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Synthesis of (+)-Boronolide from D-Glucose

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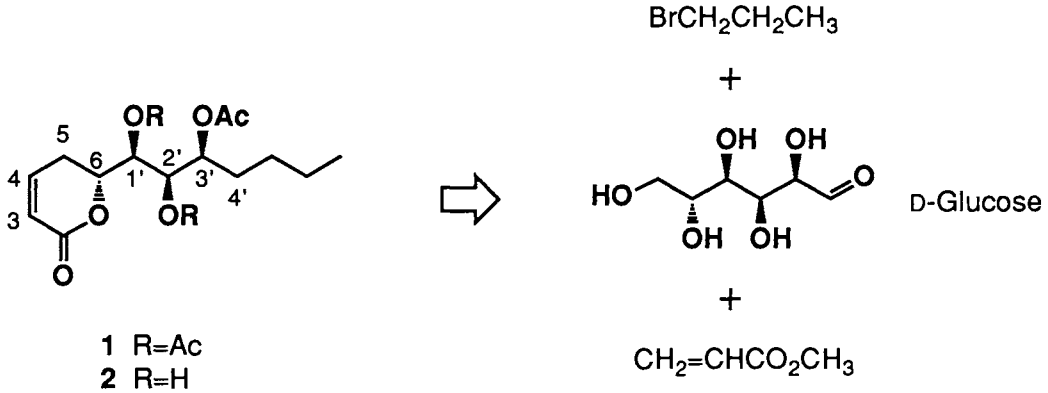
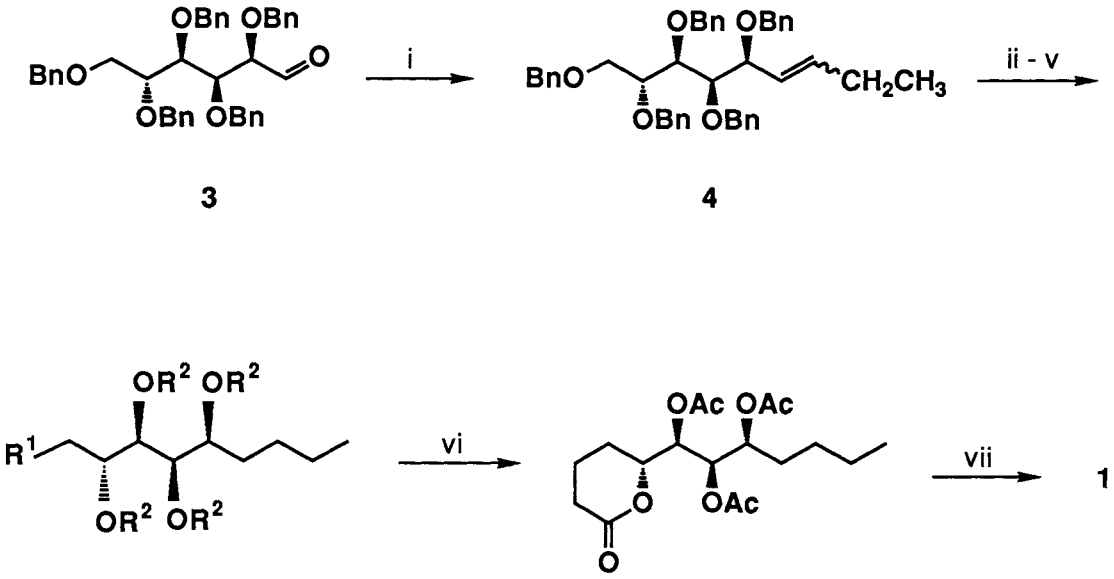
(+)-Boronolide (= (1'*R*,2'*R*,3'*S*,6*R*)-5,6-dihydro-6-[1',2',3'-tris(acetoxy)-heptyl]-2*H*-pyran-2-one) (**1**), a constituent isolated from *Tetradenia fruticosa* and *T. barberae* (Lamiaceae), was synthesized in 7 steps and in 5.2% overall yield from 2,3,4,5,6-penta-*O*-benzyl-D-glucose, whose four asymmetric centers were incorporated in **1**.

