Tetrahedron Letters, Vol. 33, No. 36, pp. 5243-5244, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

TOTAL SYNTHESIS OF CYCLOPHELLITOL STARTING FROM FURAN

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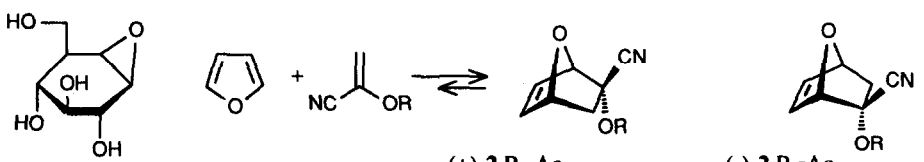
Summary: *(±)-Cyclophellitol has been prepared in a highly stereoselective fashion from the Diels-Alder adduct of furan to 1-cyanovinyl acetate.*

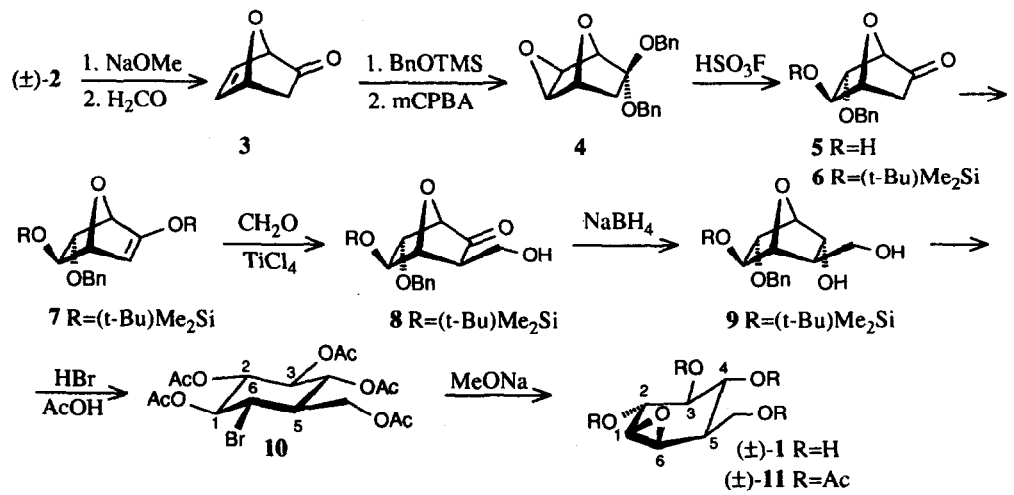
Cyclophellitol ((+)-**1**: (1S,2R,3S,4R,5R,6R)-5-hydroxymethyl-7-oxabicyclo[4.1.0]heptane-2,3,4-triol) is an unique pseudo-pyranose with an epoxide moiety; its three hydroxy groups and its hydroxymethyl



(+)-**1** (+)-**2** R=Ac (-)-**2** R=Ac
(+)-**12** R=(1S)-camphanoyl (-)-**13** R=(1R)-camphanoyl

group substitute four contiguous carbon centres with the configuration of D-glucose. This natural compound isolated from a culture filtration of a mushroom, *Phellinus* sp., strongly inhibits almond-derived β-glucosidase and thus is a potential drug against human immunodeficiency virus and metastasis.[1] A first synthesis by Tatsuta et al.[2] derived (+)-**1** from L-glucose. We report here a new approach starting from Diels-Alder adducts of furan to 1-cyanovinyl esters.[3]

The racemic Diels-Alder adduct (±)-**2**[3a] was converted into the 7-oxanorbornanone **5** following the four step procedure (65% overall yield) of Le Drian et al.[4] Silylation of its alcoholic moiety with (t-Bu)Me_2SiCl/imidazole (DMF) afforded **6** (82%; m.p. 57-58°C). The treatment of **6** with $(Me_3Si)_2NK$ and



