Synthesis of Higher-carbon Sugars *via* Cross-aldolization of 7-Oxanorbornan-2-one and Carbohydrate Aldehyde Derivatives

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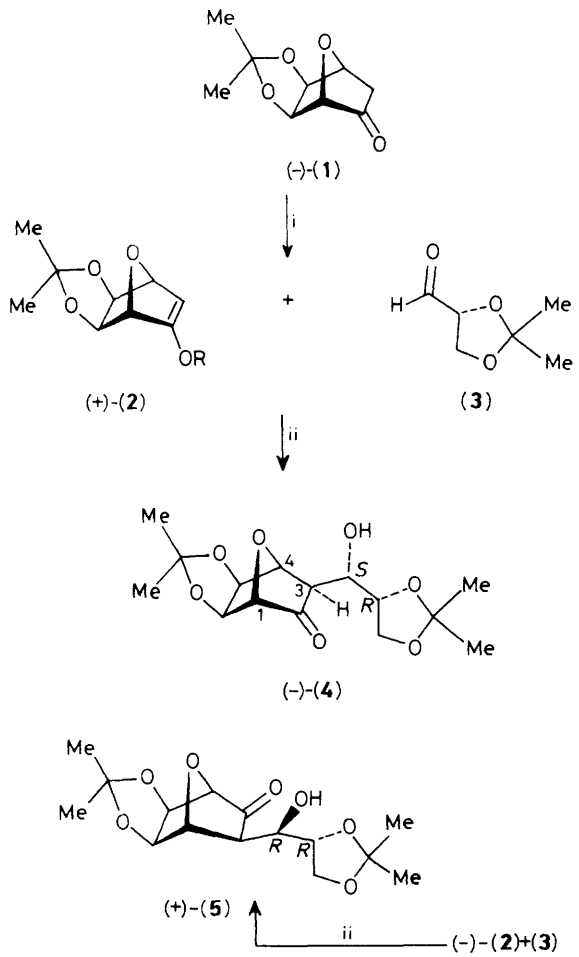
The $TiCl_4$-induced condensation of (+)-(1*S*,4*S*,5*S*,6*S*)-5,6-isopropylidenedioxy-2-t-butyldimethylsilyloxy-7-oxabicyclo[2.2.1]hept-2-ene with 2,3-*O*-isopropylidene-D-glyceraldehyde was highly stereoselective, giving a product that was converted with high stereoselectivity into protected D-*erythro*-D-*talo*-octose and D-*erythro*-L-*allo*-octose.

The discovery of important antibiotics containing higher-carbon sugars (with carbon chains containing more than six atoms) or analogues[1] has stirred a renewed interest in the synthesis of these complicated compounds.[2] We report on the application of the cross-aldolization of sugar aldehydes with 7-oxanorbornan-2-one derivatives readily obtainable in both enantiomerically pure forms.[3,4]

The $TiCl_4$-mediated condensation (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**3**) with enol ether (+)-(1*S*)-(**2**) derived from (−)-(**1**)[4,5] afforded the β-hydroxyketone (−)-(**4**) {m.p. 131—132 °C, $[\alpha]_D^{25}$ −110° (*c* 0.63, CH_2Cl_2)}. No other stereoisomers could be observed in the 360 MHz ^1H n.m.r. spectrum of the crude reaction mixture. The *exo*-configuration of the newly created C–C bond was indicated by ^3J[H–C(3), H–C(4)] *ca.* 0 Hz. The (*S*)-configuration of the alcoholic carbon centre was established as shown below. It corresponds to an *anti* mode of cross-aldolization, in agreement with the Felkin's model.[6,7] In contrast, the reaction of (**3**) with the enantiomeric enol ether (−)-(1*R*)-(**2**) gave (+)-(**5**) (61%) with the (*R*) configuration at the alcohol centre. These results can be interpreted in terms of the transition states shown in Figure 1(a) for reaction of (+)-(**2**) with (**3**) and in Figure 1(b) for reaction of (−)-(**2**) with (**3**),[7] which minimize steric repulsions between the reactants.

