Enzymatic Resolution of Cyclopropanols. An Easy Access to Optically Active Cyclohexanones Possessing an α-Quaternary Chiral Carbon

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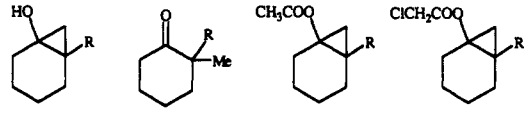
The chemistry of cyclopropanols has been thoroughly studied,[1] and useful applications of their cleavage by electrophiles have been reported.[2] However optically active cyclopropanols and derivatives are rare.[3] They have been generally obtained by chemical transformation of optically active compounds.[4] Recently, Reissig reported the enantioselective preparation of (siloxy)cyclopropanes (ee < 37%) by a copper-catalyzed cyclopropanation of silyl enol ethers.[5] Better results were obtained by Tai[6] who prepared optically active cyclopropanols by diastereoselective Simmons–Smith reactions (de: 95–99%).

In this paper we report our results on the enzymatic resolution of racemic 1-bicyclo[4.1.0]heptanol derivatives **1**, which, after opening, should allow the preparation of optically active 2,2-disubstituted cyclohexanones **2**.



1 2 3 4

Esterase-catalyzed hydrolysis of cyclopropyl acetate has been reported to occur without formation of ring-opened byproducts.[7] To obtain optically active cyclopropanols **1** we envisioned the hydrolysis of the corresponding acetates **3**. However, there are few reports in the literature concerning the reaction of tertiary alcohol derivatives. Cleavage of *tert*-butyl esters has been reported to occur with esterases at a slow rate,[8] and recently thermitase was found to be more efficient.[9] In this context, enzymatic resolutions of racemic tertiary alcohols are rare. Discrimination of α-acetoxy nitrile enantiomers was observed during hydrolysis by microorganisms,[10] and resolution of tertiary acetylenic acetate esters was accomplished with the lipase from *Candida cylindracea*.[11] These compounds are in fact activated alcohols. Cyclopropanols, owing to their chemical properties, are often compared to homoenols[2] and are more reactive than ordinary tertiary alcohols. For these reasons we decided to examine the resolution of racemic cyclopropanols **1**.

Scheme I

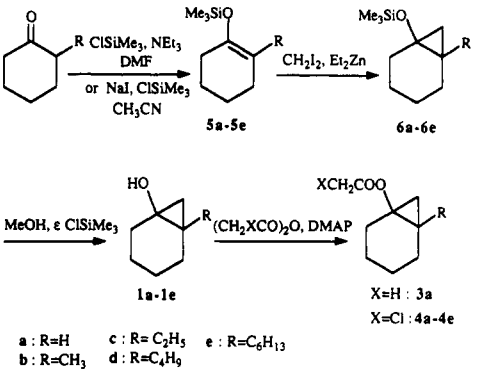


Table I. Hydrolysis of 1-Acetoxybicyclo[4.1.0]heptane (3a)

enzyme	reaction time (h)	conversn[a]	ee acetate[b] (%)	ee alcohol[b] (%)	E^a
PLE	3	0.58	91	64	14
HLE	2.5	0.31	28	61	5
CCL	5	0.51	88	86	23

[a] Conversion and E calculated according to ref 17. [b] ee measured by ^{1}H NMR (Eu(hfc)$_3$).

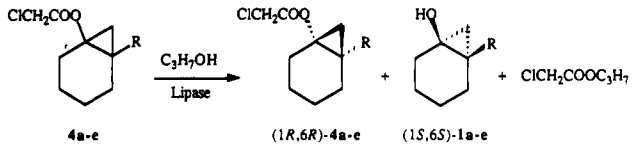
The cyclopropyl esters required for this study were prepared as shown in Scheme I. The α-substituted trimethylsilyl enol ethers **5b–5e** were obtained by reaction of 2-substituted cyclohexanones with chlorotrimethylsilane and sodium iodide in acetonitrile[12] and were cyclopropanated, as enol ether **5a**, by a diethylzinc–methylene iodide mixture[13] to give the corresponding 1-[(trimethylsilyl)oxy]bicyclo[4.1.0]heptanes **6a–6e**. Acidic cleavage of the trimethylsilyl ethers[14] gave cleanly the cyclopropanols **1a–1e** which were esterified with acetic or chloroacetic anhydride in the presence of 4-(dimethylamino)-pyridine. Acetate **3a** and chloroacetates **4a–4e** were characterized by their ^{1}H NMR, IR, and mass spectra.

