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Rearrangement Approaches to Cyclic Skeletons. XI. Chemoenzymatic Preparation of Chiral Bridged Compounds for Rearrangement Approaches[1)]

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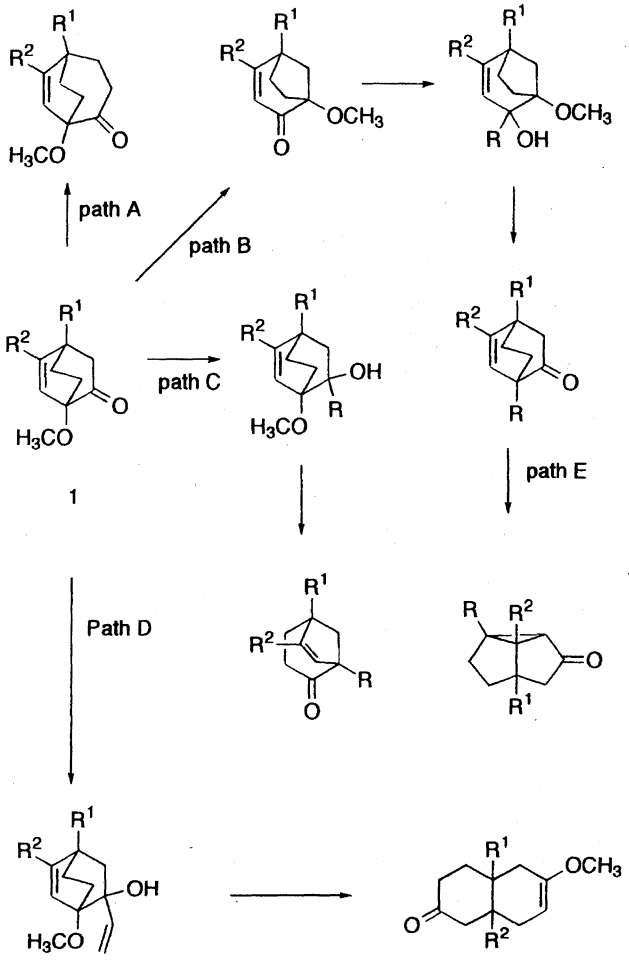
Both enantiomers of 1-methoxybicyclo[2.2.2]oct-5-en-2-ones were prepared in more than 80%ee on the basis of a chemoenzymatic reaction sequence. The optical resolution was achieved by the enantioselective hydrolysis of chloroacetyl esters 1-methoxybicyclo[2.2.2]oct-5-en-endo-2-ols using commercially available lipases.

We were able to prepare 1-methoxybicyclo[2.2.2]oct-5-en-2-ones (**1**) easily from anisoles by the Diels–Alder strategy, including Birch reduction followed by selective isomerization into 1-methoxy-1,3-cyclohexadienes.[2,3a)] As shown in Scheme 1, those ketones having a bridgehead meyhoxy group are potential substrates for the preparation of other bridged polycyclic compounds and fused-ring systems by rearrangement approaches, such as ring enlargement to bicyclo[3.2.2]non-6-en-2-ones (path A),[4)] formal bridgehead substitution giving 1-substituted bicyclo[2.2.2]oct-5-en-2-ones (path B),[5)] a pinacol-type rearrangement leading to 1-substituted bicyclo[3.2.1]oct-6-en-2-ones (path C),[1,3)] conversion into the *exo*-alcohol followed by the anionic oxy-Cope rearrangement to the [6-6] fused-ring system (path D),[2a)] and the triplet sensitized photochemical process, the [1,2] acyl migration into the [5-5] fused-ring system (path E).[6)] Under such circumstances, we need to develop efficient processes to prepare the bridgehead methoxy ketones in their chiral forms.

Many successful examples prompted us to examine enzymatic hydrolyses for the preparation of optically active compounds. Because of their commercial availability and relative stability, lipases have been widely used for the kinetic resolution of racemic alcohols and carboxylic esters.[7)] We wish to report herein on the chemoenzymatic preparation of both enantiomers of the bridgehead methoxy ketones in more than 80%ee.

Results and Discussion

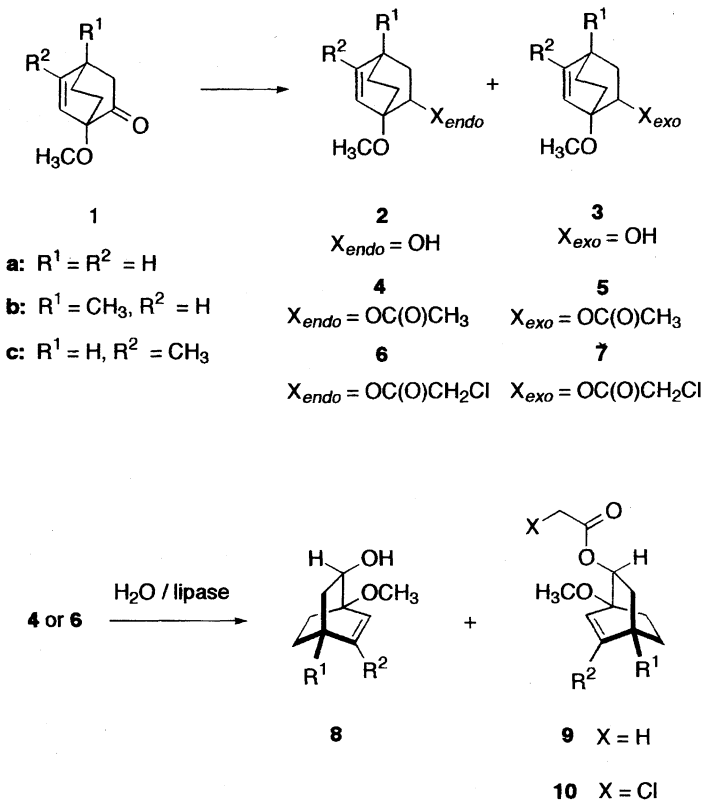
L-Selectride® reduction of ketones **1** followed by the chromatographic separation gave alcohols **2** and **3**. These alcohols were converted into the respective acetates (**4** and **5**) and chloroacetates (**6** and **7**) (Scheme 2). The stereostructures of these compounds were determined on the basis of their ^{1}H NMR spectra. Long-range coupling constants due to the W-configuration and NOE were especially informative



