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Chemical synthesis of optically active *cis*-cyclohexa-3,5-diene-1,2-diols and their 5-^{2}H-derivatives

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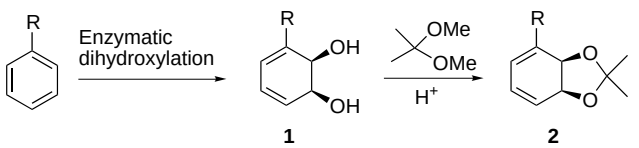
Abstract—A variety of optically active 3-substituted *cis*-cyclohexane-3,5-dien-1,2-diol acetonides were readily prepared from chiral 5-(*tert*-butyldimethylsilyloxy)-2-cyclohexenone through a seven-step reaction in good overall yield. The synthesis also allowed preparation of the acetonide having an ^{2}H-atom at the 5-position.

Enzymatic dihydroxylation of mono-substituted benzenes affords an efficient and practical method for preparing optically active cyclohexadienediols of the type **1** (Scheme 1). The compounds **1** and their hydroxy-protected derivatives, especially their acetonide **2**, have been widely utilized as starting material for synthesizing biologically active compounds, including natural products.[1] The methodology, however, with very few exceptions, allows production of only one enantiomer of **1**, and thus that of **2**, with the absolute stereochemistry shown in Scheme 1. We have now succeeded in developing an efficient and practical chemical synthesis of both enantiomers of **2**.[2]

We have recently introduced optically active 5-(*tert*-butyldimethylsilyloxy)-2-cyclohexenone (**3**) as a versatile chiral building block for synthesizing optically active cyclohexane derivatives.[3] The compound **3** was synthesized from commercially available, optically active ethyl 3-hydroxy-4-chlorobutyrate (**4**) via ethyl 3-(*tert*-butyldimethylsilyloxy)-5-hexenoate (**5**) by a six-step reaction sequence in 51% overall yield as shown in Scheme 2 (via path a).



Scheme 1.

After the development of this synthesis, we investigated another approach to **5** starting from optically active epichlorohydrin (**6**), because **6** is commercially available at lower price in comparison with **4** and the enantiomeric excess (ee) of the commercially available **6** is somewhat higher than that of **4**.[4] As shown in path b in Scheme 2, the preparation of **5** from **6** can be readily carried out by the conventional reaction sequence. Thus, **6** was treated with vinylmagnesium bromide in the presence of a catalytic amount of CuCN in THF to afford 1-chloropent-4-en-2-ol, the chlorine of which was replaced by CN by reaction with potassium cyanide in methanol, and the resulting cyanohydrin was converted to **5** by acidic ethanolysis of the cyano group and the following silylation of the hydroxy group. The olefinic ester **5**, the ee of which was determined to be more than 98%, was conclusively prepared from **6** by a four-step reaction in 77% overall yield; thus, eventually, **3** was prepared from **6** by a seven-step reaction in 52% overall yield. As all the reagents used in either method for synthesizing **3** from **4** or **6** shown in Scheme 2 are readily available and inexpensive, and the reaction procedures are operationally simple, **3** can be easily prepared in quantity.

As a part of our continuing study to apply **3** as a chiral building block in asymmetric synthesis,[3] we have now found that a variety of optically active cyclohexadienediol acetonide **2** can be readily prepared from **3**. Although we used **3** with (*S*)-configuration in the present synthesis, as its antipode (*R*)-**3** is similarly

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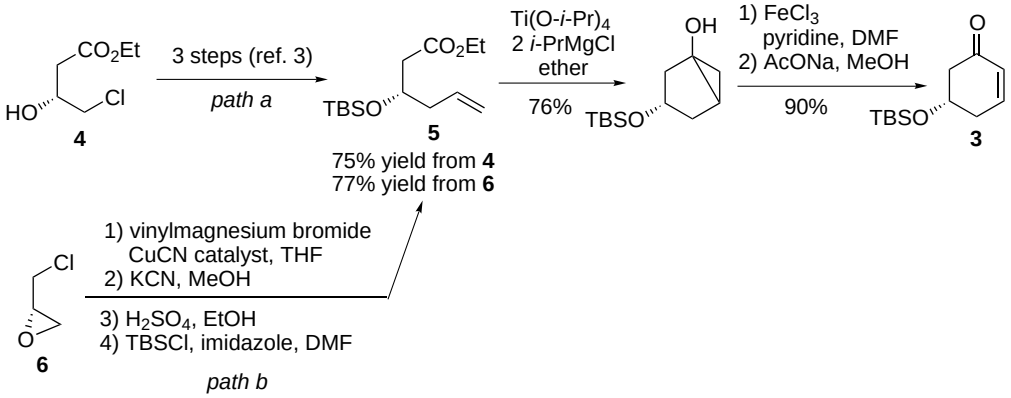


Scheme 2.

