Application of New Optically Pure Ketene Equivalents Derived from Tartaric Acids to the Total, Asymmetric Syntheses of (+)-6-Deoxycastanospermine and (+)-6-Deoxy-6-fluorocastanospermine

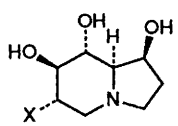
Jean-Louis Reymond and Pierre Vogel*

Section de Chimie de l'Université de Lausanne, CH-1005 Lausanne, Switzerland

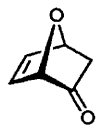
Condensation of di-*O*-acetyl-(*S,S*)-tartaric anhydride with the diethyl acetal of *N*-ethylaminoacetaldehyde gave (1*S*,5*S*,7*S*)-3-ethyl-2-oxo-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-carboxylic acid (**8**) whose 1-cyanovinyl ester (**10**) added to furan to give, after two recrystallizations, an optically pure 7-oxabicyclo[2.2.1]hept-5-en-2-yl derivative (**11**) that was converted into (+)-6-deoxycastanospermine (+)-(**2**) and (+)-6-deoxy-6-fluorocastanospermine (+)-(**3**).

Castanospermine (+)-(**1**) is a physiologically active polyhydroxylated indolizidine alkaloid isolated from seeds of *Castanospermum australe*[1] and from dried pods 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 been reported.[7] Fleet and co-workers[8] have obtained 6-epi- and 1,6-diepi-castanospermine from L-gulonolactone; Richardson and co-workers derived 1-deoxycastanospermine from D-glucose[9] and 1,8-dideoxy-6-epicastanospermine from a 2-azido-*altro*-pyranoside derivative.[10] We report here the highly stereoselective, total syntheses of 6-deoxycastanospermine (+)-(**2**) and 6-deoxy-6-fluorocastanospermine (+)-(**3**) starting with (−)-(1*S*,4*S*)-7-oxabicyclo[2.2.1]hept-5-en-2-one (−)-(**4**) a 'naked sugar'.[11] A new method for the preparation of enone (−)-(**4**) is presented. Its transformation into (+)-(**2**) and (+)-(**3**) follows an approach we had developed for the synthesis of (±)-(**1**).[12]

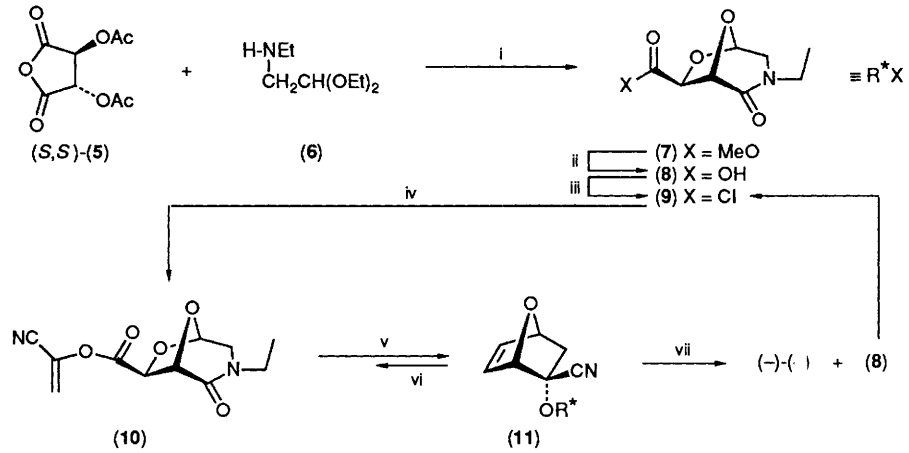
Di-*O*-acetyl-(*S,S*)-tartaric anhydride (*S,S*)-(**5**) was treated with ethylaminoacetaldehyde diethyl acetal (**6**) in CH_2Cl_2. After treatment with MeOH and $SOCl_2$, and then with H_2SO_4–SiO_2, ester (**7**) was obtained {54%, m.p. 75—78 °C, $[\alpha]_D^{20}$ +52.5° (*c* 1, CH_2Cl_2)}. Acidic hydrolysis of (**7**) (HCl–H_2O, 75 °C, 3 h) gave acid (**8**) (100%) which was transformed into (**9**) (92%) with $SOCl_2$ (75 °C, crystallization from Et_2O–light petroleum). Acyl chloride (**9**) and pyruvonitrile were condensed in CH_2Cl_2–pyridine (0 °C, 20 h) to give the new, optically pure, ketene equivalent (**10**) {86·3%, m.p. 90—91.5 °C, $[\alpha]_D^{20}$ +53.9° (*c* 1, CH_2Cl_2)}. The $ZnBr_2$-induced Diels–Alder addition of (**10**) to furan (20 °C, 7 days) gave a mixture of diastereoisomeric adducts from which pure (**11**) {m.p. 147—148 °C (decomp.); $[\alpha]_D^{20}$ −38° (*c* 1, CH_2Cl_2)} could be obtained in 35% yield [diastereoisomeric excess



