Diastereoselective Reduction of Chiral β,γ-Unsaturated α-Oxo Esters. Asymmetric Synthesis of the Fatty Acid Moiety of Symbioramide

Hideyuki Sugimura* and Kazuhiro Yoshida

The Noguchi Institute, 1-8-1, Kaga, Itabashi-ku, Tokyo 173, Japan

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Optically active α-hydroxy β,γ-unsaturated acids or esters have been synthesized by several methods, including enzymatic reduction of β,γ-unsaturated α-oxo acids[1,2] and diastereoselective vinylsilane substitution with a chiral glyoxylate.[3] Although the stereoselective reduction of α-oxo esters[4-7] or amides[8-10] has been studied using a variety of chiral auxiliaries, a chemical approach to such reduction of β,γ-unsaturated α-oxo acid derivatives has not been reported. We describe here the asymmetric synthesis of α-hydroxy β,γ-unsaturated esters by reducing β,γ-unsaturated α-oxo esters using (−)-8-phenylmenthol or (−)-*trans*-2-phenylcyclohexanol as a chiral auxiliary.

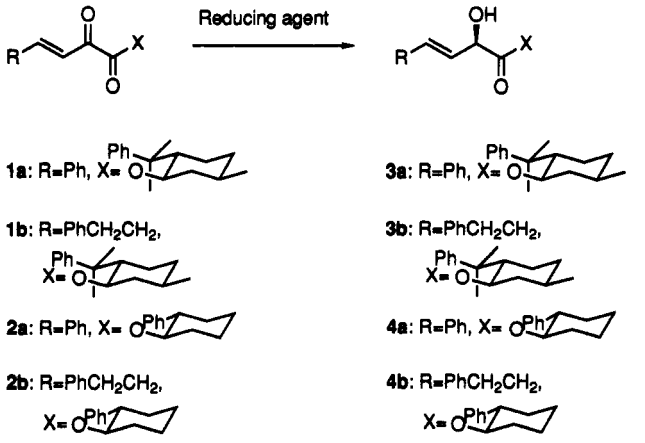
(−)-8-Phenylmenthol is an effective chiral auxiliary in the asymmetric reduction of α-oxo esters, as shown by Whitesell et al.[4] and, more recently, by Solladié-Cavallo and Bencheqroun.[7] However, high diastereoselectivity occurs when potassium triisopropoxyborohydride or potassium tributylborohydride is the reducing reagent, which is somewhat inconvenient. We initially examined the diastereoselective reduction of the β-phenyl-substituted β,γ-unsaturated α-oxo ester **1a** as a model compound with a view to obtaining a high level of selectivity, using several commercially available reducing agents. The results are summarized in Table I (runs 1-5). Very high selectivity was achieved with L-Selectride (Aldrich) in diethyl ether (run 2). The reaction in THF resulted in a lower level of stereochemical control (run 1). When K-Selectride (Aldrich) was the reducing agent, the yield was slightly decreased due to several byproducts including the saturated α-oxo ester (run 3). The reduction with aluminum hydrides was less satisfactory than that with borohydrides, with regard to diastereoselectivity (runs 4 and 5). The use of DIBAH, moreover, led to the formation of a significant amount of undesirable byproducts.

Some results of the reduction of a β,γ-unsaturated α-oxo ester bearing a β-alkyl group (R) are also summarized in Table I (runs 6-8). L-Selectride exhibited high diastereoselectivity again, and in the reaction with lithium tri-*tert*-butoxyaluminum hydride there was a considerable decrease in both yield and selectivity.

