An Approach towards Synthesis of 2-Alkyl Substituted Tetrahydroquinolines.

Thesis submitted in partial fulfillment of the requirements
for the award of the degree of

Masters of Science
In

Chemistry

Submitted by

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Roll No: -301102008

Under the guidance of

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to the

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INDIA
June 2013

Certificate

This is to certify that the project entitled **"An approach towards synthesis of 2-Alkyl-Substituted Tetrahydroquinolines"** being submitted by Poonam Sharma, Roll no. 301102008 in partial fulfillment of the requirements for the award of degree of Master of Science in School of Chemistry and Biochemistry, Thapar University, Patiala, is a bonafide work carried out under my supervision and guidance. The report has not been submitted for the award of any other degree or certificate in this or any other university.

15.07.2013

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Candidate's Declaration

I hereby declare that the work which is being presented in the dissertation entitled **"An approach towards synthesis of 2-Alkyl-Substituted Tetrahydroquinolines"** in partial fulfillment of the requirements for the award of the degree of master of science in Chemistry, School of Chemistry and Biochemistry, Thapar University, Patiala is an authentic record of my own work during a period of six months from January 2013 to July 2013, under the supervision of Dr. Satyendra Kumar Pandey, Assistant Professor, School of Chemistry and Biochemistry, Thapar University, Patiala. The report has not been submitted for the award of any other degree or certificate in this or any other university.

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Place: Patiala

Poonam Sharma

Date: 15/July/2013

This is to certify that the above statement given by the candidate is correct and true to the best of our knowledge.

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Poonam Sharma

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LIST OF CONTENT

1. Introduction

Approximately forty percent of the world's total population lives in areas where malaria is endemic, although eighty percent of cases occur in with a majority of cases in South-East Asia and South America.[1] Nitrogen-containing heterocycles have been used as medicinal compounds for centuries, and form the basis for many common drugs. Natural products and natural product derivatives have been a good source of new, biologically active compounds for centuries. Plant material has historically been made into teas and tonics for the treatment of ailments by indigenous societies, while nowadays active compounds in Western society are initially isolated from biota and become the basis for synthetic drugs.

Similarly Genus Galipea Aublet is composed of approximately 20 species including *Galipea officinalis* Hancock, a shrub indigenous to the mountains of Venezuela that is known to contain 2-substituted quinoline alkaloids. These alkaloids were formerly used in folk medicine as bitter tonic to treat dyspepsia, dysentery and chronic diarrhoea, and fever[2]. The ethanolic extract from the bark of *G. officinalis*, called angostura, possesses activity against *Mycobacterium tuberculosis*[4]. Recently, the antimalarial and cytotoxic activities of angusturiene **1**, galipeine **2**, cuspareine **3** and galipinine **4** have also been reported (Fig. 1)[3].

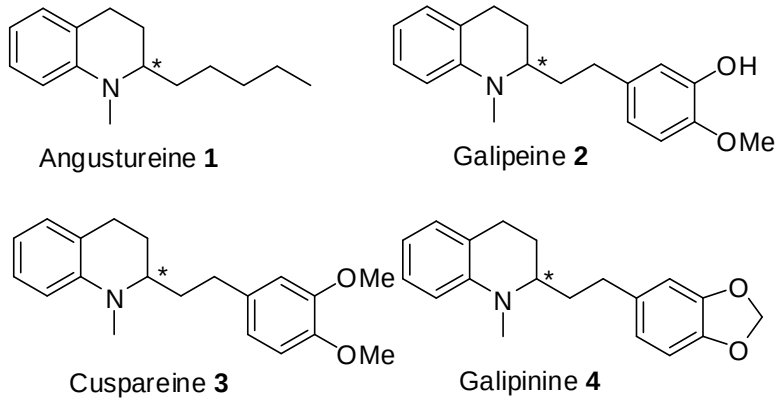


Figure 1: Examples of few naturally occurring tetrahydroquinoline alkaloids.

The unique chemical structure of this series of compounds with an array of functionalities, which contain a tetrahydroquinolines based skeleton, and their significant biological activity such as antimalarial and cytotoxic activities make them a highly attractive target for this study. A novel 2-substituted quinoline alkaloid, angusturiene **1**, was isolated from *Galipea officinalis* Hancock by Jacquemond-Collet *et al.* in 1999.[4] The same plant has

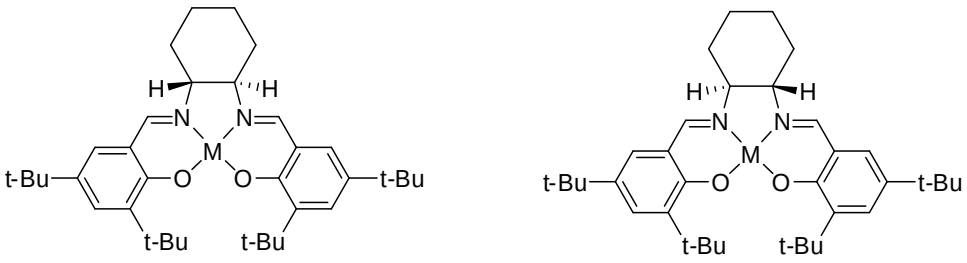
been previously investigated and five quinoline alkaloids have already been reported by Rakotoson *et al.* In 1998.[5]

Herein we wish to propose a protecting group free efficient and versatile synthetic route to the natural products containing 2-alkyl-substituted tetrahydroquinolines using (*R*)-Epichlorohydrin prepared from racemic Epichlorohydrin by Jacobsens HKR as the key step.

Protecting groups are essential in the synthesis of natural products.[6] The fact is that skeleton-building reactions in organic synthesis evolved to use mainly strongly basic reagents such as enolates, Grignard reagents, or organolithium compounds made it almost compulsory to protect hydroxyl and amino groups or carbonyl functions that were not targeted to react. Natural product synthesis with readily available substances and without using protecting groups is challenging. The protecting group introduction and removal lead to loss of material, as quantitative recovery is not possible no matter how efficient the process may be[7]. Hence, at this stage of the methodological development, protecting group-free synthesis is essentially a fantasy[7].

1.1. Hydrolytic Kinetic Resolution (HKR).

Recently Jacobsen discovered the (salen) Co complex **9** (Fig. 2) catalyzed efficient hydrolytic kinetic resolution (HKR) of a variety of terminal epoxides (**Scheme 1)**[8-10]. Since its discovery in the year 1997, HKR has got tremendous application for the synthesis of variety of compounds of biological interest[11]. Our group has recently compiled all the literature reports pertaining to the HKR application and published it in the form of a review article[12]. Racemic 1,2-epoxides are generally available directly from commercial suppliers at low cost or are obtainable in one step from inexpensive olefins or aldehydes.



M=Co: (*R*,*R*)-**9**

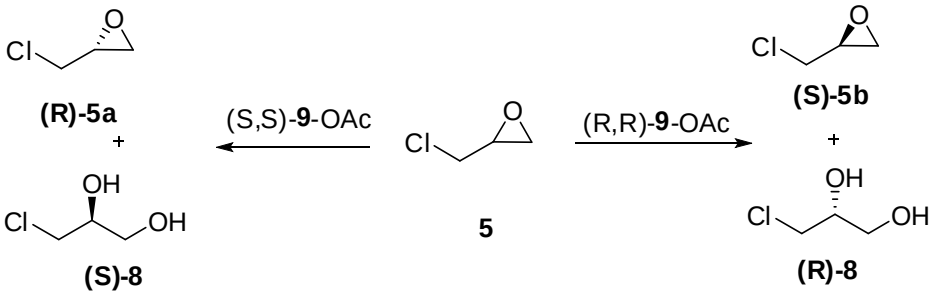
M=Co-OAc :(*R*,*R*)-**9**-OAc

M=Co: (*S*,*S*)-**9**

M=Co-OAc :(*S*,*S*)-**9**-OAc

Figure 2. Jacobsen catalyst.

The HKR has seen rapid adoption as the method of choice for the preparation of a variety of terminal epoxides in enantio-enriched form. The commercial manufacture of enantio-enriched propylene oxide, epichlorohydrin, and styrene oxide using HKR methodology has been implemented, thereby reducing the cost of these useful chiral building blocks. Jacobsen has discovered that the HKR is an extraordinarily general reaction, allowing efficient kinetic resolution of virtually any type of terminal epoxide.

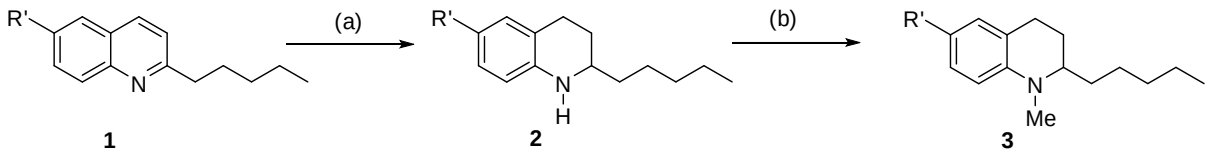


Scheme 1. Hydrolytic kinetic resolution reaction.

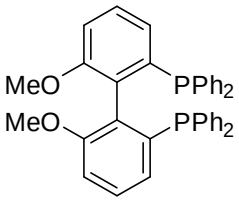
2. Review of literature

Zhou, Y-G. *et al.* (2003)[13]

Yong-gui Zhou and co-workers were reported first to synthesize tetrahydroquinoline derivatives including angustureine by direct hydrogenation of easily available quinoline derivatives **1** using Chiral iridium complex prepared in situ from $[Ir(COD)Cl]_2$ and chiral bisphosphine (*R*)-MeO-Biphep were employed as catalysts, the resulting tetrahydroquinoline **2** was methylated leading to formation of alkaloids **3**.



