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Enantioselective Synthesis of a Hydroxymethyl-*cis*-1,3-cyclopentenediol Building Block

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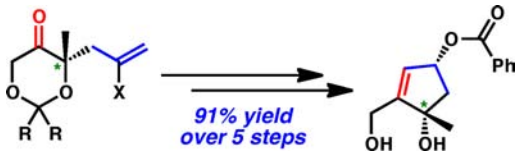
ABSTRACT



A brief, enantioselective synthesis of a hydroxymethyl-*cis*-1,3-cyclopentenediol building block is presented. This scaffold allows access to the *cis*-1,3-cyclopentanediol fragments found in a variety of biologically active natural and non-natural products. This rapid and efficient synthesis is highlighted by the utilization of the palladium-catalyzed enantioselective allylic alkylation of dioxanone substrates to prepare tertiary alcohols.

Functionalized cyclopentanol frameworks are an important structural motif in organic chemistry. Scaffolds of this type are found in many biologically active natural products,[1] pharmaceuticals,[2] and nucleoside analogs.[3] In particular, *cis*-1,3-cyclopentanediols (**1**) have been extensively employed in the synthesis of medicinally relevant natural and non-natural compounds.[3,4] For example, the biologically active prostaglandin (e.g., **2** and **3**),[2,5] furanocembranoid diterpene (e.g., **4** and **5**), and norcembranoid diterpene families of natural products (e.g., **6** and **7**)[1d,6] all contain the *cis*-1,3-cyclopentanediol motif (Figure 1).

Typically, enantioenriched carbocycles of this type have been accessed by kinetic enzymatic[7] or classical[8] resolutions. The utility of *cis*-1,3-cyclopentanediols which contain a tertiary alcohol is severely limited due to the challenges associated with the stereocontrolled formation of such chiral centers. Literature examples of the asymmetric synthesis of this moiety are limited to substrate-controlled diastereoselective alkylation[4b] or asymmetric oxidation of prochiral substrates.[9] To the best of our knowledge, the enantioselective synthesis of the *cis*-1,3-cyclopentanediol scaffold has not been accomplished through asymmetric

(1) For selected examples, see: (a) Herdewijn, P.; Balzarini, J.; De Clercq, E.; Vanderhaeghe, H. *J. Med. Chem.* **1985**, *28*, 1385–1386. (b) King, S. B.; Ganem, B. *J. Am. Chem. Soc.* **1991**, *113*, 5089–5090. (c) Ono, M.; Nishimura, K.; Tsubouchi, H.; Nagaoka, Y.; Tomioka, K. *J. Org. Chem.* **2001**, *66*, 8199–8203. (d) Kamel, H. N.; Slattery, M. *Pharm. Biol.* **2005**, *43*, 253–269.

(2) Collins, P. W.; Djuric, S. W. *Chem. Rev.* **1993**, *93*, 1533–1564.

(3) (a) Perigaud, C.; Gosselin, G.; Imbach, J. L. *Nucleosides Nucleotides* **1992**, *11*, 903–945. (b) Boyer, S. J.; Leahy, J. W. *J. Org. Chem.* **1997**, *62*, 3976–3980.

(4) (a) Bisacchi, G. S.; Chao, S. T.; Bachard, C.; Daris, J. P.; Innaimo, S.; Jacobs, G. A.; Kocy, O.; Lapointe, P.; Martel, A.; Merchant, Z. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 127–132. (b) Tsuna, K.; Noguchi, N.; Nakada, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 9452–9455.

(5) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675–5677.

(6) (a) Roethle, P. A.; Trauner, D. *Nat. Prod. Rep.* **2008**, *25*, 298–317. (b) Li, Y.; Pattenden, G. *Nat. Prod. Rep.* **2011**, *28*, 1269–1310.

(7) (a) Nakashima, H.; Sato, M.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2000**, *41*, 2639–2642. (b) Audran, G.; Acherar, S.; Monti, H. *Eur. J. Org. Chem.* **2003**, 92–98.

(8) Corey, E. J.; Schaaf, T. K.; Huber, W.; Koelliker, U.; Weinshenker, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 397–398.

(9) Niidu, A.; Paju, A.; Eek, M.; Müürisepp, A.-M.; Pehk, T.; Lopp, M. *Tetrahedron: Asymmetry* **2006**, *17*, 2678–2683.

(10) (a) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045. (b) McFadden, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 7738–7739. (c) Mohr, J. T.; Stoltz, B. M. *Chem.—Asian J.* **2007**, *2*, 1476–1491. (d) Enquist, J. A., Jr.; Stoltz, B. M. *Nature* **2008**, *453*, 1228–1231. (e) Day, J. J.; McFadden, R. M.; Virgil, S. C.; Kolding, H.; Alleva, J. L.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 6814–6818.

