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# Enantiospecific Synthesis of Cyanocyclitols and (6*R*)-6-Hydroxyshikimic Acid from Benzonitrile

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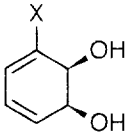
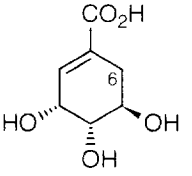
***Abstract:*** The chiral *cis*-3-cyanocyclohexa-3,5-diene-1,2-diol **5**, available by microbial oxidation of benzonitrile, is the key intermediate used in brief syntheses of the cyanocyclitols **9** and **15**, and in the synthesis of 6-hydroxyshikimic acid **20**.


There is current interest in the synthesis of cyclitols[1] and pseudo-sugars.[2] One suitable route to these molecules has been the use of dioxygenase enzymes from *Pseudomonas putida* mutants to convert arenes to cyclohexa-3,5-diene-1,2-diols **1**,[3] which are usually chiral and can be further elaborated.[4] Recent examples of this approach have even shown how the symmetrical benzene *cis*-dihydrodiol **2** can be asymmetrized[5] and used as a source of the polyoxygenated cyclohexane ring of the target molecules. The one-carbon side chain can be added to iodoalkene intermediates by Stille coupling,[6] by epoxide ring opening[7] or by carboxylation of metallated intermediates.[8] Very recently, toluene *cis*-dihydrodiol **3** has been used as the complete carbon skeleton in the synthesis of pseudo-L-fucopyranose.[9]




