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A Versatile Synthetic Route to Indolizidines, (+)-7-Deoxy-6-epicastanospermine, (-)-7,8-Dideoxy-6-epicastanospermine and (-)-*N*-Acetylslaframine

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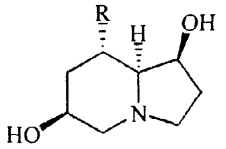
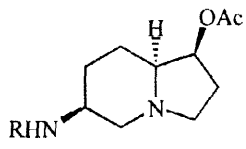
Abstract : (+)-7-Deoxy-6-epicastanospermine **1**, (-)-7,8-dideoxy-6-epicastanospermine **2** and (-)-*N*-acetylslaframine **4** have been synthesized *via* the stereoselective intramolecular iodocyclization of trichloroacetimidates generated from *cis*-olefinic allylic alcohols **7** and **15**, respectively.

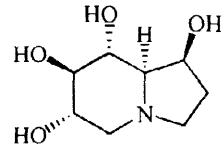
Since the bicyclic hydroxylated indolizidines retain physiologically valuable properties with the attractive chemical structures,[1] the synthesis of both the natural alkaloids and their artificial analogues has been intensively pursued.[2] Among them, (+)-7-deoxy-6-epicastanospermine **1** and (-)-7,8-dideoxy-6-epicastanospermine **2** have not been synthesized, of which the former is the only natural deoxy analogue of (+)-castanospermine **5**. (+)-7-Deoxy-6-epicastanospermine **1** isolated from *Castanospermum australe* is



1 R = OH
2 R = H



3 R = H
4 R = Ac



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known to be an inhibitor of amyloglucosidase and yeast α-glucosidase, but less potent than (+)-castanospermine **5**.[3] (-)-Slaframine **3** is a metabolite of the fungus *Rhizoctonia leguminicola*, which can infest ruminant forages.[4] When such forages are ingested by ruminants, the mycotoxin is oxidatively activated and subsequently binds to muscarinic acetylcholine receptor sites to induce excess salivation in the animals.[5] Accordingly, (-)-slaframine **3** may be clinically useful for the treatment of diseases arising from cholinergic dysfunctions.[6] Considering the alkaloids as amino alcohol derivatives, we envisioned to utilize the intramolecular iodoamidation of trichloroacetimidate derived from *cis*-olefinic allylic alcohol [7] in a stereocontrolled manner for their synthesis. Herein we wish to describe a highly enantioselective synthesis of (+)-7-deoxy-6-epicastanospermine **1**, (-)-7,8-dideoxy-6-epicastanospermine **2** and (-)-*N*-acetylslaframine **4**.[8]

The synthesis of (+)-7-deoxy-6-epicastanospermine **1** commenced with conversion of (*S*)-butane-1,2,4-triol[9] into a 7.5~8:1 mixture of 6-membered and 5-membered benzylidenes in 87% yield using *p*-anisaldehyde in the presence of pyridinium *p*-toluenesulfonate (PPTS) (Scheme 1). The inseparable mixture was oxidized under Swern conditions, [10] and then Wittig olefination with the ylid derived from phosphonium salt **6**[11] gave a 19:1 mixture of *cis*- and *trans*-olefinic 6-membered benzylidenes in 69% combined yield along with 7% of the isomeric olefins originated from 5-membered benzylidenes. After chromatographic separation, the

