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Common-Intermediate Strategy for Synthesis of Conduritols and Inositols via β-Hydroxy Cyclohexenylsilanes

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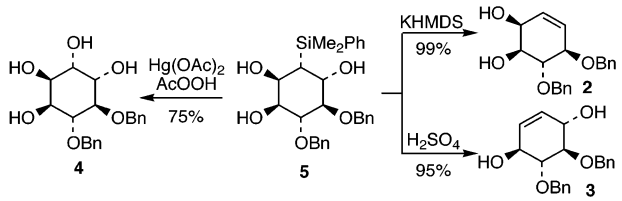
ABSTRACT



Syntheses of conduritols B–D and F and D-(+)-*chiro*- and *neo*-inositols from cyclohexenylsilane intermediates are described. The key cyclohexylsilane intermediates 5 and 14 were synthesized by stereoselective olefin dihydroxylation of the corresponding cyclohexenylsilanes. Selective Peterson elimination reactions and Fleming–Tamao oxidations of 5 and 14 then delivered the targeted cyclitol derivatives.

The conduritols[1] and the inositols[2] belong to a large and important family of natural products known as the cyclitols. Conduritol A analogues act as insulin modulators,[3] and conduritol epoxides and aminoconduritols act as glycosidase inhibitors;[4] cyclophellitols are potent inhibitors of human immunodeficiency virus (HIV) and glycosidases.[5] A number of conduritol derivatives also possess antifeedant, antibiotic, antileukemic, and growth-regulating activity.[1a] The inositols and their phosphate derivatives possess an interesting array of biological activities.[2b,6,7] In particular, D-*myo*-inositol-1,4,5-trisphosphate [Ins(1,4,5)P_3, (**1**)] is a second messenger in the intracellular signal transduction pathway that regulates the release of calcium ions in pancreatic acinar cells.[8]

Six stereoisomers are possible in the conduritol family. Two members of this group are *meso* compounds (A and D), while the remaining four are *d,l*-diastereomers (B, C, E, and F) (Figure 1). Among these, conduritols A and F are the only naturally occurring members. The inositols are 1,2,3,4,5,6-cyclohexanehexols and can exist as nine stereo-

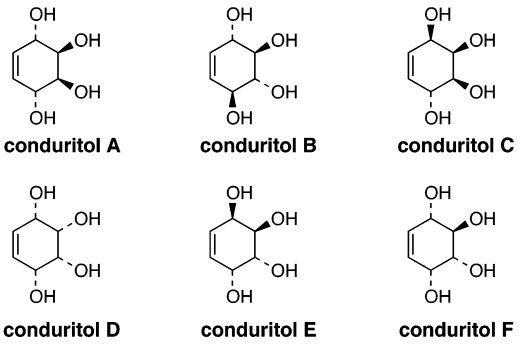


Figure 1. Conduritols A−F.

(1) (a) Balci, M. *Pure Appl. Chem.* **1997**, *69*, 97 and references therein. (b) For a recent review on the synthesis of conduritols and inositols, see: Hudlicky, T.; Entwistle, D. A.; Pitzer, K. K.; Thorpe, A. J. *Chem. Rev.* **1996**, *96*, 1195. (c) Balci, M.; Sütbeyaz, Y.; Seçen, H. *Tetrahedron* **1990**, *46*, 3715.

(2) (a) Odom, A. R.; Stahlberg, A.; Wente, S. R.; York, J. D. *Science* **2000**, *287*, 2026. (b) Potter, B. V. L.; Lampe, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1933 and references cited therein. (c) Berridge, M. J. *Nature* **1993**, *361*, 315.

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(5) (a) Atsumi, S.; Iinuma, H.; Nosaka, C.; Umezawa, K. *J. Antibiot.* **1990**, *43*, 1579. (b) Atsumi, S.; Umezawa, K.; Iinuma, H.; Naganawa, H.; Nakamura, H.; Iitaka, Y.; Takeuchi, T. *J. Antibiot.* **1990**, *43*, 49.

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isomers: *myo*, *scyllo*, *cis*, D-(+)-*chiro*, L-(−)*chiro*, *epi*, *allo*, *muco*, and *neo* inositols (Figure 2). Among this group, the *myo* (the most abundant), *scyllo*, *cis*, D-(+)-*chiro*, and L-(−)-*chiro*-inositols are naturally occurring.

