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Stereo- and Enantio-Controlled Synthesis of Two Naturally Occurring Polyoxygenated Cyclohexenemethanols, (+)-Epiepoxydon and (–)-Phyllostine, *via* Catalytic Asymmetrization of a *Meso* Substrate

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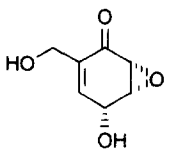
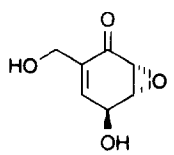
Abstract: Two naturally occurring polyoxygenated cyclohexenemethanols, (+)-epiepoxydon and (–)-phyllostine, have been first synthesized in stereo- and enantio-controlled manner using a chiral cyclohexadienol synthon prepared by catalytic asymmetrization of a *meso* substrate. The synthesis has verified the proposed absolute structures of these natural products which have been deduced by CD measurements.

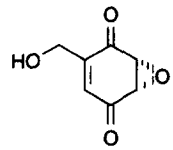
Three polyoxygenated cyclohexenemethanols, (+)-epoxydon[1,2] (**1**), (+)-epiepoxydon[3,4] (**2**), and (–)-phyllostine[5] (**3**), have been isolated so far from natural sources. They are biologically interesting for their phytotoxic, antibiotic, antitumor, and antigermination activities. However, their absolute structures have been deduced only by CD measurements though their relative configurations have been confirmed by racemic synthesis.[6,7] We wish to report here the stereo- and enantio-controlled synthesis of two of these natural products, (+)-epiepoxydon (**2**) and (–)-phyllostine (**3**), using the stereo-defined chiral cyclohexadienol synthon[8] generated *via* the Rh^{I}-(*S*)-BINAP-mediated catalytic asymmetrization[9] of the *meso* substrate, which verified the correctness of the proposed absolute structures of the three natural products.



(+)-epoxydon (**1**)



(+)-epiepoxydon (**2**)



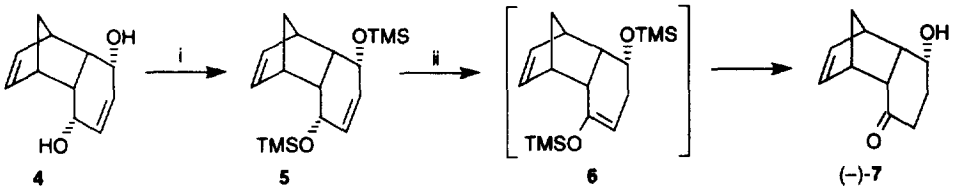
(–)-phyllostine (**3**)

Figure 1

We have recently succeeded[9] in a catalytic asymmetrization of a series of tricyclic *meso* 1,4-enediol bis-ethers including the present starting material **4** using [Rh{chiral BINAP}(COD)]$^{+}ClO_4^{-}$ (Rh^{I}-chiral BINAP)[10] as catalyst. Because the chiral Rh^{I}-BINAP-catalyzed enantiospecific isomerization has so far been limited to allyl amines in a practical sense except one example,[11] our finding implied the first breakthrough for the practical utilization of enol ether substrates in chiral synthesis. In the present synthesis we demonstrate the conversion of the *meso* 1,4-enediol (**4**) into (+)-epiepoxydon (**2**) and (–)-phyllostine (**3**) employing the Rh^{I}-(*S*)-BINAP-catalyzed asymmetrization as the key step.

Since the meso diol (**4**) itself has been found to be not an appropriate substrate,[9] its bis-trimethylsilyl ether (**5**) was refluxed with a catalytic amount of Rh^{I}-(*S*)-BINAP catalyst in 1,2-dichloroethane for 14 h to give the hydroxyketone [(–)-**7**], $[\alpha]_D^{30}$ –122.9 (*c* 1.1, $CHCl_3$), quantitatively, after hydrolytic treatment of the crude

