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 histrionicus* native to the Amazon rain forests of Southern Columbia, was first isolated by Daly, Witkop and co-workers in 1971. 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.

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\textsuperscript{2} as well as the total synthesis of histrionicotoxin alkaloids utilizing brilliant strategies.\textsuperscript{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.\textsuperscript{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\textsuperscript{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 Figure 1. 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**

![Figure 1](image)

**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\textsuperscript{5} (1) precursor was first transformed into the N-allylimine derivative (2). Subsequent C-allylation\textsuperscript{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.\textsuperscript{7} For instance, the sterically crowded 1,2-\(O\)-isopropylidene unit directs the incoming nucleophile from the \(\beta\)-face (Scheme 1)

\textbf{Scheme 1}

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme1.png}
\end{center}

\textbf{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\textsuperscript{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\textsubscript{2}O 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 \textit{via} intermediates (5-9) to produce the methyl glycoside. At first selective 5,6-acetonide deprotection of compound (3) with 1\% \(\text{H}_2\text{SO}_4\) in methanol at room temperature for 14 h followed by neutralization with \(\text{NaHCO}_3\) provided the diol derivative (5), which was protected as dibenzyl ether with benzyl bromide in \(\text{THF}\) in presence of cat. \(\text{TBAI}\) 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 \(\text{H}_2\text{SO}_4\) (6\%) to give the methyl glycoside derivative (7). The structure of \(\beta\)-methyl glycoside derivative (7) was established by the \(\text{^1H}\) and \(\text{^13C}\) NMR spectral analysis. The anomeric hydrogen of 7 resonated at 4.77 ppm, as a singlet indicating a 1,2-\textit{trans} relationship. The methyl glycoside derivative (7) on treatment with Boc\textsubscript{2}O in \(\text{CH}_2\text{Cl}_2\) in presence of DMAP furnished 8, which was converted to the corresponding carbamate (9) by using \(\text{NaOH}\) in \(\text{MeOH}:\text{THF}\) (1:1). The cyclic carbamate derivative (9) was subjected to RCM reaction using the 1\textsuperscript{st} 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$_2$SO$_4$, methanol, rt; b) benzyl bromide, NaH, TBAI, 0 °C–rt; c) 6% H$_2$SO$_4$, dry methanol, reflux; d) Boc$_2$O, DMAP, Et$_3$N, CH$_2$Cl$_2$, 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. Domino reactions are becoming a very attractive tool in this regard. Oxidative cleavage of 11 with sodium metaperiodate followed by reduction with NaBH$_4$ produced 12 which on treatment with triphenylphosphine, 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:H₂O under sonication at 45 °C 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) NaIO₄, CH₂Cl₂, 0 °C; NaBH₄, THF; b) TPP, I₂, 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 diffraction¹² 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).
Reagents and conditions: a) TBDMSOTf, lutidine, CH$_2$Cl$_2$, 0 °C; b) Grubbs’ cat., CH$_2$Cl$_2$, reflux; c) H$_2$, 10% Pd-C, 10 psi, cat. acetic acid; d) DMP, Et$_3$N, CH$_2$Cl$_2$; 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 °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 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).

Reagents and conditions: a) NaH, MEMCl, THF:DMF (1:1), 0 °C~rt; b) s-BuLi, allyl bromide, THF, 0 °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 CDCl₃ or DMSO-d₆ 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-\text{C}^3\text{-Allyl-3'}\text{N}-\text{allyl-3-deoxy-1,2:5,6-di-}\text{O}-\text{isopropylidine-}\alpha\text{-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 $-15^\circ$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$_4$Cl, 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$_2$SO$_4$), 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. $\left[\alpha\right]_D^\circ = +53^\circ$ (c 1, CHCl$_3$); $^1$H NMR (CDCl$_3$, 200 MHz): $\delta$ 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): $\delta$ 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-\text{C}^3\text{-Allyl-3'}\text{N}-\text{allyl-3-deoxy-5,6-di-}\text{O}-\text{benzyl-1,2-}\text{O}-\text{isopropylidine-}\alpha\text{-D-allofuranose (6)}

Compound (3) (8.9 g, 26.3 mmol) and 1% aqueous H$_2$SO$_4$ (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$_2$SO$_4$), 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. $\left[\alpha\right]_D^\circ = +75^\circ$ (c 1, CHCl$_3$); $^1$H NMR (acetone-d$_6$, 200 MHz): $\delta$ 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): $\delta$ 26.3, 26.7, 34.7, 48.1, 63.7,
Compound (5) (16.0 g, 53.5 mmol) in dry THF (100 mL) was cooled to 0 °C and NaH (60% dispersion in oil, 3.2 g, 80.2 mmol) was added portionwise at 0 °C. After 30 min at rt benzyl bromide (14.0 mL, 117.7 mmol) and Bu4NI (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%). [α]D = +28 ° (c 1, CHCl3); 1H NMR (CDCl3, 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); 13C NMR (CDCl3, 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 C29H37NO5: C, 72.62; H, 7.78; N, 2.92; Found: C, 72.94; H, 8.01; N, 2.85.

