Efficient Synthesis of (±)-, (+)-, and (−)-Conduritol C via Palladium(II)-Catalyzed 1,4-Diacetoxylation in Combination with Enzymatic Hydrolysis

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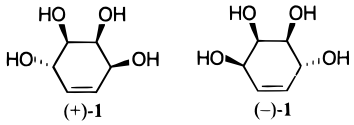
Palladium-catalyzed diacetoxylation of 5,6-isopropylendioxy-1,3-cyclohexadiene (**3**) was stereoselective and gave the *trans*-diacetate **4** (>94% trans), which after hydrolysis and deprotection, afforded (±)-conduritol. Enzymatic hydrolysis of diacetate **4** produced enantiomerically pure diol (−)-**5** (>99.5% ee) and enantiomerically pure (+)-**4** (>99.5% ee). Compounds (−)-**5** and (+)-**4** were subsequently transformed to (−)- and (+)-conduritol C, respectively.

Introduction

Conduritols constitute a class of 5-cyclohexene-1,2,3,4-tetrols with interesting biological activity including antibiotic, antileukemic, and tumor-inhibitory properties.[1] Several of the conduritol isomers are inhibitors for glycosidases.[2] Various synthetic approaches toward the different isomers of conduritols have been developed[3] including enantioselective versions.[4,5]

Conduritol C (**1**), one of the six possible diastereoisomers of 5-cyclohexene-1,2,3,4-tetrols, has been synthesized by several groups.[3−5] In 1989, Vogel et al. successfully achieved the first total synthesis of optically pure (−)-conduritol C ((−)-**1**),[4] and subsequently, others[5a−f]

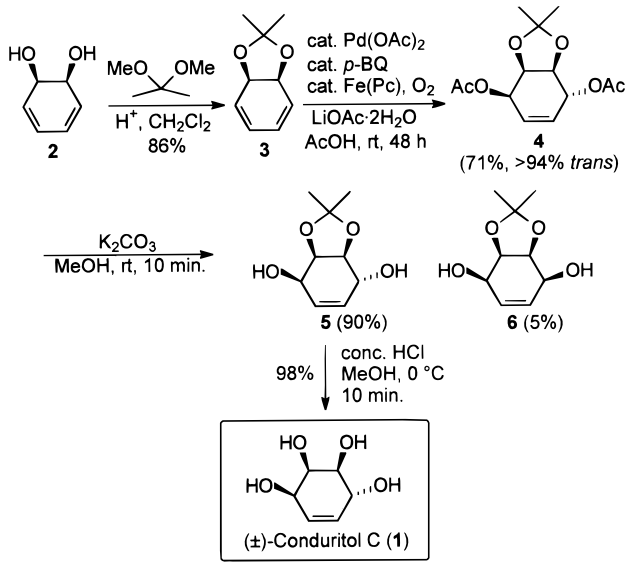


Conduritol C (1)

have reported enantioselective syntheses. Their prime synthetic strategies for introduction of the *trans*-dihydroxy groups were based on stereospecific reduction of ketones or Mitsunobu displacement reactions after enzyme-catalyzed enantioselective reaction of the *cis*-diester.

In this paper, we report on a different strategy involving a palladium-catalyzed *trans*-diacetoxylation of a protected 3,5-cyclohexadiene-1,2-diol. Kinetic resolution of the product afforded (+)- and (−)-**1** in excellent enantiomeric excess and yield.

Scheme 1. Synthesis of (±)-Conduritol C



Results and Discussion

1. 1,4-Diacetoxylations of *cis*-5,6-(Isopropylidenedioxy)-1,3-cyclohexadiene. The diene **3** was prepared from commercially available 1,2-dihydrocatechol **2** by reaction with 2,2-dimethoxypropane under acidic conditions in dichloromethane (Scheme 1).[6] Using this diene as a substrate, the palladium(II)-catalyzed 1,4-diacetoxylation was examined.[7] First, *trans*-1,4-diacetoxylation

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(2) (a) Legler, G.; Bause, E. *Carbohydr. Res.* **1973**, 28. (b) Legler, G.; Lotz, W. *Physiol. Chem.* 354, **1973**, 243. (c) Umezawa, S. *Adv. Carbohydr. Chem. Biochem.* **1974**, *30*, 111−225. (d) Atsumi, S.; Umezawa, K.; Iinuma, H.; Nakamura, H.; Iitaka, Y. *J. Antibiot.* **1989**, *43*, 49−53.

