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Facile Synthetic Routes to All Possible Enantiomeric Pairs of Conduritol Stereoisomers via Efficient Enzymatic Resolution of Conduritol B and C Derivatives

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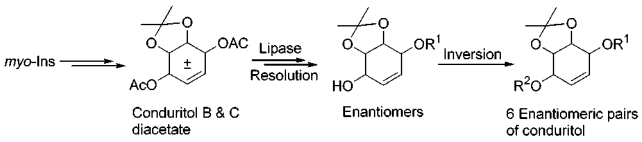
ABSTRACT



The first synthesis of all possible enantiomeric pairs of conduritol stereoisomers has been accomplished by efficient enzymatic resolution of conduritol B and C derivatives, followed by oxidation/reduction and the Mitsunobu reaction in stereo- and regioselective manners.

Conduritols and their derivatives possess interesting biological properties; conduritol epoxides and aminoconduritols act as inhibitors of glycosidases,[1] cyclophellitols have proved to be potent inhibitors of human immunodeficiency virus (HIV) and glycosidases,[2] and conduritol A analogues modulate the release of insulin from isolated pancreatic islets in the presence of varying concentrations of glucose.[3] A number of conduritol derivatives have also been found to possess antibiotic, antileukemic, and growth-regulating activities.[4] In addition, conduritols have been widely used as intermediates in chemical syntheses of inositols,[5] quercitols,[6] deoxyinositols,[7] aminoconduritols,[4,8] conduritol epoxides,[4] cyclophellitol,[9] pseudosugars,[10] amino sugar analogues,[11] sugar amino acid analogues, etc. As pointed out in the recent reviews,[4] however, a number of difficulties have been encountered in the syntheses of conduritols. Conduritols are cyclohex-5-ene-1,2,3,4-tetrols and exist as two *meso* compounds (con-

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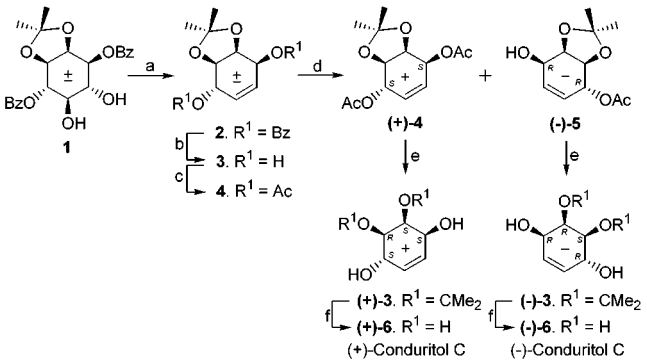
duritols A and D) and four enantiomeric pairs (conduritols B, C, E, and F). Conduritols A and F are naturally occurring. Conduritol isomers have been synthesized by several methods: microbial oxidation of benzene[12] or halobenzenes,[8b,13] followed by epoxidation-ring opening or dihydroxylation, dedihydroxylation of inositol diols,[14] and others.[7,15] Although considerable progress has been made from enantiopure unsaturated cyclic *cis*-diols, obtained by microbial oxidation of halobenzenes,[8b,13] many other approaches result in racemic mixtures. Recently, enantiopure conduritols have been prepared by employing chiral starting materials such as sugar alcohols[16] and diethyl L-tartrate.[17] Enantiopure conduritols have also been obtained by chemical[9,14b,18] or enzymatic[8a,10b,19] resolution of racemic conduritol derivatives or their precursors. However, the systematic and practical access to all enantiopure conduritols has not been realized. Thus we undertook the synthesis of all possible enantiomeric pairs of conduritol stereoisomers via efficient enzymatic resolution of conduritol B and C derivatives and herein report the results.

