HETEROCYCLES, Vol. 65, No. 12, 2005, pp. 2901 - 2916
Received, 9th August, 2005, Accepted, 13th October, 2005, Published online, 14th October, 2005

AN ENANTIOSELECTIVE SYNTHESIS OF 1-AZASPIRO[5.5]-UNDECANE RING SYSTEM OF HISTRIONICOTOXIN ALKALOIDS FROM D(+)-GLUCOSE

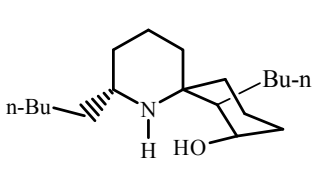
Smritilekha Bera

National Chemical laboratory, Pune 411 008, India

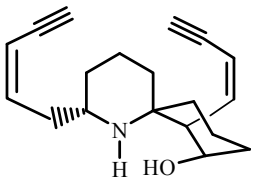
Abstract- The preparation of 1-azaspiro[5.5]undecane ring system common to histrionicotoxin alkaloids has been accomplished from D-glucose diacetonide.

INTRODUCTION

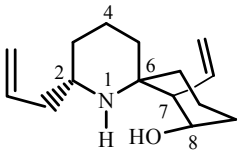
Histrionicotoxins, the archetype of a group of spiropiperidine containing alkaloids from the brightly colored poison arrow frog *Dendrobates histronicus* native to the Amazon rain forests of Southern Columbia, was first isolated by Daly, Witkop and co-workers in 1971.[1] They all share a common 1-azaspiro[5.5]undecan-8-ol ring system with unsaturated C4 or C5 side chains at both the 2 and 7 positions. The nature and length of the side chains distinguish the different members of the histrionicotoxin family.



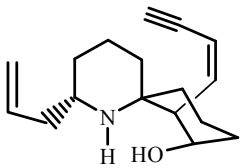
Perhydrohistrionicotoxin



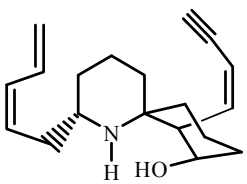
Histrionicotoxin 1



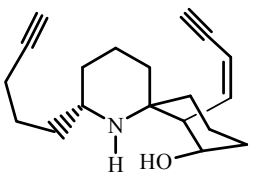
Histrionicotoxin 235A



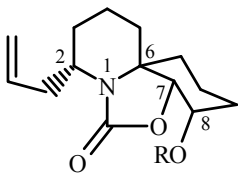
Histrionicotoxin 259A



Histrionicotoxin 285E



Histrionicotoxin 285C



22

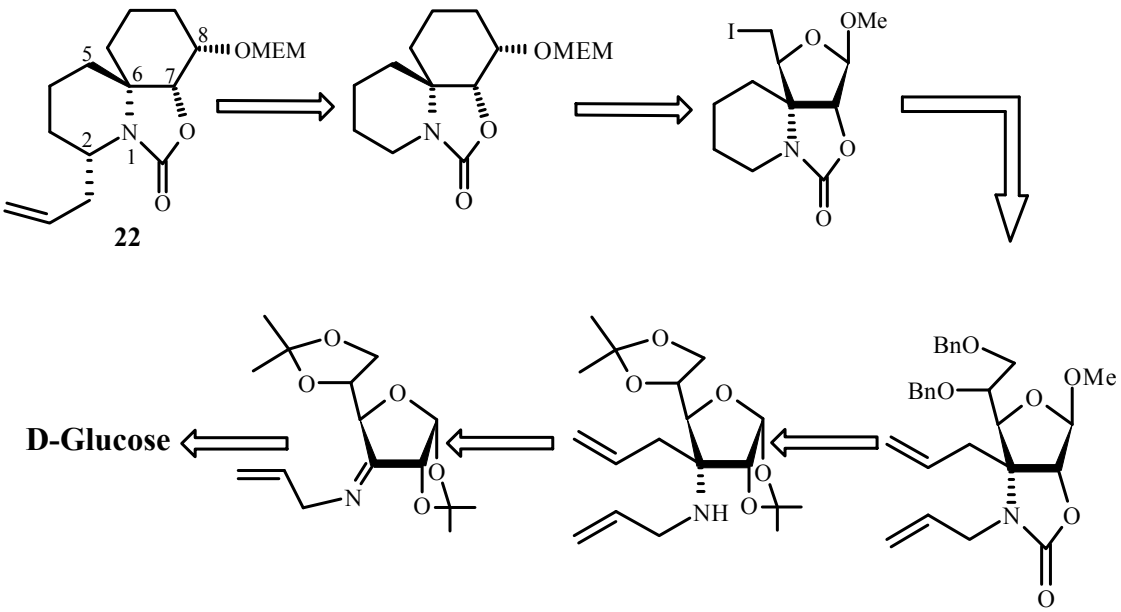
They have been shown to be potent non-competitive blockers of neuromuscular, ganglionic and central neuronal nicotinic channels, but an ever-diminishing supply of the natural material demands the synthesis

of these alkaloids. Many methods have been made to accomplish the model[2] as well as the total synthesis of histrionicotoxin alkaloids utilizing brilliant strategies.[3] A carbohydrate based synthetic approach was preluded, although we believe that a Chiron approach from a carbohydrate residue offers distinctive advantages while constructing the azaspiro undecane ring system.[4] Here we report the synthesis of commonly observed 1-azaspiro[5.5]undecane ring system (**22**) of histrionicotoxin 235A and histrionicotoxins family. The functional group distributions in **22** are exploitable for the total synthesis of these alkaloids.

Retrosynthetic analysis of histrionicotoxin 235A:

We planned from the outset to derive 1-azaspiro[5.5]undecane ring system (**22**) using Chiron[4] approach from D-glucose, a strategy that so far has never been employed in the synthesis of this compound of enduring interest. The retrosynthesis for **22** is shown in Figure1. We describe here a stereocontrolled approach for the synthesis of spiro skeleton of histrionicotoxin using two key reactions: a) addition of allyllithium to an allylimine followed by RCM; b) a zinc-mediated domino elimination–alkylation of methyl 5-iodopentofuranosides followed by RCM.

Figure 1

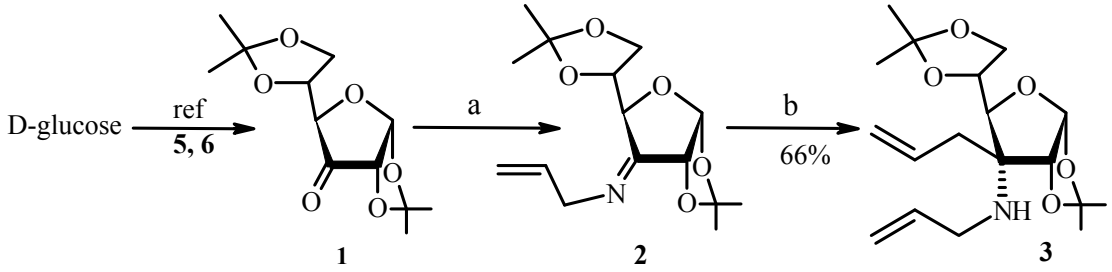


RESULTS AND DISCUSSION

Our first concern was to install the spiro-piperidine ring at C-3 of D-glucose diacetonide, and for this objective the known 1,2:5,6-di-*O*-isopropylidene-*ribo*-hexofuranose-3-ulose[5] (**1**) precursor was first transformed into the *N*-allylimine derivative (**2**). Subsequent *C*-allylation[6] of **2** with allyllithium generated compound (**3**) containing the well-defined quaternary center at C-3. The stereochemical assignment at

C-3 was gleaned from spectroscopic data coupled with literature precedent.[7] For instance, the sterically crowded 1,2-*O*-isopropylidene unit directs the incoming nucleophile from the β-face (Scheme 1)

