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A New Convergent Route to Conduritols A–F from a Common Chiral Building Block

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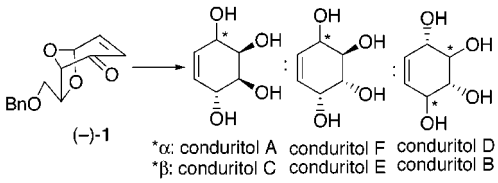
ABSTRACT



A diastereocontrolled route to conduritols A–F has been developed starting from a common chiral building block containing an oxabicyclo-[3.2.1]octane framework.

We have recently developed an efficient preparation of chiral building block **1**, which contains a bicyclo[3.2.1]octane framework, in both enantiomeric forms from furfural by employing either chemical[1] or enzymatic[2] procedures. Owing to its molecular bias, **1** exhibits inherent diastereoselectivity, while the masked formyl and 1,2-glycol functionalities in the molecule enforce its versatile applicability. The potential of **1** as a chiral building block has so far been demonstrated by a convergent synthesis of all eight of the aldohexoses[1,3] as well as the diastereocontrolled syntheses of a variety of natural products.[4] In this report, we demonstrate an alternative utilization of the chiral building block **1** for the diastereocontrolled construction of all six of the conduritol diastereomers.[5] Since there is only one precedent[6] that is capable of producing all six of the possible conduritols A−F convergently from a common cyclohexenol building block,[7] the present example constitutes the second convergent route (Scheme 1).

The synthesis began with reduction of enantiopure enone (−)-**1** by sodium borohydride−ceriumIII) chloride[8] to give *endo*-allyl alcohol[1] **3** which was protected as methoxymethyl (MOM) ether **4**, $[\alpha]^{26}_{D}$ +34.8 (*c* 1.0, $CHCl_3$). Dihydroxylation of **4** under catalytic conditions proceeded diastereoselectively from the convex face to give single *exo*-diol **5** which was transformed into tri-MOM ether **6a**, $[\alpha]^{26}_{D}$ +65.4 (*c* 2.0, $CHCl_3$), serving as the precursor of (+)-conduritol B, (−)-conduritol E, and (−)-conduritol F. Moreover, *endo*-alcohol **3** was treated under Mitsunobu conditions[9] with 4-nitrobenzoic acid[10] to give *exo*-benzoate **7** which furnished diastereoselectively *exo*-diol **8** on catalytic dihydroxylation.[1,11] On sequential debenzoylation and etherification, **8** afforded tri-MOM ether **6b**, $[\alpha]^{26}_{D}$ +44.8 (*c* 0.9, $CHCl_3$), serving as the precursor of conduritol D.

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(2) Taniguchi, T.; Takeuchi, M.; Kadota, K.; ElAzab, A. S.; Ogasawara, K. *Synthesis* **1999**, 1325.
(3) Takeuchi, M.; Taniguchi, T.; Ogasawara, K. *Chirality* **2000**, *12*, 338.
(4) (a) (+)-noviose: Takeuchi, M.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2000**, *41*, 2609. (b) FK-506 segment; Takeuchi, M.; Taniguchi, T.; Ogasawara, K. *Tetrahedron: Asymmetry* **2000**, *11*, 1601. (c) (−)-Shikimic acid: Takeuchi, M.; Taniguchi, T.; Ogasawara, K. *Synthesis* **2000**, 1375. (d) (−)-Physostigmine: ElAzab, A. S.; Taniguchi, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 2757. (e) (+)-Febrifugine: Taniguchi, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 3181. (f) Pseudomonic acid segment: Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2001**, *42*, 3359.
(5) For pertinent reviews, see: (a) Balci, M.; Secen, H. *Tetrahedron* **1990**, *46*, 3715. (b) Vogel, P.; Fattori, F.; Gasparini, F.; Le Drian, C. *Synlett* **1990**, 170. (c) Carless, H. A. J. *Tetrahedron: Asymmetry* **1992**, *3*, 795.
(6) Honzumi, M.; Hiroya, K.; Taniguchi, T.; Ogasawara, K. *Chem. Commun.* **1999**, 1985.
(7) Ogasawara, K. *J. Synth. Org. Chem. Jpn.* **1999**, *57*, 957.
(8) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
(9) Mitsunobu, O. *Synthesis* **1981**, 1.
(10) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.
(11) Matsumoto, K.; Ebata, T.; Koseki, K.; Kawakami, H. *Heterocycles* **1991**, *32*, 2225.

