LIST OF ABBREVIATIONS

Ac	acetyl
Ar	aryl
aq	aqueous
AIBN	2,2'-Azobissobutyronitrile
bp	boiling point
n-BuLi	n-butyllithium
s-BuLi	s-butyllithium
Cbz-	benzyloxycarbonyl
CSA	Camphor sulphonic acid
Comins reagent	N-(5-chloro-2-pyridyl)triflimide
DBU	1,8-diazabicylo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DIBAL-H	Diisobutylaluminium hydride
DIAD	Diisopropyl azodicarboxylate
DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
Et_3N	triethyl amine
g	gram
h	hour
IBX	*o*-iodoxybenzoic acid
LDA	lithium diisopropylamide
LAH	lithium aluminium hydride
M	molar
m-CPBA	3-chloroperoxybenzoic acid

mL	millilitre
mmol	millimole
mp	melting point
MVK	Methyl vinyl ketone
MsCl	Methanesulphonyl chloride
NMO	4-methylmorpholine N-oxide
TFA	trifluoroacetic acid
KHMDS	potassium hexamethyldisilazide
rt	room temperature
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TEA	triethyl amine
TsOH	p-toluene sulfonic acid
TsCl	p-toluene sulfonic chloride

Acknowledgement

I owe the fulfillment of this endeavor to my esteemed supervisor Dr. Ganesh Pandey for his erudite and meticulous supervision and never falling patience, which gave me constant encouragement and guidance. His painstaking efforts, immense insight, inspiring attitude, evolutionary ideas and enthusiasm enabled me to complete this research work. His thought provoking critical comments and keen insight in identifying various facets of problems have been a source of enduring patience to me without which this work could neither gather substance nor assume the present form. His scholarship, humanity made my task a joy. His efficacy led to broadcasting and deepening of my understanding of research problem. I shall always remain beholden to him.

Special thanks to all my colleagues Dr. (Mrs.) Gadre, Shrinivas, Sanjay, Balakrishna, Kishore, Keshri, Alok, Shrikant, Swarup, Gaikwad, Ravindra, Debasish, Nishant, Prasanna, Rajender, Sujit, Amrita and Anu for maintaining a warm and very cheerful atmosphere in the lab. They made working the lab very enjoyable. Special acknowledgements to Shrinivas, Bala, Nishant and Swaroop for taking trouble in bringing out the thesis.

I specially acknowledge my colleague Ravindra for the nice collaboration we had during the completion of this work. I wish him all success in his future endeavor.

Help from the spectroscopy groups of NCL is gratefully acknowledged. I sincerely thank Dr. Rajmohanan for helpful discussions and Mrs. Phalgune, Mr. Sathe and Mrs. Santakumari, Mrs. S. S. Kulkarni, Dr. Mrs. Vedabati G. Puranik for their kind cooperation.

I would like to specially thank to my senior colleagues Lahada, Sahoo, Nagesh, Murugan, Kapur, Tiwariji and all my friends from NCL for their cheerful company, which made my stay at NCL memorable one. I want to thank my friends Debdut, kartick, Dilip, Anamitra, Prabash, Soumitra, Senapati, Tikla, Sukhen, Bibhas, Roopa, Ghata, Babu-da, Deenu-da, Debu-da, Chitta-da, Ramu-da, Kamu-da, Mahu-di, Arimdam-da, Tarun, Anuradha, Samanta, Pradip, Arijit, Saikat, Bachcha, Dhona, Gach, Chanchal, Pallavi, Rahaman, Rita, Chinu, Vaku, Sougata, Amabarish, Tanushree, Nirmalya, Nabamita, Prakash, Mahesh, Sambhu, Jayanthi, Vasu and Subbu for their help whenever I needed.

I am also thankful to my teachers Debasish-da and Alok-da, who have taught me the basic chemistry and inspired me to come upto this stage.

I don't have any words to express my feelings towards my mother who has constantly encouraged me for going for higher studies, waited long enough for my return but couldn't wait anymore and left this world at beginning of my degree. May her soul rest in peace. I just can say "I love you Ma……forever."

It is equally difficult to put into words my gratitude and love to my father, brother, sisters, sister-in-law, brother-in-laws and all family members for their blessings, love, care and continuous encouragements throughout my education. I also want to thank my nice and nephews Arup, Priya and little Riya for their love and affection and also for maintaining cheering atmosphere in my home.

Finally I thank Dr. K. N. Ganesh, Head, Division of Organic Chemistry (Syn.) and Director, NCL, Pune for providing infrastructural facilities to complete my work successfully. I am also thankful to CSIR, New Delhi for the financial assistance.

Prabal Banerjee

DECLARATION

I hereby declare that the work presented in the thesis entitled **"Intra-molecular [3+2]-Cycloaddition of Non-stabilized Azomethine Ylide: Synthesis of Montanine-Type *Amaryllidaceae* Alkaloids"** submitted for Ph. D. degree to the University of Pune, has been carried out by me at The National Chemical Laboratory, Pune, under the supervision of Dr. Ganesh Pandey. The work is original and has not been submitted in part or full by me for any degree or diploma to this or any other University.

Date: (Prabal Banerjee)

Division of Organic Chemistry (Synthesis)

National Chemical Laboratory

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CONTENTS

1. Essence of Natural Product Synthesis

The task of an organic chemist is to make tools (molecules) for various uses; the method required for making these tools is called synthesis. In 1845, Kolbe used the word "synthesis" first time[1] to describe the process of assembling a chemical compound from other substances. Synthesis[2-11] forms the heart of chemistry. The formation of new substances and materials is required to meet ever changing needs and demands of the society in virtually every aspect of life—from food, clothing, shelter, to health, transportation, communications, and entertainment. Many of the substances and materials are derived from organic compounds. These forces have provided great stimulation to develop organic chemistry in general and organic synthesis in particular.

Although the practice of total synthesis and the rationale behind its pursuit have changed throughout the course of its history, its most fundamental property has remained the same. At its core, in its most essential form, natural product total synthesis is a vehicle for discovery, one that is perhaps unparalleled by any other endeavor in the realm of chemical synthesis. The reason follows: every natural product type isolated from the seemingly limitless chemical diversity in nature provides a unique set of research opportunities deriving from its distinctive three-dimensional architecture and biological properties.

As a science in its own right, organic synthesis emerged at the beginning of last century, when chemists started to master the skills of manipulating compounds in a controlled and predictable fashion eventually elaborating an arsenal of tools required for the preparation of various target products from simple starting materials. The complexity of tasks increased tremendously and by now one may safely claim that almost any compound, isolated from natural sources or conceived in the chemist's mind, can be synthesized with a reasonable amount of time and effort; such accomplishments prompts comments such as "given enough manpower and money, synthetic chemist can make any complex molecule".

As a major partner of the science as a whole, organic synthesis has contributed impressively to at least two of the most essential elements of any chemical activity: mainly, in revealing new chemistry and in understanding. Thus, one certainly quite defensible view of the role of organic synthesis is that it is an effective means for the discovery of new chemical transformations and that it fosters and improves upon old ones. In so far as the major emphasis of chemistry continues to be on chemical reactions, the necessity of discovering new or uncovering unknown aspects of previously defined reactions seems apparent. It is this role of being able to provide the means within which discovery can be made that is certainly one of the most important functions of organic synthesis. And, of course, ultimately, discovery leads to a better understanding, as such, we find in synthesis an inviting and perhaps unparalleled opportunity for expanding our knowledge of the environment in which we toil. Organic chemistry is still largely an experimental science and is likely to remain so for some time.

As a whole organic synthesis provides: great complexity and variety; challenge verging on impossibility; demand for both mental and manipulative rigor, and for dedication, persistence, and hard work; never-ending frontiers for discovery and never-ending advances in sophistication; unlimited opportunities for intellectual excitement and satisfaction; strong coupling not only with all areas of chemistry, but also with biology and medicine; relevance, at a very fundamental level to human well-being, health, and education.

"Chemical synthesis always has some element of planning in it. But, the planning should never be too rigid. Because, in fact, the specific object which the synthetic chemist uses as the excuse of his activity is often of not special importance in the general sense; rather, the important things are those that he finds out in the course of attempting to reach his objective."

R. B. Woodward[12]

The general principles that guide synthetic planning and the execution thereof are in order. The considerable task of analyzing and understanding organic synthesis as scholarly endeavor may appear rather formidable at first. The impressive and ever growing number of reactions that are at our disposal and the often justified uncertainty as to their generality may create the impression that the decisive formulation of a synthetic plan is frequently problematical. This uncertainty is largely a consequence of the fact that although a number of definite operations may be identified in the synthesis of intricate organic molecules, they are not strictly independent of one another. From the viewpoint of chemical synthesis the factors which conspire to make a synthesis difficult to plan and to execute are those which give rise to structural complexity, a point which is important, even if obvious. Less apparent, but of major significance in the development of new synthesis, is the value of understanding the roots of complexity in synthetic problem solving and the specific forms which that complexity takes. *Molecular size*, *element* and *functional-group content*, *cyclic connectivity*, *stereocenter content*, chemical *reactivity*, and structural *instability* all contribute to *molecular complexity* in the synthetic sense.

"In defining strategies and reactions to construct complex molecules, we require synthetic methods that can (i) perform a wanted structural change and none other (that is be chemoselective), (ii) orient the reacting partners in a correct fashion (be regioselective), (iii) create the correct orientation of the various parts of the molecule with respect to each other (be diastreoselective), and (iv) enable the formation of a molecule of one handedness or a mirror image isomer (be enantioselective). Such extraordinary demands are exciting challenges."

B. M. Trost[13]

For the purpose of discussion; it is of interest to depict the process of organic synthesis in general, and of total synthesis of natural products in particular, in "human terms", i.e. in an ordered set of conscious and unconscious events that are mostly

controlled by the individual investigator, from the inception of an idea to its realization. (Fig. 1)

Fig. 1. "Living" through a total synthesis:

A	Choice of Molecule	⇒	Relevance
B	Perceptive power and seeing Through the mind's eye	⇒	Personal bias, reflex, heuristic analysis, open eyed serendipity
C	Emergence of a strategy	⇒	Individual powers, creativity
D	Generation of a synthesis plan	⇒	Attention to detail, possible fixation (caution!)
E	Execution	⇒	Efficiency, practicality
F	Endurance	⇒	What price synthesis (agony and ecstasy)?
G	Contribution to science	⇒	New concepts, reactions, reagents, processes
H	Recognition	⇒	Rewards, fame, fortune, legacy

With the above perspective, it is clear that "living through" a total or partial synthesis can be an exciting, rewarding and very fulfilling endeavor. Again, with an acute sense of awareness of advances on the biological front, the synthetic organic chemist is in an ideal position to use his or her analytical, creative, and deductive skills in an effort to find target molecules for synthesis, or to provide chemical insight into complex biological phenomena through the aegis of synthesis.

Nature generates the problems

Chemistry finds solutions

Biology has the last word…

Stephen Hanessian[14]

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Experimental Section:

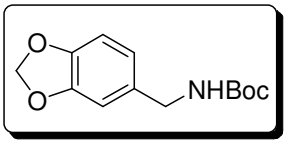
General:

All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven dried glassware (110 °C) which was cooled under argon. Solvents for anhydrous reactions were dried according to Perrin *et al*®. Benzene, DCM and triethylamine were distilled from CaH_2 and stored over molecular sieves and KOH, respectively. THF and diethyl ether were distilled over sodium benzophenone ketyl. Solvents used for chromatography were distilled at respective boiling points.

All commercial reagents were used as supplied. Progress of the reaction was monitored by TLC and gas chromatography. Column chromatography was performed on silica gel 60-120/ 100-200/ 230-400 mesh obtained from S. D. Fine Chemical Co. India or SRL India.

All melting points were uncorrected in degrees Celsius and were recorded on a Buchi melting point apparatus. IR spectra were recorded on a Perkin – Elmer infrared spectrometer model 599-B and model 1620 FT-IR. GC analysis was performed on Perkin Elmer 8700 and Varian CP 3800 gas chromatographs using a SGE BP1, BP20 and Varian Chrompack CP-Sil-5CB columns. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC-200, Bruker MSL-300 and Bruker DRX – 500 instruments. Chemical shifts are reported in δ ppm using TMS as the reference. Optical rotations were measured using JASCO 181 digital polarimeter using Na lamp. The X-ray Crystal data was obtained using Bruker SMART APEX CCD diffractometer.

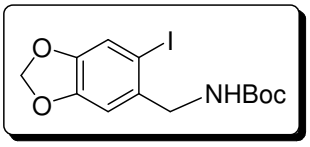
1. Preparation of *tert*-butyl benzo[d][1,3]dioxol-5-ylmethylcarbamate(208):



Piperonyl amine (5 g, 33.07mmol) was suspended in water (60 mL) and cooled with an ice bath, $(Boc)_2O$ (15.20 mL, 66.15 mmol) and sodium hydroxide (2.65 g, 66.15 mmol) were added. The ice bath was removed, and the mixture stirred overnight. The same volume of ethyl acetate was added into the flask and cooled to 0 ^oC and pH was adjusted to 2-3 with 2N HCl. The organic layer was separated with a 1M solution of $KHSO_4$ and brine, dried over $NaSO_4$ and concentrated in vacuum. The crude mass was purified by short column chromatography to obtain N-BOC protected piperonyl amine **208** as white solid (7.5 g, 90%).

mp	**:**	57-60 ^oC
IR ($CHCl_3$)	**:**	υ_{max} 3348, 2975, 1708, 1502, 1444, 1365, 1248, 1168, 1038 cm^{-1}
^1H NMR (200 MHz, $CDCl_3$)	**:**	δ 6.69 (s, 1H), 6.65 (s, 2H), 5.82(s, 2H), 5.12 (br s, 1H), 4.12 (br d, J = 5.81 Hz, 2H), 1.39 (s, 9H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ 156.1, 147.9, 146.0, 133.3, 120.8, 108.3, 101.1, 79.5, 44.6, 28.6.
Mass m/z (%)	**:**	252.23(M+1)

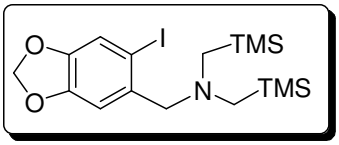
2. Preparation of *tert*-butyl (6-iodobenzo[d][1,3] dioxol-5-yl)methylcarbamate(209):



To a mixture of N-Boc piperonyl amine **208** (4.2 g, 16.73 mmol) and $AgOCOCF_3$ (4.1 g, 20.88 mmol) in choloroform (60 mL), solid iodine (4.67 g, 20.88 mmol) was added slowly via solid addition funnel over a period of 30 min and mixture was allowed to stirr at room temperature for 1 hr. Resulting reddish color mass was filtered using suction to remove yellow colored silver iodide. Filtrate was taken in a separating funnel, diluted with DCM and washed with 10% $Na_2S_2O_3$ solution (2 x 30 mL), water (2 x 30 mL) and brine (2 x 20 mL). Aqueous layer was back extracted with DCM (2 x 30 mL) and combined organic layer was dried over Na_2SO_4, concentrated under reduced pressure to afford red colored solid mass. The solid mass was transferred to a conical flask containing pet ether (50 mL) and ethyl acetate (3 mL) and contents were stirred overnight. Solid mass was filtered using suction to obtain 4.7 g (70%) of grayish colored product **209** which was pure enough to proceed for next step. Analytically pure sample was obtained by recrystallization from carbon tetrachloride.

mp	**:**	68-70 ^oC
IR ($CHCl_3$)	**:**	υ_{max} 3427, 3348, 2977, 1708, 1502, 1367, 1250, 1165, 1039 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 7.18 (s, 1H), 6.87 (s, 1H), 5.93 (s, 2H), 4.19-4.22 (br d, J = 5.87, 2H), 1.43 (s, 3H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ 155.9, 147.8, 147.9, 134.8, 118.7, 109.6, 101.9, 86.7, 49.4, 28.6.
Mass m/z (%)	**:**	378. 38(M+1)

3. (6-iodobenzo[d][1,3]dioxol-5-yl)-N,N-bis((trimethylsilyl)methyl)methaneamine(206):



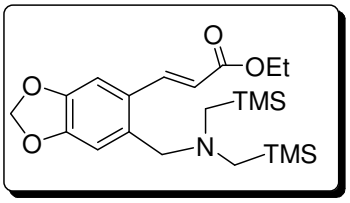
A 100 mL round bottom flask, equipped with argon gas balloon and a magnetic stir bar was charged with a solution of **208** (4 g, 10.61 mmol) in 40 mL of dry DCM and cooled to 0 ^{o}C. TFA (6.05 g, 53.05 mmol) was introduced to stirring mixture with syringe drop-wise. The mixture was allowed to stir further for 4 h. The reaction mixture was re-cooled to 0 ^{o}C and was basified with aqueous NaOH solution (pH = 10). The organic layer was separated and the aqueous layer extracted with DCM (2 x 30 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated to give crude amine, which was utilized as such without further purification for the next step.

To a stirring heterogeneous solution of crude amine and K_2CO_3 (3.75 g, 26.25 mmol) in CH_3CN (60 mL), iodo methyl trimethylsilane (3.15 mL, 21.22 mmol) was added and mixture refluxed for 10 hr. The reaction mixture was cooled to room temperature and K_2CO_3 was filtered using suction, filtrate concentrated to give a pasty mass which was dissolved into ethyl acetate and washed with water (2 x 20 mL), brine (2 x 20mL), dried over Na_2SO_4 and concentrated. The crude yellow oil was purified by silica gel column chromatography using hexane / EtOAc (95:5) as eluent to obtain **206** as pale yellow oil (3.5 g, 78%).

IR (Neat)	**:**	υ_{max} 2954, 2925, 2358, 1502, 1475, 1247, 1103, 1041 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 7.22 (s, 1H), 7.12 (s, 1H), 5.97 (s, 2H), 3.37 (s, 2H), 1.97 (s, 4H), 0.05(s, 18 H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ 148.0, 146.7, 135.6, 117.7, 109.7, 100.9, 69.4, 50.3, - 1.5.

Mass m/z (%) : 450.34 (M+1)

4. (E)-ethyl 3-(6-((bis((trimethylsilyl)methyl) amino)methyl)benzo[d][1,3]dioxol-5-yl)acrylate (205):



To a mixture of K_2CO_3 (0.55 g, 4.00 mmol), $Pd(OAc)_2$ (0.04 g, 0.16 mmol), PPh_3 (0.09g, 0.32 mmol) and **206** (1.00 g, 2.00 mmol) in 15 mL of dry CH_3CN, ethyl acrylate (1.74 mL, 16.03 mmol) was added. The mixture was purged with argon and refluxed for 10 hr under argon atmosphere. The solvent was removed under reduced pressure and whole dark-brown mass was dissolved in DCM, the organic layer was washed with 0.1N HCl (3 x 10 mL) followed by water (2 x 10 mL) and brine. The organic layer was concentrated under reduced pressure and the residue was purified by column chromatography eluting with pet ether/ethyl acetate (30:2) to afford 0.55 g (64%) of **205** as a yellow liquid.

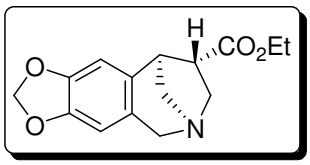
IR ($CHCl_3$) : υ_{max} 2954, 2898, 2360, 1712, 1631, 1504, 1485, 1257, 1176, 1041 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) : δ 8.12 (d, J = 15.85 Hz, 1H), 7.01 (s, 1H), 6.97 (s, 1H), 6.14 (d, J = 15.85 Hz, 1H), 5.95 (s, 2H), 4.20 (q, J = 7.07 Hz, 2H), 3.46 (s, 2H), 1.85 (s, 4H), 1.54 (t, J = 7.07 Hz, 3H), 0.27 (s, 18H).

^{13}C NMR (50 MHz,$CDCl_3$) : δ 167.0, 149.2, 146.9, 141.8, 135.3, 127.6, 117.4, 110.4, 105.6, 101.23, 63.2, 60.2, 50.7, 14.3. -1.1.

Mass m/z (%) : 422.12 (M+1)

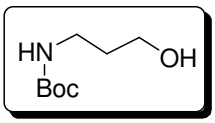
5. 4,5-Methelenedioxy-9-aza-tricyclo [7.2.1.02,7] dodeca-2,4,6-triene-11-carboxylic acid ethyl ester (204):



A solution of **205** (0.50 g, 1.90 mmol) in 30 mL of dry CH_3CN was added slowly into a argon flushed 100 mL two necked flask containing vacuum dried Ag(I)F (0.187 g, 1.48 mmol) in 10 mL dry CH_3CN. The color of the reaction mixture gradually turned to dark brown with concomitant deposition of silver on the surface of the flask in the form of a mirror. The reaction was monitored periodically by TLC. After stirring for 12h, the reaction mixture was filtered through a small plug of basic alumina and the solvent was evaporated to give a crude brown residue which was purified by silica gel column chromatography (eluent: pet. ether/ethyl acetate = 8:2) to give **204** (0.20 g, 60%) as a white solid.

mp	**:**	260-262 °C
IR ($CHCl_3$)	**:**	υ_{max} 2360, 1730, 1586, 1481, 1380 cm^{-1}
^{1}H NMR (500 MHz, $CDCl_3$)	**:**	δ 6.47 (s, 1H), 6.36 (s, 1H), 5.79 (s, 2H), 4.24 (d, J = 16.96 Hz, 1H), 4.06 (q, J = 7.34, 6.87 Hz, 2H), 3.83 (d, J = 16.96 Hz, 1H), 3.37 (dd, J = 12.83, 4.13 Hz, 1H), 3.20 (br d, J = 1.83 Hz, 1H), 3.11 (br dd, J = 11.40, 1.81 Hz, 1H), 3.04 (dd, J = 11.45, 2.29 Hz, 1H), 2.98 (d, J = 11.45 Hz, 1H), 2.96 (dd, J = 10.01, 4.32, 1H), 1.17 (t, J = 7.34, 6.87 Hz, 3H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ 172.9, 146.5, 145.8, 133.9, 124.1, 106.7, 106.3, 100.6, 60.7, 59.0, 57.4, 55.3, 54.5, 53.7, 42.0, 13.3.
Mass m/z (%)	**:**	276.32 (M+1)

6. Preparation of (3-hydroxy-propyl)-carbamic acid *tert-butyl* ester :



To a stirring solution of 3-amino propanol (15 g, 245.79 mmol) in DCM (600 ml) at 0 °C, Et_3N (47.92 mL, 294.69 mmol) was added. $(Boc)_2O$ (56.34 mL, 245.79 mmol) was added to the reaction mixture very slowly and stirring was continued for 36h at room temperature. Reaction mixture was diluted with DCM (300 mL) and washed with water (3 x 100 mL) and brine (1 x 100 mL). The organic layer was dried over Na_2SO_4 before concentrating under reduced pressure. The resultant brown colored residue was purified by vacuum distillation (b.p. 100 °C / 1mm) to obtain the product (31.5 g, 90%) as a colorless oil.

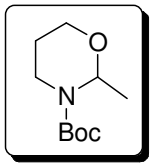
IR (Neat) : υ_{max} 3357.84, 2975.96, 2935, 1691.46, 1529.45, 1367.44, 1367.44, 1278.72, 1253.64, 1172.64, 1047.27 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 3.6 (t, J= 5.48, 5.87 Hz, 2H), 3.2 (q, J= 5.87,6.65, 2H), 1.6 (m, 2H), 1.4 (s, 9H)

^{13}C NMR (50 MHz,$CDCl_3$) : δ 156.5, 79.0, 59.0, 37.5, 32.0, 28.0

Mass m/z (%) : 176.22 (M+1)

7. Preparation of 2-mehyl- [1,3] oxazinane –3-carboxylic acid *tert*-butyl ester (211)

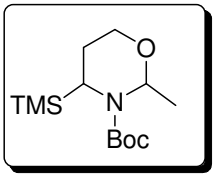


To a solution of N-Boc derivative of amino propanol (25 g, 142.85 mmol) in 425 mL of benzene and PPTS (1.8 g, 7.14 mmol), acetaldehyde diethyl acetal (24.40 mL, 171.42

mmol) was added slowly into the reaction mixture. The reaction mixture was subjected to azeotropic distillation for a period of a 10h using very long distillation head maintaining distillation teperature between 67-71 °C. The brown colored mixture was washed with saturated $NaHCO_3$ (2 x 100 mL), water (2 x 100 mL), brine (1 x 200 mL), dried over Na_2SO_4 and concentrated. The residue was purified by vacuum distillation (b.p. 64-67 °C, 1mm) to obtain **211** (24.5 g, 86%) as colorless oil.

IR (Neat)	**:**	υ_{max} 2975.96, 1703.03, 1477.37, 1407.94, 1278.12, 1155.28, 1107.16, 1024.13 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 5.46(q, J= 6.26 Hz, 1H), 3.93(dt J= 3.53,10.96,11.35 Hz, 2H), 3.54(m, 1H), 3.06(8 lines pattern, J= 3.91Hz, 1.18 Hz, 12.52 Hz.12.18 Hz, 1H), 1.41(m, lH), 1.31(s, 3H), 1.27(s, 2H), 1.24(s, 2H)
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ 153.78, 80.08, 79.16, 59.71, 36.70, 28.51, 25.53, 16.01
Mass m/z (%)	**:**	MALDI TOF 202 (M + 1)

8. Preparation of 2-methyl-trimethylsilanyl-[1,3]-oxazaninane-3-carboxylic acid *tert*-butyl ester (212):



A solution of **211** (8 g, 39.81 mmol) in 60 mL of dry THF was charged into a 250 mL two necked RB flask equipped with magnetic stirring bar and argon gas balloon and was cooled to –78 °C. TMEDA (12.07 mL, 79.64 mmol) followed by s-BuLi (1.5 M solution in cyclohexane, 53.09 mL, 79.64 mmol) were introduced to the stirring mixture drop-wise over a period of 30 min. The mixture was further allowed to stir for 4h at –78 °C. The reaction mixture was allowed to warm to room temperature and further stirred for 2h and quenched with 30 mL of saturated aqueous NH_4Cl solution. The mixture was extracted with ethyl

acetate (3 x 100 mL) and washed with brine (2 x 70 mL), dried over Na_2SO_4 and concentrated under vacuum. The yellowish colored mixture was purified by fractional distillation (b.p. 77-80 ^oC / 1 mm) to give **212** (10 g, 90-92 %) as colorless oil.

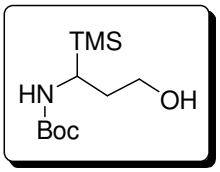
IR (Neat) : υ_{max} 2977, 2945, 2862, 1693, 1413, 1367, 1298, 1247, 1166, 1093, 844 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 5.43 (q, J = 6.06 Hz, 1H), 3.93 (m, 1H), 3.60 (m, 1H), 2.65 (dd, J = 10.74, 4.67 Hz, 1H) 1.76 (m, 2H), 1.36-1.68(broad singlet, 12H), 0.08 (s, 9H).

^{13}C NMR (50 MHz,$CDCl_3$) : δ 154.5, 81.1, 79.6, 61.1, 39.1, 28.3, 26.7, 17.5, -1.08.

Mass m/z (%) : EI-MS: 274 (M + H, 1), 258 (1), 244 (1), 230 (3), 216 (13), 202 (9), 186 (2), 158 (22), 73 (83), 57 (100).

9. Preparation of (3-hydroxy-1-trimethylsilanyl-propyl)-carbamic acid *tert*-butyl ester (213):



To a solution of the **212** (10 g, 36.63 mmol) in 250 mL of methanol and 8mL of water, PTSA (0.25 g) was added and the mixture was stirred for 4h at room temperature. Methanol was evaporated in rotary evaporator and whole mass was dissolved in ethyl acetate and washed with saturated $NaHCO_3$ solution (2 x 50 mL), water (2 x 50 mL), brine (2 x 50 mL), dried over Na_2SO_4 and concentrated under vacuum to give **213** as a white crystalline solid (8 g, quant.), which was sufficiently pure enough to proceed for the next step.

mp : 72-74 ^oC

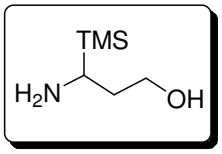
IR ($CHCl_3$) : υ_{max} 3440, 2979, 1683, 1500, 1367, 1253, 1215, 1045 cm^{-1}

^1H NMR (200 MHz, $CDCl_3$) : δ 3.58 (m, 2H), 3.21 (broad dd, J= 2.74, 12.52 Hz, 1H), 1.69(m, 1H), 1.44(s, 9H), 0.06(s, 9H).

^{13}C NMR (50 MHz,$CDCl_3$) : δ 158.1, 79.2, 58.0, 35.6, 33.6, 28.0, 3.9.

Mass m/z (%) : GC-MS 190 (M-57)

10. Preparation of amino-3-trimethylsilanyl-propan-1-ol (214):



A one Lit. RB flask was charged with 10 g (40.49 mmol) of **213**, 1,4-dioxane 200 mL and 1N HCl 100 mL. The mixture was refluxed for 45 min and cooled to RT and further cooled to 0 ^0C, neutralized with 2N NaOH solution, extracted with DCM (3 x 100 mL), dried over Na_2SO_4 and evaporated under reduce pressure to give **214** (5.2 g, 87%) as an yellowish oil. This sample was pure enough and used for next step without further purifications. The analytically pure sample was obtained by passing through a small silica gel column.

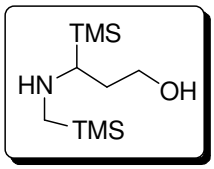
IR (Neat) : υ_{max} 3353, 3284, 1431, 1369, 1249, 1053, 838 cm^{-1}

^1H NMR (200 MHz, $CDCl_3$) : δ 3.62 (t, J= 5.81 Hz, 2H), 2.87 (br s, 3H), 2.23 (br d, J= 9.53 Hz, 1H), 1.48 (m, 1H), 1.38 (m, 1H), - 0.13 (s, 9H)

^{13}C NMR (50 MHz,$CDCl_3$) : δ 66.8, 62.8, 34.2, - 4.3.

Mass m/z (%) : GC-MS 147 (M^+).

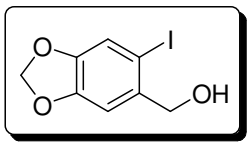
11. Preparation of trimethylsilanyl-3-(trimethyl-silanylmethyl-amino)-propan-1-ol (179) :



To a stirring heterogeneous solution of **214** (1 g, 6.79 mmol) and K_2CO_3 (2.8 g, 20.39 mmol) in CH_3CN (20 mL), iodo methyl trimethylsilane (1 mL, 6.79 mmol) was added and mixture was refluxed for 10h. The reaction mixture was cooled to room temperature and K_2CO_3 was filtered out using suction. Filtrate was evaporated off under vacuum to remove CH_3CN. The resultant pasty mass was dissolvrd in ethyl acetate and washed with water (2 x 10 mL), brine (2 x 10mL), dried over Na_2SO_4 and concentrated under vacuum to give **179** as a reddish yellow oil (1.25 g, 80%). The material was used as such for next step without further purification. The analytically pure sample was obtained by passing through a small silica gel column.

IR ($CHCl_3$)	**:**	υ_{max} 3392, 2952, 1502, 1475, 1249, 1226, 1103, 1039 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 3.81 (m, 2H), 3.53 (broad singlet, 2H), 2.37(dd, J = 8.95, 4.01 Hz,1H), 2.25 (d, J = 14.95 Hz,1H), 2.18(d, J = 14.95 Hz, 1H), 1.76(m, 2H), 0.21 (s, 9H), 0.11 (s, 9H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ 65.5, 55, 40.1, 30.1, - 0.2, - 0.3
Mass m/z (%)	**:**	GC-MS 233 (M^+)

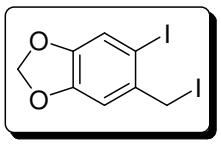
12. Preparation of (6-iodo-benzo[1,3]dioxol-5-yl)-methanol (210) :



To a mixture of piperonyl alcohol (1.5 g, 9.86 mmol), $AgOCOCF_3$ (2.6 g, 11.83 mmol) in chloroform (30 mL), iodine (3g, 11.83 mmol) was added slowly via solid addition funnel over a period of 30 min and mixture was stirred at room temperature for 1 h. Resulting reddish color mass was filtered using suction to remove yellow colored silver iodide and filtrate was taken into a separating funnel, diluted with DCM and washed with 10% $Na_2S_2O_3$ solution (2 x 20 mL), water (2 x 20 mL), brine (2 x 15 mL). Aqueous layer was back extracted with DCM (2 x 25 mL) and combined organic layer was dried over Na_2SO_4, concentrated under reduced pressure to afford red colored solid mass which was treansferred again to a mixture of pet ether (20 mL) and ethyl acetate (1 mL) and was stirred overnight. Solid mass was filtered using suction to give 1.8 g (65%) pale yellow colored product **210**, which was pure enough to carry forward to next step. Analytically pure sample was obtained by recrystalization of the above mass from carbon tetrachloride.

mp	**:**	107 –109 ^{o}C
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 7.23 (s, 1H), 6.99 (s, 1H), 5.98 (s, 2H), 4.59 (s, 2H), (1.88, br s, 1H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	148.8, 148.0, 136.5, 118.7, 109.6. 109.9, 101.96, 99.9.
Mass m/z (%)	**:**	MALDI TOF 278 (M+H)

13. Preparation of 5-Iodo-6-iodomethyl-benzo[1,3]dioxole (178) :

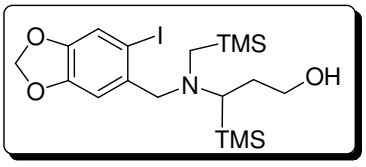


A 100 mL two necked RB flask was charged with **210** (3.6 g, 13.01 mmol) and NaI (3.3 g, 26.02 mmol), degassed thoroughly with argon and CH_3CN (40 mL) was added to it. To the vigorously stirring above solution, TMSCl (3.3 mL, 26.02 mmol) was added very slowly while continuing the stirring for further 10 min. The red brown colored reaction mixture was quenched using 10% NaS_2O_3 solution (20 mL). The reaction mixture was transferred into a separating funnel and extracted with DCM (2x50 mL), washed with 10% NaS_2O_3 solution (1 x 20 mL), water (1 x 20 mL), brine (1 x 30 mL), concentrated under reduced pressure to give **178** as a white solid (5 g, quant) which was sufficiently pure enough to be used in the next step.

mp : 75-77 ^oC

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.28 (s, 1H), 6.96 (s, 1H), 6.02 (s, 2H), 4.65 (s, 2H)

14. Preparation of 3-[(6-iodo-benzo [1,3] dioxol-5-ylmethyl)-trimethylsilanylmethyl-amino]-3-trimethyl-silanyl-propan-1-ol (215):

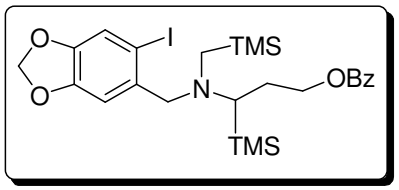


To a solution of **178** (5 g, 12.93 mmol) in 50 mL dry CH_3CN, K_2CO_3 (3.58 g, 25.87 mmol) and bissilylated amino alcohol **179** (3 g, 12.93 mmol) were added. The resultant suspension was refluxed for 7-8 h. Progress of the reaction was monitored by TLC. On completion of the reaction, mixture was cooled, filtered and the solvent was evaporated under vacuum. The resultant pasty mass was taken in ethyl acetate and washed with water (2 x 50 mL), brine (2 x 40mL), dried over Na_2SO_4 and concentrated under vacuum to give a

brown colored mass, which was purified by column chromatography (silica, pet ether-ethyl acetate, 9:1) to obtain **215** as a pale yellow oil (6.4 g, 72%).

IR (Neat)	:	υ_{max} 3348, 1502, 1475, 1248, 1217, 1039 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 7.13 (s, 1H), 6.93 (s, 1H), 5.87 (s, 1H), 5.86 (s, 1H), 3.60-3.75 (m, 3H), 3.52 (d, J = 14.15 Hz, 1H), 2.39 (dd, J = 9.57, 4.25 Hz, 1H), 2.13 (d, J = 14.52 Hz, 1H), 2.05 (d, J = 14.52 Hz, 1H), 1.81-2.02 (m, 1H), 1.32-1.50 (m, 1H), 0.11 (s, 9H), 0.00 (s, 9H).
^{13}C NMR (50 MHz,$CDCl_3$)	:	δ 149.0, 147.7, 135.1, 118.5, 109.9, 101.8, 88.1, 65.1, 64.2, 55.9, 45.4, 29.8, -0.4, -0.9.
Mass m/z (%)	:	FAB 494 (M+H)
Elemental Analysis	:	Calculated C: 43.81, H: 6.54, N: 2.84 Found C: 43.48, H: 6.16, N: 3.15.

15. Preparation of benzoic acid 3-[(6-iodo-benzo[1,3]dioxol-5-ylmethyl)-trime-thyl-silanylmethyl-amino]-3-trimethylsil-anyl-propyl ester (177):



Into a cooled (0 ^{0}C) solution of alcohol **215** (6.4 g, 12.98 mmol) in dry DCM (40 mL), was added Et_3N (2.9 mL, 19.3 mmol). BzCl (1.8 mL, 15.5 mmol) was added drop-wise to the solution, allowed to come to room temperature and stirred for 6h. The mixture was diluted with DCM (50 mL), washed with water, brine and the water layer was back extracted with DCM (2 x 20 mL). The combined DCM layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography (pet. ether / ethyl acetate = 20:1) to obtain **177** (6.2 g, 81%) as an yellowish oil.

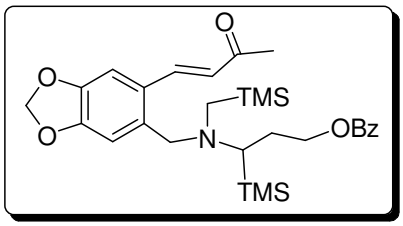
IR (Neat) : υ_{max} 1712, 1521, 1473, 1276, 1249, 1114, 1039 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 7.94 (m, 2H), 7.57 (m, 1H), 7.44 (t, J = 7.81 Hz, 2H), 7.09 (s, 1H), 7.05 (s, 1H), 5.92 (s, 1H), 5.84 (s, 1H), 4.37 (m, 2H), 3.65 (br d, J = 1.85 Hz, 2H), 2.35 (dd, J = 9.25, 4.81 Hz, 1H), 2.26 (d, J = 14.51 Hz, 1H), 2.23 (d, J = 14.51 Hz, 1H), 2.00 (m, 1H), 1.82 (m, 1H), 0.00 (s, 9H), - 0.05 (s, 9H);

^{13}C NMR (125 MHz,$CDCl_3$) : δ 166.2, 148.3, 146.9, 135.5, 132.4, 130.1, 129.2, 127.9, 117.7, 109.7, 101.2, 86.8, 63.1, 63.4, 50.0, 44.7, 26.5, - 0.4, - 1.4.

Mass m/z (%) : FAB 598 (M + H).

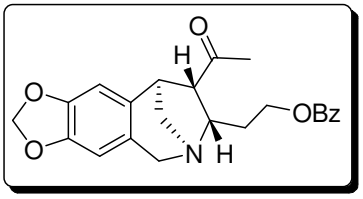
16. Preparation of benzoic acid 3-{[6-(3-oxo-but-1-enyl)-benzo[1,3]dioxol-5-ylme-thyl]-trimethyl-silanylmethyl-amino}-3-trimethylsilanyl-propyl ester (176):



To a mixture of K_2CO_3 (1.53 g, 11.04 mmol), $Pd(OAc)_2$ (0.099 g, 0.44 mmol), PPh_3 (0.23 g, 0.88 mmol) and **177** (3.3g, 5.52 mmol) in 20 mL of dry CH_3CN, methyl vinyl ketone (MVK, 3.66 mL, 44.17 mmol) was added. The mixture was degassed several times with argon and refluxed for 12 h under argon atmosphere. The solvent was removed under reduced pressure and whole dark-brown mass was dissolved in DCM, the organic layer was washed with 0.1N HCl (3 x 10 mL) followed by water (2 x 10 mL) and brine. The organic layer was concentrated under reduced pressure and the residue was purified by column chromatography eluting with pet. ether / ethyl acetate (20:2) to afford 1.79 g (60%) of **176** as an yellow solid.

mp	**:**	98-100 °C
IR ($CHCl_3$)	**:**	υ_{max} 3018, 2954, 2898, 1712, 1666, 1593, 1481, 1274, 1253, 1178, 1116, 1039 cm^{-1}**.**
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 7.81 (d, J = 16.92 Hz, 1H), 7.75 (m, 2H), 7.39 (m, 1H), 7.25 (m, 2H), 6.86 (s, 1H), 6.69 (s, 1H), 6.28 (d, J = 16.92, 1H), 5.74 (s, 1H), 5.66 (s, 1H), 4.11 (t, J = 6.44 Hz, 2H), 3.57 (s, 2H), 2.19 (s, 3H), 1.96-2.14 (m, 3H), 1.50 to 1.90 (m, 2H), 0.00 (s, 9H), -0.05 (s, 9H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ 197.7, 166.3, 149.8, 147.2, 139.9, 135.5, 132.8, 130.6, 129.5, 128.3, 127.4, 126.4, 110.4, 105.5, 101.5, 63.6, 56.7, 49.4, 45.3, 28.3, 26.6, -0.09, - 0.97.
Mass m/z (%)	**:**	TOF MS 540.2581 (M+H)
Analytical Calculations	**:**	$C_{29}H_{41}NSi_2O_5$: calculated: C, 64.52; H, 7.66; N, 2.59; found: C, 64.94; H, 7.99, N, 2.79.

17. Preparation of benzoic acid 2-(11-acetyl-4,5-methylenedioxy-9-aza-tricyclo [7.2.1.02,7]dodeca-2,4,6-trien-10-yl)-ethyl ester (174):

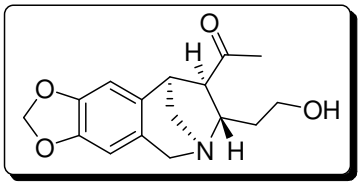


A solution of **176** (0.2 g, 0.37 mmol) in 8 mL of dry CH_3CN was introduced dropwise into an argon flushed 25 mL two necked flask containing a vacuum dried Ag(I)F (0.187 g, 1.48 mmol) in 2 mL dry CH_3CN. The color of the reaction mixture gradually turned to dark brown with concomitant deposition of silver on the surface of the flask in the form of mirror. The reaction was monitored periodically by TLC. After stirring for 12h, the reaction mixture was filtered through a small plug of basic alumina and the solvent was evaporated to give a

crude brown residue which was purified by silica gel column chromatography (eluent: pet. ether/ethyl acetate = 8:2) to give **174** (0.082 g, 56%) as an yellowish gummy liquid.

IR (Neat)	**:**	υ_{max} 3016, 1710, 1502, 1483, 1357, 1274, 1118, 1039 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$)	**:**	δ 8.05 (m, 2H), 7.58 (m, 1H), 7.46 (m, 2H), 6.49 (s, 1H), 6.46 (s, 1H), 5.90 (s, 2H), 4.58 to 4.63 (m, 1H), 4.51 to 4.55 (m, 1H), 4.32 (d, J = 17.48 Hz, 1H), 3.38 (d, J = 17.48 Hz, 1H), 3.60 (br t, J = 9.54, 9.14 Hz, 1H), 3.48 (d, J = 8.74 Hz, 1H), 3.36 (br d, J = 11.53, 1H), 3.13 (d, J = 3.18 Hz, 1H), 3.00 (d, J= 11.53, 1H), 2.21 (s, 3H), 1.65 to 1.85 (m, 2H).
^{13}C NMR (125 MHz,$CDCl_3$)	**:**	δ 207.6, 166.2, 146.4, 145.5, 132.6, 130.1, 129.2, 128.1, 106.6, 106.2, 100.4, 65.2, 64.5, 63.5, 60.2, 53.9, 43.6, 32.2, 30.9.
Mass m/z (%)	**:**	TOF MS 394.1671 (M+H).

18. Preparation of 1-[10-(2-hydroxy-ethyl)-4,5-methylenedioxy-9-aza-tricyclo [7.2.1.02,7]dodeca-2,4,6-trien-11-yl]-ethanone (217):

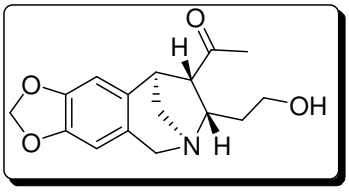


To a solution of **174** (0.25 g, 0.64 mmol) in 2 mL of MeOH, LiOH (0.023 g, 0.95 mmol) was added and the heterogeneous mixture was stirred at room temperature for 3h. The reaction mixture was evaporated under vacuum to remove MeOH. The residual mass was taken in DCM (10 mL), washed with water and brine. The aqueous layer was back extracted with DCM (2 x 5 mL), combined organic layer was dried over Na_2SO_4, evaporated under reduced pressure to give a brown colored residue. The residue was purified by silica gel column chromatography ($CHCl_3$ / MeOH = 95:5) to obtain **217** (0.175

g, almost quantitative) as a gummy liquid which on further crystallization from EtOH gave slightly reddish colored solid. Further crystallization from the same solvent gave white crystalline solid.

mp	**:**	148-150 ^{o}C
IR ($CHCl_3$)	**:**	υ_{max} 3404, 3018, 1710, 1504, 1483,1041 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$)	**:**	δ 6.47 (s, 1H), 6.41 (s, 1H), 5.91 (s, 1H), 5.90 (s, 1H), 4.31 (d, J = 16.69 Hz, 1H), 3.91 (d, J = 16.70 Hz, 1H), 3.86 (dd, J = 11.13, 1.59 Hz, 1H), 3.80 (br t, j = 3.58, 1H), 3.72 (five lines pattern, J = 5.96, 5.16, 4.37 Hz, 1H), 3.36 (dd, J = 5.17, 2.78 Hz, 1H), 3.32 (dd, J = 11.53, 2.38 Hz, 1H), 3.11 (d, J = 11.13 Hz, 1H), 3.10 (br d, J = 2.38 Hz, 1H), 2.19 (s, 3H), 1.72-1.78 (m, 1H). 1.52-1.56 (m, 1H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ 204.5, 147.0, 145.6, 129.3, 124.6, 107.1, 106.6, 100.6, 70.3, 65.9, 62.6, 59.5, 54.9, 42.9, 35.6, 30.0
Mass m/z (%)	**:**	FAB 290 (M+H)
HRMS	**:**	Calculated 289.1311408 found 289.130532 Molecular formula $C_{16}H_{19}NO_4$.

19. Preparation of 1-[10-(2-hydroxy-ethyl)-4,5-methylenedioxy-9-aza-tricyclo [7.2.1.02,7]dodeca-2,4,6-trien-11-yl]-ethanone (216):

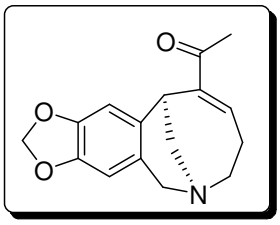


Experimental procedure was same as mention for **217** except the temperature was maintained 0 ^{o}C by using cooling machine.

^{1}H NMR (500 MHz, $CDCl_3$) : δ 6.45 (s, 1H), 6.44 (s, 1H), 5.87 (s, 2H), 4.31 (d, J = 17.59 Hz, 1H), 3.76-3.82 (m, 3H), 3.67 (br t, J = 9.96 Hz, 1H), 3.43 (d, J = 8.80 Hz, 1H), 3.35 (dd, J = 11.71, 2.93 Hz, 1H), 3.12 (d, J = 2.93 Hz, 1H), 2.98 (d, J = 11.73 Hz, 1H), 2.12 (s, 3H), 1.63-1.76 (m, 1H), 1.31-1.40 (m, 1H).

Mass m/z (%) : FAB 290 (M+H)

20. Preparation of 1-(4,5-methelenedioxy-9-aza-tricyclo[7.4.1.02,7]tetradeca-2,4,6,12-tetraen-13-yl)-ethanone (221):



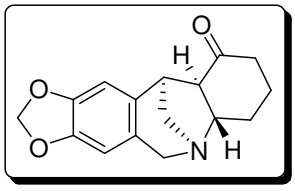
A solution **217** (0.08 g, 0.28 mmol) in 2 mL of dry DCM was charged into a 10 mL two necked RB flask equipped with magnetic stirring bar and argon gas balloon and the contents were cooled to –15 ^oC. Et_3N (0.06 mL, 0.41 mmol) followed by MsCl (0.03 mL, 0.38 mmol) were introduced into the stirring mixture drop-wise over a period of 30 min. The mixture was quenched with saturated $NaHCO_3$ (2 mL) and extracted with DCM (3 x 5mL), dried over Na_2SO_4 and concentrated under vacuum. The crude mass was purified by quick silica gel column chromatography (eluent: $CHCl_3$ / MeOH = 95:5) to give mesylated derivative of **217** (0.08 g, 77%) as a reddish colored mass which was used for next step immediately.

A solution of the crude mesylate (0.08 g, 0.22 mmol) in 5 mL of THF was transferred into a 10 mL two naked RB flask fitted with argon gas balloon and was cooled to -78 ^0C. LDA [0.33mmol, prepared by the addition of 1.5M n-BuLi in hexane (0.22 mL, 0.33 mmol) to diisopropyl amine (0.05 mL. 0.33 mmol) in 1 mL of THF at 0 ^0C)] was added dropwise and mixture was stirred at the same temperature for 1h. After bringing up the

reaction mixture to rt, it was quenched with saturated NH_4Cl solution and extracted with ethyl acetate (2 x 5mL), washed with water (2 x 2 mL), brine (2 x 3 mL) and dried over Na_2SO_4. The crude mass was purified by silica gel column chromatography (eluent: CH_3Cl / MeOH = 95:5) to produce rearranged product **221** (0.035 g, 60%) as a yellowish liquid.

IR ($CHCl_3$)	**:**	υ_{max} 2964,1668, 1485, 1421, 1363, 1041 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 6.80-6.95 (br dd, J = 4.55 and 2.90 Hz, 1H), 6.49 (s, 1H), 6.43 (s, 1H), 5.84 (s, 2H), 4.46 (d, J = 16.90 Hz, 1H), 4.37 (br s, 1H), 3.78 (d, J = 17.30Hz, 1H), 3.35-3.28 (m, 4H), 2.49-2.67 (m, 1H), 2.31 (s, 3H), 2.26 (m, 1H)
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ 198.1, 148.2, 147.7, 147.2, 142.6, 126.5, 121.6, 108.6, 105.2, 101.3, 52.8, 52.5, 50.3, 31.3, 25.5, 24.7.
Mass m/z (%)	**:**	GC-Ms 271 (M^+), 256, 242, 228, 214, 200, 186, 174.

21. Preparation of 11a(*epi*)-8,9-methylenedio-xy-5,11-methanomorphanthridin-1-one(170a):

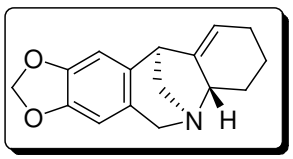


A solution of the mesylated derivative of epimerized alcohol **217** (0.2 g, 0.56 mmol) in 10 mL of THF was charged into a 25 mL two naked RB flask fitted with argon gas balloon and was cooled to -78 ^{0}C. KHMDS (2 mL of 0.8M stock solution in THF, 1.67 mmol) was added dropwise into the flask and mixture stirred at the same temperature for 1h and finally allowed to come to rt. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with ethyl acetate (2 x 8 mL), washed with water (2 x 2 mL) and brine (2 x 3 mL). The combined aqueos solution was again extracted with DCM (2 x 8 mL) and dried over Na_2SO_4. The crude mass was purified by silica gel column

chromatography (eluent: CH_3Cl/MeOH = 95:5) to produce the **170a** (0.085 g, 58%) as a gummy yellowish mass.