Baeyer–Villiger oxidation of (−)-(**4**) gave exclusively lactone (+)-(**6**) {m.p. 159—160 °C, $[\alpha]_D^{25}$ 21.8° (*c* 0.84, CH_2Cl_2)}. Treatment with dry MeOH containing a trace of K_2CO_3 furnished furanose (**7**) as a 1:2 mixture of α- and β-anomer. Selective silylation gave (**8**) (mostly β-anomer), which was reduced with $LiAlH_4$ to diol (**9**). Displacement of the primary alcohol in (**9**) with 2-$NO_2C_6H_4SeCN$ and triphenylphosphine[8] afforded (+)-(**10**) {$[\alpha]_D^{25}$ 42° (*c* 0.17, CH_2Cl_2)} after acetylation. Oxidative elimination of the selenide led to (+)-(**11**) {$[\alpha]_D^{25}$ 19° (*c* 0.18, CH_2Cl_2)} which furnished ketone (+)-(**12**) {$[\alpha]_D^{25}$ 42° (*c* 0.35, CH_2Cl_2); ^3J[*H*–C(3), H–C(4)] 1.5 Hz} upon ozonolysis. Reduction of (+)-(**12**) with $LiAlH_4$ in tetrahydrofuran (THF) (0 °C, 10 min) gave a 2.7:1 mixture of the partially protected D-*erythro*-D-*talo*-octose (**13**) {$[\alpha]_D^{25}$ 26.1° (*c* 0.23, CH_2Cl_2)} and D-*erythro*-L-*allo*-octose (**14**) {$[\alpha]_D^{25}$ 35.5° (*c* 0.2, CH_2Cl_2)} derivatives which could be separated by column chromatography on silica gel in 50 and 22% yield, respectively. With $NaBH_4$ (MeOH, 0 °C, 15 min) the selectivity was only 2:1. It was improved to 6:1 using $NaBH_4/CeCl_3$ (MeOH, −78 °C, 1 h), to 10:1 using lithium-β-isopinocampheyl-9-borabicyclo[3.3.1]nonyl hydride ('Alpine Hydride') (THF, −78 °C, 1 h), and to >20:1 with L-Selectride (THF, −78 °C, 1 h, 90%). Most interesting was the reversal of the selectivity of the reduction of (+)-(**12**) when using Bu^i_2AlH in THF. For reaction at −25 °C (3 h, 87% yield), the product ratio (**13**)/(**14**) was <1:20. Under conditions similar to those that converted (−)-(**4**) into (**13**) and (**14**), the corresponding D-*threo*-L-*talo*-



Scheme 1. *Reagents and conditions:* i, $Bu^tMe_2Si(Me)NCOCF_3$, Et_3N, dimethylformamide (DMF), 60 °C, 18 h, 85%; ii, $TiCl_4$, CH_2Cl_2, −78 °C, 5 min, 50—65%.