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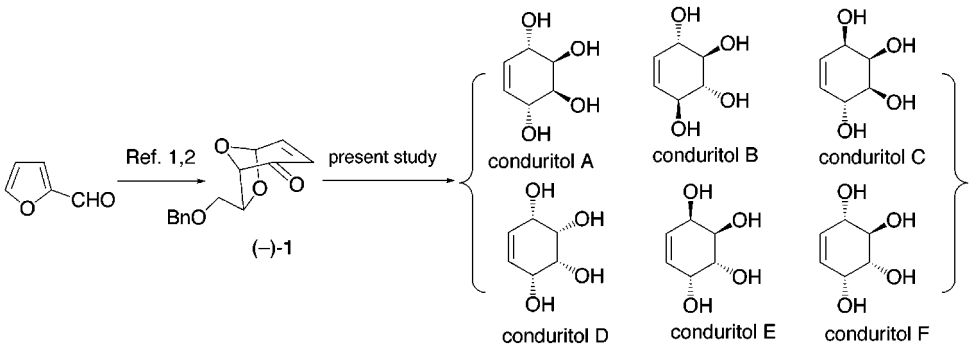
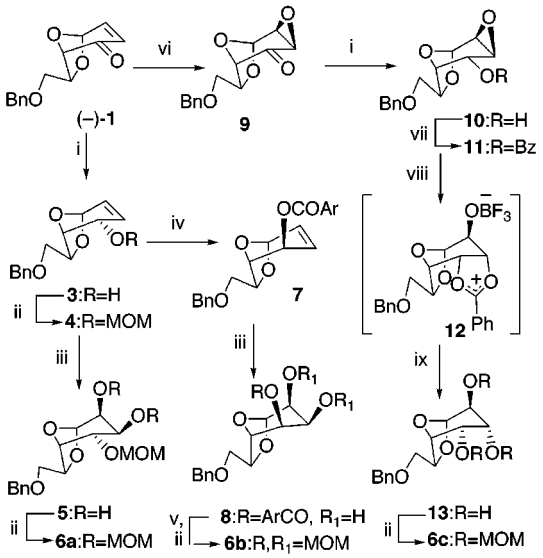
Scheme 1



On the other hand, enone (−)-**1** was first converted to *exo*-epoxide **9** which was sequentially reduced to *endo*-alcohol **10** and benzoylated to give *endo*-benzoate **11**, $[\alpha]^{25}_{D}$ +17.5 (*c* 1.4, $CHCl_3$). Upon exposure to boron trifluoride etherate, the benzoate-assisted regio- and diastereoselective epoxide cleavage[12] occurred to form oxonium intermediate **12** giving rise to single triol **13**, after alkaline methanolysis of the monobenzoate mixture, which was transformed into tri-MOM ether **6c**, $[\alpha]^{27}_{D}$ +15.2 (*c* 0.9, $CHCl_3$), serving as the precursor of conduritol A and (−)-conduritol C (Scheme 2).

Scheme 2[a]

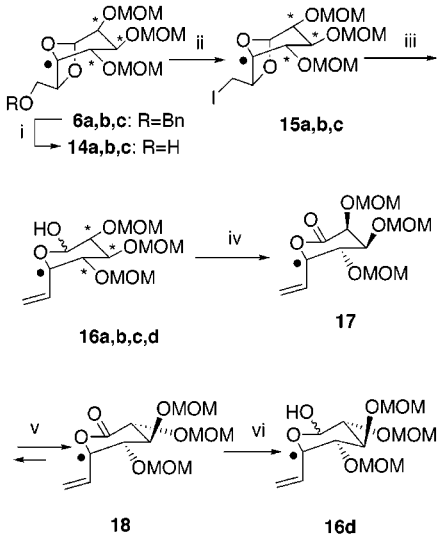


[a] Reagents and conditions: (i) $NaBH_4$−$CeCl_3$, 0 °C (90% for **3**; 75% for **11** from **1**); (ii) MOM-Cl, Hünig base, CH_2Cl_2 (94% for **4**; 95% for **6a**; 64% for **6b** from **3**; 99% for **6c**); (iii) OsO_4 (catalytic), NMO, 50% aqueous THF (95%); (iv) 4-nitrobenzoic acid, PPh_3, DIAD, THF; (v) NH_4OH−MeOH; (vi) 30% H_2O_2, aqueous NaOH−THF; (vii) benzoyl chloride, pyridine (68% from **1**); (viii) BF_3·Et_2O, toluene; (ix) NaOMe, MeOH (90% from **11**).