Scheme 1.

(Chart 1).

Pseudomonas lipases (PS and AK) were used for enzymatic hydrolyses of these esters. Table 1 shows the repre-



Scheme 2.

sentative results.

The acetates **4** were showly hydolyzed to give the alcohols **8** in moderate enantioselectivity.[8] Similar hydrolyses of chloroacetates **6** pointed to somewhat higher *E* values. The resulting alcohols **8** were benzoated prior to determination of their optical purity by HPLC using chiral stationary phase. The remaining esters, **9** and **10**, were converted into the alcohols **12** by a treatment with $LiAlH_4$, and were then benzoated to determine the optical purity.

Similar enzymatic hydrolyses of the *exo*-chloroacetate **7a** were slow reactions. Their *E* values were less than 3.

Oxidation of **8** and **12** using sulfur trioxide-pyridine[9] in DMSO gave **11** and **13**, respectively (Scheme 3). The absolute configurations of these ketones were determined on the basis of their CD and/or ORD spectra (Tables 2 and 3). The positive Cotton curves of bicyclo[2.2.2]oct-5-en-2-one have been correlated with the (1*R*)-configuration (**14**) (Chart 2).[10] The sign of the Cotton-effect curve is determined solely by the absolute disposition of the double bond relative to the carbonyl.[11] This seemed to suggest that the presence of the

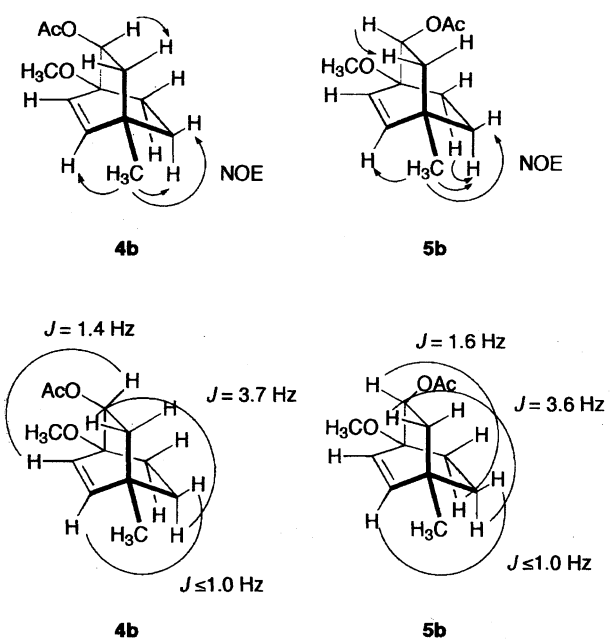
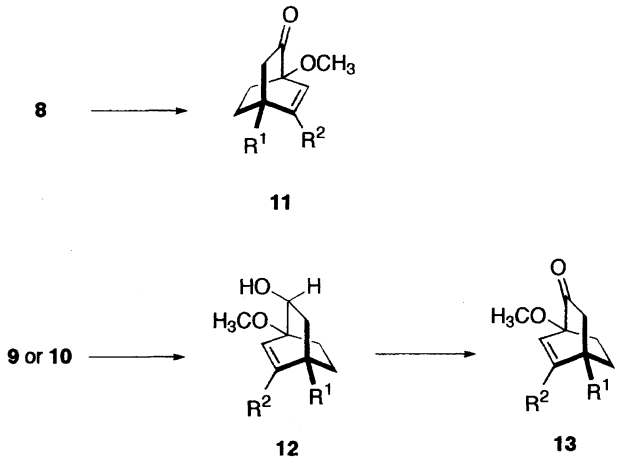


Chart 1.



Scheme 3.

