(n = 5, 6, 7) do show that stereoelectronic control is quite weak. Indeed, we have concluded above that it is so weak in the acyclic amidines of Table III that it can easily be eclipsed by other factors, such as leaving abilities.

Acknowledgment. This research was supported by the donors of The Petroleum Research Fund, administered by the American Chemical Society, and by a Venezuelan CONICIT Fellowship (to O.N.).

Enantioselective Functionalization of Prochiral Diols via Chiral Spiroketals: Preparation of Optically Pure 2-Substituted 1,3-Propanediol Derivatives and Asymmetric Synthesis of Chroman Ring and Side Chain of α-Tocopherol

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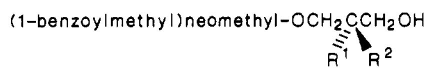
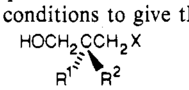
Received May 12, 1986. Revised Manuscript Received September 9, 1986

Abstract: The enantioselective functionalization of a prochiral hydroxyl group in 2-substituted 1,3-propanediols ($HOCH_2CR^1R^2CH_2OH$) is presented. The reaction of the bis(trimethylsilyl) derivative of the diol with *l*-menthone in the presence of trimethylsilyl trifluoromethanesulfonate selectively gave one of the diastereomers of the spiroketal in which the larger substituent (R^1) occupies an equatorial position. The equatorial spiroketal was treated with acetophenone enol trimethylsilyl ether in the presence of titanium tetrachloride to give the ring-cleavage product



which was produced by the selective cleavage of the equatorial C–O bond. After a proper functionalization of the hydroxyl group, the chiral auxiliary was removed under basic conditions to give the optically pure (>95% ee) derivatives **5**.



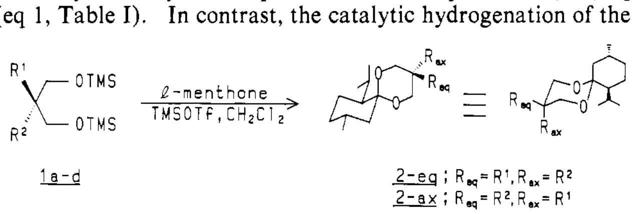
5
(X = OTHP, $OCPh_3$, SPh)

The stereoselective preparation of the axial spiroketal (R^1 = H, R^2 = Me) and its ring-cleavage are also described. The potentiality of the present method is demonstrated in an asymmetric synthesis of (2*R*,6*R*)-2,6,10-trimethylundecanol and (*S*)-6-benzyloxy-3,4-dihydro-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-methanol which are key intermediates in the total synthesis of naturally ocurring (2*R*,4′*R*,8′*R*)-α-tocopherol.

The enantioselective differentiation of a prochiral functional group in a symmetric difunctional compound is one of the efficient methods for creating new chiral centers. While this type of asymmetric synthesis is commonly observed in enzymatic transformations, examples of the chemical transformation are rare.[1] We report here a novel enantioselective functionalization of 2-substituted 1,3-propanediols (Scheme I)[2-4] utilizing a highly stereoselective ring-cleavage reaction of chiral spiroketals **2**.

Results and Discussion

A treatment of a bis(trimethylsilyl) ether **1a–c** and *l*-menthone with a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf) in dichloromethane at −85 °C[5] gave selectively the thermodynamically stable equatorial isomer of spiroketal **2(a–c)-eq** (eq 1, Table I). In contrast, the catalytic hydrogenation of the



(1)

Scheme I

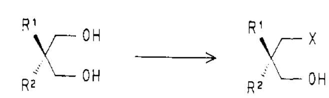
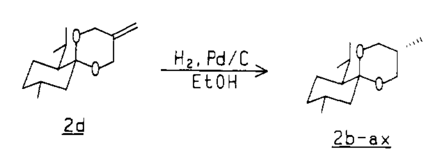


Table I. Preparation of Chiral Spiroketal

entry	starting material	products	yield (**2-eq**:**2-ax**)
1	**1a**: R^1 = Ph, R^2 = H	**2a-eq**, **2a-ax**	90% (17:1)
2	**1b**: R^1 = Me, R^2 = H	**2b-eq**, **2b-ax**	91% (5.7:1)
3	**1c**: R^1 = Ph, R^2 = Me	**2c-eq**, **2c-ax**	90% (2.6:1)
4	**1d**: R^1, R^2 = CH_2	**2d**	60%

exo methylene analogue **2d**, which was prepared by the same ketalization procedure as above, afforded the axial isomer of **2b** selectively (**2b-ax**:**2b-eq** = 20:1, 82%) (eq 2). Interestingly,



(2)

hydroboration of **2d** with 9-borabicyclo[3.3.1]nonane (9-BBN) proceeded with an opposite stereoselectivity, and after the protection of the hydroxyl group as a benzyl ether, **2e-eq** was obtained selectively (**2e-eq**:**2e-ax** = 14:1, 88% overall yield) (eq 3). It must be noted here that **2-eq** and **2-ax** can be readily separated by a flash or medium-pressure silica gel column chromatography, and

(1) For leading references see: Fuji, K.; Node, M.; Terada, S.; Murata, M.; Nagasawa, H.; Taga, T.; Machida, K. *J. Am. Chem. Soc.* **1985**, *107*, 6404.
(2) Fukuyama, T.; Wang, C.-L. J.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 260.
(3) (a) Mukaiyama, T.; Tanabe, Y.; Shimizu, M. *Chem. Lett.* **1984**, 401. (b) Ichikawa, J.; Asami, M.; Mukaiyama, T. *Ibid.* **1984**, 949.
(4) Schreiber, S. L.; Wang, Z. *J. Am. Chem. Soc.* **1985**, *107*, 5303.
(5) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.

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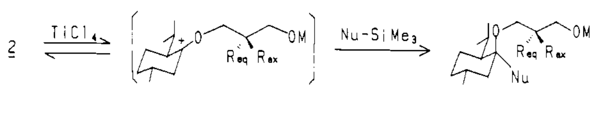
Table II. Ring-Cleavage Reaction of Spiroketal **2** and Transformation to **5** (X = OTHP or $OCPh_3$)

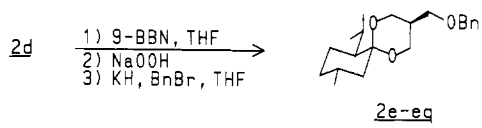
	starting material			ring-cleavage reaction		transformation to 5	
entry	2	R_{eq}	R_{ax}	product	yield (de)[a]	product	yield (ee)[d]
1	**2a-eq**	Ph	H	**3a**	94% (>95%)	**5a** (X = OTHP)[b]	77% (99%)
2	**2a-ax**	H	Ph	**3b**	73% (>95%)	**5b** (X = OTHP)[b]	76% (96%)
3	**2b-eq**	Me	H	**3c**	82% (>95%)	**5c** (X = $OCPh_3$)[c]	81% (>98%)
4	**2b-ax**	H	Me	**3d**	81% (>95%)	**5d** (X = $OCPh_3$)[c]	78% (95%)
5	**2c-eq**	Ph	Me	**3e**	96% (>95%)	**5e** (X = OTHP)[b]	75% (>98%)
6	**2c-ax**	Me	Ph	**3f**	86% (>95%)	**5f** (X = OTHP)[b]	78% (>98%)
7	**2e-eq**	$BnOCH_2$	H	**3g**	67% (>95%)		

[a] Determined by 200-MHz ^{1}H NMR measurement. [b] The transformation to **5** (X = OTHP) was carried out as follows: (1) DHP, PTS, CH_2Cl_2, room temperature, (2) $(Me_3Si)_2NK$, THF, −85 °C to a room temperature, or *t*-BuOK, *t*-BuOH, 60 °C. ^{1}H NMR spectra of the corresponding MTPA esters were measured after removal of the THP group. [c] **5** (X = $OCPh_3$) was prepared as follows: (1) Ph_3CCl, Et_3N, DMAP, CH_2Cl_2, room temperature, (2) *t*-BuOK, *t*-BuOH, 60 °C. [d] Determined by the 200-MHz ^{1}H NMR analysis of the corresponding MTPA ester.