IR ($CHCl_3$)	**:**	υ_{max} 2958, 1701, 1504, 1483, 1232, 1066, 1041cm^{-1}
^{1}H NMR (500 MHz, $CDCl_3$)	**:**	δ 6.47 (s, 1H), 6.42 (s, 1H), 5.83 (s, 1H), 5.81 (s, 1H), 4.33 (d, J = 16.26 Hz, 1H), 4.12 (8 lines pattern, J = 11.45, 4.35, 1.60 Hz, 1H), 3.86 (d, J = 16.26 Hz, 1H), 3.72 (ddd, seven lines appeared, J = 11.45, 2.39, 1.83 Hz, 1H), 3.43 (br d, J = 2.06 Hz, 1H), 3.39 (br dd, J = 11.45, 4.13, 1H), 3.04 (d, J = 10.97 Hz, 1H), 2.98 (dd, J = 11.67, 2.12 Hz, 1H), 2.23 (m, 1H), 1.80 (br d, J = 1.37 Hz, 2H), 1.64-1.72 (m, 1H), 1.50-1.60 (m, 1H).
^{13}C NMR (125 MHz,$CDCl_3$)	**:**	δ 211.7, 146.6, 146.4, 141.1, 132.0, 106.8, 106.7, 100.8, 63.6, 60.54, 59.4, 55.2, 41.4, 29.4, 26.4, 17.1.
Mass m/z (%)	**:**	LC MS 272 (M+H)

22. Preparation of $\Delta^{1\text{-}11a}$-8,9-methylenedioxy-5,11-methanomorphanthridine (220):

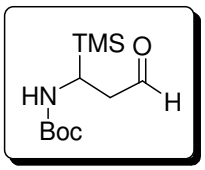


LDA [0.29 mmol, prepared by the addition of 1.5M n-BuLi in hexane (0.20 mL, 0.29 mmol) to diisopropyl amine (0.0.05 mL, 0.29 mmol) in 1 mL of THF at 0 ^{0}C)] was added dropwise to a solution of **170a** (0.064 g, 0.24 mmol) in 5 mL of THF into a 10 mL two naked RB flask fitted with argon gas balloon and which was cooled previously to -78 ^{0}C. The mixture was stirred at the same temperature for 1h and a solution of 0.14 g (0.35 mmol) of comins reagent in 2 mL of THF was added slowly. After bringing up the reaction mixture to rt over period of 5 h, it was quenched with saturated NH_4Cl solution and extracted with

ethyl acetate (2 x 5mL), washed with water (2 x 2 mL), brine (2 x 3 mL) and dried over Na_2SO_4 to give crude enol triflate (. The crude mass was purified by silica gel column chromatography (eluent: CH_3Cl / MeOH = 95:5) to produce rearranged product **221** (0.09 g) as a yellowish liquid.

To a slurry of LiCl (0.03 g, 0.71 mmol) and $Pd(PPh_3)_4$ (0.014 g, 0.02 mmol) in 5 mL of THF was added a solution 0.24 mmol of crude enol-triflate in 1.5 mL of THF in 25 mL two necked flask fitted with a reflux condenser and argon balloon system. Followed by triethylsilane (0.03 mL, 0.35 mmol) was added to the reaction mixture and flushed with argon several times and refluxed for 24 h. The reaction mixture was cooled to rt and taken in ethyl acetate and washed with water (2 x 50 mL), brine (2 x 40mL), dried over Na_2SO_4 and concentrated under vacuum to give a brown colored mass which was purified by column chromatography (silica, choloform-methanol, 9:1) to obtain **220** as a gummy yellowish mass (0.040 g, 71%). The spectral characteristic matches with the reported values in the literature.

23. tert-butyl 3-oxo-1-(trimethylsilyl)propyl-carbamate (227):



A mixture of N-Boc protected silylated aminopropanol **213** (1 g, 4.04 mmol) and IBX (1.7 g, 6.07 mmol) in 24 mL ethyl acetate was charged into a two necked RB flask equipped with magnetic stirring bar, argon balloon system and refluxed overnight. After cooling to room temperature, the solution was passed through celite pad and concentrated under vacuum to produce the corresponding aldehyde **227** (0.9 g, 90%) which was sufficiently pure enough to be used for next step.

IR ($CHCl_3$) : υ_{max} 3389, 1720, 1643, 1465, 1313, 1176 cm^{-1}

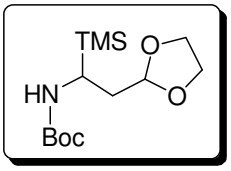
^{1}H NMR : δ 9.81 (bs, 1H), 4.53 (bs, 1H), 3.51 (m, 1H), 2.52 (m,

(200 MHz, $CDCl_3$) 2H), 1.41 (s, 9H), 0.01 (s, 9H).

^{13}C NMR (50 MHz,$CDCl_3$) : δ 202.0, 156.2, 80.3, 45.1, 37.1, 28.3, -4.3.

Mass m/z (%) : MALDI TOF 246 (M+H)

24. tert-butyl 2-(1,3-dioxolan-2-yl)-1-(trimethylsilyl)ethylcarbamate (228):



A mixture of **227** (1 g, 4.10 mmol), ethylene glycol (0.3 g, 4.90 mmol) and *p*-TSA (0.05 g) was refluxed in benzene for 8 h under Dean-Stark condition. The solvent was evaporated under reduced pressure and whole residue was dissolved in ethyl acetate (10 mL). The organic layer was washed with water (2 x 5 mL), brine and dried over Na_2SO_4. Column chromatography of the crude reaction mixture using EtOAc/hexane (9:1) as eluent afforded 1.1 g of **228** (quant.) as a white crystalline solid.

mp : 57-59 °C

IR ($CHCl_3$) : υ_{max} 3440, 3357, 1693, 1500, 1390, 1365, 1249, 1170, 1043, 1027cm^{-1}

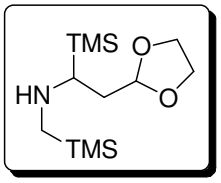
^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.86 (t, J = 4.70 Hz, 1H), 4.46 (br d, J = 9.00 Hz, 1H), 3.83 (m, 2H), 3.77 (m, 2H), 3.23 (m, 1H), 1.68 (dd, J = 9.39, 4.31 Hz, 2H), 1.37 (s, 9H), -0.02 (s, 9H).

^{13}C NMR (50 MHz,$CDCl_3$) : δ 156.3, 103.9, 79.1, 65.1, 64.6, 37.6, 35.8, 28.6, -3.2.

Mass m/z (%) : LCMS 290(M+H)

Analytical Calculations : $C_{13}H_{27}NO_4Si$: calculated: C, 53.94; H, 9.40; N, 4.84; Found: C, 53.96; H, 9.38; N, 4.70.

25. 2-(1,3-dioxolan-2-yl)-1-(trimethylsilyl)-N-((trimethylsilyl)methyl)ethanamine (226):



This experiment was performed using same procedure as described for **208**.

IR ($CHCl_3$) : υ_{max} 3346, 3166, 2954, 2896, 1679, 1612, 1415, 1253, 1192, 1132, 1041 cm^{-1}

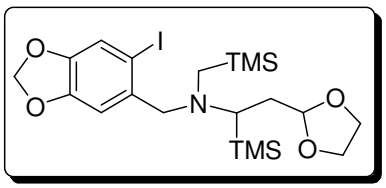
^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.95 (dd, J = 4.69, 3.52 Hz, 1H), 3.99 (m, 2H), 3.78 (m, 2H), 2.66 (br d, J = 9.45 Hz, 1H), 2.26 (d, J = 13.69 Hz, 1H), 2.04 (d, J = 13.72 Hz, 1H), 1.96 (d, J = 13.72 Hz, 1H), 1.81 (m, 1H), 1.43(m, 1H), 0.08 (s, 9H), 0.06 (s, 9H).

^{13}C NMR (50 MHz,$CDCl_3$) : δ 104.3, 65.1, 64.9, 48.3, 37.9, 30.9 -2.4, -2.7

Mass m/z (%) : LCMS 276(M+H)

Analytical Calculations : $C_{12}H_{29}NO_2Si_2$: calculated: C, 52.31; H, 10.61; N, 5.08; Found: C, 52.86; H, 10.40; N, 4.94.

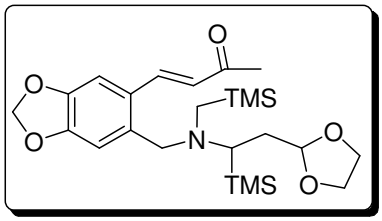
26. 2-(1,3-dioxolan-2-yl)-N-((6-iodobenzo [d][1,3] dioxol-5-yl)methyl)-1-(trimethylsi-lyl)-N-((trimethylsilyl)methyl)ethanamine (225):



This experiment was performed using same procedure as described for **215**.

IR ($CHCl_3$)	:	υ_{max} 2950, 2891, 1502, 1469, 1245, 1130, 1103, 935 cm^{-1}
^1H NMR (200 MHz, $CDCl_3$)	:	δ 7.20 (s, 1H), 7.10 (s, 1H), 5.95 (s, 2H), 5.05 (dd, J = 6.26, 3.91 Hz, 1H), 3.94 (m, 2H), 3.84 (m, 2H), 3.60 (d, J = 15.26 Hz, 1H), 3.48 (d, J = 15.26 Hz, 1H), 2.45 (dd, J = 8.60, 5.67 Hz, 1H), 2.18 (d, J = 14.48, 1H), 2.05 (d, J = 14.48, 1H), 2.01 (m, 1H), 1.65 (m, 1H), 0.13 (s, 9H), 0.05 (s, 9H).
^{13}C NMR (50 MHz,$CDCl_3$)	:	δ 148.7, 147.3, 136.1, 118.3, 110.2, 104.1, 101.6, 87.0, 64.4, 64.8, 64.9, 50.8, 45.1, 31.5, -0.7, -0.9.
Mass m/z (%)	:	TOF MS 536.1190(M+H)
Analytical Calculations	:	$C_{20}H_{34}INO_4Si_2$ Calculated: C, 44.85; H, 6.40; I, 23.70; N, 2.62; Found: C, 44.33; H, 6.01; N, 2.91.

27. (E)-4-(6-(((2-(1,3-dioxolan-2-yl)-1-(trimethylsilyl)ethyl)((trimethylsilyl)methyl)amino)methyl)benzo[d][1,3]dioxol-5-yl)but-3-en-2-one (224):



This experiment was performed using same procedure as described for **176**.

mp	:	105-107 °C
IR ($CHCl_3$)	:	υ_{max} 2850, 2593, 2360, 2341, 1666, 1593, 1479, 1251, 1039 cm^{-1}
^1H NMR (500 MHz, $CDCl_3$)	:	δ 7.80 (d, J = 15.58 Hz, 1H), 7.02 (s, 1H), 6.92 (s, 1H), 6.38 (d, J = 15.58, 1H), 5.89 (s, 1H), 5.88 (s, 1H), 4.86 (br dd, J = 5.50, 4.12, 1H), 3.81 (m, 2H),

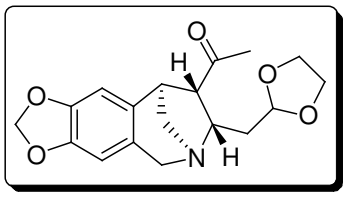
3.69 (m, 3H), 3.47 (d, J = 14.21 Hz, 1H), 2.27 (dd, J = 7.79, 5.50 Hz, 1H), 2.26 (s, 3H), 2.01 (m, 3H), 1.55(m, 1H), 0.00 (s, 9H), -0.04 (s, 9H).

^{13}C NMR (125 MHz,$CDCl_3$) : δ 197.7, 149.4, 146.5, 140.0, 135.7, 126.8, 126.2, 109.8, 105.3, 103.6, 101.0, 64.4, 64.3, 55.9, 49.5, 44.5, 30.3, 27.5, -0.8, -1.4.

Mass m/z (%) : TOF MS 478.2465(M+H)

Analytical Calculations : $C_{24}H_{39}NO_5Si_2$ Calculated: C, 60.34; H, 8.23; N, 2.93; Found: C, 59.86; H, 8.20; N, 2.73.

28. 1-(10-[1,3]Dioxolan-2-ylmethyl-4,5-methylenedioxy-9-aza-tricyclo[7.2.1.0*2, 7*]dodeca-2,4,6-trien-11α-yl)-ethanone (223):



This experiment was performed using same procedure as described for **174.**

mp : 154-156 °C

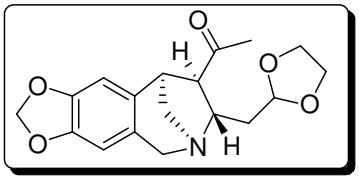
IR ($CHCl_3$) : υ_{max} 2958, 1708, 1483, 1359, 1139, 1039, cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 6.37 (s, 1H), 6.34 (s, 1H), 5.78 (s, 2H), 4.97 (dd, J = 6.88, 2.29 Hz, 1H), 4.18 (d, J = 16.96 Hz, 1H), 3.85 (m, 2H), 3.75 (m, 2H), 3.63 (d, J = 16.96 Hz, 1H), 3.53 (5 lines pattern, J = 8.71, 3.67 Hz, 1H), 3.33 (d, j = 8.71 Hz, 1H), 3.26 (dd, J = 2.52, 11.23 Hz, 1H), 2.97 (d, J = 2.52, 1H), 2.87 (d, J = 11.46 Hz, 1H), 2.06 (s, 3H), 1.80 (br t, J = 11.46, 13.29 Hz, 1H), 1.40 (m, 1H).

^{13}C NMR : δ 207.6, 146.3, 145.5, 134.9, 125.3, 106.6, 106.3,

(125 MHz,$CDCl_3$)		103.5, 100.4, 64.6, 64.5, 64.33, 64.28, 59.9, 53.9, 43.4, 35.7, 32.2.
Mass m/z (%)	**:**	TOF MS 332.1489(M+H)
Analytical Calculations	**:**	$C_{18}H_{21}NO_5$ Calculated: C, 65.24; H, 6.39; N, 4.23; Found: C, 65.14; H, 6.47; N, 4.11.

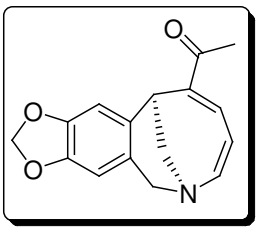
29. 1-(10-[1,3]Dioxolan-2-ylmethyl-4,5-methylenedioxy-9-aza-tricyclo[7.2.1.0*2, 7*]dodeca-2,4,6-trien-11β-yl)-ethanone (233):



A mixture of **223** (0.1 g, 0.3 mmol) and 3N HCl (1 mL) in 3 mL of THF was stirred at room temperature for 8h. The solvent was evaporated under reduced pressure and whole residue was dissolved in DCM (8 mL). The organic layer was washed with saturated $NaHCO_3$ solution (2 x 3 mL), water (2 x 3 mL), brine and dried over Na_2SO_4. Column chromatography of the crude reaction mixture with chloroform/methanol (9:1) afforded 0.09 g of **233** (90%) as a white solid.

mp	**:**	165-167 °C
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 6.38 (s, 1H), 6.28 (s, 1H), 5.81 (s, 2H), 4.85 (d, J = 5.43, 3.30 Hz, 1H), 4.26 (d, J = 16.80 Hz, 1H), 3.77-3.87 (m, 3H), 3.63-3.75 (m, 3H), 3.24 (br d, J = 8.97 Hz, 3H), 3.06 (d, 1H), 2.11-2.20 (m, 1H), 2.05 (s, 3H), 1.60-1.74 (m, 1H).

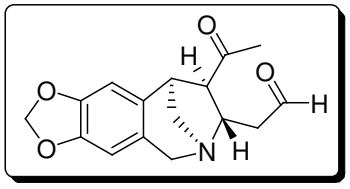
30. Preparation of 1-(4,5-methelenedioxy-9-aza-tricyclo[7.4.1.02,7]tetradeca-2,4,6,9,12-pentaen-13-yl)-ethanone (229):



To a 25 mL two necked jacketed flask 0.09 g (0.27 mmol) was taken in 10 mL of dry DCM and cooled to –20 °C. 2,6-lutidine (0.19 mL, 1.63 mmol) and TMSOTf (0.20 mL, 1.08 mmol) were added dropwise to the reaction mixture stirred for 8 h. The reaction mixture was quenched with water, extracted with DCM and washed with $NaHCO_3$, water and brine. The aqueous layer was back extracted with DCM (2 x 5 mL), combined organic layer was dried over Na_2SO_4, evaporated under reduced pressure to give a brown colored residue. The residue was purified by silica gel column chromatography (petether/acetone 7:3) to obtain **229** (0.045 g, 61%) as a gummy liquid.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 8.97 (d, J = 8.09 Hz, 1H), 7.02 (m, 1H), 6.46 (s, 1H), 6.42 (s, 1H), 5.79 (s, 2H), 5.15 (br t, J = 8.09 Hz, 1H), 4.21 (d, J = 16.42 Hz, 1H), 3.46 (br m, 1H), 3.22 (br m, 1H), 2.52 (br d, J = 6.31 Hz, 2H), 2.01 (s, 3H).

31. (11β-Acetyl-4,5-methylenedioxy-9-aza-tricyclo[7.2.1.0*2,7*]dodeca-2,4,6-trie n-10-yl)-acetaldehyde (235):

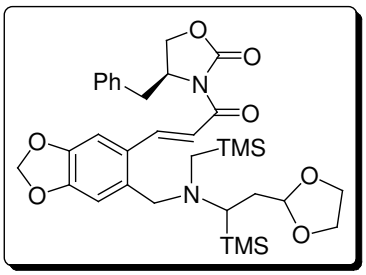


A mixture of **223** (0.2 g, 0.6 mmol) and 3N HCl (1 mL) in 4 mL of THF was heated to reflux overnight. The solvent was evaporated under reduced pressure and whole residue was taken in DCM (8 mL). The organic layer was washed with saturated $NaHCO_3$ solution (2 x 3 mL), water (2 x 3 mL), and brine, dried over Na_2SO_4. Column chromatography of the crude reaction mixture with chloroform/methanol (9:1) afforded 0.13 g of **235** (75%).

IR ($CHCl_3$) : υ_{max} 2921, 1721, 1342, 1041cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 9.76 (dd, J = 1.95, 1.57 Hz, 1H), 6.45 (s, 1H), 6.37 (s, 1H), 5.88 (s, 1H), 5.87 (s, 1H), 4.26 (d, J = 17.22 Hz, 1H), 4.00 (m, 1H), 3.91 (d, J = 17.22, 1H), 3.59-3.72 (m, 1H), 3.34 (m, 1H), 3.04-3.24 (m, 2H), 2.63-2.77 (m, 1H), (2.38-2.49 (m, 1H), 2.15 (s, 3H).

32. (4S,E)-3-(3-(6-(((2-(1,3-dioxolan-2-yl)-1-(trimethylsilyl)ethyl)((trimethylsilyl)methyl)amino)methyl)benzo[d][1,3]dioxol-5-yl)acryloyl)-4-benzyloxazolidin-2-one (295):



This experiment was performed using same procedure as described for **176**, except using **296** 1.2 equivalent.

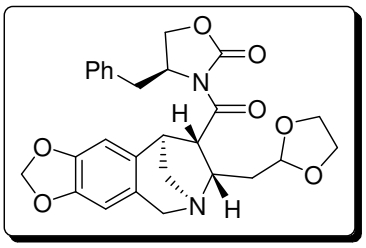
IR ($CHCl_3$) : υ_{max} 2925, 1778, 1703, 1600, 1041 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) : δ 8.22 (d, J = 15.41 Hz, 1H), 7.59 (d, J = 15.41, 1H), 7.05-7.27 (m, 7H), 5.92 (s, 2H), 4.92 (br m, 1H), 4.71 (m, 1H), 4.13 (m, 2H), 3.84 (m, 2H), 3.74 (m, 3H), 3.53 (d, J = 14.03 Hz, 1H), 3.28 (dd, J = 13.39, 3.03 Hz, 1H), 2.77 (dd, J = 13.39, 9.60 Hz, 1H), 2.32 (br t, J = 5.94 Hz, 1H), 2.13 (d, J = 13.90 Hz, 1H), 1.96 (m, 1H), 1.93 (d, J = 13.90 Hz, 1H), 1.59 (m, 1H).

^{13}C NMR (125 MHz,$CDCl_3$) : δ 172.5, 165.2, 153.6, 149.9, 146.9, 143.4, 136.4, 135.5, 129.5, 128.9, 127.4, 115.9, 109.9, 106.1, 103.9, 101.4, 66.1, 64.7, 64.6, 56.4, 55.4, 49.7, 44.7, 38.0, 30.5, 0.5, -1.0.

Mass m/z (%) : MALDI TOF 639 (M+H)

33. 4-Benzyl-3-(10-[1,3]dioxolan-2-yl methyl-4,5-methelynedioxy-9-aza-tricyclo[7.2.1.02,7]dodeca-2,4,6-triene-11-carbonyl)-oxazolidin-2-one (294):



This experiment was performed using same procedure as described for **174.**

IR ($CHCl_3$) : υ_{max} 2923, 1778, 1693, 1481, 1388, 1037 cm^{-1}

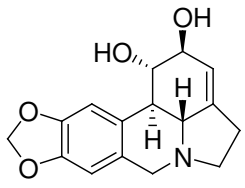
^{1}H NMR (500 MHz, $CDCl_3$) : δ 7.12-7.28 (m, 5H), 6.52 (s, 1H), 6.39 (s, 1H), 5.81 (s, 2H), 4.99 (t, J = 4.68 Hz, 1H), 4.56-4.68 (m, 1H), 4.37 (d, J = 17.05 Hz, 1H), 4.15 (m, 2H), 3.85-3.92 (m, 4H), 3.76-3.82 (m, 2H), 3.60 (dd, J = 10.12, 5.18 Hz, 1H), 3.35-3.48 (m, 3H), 3.21 (dd, J = 13.26, 3.41 Hz, 1H), 2.70 (dd, J = 13.26, 9.60 Hz, 1H), 1.85 (m, 2H)

^{13}C NMR (125 MHz,$CDCl_3$) : δ 171.4, 158.5, 152.8, 148.8, 146.0, 135.7, 134.7, 129.1, 128.7, 127.2, 107.1, 106.1, 102.2, 100.7, 69.4, 66.4, 65.2, 64.6, 64.5, 55.3, 53.5, 45.25, 41.2, 37.7, 29.4.

Mass m/z (%) : LCMS 493 (M+H)

1.1. Introduction

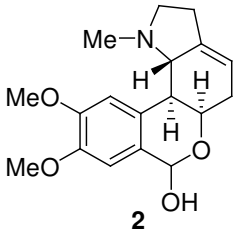
The *Amaryllidaceae* alkaloids[1-4] has long been a source of structurally intriguing target molecules that continue to challenge the capabilities of contemporary organic synthesis. Plants of the *Amaryllidaceae* family are generally considered to be source for potential drugs having a wide range of pharmacological activities. Although their structures appeared to be very different, they are known to be formed biogenetically by intramolecular oxidative coupling of norbelladines. These alkaloids encompass a functionally and structurally diverse group of bases. At present, almost two hundred alkaloids have been isolated from member of the *Amaryllidaceae* plants, and many of their structures have been determined, and most of them may be classified into eleven principal, skeletally homogeneous subgroups, although, there are several other alkaloids having structures derived from these main molecular framework. Representative alkaloids from each of these classes include lycorine (**1**), lycorenine (**2**), pancratistatine (**3**), galanthamine (**4**), crinine (**5**), latisoline (**6**), mesembrine (**7**), augustamine (**8**), montanine (**9**), latifine (**10**) and pretazettine (**11**). These alkaloids are listed below with their structural framework and pharmacological activities. (Figure-1)



1

Lycorine Class of Alkaloids: Constiuttes a group of 33 alkaloids.

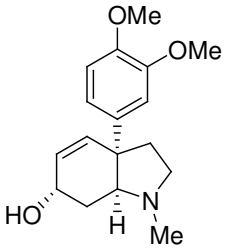
Activities: Antoviral, antineoplastic, hypotensive, Insect antifeedant.



2

Lycorenine Class of Alkaloids: Constitutes a group of 15 alkaloids.

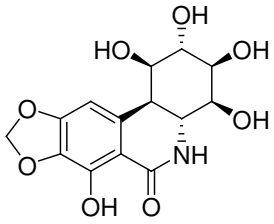
Activity: Insect antifeedant.



3

Mesembrine Type of Alkaloids: Constitutes only 2 alkaloids

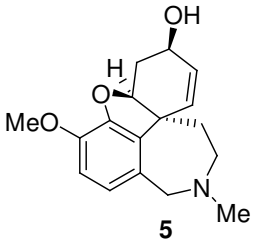
Activities: Serotonine uptake inhibitor



4

Pancratistatine Class of Alkaloids: Constitutes a group of 10 alkaloids.

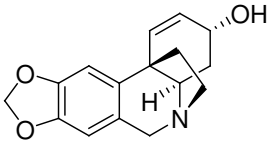
Activities: Antitumor, antiviral and antifeedant.



5

Galanthamine Class of Alkaloids: Constitutes a group of 13 alkaloids

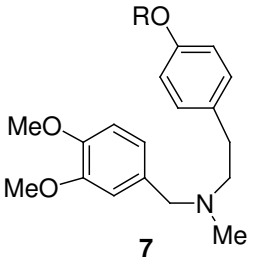
Activities: Analgesic, insectiside and hypotensive



6

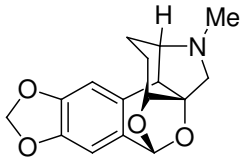
Crinine type of Alkaloids: Constitutes a group of 48 alkaloids

Activities: immunostimulant, antitumor and antiviral



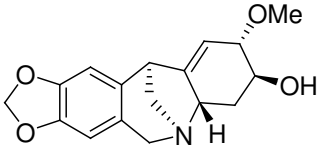
7

Latisoline class of Alkaloids: Constitutes a group of 3 alkaloids.



8

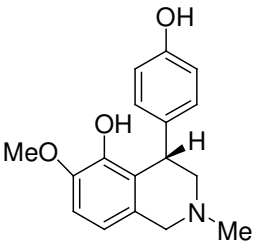
Augustamine is the only alkaloid possessing unique structure.



9

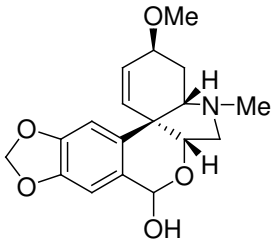
Montanine class of Alkaloids: Constitues a group of 6 alkaloids.

Activities: Convulsive and weak hypotensive activies.



10

Latifine Type of Alkaloids: Constitute 2 alkaloids.



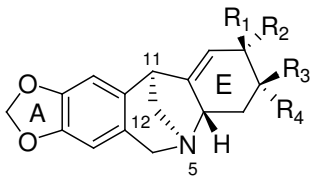
11

Petazettine Type of Alkaloids: Constitutes 4 alkaloids.

Activities: Antineoplastic

Figure-1

Since the detailed discussions on all of these alkaloids are beyond the scope of this dissertation, we will be concentrating mainly on the Montanine-type of Amaryllidaceae alkaloids. (Figure-2)



	R_1	R_2	R_3	R_4	
12	H	OH	OH	H	**(-)-pancracine**
13	H	OH	H	OH	**(-)-brunsvigine**
9	H	OMe	OH	H	**(-)-montanine**
14	OMe	H	OH	H	**(-)-coccinine**
15	H	OMe	OMe	H	**(-)-manthine**
16	H	OMe	OAc	H	**(-)-O-acetylmanthine**

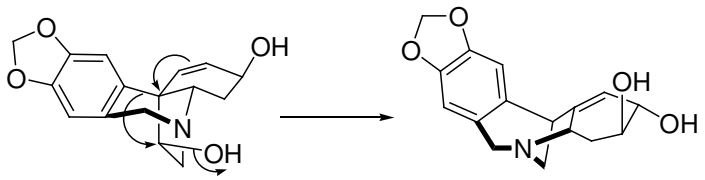
Figure-2

Three members of this class (-)-montanine (**9**), (-)-coccinine (**14**), and (-)-manthine (**15**), were first isolated in 1955 by Wildmann and co-workers from various *Haemanthus* species (*Haemanthus montanus, Haemanthus coccineus, haemanthus amarylloides*, etc.) collected in South Africa.[5] Shortly thereafter, (-)-brunsvigine (**13**) was isolated from *Brunsvigia cooperi* Baker and *Brunsvigia radulosa* Herb.[6,7] (-)-Pancracine (**12**) was found as a minor alkaloid in *Rhodophiala bifida*, a plant which is indigenous to United States, along with major alkaloid (-)-montanine (**9**).[8]

The structural assignments of the 5,11-methanomorphanthridine alkaloids were initially based on chemical degradations and interconversions.[7] In 1968, a spectroscopic study of (-)-pancracine (**12**) and some of its derivatives involving proton NMR and mass spectrometry confirmed the structure of these alkaloids. Indeed, these were found to have the structures previously attributed to them.[8] The structure of (-)-brunsvigine (**13**) is firmly based on single crystal X-ray analysis of the *bis-p*-bromobenzoate derivatve and its absolute configuration is determined by anomalous dispersion methodology.[9] In general, these alkaloids possess a common bridged pentacyclic skeleton, varying only in the

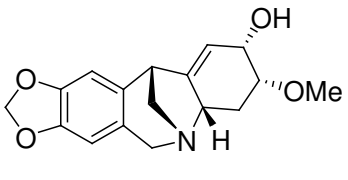
substitution (*i.e.*, methoxy or hydroxyl) and stereochemistry at C-2 and C-3. Biosynthetic labeling studies and chemical transformations support the view that the rare 5,11-methanomorphanthridine skeleton arises from the rearrangement of *Amaryllidaceae* alkaloid precursors having common 9,10-ethanophenanthridine skeleton.[10-13] This relationship is illustrated in Scheme-1 for the conversion of 11-hydroxyvittatine (normethylhaemanthidine, **17**) to (-)-pancracine (**12**).

Scheme-1



11-hydroxyvittatine (**17**) (-)-pancracine (**12**)

The seventh member of Montanine-type *Amaryllidaceae alkaloid,* montabuphine (**18**), with a β-5,11-methanomorphanthridine skeleton was found for the first time in the bulbs of *Boophane flava*[14] growing in winter rainfall area of South Africa. The structure of **18** was determined by COSY and ROESY experiments of the ^{1}H NMR, and HMQC and HMBC correlations in the ^{13}C NMR spectra.[15,16] (Figrure-3)



Montabuphine (18)

Figure-3

These *Amaryllidaceae* alkaloids display some limited biological activity. For example, (-)-coccinine (**14**) shows convulsive action in high doses [LD_{50} = 17.5 mg/kg (*in*

vivo, dog)].[17] Weak hypertensive and convulsive activities are also reported for (-)-montanine (**9**) [LD_{50} = 42 mb/kg (*in vivo*, dog)]. It may be relevant to highlight that both these physiologically active alkaloids have methyl ether functionality at the C-2 position.

Driven by their interesting pentacyclic structure and promising pharmacological potentials, these alkaloids have attracted much synthetic interest. The main challenge in the synthesis of these classes of alkaloids involve fixation of stereospecific disposition of the C-12 methylene group and controlled installation of the oxygen-functionalities around E-ring. The foregoing discussion would mainly focus on surveying the reported syntheses of these classes of alkaloids to put the dissertation in proper perspectives.

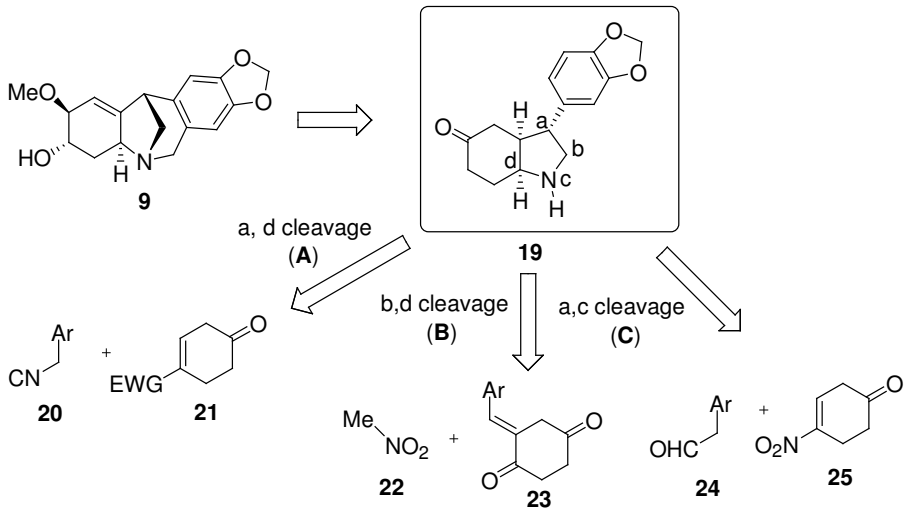
1.2. Synthetic approaches towards Montaine-type of *Amaryllidaceae* alkaloids: *Literature Reports*

In 1985 Sánchez *et al*[18] described the first synthetic efforts towards the synthesis of montanine-type of alkaloids. Hoshino and co-workers reported[19] at first the total synthesis of montanine, coccinine, pancracine, brunsvigine, and *O*-acetylmontanine in racemic form. Later on, the same group also presented an alternative approach[20] aiming towards the formal synthesis of these classes of alkaloids. The first enantioselective synthesis of these alkaloids was reported by Overmann and Shim in 1992.[21] Jin and Wienreb reported the enantioselective synthesis of (-)-coccinine and (-)-pancracine in 1997.[22] Pearson and Lian have nicely demonstrated the synthesis of (+)-coccinine, a non-natural enantiomer of (-)-coccinine.[23] Ikeda[24] and Banwell[26] have also presented formal synthesis of (±)-pancracine. First total synthesis of (-)-brunsvigine was reported by Sha and co-worker.[25] All the above-mentioned syntheses are described schematically as follows:

1.2.1. Sánchez's Approach: (*Hetrocycles*, **1985**, 23, 3033)[18]

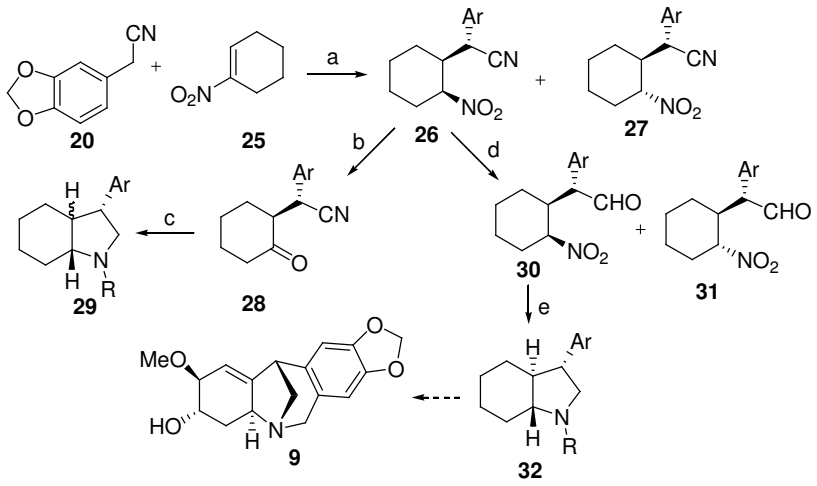
This approach is based on the use of 3-aryloctahydroindoles (**19**) as a potent synthon for the total synthesis of the montanine-type *Amarrylidaceae alkaloids* as shown in Scheme-2. Three routes have been described for the synthesis of 3-aryloctahydroindoles (**19**).

Scheme-2



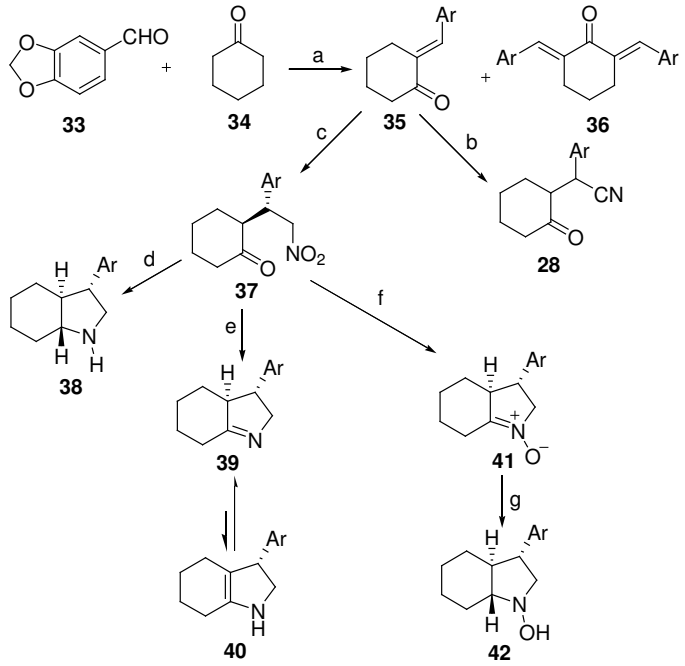
The synthesis of **19** via routes A and C utilizes the same intermediate (**26**) (Scheme-3) whereas route B proceeds via different intermediate, **35**. (Scheme-4).

Scheme-3



Reagents and conditions: *a) n-BuLi, THF, -50 °C; b) NaOMe, H_2SO_4, MeOH; c) Nickel, i-prOH, 50 psi, 45-55 °C; d) Bu_2AlH, THF, 0 °C; e) Nickel, i-PrOH, 50 psi, 45-55 °C.*

Scheme-4



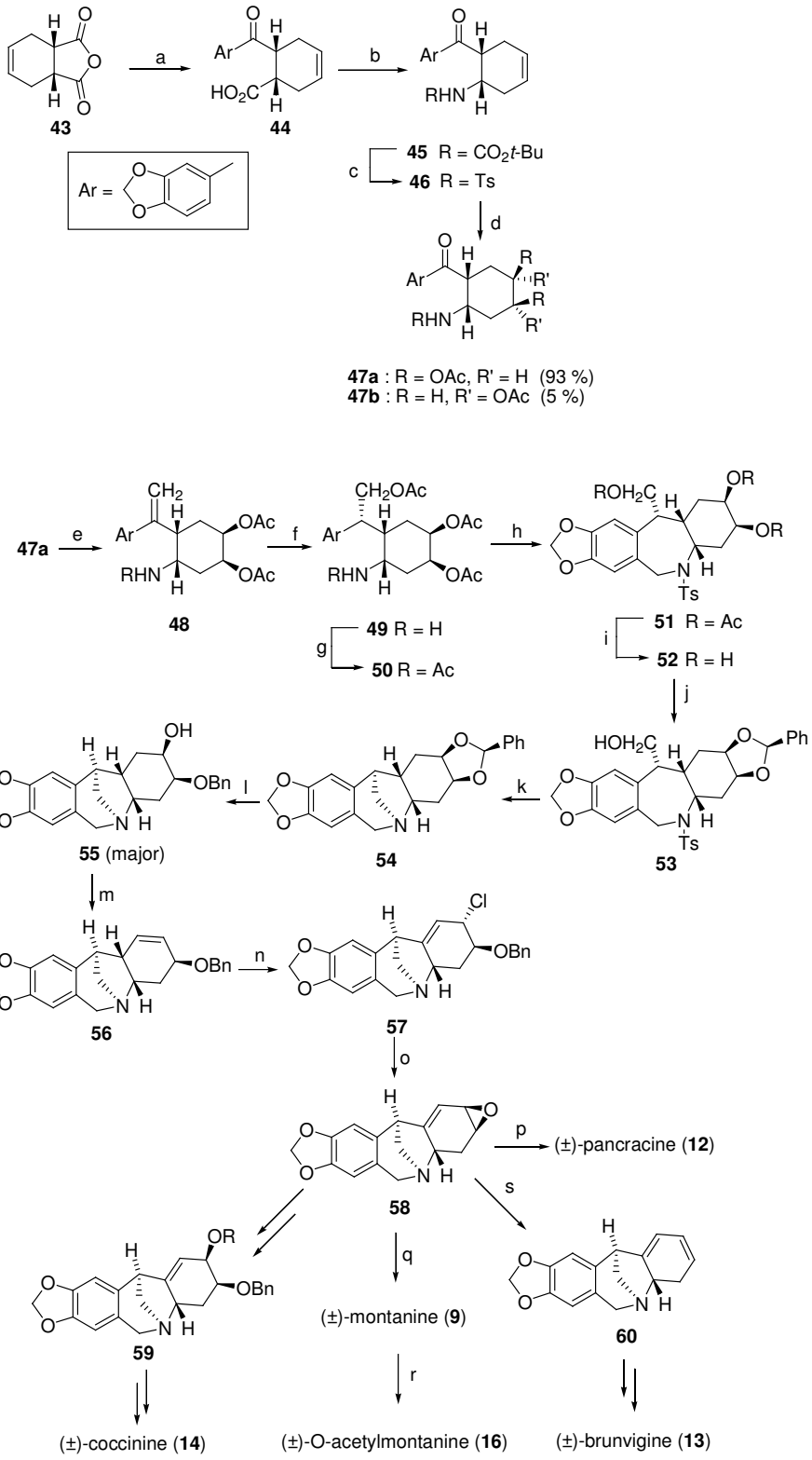
Reagents and conditions: *a) NaOH (cat), MeOH; b) KCN, benzene, acetone cyanohydrin, 18-crown-6, reflux; c) $MeNO_2$, supported TBAF cat; d) Nickel, i-PrOH, 50 psi, 45-55 ^oC; e) Zn, 1:9 v/v aqueous HOAc, rt; f) KBH_4, EtOH-H_2O; g) TiCl4, Mg amalgam, THF, rt*.

1.2.2. Hoshino's Approach

Approach-1: (J.Org.Chem. **1992**, 57, 7285)[19]

Hoshino *et al* have reported first stereoselective total syntheses of Montanine-type of alkaloids in 24 steps starting from *cis*-cyclohexanedicarboxylic acid anhydride **43**. The key feature of this synthesis involve (1) stereoselective hydroboration-oxidation of **48** to alcohol **49**, (2) cyclization of tosylamide alcohol **53** with sodium bis(2-methoxyethoxy)aluminium hydride (SMEAH), (3) conversion of **56** to allylic chloride **57** by treatment with PhSeCl in MeOH under ultrasonication followed by $NaIO_4$ oxidation and (4) finally conversion **57** to five alkaloids (montanine, coccinine, pancracine, brunsvigine, and *O*-acetylmontanine) of these group in racemic form. (Scheme-5)

Scheme-5



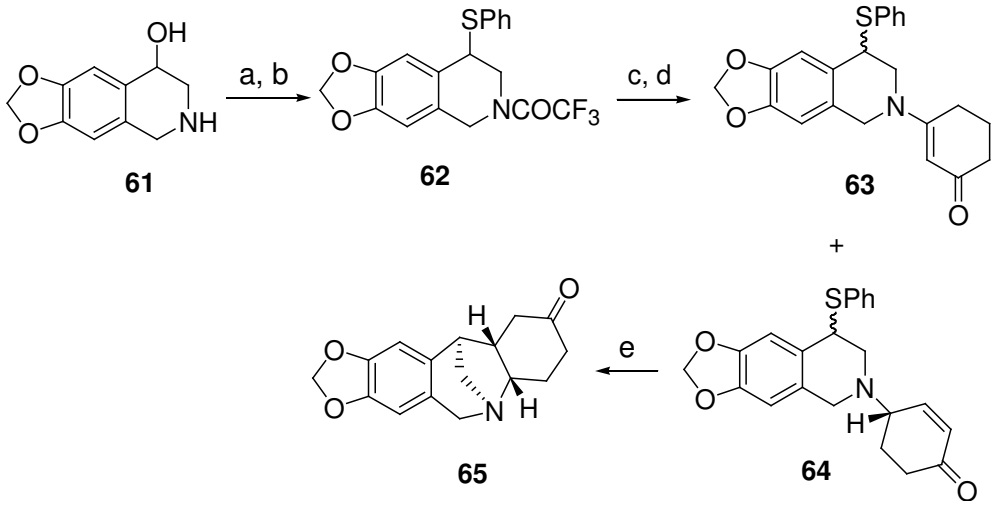
Reagents and conditions: *a) ArMgBr, THF; b) (1) $ClCO_2Et$, Et_3N; (2) NaN_3; (3) t-BuOH, reflux; c) (1) TFA, $CHCl_3$; (2) TsCl, Et_3N; d) (1) OsO_4, NMO; (2) Ac_2O, pyridine; e)*

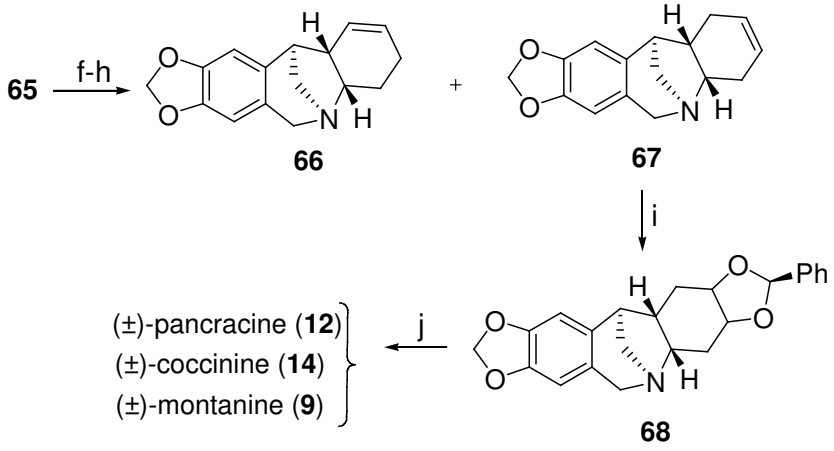
PPh_3MeBr, t-BuOK, THF; f) (1) BH_3, THF; (2) NaOH, H_2O_2; g) Ac_2O, pyridine; h) $(CH_2O)_n$, Ac_2O, $MeSO_3H$, CH_2ClCH_2Cl; i) NaOMe; j) $PhCH(OMe)_2$, p-TsOH, $CHCl_3$; k) SMEAH, o-xylene, reflux; l) DIBALH, toluene; m) (1) $MeSO_2Cl$, Et_3N, DCM, 5 °C; (2) KOt-Bu, Me_2SO, rt; n) PhSeCl, MeOH, ultrasound, 15-20 °C, then $NaIO_4$; o) Me_3SiI, $CHCl_3$, rt;p) H_2SO_4, $THF.H_2O$; q) $BF_3.OEt_2$, MeOH; r) Ac_2O, DMAP, pyridine; s) TMSCl, NaI, CH_3CN.

Approach-2: (*J. Chem. Soc. Perkin Trans. I*, **1993**, 101)[20]

A formal synthesis of these types of alkaloids was also performed by intramolecular radical cyclization of **64**. The reaction of 1,2,3,4-tetrahydro-N-(4-oxocyclohex-2-enyl)-4-phenylthioisoquinoline (**64**) with Bu_3SnH/AIBN led to 5,11-methanomorphanthridine-2-one (**65**) in 80% yield which was finally converted to 2,3-*O*-benzylidine 5,11-methanomorphanthridine (**68**). Previously **68** is converted into these types of alkaloids by the same group. (Schem-6)

Scheme-6



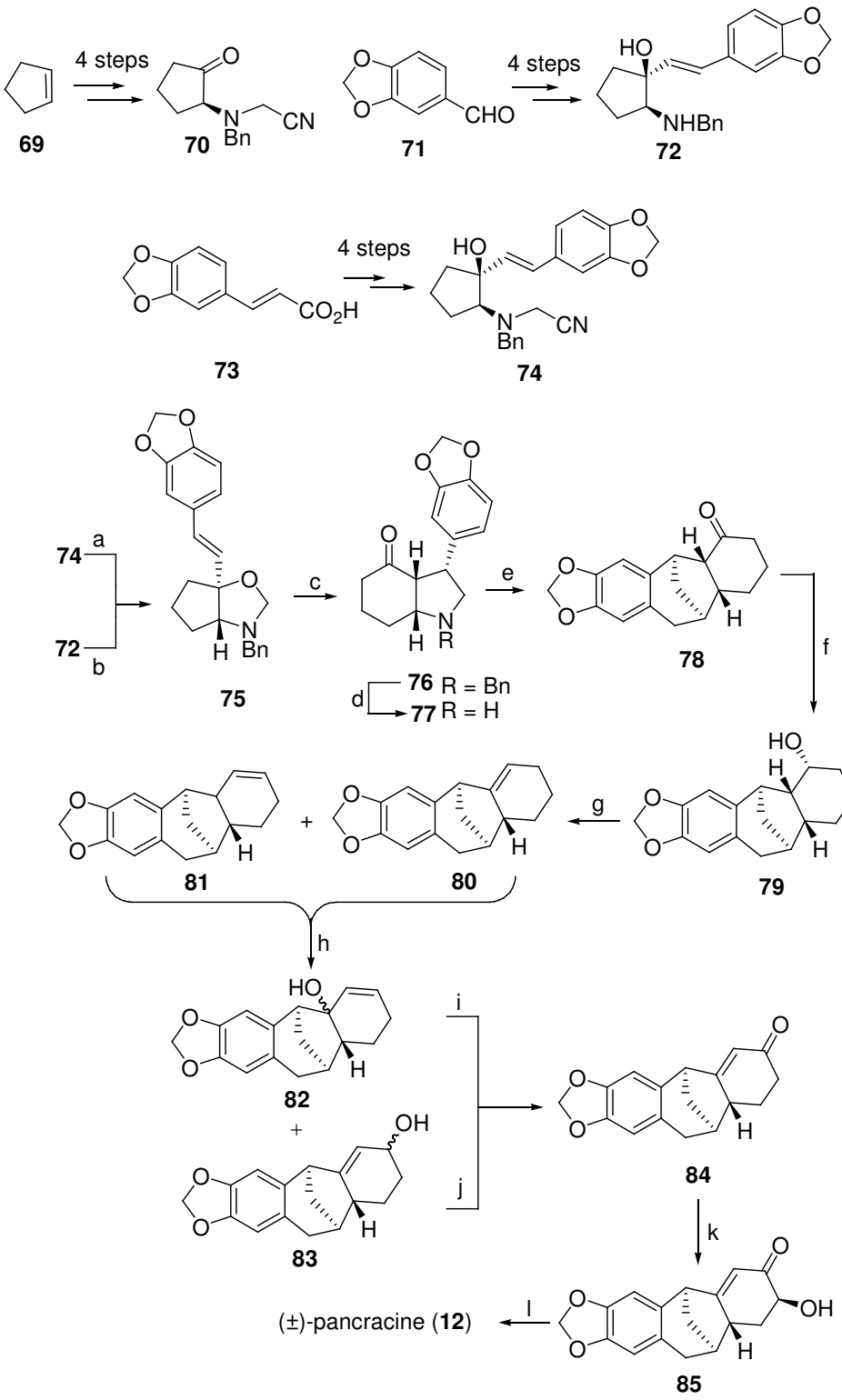


Reagents and conditions: *a) $(CF_3CO)_2O$, K_2CO_3, $CHCl_3$; then water; b) PhSH, ZnI_2, CH_2ClCH_2Cl; c) K_2CO_3, aq. MeOH; d) 4-Bromocyclohex-2-enone, Et_3N, Et_4NI, MeCN, CCl_4; e) Bu_3SnH, AIBN; f) $NaBH_4$, MeOH, 5 °C g) $MeSO_2Cl$, Et_3N, $CHCl_3$, 5 °C h) KOt-Bu, rt; i) OsO_4 (cat.), NMO; then $PhCH(OMe)_2$, p-TsOH. H_2O, CHCl3; j) ref. 22.*

1.2.3. Overman's Approach: (*J. Org. Chem*. **1993**, 58, 4662)[21]

The total synthesis of (±)-pancracine was achieved in 17 steps and 7% overall yield starting from cyclopentene with complete stereochemical control. The same group has also demonstrated first enantioselective total synthesis of (-)-pancracine which was accomplished in 13 steps and 14% overall yield from the (S)-amino ketone **86**. This later intermediate was obtained in three steps and 39% yield from 1,2-epoxy-cyclopentane. The key steps used for this synthesis involved aza-Cope rearrangement-Mannich cyclization reaction (**72** → **76**) and Pictet-Spengler reaction (**76** → **77**). (Scheme-7)

Scheme-7

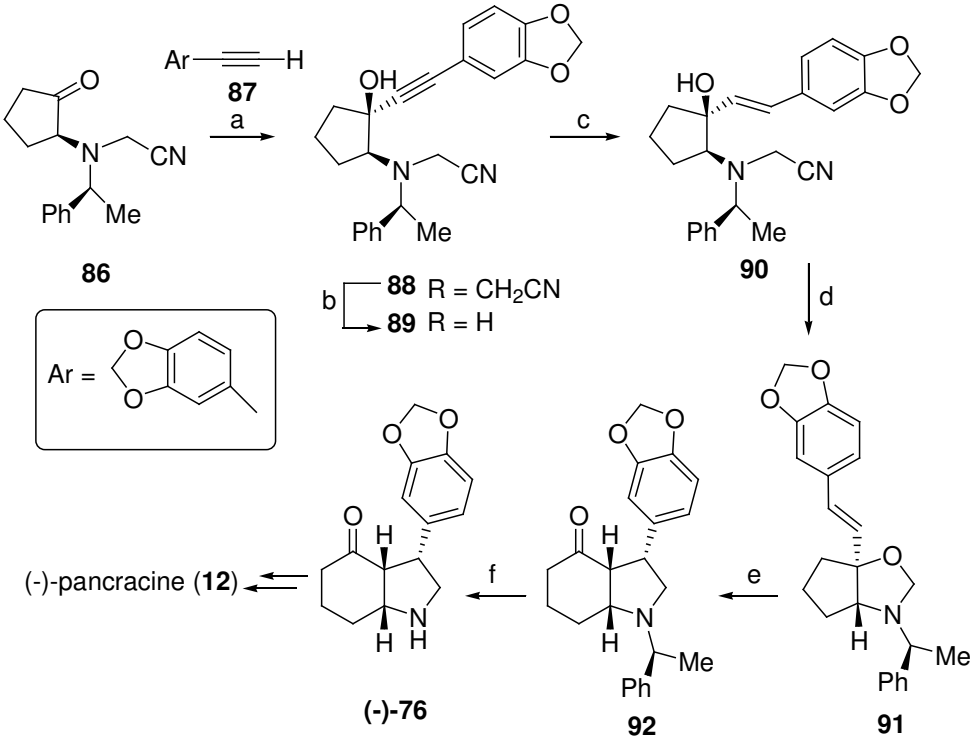


Reagent and conditions: *a) $AgNO_3$, EtOH; b) aqueous HCHO, CSA, Na_2SO_4; c) $BF_3.OEt_2$, CH_2Cl_2, -20 ^oC; d) HCl, Pd/C, H_2, MeOH; e) aqueos HCHO, Et_3N, 6 N HCl; f)*

Li(s-Bu)$_3$BH; g) SOCl$_2$, CHCl$_3$; h) SeO$_2$; i) Swern oxidation; j) PCC, 4Å molecular sieve; k) (1) Me$_3$SiOTf, Et$_3$N; (2) OsO$_4$, NMO; l) NaBH(OAc)$_3$.

