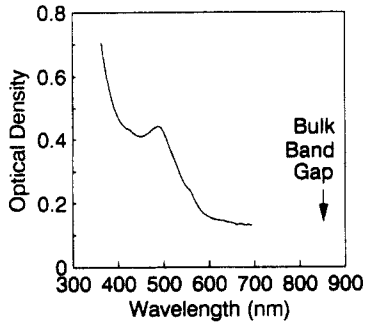


Figure 3. Optical absorption spectrum of a quinoline solution of the crystallites obtained after refluxing, but before flame annealing.

one GaAs particle taken from the field of Figure 1a, in which lattice planes can clearly be seen. Selected area electron diffraction on this region of the grid yields a diffraction pattern in which the (111), (220), and (311) zinc blende peaks of GaAs are evident, confirming the identity of the particles (Figure 1b). The widths of these peaks can be used to determine the domain size of the particles via the Debye–Scherrer formula:

$$\Delta(2\theta) = \frac{1.2\lambda}{D\cos\theta} \qquad (1)$$

where λ is the electron wavelength and D is the crystallite diameter. The best fit is obtained for $D = 24$ Å. Since the domain size determined by electron diffraction is somewhat smaller than the mean particle diameter from the real space images, we conclude that the particles are not perfectly crystalline.

X-ray diffraction on the unflamed and flamed powders also shows the (111), (220), and (311) peaks of GaAs. The domain size from X-ray diffraction matches the value obtained from electron diffraction on the unflamed powder, although the signal-to-noise ratio is much worse. The domain size is 30 Å in the flamed sample, but this improvement in crystallinity is obtained by compromising the solubility. Elemental analysis of the particles shows the presence of Ga and As in a 5:4 ratio, as well as carbon and nitrogen. These numbers are verified by XPS studies of the Ga and As core levels. The carbon and nitrogen may be from quinoline, which could bind to the Ga-rich surface via the nitrogen lone pair, and act as a capping moiety.[16] Resonance Raman scattering on powders prepared in this manner shows a single peak at 292 cm^{-1}, the frequency of the LO mode of GaAs.

Since the particles are significantly smaller than the bulk exciton diameter, we expect the onset of optical absorption to be shifted to higher energy, according to the well-known formula

$$E = E_g + \frac{\hbar^2\pi^2}{2R^2}\left(\frac{1}{m_e} + \frac{1}{m_h}\right) - \frac{1.8e^2}{\epsilon R} \qquad (2)$$

where E_g is the bulk band gap (1.52 eV), R is the particle radius, m_e (0.07) and m_h (0.68) are the effective masses of the electron and hole, e is the fundamental charge, and ϵ is the high-frequency dielectric constant (10.9).[7] For 40 Å diameter particles, this predicts a shift in the spectrum of 1.33 eV. The absorption spectrum of the nanocrystals, dissolved in quinoline, does indeed show a pronounced quantum confinement effect (1 eV, Figure 3), but not quite as large as is predicted by eq 2.[17]

We are currently exploring the large range of parameters that can be changed in this reaction, including solvent, total reactant concentration, the use of capping moieties, etc., in order to adjust the average size of the particles. In addition, we are investigating the nature of the surface derivatization.

Acknowledgment. We thank the National Center for Electron Microscopy at the Lawrence Berkeley Laboratory for the use of their electron microscope.

(16) Steigerwald, M. L.; Alivisatos, A. P.; Gibson, J. M.; Harris, T. D.; Kortan, R.; Muller, A. J.; Thayer, A. M.; Duncan, T. M.; Douglass, D. C.; Brus, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 3046.

(17) The breakdown of this formula in II–VI systems is well-known. See: Lippens, P. E.; Lannoo, M. *Phys. Rev. B* **1989**, *39*, 10935.

Efficient and Enantiodivergent Synthesis of (+)- and (−)-Pinitol

Tomas Hudlicky,*[1] John D. Price, Fan Rulin, and Toshiya Tsunoda

Department of Chemistry, Virginia Polytechnic Institute and State University Blacksburg, Virginia 24061

Received August 31, 1990

Pinitol **1** is the 3-*O*-methyl ether of chiro inositol, with both enantiomers occurring in various plant sources.[2] The structures and absolute stereochemistry of (+)- and (−)-pinitol were determined in 1952 by degradation studies[3] and confirmed later by an independent synthesis of the (−) isomer as its diacetonide.[4a] Recently (+)-pinitol has been shown to possess significant hypoglycemic and antidiabetic activity in diabetic albino mice.[5a] It also acts as a feeding stimulant for the larvae of the yellow butterfly *Eurema hecabe mandarina*[5b] and inhibits larval growth of *Heliothis zaea*.[5c,d] Ley has reported a synthesis of (±)-pinitol in which, by subsequent resolution of a racemic intermediate, he was able to achieve both antipodes.[4b,c] An enantiodivergent and a general synthesis of a large number of cyclitols, especially the important inositol phosphates[6] implicated as cell messengers,[6] would be highly desirable, especially if such an approach took into account comlete control in the stepwise functionalization of hydroxyl groups in cyclohexanehexols such as **1**.