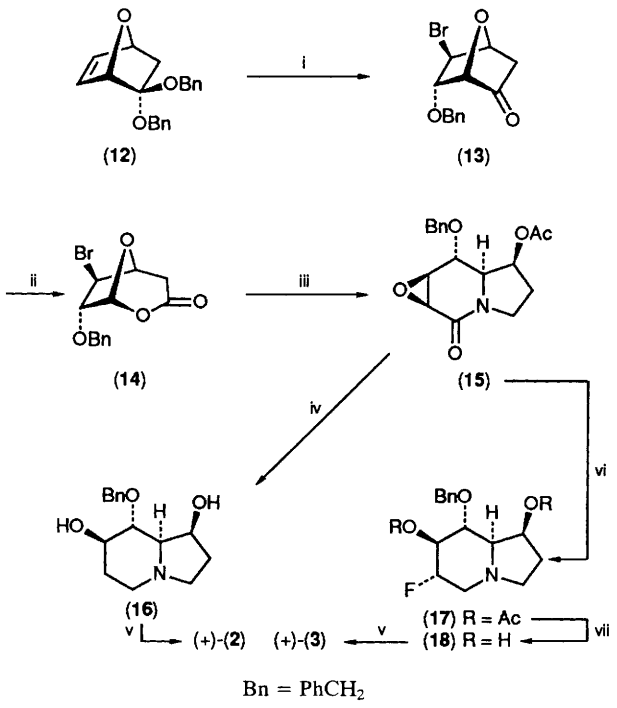
(+)-(**1**) X = OH
(+)-(**2**) X = H
(+)-(**3**) X = F



(−)-(**4**)



Scheme 1. *Reagents and conditions*: i, 20 °C, 1 h, then MeOH + $SOCl_2$, 20 °C, 24 h, then H_2SO_4– iO_2 (CH_2Cl_2), 160 °C, 54%; ii, conc. HCl–H_2O (1:20), 75 °C, 3 h, then drying *in vacuo* over P_4O_{10}; iii, $SOCl_2$, 75 °C, crystalliza..on from Et_2O–light petroleum; iv, pyruvonitrile (1 equiv.), pyridine (CH_2Cl_2), 0–20 °C, 20 h, 86.3%; v, furan (solvent), finely ground, dried 4 Å molecular sieves, $ZnBr_2$ (1 equiv.), 20 °C, 7 days, in the dark, 2 recrystallizations from AcOEt, 35%; vi, residue of mother liquors, anh. toluene, 110 °C, 33%; vii, 1 M NaOH, 40% aq. CH_2O, 20 °C, 4 h, 96%.



Scheme 2. *Reagents and conditions*: i, Br_2 (1.1 equiv.), CH_2Cl_2, −90 °C, then aq. $NaHCO_3$, −90 °C, 98%; ii, 85%-*m*-chloroperbenzoic acid, $NaHCO_3$ (CH_2Cl_2), 5 °C, 96%; iii, see ref. 12, overall yield: 43%; iv, BH_3·Me_2S (THF), 20 °C, 4 days, 25%; v, H_2–Pd–C (MeOH–HCO_2H), 20 °C, 16 h, 97%; vi, HF–Et_3N, 2-t-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine on polystyrene, 95 °C, 2 days, then Ac_2O–pyridine/4-*N*,*N*-dimethylaminopyridine (DMAP), 20 °C, 4 days, 52%; vii, BH_3·Me_2S (THF), 20 °C, 1 day; then HCl–MeOH–H_2O, 70 °C, 4 days, 83%.