Table I. Reduction of Chiral β,γ-Unsaturated α-Oxo Esters

run	ester	reducing agent	solvent	yield/%	% de[a]
1	**1a**	LiB(*s*-Bu)$_3$H	THF	92	85
2		LiB(*s*-Bu)$_3$H	Et$_2$O	90	97
3		KB(*s*-Bu)$_3$H	Et$_2$O	75[b]	96
4		LiAl(*t*-BuO)$_3$H	Et$_2$O	83[c]	70
5		Al(*i*-Bu)$_2$H	Et$_2$O	20[d]	40
6	**1b**	LiB(*s*-Bu)$_3$H	THF	82	95
7		LiB(*s*-Bu)$_3$H	Et$_2$O	81	97
8		LiAl(*t*-BuO)$_3$H	Et$_2$O	49[e]	48
9	**2a**	LiB(*s*-Bu)$_3$H	THF	95	93
10		LiB(*s*-Bu)$_3$H	Et$_2$O	96	96
11	**2b**	LiB(*s*-Bu)$_3$H	THF	88	94
12		LiB(*s*-Bu)$_3$H	Et$_2$O	84	94

[a] The diastereomeric ratios were determined by 400-MHz ^{1}H NMR. [b,c] The corresponding saturated α-oxo ester was also obtained in <8% yield. [d] The corresponding saturated α-oxo ester and α-hydroxy β,γ-unsaturated ester, formed by addition of the isobutyl group to the α-carbonyl in **1a**, were also obtained in 33 and 28% yields, respectively. [e] The corresponding saturated α-oxo ester was also obtained in 43% yield.



The diastereomeric ratios were determined by the integral of the 400-MHz ^{1}H NMR of the α-methine and vinyl protons. The 2*R* configuration of the major diastereomer **3a** was confirmed by comparing the ^{13}C NMR chemical shifts of the diastereomeric mixture to that of the (2*S*)-isomer reported by Mikami et al.[3] This stereoselectivity is in agreement with that of α-oxo esters reported by Whitesell et al.[4] and Solladié-Cavallo and Bencheqroun.[7] The configuration of **3b** was assigned by analogy with **3a**.

Optically active *trans*-2-phenylcyclohexanol is an alternative auxiliary for chiral induction whose advantage is that both enantiomers can be obtained in high enantiomeric purity.[11,12] Table I (runs 9-12) shows the results of the diastereoselective reduction using (−)-*trans*-2-phenylcyclohexanol as the chiral auxiliary. L-Selectride afforded satisfactory yields and diastereoselectivities. To determine the configuration at the 2-hydroxy position, the hydroxy esters **4a** and **4b** were converted to the corresponding unsaturated 1,2-diols by treatment with LAH. The optical rotation of either product was consistent

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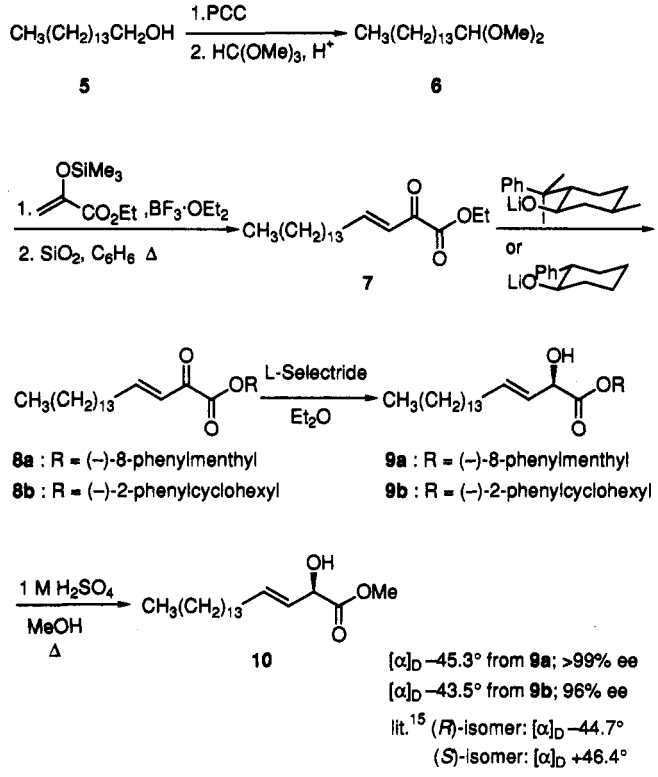
Scheme I



with that of the diols similarly derived from **3a** and **3b**. Consequently, the configuration for the major diastereomers **4a** and **4b** was assigned to be 2*R*.[13]

