Synthesis of enantiopure *cis*-decalins from microbially-derived *cis*-1,2-dihydrocatechols

Martin G. Banwell*[a] and Joseph R. Dupuche[b]

[a] *Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 0200, Australia*

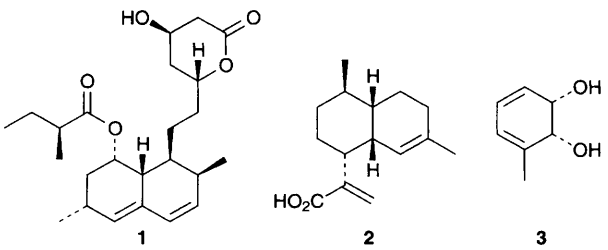
[b] *School of Chemistry, The University of Melbourne, Parkville, Victoria 3052, Australia*

The microbially-derived *cis*-1,2-dihydrocatechol 3 is converted, *via* reaction sequences involving Diels–Alder cycloaddition and anionic oxy-Cope rearrangement steps, into the enantiopure *cis*-decalins 15 and 26; using simple modifications of this chemistry the pseudo-enantiomer 22 of decalin 15 is also prepared from diol 3.

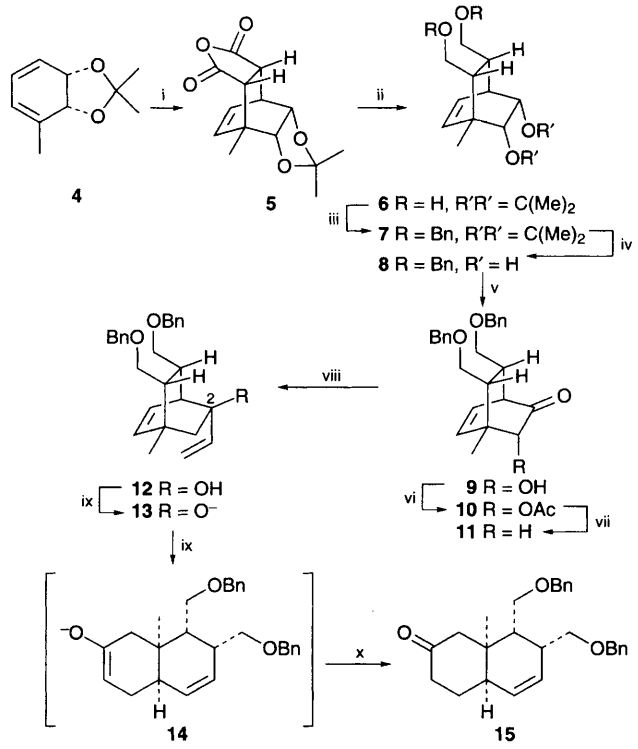
The decalin moiety is a structural subunit common to many natural products[1] including, for example, mevinolin **1**, a medicinally significant agent for reducing cholesterol in blood plasma,[2] and artemisinic acid **2**, a precursor to the important anti-malarial agent artemisinin (Qinghaosu).[3] Numerous methods for the synthesis of decalins have been developed with the Robinson annulation,[4] Diels–Alder cycloaddition,[5] Heck-type cyclisation,[6] double-Michael[7] and tandem Michael–Claisen[8] condensation procedures being especially notable. The anionic oxy-Cope rearrangement of 2-vinylbicyclo[2.2.2]oct-5-en-2-ols provides a further approach[9] but is limited by the paucity of monochiral bicyclo[2.2.2]octenyl systems which would allow for the synthesis of enantiopure decalins. The capacity of microbially-derived and monochiral *cis*-1,2-dihydrocatechols[10] such as **3**† to engage, as the 4π-component, in diastereofacially selective Diels–Alder cycloaddition reactions with the resultant formation of bicyclo[2.2.2]octenes[10c,11] has prompted us to investigate the possibility of elaborating these adducts into decalins. Preliminary results of such a study are reported herein.