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alkylation. As such, in concert with our research program dedicated to the development and application of the palladium-catalyzed asymmetric allylic alkylation,[10] we developed an efficient and general route for the enantioselective synthesis of *cis*-1,3-cyclopentanediol building block **1**.

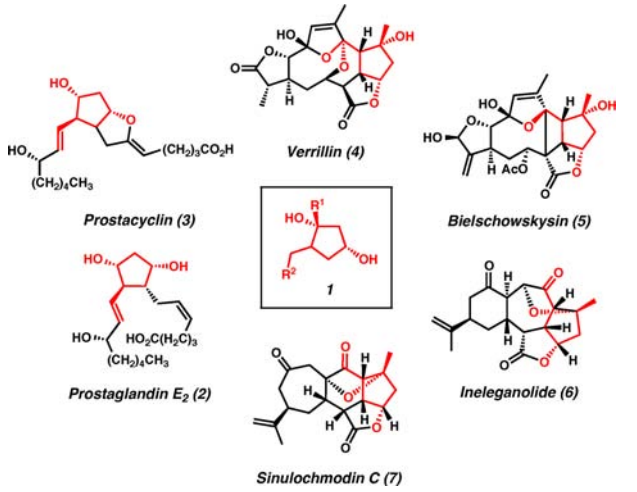
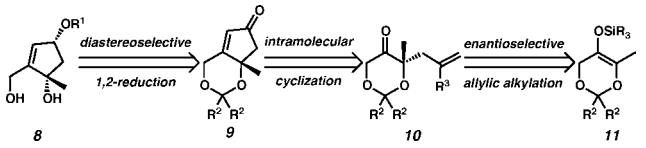


Figure 1. Representative natural products that possess a *cis*-1,3-cyclopentanediol scaffold.

We envisioned that our asymmetric catalytic preparation of a *cis*-1,3-cyclopentanediol core (**1**) with additional functional handles would serve as an enabling technology for various total synthetic efforts. Specifically, we targeted diol **8**, which can be synthesized from cyclopentenone **9** following diastereoselective reduction and ketal cleavage (Scheme 1). Intramolecular cyclization of dioxanone **10** would afford cyclopentenone **9**. In turn, chiral dioxanone **10** would be prepared by palladium-catalyzed asymmetric allylic alkylation of silyl enol ether **11**.

Our synthetic approach to *cis*-1,3-cyclopentenediol **8** was inspired by our previous report of the synthesis of related enone **14** (Scheme 2a).[10a,b,e] The palladium-catalyzed asymmetric alkylation of enol ether **12** afforded allyl ketone **13** in 95% yield with 87% ee. Wacker oxidation of the allyl fragment to the intermediate methyl ketone followed by intramolecular aldol condensation generated cyclopentenone **14** in 73% yield over two steps from allylic alkylation product **13**.

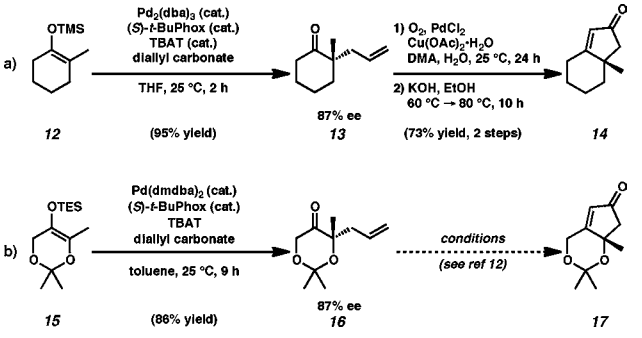
Scheme 1. Retrosynthetic Analysis of Hydroxymethyl-*cis*-1,3-cyclopentenediol **8**



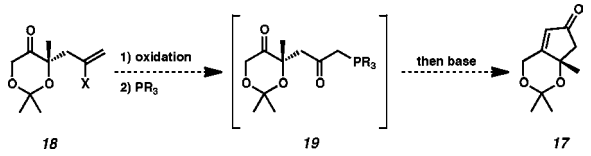
Similarly, dimethyl ketal **15** was converted to chiral ketal **16** in 86% yield and 87% ee through the enantioselective allylic alkylation procedure developed by our group (Scheme 2b).[11] However, employment of the sequential Wacker oxidation–intramolecular aldol cyclization conditions was found to be ineffective in preparing cyclopentenone ketal **17**. Despite extensive exploration of alternative conditions for this transformation, formation of enone **17** was never observed.[12]

Faced with this challenge, we envisioned the preparation of cyclopentenone **17** by an intramolecular Wittig cyclization (Scheme 3).[13] The introduction of an oxidized allyl fragment during the alkylation event to generate ketone **18** could facilitate the olefinic oxidation. Subsequent nucleophilic substitution with a phosphine would generate Wittig precursor **19**. Exposure to basic conditions could generate the phosphonium ylide, thus enabling an intramolecular Wittig cyclization to form cyclopentenone **17**.

