Tetrahedron Letters, Vol.30, No.6, pp 705-706, 1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

A HIGHLY STEREOSELECTIVE TOTAL SYNTHESIS OF (±)CASTANOSPERMINE

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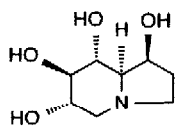
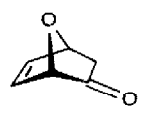
Summary: *An efficient synthesis of (±)castanospermine based on the bromine addition to 7-oxabicyclo[2.2.1]hept-5-en-2-one benzyl acetal is presented.*

Castanospermine ((+)-**1**) is a physiologically active polyhydroxylated indolizidine alkaloid isolated from seeds of *Castanospermum australe*[1] and from dried pod of *Alexa leiopetala*.[2] It is an inhibitor of several glucosidases[3] with promising anti-cancer,[4] anti-virus[5] and anti-AIDS[6] activities. Syntheses of (+)-**1** using carbohydrates as starting materials have already been proposed.[7] We present a highly stereoselective methodology which transforms 7-oxanorbonenone ((±)-**2**) into (±)-**1**.



(+)-**1**



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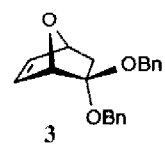

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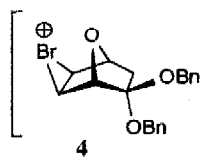
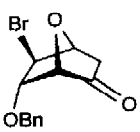
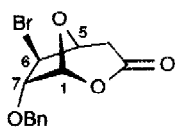


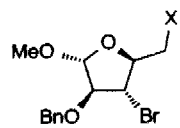
4 **5**



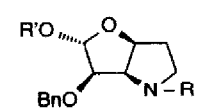
6 (m.p. 74-74.5°C)



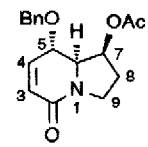
7 (107-8°C)



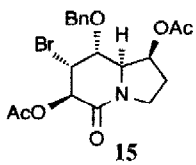
8 X=COOMe (oil)
9 X=CH_2OH (oil)
10 X=CH_2OSO_2Me (oil)



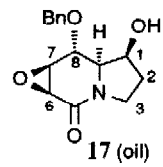
11 R=H, R'=Me (oil)
12 R=$COCH_2Cl$, R'=Me (oil)
13 R=$COCH_2Cl$, R'=Ac (oil)



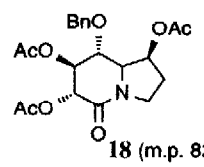
14 (91.5-92.5°C)



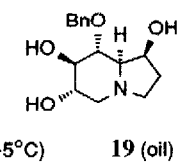
15 + **16**



17 (oil)



18 (m.p. 82-5°C)



19 (oil)

Bromination (Br_2, CH_2Cl_2, -80 °C) of the dibenzyl acetal **3** of enone **2**[8] gave the protected bromohydrine **6** (87 %) stereoselectively. The results can be interpreted in terms of formation of intermediates **4** ⇄ **5** that lead to the stereoselective migration of the *endo* BnO group of the acetal.[9] Oxidation of **6** with *m*-$ClC_6H_4CO_3H$ ($NaHCO_3$, CH_2Cl_2, 5 to 20 °C) furnished lactone **7** (96 %, ^{1}H-NMR (360 MHz, $CDCl_3$): 7.37 (br.*s*, 5H), 5.90 (*d*, *J*=4, H-C(1)); 4.74 (*d*, *J*=7, H-C(5)); 4.70 & 4.60 (*m*, ^2J=11.5); 4.56 (*d*, *J*=4, H-C(7)); 4.08 (*s*, H-C(6)); 3.13 (*dd*, ^3J=4, ^2J=18.5, H*exo*-C(4)); 2.69 (*d*, ^2J=18.5, H*endo*-C(4)). Treatment of **7** with MeOH and $SOCl_2$ (20 °C, 24 h) gave the methylfuranoside **8** (80 %, oil) and its anomer (17 %, m.p. 64-5 °C). Reduction of **8** with $(i\text{-}Bu)_2AlH$ in THF (-50 to -20 °C) afforded **9** which was esterified with CH_3SO_2Cl/Et_3N (CH_2Cl_2, 0 °C) into mesylate **10** (~100 %). Heating **10** with 12 % NH_3 in 1:1 EtOH/H_2O (70 °C, 5 h) gave **11**. The crude amine **11** was treated with $ClCH_2COCl$/pyridine (CH_2Cl_2, -5 to +8 °C) to give amide **12** (95 % based on **8**). Treatment with Ac_2O and conc.

