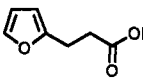
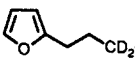
Table II. Electroreduction of Esters 1 in the Presence of *t*-BuOD[a]

run	ester 1	alcohol 2-D	yield[b] (%)	deg of deuterium incorp[c] (%)
1	$Me(CH_2)_5CO_2Me$ (1a)	$Me(CH_2)_5CD_2OH$ (2a-D)	88	93
2	$Me(CH_2)_5CH(OH)CH{=}CH(CH_2)_8CO_2Me$ (1j)	$Me(CH_2)_5CH(OH)CH{=}CH(CH_2)_8CD_2OH$ (2j-D)	93	90
3	 (1k)	 (2k-D)	86	89

[a] The reduction was performed in an undivided cell in the presence of *t*-BuOD (6 equiv relative to 1). [b] Isolated yield after 7 F/mol of electricity had been passed. [c] Determined by 200-MHz ^{1}H-NMR analysis.

present in the ester remain unaffected. The use of Al electrodes was also effective in electroreducing methyl heptanoate (**1a**) (run 2). However, the yield of alcohol was lower than that obtained by the use of Mg electrodes.

When *t*-BuOD was present instead of *t*-BuOH, the electroreduction of esters **1** gave 1,1-dideuterated alcohols (**2-D**) (Scheme I). This result is important for both synthetic and mechanistic reasons. A method by which alcohols **2-D** can be synthesized under mild conditions from esters **1** and in which *t*-BuOD serves as the deuterium source is highly economical because such alcohols are usually prepared by reducing **1** with expensive lithium aluminum deuteride.[16] The results summarized in Table II indicate that, in each case, the yield and degree of deuterium incorporation are acceptable.

That the deuterated alcohol **2-D** is formed clearly suggests a reaction pathway (Scheme I) in which the electroreduction of **1** initially yields a radical anion **3**. That species is then further reduced to an anion **4**. The intermediacy of the radical **3** and of the hemiacetal **5** is also suggested by the results shown in Schemes II and III.

The results of electroreduction of the unsaturated ester **1i** at a Mg cathode are unprecedented (Scheme II). The cathodic reduction of **1i** in the presence of *t*-BuOH afforded the cyclic alcohol **8**[17] and, in the presence of Me_3SiCl, gave the bicyclic compound **9**.[18] That a 5-membered ring, rather than a 6-membered ring, was formed exclusively suggests that the radical **6** is the key intermediate in the cyclization.[19] The intramolecular addition of a radical species to a carbon–carbon double bond is known to preferentially yield a 5-membered ring.[20]

The electroreduction of amides of aliphatic carboxylic acids is known to be difficult. However, *N,N*-dimethylamides **10** ($RCONMe_2$) can be electroreduced to alcohols **2** (RCH_2OH) at a Mg cathode in the presence of *t*-BuOH (10 equiv relative to **10**). Thus, the electroreduction of **10a** (R = n-C_6H_{13}), **10b** (R = c-C_6H_{11}), and **10c** (R = $PhCH_2CH_2$) gave the corresponding alcohols **2** in yields of 82%, 75%, and 72%, respectively.

The electroreduction of **10** can be arrested at the aldehyde stage if a smaller amount of *t*-BuOH is present. As Scheme III shows, the electroreduction of *N,N*-dimethyl 3-phenylpropionamide (**10c**) in the presence of 3.5 equiv of *t*-BuOH gave the aldehyde **11** in reasonable yield. The deuterated aldehyde **12** was similarly obtained when, instead of *t*-BuOH, *t*-BuOD was present. That compounds like **12** can be formed under such mild conditions is remarkable because the preparation of deuterated aldehydes by nonelectrochemical methods is often long and arduous.[21,22]

Registry No. **1a**, 106-73-0; **1b**, 4630-82-4; **1c**, 103-25-3; **1d**, 711-01-3; **1e**, 111-81-9; **1f**, 6203-08-3; **1g**, 69248-88-0; **1h**, 106-79-6; **1i**, 127827-61-6; **1j**, 138353-72-7; **1k**, 37493-31-5; **2a**, 111-70-6; **2a**-D, 80094-80-0; **2b**, 100-49-2; **2c**, 122-97-4; **2d**, 770-71-8; **2e**, 112-43-6; **2f**, 95-12-5; **2g**, 767-08-8; **2h**, 112-47-0; **2j**, 138353-73-8; **2k**-D, 138353-74-9; **8**, 127827-67-2; **9**, 138353-75-0; **10c**, 5830-31-9; **11**, 104-53-0; **12**, 29372-37-0; THF, 109-99-9; $LiClO_4$, 7791-03-9; Me_3SiCl, 75-77-4; *t*-BuOH, 75-65-0; Mg, 7439-95-4; *t*-BuOD, 3972-25-6.

(16) Fetizon, M.; Henry, Y.; Moreau, N.; Moreau, G.; Golfier, M.; Prange, T. *Tetrahedron* **1973**, *29*, 1011.

(17) The cis:trans ratio (13:87) was established by ^{1}H NMR analysis. **8**: IR (neat) 3350, 2910, 1450, 1060 cm^{-1}; NMR ($CDCl_3$) δ 1.04 (d, 3 H, J = 6.2 Hz), 1.00–1.95 (m, 15 H), 3.02 (d, 1 H, J = 8.5 Hz); HRMS calcd for $C_{11}H_{20}O$ 168.1515, found 168.1506.

(18) The conversion of **1i** to **9** was achieved by electrolyzing **1i** in the presence of Me_3SiCl instead of *t*-BuOH. **9**: IR (neat) 1450, 1350, 1250, 840 cm^{-1}; NMR ($CDCl_3$) δ 0.08 (s, 9 H), 0.52–0.77 (m, 3 H), 1.05–1.92 (m, 14 H); HRMS calcd for $C_{14}H_{26}OSi$ 238.1754, found 238.1733.