We first turned our attention to the hydrolysis of the acetate **3a** at pH 7.2. The products were isolated by standard procedures and purified by liquid chromatography (neutral alumina, activity III). The results are reported in Table I. With acetone powders of porcine and horse liver (PLE and HLE) the enantioselectivities were moderate to low and better results were obtained using the lipase from *C. cylindracea* (CCL). No reaction was observed with the lipase from porcine pancreas. The enantiomeric excess (ee) of the remaining acetate was measured by ^{1}H NMR spectroscopy in the presence of Eu(hfc)$_3$, and that of the cyclopropanol was determined after conversion into its acetate. The configuration of

(1) Gibson, D. H.; De Puy, C. H. *Chem. Rev.* **1974**, *74*, 605.
(2) Kuwajima, I.; Nakamura, E. *Top. Curr. Chem.* **1990**, *133*, 3.
(3) Salaün, J. *Chem. Rev.* **1989**, *89*, 1247.
(4) (a) De Puy, C. H.; Breitbeil, F. W.; De Bruin, K. R. *J. Am. Chem. Soc.* **1966**, *88*, 3347. (b) Cooke, M. D.; Fischer, E. *J. Organomet. Chem.* **1973**, *56*, 279. (c) Salaün, J.; Karkour, B.; Ollivier, J. *Tetrahedron* **1989**, *45*, 3151 and references cited therein. (d) Fadel, A.; Salaün, J. *Tetrahedron Lett.* **1988**, *29*, 6257.
(5) Kunz, T.; Reissig, H. U. *Tetrahedron Lett.* **1989**, *30*, 2079.
(6) (a) Sugima, T.; Futagawa, T.; Tai, A. *Tetrahedron Lett.* **1988**, *29*, 5775. (b) Sugimura, T.; Yoshibawa, M.; Futagawa, T.; Tai, A. *Tetrahedron* **1990**, *46*, 5955. (c) Sugimura, T.; Katagiri, T.; Tai, A. *Tetrahedron Lett.* **1992**, *33*, 367.
(7) Jongejan, J. A.; Duine, J. A. *Tetrahedron Lett.* **1987**, *28*, 2767.
(8) De Jeso, B.; Drouillard, S.; Degueil-Castaing, M.; Maillard, B. *Synth. Commun.* **1988**, *18*, 1699.
(9) Schultz, M.; Hermann, P.; Kunz, H. *Synlett* **1992**, *37*.
(10) Ohta, H.; Kimura, Y.; Sugano, Y.; Sugai, T. *Tetrahedron* **1989**, *45*, 5469 and references cited therein.
(11) O'Hagan, D.; Zaidi, N. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 947.
(12) Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron* **1987**, *43*, 2075.
(13) Furukawa, J.; Kawabata, N.; Nishimura, N. *Tetrahedron* **1968**, *24*, 53.
(14) Girard, C.; Conia, J. M. *J. Chem. Res. Miniprint* **1978**, 2351.

0022-3263/93/1958-1570$04.00/0

Scheme II



optically active cyclopropanol **1a** was determined to be 1*S*,6*S* by comparison of its chiroptical properties with those reported in the literature.[6a]

One main drawback of the enzymatic hydrolytic reactions is the tedious extraction necessary to isolate the products in satisfactory yields. An interesting method to avoid these problems is to carry out transesterifications in an organic medium.[15] We ran the transesterification in the presence of 1-propanol, starting from chloroacetates **4a–4e** instead of the less reactive acetates (Scheme II).

Using CCL, with the parent chloroacetate **4a** a low enantioselectivity (E = 8) was observed, and no reaction was noticed after 1 day with the substituted choroacetate **4d**. After preliminary experiments we chose to run the transesterification reactions using the lipase from *Mucor miehei* (lipozyme)[16] in diisopropyl ether at 35 °C. After about 50% conversion (2.5–3 h) the enzyme was filtered off and the products were separated by liquid chromatography over neutral alumina (overall yields >80%). Our results are collected in Table II.

In the cases studied, moderate to excellent ee's were found for the cyclopropanols **1** and the remaining chloroacetates **4**. The enantiomeric purities were determined by ^{1}H NMR analyses in the presence of the chiral Eu(hfc)$_3$. The ee's of alcohols **1** were measured on the corresponding acetates, and those of the chloroacetates were measured either on the methylated chloroacetate (**4b**) or after transesterification into acetate (**4a**) or after opening into methylcyclohexanones (**4c–4e**) (vide infra). The absolute configuration of cyclopropanol **1a** is known (vide supra), and the 1*R*,6*R* configuration of the nonhydrolyzed chloroacetate **4d** was ascertained by a chemical correlation with (*R*)-2-butyl-2-methylcyclohexanone (**2d**).[18] In these reactions with **4a** and **4d** the transesterification has occurred mainly with the 1*S*,6*S* enantiomer, and the same enantioselectivity of the enzyme is postulated for the cyclopropyl chloroacetates **4b**, **4c**, and **4e**. The similarity of the chiroptical properties of the optically active esters **4b–4e** is in agreement with such an assumption.[19]

It has been reported that cyclopropanol derivatives are converted in the presence of sodium hydroxide into 2-methyl ketones;[20] this reaction can be applied to the preparation of quaternary carbon centers.[21] The synthesis of optically active cyclopropyl derivatives **1c–1e** and **4c–4e** by enzymatic reaction prompted us to test their transformations by basic treatment into enantiomerically enriched ketones possessing a chiral quaternary carbon. Chemical[22–32] and enzymatic[33,34] methods have been reported to prepare such optically active compounds. A large number of these methods gave unsatisfactory results, and only a few methods offer large scope and high enantioselectivities.[27,28]

Treatment of optically active cyclopropanols **1c–1e** and cyclopropyl chloroacetates **4c–4e** with 2 equiv of aqueous sodium hydroxide in methanol at room temperature led cleanly to the corresponding enantiomerically enriched 2-alkyl-2-methylcyclohexanones **2c–2e** (yields ≥86%). The ee's of the ketones were measured by ^{1}H NMR spectroscopy in the presence of Eu(hfc)$_3$. The results are reported in Table III. Except for cyclohexanone (*R*)-**2d**[18,25] these

(15) Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 114.