Scheme 1

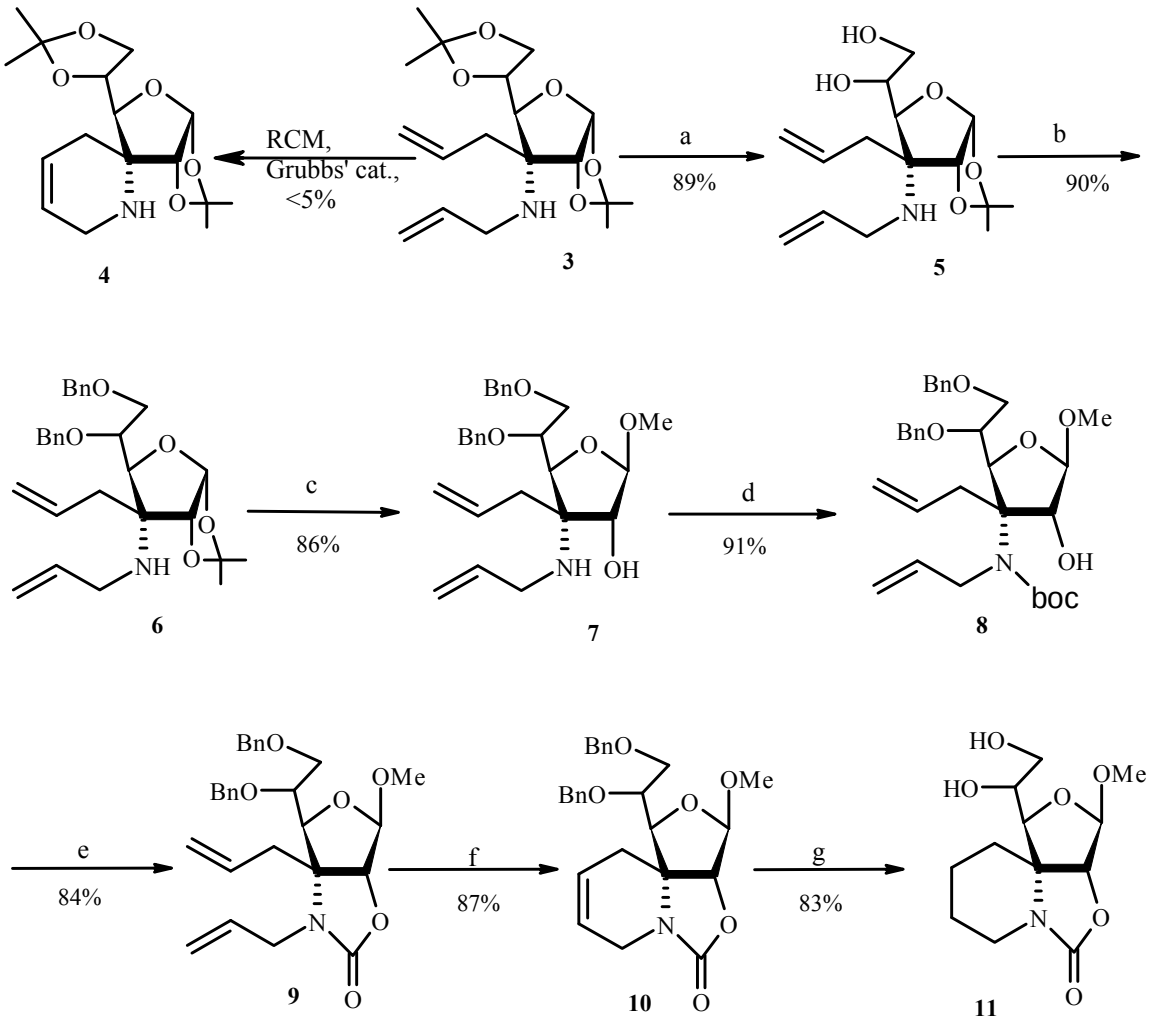


Reagents and conditions: a) allylamine, molecular sieves powder 4 Å, rt; b) allyl phenyl ether, lithium metal, cat. biphenyl.

With the advent of efficient catalysts, the ring-closing metathesis (RCM) reaction has emerged as a powerful process for cyclization of dienes[8] so we applied this method to the diene derivative (**3**) with the Grubbs' catalyst to get the spiropiperidine derivative but surprisingly, the reaction was very low yield (**4**, <5%) and most of the starting material was recovered. Anticipating an inactivation of the catalyst towards the amine, we planned to protect the secondary amino function with either Boc or Cbz groups. Astonishingly, under several conditions attempted, protection of **3** with either Boc_2O or CbzCl was found to be sluggish and resulted only with the recovery of starting material. We attributed this problem to steric crowding. However, a sequence of reactions as indicated in Scheme 2 were performed on **3** *via* intermediates (**5-9**) to produce the methyl glycoside. At first selective 5,6-acetonide deprotection of compound (**3**) with 1% H_2SO_4 in methanol at room temperature for 14 h followed by neutralization with $NaHCO_3$ provided the diol derivative (**5**)**,** which was protected as dibenzyl ether with benzyl bromide in THF in presence of cat. TBAI as usual procedure to get **6**. It is interesting to note that NH group of **5** remained unaffected during benzylation reaction, again due to steric reasons. Dibenzyl ether was then underwent deprotection of 1,2-acetonide in methanolic H_2SO_4 (6%) to give the methyl glycoside derivative (**7**)**.** The structure of β-methyl glycoside derivative (**7**) was established by the ^1H and ^{13}C NMR spectral analysis. The anomeric hydrogen of **7** resonated at 4.77 ppm, as a singlet indicating a 1,2-*trans* relationship. The methyl glycoside derivative (**7**) on treatment with Boc_2O in CH_2Cl_2 in presence of DMAP furnished **8**, which was converted to the corresponding carbamate (**9**) by using NaOH in MeOH:THF (1:1). The cyclic carbamate derivative (**9**) was subjected to RCM reaction using the 1st generation Grubbs' catalyst in benzene to obtain **10**, which underwent reduction in the presence

of 10% Pd/C and cat. acetic acid to provide the piperidine ring derivative (**11**) (Scheme 2).

Scheme 2

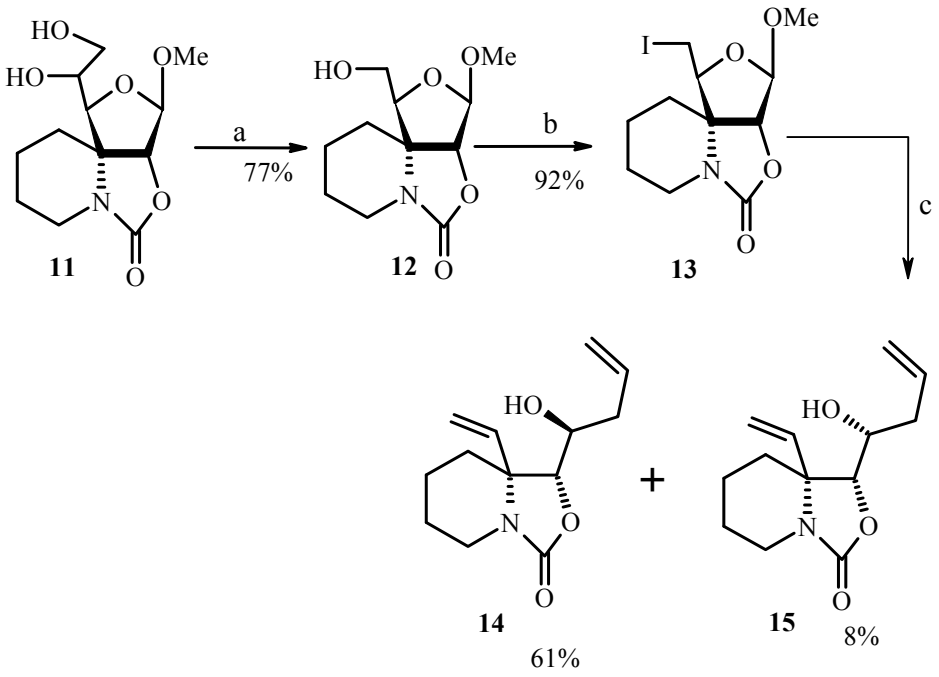


Reagents and conditions: a) 1% H_2SO_4, methanol, rt; b) benzyl bromide, NaH, TBAI, 0 °C~rt; c) 6% H_2SO_4, dry methanol, reflux; d) Boc_2O, DMAP, Et_3N, CH_2Cl_2, 0 °C~rt; e) 2 N NaOH, THF:MeOH (1:1), rt; f) Grubbs'cat., benzene, reflux; g) H_2, 10% Pd-C, 60 psi, acetic acid (cat.).