To demonstrate the synthetic potential of the above procedure, we achieved enantioselective synthesis of a (2*R*,3*E*)-2-hydroxy-3-octadecenoic acid derivative, corresponding to the fatty acid moiety of symbioramide, a novel bioactive ceramide.[14,15] As shown in Scheme I, oxidation of 1-pentadecanol (**5**) with PCC gave the corresponding aldehyde, which was subsequently used in acetalization to provide 1-pentadecanal dimethyl acetal (**6**) in 71% yield from **5** after distillation. Acetal **6** was converted to β,γ-unsaturated α-oxo ester **7** via the two-step procedure reported previously:[16] Treatment of **6** with ethyl 2-(trimethylsiloxy)acrylate in the presence of boron trifluoride etherate in dichloromethane at –78 to 0 °C followed by silica gel in refluxing benzene afforded ethyl (*E*)-2-oxo-3-octadecenoate (**7**) in 66% yield. After transesterification of the ethyl ester using lithium salts of the appropriate chiral alcohols, the resulting chiral esters **8a** and **8b** were reduced by L-Selectride in diethyl ether at –78 °C for 1 h to give the corresponding α-hydroxy β,γ-unsaturated esters **9a** and **9b** in 74 and 84% yields with >98 and 97% de, respectively. Methanolysis of **9a** and **9b** gave the known methyl ester **10** without racemization for which the assignment of the 2*R* configuration as well as the optical purity was confirmed by comparison with that reported by Nakagawa et al.[15] Thus, the optical purity of **10** was estimated as >99% ee of that derived from **9a** and 96% ee of that derived from **9b** (see Experimental Section).

In conclusion, a highly diastereoselective reduction of (–)-8-phenylmenthyl and (–)-*trans*-2-phenylcyclohexyl β,γ-unsaturated α-oxo esters was established and its utility shown by the asymmetric synthesis of the (2*R*,3*E*)-2-hydroxy-3-octadecenoic acid derivative, the fatty acid moiety of symbioramide.

Experimental Section

All melting points are uncorrected. ^1H and ^{13}C NMR spectra were measured at 400 and 100 MHz, respectively, with Me_4Si as an internal reference and $CDCl_3$ as the solvent. *J* values are given in Hz. All solvents were dried prior to use.

General Procedure for Reduction of β,γ-Unsaturated α-Oxo Esters with L-Selectride. The following is a modification of a published procedure.[7] To a solution of β,γ-unsaturated α-oxo ester (1 mmol) in 20 mL of ether was added 1.2 mL of L-Selectride (1 M in THF, 1.2 mmol) dropwise at –78 °C under Ar. After the mixture was stirred for 1 h, 1 mL of methanol, 1.5 mL of 10% aqueous NaOH, and 1.5 mL of 30% aqueous H_2O_2 were successively added, and then the reaction mixture was allowed to warm to room temperature for over 1 h. After 20 mL of water was added, the aqueous layer was separated and washed twice with 20 mL of ether. The organic layer was dried and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane–ethyl acetate) to give β,γ-unsaturated α-hydroxy esters.