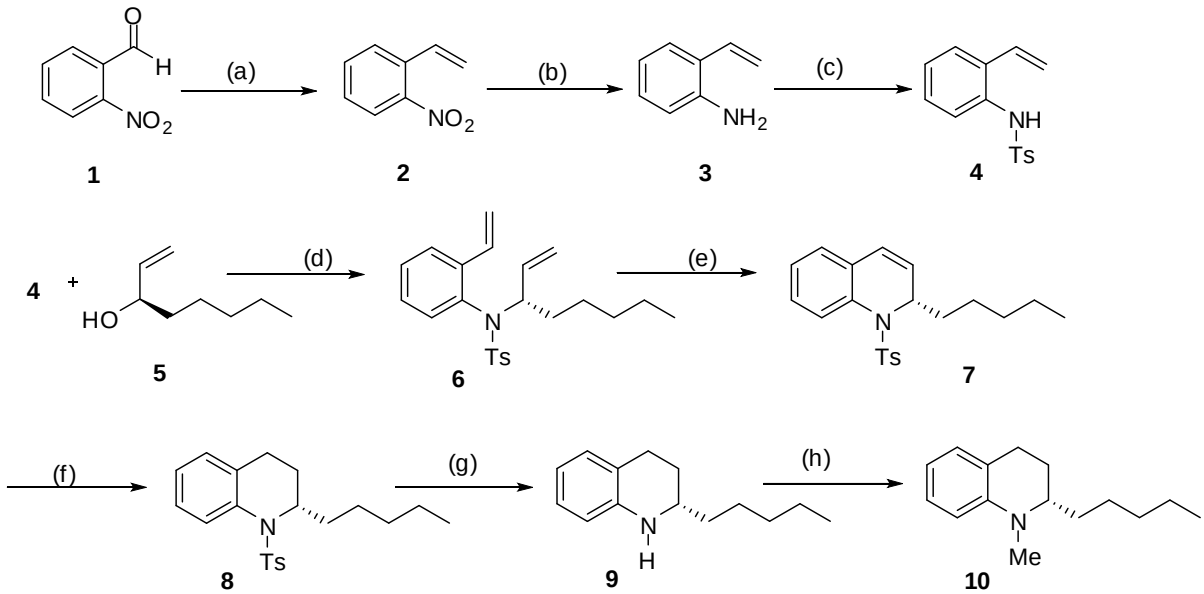
Scheme 2: (a) $[Ir(COD)Cl]_2$, (*R*)-MeO-Biphep **4**, I_2, toluene, H_2, 25°C; (b) HCHO/AcOH, $NaBH_3CN$.



(*R*)-MeO-Biphep **4**

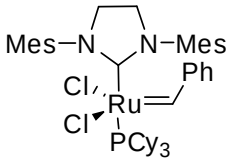
Nishida, A. *et al.* (2005)[14]

Astushi Nishida and co-workers synthesised Angustureine beginning with a Wittig olefination to convert the readily available 2-nitrobenzaldehyde **1** to olefin **2**, subsequent treatment of compound **2** with Zn powder in AcOH gave aniline **3**. Tosylation of the resulting amino group afforded tosylated aniline **4**. The C-2 side chain was installed using the Mitsunobu reaction as the first key step, with the readily available (*R*)- alcohol **5** in the presence of DEAD and PPh_3 to afford the desired α,ω-diene **6**. With substrate **6** in hand, RCM as the second key step gave a 1,2-dihydroquinoline using the second-generation Grubbs catalyst in CH_2Cl_2 (0.01 M) at 50^oC. Next, hydrogenation of dihydroquinoline **5** with PtO_2 catalyst in MeOH under an atmosphere of H_2 gave tetrahydroquinoline **8**, while subsequent detosylation resulted in tetrahydroquinoline **9**. Finally, methylation of the free nitrogen afforded (+)-(*S*)-angustureine **10**.



Scheme 3: (a) Ph_3PMeBr, $KN(TMS)_2$, THF, rt, 1h, 90%; (b) Zn powder, AcOH, rt, overnight, 72%; (c) TsCl, pyridine, CH_2Cl_2, rt, 1h, 86%; (d) DEAD, PPh_3, THF, rt, 2h, 78%;

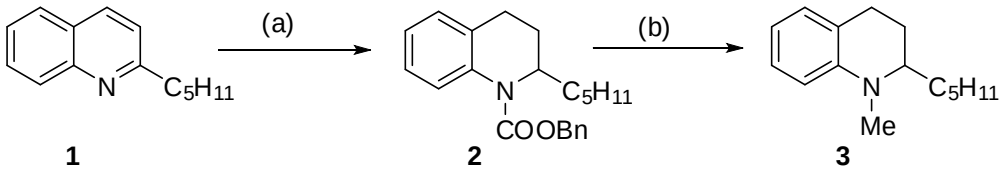
(e) Ru catalyst B, CH_2Cl_2 0.01 M, 50^oC, 1h, 92%; (f) PtO_2, H_2, MeOH, rt, 12h, 94%; (g) Anthracene sodium, DME, -65^0C, 10 min, 99%; (h) MeI, K_2CO_3, THF, reflux, 10h, 80%.



Grubbs catalyst

Zhou, Y-G. *et al.* (2006)[15]

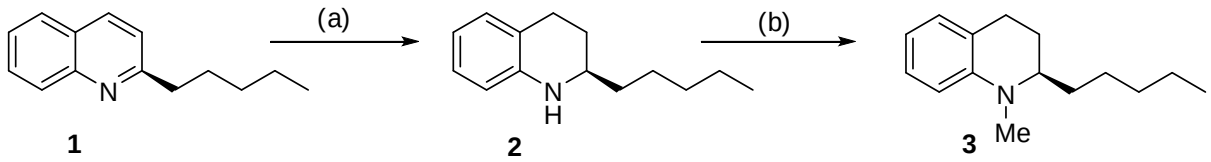
Yong-Gui Zhou and co-workers reported a novel method for synthesis of alkaloids by asymmetric hydrogenation of quinolines activated by chloroformates. Procedure involved hydrogenation of substituted quinoline derivatives under the optimized conditions with the Ir/(S)- segphos/Li_2CO_3/$ClCO_2Bn$/THF catalyst system to get 2-pentyl-3,4-dihydro-quinolin-1-carboxylic acid benzyl ester **2**, subsequent reduction of **2** with $LiAlH_4$ in Et_2O gives the *N*-methylation products angustureine **3** in high yields.



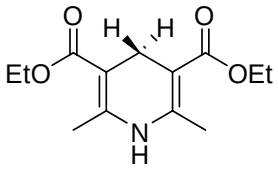
Scheme 4: (a) [{IrCl(cod)}$_2$]/(S)-segphos/Li_2CO_3/$ClCO_2Bn$/THF/H_2 ; (b) $LiAlH_4$, Et_2O.

Rueping, M. *et al.* (2006)[16]

Magnus Rueping and co-workers reported Bronsted acid catalyzed cascade transfer hydrogenation of 2-substituted quinolines **1** under optimized conditions, which were prepared by simple alkylation of 2-methylquinoline, generated the tetrahydroquinoline derivatives **2** with excellent enantioselectivity and subsequent *N*-methylation afforded the desired natural products (-)-angustureine **3** in good overall yields.



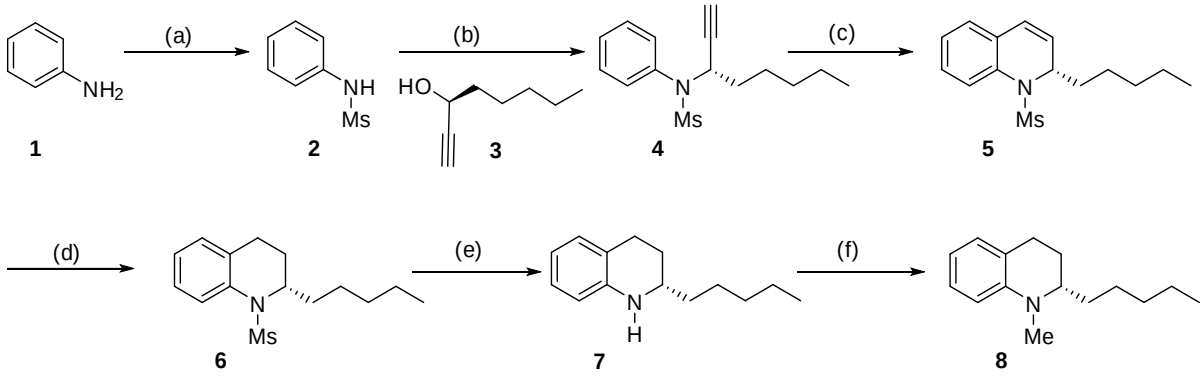
Scheme 5: (a) dihydropyridine **4**; (b) i) HCHO, AcOH; ii) $NaBH_4$.



Dihydropyridine **4**

Ryu, J-S. (2006)[17]

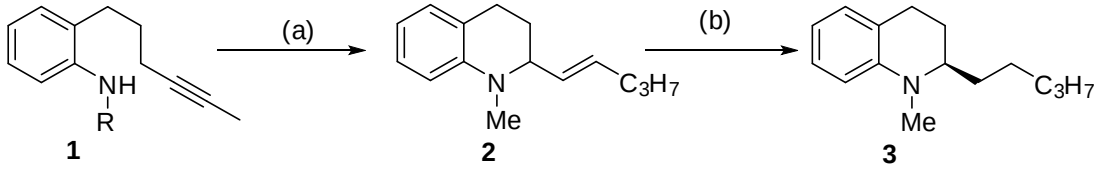
Jae-Sang Ryu reported the synthesis of angustureine using aniline **1** as starting point. The process starts with *N*-methanesulfonyl protection of aniline, followed by Mitsunobu inversion of the (R)-(+)- 1-octyn-3-ol **3** with the resulting methanesulfon-anilide **2** in the presence of DEAD/PPh_3, afforded N-propargylaniline **4**. The Mesyl-NH group served as an efficient nucleophile for Mitsunobu reaction as well as an arene-free protecting group in the next hydroarylation step with $PtCl_4$ resulting in formation of dihydroquinoline **5** followed by its reduction under standard catalytic hydrogenation conditions and removal of Ms protecting group using red-Al in toluene, ultimately affording the tetrahydroquinoline **7**. Finally, *N*-methylation completed the synthesis of (+)-(*S*)-angustureine **8**.



Scheme 6: (a) MsCl, Pyridine, CH_2Cl_2, 0^0C, 1 h, 92%; (b) (*R*)-(+)-1-Octyn-3-ol **3**, DEAD, PPh_3, THF, rt, 1h, 100%; (c) $PtCl_4$, 70^0C; (d) H_2, Pd/C, EtOH, rt, 3h, 85%; (e) Red-Al, toluene, 80^oC, 0.5h, 99%; (f) K_2CO_3, THF, CH_3I, reflux, 24 h, 99%.

Yamamoto, Y. *et al.* (2007)[17]

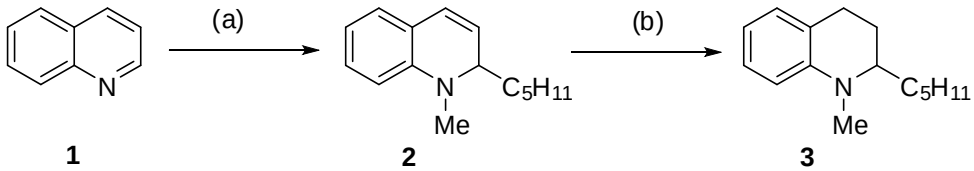
Yoshinori Yamamoto and co-workers have developed a method for the synthesis of 2-substituted tetrahydroquinolines *via* the Pd(0)-catalyzed intramolecular hydroamination of anilino-alkynes **1**. First the anilino-alkyne **1** was treated with $Pd(PPh_3)_4$ (20 mol %)/PhCOOH (50 mol %) in toluene giving the cyclization product **2**, which was in turn subjected to hydrogenation with 10% Pd/C in methanol giving rac-angustureine **3**.