The enantioselective synthesis of (-)-pancracine was achieved from **86** following the reaction sequence as described in the Scheme-8.

Scheme-8



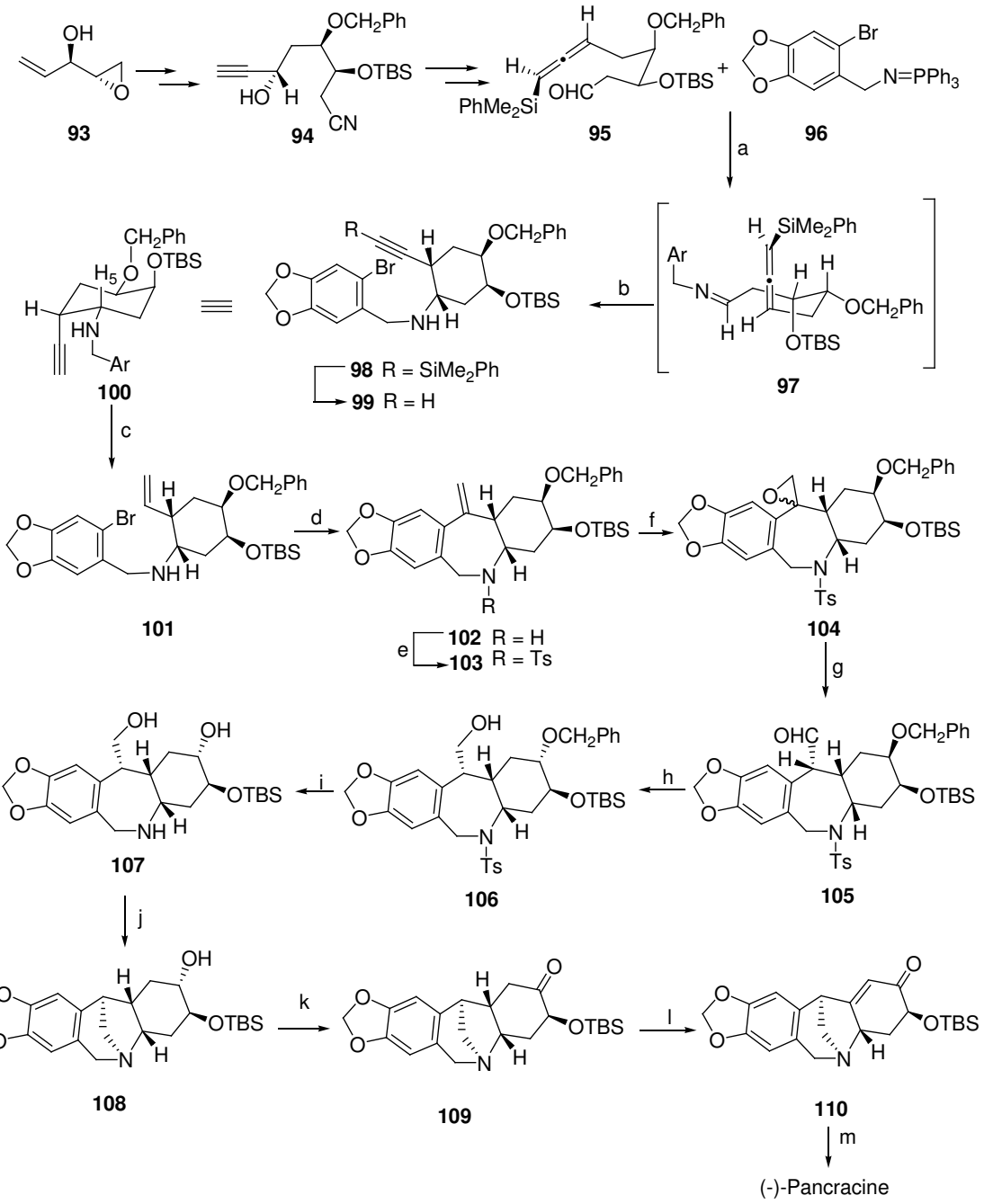
Reagents and conditions: *a) **87**, n-BuLi, CeCl$_3$; b) AgNO$_3$, EtOH, sonication c) LiAlH$_4$; d) aqueous HCHO, CSA, Na$_2$SO$_4$; e) BF$_3$.OEt$_2$, CH$_2$Cl$_2$, -20 ^{o}C; f) HCl, Pd/C, H$_2$, MeOH.*

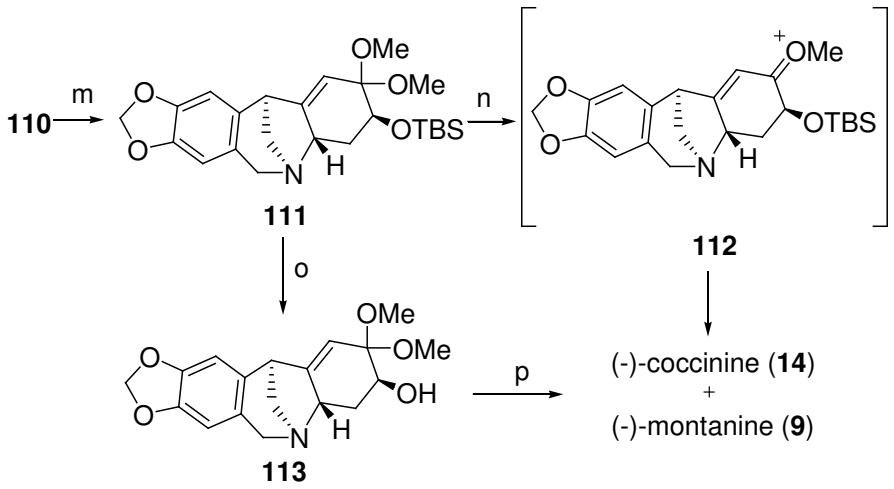
1.2.4. Weinreb's Approach: (*J. Am. Chem. Soc.* **1997**, 119, 5773)[22]

These complex pentacyclic natural products were synthesized from readily available enantiomerically pure epoxy alcohol **93** in about 25 steps. The key features of the synthetic strategy include (1) a stereospecific thermal imino ene cyclization of allenylsilane imine **97**, derived from aldehyde **95** and iminophosphorane **96,** to provide key precursor

98, (2) an intramolecular Heck reaction of bromo alkene **101** to produce a seven-membered ring containing tetracycle **102**, and (3) stereospecific formation of hydroxymethylene compound **106** *via* epoxidation of **102** followed by a Lewis acid catalyzed ring opening/rearrangement. (Scheme-9)

Scheme-9



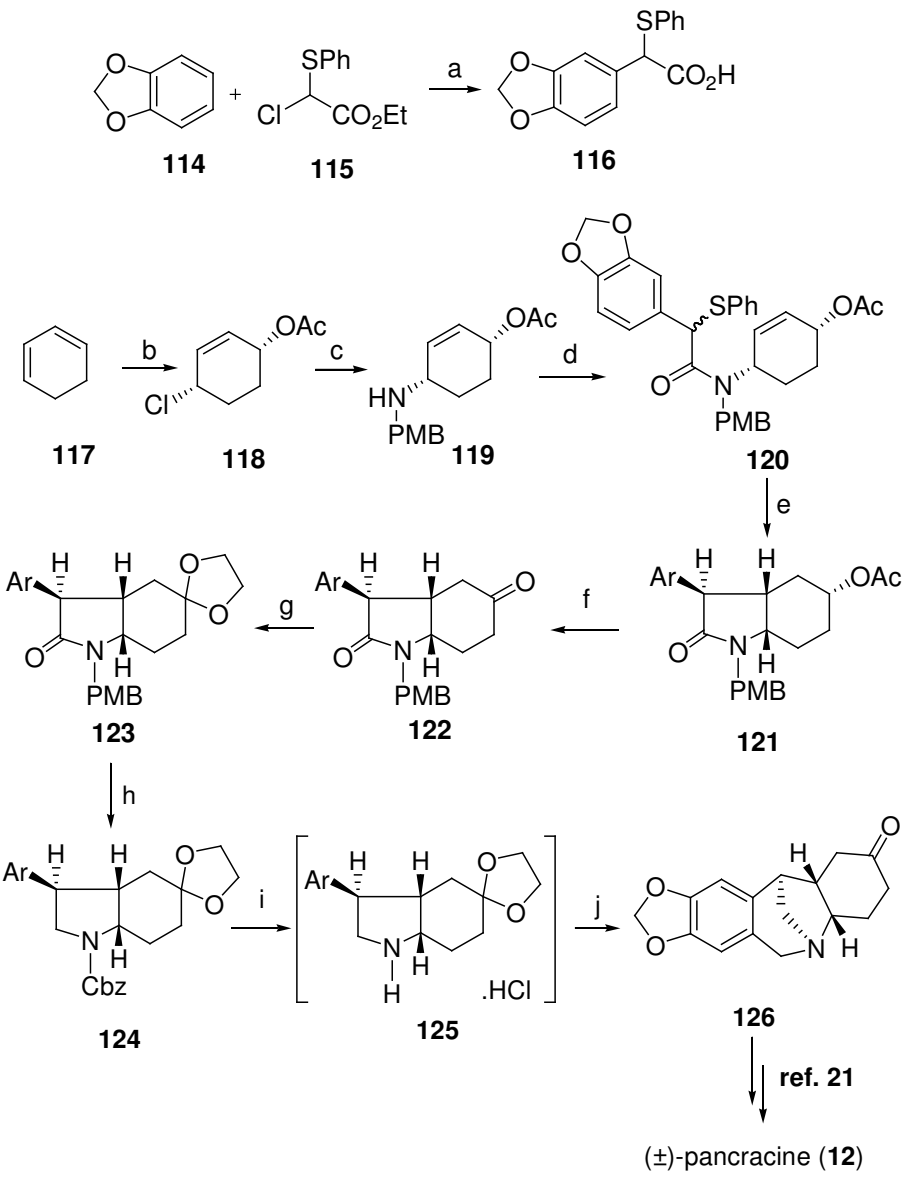


Reagents and conditions: *a) mesitylene, 50 °C-reflux; b) TBAF/THF 0 °C c) H_2, quinoline, Lindlar catalyst, MeOH; d) $Pd(PPh_3)_4$, Me_3NBnCl, TEA, MeCN, 120 °C; e) TsCl, DMAP, pyridine, 100 °C; f) dimethyl dioxirane, acetone g) $FeCl_3$, CH_2Cl_2, -78 °C h) DIBALH i) (1) H_2, Pd-C, MeOH; (2) Na, naphthalene, DME, -78 °C; j) I_2, PPh_3, imidazole, MeCN/Et_2O, 0 °C; k) TPAP, NMO, 4Å MS; l) (1) LDA, TMSCl, THF, -78 °C; (2) $Pd(OAc)_2$, MeCN; m) (1) TBAF,THF (2) $NaBH(OAc)_3$; n) p-TsOH, $CH(OMe)_3$, o) DIBALH, toluene; p) TBAF, THF.*

1.2.5. Ikeda's Approach: (*Synlett*, **1998**, 1246)[24]

Ikeda *et al* have revealed that 5-*exo-trig* radical cyclization of N-(2-cyclohexenyl)-α-aryl-α-(phenylthio)acetamides (**120**), obtained by the amidation of **116** with **119**, provides a new stereoselective strategy for the synthesis of (3*R**, 3a*S**, 7a*S**)-3-arylhydroindoles (**121**), an useful precursor for the synthesis of 5,11-methanomorphanthridine alkaloids. Simple functional group transformations of **121** provides **125**, which was finally converted to 5,11-methanomorphanthridine skeleton **126** by Pictet-Spengler cyclization. (Scheme-10)

Scheme-10

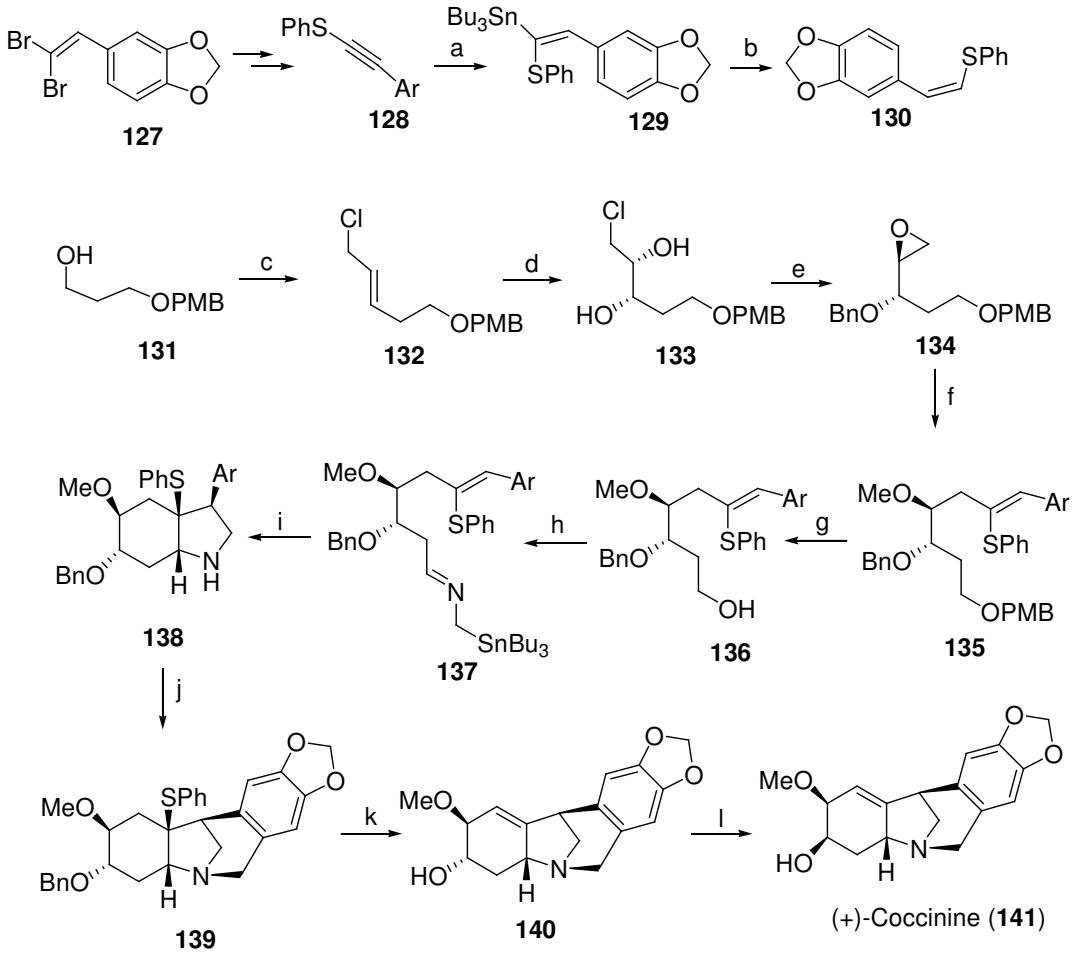


Reagents and conditions: *a) (1) $TiCl_4$, $CHCl_3$, 0 °C to rt; (2) KOH, H_2O-EtOH, reflux; b) $Pd(OAc)_2$, LiCl, $LiOAc.2H_2O$, p-benzoquinone, AcOH, rt; c) p-methoxybenzylamine, $Pd(dba)_2$, PPh_3, NEt_3, THF, rt; d)* ***116****, DCC, DMAP, DCM, rt; e) $(TMS)_3SiH$, AIBN, benzene, reflux; f) (1) $LiOH.H_2O$, H_2O-MeOH, reflux; (2) Swern Oxidation; g) ethylene glycol, TsOH, benzene, reflux; h) $AlH_3(LiAlH_4$-$AlCl_3)$, THF-Et_2O, rt; i) (1) CbzCl, benzene, reflux; (2) H_2, Pd-C, conc. HCl, MeOH, rt; j) (1) 36% formalin, NEt_3, MeOH, rt (2) 6N HCl, MeOH, 30 °C* **.**

1.2.6. Pearson's Approach: (*Angew. Chem. Int. Ed.* **1998**, 37, 1724)[23]

Pearson *et al* have reported an enantioselective total synthesis of (+)-coccinine (**141**), the non-natural enantiomer of (-)-coccinine (**14**) from readily available starting material vinylidenedibromide (**127**) in overall 21 steps. The key feature of the synthesis involved (1) the intramolecular cycloaddition of the 2-azaallyl anion generated from precursor **137** to produce key perhydroindole **138** (2) Pictet-Spengler cyclization of **138** to produce 5,11-methanomorphanthridine skeleton **139**. (Scheme-11)

Scheme-11



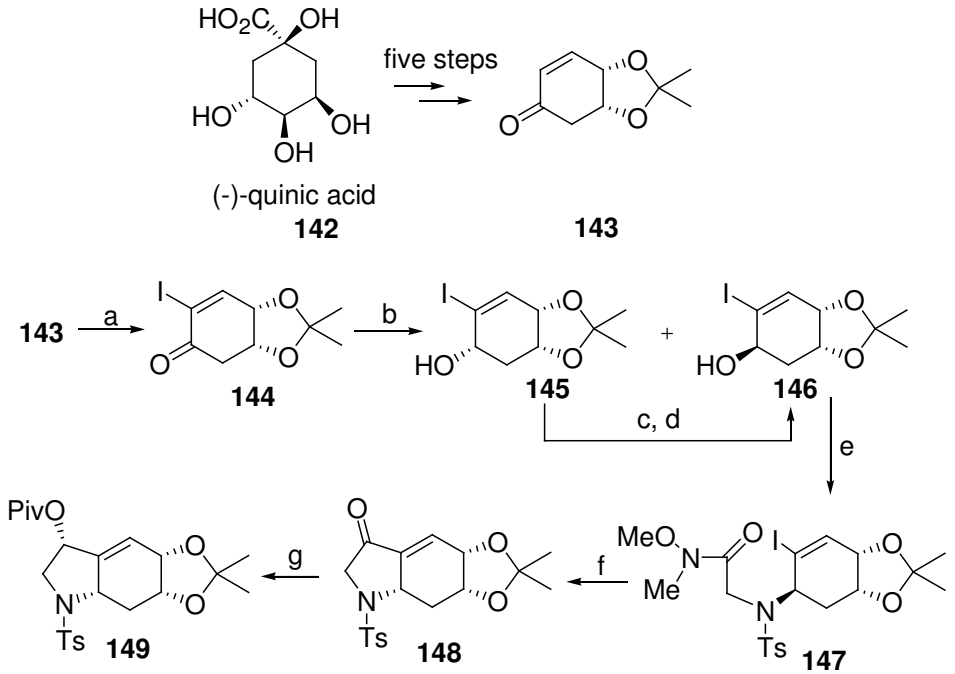
Reagents and Conditions: *a) $Pd(PPh_3)_4$ (cat), Bu_3SnH, C_6H_6, rt; b) n-BuLi (3 equiv), THF, -78 °C, 0.5h, sat. aq. NH_4Cl, rt; c) (1) Swern oxidation, (2) $(MeO)_2P(O)CH_2CO_2Me$, NaH, C_6H_6, rt ;(3) i-Bu_2AlH, toluene, THF, 0 °C→ rt; (4) MsCl, i-pr_2NEt, -23 °C, then dilute with*

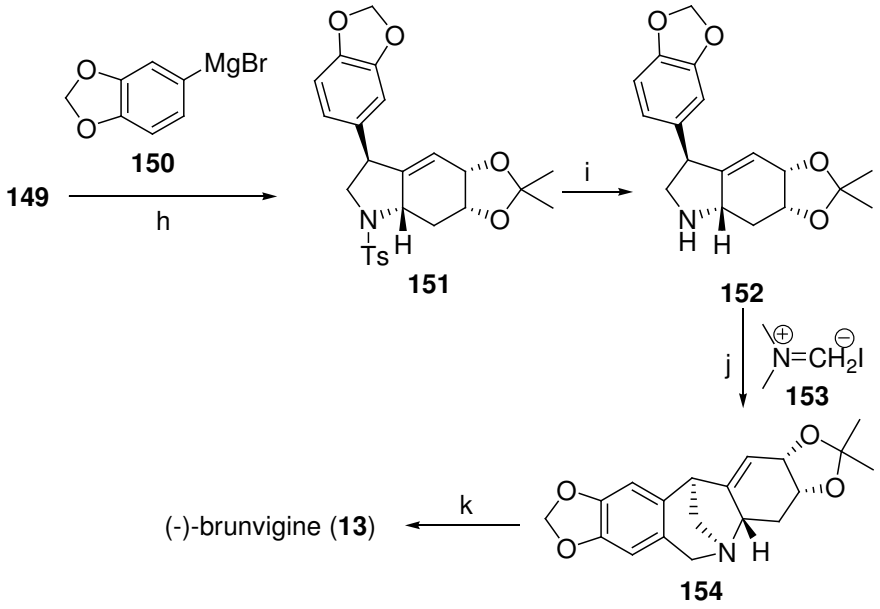
DMF, add LiCl, rt; d) AD-mix-α, THF, t-BuOH, H_2O, $MeSO_2NH_2$ e) (1) NaH, THF, DMSO, rt; (2) NaH, BnBr, THF, DMSO, 0 °C→ rt; f) (1) ***130****, t-BuLi, THF, -78 °C then* ***134****, $BF_3.OEt_2$, -78 °C ; (2) NaH, THF, 0 °C, MeI, , rt; g) EtSH, DCM, $BF_3.OEt_2$ h) (1) Swern oxidation; (2) $Bu_3SnCH_2NH_2$, Et_2O, 4Å MS; i) n-BuLi, THF, -78 °C ; j) 37 % CH_2O, MeOH, rt then 6N HCl, 80 °C ; k) (1) Et_2O, anhydrous HCl, 0 °C, concentrate under vacuo; m-CPBA, DCM, 0 °C; (2) C_6H_6, K_2CO_3, 80 0 °C; l) (1) Ms_2O, pyridine, DCM, , 0 °C; (2) CsOAc, DMF, [18] crown-6, 125 0 °C; (3) K_2CO_3, MeOH, rt, 3h.*

1.2.7. Sha's Approach: (*Organic Lett.* **2001**, 3, 2172)[25]

Sha et al have accomplished first asymmetric total synthesis of (-)-brunsvigine in 17 steps and 12% overall yield starting from (-)-quinic acid. The main features of their synthesis include (1) vinyl anion cyclization of Weinreb amide **147** to provide perhydroindole **148**, (2) stereoselective addition of Grignard reagent to the perhydroindole **149**, and (3) Pictet-Spengler cyclization of **152** which provides core structure **153** of (-)-brunsvigine. (Scheme-12)

Scheme-12



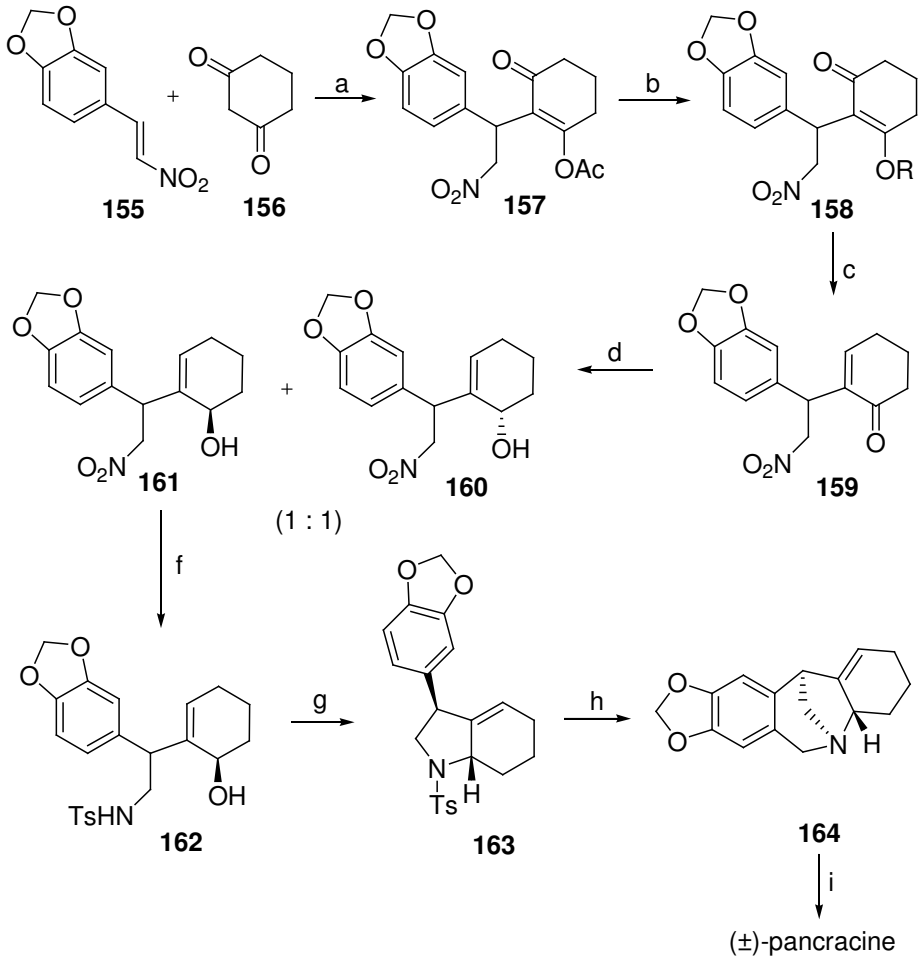


Reagents and conditions: *a) I_2, pyridine, DCM, rt; b) $NaBH_4$, $CeCl_3.7H_2O$, MeOH; c) p-NO_2PhCO_2H, PPh_3, DEAD; d) NaOH, MeOH; e) $TsNHCH_2CON(OMe)Me$, DIAD, PPh_3; f) n-BuLi, THF, -78 $^oC\rightarrow$ -30 ^oC; g) (1) $NaBH_4$, $CeCl_3.7H_2O$, MeOH; (2) PivCl, pyridine, rt; h)* ***150****, CuI, THF, rt; i) Na, naphthalene, DME, -78 ^oC; j)* ***153****, DMF, 90 ^oC; k) conc. HCl, MeOH, rt.*

1.2.8. Banwell's Approach: (*J. Chem. Soc., Perkin Trans. I*, **2001**, 1345)[26]

Banwell *et al* have demonstrated a formal total synthesis of these classes of alkaloids in 7 steps. The key features of their approach involved (1) introduction of the pivotal $\Delta^{1,11a}$ -double bond by Michael addition of cyclohexyl diketone **156** to β-nitrosostyrene **155**, (2) Mitsunobu-type intramolecular nucleophilic displacement of an allylic alcohol **162** by a tethered sulfonamide which produces key precursor **163**, (3) Pictet-Spengler cyclization of **163** to provide 5,11-methanomorphanthridine skeleton **164**.

Scheme-13

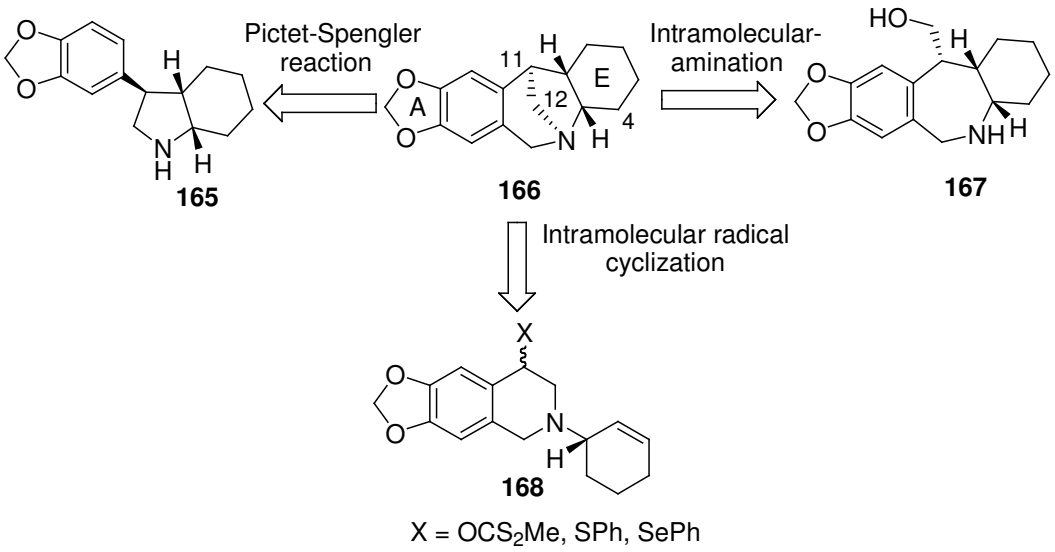


Reagents and Conditions: *a) DBU, DCM, 18 °C; b) Ac_2O, DMAP, pyridine, 18 °C; c) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, -10-18 °C then K_2CO_3, MeOH, 18 °C d) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0-18 °C; e) NiB_2, 80% aq. Hydrazine, EtOH, -78 °C then p-TsCl, DMAP, pyridine, DCM, 18 °C; f) DIAD, PPh_3, DCM. 0-18 °C; g) $C_{10}H_8Na$, DME, -78 °C; h) paraformaldehyde, HCO_2H, 80 °C.i) ref. 21.*

1.3. Summary

From the above literature survey, it is evident that there are only three strategies known to assemble 5,11-methanomorphanthridine skeleton: i) Pictet-Spengler cyclization of the precursor of type **165** ii) intramolecular cyclization from **167** ii) intramolecular radical cyclization from **168**. All these reported strategies can be briefly summarized retrosynthetically as shown in Scheme-14.

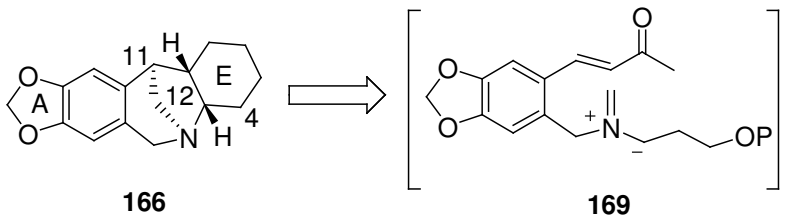
Scheme-14



However, in all these approaches, synthesis is elaborated from a precursor having proper stereochemistry at C-4a and C-11a and relative disposition of C-12 methylene group of **166** which involved its construction in stepwise manner.

We viewed the synthesis of these alkaloids differently, as depicted retro-synthetically in Scheme-15 employing [3+2]-cycloaddition of non-stabilized azomethine ylide (**169**) for the construction of suitably substituted CD-ring system in one step. Such cycloadditions were also expected to fulfill all stereochemical requirements of **166** in a single step without going through a starting material having fixed stereocenteres.

Scheme-15



166 **169**

Proceeding sections of this chapter will discuss in detail our progress towards these endeavors.

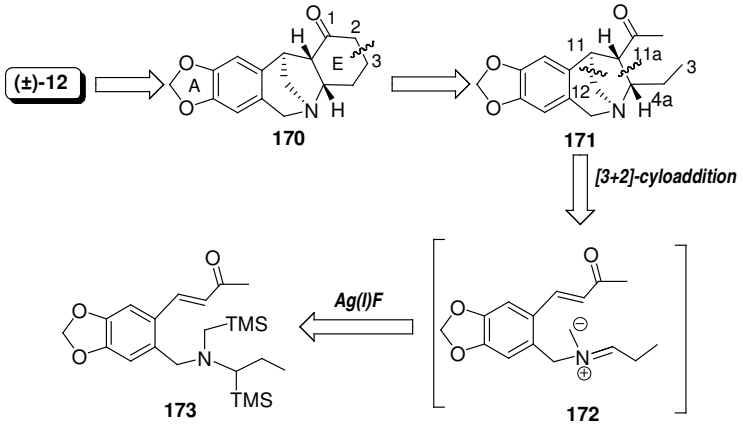
2.1. Introduction

Montanine-types of *Amaryllidaceae* alkaloids are attractive synthetic targets for synthetic organic chemist because of their unique architectures and their pharmacological promises. The main synthetic challenge to design an efficient route towards these classes of alkaloids involves creation of stereospecific disposition of the C-13 methylene group and controlled and proficient installation of the oxygen-functionalities around the periphery of E-ring. There are some synthetic journeys towards these classes of alkaloids,[18-26] as described in previous section of this chapter. Most of them suffer from (1) poor stereochemical control, (2) multiple steps, (3) poor overall yield and (4) generality. We viewed the molecular complexity of these alkaloids from totally different angle and envisaged a conceptually new synthetic route utilizing intramolecular [3 + 2]-cycloaddition of non-stabilized azomethine ylide, generated *in situ* by Ag(I)F mediated sequential one electron oxidation of α, α'-bissilylated *tert*-amine as a key step, an efficient methodology developed from our group.[27, 28]

2.2 Retrosynthetic Plan and Design

For the design of an elegant route to monatnine-type of alkaloids, retrosynthetic scission of 5,11-methanomorphanthridine skeleton **170** at C_2-C_3 bond led us to the compound **171**, which contains fused pyrrolidine ring (CD rings). It was envisaged that in our synthetic design for **171**, an intramolecular [3+2]-cycloaddition reaction of non-stabilized azomethine ylide **172**, would be an ideal approach as it would also result in the formation of C_{12}-C_{11} and C_{4a}-C_{11a} bonds in one step. (Scheme-16)

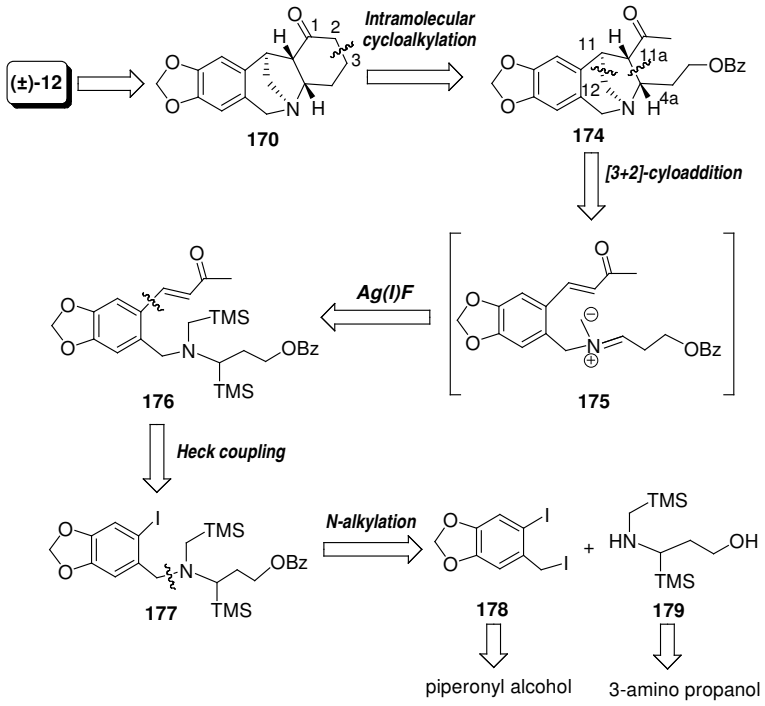
Scheme-16



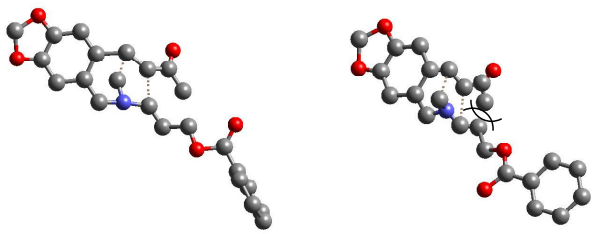
The corresponding AMY **172** could be easily generated from the α, α'-bis(trimethylsilylmethyl)alkyl amine **173** using Ag(I)F as an one electron oxidant, a protocol developed from our laboratory.[27, 28]

It is evident from the above retrosynthetic analysis that for the construction of E-ring of **170**, *i.e* for C_2-C_3 bond formation, we have to make C_3 electrophilic for effecting intramolecular carbanion cycloalkylation efficiently. Keeping this in mind, we proposed to put oxygen functionality at C_3 as a good leaving group for further manipulations. (Scheme-17)

Scheme-17



While at the drawing board of our synthetic design itself, it was very clear to us that intramolecular *endo*-attack of the *anti*-azomethine ylide **175** to the *re*-face of the α, β-unstaurated carbonyl moiety would be energetically more favoured (**A**) over the *exo*-attack (**B**) due to steric repulsion (Figure 4). Such cycloadditions were also expected to fulfill all stereochemical requirements of **170** in a single step without going through a starting material having fixed stereocenteres. Furthermore, it was envisioned that the resultant cycloadduct **174** could be equipped with a ketonic as well as protected alcohol moiety, which on proper manipulation and intramolecular carbanion-cycloalkylation would produce **170** in a very short reaction sequence. It may be appropriate to mention that Overmann *et al.*[21] have synthesized (±)-pancracine (**12**) from **170**.



A (*endo* attack of *anti*-yldide) **B** (*exo* attack of *anti*-yldide)

Figure-4. *Emprical view of the transition state **175** (hydrogens are omitted for simplicity)*

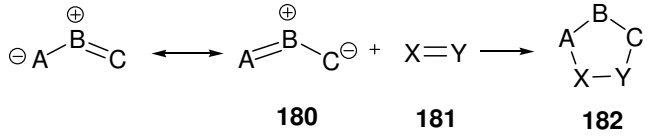
The requisite precursor **176** for the crucial transformation could be prepared by Heck coupling of corresponding iodo compound **177** and methyl vinyl ketone (MVK). The iodo compound **177** can be synthesized by alkylation of bissilylated amino alcohol **179** and diiodo compound **178**. The coupling components **178** and **179** may be obtained from commercially available piperonyl alcohol and 3-amino propanol, respectively, through simple synthetic transformations.

Since our synthetic endeavor towards montanine-type alkaloids involves [3+2]-cycloaddition of azomethine ylide as a key step, it would be appropriate to highlight the

salient features of azomethine ylide as 1,3-dipole and the protocol developed in our laboratory for its generation and trapping.

2.3 Azomethine Ylide

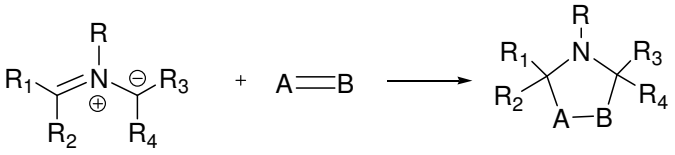
An ylide is a planer reactive intermediate where four electrons are distributed among three parallel atoms, which on cycloaddition[29-32] with a variety of dipolarophiles produces five membered hetrocyclic ring system. (Figure-5)



180 **181** **182**

Figure-5

Azomethine ylides are nitrogen-centered ylide composed of one nitrogen and two *sp*^{2} carbons. Their cycloadditions with olefin and acetylene dipolarophiles produces five membered heterocyclic compounds with concomitant formation of two sets of carbon-carbon bond in a single step. (Figure-6)



183 **184** **185**

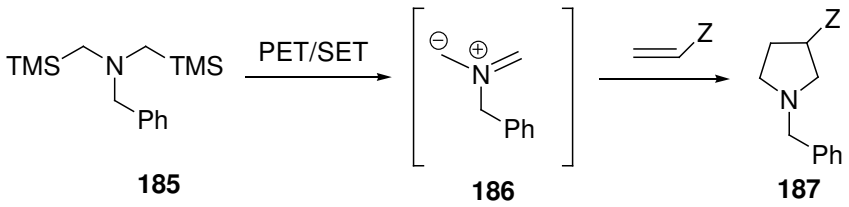
Figure-6

These 1,3-dipolar cycloaddition of azomethine ylides with an olefin has been identified as one of the most attractive strategy for the construction of pyrrolidine ring system[33-38], a frequently encountered structural unit of many synthetically challenging alkaloids. The strong preference for this reaction in the alkaloid synthesis have stemmed due to its chemo-, stereo- and regio-slectivity and reactivity[39-43]. Usually, these cycloadditions have shown preference towards *endo*-addition similar to *iso*-elcetronic Diels -Alder reaction.[42]

2.4 Our Concept and Protocol

Though there are several methods available for the generation of azomethine ylides but most of them are for stabilized azomethine ylides. Generation of non-stabilized azomethine ylides generally required heating or treatment with strong base and most importantly their generation lacks versatility. In order to overcome the pitfall involved in the generation of non stabilized azomethine ylide and to provide a general and versatile method for the generation of cyclic and acyclic azomethine ylides, our group have previously demonstrated the generation and trapping of non-stabilized azomethine ylide **186** from N, N'-bis(trimethylsylil methyl)benzyl amine **185** initiated by one electron transfer processes promoted either by PET or Ag(I)F.[27, 28] (Scheme-18)

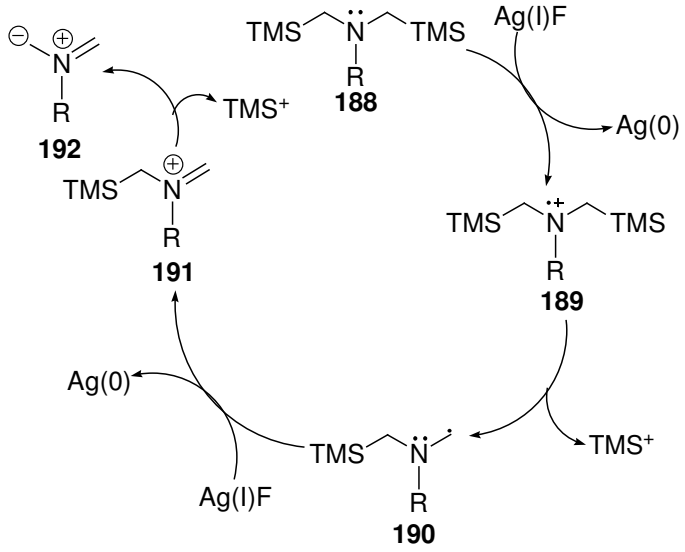
Scheme-18



185 **186** **187**

The basic concept in the generation of **186** from **185** involved sequential one electron oxidation of the lone pair of electrons located on the nitrogen and exploitation of the β-silicon effect[44] to induce sequential desilylation processes to generate azomethine ylides. (Scheme-18) Thus, one electron oxidation of N, N'-bis(trimethylsilylmethyl)alkyl amine (**188**) using Ag(I)F as one electron oxidant leads to the formation of radical cation **189**, which loses silyl cation (TMS^+) producing α-amino radical **190**. Subsequent one electron oxidation of the resultant **190** leads to generation of the iminium cation **191**. Elimination of the second silyl cation (super acid group) leads to the formation of non-stabilized azomethine ylide **192**.[27, 28] (Scheme-19)

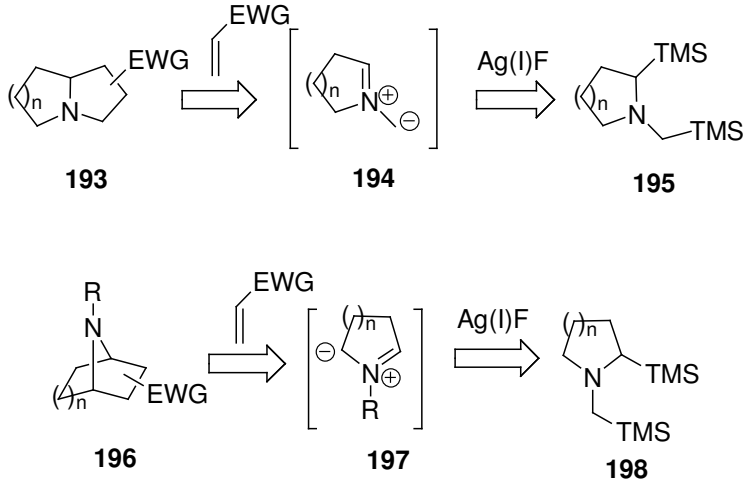
Scheme-19



The above proposed sequential one electron oxidative mechanistic pathway for the generation of azomethine ylide is supported by the fact that only N, N'-bis(trimethylsilyl methyl)alkyl amine affords the cycloadduct and not the corresponding carbamates. This mechanistic route finds further confirmation in a report published by Torii *et al*[45] where **185**, introduced from our laboratory as a precursor, is transformed to azomethine ylide *via* two electron oxidation effected electrochemically or by using one electron oxidative reagent $VO(acac)_2$ in combination with N-oxyl.

A variety of indalozidine, pyrazolidine alkaloids[27, 28, 46, 47] (**193**) and X-azabicyclo (m.2.1) alkanes[48-51] (**196**) have been synthesized using this methodology. (Scheme-20)

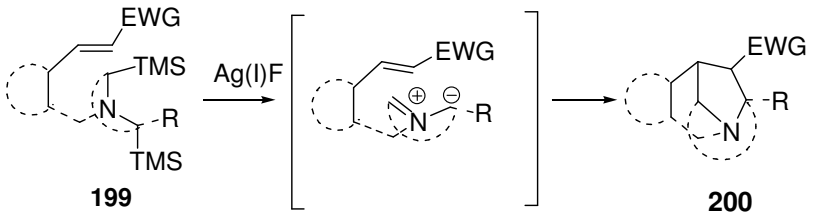
Scheme-20



2.4.1. Intramolecular 1,3-dipolar cycloaddition of azomethine ylide

The most general approach to synthesize five-membered heterocyclic compounds involve cycloaddition of a 1,3-dipole to an appropriate unsaturated substrate, the dipolarophile. Intermolecular cycloadditions result in the formation of one new ring only. However, when the 1,3-dipole and the substrate are part of the same molecule, cycloaddition is intramolecular[52] and leads to a new bicyclic ring-system. Thus, intramolecualr cycloadditions are amenable to the construction of inherently more complex products than intermolecular cycloadditions. Markedly different regioselectivity, controlled by the geometrical constraints of bringing the 1,3-dipole into correct internal alignment for the reaction with dipolarophile, is often observed in an intramolecular cycloaddition, which sometimes overwhelm the normal preferences dictated by electronic factors. The greater steric constraint inherent to intramolecular cycloaddition often affords higher diastreofacial discrimination: accordingly these reactions can exhibit very high stereoslectivity and periselectivity. Also, due to a favored entropy term compared to intermolecular variant, the reactivity of these reactions is higher in general. With all of these advantages, intramolecualr cycloadditions is certainly a powerful synthetic tool.

Intramolecular 1,3-dipolar cycloaddition of azomethine ylide[53] provides complex fused N-heterocyclic compounds, commonly encountered structural entity in many naturally occurring alkaloids. There are few reports of using this reaction in natural product synthesis. Keeping the advantages of intramolecular cycloadditions and limitations involved with the proper designing in mind, we thought of exploring an intramolecular version of our original methodology as shown schematically in Figure-7.

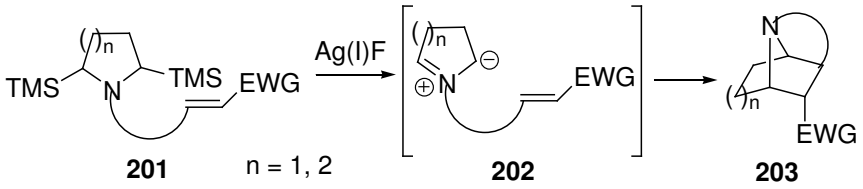


199 **200**

Figure-7

Earlier from our group, an intramolecular [3+2]-cycloaddition of non-stabilized azomethyne ylide has already been successfully demonstrated[54] for the synthesis of complex X-azatricyclo [m.n.0.0.$^{a.b}$] alkanes. (Scheme-21)

Scheme-21



With these successful background and further promises, we set upon proving the potential of our methodology for the construction of the challenging pentacyclic fused pyrolidine ring system present in Monatanine-type *Amaryllidacae* alkaloids.

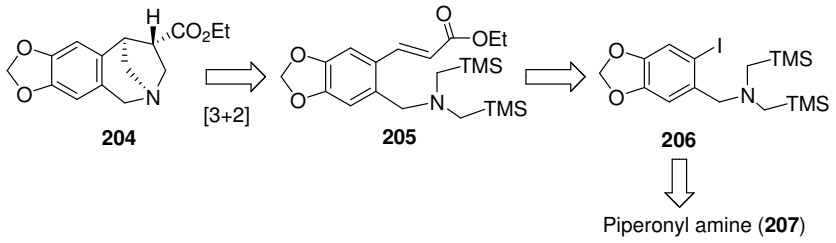
2.5. Results and Discussion

In order to check the feasibility of our approach for Montanine-type *Amaryllidaceae* alkaloids (**9**, **12-16**), we decided at first to synthesize its tetracyclic core ring structure.

2.5.1 Synthesis of Tetracyclic Core Ring Structure of Montanine-type Amaryllidaceae Alkaloids

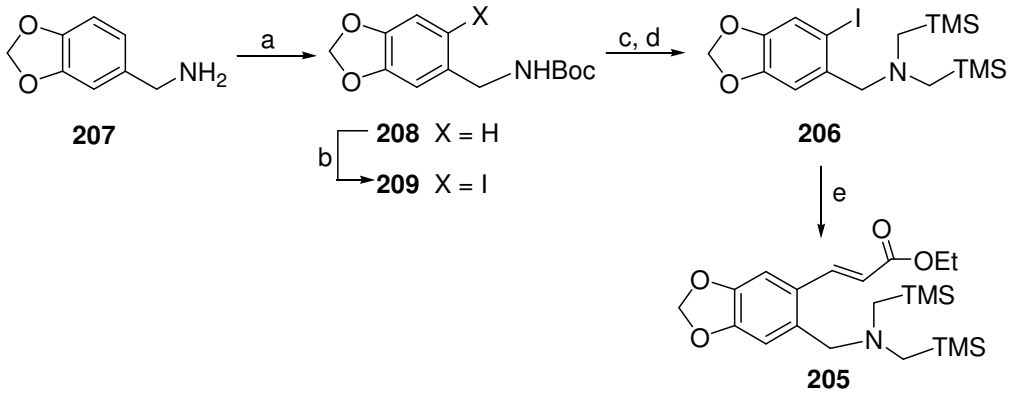
The synthesis of the core tetracyclic ring structure is based on the anticipated intramolecular [3+2]-cycloaddition of non-stabilized azomethine ylide as shown retrosynthetically in Scheme-22.

Scheme-22



The synthetic precursor **205**, for the efficient construction of the core tetracyclic ring structure **204,** was prepared from the piperonyl amine **207** following reaction sequences as shown in Scheme-23.