The next issue that needed attention was constructing the carbocyclic ring for which we sought to explore the zinc-mediated domino elimination–alkylation of the methyl 5-iodopentofuranoside derivative. Synthetic design demands high efficiency in terms of minimization of synthetic steps together with maximization of molecular complexity.[9] Domino reactions are becoming a very attractive tool in this regard.[10] Oxidative cleavage of **11** with sodium metaperiodate followed by reduction with $NaBH_4$ produced **12** which on treatment with triphenylphospine, iodine and imidazole in refluxing toluene gave the key iodo derivative (**13**). The Domino reaction of **13** with allyl bromide in presence of Zn dust in

THF:H_2O under sonication at 45 ^oC afforded the homoallylic alcohol derivatives (**14**) and (**15**) in (9:1) diastereomeric ratio (Scheme 3). The two-diastereomeric dienes were separated by silica gel column chromatography. Although the stereochemistry of the major product **(14**) was proposed based on literature,[11] conclusive proof was obtained at a later stage.

Scheme 3

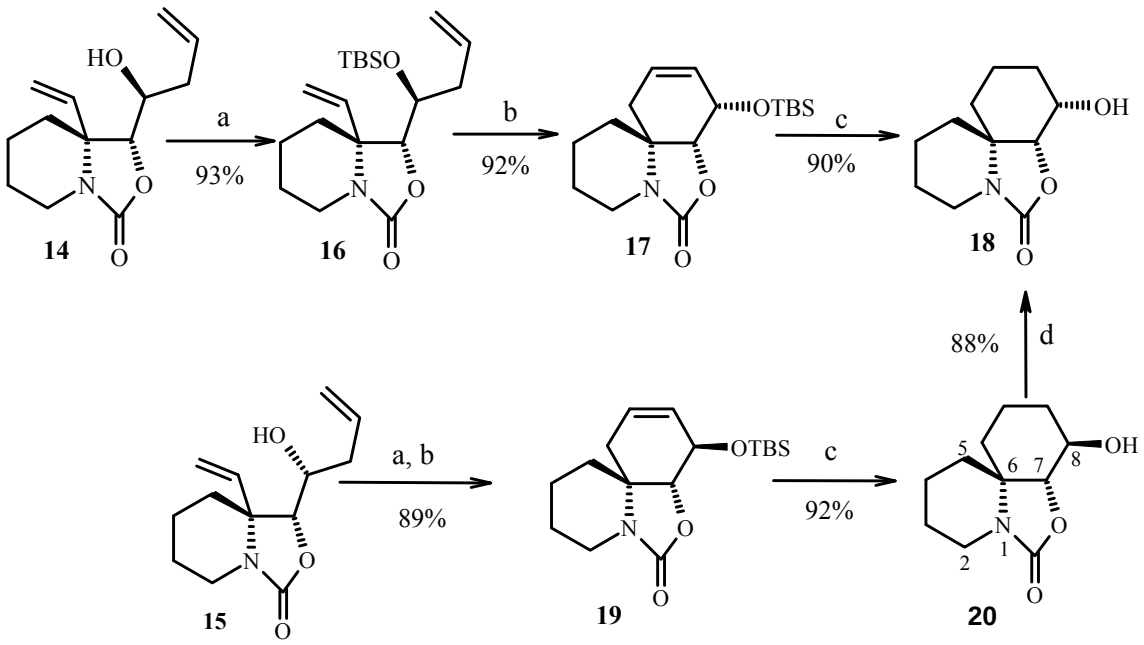


Reagents and conditions: a) $NaIO_4$, CH_2Cl_2, 0 ^oC; $NaBH_4$, THF; b) TPP, I_2, imidazole, toluene, reflux; c) Zn, allyl bromide, sonication, 40 °C.

The major isomer (**14**) was at first protected as TBS ether with TBDMSOTf and then subjected to RCM reaction using the 1st generation Grubbs' catalyst to furnish the requisite spiro-cyclic derivative (**17**). On hydrogenation of **17** over 10% Pd-C, the double bond reduction and cleavage of TBS occurred together to afford compound (**18**). The absolute structure of **18** was proved by single crystal X-Ray diffraction[12] that also assisted in identifying the two diastereomers (**14**) and (**15**) (Figure 2). The ORTEP diagram of **18** revealed the newly generated OH group in the domino reaction at C-8 and the cyclic carbamate were on the same side. This also revealed that the assigned structure of **14** and **15** were correct.

The minor isomer (**15**) was subjected to the same set of reactions as described in Scheme 3 to provide the azaspiro derivative (**20**), in which the hydroxy group at C-8 was opposite configuration to that of **18**. In order to invert the center, it was first oxidized with Dess-Martin periodinane (DMP) and then reduced with sodium borohydride. The resulting product was in complete agreement with the sample (**18**) obtained earlier (Scheme 4).

Scheme 4



Reagents and conditions: a) TBDMSOTf, lutidine, CH_2Cl_2, 0 °C; b) Grubbs' cat., CH_2Cl_2, reflux; c) H_2, 10% Pd-C, 10 psi, cat. acetic acid; d) DMP, Et_3N, CH_2Cl_2; $NaBH_4$, THF.

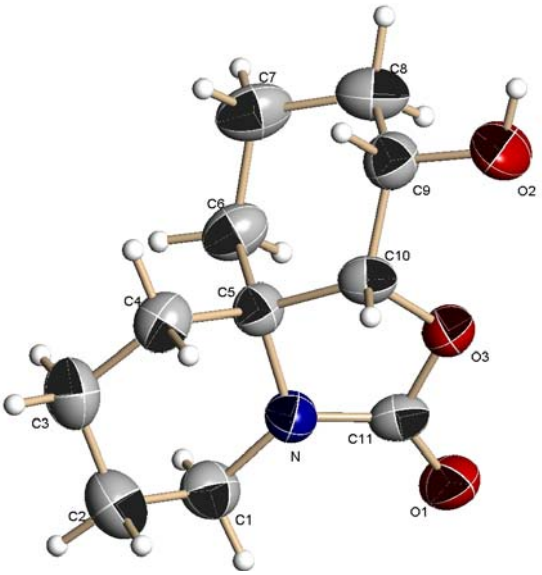


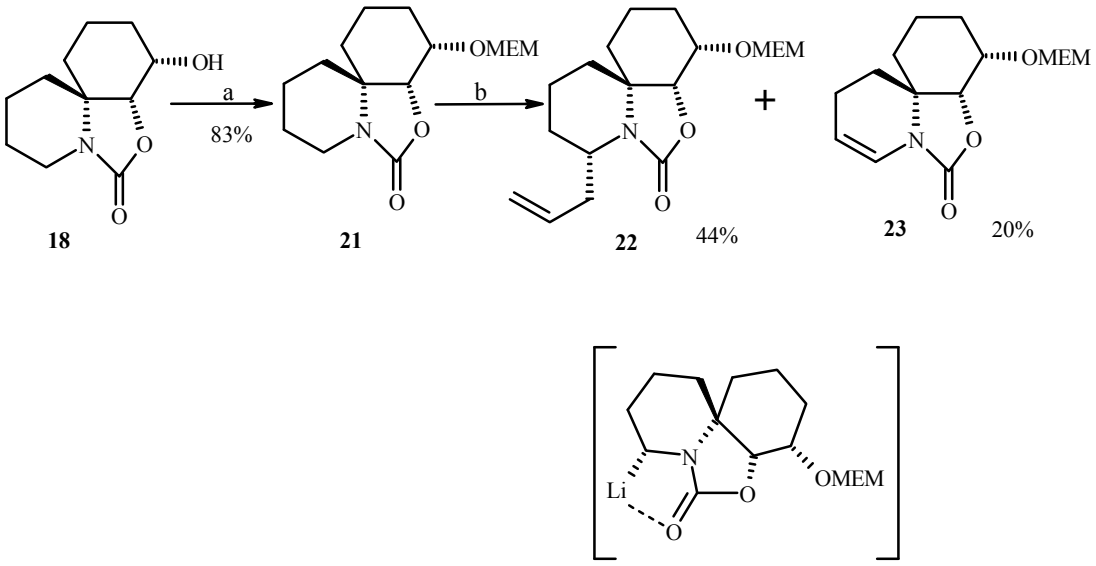
Figure 2: ***ORTEP diagram of compound 18*** (Ellipsoids are drawn at 40% probability)