(16) This enzyme was purchased from Novo Co. (Denmark). The enzyme is supported on an anionic resin.

(17) Chen, C.-S.; Wu, S.-H.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1987**, *109*, 2812.

(18) Marshall, J. A.; Flynn, K. E.; *J. Am. Chem. Soc.* **1982**, *104*, 7430.

(19) To confirm these absolute configurations, the optically active cyclopropanols **1a–e** obtained after the transesterification reactions (Scheme II) were acylated ((CH$_3$CO$_2$)O, DMAP) and examinated by ^{1}H NMR spectroscopy (C_6D_6) in the presence of Eu(hcf)$_3$. The methyl of the acetoxy group was split into two signals. In all cases except acetate **3a** the signal with the higher δ value was the minor signal.

(20) Wenkert, E.; Mueller, R. A.; Reardon, E. J.; Sathe, S. S.; Scharf, D. J.; Tosi, G. *J. Am. Chem. Soc.* **1970**, *92*, 7428. For a review see: Conia, J. M. *Pure Appl. Chem.* **1975**, *43*, 317.

(21) In the same way cleavage of cyclopropanone acetals was reported to give optically active 2,2-dialkyl esters: Isaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **1990**, *112*, 7428.

(22) Alkylation of ketones in the presence of a chiral catalyst: (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) Fiaud, J. C. *Tetrahedron Lett.* **1975**, 3495. (c) Hermann, K.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2238 and references cited therein. (d) Saigo, K.; Koda, H.; Nohira, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3119. (e) Julia, S.; Ginebreda, A.; Guixer, J.; Tomas, A. *Tetrahedron Lett.* **1980**, *21*, 3709. (f) Cram, D. J.; Sogah, G. D. Y. *J. Chem. Soc., Chem. Commun.* **1981**, 625. (g) Hughes, D. L.; Dolling, U. H.; Ryan, K. M.; Schoenewaldt, E. F.; Grabowski, E. J. J. *J. Org. Chem.* **1987**, *52*, 4745 and references cited therein. (h) Umemura, K.; Matsuyama, H.; Watanabe, N.; Kobayashi, M.; Kamigata, N. *J. Org. Chem.* **1989**, *54*, 2375. (i) Nerincke, W.; Vanderwalle, M. *Tetrahedron: Asymmetry* **1990**, *1*, 265.

(23) Alkylation of ketones using a chiral base: (a) Simpkins, N. S. *J. Chem. Soc., Chem. Commun.* **1986**, 88. (b) Cain, C. M.; Cousins, R. P. C.; Coumbarides, G.; Simpkins, N. S. *Tetrahedron* **1990**, *46*, 523.

(24) Reaction of ketone enolates with alkylating agents bearing a chiral group: (a) Murphy, W. S.; Duggan, P. G. *J. Chem. Soc., Perkin Trans. 1* **1976**, 634. (b) Annunziata, R.; Cinquini, M.; Colonna, S. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2422.

(25) Asymmetric Claisen rearrangement: Gratton, T. J.; Whitehurst, J. S. *J. Chem. Soc., Perkin Trans. 1*, **1990**, 11 and references cited therein.

(26) Reaction of chiral enamines with alkylating agents in the presence of base: (a) Hashimoto, S. i.; Koga, K. *Tetrahedron Lett.* **1978**, 573. (b) Hashimoto, S. i.; Koga, K. *Chem. Pharm. Bull.* **1979**, *27*, 2760. (c) Tomioka, K.; Ando, K.; Takemasa, Y.; Koga, K. *J. Am. Chem. Soc.* **1984**, *106*, 2719. (d) Tomioka, K.; Seo, W.; Ando, K.; Koga, K. *Tetrahedron Lett.* **1987**, *28*, 6637. Paquette, L. A.; Gilday, J. P.; Maynard, G. D. *J. Org. Chem.* **1989**, *54*, 5044.

(27) Reaction of chiral enamines with alkylating agents without additional base: (a) Tomioka, K.; Ando, K.; Yasuda, K.; Koga, K. *Tetrahedron Lett.* **1986**, *27*, 715. (b) Tomioka, K.; Yasuda, K.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1987**, 1345. (c) Brunner, H.; Kraus, J.; Lautenschlager, H. J. *Monatsch. Chem.* **1988**, *119*, 1161. (d) Guingnant, A.; Hammami, H. *Tetrahedron: Asymmetry* **1991**, *2*, 411. (e) Guingnant, A.; *Tetrahedron: Asymmetry* **1991**, *2*, 415.

(28) Reaction of chiral imines with activated olefins: (a) Pfau, M.; Revial, G.; Guingnant, A.; d'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273. For a review see: d'Angelo, J.; Desmaële, D.; Dumas, F.; Guingnant, A.; *Tetrahedron: Asymmetry* **1992**, *3*, 459. (b) Gaidarova, E. L.; Grishina, G. V. *Synlett.* **1992**, 88.