Scheme-23



Reagents and conditions: *a) $(Boc)_2O$, NaOH, H_2O, 0 $^0C\rightarrow$ rt, 90%; b) I_2, CF_3COOAg, $CHCl_3$, 70%; c) TFA, DCM, 0 $^0C\rightarrow$ rt, quant. d) ICH_2TMS, K_2CO_3, CH_3CN, reflux, 78%; e) ethyl acrylate, $Pd(OAc)_2$, PPh_3, K_2CO_3, CH_3CN, reflux, 64%.*

Piperonyl amine **207** was converted to the corresponding N-Boc derivative **208** in 90% yield by treating with di-*tert*-butyl dicarbonate and NaOH in water. The N-Boc compound **208** on aromatic electrophilic iodination[55] with I_2 in the presence of CF_3COOAg in chloroform gave corresponding iodo-derivative **209** in 70% yield. Deprotection of the N-Boc-moiety from compound **209** was achieved quantitatively by stirring with TFA in dry DCM at room temperature for 3h. The N-alkylation of the crude amine was achieved in 75-80% yield by refluxing with iodomethyltrimethylsilane in the presence of K_2CO_3 in dry CH_3CN, which gave bis-silylated compound **206**.

In the ^{1}H NMR spectrum of **206** two singlets appearing at δ 7.22 and δ 7.12, were assigned to the two aromatic protons. The methylenedioxy protons appeared as a sharp singlet at δ 5.97. A singlet at δ 3.37, integrating for two protons, was assigned to N-benzyl protons. Another singlet at δ 1.97, integrating for four protons, was assigned to (–N-C$\underline{H}_2$-

TMS) protons. A singlet at δ 0.05, integrating for eighteen protons was assigned to two the TMS group protons.

The ^{13}C spectrum of **206** displayed a total of nine signals at δ 148.05, 146.7, 135.6, 117.7, 109.7, 100.9, 69.4, 50.3, and - 1.5. In the DEPT spectrum, two aromatic methine carbons appeared at δ 117.7 and 109.7, respectively. The methylene carbon of methylenedioxy group appeared at δ 100.9. The other two methylene signals appearing at 69.4 and 50.3 were attributed to the N-benzyl and (–N-$\underline{C}H_2$-TMS) carbons, respectively. The methyl carbons of two TMS groups appeared at δ -1.5.

The mass spectrum of **206** displayed molecular ion peak at m/z 450 (M+H).

With compound **206** in hand, our next job was to create a double bond replacing the designed iodo functionality to obtain the crucial cycloaddition precursor **205**. The best thing occurred in our mind in this regard was to try Heck coupling[56, 57] of **206** with ethyl acrylate. The Heck coupling was effected by refluxing a mixture of **206** (1 equiv) with $Pd(OAc)_2$ (0.08 equiv), PPh_3 (0.16 equiv), K_2CO_3 (2 equiv) and ethyl acrylate (8 equiv) in CH_3CN for 10h which gave **205** in 65% yield.

The IR spectrum of **205** showed a strong absorption band at 1712 cm^{-1} indicating the presence of an α,β-unsaturated ester carbonyl. Furthermore, observation of an absorption band at 1631 cm^{-1}, corroborated the presence of conjugate alkene stretching vibration.

The ^1H NMR spectrum of **205** displayed two sets of doublets at δ 8.12 and 6.14 (J = 15.85 Hz) corresponding to the olefinic protons of the α,β-unsaturated carbonyl compound. Two singlets at δ 7.01 and 6.97, integrating for one proton each, were attributed to the two aromatic protons. The methylenedioxy protons appeared as a sharp singlet at δ 5.95. A quartet at δ 4.20 (J = 7.07 Hz), integrating for two protons, was assigned to (–O-C$\underline{H}_2CH_3$) protons. The N-benzyl protons appeared as a sharp singlet at δ 3.46. A singlet at δ 1.85,

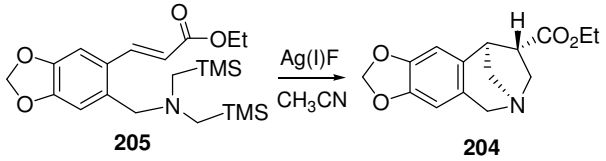
integrating for four protons, was assigned to (–N-C$\underline{H}_2$-TMS) protons. A triplet at δ 1.54, integrating for three protons, was assigned to the (–O-$CH_2C\underline{H}_3$) protons. The TMS protons appeared as sharp singlet at δ 0.00.

In the ^{13}C NMR spectrum, a total of fifteen signals at δ 167.0, 149.2, 146.9, 141.8, 135.3, 127.6, 117.4, 110.4, 105.6, 101.2, 63.2, 60.2, 50.7, 14.3, and -1.1 were observed. The most downfield peak at δ 167.0 was assigned to the carbonyl carbon of the ester moiety. The vinyl methine carbons appeared at δ 141.8 and 105.6 (suggested by DEPT experiment), respectively. The aromatic carbons appeared at δ 149.2, 146.9, 135.3, 127.6, 117.4 and 110.4. The methylenedioxy carbon appeared at δ 101.2. The carbons of (–O-CH_2CH_3) group appeared at δ 63.2 and 14.3, respectively. The benzylic carbon appeared at δ 60.2. The methylene group attached to TMS functionality was observed at δ 50.7. The carbons of TMS moiety appeared at δ -1.1.

The mass spectrum of **205** gave a peak at m/z 422 corresponding to the molecular ion.

With the cycloaddition precursor **205** in hand, we proceeded to perform the key intramolecular 1,3-dipolar cycloaddition reaction. The cycloaddition reaction involved very slow addition of **205** to a stirring heterogeneous mixture of flame dried Ag(I)F (2.5 equiv) in dry CH_3CN, which upon usual work-up and purification produced **204** in 65% yield. The cycloadduct was fully characterized by IR, ^1H NMR, ^{13}C NMR, mass spectral analyses. The stereochemistry of **204** was assigned and confirmed by 2D NMR studies. The peak assignments in the ^1H NMR spectrum were carried out with the help of COSY experiment. (Scheme-24)

Scheme-24



205 **204**

The IR spectrum of **204** showed a strong absorption band at 1730 cm^{-1} indicating the presence of an ester carbonyl moiety.

In the ^{1}H NMR spectrum of **204,** two aromatic protons appeared as singlets at δ 6.47 and 6.36. The methylenedioxy protons appeared as a sharp singlet at δ 5.79. Two sets of doublets at δ 4.26 and 3.65 (J = 16.96 Hz), integrating for one proton each, were attributed to the N-benzylic protons. The protons corresponding to (–O-C$\underline{H}_2$-CH_3) appeared as a quartet at δ 4.06 (J = 6.87 Hz). One doublet of a doublet appearing at δ 3.37 (J = 12.83, 4.13 Hz), integrating for one proton, was assigned to the (-C$\underline{H}$-CO_2Et) proton. The benzylic proton appeared as a broad doublet at δ 3.20 (J = 1.83 Hz). Another broad doublet of a doublet, integrating for one proton, at δ 3.12 (J = 11.40, 1.81 Hz), was assigned to one of the methylene bridge protons. The signal for one of the (-C$\underline{H}_2$-$CHCO_2$Et) protons appeared as a doublet of a doublet at δ 3.04 (11.45, 2.29 Hz). The other methylene bridge proton appeared as a doublet at δ 2.98 (J = 11.45). A doublet of a doublet appearing at δ 2.96 (J = 10.01, 4.32), integrating for one proton, was assigned to the other (-C$\underline{H}_2$-$CHCO_2$Et) protons.

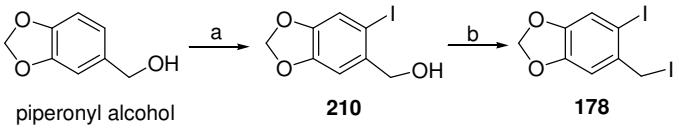
The ^{13}C NMR of **204** displayed a total of sixteen signals at δ 172.9, 146.5, 145.8, 133.9, 124.1, 106.7, 106.3, 100.6, 60.7, 59.0, 57.4, 55.3, 54.5, 53.7, 42.0, and 13.3. The most downfield peak at δ 172.9 was assigned to the carbonyl carbon of the ester moiety. The two aromatic methine carbons appeared at δ106.7 and 106.3, respectively (as per the DEPT experiment). The rest other aromatic carbons were observed at δ 146.5, 145.8, 133.9, and 124.1. The methylendioxy carbon appeared at δ 100.58. The methylene and methyl carbons of (–O-CH_2CH_3) group appeared at δ 60.7 and 13.9, respectively. The N-benzylic carbon appeared at δ 59.0. The other two methylenic carbons (methylene bridge and N-$\underline{C}H_2$-$CHCO_2$Et) were observed at δ 57.4 and 55.3, respectively. The signals at 53.6 and 42.2 were assigned to (-$\underline{C}HCO_2$Et) and benzylic carbon, respectively.

The mass spectrum of **204** displayed molecular ion peak at m/z 276.

2.5.2 Synthesis of 11a (*epi*)-8,9–methylenedioxy-5,11-methanomorphanthr-idin-1-one(170):

After successful preparation of **204**, we moved on to design the synthesis of 5,11-methanomorphanthridine skeleton **170** as a model study. Our synthesis started with the preparation of the key precursor **176**. The synthesis of **176** involved coupling of two components **178** and **179** followed by Heck reaction with methyl vinyl ketone (MVK). The synthetic route for **178** is described in Scheme-25.

Scheme-25

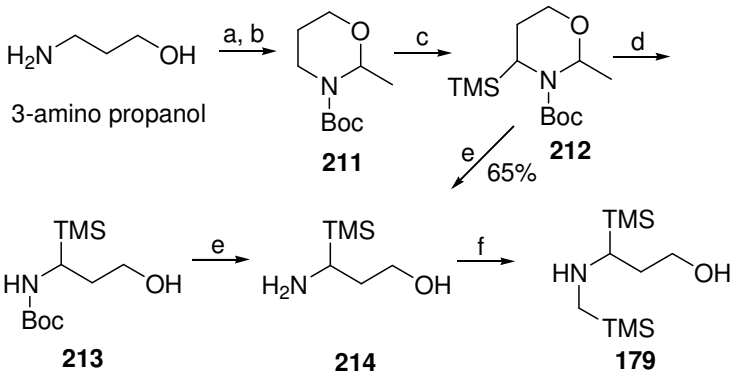


***Reagents and conditions**: a) I_2, CF_3COOAg, $CHCl_3$, rt, 65%; b) NaI, TMSCl, CH_3CN, rt, quantitative.*

Aromatic electrophilic iodination of piperonyl alcohol with iodine using silvertrifluoroacetate as Lewis acid gave **210** in 65% yield, which was finally transformed to **178** in quantitative yield by treating with NaI and TMSCl. The spectral characteristic of compounds **210** and **178** matched with the reported values in the literature.[22, 55, 58]

The other component **179**, required to accomplish precursor **176**, was achieved as shown in Scheme-26. The N-Boc protected cyclic amine **211** was synthesized very easily in two steps from commercially available 3-amino propanol. Treatment of **211** with *s*-BuLi/TMEDA at –78 ^oC in THF followed by reaction with TMSCl gave silylated compound **212** in 92% yield.[59]

Scheme-26



***Reagents and conditions**: a) $(Boc)_2O$, Et_3N, DCM, 0 $^oC \rightarrow$ rt, 90%; b) $CH_3CH(OEt)_2$, PPTS, benzene, reflux, 86%; c) s-BuLi, TMEDA,THF, -78 ^oC, then TMSCl, 92%; d) PTSA, MeOH-H_2O, rt, quant.; e) 1N HCl, Dioxane, reflux, 87%; f) ICH_2TMS, K_2CO_3, CH_3CN, reflux, 80%;*

The IR spectrum of **212** showed a strong adsorption band at 1693 cm^{-1}, suggesting the presence of an amide moiety. A sharp absorption band at 1413 cm^{-1} was attributed to the C-N stretching.

The ^1H NMR spectrum of **212** showed a quartet at δ 5.43 (J = 6.06 Hz), integrating for one proton, which was assigned to (–N-C<u>H</u>-O-) proton. Two multiplets appearing at δ 3.93 and 3.60, integrating for one proton each, were assigned to (O-C<u>H_2</u>-CH_2) protons. The (TMS-CH-) proton appeared as a doublet of a doublet at δ 2.65 (J = 10.74, 4.67 Hz). One multiplet observed at δ 1.76, integrating for two protons, was assigned to the (O-CH_2-C<u>H_2</u>-) protons. One broad singlet appearing at δ 1.52, integrating for twelve protons, was assigned to the protons of Boc and methyl groups. The protons of TMS functionality appeared at 0.08.

The ^{13}C NMR spectrum of **212** displayed a total of nine signals at δ 154.5, 81.1, 79.6, 61.1, 39.1, 28.3, 26.7, 17.5, and -1.08. The most downfield peak at δ 154.5 was assigned to the carbonyl carbon of the N-Boc moiety. The signals appearing at δ 81.1 and 79.6 were attributed to (O=C-O-<u>C</u>) and (-N-<u>C</u>H-O-) carbons, respectively. The DEPT

experiment revealed the presence of two methylenic carbons at δ 60.7 and 26.4, which were assigned to (-O-$\underline{C}H_2$-) and (TMSCH-$\underline{C}H_2$-), respectively. Two methine signals appearing at δ 38.7 and 17.2 were attributed to (TMS-$\underline{C}$H-) and (CH_3-$\underline{C}$H-) carbons, respectively. The carbons of tertiary butyl group of Boc-moiety and TMS group appeared at δ 27.9 and -1.08, respectively.

The mass spectrum of **212** displayed molecular ion peak at m/z 274 (M+H).

Deprotection of N-acetal moiety of **212** by p-TSA in methanol at room temperature produced same amino alcohol **213** in quantitative yield, which on refluxing with 1N HCl in dioxane-water produced corresponding free amine **214** in 87% yield**.** Although, direct treatment of **212** with HCl could give **214** but yield (65%) was found to be poorer compared to two steps sequence.

In the IR spectrum of **214,** two absorption bands at 3353 and 3284 cm^{-1}, suggested the presence of free hydroxyl amine functionality. A sharp peak at 1249 cm^{-1} was attributed to C-O stretching.

In the ^{1}H NMR spectrum of **214,** a triplet (J = 5.81 Hz) at δ 3.62, integrating for two protons, was assigned to (-O-C$\underline{H}_2$-) protons. A broad singlet appearing at δ 2.87, integrating for three protons, was attributed to NH_2 and OH protons. The methine proton appeared as broad doublet at δ 2.23 (J = 9.53 Hz). The other methylene protons appeared as two sets of multiplets at δ 1.48 and 1.38. The protons of TMS groups appeared at δ 0.13.

The ^{13}C NMR spectrum of **214** displayed a total of four signals at δ 66.8, 62.8, 34.2, - 4.3. The DEPT experiment showed the presence of two methylene carbons at δ 66.8 and 34.2, assigned to (O-$\underline{C}H_2$) and other remaining methylene group carbons, respectively. The methine carbon appeared at δ 62.8. The carbons of the TMS group appeared at δ -4.3.

The mass spectrum of **214** displayed molecular ion peak at m/z 147(M+).

The alkylation of **214** with iodomethyl trimethylchlorosilane in the presence of K_2CO_3 in CH_3CN gave **179** in 80% yield.

The IR spectrum of **179** showed a broad band at 3392 cm^{-1} suggesting the presence of alcoholic and amine functionality.

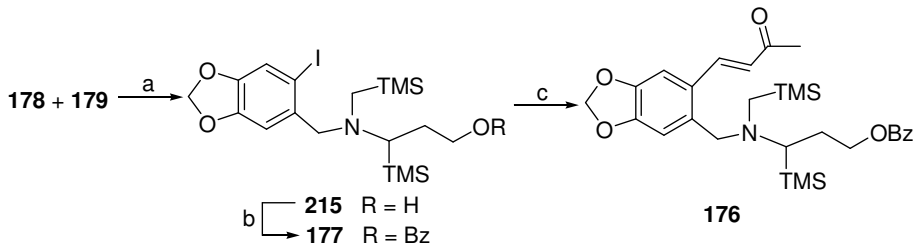
In the ^1H NMR spectrum of **179,** a multiplet at δ 3.81, integrating for two protons, was attributed to (-O-C$\underline{H}_2$-) protons. A broad singlet appearing at δ 3.53, integrating two protons, was attributed to NH and OH. The methine proton appeared as a doublet of doublet at δ 2.37 (J = 8.95 and 4.01 Hz). The methylinic protons attached to TMS group appeared as two sets of doublets at δ 2.25 and 2.18 (J = 14.95 Hz). The other methylene protons appeared as a multiplet at δ 1.76. The singlets at δ 0.21 and 0.11, integrating to nine protons each, arose from the TMS functionality.

The ^{13}C NMR spectrum displayed a total of six signals at δ 65.5, 55.1, 40.1, 30.1, -0.2, and - 0.3. The DEPT experiment revealed the presence of three methylene and one methine carbons. The peak at δ 65.5 was attributed to (-O-$\underline{C}H_2$-) carbon. The signal at δ 55.1 was assigned to (TMS-$\underline{C}$H-) carbon. The other two methylene carbons appeared at δ 40.1 and 30.1, respectively. The methyl signals appearing at δ -0.2 and -0.3 are associated with the two TMS functionality.

The molecular ion peak in the mass spectrum of **179** was observed at m/z 233(M+).

With both the fragment **178** and **179** in hand, our next task was to couple them together to achieve **215,** which was easily done in 72% yield by refluxing a mixture of **178** and **179** in dry CH_3CN in the presence of anhydrous K_2CO_3. (Scheme-27)

Scheme-27



Reagents and conditions: *a) K_2CO_3, CH_3CN, reflux, 72%; b) BzCl, Et_3N, DCM, 0 $^oC \rightarrow$ rt, 81% c) $Pd(OAC)_2$, PPh_3, K_2CO_3,, MVK, CH_3CN, reflux, 60%.*

The IR spectrum of **215** displayed an absorption band at 3348 cm^{-1}, characteristic of the -OH group.

The ^1H NMR analysis revealed the presence of two aromatic protons as a two sets of singlets at δ 7.13 and 6.93. The methylenedioxy protons appeared as two sets of singlets at δ 5.87 and 5.86. A multiplet appearing at δ 3.60 to 3.75, integrating for three protons, were assigned to (-O-C$\underline{H}_2$-) and one of the N-benzylic proton. The other N-benzylic proton appeared as a doublet at δ 3.52 (J = 14.15 Hz). A doublet of a doublet at δ 2.39 (J = 9.57, 4.25 Hz), integrating for one proton, was attributed to (TMS-C$\underline{H}$-) proton. Two sets of doublets appearing at δ 2.13 and 2.05 (J = 14.52 Hz), integrating to one proton each, were attributed to (TMS-C$\underline{H}_2$-) protons. The remaining methylene group protons appeared as two sets of multiplets at δ 1.81-2.02 and 1.32-1.50, respectively. The methyl signals at δ 0.11 and 0.00 arose due to the two TMS functionality.

The ^{13}C NMR experiment displayed a total of fourteen signals at δ 149.0, 147.7, 135.1, 118.5, 109.9, 101.8, 88.1, 65.1, 64.2, 55.9, 45.4, 29.8, -0.4, and -0.9. The DEPT experiment revealed the presence of two aromatic methine carbons at δ 118.0 and 109.2. The rest of the aromatic carbons were observed at δ 149.0, 147.7, 135.1 and 88.1. The methylendioxy carbon appeared at δ 101.32. Four methylene peaks observed at δ 65.1, 64.2, 55.9, 29.8 were assigned to the (HO-$\underline{C}H_2$-), N-benzyl, (TMS-$\underline{C}H_2$-) and (TMSCH$\underline{C}H_2$-)

carbons, respectively. The signal at δ 55.9 was attributed to the (TMS-CH-) carbon. The methyl signals at δ -0.4 and -0.9 were associated with two TMS functionality.

The mass spectrum of **215** displayed molecular ion peak at m/z 494(M+H).

In order to proceed further, it was necessary to protect the free hydroxyl group with a suitable protecting group. In this context, we thought a variety of protecting groups but found benzoyl ester as the ideal one due its easy removal and advantage of no characteristic peaks in the aliphatic region of ^{1}H NMR spectra which would help us in characterization of the products at the final step. The benzoyl protection of **215** was carried out in DCM using benzoyl chloride and triethyl amine to produce **177** in 81% yield.

In the IR spectrum of **177**, an absorption band at 1712 cm^{-1} indicated the presence of the benzoate functionality.

In the ^{1}H NMR spectrum of **177**, a set of three multiplets in the aromatic region (δ 7.94, 7.57, 7.44), integrating for a total of five protons, suggested the presence of a mono-substituted phenyl ring. The downfield shift of (O-CH_2-) protons from δ 3.60 to 4.37 indicated the protection of the free hydroxyl group.

The mass spectrum of **177** displayed a peak at m/z 598 (M+H).

With **177** in hand, our next job was to transform **177** into **176** by Heck coupling. Our initial attempt of Heck coupling between **177** and methyl vinyl ketone (MVK) by following usual reported reaction conditions such as $PdCl_2(CH_3CN)_2$ in THF[60] or $Pd(OAc)_2$ / n-Bu_4NCl in DMF[61] at room temperature, however, failed to provide **176** in satisfactory yield. Finally, with little experimentation and optimization, we succeeded in obtaining **176** in 60% yield using $Pd(OAc)_2$ as the catalyst and with the increased amount of MVK (8 equiv.).

In the IR spectrum of **176**, two absorption bands at 1712 and 1666 cm^{-1} characterized the presence of benzoate and ene-one functionality in the compound.

Similarly, presence of two sets of doublets at δ 7.81 and 6.68 (J = 16.92), integrating to one proton each, in the ^{1}H NMR spectrum of **176** confirmed the olefinic protons of the ene-one moiety. A sharp singlet at δ 2.19, integrating for three protons, was assigned for the methyl group protons.

The ^{13}C spectrum displayed a total of twenty three signals at δ 197.7, 166.3, 149.8, 147.2, 139.9, 135.5, 132.8, 130.6, 129.5, 128.3, 127.4, 126.4, 110.4, 105.5, 101.5, 63.6, 56.7, 49.4, 45.3, 28.3, 26.6, -0.09 and - 0.97. Two signals at 197.7 and 166.3 are attributed to benzoate and ketone carbonyls, respectively.

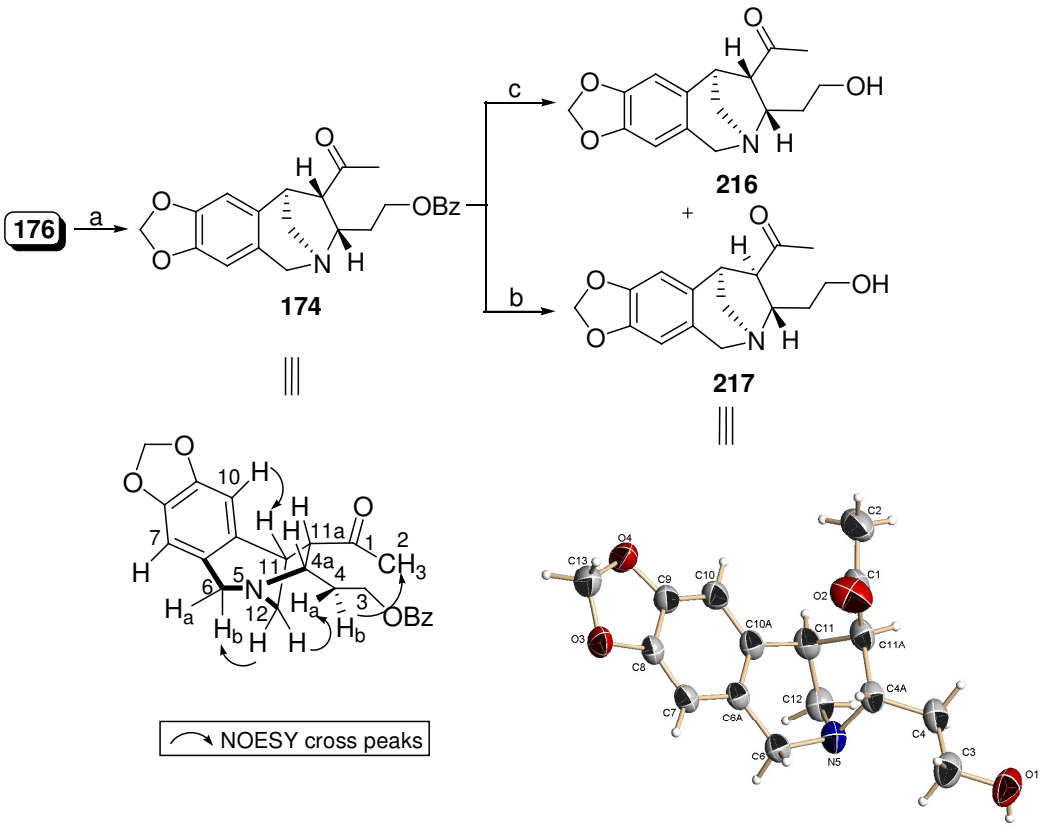
The mass spectrum of **176** displayed molecular ion peak at m/z 540 (M+H).

The above discussed spectral characterization supported the structure of **176** and the stage was set for carrying out crucial intramolecular 1,3-dipolar cycloadditon of tethered azomethine ylide.

2.5.3. Intramolecular cycloaddition reaction:

To a stirring mixture of Ag(I)F (5.9 mmol) in 10 mL of CH_3CN was added the solution **176** (1.5 mmol) in 35 mL of CH_3CN dropwise via a syringe pump over a period of one hour under argon atmosphere. The reaction mixture was allowed to stir for additional 10-12h and the progress of the reaction was monitored by TLC. After considerable consumption of starting material, the reaction mixture was filtered through a plug of basic alumina. Purification by silica gel column chromatography afforded cycloadduct **174** in 56% yield. The cycloadduct was fully characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral analyses and the stereochemistry was assigned and confirmed by 2D NMR studies. The peak assignments in the ^{1}H NMR spectrum were carried out with the help of COSY and HETCOR experiments. (Scheme-28)

Scheme-28



ORTEP diagram of **217**

***Reagents and conditions**: a) Ag(I)F, CH_3CN, RT, 9h, 56%; b) LiOH, MeOH, RT, 4h, quant; c) LiOH (1 equiv.), MeOH, 0 °C, 5h, 60%.*

2.5.4. Spectral analysis and stereochemical assignment of the cycloadduct 174:

The IR spectrum showed a sharp ketone carbonyl band at 1710 cm^{-1}.

The ^1H NMR spectrum displayed three mutiplets at δ 8.05, 7.58, 7.46, integrating for a total of five protons, which were assigned to the aromatic protons of benzoyl group. The other two protons of the aromatic ring appeared as two singlets at δ 6.49 and 6.46. The methylenedioxy protons appeared as a sharp singlet at δ 5.90. Two sets of multiplets appearing at δ 4.58 to 4.63 and 4.51 to 4.55, integrating for one proton each, were assigned to the (-C$\underline{H}_2$-OBz) protons. The N-benzylic protons appeared as two sets of doublets at δ 4.32 and 3.38 (J = 17.48 Hz). A broad triplet at δ 3.60 (J = 9.54 Hz),

integrating for one proton, was assigned for the H_{4a} proton. The H_{11a} proton was observed as a doublet at δ 3.48 (J = 8.74 Hz). One of the H_{12} protons appeared as a broad doublet at δ 3.36 (J = 11.53 Hz). The H_{11} proton appeared as a doublet at δ 3.13 (J = 3.18 Hz). The other H_{12} proton appeared as doublet at 3.03 (J = 11.53 Hz). The methyl protons appeared as a singlet at δ 2.21. The multiplets between δ 1.65-1.85, integrating for two protons, were assigned to H_4 protons.

The ^{13}C NMR spectrum displayed a total of nineteen signals at δ 207.6, 166.2, 146.4, 145.5, 132.6, 130.1, 129.2, 128.1, 106.6, 106.2, 100.4, 65.2, 64.5, 63.5, 60.2, 53.9, 43.6, 32.2 and 30.9. The DEPT experiment confirmed the signals for quaternary carbons at δ 207.6, 166.2, 146.4, 145.5 and 130.1, which were attributed to the carbonyl carbon and aromatic carbons, respectively. The rest of the aromatic methine carbons appeared at δ 132.6, 129.2, 128.1, 106.6 and 106.2. The methelynedioxy carbon appeared at δ 100.4. Four methylene carbons appearing at δ 63.5, 60.2, 53.9, and 30.9, were attributed to C_3, C_6, C_{12} and C_4 carbons, respectively. The methyl carbon appeared at δ 32.33. The C_{4a}, C_{11a} and C_{11} methine carbons appeared at δ 65.2, 64.5 and 43.6, respectively.

The mass spectrum of **174** displayed molecular ion peak at m/z 394 (M+H).

The stereochemical assignments, as shown in Scheme-28, are based on extensive COSY and NOESY NMR spectral studies. For illustration, it was noticed that there is no NOESY cross peak between H_{4a} - H_{12} and H_{11a} - H_{12}, clearly confirming the *endo*-orientation of C_{12} in **174**. The NOESY cross peak between H_{4b} and H_2 and the coupling constant of H_{11a} with H_{4a} (8.74 Hz) suggested that C_{11a} and C_{4a} are *cis*-configured.

2.5.5. Chemistry Following Cycloaddition Reaction: Construction of E-Ring

With fully characterized **174** in hand (with ABCD ring in hand), our next step towards the synthesis of 9,11-methanomorphanthridine alkaloid was to construct the E-ring. Towards this endeavor, it was necessary to make C_3-carbon electrophilic to facilitate the intramolecular cyclization reaction feasible. In this context, we thought of changing the benzoate protecting group to mesylate or tosylate at C_3-oxygen functionality. Towards this end, when **174** was subjected to usual debenzoylation reaction (LiOH/MeOH, rt), to our great surprise, it provided epimerized alcohol **217** in 98% yield (confirmed by X-ray crystallography, the ORTEP diagram of the same is shown in Scheme-28). This observation was rationalized by considering the sterically crowded *cis*-ring fusion of **174,** which favored the thermodynamic enolate formation in order to relieve the strain. Although, un-epimerized alcohol **216** could be obtain from **174** by stirring with LiOH / MeOH at 0 ^oC. (Scheme 28), we decided to proceed further with **217** itself as C_{11a} stereochemistry does not matter into the final molecule.

The IR spectrum of **217** displayed a broad absorption band at 3404 cm^{-1}, suggesting the presence of a free hydroxyl group. A sharp absorption band at 1710 cm^{-1} also revealed the presence of a ketonic carbonyl group.

In the ^1H NMR spectrum, two singlets at δ 6.47 and 6.41, integrating to one proton each, were attributed to two aromatic ring protons. The methylenedioxy protons appeared as two singlets at δ 5.91 and 5.90. Two sets of doublets at δ 4.31 and 3.91 (J = 16.70), integrating to one proton each, were attributed to the N-benzylic protons. A doublet of doublet at δ 3.36 (j = 11.13, 1.59 Hz) and one broad triplet at δ 3.80 (j = 3.58 Hz), integrating to one proton each, were attributed to C_3 protons. The C_{4a} proton appeared at δ 3.72 with a 'five lines pattern' multiplicity (J = 5.96, 5.16, 4.37 Hz). A doublet of doublet at δ 3.36 (J = 5.17, 2.78 Hz), integrating one proton, was attributed to C_{11a} proton. One of the C_{12} proton appeared as doublet of doublet at δ 3.32 (J = 11.53, 2.38 Hz). One broad doublet at δ 3.10 (J = 2.38), integrating for one proton, was assigned to the C_{11} proton. Another C_{12} proton appeared as a doublet at δ 3.11 (J = 11.13 Hz). The methyl protons

appeared as a singlet at δ 2.19. Two multiplets at δ 1.72-1.78 and 1.52-1.56 were attributed to C_4 protons.

The ^{13}C NMR spectrum displayed a total of sixteen signals at δ 204.5, 147.0, 145.6, 129.3, 124.6, 107.1, 106.6, 100.6, 70.3, 65.9, 62.6, 59.5, 54.9, 42.9, 35.6 and 30.0.

The mass spectrum of **217** displayed the molecular ion peak at m/z 290 (M+H).

Aromatic protons in the ^1H spectrum of **216** displayed two singlets at δ 6.45 and 6.44. The methylenedioxy protons appeared as a singlet at δ 5.87. A doublet at δ 4.31 (J = 17.59 Hz) was attributed to one of the N-benzylic protons. A multiplet at δ 3.76-3.82, integrating for three protons, was assigned to one of the N-benzylic proton and two H_3 protons. The H_{4a} proton appeared as a broad triplet at δ 3.67 (J = 9.96 Hz). A doublet at δ 3.43 (J = 8.80 Hz), integrating for one proton, was attributed to C_{11a} proton. One of the H_{12} proton appeared as a doublet of doublet at δ 3.35 (J = 11.71, 2.93 Hz). The H_{11} proton appeared as a doublet at δ 3.12 (J = 2.93 Hz). The other H_{12} proton was observed as a doublet at δ 2.98 (J = 11.73 Hz). The methyl protons appeared as a singlet at δ 2.12. Two multiplets appearing at δ 1.63-1.76 and δ 1.31-1.40, integrating for one proton each, were assigned to H_4 protons

Intramolecular cycloalkylation[62, 63] attempt from corresponding mesylated derivative of **217** using LDA/THF at –78 °C to rt, however, produced rearranged product **221** via thermodynamic enolate **219**. (Scheme-29)

The IR spectrum of **221** displayed an absorption band at 1668 cm^{-1}, suggesting the presence of an ene-one carbonyl functionality.

In the ^1H NMR spectrum, a doublet of doublet at δ 6.92 (J = 7.70, 4.55 Hz), integrating for one proton, was assigned to the olefinic proton of the ene-one moiety. The

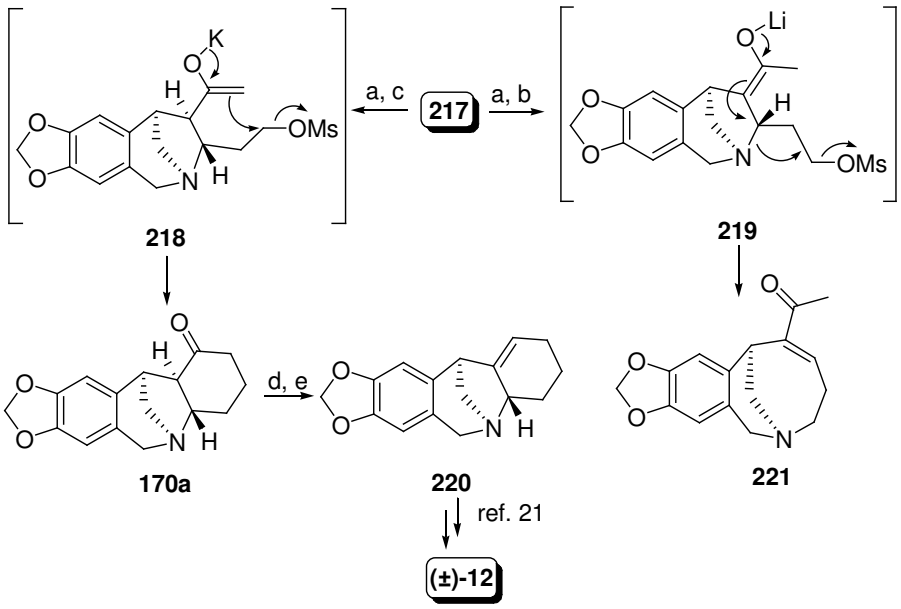
aromatic protons appeared as two singlets at δ 6.49 and 6.43. The methylenedioxy proton appeared as a singlet at δ 5.84. One of the N-benzylic proton appeared as a doublet at δ 3.78 (J = 17.30 Hz). One of the N-benzylic proton appeared as a broad singlet at δ 4.37 while the other one was spotted as a doublet at δ 3.78 (J = 17.30Hz). A multiplet at δ 3.28-3.35, integrating for four protons, was attributed to the (-N-C$\underline{H}_2$-CH-) and (-N-C$\underline{H}_2$-CH_2-) protons. Another multiplet at δ 2.49-2.67, integrating for one proton, was assigned to one of the (=CH-C$\underline{H}_2$-) protons. The methyl protons appeared as a singlet at δ 2.31. Another one proton belonging to (=CH-C$\underline{H}_2$-) was observed as a multiplet at δ 2.26.

The ^{13}C NMR spectrum indicated the presence of a total of sixteen signals at δ 198.1, 148.2, 147.7, 147.2, 142.6, 126.5, 121.6, 108.6, 105.2, 101.3, 52.8, 52.5, 50.3, 31.3, 25.5 and 24.7 in the molecule. The carbonyl carbon appeared at δ 198.14. The DEPT experiment revealed the appearance of five quaternary carbons at δ 148.2, 147.7, 147.2, 126.5 and 121.6. Two methine carbons of aromatic moiety were noticed at δ 108.6 and 105.2. The methylenedioxy carbon appeared at δ 101.3. Four methylenic carbons appeared in the aliphatic region at δ 52.8, 52.5, 50.3 and 24.7 and were assigned to N-benzylic, (-N-$\underline{C}H_2$-CH-), (-N-$\underline{C}H_2$-CH_2-) and (=CH-$\underline{C}H_2$-) carbons, respectively. The methine carbon appearing at δ 31.3 was assigned to benzyl carbon. The methyl group carbon appeared at δ 25.5.

The mass spectrum of **221** displayed the molecular ion peak at m/z 271 (M+).

At this point, we thought of exploring the possibility of generating selective kinetic enolate. In this regard, we found a method reported by Rappaort *et al*[64] to generate selective kinetic enolate by using KHMDS in THF at -78 °C. We tried the same reaction with **217** and to our delight, the reaction successfully produced cycloalkylated product **220** in 58% yield. (Scheme-29)

Scheme-29



Reagent and conditions: *a) MsCl, Et_3N, DCM, 0 °C → rt, 15min, quant.; b) LDA, THF, -78 °C → rt, 5h, 60%; (c) KHMDS, THF, -78 °C → RT, 5h, 58%. (d)* LDA, THF, Comins reagent, -78 °C → RT, 6h; *(e) $Pd(PPh_3)_4$, Et_3SiH, LiCl, THF, 60 °C, 24h, 71% over two steps.*

The IR spectrum of **170a** showed carbonyl absorption band at 1710 cm^{-1}.

The ^1H NMR spectrum of **170a** showed two singlets at δ 6.47 and 6.42, integrating for one proton each, which were attributed to the aromatic protons. The methylenedioxy protons appeared as two singlets at δ 5.83 and 5.81. The N-benzylic protons appeared as two sets of doublets at δ 4.33 and 3.86 (J = 16.26 Hz), respectively. The H_{4a} proton appeared with 'eight lines pattern' multiplicity at δ 4.12 (J = 11.45, 4.35, 1.60 Hz). The H_{11a} proton appeared with 'seven lines pattern' at δ 3.72 (11.45, 2.39, 1.83 Hz). A broad doublet appearing at δ 3.43 (J = 2.06 Hz), integrating for one proton, was assigned to H_{11} proton. One of the H_2 protons appeared as a doublet of doublet at δ 3.39 (J = 11.45, 4.13 Hz). While one of the H_{12} protons appeared as doublet at δ 3.04 (J = 10.97 Hz), the other one appeared as a doublet of doublet at δ 2.98 (j = 11.67, 2.12 Hz). A multiplet appearing at δ

2.23, integrating for one proton, was assigned to the other H_2 protons. The H_3 protons appeared as a broad doublet at 1.80 (J = 1.37 Hz). Two multiplets appearing at δ 1.64-1.72 and δ 1.50-1.60, integrating for one proton each, were attributed to H_4 protons.

The ^{13}C spectrum of **170a** displayed a total of sixteen signals at δ 211.7, 146.6, 146.4, 141.1, 132.0, 106.8, 106.7, 100.8, 63.6, 60.54, 59.4, 55.2, 41.4, 29.4, 26.4 and 17.1. The carbonyl carbon appeared at δ 211.7. The DEPT experiment revealed the presence of four quaternary carbons at δ 146.6, 146.4, 141.1 and 132.0. Two aromatic methine carbons appeared at δ 106.8 and 106.7. The methylenedioxy carbon was observed at δ 100.8. Five methylenic signals appearing at aliphatic region at 63.6, 59.4, 55.2, 29.4 and 26.4, were assigned to C_6, C_{12}, C_2, C_4 and C_3 carbons, respectively. Three methine carbon signals appearing in the aliphatic region at δ 60.6, 41.4 and 17.1 were attributed to C_{4a}, C_{11a} and C_{11} carbons, respectively.

The mass spectrum of **170a** displayed a peak at m/z 272 (M+H).

The pivotal $\Delta^{1,11a}$ double bond from **170a** leading to the formation of **220** (71% yield) and thus completing the formal total synthesis of (±)-pancracine **12** was created by the reductive elimination of the corresponding enol triflate using $Pd(PPh_3)_4$ / Et_3SiH in THF.[66] The required enol triflate from **170a** was generated by quenching the corresponding lithium enolate of **170a** with Comins reagent.[65] Overman *et al.* have reported[21] on the elaboration of **220** in couple of steps to (±)-pancracine **12**.

The spectral characterisitics of **170a** completely matches with the reported values in the literature[21].

2.6 Summary:

We have developed conceptually new and shortest synthetic route for the synthesis of 5,11-methanomorphanthridine alkaloids by using intramolecular [3 + 2]-cycloaddition of non-stabilized azomethine ylide, a methodology developed from our group.

A formal synthesis of (±)-pancracine **12** has also been demonstrated. The success of this strategy prompted us to check the efficiency of the approach by targeting total synthesis of some of the other members of this class of alkaloids. Foregoing section of this chapter will discuss our effort towards this endeavor.

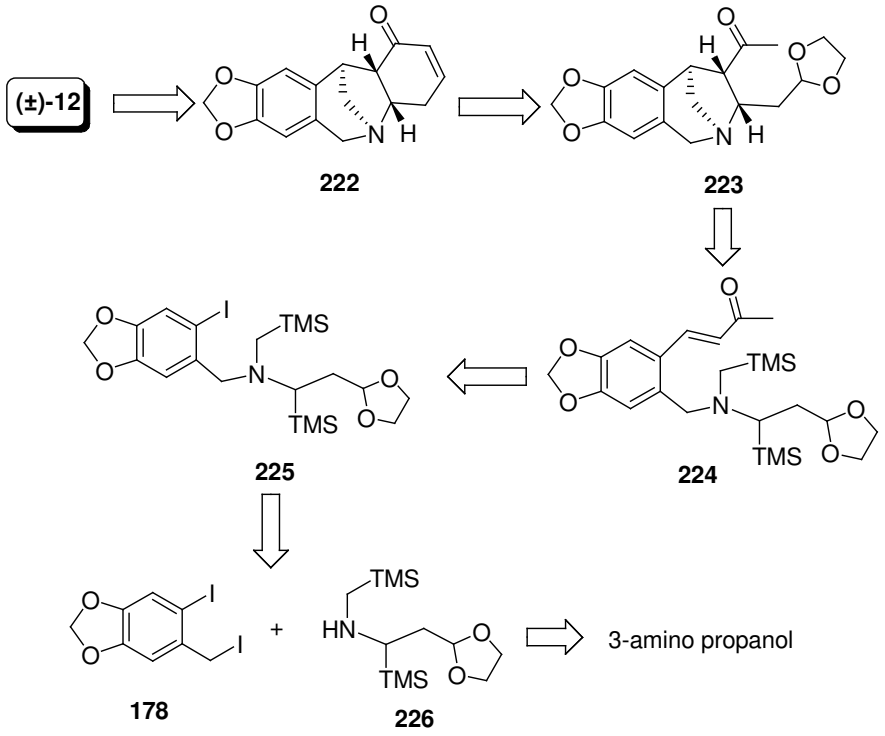
3.1. Introduction

After successful synthesis of the 5,11-methanomorphanthridine alkaloid skeleton **170**, we turned our attention towards accomplishing the total synthesis of (±)-pancracine (**1**), one of the important member of *Amaryllidaceae* class of alkaloids. In this regard, we changed our synthetic plan towards E-ring construction. Since there are varying oxygen functionality at C-2 and C-3 in the E-ring, it was essential for us to build a double bond (masked oxygen-functionality) with fixed regiochemistry in E-ring.

3.2. Retrosynthetic Analysis

Towards this end, we visualized **222** as a suitable precursor and we proposed to obtain this compound employing an intramolecualr aldol condensation as the key strategy from **223** as shown in Scheme-30.

Scheme-30

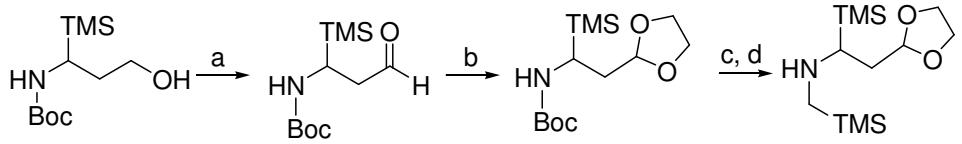


3.3. Results and Discussion

In order to synthesize proposed **222,** we envisioned **224** as an ideal precursor. It was anticipated that cycloadduct **223**, which is nicely equipped with a ketonic moiety as well as the acetyl moiety for producing **222** by intramolecular Mukiayama-type aldol reaction[67] directly without going through any functional group transformations. Furthermore, **222** was also visualized to be an advanced precursor for synthesizing some of the other members of the Montanine-type Amaryllidaceae class of alkaloids, such as (±)-brunsvigine (**13**), (±)-pancracine (**12**) and (±)-montanine (**9**).

The synthesis started with the preparation of the key precursor **224** which involved coupling of two components **178** and **226** followed by Heck reaction with methyl vinyl ketone (MVK) as described previously in the case of **176**. The detailed steps for the synthesis of **226** are summarized in Scheme-31.

Scheme-31



213 **227** **228** **226**

Reagents and conditions: *a) IBX, ethyl acetate, reflux, 90%; b) ethylene glycol, pTSA, benzene, Dean-Stark, quant.; c) TFA, DCM, 0 $^{o}C \rightarrow$ rt, Quant.; d) ICH_2TMS, K_2CO_3, CH_3CN, reflux, 77%.*

Oxidation of the primary alcohol **213** by refluxing with IBX[68] in ethyl acetate provided aldehyde **227,** which on protection with ethylene glycol employing usual experimental condition gave **228** in 90% yield. Deprotection of N-Boc-moiety from **228** by stirring with TFA followed by the alkylation of the crude amine with idomethyl trimethylsilane provided the bissilylated compound **226** in 77% yield.

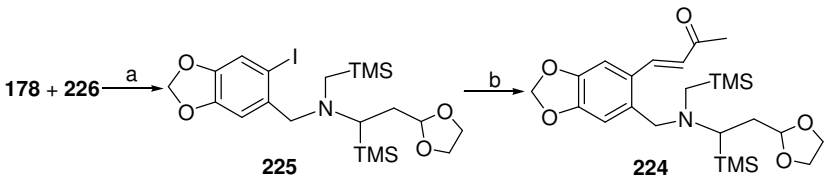
The compound **227** was fully characterized by spectral analysis.

The characteristic feature of the ^{1}H NMR spectrum of **228** was the absence of aldehydic proton and the appearance of a triplet at δ 4.86 (J = 4.70 Hz), for the (-O-C<u>H</u>-O-) proton. The ^{13}C NMR spectrum also displayed the signal for the (-O-<u>C</u>H-O-) at δ 103.9. The mass spectrum of **228** displayed a peak at m/z 290 (M+H).

Similarly, in the ^{1}H NMR spectrum of **226**, a doublet of doublet at δ 4.95 (J = 4.69, 3.52 Hz), integrating for one proton, characterized the (O-C<u>H</u>-O) proton. The absence of Boc group protons and appearance of two doublets at δ 2.04 and 1.96 (J = 13.72 Hz) characterized the (TMS-C<u>H</u>$_2$-N) protons. The ^{13}C NMR experiment confirmed the presence of methine (O-<u>C</u>H-O) and methylene (TMS-<u>C</u>H$_2$-N) carbons at δ 104.3 and 37.9, respectively. The mass spectrum of **226** displayed the molecular ion peak at m/z 276 (M+H).

Usual heating of a mixture of **178** with **226** in CH_3CN in the presence of anhydrous K_2CO_3 produced **225** (85% yield). (Scheme-32)

Scheme-32



Reagents and conditions: *a) K_2CO_3, CH_3CN, reflux, 85%; b) $Pd(OAC)_2$, PPh_3, K_2CO_3,, methyl vinyl ketone, CH_3CN, reflux, 65%.*

The ^{1}H NMR spectrum of **225** displayed two aromatic singlets at δ 7.20 and 7.10. The methylenedioxy protons appeared as a singlet at δ 5.95. The doublet of doublet appearing at δ 5.05 and integrating for one proton was assigned to (O-C<u>H</u>-O) proton. Two multiplets at δ 3.94 and 3.54, integrating for two protons each, were attributed to the

methylinic protons. Two sets of doublets at δ 3.60 and 3.48 (J = 15.26 Hz), integrating to one proton each, were assigned to the N-benzyl protons. The (TMS-CH-) proton appeared as a doublet of doublet at δ 2.45 (J = 8.60, 5.67 Hz). Two sets of doublets appearing at δ 2.15 and 2.05 (J = 14.48 Hz), integrating for one proton each, were assigned to the (TMS-CH_2-) protons. The (TMS-CH-CH_2-) protons appeared as two multiplets at δ 1.65 and 2.01. Two singlets appearing at δ 0.13 and 0.05, integrating for nine protons each, were assigned to TMS functionalities.

The ^{13}C NMR spectrum of **225** displayed a total of sixteen signals at δ 148.7, 147.3, 136.1, 118.3, 110.2, 104.1, 101.6, 87.0, 64.9, 64.8, 64.4, 50.8, 45.1, 31.5, -0.7 and -0.9. The DEPT experiment revealed the presence of four quaternary carbons at δ 148.7, 147.3, 136.1 and 87.0, which were assigned to four aromatic quaternary carbons. Two aromatic methine signals were observed at δ 118.3 and 110.2. The methylenedioxy carbon appeared at δ 101.6. A group of five methylene signals appeared at δ 64.9, 64.8, 64.4, 45.1 and 31.5 and were assigned to two methylinic, N-benzylic, (TMS-CH_2-) and (O-CH-CH_2-) carbons, respectively. The signal for (TMS-CH-) carbon was observed at δ 50.8. The methyl group signals of TMS functionalities were observed at δ -0.7 and -0.9.

The mass spectrum of **225** displayed molecular ion peak at m/z 536 (M+H).

The Heck coupling of **225** with MVK, using the conditions as described earlier, gave **224** in 65% yield (Scheme-32).

In the IR spectrum of **224**, an absorption band at 1666 cm^{-1} clearly suggested the presence of ene-one carbonyl functionality.

In the 1H NMR spectrum, two sets of doublets appearing at δ 7.80 and 6.38 (J = 15.58 Hz), integrating for one proton each, could easily be assigned to the ene-one olefinic protons. The methyl protons appeared as a singlet at δ 2.26

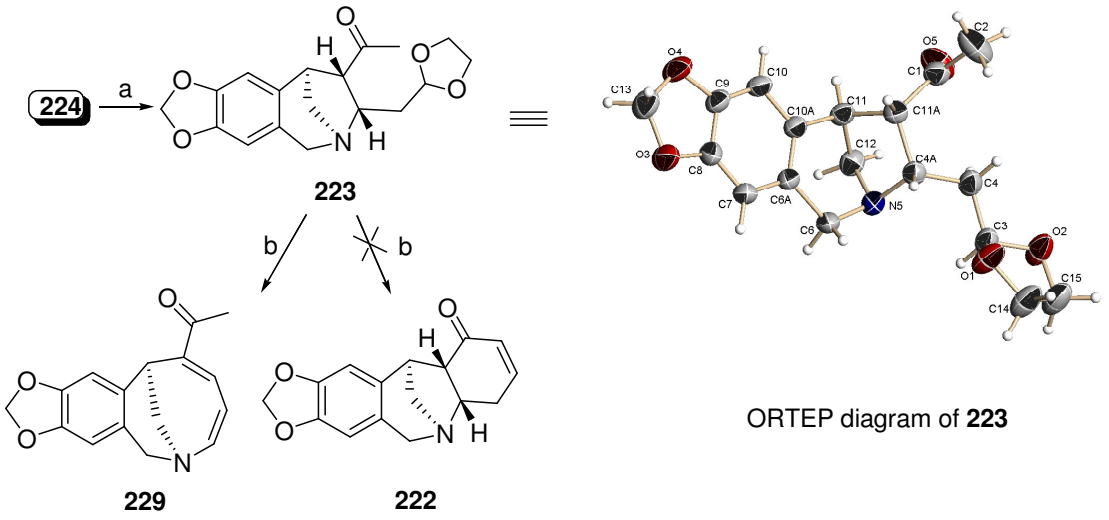
The ^{13}C spectrum of **224** showed a total of twenty signals at δ 197.7, 149.4, 146.5, 140.0, 135.7, 126.8, 126.2, 109.8, 105.3, 103.6, 101.0, 64.4, 64.3, 55.9, 49.5, 44.5, 30.3, 27.5, -0.8 and -1.4.