Scheme II

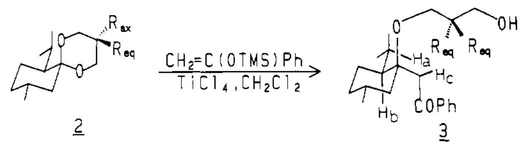


their stereochemistry was unambiguously established on the basis of the analysis by 200-MHz ^{1}H NMR spectra.



(3)

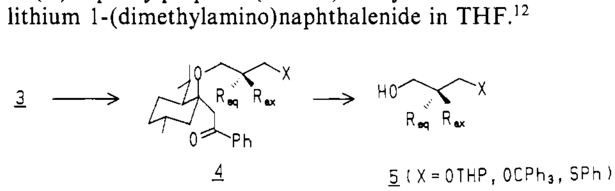
Titanium tetrachloride promoted ring-cleavage[6,7] of the spiroketal **2** by acetophenone enol trimethylsilyl ether (CH_2Cl_2, at −85 °C) proceeded with a remarkably high stereoselectivity to give the monoprotected propanediol **3**, the only one of the four possible isomers (eq 4, Table II). The stereochemical bias of the ring-cleavage reaction was not affected by the difference in equatorial/axial stereochemistry of the spiroketal **2**: for example, epimeric **3a** and **3b** were selectively formed in the reaction of **2a-eq** and **2a-ax**, respectively.



(4)

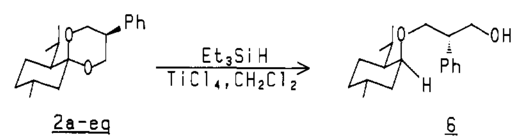
The stereochemistry of **3** at C(1) of the neomenthyl moiety was determined on the basis of the following observations. In the ^{1}H NMR spectra of **3a** and **3b**, small values of the coupling constant (1.1 and 1.2 Hz, respectively) between the isopropyl methine proton (H_a) and the vicinal ring proton (H_b) were observed, and irradiation of H_a caused the NOE enhancement (7.2% and 8.0%, respectively) of one of the methylene protons α to benzoyl group (H_c). These observations are expected only in the conformers of **3a** and **3b** as depicted in eq 4.

After a proper protection or functionalization of the hydroxyl group of **3a–f**, the (1-benzoylmethyl)neomenthyl group was readily removed under basic conditions to give optically pure **5a–f** (X = OTHP, $OCPh_3$, SPh) in high yield (eq 5, Table II). For example, mesylation of **3a** followed by treatment with sodium benzenethiolate in THF–EtOH and the subsequent removal of the chiral moiety in refluxing aq KOH in THF–MeOH gave sulfide alcohol **5a** (X = SPh) in 80% overall yield. The absolute stereochemistry of **5a** (X = SPh) was determined after converting **5a** (X = SPh) to (*R*)-2-phenylpropanol (96% ee)[8-10] by the desulfurization with lithium 1-(dimethylamino)naphthalenide in THF.[12]



(5)

We should explain the origin of the present high stereoselectivity in terms of the mechanism of the Lewis acid promoted ring-cleavage reaction of ketals and acetals. Recently, Johnson and co-workers have reported a highly stereoselective ring-cleavage and alkylation reaction of chiral cyclic acetals promoted by titanium tetrachloride, and they proposed a mechanism in which the attack of nucleophiles proceeds with inversion of configuration.[6b] In contrast, the present reaction of spiroketal **2** proceeds unambiguously with the selective cleavage of the equatorial C–O bond followed by the attack of a nucleophile with retention of configuration (Scheme II).[13] Moreover, reaction of **2a-eq** with Et_3SiH in the presence of titanium tetrachloride in CH_2Cl_2 at −85 °C also proceeded with the same stereoselectivity to give **6** (94% yield, >95% de) (eq 6). The axial stereochemistry of **6** was determined by the ^{1}H NMR signal (δ 3.67) of the proton attached to C(1) of the neomenthyl moiety which appears as a broad singlet (W_H = ~9 Hz). The determination of the stereochemistry on the C(2) of the propanediol moiety is based on its transformation to (*R*)-2-phenylpropanol (96% ee)[11] according to the following procedures; (1) MsCl, Et_3N, CH_2Cl_2, (2) PhSNa, THF, EtOH, (3) $Li[Naph]^{•-}$, THF, (4) Ac_2O, $FeCl_3$, and (5) aq NaOH, MeOH.



(6)

The stereoselectivity observed in the present study is rationalized as follows: Coordination of titanium tetrachloride with a less hindered equatorial oxygen may be preferred and, in a similar sense, the equatorial attack of a nucleophile on the positively charged sp^2-hybridized C(1) carbon of the menthone skeleton becomes highly preferable (though not essential to the enantioselectivity of the diol).[14]

(6) (a) McNamara, J. M.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7371. (b) Bartlett, P. A.; Johnson, W. S.; Elliott, J. D. *Ibid.* **1983**, *105*, 2088. (c) Johnson, W. S.; Carckett, P. H.; Elliott, J. D.; Jagodzinsky, J. J.; Lindell, S. D.; Natarjan, S. *Tetrahedron Lett.* **1984**, *25*, 3951 and references cited therein.

(7) Mukaiyama, T. *Org. React.* **1982**, *28*, 203.

(8) $[\alpha]^{17}_D$ 17.5 (*c* 0.476, benzene). For (*S*)-(−) isomer, $[\alpha]^{19}_D$ −19 (*c* 0.83, benzene) was reported.[9]

(9) Suzuki, K.; Kitayama, E.; Matsumoto, T.; Tsuchihashi, G. *Tetrahedron Lett.* **1984**, *25*, 3715.

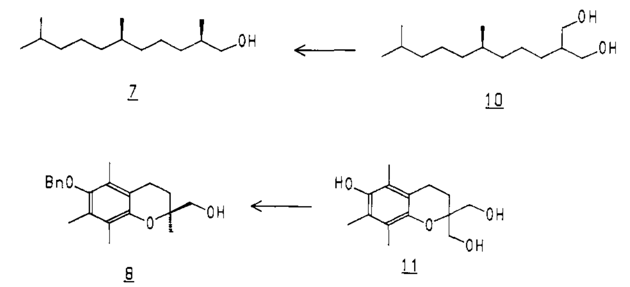
(10) The value was determined after the conversion to the corresponding (*S*)-(−)-MTPA ester.[11]

(11) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

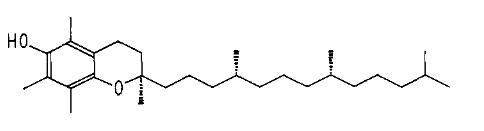
(12) Matz, J. R.; Cohen, T. *J. Am. Chem. Soc.* **1980**, *102*, 6900.