Compound (**18**) is a key intermediate i.e. 1-azaspiro[5.5]undecan-8-ol ring system which is present in all the histrionicotoxin alkaloids family.

Now to install the allyl group at C-2 for the synthesis of histrionicotoxin 235A, **18** was at first converted to its MEM ether and then treated with allyl bromide in the presence of s-BuLi and TMEDA at 0 ^{o}C to

give only one stereoselective product (**22**) along with the eliminated product (**23**). The determination of correct stereochemistry of a newly formed stereogenic center was very intricate. From the COSY and NOESY spectral experiment it was expected that the hydrogens at C-2 and C-7 should show some spatial interaction between them but it didn't show any interaction probably due to longer spacing. Based on literature[13a,b] precedent and complex-induced proximity effects, we concluded that the allylic group occupied α-position with the same face of the carbamate ring. It is obvious that the carbonyl group of the carbamate first complexes with *s*-BuLi to influence the lithiation from the same face of the ring system (**22**) (Scheme 5).

Scheme 5



Reagents and conditions: a) NaH, MEMCl, THF:DMF (1:1), 0 ^{o}C~rt; b) *s*-BuLi, allyl bromide, THF, 0 ^{o}C.

Compound (**22**) was an advanced intermediate for the synthesis of histrionicotoxin 235A, which exemplifies a formal synthesis of this alkaloid.

CONCLUSION

In summary the carbohydrate-based synthesis of key azaspiro[5.5]undecane-8-ol ring system present in histrionicotoxin group of alkaloids family and the formal synthesis of histrionicotoxin 235A was successfully achieved from easily accessible D-glucose.

EXPERIMENTAL

NMR spectra were recorded on Bruker AC 200, MSL 300 or DRX 500 MHz instruments in $CDCl_3$ or DMSO-d_6 using TMS as an internal standard. EIMS spectra were recorded on a Finnigan MAT-1020.

Optical rotations were measured with a JASCO DIP 370 digital polarimeter. Microanalysis was carried out on Carbo-Elba elemental analyzer. Melting points were measured on a Buchi B-540 apparatus and are uncorrected. Solvents were distilled over drying agents under argon or nitrogen. All reactions were monitored by TLC carried out on 0.25 m E. Merck silica gel plates (60F-254) using UV light as visualizing agent and anisaldehyde in ethanol as developing agent. Silica gel (60-120) was purchased from Acme Chemical Company.

3-*C*-Allyl-3'-*N*-allyl-3-deoxy-1,2:5,6-di-*O*-isopropylidine-α-D-allofuranose (3)

Compound (**1**) (10.0 g, 38.7 mmol), allylamine (3.2 g, 42.6 mmol) and molecular sieves powder (2.0 g) were stirred for 1 h at rt, filtered through celite, washed with benzene and concentrated to give **2** (10.9 g), as a brown liquid which was directly used for next reaction.

A suspension of freshly cut lithium pieces (2.54 g, 0.37 g.- atom) and biphenyl (5.0 mg) in THF (50 mL), was cooled to –15 ^{o}C and then allyl phenyl ether (25.2 mL, 183 mmol) in anhydrous THF (26 mL) was added dropwise. After 45 min the cooling bath was removed and the reaction mixture was stirred for an additional 15 min. The dark red solution of allyllithium was cannulated to a new flask. Compound (**2**) (10.9 g) in THF (50 mL) was introduced. After stirring at rt for 2 h the reaction was quenched with saturated NH_4Cl, filtered through celite and washed with ethyl acetate-hexane. The combined filtrate was washed with 1 N NaOH (2 x 30 mL), brine, dried (over Na_2SO_4), and concentrated. The residue was purified on silica gel by using EtOAc-hexane (1:9) to give **3** (8.2 g, 66%), as a yellow liquid. $[\alpha]_D$ = +53 ^{o} (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.31 (s, 3 H), 1.34 (s, 3 H), 1.42 (s, 3 H), 1.54 (s, 3 H), 2.18 (dd, 1 H, *J* = 6.8, 1.2 Hz), 2.46 (dd, 1 H, *J* = 6.8, 0.9 Hz), 3.26 (ddt, 1 H, *J* = 2.3, 5.4, 14.7 Hz), 3.49 (ddt, 1 H, *J* = 2.3, 6.2, 12.0 Hz), 3.85 (m, 2 H), 4.10 (m, 2 H), 4.33 (d, 1 H, *J* = 3.0 Hz), 5.01-5.22 (m, 4 H), 5.51 (d, 1 H, *J* = 3.0 Hz), 5.82-6.09 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 24.7, 25.6, 25.8, 26.2, 34.1, 45.5, 65.6, 67.5, 72.3, 73.8, 83.3, 102.5, 108.6, 114.5, 117.4, 127.5, 132.7, 136.8; Ms: *m/z* 340 (M+ 1). *Anal.* Calcd for $C_{18}H_{29}NO_5$: C, 63.69; H, 8.61; N, 4.13; Found: C, 63.84; H, 8.42; N, 4.03.

3-*C*-Allyl-3'-*N*-allyl-3-deoxy-5,6-di-*O*-benzyl-1,2-*O*-isopropylidine-α-D-allofuranose (6)

Compound (**3**) (8.9 g, 26.3 mmol) and 1% aqueous H_2SO_4 (30 mL) in methanol (30 mL) were stirred at rt for 14 h, neutralized with $NaHCO_3$, filtered and concentrated. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried (over Na_2SO_4), and concentrated. The crude residue was purified on silica gel by eluting with EtOAc-hexane (1:1) to give **5** (7.0 g, 89%), as a liquid. $[\alpha]_D$ = +75 ^{o} (*c* 1, $CHCl_3$); ^{1}H NMR (acetone-d_6, 200 MHz): δ 1.32 (s, 3 H), 1.50 (s, 3 H), 2.42 (m, 2 H), 3.22-3.52 (m, 5 H), 3.72 (m, 2 H), 3.89 (m, 1 H), 4.50 (d, 1 H, *J* = 3.9 Hz), 5.0-5.29 (m, 4 H), 5.67 (d, 1 H, *J* = 3.9 Hz), 5.84-6.17 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 26.3, 26.7, 34.7, 48.1, 63.7,

66.5, 69.4, 78.3, 81.0, 104.1, 111.5, 115.9, 118.3, 132.5, 135.8; MS: *m/z* 300 (M^++1); *Anal.* Calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68; Found: C, 59.84; H, 8.31; N, 4.73.