(29) Alkylation of β-dicarbonyl compounds in the presence of palladium salts bearing chiral ligands: (a) Hayashi, T.; Kanehira, K.; Hagihara, T.; Kumada, M. *J. Org. Chem.* **1988**, *53*, 113 and references cited therein. (b) Sawamura, M.; Nagata, H.; Sakamoto, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2586.

(30) Reaction of silyl enol ethers with activated olefins: (a) Duhamel, P.; Hennequin, L.; Poirier, J. M.; Tavel, G.; Vottero, C. *Tetrahedron* **1986**, *42*, 4777. (b) Michelon, F.; Pouilhès, A.; Van Bac, N.; Langlois, N. *Tetrahedron Lett.* **1992**, *33*, 1743.

(31) Diastereoselective [2 + 2] cycloadditions: Greene, A. E.; Charbonnier, F.; Luche, M. J.; Moyano, A. *J. Am. Chem. Soc.* **1987**, *109*, 4752.

(32) Rearrangement of optically active oxaspiropentanes: Nemoto, H.; Ishibashi, H.; Nagamochi, M.; Fukumoto, K. *J. Org. Chem.* **1992**, *57* 1707.

(33) Reduction of 2,2-disubstituted-1,3-diketones by yeasts: (a) Gibian, H.; Kieslich, K.; Koch, H. J.; Kosmol, H.; Rufer, C.; Schröder, E.; Vössing, R. *Tetrahedron Lett.* **1966**, 2321. (b) Brooks, D. W.; Grothaus, P. G.; Irwin, W. I. *J. Org. Chem.* **1982**, *47*, 2820. (c) Brooks, D. W.; Mazdiyasni, H.; Chakrabarti, S. *Tetrahedron Lett.* **1984**, *25*, 1241. (d) Brooks, D. W.; Mazdiyasni, H.; Grothaus, P. G. *J. Org. Chem.* **1987**, *52*, 3223. (e) Mori, K.; Fujiwhara, M. *Tetrahedron* **1988**, *44*, 343. (f) Mori, K.; Fujiwhara, M. *Liebigs Ann. Chem.* **1989**, 41. (g) Mori, K.; Fujiwhara, M. *Liebigs Ann. Chem.* **1990**, 369.

(34) Hydrolysis of the 2,2-bis(acetoxymethyl)cyclopentanone with an esterase: Suemune, H.; Harabe, T.; Xie, Z.; Sakai, K. *Chem. Pharm. Bull.* **1988**, *36*, 4337.

Table II. Transesterification of Chloroacetates 4a–4e in the Presence of Lipase from *M. miehei* and 1-Propanol

	substrate 4		chloroacetate 4			alcohol 1		
entry	R	conversn[a]	$[\alpha]^{25}_{D}$[b] (deg)	ee[c] (%)	conf.[d]	$[\alpha]^{25}_{D}$[b] (deg)	ee[c] (%)	E[a]
a	H	0.51	+10.4	84	1*R*,6*R*	+5.7	79	22
b	Me	0.57	+30.2	95	(1*R*,6*R*)	-18.7	72	22
c	ethyl	0.53	+18.5	91	(1*R*,6*R*)	-10.5	80	28
d	butyl	0.51	+18.5	90	1*R*, 6*R*	-11.6	86	38
e	hexyl	0.56	+13.0	86	(1*R*,6*R*)	-8.0	66	13

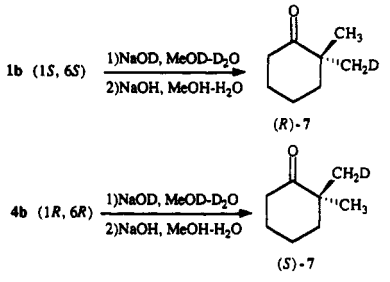
[a] Conversion and E calculated according to ref 17. [b] $c = 1$ (THF). [c] ee measured by ^{1}H NMR (Eu(hfc)$_3$), see text. [d] Configurations in parentheses are postulated.

Table III. Preparation of (*R*)- and (*S*)-2-Alkyl-2-methylcyclohexanones 2c–2e

substrate	product	ee (%)	conf.[a]	yield (%)
1c	(*S*)-2c	80	(*S*)	86
4c	(*R*)-2c	91	(*R*)	87
1d	(*S*)-2d	86	*S*	86
4d	(*R*)-2d	90	*R*	85
1e	(*S*)-2e	66	(*S*)	86
4e	(*R*)-2e	86	(*R*)	88

[a] Configurations in parentheses are postulated.

Scheme III

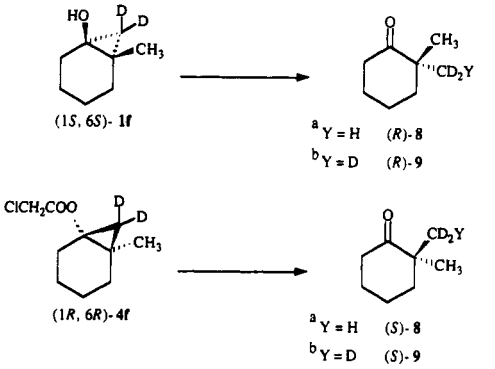


ketones have not yet been obtained in an enantiomerically enriched form. The simplicity of our method shows its usefulness.