Methyl 3-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. H2SO4 (3 mL) in dry methanol (80 mL) was refluxed for 6 h, neutralized with K2CO3, filtered and concentrated. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried (over Na2SO4) 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. [α]D = −69 ° (c 1, CHCl3); 1H NMR (CDCl3, 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); 13C NMR (CDCl3, 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 C27H35NO5: 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), Boc2O (4.8 g, 21.2 mmol), and DMAP (10.0 mg, 0.09 mmol) in CH2Cl2 (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%). [α]D = −18 ° (c 1, CHCl3); 1H NMR (CDCl3, 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); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 50 MHz): \(\delta\) 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\(^{+2}\)); \textit{Anal.} Calcd for C\textsubscript{32}H\textsubscript{43}NO\textsubscript{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(3H)-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\textsubscript{2}SO\textsubscript{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 °C [recrystallized from ethyl acetate-hexane]; [\(\alpha\)]\textsubscript{D} = \(-49^\circ\) (c 1, CHCl\textsubscript{3}); \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 200 MHz): \(\delta\) 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); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 50 MHz): \(\delta\) 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\(^{-1}\); \textit{Anal.} Calcd for C\textsubscript{28}H\textsubscript{33}NO\textsubscript{6}: C, 70.13; H, 6.94; N, 2.92; Found: C, 69.96; H, 7.13; N, 2.92.

1-[1,2-bis-Benzylxyethyl]-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 eluting with EtOAc-hexane (1:9) as eluent to give 10 (4.1 g, 87%), as a yellow liquid. [\(\alpha\)]\textsubscript{D} = \(-37^\circ\) (c 1, CHCl\textsubscript{3}); \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 200 MHz): \(\delta\) 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); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 50 MHz): \(\delta\) 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\(^{+1}\)); \textit{Anal.} Calcd For C\textsubscript{26}H\textsubscript{29}NO\textsubscript{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 °C [recrystallized from ethyl acetate-hexane]; [α]D = −105 ° (c 1, CHCl3); 1H NMR (CDCl3, 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); 13C NMR (CDCl3, 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 C12H19NO6: 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 CH2Cl2 (20 mL) were stirred at rt for 30 min and filtered. Organic layer was washed with 5% Na2S2O3, brine, dried (over Na2SO4) and concentrated to give aldehyde (4.0 g, 91%). It was dissolved in THF (20 mL) and then NaBH4 (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. NH4Cl, filtered, washed with ethyl acetate and the total organic layer was dried (over Na2SO4) 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 °C [recrystallized from ethyl acetate-hexane]; [α]D = −115 ° (c 1, CHCl3); 1H NMR (CDCl3, 200 MHz): δ 1.44-1.77 (m, 5 H), 1.96 (m, 1 H), 2.25 (m, 1 H), 2.89-3.03 (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), 4.46 (t, 1 H, J = 3.1 Hz), 5.0 (s, 1 H); 13C NMR (CDCl3, 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 C12H17NO5: 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), I2 (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% NaHCO3, 5% Na2S2O3, and brine, dried (over Na2SO4), and concentrated. The residue was purified on silica gel by using EtOAc-hexane (1:1) to get a solid compound (13) (4.0 g, 92%). mp = 170 °C [recrystallized from ethyl acetate-hexane]; [α]D = −3 ° (c 1, CHCl3); 1H NMR (CDCl3, 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); 13C NMR (CDCl3, 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 C11H16NO4I: C, 37.41; H, 4.57; N, 3.97; Found: C, 37.15; H 4.50; N, 3.90.
(1R,8aR)-1-[(1S)-1-Hydroxybut-3-en-1-yl]-8a-vinylhexahydro[1,3]oxazolo[3,4-a]pyridin-3-one (14) and (1R,8aR)-1-[(1R)-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:H2O (3:1, 30 mL) under argon atmosphere were sonicated at 40 °C 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: [α]D = +5 ° (c 1, CHCl3); 1H NMR (CDCl3, 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); 13C NMR (CDCl3, 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 C13H19NO3: 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: [α]D = –3 ° (c 1, CHCl3); 1H NMR (CDCl3, 200 MHz): δ 1.38-1.81 (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); 13C NMR (CDCl3, 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.