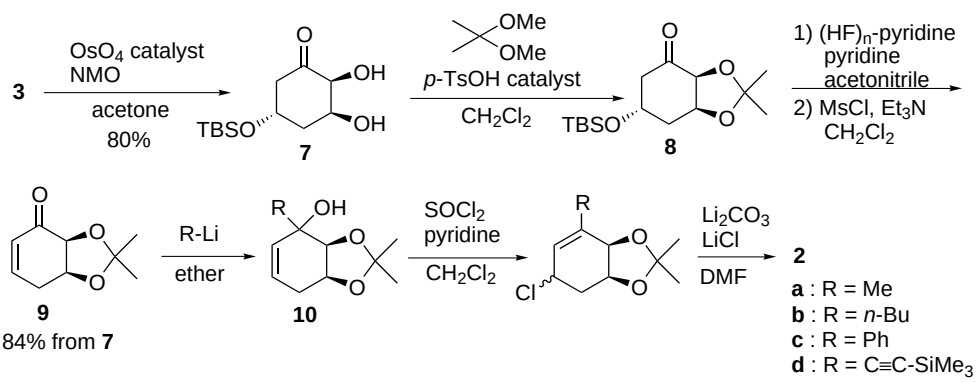
preparable because both enantiomers of **4** and **6** are, respectively, commercially available, the present method allows access to both enantiomers of **2**.

The preparation of **2** from **3** was carried out according to the procedure shown in Scheme 3. Thus, the dihydroxylation of **3** with catalytic osmium tetraoxide–NMO gave **7** exclusively in 80% yield as previously reported,[3e] which in turn was converted quantitatively to the acetonide **8**, and the crude of which was used for the next reaction. Desilylation of **8** with $(HF)_n$-pyridine and the following mesylation of the resulting hydroxy group with MsCl and Et_3N was accompanied with β-elimination to furnish enone **9**[5] in 84% overall yield from **7**, thus, eventually, in 67% yield from **3**. From **9**, substituted cyclohexadienediol acetonides **2a–d** could be prepared by a three-step reaction which involves 1,2-addition of the corresponding organolithium reagent to **9**, migrative chlorination of the resulting **10** with thionyl chloride, and the following elimination reaction using Li_2CO_3/LiCl[6] as a base. The yield of **2** from **9** and their $[\alpha]_D$ values are summarized in Table 1. In conclusion, a variety of optically active acetonides **2a–d** were prepared in 41, 47, 50, or 43% overall yield from **3**, respectively.[7,8] It is worth mentioning here that, at first, we were anxious about the successful conversion of **10** to **2** because further elimination of the resulting **2** to the corresponding phenol derivative was easily conceivable. Actually, the direct dehydration of **10** to **2** was unsuccessful. For example, treatment of **10** with *p*-TsOH catalyst or with Tf_2O/DBU gave a complicated mixture including the phenol derivative(s). Finally, to our delight, we were able to find the conditions enabling the conversion of **10** to **2** by the two-step procedure shown in Scheme 3; under these conditions, phenol derivative(s) was produced in less than 2% yield, if any.

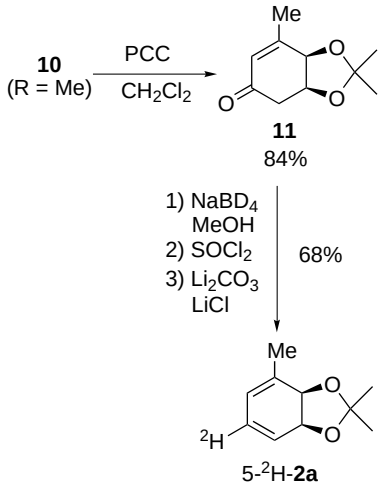
As many biologically important compounds have been prepared by using **2** as a starting material,[1] we next attempted to prepare **2** labeled with ^2H, which eventually allows access to those biologically important compounds labeled with ^2H. The preparation of **2** with ^2H at the 5-position was easily carried out as exemplified by the synthesis 5-^{2}H-**2a** as shown in Scheme 4. Thus,

Table 1.