(13) Reductive cleavage of the chiral ketals derived from (2*R*,4*R*)-2,4-pentanediol with use of organoaluminum reagents has been reported to proceed with the opposite stereoselectivity to that observed by Johnson et al. Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4581.

Scheme III



The potentiality of the present enantioselective functionalization of 2-substituted 1,3-propanediols is demonstrated by the efficient asymmetric synthesis of (2*R*,6*R*)-2,6,10-trimethylundecanol (**7**) and (*S*)-6-benzyloxychroman-2-methanol (**8**) which are key intermediates in the total synthesis of naturally occurring (2*R*,4′*R*,8′*R*)-α-tocopherol (**9**).[15-17] As shown in Scheme III, our strategy is based on the enantioselective partial deoxygenation of the readily accessible 1,3-propanediol derivatives **10** and **11**.



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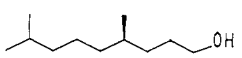
(*R*)-4,8-Dimethyl-1-nonanol (**12**) which was easily prepared from D-(+)-citronellal[18] was converted into the required diol **10** in high yields (>90%) via a three-step sequence: (1) aq HBr, H_2SO_4, (2) $NaCH(CO_2Et)_2$, MeOH, and (3) $LiAlH_4$, THF. Bis-trimethylsilylation of diol **10** ($(Me_3Si)_2NH$ (4 equiv), Me_3SiCl (cat.)) followed by the reaction with *l*-menthone in the presence



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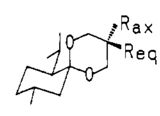
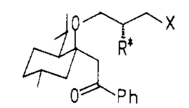


13; Req = R*, Rax = H
14; Req = H, Rax = R*
(R* = (R)-4,8-dimethyl-nonyl)

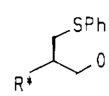
of Me_3SiOTf (10 mol %) in CH_2Cl_2 at −85 °C for 14 h gave equatorial spiroketal **13** (76%) selectively together with the minor axial isomer **14** (14%). After removing the minor isomer **14** by medium-pressure column chromatography, the spiroketal **13** was subjected to the ring-cleavage reaction, the critical stage of this synthesis. Thus, the treatment of **13** with acetophenone enol trimethylsilyl ether in the presence of titanium tetrachloride in CH_2Cl_2 at −85 °C afforded the keto alcohol **15** (93%) as the sole stereoisomer detectable by 200-MHz ^1H NMR measurement.



15; X = OH
16; X = SPh

The transformation of the enantiotropically differentiated hydroxymethyl group in **15** into a methyl group and the removal of neomenthyl moiety were achieved effectively in four steps (70% overall yield). Thus, mesylation of **15** followed by the reaction with PhSNa in THF-EtOH gave the sulfide **16** in 86% yield. The treatment of **16** with a hot aqueous KOH–MeOH–THF solution gave the sulfide alcohol **17** (87%), which finally was desulfurized by lithium naphthalenide in THF to give chiral side chain alcohol **7** ($[\alpha]^{25}_D$ 9.02 (*c* 0.665, hexane))[19] in 93% yield. The high-field (100.5-MHz) ^{13}C NMR analysis of **7** showed that the diastereomeric purity of **7** is more than 98%.[20]

The asymmetric synthesis of chroman alcohol **8** starts with trimethylhydroquinone. The reaction of the hydroquinone and acrylonitrile in the presence of $AlCl_3$ and gaseous HCl,[21] followed by the protection of the phenolic hydroxyl group by *tert*-butylchlorodimethylsilane (with imidazole in DMF), afforded chromanone **18** in 38% overall yield. **18** was allowed to react with $LiCH_2OCH(CH_3)OC_2H_5$ (4.4 equiv)[22] in THF to give the adduct **19** in 74% yield. From **19**, the expected diol **11** was prepared by a single-flask operation; the deprotection of **19** in a refluxing 2 N aqueous HCl–MeOH solution followed by the displacement of benzene for water and methanol by the azeotropic distillation and the subsequent treatment of the benzene solution with *p*-TsOH (cat.) at 80 °C, afforded diol **11** in 78% yield. It should be noted that the free phenolic hydroxyl group at the 6 position is indispensable to the successful cyclodehydration.[15b] In this regard, the attempted cyclization of the 6-benzyloxy derivative of **19** (R = H) gave a complex mixture.



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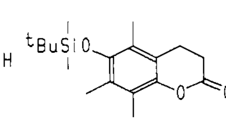

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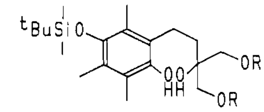
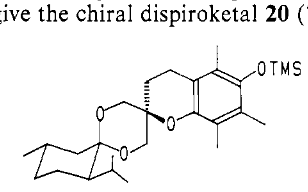


19; R = ethoxyethyl

After converting **11** to the tris(trimethylsilyl) derivative (93%), a ketalization reaction was performed employing *d*-menthone (*not l-menthone*) to give the chiral dispiroketal **20** (70%) which was



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separated from the minor isomer **21** (23%) by flash chromatography. The stereoselective ring-cleavage reaction of dispiroketal **20** was performed under the same conditions as described before to give **22** (67%) as the sole diastereomer. After converting **22**

(14) (a) Harada, T.; Nozaki, Y.; Yamaura, Y.; Oku, A. *J. Am. Chem. Soc.* **1985**, *107*, 2189. (b) Ashby, E. C.; Laemmele, J. T. *Chem. Rev.* **1975**, *75*, 521.

(15) (a) Cohen, N.; Eichel, W. F.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3505. (b) Cohen, N.; Lopresti, R. J.; Saucy, G. *J. Am. Chem. Soc.* **1979**, *101*, 6710. (c) Cohen, N.; Scott, C. G.; Neukom, C.; Lopresti, R. J.; Weber, G.; Saucy, G. *Helv. Chim. Acta* **1981**, *64*, 1158.

(16) For the previous asymmetric syntheses of side chains, see: (a) Scott, J. W.; Bizzarro, F. T.; Parrish, D. R.; Saucy, G. *Helv. Chim. Acta* **1976**, *59*, 290. (b) Schmid, M.; Barner, R. *Ibid.* **1979**, *62*, 464. (c) Leuenberger, H. G. W.; Bouguth, W.; Barner, R.; Schmid, M.; Zell, R. *Ibid.* **1979**, *62*, 454. (d) Zell, R. *Ibid.* **1979**, *62*, 474. (e) Trost, B. M.; Klun, T. P. *J. Am. Chem. Soc.* **1981**, *103*, 1864. (f) Helmchan, G.; Schmierer, R. *Tetrahedron Lett.* **1983**, *24*, 1235. (g) Koreeda, M.; Brown, L. *J. Org. Chem.* **1983**, *48*, 2122. (h) Fujiwara, J.; Fukutani, Y.; Hasegawa, M.; Maruoka, K.; Yamomoto, H. *J. Am. Chem. Soc.* **1984**, *106*, 5004. (i) Bérubé, G.; Deslongchamps, P. *Can. J. Chem.* **1984**, *62*, 1558.

(17) For the previous asymmetric syntheses of the chroman ring, see: (a) Reference 15. (b) Fuganti, C.; Grasselli, P. *J. Chem. Soc., Chem. Commun.* **1982**, 205. (c) Akkerman, J. M.; De Koning, H.; Huisman, H. O. *Heterocycles* **1981**, *15*, 797. (d) Solladie, G.; Moine, G. *J. Am. Chem. Soc.* **1984**, *106*, 6097.