Scheme 7: (a) $Pd(PPh_3)_4$ (20 mol %)/PhCOOH, (*R*,*R*)-RENORPHOS, toluene, 120°C, 4h; (b) H_2, 10% Pd/C, MeOH, 12h.

Evans, P. *et al.* (2008)[19]

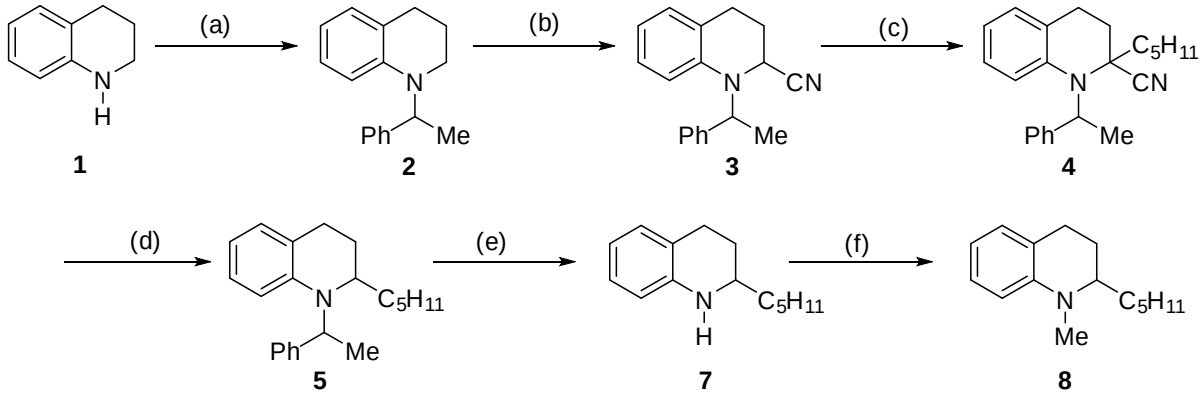
Paul Evans and co-workers reported one-pot method for preparation of Galipea alkaloids. This method featured the treatment of quinoline **1** in THF under nitrogen at 0^oC with organolithium reagent i.e. *N*-pentyllithium, (which was generated from n-pentylbromide and lithium metal in pentane) leading to formation of the 2-substituted anilide, methyliodide was then added, the resultant dihydroquinoline **2** was then converted to Angustureine **3** following palladium-catalysed hydrogenation.



Scheme 8: (a) i) $C_5H_{11}Li$ (1.5-2 equiv.), THF, 0°C; (ii) MeI, 0°C; (b) H_2, Pd/C (10 mol%), EtOH.

Hurvois, J-P. *et al.* (2008)[20]

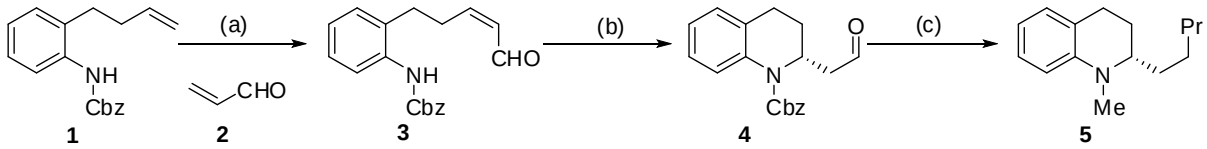
Jean-Pierre Hurvois and co-workers reported a new method for the synthesis of Galipea alkaloids by alkylation of an α-Amino Nitrile **3**. Synthesis began with the condensation of lithiated tetrahydroquinoline with (1-bromoethyl)benzene and obtained 1-(1-phenylethyl)-tetrahydroquinoline **2**, which was dissolved in methanol containing lithium acetate and sodium cyanide and the α-amino nitrile **3** was obtained followed by the addition of LDA and 1-iodopentane led to the rapid formation of **4.** The reductive decyanation of α-amino nitriles **4** consists of the replacement of the cyano group by a hydrogen atom. In the penultimate step, the *N*-benzyl bond in amines **6** was cleaved by catalytic hydrogenolysis in the presence of $Pd(OH)_2$-C in a mixture of methanol and ethyl acetate under hydrogen, and obtained amines **7,** Methylation of the free nitrogen atom of **7** led to the formation of rac-angustureine **8**.



Scheme 9: (a) i) *n*-BuLi, THF; ii) $PhCH_2BrCH_3$; (b)NaCN, MeOH, MeCOOLi; (c) i) LDA,THF; ii) $C_5H_{11}I$; (d) $NaBH_4$, EtOH; (e) $H_2/Pd(OH)_2$-C, MeOH; (f) MeI, K_2CO_3, THF.

Fustero, S. *et al.* **(2008)**[21]

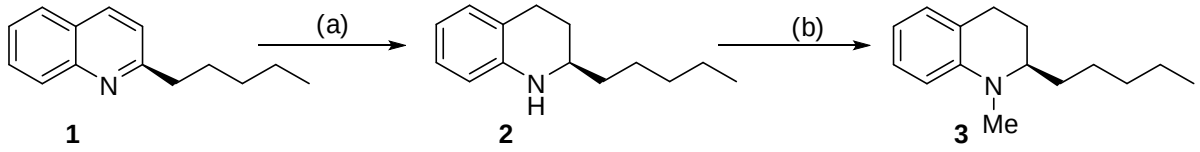
Santos Fustero and co-workers employed intra molecular aza michael reaction (IMAMR) to synthesize Angustureine. Approach started with a cross metathesis (CM) reaction of the terminal alkenylic chain of ortho-substituted N-protected anilines **1** with acrolein **2** to afford the corresponding α,β-unsaturated derivative **3** and subsequent aldehyde reduction gave **4**. Subsequent Wittig reaction with propyltriphenylphosphonium bromide, followed by carbamate reduction with $LiAlH_4$ and palladium-catalyzed hydrogenation, afforded the desired natural product (*S*)-(+)- angustureine **4**.



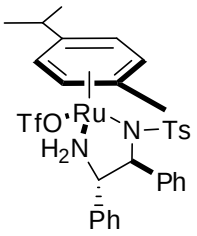
Scheme 10: (a) CH_2Cl_2, $Cl_2(IMes)Ru{=}CH(o\text{-}iPrOC_6H_4)$, 12h; (b) I_2, PhCOOH, $CHCl_3$, -30^oC, 24h; (c) i) Ph_3PPrBr, toluene, $NaN(TMS)_2$; ii) $LiAlH_4$, Et_2O; iii) H_2, Pd/C, EtOAc.

Fan, Q-H. et al. (2009)[22]

Qing-Hua Fan and co-workers carried out hydrogenation of quinolines under solvent-free or highly concentrated conditions. Asymmetric hydrogenation of 2-pentyl substituted quinoline **1** was carried out on a gram scale at a catalyst loading of 0.1 mol%, giving the tetrahydroquinoline derivative **2** in quantitative conversion with 94% ee. Subsequent *N*-methylation of the hydrogenated product afforded the desired natural product (-)-angustureine **3** in 96% overall yield.



Scheme 11: (a) Ru catalyst **I**, 80 atm, H_2, solvent free, 72h; (b) HCHO/AcOH, $NaBH_3CN$.



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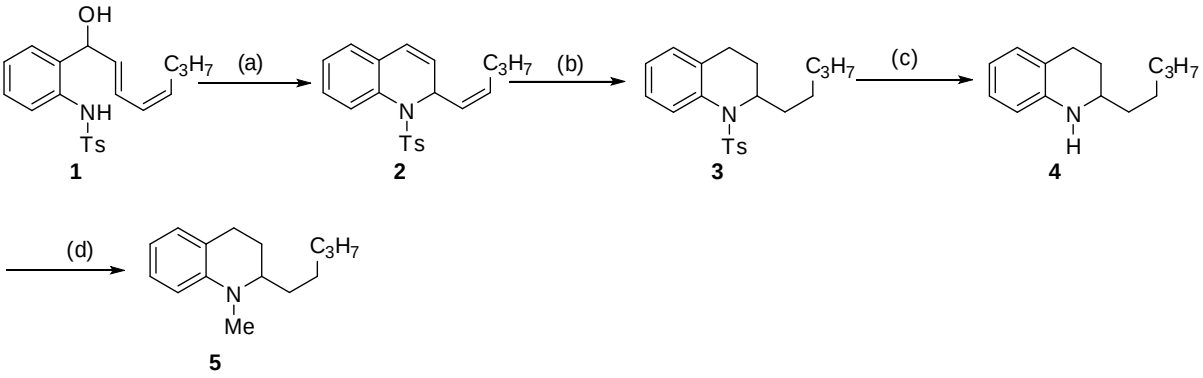
Chan, P. W. H. *et al.* (2009)[23]

Philip Wai Hong Chan and co-workers synthesized tetrahydroquinoline *via* synthetic route that relies on $AuCl_3/AgSbF_6$-catalyzed intramolecular allylic amination of 2-tosylaminophenylprop-1-en-3-ols **1.** Synthesis begins with the treatment of one equiv of 2-

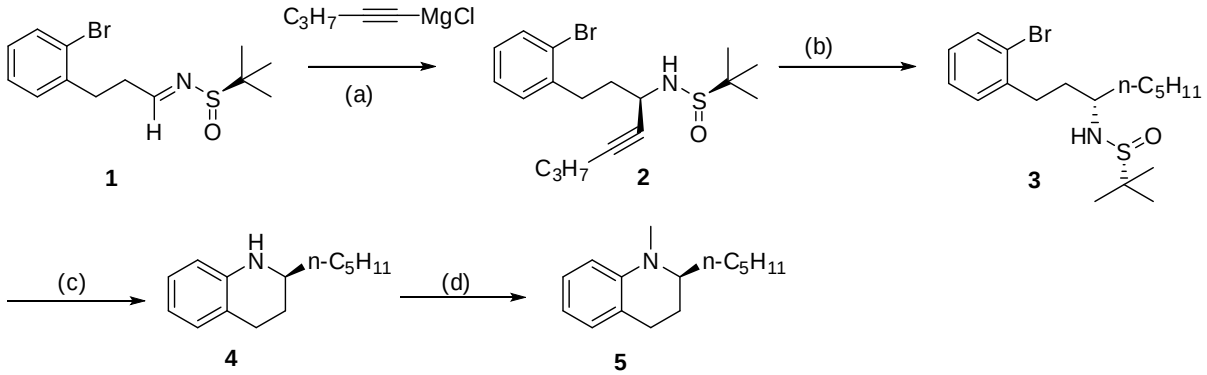
tosylaminophenylprop-1-en-3-ol **1** with 5 mol% of $AuCl_3$ and 15 mol% of $AgSbF_6$ in toluene gave the best result. Under these conditions, 1,2-dihydroquinoline **2** was furnished, Pd/ C-mediated hydrogenation of **2** in MeOH gave the tetrahydroquinoline **3** in 96% yield. Subsequent treatment of this newly formed intermediate with a methanolic solution containing an excess amount of magnesium powder furnished the detosylated tetrahydroquinoline **4** in 98% yield. Finally, *N*-methylation of this adduct with MeI and K_2CO_3 gave (-)-Angustureine **5** in 96% yield.