**1**
**2** X = H
**3** X = $CH_3$

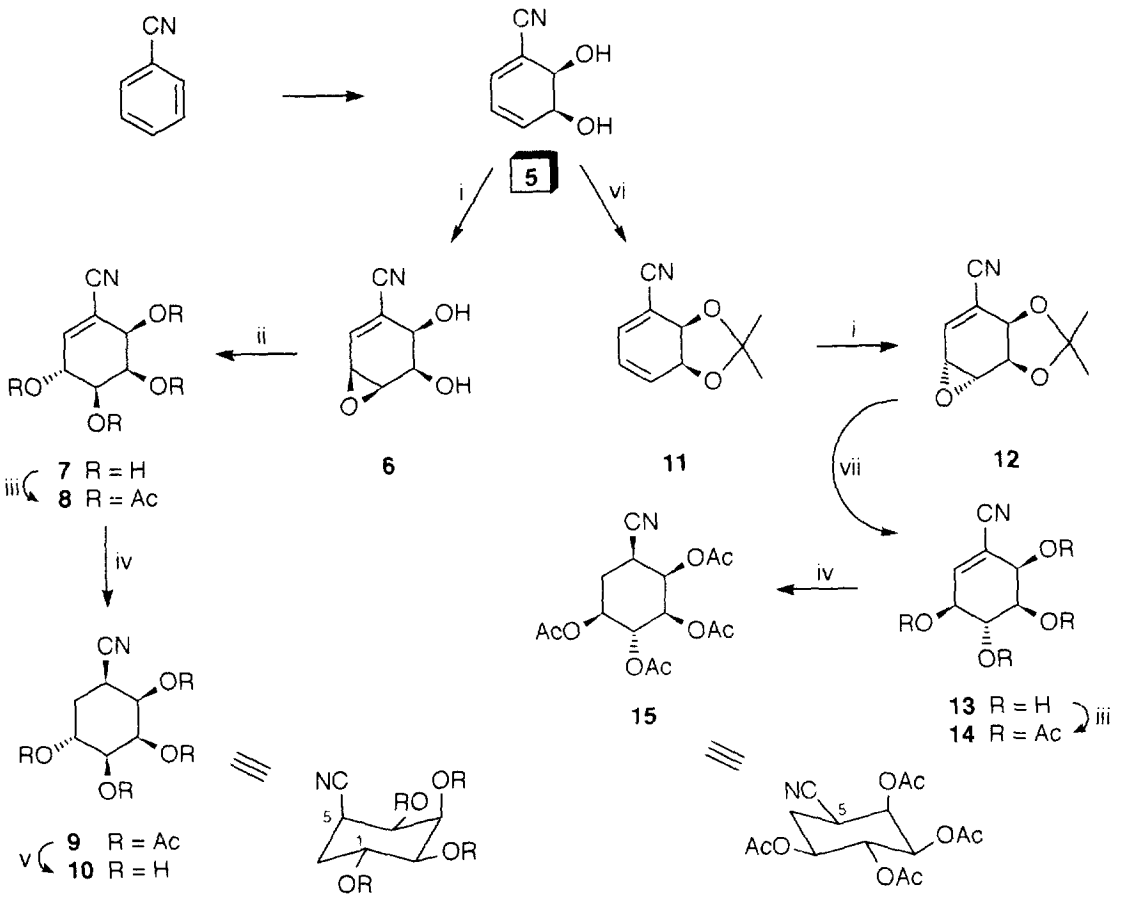



**4**

Shikimic acid **4**, the biogenetic precursor of the aromatic amino-acids, has also been the object of synthetic attention in a number of laboratories,[6,7,10,11] and 6-fluoro analogues having antimicrobial activity have been reported.[12]

We now describe the first examples of cyclitol synthesis *via* the use of benzonitrile as a substrate for *Pseudomonas putida*, where the cyano- group provides the one-carbon source suitable for direct conversion to the pseudo-sugar and shikimic acid skeleton.

The microbial oxidation product **5**,[13] having ≥98% ee and the absolute configuration shown, provides the key intermediate for the preparation of two cyanoconduritol isomers and the corresponding cyanocyclitols shown in Scheme 1. Peracid epoxidation of **5** by MCPBA occurred both stereoselectively and regioselectively to give the *syn*-epoxide **6** in 71% yield. Formation of this stereoisomer reflects attack at the more electron-rich



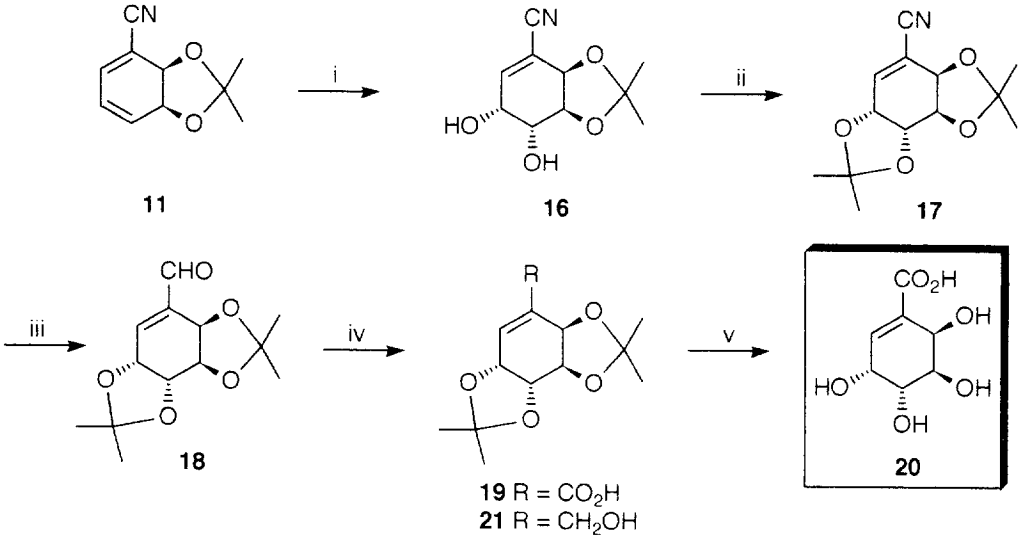

**Scheme 1** *Reagents*: i, MCPBA (1.3 equiv.), $CH_2Cl_2$; ii, $CF_3CO_2H$:$H_2O$, 1:20 v/v, 20°C, 4 h; iii, $Ac_2O$/pyridine; iv, Rh (5%) on C, $H_2$ (Compound **8**: 35 psi, 8h), (Compound **14**: 40 psi, 10 h); v, $K_2CO_3$/ $CH_3OH$, 4 h; vi, $Me_2CO$, $(MeO)_2CMe_2$, $CF_3CO_2H$, 20°C; vii, $CF_3CO_2H$, $Me_2CO$, $H_2O$, (0.03:1:1 v/v), reflux, 4 h.