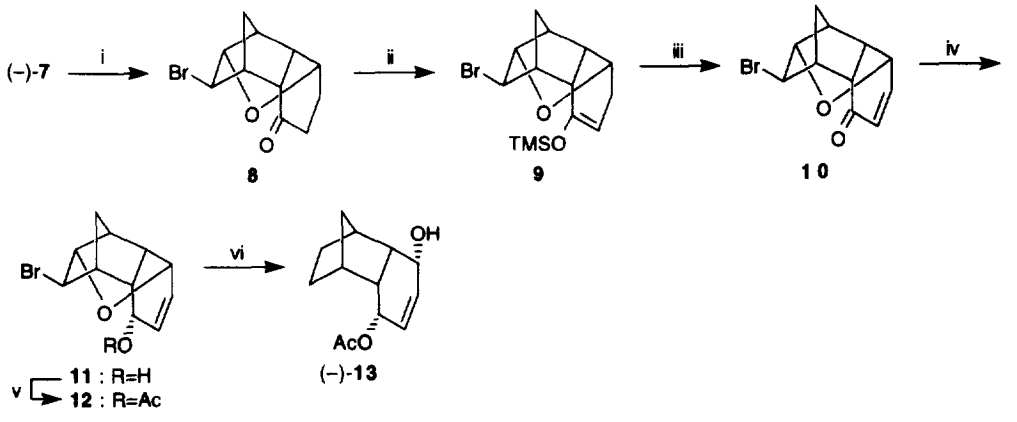
isomerization product (**6**). Optical purity of the product (**7**) was determined to be 93.5% ee by hplc using chiral column (CHIRALCEL OD; elution *i*-PrOH/hexane, 1:99 v/v) after converting it into the mono-benzoate (**Scheme 1**).



Scheme 1

Reagents and conditions: i. TMSCl, Et_3N, THF, 96%; ii. Rh(I)-(*S*)-BINAP (2 mol%), $ClCH_2CH_2Cl$, reflux, 14 h, then aq. TBAF, THF, ~100%, 93.5% ee.

Without further purification, the optically enriched hydroxyketone [(–)-**7**] was treated with *N*-bromosuccinimide (NBS) to give the optically pure bromo ether (**8**), mp 58-59 °C, $[\alpha]_D^{29}$ –203.5 (*c* 0.6, $CHCl_3$), after recrystallization (Et_2O-hexane). Employing the Saegusa conditions,[12] the ketone (**8**) was transformed into the α,β-unsaturated ketone (**10**), mp 133-134 °C, $[\alpha]_D^{28}$ –262.2 (*c* 0.7, $CHCl_3$), *via* the trimethylsilyl ether (**9**). Reduction of **10** with $NaBH_4$-$CeCl_3$[13] gave stereoselectively the *endo*-alcohol (**11**), mp 127 °C, $[\alpha]_D^{25}$ –115.1 (*c* 1.1, $CHCl_3$) which, after conversion into the acetate (**12**), was refluxed with zinc dust in methanol in the presence of acetic acid to afford the tricyclic monoacetate [(–)-**13**], mp 86.5-87.5 °C, $[\alpha]_D^{27}$ –68.8 (*c* 1.0, $CHCl_3$). The acetate [(–)-**13**] generated was identical in all respects, except the direction of optical rotations, with its enantiomer [(+)-**13**], mp 87-88 °C, $[\alpha]_D^{30}$ +70.1 (*c* 1.02, $CHCl_3$), obtained by lipase-mediated asymmetric acetylation,[14] which has been used as either chiral cyclohexadienol synthon or chiral cyclohexadienone synthon.[8] Overall yield of (–)-**13** from **4** was 49% (**Scheme 2**).