Scheme 12: (a) $AuCl_3/AgSbF_6$, toluene, 1h; (b) Pd/C, MeOH, 3h; (c) Mg powder, MeOH, 18h; (d) MeI, K_2CO_3, THF, Δ, 12h.

Wang B. *et al.* (2010)[24]

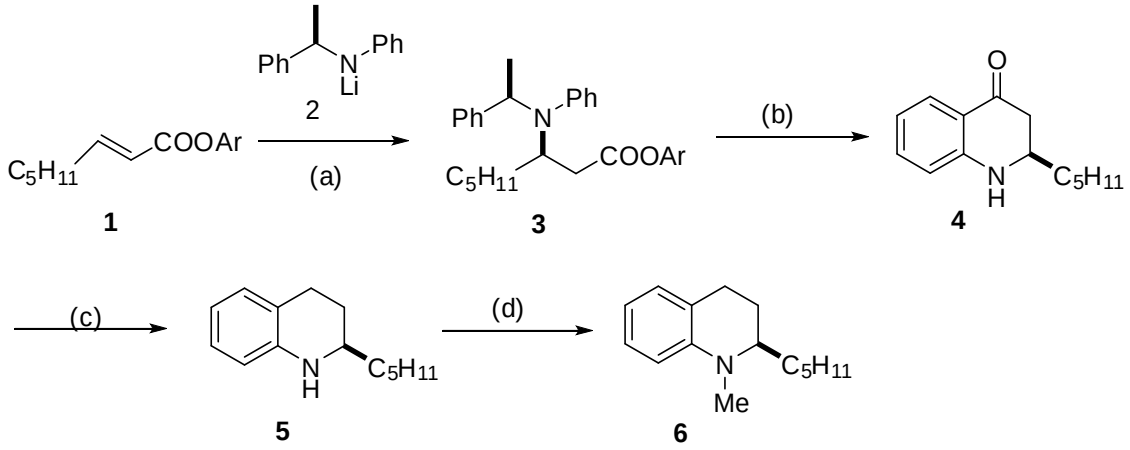
Bing Wang and group synthesized Angustureine by addition of pentynylmagnesium chloride to *N*-*tert*-Butanesulfinyl aldimine **1** to form the adduct **2**. Saturation of triple bond of **2** afforded **3**, which was then subjected to Buchwald-Hartwig amination reaction followed by reductive N-methylation to get (+)-angustureine **5**.



Scheme 13: (a) DCM, -78^{0}C; (b) H_2, cat. PtO_2; (c) cat. $Pd(OAc)_2$, BINAP, Cs_2CO_3, Toluene Reflux; (d) $(CH_2O)_n$, $NaBH_3CN$, MeCN, AcOH.

Davies, S. G. *et al.* (2011)[25]

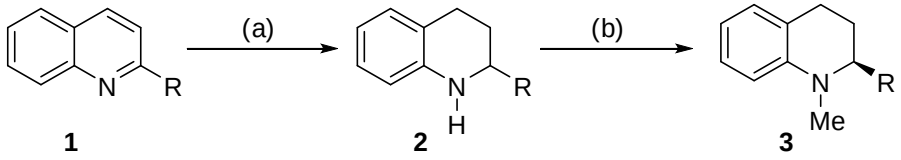
Stephen G. Davies and co-workers reported the synthesis of (*R*)-(-)-angustureine by the application of conjugate addition of lithium *N*-Phenyl-*N*-(α-methylbenzyl)amide **1** to α,β-unsaturated ester **2** under optimal conditions to get corresponding β-amino ester **3** followed by its saponification with aqueous LiOH gave corresponding β-amino acid which upon exposure to PPA, underwent cyclization with loss of an α-methylbenzyl group to give 2-pentyl-2,3-dihydroquinolin-4-one **4** followed by its reduction with $LiAlH_4$ and N-methylation upon reflux in THF in the presence of MeI and K_2CO_3 to give (R)-(-)-angustureine **6**.



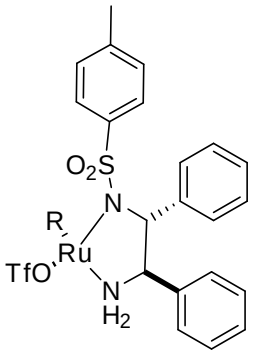
Scheme 14: (a) THF, -78^{o}C, 2h; (b) i) LiOH, THF/H_2O, 40^{o}C, 3h; ii) PPA, 100^{o}C, 16h; **(c)** $LiAlH_4$, THF reflux, 16h; (d) MeI, K_2CO_3, THF, reflux, 16h.

Fan Q-H. and Yu Z-X *et al.* (2011)[26]

Qing-Hua Fan and co-workers synthesized (-)-angustureine by enantioselective hydrogenation of quinolines **1** using phosphinine-free chiral cationic ruthenium catalysts in ionic liquids or under solvent free conditions with unprecedented reactivity and selectivity. Subsequent N-methylation leads to the formation of (-)-angustureine **3**.



Scheme 15: (a) H_2, 0.2 mol% Ru catalyst**,** MeOH, 12-14 h; (b) i) HCHO, CH_3CN; ii) $NaBH_3CN$, AcOH.

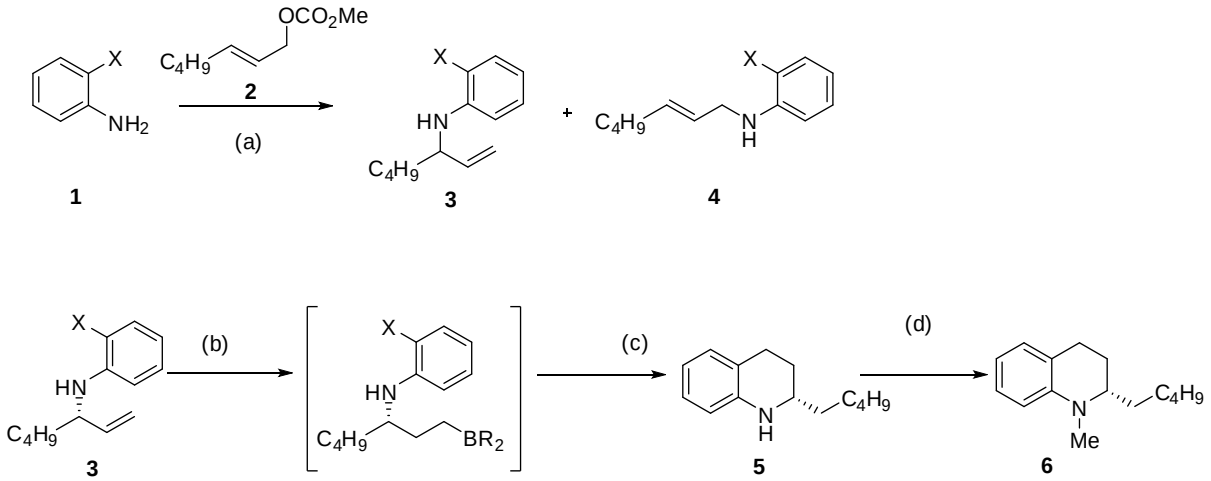


Ru Catalyst

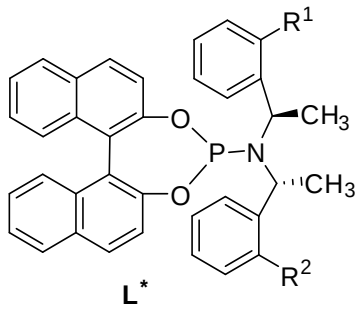
R= hexamethyl benzene

Satyanarayan G. *et al.* (2011)[27]

Gedu Satyananarayan and co-workers synthesized Angustureine using Iridium catalyzed allylic substitutions. (+)-Angustureine was prepared by the reaction between 2-iodoaniline **1** and carbonate **2** under standard conditions to get **3**, which was then treated with 9-BBN in THF and followed by Suzuki-Miyaura coupling and N-Methylation to give (+)-angusturiene **6**.



Scheme 16: (a) [$Ir(COD)Cl]_2$/L*, TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene), dry THF at 50°C; (b) 9-BBN, THF; (c) $Pd(dppf)Cl_2$, $AsPh_3$, Cs_2CO_3, DMF/H_2O, Δ or μw; (d) $(CH_2O)n$/AcOH, $Na(CN)BH_3$, CH_3CN.



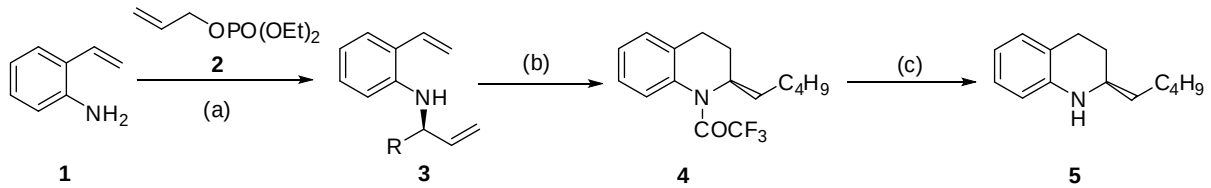
L*

L^1 : $R^1 = R^2 = H$
L^2 : $R^1 = R^2 = OMe$
L^3 : $R^1 = H$; $R^2 = OMe$

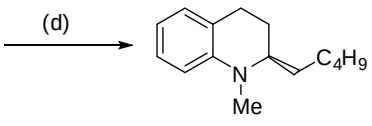
Ligand used for allylic amination

Shu-li You *et al.* (2011)[28]

Shu-li You and co-workers employed Ir-catalyzed reactions of allyl diethyl phosphates with o- aminostyrene derivatives **1** proceeding via an allylic amination pathway. A subsequent ring-closing metathesis (RCM) reaction of the amination products led to a series of enantiomerically enriched 1,2-dihydroquinoline derivatives **4**. Subsequent catalytic hydrogenation followed by methylation leads to highly enantioenriched tetrahydroquinolines, in particular (-)-angustureine **6**.