Compound (**5**) (16.0 g, 53.5 mmol) in dry THF (100 mL) was cooled to 0 ^oC and NaH (60% dispersion in oil, 3.2 g, 80.2 mmol) was added portionwise at 0 ^oC. After 30 min at rt benzyl bromide (14.0 mL, 117.7 mmol) and Bu_4NI (98.0 mg, 0.25 mmol) were added and the mixture was stirred for 3 h. After usual work up the residue was purified on silica gel by eluting with EtOAc-hexane (1:19) to afford a yellow liquid **6** (23.0 g, 90%). $[\alpha]_D$ = +28 ^{o} (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.31 (s, 3 H), 1.52 (s, 3 H), 1.98 (br s, 1 H), 2.21 (dd, 1 H, *J* = 6.8, 14.6 Hz), 2.34 (dd, 1 H, *J* = 7.8, 14.6 Hz), 3.18-3.39 (m, 2 H), 3.66 (dd, 1 H, *J* = 6.1, 9.7 Hz), 3.81-4.02 (m, 3 H), 4.30 (d, 1 H, *J* = 3.6 Hz), 4.56 (br t, 3 H, *J* = 4.2 Hz), 4.83-5.11 (m, 5 H), 5.57 (d, 1 H, *J* = 3.6 Hz), 5.74-6.02 (m, 2 H), 7.32 (m, 10 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 26.4, 26.8, 35.8, 46.4, 66.5, 71.7, 72.0, 73.2, 76.7, 80.4, 83.7, 103.0, 111.5, 114.8, 117.4, 127.4, 127.7, 128.0, 128.1, 133.8, 137.3, 138.3; MS: *m/z* 480 (M^++1); *Anal.* Calcd for $C_{29}H_{37}NO_5$: C, 72.62; H, 7.78; N, 2.92; Found: C, 72.94; H, 8.01; N, 2.85.

Methyl 3-*C*-allyl-3'-*N*-allyl- 3-deoxy-5,6-di-*O*-benzyl-β-D-allofuranoside (7)

A solution of compound (**6**) (6.3 g, 13.2 mol) and conc. H_2SO_4 (3 mL) in dry methanol (80 mL) was refluxed for 6 h, neutralized with K_2CO_3, filtered and concentrated. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried (over Na_2SO_4) and concentrated to give a residue, which was purified on silica gel by eluting with EtOAc-hexane (1:9) to give **7** (5.1 g, 86%), as a yellow liquid. $[\alpha]_D$ = –69 ^{o} (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 2.41 (ddt, 1 H, *J* = 1.6, 3.4, 5.4 Hz), 2.61 (q, 1 H, *J* = 7.6 Hz), 2.90 (ddt, 1 H, *J* = 1.5, 3.4, 4.8 Hz), 3.16-3.30 (m, 1 H), 3.35 (s, 3 H), 3.61 (dd, 1 H, *J* = 3.4, 10.4 Hz), 3.69 (s, 1 H), 3.78-3.93 (m, 3 H), 4.42 (d, 1 H, *J* = 11.2 Hz), 4.58 (s, 2 H), 4.77 (s, 1 H), 4.83 (d, 1 H, *J* = 11.2 Hz), 4.97-5.16 (m, 4 H), 5.66-5.96 (m, 2 H), 7.32 (m, 10 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 34.9, 45.5, 55.0, 64.1, 70.7, 70.9, 72.8, 77.2, 77.4, 81.2, 109.1, 114.9, 117.1, 127.1, 127.7, 134.1, 135.7, 137.8; MS: *m/z* 454 (M^++1); *Anal*. Calcd for $C_{27}H_{35}NO_5$: C, 71.50; H, 7.78; N, 3.09; Found: C, 71.56, H, 7.54; N, 2.96.

Methyl 3-*C*-allyl-3'-(*N*-allyl-*N*'-*tert*-butoxycarbonyl)-3-deoxy-5,6-di-*O*-benzyl-β-D-allofuranoside (8)

7 (8.0 g 17.6 mmol), triethylamine (7.3 mL, 53.0 mmol), Boc_2O (4.8 g, 21.2 mmol), and DMAP (10.0 mg, 0.09 mmol) in CH_2Cl_2 (30 mL) were stirred at rt for 30 min and concentrated. The crude residue was purified on silica gel by eluting with EtOAc-hexane (1:9) to afford a yellow liquid (**8**) (8.9 g, 91%). $[\alpha]_D$ = –18 ^{o} (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.47 (s, 9 H), 2.45 (dd, 1 H, *J* = 6.3, 10.5 Hz), 2.66

(dd, 1 H, *J* = 6.8, 11.5 Hz), 3.10 (dd, 1 H, *J* = 5.8, 13.3 Hz), 3.27 (dd, 1 H, *J* = 5.8, 14.1 Hz), 3.36 (s, 3 H), 3.62-3.67 (m, 2 H), 3.88 (d, 1 H, *J* = 8.9 Hz), 4.08 (d, 1 H, *J* = 8.9 Hz), 4.48 (d, 1 H, *J* = 11.2 Hz), 4.59 (br d, 2 H, *J* = 2.0 Hz), 4.80 (br d, 1 H, *J* =1.4 Hz), 4.86 (br d, 2 H, *J* =1.4 Hz), 4.92-5.17 (m, 4 H), 5.69-5.99 (m, 2 H), 7.32 (m, 10 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 27.6, 34.9, 45.8, 55.4, 64.7, 71.2, 71.6, 73.3, 77.8, 82.1, 82.1, 83.5, 106.9, 114.6, 117.8, 127.3, 127.4, 127.7, 128.1, 133.8, 137.3, 138.3, 152.4; MS: *m/z* 555 (M^++2); *Anal.* Calcd for $C_{32}H_{43}NO_7$: C, 69.42; H, 7.83; N, 2.53; Found: C, 69.22; H, 7.90; N, 2.71.

3,3a-Diallyl-4-[1,2-*bis*-benzyloxyethyl]-6-methoxytetrahydrofuro[3,4-*d*][1,3]oxazol-2(3*H*)-one (9)

8 (3.0 g, 5.4 mmol) and NaOH (12.0 mg, 0.32 mmol) in THF:MeOH (1:1, 15 mL) were stirred at rt for 3 h, quenched with acetic acid and concentrated. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried (over Na_2SO_4), and concentrated**.** The residue was purified on silica gel by eluting with EtOAc-hexane (1:9) to furnish **9** (2.2 g, 84%), as a white solid. mp = 79 ^{o}C [recrystallized from ethyl acetate-hexane]; $[\alpha]_D$ = – 49 ^{o} (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.24 (dd, 1 H, *J* = 7.9, 14.9 Hz), 2.95 (dd, 1 H, *J* = 5.5, 13.6 Hz), 3.18-3.41 (m, 1 H), 3.31 (s, 3 H), 3.59-3.73 (m, 2 H), 3.75 (d, 1 H, *J* = 5.9 Hz), 3.90 (d, 1 H, *J* = 9.2 Hz), 4.20 (d, 1 H, *J* = 9.2 Hz), 4.40 (d, 1 H, *J* = 11.5 Hz), 4.50-4.65 (m, 3 H), 4.88 (d, 2 H, *J* = 14.1 Hz), 4.95-5.22 (m, 4 H), 5.54-5.95 (m, 2 H), 7.34 (m, 10 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 34.0, 43.7, 55.9, 69.5, 71.3, 72.4, 73.1, 77.7, 83.7, 84.6, 108.0, 117.5, 120.0, 126.5, 126.9, 127.4, 127.5, 127.6, 128.1, 131.6, 132.7, 137.7, 137.5, 137.8, 156.2; MS: *m/z* 480 (M^++1); IR: 1752 cm^{-1}; *Anal.* Calcd for $C_{28}H_{33}NO_6$: C, 70.13; H, 6.94; N, 2.92; Found: C, 69.96; H, 7.13; N, 2.92.