(d.e.) >99% by 360 MHz ^{1}H NMR] after two recrystallizations from AcOEt. When the residue of the mother liquors was heated in toluene (115 °C, 12 h), (**10**) was recovered in 33% yield. Saponification of (**11**) (NaOH, H_2O, CH_2O, 20 °C) afforded enone (−)-(**4**) (96%) and the chiral auxiliary (**8**) (78%). This method of preparation of (−)-(**4**) was more practical and easier to scale up than that based on the ZnI_2-induced Diels–Alder addition of furan to 1-cyanovinyl (1*R*)-camphanate[11] [(1*R*)-camphanic acid as chiral auxiliary].

Bromination of the dibenzyl acetal (**12**) derived from (−)-(**4**)[13] afforded (**13**) {98%, m.p. 92—92.5 °C, $[\alpha]_D^{20}$ +69° (*c* 1, CH_2Cl_2)}. Baeyer–Villiger oxidation of (**13**) gave the β-L-*arabino*-hexofuranosidurono-6,1-lactone derivative (**14**) {96%, m.p. 115—116 °C, $[\alpha]_D^{20}$ +135° (*c* 1, CH_2Cl_2)} which was then converted into epoxy-lactam (**15**) (43%, oil).[12] Treatment of (**15**) with BH_3·Me_2S in anhydrous tetrahydrofuran (THF) led to a mixture of compounds from which (**16**) {25%, oil, $[\alpha]_D^{25}$ +3.2° (*c* 0.62, CH_2Cl_2)} was the only amine that could be isolated (by column chromatography, Dowex-H^+, then silica gel). Hydrogenolysis of the benzylic ether gave (+)-(**2**) {97%, oil $[\alpha]_D^{25}$ +36° (*c* 2.5, EtOH)}.

The reaction of (**15**) with HF·Et_3N (95 °C, 2 days) led to a stereoselective ring opening of the epoxide moiety with attack on C(6) by the fluoride anion. After acetylation, (Ac_2O–pyridine), (**17**) {52%, m.p. 178—179 °C, $[\alpha]_D^{25}$ +162° (*c* 1, CH_2Cl_2)} was isolated. Reduction of (**17**) with BH_3·Me_2S in THF, followed by hydrolysis of the acetates (HCl, H_2O–MeOH, 70 °C) afforded the partially protected 6-deoxy-6-fluorocastanospermine (**18**) {83%, oil, $[\alpha]_D^{25}$ +52° (*c* 0.42, CH_2Cl_2)}. Hydrogenolysis of the benzylic ether gave (+)-(**3**) {93%, colourless crystals, m.p. 142—143 °C, $[\alpha]_D^{25}$ +88° (*c* 0.16, EtOH)}.[14]

The structures of (+)-(**2**), (+)-(**3**), and derivatives (**16**)—(**18**) were confirmed by their spectral data and by comparison with those reported for (+)-(**1**)[1,7,12] [*e.g.* ^{1}H NMR ($CDCl_3$, 250 MHz) of (**16**): δ 3.56 (ddd, ^3J 11.0, 9.0, 5.0 Hz, 7-H), 3.50 (t, ^3J 9.0, 8-H); of (**18**): δ 4.54 (dddd, $^2J_{H,F}$ 51, $^3J_{H,H}$ 14, 8.5, 5.5, 6-H), 4.30 (m, 1-H), 3.75 (ddd, $^3J_{H,F}$ 15, $^3J_{H,H}$ 9, 8.5, 7-H), 3.60 (t, $^3J_{H,H}$ 9.0, 8-H), 3.33 (ddd, $^2J_{H,H}$ 10, $^3J_{H,F}$ = 5.5, $^3J_{H,H}$ = 2.0, 5-H_{eq}]. For all these compounds, the ^{1}H NMR spectra suggested conformations ($^NC_7$ chair for the six-membered ring) similar to that of (+)-(**1**).[1,7]

The pK_a values of the conjugate acids of (+)-(**1**), (+)-(**2**), and (+)-(**3**) have been determined by the titrimetric method to be 6.01 ± 0.01, 7.31 ± 0.02, and 5.09 ± 0.01, respectively, at 25 °C (H_2O).[15] The enhanced acidity of (+)-(**3**)-H^+ compared with that of (+)-(**1**)-H^+ and (+)-(**2**)-H^+ was

expected and can be attributed to the inductive effect of the fluoro substituent.

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