Having obtained the three intermediates **6a**−**c** with the stereochemistry requisite for the construction of all six of the conduritol diastereomers, their conversion into the 1,7-diene substrates for the key ring-closing olefin metathesis reaction[13] was next examined. Thus, MOM ethers **6a**−**c** were transformed[14] into the iodides **15a**−**c**, via alcohols **14a**−**c**, which were further transformed into hemiacetals **16a**−**c** on exposure to zinc in methanol in the presence of acetic acid.[1]

Of the hemiacetals **16a**−**c** thus obtained, **16a** was oxidized[15] to give *δ*-lactone **17** with α-axial alkoxy functionality. When **17** was refluxed in benzene with 1,4-diazabicyclo-[2.2.2]octane (DABCO),[1] epimerization occurred to give α-equatorial epimer **18** in 44% yield with unchanged **17** in 50% recovery yield, the latter of which was recycled. The former lactone **18** was reduced with diisobutylaluminum hydride (DIBAL) to yield the fourth hemiacetal **16d** (Scheme 3).

Scheme 3[a]

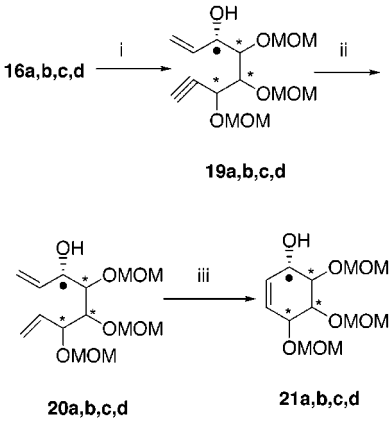


[a] Reagents and conditions: (i) H_2, 10% Pd−C, AcOEt (93% for **14a**; 85% for **14b**; 99% for **14c**); (ii) I_2, PPh_3, imidazole, THF (90% for **15a**; 81% for **15b**; 89% for **15c**); (iii) Zn, AcOH−MeOH (1:10), rt (96% for **16a** and **16b**; 98% for **16c**); (iv) TPAP (catalytic), NMO, CH_2Cl_2 (88%); (v) DABCO, benzene, reflux (44% of **18** and 50% recovery of **17**). DIBAL, CH_2Cl_2, −78 °C (93%).

(12) Prystas, M.; Gustafsson, H.; Sorm, F. *Collect. Czech. Chem. Commun.* **1971**, *36*, 1487.

Transformation of hemiacetals **16a**−**d** thus obtained into the corresponding 1,7-dienes **20a**−**d** was, however, found to be unexpectedly difficult under standard Wittig olefination conditions. Under these conditions, the yield did not exceed 20%. We, therefore, employed a two-step procedure involving the conversion of hemiacetals **16a**−**d** first into 1,7-enyne intermediates **19a**−**d** on treatment with trimethylsilyldiazomethane[16] in the presence of lithium diisopropylamide (LDA). Enynes **19a**−**d** were then hydrogenated over Lindlar catalyst to obtain the desired dienes **20a**−**d** in acceptable overall yields. A ring-closing olefin metathesis reaction of **20a**−**d** under standard conditions using Grubbs' catalyst[17] proceeded without difficulty to yield the corresponding cyclohexenols **21a**−**d** in satisfactory yields (Scheme 4).

Scheme 4[a]

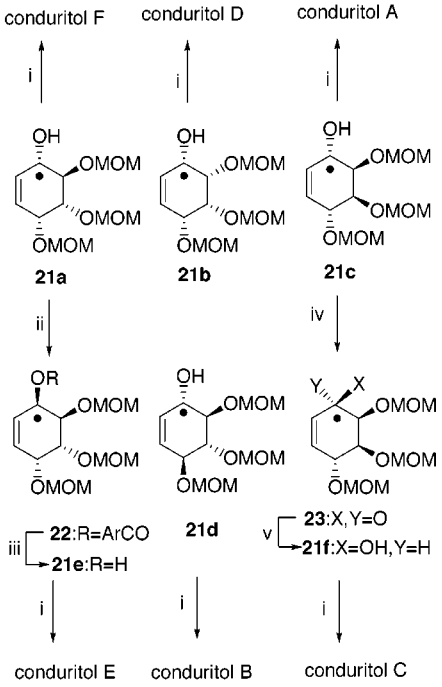


[a] Reagents and conditions: (i) $TMSCHN_2$, LDA, THF, −78 °C to rt (61% for **19a**; 62% for **19b**; 60% for **19c**; 61% for **19d**); (ii) H_2, 5% Pd−$BaSO_4$, quinoline (catalytic), AcOEt; (iii) Grubbs' catalyst (10 mol %), benzene, reflux (two steps: 71% for **21a** and **21b**; 72% for **21c**; 69% for **21d**).