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (2*R*,3*E*)-2-hydroxy-4-phenyl-3-butenoate (3a): mp 107.0–107.5 °C (hexane); ^1H NMR δ 0.86 (d, 3H, *J* = 6.3), 0.99–1.36 (m, 3H), 1.22 (s, 3H), 1.31 (s, 3H), 1.46 (m, 1H), 1.58–1.70 (m, 2H), 1.90 (m, 1H, *J* = 11.7), 2.09 (dt, 1H, *J* = 3.4, 10.7), 2.05–2.13 (br, 1H), 4.49 (d, 1H, *J* = 5.4), 4.93 (dt, 1H, *J* = 4.4, 10.7), 6.15 (dd, 1H, *J* = 5.4, 16.1), 6.73 (d, 1H, *J* = 16.1), 7.15–7.42 (m, 10H); ^{13}C NMR δ 21.7, 26.1, 26.7, 27.3, 31.3, 34.4, 39.9, 41.5, 50.2, 71.9, 76.8, 124.8, 125.5, 126.6, 127.8, 128.1, 128.5, 132.1, 136.2, 151.4, 171.5; IR (KBr) 3460, 1720 cm^{-1}. Anal. Calcd for $C_{26}H_{32}O_3$: C, 79.55; H, 8.22. Found: C, 79.52; H, 8.47.

The ^1H NMR signals for the α-methine and vinyl protons of the *S* isomer appeared at δ 3.79 (d, *J* = 5.4), 5.81 (dd, *J* = 5.4, 16.1), 6.49 (d, *J* = 16.1).

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (2*R*,3*E*)-2-hydroxy-6-phenyl-3-hexenoate (3b): ^1H NMR δ 0.87 (d, 3H, *J* = 6.8), 0.97–1.15 (m, 3H), 1.22 (s, 3H), 1.31 (s, 3H), 1.46 (m, 1H), 1.57–1.68 (m, 2H), 1.88 (m, 1H), 1.94 (br, 1H), 2.06 (ddd, 1H, *J* = 3.4, 10.7, 12.2), 2.34 (dt, 2H, *J* = 6.8, 7.8), 2.67 (t, 2H, *J* = 7.8), 4.26 (m, 1H, *J* = 1.5, 5.9), 4.89 (dt, 1H, *J* = 4.4, 10.7), 5.43 (dd, 1H, *J* = 5.9, 15.6), 5.86 (ddt, 1H, *J* = 1.5, 6.8, 15.6), 7.1–7.2 (m, 4H), 7.2–7.35 (m, 6H); ^{13}C NMR δ 21.7, 26.2, 26.7, 27.2, 31.3, 34.0, 34.4, 35.2, 40.0, 41.9, 50.1, 72.0, 76.5, 125.5, 125.9, 126.0, 128.1, 128.3, 133.7, 141.6, 151.3, 171.9; IR (neat) 3500, 1725 cm^{-1}. Anal. Calcd for $C_{28}H_{36}O_3$: C, 79.96; H, 8.63. Found: C, 79.89; H, 8.75.

The ^1H NMR signals for the α-methine and vinyl protons of the *S* isomer appeared at δ 3.57 (dd, *J* = 5.9), 5.16 (dd, *J* = 5.9, 15.6), 5.62 (ddt, *J* = 1.5, 6.8, 15.6).

(1*R*,2*S*)-2-Phenyl-1-cyclohexyl (2*R*,3*E*)-2-hydroxy-4-phenyl-3-butenoate (4a): white crystalline, mp 109.0–110.0 °C (hexane); ^1H NMR δ 1.20–1.62 (m, 4H), 1.80 (m, 1H), 1.83–1.98 (m, 2H), 2.17–2.25 (m, 1H), 2.70 (dt, 1H, *J* = 3.4, 12.2), 2.89 (d, 1H, *J* = 5.9), 4.60 (m, 1H), 5.07 (dt, 1H, *J* = 4.4, 10.3), 5.49 (dd, 1H, *J* = 5.4, 15.6), 6.53 (dd, 1H, *J* = 1.5, 15.6), 6.99–7.36 (m, 10H); ^{13}C NMR δ 25.3, 26.3, 32.9, 34.6, 50.4, 71.7, 79.0, 126.0. 127.3, 127.4, 128.0, 128.3, 128.9, 129.0, 132.2, 143.0, 173.4; IR (KBr) 3460, 1730 cm^{-1}. Anal. Calcd for $C_{22}H_{24}O_3$: C, 78.54; H, 7.19. Found: C, 78.21; H, 7.24.