double bond of **5**, from a direction assisted by the adjacent allylic hydroxyl and homoallylic hydroxyl groups. Epoxide **6** underwent facile hydrolysis by aqueous trifluoroacetic acid at room temperature to provide the 5-cyanoconduritol C **7** as a single stereoisomer (82%). Routine acetylation of tetrol **7** gave the tetra-acetate **8** in 76% yield after purification. Stereoselective hydrogenation of the double bond in **8** was achieved using rhodium on carbon as catalyst, and the major product was further purified to give the cyanotetra-acetate **9** (58%), having the stereochemistry of the pseudo-α-L-talopyranose series.[2] The configuration and conformation of **9** shown in Scheme 1 were evident from its $^1H$ nmr spectrum, which showed H-5 as a quartet ($J$ 5 Hz) and H-1 as a double triplet having two diaxial couplings ($J$ 4.3, 8.6 and 9.3 Hz). Deacetylation of **9**, followed by column chromatography, gave the polar cyanocyclitol **10** in 66% yield.

A complementary approach to cyclitols was achieved *via* initial isopropylidenation of the dihydrodiol **5** (90%). Peracid epoxidation of the protected diol **11** occurred *anti* to the isopropylidene group, to give the epoxide **12** (43%) as a single isomer formed in a regiospecific reaction. There was some competing [2+4]

dimerisation of **11**, particularly at higher concentration.[14] Acid-catalysed ring opening of the allylic epoxide **12** with concomitant removal of the isopropylidene group produced the 5-cyanoconduritol F isomer **13** (62%), and a subsequent acetylation step provided the tetra-acetate **14** (57%). Catalytic hydrogenation of **14** using rhodium/carbon (as for **8**) was also stereoselective; this example yielded the cyanotetra-acetate **15**, in which the stereochemistry of the pseudo-β-L-galactopyranose series was adopted.

The versatility of the cyano-group as a one-carbon synthon is shown by the use of protected diol **11** in a brief synthesis of (6*R*)-6-hydroxyshikimic acid **20**, as shown in Scheme 2.[15] Catalytic osmylation of **11**




**Scheme 2** *Reagents:* i, NMO (2 equiv.), $OsO_4$, $Me_2CO$:$H_2O$, 5:1 v/v, 4 days; ii, $Me_2CO$, $(MeO)_2CMe_2$, $CF_3CO_2H$, 20°C, 14 h; iii, DIBAL-H (5 equiv.), $Et_2O$, -78°C; iv, $NaClO_2$ (8 equiv.), $Bu^tOH$:2-methylbut-2-ene, 10:3 v/v, $NaH_2PO_4$ buffer; v, $CF_3CO_2H$, $Me_2CO$, $H_2O$, (0.03:1:1 v/v), reflux, 1 h.

proceeded regio- and stereoselectively to give the diol **16**, isolated in 55% yield. Subsequent isopropylidenation of the diol gave the full protected derivative **17** (81%), which was most effectively reduced by di-isobutylaluminium hydride to the unsaturated aldehyde **18** (47%). The latter was an effective intermediate in that it could be oxidised to the corresponding carboxylic acid **19**, using sodium chlorite[16] (96%). Deprotection then gave (6*R*)-6-hydroxyshikimic acid **20**. Alternatively, aldehyde **19** could be reduced in high yield using sodium borohydride to afford the primary alcohol **21**, which has the complete pseudo-sugar skeleton.[2,8]

## REFERENCES AND NOTES

1. Balci, M.; Sütbeyaz, Y.; Seçen, H. *Tetrahedron*, **1990**, *46*, 3715; Hudlicky, T.; Cebulak, M. *Cyclitols and Their Derivatives*, VCH, New York, **1993**.
2. Suami, T.; Ogawa, S. *Adv. Carbohydr. Chem. Biochem.*, **1990**, *48*, 21; Suami, T. *Top. Curr. Chem.*, **1990**, *154*, 257.
3. Reviews: Widdowson, D. A.; Ribbons, D. W.; Thomas, S. D. *Janssen Chim. Acta*, **1990**, *8* (*No. 3*), 3; Carless, H. A. J. *Tetrahedron: Asymmetry*, **1992**, *3*, 795; Sheldrake, G. N. in *Chirality in Industry*, ed.

Collins, A. N.; Sheldrake, G. N.; Crosby, J.; Wiley, Chichester, **1992**, 127; Brown, S. M.; Hudlicky, T.; in *Organic Synthesis: Theory and Applications*, ed. Hudlicky, T.; JAI Press, Greenwich, Connecticut, **1993**, vol.2, 113.