(18) D-(+)-Citronellal ($[\alpha]^{24}_D$ 16.2, neat) was kindly supplied from Takasago Perfumery Co., Ltd.

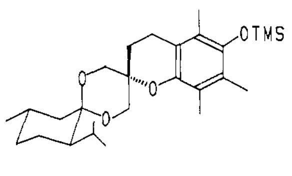
(19) Lit. $[\alpha]^{25}_D$ 9.36 (*c* 2.02, hexane).[15a]

(20) Heathcock, C. H.; Jarvi, E. T. *Tetrahedron Lett.* **1982**, *23*, 2825.

(21) Sato, K.; Amakasu, T.; Abe, S *J. Org. Chem.* **1964**, *29*, 2971.

(22) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481.

to the benzyl tetrahydropyranyl derivative **23** in two steps (84%)[23]—(1) $Bu_4N^+F^-$, BnBr, (2) DHP, PTS—menthyl moiety was removed under basic conditions to give the chiral chroman alcohol **24** in a quantitative yield. The conversion of the free hydroxymethyl group in **24** into a methyl group was achieved as follows: (1) the reaction of **24** with $P(NMe_2)_3$–CCl_4 in THF, (2) reduction of the produced oxophosphonium salts with $LiEt_3BH$, and (3) the deprotection of the THP group (PTS, MeOH).[24,25] The chiral chroman alcohol **8** was obtained in 60% yield, and the optical purity determined by the ^{1}H NMR measurement of the corresponding (*S*)-(−)-MTPA ester is >95%.[26,27]



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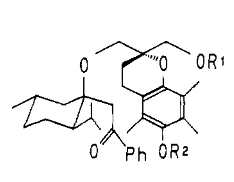
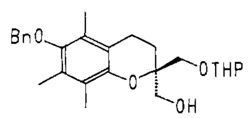


22; R1=H, R2=TMS
23; R1=THP, R2=Bn



24

In summary, we have shown some examples of the effective enantioselective differentiation of the hydroxymethyl groups in 2-substituted 1,3-propanediols. This method consisting of the selective cleavage of chiral spiroketals must be viable in asymmetric organic synthesis, and its application to the other types of prochiral diols seems to be promising.

Experimental Section

Infrared spectra were measured on a JASCO IRA-1 grating spectrophotometer. ^{1}H NMR (200 MHz) and ^{13}C NMR (100.5 MHz) spectra were obtained with Varian XL-200 and JEOL GX-400,[28] respectively. Mass spectra were measured on a Hitachi M-80 mass spectrometer. GLC analyses were performed by using an OV-101 (30 m) capillary column. Unless otherwise noted, flash chromatography was performed by using silica gel (Wakogel C-300) as an adsorbent and ethyl acetate in petroleum ether as an eluent, whose concentration is indicated in the parentheses. Medium-pressure column chromatography was performed by using a Merck Lobar column packed with 40–63 μm LiChroprep SI 60. *l*-Menthone was purchased from Norse Laboratories Inc. and used after purification by flash chromatography (1% ether/petroleum ether). *d*-Menthone was prepared by the PCC oxidation of *d*-menthol purchased from Nakarai Chemicals Co.

General Procedure for the Preparation of Spiroketal 2.[5] To a solution of bis(trimethylsilyl) ether (**1**) (5.00 mmol) and *l*-menthone (5.05 mmol) in CH_2Cl_2 (4 mL) was added trimethylsilyl trifluoromethanesulfonate (TMSOTf) (0.20 mmol) at −85 °C under a nitrogen atmosphere, and the resulting solution was stirred for 10–24 h at the same temperature. The reaction was quenched by the successive additions of pyridine (0.2 mL) and 0.5% NaOH in methanol (3 mL), and the resulting mixture was stirred at room temperature for 1 h. After addition of water followed by extraction with petroleum ether, the combined organic layer was washed twice with water, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by flash or medium-pressure column chromatography (1-2% ether/petroleum ether) to give **2-eq** and **2-ax**.

Hydrogenation of Exo Methylene Spiroketal 2d. A mixture of **2d** (128.4 mg, 0.573 mmol) and 10% Pd/C (70 mg) in 3 mL of ethanol was stirred under a hydrogen atmosphere (1 atm) at 0 °C for 24 h. After the usual workup followed by flash chromatography (2%), a 20:1 mixture of **2b-ax** and **2b-eq** (101.2 mg, 82%) was obtained. **2b-ax**: ^{1}H NMR ($CDCl_3$) δ 0.64 (1 H, dd, *J* = 13.6 and 12.8 Hz), 0.89 (3 H, d, *J* = 7.0 Hz), 0.90 (3 H, d, *J* = 6.4 Hz), 0.92 (3 H, d, *J* = 7.0 Hz), 1.09–1.56 (9 H, m, including 3 H at 1.23 (d, *J* = 7.0 Hz)), 1.69 (1 H, br d, *J* = ∼13 Hz), 2.49 (1 H, sept d, *J* = 7.0 and 1.8 Hz), 2.74 (1 H, ddd, *J* = 13.6, 3.6, and 2.6 Hz), 3.43 (1 H, dt, *J* = 12.1 and ∼2 Hz), 3.47 (1 H, dt, *J* = 11.6 and ∼2 Hz), 4.04 (1 H, dd, *J* = 12.1 and 3.3 Hz), 4.26 (1 H, dd, *J* = 11.6 and 3.2 Hz); IR (liquid film) 1170 (s), 1120 (s), 1015 (s) cm^{-1}; mass spectrum, *m/z* (relative intensity) 226 (M^+, 19), 211 (42), 169 (81), 141 (100), 69 (61), 55 (80); exact mass calcd for $C_{14}H_{26}O_2$ 226.1934, found 226.1933. **2b-eq**: ^{1}H NMR ($CDCl_3$) δ 0.64 (1 H, dd, *J* = 13.6 and 12.8 Hz), 0.68 (3 H, d, *J* = 7.0 Hz), 0.87 (3 H, d, *J* = 7.0 Hz), 0.88 (3 H, d, *J* = 7.2 Hz), 1.10–1.59 (4 H, m), 1.67 (1 H, br d, *J* = 12.8 Hz), 1.99 (1 H, m), 2.36 (1 H, sept d, *J* = 7.2 and 2.2 Hz), 2.68 (1 H, ddd, *J* = 13.8, 3.6, and 2.2 Hz), 3.39 (1 H, t, *J* = 11.6 Hz), 3.60 (1 H, t, *J* = 11.6 Hz), 3.66 (1 H, ddd, *J* = 11.6, 5.6, and 1.8 Hz), 3.70 (1 H, ddd, *J* = 11.6, 5.6, and 1.8 Hz); IR (liquid film) 1120 (s), 1080 (s), 1040 (s) cm^{-1}; mass spectrum, *m/z* (relative intensity) 226 (M^+, 30), 211 (48), 169 (90), 141 (100); exact mass calcd for $C_{14}H_{26}O_2$ 226.1934, found 226.1930.