2	R	Yield from 9 (%)	$[\alpha]_D$ Value
2a[7,9]	Me	62	$[\alpha]_D^{29}$ +93 (*c* 0.27, MeOH) lit.[7a] $[\alpha]_D^{29}$ +93.7 (*c* 2.98, MeOH)
2b	*n*-Bu	70	$[\alpha]_D^{26}$ +101 (*c* 0.50, $CHCl_3$)
2c[7]	Ph	75	$[\alpha]_D^{26}$ +204 (*c* 0.12, $CHCl_3$)
2d	$Me_3Si{\cdot}C{\equiv}C$	64	$[\alpha]_{28}^{D}$ +131 (*c* 0.32, $CHCl_3$)



Scheme 3.



Scheme 4.

PCC-oxidation of **10** (R = Me), derived from **9** and MeLi, afforded ketone **11** in 84% yield. The reduction of **11** with $NaBD_4$ and the successive treatment of the product with thionyl chloride and $LiCO_3$/LiCl afforded the acetonide of 3-methyl-5-deutero-cyclohexa-3,5-dien-1,2-diol (5-^{2}H-**2a**) with more than 93% of deuterium incorporation[10] in 68% overall yield.

Acknowledgements

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4. Compounds **4** with 97% ee and **6** with >98% ee are commercially available from Aldrich.
5. $[\alpha]_D$ of **9** was $[\alpha]_D^{26}$ +101 (*c* 0.22, $CHCl_3$) and the ee was found to be 97% by GC analysis with the use of a chiral column (Chirasil-DEX CB, 0.25 mm×25 m, Chrompack). Landais et al. reported the preparation of non-racemic **9** with $[\alpha]_D^{25}$ +76.3 (*c* 0.94, $CHCl_3$) from chlorodimethylphenylsilane in 38% yield through a five-step reaction, which involves the Sharpless asymmetric dihydroxylation of 3-(hydroxydimethylsilyl)-1,4-cyclohexadiene: Angelaud, R.; Babot, O.; Charvat, T.; Landais, Y. *J. Org. Chem.* **1999**, *64*, 9613–9624.
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7. Spectral data of **2a** and **2c** thus prepared were in good agreement with those reported. For **2a**, see: (a) Hudlicky, T.; Luna, H.; Barbieri, G.; Kwart, L. D. *J. Am. Chem. Soc.* **1998**, *120*, 4735–4741. For **2c**, see: (b) Gibson, D. T.; Roberts, R. L.; Wells, M. C.; Kobal, V. M. *Biochem. Biophys. Res. Commun.* **1973**, *50*, 211–219.
8. Compound **2b**: ^{1}H NMR δ 5.98 (dd, J = 5.7, 9.6 Hz, 1H), 5.78 (dd, J = 3.9, 9.6 Hz, 1H), 5.71 (d, J = 5.7 Hz, 1H), 4.65 (dd, J = 3.9, 8.7 Hz, 1H), 4.53 (d, J = 8.7 Hz, 1H), 2.14-2.31 (m, 2H), 1.25–1.58 (m, 4H), 1.39 and 1.41 (2s, each 3H), 0.92 (t, J = 7.5 Hz, 3H); ^{13}C NMR δ 138.7, 124.8, 122.3, 118.0, 105.2, 73.5, 71.3, 33.3, 29.4, 27.0, 25.2, 22.6, 14.1; IR (neat) 2958, 2878, 1603, 1458, 1369, 1258, 1048, 868, 804 cm^{-1}. Anal. calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.22; H, 9.67%. Compound **2d**: ^{1}H NMR δ 6.35 (d, J = 5.7 Hz, 1H), 6.01 (dd, J = 5.7, 9.6 Hz, 1H), 5.92 (dd, J = 3.3, 9.6 Hz, 1), 4.71 (dd, J = 3.3, 8.1 Hz, 1H), 4.54 (d, J = 8.1 Hz, 1H), 1.43 and 1.42 (2s, each 3H), 0.10 (s, 9H); ^{13}C NMR δ 130.6, 126.9, 123.3, 119.7, 105.9, 104.2, 98.8, 72.3, 71.4, 26.9, 25.3, 0.10; IR (neat) 2960, 2142, 1379, 1250, 1034, 844 cm^{-1}. Anal. calcd for $C_{14}H_{20}O_2Si$: C, 67.70; H, 8.12. Found: C, 67.38; H, 8.49%.
9. Comparison of the $[\alpha]_D$ value of **2a** thus prepared with the reported one indicates that no racemization occurred during conversion of **9** to **2**.
10. Determined by ^{1}H NMR analysis.