Table 1. Lipase-Catalyzed Enantioselective Hydrolysis of **4** and **6**[a]

Substrate	Lipase	Time h	c[b]	Product **8**	%ee[c] (yield, %)[d]	Remaining ester	%ee[c] (yield, %)[d]	E[e]
4a	PS	5	0.33	**8a**	80 (17)	**9a**	40 (62)	14
4a	AK	7	0.32	**8a**	91 (28)	**9a**	43 (53)	33
4b	PS	144	0.39	**8b**	36 (21)	**9b**	23 (73)	3
4b	AK	42	0.47	**8b**	82 (38)	**9b**	78 (50)	23
6a[f]	PS	6	0.41	**8a**	90 (27)	**10a**	63 (46)	39
6a[f]	PS	22	0.54	**8a**	85 (26)	**10a**	98 (31)	56
6a[f]	AK	6	0.54	**8a**	70 (33)	**10a**	81 (42)	14
6b[g]	PS	48	0.64	**8b**	60 (50)	**10b**	72 (39)	8
6b[g]	AK	24	0.54	**8b**	83 (50)	**10b**	98 (42)	48
6c[g]	PS	24	0.53	**8c**	82 (48)	**10c**	92 (44)	33
6c[g]	AK	48	0.59	**8c**	59 (57)	**10c**	87 (36)	11

a) Acetates **4** (200 mg) were hydrolyzed by a lipase (400 mg) in 20 ml of buffer, pH 7.0, and 4 ml of THF at 40 °C as described in the Experimental Section. b) Conversion $c=ee_s/(ee_s+ee_p)$. c) Determined by HPLC. d) Isolated yield. e) Enantiomeric ratio $(E)=\ln[(1-c)(1-ee_s)]/\ln[(1-c)(1+ee_s)]$. f) Chloroacetate **6a** (400 mg) was hydrolyzed by a lipase (200 mg) at 35 °C. g) Chloroacetates **6b** and **6c** (600 mg) were hydrolyzed by a lipase (300 mg) at 35 °C.

Table 2. CD Spectra of Chiral β,γ-Unsaturated Ketones in Isooctane

Ketone	(ee%)	CD				
11b	(87)	(c 3.17×10^{-4}, 20 °C),	$[\theta]_{307}$ +3.01,	$[\theta]_{299}$ +2.94,	$[\theta]_{240}$ 0,	and $[\theta]_{222}$ +0.61
13b	(78)	(c 2.76×10^{-4}, 20 °C),	$[\theta]_{307}$ −2.76,	$[\theta]_{300}$ −2.58^{sh},	$[\theta]_{240}$ 0,	and $[\theta]_{224}$ −0.56
15b	(78)	(c 5.58×10^{-4}, 20 °C),	$[\theta]_{303}$ −2.75,	$[\theta]_{293}$ −2.91,		and $[\theta]_{231}$ −0.01

Table 3. ORD Spectra of Chiral Ketones **11** and the Related Ones in Isooctane

Ketone	(ee%)[a]	ORD			
11a	(88)	(c 3.95×10^{-3}, 20 °C),	$[\Phi]_{589}$ +490°,	$[\Phi]_{326}$ +17300°,	and $[\Phi]_{305}$ 0°
13a	(91)	(c 4.89×10^{-3}, 20 °C),	$[\Phi]_{589}$ −498°,	$[\Phi]_{324}$ −17100°,	and $[\Phi]_{302}$ 0°
11b	(87)	(c 5.27×10^{-3}, 20 °C),	$[\Phi]_{589}$ +489°,	$[\Phi]_{326}$ +18300°,	and $[\Phi]_{306}$ 0°
13b	(78)	(c 4.58×10^{-3}, 20 °C),	$[\Phi]_{589}$ −439°,	$[\Phi]_{324}$ −17000°,	and $[\Phi]_{306}$ 0°
11c	(80)	(c 7.91×10^{-3}, 20 °C),	$[\Phi]_{589}$ +460°,	$[\Phi]_{326}$ +18600°,	and $[\Phi]_{304}$ 0°
13c	(95)	(c 4.87×10^{-3}, 20 °C),	$[\Phi]_{589}$ −531°,	$[\Phi]_{326}$ −21200°,	and $[\Phi]_{305}$ 0°
15b	(78)	(c 7.59×10^{-3}, 20 °C),	$[\Phi]_{589}$ −387°,	$[\Phi]_{322}$ +17600°,	$[\Phi]_{314}$ −11300°,
			$[\Phi]_{308}$ −14400°,	and $[\Phi]_{300}$ 4400°	

a) Determined by HPLC.

14 **15b**

Chart 2.

C-1 methoxy group does not change the sign of the Cotton-effect curves. Ketone **15b**, derived from **13b** according to the path B in Scheme 1, showed a similar negative Cotton-effect curve to that of **13b**.

Griengl and his co-workers reported on the hydrolyses of the esters derived from more simple bicyclo[2.2.2]oct-5-en-2-ols than **8** by *Candia cyclidracea* lipase,[12] and proposed a substrate model for the enzymatic resolution.[13] The present results can be explained based on the substrate model. In other words, no hindrance effects caused by a bridgehead methoxy group exist in the hydrolyses using lipase PS or AK.

There are many examples of an enantiopurity enhancement by appropriate *sequential* kinetic resolutions.[14] The procedure should be applicable to the optical-purity enhancement of **8**. Thus, our results open the door to rearrangement approaches to chiral cyclic skeletons.

