Integrated synthesis of conduritols A–F using a single chiral building block

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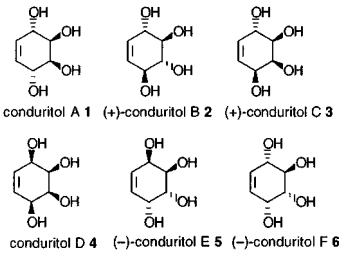
Six possible diastereomers of conduritols have been synthesized diastereoselectively in an integrated manner starting from a single chiral precursor, which served as a synthetic equivalent of chiral *cis*-1,4-dihydroxycyclohexa-2,5-diene.

Although only two conduritols, A **1** and F **6**, occur in Nature, four other possible diastereomers, conduritols B **2**, C **3**, D **4** and E **5**, are known[1]. Since they are useful for the preparation of

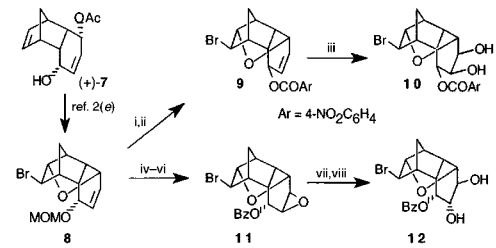


physiologically active cyclitols and their derivatives, a considerable number of syntheses have been reported to date.[2] The majority of syntheses, however, are limited to preparation of particular members of conduritols and there has been no precedent which is capable of producing all six conduritols diastereoselectively from a single precursor in an integrated manner. As we have developed an efficient preparation[3] of the tricyclic monoacetate **7** serving as a synthetic equivalent of chiral *cis*-1,4-dihydroxycyclohexa-2,5-diene in both enantiomeric forms by lipase-mediated asymmetric desymmetrization of a *meso* precursor, we examined diastereocontrolled preparation of all six conduritols on the basis of inherent steric and chemical functionalities comprised in this chiral building block.[4] We report herein the first integrated synthesis of conduritols A–F **1**–**6** starting from the single chiral compound (+)-**7** using a methoxymethyl (MOM) ether as the common protecting group.

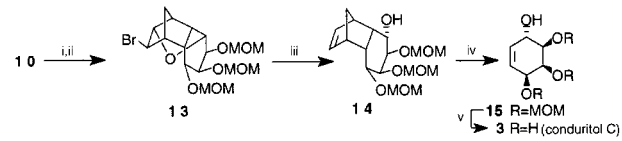
The acetate[3] **7** was first transformed into the bromo ether **8** in three steps[2e] to discriminate one of two olefin functionalities and to block the secondary hydroxy functionality in the molecule. On acid-catalyzed removal of the MOM protecting group, followed by the Mitsunobu reaction,[5], **8** afforded the *exo*-benzoate **9**, mp 135–136 °C, $[\alpha]_D^{28}$ −260.1 (*c* 1.02, $CHCl_3$), whose dihydroxylation occurred from the convex face to furnish the *exo-cis*-diol **10**, $[\alpha]_D^{30}$ −66.6 (*c* 0.96, $CHCl_3$), diastereoselectively. On the other hand, **8** was transformed into the single *trans*-diol **12**, $[\alpha]_D^{26}$ −60.5 (*c* 1.18, $CHCl_3$), through the *exo*-epoxide **11**, mp 93–94 °C, $[\alpha]_D^{28}$ +0.9 (*c* 1.02, $CHCl_3$), on sequential MOM deprotection, benzoylation, convex face selective epoxidation and acid treatments. In the latter conversion, the epoxide **11** was cleaved diastereo- and regioselectively by the participation[6] of the benzoate functionality in the presence of a Lewis acid to give a mixture of two regioisomeric benzoates, which, however, converged on the single isomer **12** on stirring with TsOH in CH_2Cl_2 (Scheme 1).