Hydroboration of Exo Methylene Spiroketal 2d. To a solution of **2d** (101.4 mg, 0.450 mmol) in THF (0.5 mL) was added 9-BBN (2.6 mL, 0.78 M in THF, 2.0 mmol), and the mixture was heated under reflux for 4 days. After successive additions of 6 N aqueous NaOH (0.6 mL) and 30% aqueous hydrogen peroxide (1.2 mL) at 0 °C, the resulting mixture was stirred for 30 min. Aqueous workup and the purification of the residue by flash chromatography (10%) gave 102.2 mg (93%) of a mixture of stereoisomers of spiroketal **2** (R_{eq}, R_{ax} = CH_2OH, H). To a suspension of oil-free KH (0.50 mmol) in THF (0.5 mL) was added a THF (0.5 mL) solution of the spiroketal (79.5 mg, 0.329 mmol) and benzyl bromide (71 μL, 0.60 mmol) at room temperature, and the mixture was stirred for 1 h. The usual workup followed by the purification by flash chromatography (1%) gave a 14:1 mixture of **2e-eq** and **2e-ax** (104.4 mg, 95%). **2e-eq**: ^{1}H NMR (C_6D_6) δ 0.73 (1 H, dd, *J* = 13.4 and 12.6 Hz), 0.82–1.02 (4 H, m, including 3 H at 0.89 (d, *J* = 6.5 Hz)), 1.14 (3 H, d, *J* = 7.1 Hz), 1.26 (3 H, d, *J* = 7.0 Hz), 1.32–1.83 (5 H, m), 2.27 (1 H, m), 2.73 (1 H, ddd, *J* = 13.4, 3.4, and 1.8 Hz), 2.82 (2 H, d, *J* = 6.0 Hz), 2.90 (1 H, sept d, *J* = 7.0 and 2.1 Hz), 3.57 (1 H, t, *J* = 10.8 Hz), 3.83 (3 H, m), 4.18 (2 H, s), 7.18 (5 H, m); IR (liquid film) 1175 (s), 1135 (s), 750 (s), 710 (s) cm^{-1}. **2e-ax**: ^{1}H NMR ($CDCl_3$) δ 0.66 (1 H, t, *J* = 10.2 Hz), 0.81 (3 H, d, *J* = 7.0 Hz), 0.85 (3 H, d, *J* = 7.1 Hz), 0.89 (3 H, d, *J* = 6.6 Hz), 1.10–1.78 (7 H, m), 2.32 (1 H, sept d, *J* = 6.9 and 1.6 Hz), 2.79 (1 H, ddd, *J* = 14.4, 3.3, and 1.9 Hz), 3.62–3.88 (4 H, m), 4.04 (1 H, dd, *J* = 12.0 and 3.3 Hz), 4.14 (1 H, dd, *J* = 12.0 and 3.3 Hz), 4.54 (1 H, d, *J* = 11.2 Hz), 4.60 (1 H, d, *J* = 11.2 Hz), 7.32 (5 H, m); IR (liquid film) 1175 (s), 1170 (s), 1125 (s), 760 (s), 705 (s) cm^{-1}.

General Procedure for the Ring-Cleavage Reaction of Spiroketal 2. To a solution of spiroketal **2** (1 mmol) and acetophenone enol trimethylsilyl ether (1.05 mmol) in CH_2Cl_2 (30 mL) was added $TiCl_4$ (1.05 mmol, 1 M solution in CH_2Cl_2) at −85 °C, and the resulting yellow solution was stirred at the same temperature for 30–45 min. After the addition of pyridine (0.2 mL), the mixture was poured into brine and extracted twice with petroleum ether–ethyl acetate. The extract was washed with aqueous $NaHCO_3$, dried over sodium sulfate, and concentrated in vacuo to give a crude oil, from which **3** was isolated by flash chromatography.

Conversion of 3a to (*R*)-2-Phenyl-3-(phenylthio)propanol (5a: X = SPh). To a solution of **3a** (443 mg, 1.08 mmol) in 5 mL of CH_2Cl_2 was added triethylamine (0.17 mL, 1.2 mmol) and methanesulfonyl chloride (94 μL, 1.2 mmol) at 0 °C. After the mixture was stirred for 30 min, petroleum ether (50 mL) and magnesium sulfate (2 g) were added. Filtration through a cotton plug followed by the removal of solvents in vacuo gave a crude mesylate, which was dissolved in ethanol (2 mL); the solution was added at 0 °C to a THF solution (2.6 mL) of sodium phenylthiolate which was prepared from 113 mg (2.83 mmol) of NaH (60% suspension in oil) and 0.33 mL (3.2 mmol) of thiophenol, and the mixture was stirred for 15 h at room temperature. After the usual workup, the crude material was purified by flash chromatography (2.5%) to give 514 mg (95%) of **4** (R_{eq} = Ph, R_{ax} = H, X = SPh): ^{1}H NMR ($CDCl_3$) δ 0.67 (3 H, d, *J* = 7.6 Hz), 0.75 (3 H, d, *J* = 6.8 Hz), 0.86 (3 H, d, *J* = 7.6 Hz), 1.21–1.96 (9 H, m), 3.00 (1 H, d, *J* = 16.1 Hz), 3.20 (1 H, m), 3.5 (1 H, d, *J* = 16.1 Hz), 3.27 (1 H, dd, *J* = 13.0 and 8.0 Hz), 3.49 (1 H, dd, *J* = 13.0 and 6.9 Hz), 3.56–3.70 (2 H, m), 7.10–7.61 (13 H, m), 7.81 (2 H, m); IR (liquid film) 1705 (s), 1225 (s),

(23) Substitution of a benzyloxy group for the trimethylsilyloxy group was achieved in a single flask operation by this procedure. For the use of tetramethylammonium fluoride as a Lewis base in the protection of phenols, see: Miller, J. M.; So, K. H.; Clark, J. H. *Can. J. Chem.* **1979**, *57*, 1887.

(24) Simon, P.; Ziegler, C. J.; Gross, B. *Synthesis* **1979**, 951.

(25) The reactivity of **22** and **24** on their carbinyl carbon toward nucleophilic substitution is very low. Thus, $LiEt_3BH$ reduction of the tosylate of **24** mainly gave **24** with a minor formation of **8**. The mesylate of **22** was recovered in the reaction with PhSNa in THF-EtOH.

(26) Collins oxidation of **8** (79%) gave the corresponding aldehyde which shows $[\alpha]^{23}_D$ 12.3 (*c*, 0.323, $CHCl_3$). Lit. $[\alpha]^{20}_D$ 12.5 (*c* 2.8, $CHCl_3$).[17d]

(27) Racemic **8** was prepared form (±)-**24** which was obtained by the monoprotection of diol **11** followed by benzylation of the phenolic hydroxyl group.

(28) The 100.5-MHz ^{13}C NMR spectra were measured at the Fuculty of Science, Kyoto University.

1100 (s), 1080 (s), 1010 (s), 760 (s), 745 (s), 710 (s), 700 (s) cm^{-1}; mass spectrum, m/z (relative intensity) 500 (M+, 9), 482 (7), 244 (18), 227 (27), 123 (100), 105 (98); exact mass calcd for $C_{33}H_{40}SO_2$ 500.2749, found 500.2748.

To a solution of **4** (R_{eq} = Ph, R_{ax} = H, X = SPh) (254.0 mg, 0.51 mmol) in a mixed solvent of methanol (1.6 mL) and THF (3.2 mL) was added 7.5 N aqueous KOH (0.8 mL), and the mixture was heated at 55 °C for 24 h. Aqueous workup and the purification of the residue by flash chromatography (10%) gave 115.6 mg (93%) of **5a** (X = SPh): ^1H NMR ($CDCl_3$) δ 1.57 (1 H, s), 2.87–3.43 (3 H, m), 3.87 (2 H, br d, J = ~5 Hz), 7.03–7.43 (10 H, m); IR (liquid film) 3400 (br), 1040 (s), 1065 (s), 750 (s), 705 (s) cm^{-1}; mass spectrum, m/z (relative intensity) 244 (M^+, 81), 135 (23), 123 (100), 110 (32); exact mass calcd for $C_{15}H_{16}SO$ 244.0922, found 244.0925.