Basic treatment of optically active cyclopropyl derivatives **1a** and **4a** under the conditions reported above should lead to racemic 2-methylcyclohexanone. However, by acidic treatment of bicycloheptanol (**1a**) enantiomerically enriched 2-methylcyclohexanone was prepared with partial racemization.[6a,35] Opening of optically active compounds **1b** and **4b** would lead to achiral 2,2-dimethylcyclohexanone. However, in these latter cases when the cleavage was performed with sodium deuteroxide in a mixture of MeOD–D_2O optically active (*R*)- and (*S*)-2-methyl-2-(methyl-*d*)cyclohexanones-6-d_2 were obtained, which gave (*R*)- and (*S*)-2-methyl-2-(methyl-*d*)cyclohexanone **7** after removal of the deuterium atoms in α' position to the carbonyl group by treatment with basic aqueous methanol (Scheme III, 80% yields). The deuterium incorporation, checked by mass spectroscopy was > 97%. Enantiomeric excesses of cyclohexanones **7** measured by ^{2}H NMR analyses in a cholesteric phase[36] are in agreement with those of the corresponding cyclopropanic compounds **1b**, **4b**. It should be emphasized that this NMR technique allows the visualisation of enantiomers although the deuterium atom was in α position of the chiral center.

Such isotopically labeled chiral cyclohexanones with two and three deuterium atoms on the same methyl group have also been prepared. Reaction of silyl enol ether **5b** with CD_2I_2 in the presence of diethylzinc in ether gave the corresponding 6-methyl-1-[(trimethylsilyl)oxy]bicyclo-[4.1.0]heptane-7-d_2 (**6f**) in good yield. Transesterification of the corresponding deuterated cyclopropyl chloroacetate **4f** with 1-propanol in the presence of the lipase from *M. miehei* gave results (E = 15) close to those reported for the corresponding non-deuterated compound **4b** (Scheme II and Table II).

Scheme IV[a]



[a] Key: (a) NaOH, MeOH–H_2O; (b) (1) NaOD, MeOD–D_2O, (2) NaOH, MeOH–H_2O.

In the first experiment the corresponding optically active chloroacetate **4f** and cyclopropanol **1f** were treated with aqueous sodium hydroxide in methanol to give the (*R*)- and (*S*)-2-methyl-2-(methyl-d_2)cyclohexanones **8** (Scheme IV, 85–90% yields). Sequential treatment of the same compounds **1f** and **4f** with sodium deuteroxide in a mixture MeOD–D_2O, followed by aqueous sodium hydroxide in methanol, led to the enantiomerically enriched 2-methyl-2-(methyl-d_3)cyclohexanones **9** (Scheme IV, 80% yields). The synthesis of (*R*)- and (*S*)-cyclohexanones **9** (ee < 50%) has been already achieved in 10 steps by degradation of natural products.[37]

In conclusion, the lipase resolution of 1-bicyclo[4.1.0]-heptanol derivatives appears to be a versatile and useful method to generate optically active cyclohexanones with an α-quaternary chiral center. The unusual reactivity of these tertiary alcohol derivatives is probably an indication of the homology of these cyclopropyl esters with vinyl esters which are generally more reactive than the corresponding alkyl esters. Application of this methodology to cyclanones of various ring sizes is under investigation.

Experimental Section

General. ^{1}H NMR spectra were recorded at 200 MHz. Mass spectra were determined at an ionizing voltage of 70 eV. GC analyses were recorded with 10% SE-30 2-m column. Column

(35) The opening of the cyclopropanol **1a** was made using a trace of *p*-toluenesulfonic acid, and a slight isomerization was observed. A large excess of acid was necessary in the case reported by Tai and al.[6a]

(36) Lafontaine, E.; Pechiné, J. M.; Courtieu, J.; Mayne, C. L. *Liq. Cryst.* **1990**, *7*, 293. Bayle, J. P.; Courtieu, J.; Loewenstein, A.; Pechiné, J. P. *New J. Chem.* **1992**, *16*, 837.

(37) Lee, S. F.; Edgar, M.; Pak, C. S.; Barth, G.; Djerassi, C. *J. Am. Chem. Soc.* **1980**, *102*, 4784.

chromatography was performed with silica gel (70–230 mesh) or neutral alumina. TLC was performed on 0.25-mm silica gel (Merck 60 F_{254}). Dry solvents were obtained as follows: diethyl ether was distilled over $LiAlH_4$, THF was distilled over sodium–benzophenone, and hexane was distilled over P_2O_5. DMF was purified by distillation over CaH_2 and chlorotrimethylsilane by distillation over quinoline under argon. Other reagents were distilled before use. 1-[(Trimethylsilyl)oxy]cyclohexene (**5a**) was prepared according to ref 38 and 2-alkyl-1-[(trimethylsilyl)oxy]-cyclohexenes **5b–5e** were prepared according to ref 12. These silyl enol ethers are known: **5a–5b**,[38] **5c–5e**.[39] 1-[(Trimethylsilyl)-oxy]bicyclo[4.1.0]heptanes **6a–6f** were prepared according to a literature procedure.[6b] 1-[(Trimethylsilyl)oxy]bicyclo[4.1.0]-heptane (**6a**) and 1-[(Trimethylsilyl)oxy]-6-methylbicyclo[4.1.0]-heptane (**6b**) are known.[14] PLE, HLE (acetone powders), and CCL were purchased from Sigma. The lipase from *M. miehei* (lipozyme) was obtained from Novo.