1 **3** **4** **5**

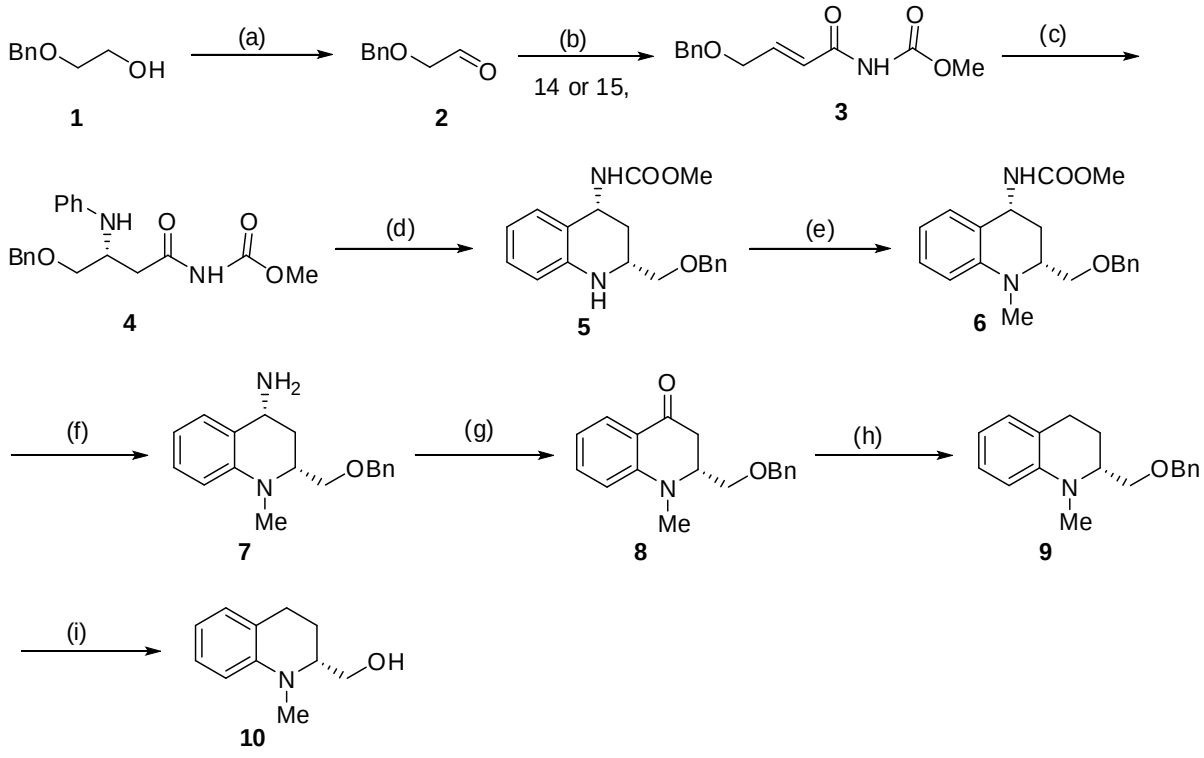


6

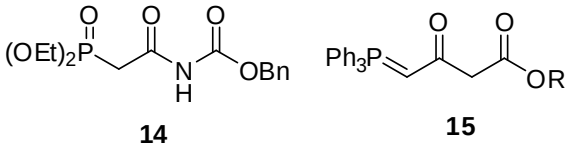
Scheme 17: (a) $[Ir(dbcot)Cl]_2$(2mol%), Ligand 7 (4mol%), K_3PO_4 (110 mol%), THF, 50°C, (b) i) TFAA, Et_3N, CH_2Cl_2, 0°C to rt; ii) Zhan-1 B(2mol%), toluene, 80°C, (c) i) Pd/C(10 mol%), MeOH, H_2, rt; ii) K_2CO_3, 50°C, MeOH/H_2O, (d) K_2CO_3, MeI, THF, reflux.

Hii, K. K. *et al.* (2012)[29]

King Kuok Hii and co-workers synthesized Galipea alkaloids by preparing an optically active tetrahydroquinoline intermediate from monoprotected ethylene glycol **1**, using a Pd-catalysed Aza-Michael reaction to form key intermediate **3**, which is then transformed into three galipea alkaloids. The process (Scheme 18) involved preparation of Michael acceptor from *O*-protected ethylene glycol **1** by its oxidation under Swern conditions to form protected beta-hydroxy aldehydes **2** which was further subjected to one pot oxidation-olefination procedure by using DMP as oxidant and phosphonium ylides **14** to form Michael acceptor **3**, which in turn was subjected to Aza- Michael reaction with aniline to form adduct **4**. The formation of heterocycles was achieved by reductive cyclization of **4** to form 4-amino-2-substituted tetrahydroquinoline **5**, followed by methylation at N-1 and deprotection of N-2 to form compound **7**, which was subjected to transamination to form 4-keto derivative **8**, followed by reduction to get key intermediate **9**, which was hydrogenated to form tetrahydroquinoline **10**. Finally, **10** was transformed into the galipea alkaloids by a sequence of oxidation-wittig-reduction reactions (Scheme 19).

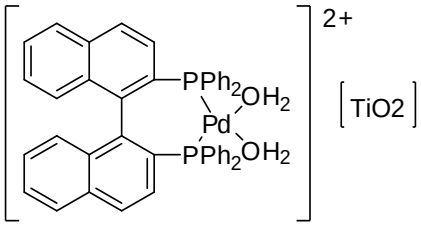


Scheme 18: (a) Swern, (b) phosphinium ylides 14/15&base, (c) cat.16, $PhNH_2$, Toluene, (d) $MgCl_2$, $NaBH_4$, EtOH-THF, -10^0C, 87%, (e) HCHO, $NaCNBH_3$, AcOH, CH_3CN, 0^0C, (f) TMSI, CH_3CN, (g) 4-formyl-1-methylpyridinium benzenesulfonate, DBU, DCM-DMF, (h) $LiAlH_4$, $AlCl_3$, THF, (i) RANEY Ni, H_2, EtOH-THF, reflux.

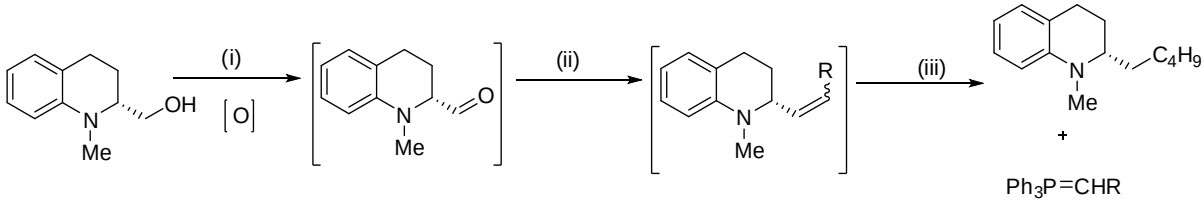


14

15



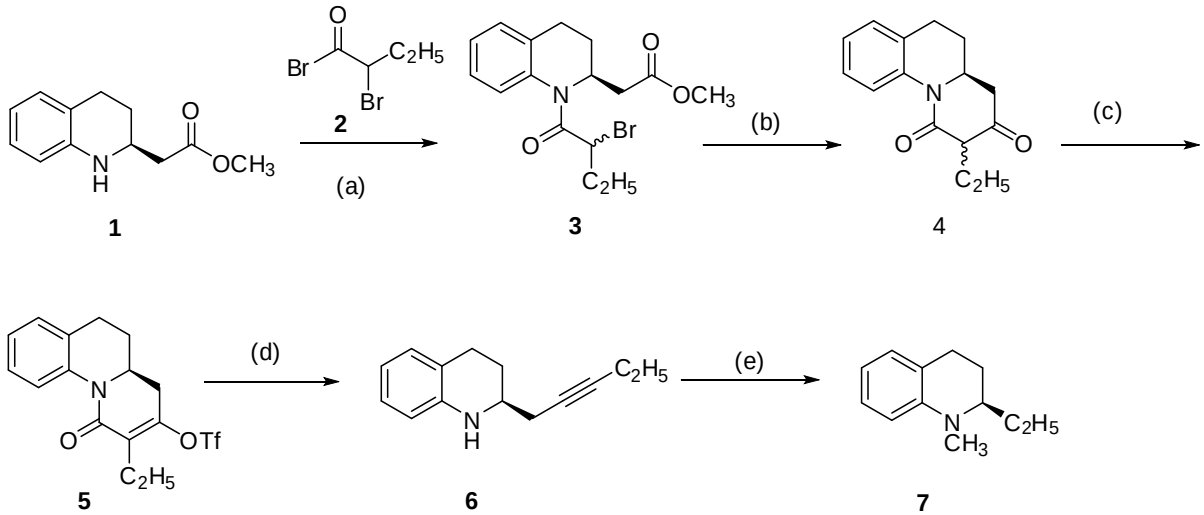
Cat 16



Scheme 19: (i) Oxidation, (ii) Wittig reaction, Ph_3PCHR, (iii) Reduction, Pd/C, H_2.

Dudley, G. B. *et al.* (2013)[30]

Gregory B. Dudley and co-workers synthesized (-)-angustureine **7** by formal alkynylation of a chiral β-amino ester **1**. The synthesis begins with three step annulation sequence to dihydropyridone(DHPD) triflate **5**, followed by a domino sequence in which addition, fragmentation, and deacylation are all accomplished under a unified set of conditions. DHDP triflate **5** was subjected to 3.0 equiv. of methyllitium yielded amine **6**, the remaining two functional group manipulations i.e hydrogenation using Pd on carbon and methylation leads to formation of (-)-angustureine **7**.



1 **3** 4 **5** **6** **7**

Scheme 20: (a) DMAP, CH_2Cl_2, 60^0C; (b) t-BuMgCl, THF, 60^0C; (c) Tf_2O, Et_3N, CH_2Cl_2, -78 ^0C; (d) MeLi, $PhCH_3$; (e) H_2, 5% Pd/C, CH_2Cl_2; CH_3I, K_2CO_3, acetone.

