Pergamon

Tetrahedron Letters, Vol. 35, No. 42, pp. 7735-7738, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01663-1

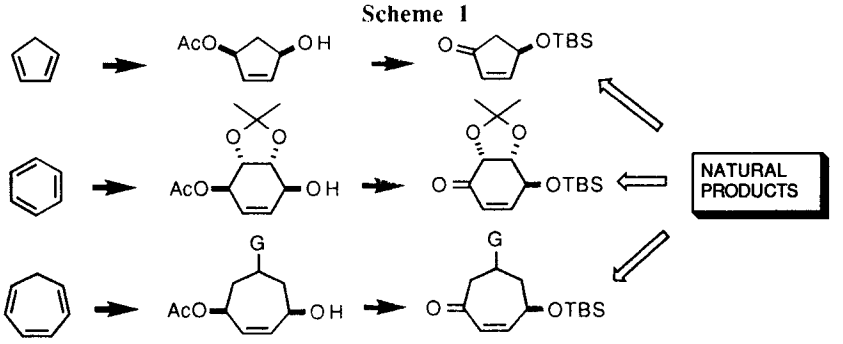
Enantioselective Synthesis of 7-Cycloocten-1,3,5,6-tetraol Derivatives by Enzymatic Asymmetrization

Carl R. Johnson,* Lalgudi S. Harikrishnan and Adam Golebiowski
Department of Chemistry, Wayne State University, Detroit, Michigan 48202-3489

Abstract: *meso*-Diol **4**, derived from 1,5-cyclooctadiene, in the presence of *Pseudomonas cepacia* lipase in isopropenyl acetate, afforded enantiopure **5**, an attractive intermediate for the synthesis of sugars and related compounds.

We are engaged in a program directed toward development of chemoenzymatic syntheses of polyhydroxylated natural products and related bioactive compounds.[1] Using enzymatic asymmetrization[2] and resolution[3] methodologies we have transformed simple hydrocarbons (*e.g.*, cyclopentadiene, benzene or cycloheptatriene) into enantiopure intermediates, which were further elaborated[4] into various targets including sugars and related molecules (Scheme 1).[5]

Scheme 1

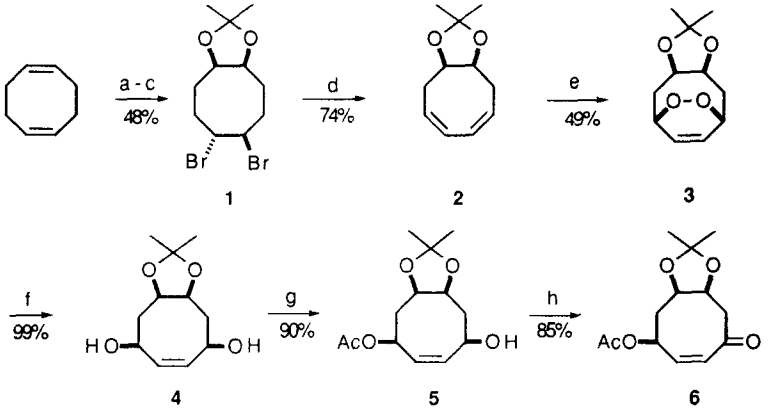


1,5-Cyclooctadiene, a dimer of 1,3-butadiene and a readily available, inexpensive substance, appeared to be a logical substrate for progression of this strategy. We envisioned that the eight-membered ring intermediate **5** could be a useful starting material for the synthesis of higher sugars and other polyhydroxylated bioactive targets.

Monobromination of cyclooctadiene followed by *cis*-dihydroxylation gave acetonide **1** after acid-catalysed acetalization.[6] Bis-elimination of HBr gave diene **2** (Scheme 2). Examination of molecular models (Figure 1) lead to the prediction that singlet oxygen addition to **2** from the face *syn* to the existing acetonide would be favored. The single peroxide diastereomer **3** formed on exposure of **2** to singlet oxygen[7] had the all *syn* stereochemistry of oxygen substituents in accord with our prediction (vide infra).

Zinc and acetic acid reduction of the peroxide **3** led to diol **4**, which was treated with lipase from *Pseudomonas cepacia* (Amano P-30) in isopropenyl acetate at 50 °C for 4 days.[8] Collection of the the enzyme by filtration and evaporation of solvent gave monoacetate **5** in 90% yield. Monacetate **5** was found to be >98% enantiopure by converting alcohol **5** into enone **6** which was analyzed using chiral HPLC.[9] The absolute and relative stereochemistry of **5** was established by chemical correlation to 3-deoxy-D-*ribo*-hexitol pentaacetate (**9**) (Scheme 3).