1-[(Trimethylsilyl)oxy]-6-ethylbicyclo[4.1.0]heptane (6c): IR (neat) 3060, 2940, 2860, 1455, 1250, 1200, 995 cm^{-1}; ^1H NMR δ 2.12–1.00 (m, 10 H), 0.95 (t, J = 6.6 Hz, 3 H), 0.60–0.40 (m, 2 H), 0.15 (s, 9 H). Anal. Calcd for $C_{13}H_{24}OSi$: C, 66.60; H, 11.18. Found: C, 66.87; H, 11.52.

1-[(Trimethylsilyl)oxy]-6-butylbicyclo[4.1.0]heptane (6d): IR (neat) 3060, 2940, 2860, 1455, 1250, 1210, 990 cm^{-1}; ^1H NMR (C_6D_6) δ 2.15–1.95 (m, 2 H), 1.82–1.10 (m, 11 H), 1.08–0.95 (m, 4 H), 0.54 (d, J = 5.1 Hz, 1 H), 0.48 (d, J = 5.1 Hz, 1 H), 0.18 (s, 9 H). Anal. Calcd for $C_{13}H_{26}OSi$: C, 68.96; H, 11.57. Found: C, 64.47; H, 11.82.

1-[(Trimethylsilyl)oxy]-6-hexylbicyclo[4.1.0]heptane (6e): IR (neat) 3060, 2940, 1455, 1250 cm^{-1}; ^1H NMR δ 2.12–1.00 (m, 18 H), 0.90 (t, J = 6.6 Hz, 3 H), 0.50–0.40 (m, 2 H), 0.15 (s, 9 H). Anal. Calcd for $C_{15}H_{30}OSi$: C, 70.80; H, 11.88. Found: C, 71.18; H, 12.10.

Preparation of Racemic 1-Bicyclo[4.1.0]heptanol (1a). Representative Procedure. Silyloxycyclopropane **6a** (1.84 g, 10 mmol) was stirred under argon at 0 °C as dry methanol (10 mL) and a drop of $ClSiMe_3$ were added. After 10 min, TLC analysis showed that the reaction was over, methanol was evaporated under reduced pressure, and the cyclopropanol **1a** was used without purification for the next step (1.10 g, 98%). Cyclopropanols **1b–1e** were prepared following the same procedure. All these compounds were sensitive in pure form, and their NMR spectra in $CDCl_3$ rapidly showed the presence of irrelevant signals. Cyclopropanols **1a** and **1b** are known.[14]

Preparation of Racemic 1-(Chloroacetoxy)bicyclo[4.1.0]-heptane (4a). Representative Procedure. A solution of cyclopropanol **1a** (1.10 g, 9.8 mmol) in CH_2Cl_2 (10 mL) under argon was stirred at 0 °C as a solution of DMAP (1.34 g, 11 mmol) and chloroacetic anhydride (1.70 g, 10 mmol) in CH_2Cl_2 (20 mL) was added dropwise. After 1 h at 0 °C, the reaction mixture was diluted with ether (50 mL) and the organic solution was washed successively with 10% $NaHCO_3$ (5 mL) and 1 M HCl solution (5 mL) and then dried (Na_2SO_4). The solvents were evaporated, and the product was purified by column chromatography on silica gel (pentane/ether (97/3)) to give the pure chloroacetate **4a** (1.47 g, 80%): IR (neat) 3060, 2940, 2860, 1770, 1745, 1450, 1150 cm^{-1}; ^1H NMR δ 3.99 (s, 2 H), 2.23 (ddd, J = 5.2, 7.3, 13.5 Hz, 1 H), 2.14–1.90 (m, 2 H), 1.45–1.05 (m, 6 H), 0.98 (ddd, J = 1.1, 6.3, 11 Hz, 1 H), 0.58 (dd, J = 6.5, 6.5 Hz, 1 H); EI-MS m/z 153, 139, 121, 111, 97, 94, 93, 79, 55(100). Anal. Calcd for $C_9H_{13}O_2Cl$: C, 57.30; H, 6.95. Found: C, 57.52; H, 6.78. Chloroacetates **4b–4f** and the known acetate **3a**[40] were prepared following the same procedure.

1-(Chloroacetoxy)-6-methylbicyclo[4.1.0]heptane (4b): 1.65 g, 85%; IR (neat) 3060, 2940, 2860, 1770, 1745, 1455, 1150 cm^{-1}; ^1H NMR δ 4.02 (s, 2 H), 2.18–1.97 (m, 2 H), 1.73–1.65 (m, 2 H), 1.63–1.41 (m, 2 H), 1.41–1.25 (m, 1 H), 1.14 (s, 3 H), 1.12–0.97 (m, 1 H), 0.69 (d, J = 6.2 Hz, 1 H), 0.65 (dd, J = 6.2, 0.8, 1 H); EI-MS m/z 167, 153, 125, 109, 93, 77, 55 (100). Anal. Calcd for $C_{10}H_{15}O_2Cl$: C, 59.26; H, 7.46. Found: C, 59.48; H, 7.52.