1-[1,2-*bis*-Benzyloxyethyl]-3-methoxy-3,3a,7,10-tetrahydrofuro[3′,4′:4,5][1,3]oxazolo[3,4-*a*]pyridin-5-one (10)

Compound (**9**) (5.0 g, 10.4 mmol) and Grubbs' cat. (85.0 mg, 1 mol%) in benzene (80 mL) was degassed under argon atmosphere and then refluxed for 30 h. After that additional Grubbs' cat. (60.0 mg, 0.7 mol%) was added and further refluxed for 12 h. The solvent was evaporated and the residue was purified on silica gel by using EtOAc-hexane (1:9) as eluent to give **10** (4.1 g, 87%), as a yellow liquid. $[\alpha]_D$ = –37 ^{o} (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.42 (m, 2 H), 3.30 (s, 3 H), 3.61 (dd, 1 H, *J* = 2.1, 9.9 Hz), 3.72 (m, 1 H), 3.85 (dd, 1 H, *J* = 2.0, 9.9 Hz), 4.13 (m, 1 H), 4.20 (d, 1 H, *J* = 9.9 Hz), 4.36 (s, 1 H), 4.40 (d, 2 H, *J* = 9.9 Hz), 4.53 (t, 2 H, *J* = 9.6 Hz), 4.77 (d, 1 H, *J* = 10.9 Hz), 4.92 (t, 1 H, *J* = 9.6 Hz), 5.43 (m, 2 H), 7.31 (m, 10 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 27.9, 39.2, 56.0, 69.5, 71.5, 73.3, 78.3, 81.9, 88.1, 109.0, 121.5, 124.2, 127.5, 127.6, 128.1, 128.2, 137.9, 137.9, 154.9; Ms: *m/z* 452 (M+ 1); *Anal.* Calcd For $C_{26}H_{29}NO_6$: C, 69.16; H, 6.47; N, 3.10; Found: C, 68.86; H, 6.33; N, 3.02.

1-Hydroxymethyl-3-methoxyhexahydro-2,4-dioxa-5a-azacyclopenta[*c*]inden-5-one (12)

A suspension of **10** (2.0 g, 4.4 mmol), cat. acetic acid and 10% Pd/C (0.2 g) in methanol (30 mL) was hydrogenated at rt under 60 psi. The reaction was completed in 6 h, and filtered through celite, concentrated. The residue was purified on silica gel by using EtOAc-hexane (1:9) to afford a white solid **11** (1.0 g, 83%). mp = 161 ^{o}C [recrystallized from ethyl acetate-hexane]; $[\alpha]_D$ = –105 ^{o} (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.49-1.87 (m, 6 H), 2.27 (d, 1 H, *J* = 11.5 Hz), 2.59 (br s, 2 H), 2.96 (dt, 1 H, *J* = 2.9, 12.8 Hz), 3.42 (s, 3 H), 3.81 (m, 3 H), 4.18 (d, 1 H, *J* = 8.6 Hz), 4.37 (s, 1 H), 4.92 (s, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.8, 23.7, 28.4, 39.6, 55.7, 63.5, 69.7, 70.4, 83.2, 87.5, 108.2, 155.1; MS: *m/z* 274 (M^++1); *Anal.* Calcd for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.01; N, 5.13; Found: C, 52.88; H, 6.91; N, 5.02.

Compound (**11**) (5.0 g, 18.3 mmol) and sodium metaperiodate (5.9 g, 27.4 mmol) in water (3 mL) and CH_2Cl_2 (20 mL) were stirred at rt for 30 min and filtered. Organic layer was washed with 5% $Na_2S_2O_3$, brine, dried (over Na_2SO_4) and concentrated to give aldehyde (4.0 g, 91%). It was dissolved in THF (20 mL) and then $NaBH_4$ (0.18 g, 4.6 mmol) was added portionwise and the mixture was stirred at rt for 2 h. The reaction mixture was quenched with sat. NH_4Cl, filtered, washed with ethyl acetate and the total organic layer was dried (over Na_2SO_4) and concentrated. The residue was purified on silica gel by using EtOAc-hexane (1:1) to get a white solid (**12**) (3.1 g, 77%). mp = 116 ^{o}C [recrystallized from ethyl acetate-hexane]; $[\alpha]_D$ = –115 ^{o} (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.44-1.77 (m, 5 H), 1.96 (m, 1 H), 2.25 (m, 1 H), 2.88-3.03 (m, 1 H), 3.49 (s, 3 H), 3.38-4.02 (m, 1 H), 3.66 (br s, 1 H), 3.77-3.96 (m, 1 H), 4.42 (s, 1 H), 4.46 (t, 1 H, *J* = 3.1 Hz), 5.0 (s, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.2, 24.3, 28.0, 39.4, 55.4, 62.4, 69.0, 84.1, 86.9, 108.6, 154.8; MS: *m/z* 244 (M^++1); *Anal.* Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76; Found: C, 54.48; H, 7.06; N, 5.71.

1-Iodomethyl-3-methoxyhexahydro-2,4-dioxa-5a-azacyclopenta[*c*]inden-5-one (13)

12 (3.0 g, 12.3 mmol), TPP (6.5 g, 24.7 mmol), I_2 (6.3 g, 24.7 mmol) and imidazole (1.7 g, 24.7 mmol) in toluene (15 mL) were refluxed for 4 h. Toluene was removed, the residue partitioned between water and ethyl acetate. The organic phase was washed with 5 % $NaHCO_3$, 5 % $Na_2S_2O_3$, and brine, dried (over Na_2SO_4), and concentrated. The residue was purified on silica gel by using EtOAc-hexane (1:4) to get a solid compound (**13**) (4.0 g, 92%). mp = 170 ^{o}C [recrystallized from ethyl acetate-hexane]; $[\alpha]_D$ = –3 ^{o} (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.32-2.03 (m, 6 H), 2.89 (m, 1 H), 3.29 (dd, 1 H, *J* = 2.9, 10.3 Hz), 3.45 (dd, 1 H, *J* = 10.3, 11.8 Hz), 3.47 (s, 3 H), 3.89 (br d, 1 H, *J* =14.1 Hz), 4.44 (s, 1 H), 4.45 (dd, 1 H, *J* = 2.9, 11.8 Hz), 4.96 (s, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 6.3, 21.1, 24.1, 28.8, 39.4, 56.7, 68.5, 84.3, 87.3, 108.4, 154.4; Ms: *m/z* 354 (M^++ 1); *Anal.* Calcd for $C_{11}H_{16}NO_4I$: C, 37.41; H, 4.57; N, 3.97; Found: C, 37.15; H 4.50; N, 3.90.

(1*R*,8a*R*)-1-[(1*S*)-1-Hydroxybut-3-en-1-yl]-8a-vinylhexahydro[1,3]oxazolo[3,4-*a*]pyridin-3-one (14) and (1*R*,8a*R*)-1-[(1*R*)-1-Hydroxybut-3-en-1-yl]-8a-vinylhexahydro[1,3]oxazolo[3,4-*a*]pyridin-3-one (15)

Zn powder (6.3 g, 96.0 mmol), allyl bromide (2.4 g, 28.8 mmol) and iodofuranoside (**13**) (3.4 g, 9.6 mmol) in THF:H_2O (3:1, 30 mL) under argon atmosphere were sonicated at 40 ^oC until TLC revealed full consumption of the starting material. It took 3 h. The reaction mixture was filtered through celite and washed with ether. Removal of solvent gave the residue, which was purified on silica gel by using EtOAc-hexane (1:4) to afford one isomer (**14**) (1.4 g, 61%), as an oil. **14**: $[\alpha]_D$ = +5 ^{o} (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.30-1.74 (m, 6 H), 2.02-2.25 (m, 2 H), 2.48 (m, 1 H), 2.87 (m, 1 H), 3.69 (m, 2 H), 3.76 (dd, 1 H, *J* = 9.3, 1.3 Hz), 5.11 (m, 3 H), 5.57 (d, 1 H, *J* = 9.3 Hz), 5.62-5.80 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.3, 24.0, 35.9, 38.3, 38.5, 63.5, 68.1, 86.6, 118.1, 118.4, 133.2, 134.8, 155.9; Ms: *m/z* 238 (M^++ 1); *Anal.* Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90; Found: C, 65.78; H, 8.18; N, 5.76.