3 **4** **5** R=H
6 R=(t-Bu)Me_2Si
7 R=(t-Bu)Me_2Si **8** R=(t-Bu)Me_2Si **9** R=(t-Bu)Me_2Si
10
(±)-**1** R=H
(±)-**11** R=Ac

(t-Bu)Me_2SiCl (-78°C, THF) yielded the silyl enol ether **7** (87%).[5] Monomeric formaldehyde (2.5 equivalents) was added to **7** (-78°C, CH_2Cl_2), followed by the addition of freshly distilled $TiCl_4$.[6] After 2 hours at -78°C, the *exo* aldol **8** was isolated (89%).[7] Reduction of **8** with $NaBH_4$ (0°C, MeOH) afforded the *endo* alcohol **9** (95%). Heating **9** in 30% HBr/AcOH (+ 2 drops of Ac_2O)[8] to 60°C for 20 hours furnished the bromocyclohexane derivative **10** (69%) in which the six substituents occupy equatorial positions as shown by ^{1}H-NMR.[9] The treatment of **10** with 8 equivalents of MeONa in anhydrous MeOH (20°C, 3.5 h) led to (±)-**1** which was characterized as its tetraacetate (±)-**11** obtained by treatment with Ac_2O, pyridine and 4-dimethylaminopyridine (90%).[10] The structures of **6** - **10** were confirmed by their spectral data and elemental analyses.[11] The vicinal H-H coupling constants in ^{1}H-NMR spectrum of (±)-**11**[10] suggested a "sofa" conformation for its six-membered ring.

Since the optically pure 7-oxabicyclo[2.2.1]hept-5-en-2-yl derivatives (+)-**12** and (+)-**13**[3b] ("naked sugars")[12] are readily available, our total synthesis can be applied, in principle, to the preparation of cyclophellitol ((+)-**1**) and its enantiomer (-)-**1** with the same ease.[11]

Acknowledgments. We thank *F. Hoffmann-La Roche & Co.*, AG (Basel), the *Fonds Herbette* (Lausanne) and the *Swiss National Science Foundation* for financial support and Dr. R. M. Bimwala for his advice.