Scheme 2[a]



[a]Reagents and conditions: (a) Br_2, $CHCl_3$, - 78 °C; (b) OsO_4-cat, NMO, THF, rt; (c) 2,2-dimethoxypropane, p-TsOH-cat, rt; (d) DBU, toluene, reflux; (e) O_2, TPP, hυ, 10 °C, $CHCl_3$:MeOH - 3:1; (f) Zn(activated), HOAc, EtOAc; (g) isopropenyl acetate, *Pseudomonas cepacia* lipase (Amano P-30) 2 wt. equiv, 50 °C, 4 d

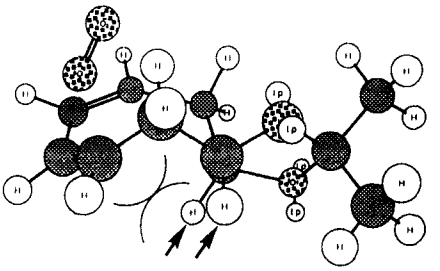
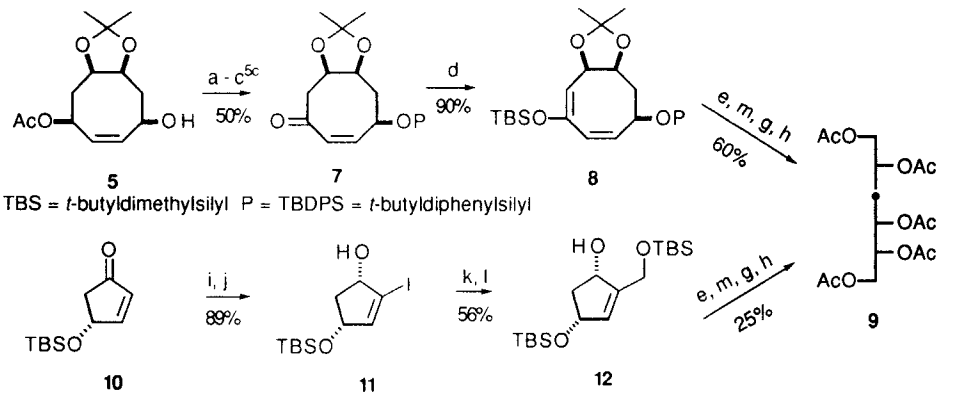


Figure 1. Transannular hydrogens shield approach of $^1O_2$ anti to acetonide of **2** (mimimized Chem3D™ structure shown).

Silylation of the free hydroxy of **5** with TBDPSCl followed by removal of the acetate with KOH/MeOH and PDC oxidation gave enone **7** in 50% yield. Enone **7** was quantitatively converted to the *t*-butyldimethylsilyloxy diene **8**. Ozonolysis of **8** followed in sequence by reductive work-up (dimethyl sulfide), sodium borohydride reduction of the dialdehyde, acidic (1*N* HCl) removal of protective groups and peracetylation gave (+)-3-deoxy-*ribo*-hexitol pentatacetate (**9**). The spectral data for this compound was identical to that previously reported.[10] The production of diastereomer **9** established the relative stereochemistry of the singlet oxygen addition product **3** and polyols **4** and **5** derivatives as having all syn oxygens.

The absolute stereochemistry was established by conversion of the prostaglandin presursor **10**[11] of known absolute stereochemistry to pentaacetate **9**. α-Iodination of enone **10**,[4a] followed by Luche reduction,[12] afforded alcohol **11** as a major product (*syn* : *anti*; 8:1).[5c] One carbon homologation with carbon monoxide[5c,13] followed by reduction and selective silylation of the primary alcohol gave cyclopentenol **12**. Ozonolysis of **12** followed by reductive work-up led to a keto-aldehyde, which was immediately subjected to *anti*-selective reduction with sodium triacetoxyborohydride (*anti* : *syn*; >20:1).[14] Acidic removal of the silyl groups and peracetylation again afforded (+)-pentaacetate **9**, establishing the absolute confirguration of compounds **5** - **9** as shown.