Scheme 2. Enantioselective Allylic Alkylation and Elaboration of Cyclohexanone and Dioxanone Substrates [TBAT = $Bu_4NPh_3SiF_2$, DMA = *N*,*N*-Dimethylacetamide]



Scheme 3. Construction of Cyclopentenone **17** Using an Intramolecular Wittig Cyclizaton



To explore this pathway, we began with chloroallylketone **20** which was prepared by palladium-catalyzed asymmetric allylic alkylation in 59% yield and 92% ee

(11) Seto, M.; Roizen, J. L.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6873–6876.

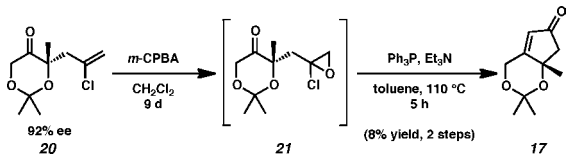
(12) A variety of conditions were found to be ineffective in the formation of desired product **17** including: KOH/xylenes/110 °C, NaH/110 °C, $Ba(OH)_2 \cdot 8H_2O$/water/methoxyethanol, LDA/THF/−78 °C, NaO*t*-Bu/HO*t*-Bu, KF/18-crown-6/xylenes, TMSOTf/EtN(*i*-Pr)$_2$/0 °C then TBAF.

(13) (a) Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **1980**, *102*, 5699–5700. (b) VanBrunt, M. P.; Ambenge, R. O.; Weinreb, S. M. *J. Org. Chem.* **2003**, *68*, 3323–3326.

(14) The specific procedure for the conversion of silyl enol ether **15** to chloroallylketone **20** with the associated characterization data has been reported by our group; see ref 11.

by a known procedure (Scheme 4).[14] Epoxidation of ketone **20** with *m*-CPBA generated intermediate epoxide **21**. Nucleophilic epoxide opening then formed the α-phosphinoketone in situ, enabling the construction of enone **17** by intramolecular Wittig cyclization. Although the yield for the two-step sequence was low and varied unpredictably, the desired cyclopentenone **17** could be isolated in small quantities.

Scheme 4. Construction of Enone **17** by Epoxidation of Chloroallylketone **20**

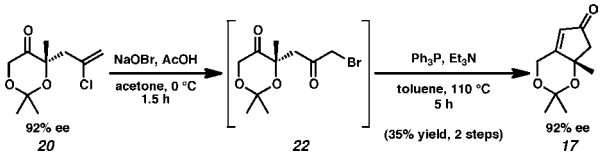


Having accomplished the proof of principle, we turned our attention to optimization. Despite the fact that a variety of epoxidation conditions had been screened,[15] the synthesis of intermediate **21** proved difficult and remained low yielding. The Wittig cyclization had similar constraints, furnishing cyclopentenone **17** in variable, unsatisfactory yields.

In spite of this failed optimization, we remained inspired by the successful isolation of the desired enone **17**. As an alternative, we decided to explore the synthesis of other Wittig cyclization precursors. One appealing option was to target intermediate α-bromoketone **22** (Scheme 5).[13] Oxidative bromination of vinyl chloride **20** with NaOBr in AcOH resulted in the formation of intermediate bromide **22**. In situ displacement of the bromide by triphenylphosphine and subsequent intramolecular Wittig cyclization furnished cyclopentenone **17** with no erosion of enantiomeric excess, albeit in comparably unpredictable yields.

Synthetic advancement of dioxanone **20** through α-bromoketone **22** was plagued by vast inconsistencies, and optimization proved difficult. The two-step sequence offered a range of yields from 0% to 82%. A variety of oxidative bromination conditions were attempted,[15] yet consistent yields could not be achieved. Importantly, when intermediate **22** was successfully formed,[16] conversion to cyclopentenone **17** could be reproducibly accomplished with moderate success, indicating that the oxidative bromination was the problematic step in the sequence.

Scheme 5. Construction of Enone **17** by Oxidative Bromination of Chloroallylketone **20**

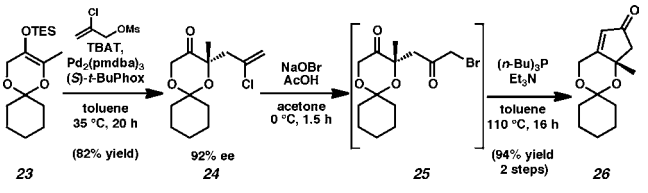


Upon closer inspection of the oxidative α-bromination procedure, we identified two possible sources of inconsistency. First, we suspected that exposure of substrate **20** and intermediate **22** to acetic acid was causing the ketal cleavage of both compounds throughout the reaction, resulting in decomposition. Direct observation of this hypothesis was challenging, as the cleavage of the dimethyl ketal simply generated additional quantities of the reaction solvent, acetone. An additional source of variability arose as the scale of the reaction was increased. Over the lengthy time course of addition on a greater scale (2 h), the NaOBr solution decomposes, lowering the reaction yield in the process.