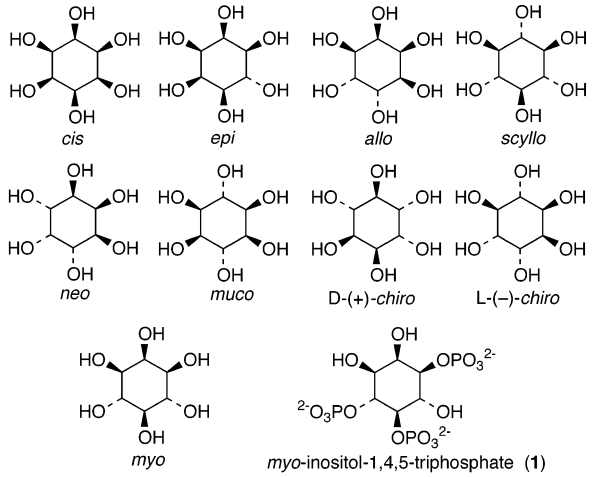


Figure 2. Inositols and Ins(1,4,5)P_3.

Considerable effort has been devoted toward the synthesis of all of the conduritol and inositol stereoisomers.[1a,9] Recently, syntheses of optically pure conduritols have been developed starting from sugars[10] and tartrate derivatives,[11] by sequences involving ring-closing metathesis (RCM) reactions. The use of chemical[12] or enzymatic[13] resolution of racemic conduritols or their precursors has also provided access to enantiomerically pure cyclitol derivatives.

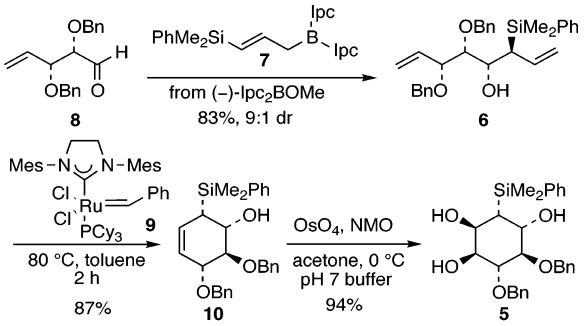
Various approaches for the synthesis of inositols and their phosphate derivatives have been developed, including the use of commercially available inositols[14c−e,h,15] and sugars,[10e,14a] microbial oxidation of arenes,[14f] and hydrogenation of tetrahydroxyquinone.[14g] Landais has synthesized several cyclitol derivatives via the desymmetrization of cyclohexadienylsilanes.[14b] Continued exploration of the structure−activity relationships of inositol phosphates and their biomacromolecule targets has fueled an ongoing interest in the development of efficient syntheses of these compounds.[2b,15]

In the preceding paper,[16] we described a strategy for synthesis of enantiomerically pure cyclohexenylsilanes via a stereoselective aldehyde γ-silylallylboration followed by a RCM reaction sequence. Here we report the application of this procedure to the synthesis of highly functionalized cyclohexenylsilanes that serve as intermediates in the synthesis of several conduritols (B, C, E, and F) and inositols (D-(+)-*chiro* and *neo*).

An important feature of our strategy was the recognition that members of the conduritol or inositol family could be synthesized from cyclohexenylsilane intermediates by simple trifurcation of the synthetic sequence. As illustrated in Figure 3, conduritols F and B and D-(+)-*chiro*-inositol can be accessed from β-hydroxy cyclohexylsilane **5**. The two stereochemically distinct β-hydroxy silane units in **5** are substrates for regioselectively distinct Peterson elimination reactions,[17] while the silyl group can serve as a hydroxyl surrogate via Fleming−Tamao oxidation.[18] β-Hydroxy cyclohexylsilane **5** would derive from diene **6** via RCM followed by a catalytic olefin dihydroxylation reaction. We anticipated that diene **6**, in turn, would be prepared by stereoselective γ-allylboration of aldehyde **8**[16] with chiral γ-silylallylborane **7**.[19] In addition, we recognized that conduritols C and E and *neo*-inositol could be accessed by an analogous sequence simply by employing the enantiomeric silylallylborating reagent, *ent*-**7**, in the allylboration of **8**.