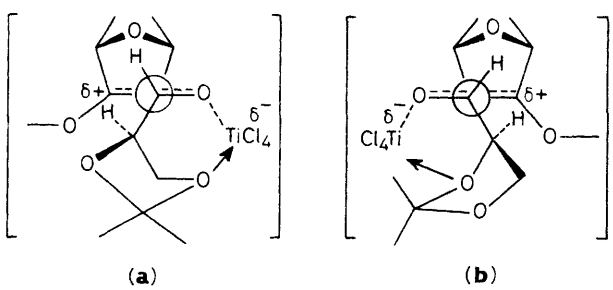
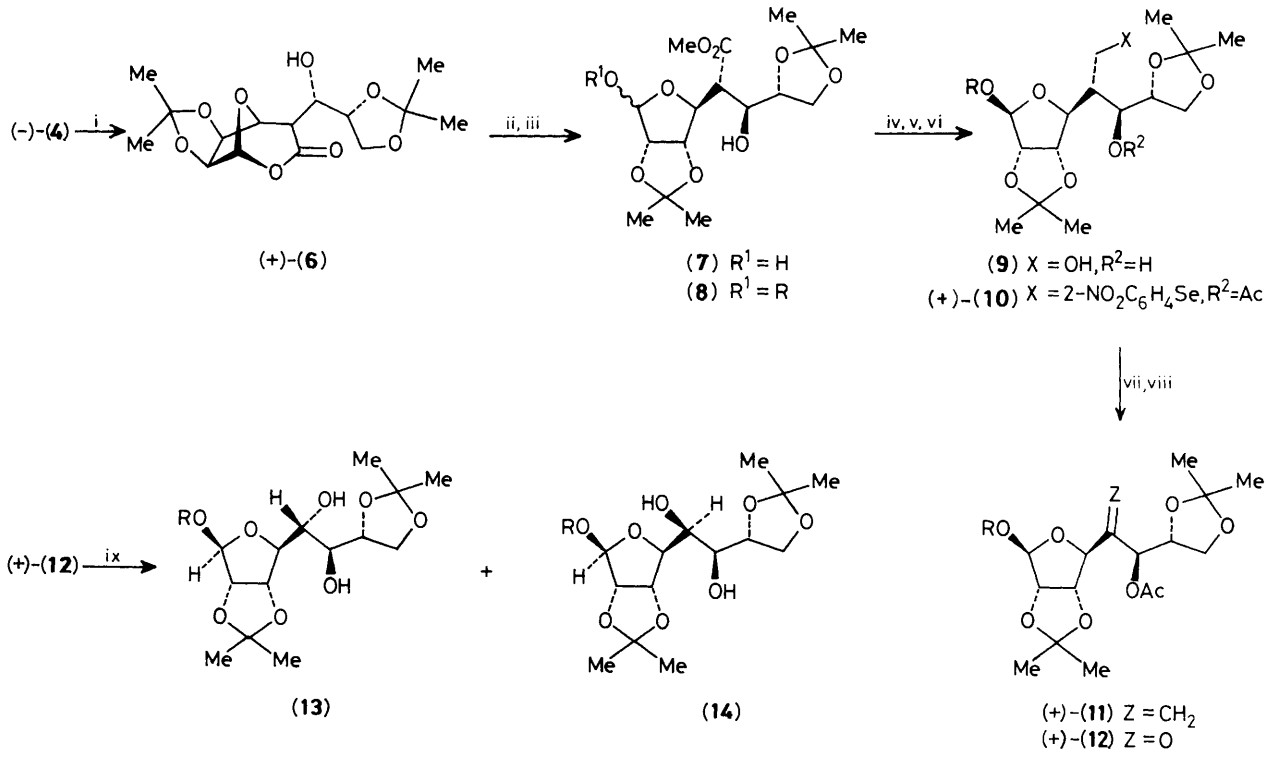
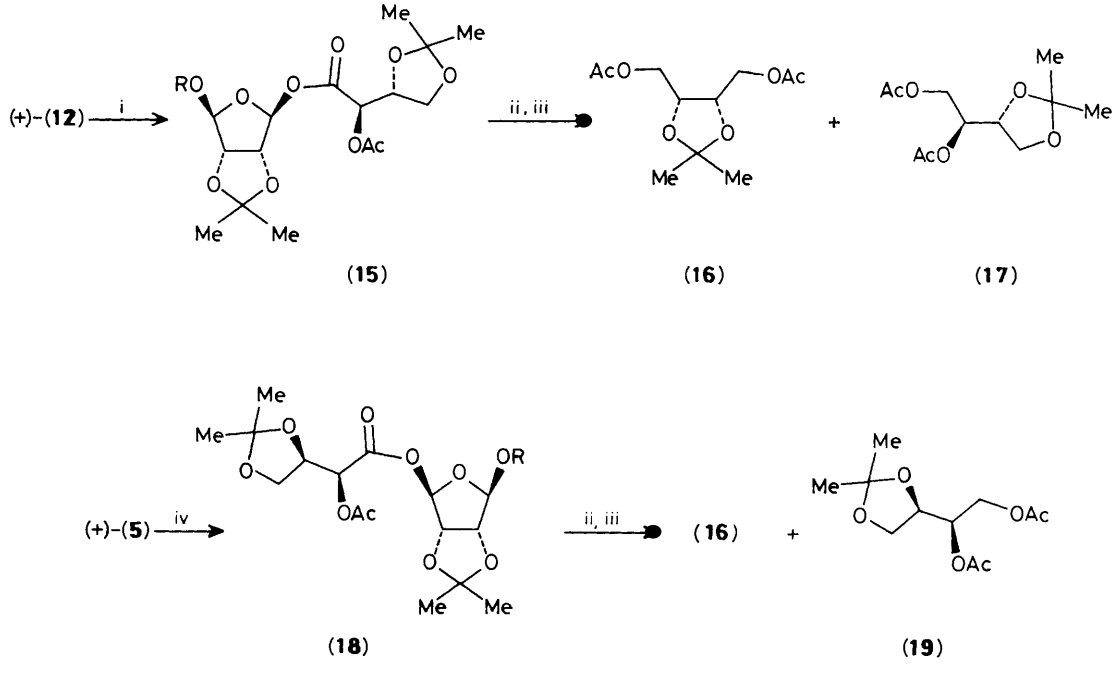


