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# Highly Enantio- and Diastereo-selective Synthesis of $C_2$-Symmetric 3,5-Cyclohexadiene-1,2-diol and $D_2$-Symmetric Cyclohexane-1,2,4,5-tetrol

**Hiroshi Suemune,[a,] * Atsushi Hasegawa[a] and Kiyoshi Sakai[b,] ***

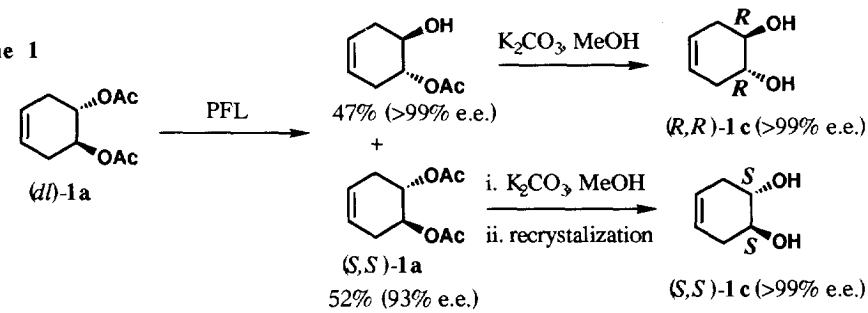
[a] Faculty of Pharmaceutical Sciences, Kyushu University, Fukuoka 812, Japan

[b] Kyushu Women's University, Kitakyushu 807, Japan

**Abstract:** Highly enantio- and diastereo-selective synthesis of $C_2$-symmetric 3,5-cyclohexadiene-1,2-diol **5** and $D_2$-symmetric cyclohexane-1,2,4,5-tetrol related compounds **7a,b, 10, 11** has been achieved using optically active 4-cyclohexene-1,2-diol (*S,S*)-**1c** prepared by an enzymatic procedure.

Previously, we reported that *Pseudomonas fluorescens* lipase (PFL) is effective for the highly enantioselective hydrolysis of (*dl*)-1,2-diacetoxy-4-cyclohexene (*dl*)-**1a** to afford (1*R*,2*R*)-monoacetate of >99% e.e. (47% yield) and (*S,S*)-**1a** of 93% e.e. (52% yield).[1] Both products were easily converted to enantiomerically pure diols (*R,R*)- and (*S,S*)-**1c** (Scheme 1). Thus, the obtained optically active **1c** was considered to be a versatile synthetic intermediate for various six-membered oxy-functionalized compounds.

**Scheme 1**




In this report, we wish to describe highly enantio- and diastereo-selective syntheses of $C_2$-symmetric (*S,S*)-3,5-cyclohexadiene-1,2-diol **5** and $D_2$-symmetric (*S,S,S,S*)-cyclohexane-1,2,4,5-tetrol **11**, and related compounds **7a,b**, **10** starting from (*S,S*)-**1c**. Enantiomers of these compounds have also been synthesized in the same manner starting from (*R,R*)-**1c**.

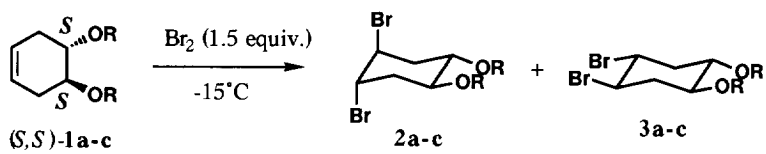
### Synthesis of (*S,S*)-3,5-cyclohexadiene-1,2-diol

Compound (*dl*)-**5**, which was prepared by Platt *et al.*[2] from cyclohexa-1,4-diene, had been used for the synthesis of highly functionalized cyclohexane derivatives such as inosamine, fortamine and conduritols in racemic form.[3] In these syntheses, the key process was the hetero Diels-Alder reaction between the diene system

in (*dl*)-**5** and N=O, N=N, O=O systems, respectively. Preparation of **5** in enantiomerically pure form[4] might expand the usefulness of this compound for asymmetric synthesis.

