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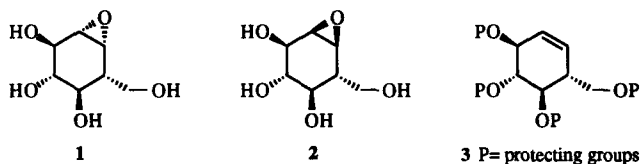
## A Stereodivergent Synthesis of (±)-Cyclophellitol and (1*R*\*,6*S*\*)-Cyclophellitol from the 7-Oxabicyclo-[2.2.1]hept-5-ene-2-*endo*-carboxylic Acid.‡

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**Abstract:** A concise, stereodivergent synthesis of (±)-cyclophellitol **1** and its unnatural diastereoisomer (1*R*\*,6*S*\*)-cyclophellitol **2** starting from the Diels-Alder adduct of furan and acrylic acid is reported. The stereochemistry of the key step (the epoxidation of alkene **3**) is controlled by the nature of the hydroxyl protecting groups. Copyright © 1996 Elsevier Science Ltd

Cyclophellitol **1** is a carbasugar derivative isolated from the culture filtrates of a mushroom, *Phellinus* *sp.*<sup>1</sup> The biological properties of this compound include a strong β-glucosidase inhibitory action and a potential therapeutic activity against HIV and metastasis.<sup>1</sup> On the other hand, its unnatural diastereoisomer (1*R*,6*S*)-cyclophellitol **2** is inhibitor of α-glucosidase.<sup>2</sup> Although there are several synthetic approaches to **1** and **2** starting from sugars,<sup>2,3</sup> other natural cyclitols<sup>4</sup> and furan derivatives,<sup>5</sup> only in a few cases the epoxidation of an alkene precursor **3** has been used for the divergent synthesis of both **1** and **2**.<sup>3b,3d,4b,6</sup> In this letter we wish to report a shorter route to **1** and **2** through a suitable alkene intermediate **3** in which a delicate stereochemical control of the epoxidation process is performed by rational manipulation of the hydroxyl protecting groups.

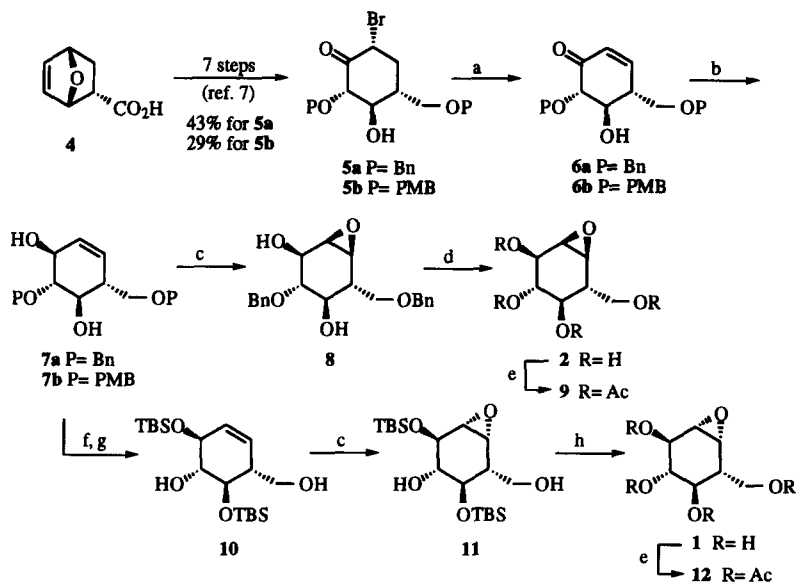


Our synthesis started from the bromoketone **5a**, readily available in seven steps through a route previously developed in our laboratory<sup>7</sup> from the acid **4**, the Diels-Alder adduct of furan and acrylic acid (Scheme 1). Although this sequence has been carried out using racemic compounds it is also possible to obtain the final products in enantiomerically pure form since the optical resolution of **4** has been previously described.<sup>8</sup>

Dehydrohalogenation of **5a** with CaCO<sub>3</sub> in refluxing DMF yielded the enone **6a**.<sup>9</sup> Carbonyl reduction of **6a** under Luche's conditions<sup>10</sup> gave the diol **7a**. Its subsequent epoxidation using *m*-CPBA was controlled by the free allylic hydroxyl group<sup>11</sup> producing **8** as a single product, which after debenzoylation gave rise to (1*R*\*,6*S*\*)-cyclophellitol **2**. Peracetylation of **2** afforded the fully protected derivative **9**.