The mass spectrum of **224** displayed the molecular ion peak at m/z 478 (M+H).

3.3.1. Intramolecular cycloaddition of 224

Generation of azomethine ylide from **224** by following identical reaction sequence as enumerated earlier for **176,** provided cycloadduct **223** in 51% yield. The stereochemistry of **223** was assigned by detailed 2D-NMR studies and was further confirmed by single crystal X-Ray crystallography (the ORTEP-diagram of the same is shown in Scheme-33). The peak assignments in the ^{1}H NMR spectrum were carried out with the help of COSY and HETCOR experiments.

Scheme-33



***Reagents and conditions**: a) Ag(I)F, CH_3CN, rt, 51%; b) TMSOTf, 2,6-lutidine, DCM, -20 $^oC \rightarrow$ rt, 62%.*

The IR spectrum of **223** displayed an absorption band at 1708 cm-1, suggesting the presence of a ketonic carbonyl functionality.

In the ^1H NMR spectrum of **223**, two singlets at δ 6.37 and 6.34, integrating to one proton each, were assigned to the aromatic protons. The methylenedioxy protons appeared as a singlet at δ 5.78. A doublet of a doublet, integrating for one proton at δ 4.97 (J = 6.88, 2.29 Hz) was assigned to the (O-C<u>H</u>-O) proton. The N-benzylic protons appeared as two sets of doublets at δ 4.18 and 3.63 (J = 16.96 Hz). Two multiplets at δ 3.85 and 3.75, integrating for two protons each, were assigned to the methylenic protons. The H_{4a} appeared at δ 3.53 with 'five lines pattern' multiplicity (J = 8.71, 3.67 Hz). The H_{11a} proton appeared as a doublet at δ 3.33 (J = 8.71 Hz). Another doublet of doublet at δ 3.26 (J = 2.52, 11.23 Hz), integrating for one proton, was assigned to one of the H_{12} protons. The H_{11} proton appeared as a broad doublet at δ 2.97 (J = 2.52 Hz). Another H_{12} proton appeared as a doublet at δ 2.97 (J = 11.46 Hz). The methyl group protons appeared as a singlet at δ 2.06. Two multiplets appearing at δ 1.80 and 1.40, integrating for one proton each, were assigned for the H_4 protons.

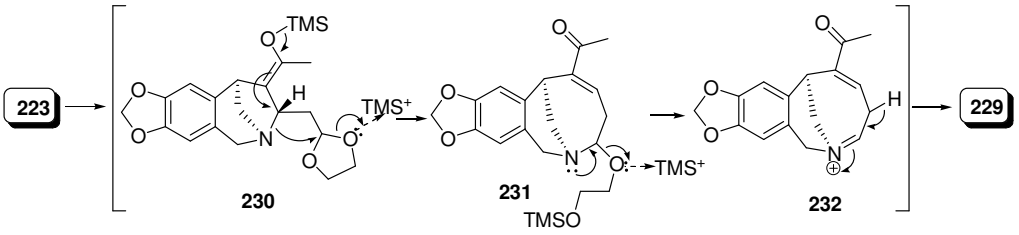
The ^{13}C NMR spectrum of **223** displayed a total of eighteen signals at δ 207.6, 146.3, 145.5, 134.9, 125.3, 106.6, 106.3, 103.5, 100.4, 64.6, 64.5, 64.33, 64.28, 59.9, 53.9, 43.4, 35.7 and 32.2. The most downfield signal appearing at δ 207.6 was attributed to the carbonyl carbon. The DEPT experiment revealed the presence of four quaternary aromatic carbons at δ 146.3, 145.5, 134.9 and 125.3. Two aromatic methine and (O-<u>C</u>H-O) carbons appeared at δ 106.6, 106.3 and 103.5, respectively. The methylenedioxy carbon appeared at δ 100.4. Five methylene carbon signals appearing at δ 64.6, 64.33, 59.9, 53.9 and 35.7 were attributed to ethylinic, C_6, C_{12} and C_4 carbons, respectively. Three methine carbons, appearing at δ 64.5, 64.28 and 43.4 were attributed to C_{4a}, C_{11a} and C_{11}, respectively. The methyl carbon signal appeared at δ 32.2.

The mass spectrum of **223** displayed molecular ion peak at m/z 332(M+H)

3.3.2. Chemistry following cycloaddition reaction:

With fully characterized **223** in hand, our next job was to construct the E-ring, *i.e.* the synthesis of common intermediate **222**. In this context, we tried our preplanned intramolecular Mukiayama-type aldol reaction using TMSOTf[69] and 2,6-lutidine at -20 °C. (Scheme-33) However, to our dismay, we did not get aldol product **222**; instead we got a compound with a probable structure **229**. The formation of **229** was rationalized by considering the formation of thermodynamic TMS-enol ether **230**, which on rearrangement produced **229** as shown in Scheme-34.

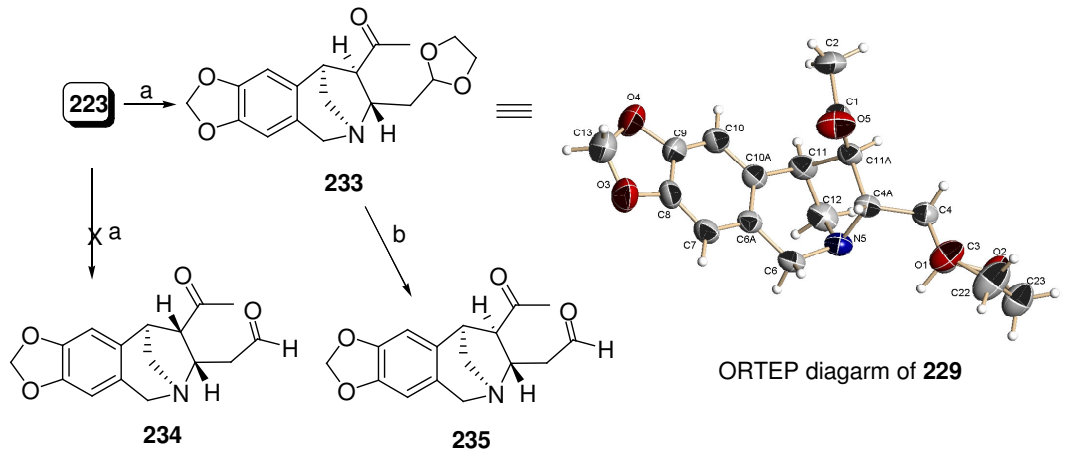
Scheme-34



In the ^{1}H spectrum of **229**, a doublet appearing at δ 8.97 (J = 8.09 Hz), integrating for one proton was assigned to the (N-C<u>H</u>-CH) proton. The (C<u>H</u>-C-CO) proton appeared as a multiplet at δ 7.02. Two aromatic protons appeared as two singlets at δ 6.46 and 6.42. The methylenedioxy protons appeared as a singlet at δ 5.79. One broad triplet appearing at δ 5.15 (J = 8.09 Hz), integrating for one proton was assigned to the (N-CH-C<u>H</u>) proton. One of the N-benzylic proton appeared as a doublet at δ 4.12 (J = 16.42 Hz). While the other one appeared as a broad multiplet at δ 3.46. Another broad multiplet appeared at 3.22, integrating for one proton, was assigned for the benzylic proton. The (N-C<u>H$_2$</u>-CH) protons appeared as a doublet at δ 2.52 (J = 6.31 Hz). The methyl group protons appeared as a singlet at δ 2.01.

With this un-anticipated failure of the strategy, we decided to deprotect the dioxolane moiety to get free aldehyde and try the classical acid/base catalyzed intramolecular aldol reaction.[70] In this context, when the cycloadduct **223** was stirred with 3N HCl in THF-H_2O at room temperature, we expected to obtain product **234.** However, detailed spectroscopic analysis of the product **233** indicated to be epimerized product of **223**. The single crystal X-Ray crystallography confirmed the structure of the product as **233** (the ORTEP-diagram of **233** is shown in Scheme-35). However, when **223** was refluxed with 3N HCl in for 10h, the epimerized aldehyde **235** was obtained in 75% yield. (Scheme-35) In order to get the unepimerized aldehyde **234**, **223** was subjected to a much milder conditions[71] (PPh_3, CBr_4, THF, 0 °C) but only starting material could be recovered. Therefore, we decided to go ahead with the epimerized aldehyde **235** only.

Scheme-35

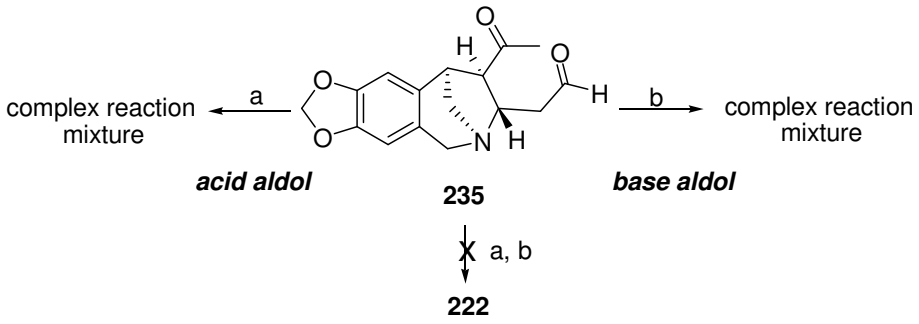


***Reagents and conditions**: a) 3N, HCl, THF-H_2O, rt, 8 h, 90%; b) 3N HCl, THF-H_2O, reflux. 10 h, 75%.*

The aldehyde **235** was treated to a variety of acidic [i) 3N HCl/THF-H_2O, reflux for long time, ii) CSA/xylene reflux[72]] and basic[73] [i) DBU/benzene ii) pyridine iii) NaOMe/methanol iv) KOH/MeOH v) KHMDS/THF] conditions, but, to our surprise, none of

these reaction conditions produced expected aldol product **222**, instead a complex reaction mixture was formed in each case, from which no conclusion could be drawn.

Scheme-36



***Reagents and conditions**: a) i) 3N HCl/THF-H_2O, reflux for long time, ii) CSA/xylene reflux b) i) DBU/benzene ii) pyridine iii) NaOMe/methanol iv) KOH/MeOH v) KHMDS/THF*

With this major setback, we are now modifying our approach and further studies in this direction are actively in progress.

3.4. Summary:

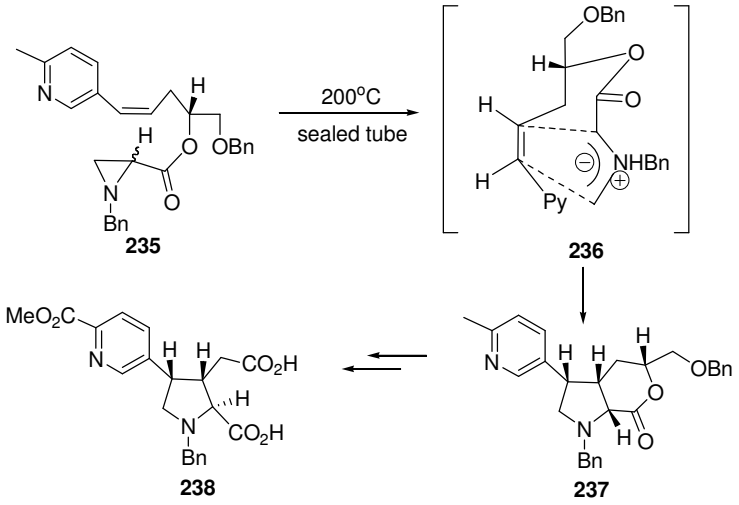
We have attempted to develop a modified strategy towards the total synthesis of 5,11-methanomorphanthridine alkaloids. The failure to construct the E-ring by proposed strategy was attributed to the skeletal rearrangement initiated by thermodynamic silyl-enol ether. However, these observations have led us to know the competitive reactivity of acyl moiety towards enolization and further studies to overcome this problem are under process.

4.1. Introduction

Asymmetric 1,3-dipolar cycloaddition of azomethine ylides to a variety of alkenes has emerged as one of the most powerful strategy for the construction of enantiopure pyrrolidines ring system.[74-76] The intramolecular asymmetric 1,3-dipolar cycloaddition of azomethine ylide leads to the formation of enantiopure complex fused pyrrolidine ring system, a commonly encountered structural entity in naturally occurring alkaloids. The quest for the development of a new general asymmetric route for the construction of enantiopure 5,11-methanomorphanthridine alkaloids skeleton led us to envision an unprecedented intramolecular[1] asymmetric [3+2]-cycloaddition strategy involving non-stabilized azomethine ylide and tethered chiral dipolarophile or achiral dipolarophile complexed with chiral ligand. Before going into the details of our own work, it would be appropriate to discuss some of the existing approaches pertaining to the intramolecular asymmetric [3+2]-cycloaddition reaction of azomethine ylide in order to evaluate the merit of our approach.

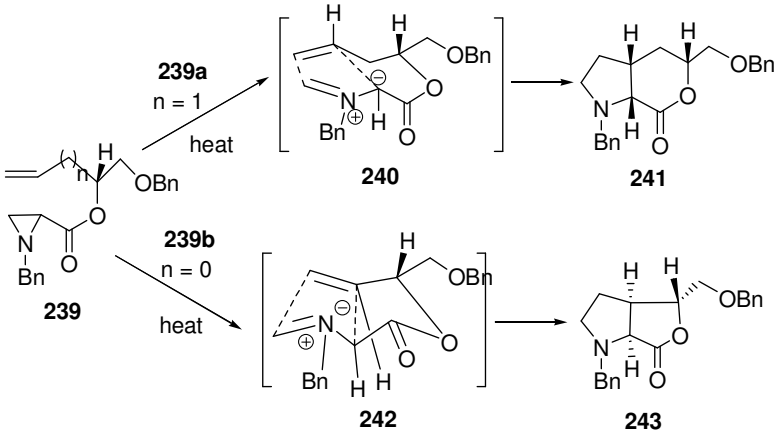
Possibly, the first example in the above context could be traced to an intramolecular cycloaddition of a chiral non-stabilized azomethine ylide **236**, produced by the thermolysis of **235**, which underwent highly diastereoselective cycloaddition reaction producing diastereomerically pure cycloadduct **237**; out of four possible isomers, with all *syn*-stereochemistry[77]. The extremely higher diastereofacial selectivity for the cycloaddition of **235** is best in accord with the *anti*-azomethine ylide **236** as the reactive conformer in which the bulky benzyloxymethyl group takes the most stable six membered chair like arrangement to give all *syn*-**3.** This strategy was utilized for the synthesis of acromalic acid-A (**238**). (Scheme-37)

Scheme-37



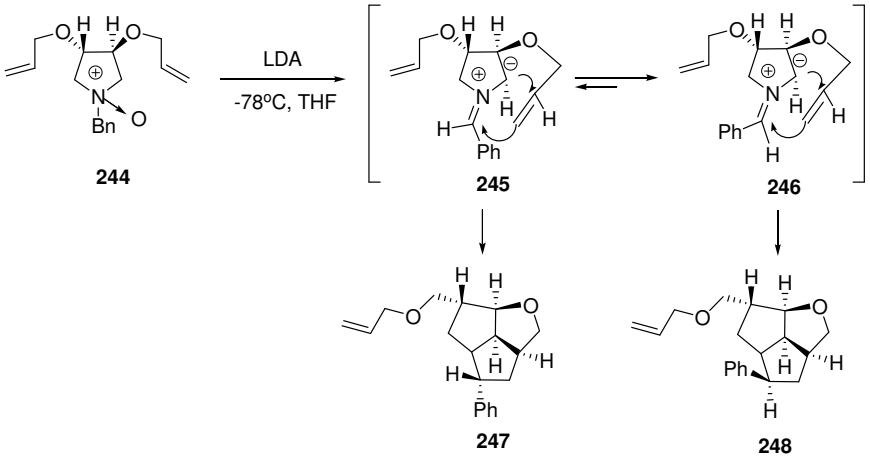
The same group afterwards also extended[78] this strategy to synthesize diastereomerically pure **241** and **243** from the intramolecular cycloaddition of corresponding azomethine ylides **240** and **242,** respectively. (Scheme-38)

Scheme-38



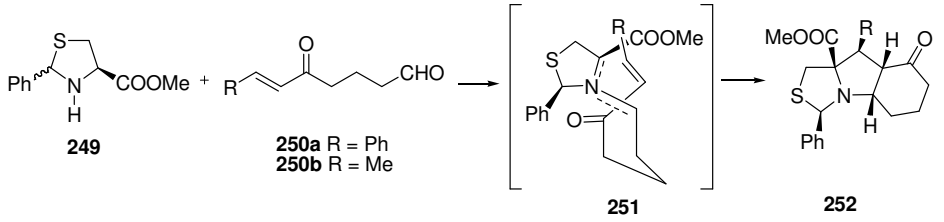
Complete diastereoselective intramolecular cycloaddition is observed[79] from an ylide possessing C_2-symmetric structure **246,** providing only **248** as the product. The observed stereochemistry of **248** is explained considering the involvement of benzylidene azomethine ylide **246** having Z-configuration giving rise to *endo*-phenyl adduct selectively instead of forming the *exo*-phenyl adduct **247** *via* the alternative E-ylide **245,** presumably due to steric congestion. (Scheme-39)

Scheme-39



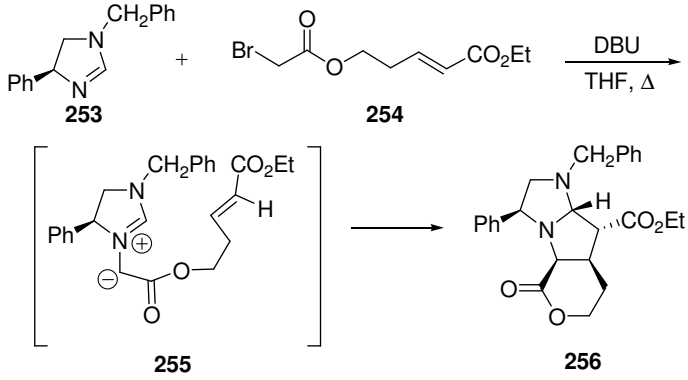
Kanemasa *et al*. have reported[80] stereoselective intramolecular cycloaddition of an *in situ* generated azomethine ylide **251** by the reaction of 2-phenyl-4-thiazolidine-carboxylate **249** and *enone* **250a-250b** to produce cycloadducts **252a-252b**, respectively. (Scheme-40)

Scheme-40



Similar diastereoselectivity is also recorded by Jones *et al*.[81] in the intramolecular cycloaddition of **255** to obtain **256** as the only product (yield 40 %). (Scheme-41)

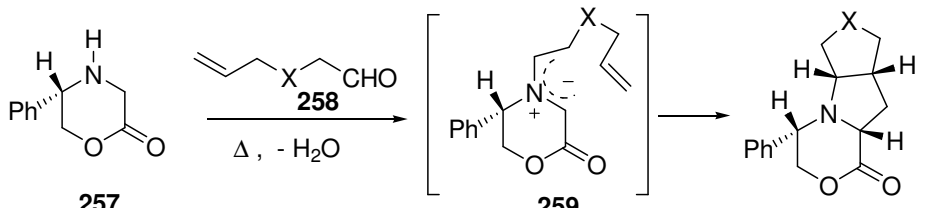
Scheme-41



The excellent stereochemical results are explained by considering the identical transition state model as described for the intermolecular cycloadditions by these authors.

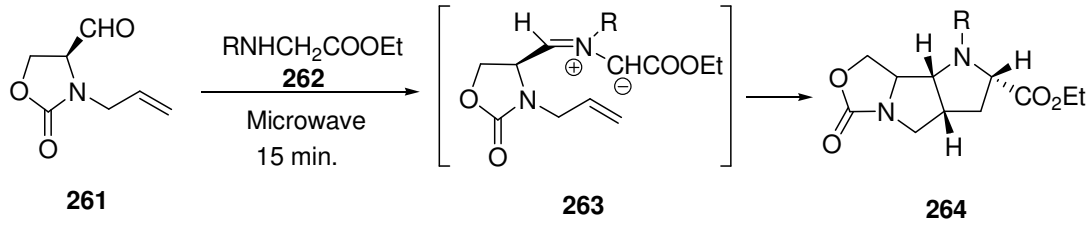
Harwood *et al*. have also shown[82-85] excellent diastereoselectivity in the intramolecular cycloaddition of *in situ* generated azomethine ylide **259**, produced by the reaction of 5-phenyloxazolidinone **257** and an aldehyde **258** (Scheme-42), producing **260** as the only product.

Scheme-42



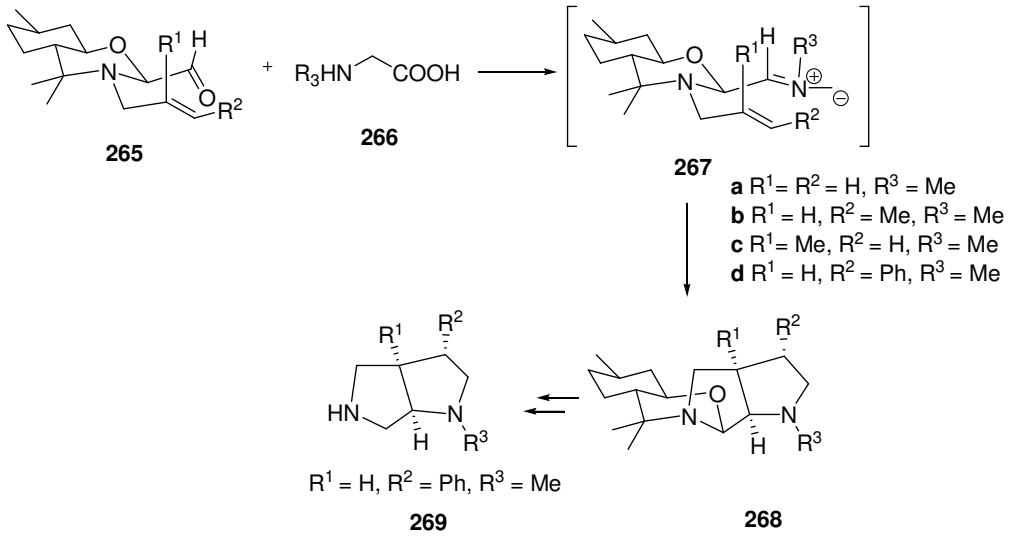
Semi-empirical and quantum mechanical calculations have suggested that most favorable transition state involves the *anti*-addition to the E-ylide (E_{act} ~ 12 kcal/mole). Similar results are also reported[86] from the cycloaddition of **263** (Scheme-43) giving rise to only **264** as the product.

Scheme-43



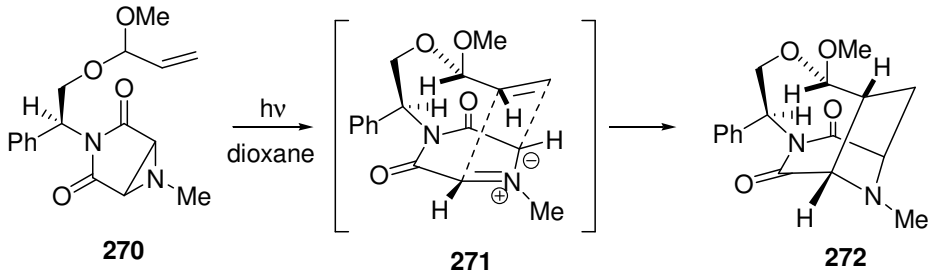
Stereospecific cycloaddition leading to a single diastereoisomeric octahydropyrrolo[3, 4]pyrrole derivatives **268** in each case is reported[87] by the intramolecular cycloaddition of an azomethine ylide **267** generated on to a chiral perhydro-1,3-benzoxazines **265** by the reaction with N-substituted glycines **266** (Scheme-44)**.**

Scheme-44



Asymmetric entry into the 3, 8-diazabicyclo[3.2.0]octane nucleus of napthyridinomycin is reported[88] by the stereospecific intramolecular cycloaddition of the chiral non-stabilized azomethine ylide **271** equipped with the tethered dipolarophile with acetal linkage. (Scheme-45)

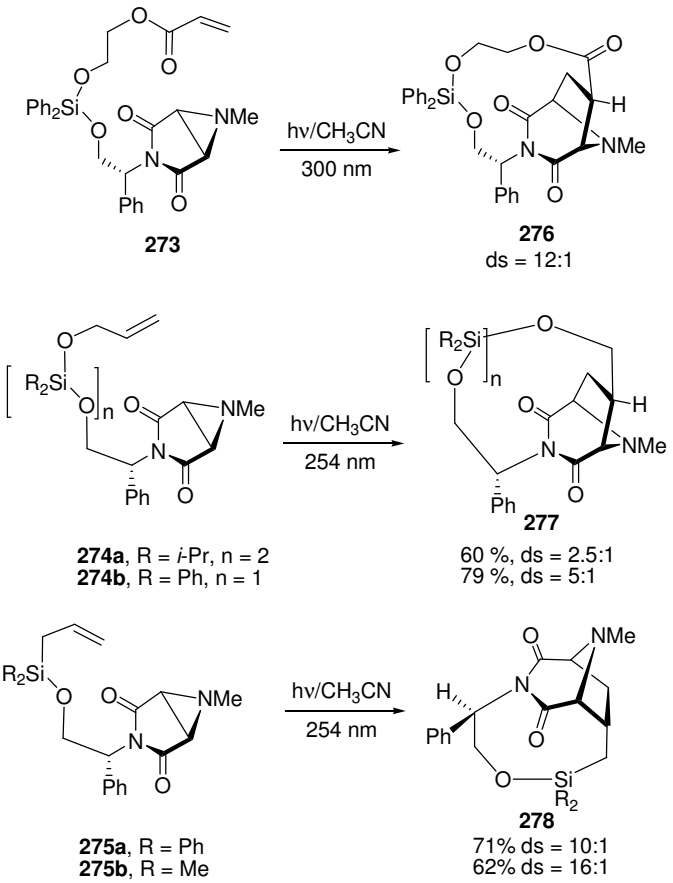
Scheme-45



In this cycloaddition, *si*-diastreofacial preference is forced by the steric repulsion between the aromatic ring and one of the imide carbonyl in the *endo*-transition state **271**. Furthermore, these groups have reported[89] a novel strategy of controlling the diastereofacial selectivity in an intramolecular dipolar cycloadditions of corresponding azomethine ylides from **273-275**, by varying the structure of the silicon-based tether. A correlation is found between the lengths of the tether dipolarophile conjugate (TDC) and the observed sense of diastereocontrol. For example, azomethine ylides incorporating

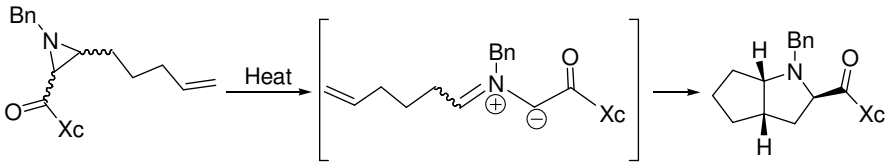
longer TDC such as **274a-b** favour *endo si* - attack while shorter TDC **275** leads to the reversal of selectivity giving *endo- re-* product **278**. (Scheme-46)

Scheme-46



Dogan *et al.* have observed[90] relatively poor diastereoselectivity (*de* = 50%) in the intramolecular cycloaddition of camphorsultam derived azomethine ylide **280**, generated by heating the aziridine **279,** which furnished the fused bicycles **281** (Scheme-47) albeit in good chemical yields.

Scheme-47



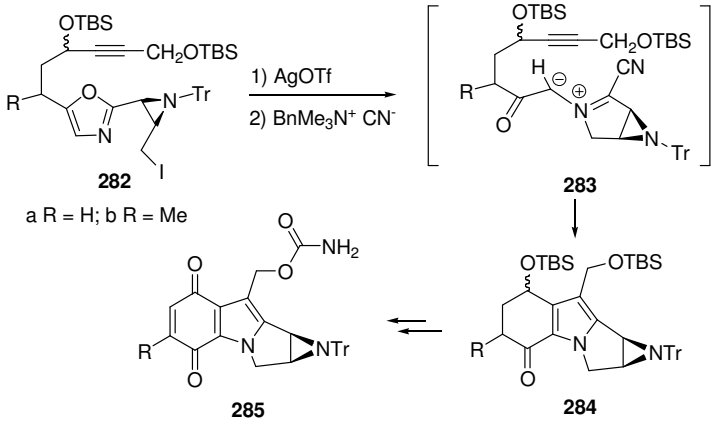
279
Xc = (1R)-(+)-camphorsultam

280

281

An enantiocontrolled synthetic route for aziridinomitosenes **285** is reported[91] by Vedejs *et al.* from a highly diastereoselective intramolecular cycloaddition of azomethine ylide **283**. (Scheme-48)

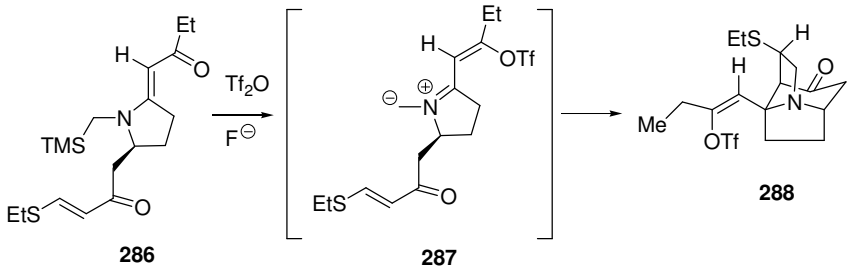
Scheme-48



The dipole generation was based on silver ion-assisted intramolecular oxazole alkylation and cyanide – induced reaction.

Enantiospecific synthesis of the bridged pyrrolizidine core of asparagamine-A is synthesized[92] by the intramolecular cycloaddition of an azomethine ylide **287**, generated from **286** as shown in Scheme-1. The cycloadduct **288** was isolated as 6:1 mixture of E and Z isomers. (Scheme-49)

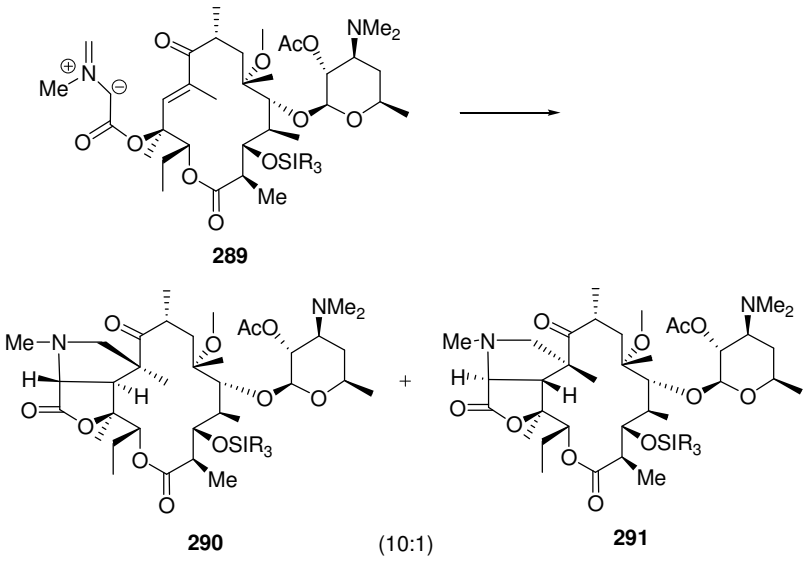
Scheme-49



Although most of the above examples pertaining to asymmetric azomethine ylides have involved chiral ylide in the cycloaddition processes, a lone report in which the chirality is remotely placed on the dipolarophile unit is also known. Giu research group[93] have synthesized analogues of antibacterial agent Cethromycin by involving intramolecular

cycloaddition strategy of azomethine ylide **289** for the pyrrolidine ring system construction at C11 and C12 of the macrolide core, however, two isomers **290** and **291** obtained were in 10:1 ratio as non-separable mixture. (Scheme-50)

Scheme-50



From the above discussion, it is accredited that though diastereofacial control in intramolecular asymmetric 1,3-dipolar cycloaddition involving either chiral azomethine ylide or chiral dipolarophiles is a subject of much discussion, there has been very limited use of a removable chiral auxiliary or catalyst. Thus the aforementioned reports are conceptually attractive and deserve much credit due to their pioneering nature but they are inappropriate to initiate a complex total synthesis.

In the quest of designing a conceptually attractive asymmetric route towards 5,11-methanomorphanthridine, we viewed that chirality in our case can be induced in two ways according to our synthetic plan:

(a) using chiral dipolarophile

(b) using chiral catalyst. (Figure-7)

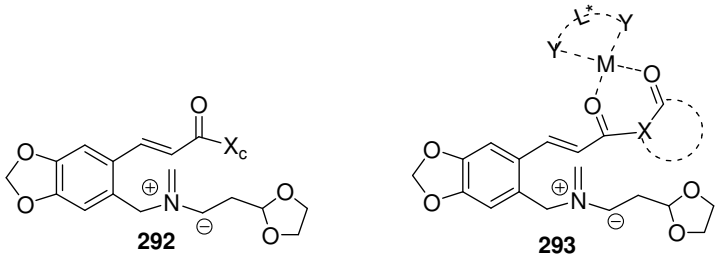


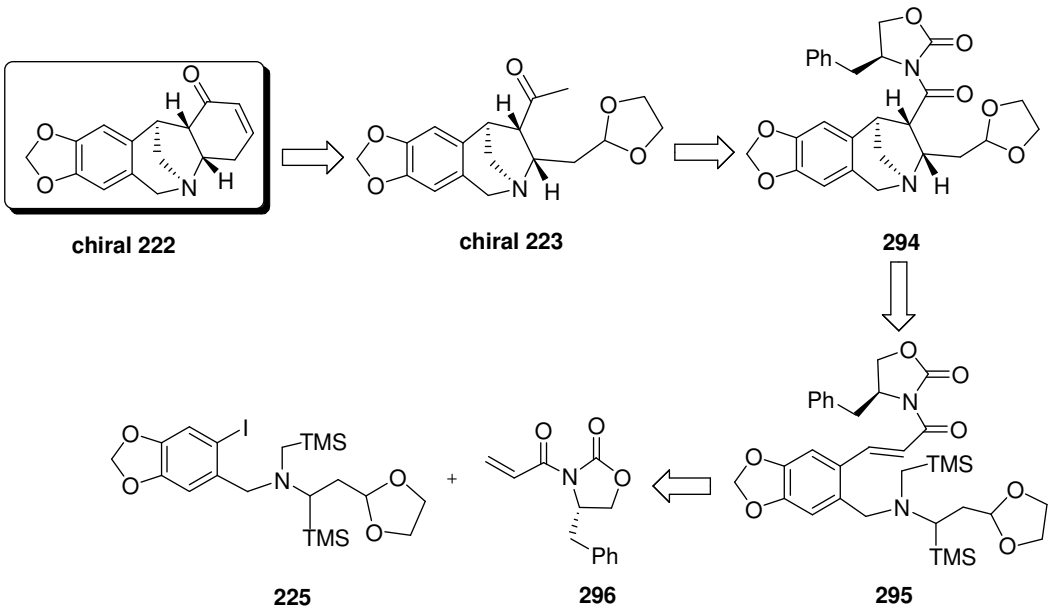
Figure-7

Although, we in our group have started synthesizing 5,11-methanomorphanthrine skeleton in optically pure for using both these approaches, I would present here only our initial results with chiral auxiliary approach.

4.2. Results and Discussion

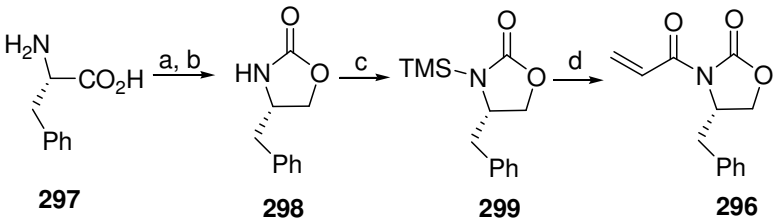
We thought of checking the efficiency of our proposed strategy by using Evan's oxazolidinone chiral auxiliary at first. The details of our approach is depicted retrosynthetically in Scheme-51.[94]

Scheme-51



The synthetic journey commenced with the preparation of the key precursor **295** which involved the Heck coupling of **225** with Evan's acryloyl oxazolidione **296**. The compound **296** was prepared from L-phenyl alanine **297** using literature procedure.[94](Scheme-52)

Scheme-52

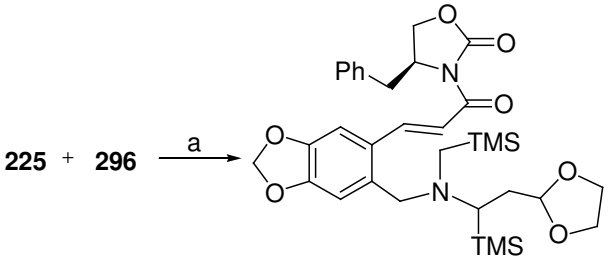


297 **298** **299** **296**

Reagents and conditions: *a) $NaBH_4$, I_2, THF, reflux, 18h, 85%; b) $(CH_3O)_2CO$, K_2CO_3, THF, reflux, 8h, 90%; c) TMSCl, Et_3N, CH_3CN, 14h, 91%; d) propenoyl chloride, 0.1mol $CuCl_2$ (anhyd.), benzene, reflux, 16h, 94%.*

The Heck coupling of **225** with **296** by following the identical reaction conditions as described earlier for **175,** produced **295** in 60 % yield. (Scheme-53)

Scheme-53



295

Reagents and conditions: a) *$Pd(OAC)_2$, PPh_3, K_2CO_3,, CH_3CN, reflux, 65%.*

The IR spectrum of **295** displayed two absorptions bands at 1778 and 1703 cm^{-1}, suggesting the presence of carbonyl functionality of oxazolidinone and amide, respectively.

In the 1H NMR spectrum of **295** two sets of doublets appearing at δ 8.22 and 7.59 (J = 15.41 Hz), integrating for one proton each, were assigned to the ene-one olefinic protons. The aromatic protons appeared as a multiplet at δ 7.05-7.27. The methylenedioxy protons appeared at δ 5.92. One broad multiplet appearing at δ 4.92, integrating for one proton, was assigned to the (O-C<u>H</u>-O) proton. The (PhCH_2-C<u>H</u>-) proton was observed as a multiplet at δ 4.71. Three multiplets appearing at δ 4.14 (2H), 3.84 (2H) and 3.74 (3H), were assigned to the (CH-C<u>H_2</u>-O), (O-C<u>H_2CH_2</u>-O) and one of the N-benzylic protons. The other N-benzylic proton appeared as a doublet at δ 3.53 (J = 14.03 Hz). One of the (Ph-C<u>H_2</u>CH-) proton appeared as a doublet of doublet at δ 3.28 (J = 13.39, 3.03 Hz), while the other one was observed as a doublet of doublet at δ 2.77 (J = 13.39, 9.60 Hz). A broad triplet at δ 2.32 (J = 5.94 Hz), integrating for one proton, was assigned to the (TMS-C<u>H</u>-N) proton. Two (TMS-C<u>H_2</u>-N) protons appeared as two sets of doublets at δ 2.13 and 1.93 (J = 13.90). The ((TMS-CH-C<u>H_2</u>-) protons appeared as two sets of multiplets at δ 1.96 and 1.59.

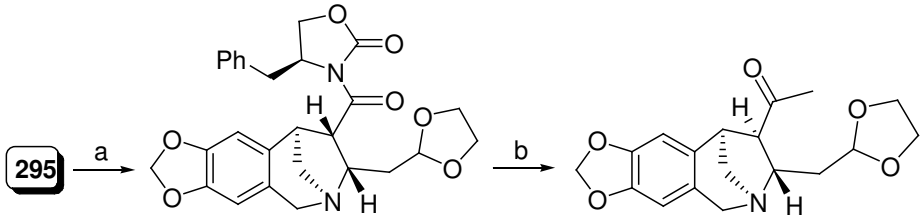
The ^{13}C NMR spectrum displayed a total of twenty seven signals at δ 172.5, 165.2, 153.6, 149.9, 146.9, 143.4, 136.4, 135.5, 129.5, 128.9, 127.4, 115.9, 109.9, 106.1, 103.9, 101.4, 66.1, 64.7, 64.6, 56.4, 55.4, 49.7, 44.7, 38.0, 30.5, 0.5, -1.0. Two most downfield signals appearing at δ 172.5 and 165.2 were attributed to two carbonyl carbons. The carbons of ene-one olefinic moiety were observed at δ 143.4 and 115.9. The DEPT experiment revealed the presence of five aromatic quaternary carbons at δ 153.6, 149.9, 146.9, 136.4 and 135.5. The methine signals of mono substituted benzene ring appeared at 129.5, 128.9 and 127.4, respectively. The other two methine signals of aromatic region were noticed at δ 109.9 and 106.1. The methylenedioxy carbon appeared at δ 101.4. The carbon of (O-<u>C</u>H-O) was observed at δ 103.9. The DEPT experiment confirmed the appearance of seven methylene carbon signals in aliphatic region at δ 66.1, 64.7, 64.6, 56.4, 44.7, 38.0 and 30.5, which were assigned to N-benzylic, (O-<u>C</u>H_2-<u>C</u>H_2-O), (CH-<u>C</u>H_2-O), (N-<u>C</u>H_2CH), (Ph-<u>C</u>H_2-CH) and (-<u>C</u>H_2-CHO) carbons, respectively. Two methine signals

appearing at δ 55.4 and 49.7 were assigned to (Ph-CH_2-CH-) and (N-CH-TMS), respectively. The signals for TMS functionalities appeared at δ 0.5 and –1.0.

The mass spectrum of **295** displayed the molecular ion peak at m/z 639 (M+H).

With fully characterized **295** in hand, we proceeded for the crucial intramolecular asymmetric cycloaddition reaction. The cycloaddition was performed using the same experimental procedure as described earlier to produce **294** as single isomer. (Scheme-54)

Scheme-54



Reagents and conditions: *a) Ag(I)F, CH3CN, rt, 53%; b) MeLI, THF, 0 °C→ rt. 60%.*

The IR spectrum of **294** displayed two absorption bands at 1778 and 1693 cm^{-1}, suggesting the presence of oxazolidinone and amide ketonic carbonyl groups, respectively.

In the ^1H NMR spectrum of **294**, a multiplet appearing at δ 7.12-7.28, integrating for five protons was assigned to mono-substituted phenyl ring protons. The two aromatic protons appeared as two singlets at δ 6.52 and 6.39. The methylenedioxy protons appeared as a singlet at δ 5.81. The (O-CH-O) proton appeared as a triplet at δ 4.99 (J = 4.68 Hz). A multiplet appearing at δ 4.56-4.68, integrating for one proton, was assigned to the (Ph-CH_2-CH-) proton. One of the N-benzylic proton appeared as a doublet at δ 4.37 (J = 17.05 Hz). The (CH-CH_2-O) proton appeared as a multiplet at δ 4.15. One multiplet corresponding to four protons appeared at δ 3.85-3.92, which could be assigned to another N-benzylic proton, two of (O-CH_2-CH_2-O) and (N-CH-CH_2) protons, respectively. Another two (O-CH_2-CH_2-O) protons appeared as a multiplet at δ 3.76-3.82. One of the (N-CH_2-CH) protons appeared as a doublet of doublet at δ 3.60 (J = 10.12, 5.18 Hz). Another multiplet

appearing at δ 3.35-3.48, integrating for three protons was assigned to the other remaining (N-C<u>H</u>$_2$-CH-), (Ar-C<u>H</u>-CH-) and (Ar-C<u>H</u>-CH-) protons. One of the (Ph-C<u>H</u>$_2$-CH-) proton appeared as a doublet of a doublet at δ 3.21 (J = 13.26, 3.41 Hz) while the other one was observed as doublet of doublet at δ 2.70 (J = 13.26, 9.60 Hz). The (-CH-C<u>H</u>$_2$-CH-) protons appeared as a multiplet at δ 1.85.

The ^{13}C NMR spectrum displayed a total of twenty-five signals at δ 171.4, 158.5, 152.8, 148.8, 146.0, 135.7, 134.7, 129.1, 128.7, 127.2, 107.1, 106.1, 102.2, 100.7, 69.4, 66.4, 65.2, 64.6, 64.5, 55.3, 53.5, 45.25, 41.2, 37.7 and 29.4. The most downfield signals appearing at δ 171.4 and 158.5 were attributed to two carbonyls. The DEPT experiment revealed the presence of five aromatic quaternary carbons at δ 152.8, 148.8, 146.0, 135.7 and 134.7. The methine signals of mono-substituted phenyl ring appeared at δ 129.1, 128.7,and 127.2. Another two aromatic methine signals were observed at δ 107.1 and 106.1. The (O-CH-O) carbon appeared at δ 102.2. The methylenedioxy signal was observed at δ 100.7. The DEPT experiment revealed the presence of seven-methylene group in aliphatic region at δ 69.4, 66.4, 64.6 and 64.5 corresponding to (CH-<u>C</u>H$_2$-O), N-benzyl, Two (O-<u>C</u>H$_2$-<u>C</u>H$_2$-O), (N-<u>C</u>H$_2$CH), (Ph<u>C</u>H$_2$-CH) and (CH-<u>C</u>H$_2$-CH), respectively. Four methine signals appearing at δ 65.2, 55.3, 53.5 and 45.3, were assigned to (PhCH$_2$-<u>C</u>H), (N-<u>C</u>H-CH$_2$), (N-CH-<u>C</u>H) and (Ar-<u>C</u>H-CH), respectively.

The mass spectrum of **294** displayed the molecular ion peak at m/z 493 (M+H).

The chiral auxiliary was removed successfully by treating **294** with methyl lithium at 0 ^{o}C which produced chiral epimerized product **233** in 60% yield.[95] $[\alpha]_D^{25}$ = -20.5^{o} (C 0.7, $CHCl_3$).

4.3 Summary

We have developed an asymmetric route for the sterereospecific construction of 5,11-methonomorphanthridine alkaloids. This commending methodology not only holds promise to be extremely useful in the synthesis of natural product targets, but also makes a new entry into the field of intramolecular asymmetric 1,3-dipolar cycloaddition.