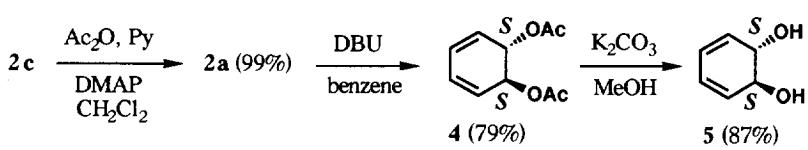
Easy access to cyclohexadiene derivatives from cyclohexenes might be accomplished by addition of bromine and subsequent elimination of hydrogen bromide. At first, diastereoselectivity of addition of bromine was studied by using (*S,S*)-**1a-c** (Scheme 2). Reaction of (*S,S*)-**1a,b** with bromine (1.5 equiv.) in $CCl_4$ at -15°C afforded an inseparable mixture of **2a,b** and **3a,b** in 87-90% yields with low diastereoselectivity. In contrast to the above results, reaction of (*S,S*)-**1c** under similar conditions afforded **2c** (95%) in a completely diastereoselective manner.[5] Compound **2c** was converted to **2a** (99%) by usual acetylation procedures. Subsequent elimination of hydrogen bromide proceeded by treatment with DBU (2.5 equiv.) in benzene at room temperature to afford the desired **4** (79%).[6] Deacetylation of **4** by treatment with $K_2CO_3$/MeOH afforded the corresponding diol **5** in 87% yield (Scheme 3).

**Scheme 2**




| Substrate | R | Solvent | Yield (2+3) | D.r. (2 : 3) |
|---|---|---|---|---|
| **1a** | Ac | $CCl_4$ | 87% | 66 : 34 |
| **1b** | TBDMS | $CCl_4$ | 90% | 63 : 37 |
| **1c** | H | $CHCl_3$ | 95% | 100 : 0 |

**Scheme 3**



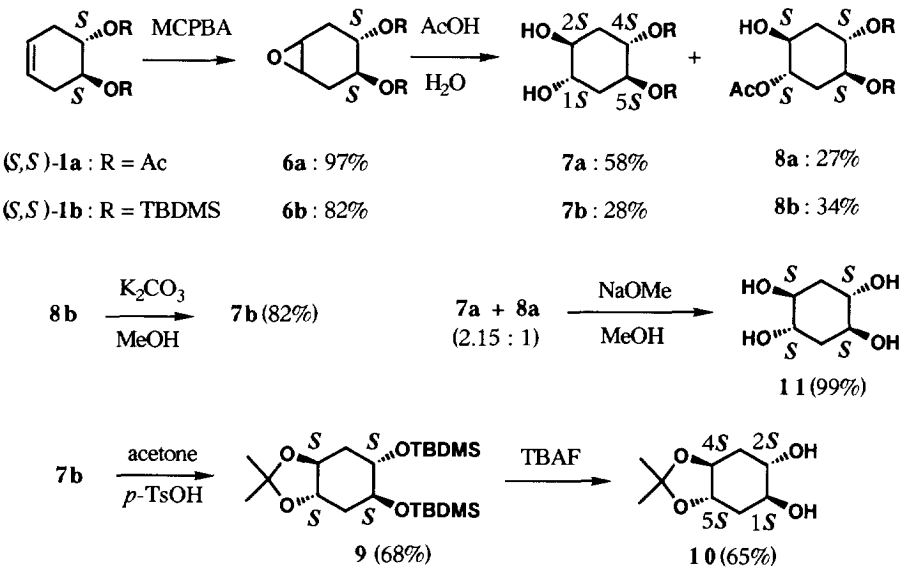

**Synthesis of *D2*-symmetric cyclohexanetetrol and related compounds**

(*S,S,S,S*)-Cyclohexane-1,2,4,5-tetrol **11** had been isolated from sugar beet molasses in 1966 by Ramanathan *et al.* and its absolute configuration had been assigned by CD.[7] We made note of the *D2*-symmetric structure of **11**. Since compound **11** had two *C2*-axes, symmetric protection of two hydroxy groups (1,2-*O*-protection or 1,5-*O*-protection) might afford two types of *C2*-symmetric diols. In the case of 1,2-*O*-protection of **11**, selection of the protecting group might fix the conformation of the remaining diols as *trans*-diequatorial or *trans*-diaxial. As a basic study for development of a novel asymmetric reaction using these conformationally fixed compounds as chiral ligand or chiral auxiliary, enantio- and diastereo-selective synthesis of **7a,b** and **10** including **11** has been investigated (Scheme 4).

Epoxidation of *C2*-symmetric (*S,S*)-**1a,b** with MCPBA gave **6a,b** in 97 and 82% yields, respectively. Diastereoselective epoxy ring opening of **6** was performed by treatment with AcOH/$H_2O$ (4:1) to afford **7a,b** and **8a,b**. Compound **8b** was easily converted to **7b** (82%) by treatment with $K_2CO_3$/MeOH at room temperature. Stereochemistry of **7a** was determined by the $^1$H-NMR spectrum, in which C(4 and 5)-H were

observed at δ 5.02 (Wh 7.4 Hz) and C(1 and 2)-H at δ 3.77 (Wh 15.5 Hz). These observations suggested that 4,5-diacetates occupied *trans*-diaxial orientation and 1,2-diols *trans*-diequatorial orientation based on chair conformation of the cyclohexane skeleton. Similarly, $^1$H-NMR spectrum of **8b** showed that the acetate and hydroxy groups have *trans*-diequatorial orientation and bis-TBDMS ether *trans*-diaxial orientation.[8]