Experimental

General. The ^{1}H NMR spectra were measured at 300 and 600 MHz in $CDCl_3$ using TMS [$(CH_3)_4Si$] as the internal standard. COSY and NOESY experiments were frequently employed in order to assign the stereostructures. HRMS were determined with a JEOL JMS-HX110 mass spectrometer. CD and ORD spectra were measured with a JASCO J-405 spectrometer and a JASCO model ORD/UV-5 optical rotatory dispersion recorder, respectively. THF

and diethyl ether were distilled from diphenylketyl under argon immediately prior to use. Benzene was distilled from P_2O_5. Dichloromethane was distilled from CaH_2 under argon immediately prior to use. L-Selectride® was from Aldrich. *Pseudomonas* Lipases (PS and AK) were available from Amano Pharmaceutical Co., Ltd. All of the preparative reactions were monitored by analytical TLC using Merck pre-coated silica-gel $60F_{254}$ plates. VPC was carried out on a fused-silica capillary column (Shimadzu CPB1-M-25-025). Column chromatography was performed using Merck silica-gel 60 (70—230 mesh ASTM). Flash chromatography was carried out on Cica-Merck silica-gel 60 (230—400 mesh ASTM). The optical purities were determined on HPLC equipped with a chiral column (Daicel CHIRALCEL OJ®). Semi-preparative HPLC was performed using a Merck Hiber prepacked column RT (250×10 mm).

(±)-1-Methoxybicyclo[2.2.2]oct-5-en-*endo*-2-ol (2a) and the *exo* Isomer (3a), (As a General Procedure for L-Selectride® Reduction). To a mixture of THF (60.0 cm^3) and L-Selectride® (1.00 M solution in THF, 20.0 cm^3, 1 M = 1 mol dm^{-3}) in a 200 ml flask was added dropwise a solution of a ketone **1a** (2.50 g, 16.4 mmol) in THF (30.0 cm^3) over a period of 30 min at −78 °C under argon. The mixture was stirred for 6 h at −78 °C, and then allowed to warm to room temperature. After stirring for 1 h at room temperature, the mixture was cooled at 0 °C, and then treated with water (2.14 cm^3). To the reaction mixture were added ethanol (8.04 cm^3), a 6.0 M aqueous NaOH solution (5.36 cm^3), and 30% hydrogen peroxide (8.04 M cm^3). The resulting mixture was stirred overnight at room temperature. The mixture was saturated with potassium carbonate, and extracted with three portions of ether. The combined extracts were washed with saturated brine, dried over $MgSO_4$, and concentrated. Flash chromatography of the remaining oil (4.17 g) on silica gel (50 mm×200 mm, 3 : 1 hexane–ethyl acetate) gave **2a** (1.69 g, 11.0 mmol, 67%) and **3a** (273 mg, 1.77 mmol, 11%).

2a: A colorless oil; IR (neat) 3450, 3050, 2950, 2853, 2825, and 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.25 (1H, ddd, $J_{3endo,3exo}$ = 13.5, $J_{3endo,4}$ = 6.0, and $J_{3endo,2exo}$ = 3.3 Hz, H_{3endo}), 1.30—1.41 (2H, m), 1.52—1.64 (2H, m), 2.02 (1H, ddd, $J_{3exo,3endo}$ = 13.5, $J_{3exo,2exo}$ = 8.4, and $J_{3exo,4}$ = 2.4 Hz, H_{3exo}), 2.23 (1H, d, J = 2.4 Hz, OH), 2.52 (1H, m, H_4), 3.41 (3H, s, OCH_3), 3.92 (1H, dddd, $J_{2exo,3exo}$ = 8.4, $J_{2exo,3endo}$ = 3.3, $J_{2exo,OH}$ = 2.4, and $J_{2exo,6}$ = 2.3 Hz, H_{2exo}), 6.14 (1H, broad d, $J_{6,5}$ = 8.7 Hz, $W_{1/2}$ = 3.6 Hz, H_6), and 6.36 (1H, dd, $J_{5,6}$ = 8.7 and $J_{4,5}$ = 6.3 Hz, H_5). Found: *m/z* 154.1016. Calcd for $C_9H_{14}O_2$: M, 154.0994.

The Benzoate of 2a: Colorless oil; IR (neat) 1710 cm^{-1}. Found: *m/z* 258.1250. Calcd for $C_{16}H_{18}O_3$: M, 258.1256.

3a: Colorless oil; IR (neat) 3450, 3050, 2950, 2853, 2825, and 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.30 (1H, ddd, J = 13.2, 2.7, and 2.4 Hz), 1.33—1.43 (2H, m), 1.73 (1H, ddd, J = 9.7, 8.6, and 2.7 Hz), 1.87 (1H, dddd, J = 13.5, 10.2, 6.3, and 3.0 Hz), 1.99 (1H, dd, $J_{3endo,2endo}$ = 9.9 and $J_{3endo,4}$ = 7.4 Hz, H_{3endo}), 2.29 (1H, s, OH), 2.48 (1H, m, H_4), 3.38 (3H, s, OCH_3), 3.78 (1H, broad d, $J_{2endo,3endo}$ = 9.9 Hz, $W_{1/2}$ = 4 Hz, H_{2endo}), 6.24 (1H, broad d, $J_{6,5}$ = 8.7 Hz, H_6), and 6.27 (1H, dd, $J_{5,6}$ = 8.7 and $J_{4,5}$ = 6.3 Hz, H_5).

The Benzoate of 3a: Colorless oil; IR (neat) 1710 cm^{-1}. Found: *m/z* 258.1254. Calcd for $C_{16}H_{18}O_3$: M, 258.1256.