Scheme 3[a]



[a]Reagents and conditions: (a) TBDPSCl, imidazole, DMF, RT; (b) KOH, MeOH; (c) PDC, CH_2Cl_2, molecular sieves 4 Å; (d) TBSOTf, Et_3N, Et_2O, RT; (e) O_3, MeOH, -78 °C then DMS, 20 °C; (f) $NaBH_4$, MeOH; (g) 1N HCl, MeOH, rt; (h) Ac_2O, pyridine, DMAP, rt ; (i) I_2, (1.8 eq.), pyridine/CCl_4 ; (j) $NaBH_4$, $CeCl_3$, MeOH, -78 °C; (k) CO (1 atm.), Bu_3SnH, $Pd(Ph_3P)_4$ 5 mol%, THF; then $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, -78 °C; (l) TBSCl, Et_3N, CH_2Cl_2, RT; (m) $NaBH(OAc)_3$, AcOH, CH_2Cl_2

The absolute stereochemistry at the acetoxy-substituted stereogenic center of **5** is consistent with that predicted by empirical rules for *Pseudomonas cepacia* lipase catalysis at such secondary centers.[2d,15] Enantiopure intermediate **5** as well as derived enone **7** and diene **8** should prove useful in the synthesis of higher sugars and related polyols.[16]

Acknowledgment. This work was supported by grant CHE-9223011 from the National Science Foundation.

References and Notes

1. Johnson, C. R.; Adams, J. P.; Bis, S. J.; De Jong, R. L.; Golebiowski, A.; Medich, J. R.; Penning, T. D.; Senanayake, C. H.; Steensma, D. H.; Van Zandt, M. C. *Pure & Appl. Chem.* **1992**, *64*, 1115.

2. (a) Johnson, C. R.; Penning, T. D. *J. Am. Chem. Soc.* **1988**, *110*, 4726; (b) Medich, J. R.; Kunnen, K. B.; Johnson, C. R. *Tetrahedron Lett.* **1987**, *28*, 4131; (c) Johnson, C. R.; Senanayake, C. H. *J. Org. Chem.* **1989**, *54*, 735; (d) Johnson, C. R.; Golebiowski, A.; McGill, T. K.; Steensma, D. H. *Tetrahedron Lett.* **1991**, *32*, 2597; (e) Johnson, C. R.; Ple, P. A.; Su, L.; Heeg, M. J.; Adams, J. P. *Synlett* **1992**, 388.

3. Johnson, C. R.; Sakaguchi, H. *Synlett* **1992**, 813; Sundram, H.; Golebiowski, A.; Johnson, C. R. *Tetrahedron Lett.* **1994**, *35*, (in press).

4. For examples of new synthetic methodologies developed in the course of this project see: (a) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B.; Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron Lett.* **1992**, *33*, 919; (b) Bakale, R. P.; Johnson, C. R.; Scialdone, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 6729; (c) Johnson, C. R.; Golebiowski, A.; Steensma, D, H.; Scialdone, M. A. *J. Org. Chem.* **1993**, *58*, 7185; (d) Johnson, C. R.; Raheja, R. K. *J. Org. Chem.* **1994**, *59*, 2287.

5. (a) Johnson, C. R.; Golebiowski, A.; Steensma, D, H. *J. Am. Chem. Soc.* **1992**, *114*, 9414; (b) Johnson, C. R.; Adams, J. P.; Collins, M. A. *J. Chem. Soc. Perkin Trans. 1* **1993**, 1; (c)

Johnson, C. R.; Golebiowski, A.; Braun, M. P.; Sundram, H. *Tetrahedron Lett.* **1994**, *35*, 1833; (d) Johnson, C. R.; Kozak, J. *J. Org. Chem.* 1994, *59*, 2910.

6. This part of the synthesis was done in analogy to the previously reported 1,4-cyclohexadiene functionalization (see ref. 2e).
7. All syn oxygen products are dominant in additions of singlet oxygen to 6-silyloxy-1,4cycloheptadienes (see ref. 2c, 2d, 5a). For a recent review on singlet oxygen cycloadditions see: Clennan, E. L. *Tetrahedron* **1991**, *47*, 1343.
8. For a recent review on the use of lipases in the presence of isopropenyl acetate see Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry;* Pergamon : Oxford, 1994
9. Chiral HPLC: CHIRALCEL OB (J. T. Baker); 40% isopropyl alcohol in hexane at 0.5 mL/min; **ent-6** 13.6 min; **6**, 15.5 min. A racemic sample of **6** was prepared from **4**.
10. Moore, R. E.; Barchi, J. J.; Bartolini, G. *J. Org. Chem.* **1985**, *50*, 374. No polarimetric data is given for 3-deoxy-D-*ribo*-hexitol.
11. Johnson, C.R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014.
12. Gemal, A. L.; Luche, J-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
13. Baillargeon, V. P.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 7176.
14. Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273. For an excelent review on substrate-directable reactions see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.
15. Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656.
16. **Selected Spectral and Polarimetric Data:**