***(R)*-2-Phenylpropanol.** To lithium (102.1 mg, 14.8 mmol) in THF (15 mL) was added 1-(dimethylamino)naphthalene (2.4 mL, 15 mmol) at −85 °C under a nitrogen atmosphere, and the resulting dark blue mixture was slowly warmed to −35 °C. After the addition of a THF (2 mL) solution of **5a** (X = SPh) (219.2 mg, 0.90 mmol), the reaction mixture was warmed up to −20 °C over 1 h and quenched by the addition of ethanol. After the usual workup, the purification by flash chromatography (10%) gave 94.9 mg (77%) of (*R*)-2-phenylpropanol:[8,9] $[\alpha]^{17}_D$ 17.5 (*c* 0.476, benzene); ^1H NMR ($CDCl_3$) δ 1.23 (3 H, d, J = 7.2 Hz), 1.67 (1 H, br s), 2.50–3.27 (1 H, m), 3.57 (2 H, d, J = 6.2 Hz), 7.17 (5 H, m). (*R*)-2-Phenylpropyl (*S*)-α-methoxy-α-trifluoromethylphenylacetate; ^1H NMR ($CDCl_3$) δ 1.30 (3 H, d, J = 7.2 Hz), 3.18 (1 H, m), 3.42 (3 H, br s), 4.34 (1 H, dd, J = 10.6 and 6.7 Hz), 4.50 (1 H, dd, J = 10.6 and 7.6 Hz), 7.20–7.45 (10 H, m). (±)-2-Phenylpropyl (*S*)-α-methoxy-α-trifluoromethylphenylacetate: ^1H NMR ($CDCl_3$) 1.30 (3 H, d, J = 7.2 Hz), 3.18 (1 H, m), 3.22 (1 H, m), 3.42 (3 H, br s), 3.45 (3 H, br s), 4.33 (1 H, dd, J = 10.8 and 6.8 Hz), 4.34 (1 H, dd, J = 10.6 and 6.7 Hz), 4.50 (1 H, dd, J = 10.6 and 7.6 Hz), 4.53 (1 H, dd, J = 10.8 and 6.5 Hz), 7.20–7.45 (10 H, m).

General Procedure for the Conversion of 3 to 5 (X = OTHP, $OCPh_3$). A CH_2Cl_2 (5 mL) solution of **3** (1.00 mmol), dihydropyran (1.5–10 mmol), and pyridinium *p*-toluenesulfonate (PTS) (0.01 mmol) was stirred overnight at room temperature. The usual workup followed by flash chromatography gave **4** (X = OTHP).

A CH_2Cl_2 (10 mL) solution of **3** (1.00 mmol), chlorotriphenylmethane (1.2 mmol), and triethylamine (2.4 mmol) was stirred in the presence of 4-(dimethylamino)pyridine (10 mg) at room temperature for 2 days. After the usual workup, the obtained crude **4** (X = $OCPh_3$) was used without further purification.

4 (X = OTHP or $OCPh_3$) obtained above was treated by a 0.5 N solution of *t*-BuOK (5–10 equiv) in *t*-BuOH at 60 °C for 1 h. The usual workup and the purification by flash chromatography gave **5** (X = OTHP or $OCPh_3$).

Spiroketal 13. To a solution of diol **10** (714 mg, 3.10 mmol) and hexamethyldisilazane (2.6 mL, 12 mmol) in THF was added 0.1 mL of chlorotrimethylsilane, and the resulting white suspension was stirred at room temperature for 20 h. After dilution with petroleum ether (100 mL), the mixture was washed twice with cold water, dried, and concentrated. Purification of the residue by flash chromatography (petroleum ether) gave 1.11 g (96%) of the bis(trimethylsilyl) ether, which was converted to the spiroketal **13** by a similar procedure to that described before. The crude material was purified by medium-pressure column chromatography (2% ether/petroleum ether) to give 862 mg (79%) of **13** and 170 mg (15%) of **14**. **13**: ^1H NMR ($CDCl_3$) δ 0.62 (1 H, t, J = 13.1 Hz), 0.84 (18 H, m), 0.94–1.60 (19 H, m), 1.66 (1 H, br d, J = 12.8 Hz), 1.87 (1 H, m), 2.37 (1 H, d sept, J = 1.8 and 7.1 Hz), 2.68 (1 H, br d, J = 13.1 Hz), 3.42 (1 H, t, J = 12.3 Hz), 3.69 (3 H, m); IR (liquid film) 2960 (s), 1175 (s), 1145 (s), 1130 (s) cm^{-1}; mass spectrum, m/z (relative intensity) 366 (M^+, 37), 351 (30), 309 (32), 281 (39), 44 (100); exact mass calcd for $C_{24}H_{46}O_2$ 366.3500, found 366.3493. **14**: ^1H NMR ($CDCl_3$) δ 0.61 (1 H, t, J = 12.8 Hz), 0.85 (18 H, m), 0.95–1.72 (21 H, m), 2.50 (1 H, d sept, J = 1.4 and 7.4 Hz), 2.74 (1 H, ddd, J = 1.5, 2.8, and 13.3 Hz), 3.56 (2 H, m), 3.97 (1 H, dd, J = 2.8 and 11.7 Hz), 4.19 (1 H, dd, J = 2.8 and 11.7 Hz); IR (liquid film) 2960 (s), 1170 (s), 1130 (s), 1115 (s) cm^{-1}; mass spectrum, m/z (relative intensity) 366 (M^+, 47), 351 (25), 309 (44), 281 (53), 44 (100); exact mass calcd for $C_{24}H_{46}O_2$ 366.3500, found 366.3484.

Ring-Cleavage Product 15. Spiroketal **13** was cleaved to give **15** (93%) by a similar procedure to that described before; ^1H NMR ($CDCl_3$) δ 0.70 (3 H, d, J = 7.0 Hz), 0.84 (15 H, m), 1.00–2.00 (19 H, m), 3.20 (1 H, d, J = 15.6 Hz), 3.47 (3 H, m), 3.63 (1 H, dd, J = 5.9 and 10.4 Hz), 3.76 (1 H, dd, J = 3.7 and 10.4 Hz), 7.40–7.59 (3 H, m), 7.92 (2 H, m); IR (liquid film) 3460 (br), 2945 (s), 1690 (s), 1070 (s), 1045 (s) cm^{-1}; mass spectrum, m/z (relative intensity) 486 (M^+, 12), 401 (7), 380 (10), 367 (47), 281 (76), 105 (100), 44 (98); exact mass calcd for $C_{32}H_{54}O_3$ 486.4075, found 486.4062.

