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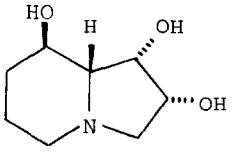
TOTAL SYNTHESIS OF (+)-CASTANOSPERMINE FROM D-MANNOSE

Hiroyuki Setoi, Hidekazu Takeno, and Masashi Hashimoto*

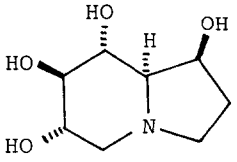
Exploratory Research Laboratories, Fujisawa Pharmaceutical Co., Ltd.
2-1-6 Kashima, Yodogawa-ku, Osaka 532, Japan

Summary: A total synthesis of (+)-castanospermine (2) has been achieved starting from D-mannose by a route adopting a double-cyclization process (5c → 6) as the key step.

Considerable effort has been directed recently towards the total synthesis of swainsonine (1)[1] and castanospermine (2)[2], the two representative polyhydroxylated-indolizidine alkaloids[3] which exhibit glucosidase-inhibitory activities. In the preceding paper,[4] we have demonstrated that the indolizidine ring of swainsonine can be formed via a double cyclization of the epoxy amino ester 3 (as depicted in 3). We now report a total synthesis of (+)-castanospermine (2) from D-mannose by a route adopting a similar cyclization process as the key step. A noteworthy feature of this cyclization reaction is that, unlike the indolizidinone-forming reaction in the synthesis of swainsonine, the first step is the piperidine ring closure (as depicted in 5 by arrow *a*) which is set up by the acetonide protection of the 6,7-trans-diol, and is subsequently followed by the pyrrolidone ring formation (arrow *b*).