Treatment of (*E*)-γ-silylallylborane **7** with aldehyde **8**[16] gave hydroxysilane **6** in 83% yield with 9:1 diastereoselectivity (Scheme 1). Subsequent RCM of **6** using Grubbs' catalyst **9**[20] provided cyclohexenylsilane **10**, which was subjected to catalytic dihydroxylation conditions[21] to provide trihydroxysilane **5** as a single isomer in 94% yield. As expected, the dihydroxylation reaction proceeded in an anti manner to both the allylic dimethylphenylsilyl and benzyloxy substituents.

Scheme 1



(7) (a) Hanck, T.; Stricker, R.; Krishna, U. M.; Falck, J. R.; Chang, Y. T.; Chung S. K.; Reiser, G. *Eur. J. Biochem.* **1999**, *261*, 577. (b) Chung, S. K.; Shin, B. G.; Chang, Y. T.; Suh, B. C.; Kim, K. T. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 659.

(8) For a review, see: Berridge, M. J.; Irvine, R. F. *Nature* **1989**, *341*, 197.

(9) For recent examples, see: (a) de Sousa, S. E.; O'Brien, P.; Pilgram, C. D. *Tetrahedron* **2002**, *58*, 4643. (b) Kadota, K.; Takeuchi, M.; Taniguchi, T.; Ogawawara, K. *Org. Lett.* **2001**, *3*, 1769. (c) Ceré, V.; Mantovani, G.; Peri, F.; Pollicino, S.; Ricci, A. *Tetrahedron* **2000**, *56*, 1225. (d) Ley, S. V.; Parra, M.; Redgrave, A. J.; Sternfeld, F. *Tetrahedron* **1990**, *46*, 4995.

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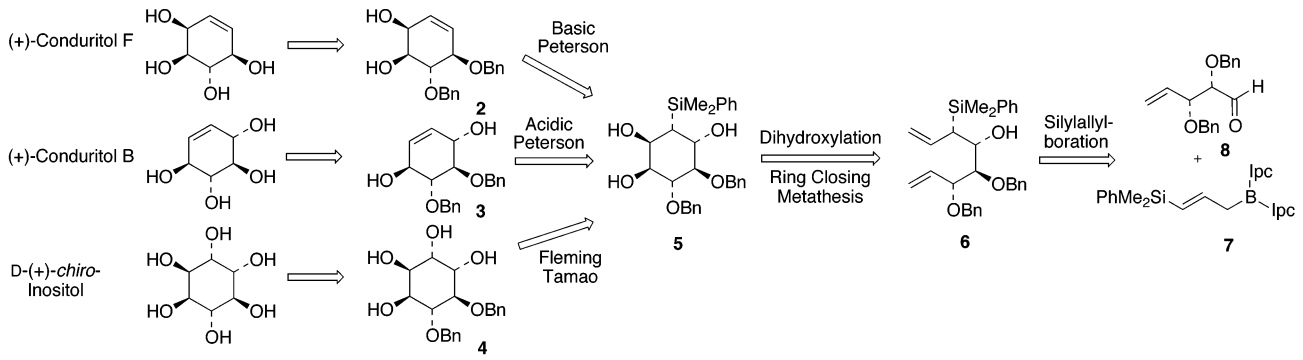
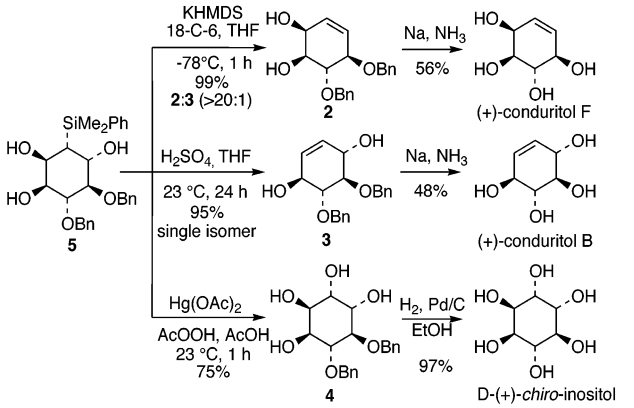


Figure 3. Retrosynthetic Analysis.