1-(Chloroacetoxy)-6-ethylbicyclo[4.1.0]heptane (4c): 1.82 g, 86%; IR (neat) 3070, 2940, 2860, 1770, 1745, 1450, 1160 cm^{-1}; ^1H NMR δ 4.00 (s, 2 H), 2.18 (ddd, J = 5, 8, 13.5 Hz, 1 H), 1.96 (ddd, J = 6.5, 6.5, 13.5 Hz, 1 H), 1.80–1.04 (m, 8 H), 0.98 (t, J = 6.5 Hz, 3 H), 0.72 (d, J = 5 Hz, 1 H), 0.68 (d, J = 5 Hz, 1 H); EI-MS m/z 167, 140, 139, 125, 111, 107, 97, 96, 95, 77, 69 (100). Anal. Calcd for $C_{11}H_{17}O_2Cl$: C, 60.97; H, 7.91. Found: C, 60.78; H, 7.52.

6-Butyl-1-(chloroacetoxy)bicyclo[4.1.0]heptane (4d): 2.15 g, 90%, IR (neat) 3070, 2940, 2860, 1770, 1750, 1455, 1290, 1165 cm^{-1}; ^1H NMR (C_6D_6) δ 3.41 (s, 2 H), 2.14 (ddd, J = 5, 8, 13.5 Hz, 1 H), 1.95 (ddd, J = 6.5, 6.5, 13.5 Hz, 1 H), 1.68–1.00 (m, 12 H), 0.92 (t, J = 6.5 Hz, 3 H), 0.62 (d, J = 6 Hz, 1 H), 0.51 (d, J = 6 Hz, 1 H); EI-MS m/z 209, 195, 167, 151, 150, 121, 111(100), 108, 93, 79, 77, 55. Anal. Calcd for $C_{13}H_{21}O_2Cl$: C, 63.79; H, 8.65. Found: C, 63.98; H, 8.97.

1-(Chloroacetoxy)-6-hexylbicyclo[4.1.0]heptane (4e): 2.40 g, 88%; IR (neat) 3060, 2940, 2860, 1770, 1750, 1460, 1270 cm^{-1}; ^1H NMR δ 4.00 (s, 2 H), 2.27–2.10 (m, 1 H), 2.05–1.99 (m, 1 H), 1.80–1.00 (m, 16 H), 0.90 (t, J = 6.5 Hz, 3 H), 0.70 (d, J = 6 Hz, 1 H), 0.66 (d, J = 6 Hz, 1 H); EI-MS m/z 223, 188, 163, 152, 112, 108, 96 (100) 93. Anal. Calcd for $C_{15}H_{25}O_2Cl$: C, 66.04; H, 9.24. Found: C, 66.28; H, 9.42.

1-(Chloroacetoxy)-6-methylbicyclo[4.1.0]heptane-7-d_2 (4f): 1.62 g, 83%; IR (neat) 3060, 2940, 2860, 1770, 1750, 1455, 1150 cm^{-1}; EI-MS m/z 204 (M^+) 169, 128, 113, 111, 110, 94, 93 (100).

Enzymatic Hydrolysis of 1-Acetoxybicyclo[4.1.0]heptane (3a). In an Erlenmeyer flask were placed water (10 mL) and the racemic acetate **3a** (0.771 g, 5 mmol). The pH was adjusted at 7.2 with 2 M NaOH, and the enzyme was added (0.5 g of crude PLE, HLE or CCL). The reaction started immediately. After NaOH consumption corresponding to 50–60% conversion (monitored using a pH meter) had been noted, Celite (1 g) was added. The mixture was filtered over Celite, the cake was washed with ether (2 × 5 mL), and the aqueous phase was extracted with ether (4 × 5 mL). The organic phase was dried (Na_2SO_4) and concentrated. The resulting crude mixture was purified by liquid chromatography (neutral alumina, activity III) to give 1-acetoxybicyclo[4.1.0]heptane (**3a**) (0.360–0.390 g, 38–45%): $[\alpha]_D$ +16.5° (c, 3.6, THF, ee 91%) and cyclopropanol **1a** (0.210–0.250 g, 38–45%): $[\alpha]_D$ +5.4° (c 3.0, THF, ee 64%).

Enzymatic Transesterification of 1-(Chloroacetoxy)-bicyclo[4.1.0]heptane (4a). Representative Procedure. Chloroacetate **4a** (1.88 g, 10 mmol) dissolved in diisopropyl ether (3 mL) was added to a mixture of supported *M. miehei* lipase (lipozyme, 1.5 g) and 1-propanol (0.6 mL). After 3 h at 35 °C, the reaction mixture was filtered and the solid was washed with ether. After concentration under vacuum, the reaction products were separated by column chromatography on neutral alumina activity III (pentane/ether (90/10)) to give 0.829 g (45%) of remaining chloroacetate **4a** and 0.514 g of cyclopropanol **1a** (44%). Transesterifications of the chloroacetates **4g–4f** were made following the same procedure (overall yields 80–90%). Optical properties of compounds **1a–1e** and **4a–4e** are reported Table II.