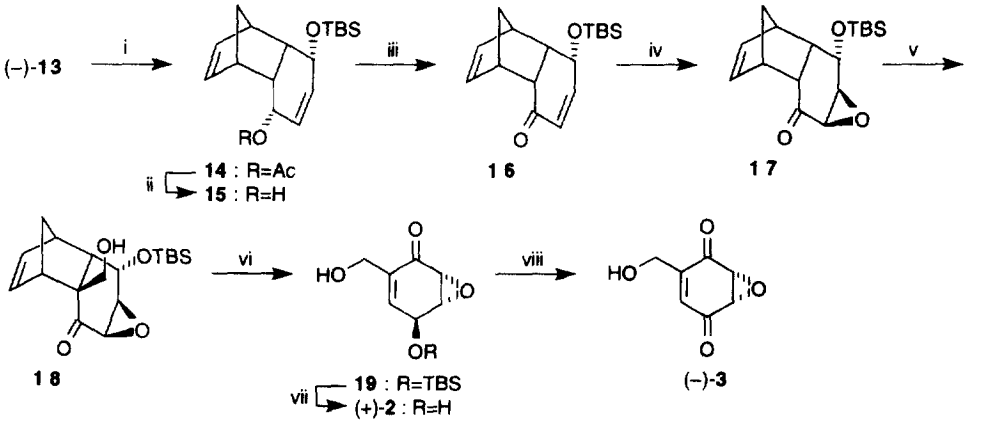


Scheme 2

Reagents and conditions: i. NBS (1.1 equiv.), CH_2Cl_2, 0 °C, 1 h, 92%; ii. *i*-Pr_2NEt, TMSOTf, CH_2Cl_2, 0 °C, 2.5 h; iii. $Pd(OAc)_2$, MeCN, room temp., 26 h, 80%; iv. $NaBH_4$, $CeCl_3 \cdot 7H_2O$, EtOH, –78 °C, 4.5 h, 92%; v. Ac_2O, Et_3N, DMAP (cat.), CH_2Cl_2, 0–25 °C, 12 h; vi. Zn, AcOH, MeOH, reflux, 7 h, 76%.

Having confirmed the stereochemistry, the acetate [(–)-**13**] was transformed into the known siloxy enone[15] [(–)-**16**], $[\alpha]_D^{30}$ –241.7 (*c* 1.1, $CHCl_3$), *via* **14** and **15**. Treatment of **16** with alkaline aqueous hydrogen peroxide afforded the *exo*-epoxide[15] (**17**), mp 65.5-66.5 °C, $[\alpha]_D^{29}$ –54.9° (*c* 1.1, $CHCl_3$), in 67% overall yield from (–)-**13** as a single product. The epoxide (**17**) was next treated with formalin in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[16] to introduce the hydroxymethyl group regioselectively, affording the hydroxy ketone (**18**), mp 72-73 °C, $[\alpha]_D^{29}$ +38.5° (*c* 0.9, $CHCl_3$), nearly in quantitative yield. Upon thermolysis in refluxing with diphenyl ether, **18** furnished the cyclohexenone (**19**), mp 39.5-41 °C, $[\alpha]_D^{29}$ +233.5° (*c* 0.9, $CHCl_3$), equipped with the requisite functionalities cleanly regenerating the double bond with facile removal of the cyclopentene bridge by retro-Diels-Alder cleavage. The α-epoxyketone functionality was found to be intact under the above strong alkaline and these thermal conditions.[16] Brief treatment of **19** with hydrofluoric acid in acetonitrile[17] allowed facile removal of the silyl protecting group to give (+)-epiepoxydon (**2**) as an amorphous solid, $[\alpha]_D^{27}$ +256.4° (*c* 0.8, EtOH), in 73% overall yield from **17**. Since its direction of optical rotations was identical with that of the natural product (amorphous solid, $[\alpha]_D^{24}$ +194 (*c* 1.57, EtOH)[3]; mp 53 °C, $[\alpha]_D^{32}$ +206 (*c* 0.17, MeOH)[4]), the absolute structure deduced by CD measurements has been verified.

We next examined the selective oxidation of one of the two allylic hydroxy groups of (+)-epiepoxydon (**2**) to obtain (–)-phyllostine (**3**). We found that the selective oxidation occurred in the desired way when (+)-**2** was treated with pyridinium dichromate (PDC) in *N,N*-dimethylformamide (DMF). Thus, treatment of (+)-**2** with PDC in DMF at 0 °C afforded (–)-phyllostine (**3**), mp 54.5-55.0 °C, $[\alpha]_D^{31}$ –100.4 (*c* 0.6, EtOH), in 37% yield by selective oxidation of the secondary center. Since the direction of optical rotations of the synthetic material was identical with that of natural (–)-phyllostine (**3**), (mp 56 °C, $[\alpha]_D^{20}$ –105.6 (*c* 1, EtOH)[5]), the absolute structure deduced by CD measurements has also been verified (**Scheme 3**).



Scheme 3

Reagents and conditions: i. TBSCl, imidazole, DMF; ii. K_2CO_3, MeOH, room temp.; iii. 30% H_2O_2, Triton B, 0 °C (80% overall); iv. 35% formalin, DBU, THF, 0 °C (98%); v. diphenyl ether, reflux (87%); vi. 46% HF-MeCN (1:19), 0 °C (86%); vii. PDC, DMF, 0 °C (37%).