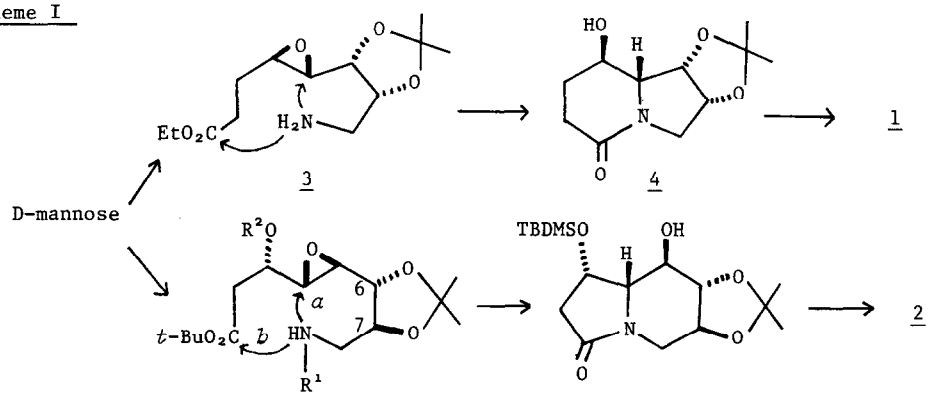
1



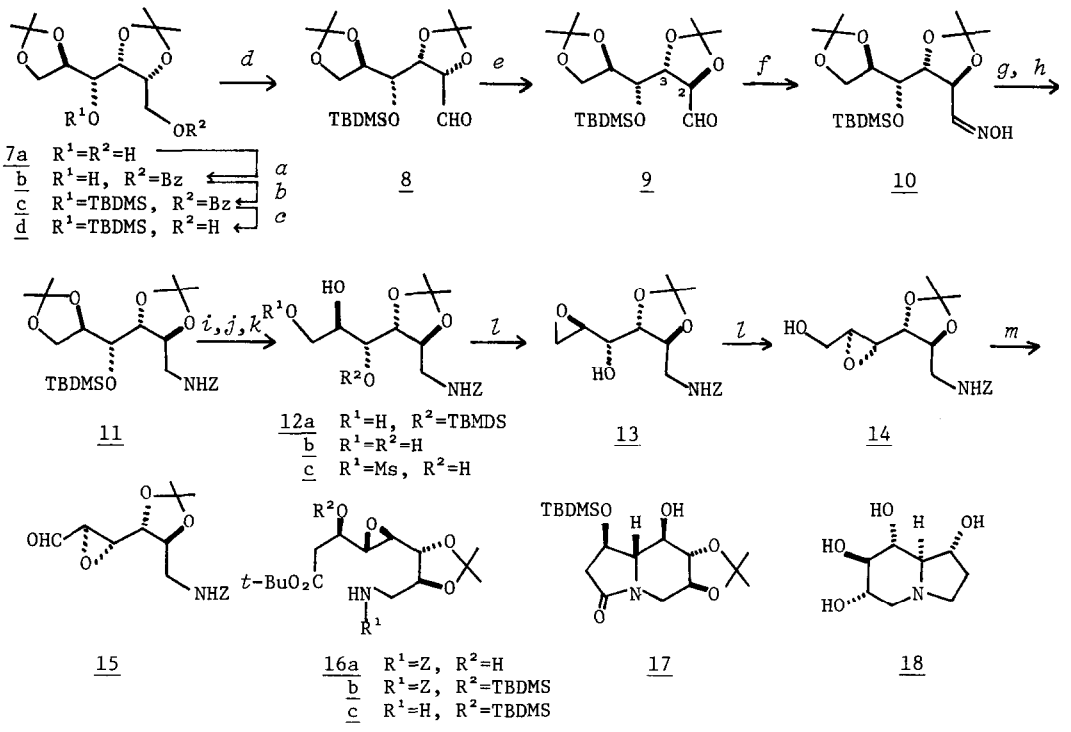
2

The requisite intermediate 5a was prepared as follows. Selective benzoylation of the diol 7a, readily prepared from D-mannose,[5] gave the monobenzoate 7b (62%). Protection of the hydroxy group in 7b with *t*-butyldimethylsilyl (TBDMS) chloride was followed by removal of the

Scheme I



Scheme II



a) BzCl/pyridine, room temp; *b*) TBDMSCl/imidazole/DMF, 80°C; *c*) 1N NaOH/MeOH, room temp; *d*) DMSO/DCC/TFA/pyridine/benzene, room temp; *e*) K_2CO_3 (3 equiv)/MeOH, room temp; *f*) $H_2NOH \cdot HCl$/$NaHCO_3$/EtOH-H_2O, 60°C; *g*) $LiAlH_4$/THF, room temp; *h*) ZCl/THF-H_2O, 0°C; *i*) TsOH (0.1 equiv)/MeOH-H_2O (9:1), 15°C; *j*) *n*-Bu_4NF/THF, 0°C; *k*) MsCl/pyridine, 5°C; *l*) MeONa (1.4 equiv)/MeOH, 20°C; *m*) $CrO_3 \cdot 2$pyridine/CH_2Cl_2, 5°C.

benzoyl group by alkaline hydrolysis to give the alcohol 7d (99% from 7b). Moffatt oxidation of 7d and successive treatment of the resulting aldehyde 8 (91%) with K_2CO_3 in MeOH,[6] afforded the 2,3-trans aldehyde 9 (87%). This compound was derived to the oxime 10 (*E*/*Z* mixture, 99%), which was then subjected to $LiAlH_4$ reduction followed by carbobenzyloxylation, yielding the protected amine 11 (78%). Partial hydrolysis of 11 by treatment with TsOH in aqueous MeOH produced the diol 12a (41%) and the triol 12b (21%), along with a 26% recovery of the starting material 11. The TBDMS ether in 12a was easily removed by treatment with *n*-Bu_4NF to also give 12b (85%). The primary hydroxy group in 12b was mesylated and the resulting monomesylate 12c (68%) was successively treated with MeONa in MeOH to provide the epoxide 14[10] (60%), together with the intermediary end-epoxide 13[10] (13%) which was converted to 14 by further treatment with MeONa (64%).[7] Oxidation of 14 with Collins' reagent gave the aldehyde 15, which without isolation was allowed to react with *t*-butyl lithioacetate, providing a mixture of the diastereoisomers 5a[10] and 16a[10] (24% from 14) in a ratio of 3:2.[8] Since the isolation of the desired product 5a at this stage was found to be rather difficult, we decided to directly subject the mixture to the following reactions.

The stage was now set to investigate the key double-cyclization reaction. After protection of the hydroxy groups in 5a and 16a with TBDMS in a manner similar to that for 7c, the mixture was subjected to catalytic reduction on 10% Pd-C in EtOH for removal of the Z groups, yielding a mixture of the amines 5c and 16c, which was then refluxed in methoxyethanol to afford as expected the indolizidinones 6 and 17 in a ratio reflecting that of the starting mixture. A silica gel chromatography (hexane-AcOEt) separated 6 and 17 in 31% and 20% yields from the mixture of 5a and 16a, respectively. The structures of these products were characterized by their spectral properties[10] and further confirmed by conversion to 2 and its isomer 18. The versatility of the above cyclization process was thus discerned.

Finally, the compound 6 was subjected to reduction using borane-THF complex (THF, reflux) followed by treatment with 6N HCl (THF, reflux) to afford in 83% yield (+)-castanospermine (2)[10] [mp 207-210°C dec, $[\alpha]_D^{19}$ +79.0° (c 0.2, H_2O)], identical with an authentic sample[9] in all respects. 1-Epicastanospermine (18)[10] [oil, $[\alpha]_D^{22}$ -39.1° (c 0.4, H_2O)] was also obtained by the same treatments of 16 in 78% yield.

The results described here illustrate the potential flexibility of our double-cyclization approach to the synthesis of the polyhydroxylated indolizidine alkaloids.