Diels–Alder cycloaddition (Scheme 1) of maleic anhydride with the acetonide **4**, readily prepared[12] from diol **3**, afforded adduct **5**‡ (68%) {mp = 104–105 °C (sealed tube); $[\alpha]_D$ = +15 (*c* 1.0, 15 °C)§}. Lithium aluminium hydride reduction of anhydride **5** gave the expected diol **6** (88%) {mp = 155–156 °C; $[\alpha]_D$ = +24 (*c* 1.0, 14 °C)} which was subsequently protected as its bis-benzyl ether **7** (99%) {$[\alpha]_D$ = +32 (*c* 1.6, 15 °C)}. Hydrolysis of the acetonide unit within compound **7** gave diol **8** (100%) {$[\alpha]_D$ = +44 (*c* 1.1, 14 °C)} which was oxidised, in a regioselective fashion, to the acyloin **9** (97%) {$[\alpha]_D$ = −40 (*c* 1.0, 14 °C)} using the sterically demanding oxoammonium salt derived from 4-acetamido-TEMPO (4-AcNH-TEMPO) and toluene-*p*-sulfonic acid (*p*-TsOH).[13] Deoxygenation of the derived acetate **10** (92%) {$[\alpha]_D$ = −19 (*c* 1.1, 13 °C)} was achieved with freshly prepared samarium diiodide in THF–acetic acid.[14] The resulting ketone **11** (88%) {$[\alpha]_D$ = −129 (*c* 1.6, 15 °C)} was then reacted with vinylmagnesium bromide to give a mixture of alcohol **12** (61%) {$[\alpha]_D$ = +7 (*c* 1.0, 14 °C)} and its C-2 epimer (20%) {$[\alpha]_D$ = +4 (*c* 0.8, 14 °C)} which could be separated from one another chromatographically. Compound **12** was then treated with potassium hydride and 18-crown-6 (18-C-6) to give anion **13** which underwent smooth rearrangement to enolate **14**. Subsequent protonation of this latter species then afforded decalin **15** (80% from **12**) {$[\alpha]_D$ = +80 (*c* 0.6, 14 °C)}.

A complementary approach to decalins is shown in Scheme 2. Thus, diol **8** was selectively converted into the *tert*-butyldimethylsilyl ether **16** (68%) {$[\alpha]_D$ = +39 (*c* 0.9, 18 °C)} Swern oxidation[15] of which gave ketone **17**. Desilylation of the latter compound with *tetra*-butylammonium fluoride (TBAF) gave acyloin **18** (90% from **16**) {$[\alpha]_D$ = +126 (*c* 1.4, 17 °C)} which was deoxygenated *via* the corresponding acetate **19**. The resulting ketone **20** (86% from **18**) {$[\alpha]_D$ = +224 (*c* 0.9, 14 °C)} was then reacted with vinylmagnesium bromide to give an inseparable 1 : 1 mixture of alcohol **21** and its C-2 epimer (85% combined yield). Subjection of these compounds to



1 **2** **3**



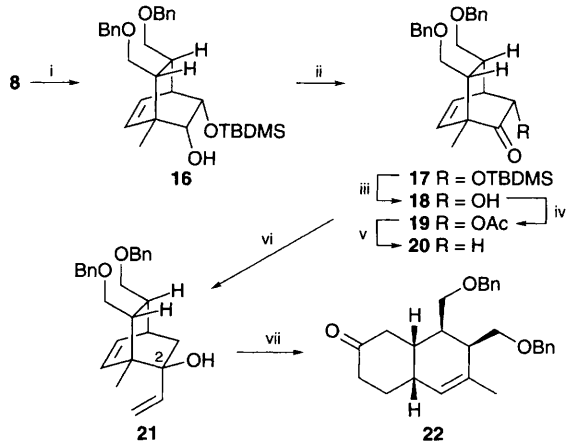
4 **5** **6** R = H, R′R′ = C(Me)$_2$; **7** R = Bn, R′R′ = C(Me)$_2$; **8** R = Bn, R′ = H; **9** R = OH; **10** R = OAc; **11** R = H; **12** R = OH; **13** R = O$^-$; **14** **15**

Scheme 1 *Reagents and conditions*: i, maleic anhydride, CH_2Cl_2, 0–18 °C, 24 h; ii, $LiAlH_4$, THF, 66 °C, 3 h; iii, BnBr, NaH, Bu_4NI, DMF, 0–18 °C, 18 h; iv, AcOH, H_2O, 80 °C, 16 h; v, 4-AcNH-TEMPO, *p*-TsOH, CH_2Cl_2, 18 °C, 3 h; vi, Ac_2O, pyridine, CH_2Cl_2, 18 °C, 18 h; vii, SmI_2, AcOH, THF, 18 °C, 20 min; viii, H_2C=C(H)MgBr, THF, 0 °C, 3 h; ix, KH, 18–C–6, THF, 60 °C, 2 h; x, aqueous workup. Bn = benzyl.