Utilizing the *cis*-diol **10**, (+)-conduritol C **3** was first prepared. On alkaline methanolysis followed by MOM protection, **10** gave the tri-MOM ether **13**, $[\alpha]_D^{29}$ −101.4 (*c* 1.05, $CHCl_3$), whose bromo ether linkage was reductively cleaved with zinc in the presence of acetic acid[2e] to regenerate the olefin and the hydroxy functionalities to give rise to the tricyclic alcohol **14**, $[\alpha]_D^{31}$ +14.4 (*c* 1.02, $CHCl_3$). Thermolysis of **14** was carried out at this stage in refluxing Ph_2O in the presence of $NaHCO_3$[7] to give the cyclohexenol **15**, $[\alpha]_D^{28}$ +123.5 (*c* 0.54, $CHCl_3$), by retro-Diels–Alder reaction. When the carbonate was absent, the yield of **15** was diminished considerably. Stirring **15** with saturated methanolic HCl at room temperature[8] induced smooth MOM deprotection to give (+)-conduritol C **3**, mp 129–130 °C, $[\alpha]_D^{30}$ +209.1 (*c* 0.62, H_2O) [lit.,[2f] mp 128–129 °C, $[\alpha]_D^{20}$ +215 (*c* 2.01, H_2O)]. As shown below, under these acid-catalyzed conditions, the MOM protecting group of the other conduritols was neatly removed to afford the corresponding conduritols after removal of low volatiles under reduced pressure followed by washing the residue with an appropriate solvent (Scheme 2).

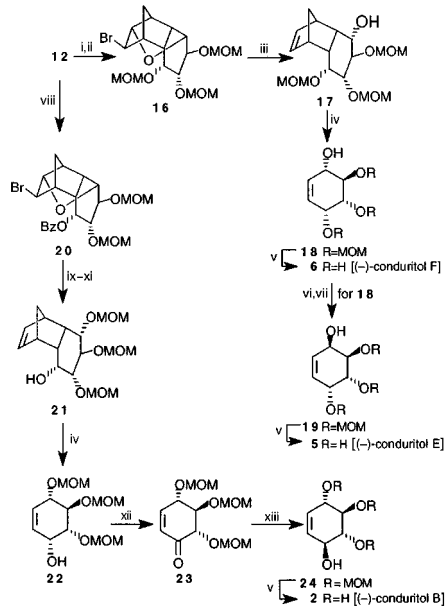
The *trans*-diol **12** was served as the precursor for the synthesis of three conduritols, (+)-B **2**, (−)-E **5** and (−)-F **6**. Thus, **12** was first transformed into the tri-MOM ether **16**, $[\alpha]_D^{30}$ −78.0 (*c* 1.15, $CHCl_3$), by sequential debenzoylation and MOM protection. Reductive cleavage of **16**, followed by thermolysis of the resulting **17**, $[\alpha]_D^{31}$ −80.8 (*c* 0.94, $CHCl_3$), afforded the cyclohexenol **18**, $[\alpha]_D^{27}$ +55.5 (*c* 0.79, $CHCl_3$), which gave (−)-conduritol F **6**, mp 129–130 °C, $[\alpha]_D^{28}$ −70.2 (*c* 0.15, MeOH) [lit.[2g] for (+)-enantiomer: mp 128–130 °C, $[\alpha]_D^{23}$ +75.1 (*c* 0.33, MeOH)], on MOM deprotection. The alcohol **18**, on the other hand, was first treated with 4-nitrobenzoic acid[9] under Mitsunobu conditions[5] to give the epimeric alcohol **19**, $[\alpha]_D^{30}$ −106.6 (*c* 1.07, $CHCl_3$), after alkaline methanolysis, which on MOM-deprotection, afforded (−)-conduritol E **5**, mp 191–192 °C, $[\alpha]_D^{29}$ −330.3 (*c* 0.18, H_2O) [lit.[2g] for (+)-enantiomer: mp 192–194 °C, $[\alpha]_D^{30}$ +327 (*c* 0.22, H_2O)].



Scheme 1 *Reagents and conditions*: i, conc. HCl–MeOH–THF (91%); ii, 4-$NO_2C_6H_4CO_2H$, DIAD, PPh_3, THF (86%); iii, OsO_4 (cat.), NMO, aq. THF (97%); iv, conc. HCl–MeOH–THF (91%);. v, BzCl, pyridine, DMAP (cat.), CH_2Cl_2 (99%); vi, MCPBA, CH_2Cl_2 (91%); vii, $BF_3{\cdot}OEt_2$, toluene (100%); viii, TsOH (cat.), CH_2Cl_2, room temp., 3 d (76%).



Scheme 2 *Reagents and conditions*: i, NaOMe, MeOH; ii, MOMCl, Pr^i_2NEt, CH_2Cl_2 (89%); iii, Zn, AcOH, MeOH (85%); iv, $NaHCO_3$, Ph_2O, reflux, 30 min (84%); v, sat. HCl–MeOH (93%).