In summary, we have verified unambiguously the absolute structures of (+)-epiepoxydon (**2**) and (–)-phyllostine (**3**) as have been deduced by the stereo- and enantio-controlled synthesis using the chiral

cyclohexadienol synthon **13** obtained by catalytic asymmetrization. The present synthesis has also clarified the absolute structure of (+)-epoxydon (**1**) as proposed since natural (+)-epoxydon (**1**) afforded (–)-phyllostine (**3**) on oxidation.[5]

References and Notes

1. Closse, A.; Mauli, R.; Sigg, H. P. *Helv. Chim. Acta* **1966**, *49*, 204.
2. Sakamura, S.; Niki, H.; Obata, Y.; Sakai, R.; Matsumoto, T. *Agr. Biol. Chem.* **1969**, *33*, 698.
3. Nagasawa, H.; Suzuki, A.; Tamura, S. *Arg. Biol. Chem.* **1978**, *42*, 1303.
4. Sekiguchi, J.; Gaucher, G. M. *Biochem. J.* **1979**, *182*, 445.
5. Sakamura, S.; Ito, J.; Sakai, R. *Agr. Biol. Chem.* **1970**, *34*, 153; **1971**, *35*, 105.
6. Racemic syntheses: a) Ichihara, A.; Oda, K.; Sakamura, S. *Tetrahedron Lett.* **1972**, 5105. b) Ichihara, A.; Kimura, R.; Oda, K.; Sakamura, S. *Tetrahedron Lett.* **1976**, 4741. c) Ichihara, A.; Kimura, R.; Oda, K.; Moriyasu, K.; Sakamura, S. *Arg. Biol. Chem.* **1982**, *46*, 1879.
7. Pertinent reviews, see: a) Ichihara, A. *J. Syn. Org. Chem. Jpn.* **1982**, *40*, 102. b) Ichihara, A. *Synthesis* **1987**, 207.
8. Ogasawara, K. *Pure & Appl. Chem.* **1994**, *66*, 2119.
9. Hiroya, K.; Kurihara, Y.; Ogasawara, K. *Angew. Chem. Int. Ed. Engl.* in press.
10. Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932; Miyashita, A.; Takaya, H.; Souchi, T.; Noyori, R. *Tetrahedron* **1984**, *40*, 1245; Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629.
11. Kitamura, M.; Manabe, M.; Noyori, R.; Takaya, H. *Tetrahedron Lett.* **1987**, *28*, 4719. Pertinent reviews: Otsuka, S.; Tani, K. In *Asymmetric Synthesis*; Morrison, J. D. Ed.; Academic Press: New York, 1985; Vol. 5, 171; Noyori, R.; Kitamura, M. *Modern Synthetic Methods*; Schefford, R. Ed.; Springer: Heidelberg, 1989; Vol. 5, 115.; Otsuka, S.; Tani, K. *Synthesis* **1991**, 665.
12. Ito, Y.; Hirano, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
13. Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
14. Takano, S.; Higashi, Y.; Kamikubo, T.; Moriya, M.; Ogasawara, K. *Synthesis* **1993**, 948.
15. Kamikubo, T.; Ogasawara, K. *Tetrahedron Lett.* **1995**, *36*, 1685. In this report was described the transformation of the enzymatically prepared (+)-**13** into **17** *via* **16**.
16. a) Takano, S.; Moriya, M.; Ogasawara, K. *Synlett* **1993**, 601. b) Kamikubo, T.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1995**, 1951.
17. Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3981.
18. NMR spectra of the synthetic natural products: (+)-epiepoxydon (**2**) — ^{1}H-NMR (300 MHz, acetone-d_6): δ 3.40 (dd, 1H, *J*=3.8 and 1.1 Hz), 3.77-3.79 (m, 1H), 4.03-4.07 (m, 1H), 4.10-4.32 (m, 2H), 4.64-4.69 (m, 1H), 4.82-4.85 (m, 1H), 6.70-6.74 (m, 1H). ^{13}C-NMR (125 MHz, acetone-d_6): δ 54.58, 59.28, 59.52, 63.79, 137.60, 139.77, 194.84. (–)-phyllostine (**3**) — ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.03 (br s, 1H), 3.82-3.85 (m, 2H), 4.41 (dd, 1H, *J*=17.5 and 1.7 Hz), 4.59 (dd, 1H, *J*=17.5 and 1.9 Hz), 6.69 (dd, 1H, *J*=3.8 and 1.9 Hz).

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