One of the frequently cited disadvantages of enzyme-mediated synthesis is that usually only one enantiomer of a given target may be prepared. The chiral auxiliary approaches to enantiodivergent synthesis are frequently inefficient and long and rely on known sources of chirality. In this communication we report a short synthesis of both enantiomers of pinitol **1**, based on a novel concept of designing enantiodivergent synthesis as an indication that, with proper consideration of symmetry,[7] *both enantiomers may become available from a single isomer generated by biocatalytic means.*

Our enantiodivergent approach to (+)- and (−)-**1** centered upon elaboration of a new cis-diol **2** obtained by the microbial oxidation of bromobenzene by the bacteria *Pseudomonas putida* 39-D.[8]

(1) Recipient of the Research Career Development Award, 1984–1989, National Institutes of Health (AI-00564).

(2) For leading references concerning isolation, see: (a) Pereira, M.; Correa, C.; Rego de Sousa, J. Teixeira, M. *Quim. Nova* **1988**, *11*, 196. (b) Calle, J.; Rivera, A.; Joseph-Nathan, P. *Planta Med.* **1987**, *53*, 303. (c) Rao, C.; Gunasekar, D. *Acta Cienc. Indica, Chem.* **1987**, *13*, 169. (d) Sharma, N.; Guupta, R. K. *Fitoterapia* **1985**, *56*, 122. (e) Adinarayana, D.; Chetty, P. R. *Indian J. Chem., Sect. B* **1985**, *24B*, 453. (f) Iribarren, A. M.; Pomilio, A. B. *J. Nat. Prod.* **1983**, *46*, 752. (g) Davis, L. C.; Nordin, P. *Plant Physiol.* **1983**, *72*, 1051. (h) Adinarayana, D.; Syamasundar, K. V. *Curr. Sci.* **1982**, *51*, 936. (i) Balabanova-Radonova, E. *Dokl. Bulg. Akad. Nauk* **1982**, *35*, 463. (j) Adinarayana, D.; Pamachandraia, P. *J. Nat. Prod.* **1985**, *48*, 156.

(3) (a) Anderson, A. B.; MacDonald, D. L.; Fischer, H. O. L. *J. Am. Chem. Soc.* **1952**, *74*, 1479. (b) Angya, S. J.; Macdonald, C. G. *J. Chem. Soc.* **1952**, 686.

(4) (a) Angyal, S. J.; Macdonald, C. G.; Matheson, N. K. *J. Chem. Soc.* **1953**, 3321. (b) Ley, S. V.; Sternfeld, F. *Tetrahedron* **1989**, *45*, 3463. (c) Ley, S. V.; Sternfeld, F.; Taylor, S. *Tetrahedron Lett.* **1987**, *28*, 225.

(5) (a) Narayanan, C. R.; Joshi, D. D.; Miyumdar, A. M.; Dhekne, V. V. *Curr. Sci.* **1987**, *56*, 139. (b) Namata, A.; Hokimoto, K.; Shimada, A.; Yamaguchi, H.; Takaishi, K. *Chem. Pharm. Bull.* **1979**, *27*, 602. (c) Reece, J. C.; Chan, B. G.; Waiss, A. C., Jr. *J. Chem. Ecol.* **1982**, *8*, 1429. (d) Drewer, D. L.; Binder, R. G.; Chan, B. G.; Waiss, A. S., Jr.; Hartwig, E. E.; Beland, G. L. *Experientia* **1979**, *35*, 1182.

(6) For a recent review, see: Billington, D. C. *Chem. Soc. Rev.* **1989**, *18*, 83.

(7) The enantiomers of **1** are related by a plane of chirality (Figure 1) and may be interconverted (and/or racemized) via a hypothetical [2, 3] methoxy transposition. Diol **2** possesses a similar chirality plane. Thus, enantiodivergence from **2** to **1** is realized by differentiating between olefin a and olefin b at the time of functionalization without destroying this plane of chirality. With meso diene diols, the olefins are enantiotopic and cannot be differentiated except by use of chiral reagents. This property (i.e., possessing a "latent" plane of symmetry, the creation of which is a function of only a single chemical operation) also exists in **2**, where the reduction of bromine at C2 or bromination of C4 would render this enantiomer meso. We would therefore like to refer to olefins in compounds such as **2** as "proenantiotopic", indicating that a carefully controlled sequence of operations can lead to enantiomeric distinction between the D and L series of the target molecule.