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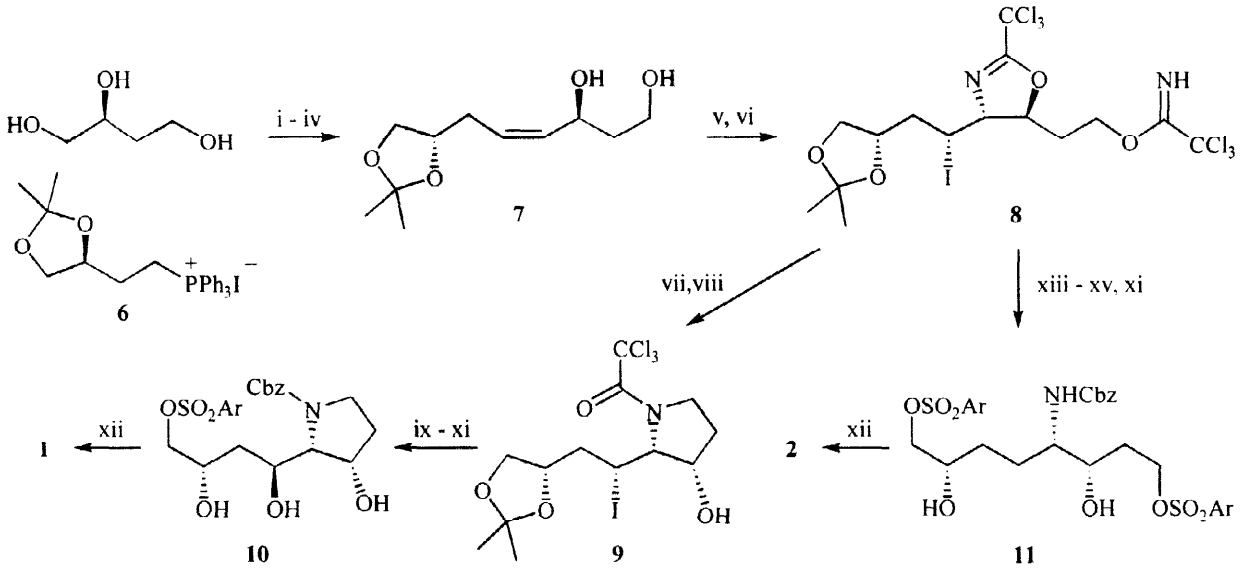
Scheme 1