Side Chain Alcohol 7. The transformation of **15** to side chain alcohol **7** was performed by a similar procedure to that described in the conversion of **3a-eq** to (*R*)-2-phenylpropanol. Spectral data of the intermediates **10** and **7** are as follows. **10**: ^1H NMR ($CDCl_3$) δ 0.70 (3 H, d, J = 6.9 Hz), 0.85 (15 H, m), 1.00–2.00 (23 H, m), 2.98 (1 H, dd, J = 5.7 and 13.0 Hz), 3.09 (1 H, dd, J = 6.7 and 13.0 Hz), 3.14 (1 H, d, J = 15.8 Hz), 3.39 (3 H, m), 7.04–7.60 (8 H, m), 7.89 (2 H, m); IR (liquid film) 2945 (s), 1695 (s), 1080 (s), 755 (s), 745 (s), 700 (s) cm^{-1}; mass spectrum, m/z (relative intensity) 578 (M^+, 2.2), 559 (8.0), 322 (37), 305 (56), 138 (68), 105 (100); exact mass calcd for $C_{38}H_{58}O_2S$ 578.4160, found 578.4149. **7**: $[\alpha]^{25}_D$ 9.02 (*c* 0.665, hexane), lit. $[\alpha]^{25}_D$ 9.36 (*c* 2.02, hexane);[16a] ^1H NMR ($CDCl_3$) δ 0.82 (3 H, d, J = 6.4 Hz), 0.84 (6 H, d, J = 6.6 Hz), 0.88 (3 H, d, J = 6.7 Hz), 0.95–1.70 (15 H, m), 1.92 (1 H, br), 3.36 (1 H, dd, J = 6.5 and 10.5 Hz), 3.45 (1 H, d, J = 5.8 Hz); ^{13}C NMR ($CDCl_3$) δ 16.46, 19.53, 22.42, 22.51, 24.24, 24.50, 27.79, 32.58, 33.35, 35.60, 37.09, 37.21, 39.19, 68.10; IR (liquid film) 3320 (br), 2940 (s), 1030 (s) cm^{-1}.

Spiroketal 20. Transformation of **11** to **20** was performed by a similar method to that described before employing *d*-menthone instead of *l*-menthone. The crude mixture was purified by flash chromatography (2%) to give pure **20** and **21**. **20**: ^1H NMR (C_6D_6) δ 0.21 (9 H, s), 0.64 (1 H, t, J = 13.0 Hz), 0.82 (3 H, d, J = 6.5 Hz), 0.90 (1 H, m), 1.14 (3 H, d, J = 7.1 Hz), 1.20 (3 H, d, J = 7.0 Hz), 1.28–1.74 (5 H, m), 2.09 (3 H, s), 2.14 (2 H, m), 2.19 (3 H, s), 2.24 (3 H, s), 2.44 (2 H, m), 2.85 (2 H, m), 3.66 (1 H, dd, J = 2.0 and 12.8 Hz), 3.75 (1 H, dd, J = 2.0 and 13.0 Hz), 3.82 (1 H, d, J = 12.8 Hz), 4.07 (1 H, d, 13.0 Hz); IR (KBr disk) 1260 (s), 1095 (s), 840 (s), 805 (s) cm^{-1}; mass spectrum, m/z (relative intensity) 460 (M^+, 62), 445 (4), 403 (5), 375 (5), 306 (22), 73 (100); exact mass calcd for $C_{27}H_{44}SiO_4$ 460.3010, found 460.2995. **21**: ^1H NMR (C_6D_6) δ 0.232 (9 H, s), 0.72 (1 H, t, J = 12.8 Hz), 0.93 (3 H, d, J = 6.6 Hz), 1.08 (2 H, t, J = 7.2 Hz), 1.17 (3 H, d, J = 7.1 Hz), 1.34 (3 H, d, J = 7.0 Hz), 1.40–1.84 (9 H, m), 2.14 (3 H, s), 2.21 (3 H, s), 2.50 (3 H, s), 3.17 (1 H, d sept, J = 1.6 and ~7 Hz), 3.40 (1 H, d, J = 13.1 Hz), 3.62 (1 H, d, J = 13.0 Hz), 3.71 (1 H, dd, J = 2.7 and 13.1 Hz), 3.84 (1 H, dd, J = 2.7 and 13.0 Hz); IR (KBr disk) 1260 (s), 1100 (s), 910 (s), 840 (s) cm^{-1}; mass spectrum, m/z (relative intensity) 460 (M^+, 28), 366 (7), 261 (23), 220 (24), 205 (86), 73 (100); exact mass calcd for $C_{27}H_{44}SiO_4$ 460.3010, found 460.3000.

Ring-Cleavage Product 22. Spiroketal **20** was converted to **22** by a similar procedure to that described before. **22**: ^1H NMR (C_6D_6) 0.80 (3 H, d, J = 6.8 Hz), 0.88 (3 H, d, J = 7.2 Hz), 1.07 (3 H, d, J = 6.9 Hz), 1.38–2.17 (21 H, m), 2.20 (6 H, s), 2.23 (3 H, s), 2.53 (2 H, m), 2.89 (1 H, d, J = 16.0 Hz), 3.18 (1 H, d, J = 16.0 Hz), 3.43 (1 H, d, J = 8.8 Hz), 3.61 (1 H, d, J = 8.8 Hz), 3.84 (2 H, m), 7.08 (3 H, m), 7.86 (2 H, m); IR (KBr disk) 3480 (br), 1700 (s), 1270 (s), 1090 (s), 945 (s), 895 (s), 840 (s), 800 (s), 755 (s), 690 (s) cm^{-1}; mass spectrum, m/z (relative intensity) 580 (M^+, 31), 503 (1), 460 (5), 324 (14), 306 (12), 137 (30), 105 (71), 73 (100); exact mass calcd for $C_{35}H_{52}SiO_5$ 580.3586, found 580.3563.

Chroman Alcohol 24. To a solution of **22** (91.5 mg, 0.158 mmol) in THF (2 mL) was added tetrabutylammonium fluoride (1 N solution in THF, 0.473 mmol) at room temperature. After 30 min, benzyl bromide (0.56 mL, 0.48 mmol) was added, and the resulting solution was stirred for 3 h. After the usual workup followed by purification by flash chromatography (15%), the product was dissolved in CH_2Cl_2 (1 mL) containing dihydropyran (0.12 mL, 1.3 mmol) and PTS (5 mg), and the resulting solution was stirred at room temperature for 16 h. The usual workup followed by the purification by flash chromatography (7%) gave 90.9 mg (84%) of the benzyl tetrahydropyranyl derivative **23**. To a THF (2 mL) solution of **23** was added $KN(SiMe_3)_2$ (1 M solution in THF, 0.158 mmol) at −85 °C, and the reaction mixture was stirred at room temperature for 45 min. After the usual workup, the mixture was purified by flash chromatography (15–30%) to give 46.3 mg (103%) of **24**: ^1H NMR ($CDCl_3$) δ 1.40–1.88 (7 H, m), 2.00 (2 H, m), 2.10 (3 H, s), 2.16 (3 H, s), 2.21 (3 H, s), 2.64 (2 H, m), 3.43–3.97 (6 H, m), 4.61 (1 H, m), 4.68 (2 H, m), 7.33–7.55 (5 H, m); IR (liquid film) 3400 (br), 1250 (s), 1030 (s), 905 (s) cm^{-1}; mass spectrum, m/z (relative intensity) 426 (M^+, 10), 335 (8), 251 (100), 91 (97), 85 (99); exact mass calcd for $C_{26}H_{34}O_5$ 426.2397, found 426.2402.