**Scheme 4**




Synthesis of acetonide derivative **10** by a similar sequence of reactions (i. acetonide formation of (*S,S*)-**1c**; ii. epoxy ring opening) did not give satisfactory results, because the corresponding acetonides derived from (*S,S*)-**1c** and **6c** (R=H) were so volatile that their isolated yields were low. Compound **10** was synthesized from **7b** *via* **9** by usual acetonide formation (68%) and subsequent deprotection of TBDMS ether (65%). Conformational analysis of **10** was performed based on $^1$H-NMR spectrum. The C(4 and 5)-H (δ 3.69, Wh 15.8 Hz) were fixed as *trans*-diaxial because of stereochemical requirement, and the dihydroxy groups on C(1 and 2) consequently had *trans*-diaxial orientation ((C1 and 2)-H: δ 3.95, Wh 4.5 Hz).

(*S,S,S,S*)-Cyclohexane-1,2,4,5-tetrol **11** was synthesized by solvolysis of a mixture of **7a** and **8a** (2 : 1) in 99% yield. The specific rotation value ($[\alpha]_D^{22}$ +18.9 (*c* 1.5, $H_2O$)) of **11** synthetically reconfirmed the absolute configuration of natural **11** ($[\alpha]_D^{21}$ +22.5 (*c* 1.06, $H_2O$))[7] to be *S,S,S,S*.

Further studies for synthetic application of enantiomerically pure **5** and for asymmetric reactions using **7a,b** and **10** as chiral ligands are currently under way.

## References and Notes

1. a) Suemune, H.; Hizuka, M.; Kamashita, T.; Sakai, K. *Chem. Pharm. Bull.*, **1989**, 37, 1379. "Amano lipase P" (PFL) had been renamed "Amano lipase PS" (*Pseudomonas cepacia*).
2. Platt, K. L.; Oesch, F. *Synthesis*, **1977**, 449.
3. a) Kresze, G.; Dittel, W. *Liebigs Ann. Chem.*, **1981**, 610; b) Kuo, C. H.; Wendler, N. L. *Tetrahedron Lett.*, **1984**, *25*, 2291; c) Seçen, H.; Sübeyaz, Y.; Balci, M. *Tetrahedron Lett.*, **1990**, *31*, 1323.

4. Ganey, M. V.; Padykula, R. E.; Berchtold, G. A.; Braun, A. G. *J. Org. Chem.*, **1989**, *54*, 2787.
5. These results suggest that conformation of **1c** with hydrogen bonding, in which diols have *psuedo*-equatorial orientation, is highly stabilized.
6. Elimination of hydrogen bromide of **2c** with DBU gave a complex mixture, and that of **3a** did not proceed at all.
7. Ramanathan, J. D.; Craigie, J. S.; McLchlan, J.; Smith, D. G.; McInnes, A. G. *Tetrahedron Lett.*, **1966**, *14*, 1527.

8. **Selected Spectroscopic Data**

**(*S,S*)-4-Cyclohexene-1,2-diol** (*S,S*)-(**1c**): Colorless needles, mp 100-102°C (AcOEt), $[\alpha]_D^{25}$ +143.5 (*c* 1.2, $CHCl_3$).[1a]

**(1*S*,2*S*,4*S*,5*S*)-4,5-Dibromocyclohexane-1,2-diol (2c)**: Colorless needles, mp 118-120°C ($CHCl_3$), $[\alpha]_D^{27}$ +54.1 (*c* 1.2, $CHCl_3$), $^1$H-NMR (270 MHz, $CD_3OD$) δ 4.60 (2H, br.s, 4,5-H), 3.82 (2H, ddd, *J* 10.9, 7.2, 3.6 Hz, 1,2-H). EIMS (*m/z*): 274 ($M^+$), 272, 195, 193, 177, 113.

**(1*S*,2*S*,4*S*,5*S*)-1,2-Diacetoxy-4,5-dibromocyclohexane (2a)**: Colorless oil, $[\alpha]_D^{27}$ +38.2 (*c* 1.3, $CHCl_3$), $^1$H-NMR (270 MHz, $CDCl_3$) δ 5.25 (2H, ddd, *J* 11.5, 7.9, 3.6 Hz, Wh 13.0 Hz, 1,2-H), 4.50 (2H, br.s, Wh 9.1 Hz, 4,5-H), 2.07 (6H, s, Ac). EIMS (*m/z*): 359 ($M^+$+1), 315, 298, 258.