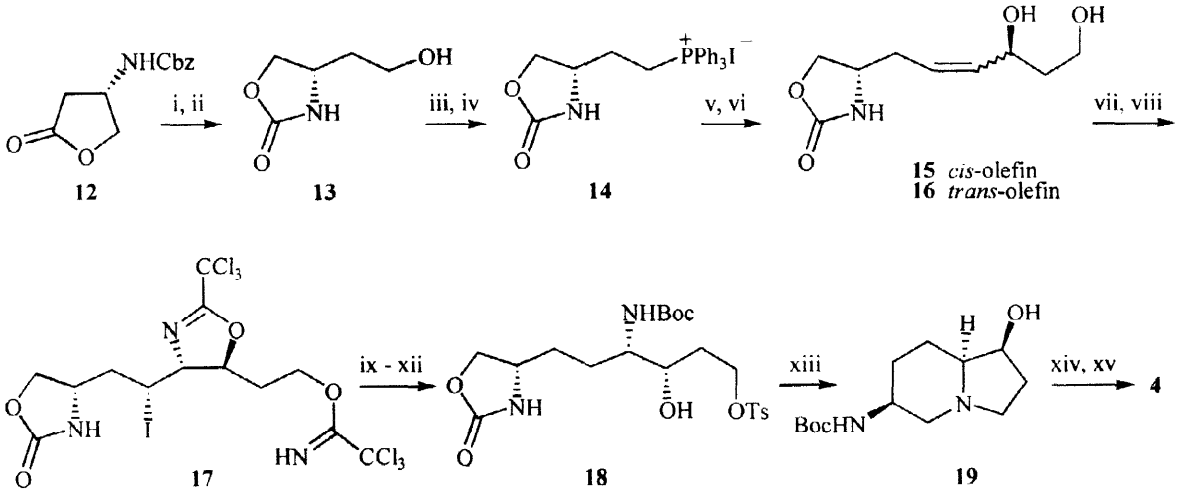


Reagents : i) *p*-$MeOC_6H_4CHO$, PPTS, PhMe, Dean-Stark trap, 120°C. ii) Swern ox. iii) **6**, *n*-BuLi, HMPA,THF, -78~0°C. iv) PPTS, MeOH, 0°C. v) Cl_3CCN(3 equiv.), DBU(1.5 equiv.), MeCN, 0°C. vi) IBr(2.5 equiv.), K_2CO_3(1.1 equiv.), EtCN, -78°C. vii) PPTS, MeOH, rt. viii) DEAD, Ph_3P, THF, 0°C. ix) aq. CF_3COOH, reflux. x) BnOCOCl, $NaHCO_3$, MeOH, 0°C. xi) 2,4,6-$Me_3C_6H_2SO_2Cl$, Py, 0°C. xii) H_2, 10% Pd/C, MeOH, then Et_3N, reflux. xiii) 6N HCl, MeOH, rt. xiv) BnOCOCl, $NaHCO_3$, MeOH, 0°C. xv) Ph_3SnH, Et_3B, THF, 0°C.

desired *cis*-olefinic dioxane was chemoselectively hydrolyzed under acidic conditions to provide *cis*-olefinic allylic alcohol **7**, $[\alpha]_D^{27}$ +9.9 (*c* 1.30, $CHCl_3$), in 86% yield. The next pivotal functionalization was conducted by sequential treatment of **7** with trichloroacetonitrile in the presence of DBU at 0°C and iodine monobromide at -78°C to furnish *trans*-oxazoline **8**, $[\alpha]_D^{19}$ -76.8 (*c* 1.65, $CHCl_3$), as a single stereoisomer in 86% yield. Partial hydrolysis of **8** with PPTS in aqueous methanol yielded dihydroxyl trichloroacetamide, which was cyclized under Mitsunobu conditions[12] to produce pyrrolidine **9**, $[\alpha]_D^{18}$ +82.6 (*c* 0.85, $CHCl_3$), in 82% overall yield. Refluxing **9** in aqueous trifluoroacetic acid effected substitution of its iodo group by hydroxyl group with complete inversion, which was probably assisted by trichloroacetyl oxygen, and the concomitant deproctection. The generated pyrrolidine tetraol was sequentially subjected to benzyl chloroformate and mesitylenesulfonyl chloride to afford sulfonate **10**, $[\alpha]_D^{21}$ +29.8 (*c* 1.10, $CHCl_3$), in 79% overall yield. After removal of benzyloxycarbonyl group of **10** by hydrogenation, triethylamine was added and the resulting mixture was refluxed for the *in situ* cyclization to give (+)-7-deoxy-6-epicastanospermine **1**, mp 152~153°C (decomposition), $[\alpha]_D^{16}$ +28.0 (*c* 0.80, MeOH){lit.,[3] $[\alpha]_D^{26}$ +18.3 (*c* 0.712, MeOH)}, in 69% yield, of which the spectroscopic data was identical to the reported.[3]

For the synthesis of (-)-7,8-dideoxy-6-epicastanospermine **2**, oxazoline **8** was completely hydrolyzed and the unmasked amino group was protected as benzyl carbamate. The pendent iodine was efficiently reduced by radical process[13] and finally the two primary hydroxy groups were sulfonated with mesitylenesulfonyl chloride to provide disulfonate **11**, $[\alpha]_D^{20}$ -8.2 (*c* 1.10, $CHCl_3$), in 68% overall yield. Treatment of **11** under the same conditions as described in the formation of **1** from **10** furnished (-)-7,8-dideoxy-6-epicastanospermine **2**,[14] $[\alpha]_D^{17}$ -2.7 (*c* 0.75, MeOH), in 73% yield.