Further elution gave another isomer (**15**) (0.02 g, 8%), as an oil.

15: $[\alpha]_D$ = –3 ^{o} (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ1.38-1.81 (m, 6 H), 2.04 (m, 1 H), 2.28 (m, 2 H), 2.58 (br s, 1 H), 2.88 (m, 1 H), 3.75 (m, 1 H), 3.95 (d, 1 H, *J* = 5.4 Hz), 5.05-5.18 (m, 2 H), 5.25 (d, 1 H, *J* = 17.4 Hz), 5.52 (d, 1 H, *J* = 10.9 Hz), 5.67-5.92 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.7, 24.3, 34.6, 37.2, 38.9, 62.9, 69.1, 86.4, 118.2, 120.1, 133.4, 134.5, 156.4.

(4*S*,4a*R*,11a*R*)-4-(*tert*-Butyldimethylsilyloxy)-4,4a,8,9,10,11-hexahydro-1*H*-pyrido[1,2-*c*][1,3]-benzoxazol-6-one (17)

14 (1.4 g, 5.9 mmol), lutidine (1.4 mL, 11.8 mmol) and TBDMSOTf (2.0 mL, 8.9 mmol) in CH_2Cl_2 (10 mL) were stirred for 45 min. The reaction mixture was diluted with CH_2Cl_2, washed with 2 N HCl (30 mL), and the combined organic layer was dried (over Na_2SO_4), concentrated and the residue was purified on silica gel by eluting with EtOAc-hexane (1:9) to furnish **16** (1.93 g, 93%) as a syrup. $[\alpha]_D$ = +15 ^{o} (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 0.09 (s, 3 H), 0.13 (s, 3 H), 0.91 (s, 9 H), 1.30-1.79 (m, 6 H), 2.10 (m, 1 H), 2.45 (m, 1 H), 2.89 (dd, 1 H, *J* = 3.5, 12.8 Hz), 3.77 (m, 1 H), 4.02 (m, 2 H), 5.10-5.23 (m, 3 H), 5.45 (dd, 1 H, *J* = 1.2, 10.7 Hz), 5.55 (dd, 1 H, *J* = 10.5, 16.1 Hz), 5.79 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ – 4.8, –3.7, 17.7, 19.4, 24.1, 25.7, 35.9, 37.2, 38.1, 62.8, 69.8, 85.2, 118.2, 118.7, 132.0, 134.9, 155.4; Ms: *m/z* 352 (M^++ 1); *Anal.* Calcd for $C_{19}H_{33}NO_3Si$: C, 64.91; H, 9.46; N, 3.98; Found: C, 64.82; H, 9.44; N, 3.98.

16 (0.2 g, 0.56 mmol) and Grubbs' cat. (4.6 mg, 0.1 mol%) in CH_2Cl_2 (40 mL) was refluxed for 24 h under argon atmosphere. After that additional Grubbs' cat. (3.0 mg, 0.06 mol%) was added and further refluxed for 16 h. The solvent was evaporated and the residue was purified on silica gel by using EtOAc-

hexane (1:9) to give a white crystalline solid (**17**) (0.17 g, 92%). mp = 136 °C [recrystallized from ethyl acetate-hexane]; $[\alpha]_D$ = –72 ° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.09 (s, 6 H), 0.80 (s, 9 H), 1.44-1.85 (m, 6 H), 2.09-2.23 (m, 1 H), 2.41 (ddt, 1 H, *J* = 2.4, 6.8, 9.2 Hz), 2.90 (ddd, 1 H, *J* = 3.0, 12.6, 22.6 Hz), 3.70 (m, 1 H), 3.96 (ddd, 1 H, *J* = 2.5, 5.7, 9.7 Hz), 4.18 (br d, 1 H, *J* = 2.2 Hz), 5.75 (ddd, 1 H, *J* = 2.5, 5.7, 10.2 Hz), 5.94 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ –5.1, – 4.9, 17.7, 19.0, 24.0, 25.4, 29.4, 34.5, 37.7, 58.9, 66.7, 83.9, 123.1, 126.3, 155.5; Ms: *m/z* 324 (M^+ + 1); *Anal.* Calcd for $C_{17}H_{29}NO_3Si$: C, 63.12; H, 9.04; N, 4.33. Found: C, 63.29; H, 9.01; N, 4.22.

(4*R*,4a*R*,11a*R*)-4-(*tert*-Butyldimethylsilyloxy)-4,4a,8,9,10,11-hexahydro-1*H*-pyrido[1,2-*c*][1,3]-benzoxazol-6-one (19)

Compound (**19**) was obtained from **15** in 89% yield, as a syrup following the above procedure.

19: $[\alpha]_D$ = –20 ° (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.09 (s, 6 H), 0.90 (s, 9 H), 1.47-1.90 (m, 6 H), 2.18 (m, 1 H), 2.46 (ddt, 1 H, *J* = 2.8, 5.2, 9.8 Hz), 2.81-2.97 (m, 1 H), 3.62-3.76 (m, 1 H), 3.90-4.00 (ddd, 1 H, *J* = 2.5, 5.7, 9.4 Hz), 4.20 (br t, 1 H, *J* = 1.3 Hz), 5.78 (ddd, 1 H, *J* = 2.5, 5.7, 10.2 Hz), 5.90-5.99 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ –4.6, –4.4, 18.2, 19.5, 24.4, 25.8, 29.9, 34.9, 36.1, 59.3, 67.1, 84.4, 123.3, 126.8, 156.0.

(4*S*,4a*R*,11a*R*)-4-Hydroxyoctahydro-1*H*-pyrido[1,2-*c*][1,3]benzoxazol-6-one (18)

Compound (**17**) (0.12 g, 0.37 mmol), acetic acid (cat.) and 10% Pd/C (0.02 g) in methanol (10 mL) were hydrogenated at rt under 10 psi. The reaction was completed in 8 h, filtered through celite and concentrated. The residue was purified on silica gel by using EtOAc-hexane (1:9) to afford **18** (70.0 mg, 90%) as a white solid. mp = 112 °C [recrystallized from ethyl acetate-hexane]; $[\alpha]_D$ = – 40 ° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.25-1.92 (m, 12 H), 2.81 (t, 1 H, *J* = 12.8 Hz), 3.25 (br s, 1 H), 3.56-3.90 (m, 2 H), 4.17 (d, 1 H, *J* = 3.6 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 17.6, 18.7, 23.7, 26.4, 26.9, 31.0, 37.4, 58.9, 66.6, 83.7, 155.9; MS: *m/z* 212 (M^++1); *Anal.* Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63; Found: C, 62.26; H, 8.16; N, 6.52.

(4*R*,4a*R*,11a*R*)-4-Hydroxyoctahydro-1*H*-pyrido[1,2-*c*][1,3]benzoxazol-6-one (20)

Compound (**20**) was obtained from **19** in 92% yield, as an oil following the above procedure.

(4*S*,4a*R*,11a*R*)-4-Hydroxyoctahydro-1*H*-pyrido[1,2-*c*][1,3]benzoxazol-6-one (18 from 20)

To a solution of **20** (0.56 g, 2.6 mmol) in CH_2Cl_2 (10 mL) was added DMP (1.35 g, 3.2 mmol) at 0 °C. After 5 min, the reaction mixture was allowed to warm to rt and stirred for 1 h. The mixture was cooled down to 0 °C and washed with a sat. solution (10 mL) of $NaHCO_3/Na_2S_2O_3$ (1:1). The organic layer was washed with brine, dried (over Na_2SO_4) and concentrated. The crude residue was dissolved in THF (20

mL) and then $NaBH_4$ (0.1 g, 2.6 mmol) was added portionwise and stirred at rt for 3 h. The reaction mixture was quenched with sat. NH_4Cl, filtered, washed with ethyl acetate and the total organic layer was concentrated. The residue was purified on silica gel by using EtOAc-hexane (1:1) to get a white solid (**18**) (0.49 g, 88%).