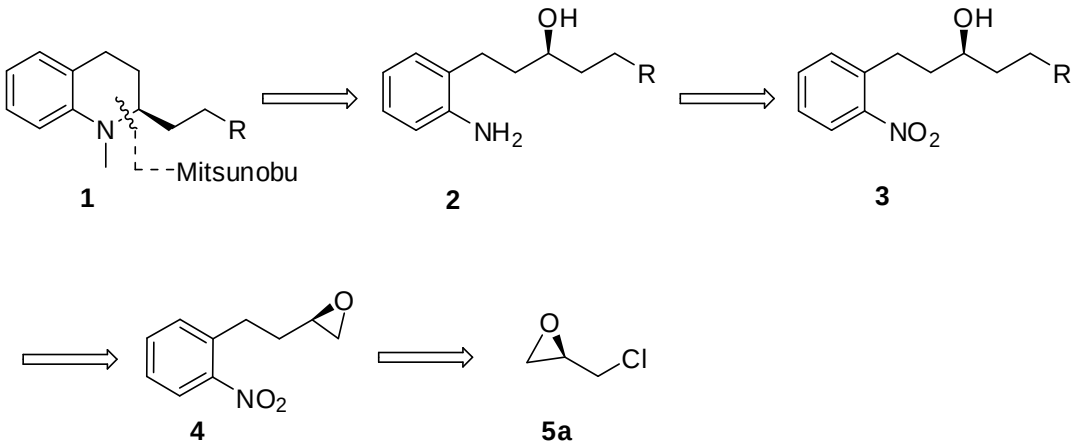
3. Present Work

3.1. Objective:

Various methods for the synthesis of (*S*)-Angustureine have been documented in the literature. Most of these approaches employ chiral pool starting materials. As part of our research program aimed at developing enantioselective synthesis of naturally occuring antimalarial and cytotoxic agents, we became interested to develop a new and highly enantioselective synthesis of (*S*)-Angustureine employing Jacobsen's catalyst, Grignard reaction and epoxide formation as the key steps.

3.2 Retro Synthetic Approach:

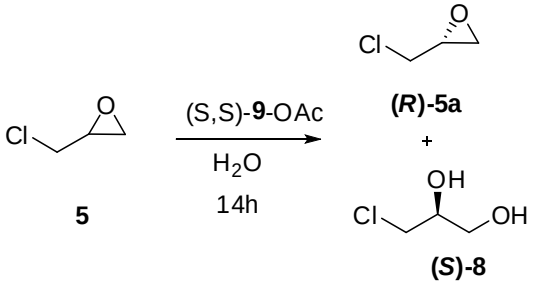
The retrosynthesis of 2-alkyl-substituted tetrahydroquinolines is outlined in Scheme 21. The tetrahydroquinolines ring system could be effectively prepared using the Mitsunobu reaction to establish the (*S*)- and/or (*R*)-configuration of the side chain (**2**→**1**). The amino-hydroxy derivative **2** was visualized as a synthetic intermediate from which tetrahydroquinolines ring system could be synthesized. The amino-hydroxy derivative **2** could be obtained from alcohol **3** *via* reduction of nitro group. Alcohol **3** could be easily synthesized from the epoxide **4** prepared from enantiomerically pure (*R*)-epichlorohydrin **5a** by Grignard reaction with 2-nitrobenzyl magnesium bromide.



Scheme 21: Retrosynthesis of (*S*)-angustureine **1.**

4. Results and discussion

A synthesis has been designed herein from (*R*)-epichlorohydrin **5a** which was prepared from the commercially available racemic epichlorohydrin as shown in the Scheme-22. Epichlorohydrin **5** was subjected to Jacobsen's HKR using (*S,S*)-Salan-Co-(OAc) catalyst to give (*R*)-epichlorohydrin **5a** as a single isomer, which was easily isolated from the more polar diol (*S*)-**8** by distillation. The completion of reaction was confirmed by GC-MS. The ^{1}H NMR spectrum of (*R*)-Epichlorohydrin **5a** showed methylene protons in oxirane ring at 2.69 (doublet of doublet, *J*=2.76. 5.04 Hz,1H), 2.90 (triplet, *J*=4.60 Hz, 1H), methine proton at 3.23-3.26 (multiplet, 1H), and methylene protons adjacent to chlorine atom appeared at 3.55 (doublet of doublet, *J*=5.96, 11.92 Hz, 1H), 3.62 (dublet of doublet, *J*=4.60, 11.92 Hz, 1H) ppm. The ^{13}C NMR spectrum of (*R*)-Epichlorohydrin **5a** showed methylene carbon in oxirane ring at 46.7, chiral carbon at 51.1, and carbon adjacent to chlorine atom appeared at 44.9 ppm

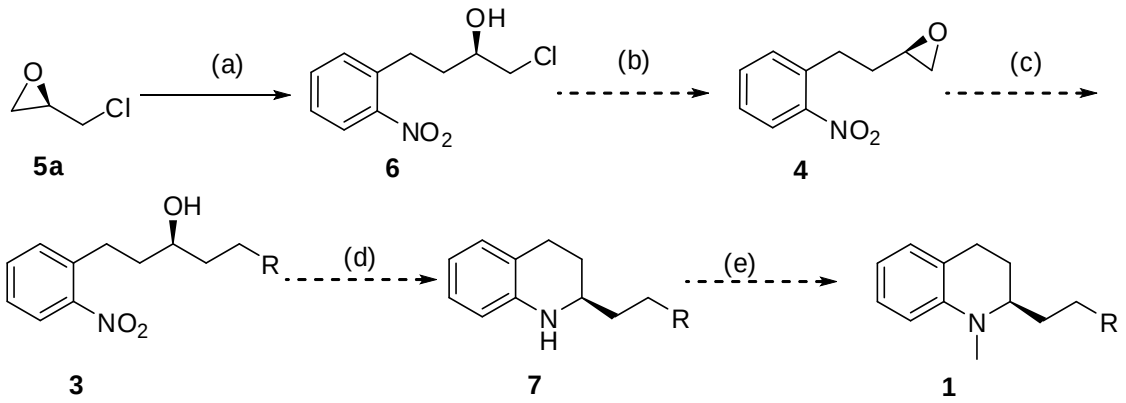


.

Scheme 22:

Racemic epichlorohydrin **5** was subjected to copper-catalysed (CuI) regioselective ring-opening with 2-nitrobenzyl magnesium bromide to give the chloro-alcohol intermediade **6**. The ^{1}H NMR spectrum of 1-chloro-4-(2-nitrophenyl)butan-2-ol **6** showed benzylic proton at 2.87 (triplet, *J*=3.82 Hz, 2H), methylene protons adjacent to chlorine atom at 2.94-3.01 (multiplet, 1H) and methine proton attached to hydroxyl group appeared at 3.20-3.27 (multiplet, 2H) ppm. The ^{13}C NMR spectrum of 1-chloro-4-(2-nitrophenyl)butan-2-ol **6** showed benzylic carbons at 25.1, chiral carbon at 71.4, and carbon adjacent to chlorine atom at 50.5 ppm.

Epoxide **4** would be the common intermediate to synthesize all 2-alkyl-substituted tetrahydro quinolines derivative just by changing the suitable side chain of the Grignard reagents. The hydroxyl-nitro derivative **3** on reduction with H_2/Pd-C would furnish the amino-alcohol

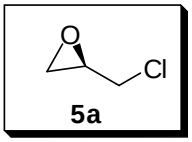


Scheme 22: Synthesis of (*S*)-Angustureine **1**. (a) 2-Nitrobenzylbromide, Mg turnings, 1,2-Dibromoethane, CuI, I_2, THF; (b) KOH, THF; (c) Butyl magnesium bromide, THF; (d) i) H_2 Pd/C; ii) DEAD,PPh_3; (e) MeI, K_2CO_3, THF.

which on Mitsunobu inversion will give the cyclised products **7** which on methylation will give the target compounds 2-alkyl-substituted tetrahydroquinolines **1**.

5. Experimental Section

5.1. (*R*)-2-(chloromethyl)oxirane 5a



A solution of the catalyst ((*S*,*S*), 484 mg, 800 μmol, 0.005 equiv) in 10mL DCM was treated with 500 μL AcOH. The crude catalyst residue obtained after concentration was treated with (±)-epichlorohydrin (12.52 mL, 14.80 g, 160 mmol) and 1.6 mL THF. The solution was cooled to 0 ^{0}C and treated with H_2O (1600 μL, 88 mmol, 1.10 equiv) and the reaction was maintained at 0 –4 ^{0}C for 16h. (*R*)-Epichlorohydrin **5a** was isolated by vacuum transfer (25 ^{0}C & 0.25 torr) from reaction mixture into a cooled receiving flask. The recovered epoxide was determined to be >99% ee by GC analysis.

Yield: 7.40 g, 100%

Mol. Formula: C_3H_5OCl

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.69 (dd, *J*=2.76, 5.04Hz, 1H), 2.90 (t, *J*=4.60 Hz, 1H), 3.23-3.26 (m, 1H), 3.55 (dd, *J*=5.96, 11.92 Hz, 1H), 3.62 (dd, *J*=4.60, 11.92 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 44.9, 46.7, 51.1 ppm.

5.2. 1-chloro-4-(2-nitrophenyl)butan-2-ol 6.

Synthesis of 1-chloro-4-(2-nitrophenyl)butan-2-ol **6** was carried out under different conditions shown in Table 1. So far best results were obtained with entry no.5. To a stirred solution of epichlorohydrin **5a** (427 mg, 4.65 mmol) and CuI (89 mg, 0.465 mmol) in dry THF (20 mL), was added a solution of 2-Nitrobenzylmagnesiumbromide prepared form 2-Nitrobenzylbromide (1.0 g, 4.65 mmol) and Mg-turning (0.696g, 27.9 mmol) in dry THF, dropwise at –78 °C. The mixture was warmed to -20 °C over 12h and poured into a saturated NH_4Cl solution. The layers were separated and the aqueous layer was extracted with Ethyl acetate (3 x 50 mL). The combined extracts were dried over Na_2SO_4. The extracts were concentrated to near dryness and purified on silica gel column chromatography (EtOAc/Hexane, 1:9) to afford **6** as dark brown liquid.

Table 1. Optimization of Grignard Reaction

S.No.	Solvent used	Reaction conditions	Product
1.	THF	0^0C for 6h, then rt for 8-10h	Complex reaction mixture
2.	Ether	0^0C for 6h, then rt for 8-10h	Complex reaction mixture
3.	THF and Ether	0^0C for 6h, then rt for 8-10h	Complex reaction mixture
4.	Dry THF	0^0C for 6h, then rt for 8-10h	Grignard reagent was generated but second step leads to Complex reaction mixture
5.	Dry THF	liquid N_2 to rt for 8-10h	45.5% yield

Yield: 485 mg 45.5%

Mol. Formula: $C_{10}H_{12}O_3NCl$

^{1}H NMR(400 MHz, $CDCl_3$): δ 1.25 (m, 2H), 1.58 (s, 1H), 2.87(t, *J*=3.82 Hz, 2H), 2.94-3.01 (m, 2H), 3.20-3.27(m,2H), 7.03-7.26(m, 4H) ppm.