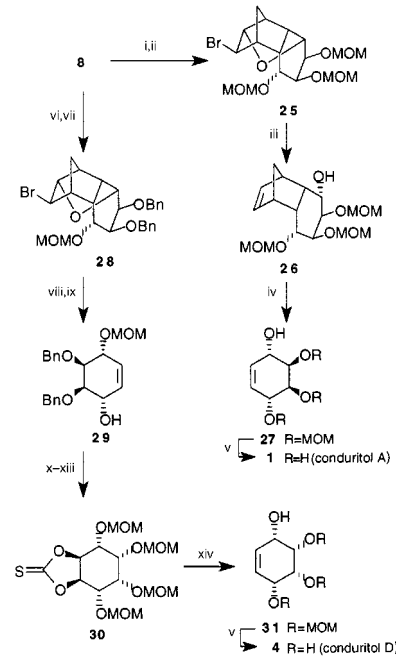
Scheme 3 *Reagents and conditions*: i, NaOMe, MeOH; ii, MOM-Cl, Pr^i_2NEt, $(CH_2Cl)_2$ (92%); iii, Zn, AcOH, MeOH (91%); iv, $NaHCO_3$, Ph_2O, reflux, 30 min (77% for **18**; 96% for **22**); v, sat. HCl–MeOH (100% for **2**, **5**, **6**); vi, 4-$NO_2C_6H_4CO_2H$, DIAD, PPh_3, THF (74%); vii, K_2CO_3, MeOH (94%); viii, MOMCl, Pr^i_2NEt, CH_2Cl_2 (97%); ix, Zn, AcOH, MeOH (99%); x, MOMCl, Pr^i_2NEt, CH_2Cl_2 (82%); xi, K_2CO_3, MeOH (94%); xii, PCC, CH_2Cl_2 (94%); xiii, $NaBH_4$–$CeCl_3$ (93%).

On the other hand, the *trans*-diol **12** was first transformed into the di-MOM ether **20**, $[\alpha]_D^{30}$ −73.6 (*c* 1.01, $CHCl_3$), which was further transformed into the tricyclic alcohol **21**, $[\alpha]_D^{31}$ −8.0 (*c* 1.04, $CHCl_3$), by sequential reductive cleavage, MOM protection and debenzoylation. Themolysis of **21** afforded the cyclohexenol **22**, $[\alpha]_D^{28}$ +24.5 (*c* 1.01, $CHCl_3$), which was epimerized to **24**, $[\alpha]_D^{29}$ +142.1 (*c* 1.03, $CHCl_3$), *via* the cyclohexenone **23**, $[\alpha]_D^{30}$ +41.4 (*c* 1.05, $CHCl_3$), by oxidation followed by diastereoselective 1,2-reduction in the presence of cerium(III) chloride.[10] Compound **24** afforded (+)-conduritol B **2**, mp 174–175 °C, $[\alpha]_D^{28}$ +153.5 (*c* 0.31, MeOH) [lit.[2c] mp 174–175 °C, $[\alpha]_D^{20}$ −179 (*c* 1.2, MeOH)], on MOM deprotection (Scheme 3).

Although enantiocontrol is not required for the construction of the two remaining conduritols, A **1** and D **4**, having *meso* structures, the same intermediate **8** was used as the starting material to demonstrate the potential of our building block. Thus, **8** was first transformed into the tri-MOM ether **25**, $[\alpha]_D^{26}$ −33.0 (*c* 1.01, $CHCl_3$), which was then converted to the cyclohexenol **27**, $[\alpha]_D^{25}$ −8.7 (*c* 1.11, $CHCl_3$), by sequential MOM protection, reductive cleavage and thermolysis. Compound **27** afforded conduritol A **1**, mp 141–142 °C (lit.,[2a] mp 140–141 °C), on MOM deprotection.

Compound **8**, on the other hand, was first transformed into the dibenzyl ether **28**, mp 91–92 °C, $[\alpha]_D^{29}$ −63.1 (*c* 1.32, $CHCl_3$), which, on sequential reductive cleavage and thermolysis, gave the cyclohexenol **29**, $[\alpha]_D^{27}$ +12.8 (*c* 1.05, $CHCl_3$). On sequential diastereoselective dihydroxylation, MOM protection, debenzylation and thiocarbonylation, **29** furnished the *meso* cyclohexane **30**. Refluxing **30** with trimethyl phosphite[11,12] allowed smooth dethiocarbodioxylation to give the cyclohexene **31** which afforded conduritol D **4**[2b] on MOM deprotection (Scheme 4).

