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A new and concise synthetic route to an enantiopure (+)-conduritol-E derivative from diethyl L-tartrate

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Abstract

(+)-(1*R*,2*R*,3*S*,6*S*)-3,6-Di-*O*-methyl conduritol-E was efficiently synthesized in enantiomerically pure form starting from diethyl L-tartrate in 33% total yield using a ring-closing olefin metathesis reaction as one of the key steps.

A series of conduritols such as conduritol-E **1** and their derivatives are a prominent class of biologically active compounds.[1] Several of these cyclitols have been shown to inhibit the action of glycosidases.[2] Moreover, they serve as versatile building blocks for the synthesis of compounds of biological significance such as inositols and their analogs. This has stimulated considerable efforts toward the synthesis of this class of compounds with high enantiomeric excess.[3] Optically active conduritol-E **1** or its derivatives, one of the six possible diastereomers of 5-cyclohexene-1,2,3,4-tetraols, have been prepared either from *meso*-benzene-derived dienediols or from inositol derivatives already equipped with all the necessary stereogenic centers.[4] However, successes in these synthetic approaches critically rely either on the reliability of kinetic resolution to provide the required stereogenic centers or on the efficiency of tedious protection/deprotection sequences. This report describes a short and concise strategy for the synthesis of an enantiomerically pure conduritol-E derivative using ring-closing olefin metathesis as one of the key steps.

As outlined in Scheme 1, a brief analysis of the structure of conduritol-E **1** indicated that the cycloolefinic skeleton could be accessible by ring-closing olefin metathesis of a symmetric dialkenyl precursor **2** (or in its protected form). The required dienyl tetraol **2** was envisioned to be readily prepared by a stereoselective bis-addition of a vinyl nucleophile onto 2,3-dihydroxy butanedialdehyde (or its equivalent) which in turn could be derived from the enantiomerically pure tartrate ester **3**. The realization of this approach is shown in Scheme 2.[5] It has been known that partial reduction of the two ester groups in **4** with DIBAL-H at low temperature provides a corresponding dialuminate which in turn, as an aldehyde equivalent, reacts under Wittig conditions to afford diolefinic compounds in good yields.[6] We anticipated

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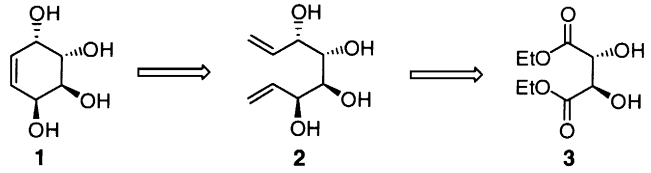
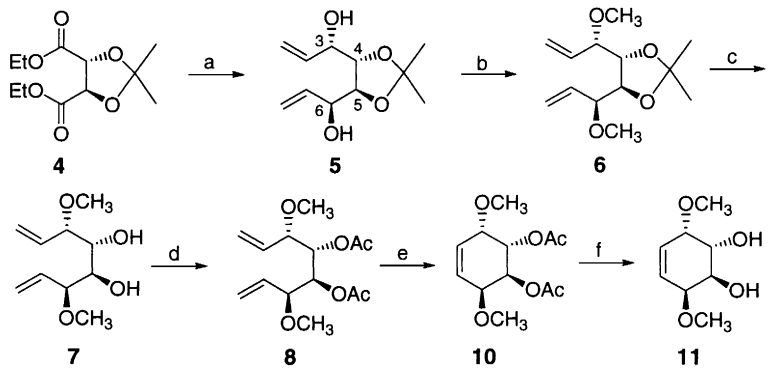
that an addition product could be obtained with a marginal facial selectivity by the treatment of the dialdehyde equivalent with nucleophiles such as a Grignard reagent.



Scheme 1.