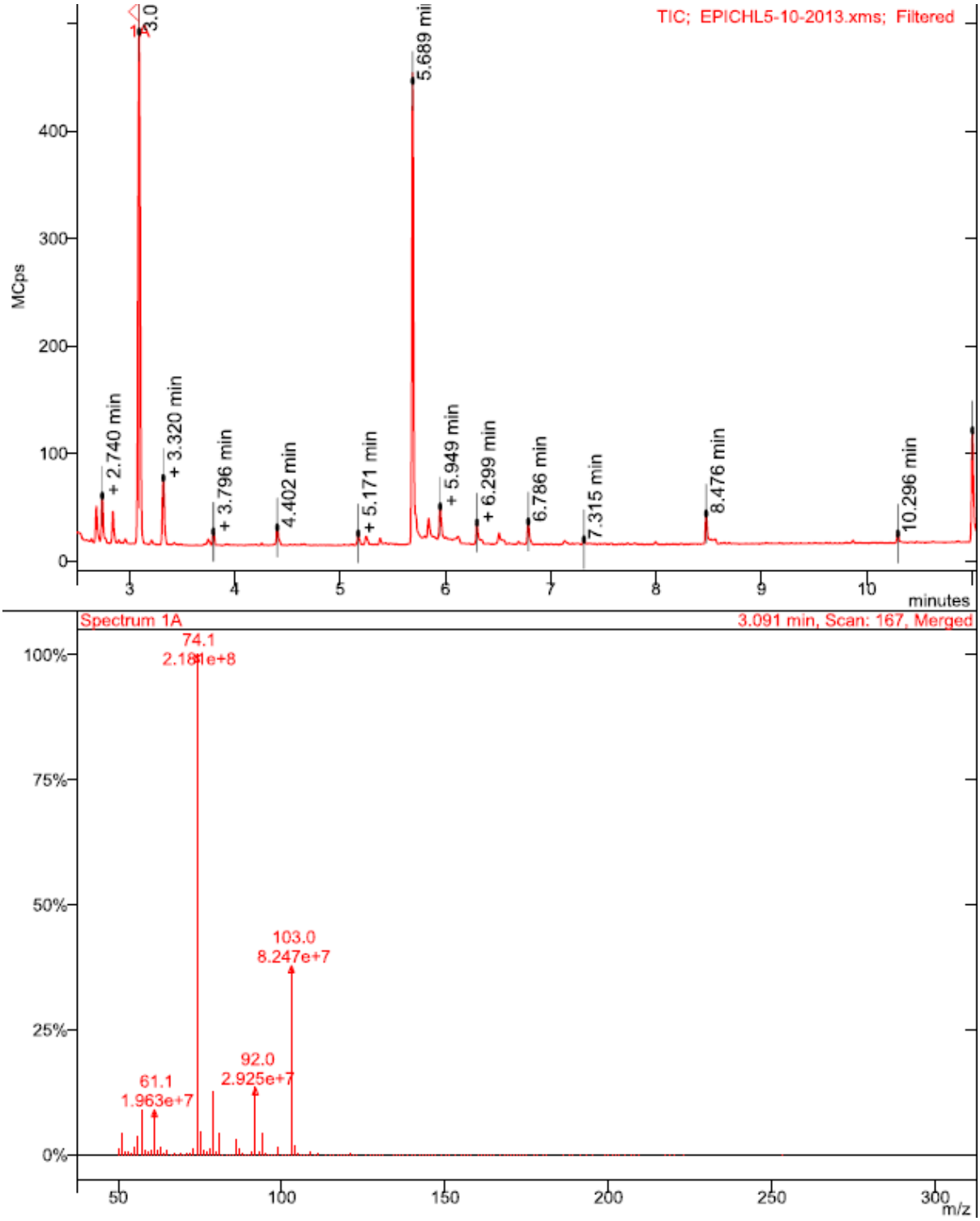
^{13}C NMR(100 MHz, $CDCl_3$): δ 25.1, 34.1, 50.5, 71.4, 126.2, 128.2, 128.9, 132.3, 134.3, 149.0 ppm.

6. Conclusion.

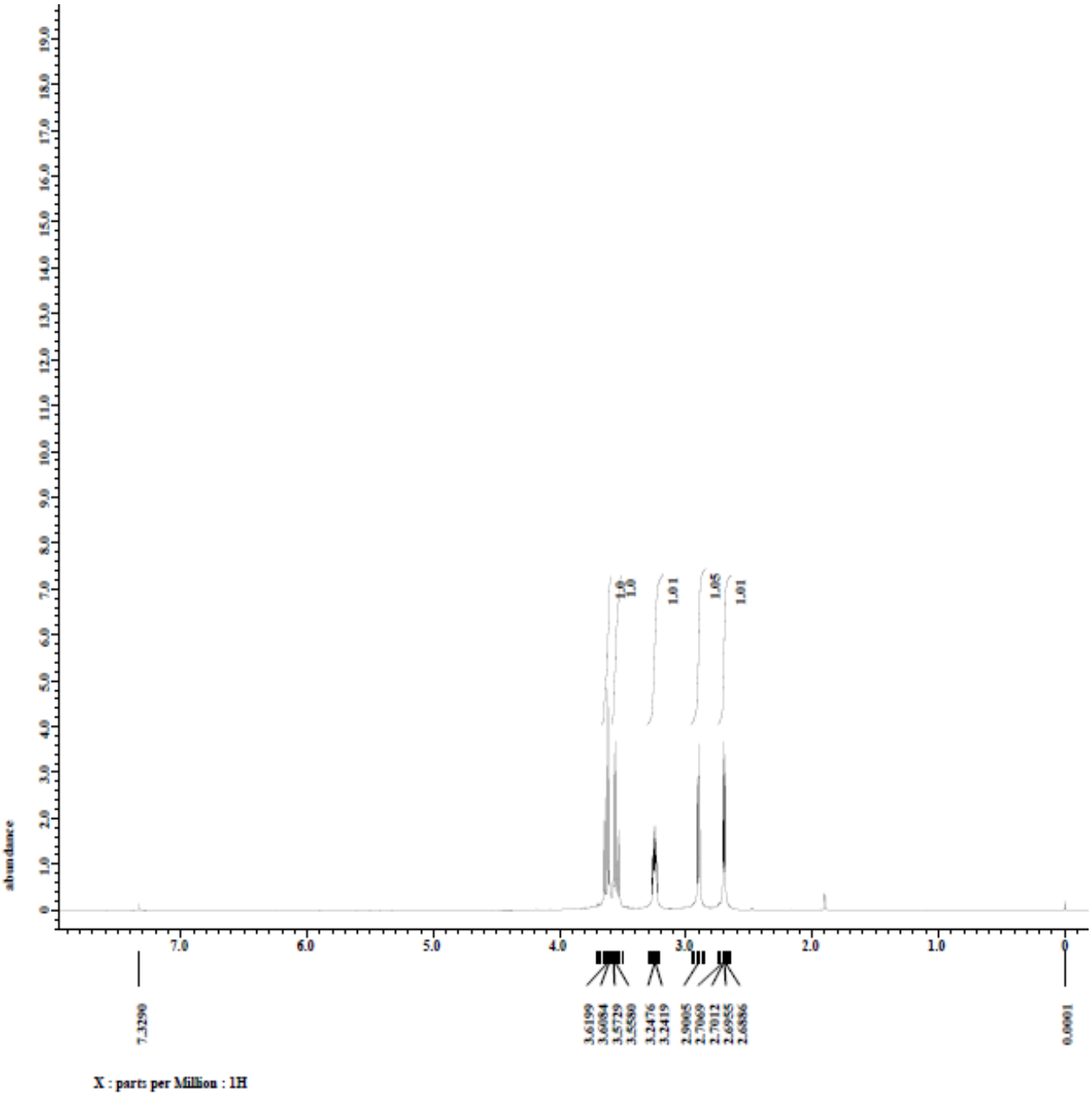
In conclusion a practical and enantioselective synthesis of (*S*)-Angustureine has been targeted from (*R*)-Epichlorohydrin **5a** employing jacobsen's HKR, Grignard reaction as the key steps. We have successfully completed the trial reaction for intermediate **6**. The work is under progress in further direction to achieve the target compounds. The merits of this synthetic approach is high yielding reaction steps. This synthetic strategy has significant potential for further extension to synthesis of galipeine **2**, cuspareine **3** and galipinine **4.**