In order to reverse the selectivity of the epoxidation, the change of protecting groups in **7a** by means of a protection-debenzylation sequence was proposed. However, the benzyl groups were not easily removed in the presence of the double bond and the other protecting groups. Therefore, we decided to repeat the route with the corresponding *p*-methoxybenzyl ether derivatives prepared in identical manner as before.

The synthesis of (±)-cyclophellitol was then addressed from diol **7b**. Thus, its protection with TBSOTf followed by clean removal of the PMB groups using DDQ gave **10**. Its epoxidation afforded selectively the protected (±)-cyclophellitol **11**. Finally, removal of silyl groups using TBAF yielded (±)-cyclophellitol **1** which



Reagents and conditions: a)  $\text{CaCO}_3$  (5 equiv), DMF,  $150^\circ\text{C}$ , 2.5 h, 70% for 6a, 58% for 6b. b)  $\text{NaBH}_4$ ,  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ , MeOH,  $-78^\circ\text{C}$  to rt, 2 h, 83% for 7a, 80% for 7b. c) *m*-CPBA,  $\text{CH}_2\text{Cl}_2$ , rt, 36 h, 71% for 8, 81% for 11. d)  $\text{H}_2$ , 10% Pd-C, MeOH, rt, 24 h. e)  $\text{Ac}_2\text{O}$ , pyr, DMAP, rt, 12 h, 80% for 9 (2 steps), 75% for 12 (2 steps). f) TBSOTf,  $\text{Et}_3\text{N}$ , THF,  $-78^\circ\text{C}$ , 1 h, quant. g) DDQ,  $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$  20:1, rt, 4 h, 75%. h) TBAF, THF, rt, 30 min.

Scheme 1

was further identified as pentaacetate 12. The spectral features of 9 and 12 were identical to those reported in the literature.<sup>4b</sup>

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#### References and notes.

- §. Dedicated to Prof. Charles W. Jefford.
1. Atsumi, S.; Umezawa, K.; Iinuma, H.; Nagawawa, H.; Nakamura, H.; Iitaka, Y.; Takeuchi, T. *J. Antibiot.* **1990**, *43*, 49-53.
2. Tatsuta, K.; Niwata, Y.; Umezawa, K.; Toshima, K.; Nakata, M. *J. Antibiot.* **1991**, *44*, 456-458.
3. a) Tatsuta, K.; Niwata, Y.; Umezawa, K.; Toshima, K.; Nakata, M. *Tetrahedron Lett.* **1990**, *31*, 1171-1172. b) Sato, K.; Bokura, M.; Moriyama, H.; Igarashi, T. *Chem. Lett.* **1994**, 37-40. c) McDevitt, R. E.; Fraser-Reid, B. *J. Org. Chem.* **1994**, *59*, 3250-3252. d) Jung, M. E.; Choe, S. W. T. *J. Org. Chem.* **1995**, *60*, 3280-3281.
4. a) Akiyama, T.; Ohnari, M.; Shima, H.; Ozaki, S. *Synlett* **1991**, *66*, 831-832. b) Shing, T. M. K.; Tai, V. W.-F. *J. Chem. Soc.; Perkin Trans. 1* **1994**, 2017-2025.
5. a) Moritz, V.; Vogel, P. *Tetrahedron Lett.* **1992**, *33*, 5243-5244. b) Schlessinger, R. H.; Bergstrom, C. P. *J. Org. Chem.* **1995**, *60*, 16-17. c) It should be noted that protected derivatives of 1 and 2 were prepared by Ogawa *et al* in their synthesis of valienamine. See: Ogawa, S.; Chida, N.; Suami, T. *J. Org. Chem.* **1983**, *48*, 1203-1207.
6. For the synthesis of a tetraacetyl alkene 3 (P= Ac) in racemic form, see: Barton, D. H. R.; Dalko, P.; Gero, S. D. *Tetrahedron Lett.* **1991**, *32*, 2471-2474.
7. a) Aceña, J. L.; Arjona, O.; Fernández de la Pradilla, R.; Plumet, J.; Viso, A. *J. Org. Chem.* **1992**, *57*, 1945-1946. b) Aceña, J. L.; Arjona, O.; Fernández de la Pradilla, R.; Plumet, J.; Viso, A. *J. Org. Chem.* **1994**, *59*, 6419-6424.
8. Ogawa, S.; Iwasawa, Y.; Nose, T.; Suami, T.; Ohba, S.; Ito, M.; Saito, Y. *J. Chem. Soc.; Perkin Trans. 1* **1985**, 903-906.
9. All new compounds showed spectroscopic and analytical data consistent with the assigned structures.
10. Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454-5459.
11. a) Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1957**, 1958-1965. b) Kocovsky, P. *J. Chem. Soc.; Perkin Trans. 1* **1994**, 1759-1763.

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