Chroman Alcohol 8. To a solution of **26** (16.5 mg, 0.0387 mmol) and CCl_4 (24 μL, 0.25 mmol) in THF (1 mL) was added hexamethylphosphoric triamide (34 μL, 0.19 mmol) at −45 °C under a nitrogen atmosphere, and the resulting mixture was stirred for 30 min. To this was added lithium triethylborohydride (1 M solution in THF, 1.1 mmol) at −45 °C, and the mixture was heated at 50 °C for 3 h. After the usual workup, the deoxygenated product was isolated by flash chromatography (10%) and dissolved in 1 mL of methanol containing 5 mg of PTS, and the mixture was heated at 60 °C for 4 h. The usual workup followed by the purification by flash chromatography (20%) gave 7.6 mg (60%) of **8**: ^1H NMR ($CDCl_3$) δ 1.24 (3 H, s), 1.64–2.06 (3 H, m), 2.10 (3 H, s), 2.18 (3 H, s), 2.22 (3 H, s), 2.64 (2 H, m), 3.58 (1 H, d, J = 11.8 Hz), 3.67 (1 H, d, J = 11.8 Hz), 4.69 (2 H, s), 7.29–7.53 (5 H, m); IR (liquid film) 3240 (br), 1265 (s), 1130 (s), 1040 (s), 910 (s), 870 (s), 815 (s), 715 (s), 700 (s) cm^{-1}. (S)-(−)-MTPA ester derivative of (S)-**8**: ^1H NMR ($CDCl_3$) δ 1.1–1.9 (4 H, m), 2.04 (3 H, s), 2.15 (3 H, s), 2.20 (3 H, s), 2.60 (2 H, m), 3.56 (3 H, q, J = 1.1 Hz), 4.28 (1 H, d, J = 11.2 Hz), 4.41 (1 H, d, J = 11.2 Hz), 4.68 (2 H, s), 7.29–7.60 (10 H, m). (S)-(−)-MTPA ester derivative of (±)-**8**:[27] ^1H NMR ($CDCl_3$) δ 1.1–1.9 (4 H, m), 2.01 (3 H, s), 2.04 (3 H, s), 2.15 (3 H, s), 2.20 (3 H, s), 2.60 (2 H, m), 3.55 (3 H, q, J = 1.1 Hz), 3.56 (3 H, q, J = 1.1 Hz), 4.26 (1 H, d, J = 11.2 Hz), 4.28 (1 H, d, J = 11.2 Hz), 4.41 (1 H, d, J = 11.2 Hz), 4.47 (1 H, d, J = 11.2 Hz), 4.68 (2 H, s), 7.29–7.60 (10 H, m).

8 (18.7 mg, 0.0574 mmol) was oxidized by Collins reagent as described by Cohen et al.[15b] to give 14.7 mg (79%) of the chroman aldehyde: $[\alpha]^{23}_D$ 12.3 (c 0.323, $CHCl_3$), lit. $[\alpha]^{20}_D$ 12.5 (c 2.8, $CHCl_3$),[17d] the ^1H NMR spectrum of this aldehyde was identical with their reported values.[15b]

Acknowledgment. This work was supported partially by Grant-In-Aid for Scientific Research from the Japan Ministry of Education, Science and Culture (No. 61750821).

Supplementary Material Available: Reaction of **2a-eq** with Et_3SiH–$TiCl_4$ and the conversion of the product **6** to (R)-2-phenylpropanol; preparation of **10** and **11**; ^1H NMR, IR, mass and high resolution mass spectral data of **2a-eq, 2a-ax, 2c-eq, 2c-ax, 2d**, and **3a–e**; ^1H NMR spectral data of **3f, 3g**, and the MTPA esters of **5a–f** (10 pages). Ordering information is given on any current masthead page.

Studies on the Radical Species of 9-Decarboxymethoxatin

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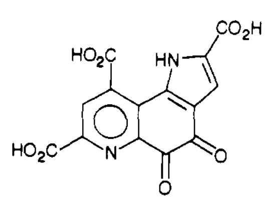
Abstract: Spectrophotometric titrations have been employed to determine the pK_a values of the acid–base species of 9-decarboxymethoxatin (A = $\mathbf{1}_{ox}H_3^+ + \mathbf{1}_{ox}H_2 + \mathbf{1}_{ox}H^- + \mathbf{1}_{ox}^{2-}$; eq 1) and its quinol 2e$^-$ reduction product (B = $\mathbf{1}_{red}H_4 + \mathbf{1}_{red}H_3^- + \mathbf{1}_{red}H_2^{2-} + \mathbf{1}_{red}H^{3-} + \mathbf{1}_{red}^{4-}$; eq 3) as well as the equilibrium constants for the pH-dependent hydration of 9-decarboxymethoxatin (to provide the species C = $\mathbf{1}_{ox}(OH)^{3-} + \mathbf{1}_{ox}(H_3O_2)^{3-}$; eq 4). The pH dependence of the concentrations of paramagnetic semiquinone species present in solutions of half-reduced methoxatin at basic pH values (D = $\mathbf{1}_{rad}H^{2-} + \mathbf{1}_{rad}^{3-}$) was determined by EPR measurements, and from these concentrations the pH-dependent equilibrium constants (K_{pH}) were calculated for disproportionation of quinone and quinol species. A plot of log K_{pH} vs. pH was found to have a bell shape with ascending and descending legs of slope +1 and −1, respectively. The experimental points of the log K_{pH} vs. pH profile were fitted by an equation which takes into account the pH dependence of the concentrations of all quinone, quinol, and semiquinone species ($K_{eq} = [D]^2/[A + C][B]$). Fitting of the equation to the experimental points was carried out by iteration of the value of $K = [\mathbf{1}_{rad}^{2-}]/[\mathbf{1}_{ox}^{2-}][\mathbf{1}_{red}H_2^{2-}]$ = 3.3 and the pK_a of the semiquinone ($\mathbf{1}_{rad}H^{2-}$) hydroxyl proton as 7.52. The sharp decrease in semiquinone formation above pH 12.5 is explained by quinone hydration. Spectral evidence is presented which supports the dimerization in aqueous solution of the paramagnetic semiquinone to a diamagnetic species. Analysis of the EPR spectrum of $\mathbf{1}_{rad}^{3-}$ and comparison to the EPR spectrum of the analogous methoxatin semiquinone shows that there are no major alterations in spin density in the heterocyclic trinuclear ring system on replacement of the 9-position carboxylate functionality in the naturally occurring methoxatin with a proton.

The compound 4,5-dihydro-4,5-dioxo-1H-pyrrolo[2,3-f]-quinoline-2,4,9-tricarboxylic acid (trivial name methoxatin) was first recognized to be a cofactor in methyltrophic bacteria (1979).[1]



methoxatin

For these aerobic organisms, methoxatin-containing enzymes (quinoenzymes) serve in place of the nicotinamide cofactor requiring enzymes and flavoenzymes in the oxidation of alcohols, hexoses, aldehydes, and methylamine.[2] More recently, methoxatin has been found[3] as a cofactor in *E. coli*, an aerobic organism, and to (most likely) represent the long sought-after cofactor for mammalian plasma amine oxidase.[4] Quinoenzymes would appear, therefore, to represent a new and widely distributed class of oxidase enzymes.

Knowledge of the chemistry of a methoxatin semiquinone species is important to an understanding of the biological role of methoxatin. In the metabolism of methyltrophs, methoxatin is proposed to undergo 2e$^-$ reduction by substrate and to pass on 1e$^-$ at a time to cytochrome c^{5a} via ubiquinone.[5b] Such a 2e$^-$-to-1e$^-$ switching mechanism must involve a methoxatin radical intermediate. Step-down electron switching mechanisms have previously been associated with a number of flavoenzymes (e.g., succinic acid dehydrogenase).[6] The mechanisms of 2e$^-$ oxidations of substrates by methoxatin and quinoenzymes are poorly understood, and as is the case with flavin and flavoenzyme oxidations,

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