0002-7863/90/1512-9439$02.50/0

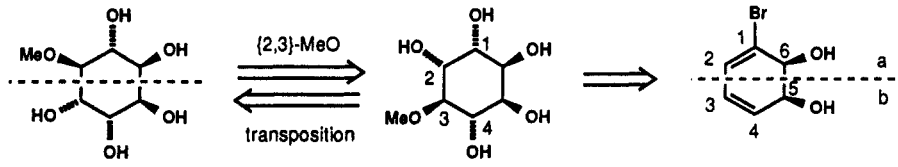
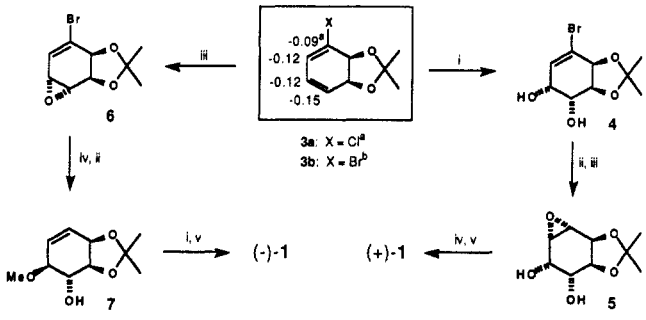


Figure 1.

Scheme I



Reagents: i. OsO_4, MNO, H_2O, acetone; ii. $LiAlH_4$, THF; iii, mCPBA, CH_2Cl_2; iv. MeOH, Al_2O_3; v. HCl, H_2O, acetone. (a) Formal charges determined for X = Cl. (b) HOMO coefficients determined for X = Br: C1 = -0.499, C2 = -0.415, C3 = +0.347, C4 = +0.475; formal charges for X = Br: C1 = -0.19, C2 = -0.08, C3 = -0.13, C4 = -0.14 (results from AM1 calculations).

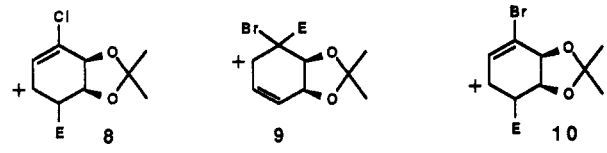
Several natural products have recently been synthesized from other arene cis-diols in Ley's[4a,b,9] as well as our laboratories.[10] A number of points should be addressed regarding the versatility of diene diols such as **2**. (1) The diene diol is well suited for subsequent functionalization to cyclitols by employing precisely defined osmylation/epoxidation sequences. (2) The cis-diol moiety required for both enantiomers of **1** (see Figure 1) is established in the biotransformation step. (3) Protection of the diol in **2** with a rigid acetonide confers facial selectivity during subsequent transformations. (4) The presence of a substituent at C1 leads not only to optically active starting material in contrast to meso-diols, but (5) it also allows for differentiation of the two double bonds leading to regioselectivity in reactions with specific electronic requirements (such as osmylation and/or epoxidation reactions). The first four factors alone should be sufficient to allow for an enantiocontrolled approach to **1**. However, by differentiation of the double bond reactivity, and the appropriate ordering of subsequent oxidation steps (osmylation vs epoxidation), a divergent approach to both enantiomers of **1** is realized.

Specifically, initial osmylation of the more electron rich olefin (C3–C4) (see Scheme I for formal electron charges determined for **3**) followed by dehalogenation, epoxidation, and ring opening would lead to (+)-**1**. Alternatively, initial epoxidation of the same olefin followed by ring opening, dehalogenation, and osmylation of the C1–C2 double bond would lead to (-)-**1**. Our results are shown in Scheme I.

Treatment of acetonide **3b** prepared quantitatively from **2** ($(MeO)_2C(CH_3)_2$, *p*-TsOH) with catalytic OsO_4 resulted in formation of a single diol **4** (85%), as determined by ^1H NMR and GC analysis, with complete control of stereo- and regiochemistry. Reduction of the vinyl bromide with $LiAlH_4$ proceeded smoothly to afford an olefin (85%) that is ideally suited for conversion to the epoxide (*m*-CPBA, 86%) at the α face (anti to the isopropylidene, syn to the directing free hydroxyl). Methanolysis of **5** (90%) followed by deprotection afforded (+)-pinitol, whose spectral data and optical rotation ($[\alpha]_D$ = +64.6° (*c*, 1.0, H_2O), (lit.[4b] $[\alpha]_D$ = +66.8° (*c*, 25 (H_2O)), were in agreement with literature values.[4b,11]