(3) For excellent reviews on preparation of conduritols, see: (a) BalcI, M.; Sütbeyaz, Y.; Seçen, H. *Tetrahedron* **1990**, *46*, 3715−3742. (b) Hudlicky, T.; Reed, J. W. In *Advances In Asymmetric Synthesis*; JAI Press Inc.: London, 1995; Vol. 1, p 271−312. (c) Balcı, M. *Pure Appl. Chem.* **1997**, *69*, 97−104.

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(5) For more recent examples, see: (a) Johnson, C. R.; Plé, P. A.; Adams, J. P. *J. Chem. Soc., Chem. Commun.* **1991**, 1006−1007. (b) Dumortier, L.; Liu, P.; Dobbelaere, S.; Van der Eycken, J.; Vandewalle, M. *Synlett* **1992**, 243−245. (c) Patti, A.; Sanfilippo, C.; Piatteri, M.; Nicolosi, G. *Tetrahedron: Asymmetry* **1996**, *7*, 2665−2670 (conduritol C and D). (d) Carless, H. A. J.; Oak, O. Z. *J. Chem. Soc., Chem. Commun.* **1991**, 61−62. (e) McIntosh, M. C.; Weinreb, S. M. *J. Org. Chem.* **1991**, *56*, 5010−5012. (f) Carless, H. A. J. *J. Chem. Soc., Chem. Commun.* **1992**, 234−235. (g) Innes, J. E.; Edwards, P. J.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1997**, 795−796 ((+)-D-conduritol B).

(6) (a) Yang, N. C.; Chen, M.-J.; Chen, P. J. *J. Am. Chem. Soc.* **1984**, *106*, 7310−7315. (b) Ramesh, K.; Wolfe, M. S.; Lee, Y.; Velde, D. V.; Borchardt, R. T. *J. Org. Chem.* **1992**, *57*, 5861−5868.

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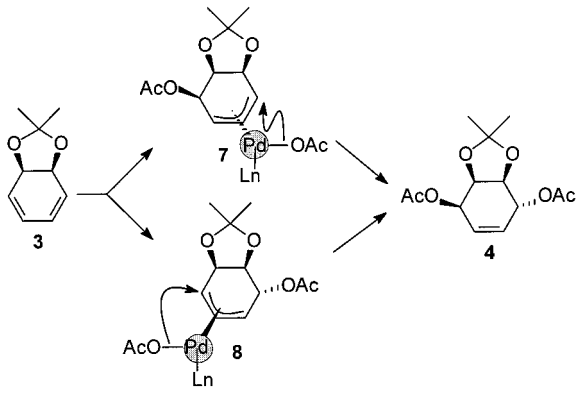
Table 1. Examination of *trans*-1,4-Diacetoxylation[a]

run	oxidant	temp	yield (%)[b]	ratio (trans %)[c]
1	MnO_2	rt	69	87
2	MnO_2	40 °C	51	88
3	Fe(Pc)/O_2	rt	71	94

[a] All reactions were carried out for 48 h. [b] Isolated yield. [c] Ratio was determined by ^{1}H NMR spectrum.

Scheme 2



was studied by employing 5 mol % of palladium diacetate [$Pd(OAc)_2$], 10 mol % of *p*-benzoquinone, 1.2 equiv of lithium acetate dihydrate ($LiOAc·2H_2O$), and 1.2 equiv of manganese(IV) oxide (MnO_2) in acetic acid at room temperature for 48 h (Table 1, run 1).[7b] The desired product *trans*-1,4-diacetate **4** was obtained in 69% yield in a trans/cis ratio of 87:13. When the temperature was raised to 40 °C, the yield dropped to 51% (run 2). Using 3 mol % of iron(II) phthalocyanine [Fe(Pc)] as a dioxygen activating agent under an oxygen atmosphere[7c] afforded **4** in 71% yield and with >94% trans selectivity (run 3).