**(*S,S*)-1,2-Diacetoxy-3,5-cyclohexadiene (4):** Colorless oil, $[\alpha]_D^{27}$ +464.6 (*c* 0.1, $CHCl_3$), $^1$H-NMR (270 MHz, $CDCl_3$) δ 6.08 (2H, dd, *J* 7.6, 3.0 Hz, 4,5-H), 5.85 (2H, m, 3,6-H), 5.58 (2H, dd, *J* 2.3, 1.3 Hz, 1,2-H), 2.08 (6H, s, Ac). $^{13}$C-NMR (67.8 MHz, $CDCl_3$) δ 170.2 (s), 125.7 (d), 124.8 (d), 71.2 (d), 21.0 (q). EIMS (*m/z*): 197 ($M^+$+1), 172, 130, 112.

**(*S,S*)-3,5-Cyclohexadiene-1,2-diol (5):** Colorless oil, $[\alpha]_D^{24}$ +344 (*c* 0.37, 99% EtOH), lit.[4] $[\alpha]_D^{20}$ +360 (*c* 0.036, 95% EtOH). $^1$H-NMR (270 MHz, $CDCl_3$) δ 5.90 (4H, s, olefinic H), 4.46 (2H, s, 1,2-H), 2.53 (2H, br.s, OH). $^{13}$C-NMR (67.8 MHz, $CDCl_3$) δ 130.6 (d), 124.3 (d), 74.8 (d). EIMS (*m/z*): 112 ($M^+$), 94, 83, 66.

**(1*S*,2*S*,4*S*,5*S*)-4,5-Diacetoxycyclohexane-1,2-diol (7a)**: Colorless oil, $[\alpha]_D^{26}$ +31.1 (*c* 0.8, $CHCl_3$), $^1$H-NMR (270 MHz, $CDCl_3$) δ 5.02 (2H, dt, *J* 3.9, 2.0 Hz, Wh 7.4 Hz, 4,5-H), 3.77 (2H, m, Wh 15.5 Hz, 1,2-H), 2.97 (2H, br, OH), 2.07 (6H, s, Ac). EIMS (*m/z*): 233 ($M^+$+1), 215, 189, 172, 154, 144.

**(1*S*,2*S*,4*S*,5*S*)-4,5-Bis(*tert*-butyldimethylsiloxy)cyclohexane-1,2-diol (7b)**: Colorless needles, mp. 156-158°C (hexane), $[\alpha]_D^{24}$ +11.3 (*c* 1.2, $CHCl_3$), $^1$H-NMR (270 MHz, $CDCl_3$) δ 3.70-3.77 (4H, m, 1,2,4,5-H), 2.04 (2H, br.s, OH). EIMS (*m/z*): 377 ($M^+$+1), 359, 280. $^1$H-NMR of diacetate of **7b** (270 MHz, $CDCl_3$) δ 5.16 (2H, m, Wh 17.0 Hz, 1,2-H), 3.73 (2H, br.s, Wh 6.1 Hz, 4,5-H), 2.01 (6H, s, Ac). $^1$H-NMR of **8b** (270 MHz, $CDCl_3$) δ 4.94 (1H, ddd, *J* 11.2, 9.6, 4.9 Hz, Wh 25.0 Hz, 1-H), 3.91 (1H, m, Wh 22.0 Hz, 2-H), 3.72 (2H, br.s, Wh 6.7 Hz, 4,5-H), 2.09 (3H, s, Ac).

**(1*S*,2*S*,4*S*,5*S*)-4,5-(2,2-Propanedioxy)cyclohexane-1,2-diol (10)**: Colorless solids, mp. 130-133°C, $[\alpha]_D^{24}$ +25.9 (*c* 1.0, MeOH), $^1$H-NMR (270 MHz, $CD_3OD$) δ 3.95 (2H, dd, *J* 4.0, 1.7 Hz, Wh 4.5 Hz, 1,2-H), 3.69 (2H, m, Wh 15.8 Hz, 4,5-H), 2.10 (2H, m, 3,6-eq-H), 1.84 (2H, m, 3,6-ax-H), 1.38 (6H, s, Me). FDMS (*m/z*): 189 ($M^+$+1), 173, 130.

**(*S,S,S,S*)-1,2,4,5-cyclohexanetetrol (11)**: Colorless powder, mp. 206-208°C (MeOH), $[\alpha]_D^{22}$ +18.9 (*c* 1.5, $H_2O$), lit.[7] $[\alpha]_D^{21}$ +22.5 (*c* 1.06, $H_2O$). $^1$H-NMR (270 MHz, DMSO-*d6*) δ 4.44 (4H, br, OH), 3.49 (4H, s, 1,2,4,5-H), 2.50 (4H, s, 3,6-H). EIMS (*m/z*): 149 ($M^+$-1), 130, 112, 73.

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