To obtain enantiopure conduritol stereoisomers, enantioselective enzyme-catalyzed hydrolysis of conduritol B and C derivatives was explored. First, conduritol C derivative (**2**) was prepared from *myo*-inositol diol **1**[20] under the Samuelsson conditions.[21,22] The diacetate **4**, which was derived from **2**, was exposed to lipase from *Candida rugosa* (CRL, Sigma) in a phosphate buffer (pH 7) according to the Kazlauskas' procedure.[23] After 3 h the conversion reached ca. 50% and the reaction mixture contained the unreacted diacetate **(+)-4** (49%, >95% ee) and the monoacetate **(−)-5** (48%, 95% ee) (Scheme 1).

Scheme 1[a]



[a] (a) PPh_3, imidazole, I_2, toluene, ↑↓, 77%; (b) NaOMe, MeOH, ↑↓, 96%; (c) Ac_2O, pyridine 97.5%; (d) see Table 1; (e) NaOMe, MeOH, quant; (f) 80% aq. AcOH, 100 °C, quant.

This observation was at minor variance with Bäckvall's results, which indicated the enzymatic resolution of the diacetate **4** by CRL produced the unreacted diacetate **(+)-4** and the diol **(−)-3**.[19c] It is clear that CRL shows *R* stereopreference. Methanolysis and successive acid-catalyzed hydroysis of compounds **(+)-4** and **(−)-5** afforded (+)-conduritol C [**(+)-6**] and (−)-conduritol C [**(−)-6**], respectively.[7b,13e,19c] The reaction catalyzed by lipase from *Pseudomonas cepacia* (PCL, Amano) also gave comparable results in terms of products, enantioselectivity, and reaction rate. However, the alcoholysis of the diacetate **4** with Novozym 435 (CAL, immobilized lipase from *Candida antarctica*, Novo Nordisk) or Lipozyme RM IM (RML, immobilized lipase from *Rhizomucor miehei*, Novo Nordisk) in *t*-BME did not work at all (Table 1).

To obtain enantiopure conduritol B derivatives, the conduritol B derivative **10** was prepared according to Samuelsson's olefination procedure[21] from compound **9**,[20] which was derived from compound **7**[20] (Scheme 2). The diacetate **12**, prepared by methanolysis and subsequent acetylation of compound **10**, was exposed to CRL and PCL in a phosphate buffer (pH 7), but the optical resolutions did not result.

We then investigated the system with Novozym 435 and *n*-BuOH in *t*-BME at 45 °C. After 30 min, the reaction mixture was found to contain the unreacted diacetate **(+)-12**, the monoacetate **(−)-13**, and the diol **(−)-11**. The monoacetate **(−)-13** was slowly converted to **(−)-11.** This reveals that this enzyme also has *R* stereopreference and can recognize both acetyl groups since the diacetate **(−)-12** has a C_2 symmetry axis. After 3 h, the reaction mixture contained **(+)-12** (49.5%, 98% ee) and **(−)-11** (48.5%, >99% ee). Compound **(+)-12** was treated with NaOMe in MeOH to

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Table 1. Lipases-Catalyzed Resolution of Conduritol B and C Derivatives

substrate	lipase	time (h)[c]	yield (%)	enantioselectivity of products (% ee)[d]
4	CRL[a]	3	48	95 (>99)[e]
4	PCL[a]	3	48	95 (>99)[e]
4	CAL[b]	no rxn		
4	RML[b]	no rxn		
12	CRL[a]	no rxn		
12	PCL[a]	no rxn		
12	CAL[b]	3	48.5	>99
12	RML[b]	36	48.5	>99