(+)-Boronolide (**1**) is a C_{12}-lactone isolated from the bark and branches of *Tetradenia fruticosa* Beth. (Lamiaceae) which is used as a local folk medicine in Madagascar[1] and from the leaves of *T. barberae* (N. E. Br) Codd.[2] 1',2'-Dideacetylboronolide (**2**) has furthermore been isolated from *T. riparia* (formerly *Iboza*), a medicinal plant of Ruwanda.[3] The absolute configuration of (+)-boronolide has been determined by X-ray analysis[4] and by chemical degradation[2] as (1'*R*, 2'*R*, 3'*S*, 6*R*)-5,6-dihydro-6-[1', 2', 3'-tris (acetoxy)-heptyl]-2*H*-pyran-2-one. The total synthesis of (±)-boronolide has recently been reported.[5] We now report the synthesis of (+)-boronolide (**1**) from 2,3,4,5,6-penta-*O*-benzyl-D-glucose (**3**).[6,7]



1 R=Ac
2 R=H



5 R^1=OH, R^2=H
6 R^1=OTs, R^2=Ac
7 R^1=I, R^2=Ac
8 R^1=$CH_2CH_2CO_2CH_3$, R^2=Ac
9 R^1=H, R^2=Ac
10 R^1=$CH_2CH(CH_2CH_2CO_2CH_3)CO_2CH_3$, R^2=Ac

Scheme 1. *Reagents and conditions*: i, $Ph_3P^+CH_2CH_2CH_3Br^-$, BuLi, THF, 0 °C; ii, H_2, 10% Pd-C, ethanol; iii, a) *p*-toluenesulfonyl chloride, pyridine, 0 °C, b) acetic anhydride; iv, NaI, acetone, reflux; v, Bu_3SnH, $CH_2=CHCO_2CH_3$, hν, ether, reflux; vi, a) K_2CO_3, b) dilute HCl, c) aqueous $NaHCO_3$, d) acetic anhydride, pyridine; vii, $(PhSeO)_2O$, chlorobenzene, reflux.

A retrosynthetic analysis of the structure of (+)-boronolide shows that D-glucose may be used as its central C_6-segment (C5 - C4'). In this planning all four asymmetric centers of D-glucose are incorporated in the target molecule. Three carbon extension of the central segment was at first performed by the Wittig reaction of 2,3,4,5,6-penta-*O*-benzyl-D-glucose (**3**) with propylidene(triphenyl)phosphorane to give the olefin **4** as a mixture of *Z* (predominant; ^{1}H-NMR, δ=5.43 (1H, dd, *J*=11.0 and 9.5 Hz, olefinic proton)) and *E* isomers in 75% yield.[8] The olefin **4** was then treated with 10% Pd-C in ethanol to adsorb impurities poisoning the catalyst. After the catalyst was filtered out, 10% Pd-C was added again and the catalytic hydrogenation and hydrogenolysis of **4** were performed to give the tetraol **5** in 96% yield.[9] Selective tosylation of the primary hydroxyl group of **5** with *p*-toluensulfonyl chloride (1.2 mol equiv.) in pyridine at 0 °C and subsequent

acetylation of the secondary hydroxyl groups with acetic anhydride gave **6** in 54% yield. The tosylate **6** was then transformed to the iodide **7** with sodium iodide in refluxing acetone in 67% yield.[10] Introduction of the second three carbon unit to **7** was performed by the intermolecular radical C-C bond forming reaction.[11] Slow addition of tributyltin hydride to a solution of **7** and methyl acrylate in diethyl ether under irradiation gave the desired product **8** in 45% yield together with the reductive deiodination product **9** (27%) and the product of trapping of two molecules of methyl acrylate **10** (18%).[12] Compound **8** was hydrolyzed with potassium carbonate in aqueous methanol at room temperature and then the reaction mixture was acidified with dilute hydrochloric acid and stirred at room temperature. After neutralization with sodium hydrogencarbonate, the solvent was evaporated and the residue was acetylated with acetic anhydride in pyridine to give the lactone **11** in 69% yield.[13] Transformation of (±)-**11** to (±)-boronolide has already reported.[5] Following the reported procedure the lactone **11** was dehydrogenated with benzeneselenic anhydride to give (+)-boronolide (**1**), mp 89.4 - 90.5 °C (lit[1, 2] mp 90 °C); $[\alpha]_D$ + 25.7° (*c* 0.54, ethanol) (lit[1]) $[\alpha]_D$+ 25° and lit[2]) $[\alpha]_D$ + 28°), in 64 % yield. The spectral data (^{1}H-NMR, ^{13}C-NMR, and MS) of **1** were identical with those reported.[1, 2, 5]

References

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7) (+)-Anamarine, a C_{12}-lactone, has recently been synthesized from D-gulonolactone and diethyl L-tartrate. K. Lorenz and F. W. Lichtenthaler, *Tetrahedron Lett.*, **28**, 6437 (1987).