(±)-1-Methoxy-4-methylbicyclo[2.2.2]oct-5-en-*endo*-2-ol (2b) (63% yield): Colorless oil; IR (neat) 3450, 3050, 2950, 2853, 2825, 1100, and 685 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.15 (3H, s, 4-CH_3), 1.20— 1.29 (1H, m), 1.40 (2H, m), 1.56—1.68 (2H, m), 1.87 (1H, dd, $J_{3exo,3endo}$ = 13.2 and $J_{3exo,2exo}$ = 8.4 Hz, H_{3exo}), 2.25 (1H, d, J = 2.7 Hz, OH), 3.40 (3H, s, OCH_3), 3.94 (1H, broad d, J = 8.4 Hz, $W_{1/2}$ = 6 Hz, H_{2exo}), 6.09 (1H, d, $J_{6,5}$ = 8.7 Hz, H_6), and 6.10 (1H, d, $J_{5,6}$ = 8.7, H_5). Found: *m/z* 140.0837. Calcd for $C_{10}H_{14}O$: M–H_2O, 140.0837.

The Benzoate of 2b: Colorless oil; IR (neat) 1710 cm^{-1}. Found: *m/z* 272.1406. Calcd for $C_{17}H_{20}O_3$: M, 272.1412.

(±)-1-Methoxy-4-methylbicyclo[2.2.2]oct-5-en-*exo*-2-ol (3b) (13% yield): Colorless oil ; IR (neat) 3450, 3050, 2950, 2853, 2825, 1080, and 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.11 (3H, s, 4-CH_3), 1.22 (2H, m), 1.43 (1H, dddd, J = 11.9, 11.9, 3.8, and 2.2 Hz), 1.56 (1H, ddd, J = 10.7, 10.7, and 3.7 Hz), 1.72 (1H, ddd, J = 13.5, 10.1, and 3.5 Hz), 2.03 (1H, ddd, J = 11.2, 9.9, and 4.5 Hz), 2.26 (1H, s, OH), 3.38 (3H, s, OCH_3), 3.80 (1H, broad d, J = 9.9 Hz, $W_{1/2}$ = 4 Hz, H_{2endo}), 5.97 (1H, d, J = 9.0 Hz, H_6), and 6.19 (1H, d, J = 9.0 Hz, H_5).

The Benzoate of 3b: Colorless oil; IR (neat) 1710 cm^{-1}. Found: *m/z* 272.1412. Calcd for $C_{17}H_{20}O_3$: M, 272.1412.

(±)-1-Methoxy-5-methylbicyclo[2.2.2]oct-5-en-*endo*-2-ol (2c) (62% yield): Colorless oil; IR (neat) 3450, 3050, 2950, 2853, 2825, 1650, and 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.21—1.41 (3H, m), 1.49—1.62 (2H, m), 1.85 (3H, d, J = 1.5 Hz, CH_3), 2.01 (1H, ddd, J = 13.8, 8.2, and 2.4 Hz), 2.24 (1H, d, J = 2.4 Hz, OH), 2.30 (1H, broad s, $W_{1/2}$ = 9 Hz, H_4), 3.40 (3H, s, OCH_3), 3.90 (1H, broad d, J = 8.4 Hz, $W_{1/2}$ = 5.9 Hz, H_{2exo}), and 5.75 (1H, broad s, $W_{1/2}$ = 5.4 Hz, H_6).

The Benzoate of 2c: Colorless oil; IR (neat) 1710 cm^{-1}. Found: *m/z* 272.1418. Calcd for $C_{17}H_{20}O_3$: M, 272.1412.

(±)-1-Methoxy-5-methylbicyclo[2.2.2]oct-5-en-*exo*-2-ol (3c) (17% yield): Colorless oil; IR (neat) 3450, 3050, 2950, 2853, 2825, 1650, and 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.25 (1H, ddd, $J_{3endo,3exo}$ = 13.2, $J_{3endo,2exo}$ = 3.0, and $J_{3endo,4}$ = 2.4 Hz, H_{3endo}), 1.30—1.40 (2H, m), 1.56 (1H, broad s, $W_{1/2}$ = 4 Hz, OH), 1.68 (1H, m, H_8), 1.76 (3H, d, J = 1.5 Hz, CH_3), 1.88 (1H, dddd, J = 13.2, 9.3, 3.3, and 2.4 Hz), 1.97 (1H, broad dd, $J_{7exo,7endo}$ = 10.2 and $J_{7exo,8exo}$ = 6.9 Hz, H_{7exo}), 2.20 (1H, broad s, $W_{1/2}$ = 7.2 Hz, H_4), 3.42 (3H, s, OCH_3), 3.73 (1H, broad d, $J_{2endo,3exo}$ = 9.3 Hz, $W_{1/2}$ = 7.2 Hz, H_{2endo}), and 5.79 (1H, broad s, $W_{1/2}$ = 5.5 Hz, H_6). Found: *m/z* 150.1040. Calcd for $C_{10}H_{14}O$: M–H_2O, 150.1045.

(±)-1-Methoxybicyclo[2.2.2]oct-5-en-*endo*-2-yl Acetate (4a) (90% yield): Colorless oil; ^1H NMR ($CDCl_3$) δ = 1.24 (1H, ddd, $J_{3endo,3exo}$ = 13.8, $J_{3endo,4}$ = 5.7, and $J_{3endo,2exo}$ = 2.4 Hz, H_{3endo}), 1.30—1.67 (4H, m), 2.03 (3H, s, OAc), 2.17 (1H, ddd, $J_{3exo,3endo}$ = 13.8, $J_{3exo,2exo}$ = 8.4, and $J_{3exo,4}$ = 2.4 Hz, H_{3exo}), 2.54 (1H, m, H_4), 3.35 (3H, s, OCH_3), 5.13 (1H, ddd, $J_{2exo,3exo}$ = 8.4, $J_{2exo,3endo}$ = 2.4, and $J_{2exo,6}$ = 1.5 Hz, H_{2exo}), 6.15 (1H, braod d, $J_{6,5}$ = 8.7 Hz, $W_{1/2}$ = 3.6 Hz, H_6), and 6.32 (1H, dd, $J_{5,6}$ = 8.7 and $J_{4,5}$ = 6.3 Hz, H_5).