Partial reduction of diethyl (*2R,3R*)-2,3-*O*-isopropylidenetartrate **4** was performed by the action of 2.1 equiv. of DIBAL-H at −78°C. The dialdehyde equivalent generated was unstable and thus was treated in situ with vinylmagnesium bromide at low temperature to afford the bis-allyl alcohol **5** and its diastereomers as a mixture in 65–75% combined yields. We were pleased to observe that the (bis)*syn*-product **5** was produced with predominance over the other diastereomers in a ratio of 77:23 (**5**:other three diastereomers) based on the ^{1}H NMR integration of the crude reaction mixture.[7] In the addition reaction, several attempts were made to achieve better selectivity such as use of different solvent systems, addition of vinyllithium instead of vinylmagnesium bromide, or use of some additives ($MgBr_2$ or $ZnCl_2$). The resultant selectivities, however, were less satisfactory. The value of coupling constants ($J_{H3–H4}$=$J_{H5–H6}$=4.4 Hz) of **5** separated by column chromatography on silica gel confirmed a *cis* relationship for the two pairs of protons (H3/H4 and H5/H6).[8] This is the first example, to the best of our knowledge, of a stereoselective bis-addition of a nucleophile to a dialdehyde equivalent derived from a tartrate moiety.[9]



Scheme 2. Reagents and conditions. (a) (i) DIBAL-H (2.1 equiv.)/toluene, −78°C, 2.5 h,(ii) CH_2=CHMgBr (3.0 equiv.), −78°C to rt (54% in two steps); (b) NaH (3.0 equiv.)/CH_3I (4.0 equiv.)/DMF (94%); (c) 10% HCl/MeOH (99%); (d) Ac_2O/Et_3N/DMAP (92%); (e) **9** (12 mol%)/CH_2Cl_2, 45°C, 18 h (73%); (f) K_2CO_3/MeOH (99%)

Although ring-closing olefin metathesis (RCM) has recently proven to be a very powerful tool for the synthesis of carbocycles and heterocycles,[10] direct cyclization of the dienyl compound **5** was unsuccessful using the Grubbs' Ru–benzylidene complex $Cl_2(PCy_3)_2Ru$=CHPh (**9**) as the catalyst.[11] Treatment of **5** with the catalyst **9** produced the corresponding fused cyclic diol in less than 5% yield under a variety of reaction conditions. Low reactivity exhibited by the dienyl compound **5** for RCM was not unexpected considering that the substrate is conformationally restrained for ring closure and the nearby free hydroxyl group may deactivate the catalyst by coordination. The *trans*-acetonide protecting group in **5** would force the two ethylenic appendages in a *trans* orientation to each other and this unfavorable conformation of **5** may contribute in part to the lack of reactivity of this diolefinic compound to the metathesis reaction.[12] This led us to protect the allylic hydroxyl group of **5** and subsequent

conversion of the cyclic *trans*-acetonide of **5** to a different acyclic protecting group. The three successive protection/deprotection steps (**5**–**8**) proceeded with high efficiency (86% yield over three steps). RCM of the fully protected dienyl compound **8** was effected in refluxing CH_2Cl_2. The cyclohexenyl product **10** was isolated in 73% yield using 12 mol% of the catalyst **9**, which was fed to the reaction mixture in three portions over 18 h. Deacetylation of **10** provided 3,6-di-*O*-methyl conduritol-E **11** in an almost quantitative yield. Its analytical data were completely identical to those reported in the literature[4c] and its enantiomeric excess was determined to be >99.7%.[13]

In conclusion, an enantiomerically pure conduritol-E derivative **11** was efficiently synthesized in 33% total yield from a cheap and accessible starting chiral compound through a series of routine organic reactions and eventual RCM process that is currently prevailing.