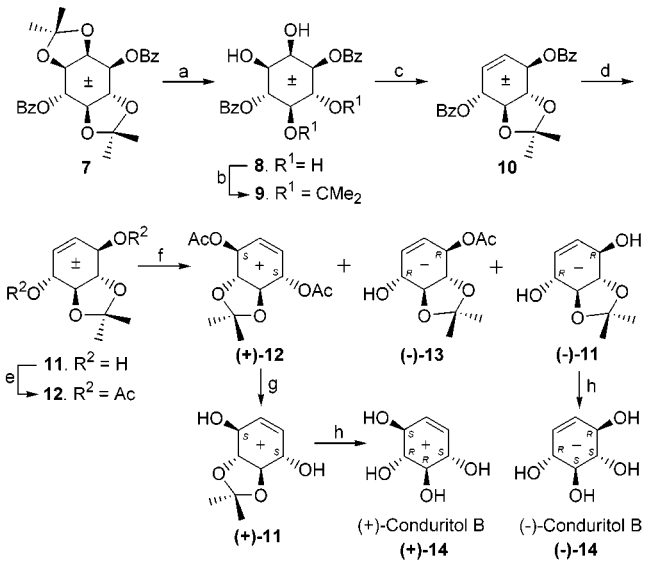
[a] CRL, lipase from *Candida rugosa* (Sigma); PCL, lipase from *Pseudomonas cepacia* (Amano). Experimental conditions, enzyme (100 mg/substrate 1 mmol), 0.5 N buffer (pH 7.0, 5 mL/substrate 1 mmol), 0.5 N NaOH, rt. [b] CAL, Novozym 435 (immobilized lipase from *Candida antarctica*, Novo Nordisk); RML, Lipozyme RM IM (immobilized lipase from *Rhizomucor miehei*, Novo Nordisk). Experimental conditions: enzyme (300 mg/substrate 1 mmol), *n*-BuOH (10 mmol/substrate 1 mmol), *t*-BME (15 mL/substrate 1 mmol), 45 °C. [c] At ca. 50% conversion. [d] Determined by NMR analysis of the diacetates using $Eu(hfc)_3$ as the NMR shift agent. [e] After recrystallization.

give **(+)-11**. The reaction catalyzed by Lipozyme RM IM gave comparable results in terms of products and enantioselectivity but showed a lower reaction rate (Table 1). The enantiomerically pure *trans*-diols **(+)-11** and **(−)-11** were hydrolyzed in 80% aqueous AcOH to yield (+)-conduritol B [**(+)-14**] and (−)-conduritol B [**(−)-14**], respectively.[7a,14d]

Conversions of the enantiomeric diols **(+)-3**/**(−)-3** and **(+)-11**/**(−)-11** to enantiomeric pairs of conduritol stereoisomers follow the same procedures except that the corresponding products involved in each route have opposite configurations. Accordingly, the procedures starting from **(+)-3** and **(+)-11** only are described as the representative.

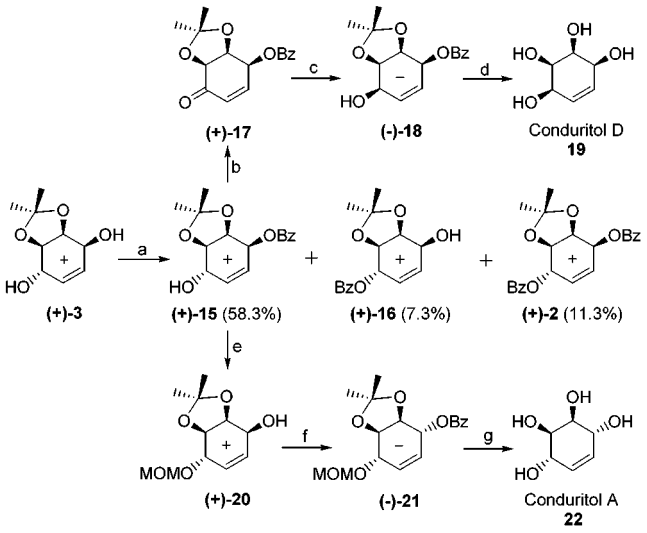
Because our initial synthetic plan for enantiopure conduritol stereoisomers involved the inversion of the allylic alcohol stereochemistry in selectively protected conduritol derivatives under the Mitsunobu conditions, the monobenzoate **(+)-15** was preferentially prepared by treatment of **(+)-3** with BzCl (1.0 equiv) in pyridine (Scheme 3).