Treatment of **3b** with *m*-CPBA also resulted in formation of a single epoxide **6** (80%), once again with complete stereo- and regiocontrol. Methanolysis (89%) and dehalogenation (85%) afforded olefin **7**. Osmylation (63%) gave a single product, which after deprotection yielded (-)-pinitol whose spectral data[11] and optical rotation ($[\alpha]_D$ = -61.5° (*c*, 0.19, H_2O) (lit.[4b] $[\alpha]_D$ = -61.4° (*c*, 2.5, H_2O)) were identical with literature values. The above syntheses were also accomplished by using **3a** derived from chlorobenzene, with the only difference being the slightly lower yield of the dehalogenation steps.

The exclusive regioselectivity of either epoxidation or osmylation of **3a** and **3b** is interesting. Calculations indicated that C4 of **3a** and C1 of **3b** have the largest π electron densities as evident from either formal charges or HOMO coefficients, which were calculated for fully optimized geometries by using the AM1 approximation developed by Dewar et al.[12] and implemented through MOPAC, version 5.0 (*QCPE* **1989**, *No. 455*). One would therefore expect the electrophilic interaction to lead to **8** in the



case of chlorodiene **3a** and to **9** in the case of bromodiene **3b**. However, the transition state leading to cation **9**, in addition to possible steric complications, does not enjoy the resonance stabilization of **10** and would therefore be less favorable. The differences in charge densities at C1 and C4 in **3a** and **3b** may be exploitable in cycloadditions of unsymmetrical dienophiles.

In summary, short (six steps from **2**), stereocontrolled, and enantiodivergent syntheses of (+)- and (-)-pinitol have been achieved.[13] Microbial oxidation of bromobenzene leads to a versatile chiral synthon allowing for complete control of diastereoselectivity (α- vs β-face attack) as well as complete regiocontrol in subsequent oxidation steps.

Acknowledgment. We express our gratitude to the following agencies for their generous financial support: the donors of the Petroleum Research Fund, administered by the American Chemical Society, the National Institutes of Health (AI-00564, GM-40648), and the Jeffress Trust Fund. Continuing advice and interest of Professor Gibson and his group (University of Iowa) are greatly appreciated. We would also like to thank Dr. James Tanko (VPI) for his helpful discussions and AM1 molecular orbital calculations.

Supplementary Material Available: Spectra of relevant compounds (17 pages). Ordering information is given on any current masthead page.

(8) (a) Gibson, D. T.; Hensley, M.; Yoshika, H.; Mabry, R. J. *Biochemistry* **1970**, *9*, 1626. (b) Gibson, D. T.; Mahaderan, V.; Davey, J. F. *J. Bacteriol.* **1974**, *119*, 1626. (c) Gibson, D. T.; Koch, J. R.; Dallio, R. E. *Biochemistry* **1968**, *7*, 2653.

(9) (a) D- and L-*myo*-inositol 1,4,5-triphosphate: Ley, S. V.; Parra, M.; Redgrave, A. J.; Sternfeld, F. *Tetrahedron* **1990**, *46*, 4995. (b) 6-Deoxy-*myo*-inositol 1,4,5-triphosphate: Ley, S. V.; Parra, M.; Redgrave, A. J.; Sternfeld, F.; Vidal, A. *Tetrahedron Lett.* **1989**, *30*, 3557.

(10) (a) $PGE_{2\alpha}$: Hudlicky, T.; Luna, H.; Barbieri, C.; Kwart, L. D. *J. Am. Chem. Soc.* **1988**, *110*, 4735. (b) (-)-Zeylena: Hudlicky, T.; Seoane, G.; Pettus, T. *J. Org. Chem.* **1989**, *54*, 4239. (c) (+)- and (-)-Erythrose: Hudlicky, T.; Luna, H.; Price, J. D.; Rulin, F. *Tetrahedron Lett.* **1989**, *30*, 4053. (d) (+)- and (-)-Ribonolactone: Hudlicky, T.; Price, J. *Synlett* 1990, 159. (e) (-)-Dihydroconduritol C: Hudlicky, T.; Price, J. D.; Luna, H.; Andersen, C. M. *Synlett* **1990**, 309. (f) (+)- and (-)-Trihydroxyheliotridane: Hudlicky, T.; Luna, H.; Price, J. D.; Rulin, F. *J. Org. Chem.* **1990**, *55*, 4683.

(11) Angyal, S. J.; Odier, L. *Carbohydr. Res.* **1983**, *123*, 23.

(12) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3092.

(13) Contained in a pending U.S. patent application, VPI.