(±)-1-Methoxy-4-methylbicyclo[2.2.2]oct-5-en-*endo*-2-yl Acetate (4b) (96% yield): Colorless oil; ^1H NMR ($CDCl_3$) δ = 1.12 (1H, ddd, $J_{3endo,3exo}$ = 13.8, $J_{3endo,8endo}$ = 3.7, and $J_{3endo,2exo}$ = 2.4 Hz, H_3), 1.14 (3H, s, 4-CH_3), 1.23 (1H, dddd, $J_{8endo,8exo}$ = 12.2, $J_{8endo,7endo}$ = 12.2, $J_{8endo,7exo}$ = 4.8, and $J_{8endo,3endo}$ = 3.7 Hz, H_{8endo}), 1.40 (1H, ddd, $J_{8exo,8endo}$ = 12.2, $J_{8exo,7exo}$ = 10.2, $J_{8exo,7endo}$ = 3.9, and $J_{8exo,5}$ < 1.0 Hz, H_{8exo}), 1.53 (1H, ddd, $J_{7endo,7exo}$ = 12.2, $J_{7endo,8endo}$ = 12.2, and $J_{7endo,8exo}$ = 3.9 Hz, H_{7endo}), 1.68 (1H, dddd, $J_{7exo,7endo}$ = 12.2, $J_{7exo,8exo}$ = 10.2, $J_{7exo,8endo}$ = 4.8, and $J_{7exo,6}$ < 1.0 Hz, H_{7exo}), 2.025 (1H, dd, $J_{3exo,3endo}$ = 13.8 and $J_{3exo,2exo}$ = 8.5 Hz, H_{3exo}), 2.03 (3H, s, OAc), 3.35 (3H, s, OCH_3), 5.13 (1H, ddd, $J_{2exo,3exo}$ = 8.5, $J_{2exo,3endo}$ = 2.4, and $J_{2exo,6}$ = 1.4 Hz, H_{2exo}), 6.20 (1H, broad d, $J_{5,6}$ = 8.7 Hz, $W_{1/2}$ = 2 Hz, H_5), and 6.21 (1H, broad d, $J_{6,5}$ = 8.7 Hz, $W_{1/2}$ = 3 Hz, H_6). Found: *m/z* 210.1252. Calcd for $C_{12}H_{18}O_3$: M, 210.1256.

(±)-1-Methoxy-4-methylbicyclo[2.2.2]oct-5-en-*exo*-2-yl Acetate (5b) (90% yield): Colorless oil; ^1H NMR ($CDCl_3$) δ = 1.12

(3H, s, 4-CH_3), 1.15 (1H, broad dd, $J_{3exo,3endo}$=13.5 and $J_{3exo,2endo}$= 2.2 Hz, ($J_{3exo,5}$ < 1.0 Hz), H_{3exo}), 1.29 (1H, dddd, $J_{8endo,8exo}$ = 12.2, $J_{8endo,7endo}$=11.8, $J_{8endo,7exo}$=4.0, and $J_{8endo,3endo}$=3.6 Hz, H_{8endo}), 1.40 (1H, dddd, $J_{7endo,7exo}$=11.8, $J_{7endo,8endo}$=11.8, $J_{7endo,8exo}$=4.3, and $J_{7endo,2endo}$ = 1.6 Hz, H_{7endo}), 1.54 (1H, ddd, $J_{8exo,8endo}$ = 12.2, $J_{8exo,7exo}$ = 10.1, and $J_{8exo,7endo}$ = 4.3 Hz, H_{8exo}), 1.89 (1H, ddd, $J_{3endo,3exo}$=13.5, $J_{3endo,2endo}$=9.9, and $J_{3endo,8endo}$=3.6 Hz, H_{3endo}), 2.10 (3H, s, OAc), 2.13 (1H, dddd, $J_{7exo,7endo}$=11.8, $J_{7exo,8exo}$=10.1, $J_{7exo,8endo}$ = 4.0, and $J_{7exo,6}$ < 0.5 Hz, H_{7exo}), 3.35 (3H, s, OCH_3), 4.94 (1H, ddd, $J_{2endo,3endo}$ = 9.9, $J_{2endo,3exo}$ = 2.2, and $J_{2endo,7endo}$ = 1.6 Hz, H_{2endo}), 6.00 (1H, broad d, $J_{5,6}$ = 8.7 Hz, $W_{1/2}$ = 2 Hz, H_5), and 6.21 (1H, broad d, $J_{6,5}$ = 8.7 Hz, $W_{1/2}$ = 3 Hz, H_6). Found: *m/z* 210.1252. Calcd for $C_{12}H_{18}O_3$: M, 210.1256.