Opening of Cyclopropanol 1c and Chloroacetate 4c into Cyclohexanone 2c. Representative Procedure. To the chloroacetate **4c** (0.216 g, 1 mmol) dissolved in methanol (2 mL) was added aqueous 2 M NaOH (1 mL), and the reaction mixture was stirred 4 h at 60 °C. The product was extracted with ether (2 × 25 mL), and the organic solution was washed with brine and dried ($MgSO_4$). The crude 2-ethyl-2-methylcyclohexanone (**2c**) was purified by column chromatography on silica gel (pentane/ether (97/3)) to give 0.126 g (90%) of **2c**. The same procedure was used starting from cyclopropanol **1c** (Yield 85%). Following this procedure the cyclohexanones **2d**, **2e**, and **8** were also obtained in good yields (80–90%).

2-Ethyl-2-methylcyclohexanone (2c).[41] (*R*): $[\alpha]_D$ −25.5° (c 1, THF, ee 91%). (*S*): $[\alpha]_D$ +24.4° (c 1, THF, ee 80%).

2-Butyl-2-methylcyclohexanone (2d). (*R*): $[\alpha]_D$ −61.5° (c 1.4, $CHCl_3$, ee 90%); $[\alpha]_D$ −46.3° (c 1, THF, ee 90%). (*S*): $[\alpha]_D$ +60.3 (c 1, $CHCl_3$, ee 86%); $[\alpha]_D$ +45.0° (c 1, THF, ee 86%). (lit.[24] (*R*) $[\alpha]_D$ −73.2° ($CHCl_3$, c 1.4, ee 100%)).

(38) House, H. O.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1971**, *36*, 2361.
(39) Hooz, J.; Oudenes, J. *Tetrahedron Lett.* **1983**, *24*, 5695.
(40) Ryu, I.; Murai, S.; Otani, S.; Sonoda, N. *Chem. Lett.* **1976**, 93.
(41) Crouzet, J.; Giral, L.; Cauquil, G.; Rouzaud, J. *Bull. Soc. Chim. Fr.* **1967**, 3722.

2-Hexyl-2-methylcyclohexanone (2e): IR (CCl_4) 2940, 2860, 1715, 1470, 1380, 1235 cm^{-1}; ^1H NMR δ 2.17 (m, 2 H), 1.7–1.1 (m, 16 H), 1.03 (s, 3 H), 0.90 (t, J = 6 Hz, 3 H); EI-MS m/z 196 (M^+), 181, 167, 112 (100), 111, 97, 85, 83, 69. Anal. Calcd for $C_{13}H_{24}O$: C, 79.52; H, 12.33. Found: C, 79.78; H, 12.52. (*R*): $[\alpha]_D$ −31.5° (*c* 1, THF, ee 86%). (*S*): $[\alpha]_D$ +28.5° (*c* 1, THF, ee 66%).

2-Methyl-2-(methyl-d_2)cyclohexanone (8): IR (neat) 2940, 2885, 1715, 1450, 1140 cm^{-1}; EI-MS m/z 128 (M^+), 113, 111, 100, 99, 71, 70, 69 (100), 68. (*R*) isomer: $[\alpha]_D$ +0.80° (*c* 1, THF, ee 70%). Deuterium incorportion >97%. (*S*) isomer: $[\alpha]_D$ −1.30° (*c* 1, THF, ee 90%). Deuterium incorporation >97%.

Opening of Cyclopropanol 1b and Chloroacetate 4b into 2-Methyl-2-(methyl-*d*)cyclohexanone (7). Cyclopropanol **1b** (0.126 g, 1 mmol) or chloroacetate **4b** (0.212 g, 1 mmol) dissolved in CH_3OD (1 mL) was added to a mixture of NaOD (2 mmol) in CH_3OD (1 mL), and the solution was heated at 60 °C for 4 h. The product was extracted with ether (2 × 5 mL), the solvent was evaporated, and the intermediate was stirred at 60 °C with aqueous 2 M NaOH (1 mmol) in methanol for 2 h. The reaction mixture was extracted with ether (2 × 5 mL), and the organic layer was washed with brine and then dried over $MgSO_4$. After evaporation of the solvent, the product was purified by chromatography on silica gel (pentane/ether (97/3)) to give 0.101–0.115 g (40–45%) of (*R*)- and (*S*)-2-methyl-2-(methyl-*d*)-cyclohexanones (**7**): IR (CCl_4) 2940, 1715, 1450, 1120 cm^{-1}; EI-MS m/z 127 (M^+), 100, 99, 98, 71, 70, 69 (100). (*R*) isomer: $[\alpha]_D$ +0.64° (*c* 1, THF, ee 72%). Deuterium incorporation >97%. (*S*) isomer: $[\alpha]_D$ −0.82° (*c* 1, THF, ee 95%). Deuterium incorporation >97%.

The same procedure applied to cyclopropanol **1f** and chloroacetate **4f** led to the formation of (*R*)- and (*S*)-2-methyl-2-(methyl-d_3)cyclohexanones (**9**).[37] (*R*) isomer: $[\alpha]_D$ +0.90° (*c* 1, THF, ee 70%). Deuterium incorporation >97%. (*S*) isomer: $[\alpha]_D$ −1.60° (*c* 1, THF, ee 90%). Deuterium incorporation >97%.

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Supplementary Material Available: ^1H NMR spectra for compounds **4f**, **7**, and **8** (3 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.