5. References:

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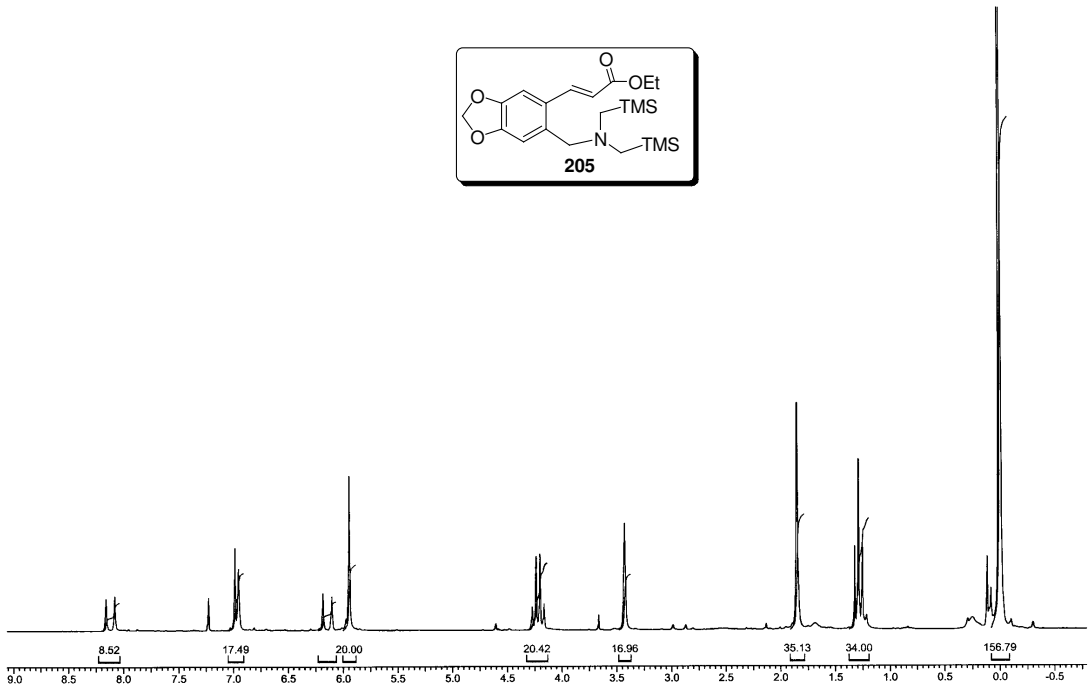
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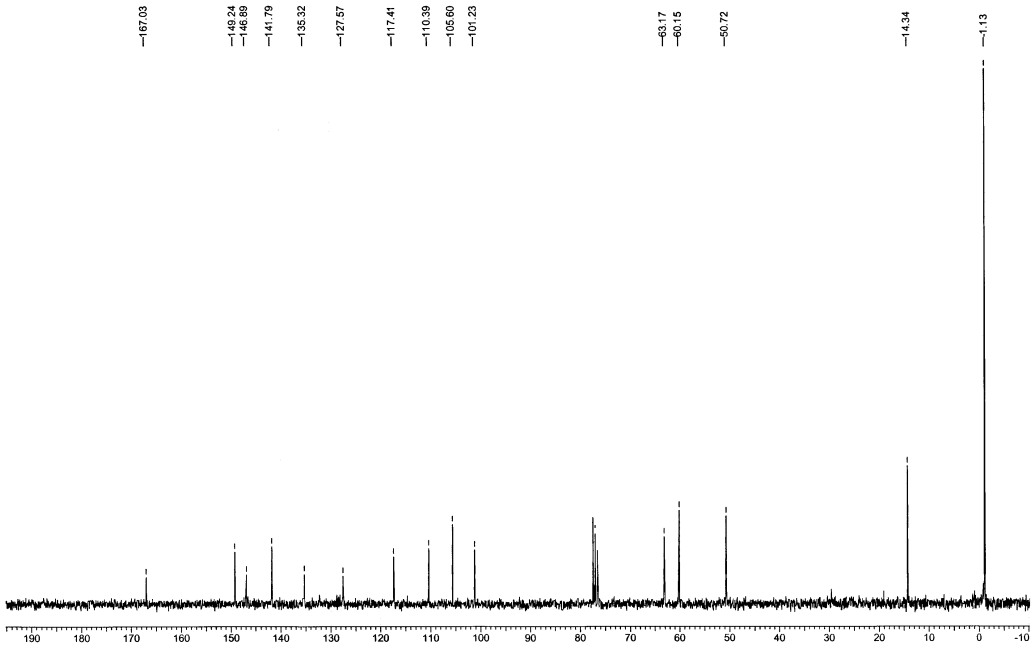
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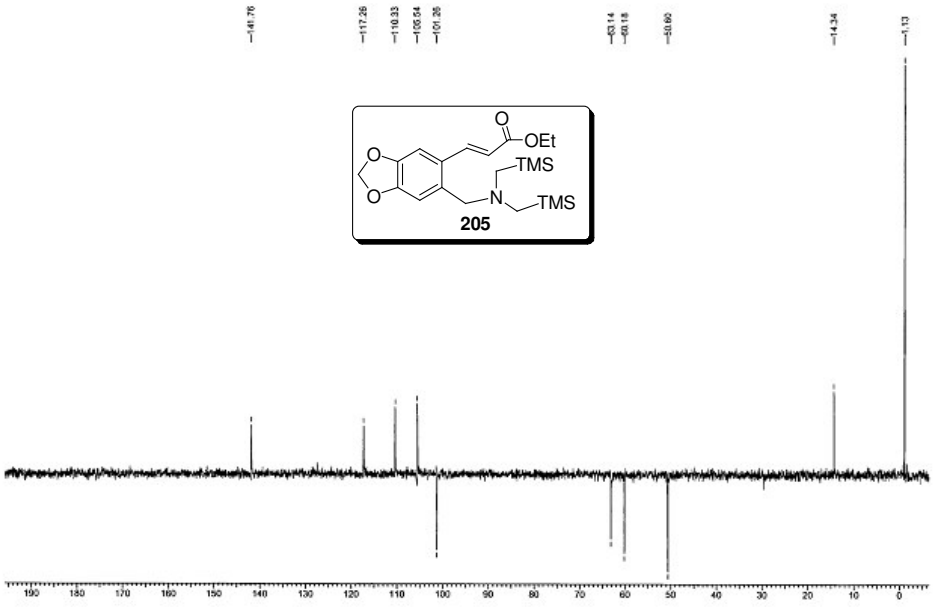
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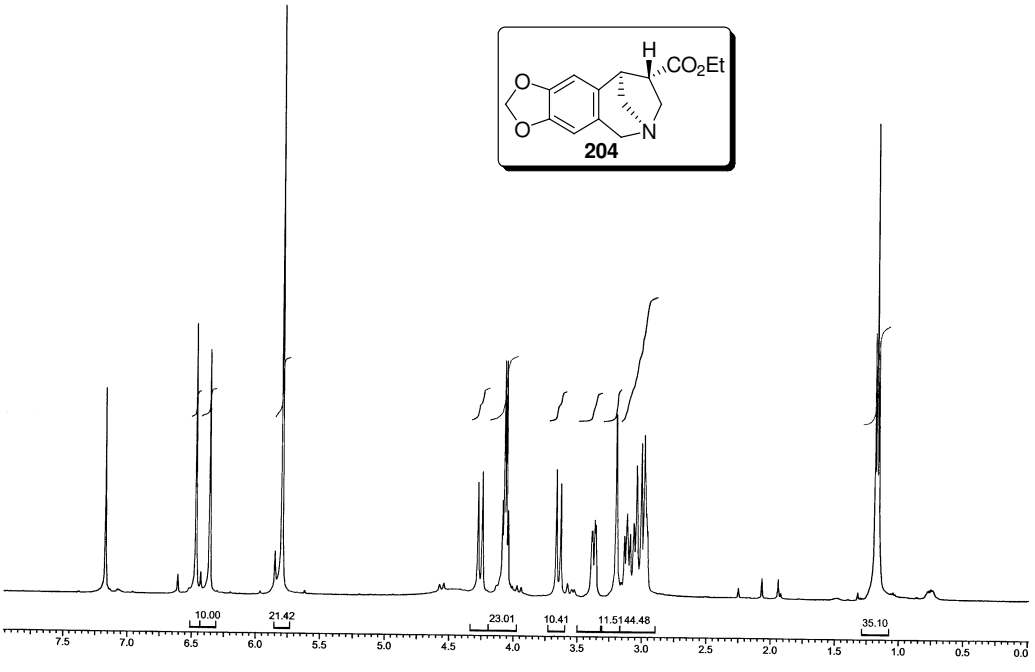
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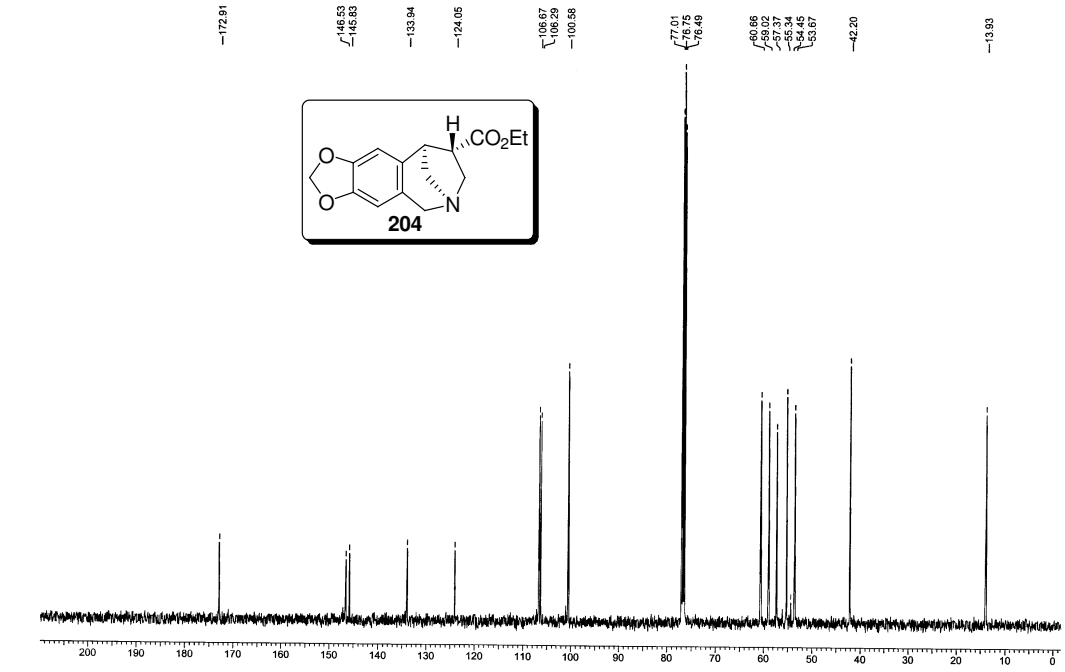
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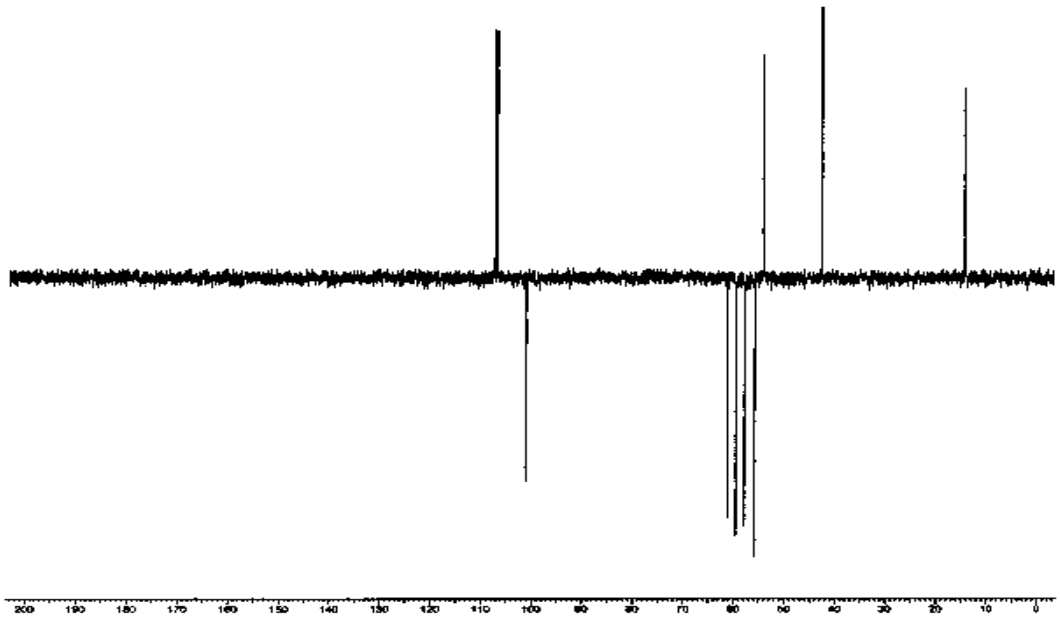

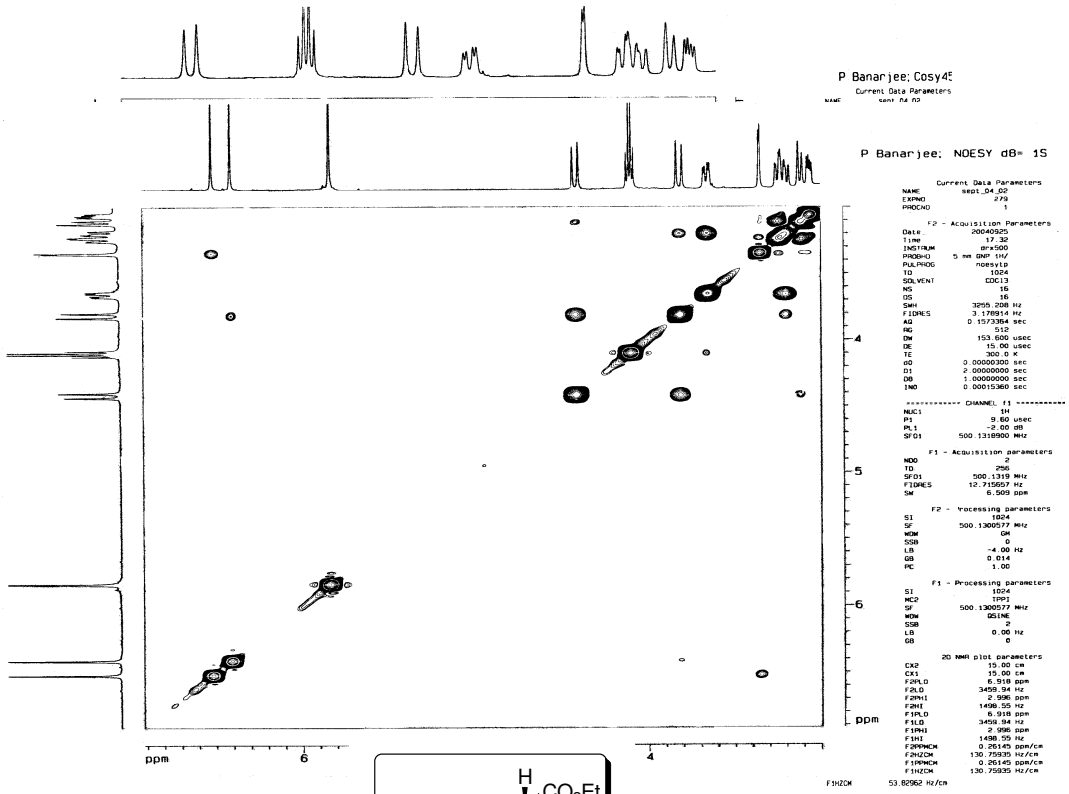
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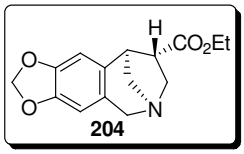
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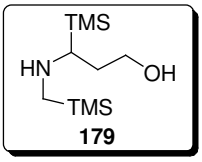
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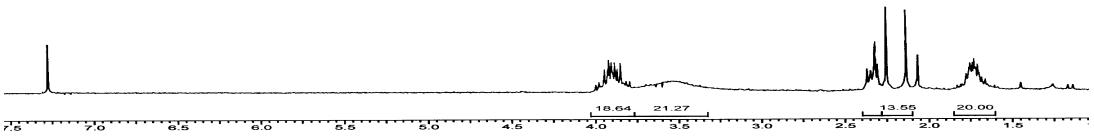
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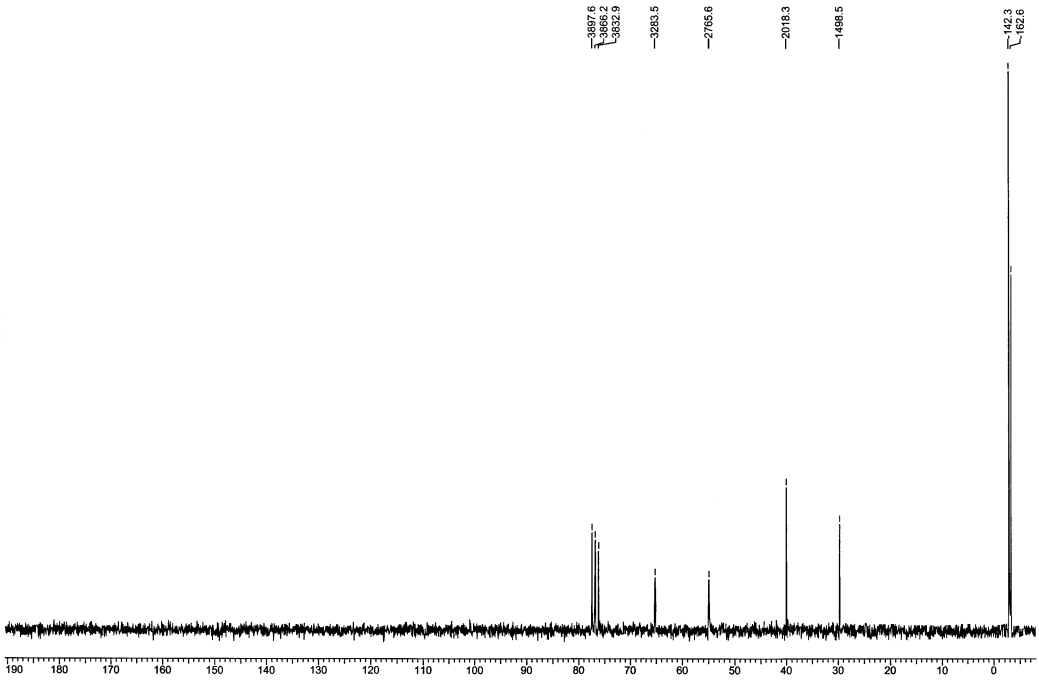
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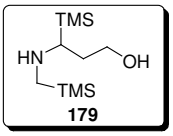
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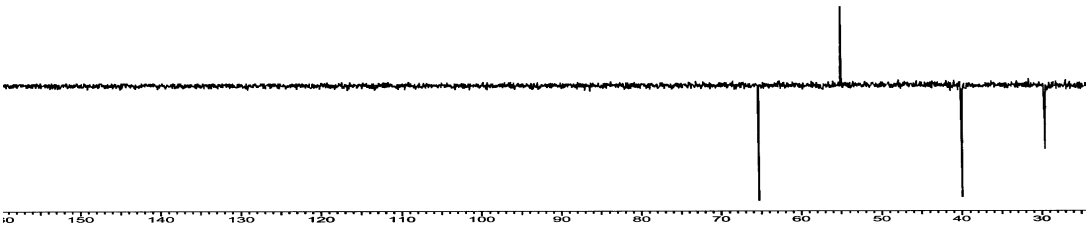
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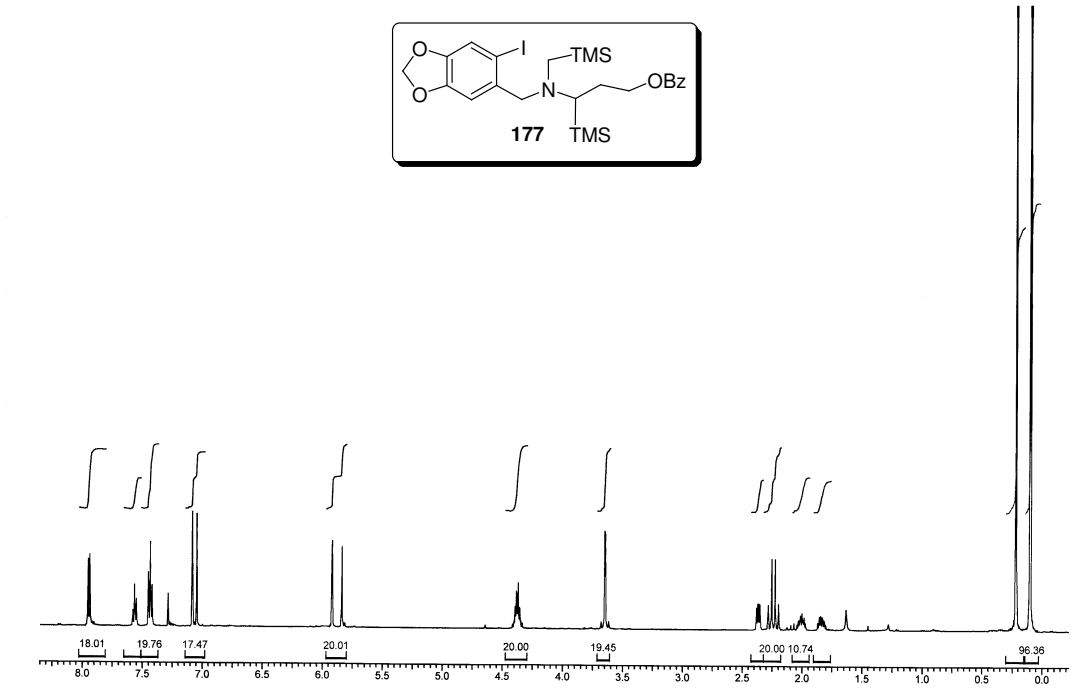
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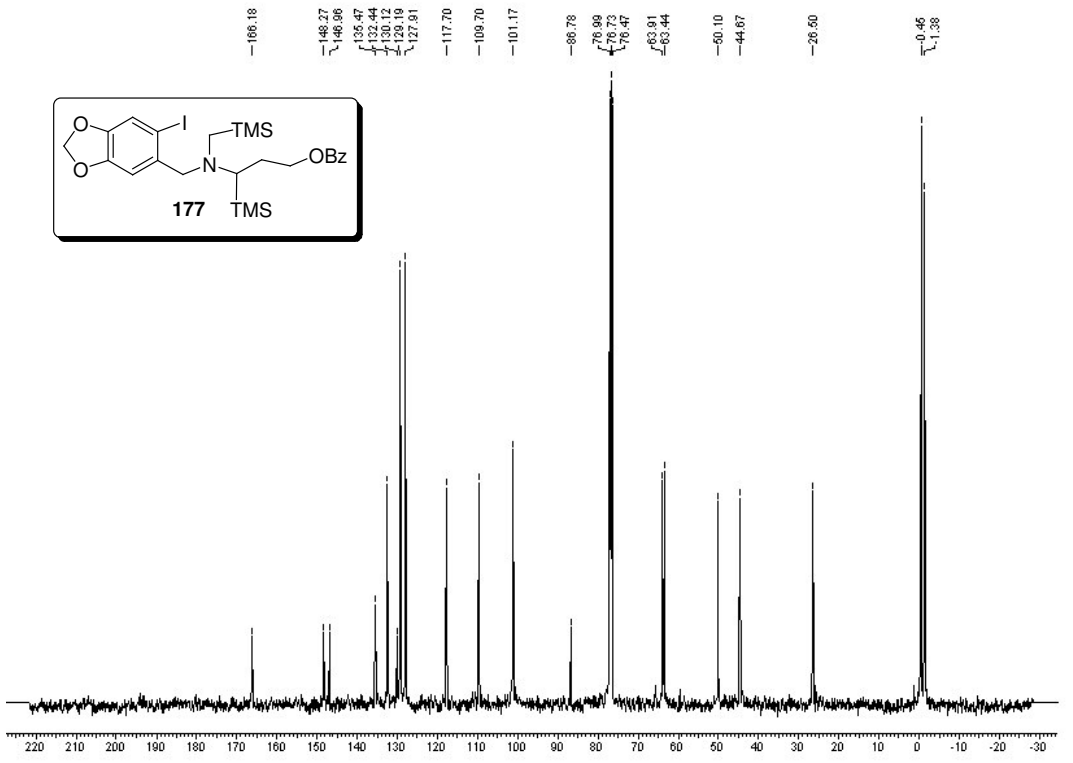
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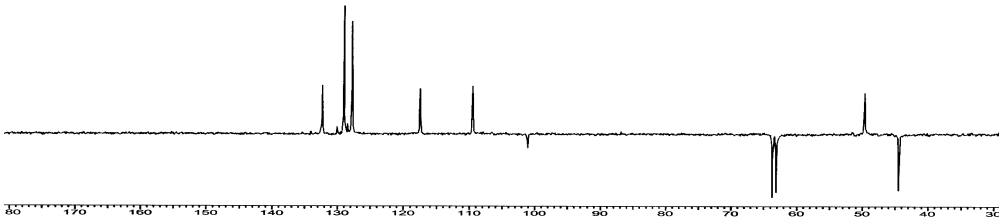

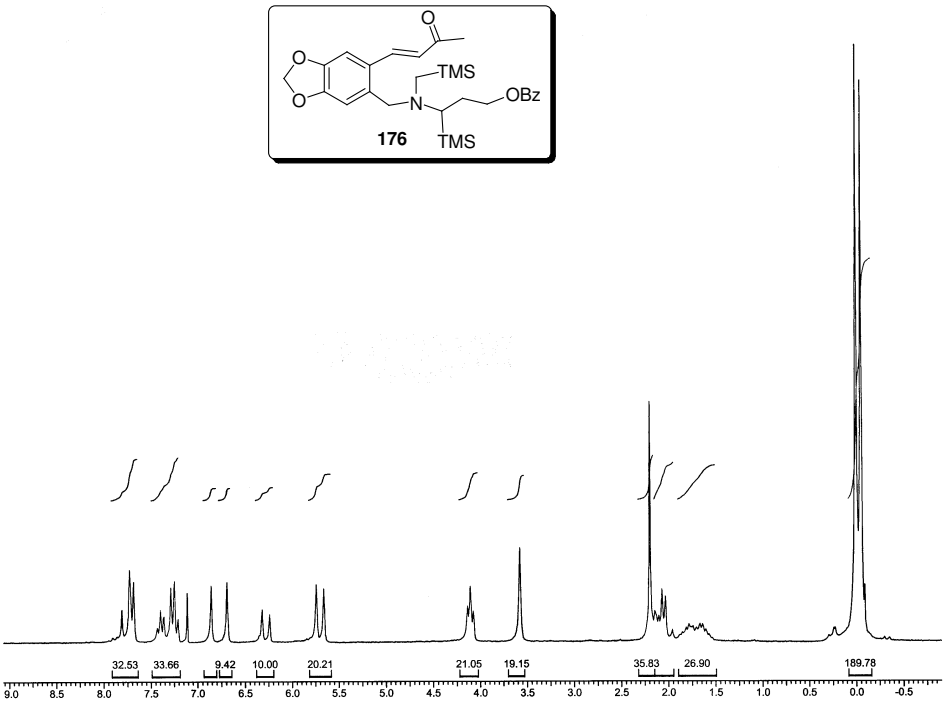
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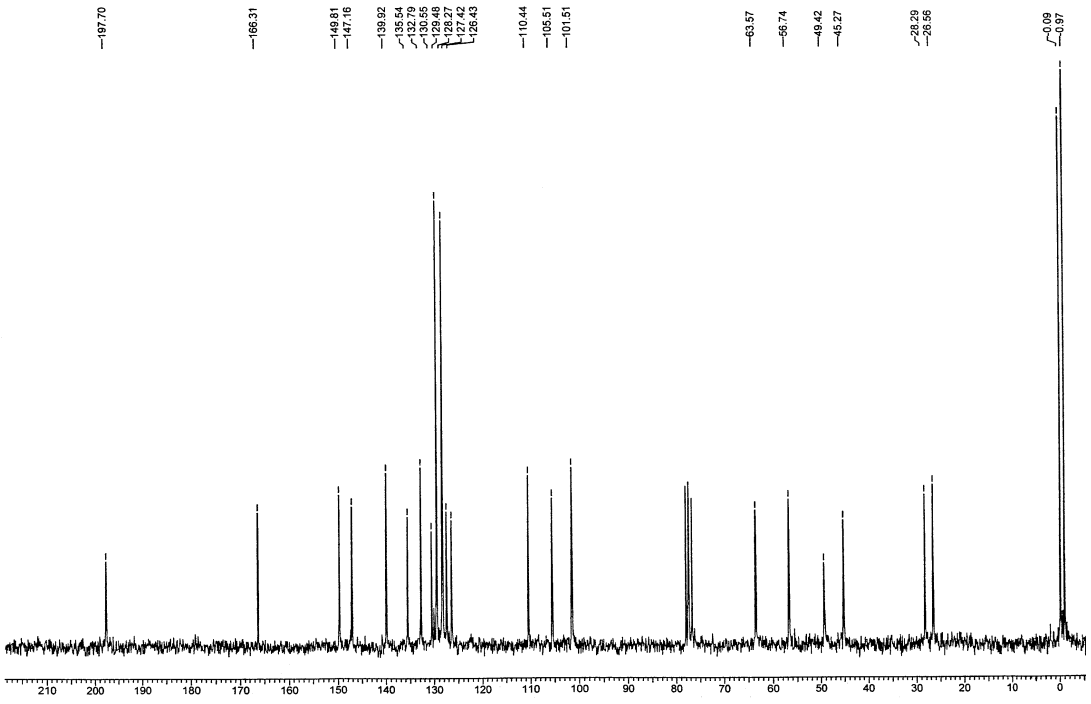
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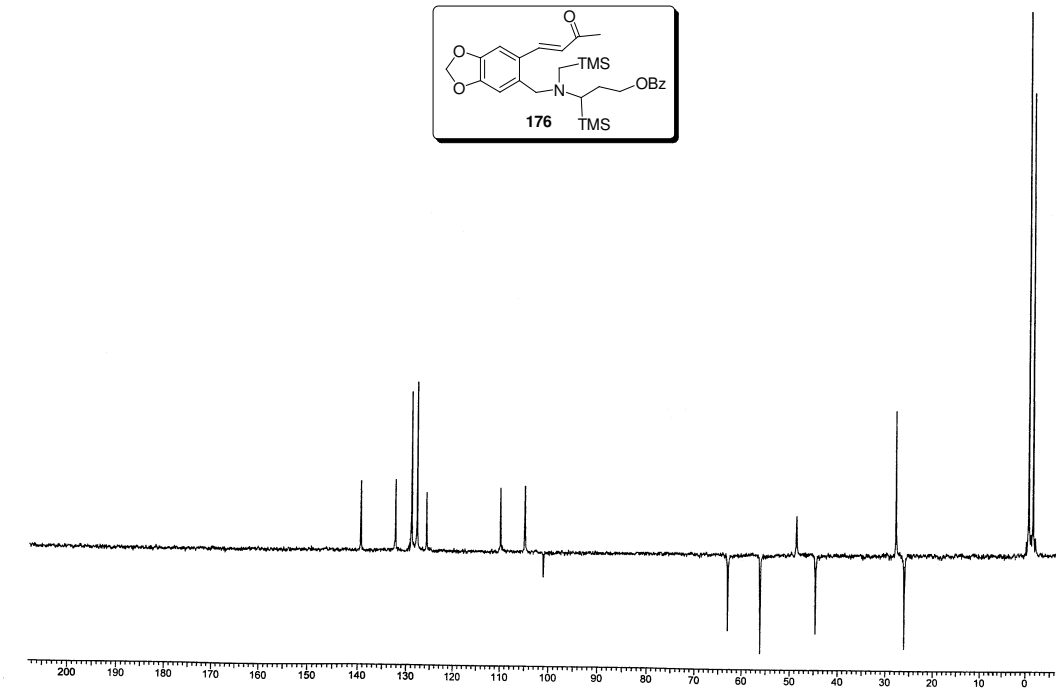
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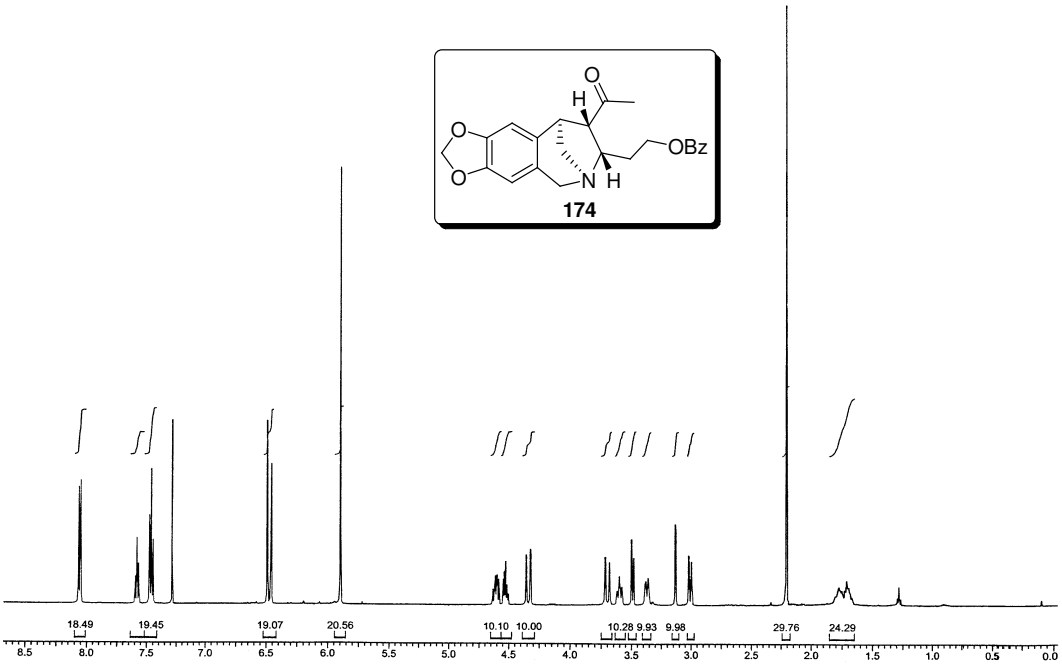
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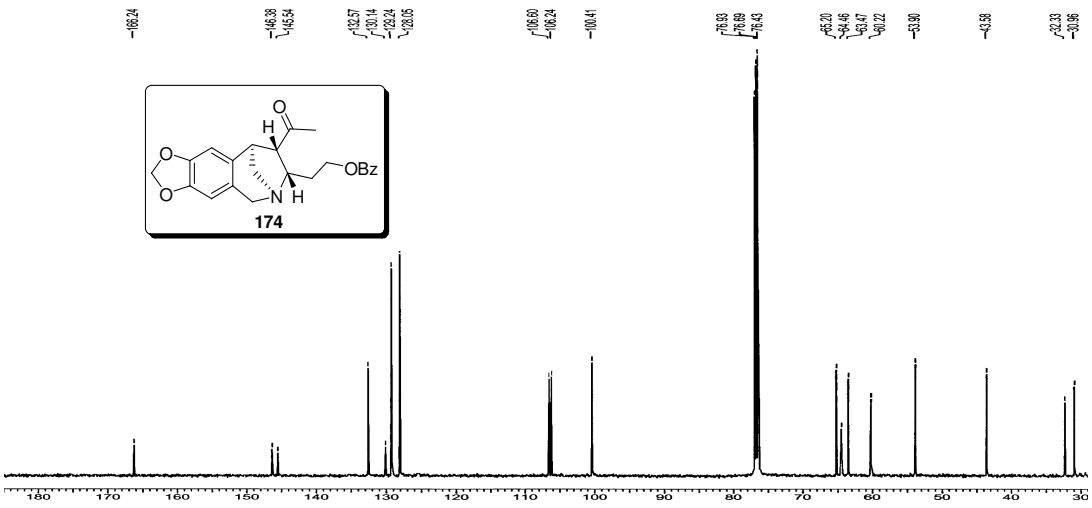
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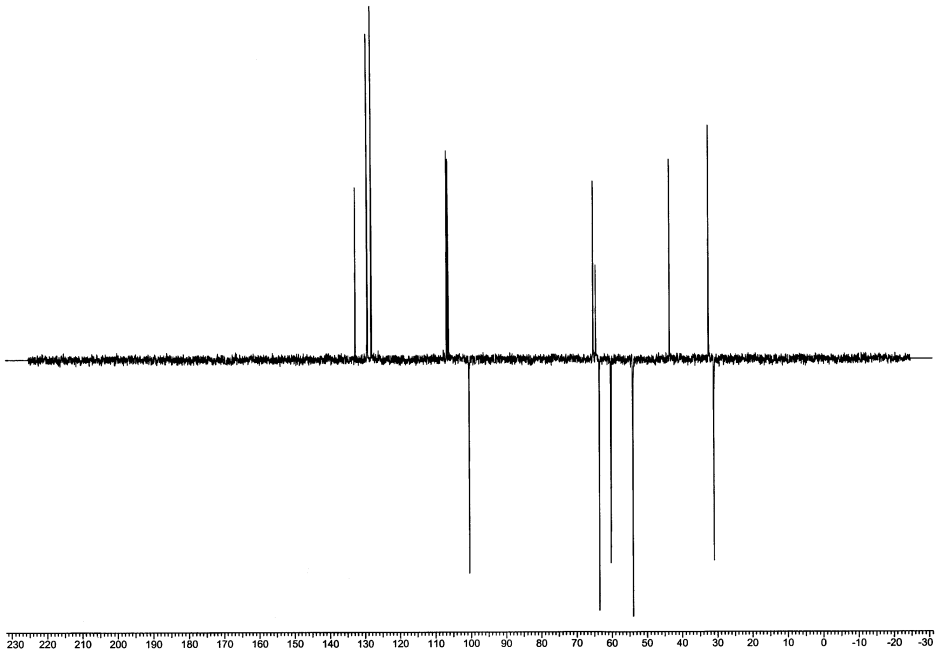

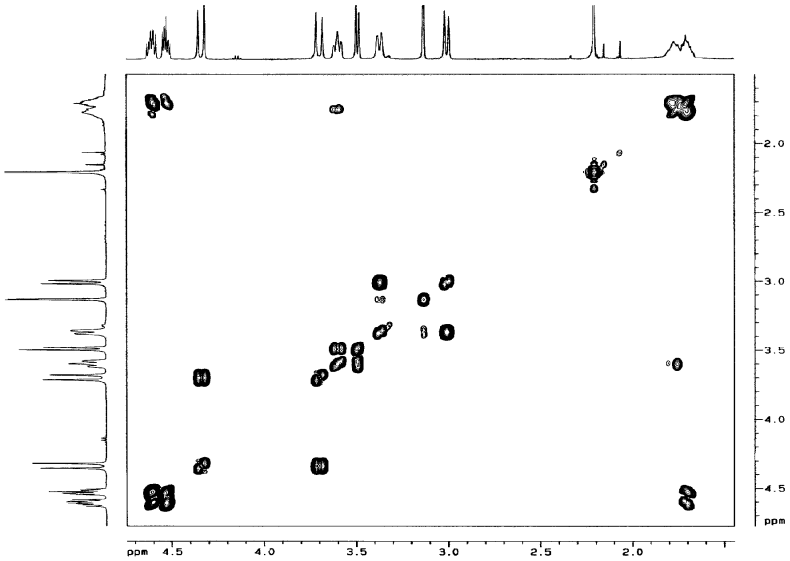

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PROCNO	1

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INSTRUM	drx500
PROBHD	5 mm BBP 1H/
PULPROG	cosy45
TD	1024
SOLVENT	CDCl3
NS	16
DS	16
SWH	4006.410 Hz
FIDRES	3.912510 Hz
AQ	0.1278452 sec
RG	400
DW	124.800 usec
DE	6.00 usec
TE	300.0 K
d0	0.00000300 sec
d1	2.00000000 sec
IN0	0.00024960 sec

CHANNEL f1

NUC1	1H
P1	9.60 usec
PL1	-2.00 dB
SFO1	500.1324600 MHz

F1 - Acquisition parameters

MDD	2
TD	256
SFO1	500.1325 MHz
FIDRES	15.626040 Hz
SW	8.011 ppm

F2 - Processing parameters

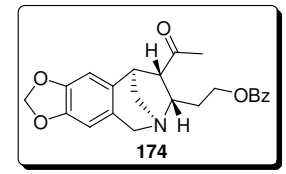
SI	1024
SF	500.1300000 MHz
WDW	QSINE
SSB	10
LB	0.00 Hz
GB	0
PC	1.00

F1 - Processing parameters

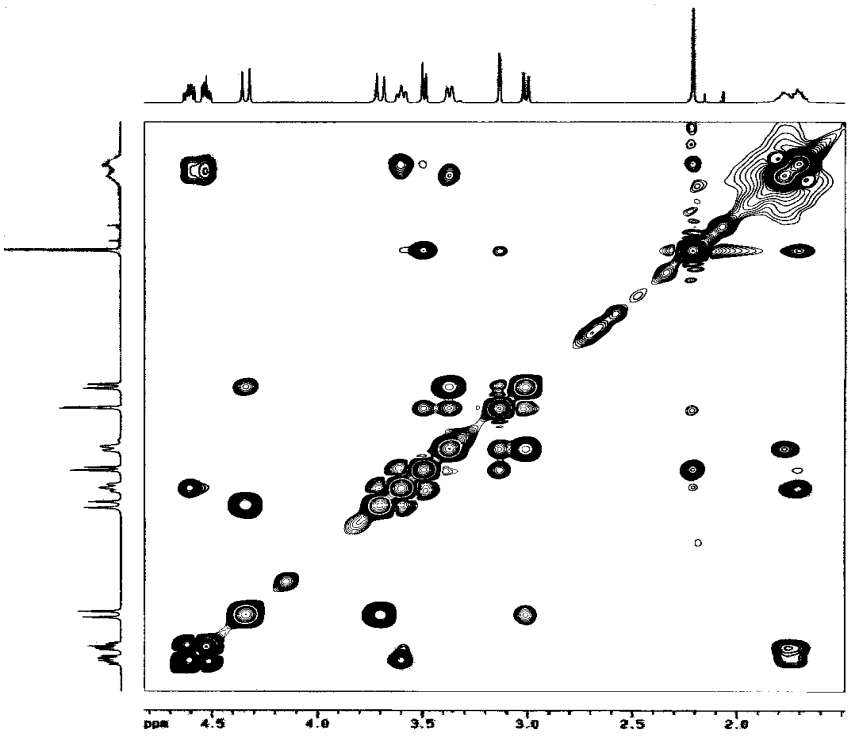
SI	1024
MC2	QF
SF	500.1300000 MHz
WDW	QSINE
SSB	8
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	4.747 ppm
F2LO	2373.59 Hz
F2PHI	1.445 ppm
F2HI	722.65 Hz
F1PLO	4.778 ppm
F1LO	2389.58 Hz
F1PHI	1.500 ppm
F1HI	750.23 Hz
F2PPMCM	0.28909 ppm/cm
F2HZCM	119.07185 Hz/cm
F1PPMCM	0.21852 ppm/cm
F1HZCM	109.28944 Hz/cm



174



Prabal B.
PBAMDCA; NOESY d8= 1S

Current Data Parameters

NAME	Dec_3-02
EXPNO	50
PROCNO	1

F2 - Acquisition Parameters

Date_	20021205
Time	22.04
INSTRUM	drx500
PROBHD	5 mm BBP 1H/
PULPROG	noesytp
TD	1024
SOLVENT	CDCl3
NS	16
DS	16
SWH	4006.410 Hz
FIDRES	3.912510 Hz
AQ	0.1278452 sec
RG	400
DW	124.800 usec
DE	6.00 usec
TE	300.0 K
d0	0.00000300 sec
d1	2.00000000 sec
d8	1.00000000 sec
IN0	0.00012480 sec

CHANNEL f1

NUC1	1H
P1	9.60 usec
PL1	-2.00 dB
SFO1	500.1324600 MHz

F1 - Acquisition parameters

MDD	2
TD	256
SFO1	500.1325 MHz
FIDRES	15.626040 Hz
SW	8.011 ppm

F2 - Processing parameters

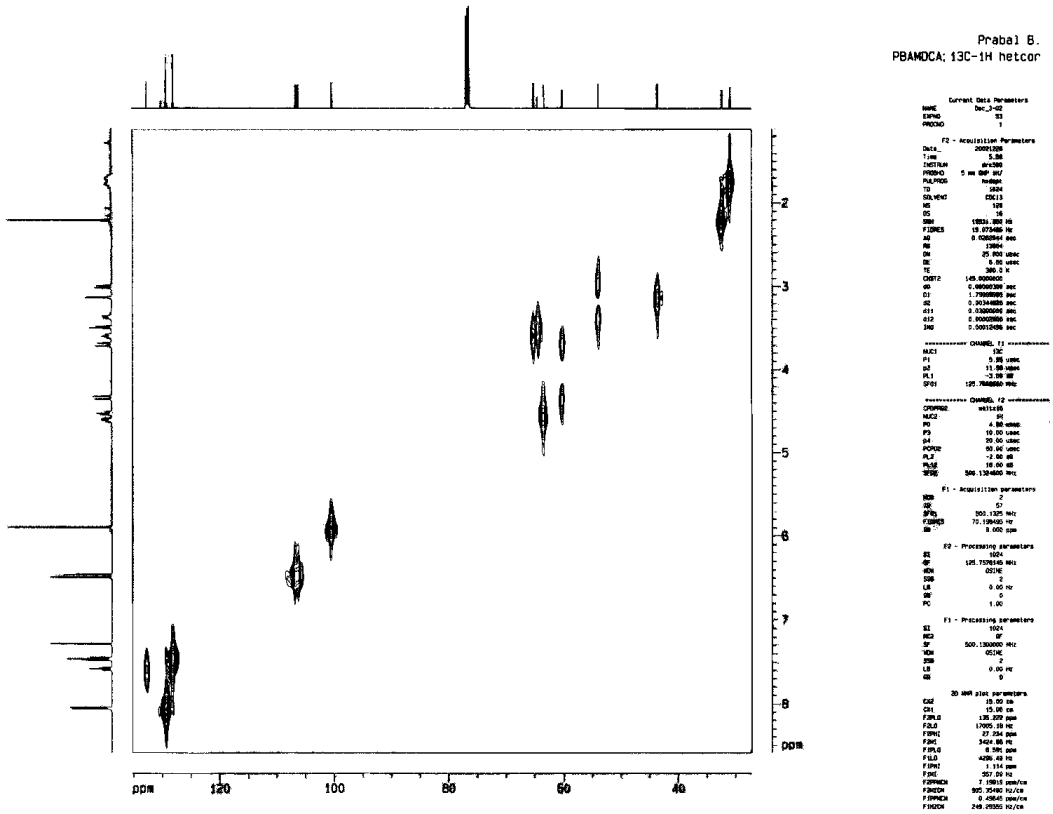
SI	1024
SF	500.1300000 MHz
WDW	SN
SSB	0
LB	-4.00 Hz
GB	0.814
PC	1.00

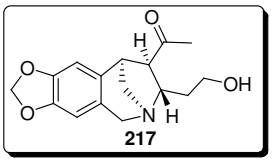
F1 - Processing parameters

SI	1024
MC2	TPPI
SF	500.1300000 MHz
WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0

2D NMR plot parameters

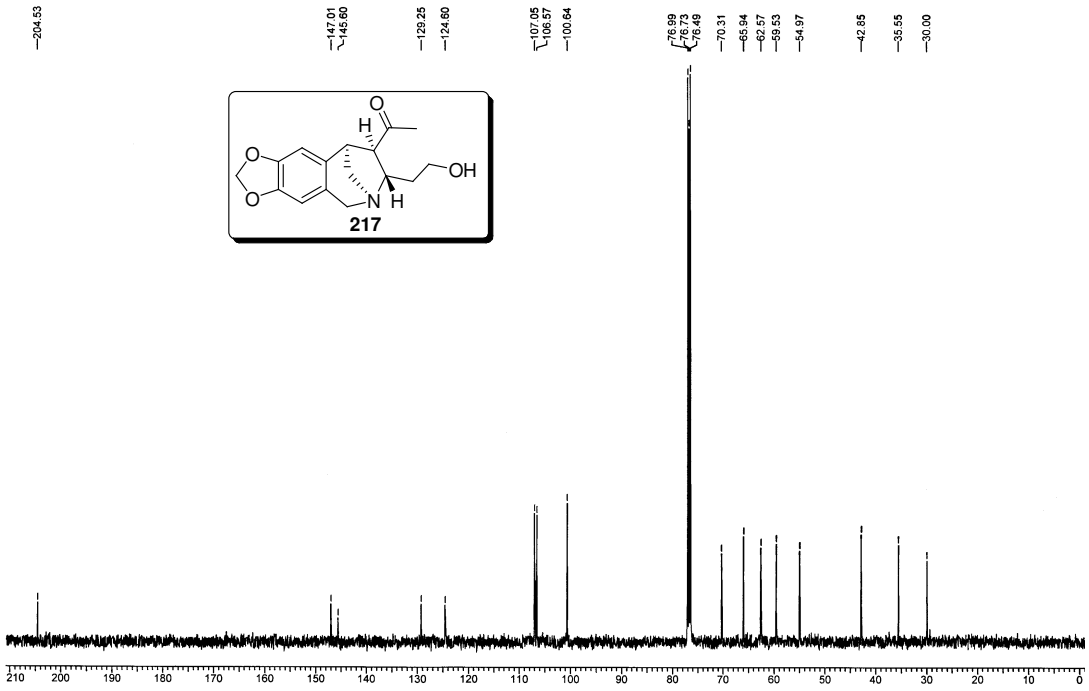
CX2	15.00 cm
CX1	15.00 cm
F2PLO	4.825 ppm
F2LO	2413.05 Hz
F2PHI	1.484 ppm
F2HI	742.41 Hz
F1PLO	4.784 ppm
F1LO	2392.45 Hz
F1PHI	1.461 ppm
F1HI	730.97 Hz
F2PPMCM	0.22269 ppm/cm
F2HZCM	111.37812 Hz/cm
F1PPMCM	0.22217 ppm/cm
F1HZCM	111.11526 Hz/cm

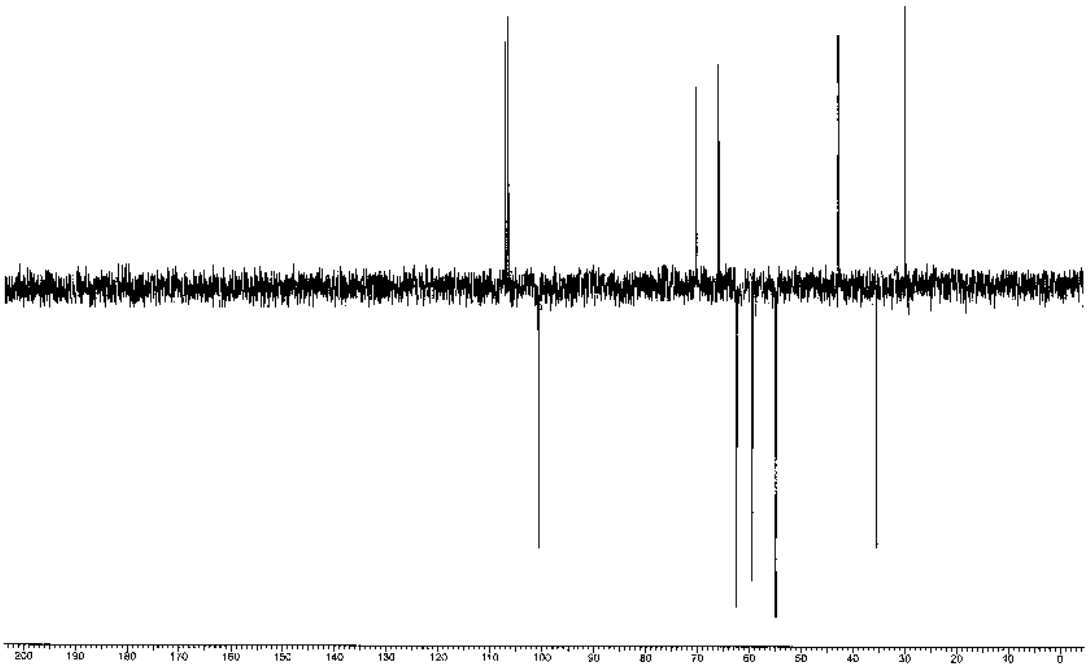

Prabal B.
PBAMDCA: 13C-1H hetcor
ppm
120
100
80
60
40
2
3
4
5
6
7
8
ppm

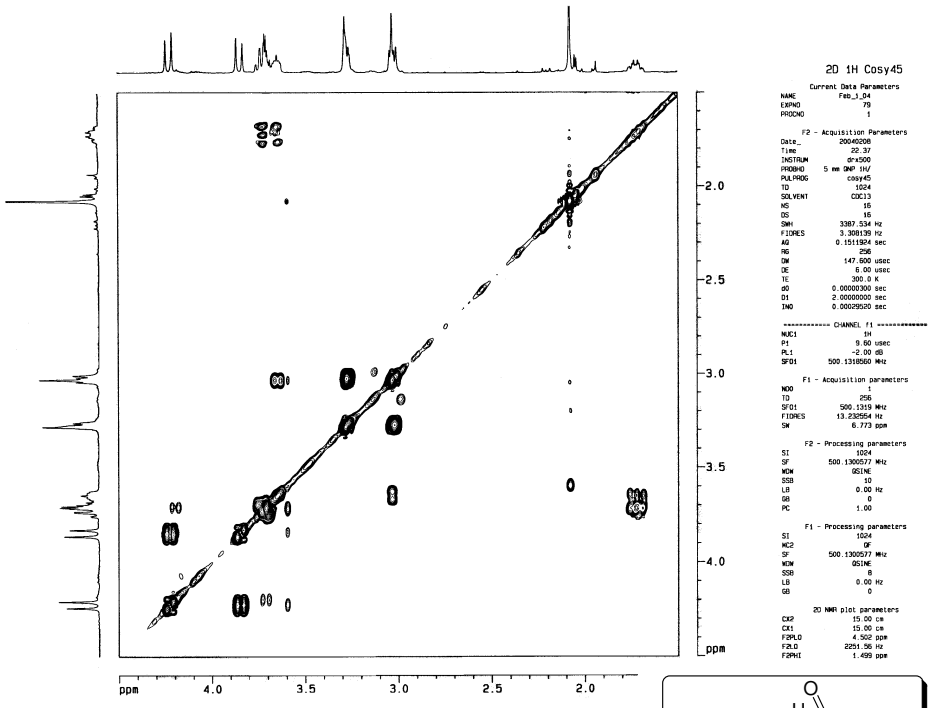

O
H
O
O
OH
N H

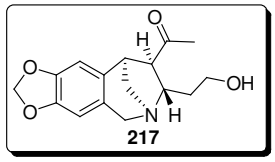
217

9.35
20.00
12.59
11.14
12.25
9.79
17.99
25.82
11.70
10.39
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

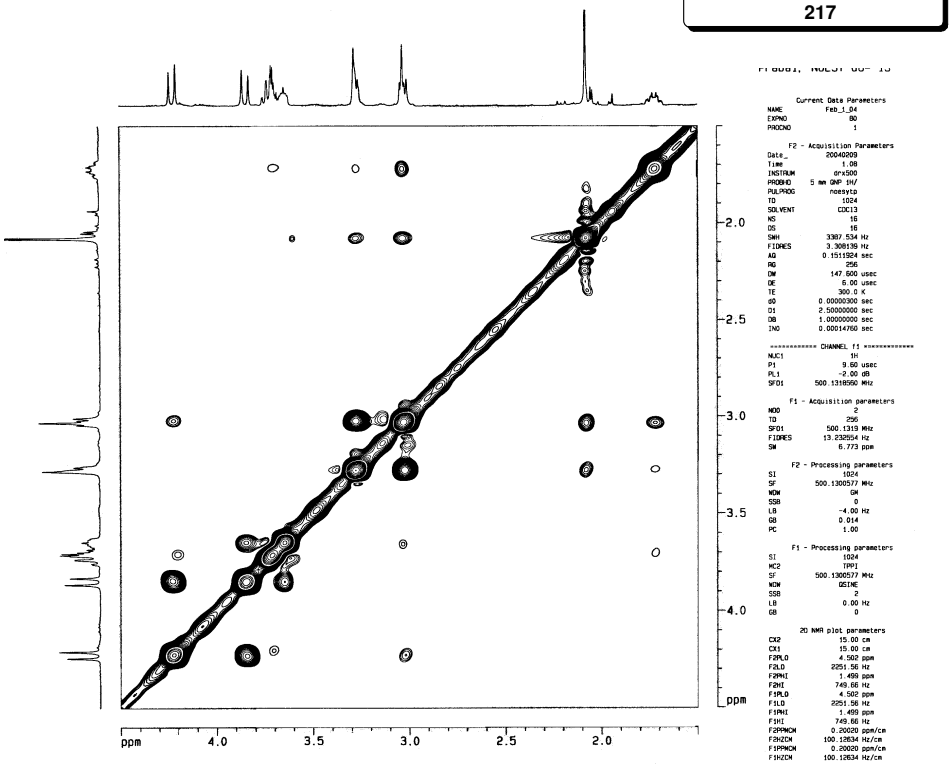

204.53
147.01
145.60
129.25
124.60
107.05
106.57
100.84
76.99
76.73
76.49
70.31
65.94
62.57
59.53
54.97
42.85
35.55
30.00
O
H
O
O
OH
N H
217