H_2SO_4 (5 °C, 2 h) afforded acetate **13** (+ anomer) which was converted into lactame **14** (47%, ^{1}H-NMR ($CDCl_3$): 7.35 (*m*, 5H); 6.62 (*dd*, *J*=10, 1.5, H-C(4)); 5.92 (*dd*, *J*=10, 2, H-C(3)); 5.44 (*ddd*, *J*=3.6, 3.5, 3.4, H-C(7)); 4.68 & 4.50 (*m*, ^2J=12, 2H)); 4.46 (*ddd*, *J*=11.5, 2.0, 1.5, H-C(5)); 3.86 (*dd*, *J*=11.5, 3.5, H-C(6)); 3.74 (*ddd*, *J*=11, 9.5, 1.5) & 3.48 (*ddd*, *J*=11, 10.8, 7.5, $H_2C(9)$); 2.08 (*m*, $H_2C(8)$); 1.88 (*s*, Ac)) through an intramolecular Wittig-Horner condensation on heating with $(EtO)_3P$ to 130 °C (7 h), followed by treatment with K_2CO_3/EtOH (20 °C, 12 h) and acetylation (Ac_2O/pyridine, 4-dimethylaminopyridine, 20 °C, 48 h). Bromination of **14** (Br_2, 1:2 AcOH/Ac_2O containing AgOAc, 9 °C) gave a 1.5:1 mixture of **15/16** which were converted into epoxide **17** (^{1}H-NMR ($CDCl_3$): 7.4 (*m*, 5H); 4.86 & 4.64 (*m*, ^2J=12, 2H); 4.35 (*m*, H-C(1)); 3.88 (*dd*, *J*=10, 0.7, H-C(8)); 3.76 (*dd*, *J*=10, 3, H-C(8a)); 3.66 (*ddd*, *J*=11.5, 8.5, 2) & 3.56 (*dd*, *J*=3.5, 0.7, H-C(7)); 3.43 (*dd*, *J*=11.5, 7.5, $H_2C(3)$); 3.38 (*d*, *J*=3.5, H-C(6)); 1.96 (*m*, $H_2C(2)$); 1.54 (br.*d*, *J*=4, OH)) with MeOH and $SOCl_2$ (20 °C, 17 h) followed by treatment with 2-*tert*butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine on polystyrene (CH_3CN, 20 °C, 35 min). After addition of H_2O, the mixture was heated to 100 °C (4 ½ h: hydrolysis of the epoxide). Filtration, followed by treatment with pyridine/Ac_2O and 4-dimethylaminopyridine (20 °C, 48 h) led to triacetate **18** (42 % based on **14**). Reduction of **18** with BH_3·Me_2S in THF (20 °C, 15 h) furnished **19** (95 %) which was debenzylated (H_2, 10 % Pd-C, 5:1 THF/H_2O, 20 °C, 24 h) to give (±)-**1** (97 %, m.p. 189 - 190 °C) whose spectral characteristics were identical to those reported for castanospermine.[1,10]

Since both (-)-(1S)-7-oxanorborn-5-en-2-one ((-)-**2**) and (+)-(1R)-**2** ("naked sugars"[11]) are readily obtained optically pure,[12] our methodology can be used to prepare both the natural castanospermine (+)-**1** and its epimer (-)-**1**, respectively. Synthetic intermediates such as **14** and **17** are expected to be starting materials for the preparation of stereoisomers and analogues of **1**.[13]

Acknowledgments. We are grateful to the *Swiss National Science Foundation*, the *Fonds Herbette*, Lausanne, *Hoffmann - La Roche* & Co., AG, Basel and *E. I. Du Pont de Nemours* & Co., Wilmington for generous support.

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13. Details will be given in our full paper.

(Received in France 23 November 1988)