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References

1. (a) Külber, K. *Arch. Pharm*. **1908**, *346*, 620. (b) Manni, P. E.; Sinsheimer, J. E. *J. Pharm. Sci*. **1965**, *54*, 1541. (c) Legler, G. *Mol. Cell. Biochem*. **1973**, *2*, 31.
2. For a recent review, see: Look, G. C.; Fotsch, C. H.; Wong, C. H. *Acc. Chem. Res*. **1993**, *26*, 182.
3. Hudlicky, T.; Entwistle, D. A.; Pitzer, K. K.; Thorpe, A. J. *Chem. Rev*. **1996**, *96*, 1195.
4. (a) Hudlicky, T.; Price, J. D.; Olivo, H. *Synlett* **1991**, 645. (b) Takano, S.; Yoshimitsu, T.; Ogasawara, K. *J. Org. Chem*. **1994**, *59*, 54. (c) Cere, V.; Peri, F.; Pollicino, S. *Tetrahedron Lett*. **1997**, *38*, 7797. (d) Sanfilippo, C.; Patti, A.; Piattelli, M.; Nicolosi, G. *Tetrahedron: Asymmetry* **1998**, *9*, 2809.
5. All new compounds were fully characterized by spectroscopic means: ^{1}H and ^{13}C NMR, IR and HRMS.
6. (a) Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc*. **1992**, *114*, 2524. (b) Naito, H.; Kawahara, E.; Maruta, K.; Maeda, M.; Sasaki, S. *J. Org. Chem*. **1995**, *60*, 4419.
7. (Bis)*syn*-product **5**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.99–5.92 (m, 2H), 5.42–5.27 (m, 4H), 4.19 (br s, 2H), 3.90 (dd, *J*=4.4, 1.5 Hz, 2H), 1.55 (br s, 2H), 1.41 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 137.2, 117.5, 109.9, 82.4, 74.3, 27.5; IR (CH_2Cl_2) cm^{-1} 3368 (broad), 2989, 2891, 1645, 1429, 1166, 996, 930; HRMS (CI) calcd for $C_{11}H_{19}O_4$ $[M+H]^+$ 215.1284, found 215.1286; $[\alpha]_D^{25}=-23.6$ (*c* 1.0, CH_2Cl_2). (Bis)*anti*-isomer of **5**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.95–5.87 (m, 2H), 5.40–5.25 (m, 4H), 4.31 (dd, *J*=14.2, 6.3 Hz, 2H), 4.03 (m, 2H), 2.88 (bs, 2H), 1.44 (s, 6H).
8. (a) Laib, T.; Chastanet, J.; Zhu, J. *J. Org. Chem*. **1998**, *63*, 1709. (b) Mukaiyama, T.; Suzuki, K.; Yamada, T.; Tabusa, F. *Tetrahedron* **1990**, *46*, 265.
9. For some examples on stereoselective addition of various nucleophiles to mono-aldehyde derived from tartrate ester, see: (a) Majewski, M.; Shao, J.; Nelson, K.; Nowak, P.; Irvine, N. M. *Tetrahedron Lett*. **1998**, *39*, 6787. (b) Chattopadhyay, A.; Dhotare, B. *Tetrahedron: Asymmetry* **1998**, *9*, 2715.
10. Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.
11. For some recent examples on the application of RCM to cyclitols or carbohydrates, see: (a) Sellier, O.; Weghe, P. V.; Nouen, D. L.; Strehler, C.; Eustache, J. *Tetrahedron Lett*. **1999**, *40*, 853. (b) Ovaa, H.; Codee, J. D. C.; Lastdrager, B.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett*. **1999**, *40*, 5063. (d) Kapferer, P.; Sarabia, F.; Vasella, A. *Helv. Chim. Acta* **1999**, *82*, 645. (d) Kornienko, A.; d'Alarcao, M. *Tetrahedron: Asymmetry* **1999**, *10*, 827.
12. (a) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc*. **1996**, *118*, 9606. (b) Holder, S.; Blechert, S. *Synlett* **1996**, 505. (c) Hammer, K.; Undheim, K. *Tetrahedron* **1997**, *53*, 5925.
13. $[\alpha]_D^{25}=+233.40$ (*c* 1.00, $CHCl_3$) [lit.[4c] $[\alpha]_D^{27}=-234.04$, the enantiomer of **11** (*c* 1.00, $CHCl_3$)].