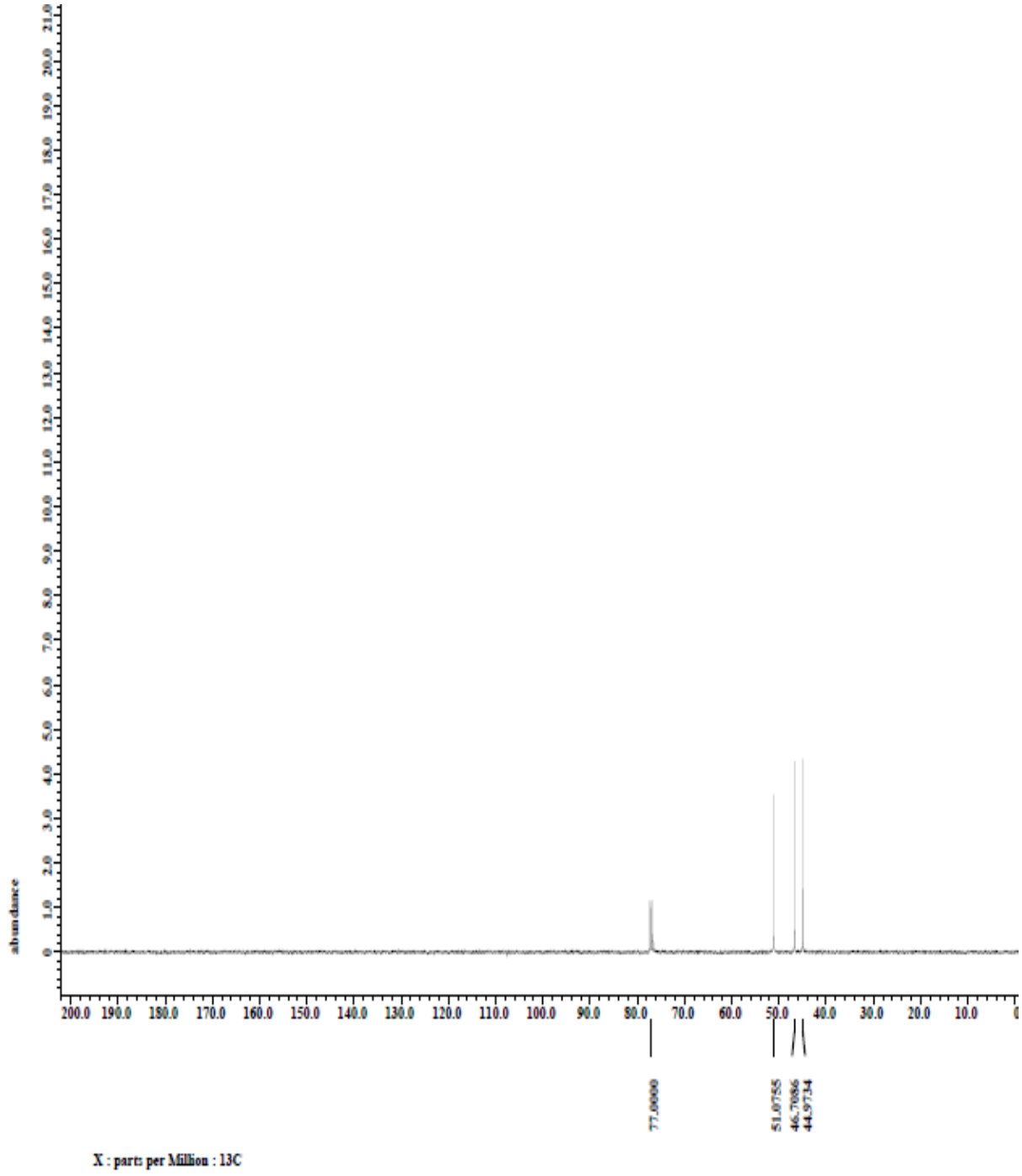
7. SPECTRA :-

1. Mass spectra of **5a.**
2. ^{1}H, ^{13}C NMR spectra of **5a**.
3. ^{1}H, ^{13}C NMR spectra of **6**.

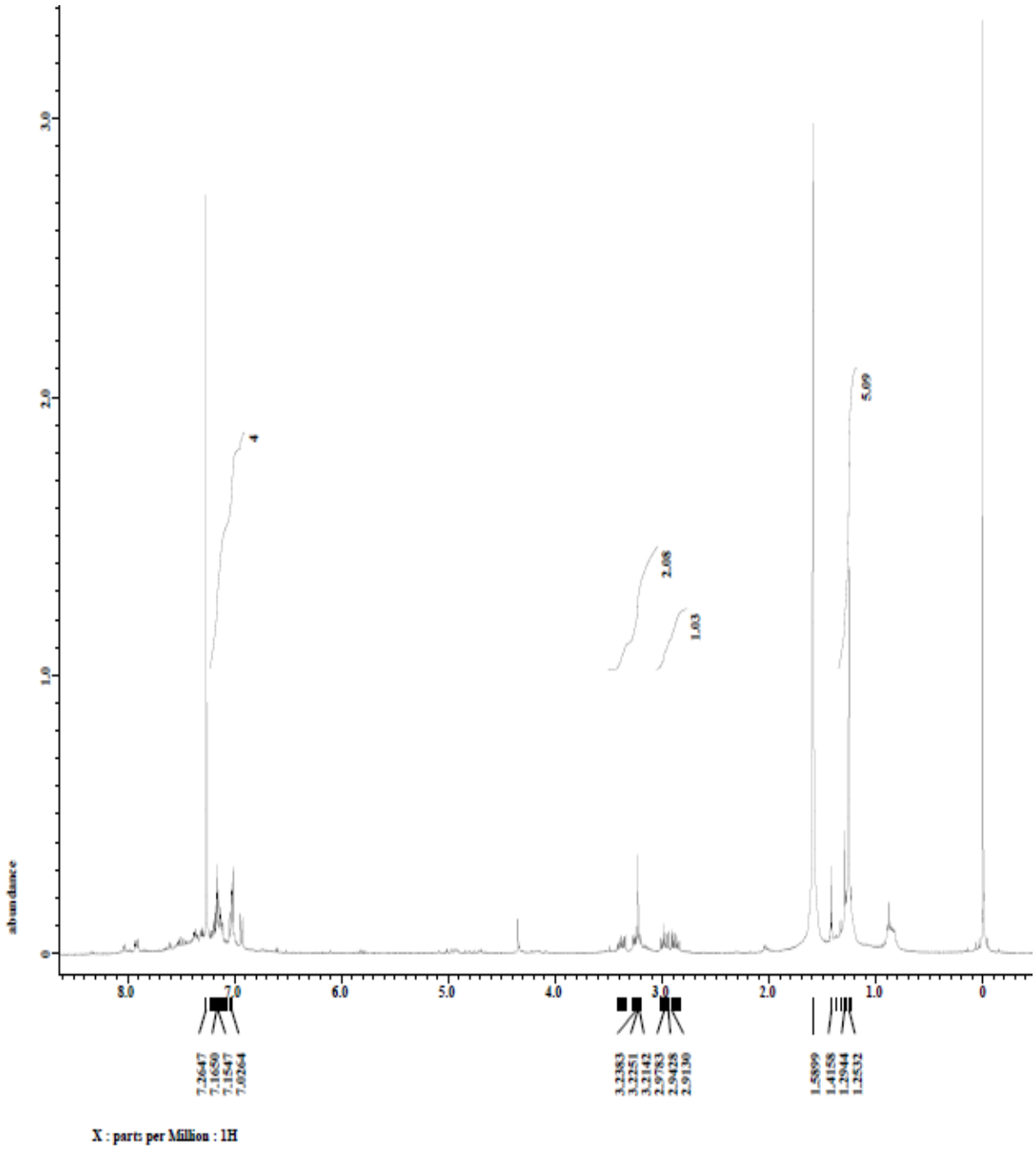

TIC; EPICHL5-10-2013.xms; Filtered
MCps
minutes
+ 2.740 min
+ 3.320 min
+ 3.796 min
4.402 min
+ 5.171 min
5.689 mi
+ 5.949 min
+ 6.299 min
6.786 min
7.315 min
8.476 min
10.296 min
Spectrum 1A
3.091 min, Scan: 167, Merged
74.1
103.0
8.247e+7
92.0
2.925e+7
61.1
1.963e+7
m/z

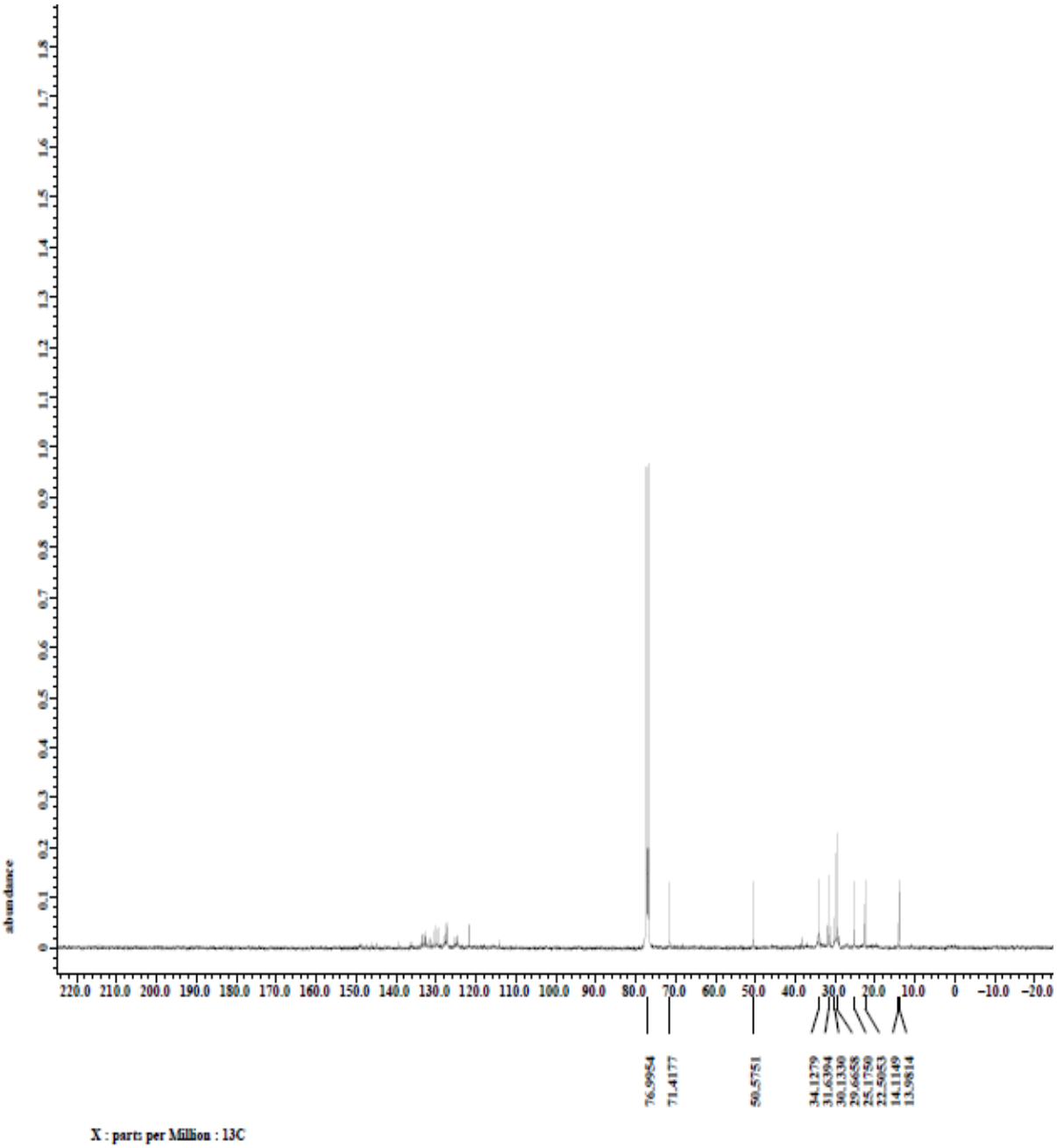
^{1}H, ^{13}C NMR spectra of **5a**.




abundance
0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
14.0
15.0
16.0
17.0
18.0
19.0
20.0
21.0
200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0
77.0000
51.0755
46.7086
44.9734
X : parts per Million : 13C

^{1}H, ^{13}C NMR spectra of **6**.




abundance
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50.5751
34.1279
31.6394
30.1330
29.6658
25.1750
22.5053
14.1149
13.9814
X : parts per Million : 13C

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