1: mp 99 °C; ^{1}H NMR ($CDCl_3$) δ: 4.63-4.51 (m, 2H); 4.40-4.31 (m, 2H); 2.28-1.93 (m, 8H); 1.44 (s, 3H); 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 107.1, 76.6, 58.0, 31.5, 30.0, 27.7, 25.4. **3**: IR (film) : 1450, 1431, 1395, 1357, 1200, 1157 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 6.39 (dd, 2H,J = 3.7 Hz, 2.15 Hz); 4.80-4.76 (m, 2H); 4.32-4.23 (m, 2H); 2.56-2.51 (m, 4H); 1.47 (s, 3H); 1.28 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 130.6, 105.4, 74.7, 73.7, 37.9, 27.4, 23.9. **4**: mp 127-128 °C; IR (film) : 3404, 3337, 1645, 1210, 1070, 1024 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 5.75 (d, 2H, *J* =3 Hz); 4.41-4.36 (m, 4H); 2.38-2.15 (m, 6H); 1.42 (s, 3H); 1.30 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 134.1, 102.1, 76.3, 66.4, 40.3, 27.3, 24.4. **5**: Oil; $[\alpha]_D$ +23.2 (*c* 1, $CHCl_3$); IR (neat) : 3454, 2978, 1730, 1711, 1366, 1241, 1027 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 5.76 (ddd, 1H, *J* = 11.5, 5.5, 1.8 Hz); 5.63 (ddd, 1H, J = 11.5, 5.5, 1.8 Hz); 5.29-5.22 (m, 1H); 4.59-4.48 (m, 2H); 4.40-4.35 (m, 1H); 2.34-2.07 (m, 5H); 2.06 (s, 3H); 1.40 (s, 3H); 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 170.3, 135.5, 129.8, 107.7, 76.9, 76.7, 68.7, 66.9, 41.7, 39.0, 27.4, 24.6, 21.1. **6**: mp 49-52 °C; ; $[\alpha]_D$ -14.9 (*c* 1, $CHCl_3$); IR (cast film) : 1733, 1636, 1366, 1229, 1059, 1016 cm^{-1}; ^{1}H NMR ($CDCl_3$) d: 6.12 (ddd, 1H, *J* =13.3, 4.8, 1.1 Hz); 5.97 (d, 1H, J = 13.8 Hz); 5.55-5.48 (m, 1H); 4.52 (ddd, 1H, *v*= 10.8, 5.3, 3.3 Hz); 4.35 (ddd, 1H, J = 10.7, 5.2, 3.7 Hz); 2.98 (dd, 1H, J = 17.7, 10.8 Hz); 2.73 (dd, 1H, J = 18.2, 3.4 Hz); 2.34 (ddt, 1H, J = 14.6, 3.7, 1.4 Hz); 2.07 (s, 3H); 1.43 (s, 3H); 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 201.7, 169.6, 134.9, 131.4, 107.8, 74.5, 73.1, 67.9, 44.4, 32.0, 27.7, 25.5, 20.7. **9** (from cyclooctadiene **8**): $[\alpha]_D$ +0.4, $[\alpha]_{400}$ +1.6 (*c*1, $CHCl_3$); **9** (from cyclopentene **12**): $[\alpha]_D$ +0.4 (*c* 3.6, $CHCl_3$), $[\alpha]_{400}$ +1.8 (*c*2.1, $CHCl_3$); The following spectral data were identical in both cases: IR (neat) : 1742, 1433, 1370, 1235, 1045, 948 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 5.21-5.28 (m, 3H); 4.28 (dd, 1H, J =4.7, 3.7 Hz); 4.24 (dd, 1H, J = 4.7, 3.7 Hz); 4.12 (dd, 1H, J = 12.2, 6.1 Hz); 4.03 (dd, 1H, J = 12.2, 6.1 Hz); 2.04 - 2.07 (m, 17H); ^{13}C NMR ($CDCl_3$) δ: 170.5, 170.0, 170.2, 71.5, 68.4, 68.3, 64.3, 61.6, 31.2, 20.9, 20.8, 20.6

(*Received in USA* 1 *August* 1994; *revised* 23 *August* 1994; *accepted* 26 *August* 1994)