(4*S*,4a*R*,11a*R*)-4-[2-Methoxyethoxymethoxy]octahydro-1*H*-pyrido[1,2-*c*][1,3]benzoxazol-6-one (21)

18 (0.38 g, 1.8 mmol) in dry THF:DMF (9:1, 12 mL) mixture was cooled to 0 °C, and NaH (60% dispersion in oil, 0.14 g, 3.6 mmol) was added portionwise. After 30 min MEMCl (0.32 mL, 2.7 mmol) was added and the mixture was stirred for 12 h. After usual work up the residue was purified on silica gel by using EtOAc-hexane (1:4) to get **21** (0.45 g, 83%) as an oil; $[\alpha]_D = -30$ ° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.25 (m, 1 H), 1.35-1.56 (m, 4 H), 1.67-1.90 (m, 7 H), 2.80 (dt, 1 H, *J* = 3.1, 13.3 Hz), 3.45 (s, 3 H), 3.55 (t, 2 H, *J* = 4.5 Hz), 3.68 (t, 1 H, *J* = 4.5 Hz), 3.70 (t, 1 H, *J* = 4.6 Hz), 3.75 (m, 1 H), 3.80 (m, 1 H), 4.25 (d, 1 H, *J* = 13.7 Hz), 4.87 (s, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 17.7, 18.9, 23.9, 24.8, 26.8, 31.8, 37.6, 58.5, 58.6, 66.6, 71.3, 72.3, 82.1, 93.8, 155.5; *Anal.* Calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68; Found: C, 60.34; H, 8.32; N, 4.58.

(4*S*,4a*R*,8*S*,11a*R*)-8-Allyl-4-[2-methoxyethoxymethoxy]octahydro-1*H*-pyrido[1,2-*c*][1,3]benzoxazol-6-one (22)

To a solution of **21** (0.1 g, 0.33 mmol) and TMEDA (0.05 mL, 0.33 mmol) in THF (5 mL) at 0 °C, *s*-BuLi (0.4 mL, 0.5 mmol) in hexane was added. After 40 min allyl bromide (0.06 mL, 0.5 mmol) in THF (3 mL) was introduced and the mixture was stirred for 2 h. The reaction mixture was quenched with sat. NH_4Cl and extracted with ethyl acetate. The organic layer was washed with brine, dried (over Na_2SO_4), and concentrated. The residue was purified on silica gel by using EtOAc-hexane (1:9) to get **22** (0.05 g, 44%) as an oil. $[\alpha]_D = -39$ ° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.27 (m, 2 H), 1.42 (m, 2 H), 1.72 (m, 6 H), 1.84 (m, 1 H), 1.98 (dt, 1 H, *J* = 4.3, 11.8 Hz), 2.70 (quintet, 1 H, *J* = 7.4 Hz), 3.06 (m, 1 H), 3.20 (m, 1 H), 3.38 (s, 3 H), 3.56 (t, 2 H, *J* = 8.6 Hz), 3.70 (m, 1 H), 3.78 (m, 1 H), 3.83 (m, 1 H), 4.13 (d, 1 H, *J* = 5.4 Hz), 4.80 (s, 2 H), 5.07 (m, 2 H), 5.77 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 18.7, 19.5, 25.9, 27.7, 30.6, 36.2, 51.4, 58.9, 61.8, 67.1, 71.9, 72.7, 80.9, 94.3, 117.5, 134.9, 156.2; *Anal.* Calcd for $C_{18}H_{29}NO_5$: C, 63.69; H 8.61; N, 4.13; Found: C, 63.72, H, 8.51, N, 4.25.

Further elution gave another side product (**23**) (0.02 g, 20%) as an oil. $[\alpha]_D = -36$ ° (*c* 1.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.29-2.01 (m, 8 H), 2.23 (m, 2 H), 3.39 (s, 3 H), 3.49 (m, 2 H), 3.66 (t, 1 H, *J* = 4.4 Hz), 3.75 (m, 2 H), 4.35 (d, 1 H, *J* = 3.2 Hz), 4.82 (s, 2 H), 4.97 (m, 1 H), 6.57 (dt, 1 H, *J* = 2.1, 8.3 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 18.2, 18.7, 25.4, 27.9, 29.2, 58.9, 67.2, 71.8, 72.8, 82.9, 94.3, 105.3, 120.8, 121.0, 150.9. *Anal.* Calcd for $C_{15}H_{23}NO_5$: C, 60.59; H 7.80; N, 4.71; Found: C, 60.71, H, 7.51, N, 4.77.

ACKNOWLEDGMENT

The author expresses her thanks to Dr. M. K. Gurjar for his guidance and CSIR, New Delhi for providing financial assistance in the form of senior research fellowship.

REFERENCES AND NOTES

1. J. W. Daly, I. Karle, C. W. Myers, T. Tokuyama, J. A. Waters, and B. Witkop, *Proc. Natl. Acad. Sci. U.S.A.,* 1971, **68**, 1870.

2. (a) D. J. Wardrop, W. Zhang, and C. L. Landrie, *Tetrahedron Lett.,* 2004, **45**, 4229. (b) J. J. Venit, M. DiPierro, and P. Magnus, *J. Org, Chem.,* 1989, **54**, 4298.

3. (a) D. Tanner and L. Hagberg, *Tetrahedron,* 1998, **54**, 7907 and references therein. (b) R. A. Stockman, *Tetrahedron Lett*., 2000, **41**, 9163. (c) S. C. Carey, M. Aratani, and Y. Kishi, *Tetrahedron Lett.,* 1985, ***26***, 5887. (d) G. Stork and K. Zhao, *J. Am. Chem. Soc.,* 1990, **112**, 5875. (e) G. M. Williams, S. D. Roughley, J. E. Davies, and A. B. Holmes, *J. Am. Chem. Soc*., 1999, **121**, 4900. (f) E. C. Davison, M. E. Fox, A. B. Holmes, S. D. Roughley, C. J. Smith, G. M. Williams, J. E. Davies, P. R. Raithby, J. P. Adams, I. T. Forbes, N. J. Press, and M. J. Thompson, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1494.

4. S. Hanessian, Total Synthesis of Natural Products, The Chiron Approach, Pergamon Press, New York, 1983.

5. (a) O. T. Smidt, *Methods in Carbohydr. Chem.,* 2, 319. (b) G. H. Jones and J. G. Moffatt, *Methods in Carbohydr. Chem*., 1972, **6**, 315.

6. J. J. Eisch and A. M. Jacobs, *J. Org. Chem.,* 1963, **28**, 2145.

7. (a) D. Postel, A. N. Van Nhien, M. Pillon, P. Villa, and G. Ronco, *Tetrahedron Lett.,* 2000, **41**, 6403. (b) R. Patra, N. C. Bar, A. Roy, B. Achari, N. Ghoshal, and S. B. Mandal, *Tetrahedron,* 1996, **52**, 11265.

8. For a general review, see: R. H. Grubbs, *Tetrahedron,* 2004, **60,** 7117.

9. (a) R. Madsen and C. S. Poulsen, *J. Org. Chem.* 2002, **67**, 4441. (b) L. Hyldtoft and R. Madsen, *J. Am. Chem. Soc.,* 2000, **122**, 8444.

10. L. F. Tietze, *Chem. Rev.,* 1996, **96**, 115.

11. (a) M. Che´rest, H. Felkin, and N. Prudent, *Tetrahedron Lett.,* 1968, 2199. (b) N. T. Anh, *Top. Curr. Chem.,* 1980, **88**, 145.

12. Crystallographic data for the structure (**18**) in this paper have been deposited with the Cambridge Crystallographic data Centre as supplementary publication number CCDC-246855. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, UK.

13. (a) P. Beak and W. Zaidel, *Chem. Rev.,* 1984, **84**, 471. (b) K. M. Bertini and P. Beak, *J. Am. Chem. Soc*., 2001, **123**, 315.