Scheme 2[a]



[a] (a) 80% aq. AcOH, 100 °C, quant; (b) 2-methoxypropene, TSA, DMF, 43%; (c) PPh_3, imidazole, I_2, toluene, ↑↓, 78%; (d) NaOMe, MeOH, ↑↓, 97.4%; (e) Ac_2O, pyridine 98.8%; (f) see Table 1; (g) NaOMe, MeOH, quant; (h) 80% aq. AcOH, 100 °C, quant.

Scheme 3[a]



[a] (a) BzCl (1.0 equiv), pyridine; (b) SO_3−pyridine complex, TEA, DMSO; (c) $NaBH_4$, MeOH−CH_2Cl_2, 74.5% from **(+)-15**; (d) (i) NaOMe, MeOH, ↑↓, (ii) 80% aq. AcOH, 100 °C, 92%; (e) (i) MOMCl, $(i\text{-Pr})_2NEt$, (ii) NaOMe, MeOH, ↑↓, 97.1%; (f) BzOH, Ph_3P, DEAD, toluene, 97.1%; (g) (i) NaOMe, MeOH, ↑↓, (ii) 80% aq. AcOH, 100 °C, 89%.

In the preliminary experiment, the Mitsunobu reaction of the racemic monobenzoate **15** with BzOH, Ph_3P, and DEAD in toluene at room temperature was found to give the expected conduritol D derivative **25** (8.5%) as the minor product and the rearranged conduritol C derivative **26** (73.1%) as the major product in stereo- and regioselective fashions. That is, the reaction was found to proceed predominantly with both inversion and allylic rearrangement, presumably via the intermediate **24** by S_N2' replacement to afford compound **26** (Scheme 4). These unexpected results suggest that the reaction of a carboxylate anion with an alkoxy phosphonium salt is better described as proceeding through an intimate ion pair rather than a free allylic carbonium ion.[24] When (±)-(1,2,3/4)-1-*O*-methoxymethyl-2,3-*O*-isopropylidene-cyclohex-5-ene-1,2,3,4-tetrol and (±)-(1,2,3/4)-1,2,3-tri-*O*-methoxymethylcyclohex-5-ene-1,2,3,4-tetrol, derived from the racemate **3**, were subjected to the Mitsunobu conditions, similar results were obtained, indicating that the nature of the protecting groups made little difference. The stereochemistry of the transformation does not significantly depend on steric and electronic effects but rather on the substrate structure.

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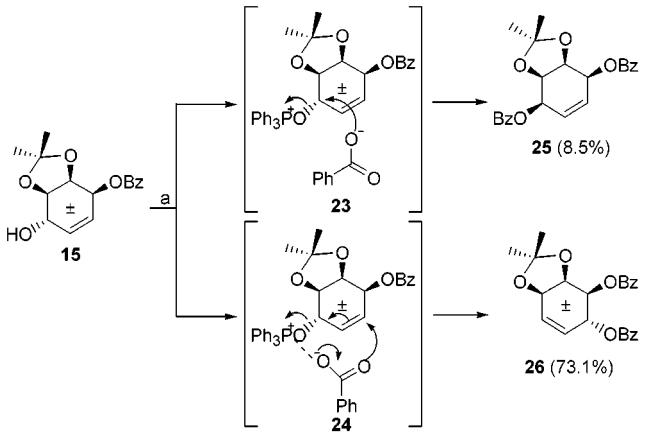
Scheme 4[a]



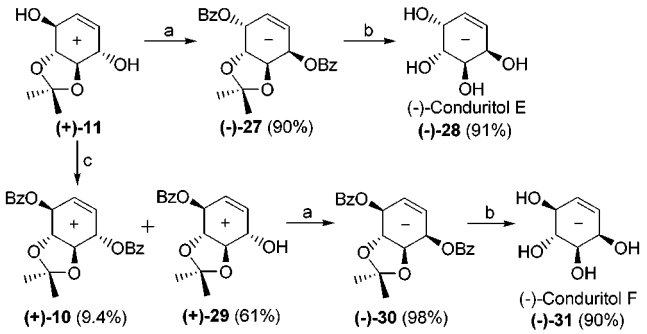
[a] (a) BzOH, Ph_3P, DEAD, toluene.