Figure 1. Transition states for reactions of (**2**) with (**3**).



Scheme 2. *Reagents and conditions:* i, *m*CPBA (*m*-chloroperbenzoic acid), CH_2Cl_2, 20 °C, 24 h, 81%; ii, K_2CO_3, MeOH, 20 °C, 20 min, 99%; iii, 2,6-lutidine, $Bu^tMe_2SiOSO_2CF_3$, CH_2Cl_2, 0 °C, 1 h, 83%; iv, $LiAlH_4$, THF, 0—20 °C, 30 min, 92%; v, 2-$NO_2C_6H_4SeCN$, THF, then Bu_3P, 50 °C, 45 min, 63%; vi, pyridine, Ac_2O, trace of 2-dimethyl-aminopyridine (DMAP), 20 °C, 2 h, 92%; vii, *m*CPBA, CH_2Cl_2, 5 min, 64%; viii, O_3, CH_2Cl_2–MeOH, 5:2, −78 °C, then Me_2S, 20 °C, 1 h, 91%; ix, see text.



Scheme 3. *Reagents and conditions:* i, $NaHCO_3$, *m*CPBA, CH_2Cl_2, 20 °C, 15 h; ii, $LiBH_4$, THF, 40 °C, 1 h; iii, Ac_2O, pyridine, DMAP as catalyst; iv, see Scheme 2.

octose and D-*threo*-D-*allo*-octose derivatives can be prepared from (+)-(**5**).†

The configuration of C(6) in (**13**) and (**14**) was established as shown in Scheme 3. Baeyer–Villiger oxidation of ketone (+)-(**12**) gave exclusively (**15**). Reduction with $LiBH_4$, followed by acetylation gave a 1:1 mixture of (**16**) and (**17**), which were readily separated by column chromatography on silica gel. The non-symmetrical compound (**17**) was hydrolysed (90% aq. AcOH), then acetylated (Ac_2O, pyridine) to give *meso*-erythritol tetra-acetate. Under similar conditions, (+)-(**5**) led to (**18**) and then to a 1:1 mixture of (**16**) (76%) and (**19**) (68%, isolated). Acidic hydrolysis of (**19**), followed by acetylation afforded pure D-threitol tetra-acetate, thus confirming the (*R*)-configuration of the alcoholic carbon centre in (+)-(**5**). The relative configuration of C(5) in (**13**) and (**14**) was given by the 360 MHz ^1H n.m.r. spectra of the corresponding carbonates obtained on treatment with phosgene (CH_2Cl_2, pyridine, 0—15 °C, 1 h). The carbonate derived from (**13**) showed ^3J[H–C(5), H–C(6)] 8.0 Hz (*cis*), while that derived from (**14**) displayed ^3J[H–C(5), H–6(6)] 4.0 Hz (*trans*).‡

The $TiCl_4$-mediated condensation of methyl 2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanoside with enol ether (−)-(**2**) gave only one unique compound.[9] Work is underway to convert it into decose derivatives. We also plan to generate branched nonose derivatives[10] by double hydroxylation of (+)-(**11**) and its analogues.