Treatment of **5** with KHMDS at −78 °C in the presence of 18-crown-6 provided the conduritol F derivative **2**[22] via Peterson elimination of the *cis*-hydroxysilane with high selectivity (>20:1 dr) (Scheme 2). We had anticipated that

Scheme 2



the base-promoted Peterson elimination reaction would proceed via a concerted reaction mechanism[23] and that cyclic β-hydroxy silanes such as **5** would undergo syn elimination with excellent stereoselectivity. However, subjection of **5** to a variety of basic reaction conditions afforded a mixture of elimination products **2** and **3**.[24] The base-promoted Peterson elimination of the *trans*-β-hydroxysilane unit in **5** (leading to **3**) must occur via a stepwise pathway.[23]

On the other hand, treatment of **5** with sulfuric acid furnished conduritol B derivative **3** as the sole product via Peterson elimination of the *trans*-hydroxysilane. Removal of the benzyl ether protecting groups in **2** and **3** under dissolving metal conditions[25] provided conduritols F and B, respectively.[26] Hydroxysilane **5** was also converted to D-(+)-*chiro*-inositol via Fleming−Tamao oxidation followed by hydrogenolytic debenzylation of tetrol **4**.

To extend this strategy to the synthesis of conduritols C and E and *neo*-inositol, we targeted the diastereomeric β-hydroxy cyclohexylsilane **14** as a key intermediate. Silylallylboration of aldehyde **8** with *ent*-**7**, prepared from (+)-Ipc$_2$BOMe, afforded the β-hydroxyallylsilane diastereomers **6** and **11** as a 1:1 mixture (Scheme 3).[27] After separation of the two products by column chromatography, RCM cyclization of **11** provided cyclohexene **12** in 87% yield. Treatment

(14) For recent examples, see: (a) Takahashi, H.; Kittaka, H.; Ikegami, S. *J. Org. Chem.* **2001**, *66*, 2705. (b) Angleaud, R.; Babot, O.; Charvat, T.; Landais, Y. *J. Org. Chem.* **1999**, *64*, 9613. (c) Riley, A. M.; Jenkins, D. J.; Potter, B. V. L. *Carbohydr. Res.* **1998**, *314*, 277. (d) Husson, C.; Odier, L.; Vottéro, P. J. A. *Carbohydr. Res.* **1998**, *307*, 163. (e) Gigg, J.; Gigg, R. *Carbohydr. Res.* **1997**, *299*, 77. (f) Desjardins, M.; Brammer, L. E., Jr.; Hudlicky, T. *Carbohydr. Res.* **1997**, *304*, 39. (g) Angyal, S. J.; Odier, L.; Tate, M. E. *Carbohydr. Res.* **1995**, *266*, 143. (h) Bruzik, K. S.; Tsai, M.-D. *J. Am. Chem. Soc.* **1992**, *114*, 6361.

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(21) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *23*, 1973.

(22) Compound **2** constitutes a formal synthesis of D-*myo*-inositol-1,4,5-triphosphate **1** (Figure 2) and was in agreement with reported spectral data; see ref 9d.

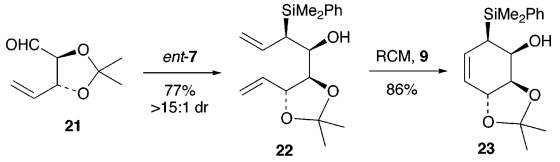
(23) Staden, L. F.; Gravestock, D.; Ager, D. J. *Chem. Soc. Rev.* **2002**, *31*, 195 and references cited therein.

(24) (a) KH, THF, 0 °C, 8 h; 80% (**2**:**3** = 16:1). (b) KHMDS, THF, −78 °C, 6 h; 50−88% (**2**:**3** = 6−20:1). (c) KO^{t}Bu, THF, 0 °C, 2 h; 33% (**2**:**3** = 6:1). (d) KO^{t}Bu, 18-C-6, THF, 0 °C, 1 h; 58% (**2**:**3** = 16:1).