8) Compound **4**: colorless oil; IR (neat) 1500, 1460, 1095, 1070, 1030, 735, and 700 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) *Z*-isomer δ=7.35 - 7.18 (25H, m), 5.62 (1H, m), 5.43 (1H, dd, *J*=11.0 and 9.5 Hz), 4.83 - 4.26 (11H, m), 4.00 (1H, dd, *J*=4.8 and 4.8 Hz), 3.82 (2H, m), 3.74 (1H, dd, *J*=5.4 and 5.4 Hz), 3.65 (1H, dd, *J*=11.3 and 6.3 Hz), 2.08 - 1.80 (2H, m), and 0.87 (3H, t, *J*=7.5 Hz); MS *m/z* (rel intensity) 565 (M^+ - C_7H_7, 0.02%), 481 (0.7), 181 (10), and 91 (100).

9) Compound **5**: colorless solid, IR (Nujol) 3300 cm^{-1}; MS *m/z*209 (M^+ + 1, 0.8), 191 (M^+ - H_2O +

1, 0.8), 173 (M^+ - $2H_2O$ + 1, 2), 159 (4), 147 (3), 129 (10), 117 (9), 87 (11), 73 (100), and 55 (31).

10) Compound **7**: colorless oil; IR (neat) 1745, 1425, 1375, 1210, and 1030 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ=5.34(1H, dd, *J*=6.6 and 4.2 Hz), 5.22 (1H, dd, *J*=6.8 and 4.2 Hz), 4.99 (1H, dt, =7.1 and 4.9 Hz), 4.90(1H, dt, *J*=6.6 and 3.9 Hz), 3.36 (1H, dd, *J*=11.2 and 3.9 Hz), 3.21 (1H, dd, *J*=11.2 and 6.8 Hz), 2.15 (3H, s), 2.09 (3H, s), 2.07 (3H, s), 2.06 (3H, s), 1.60(2H, m), 1.28 (4H, m), and 0.89 (3H, t-like, *J*=7.0 Hz).

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12) To a refluxing solution of iodide **7** (232 mg, 0.48 mmol) and methyl acrylate (0.41 ml, 4.6 mmol) in dry diethyl ether (17 ml) was added a solution of Bu_3SnH (0.25 ml, 0.91 mmol) in dry diethyl ether (6 ml) via syringe pump over a 6 h period under irradiation (100 W tungsten lamp). KF (1.2 g) and few drops of water were then added and the mixture was stirred overnight. The crude product was chromatographed on silica gel (hexane - ethyl acetate 4 : 1) to give **8** (96 mg, 45%), **9** (46 mg, 27%), and **10** (47 mg, 18%). Compound **8**: colorless oil, IR (neat) 1745, 1440, 1375, 1250, 1220, and 1025 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ=5.30 (1H, t, *J*=5.4 Hz), 5.21 (1H, t, *J*=5.4 Hz), 4.99 (1H, q, *J*=6.1 Hz), 4.91 (1H, m), 3.67 (3H, s), 2.32 (2H, t, *J*=6.5 Hz), 2.11 (3H, s), 2.10 (3H, s), 2.07 (3H, s), 2.02 (3H, s), 1.78 - 1.48 (6H, m), 1.40 - 1.20 (4H, m), and 0.88 (3H, t-like, *J*=7.0 Hz); ^{13}C-NMR δ=173.37, 170.46, 170.22, 170.00 (2C), 71.34, 71.31, 71.07, 70.35, 51.50, 33.27, 30.13, 28.58, 26.97, 22.30, 20.83, 20.80, 20.69, 20.57, 20.42, and 13.79; MS *m/z*415 (M^+ - OCH_3, 3), 387 (M^+ - CO_2CH_3, 1), 373 (M^+ - $CH_2CO_2CH_3$, 6), 215 (100), 173 (71), 156 (47), 131 (36), 111 (32), and 99 (24).

13) Compound **11**: colorless oil, $[\alpha]_D^{24}$ - 19.3° (*c* 0.55, ethanol) (lit.[1] $[\alpha]_D$ -10° (ethanol)); IR (neat) 1745, 1375, 1220, 1050, and 1030 cm^{-1}; ^{13}C-NMR ($CDCl_3$) δ=170.37, 169.93, 169.67 (2C), 77.75, 71.72, 71.27, 70.61, 30.22, 29.47, 26.98, 23.40, 22.29, 20.83, 20.65, 20.54, 18.11, and 13.76. ^{1}H-NMR and MS spectral data of **11** were identical with those reported in Ref. 5.

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