In conclusion, the present synthesis provides the first integrated route to all possible conduritol diastereomers with complete diastereocontrol starting from a single chiral building block by using MOM ether as the common protecting group.



Scheme 4 *Reagents and conditions*: i, OsO_4 (cat.), NMO, aq. THF (97%); ii, MOMCl, Pr^i_2NEt, CH_2Cl_2 (95%); iii, Zn, AcOH, MeOH (91%); iv, $NaHCO_3$, Ph_2O, reflux, 30 min (93%) (90% for **29**); v, sat. HCl–MeOH (100% for **1** and **4**); vi, OsO_4 (cat.), NMO, aq. THF (97%); vii, BnBr, NaH, reflux, 30 min, Bu_4NI, THF (97%); viii, Zn, AcOH, MeOH (98%); ix, $NaHCO_3$, Ph_2O, (90%); x, OsO_4 (cat.), NMO, aq. THF; xi, MOMCl, Pr^i_2NEt, CH_2Cl_2 (96%); xii, H_2, $Pd(OH)_2$, MeOH (93%); xiii, $Im_2C{=}S$, toluene (94%); xiv, $(MeO)_3P$, reflux (97%).

Notes and references

† Satisfactory analytical (combustion and/or high resolution mass) and spectroscopic (IR, ^1H and ^{13}C NMR, MS) data were obtained for isolable new compounds.

1 Pertinent reviews, see: M. Balci, Y. Sütbeyaz and H. Seçen, *Tetrahedron*, 1990, **46**, 3715; P. Vogel, D. Fattori, F. Gasparini and C. Le Drian, *Synlett*, 1990, 173; H. A. J. Carless, *Tetrahedron: Asymmetry*, 1992, **3**, 795; M. Balci, *Pure Appl. Chem*., 1997, **69**, 97.

2 Some recent examples, see: (*a*) Y. Sütbeyaz, H. Seçen and M. Balci, *J. Chem. Soc., Chem. Commun*., 1988, 1330 (A); (*b*) H. A. J. Carless and O.Z. Oak, *Tetrahedron Lett.*, 1989, **30**, 1719 (A and D); (*c*) C. Le Drian, J. P. Vionnet and P. Vogel, *Helv. Chim. Acta*, 1990, **73**, 161 (B and F); (*d*) B. M. Trost and E. J. Hembre, *Tetrahedron Lett.*, 1999, **40**, 219 (B); (*e*) S. Takano, M. Moriya, Y. Higashi and K. Ogasawara, *J. Chem. Soc., Chem. Commun*., 1993, 177 (C); (*f*) H. Yoshizaki and J.-E. Bäckvall, *J. Org. Chem*., 1998, **63**, 9339 (C); (*g*) T. Yoshimitsu and K. Ogasawara, *Synlett*, 1995, 257 (E and F).

3 S. Takano, Y. Higashi, T. Kamikubo, M. Moriya and K. Ogasawara, *Synthesis*, 1993, 948; H. Konno and K. Ogasawara, *Synthesis*, 1999, 1135.

4 K. Ogasawara, *Pure Appl. Chem.*, 1994, **66**, 2119: K. Ogasawara, *J. Synth. Org. Chem. Jpn.*, in the press.

5 O. Mitsunobu, *Synthesis*, 1981, 1.

6 M. Prystas, H. Gustafsson and F. Sorm, *Collect. Czech. Chem. Commun.*, 1971, **36**, 1487.

7 T. Kamikubo and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1995, 1951.

8 T. Kamikubo and K. Ogasawara, *Chem. Lett.*, 1996, 987.

9 S. F. Martin and J. A. Dodge, *Tetrahedron Lett.*, 1991, **32**, 3017.

10 A. L. Gemal and J. L. Luche, *J. Am. Chem. Soc.*, 1981, **103**, 5454.

11 E. J. Corey and R. A. E. Winter, *J. Am. Chem. Soc.*, 1963, **85**, 2677.

12 T. L. Nagabhushan, *Can. J. Chem.*, 1970, **48**, 383.

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