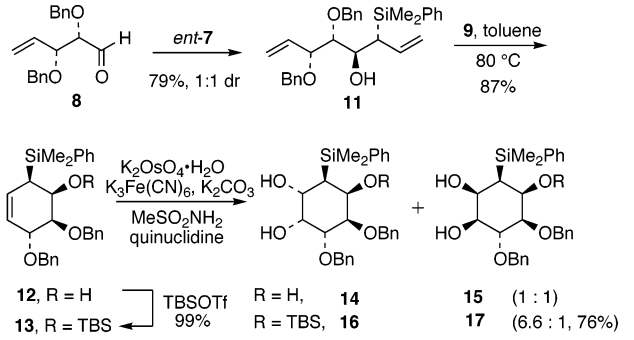
(25) Sulikowski, M. M.; Ellis Davies, G. E. R.; Smith, A. B., III. *J. Chem. Soc., Perkin Trans. 1* **1992**, 979.

(26) All known compounds exhibited acceptable ^{1}H NMR, ^{13}C NMR, optical rotation, and HRMS compared to literature values.

(27) Diastereoselectivity of silylallylboration en route to the stereotetrad in **11** has been improved by using the acetonide-protected aldehyde **21** (cf. **8**), which gave β-hydroxyallylsilane **22** with >15:1 dr. Compound **22** readily underwent RCM to provide cyclohexene **23** in good yield. Further elaboration of **23** to cyclitol derivatives will be reported in our subsequent papers in this series.



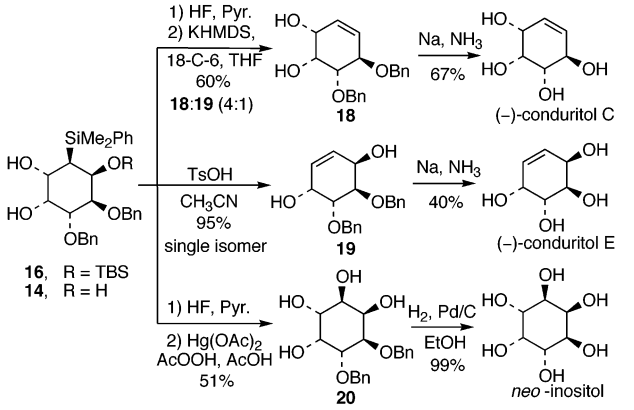
Scheme 3



of **12** under a variety of dihydroxylation conditions[28] failed to provide **14** with acceptable levels of diastereoselectivity. Consequently, we protected the free hydroxyl group of **12** as the *tert*-butyldimethylsilyl ether to block the β-face. Silyl ether **13** was then subjected to catalytic olefin dihydroxylation conditions[29] to provide hydroxysilanes **16** and **17** with good selectivity (6.6:1 dr).

Treatment of **16** with HF-pyridine gave the corresponding alcohol **14** in 70% yield along with small amounts of the elimination product **19** (<10%) (Scheme 4). Subsequent

Scheme 4



Peterson elimination of **14** under the basic conditions developed previously (KHMDS, 18-C-6, THF, −78 °C) for the conversion of **5** to **2** provided a 4:1 mixture of **18** and **19**. Purification of **18** using HPLC followed by removal of the benzyl protecting groups under dissolving metal conditions provided conduritol C.[26]

The surprising formation of **19** from **14** under basic conditions again strongly implicates a stepwise mechanism for the base-promoted Peterson elimination reaction.[23] However, at present, the factors that influence the partition between the base-promoted syn and anti elimination pathways are uncertain. Studies probing the unexpected lack of stereoselectivity in these elimination reactions are in progress and will be reported separately.

For the synthesis of conduritol E, concomitant removal of the TBS protecting group and acidic Peterson elimination occurred when **16** was treated with TsOH/CH_3CN. This provided **19** as a single isomer in 95% yield. Subsequent removal of the benzyl protecting groups afforded conduritol E. Finally, subjection of **14** to Fleming−Tamao oxidation and hydrogenolysis of **20** provided *neo*-inositol in good overall yield.

In summary, we have synthesized a variety of cyclitol derivatives in a highly divergent manner utilizing cyclohexenylsilanes as common intermediates. The unique reactivity of the silane moiety permitted trifurcation of the synthetic sequence such that the three cyclitols were accessed from a single cyclohexenylsilane intermediate. Further applications of cyclohexenylsilanes in organic synthesis will be reported in due course.

Acknowledgment. We thank the National Institutes of Health (GM 38907) for financial support.

Supporting Information Available: Experimental procedures and spectral data for compounds **2**−**6** and **10**−**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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