References and Notes

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5. W.M.Doane, B.S.Shasha, C.R.Russell, and C.E.Rist, J. Org. Chem., 32, 1080 (1967).
6. For base-catalyzed epimerization of the acetonides of the *erythro*-2,3-dihydroxy aldehydes or esters to the corresponding *threo* compounds, see e.g. (a) M.Hashimoto, Y.Saito, H.Seki, and T.Kamiya, Tetrahedron Lett., 1359 (1970); (b) A.W.M.Lee, V.S.Martin, S.Masamune, K.B.Sharpless, and F.J.Walker, J. Am. Chem. Soc., 104, 3515 (1982).
7. For conversion of the 1,2,3-triols such as 12b to the primary epoxy-alcohols via secondary ones, see e.g. J.Rokach, R.Zamboni, C.-K.Lau, and Y.G.Guindon, Tetrahedron Lett., 22, 2759 (1981).
8. The ratio was estimated from the ^{1}H NMR spectrum ($CDCl_3$) of the mixture, in which the C-2 methylene protons were observed at δ 2.50(d, J=5Hz, 6/5H) and 2.48(d, J=5Hz, 4/5H). The desired compound 5a was found, after conversion of the mixture to 6 and 17, to be the major one.
9. We are grateful to Professor E.A.Bell of King's College and Mr. R.J.Nash of Royal Botanic Gardens for an authentic sample of (+)-castanospermine.
10. The selected physical data. 13: oil; ^{1}H NMR ($CDCl_3$) δ 2.76(dd, J=2, 5Hz, 1H), 2.83(dd, J=3, 5Hz, 1H), 3.08(m, 1H), 3.47(dd, J=4, 6Hz, 2H), 3.54(m, 1H), 3.92(dd, J=4,9Hz, 1H), 4.15(q, J=4Hz, 1H). 14: oil; ^{1}H NMR ($CDCl_3$) δ 3.13(dd, J=2, 5Hz, 1H), 3.24(m, 1H), 3.47(dd, J=4, 6Hz, 2H), 3.66(dd, J=5, 8Hz, 1H), 3.73(dd, J=3, 13Hz, 1H), 3.92(dd, J=2, 13Hz, 1H), 4.0(dt, J=4, 8Hz, 1H). 5a and 16a: oil; ^{1}H NMR ($CDCl_3$) δ 2.48(d, J=5Hz, 4/5H), 2.50(d, J=5Hz, 6/5H), 3.1-3.2(m, 2H), 3.47(dd, J=5, 7Hz, 2H), 3.65(m, 1H), 4.0-4.2(m, 2H). 6: mp 168-170°C; $[\alpha]_D^{21}$ +81.2° (c 0.5, $CHCl_3$); IR (Nujol) 1675 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.40(dd, J=4, 17Hz, 1H), 2.68(dd, J=7, 17Hz, 1H), 2.73(t, J=12Hz, 1H), 3.32(ddd, J=5, 10, 12Hz, 1H), 3.44(dd, J=7, 10Hz, 1H), 3.57(t, J=10Hz, 1H), 4.08(t, J=10Hz, 1H), 4.49(dd, J=5,12Hz, 1H), 4.68(dt, J=4, 7Hz, 1H). 17: mp 174-177°C; $[\alpha]_D^{17}$ +32.7° (c 0.3, $CHCl_3$); IR (Nujol) 1665 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.44(dd, J=4, 17Hz, 1H), 2.70(dd, J=8, 17Hz, 1H), 2.80(t, J=11Hz, 1H), 3.22(ddd, J=5, 9, 11Hz, 1H), 3.26(dd, J=3, 10Hz, 1H), 3.48(dd, J=9, 10Hz, 1H), 3.49(t, J=3Hz, 1H), 4.42(ddd, J=3, 4, 8Hz, 1H), 4.52(dd, J=5, 11Hz, 1H). 2: ^{1}H NMR (D_2O) δ 1.73(m, 1H), 2.05(dd, J=5, 10Hz, 1H), 2.08(t, J=10Hz, 1H), 2.24(q, J=10Hz, 1H), 2.36(m, 1H), 3.11(dt, J=2, 10Hz, 1H), 3.20(dd, J=5, 10Hz, 1H), 3.34(t, J=9Hz, 1H), 3.62(dd, J=9, 10Hz, 1H), 3.65(m, 1H), 4.43(m, 1H). 18: ^{1}H NMR (D_2O) δ 1.67(m, 1H), 2.13(t, J=9Hz, 1H), 2.24(t, J=11Hz, 1H), 2.28(m, 1H), 2.58(q, J=9Hz, 1H), 2.95(dt, J=2, 10Hz, 1H), 3.15(dd, J=5, 11Hz, 1H), 3.32(t, J=9Hz, 1H), 3.38(t, J=9Hz, 1H), 3.60(m, 1H), 4.23(m, 1H).

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