(4S,4aR,11aR)-4-(tert-Butyldimethylsilyloxy)-4,4a,8,9,10,11-hexahydro-1H-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 CH2Cl2 (10 mL) were stirred for 45 min. The reaction mixture was diluted with CH2Cl2, washed with 2 N HCl (30 mL), and the combined organic layer was dried (over Na2SO4), 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. [α]D = +15 ° (c 1, CHCl3); 1H NMR (CDCl3, 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); 13C NMR (CDCl3, 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 C19H33NO3Si: 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 CH2Cl2 (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]; \([\alpha]_D = -72^\circ\) (c 1, CHCl₃); \(^1\)H NMR (CDCl₃, 200 MHz): S 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, J = 2.4, 6.8, 9.2 Hz), 2.90 (ddd, J = 3.0, 12.6, 22.6 Hz), 3.70 (m, 1 H), 3.96 (ddd, J = 2.5, 5.7, 9.7 Hz), 4.18 (br d, J = 2.2 Hz), 5.75 (ddd, J = 2.5, 5.7, 10.2 Hz), 5.94 (m, 1 H); \(^13\)C NMR (CDCl₃, 50 MHz): S –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 C₁₇H₂₉NO₃Si: C, 63.12; H, 9.04; N, 4.33. Found: C, 63.29; H, 9.01; N, 4.22.

(4R,4aR,11aR)-4-(tert-Butyldimethylsilyloxy)-4,4a,8,9,10,11-hexahydro-1H-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: \([\alpha]_D = -20^\circ\) (c 1.4, CHCl₃); \(^1\)H NMR (CDCl₃, 200 MHz): S 0.09 (s, 6 H), 0.90 (s, 9 H), 1.47-1.90 (m, 6 H), 2.18 (m, 1 H), 2.46 (dt, 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, J = 2.5, 5.7, 9.4 Hz), 4.20 (br t, J = 1.3 Hz), 5.78 (ddd, J = 2.5, 5.7, 10.2 Hz), 5.90-5.99 (m, 1 H); \(^13\)C NMR (CDCl₃, 50 MHz): S –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.

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

Compound (17) (0.11 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]; \([\alpha]_D = -40^\circ\) (c 1, CHCl₃); \(^1\)H NMR (CDCl₃, 200 MHz): S 1.25-1.92 (m, 12 H), 2.81 (t, J = 12.8 Hz), 3.25 (br s, 1 H), 3.56-3.90 (m, 2 H), 4.17 (d, J = 3.6 Hz); \(^13\)C NMR (CDCl₃, 50 MHz): S 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 C₁₁H₁₇NO₃: C, 62.54; H, 8.11; N, 6.63; Found: C, 62.26; H, 8.16; N, 6.52.

(4R,4aR,11aR)-4-Hydroxyoctahydro-1H-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.

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

To a solution of 20 (0.56 g, 2.6 mmol) in CH₂Cl₂ (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 NaHCO₃/Na₂S₂O₅ (1:1). The organic layer was washed with brine, dried (over Na₂SO₄) and concentrated. The crude residue was dissolved in THF (20
mL) and then NaBH₄ (0.1 g, 2.6 mmol) was added portionwise and stirred at rt for 3 h. The reaction mixture was quenched with sat. NH₄Cl, 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%).

(4S,4aR,11aR)-4-[2-Methoxyethoxymethoxy]octahydro-1H-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; [α]D = –30 ° (c 1, CHCl₃); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 C₁₅H₂₅NO₅: C, 60.18; H, 8.42; N, 4.68; Found: C, 60.34; H, 8.32; N, 4.58.

(4S,4aR,8S,11aR)-8-allyl-4-[2-methoxyethoxymethoxy]octahydro-1H-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. NH₄Cl and extracted with ethyl acetate. The organic layer was washed with brine, dried (over Na₂SO₄), 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; [α]D = –39 ° (c 1, CHCl₃); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 C₁₈H₂₉NO₅: 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. [α]D = –36 ° (c 1.8, CHCl₃); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 C₁₅H₂₃NO₅: C, 60.59; H, 7.80; N, 4.71; Found: C, 60.71, H, 7.51, N, 4.77.
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REFERENCES AND NOTES


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 1EZ, UK.