In order to address these concerns, we first sought to alter the ketal. The introduction of additional steric bulk was hypothesized to impart additional stability to the protecting group and thus its tolerance to the oxidative bromination conditions. Gratifyingly, the selection of the cyclohexyl ketal proved to have no deleterious effects on the asymmetric allylic alkylation of enol ether **23** (Scheme 6).[17] Under optimized conditions,[18] chloroallylketone **24** was generated in a greatly improved 82% yield and duplicated 92% ee in comparison to the dimethyl ketal allylic alkylation product **20**.

Attempts to convert cyclohexyl ketal **24** to α-bromoketone **25** were met with consistent results and complete conversion could be reliably accomplished under optimized conditions,[19] affording bromide **25** in nearly quantitative yield.[20] As such, α-bromoketone was immediately advanced as a crude oil to cyclopentenone **26**. Application of standard conditions for this transformation afforded enone **26**, albeit in 35–40% yield.[21] Modification of these conditions, including the use of $(n\text{-Bu})_3P$, enabled the conversion of bromide **25** to the desired cyclopentenone **26** in 94% yield over two steps from chloroallylketone **24**.

Scheme 6. Synthetic Route Enabled by the Crucial Choice of the Cyclohexyl Ketal Group



With the establishment of a scalable, reliable route for the production of cyclopentenone **26**, we sought to advance toward the desired *cis*-1,3-cyclopentenediol **8**. Diastereoselective 1,2-reduction of enone **26** with diisobutylaluminum

(15) For full details and optimized procedure, see Supporting Information.

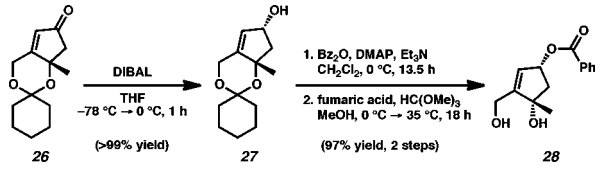
(16) Determined by ^{1}H NMR studies of the crude mixture.

(17) For details concerning the synthesis of silyl enol ether **23**, see Supporting Information.

(18) Optimized conditions for the transformation of silyl enol ether **23** to chloroallylketone **24** are displayed in Scheme 6. For full details, see Supporting Information.

(19) The decomposition of NaOBr was avoided by accomplishing the addition with a plastic syringe, without suspending the reagent over the reaction headspace. For full details, see Supporting Informaton.

Scheme 7. Synthetic Advancement toward the Desired Hydroxymethyl-*cis*-1,3-cyclopentenediol Framework



hydride (DIBAL) cleanly furnished allylic alcohol **27** in excellent yield as a single diastereomer (Scheme 7).[22] Sequential benzoylation of alcohol **27** and fumaric acid mediated ketal cleavage yielded protected alcohol **28**, a surrogate for the targeted cyclopentene **8**. This three-step transformation from cyclopentenone **26** not only provided *cis*-1,3-cyclopentenediol building block **28** in 97% yield but also proved to be scalable, allowing access the desired product in gram quantities.[23]

In summary, we have disclosed a highly efficient and scalable route for the construction of a *cis*-1,3-cyclopentenediol building block, enabling access to the *cis*-1,3-cyclopentanediol framework found in a variety of natural products and natural product analogs. The enantioselective palladium-catalyzed allylic alkylation has been used effectively to generate the desired chiral tertiary alcohol stereocenter. Judicious choice of the ketal protecting group allowed for successful optimization of the diastereoselective formation of the *cis*-1,3-diol framework, generating diol **28** in 91% yield over five steps from allylic alkylation product **24**. Efforts are currently underway to employ this building block in the synthesis of members of the norcembranoid diterpene family of natural products.

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Supporting Information Available. Experimental details and NMR spectra of all intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

(20) This transformation has been performed on scales up to 1.40 g of starting material **24**. For full details, see Supporting Information.

(21) See Scheme 5. Also, see ref 13.

(22) Only one diastereomer is observed as a product. The stereochemistry of the reduction has been confirmed by NOE studies of alcohol **27** after benzoylation. See Supporting Information.

(23) This transformation has been performed on scales up to 3.30 g of starting material **26**. For full details, see Supporting Information.

The authors declare no competing financial interest.