The diacetate **4** obtained from 1,4-diacetoxylation of diene **3** was hydrolyzed, and the purified *trans*-diol obtained was subsequently deprotected to afford the (±)-conduritol ((±)-**1**). The overall yield of (±)-**1** from commercially available diol **2** was 54% (Scheme 1).

cis-1,4-Diacetoxylation of **3** was also studied by employing 5 mol % of $Pd(OAc)_2$, 20 mol % of *p*-benzoquinone, 20 mol % of lithium chloride (LiCl), 30 mol % of $LiOAc·2H_2O$, and 1.2 equiv of MnO_2 in acetic acid at room temperature.[7b] The desired *cis*-diacetate was not obtained, and instead, the Diels−Alder adduct between diene and quinone was produced.

In the diacetoxylation of **3**, the reaction may proceed via two different (π-allyl)palladium complexes (Scheme 2). Palladium can coordinate either from the same or from the opposite side of the acetonide. Subsequent nucleophilic attack by the first nucleophile would give the (π-allyl)palladium intermediates **7** and **8**. A cis migration from the latter complexes would produce the *trans*-diacetate. It is likely that **7** is the intermediate π-allyl complex in this reaction. This was supported by the fact that the *cis*-diacetate obtained as a minor isomer (diacetate of **6**) was found to have the diacetoxy groups cis to the oxygens in the acetonide (J_{23} = 3.3 Hz, see Experimental Section). This diacetate would be formed from external attack by acetate on intermediate **7**.

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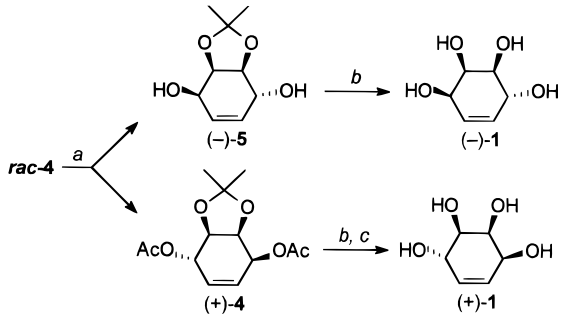
Scheme 3. Synthesis of Optically Pure (+)- and (−)-Conduritol C[a]



[a] Reagents and conditions: (a) lipase (from *Candida rugosa*), phosphate buffer (pH 7.0), rt, 18 h ((−)-**5**: 49%). (b) Conc. HCl aq, MeOH, 0 °C, 10 min (98%). (c) K_2CO_3, MeOH, rt, 10 min (99%).

2. Enantiomerically Pure (+)- and (−)-Conduritol C. Enantioselective enzyme-catalyzed hydrolysis of *trans*-diacetate **4** obtained from 1,4-diacetoxylation of **3** was studied in an attempt to obtain enantiomerically pure conduritol C.

In the planning of this synthesis, a significant question was if the enzyme could recognize both of two acetates simultaneously. If not, four compounds, one diacetate, one diol, and two monoacetates, would be produced and resolution would fail. However, according to the principle of enzymatic hydrolysis,[8,9] it appeared to be possible in this case.

The diacetate obtained from *trans*-1,4-diacetoxylation of diene **3** having the acetonide function was hydrolyzed by lipase from *Candida rugosa*,[9] in a phosphate buffer (pH 7), according to Kazulauskas' procedure.[9] Fortunately, the acetonide function could be effectively distinguished by the enzyme, and the optical resolution proceeded smoothly and quantitatively. In this step, the hydrolyzed *trans*-diol (−)-**5** and *trans*-diacetate (+)-**4** were obtained in 49% and 48% yields, respectively. The enantiomeric excesses (ees) of the products were determined by chiral HPLC analysis after derivatization of the *trans*-diols (+)- and (−)-**5** into *trans*-dibenzoate. In each case, the ees were >99.5%, showing that the enzyme-catalyzed kinetic resolution was highly efficient (Scheme 3).