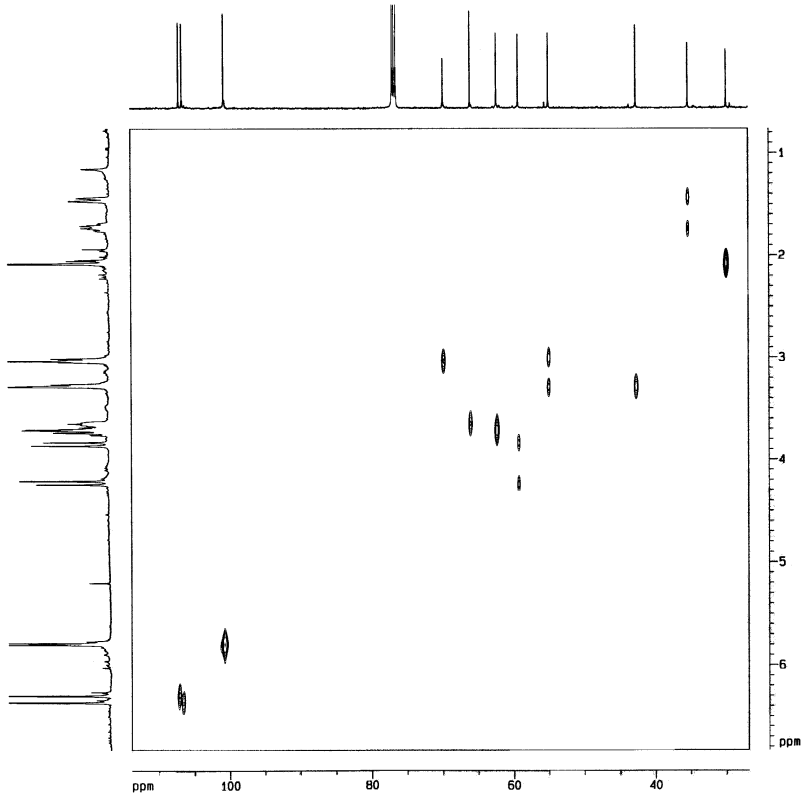



2D 1H Cosy45
Current Data Parameters
NAME Feb_1_04
EXPNO 79
PROCNO 1
F2 - Acquisition Parameters
Date_ 20040208
Time 22.37
INSTRUM drx500
PROBHD 5 mm QNP 1H/
PULPROG cosy45
TD 1024
SOLVENT CDCl3
NS 16
DS 16
SWH 3387.534 Hz
FIDRES 3.308139 Hz
AQ 0.1511924 sec
RG 256
DW 147.600 usec
DE 6.00 usec
TE 300.0 K
d0 0.00000300 sec
D1 2.00000000 sec
INO 0.00029520 sec
CHANNEL f1
NUC1 1H
P1 9.60 usec
PL1 -2.00 dB
SFO1 500.1318560 MHz
F1 - Acquisition parameters
MOD 1
TD 256
SFO1 500.1319 MHz
FIDRES 13.232554 Hz
SW 6.773 ppm
F2 - Processing parameters
SI 1024
SF 500.1300577 MHz
WDW QSINE
SSB 10
LB 0.00 Hz
GB 0
PC 1.00
F1 - Processing parameters
SI 1024
MC2 QF
SF 500.1300577 MHz
WDW QSINE
SSB 0
LB 0.00 Hz
GB 0
2D NMR plot parameters
CX2 15.00 cm
CX1 15.00 cm
F2PLO 4.502 ppm
F2LO 2251.56 Hz
F2PHI 1.499 ppm
ppm
4.0
3.5
3.0
2.5
2.0


O
H
O
O
OH
N H

217


Current Data Parameters
NAME Feb_1_04
EXPNO 80
PROCNO 1
F2 - Acquisition Parameters
Date_ 20040209
Time 1.08
INSTRUM drx500
PROBHD 5 mm QNP 1H/
PULPROG noesytp
TD 1024
SOLVENT CDCl3
NS 16
DS 16
SWH 3387.534 Hz
FIDRES 3.308139 Hz
AQ 0.1511924 sec
RG 256
DW 147.600 usec
DE 6.00 usec
TE 300.0 K
d0 0.00000300 sec
D1 2.50000000 sec
D8 1.00000000 sec
INO 0.00014760 sec
CHANNEL f1
NUC1 1H
P1 9.60 usec
PL1 -2.00 dB
SFO1 500.1318560 MHz
F1 - Acquisition parameters
MOD 2
TD 256
SFO1 500.1319 MHz
FIDRES 13.232554 Hz
SW 6.773 ppm
F2 - Processing parameters
SI 1024
SF 500.1300577 MHz
WDW GM
SSB 0
LB -4.00 Hz
GB 0.014
PC 1.00
F1 - Processing parameters
SI 1024
MC2 TPPI
SF 500.1300577 MHz
WDW QSINE
SSB 2
LB 0.00 Hz
GB 0
2D NMR plot parameters
CX2 15.00 cm
CX1 15.00 cm
F2PLO 4.502 ppm
F2LO 2251.56 Hz
F2PHI 1.499 ppm
F2HI 749.66 Hz
F1PLO 4.502 ppm
F1LO 2251.56 Hz
F1PHI 1.499 ppm
F1HI 749.66 Hz
F2PPMCM 0.20020 ppm/cm
F2HZCM 100.12634 Hz/cm
F1PPMCM 0.20020 ppm/cm
F1HZCM 100.12634 Hz/cm
ppm
4.0
3.5
3.0
2.5
2.0



alcohol; 13C-1H hetcor

Current Data Parameters
NAME Feb_1_04
EXPNO 90
PROCNO 1

F2 - Acquisition Parameters
Date_ 20040209
Time 21.13
INSTRUM drx500
PROBHD 5 mm QNP 1H/
PULPROG hxdqgp1
TD 1024
SOLVENT CDCl3
NS 256
DS 16
SWH 15151.516 Hz
FIDRES 14.796402 Hz
AQ 0.0338426 sec
RG 32768
DW 33.000 usec
DE 6.00 usec
TE 300.0 K
CNST2 145.0000000
d0 0.00000300 sec
D1 1.79999995 sec
d2 0.00344828 sec
d11 0.03000000 sec
d12 0.00002000 sec
IN0 0.00009997 sec

CHANNEL f1
NUC1 13C
P1 5.95 usec
p2 11.90 usec
PL1 -3.00 dB
SFO1 125.7663990 MHz

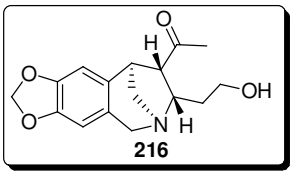
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
P0 4.80 usec
P3 10.00 usec
p4 20.00 usec
PCPD2 80.00 usec
PL2 -2.00 dB
PL12 18.00 dB
SFO2 500.1321430 MHz

F1 - Acquisition parameters
NDO 2
TD 94
SFO1 500.1321 MHz
FIDRES 53.204792 Hz
SW 10.000 ppm

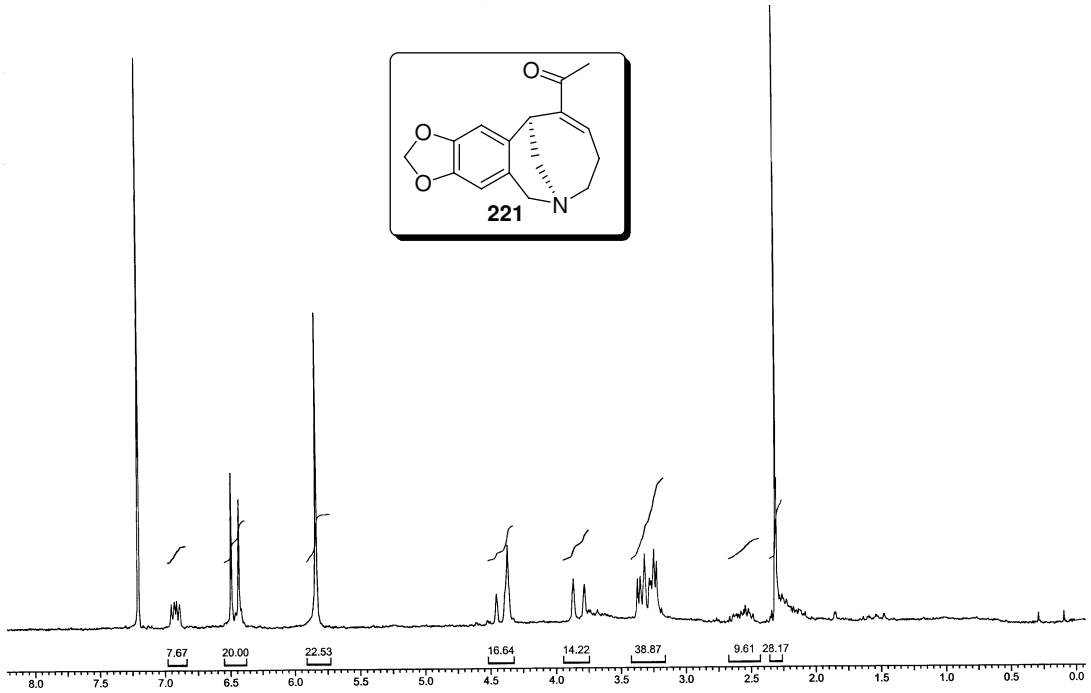
F2 - Processing parameters
SI 1024
SF 125.7578253 MHz
WDW QSINE
SSB 2
LB 0.00 Hz
GB 0
PC 1.00

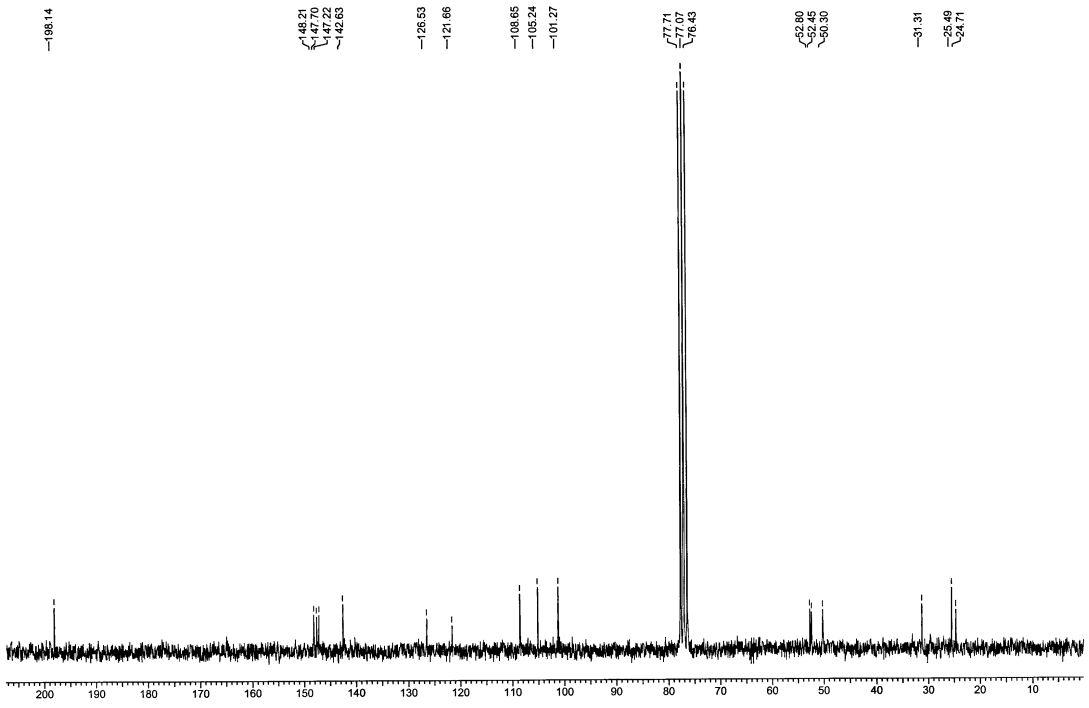
F1 - Processing parameters
SI 1024
MC2 QF
SF 500.1300576 MHz
WDW QSINE
SSB 2
LB 0.00 Hz
GB 0

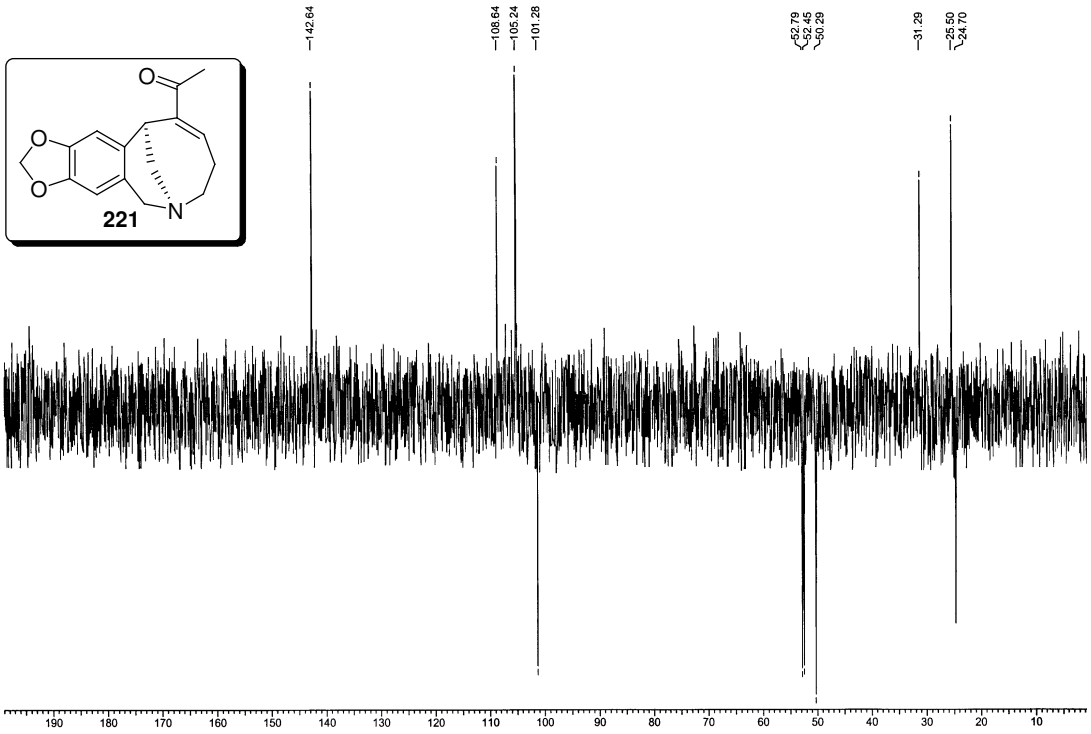
2D NMR plot parameters
CX2 15.00 cm
CX1 15.00 cm
F2PLO 113.826 ppm
F2LO 14314.70 Hz
F2PHI 26.676 ppm
F2HI 3380.16 Hz
F1PLO 6.836 ppm
F1LO 3418.74 Hz
F1PHI 0.752 ppm
F1HI 380.87 Hz
F2PPMCM 5.79861 ppm/cm
F2HZCM 726.96936 Hz/cm
F1PPMCM 0.40484 ppm/cm
F1HZCM 202.52460 Hz/cm

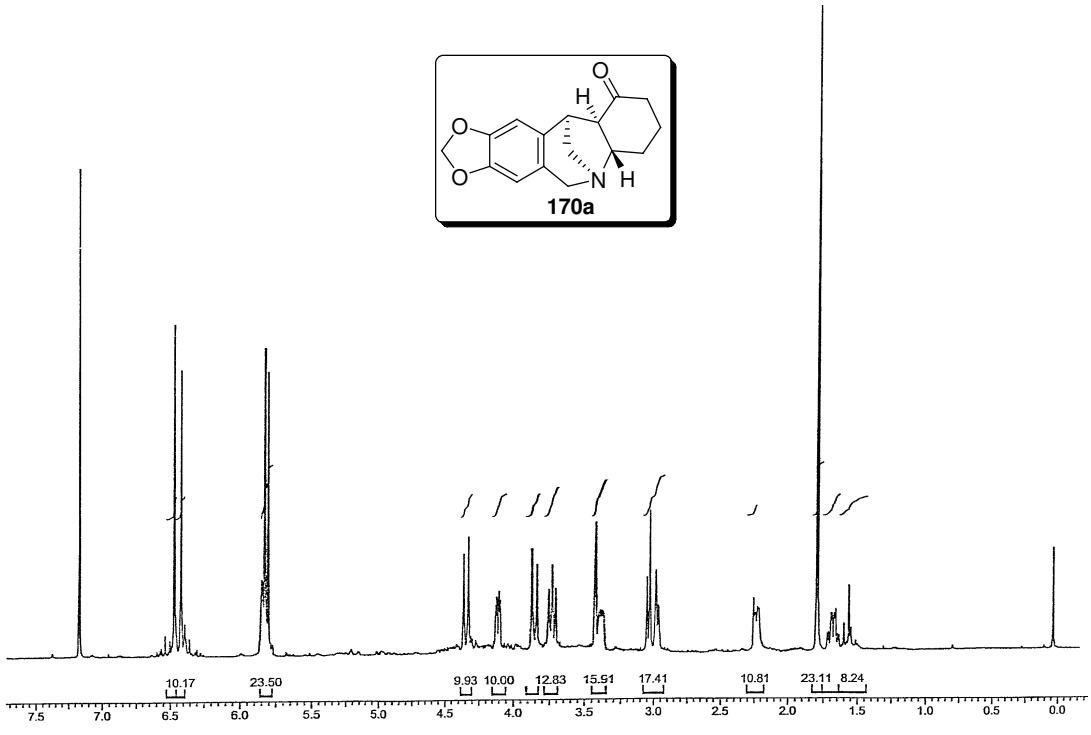


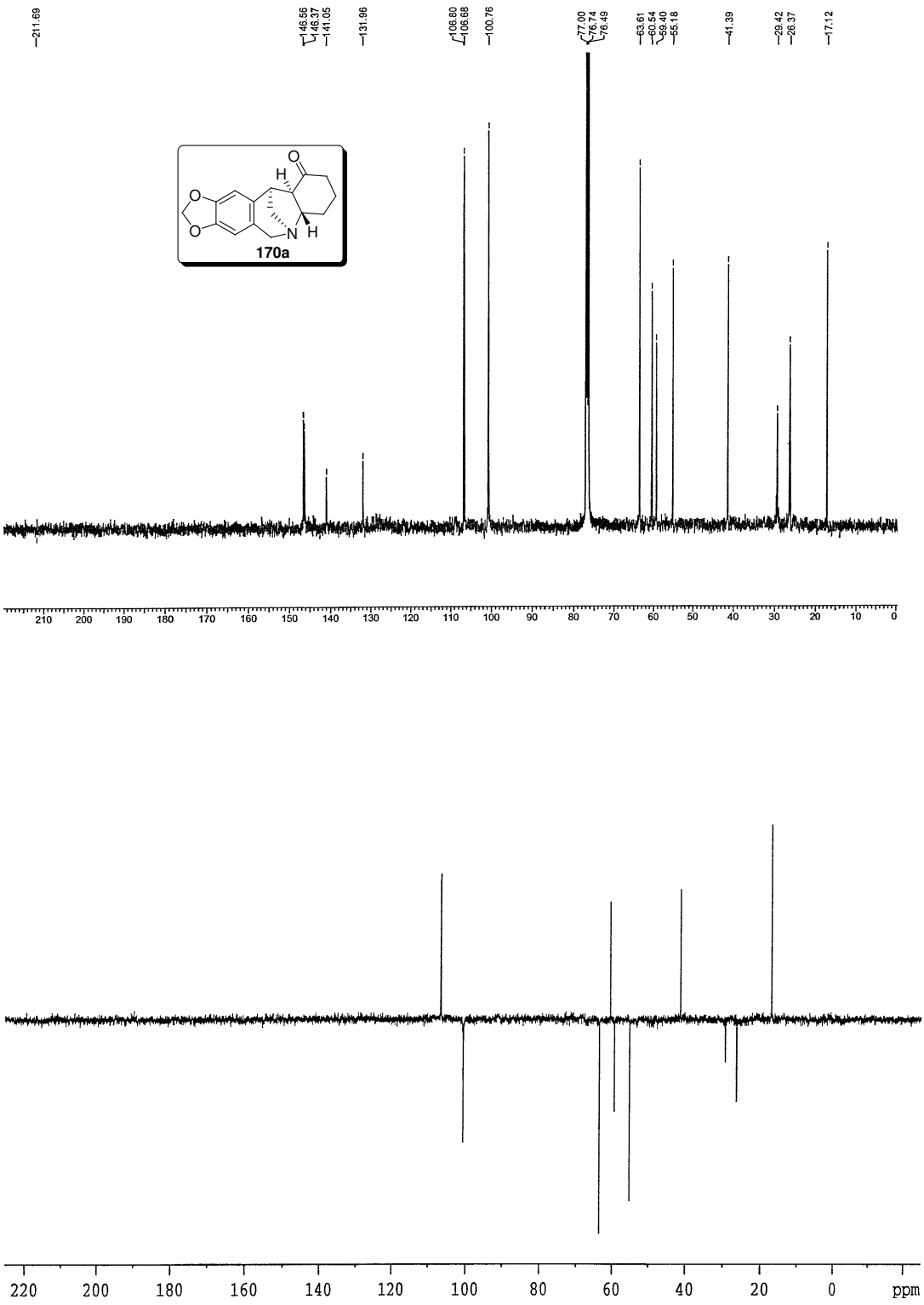
216

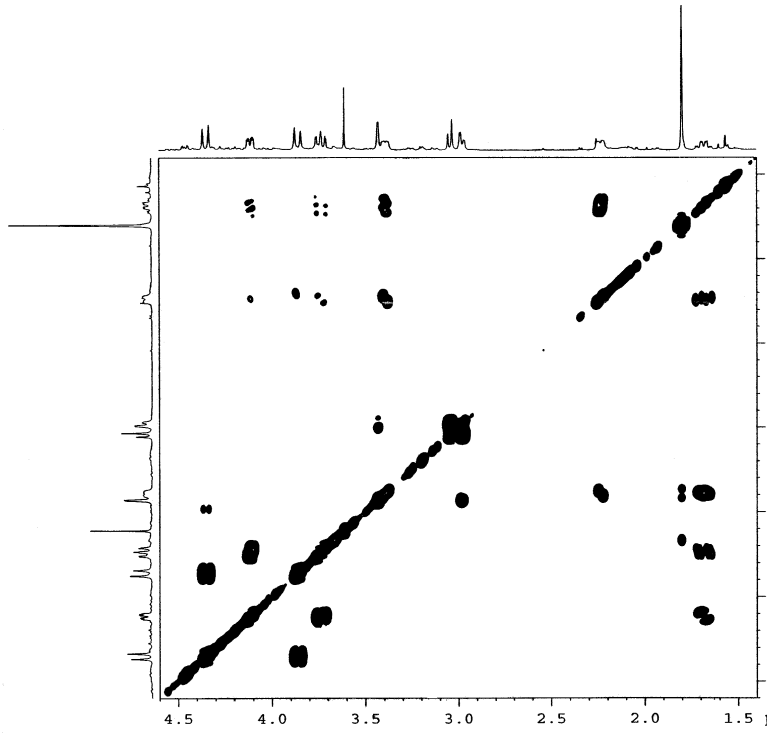

O
O
O
N
221
7.67
20.00
22.53
16.64
14.22
38.87
9.61
28.17
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


198.14
148.21
147.70
147.22
142.63
126.53
121.66
108.65
105.24
101.27
77.71
77.07
76.43
52.80
52.45
50.30
31.31
25.49
24.71
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


142.64
108.64
105.24
101.28
52.79
52.45
50.29
31.29
25.50
24.70
221


170a
10.17
23.50
9.93
10.00
12.83
15.91
17.41
10.81
23.11
8.24


211.69
146.56
146.37
141.05
131.96
106.80
106.68
100.76
77.00
76.74
76.49
63.61
60.54
59.40
55.18
41.39
29.42
26.37
17.12
O
H
O
O
N
H
170a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
220 200 180 160 140 120 100 80 60 40 20 0 ppm



P Banarjee; COSY

Current Data Parameters
NAME Feb_3_05-ep
EXPNO 49
PROCNO 1

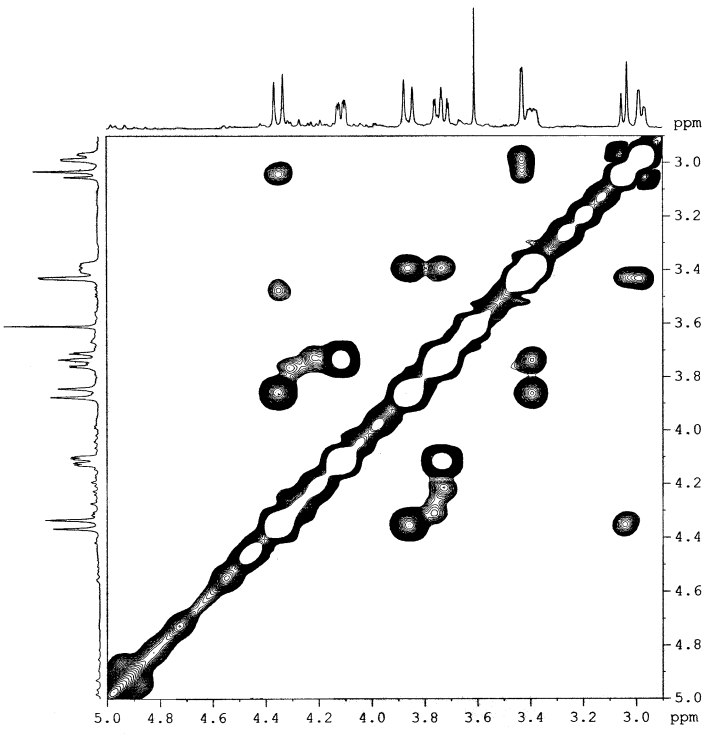
F2 - Acquisition Parameters
Date_ 20050221
Time 22.03
INSTRUM drx500
PROBHD 5 mm QNP 1H/15
PULPROG cosyqf45
TD 1024
SOLVENT CDCl3
NS 16
DS 16
SWH 3333.333 Hz
FIDRES 3.255208 Hz
AQ 0.1538000 sec
RG 512
DW 150.000 usec
DE 6.00 usec
TE 666.5 K
d0 0.00000300 sec
D1 2.00000000 sec
IN0 0.00030022 sec
MCREST 0.00000000 sec
MCWRK 2.00000000 sec

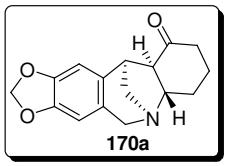
======== CHANNEL f1 ========
NUC1 1H
P1 9.60 usec
PL1 -2.00 dB
SFO1 500.1318910 MHz

F1 - Acquisition parameters
ND0 1
TD 256
SFO1 500.1319 MHz
FIDRES 13.011075 Hz
SW 6.660 ppm
FnMODE QF

F2 - Processing parameters
SI 1024
SF 500.1300570 MHz
WDW QSINE
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

F1 - Processing parameters
SI 1024
MC2 QF
SF 500.1300570 MHz
WDW QSINE
SSB 0
LB 0.00 Hz
GB 0





170a

EXPNO 50
PROCNO 1

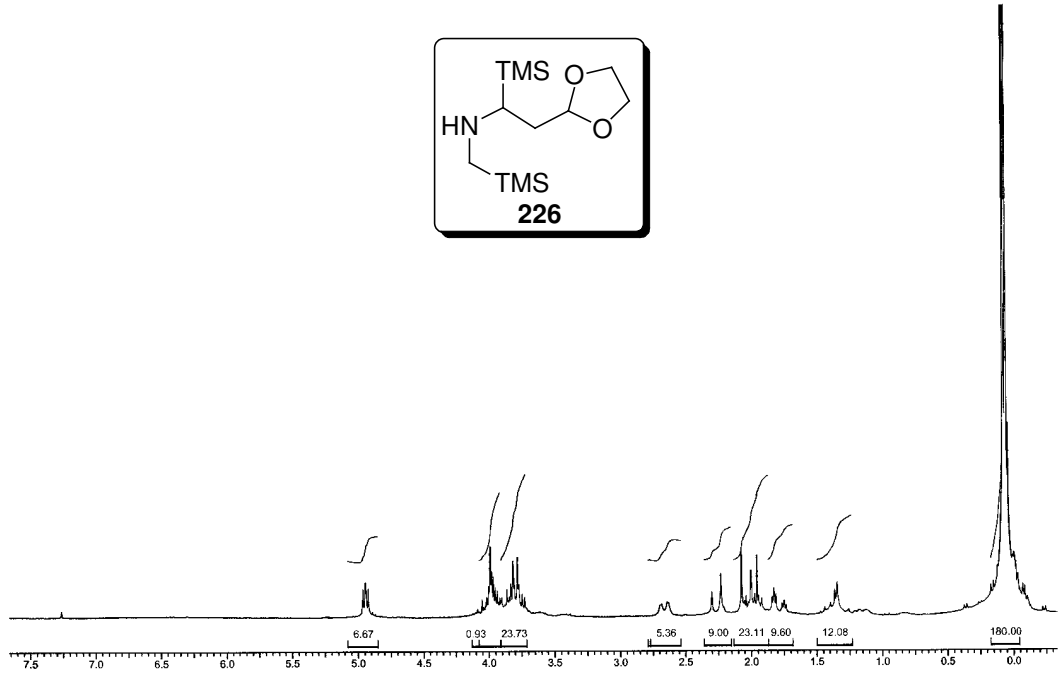
F2 - Acquisition Parameters
Date_ 20050222
Time 0.34
INSTRUM drx500
PROBHD 5 mm QNP 1H/15
PULPROG noesyph
TD 1024
SOLVENT CDCl3
NS 16
DS 16
SWH 3333.333 Hz
FIDRES 3.255208 Hz
AQ 0.1538000 sec
RG 512
DW 150.000 usec
DE 6.00 usec
TE 666.5 K
d0 0.00013789 sec
D1 2.00000000 sec
D8 1.00000000 sec
IN0 0.00030022 sec
MCREST 0.00000000 sec
MCWRK 2.00000000 sec

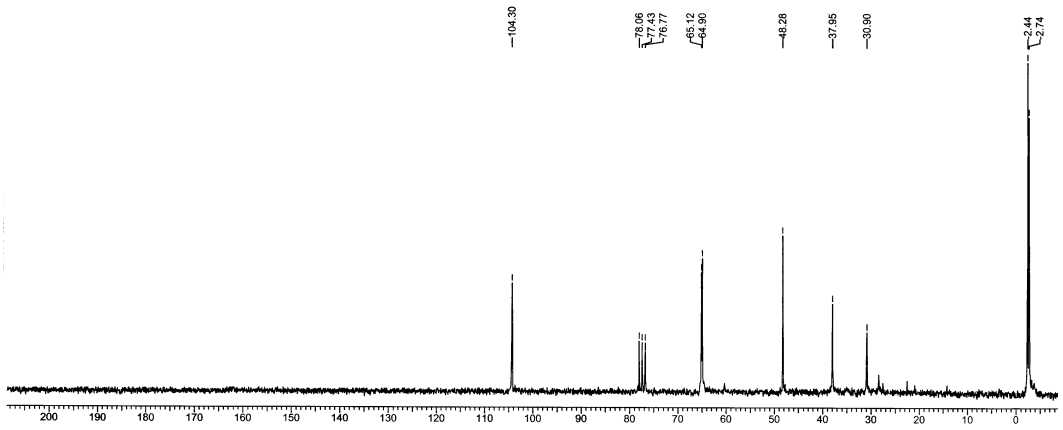
======== CHANNEL f1 ========
NUC1 1H
P1 9.60 usec
PL1 -2.00 dB
SFO1 500.1318910 MHz

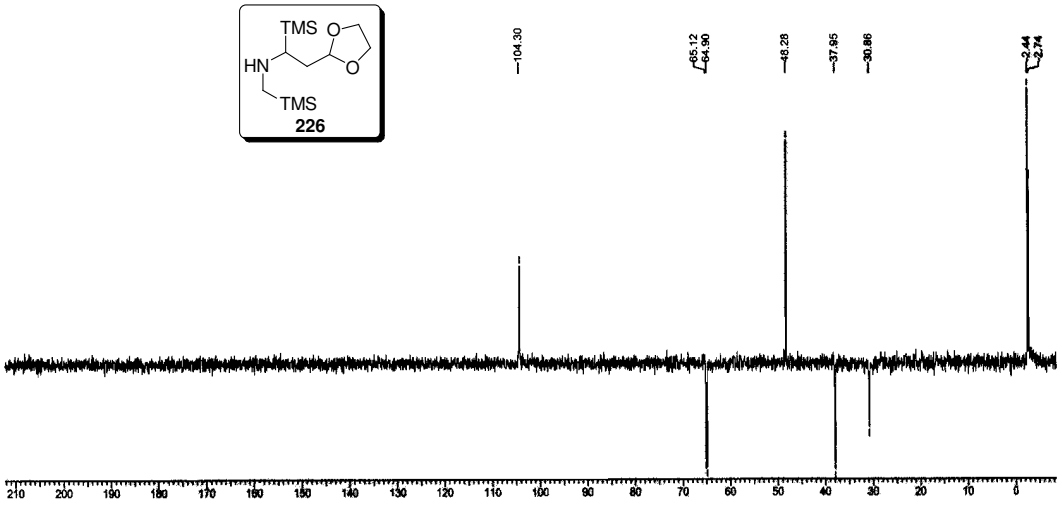
F1 - Acquisition parameters
ND0 1
TD 256
SFO1 500.1319 MHz
FIDRES 13.011075 Hz
SW 6.660 ppm
FnMODE TPPI

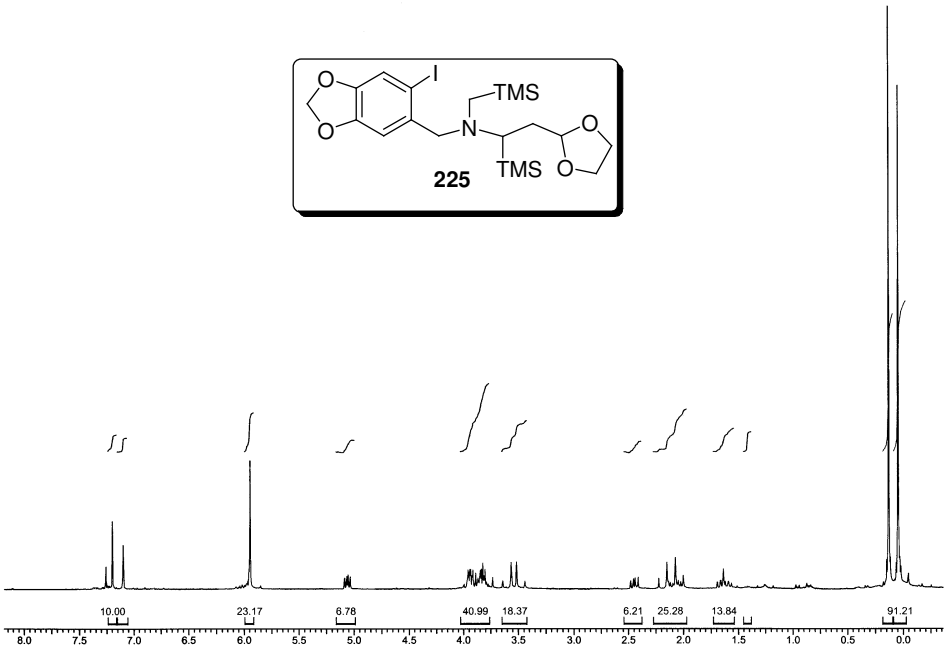
F2 - Processing parameters
SI 1024
SF 500.1300570 MHz
WDW GM
SSB 0
LB -4.00 Hz
GB 0.014
PC 1.40

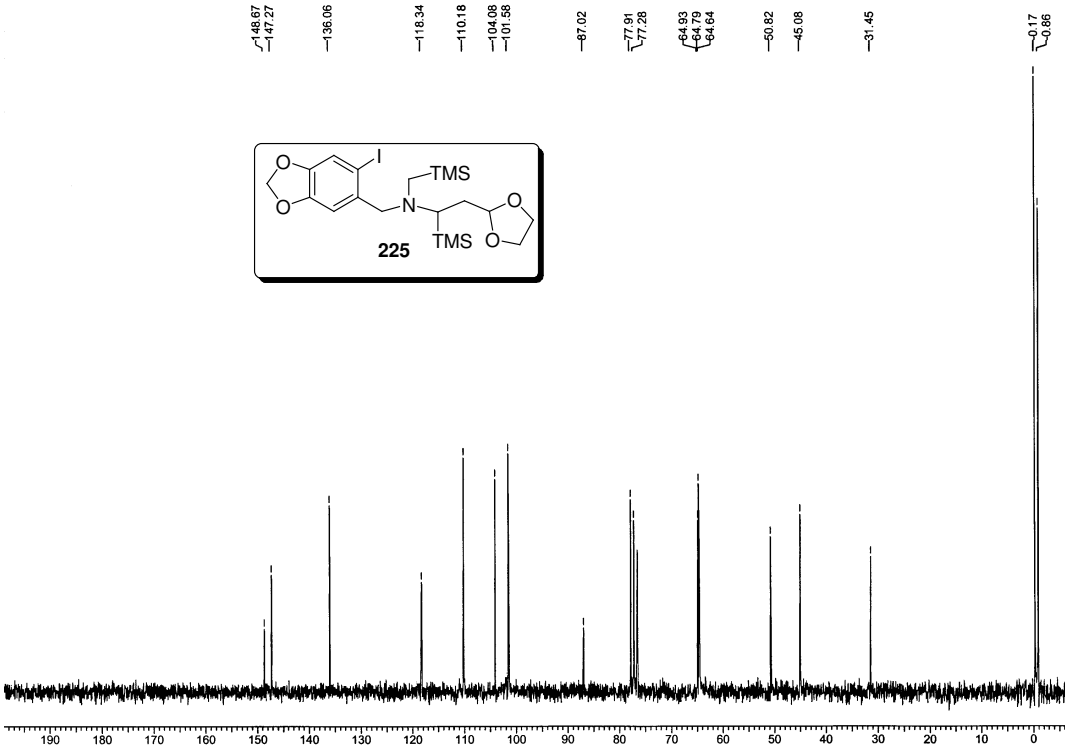
F1 - Processing parameters
SI 1024
MC2 TPPI
SF 500.1300570 MHz
WDW QSINE
SSB 2
LB 0.00 Hz
GB 0

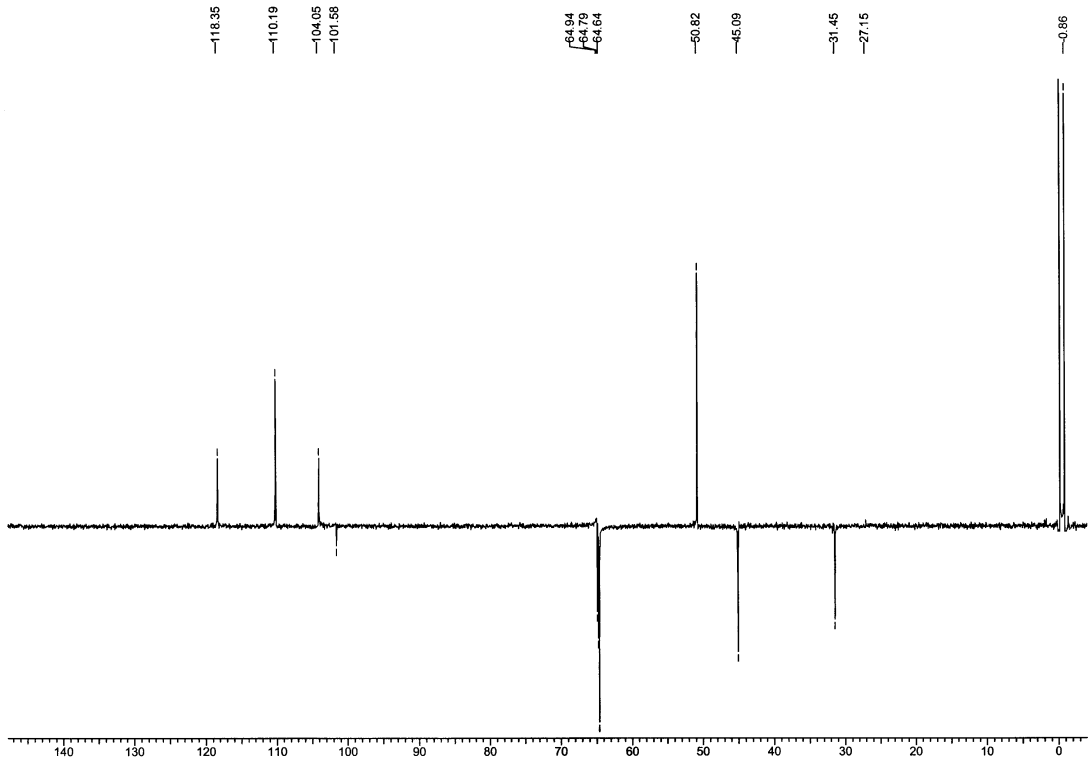

TMS
O
HN
O
TMS
226
6.67
0.93
23.73
5.36
9.00
23.11
9.60
12.08
180.00

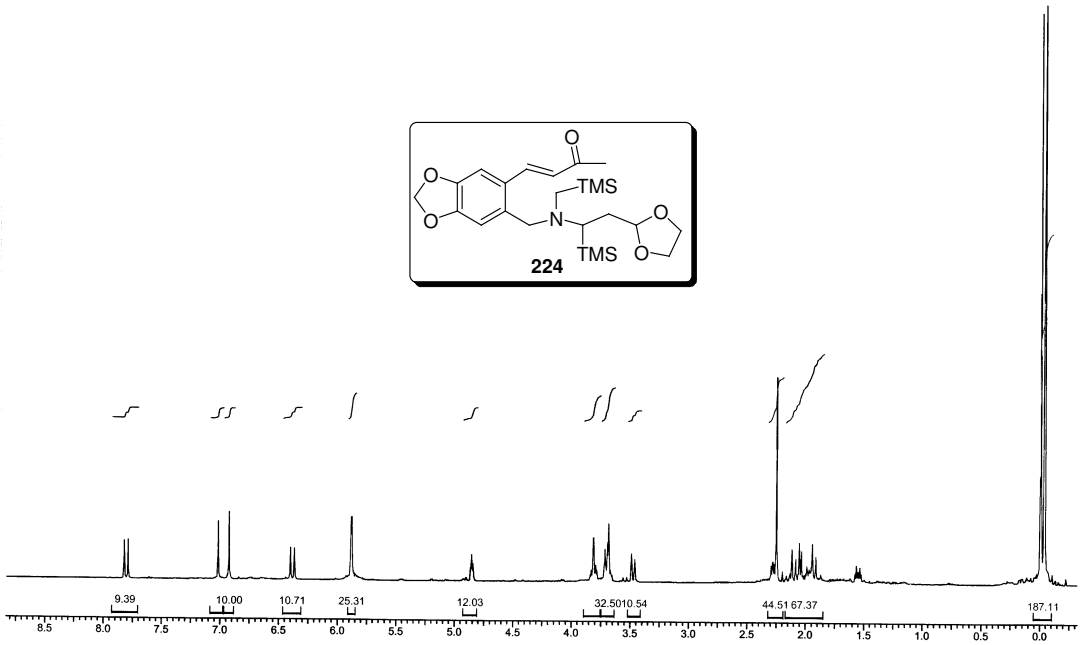

104.30
78.06
77.43
76.77
65.12
64.90
48.28
37.95
30.90
2.44
2.74

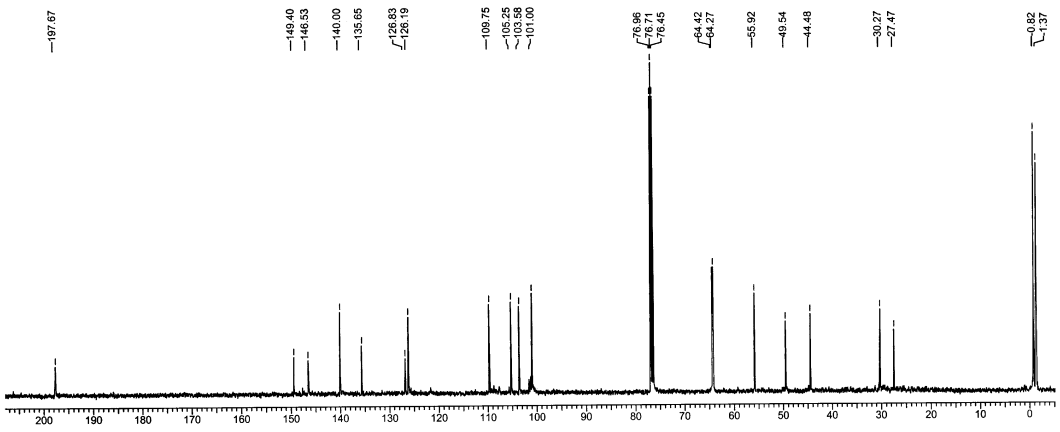

TMS
O
HN
O
TMS
226
104.30
65.12
64.90
48.28
37.95
30.86
2.44
2.74

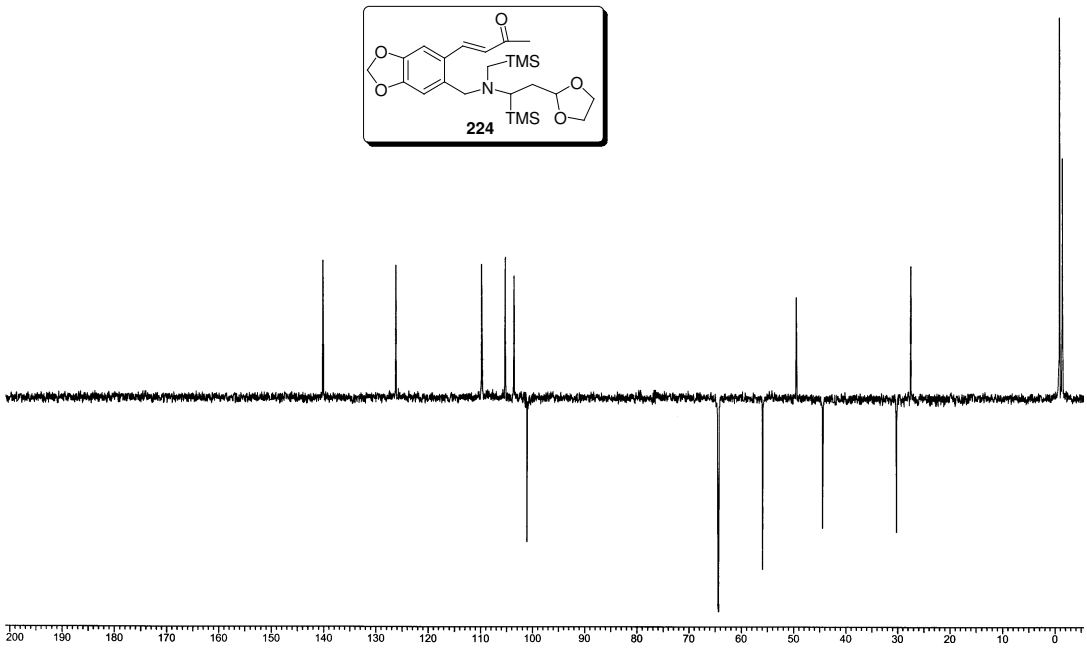

O
O
I
TMS
N
O
TMS
O
225
10.00
23.17
6.78
40.99
18.37
6.21
25.28
13.84
91.21

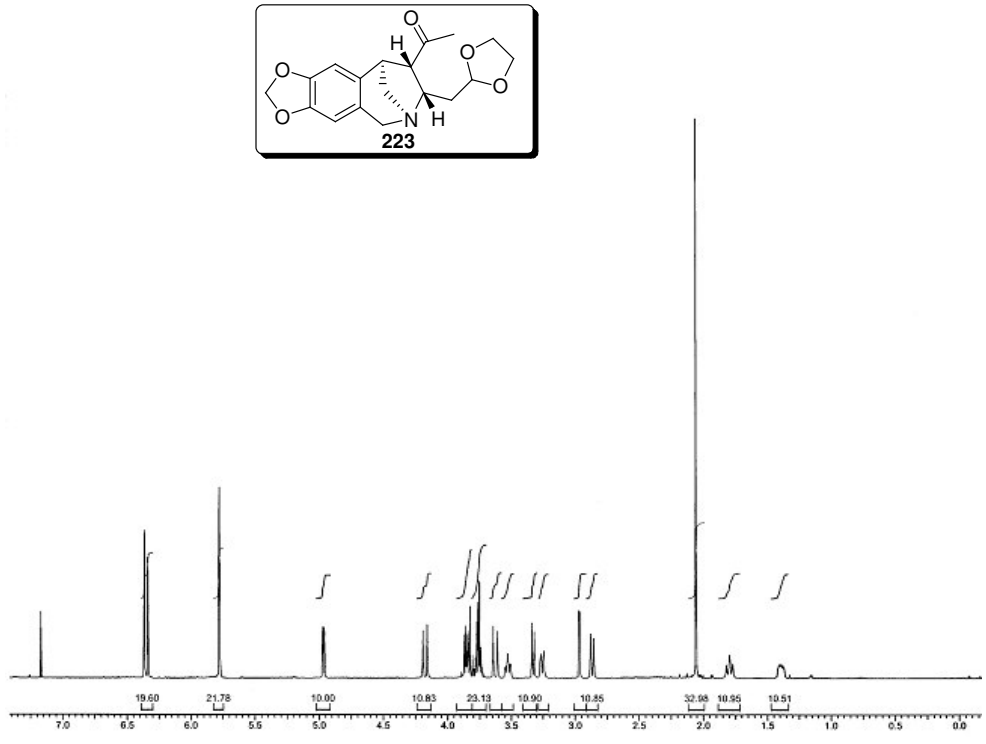

148.67
147.27
136.06
118.34
110.18
104.08
101.58
97.02
77.91
77.28
64.93
64.79
64.64
50.82
45.08
31.45
0.17
0.86
I
TMS
N
TMS
O
O
O
O
225