(±)-1-Methoxybicyclo[2.2.2]oct-5-en-*endo*-2-yl Chloroacetate (6a). (As a General Procedure for Chloroacetylation). To a solution of an alcohol **2a** (1.32 g, 8.58 mmol) and pyridine (1.80 cm^3, 14.3 mmol) in dichloromethane (18 cm^3) was added dropwise chloroacetyl chloride (1.07 ml, 13.2 mmol) at 0 °C under argon. The mixture was stirred for 1 h at 0 °C, diluted with dichloromethane (18 cm^3), and stirred with water (12 cm^3) for 30 min. The resulting mixture was extracted with two portions of ether (100 cm^3 each). The organic layers were combined, washed with two portions of 5% aqueous HCl, with saturated aqueous $NaHCO_3$, and with saturated brine, and dried over $MgSO_4$. Evaporation of the solvents gave a pale yellow oil (2.31 g). Chromatography of the oil on silica gel (100 g, 5 : 1 hexane–ethyl acetate) gave **6a** (1.83 g, 7.91 mmol, 92%) as a colorless oil.

6a: IR (neat) 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.28 (1H, ddd, $J_{3endo,3exo}$ = 13.8, J =$_{3endo,2exo}$= 2.4, and $J_{3endo,4}$ = 2.1 Hz, H_{3endo}), 1.30—1.67 (4H, m), 2.18 (1H, ddd, $J_{3exo,3endo}$=13.8, $J_{3exo,2exo}$=8.4, and $J_{3exo,4}$ = 2.1 Hz, H_{3exo}), 2.57 (1H, m, H_4), 3.34 (3H, s, OCH_3), 4.00 (1H, d, J = 15.0 Hz, –C<u>H</u>HCl), 4.06 (1H, d, J = 15.0 Hz, –CH<u>H</u>Cl), 5.23 (1H, ddd, $J_{2exo,3exo}$=8.4, $J_{2exo,3endo}$=2.4, and J=1.5 Hz, H_{2exo}), 6.12 (1H, broad d, $J_{6,5}$ = 8.7 Hz, H_6), and 6.33 (1H, dd, $J_{5,6}$ = 8.7 and $J_{4,5}$ = 6.3 Hz, H_5). Found: *m/z* 230.0708. Calcd for $C_{11}H_{15}ClO_3$: M, 230.0710.

(±)-1-Methoxy-4-methylbicyclo[2.2.2]oct-5-en-*endo*-2-yl-Chloroacetate (6b) (90% yield): Colorless oil; IR (neat) 1750 cm^{-1}; ^1H NMR ($CDCl_3$ δ = 1.12 —1.21 (1H,m), 1.16 (3H, s, 4-CH_3), 1.27 (1H, dddd, $J_{8endo,8exo}$ = 12.0, $J_{8endo,7endo}$ = 12.0, $J_{8endo,7exo}$ = 5.4, and $J_{8endo,3endo}$ = 3.6 Hz, H_{8endo}), 1.42 (1H, ddd, $J_{8exo,8endo}$=12.0, $J_{8exo,7exo}$=9.8, and $J_{8exo,7endo}$=3.6 Hz, H_{8exo}), 1.56 (1H, ddd, $J_{7endo,7exo}$ = 12.0, $J_{7endo,8endo}$ = 12.0, and $J_{7endo,8exo}$ = 3.6 Hz, H_{7endo}), 1.67 (1H, ddd, $J_{7exo,7endo}$ = 12.0, $J_{7exo,8exo}$ = 9.8, and $J_{7exo,8endo}$ = 5.4 Hz, H_{7exo}), 2.04 (1H, dd, $J_{3exo,3endo}$ = 13.8 and $J_{3exo,2exo}$ = 8.4 Hz, H_{3exo}), 3.34 (3H, s, OCH_3), 4.00 (1H, d, J = 15.0 Hz, –C<u>H</u>HCl), 4.06 (1H, d, J = 15.0 Hz, –CH<u>H</u>Cl), 5.23 (1H, ddd, $J_{2exo,3exo}$ = 8.4, $J_{2exo,3endo}$ = 2.4, and $J_{2exo,6}$ = 1.2 Hz, H_{2exo}), 6.05 (1H, broad d, $J_{5,6}$ = 8.7 Hz, $W_{1/2}$ = 2 Hz, H_5), and 6.09 (1H, broad d, $J_{6,5}$ = 8.7 Hz, $W_{1/2}$ = 3 Hz, H_6). Found :*m/z* 244.0858. Calcd for $C_{12}H_{17}ClO_3$: M, 244,0866.

(±)-1-Methoxy-5-methylbicyclo[2.2.2]oct-5-en-*endo*-2-yl Chloroacetate (6c) (90% yield): Colorless oil; IR (neat) 1750 cm^{-1}; ^1H MNR ($CDCl_3$) δ = 1.26 (1H, ddd, $J_{3endo,3exo}$ = 13.8, $J_{3endo,2exo}$ = 5.7, and $J_{3endo,4}$ = 2.4 Hz, H_{3endo}), 1.30—1.60 (4H, m), 1.85 (3H, d, J = 1.8 Hz, 5-CH_3), 2.17 (1H, ddd, J = 14.1, 8.4, and 2.1 Hz), 2.33 (1H, broad s, $W_{1/2}$ = 7.2 Hz, H_4), 3.33 (3H, s, OCH_3), 4.03 (1H, d, J = 15.0 Hz –C<u>H</u>HCl), 4.07 (1H, d, J = 15.0 Hz, –CH<u>H</u>Cl), 5.18 (1H, broad d, J = 8.7 Hz, $W_{1/2}$ = 3.6 Hz, H_{2exo}), and 5.72 (1H, broad s, $W_{1/2}$ = 5.5 Hz, H_6). Found: *m/z* 244.0863. Calcd for $C_{12}H_{17}ClO_3$: M, 244.0866.