The enantiomerically pure *trans*-diol (−)-**5** was deprotected to give (−)-**1**, and the diacetate (+)-**4** was hydrolyzed−deprotected to give (+)-**1**. The overall yields of (+)- and (−)-**1** from **2** were 29% and 30%, respectively. The ^{1}H and ^{13}C NMR spectra and optical rotations were in good agreement with literature data.[4]

In this manner, a short and efficient synthesis of enantiomerically pure (+)- and (−)-conduritol C was achieved. We have demonstrated the utility of palladium-catalyzed 1,4-*trans*-diacetoxylation for introduction of functional groups, as well as the enzyme-catalyzed hydrolysis as a powerful tool for obtaining optically active materials.

Experimental Section

(1*R,4*R**,5*S**,6*R**)-1,4-Diacetoxy-5,6-(isopropylidenedioxy)-2-cyclohexene (4).** To a solution of palladium diacetate (161.2 mg, 0.718 mmol), *p*-benzoquinone (155.2 mg, 1.436

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mmol), iron phthalocyanine (272.1 mg, 0.431 mmol), and $LiOAc \cdot 2H_2O$ (1.81 g, 17.23 mmol) in acetic acid (45 mL) at 20 °C was added *cis*-5,6-(isopropylidenedioxy)-1,3-cyclohexadiene (**3**, 2.18 g, 14.36 mmol) during 3 h with a syringe pump. Stirring was continued for another 48 h at this temperature. The reaction mixture was filtered through Celite under reduced pressure and washed with 2 M aqueous sodium hydroxide solution (5 × 50 mL), and the aqueous phase was re-extracted with ethyl acetate. The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give the crude product. Purification of the crude product by flash column chromatography (petroleum ether/AcOEt, 5:1) afforded 2.63 g (71%) of *trans*-1,4-diacetate **4** (>94% trans) as a colorless liquid. R_f: 0.37 (AcOEt). ^{1}H NMR (270 MHz, $CDCl_3$): δ (ppm) 1.37 (s, 3H), 1.44 (s, 3H), 2.04 (s, 3H), 2.07 (s, 3H), 4.42 (dd, J = 6.2, 8.0 Hz, 1H), 4.71 (dd, J = 3.7, 9.5 Hz, 1H), 5.18 (dd, J = 3.7, 8.1 Hz, 1H), 5.49 (t, J = 4.1 Hz, 1H), 5.93 (ddd, J = 0.9, 4.0, 9.9 Hz, 1H), 6.07 (dd, J = 3.7, 9.9 Hz, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ (ppm) 20.8, 20.9, 25.7, 27.6, 66.0, 71.0, 72.0, 72.8, 110.0, 126.6, 129.3, 170.1, 170.4.

(1*R,4*S**,5*R**,6*S**)-1,4-Diacetoxy-5,6-(isopropylidenedioxy)-2-cyclohexene (Minor Isomer, Diacetate of 6).** R_f: 0.37 (petroleum ether/AcOEt, 5:1). ^{1}H NMR (270 MHz, $CDCl_3$): δ (ppm) 1.38 (s, 3H), 1.49 (s, 3H), 2.14 (s, 6H), 4.28 (dd, J = 1.4, 3.3 Hz, 2H), 5.29 (dd, J = 1.1, 3.3 Hz, 2H), 5.73 (s, 2H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ (ppm) 21.3, 25.3, 27.3, 71.8, 75.6, 109.9, 128.4, 170.4.