Transformation of the four cyclohexenols **21a**−**d** to conduritols was carried out by removal of the MOM-protecting group just by stirring in hydrogen chloride-saturated methanol at room temperature. Under these conditions, the MOM-protecting group was removed by forming volatile acetal byproducts, leaving conduritols virtually in quantitative yield on evaporation under reduced pressure. Thus, (−)-conduritol F, mp 128−129 °C, $[\alpha]^{25}_D$ −69.4 (*c* 1.0, MeOH) {lit.[6] mp 129−130 °C, $[\alpha]^{28}_D$ −70.2 (*c* 0.15, MeOH)}, from **21a**, $[\alpha]^{25}_D$ +55.7 (*c* 0.4, $CHCl_3$), conduritol D as an oil from **21b**, $[\alpha]^{27}_D$ +1.0 (*c* 0.5, $CHCl_3$), conduritol A, mp 141−142 °C (lit.[6] mp 141−142 °C) from **21c**, $[\alpha]^{28}_D$ −9.3 (*c* 0.7, $CHCl_3$), and (+)-conduritol B, mp 174−175 °C, $[\alpha]^{24}_D$ +173.0 (*c* 0.3, MeOH) {lit.[6] mp 174−175 °C, $[\alpha]^{28}_D$ +153.5 (*c* 0.31, MeOH)}, from **21d**, $[\alpha]^{24}_D$ +140.0 (*c* 0.9, $CHCl_3$), were obtained in excellent yields under these conditions, respectively.

The remaining two conduritols could also be obtained from cyclohexenols **21a** and **21c** by inversion of the stereogenic center of the hydroxy functionality of each compound. Thus, the Mitsunobu reaction of **21a** using 4-nitrobenzoic acid[10] brought about inversion to give the fifth cyclohexenol **21e**, $[\alpha]^{27}_D$ +109.0 (*c* 0.9, $CHCl_3$), via the benzoate **22**, which afforded (−)-conduritol E, mp 191 °C, $[\alpha]^{27}_D$ −314.0 (*c* 0.6, H_2O) {lit.[6] mp 191−192 °C, $[\alpha]^{29}_D$ −330.3 (*c* 0.18, H_2O)}, by sequential debenzoylation and de-MOM protection. Meanwhile, the inversion of **21c** was carried out by sequential oxidation and reduction through the enone **23** to give the sixth cyclohexenol **21f**, $[\alpha]^{24}_D$ −68.3 (*c* 0.9, $CHCl_3$), which afforded (−)-conduritol C, mp 128−129 °C, $[\alpha]^{24}_D$ −213.0 (*c* 0.4, H_2O){lit. for (+)-enantiomer,[6] mp 129−130 °C, $[\alpha]^{28}_D$ +209.1 (*c* 0.62, H_2O)}, by de-MOM protection (Scheme 5).

Scheme 5[a]



[a] Reagents and conditions: (i) saturated HCl−MeOH (∼100%); (ii) 4-nitrobenzoic acid, PPh_3, DIAD, THF; (iii) K_2CO_3, MeOH (81% from **21a**); (iv) PCC, NaOAc, CH_2C_{l2} (94%); (v) DIBAL, CH_2Cl_2, −78 °C (97%).

In conclusion, a new convergent route to all six of the conduritols has been developed, starting from a common chiral building block, on the basis of its inherent diastereo-

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selectivity and high functionality. Although we have demonstrated the synthesis of single enantiomeric products, the present procedure constitutes formal production of their alternative enantiomers since the enantiomer of the starting material has also been prepared. Since the biological importance of cyclitols has been well recognized recently,[18] the present convergent method for the construction of all conduritol diastereomers may be useful in the synthesis of a variety of derivatives for biological evaluation.

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