(±)-1-Methoxybicyclo[2.2.2]oct-5-en-*exo*-2-yl-Chloroacetate (7a) (89% yield): IR (neat) 1750 cm^{-1}; ^1H MNR ($CDCl_3$) δ = 1.30—1.50 (4H, m), 1.72 (1H, dddd, J = 12.0, 12.0, 4.2, and 2.4 Hz), 2.00—2.12 (2H, m), 2.56 (1H, m, H_4), 3.35 (3H, s, OCH_3), 4.11 (1H, d, J = 15.0 Hz, –C<u>H</u>HCl), 4.12 (1H, d, J = 15.0 Hz, –CH<u>H</u>Cl), 5.04 (1H, ddd, $J_{2exo,3exo}$=9.9, $J_{2exo,3endo}$=2.4, and J=2.4 Hz, H_{2exo}), 6.26 (1H, broad d, $J_{6,5}$ = 8.7 Hz, H_6), and 6.33 (1H, dd, $J_{5,6}$ = 8.7 and $J_{4,5}$ = 6.3 Hz, H_5). Found *m/z* 230.0708. Calcd for $C_{11}H_{15}ClO_3$: M, 230.0710.

Enzymatic Hydrolysis of 6a (As a General Procedure): To an emulsion of the enzyme (PS, 200 mg) in 0.067 M sodium phosphate buffer (pH 7.0, 20 cm^3) was added a solution of **6a** (400 mg, 1.74 mmol) in THF (4 cm^3) at 35 °C. This mixture was stirred continuously and the reaction was monitored by VPC. After 22 h, the reaction mixture was extracted with ether (3×50 cm^3). The combined extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Chromatography of the residue (214 mg) on silica gel (12.5 g, 5 : 1 hexane–ethyl acetate) gave **8a** (69.4 mg, 0.462 mmol, 26%) and **10a** (124.2 mg, 0.540 mmol, 31%). The alcohol **8a** was transformed into the benzoate, and its optical purity (85%ee) determined. The ester **10a** was reduced by $LiAlH_4$, and the resulting alcohol was converted into the benzoate (98%ee).

(+)-1-Methoxy-4-methylbicyclo[2.2.2]oct-5-en-2-one (11b). (As a General Procedure for Oxidation of Alcohols 8 and 12). To a solution of an alcohol **8b** (87%ee, 65.7 mg, 0.312 mmol) and triethylamine (0.35 cm^3, 2.54 mmol) in DMSO (2 cm^3) was added dropwise a solution of sulfur trioxide–pyridine (186.2 mg, 1.17 mmol) in DMSO (2 cm ^{3}) at room temperature under argon. The mixture was stirred for 20 min, diluted with water (3 cm^3), and extracted with three portions of ether. The organic layers were combined, washed with two portions of 5% aqueous HCl, with saturated aqueous $NaHCO_3$, and with saturated brine, and dried over $MgSO_4$. Evaporation of the solvents gave an oil (58.6 mg). Chromatography of the oil on silica gel (5 g, 3 : 1 hexane–ethyl acetate) gave **11b** (51.7 mg, 0.311 mmol, 80%) as a colorless oil. The IR and ^1H NMR spectra of **11b** were identical to those of **1b**.[3a] The CD and ORD spectra of **11b** are listed in Tables 2 and 3, respectively.

(−)-4-Methylbicyclo[2.2.2]oct-5-en-2-one (15b). To a stirred solution of a chiral ketone **13b** (92%ee, 140 mg, 0.843 mmol) in dichloromethane (7.0 cm^3) was added boron trifluoride–methanol (0.060 cm^3, 0.56 mmol) at 20 °C under argon. The mixture was stirred for 2 h and then diluted with dichloromethane. The solution was washed with a saturated aqueous $NaHCO_3$ solution, water, and saturated brine, and dried over $MgSO_4$. Evaporation of the solvent under vacuum gave a colorless oil (103.7 mg, 0.624 mmol, 74%). To a stirred solution of the oil in hexane (4.0 cm^3) was added diisobutylaluminium hydride (1 M toluene solution, 1.4 cm^3, 1.4 mmol) at 0 °C under argon. The mixture was allowed to warm to room temperature. To this solution was added an aqueous NH_4Cl solution. The resulting mixture was extracted with three portions of ether. The combined extracts were washed with saturated brine, dried over $MgSO_4$, and concentrated to an oil (109 mg). To a solution of this oil benzene (10 cm^3) was added *p*-toluenesulfonic acid (12.4 g, 0.065 mmol). The mixture was heated under reflux for 1 h and then treated with a saturated aqueous $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with two portions of ether. The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and carefully concentrated to an oil. Chromatography of this oil on silica gel (10 g, 10 : 1 hexane–ether) gave **15b** (48.2 mg, 0.354 mmol, 42%) as a colorless oil. The IR and ^1H NMR spectra of **15b** were identical with those of (±)-**15b**.[5]

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