The ^1H NMR signals for the α-methine and vinyl protons of the *S* isomer appeared at δ 4.44(m), 6.06 (dd, *J* = 5.4, 15.6), 6.67 (dd, *J* = 1.5, 15.6).

(1*R*,2*S*)-2-Phenyl-1-cyclohexyl (2*R*,3*E*)-2-hydroxy-6-phenyl-3-hexenoate (4b): ^1H NMR δ 1.28–1.62 (m, 4H), 1.79 (m, 1H, *J* = 13.2), 1.86–1.98 (m, 2H), 2.09 (dt, 2H, *J* = 6.8, 8.3), 2.18 (m,

(13) The optical rotations are as follows. (*R*)-PhCH=CHCH(OH)-CH_2OH (from 93% de of **4a**): $[\alpha]^{25}_D$ –28° ($CHCl_3$, *c* 0.57). (*R*)-$PhCH_2$-CH_2CH=CHCH(OH)CH_2OH (from 94% de of **4b**): $[\alpha]^{24}_D$ –13° ($CHCl_3$, *c* 0.94).

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1H), 2.50 (t, 2H, J = 8.3), 2.68 (ddd, 1H, J = 3.9, 10.7, 12.2), 2.73 (d, 1H, J = 6.4), 4.36 (dd, 1H, J = 5.4, 6.4), 4.80 (dd, 1H, J = 5.4, 15.1), 5.05 (dt, 1H, J = 4.4, 10.7), 5.59 (dt, 1H, J = 6.8, 15.1), 7.10–7.32 (m, 10H); ^{13}C NMR δ 24.7, 25.7, 32.2, 33.8, 34.0, 35.2, 49.9, 71.0, 78.0, 125.9, 126.6, 127.5, 128.3, 132.6, 141.8, 142.7, 173.1; IR (neat) 3500, 1725 cm^{-1}. Anal. Calcd for $C_{24}H_{28}O_3$: C, 79.09; H, 7.74. Found: C, 79.16; H, 7.90.

The ^{1}H NMR signals for the α-methine and vinyl protons of the *S* isomer appeared at δ 4.21 (dd, J = 5.4, 5.9), 5.35 (dd, J = 5.4, 15.1), 5.77 (dt, J = 6.8, 15.1).

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (2*R*,3*E*)-2-Hydroxy-3-octadecenoate (9a). According to the general procedure, **8a** was reduced to yield **9a** as a colorless oil (74%, >98% de): ^{1}H NMR δ 0.87 (d, 3H, J = 6.8), 0.88 (t, 3H, J = 6.8), 0.98–1.13 (m, 2H), 1.17–1.38 (m, 28H), 1.31 (s, 3H), 1.45 (m, 1H), 1.57–1.66 (m, 2H), 1.89 (m, 1H, J = 12.2), 1.97–2.09 (m, 4H), 4.27 (dd, 1H, J = 5.1, 6.3), 4.88 (dt, 1H, J = 4.4, 10.7), 5.37 (dd, 1H, J = 6.3, 15.1), 5.80 (dt, 1H, J = 6.8, 15.1), 7.15–7.20 (m, 1H), 7.23–7.34 (m, 4H); ^{13}C NMR δ 14.1, 21.7, 22.7, 26.5, 26.7, 27.0, 28.8, 29.1, 29.3, 29.4, 29.5, 29.6, 31.3, 31.9, 32.1, 34.4, 39.8, 41.5, 50.1, 72.1, 76.4, 125.3, 125.4, 125.5, 128.0, 134.9, 151.2, 172.1; IR (neat) 3550, 1730 cm^{-1}. Anal. Calcd for $C_{34}H_{56}O_3$: C, 79.63; H, 11.01. Found: C, 79.90; H, 11.21.