Thus, the possibility of obtaining conduritol D by way of oxidation and subsequent stereoselective reduction of **(+)-15** was investigated (Scheme 3). Compound **(+)-15** was treated with SO_3−pyridine complex and TEA in DMSO to furnish an enone **(+)-17**. Although conduritol D itself is a meso compound, reduction of the enone **(+)-17** with $NaBH_4$ gave stereoselectively an enantiopure conduritol D derivative **(−)-18** in 74.5% overall yield from **(+)-15**. Methanolysis and successive acid-catalyzed hydrolysis of **(−)-18** provided achiral conduritol D (**19**).[7b,12d,13a]

On the other hand, the allylic alcohol **(+)-20**, derived from **(+)-15** by treatment with MOMCl and $(i\text{-Pr})_2NEt$ in $CHCl_3$, followed by debenzoylation, was treated with BzOH, Ph_3P, and DEAD in toluene to afford the conduritol A derivative **(−)-21** with inversion of the stereochemistry but no allylic rearrangement in 97.1% yield. All protecting groups of **(−)-21** were removed by treatment with NaOMe and subsequent acid-catalyzed hydrolysis to give achiral conduritol A (**19**).[12d,15a]

The double inversion of two allylic hydroxyl groups of **(+)-11** might be expected to give the conduritol E derivative. The treatment of **(+)-11** with BzOH, Ph_3P, and DEAD in toluene at room temperature indeed provided the (−)-conduritol E derivative [**(−)-27**] without allylic rearrangement in 90% yield. The protecting groups of **(−)-27** were removed by successive reactions with NaOMe in MeOH and 80% aqueous AcOH to yield (−)-conduritol E [**(−)-28**]

Scheme 5[a]



[a] (a) BzOH, Ph_3P, DEAD, toluene; (b) (i) NaOMe, MeOH, ⇅, (ii) 80% aq. AcOH, 100 °C, 90%; (c) BzCl (1.05 equiv), pyridine.

(Scheme 5).[8b,16b] The monobenzoate **(+)-29** was obtained by treatment of the diol **(+)-11** with BzCl (1.05 equiv) in pyridine in 61% yield. The Mitsunobu reaction of **(+)-29** with BzOH, Ph_3P, and DEAD in toluene provided the conduritol F derivative **(−)-30** in 98% yield. All protecting groups of **(−)-30** were removed by methanolysis and subsequent acid-catalyzed hydrolysis to yield conduritol F, **(−)-31**.[7a,13d,14d,16b]

In sum, we successfully developed synthetic routes to enantiomeric pairs of all possible stereoisomeric conduritol derivatives by efficient enzymatic resolution of conduritol B and C derivatives, followed by oxidation/reduction and the Mitsunobu reaction in stereo- and regioselective manners. We are currently examining the utility of enantiopure conduritol stereoisomers in the syntheses of inositol stereoisomers and various cyclitols.

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Supporting Information Available: Experimental procedures and full characterization for compounds **2**−**4**, **(+)-4**, **(−)-5**, **(+)/(−)-3**, **10**−**12**, **(+)-12**, **(−)-13**, **(+)/(−)-11**, **(+)/(−)-15**, **(+)/(−)-16**, **(+)/(−)-2**, **(+)/(−)-17**, **(+)/(−)-18**, **(+)/(−)-20**, **(+)/(−)-21**, **25**, **26**, **(+)/(−)-27**, **(+)/(−)-29**, **(+)/(−)-10**, and **(+)/(−)-30**. This material is available free of charge via the Internet at http://pubs.acs.org.

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