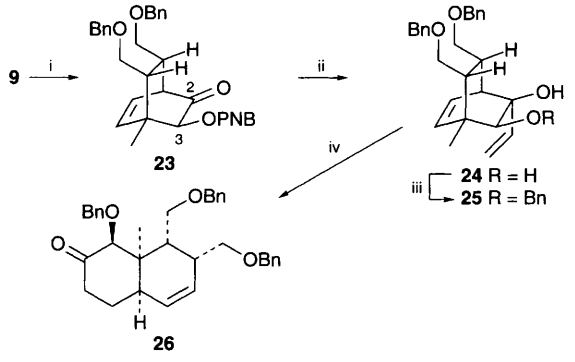
standard anionic oxy-Cope rearrangement conditions gave decalin **22** (55%) {$[\alpha]_D$ = −48 (*c* 0.7, 18 °C)}.¶ Compound **22** is a pseudo-enantiomer of decalin **15**.

Modification of the synthetic sequences described above enabled preparation of a more functionalised decalin derivative (Scheme 3). Thus, subjection of compound **9** to a Mitsunobu reaction using *p*-nitrobenzoic acid as nucleophile[16] afforded the labile ester **23** (60%) {$[\alpha]_D$ = −1.7 (*c* 0.8, 20 °C)}. In contrast to the previous cases (Schemes 1 and 2), addition of vinylmagnesium bromide to the ketone carbonyl in compound **23** proceeded with excellent diastereoselectivity and in the desired sense. Vinylation was accompanied by ester cleavage and the resultant diol **24** was then selectively converted into monobenzyl ether **25** (50% from **23**) {$[\alpha]_D$ = +51 (*c* 1.1, 15 °C)} under standard conditions. Upon treatment with potassium hydride and 18-C-6, compound **25** underwent rearrangement to decalin **26** (60%) {$[\alpha]_D$ = +155 (*c* 0.4, 20 °C)}.

We acknowledge financial support from the Australian Research Council. J. R. D. is the grateful recipient of an Australian Post Graduate Research Award. We thank Dr Gregg Whited of Genencor International (South San Francisco) for his continued interest in this work and the provision of generous samples of various *cis*-1,2-dihydrocatechols.



Scheme 2 *Reagents and conditions*: i, TBDMSCl, imidazole, DMF, 18 °C, 24 h; ii, Me_2SO, TFAA, CH_2Cl_2, −60 °C, 1 h; iii, TBAF, THF, CH_2Cl_2, 18 °C, 18 h; iv, Ac_2O, pyridine, CH_2Cl_2, 18 °C, 18 h; v, SmI_2, AcOH, THF, 18 °C, 20 min; vi, H_2C=C(H)MgBr, THF, 0 °C, 3 h; vii, KH, 18-C-6, THF, 60 °C, 2 h then aqueous workup. TBDMSCl = *tert*-butyldimethylsilyl chloride; TFAA = trifluoroacetic anhydride.



Scheme 3 *Reagents and conditions*: i, PPh_3, DEAD, *p*-$O_2NC_6H_4CO_2H$, 0–18 °C, 0.5 h; ii, H_2C=C(H)MgBr, THF, 0 °C, 3 h; iii, BnBr, NaH, DMF, 0–18 °C, 2 h; iv, KH, 18-C-6, THF, 60 °C, 2 h then aqueous workup. PNB = *p*-nitrobenzoate; DEAD = diethyl azodicarboxylate.

Footnotes

† Around 20 such *cis*-1,2-dihydrocatechols are now available commercially from the following sources: Genencor International Inc., South San Francisco, CA; ICI Fine Chemicals, Manchester, U.K.; Enzymatix, Cambridge, U.K.; Janssen Chimica, Geel, Belgium.