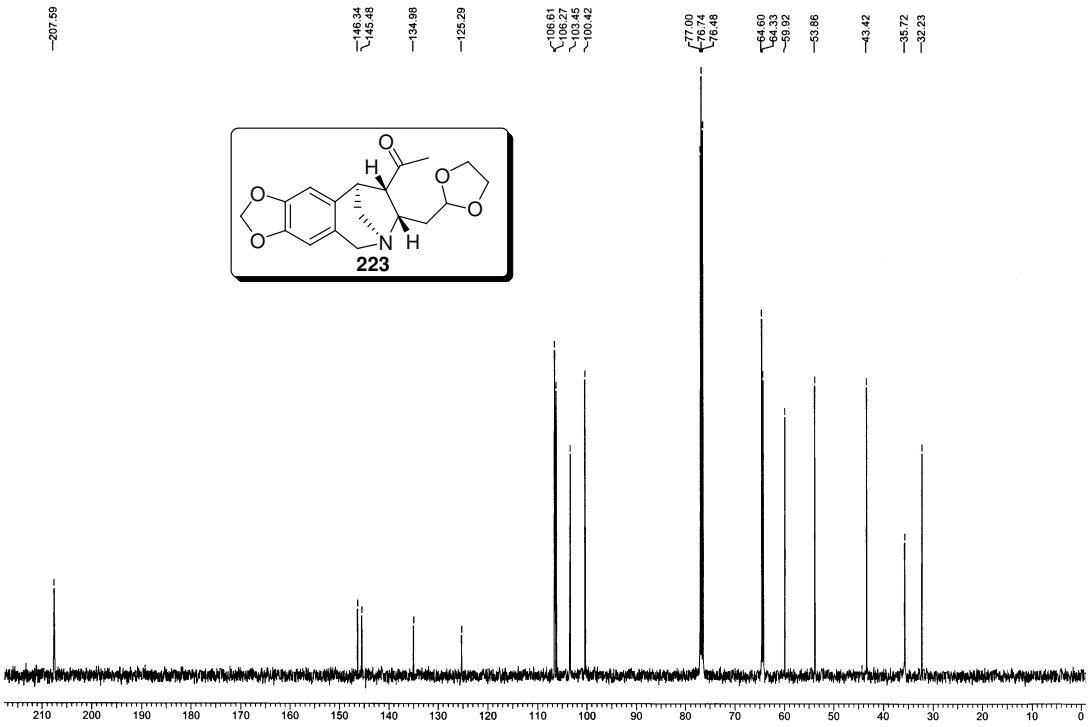

118.35
110.19
104.05
101.58
64.94
64.79
64.64
50.82
45.09
31.45
27.15
0.86

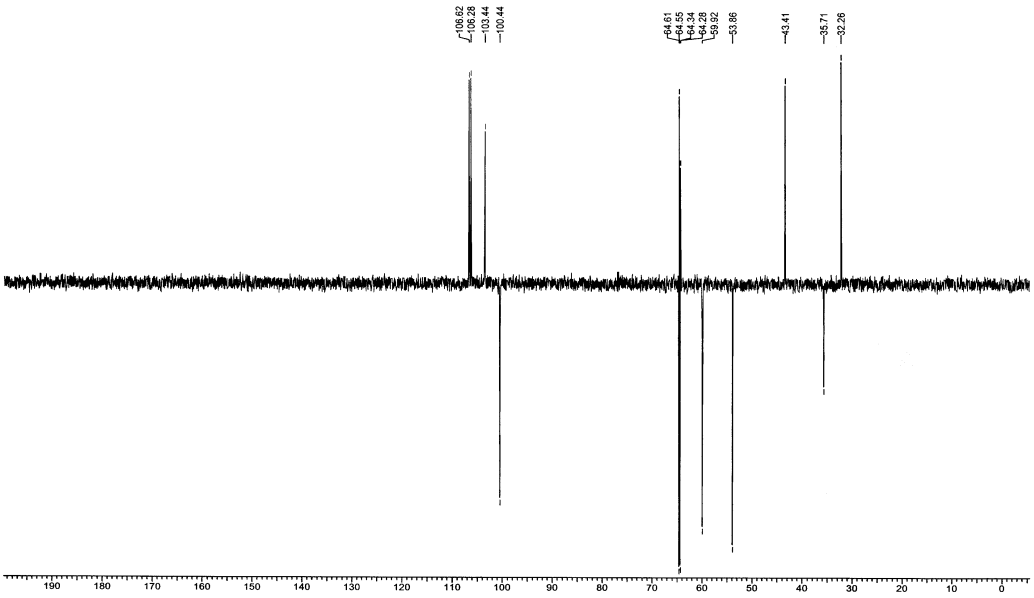

O
O
O
TMS
N
TMS
O
O
224
9.39
10.00
10.71
25.31
12.03
32.50
10.54
44.51
67.37
187.11

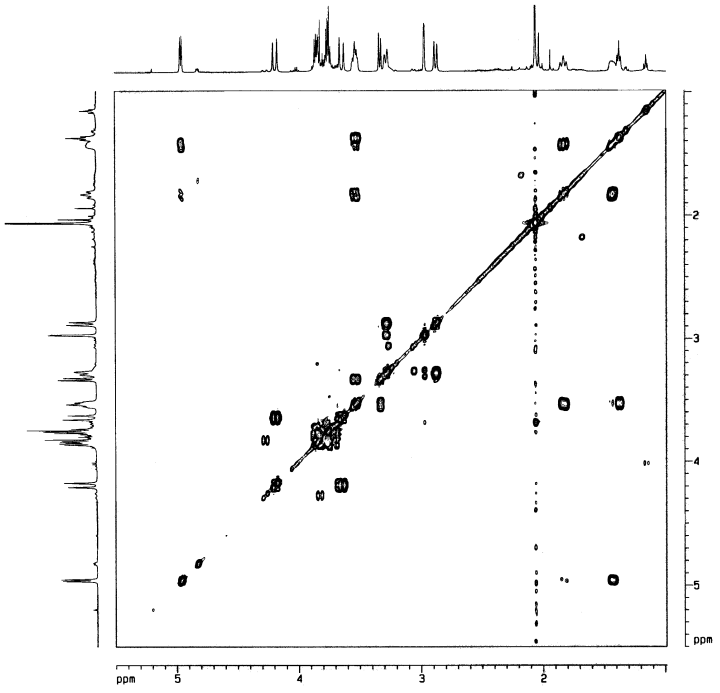

197.67
149.40
146.53
140.00
135.65
126.83
126.19
109.75
105.25
103.58
101.00
76.96
76.71
76.45
64.42
64.27
55.92
49.54
44.48
30.27
27.47
0.82
1.37


O
O
O
TMS
N
TMS
O
O
224
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


O
H
O
O
O
O
N
H
223
19.60
21.78
10.00
10.83
23.13
10.90
10.85
32.98
10.95
10.51
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


207.59
146.34
145.48
134.98
125.29
106.61
106.27
103.45
100.42
77.00
76.74
76.48
64.60
64.33
59.92
53.86
43.42
35.72
32.23
223


106.62
106.28
103.44
100.44
64.61
64.55
64.34
64.28
59.92
53.86
43.41
35.71
32.26



CA New; Cosy45

Current Data Parameters

NAME	Feb_1_04
EXPNO	33
PROCNO	1

F2 - Acquisition Parameters

Date_	20040204
Time	21.07
INSTRUM	drx500
PROBHD	5 mm QNP 1H/
PULPROG	cosy45
TD	1024
SOLVENT	CDCl3
NS	16
DS	16
SWH	3255.208 Hz
FIDRES	3.178914 Hz
AQ	0.1573364 sec
RG	128
DW	153.600 usec
DE	6.00 usec
TE	300.0 K
d0	0.00000300 sec
D1	2.00000000 sec
IN0	0.00030720 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	9.60 usec
PL1	-2.00 dB
SFO1	500.1319000 MHz

F1 - Acquisition parameters

NDO	1
TD	256
SFO1	500.1319 MHz
FIDRES	12.715657 Hz
SW	6.509 ppm

F2 - Processing parameters

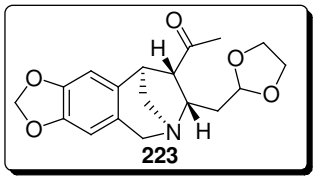
SI	1024
SF	500.1300577 MHz
WDW	QSINE
SSB	10
LB	0.00 Hz
GB	0
PC	1.00

F1 - Processing parameters

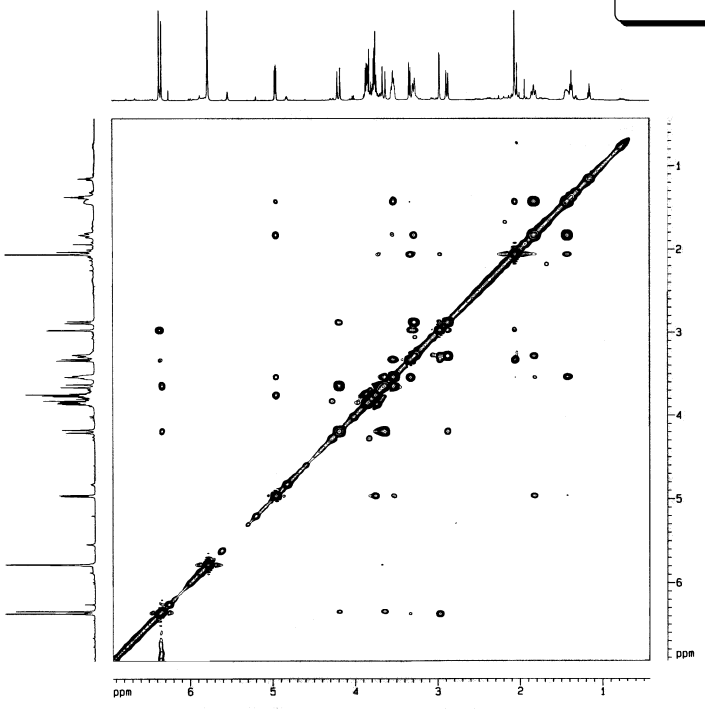
SI	1024
MC2	QF
SF	500.1300577 MHz
WDW	QSINE
SSB	0
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	5.502 ppm
F2LO	2751.47 Hz
F2PHI	0.989 ppm
F2HI	494.44 Hz
F1PLO	5.502 ppm
F1LO	2751.47 Hz
F1PHI	0.989 ppm



223



CA New; NOESY d8= 1S

Current Data Parameters

NAME	Feb_1_04
EXPNO	34
PROCNO	1

F2 - Acquisition Parameters

Date_	20040204
Time	23.38
INSTRUM	drx500
PROBHD	5 mm QNP 1H/
PULPROG	noesyld
TD	1024
SOLVENT	CDCl3
NS	16
DS	16
SWH	3255.208 Hz
FIDRES	3.178914 Hz
AQ	0.1573364 sec
RG	256
DW	153.600 usec
DE	6.00 usec
TE	300.0 K
d0	0.00000300 sec
D1	2.50000000 sec
D8	1.00000000 sec
IN0	0.00015360 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	9.60 usec
PL1	-2.00 dB
SFO1	500.1319000 MHz

F1 - Acquisition parameters

NDO	2
TD	256
SFO1	500.1319 MHz
FIDRES	12.715657 Hz
SW	6.509 ppm

F2 - Processing parameters

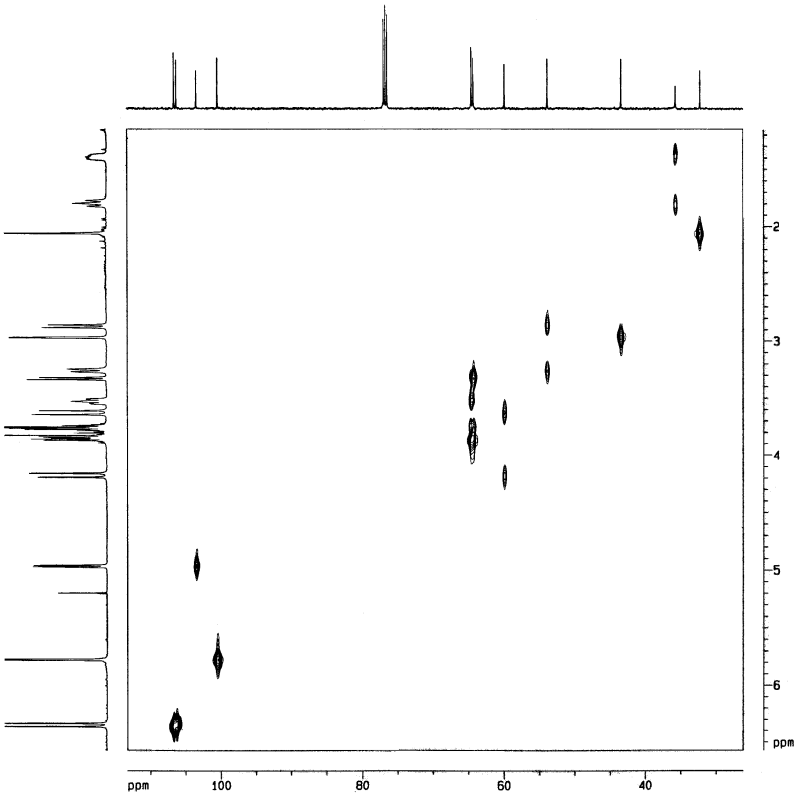
SI	1024
SF	500.1300577 MHz
WDW	GM
SSB	0
LB	-4.00 Hz
GB	0.014
PC	1.00

F1 - Processing parameters

SI	1024
MC2	TPPI
SF	500.1300577 MHz
WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	6.938 ppm
F2LO	3469.90 Hz
F2PHI	0.429 ppm
F2HI	214.70 Hz
F1PLO	6.938 ppm
F1LO	3469.90 Hz
F1PHI	0.429 ppm
F1HI	214.70 Hz
F2PPMCM	0.43391 ppm/cm
F2HZCM	217.01390 Hz/cm
F1PPMCM	0.43391 ppm/cm
F1HZCM	217.01390 Hz/cm



C New; 13C-1H hetcor

Current Data Parameters

NAME	Feb_1_04
EXPNO	156
PROCNO	1

F2 - Acquisition Parameters

Date_	20040214
Time	16.18
INSTRUM	drx500
PROBHD	5 mm BBF in/
PULPROG	hxdept
TD	1024
SOLVENT	CDCl3
NS	32
DS	16
SWH	15151.516 Hz
FIDRES	14.795402 Hz
AQ	0.0338420 sec
RG	32768
DW	33.000 usec
DE	6.00 usec
TE	300.0 K
CNST2	145.0000000
d0	0.00000300 sec
D1	1.79999995 sec
d2	0.00344828 sec
d11	0.03000000 sec
d12	0.00002000 sec
IN0	0.00015869 sec

CHANNEL f1

NUC1	13C
P1	5.95 usec
p2	11.90 usec
PL1	-3.00 dB
SFO1	125.7663998 MHz

CHANNEL f2

CPDPRG2	waltz16
NUC2	1H
P0	4.80 usec
P3	10.00 usec
p4	20.00 usec
PCPD2	80.00 usec
PL2	-2.00 dB
PL12	16.00 dB
SFO2	500.1321430 MHz

F1 - Acquisition parameters

NDO	2
TD	88
SFO1	500.1321 MHz
FIDRES	35.402775 Hz
SW	6.300 ppm

F2 - Processing parameters

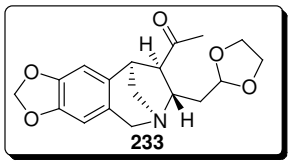
SI	1024
SF	125.7576253 MHz
WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0
PC	1.00

F1 - Processing parameters

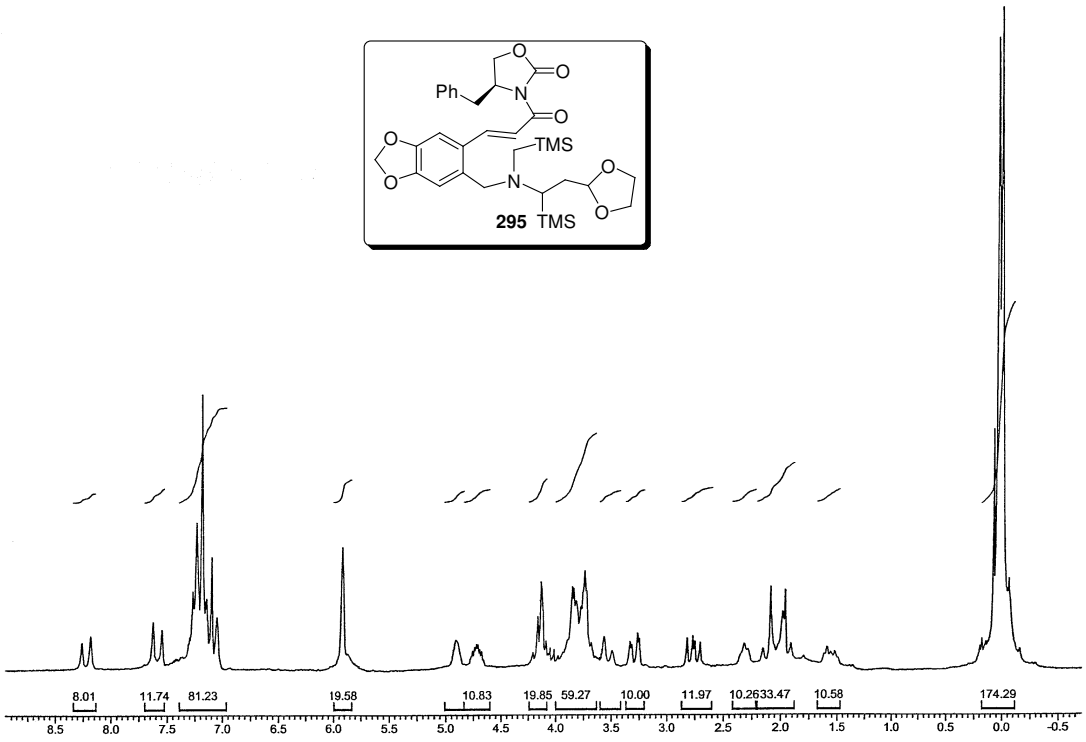
SI	1024
MC2	QF
SF	500.1300576 MHz
WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0

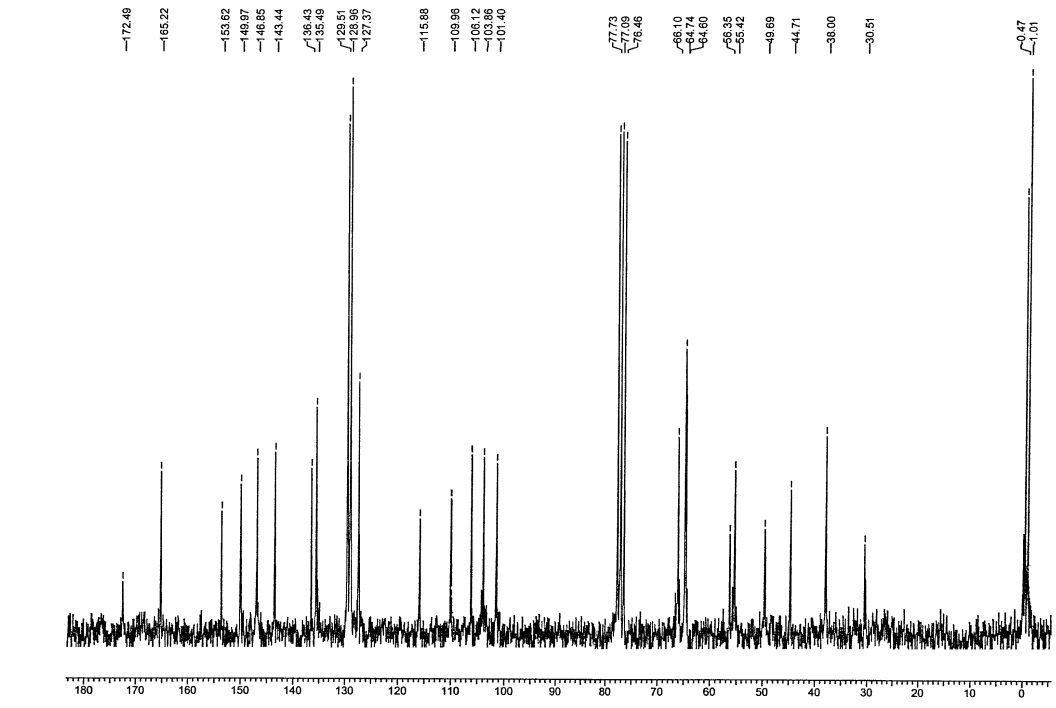
2D NMR plot parameters

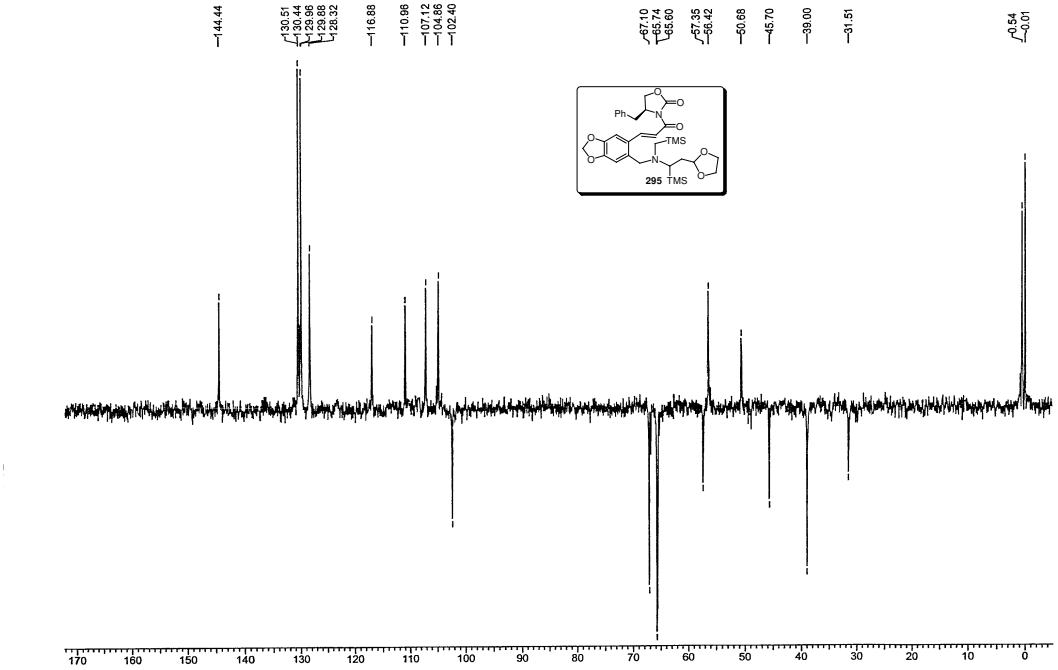
CX2	15.00 cm
CX1	15.00 cm
F2PLO	113.238 ppm
F2LO	14240.72 Hz
F2PHI	26.172 ppm
F2HI	3291.38 Hz
F1PLO	8.575 ppm
F1LO	3288.51 Hz
F1PHI	1.149 ppm
F1HI	574.59 Hz
F2PPMCM	5.90446 ppm/cm
F2HZCM	729.95081 Hz/cm
F1PPMCM	0.36178 ppm/cm
F1HZCM	180.92754 Hz/cm

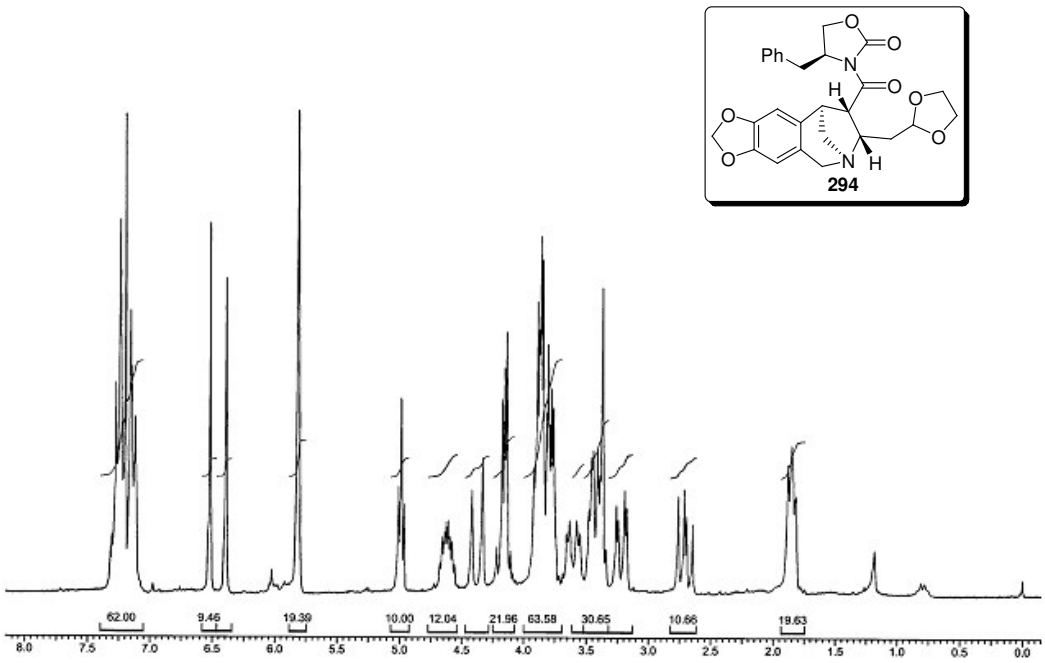


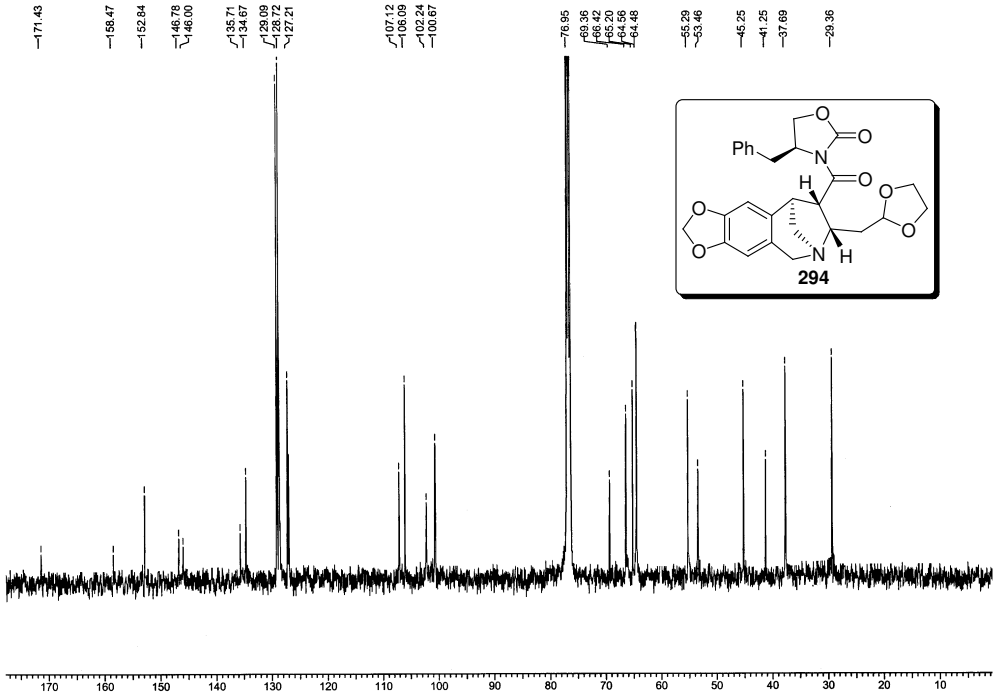
233

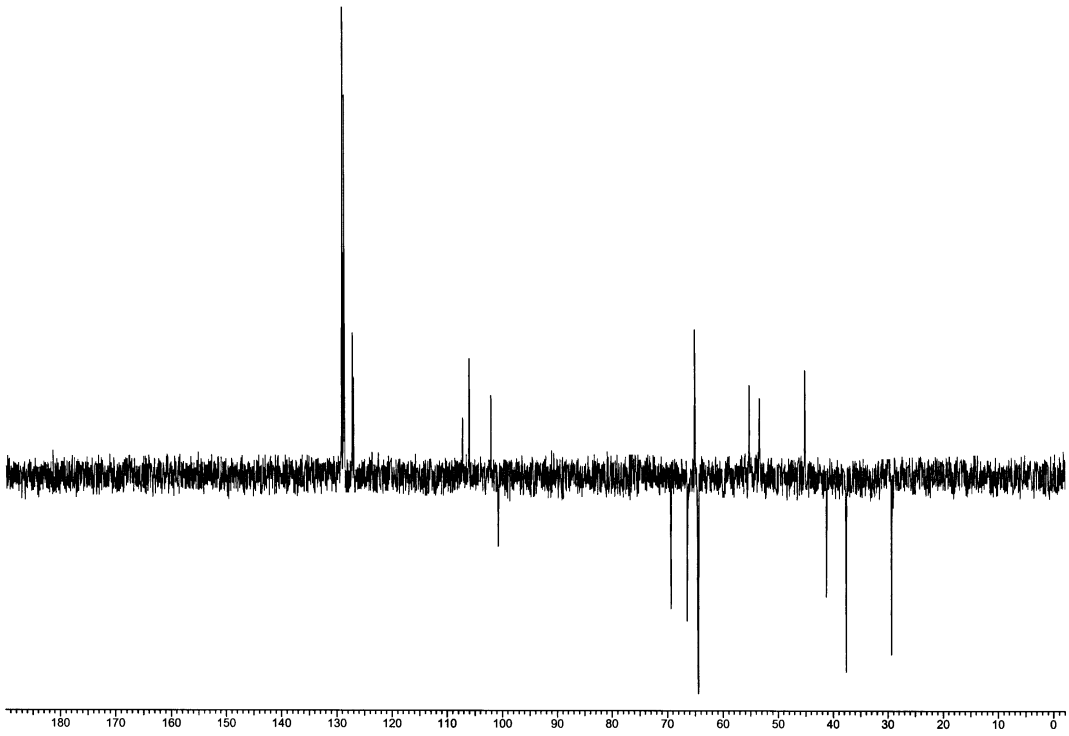

Ph
TMS
TMS
295
8.01
11.74
81.23
19.58
10.83
19.85
59.27
10.00
11.97
10.26
33.47
10.58
174.29


172.49
165.22
153.62
149.97
148.85
143.44
136.43
135.49
129.51
128.96
127.37
115.88
109.96
108.12
103.86
101.40
77.73
77.09
76.46
66.10
64.74
64.60
56.35
55.42
49.69
44.71
38.00
30.51
0.47
-1.01


144.44
130.51
130.44
129.96
129.88
128.32
116.68
110.96
107.12
104.86
102.40
67.10
65.74
65.60
57.35
56.42
50.68
45.70
39.00
31.51
0.54
0.01
Ph
TMS
TMS
295


Ph
H
H
294
62.00
9.46
19.39
10.00
12.04
21.96
63.58
30.65
10.66
19.63


171.43
158.47
152.84
146.78
146.00
135.71
134.67
129.09
128.72
127.21
107.12
106.09
102.24
100.67
76.95
69.36
66.42
65.20
64.56
64.48
55.29
53.46
45.25
41.25
37.69
29.36
Ph
O
N
H
O
O
O
O
O
N
H
294
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

Appendix

1. Crystal data and structure refinement for 217:

Table-1. General

Empirical formula	$C_{16}H_{19}NO_4$
Formula weight	289.32
Temperature	568(2) K
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 5.7666(5) Å α = 98.029(1) deg. b = 9.7162(8) Å β = 100.091(1) deg. c = 13.4268(11)Å χ = 97.602(1) deg.
Volume	723.85(10) $Å^3$
Z, Calculated density	2, 1.327 Mg/m^3
Crystal size	0.40 x 0.38 x 0.13 mm
θ range for data collection	1.56 to 25.00 deg.
Reflections collected / unique	7005 / 2539 [R(int) = 0.0191]
Completeness to θ = 25.00	99.7 %
Goodness-of-fit on F^2	1.039
Final R indices [I>2sigma(I)]	R_1 = 0.0441, wR2 = 0.1167
R indices (all data)	R_1 = 0.0593, wR2 = 0.1254

Table 2. Bond lengths [A] and angles [deg] for 217.

O(1)-C(3)	1.412(2)	N(5)-C(4A)-C(4)	110.61(14)
O(2)-C(1)	1.203(2)	N(5)-C(4A)-C(11A)	107.03(13)
O(3)-C(8)	1.382(2)	C(4)-C(4A)-C(11A)	113.31(14)
O(3)-C(13)	1.422(2)	C(10A)-C(6A)-C(7)	120.39(15)
O(4)-C(9)	1.381(2)	C(10A)-C(6A)-C(6)	119.82(14)
O(4)-C(13)	1.422(2)	C(7)-C(6A)-C(6)	119.78(14)
N(5)-C(6)	1.475(2)	C(8)-C(7)-C(6A)	117.58(15)
N(5)-C(12)	1.477(2)	C(7)-C(8)-C(9)	121.97(15)
N(5)-C(4A)	1.496(2)	C(7)-C(8)-O(3)	128.35(15)
C(1)-C(2)	1.493(3)	C(9)-C(8)-O(3)	109.61(15)
C(1)-C(11A)	1.514(3)	C(10)-C(9)-C(8)	121.87(17)
C(3)-C(4)	1.498(3)	C(10)-C(9)-O(4)	128.32(16)
C(4)-C(4A)	1.518(2)	C(8)-C(9)-O(4)	109.76(15)
C(4A)-C(11A)	1.536(3)	C(9)-C(10)-C(10A)	117.65(16)
C(6)-C(6A)	1.513(2)	C(6A)-C(10A)-C(10)	120.48(15)

C(6A)-C(10A)	1.392(2)	C(6A)-C(10A)-C(11)	118.74(15)
C(6A)-C(7)	1.397(2)	C(10)-C(10A)-C(11)	120.78(15)
C(7)-C(8)	1.361(2)	C(10A)-C(11)-C(12)	108.84(14)
C(8)-C(9)	1.368(2)	C(10A)-C(11)-C(11A)	111.30(13)
C(9)-C(10)	1.361(2)	C(12)-C(11)-C(11A)	98.88(14)
C(10)-C(10A)	1.396(2)	C(1)-C(11A)-C(4A)	115.65(15)
C(10A)-C(11)	1.511(2)	C(1)-C(11A)-C(11)	114.20(15)
C(11)-C(12)	1.515(3)	C(4A)-C(11A)-C(11)	103.13(13)
C(11)-C(11A)	1.552(2	N(5)-C(12)-C(11)	103.35(13)
		O(3)-C(13)-O(4)	107.90(15)

Table 3. Torsion angles [deg] for 217.

O(1)-C(3)-C(4)-C(4A)	179.80(14)	C(13)-O(4)-C(9)-C(8)	10.2(2)
C(6)-N(5)-C(4A)-C(4)	139.46(15)	C(8)-C(9)-C(10)-C(10A)	-1.5(3)
C(12)-N(5)-C(4A)-C(4)	105.30(16)	O(4)-C(9)-C(10)-C(1)	178.46(17)
C(6)-N(5)-C(4A)-C(11A)	96.67(15)	C(7)-C(6A)-C(10A)-C(10)	0.9(2)
C(12)-N(5)-C(4A)-C(11A)	18.57(16)	C(6)-C(6A)-C(10A)-C(10)	179.54(15)
C(3)-C(4)-C(4A)-N(5)	-2.30(19)	C(7)-C(6A)-C(10A)-C(11)	179.60(14)
C(3)-C(4)-C(4A)-C(11)	67.52(15)	C(6)-C(6A)-C(10A)-C(11)	-0.9(2)
C(12)-N(5)-C(6)-C(6A)	45.66(17)	C(9)-C(10)-C(10A)-C(6A)	1.1(3)
C(4A)-N(5)-C(6)-C(6A)	66.83(17)	C(9)-C(10)-C(10A)-C(11)	178.43(15)
N(5)-C(6)-C(6A)-C(10A)	8.1(2)	C(6A)-C(10A)-C(11)-C(12)	30.6(2)
N(5)-C(6)-C(6A)-C(7)	-73.20(13)	C(10)-C(10A)-C(11)-C(12)	149.87(16)
C(10A)-C(6A)-C(7)-C(8)	-2.4(2)	C(6A)-C(10A)-C(11)-C(11)	77.33(19)
C(6)-C(6A)-C(7)-C(8)	78.93(14)	C(10)-C(10A)-C(11)-C(11)	102.18(19)
C(6A)-C(7)-C(8)-C(9)	2.0(2)	O(2)-C(1)-C(11A)-C(4A)	-11.3(3)
C(6A)-C(7)-C(8)-O(3)	178.94(15)	C(2)-C(1)-C(11A)-C(4A)	170.17(15)
C(13)-O(3)-C(8)-C(7	172.65(17)	O(2)-C(1)-C(11A)-C(11)	108.2(2)
C(13)-O(3)-C(8)-C(9)	10.15(19)	C(2)-C(1)-C(11A)-C(11)	-70.3(2)
C(7)-C(8)-C(9)-C(10)	-0.1(3)	N(5)-C(4A)-C(11A)-C(11)	137.11(14)
O(3)-C(8)-C(9)-C(10)	177.50(16)	C(4)-C(4A)-C(11A)-C(1)	100.69(17)
C(7)-C(8)-C(9)-O(4)	177.39(15)	N(5)-C(4A)-C(11A)-C(11)	11.73(16)
O(3)-C(8)-C(9)-O(4)	0.0(2)	C(4)-C(4A)-C(11A)-C(11)	133.93(14)
C(13)-O(4)-C(9)-C(10)	172.55(19)	C(10A)-C(11)-C(11A)-C(1)	-48.3(2)
		C(12)-C(11)-C(11A)-C(1)	162.60(15)

2. Crystal data and structure refinement for 223.

Table 4. General

Empirical formula	$C_{18}H_{21}NO_5$
Formula weight	331.36
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P21/c
Unit cell dimensions	a = 6.5866(6) Å b = 24.702(2) Å β = 100.850(2) deg. c = 10.0072(9) Å
Volume	1599.1(3) $Å^3$

Z, Calculated density	4, 1.376 Mg/m^3
Crystal size	0.43 x 0.32 x 0.28 mm
θ range for data collection	1.65 to 25.00 deg.
Reflections collected / unique	7978 / 2801 [R(int) = 0.0179]
Completeness to θ = 25.00	99.9 %
Goodness-of-fit on F^2	1.040
Final R indices [I>2sigma(I)]	R_1 = 0.0424, wR2 = 0.1070
R indices (all data)	R_1 = 0.0480, wR2 = 0.1109

Table 5. Bond lengths [A] and angles [deg] for 223.

O(1)-C(3)	1.403(2)	C(2)-C(1)-C(11A)	117.60(15)
O(1)-C(14)	1.415(2)	O(2)-C(3)-O(1)	105.19(13)
O(2)-C(3)	1.402(2)	O(2)-C(3)-C(4)	111.70(14)
O(2)-C(15)	1.419(2)	O(1)-C(3)-C(4)	110.71(15)
O(3)-C(8)	1.378(2)	C(3)-C(4)-C(4A)	112.22(13)
O(3)-C(13)	1.426(2)	N(5)-C(4A)-C(4)	109.57(13)
O(4)-C(9)	1.3784(19)	N(5)-C(4A)-C(11A)	106.19(11)
O(4)-C(13)	1.424(2)	C(4)-C(4A)-C(11A)	114.54(12)
O(5)-C(1)	1.202(2)	C(6)-N(5)-C(12)	108.71(12)
C(1)-C(2)	1.485(3)	C(6)-N(5)-C(4A)	112.65(12)
C(1)-C(11A)	1.517(2)	C(12)-N(5)-C(4A)	103.49(12)
C(3)-C(4)	1.501(2)	N(5)-C(6)-C(6A)	115.50(13)
C(4)-C(4A)	1.526(2)	C(10A)-C(6A)-C(7)	120.89(14)
C(4A)-N(5)	1.480(2)	C(10A)-C(6A)-C(6)	119.41(14)
C(4A)-C(11A)	1.591(2)	C(7)-C(6A)-C(6)	119.69(13)
C(4A)-H(4')	0.9800	C(8)-C(7)-C(6A)	117.25(14)
N(5)-C(6)	1.472(2)	C(7)-C(8)-O(3)	127.98(15)
N(5)-C(12)	1.473(2)	C(7)-C(8)-C(9)	121.96(15)
C(6)-C(6A)	1.519(2)	O(3)-C(8)-C(9)	110.06(14)
C(6A)-C(10A)	1.392(2)	C(10)-C(9)-C(8)	122.06(14)
C(6A)-C(7)	1.402(2)	C(10)-C(9)-O(4)	128.18(15)
C(7)-C(8)	1.366(2)	C(8)-C(9)-O(4)	109.76(14)
C(8)-C(9)	1.377(2)	C(9)-C(10)-C(10A)	117.34(14)
C(9)-C(10)	1.365(2)	C(6A)-C(10A)-C(10)	120.50(14)
C(10)-C(10A)	1.405(2)	C(6A)-C(10A)-C(11)	118.24(13)
C(10A)-C(11)	1.508(2)	C(10)-C(10A)-C(11)	121.26(14)
C(11)-C(12)	1.527(2)	C(10A)-C(11)-C(12)	108.60(13)
C(11)-C(11A)	1.541(2)	C(10A)-C(11)-C(11A)	110.41(12)
C(14)-C(15)	1.500(3)	C(12)-C(11)-C(11A)	101.57(12)
C(3)-O(1)-C(14)	106.65(14)	C(1)-C(11A)-C(11)	112.61(13)
C(3)-O(2)-C(15)	105.17(13)	C(1)-C(11A)-C(4A)	114.34(13)
C(8)-O(3)-C(13)	105.50(13)	C(11)-C(11A)-C(4A)	102.51(12)
C(9)-O(4)-C(13)	105.72(13)	N(5)-C(12)-C(11)	102.46(12)
O(5)-C(1)-C(2)	120.30(16)	O(4)-C(13)-O(3)	108.72(13)
O(5)-C(1)-C(11A)	122.08(15)	O(1)-C(14)-C(15)	105.26(15)
		O(2)-C(15)-C(14)	104.15(15)

Table 6. Torsion angles [deg] for 223.

C(15)-O(2)-C(3)-O(1)	37.9(2)	C(7)-C(6A)-C(10A)-C(10)	1.1(2)
C(15)-O(2)-C(3)-C(4)	158.09(17)	C(6)-C(6A)-C(10A)-C(10)	179.92(14)
C(14)-O(1)-C(3)-O(2)	-32.4(2)	C(7)-C(6A)-C(10A)-C(11)	-179.17(14)
C(14)-O(1)-C(3)-C(4)	-153.18(16)	C(6)-C(6A)-C(10A)-C(11)	-0.4(2)
O(2)-C(3)-C(4)-C(4A)	-177.09(14)	C(9)-C(10)-C(10A)-C(6A)	-0.8(2)
O(1)-C(3)-C(4)-C(4A)	-60.23(19)	C(9)-C(10)-C(10A)-C(11)	179.48(14)
C(3)-C(4)-C(4A)-N(5)	-62.98(17)	C(6A)-C(10A)-C(11)-C(12)	33.67(18)
C(3)-C(4)-C(4A)-C(11A)	177.83(13)	C(10)-C(10A)-C(11)-C(12)	-146.62(14)
C(4)-C(4A)-N(5)-C(6)	146.32(13)	C(6A)-C(10A)-C(11)-C(11A)	-76.88(17)
C(11A)-C(4A)-N(5)-C(6)	-89.47(14)	C(10)-C(10A)-C(11)-C(11A)	102.82(16)
C(4)-C(4A)-N(5)-C(12)	-96.45(14)	O(5)-C(1)-C(11A)-C(11)	-28.5(2)
C(11A)-C(4A)-N(5)-C(12)	27.75(14)	C(2)-C(1)-C(11A)-C(11)	149.90(17)
C(12)-N(5)-C(6)-C(6A)	-41.00(18)	O(5)-C(1)-C(11A)-C(4A)	88.0(2)
C(4A)-N(5)-C(6)-C(6A)	73.08(17)	C(2)-C(1)-C(11A)-C(4A)	-93.62(19)
N(5)-C(6)-C(6A)-C(10A)	3.3(2)	C(10A)-C(11)-C(11A)-C(1)	-150.18(13)
N(5)-C(6)-C(6A)-C(7)	-177.91(14)	C(12)-C(11)-C(11A)-C(1)	94.76(14)
C(10A)-C(6A)-C(7)-C(8)	-0.8(2)	C(10A)-C(11)-C(11A)-C(4A)	86.47(14)
C(6)-C(6A)-C(7)-C(8)	-179.61(14)	C(12)-C(11)-C(11A)-C(4A)	-28.59(14)
C(6A)-C(7)-C(8)-O(3)	179.69(16)	N(5)-C(4A)-C(11A)-C(1)	-120.83(14)
C(6A)-C(7)-C(8)-C(9)	0.3(3)	C(4)-C(4A)-C(11A)-C(1)	0.23(19)
C(13)-O(3)-C(8)-C(7)	177.55(17)	N(5)-C(4A)-C(11A)-C(11)	1.35(14)
C(13)-O(3)-C(8)-C(9)	-2.97(19)	C(4)-C(4A)-C(11A)-C(11)	122.41(14)
C(7)-C(8)-C(9)-C(10)	0.0(3)	C(6)-N(5)-C(12)-C(11)	73.15(15)
O(3)-C(8)-C(9)-C(10)	-179.52(15)	C(4A)-N(5)-C(12)-C(11)	-46.81(15)
C(7)-C(8)-C(9)-O(4)	179.57(15)	C(10A)-C(11)-C(12)-N(5)	-69.24(15)
O(3)-C(8)-C(9)-O(4)	0.0(2)	C(11A)-C(11)-C(12)-N(5)	47.15(14)
C(13)-O(4)-C(9)-C(10)	-177.56(17)	C(9)-O(4)-C(13)-O(3)	-4.73(19)
C(13)-O(4)-C(9)-C(8)	2.91(19)	C(8)-O(3)-C(13)-O(4)	4.75(19)
C(8)-C(9)-C(10)-C(10A)	0.3(2)	C(3)-O(1)-C(14)-C(15)	14.3(2)
O(4)-C(9)-C(10)-C(10A)	-179.21(15)	C(3)-O(2)-C(15)-C(14)	-28.1(2)
		O(1)-C(14)-C(15)-O(2)	8.5(2)

3. Crystal data and structure refinement for 233.

Table 7. General

Empirical formula	$C_{18}H_{21}NO_5$
Formula weight	331.36
Temperature	568(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P21/c
Unit cell dimensions	a = 12.0026(11) Å b = 5.7261(5) Å β = 103.928(2) deg. c = 24.210(2) Å
Volume	1615.0(2) $Å^3$
Z, Calculated density	4, 1.363 Mg/m^3

Crystal size	0.32 x 0.15 x 0.06 mm
θ range for data collection	2.74 to 24.99 deg.
Reflections collected / unique	11122 / 2833 [R(int) = 0.0397]
Completeness to θ = 24.99	99.7%
Goodness-of-fit on F^2	1.037
Final R indices [I>2sigma(I)]	R_1 = 0.0522, wR2 = 0.1214
R indices (all data)	R_1 = 0.0863, wR2 = 0.1386

Table 8. Bond lengths [A] and angles [deg] for 233.

N(5)-C(6)	1.463(3)	C(6)-N(5)-C(12)	107.99(19)
N(5)-C(12)	1.470(3)	C(6)-N(5)-C(4A)	112.66(18)
N(5)-C(4A)	1.485(3)	C(12)-N(5)-C(4A)	102.88(18)
C(4A)-C(4)	1.517(3)	N(5)-C(4A)-C(4)	109.40(19)
C(4A)-C(11A)	1.547(3)	N(5)-C(4A)-C(11A)	107.08(17)
C(6A)-C(10A)	1.391(3)	C(10)-C(10A)-C(11)	121.1(2)
C(6A)-C(7)	1.396(3)	C(1)-C(11A)-C(4A)	115.9(2)
C(6A)-C(6)	1.515(3)	C(1)-C(11A)-C(11)	114.2(2)
O(2)-C(3)	1.395(3)	C(4A)-C(11A)-C(11)	103.03(18)
O(2)-C(23)	1.424(3)	C(3)-O(1)-C(22)	107.2(2)
C(10A)-C(10)	1.394(4)	N(5)-C(6)-C(6A)	114.81(19)
C(10A)-C(11)	1.509(3)	C(10A)-C(11)-C(12)	109.2(2)
C(11A)-C(1)	1.510(3)	C(10A)-C(11)-C(11A)	111.43(19)
C(11A)-C(11)	1.551(3)	C(12)-C(11)-C(11A)	98.37(19)
O(1)-C(3)	1.404(3)	O(5)-C(1)-C(2)	121.1(3)
O(1)-C(22)	1.406(3)	O(5)-C(1)-C(11A)	122.9(2)
C(11)-C(12)	1.525(4)	C(2)-C(1)-C(11A)	116.0(2)
C(1)-O(5)	1.206(3)	C(9)-O(4)-C(13)	105.1(2)
C(1)-C(2)	1.496(4)	C(9)-C(10)-C(10A)	117.8(2)
O(4)-C(9)	1.387(3)	C(8)-C(9)-C(10)	122.1(3)
O(4)-C(13)	1.417(4)	C(8)-C(9)-O(4)	109.5(3)
C(10)-C(9)	1.364(4)	C(10)-C(9)-O(4)	128.4(3)
C(9)-C(8)	1.362(4)	O(2)-C(3)-O(1)	106.7(2)
C(3)-C(4)	1.494(3)	O(2)-C(3)-C(4)	111.4(2)
C(7)-C(8)	1.365(4)	O(1)-C(3)-C(4)	111.9(2)
O(3)-C(8)	1.377(3)	C(8)-C(7)-C(6A)	117.9(2)
O(3)-C(13)	1.414(4)	N(5)-C(12)-C(11)	103.26(18)
C(23)-C(22)	1.460(4)	C(8)-O(3)-C(13)	105.1(2)
C(4)-C(4A)-C(11A)	112.14(19)	C(3)-C(4)-C(4A)	113.3(2)
C(10A)-C(6A)-C(7)	120.4(2)	C(9)-C(8)-C(7)	121.5(2)
C(10A)-C(6A)-C(6)	119.6(2)	C(9)-C(8)-O(3)	110.4(2)
C(7)-C(6A)-C(6)	120.0(2)	C(7)-C(8)-O(3)	128.0(3)
C(3)-O(2)-C(23)	106.1(2)	O(2)-C(23)-C(22)	103.9(2)
C(6A)-C(10A)-C(10)	120.3(2)	O(3)-C(13)-O(4)	109.1(3)
C(6A)-C(10A)-C(11)	118.5(2)	O(1)-C(22)-C(23)	107.2(2)

Table 9. Torsion angles [deg] for 233.

C(6)-N(5)-C(4A)-C(4)	143.16(19)	C(10A)-C(10)-C(9)-C(8)	-0.9(4)
C(12)-N(5)-C(4A)-C(4)	-100.8(2)	C(10A)-C(10)-C(9)-O(4)	-179.6(3)
C(6)-N(5)-C(4A)-C(11A)	-95.1(2)	C(13)-O(4)-C(9)-C(8)	5.5(3)
C(12)-N(5)-C(4A)-C(11A)	20.9(2)	C(13)-O(4)-C(9)-C(10)	-175.6(3)
C(7)-C(6A)-C(10A)-C(10)	-0.2(4)	C(23)-O(2)-C(3)-O(1)	30.3(3)
C(6)-C(6A)-C(10A)-C(1)	178.4(2)	C(23)-O(2)-C(3)-C(4)	152.7(2)
C(7)-C(6A)-C(10A)-C(11)	178.0(2)	C(22)-O(1)-C(3)-O(2)	-20.6(3)
C(6)-C(6A)-C(10A)-C(11)	-3.4(3)	C(22)-O(1)-C(3)-C(4)	-142.7(3)
N(5)-C(4A)-C(11A)-C(1)	135.4(2)	C(10A)-C(6A)-C(7)-C(8)	-1.8(4)
C(4)-C(4A)-C(11A)-C(1)	-104.6(2)	C(6)-C(6A)-C(7)-C(8)	179.6(2)
N(5)-C(4A)-C(11A)-C(11)	9.9(2)	C(6)-N(5)-C(12)-C(11)	74.4(2)
C(4)-C(4A)-C(11A)-C(11)	130.0(2)	C(4A)-N(5)-C(12)-C(11)	-44.9(2)
C(12)-N(5)-C(6)-C(6A)	-46.9(3)	C(10A)-C(11)-C(12)-N(5)	-66.1(2)
C(4A)-N(5)-C(6)-C(6A)	66.0(2)	C(11A)-C(11)-C(12)-N(5)	50.1(2)
C(10A)-C(6A)-C(6)-N(5)	10.5(3)	O(2)-C(3)-C(4)-C(4A)	166.8(2)
C(7)-C(6A)-C(6)-N(5)	-170.9(2)	O(1)-C(3)-C(4)-C(4A)	-73.8(3)
C(6A)-C(10A)-C(11)-C(12)	31.6(3)	N(5)-C(4A)-C(4)-C(3)	-69.3(3)
C(10)-C(10A)-C(11)-C(12)	-150.2(2)	C(11A)-C(4A)-C(4)-C(3)	172.0(2)
C(6A)-C(10A)-C(11)-C(11A)	-76.1(3)	C(10)-C(9)-C(8)-C(7)	-1.2(4)
C(10)-C(10A)-C(11)-C(11A)	102.2(3)	O(4)-C(9)-C(8)-C(7)	177.8(3)
C(1)-C(11A)-C(11)-C(10A)	-47.3(3)	C(10)-C(9)-C(8)-O(3)	-179.5(3)
C(4A)-C(11A)-C(11)-C(10A)	79.3(2)	O(4)-C(9)-C(8)-O(3)	-0.5(3)
C(1)-C(11A)-C(11)-C(12)	-161.9(2)	C(6A)-C(7)-C(8)-C(9)	2.5(4)
C(4A)-C(11A)-C(11)-C(12)	-35.3(2)	C(6A)-C(7)-C(8)-O(3)	-179.5(2)
C(4A)-C(11A)-C(1)-O(5)	-9.4(3)	C(13)-O(3)-C(8)-C(9)	-4.7(3)
C(11)-C(11A)-C(1)-O(5)	110.1(3)	C(13)-O(3)-C(8)-C(7)	177.2(3)
C(4A)-C(11A)-C(1)-C(2)	169.9(2)	C(3)-O(2)-C(23)-C(22)	-27.5(3)
C(11)-C(11A)-C(1)-C(2)	-70.5(3)	C(8)-O(3)-C(13)-O(4)	8.1(4)
C(6A)-C(10A)-C(10)-C(9)	1.5(4)	C(9)-O(4)-C(13)-O(3)	-8.4(4)
C(11)-C(10A)-C(10)-C(9)	-176.6(2)	C(3)-O(1)-C(22)-C(23)	3.2(4)
		O(2)-C(23)-C(22)-O(1)	14.9(4)