(1*R*,2*S*)-2-Phenyl-1-cyclohexyl (2*R*,3*E*)-2-Hydroxy-3-octadecenoate (9b). According to the general procedure, **8b** was reduced to yield **9b** as a colorless oil (84%, 96% de): ^{1}H NMR δ 0.88 (t, 3H, J = 6.4), 1.15–1.42 (m, 28H), 1.43–1.62 (m, 2H), 1.70–1.83 (m, 2H), 1.85–1.98 (m, 2H), 2.17 (m, 1H), 2.68 (ddd, 1H, J = 3.9, 10.7, 12.2), 4.34 (dd, 1H, J = 5.9, 6.3), 4.73 (dd, 1H, J = 5.9, 15.1), 5.04 (dt, 1H, J = 4.4, 10.7), 5.53 (ddt, 1H, J = 1.5, 6.8, 15.1), 7.13–7.19 (m, 3H), 7.21–7.27 (m, 2H); ^{13}C NMR δ 14.1, 22.7, 24.7, 25.7, 28.8, 29.3, 29.4, 29.6, 29.7 × 2, 32.0, 32.1, 32.3, 34.0, 49.8, 71.1, 77.9, 125.7, 126.6, 127.5, 128.3, 133.7, 142.7, 173.2; IR (neat) 3500, 1720 cm^{-1}. Anal. Calcd for $C_{30}H_{48}O_3$: C, 78.89; H, 10.59. Found C, 78.63; H, 10.58.

The ^{1}H NMR signals for the α-methine and vinyl protons of the *S* isomer appeared at δ 4.23 (dd, J = 5.8, 6.3), 5.30 (dd, J = 5.8, 15.1), 5.72 (ddt, J = 1.5, 6.8, 15.1).

Methanolysis of 9a and 9b. From 9a. **9a** (121 mg, 0.24 mmol) was dissolved in 6 mL of 1 M H_2SO_4 in MeOH–THF (5:1), and the solution was stirred under reflux for 12 h. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted three times with 10 mL of ether. The combined organic layer was dried and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane–ethyl acetate (19:1)) to give 63 mg of methyl ester **10** (93%) as a white solid accompanied by 53 mg of (–)-8-phenylmenthol (96%): mp 42 °C; $[\alpha]^{29}_D$ –45.3° ($CHCl_3$, c 0.696) (lit.[15] $[\alpha]_D$ = –44.7°); ^{1}H NMR δ 0.90 (t, 3H, J = 6.4), 1.20–1.40 (m, 24H), 2.06 (dt, 2H, J = 6.8, 7.3), 2.85 (d, 1H, J = 6.4), 3.80 (s, 3H), 4.61 (dd, 1H, J = 6.4), 5.50 (dd, 1H, J = 6.4, 15.6), 5.88 (dt, 1H, J = 6.8, 15.6); ^{13}C NMR δ 14.1, 22.7, 28.8, 29.2, 29.4, 29.5, 29.6, 29.7, 31.9, 32.2, 52.8, 71.5, 125.9, 135.1, 174.3; IR (KBr) 3450, 1740 cm^{-1}. Anal. Calcd for $C_{19}H_{36}O_3$: C, 73.03; H, 11.61. Found; C, 73.09; H, 11.61.

From **9b**. Similarly, the reaction of **9b** (230 mg, 0.50 mmol) in 12 mL of 1 M H_2SO_4 (MeOH–THF (5:1)) under reflux for 1 h afforded 154 mg of **10** (98%) accompanied by 88 mg of (–)-2-phenylcyclohexanol (99%): $[\alpha]^{28}_D$ –43.5° ($CHCl_3$, c 1.46).

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Supplementary Material Available: Experimental procedures and characterization data for compounds **1a,b**, **2a,b**, **6**, **7**, and **8a,b** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.