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† All new compounds gave satisfactory elemental analyses and spectral data consistent with assigned structures.

‡ Further evidence for the stereochemical assignments was obtained from nuclear Overhauser enhancement experiments.

References

1 See, *e.g.*: (a) K. Sakata, J. Uzawa, and A. Sakurai, *Org. Magn. Reson.*, 1977, **10**, 230; N. B. Perry, J. W. Blunt, M. H. G. Munro, and L. K. Pannell, *J. Am. Chem. Soc.*, 1988, **110**, 4850; S. Sakemi, T. Ichiba, S. Kohmoto, G. Saucy, and T. Higy, *ibid.*, 1988, **110**, 4851; X. Ye and Y. Quiang, *Weishengwu Xuebao*, 1987, **27**, 156 (*Chem. Abstr.*, 1987, **107**, 112294h).

2 For other syntheses of higher-carbon sugars, see *e.g.*: S. J. Daniskefsky and M. P. DeNinno, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 15, and references cited therein; V. Bilik, L. Petrus, and J. Alfoldi, *Chem. Zvesti*, 1976, **30**, 698; H. Paulsen, K. Roden, V. Sinnwell, and P. Luger, *Liebigs Ann. Chem.*, 1981, 2009; A. Dondoni, G. Fantin, M. Fogagnolo, and A. Medici, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 835; N. K. Kochetkov and B. A. Dmitriev, *Tetrahedron*, 1965, **21**, 803; J. A. Secrist and S. R. Wu, *J. Org. Chem.*, 1979, **44**, 1434; H. C. Jarrell and W. A. Szarek, *Can. J. Chem.*, 1978, **56**, 144; 1979, **57**, 924; J. S. Brimacombe, R. Hanna, A. K. M. S. Kabir, F. Bennet, and I. D. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 1986, 815; M. D. Bednarski, H. J. Waldmann, and G. M. Whitesides, *Tetrahedron Lett.*, 1986, **27**, 5807; S. A. Babirad, Y. Wang, and Y. Kishi, *J. Org. Chem.*, 1987, **52**, 1370; B. Fraser-Reid, B. F. Molino, L. Magdzinski, and D. R. Moctoo, *ibid.*, 1987, **52**, 4505; B. Giese, M. Hoch, C. Lamberth, and R. R. Schmidt, *Tetrahedron Lett.*, 1988, **29**, 1375; R. Couk, M. Hugener, and A. Vasella, *Helv. Chim. Acta*, 1988, **71**, 609.

3 A. Warm and P. Vogel, *J. Org. Chem.*, 1986, **51**, 5348; *Helv. Chim. Acta*, 1987, **70**, 690.

4 J. Wagner, E. Vieira, and P. Vogel, *Helv. Chim. Acta*, 1988, **71**, 624.

5 Y. Auberson and P. Vogel, *Helv. Chim. Acta*, 1989, **72**, 278.

6 M. Cherest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, 1968, 2201; M. Cherest and H. Felkin, *ibid*, 1968, 2205.

7 J. Jurczak, S. Pikul, and T. Bauer, *Tetrahedron*, 1986, **42**, 447.

8 P. A. Grieco, S. Gilman, and M. Nishizwa, *J. Org. Chem.*, 1976, **41**, 1485.

9 For recent examples of cross-aldolization using sugar derivatives, see *e.g.*: S. Handa, R. Tsang, A. McPhail, and B. Fraser-Reid, *J. Org. Chem.*, 1987, **52**, 3489; Y. Chapleur, F. Longchambon, and H. Gillier, *J. Chem. Soc., Chem. Commun.*, 1988, 564.

10 See *e.g.* the calditols: M. De Rosa, S. De Rosa, A. Gambacorta, and J. D. Bu'Lock, *Phytochemistry*, 1980, **19**, 249.