(1*R*,4*R*,5*S*,6*R*)-1,4-Dihydroxy-5,6-(isopropylidenedioxy)-2-cyclohexene ((−)-5). A suspension of racemate **4** (4.66 g, 18.04 mmol) and lipase in phosphate buffer (40 mL) at pH 7.0 was vigorously stirred for 18 h at room temperature. After addition of ethyl acetate (40 mL), this suspension was filtered through Celite and the mixture was extracted 4 times with ethyl acetate. The combined extracts were washed with saturated aqueous sodium bicarbonate, water, and brine, dried over magnesium sulfate, and concentrated. After purification by flash column chromatography (petroleum ether/AcOEt, 1:1−1:2), 2.23 g (48%) of trans-1,4-diacetate (+)-**4** (>99.5% ee) and 1.64 g (49%) of *trans*-diol (−)-**5** (>99.5% ee) were obtained Recrystallization of (−)-**5** from *n*-hexane and ether gave 1.41 g (86%) of colorless crystals. ^{1}H NMR (270 MHz, $CDCl_3$): δ (ppm) 1.38 (s, 3H), 1.44 (s, 3H), 2.98 (brs, 1H), 3.16 (brs, 1H), 3.96−3.98 (m, 1H), 4.30 (brs, 1H), 4.37 (t, J = 6.2 Hz, 1H), 4.67 (brd, J = 5.9 Hz, 1H), 5.92−5.94 (m, 2H). ^{13}C NMR (67.9 MHz, $CDCl_3$): δ (ppm) 26.1, 28.1, 66.1, 71.3, 72.0, 75.9, 109.7, 127.6, 130.1. (+)-**4**: $[\alpha]^{20}_D$ +154.7 (*c* 1.106, $CHCl_3$). (−)-**5**: $[\alpha]^{20}_D$ −157.2 (*c* 0.998, $CHCl_3$).

Determination of Enantiomeric Purity of Compounds (+)-4 and (−)-5. Diol (−)-**5** was transformed to the dibenzoate by reaction with benzoyl chloride and pyridine. Analysis of the dibenzoate with chiral HPLC (Chiracel OD-H, hexane/2-propanol = 90:10) showed that the product was of >99.5% ee. The diacetate (+)-**4** was hydrolyzed, and the diol was dibenzoylated. Chiral HPLC analysis as above showed that the ee was >99.5%.

(1*R*,4*R*,5*S*,6*R*)-5-Cyclohexene-1,2,3,4-tetrol and (1*S*,4*S*,-5*R*,6*S*)-5-Cyclohexene-1,2,3,4-tetrol [(+)-1 and (−)-1]. To a methanol solution (20 mL) of *trans*-diol (−)-**5** (1.0 g, 5.37 mmol), two drops of concentrated hydrochloric acid (37%) was added dropwise, and the solution was stirred for 10 min at 0 °C. The reaction mixture was neutralized with saturated aqueous sodium bicarbonate. This suspension was evaporated under reduced pressure, and the residue was suspended with methanol. The filtrate was left overnight at −30 °C to yield 776.1 mg (99%) of colorless crystals. Recrystallization from methanol and ether gave 621.5 mg (80%) of colorless crystals, mp 128−129 °C (lit.[4] 129−130 °C). (−)-**1**: $[\alpha]^{20}_D$ −213° (*c* 1.996, H_2O) [lit.[4] $[\alpha]^{25}_D$ −209° (*c* 2, H_2O)]. (+)-**1**: $[\alpha]^{20}_D$ +215° (*c* 2.008, H_2O) [lit.[5d] $[\alpha]^{25}_D$ +213° (*c* 0.4, H_2O)]. ^{1}H NMR (270 MHz, CD_3OD): δ (ppm) 3.57 (dd, J = 3.7, 6.6 Hz, 1H), 3.85 (brt, J = 3.1 Hz, 1H), 4.00 (t, J = 6.2 Hz, 1H), 4.30 (dd, J = 3.3, 5.9 Hz, 1H), 5.45 (ddd, J = 0.9, 3.6, 10.2 Hz, 1H), 5.54 (dd, J = 3.6, 10.2 Hz, 1H). ^{13}C NMR (67.9 MHz, CD_3OD): δ (ppm) 69.2, 72.3, 73.5, 77.6, 127.7, 132.3.

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Supporting Information Available: Copies of NMR spectra of **4**, **5**, the diacetate of **6**, and conduritol C (**1**) (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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