4. For recent synthetic applications, and in cyclitol synthesis, see Boyd, D. R.; Sharma, N. D.; Barr, S. A.; Dalton, H.; Chima, J.; Whited, G.; Seemayer, R. *J. Am. Chem. Soc.*, **1994**, *116*, 1147; Hudlicky, T.; Thorpe, A. J. *Synlett*, **1994**, 899; Roberts, S. M.; Sutton, P. W. *J. Chem. Soc., Perkin Trans. 1*, **1995**, 1499; Jenkins, G. N.; Ribbons, D. W.; Widdowson, D. A.; Slawin, A. M. Z.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1*, **1995**, 2647; for an alternative approach to cyclitols from arenes, see Motherwell, W. B.; Williams, A. S. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2031.
5. Nicolosi, G.; Patti, A.; Piattelli, M.; Sanfilippo, C. *Tetrahedron Lett.*, **1995**, *36*, 6545; earlier resolutions of intermediates derived from **2**: Johnson, C. R.; Plé, P. A.; Adams, J. P. *J. Chem. Soc., Chem. Commun.*, **1991**, 1006; Ley, S.V.; Yeung, L. L. *Synlett*, **1992**, 997.
6. Johnson, C. R.; Adams, J. P.; Collins, M. A. *J. Chem. Soc., Perkin Trans. 1*, **1993**, 1.
7. Dumortier, L.; Van der Eycken, J.; Vandewalle, M. *Synlett*, **1992**, 245.
8. Entwistle, D. A.; Hudlicky, T. *Tetrahedron Lett.*, **1995**, *36*, 2591.
9. Carless, H. A. J.; Malik, S. S. *J. Chem. Soc., Chem. Commun.*, **1995**, 2447.
10. Review: Campbell, M. M.; Sainsbury, M.; Searle, P. A. *Synthesis*, **1993**, 179.
11. Recent examples: Wood, H. B., Jr.; Ganem, B. *Tetrahedron Lett.*, **1993**, *34*, 1403; Jiang, S.; Mekki, B.; Singh, G.; Wightman, R. H.; *Tetrahedron Lett.*, **1994**, *35*, 5505; Meier, R. M.; Ganem, B. *J. Org. Chem.*, **1994**, *59*, 5436.
12. Synthesis: (a) Sutherland, J. K.; Watkins, W. J.; Bailey, J. P.; Chapman, A. K.; Davies, G. M. *J. Chem. Soc., Chem. Commun.*, **1989**, 1386; (b) Sutherland, J. K.; Whitehead, R. C.; Davies, G. M. *J. Chem. Soc., Chem. Commun.*, **1993**, 464; (c) Bowles, S. A.; Campbell, M. M.; Sainsbury, M.; Davies, G. M. *Tetrahedron*, **1990**, *46*, 3981; Activity: (d) Ewart, C. D. C.; Jude, D. A.; Thain, J. L.; Nichols, W. W. *Antimicrob. Agents Chemotherapy*, **1995**, *39*, 87; (e) Davies, G. M.; Barrettbee, K. J.; Jude, D. A.; Lehan, M.; Nichols, W. W.; Pinder, P. E.; Thain, J. L.; Watkins, W. J.; Wilson, R. G. *Antimicrob. Agents Chemotherapy*, **1994**, *38*, 403.
13. Benzonitrile *cis*-dihydrodiol, 3-cyanocyclohexa-3,5-diene-1,2-diol, has (1*S*,2*R*) configuration: Boyd, D. R.; Hand, M. V.; Sharma, N. D.; Chima, J.; Dalton, H.; Sheldrake, G. N. *J. Chem. Soc., Chem. Commun.*, **1991**, 1630; it is commercially available (product GC 904) from Genencor International Inc., Rochester, NY, 14618, USA.
14. Related Diels-Alder type dimerisations of such isopropylidenated dienediols have been observed: **1**, X = $CF_3$, Pittol, C. A.; Pryce, R. J.; Roberts, S. M.; Ryback, G.; Sik, V.; Williams, J. O. *J. Chem. Soc., Perkin Trans. 1*, **1989**, 1160; **1**, X = Cl, Hudlicky, T.; Olivo, H. F.; McKibben, B. *J. Am. Chem. Soc.*, **1994**, *116*, 5108 and references therein.
15. See reference 12(b) for a previous multi-step route to **20** from quinic acid.
16. Bal, S. B.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron*, **1981**, *37*, 2091.

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