Scheme 2



Reagents : i) 6N NaOH, MeOH, 20°C, then CH_2N_2 after neutralization. ii) $LiBH_4$, THF, 0~20°C. iii) I_2, Ph_3P, imidazole, DMF, 20°C. iv) Ph_3P, MeCN, reflux. v) *n*-BuLi, HMPA, THF, 0°C, then aldehydes, -78~20°C. vi) H_5IO_6, aq. MeOH, 20°C. vii) Cl_3CCN(2.5 equiv.), DBU(1.2 equiv.), MeCN, 0°C. viii) IBr(3.5 equiv.), K_2CO_3(1.1 equiv.), EtCN, -78°C. ix) 6N HCl, MeOH, 20°C. x) Boc_2O, $NaHCO_3$, MeOH, 0°C. xi) Ph_3SnH, Et_3B, THF, 0°C. xii) TsCl, Py, CH_2Cl_2, 0°C. xiii) 180°C, then Boc_2O, $NaHCO_3$, MeOH. xiv) CF_3COOH, CH_2Cl_2, 20°C. xv) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 20°C.

Since (-)-slaframine comprises 6β-amino group, the known lactone **12**[15] containing the requisite amino group was employed (Scheme 2). Ring opening of **12** followed by esterification and the ensuing lithium borohydride reduction produced alcohol **13** in 80% yield. By the conventional procedure, **13** was converted into phosphonium salt **14** in 54% overall yield *via* the formation of iodide. Wittig olefination of **14** was carried out using 2 equiv. of *n*-BuLi with the aforementioned aldehydes prepared form (*S*)-butane-1,2,4-triol and *p*-anisaldehyde. The resulting mixture was treated with periodic acid in aqueous methanol to provide a 10:1 inseparable mixture of olefins **15** and **16** in 64% combined overall yield *via* chemoselective hydrolysis of benzylidene groups and oxidative removal of the minor vicinal diols derived from 5-membered benzylidenes. The isomeric olefins were readily separated by converting them into bis(trichloroacetimidate)s. The purified *cis*-oleifinc allylic imidate was cyclized with iodine monobromide at -78°C to furnish an isomerically pure *trans*-oxazoline **17**, $[\alpha]_D^{24}$ -13.6 (*c* 1.00, $CHCl_3$), in 83% overall yield. Hydrolysis of **17** and the subsequent protection of the generated amino group produced the desired iodo carbamate in 64% yield along with 27% of the corresponding aziridine. Reductive removal of the iodo group and the following sulfonation of the primary hydroxy group afforded tosylate **18**, $[\alpha]_D^{25}$ -21.6 (*c* 1.00, $CHCl_3$), in 86% yield. Pyrolytic[16] double cyclization of **18** at 180°C gave deacetylated slaframine, of which the amino group was protected with di-*t*-butyl dicarbonate to provide indolizidine **19** in 74% yield. For the purpose of identification, **19** was deprotected and then acetylated to yield the known *N*-acetyl-slaframine **4**, $[\alpha]_D^{24}$ -12.8 (*c* 1.00, EtOH) {lit.,[8c] $[\alpha]_D^{19}$ -15.7 (*c* 0.14, EtOH); lit.,[17] $[\alpha]_D^{25}$ -11.2 (*c* 1.45, EtOH)}, quantitatively, of which the spectroscopic data matched those reported in the literatures.[18, 19]

In conclusion, we have developed a divergent synthetic route to indolizidines **1**, **2**, and **4** applying the intramolecular iodoamidation of *cis*-olefinic allylic trichloroacetimidate to the diastereoselective introduction of the indispensable amino group.

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14. *Spectroscopic data* for **2** : IR ν_{max}/cm^{-1}($CHCl_3$) 3353, 2935, 1446, 1337, 1120 and 971. ^1H NMR (300 MHz, CD_3OD) δ 1.35–1.87 (6H, m), 1.98 (1H, dd, J 8.8, 17.6), 2.10 (1H, dd, J 1.9, 11.6), 2.16 (1H, m), 3.01 (1H, dt, J 2.2, 8.9), 3.09 (1H, md, J 11.6), 3.86 (1H, m) and 4.06 (1H, m). ^{13}C NMR (75.5 MHz, CD_3OD) δ 20.7, 31.4, 33.7, 53.7, 59.7, 66.3, 69.4 and 73.6. HRMS(M^+) calcd 157.1103 for $C_8H_{15}NO_2$, found 157.1122.
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