References and Notes

1. Atsumi, S.; Umezawa, K.; Iinama, H.; Naganawa, H.; Nakamura, H.; Iitaka, Y.; Takeuchi, T. *J. Antibiotics* **1990**, *43*, 49.
2. Tatsuta, K.; Niwata, Y.; Umezawa, K.; Toshima, K.; Nakata, M. *Tetrahedron Lett.* **1990**, *31*, 1171.
3. a) Vieira, E.; Vogel, P. *Helv. Chim. Acta* **1982**, *65*, 1700; b) Vieira, E.; Vogel, P. *Ibid.* **1983**, *66*, 1865; Black, K. A.; Vogel, P. *Ibid.* **1984**, *67*, 1612; Reymond, J.-L.; Vogel, P. *Tetrahedron: Asymmetry* **1990**, *1*, 729.
4. Le Drian, C.; Vionnet, J.-P.; Vogel, P. *Helv. Chim. Acta* **1990**, *73*, 161.
5. Data of **7**: m.p. 44-45.5°C, ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H: 7.35-7.25 (*m*, 5H); 4.92 (*d*, ^3J = 2.5 Hz, H-C(3)); 4.61, 4.49 (AB, 2H, ^2J = 11.5 Hz); 4.65-4.39 (*m*, 3H); 3.37 (*m*, 1H); 0.94, 0.80 (2*s*, 2 t-Bu); 0.22-0.05 (*m*, 2 Me_2Si).
6. Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7505.
7. Data of **8**: colourless oil; IR (CH_2Cl_2) ν: 3680, 3610, 3050, 2950, 2925, 2855, 1715, 1605, 1470, 1462, 1455, 1245, 1115 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H: 7.33-7.25 (*m*, 5H); 4.59, 4.43 (AB, 2H, ^2J = 11.5 Hz); 4.47 (*m*, H-C(1), H-C(5)); 4.07 (*d*, ^3J = 1 Hz, H-C(4)); 3.95 (*m*, H-C(6)); 3.81 (*m*, CH_2OH); 2.33 (*t*, ^3J = 8 Hz, H-C(3)); 2.07 (br. *s*, OH); 0.89 (*s*, t-Bu); 0.12, 0.10 (2*s*, Me_2Si); ^{13}C-NMR (100.7 $CDCl_3$) δ_C: 171.1, 136.6 (2*s*); 128.5, 128.1, 85.4, 85.1, 81.1, 79.8, 72.6 (7*d*), 60.7 (*t*, ^1J(C,H) = 148 Hz), 50.5 (*d*, ^1J(C,H) = 135 Hz); 25.8 (*q*), 18.0 (*s*), -4.7 (*q*,).
8. For related examples, see e.g.: Kowarski, R.; Sarel, S. *J. Org. Chem.* **1973**, *38*, 117; Ogawa, S.; Vemura, M.; Fujita, T. *Carbohydr. Res.* **1988**, *177*, 213; Eynard, E.; Reymond, J.-L.; Vogel, P. *Synlett* **1991**, 469.
9. Data of **10**: colourless oil; IR (CH_2Cl_2) ν: 3050, 2975, 1755, 1712, 1425, 1365, 1225 cm^{-1}; ^{1}H-NMR (250 MHz, C_6D_6) δ_H: 5.36 (*dd*, ^3J = 10, 11 Hz, H-C(1)); 5.28, 5.23, 5.10 (3*dd*, ^3J = 10, 10.5 Hz, H-C(4), H-C(2), H-C(3)); 4.34, 4.08 (2*dd*, ^2J = 12 Hz, ^3J = 2 Hz, H_2C-C(5)); 3.80 (*t*, ^3J = 11 Hz, H-C(6)); 1.9 (*m*, 16H, 5 Ac, H-C(5)); ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ_C: 170.4, 169.6, 169.3 (3*s*), 74.1, 72.1, 70.9, 67.7 (3*d*); 59.9 (*t*), 47.1, 44.3 (2*d*); 20.7, 20.6, 20.5 (3*q*).
10. Data of (±)-**11**: oil; IR ($CHCl_3$) ν: 3010, 1745, 1365, 1195, 1084, 1058, 1035 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H: 5.12 (*dd*, ^3J = 10, 8.5 Hz, H-C(3)); 5.07 (*d*, ^3J = 8.5 Hz, H-C(2)); 5.00 (*t*, ^3J = 10 Hz, H-C(4)); 4.28 (*dd*, ^2J = 10 Hz, ^3J = 4 Hz) & 4.11 (*dd*, ^2J = 10 Hz, ^3J = 7.5 Hz, H_2C-C(5)); 3.41 (*dd*, ^3J = 3.5, 1.5 Hz, H-C(6)); 3.11 (*d*, ^3J = 3.5 Hz, H-C(1)); 2.49 (*dddd*, ^3J = 10, 7.5, 4, 1.5 Hz, H-C(5)); 2.07, 2.06, 2.04, 2.00 (4*s*, 4 AcO); ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ_C: 170.1, 170.1, 169.9, 169.7 (4*s*); 72.3 (*d*, ^1J(C,H) = 152 Hz); 70.9 (*d*, ^1J(C,H) = 155 Hz); 66.4 (*d*, ^1J(C,H) = 148 Hz); 62.1 (*t*, ^1J(C,H) = 150 Hz); 54.7 (*d*, ^1J(C,H) = 175 Hz, C(1)); 53.2 (*d*, ^1J(C,H) = 180 Hz, C(6)), 39.7 (*d*, ^1J(C,H) = 130 Hz, C(5)); 20.8, 20.6 (2*q*, ^1J(C,H) = 127 Hz).
11. Details will be given in a full-paper.
12. Vogel, P.; Fattori, D.; Gasparini, F.; Le Drian, C. *Synlett* **1990**, 173; Vogel, P. *Bull. Soc. Chim. Belg.* **1990**, *99*, 395.

(Received in France 23 July 1992)