‡ All new compounds had spectroscopic data [IR, UV, NMR, mass spectrum] consistent with the assigned structure. Satisfactory combustion and/or high resolution mass spectral analytical data were obtained for new compounds and/or suitable derivatives.

§ All optical rotations were determined using chloroform as solvent.

¶ 2-*epi*-**21**, which is incapable of undergoing Cope rearrangement, could not be isolated from the reaction mixture and, at present, the fate of this compound is unknown.

References

1 J. R. Hanson, *Nat. Prod. Rep.*, 1992, **9**, 139 and references cited therein.
2 Y. Chapleur, *The Chemistry and Total Synthesis of Mevinolin and Related Compounds*, in *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*, vol. 2, ed. G. Lukacs, Springer-Verlag: Berlin, 1993, pp. 829–937; T. Rosen, *Naturally Occurring Mevinic Acids—Synthesis Studies*, in *Studies in Natural Products Chemistry*, vol. 13, ed. Atta-ur-Rahman, Elsevier Science Publishers B. V., 1993, pp. 553–627.
3 A. R. Butler and Y.-L. Wu, *Chem. Soc. Rev.*, 1992, 85.
4 M. E. Jung, *Tetrahedron*, 1976, **32**, 2; R. E. Gawley, *Synthesis*, 1976, 777.
5 J. F. Lavallee and P. Deslongchamps, *Tetrahedron Lett.*, 1988, **29**, 6033 and references cited therein; G. Muller and G. Jas, *Tetrahedron Lett.*, 1992, **33**, 4417; H.-J. Liu and Y. Han, *Tetrahedron Lett.*, 1993, **34**, 423 and references cited therein; J. Schnaubelt and H.-U. Reissig, *Synlett*, 1995, 452; C. Taillefumier, Y. Chapleur, D. Bayeul and A. Aubry, *J. Chem. Soc., Chem. Commun.*, 1995, 937; D. A. Singleton and Y.-K. Lee, *Tetrahedron Lett.*, 1995, **36**, 3473.
6 Y. Sato, S. Watanabe and M. Shibasaki, *Tetrahedron Lett.*, 1992, **33**, 2589.
7 H. Hagiwara, T.Nakano, M. Kon-no and H. Uda, *J. Chem. Soc., Perkin Trans. 1*, 1995, 777.
8 O. Z. Pereira and T. H. Chan, *J. Org. Chem.*, 1994, **59**, 6710.
9 D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.*, 1975, **97**, 4765; For comprehensive reviews on this topic see: L. A. Paquette, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 609; L. A. Paquette, *Synlett*, 1990, 67; L. A. Paquette, *Chem. Soc. Rev.*, 1995, 9.
10 For reviews on the applications of *cis*-1,2-dihydrocatechols in synthesis see: (*a*) H. A. J. Carless, *Tetrahedron Asymmetry*, 1992, **3**, 795; (*b*) D. A. Widdowson, D. W. Ribbons and S. D. Thomas, *Janssen Chimica Acta*, 1990, 3; (*c*) S. M. Brown and T.Hudlicky, *The Use of Arene* cis-*Diols in Synthesis*, in *Organic Synthesis: Theory and Practice*, vol. 2, ed. T. Hudlicky, JAI Press, 1993, 113.
11 T. Hudlicky, H. F. Olivo and B. McKibben, *J. Am. Chem. Soc.*, 1994, **116**, 5108 and references cited therein.
12 M. G. Banwell and M. P. Collis, *J. Chem. Soc., Chem. Commun.*, 1991, 1343.
13 M. G. Banwell, V. S. Bridges, J. R. Dupuche, S. L. Richards and J. M. Walter, *J. Org. Chem.*, 1994, **59**, 6338.
14 G. A. Molander and G. Hahn, *J. Org. Chem.*, 1986, **51**, 1135; G. I. Georg and Z. S. Cheruvallath, *J. Org. Chem.*, 1994, **59**, 4015.
15 C. M. Amon, M. G. Banwell and G. L. Gravatt, *J. Org. Chem.*, 1987, **52**, 4851.
16 J. A. Dodge, J. I. Trujillo and M. Presnell, *J. Org. Chem.*, 1994, **59**, 234.

Received, 20th December 1995; Com. 5/08268D