(19) The mechanism of the formation of **8** and **9** from **7** will be discussed in a forthcoming paper.

(20) For example, see: Julia, M. *Acc. Chem. Res.* **1971**, *4*, 386.

(21) Degani, I.; Fochi, R.; Regondi, V. *Tetrahedron Lett.* **1981**, *22*, 1821.

(22) Kalvin, D. M.; Woodard, R. W. *Tetrahedron* **1984**, *18*, 3387 and references cited therein.

Enzyme-Catalyzed Formation of Chiral Monosubstituted Mixed Diesters and Half Esters of Malonic Acid in Organic Solvents

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Summary: Enzymes in organic solvents were used to develop a strategy for the formation of heretofore unknown chiral monosubstituted malonate diesters and half esters. This enzymatic approach is not feasible in aqueous solutions because the activated malonic hydrogen invariably undergoes fast exchange accompanied by racemization.

Optically active monosubstituted half esters of malonic acid (1) would be useful as chiral synthons and substrates for mechanistic and kinetic studies on racemization, but their synthesis has not yet been reported. The failure to prepare these compounds in optically active form was due to the inapplicability of the conventional approach, i.e.,

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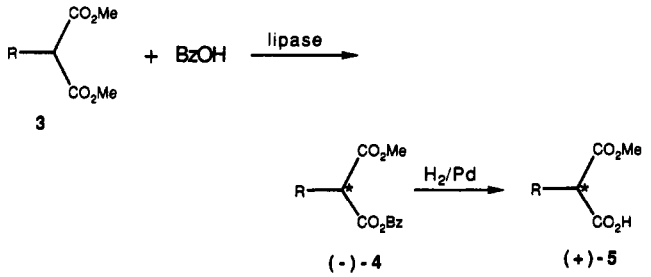
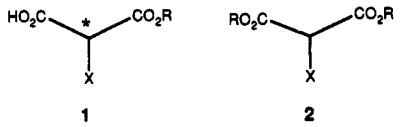
Scheme I[a]



[a] Key: (a) R = OCH_3; (b) R = CH_3.

enzymatic hydrolysis of the corresponding symmetrical monosubstituted diesters **2**. Although successfully used for the synthesis of chiral disubstituted malonates,[1] this approach was bound to fail for the monosubstituted malonates because under aqueous conditions the activated malonic hydrogen undergoes fast exchange accompanied by racemization.[1,2]



It is now well-established that hydrolytic enzymes can act also in anhydrous organic solvents, where they catalyze ester synthesis and ester exchange rather than hydrolysis.[3] Since the substrate specificity and stereoselectivity of enzymes in organic solvents may be different from that in water,[4] in most cases of asymmetric resolution both the aqueous and organic alternatives should be considered.[5] Recently, we emphasized the importance of the organic solvents approach by exploiting enzymatic prochiral selectivity for the synthesis of optically active lactones and polyesters which could not be accomplished in aqueous solution and where work in organic solvents was an absolute necessity.[6]

In the present work we designed a novel strategy, which enables the preparation of the heretofore unknown optically active monosubstituted malonates with enzymes in organic solvents. Initially, we examined the transesterification of prochiral symmetrical methyl- and methoxy-substituted dimethyl malonates **3** in organic solvents. Screening of several commercially available lipase preparations revealed that the lipase from *Candida cylindracea*[7] is highly efficient and stereoselective in catalyzing the transesterification reaction with various alcohols in anhydrous hexane. The use of benzyl alcohol was particularly rewarding as it afforded the chiral methyl benzyl ester **4**, which can be easily converted to the chiral half ester **5** by catalytic hydrogenation (Scheme I). Possessing two readily distinguishable functional groups such half esters may provide versatile chiral building blocks.

Table I. Asymmetric Transesterification of Monosubstituted Dimethyl Malonates with Lipase in Organic Solvents[a]

substrate	initial rate[b]	reaction time (h)	% conversion to 4[c]	$[\alpha]^{28}_D$ (c in $CHCl_3$) (deg)	% ee[d]
3a	0.46	3.5	53	−17.4 (1.43)	98
3a		18.5	64	−16.2 (0.87)	91
3b	0.50	3.5	48	−6.1 (1.08)	*e*
3b		18.5	55	−6.1 (2.25)	*e*

[a] The experimental protocol was the same as described in the text for **3a**. No reaction took place in the absence of enzyme under the conditions used. [b] In μmol h^{-1} (mg enzyme). [c] Reaction progress was monitored by integration of ^1H NMR signals, which enabled quantitative determination of the remaining dimethyl ester **3** and the mixed benzyl methyl diester **4**. [d] Determined by HPLC on a chiral column (Chiralcel OJ, Daicel) with a mixture of hexane and 2-propanol (95:5) as the mobile phase at the flow rate of 0.9 mL/min using detection at 258 nm. The R_f values were 85 min for the (−)-enriched enantiomer and 99 min for the (+)-enriched enantiomer. [e] Conditions for separating enantiomers of **4b** have not yet been found.

In a typical enzymatic experiment 4 g of powdered lipase preparation from *Candida cylindracea* was added to a solution of 1 g of methoxydimethyl malonate (**3a**) and 2.9 mL of benzyl alcohol in 30 mL of hexane, and the suspension was vigorously shaken at 40 °C at 200 rpm. The reaction was terminated by filtration to remove the enzyme, followed by evaporation of the solvent and separation of the remaining benzyl alcohol and dimethyl ester **3** from the optically active product **4a** by bulb to bulb distillation.[8] Palladium oxide catalyzed hydrogenation of **4a** in dry methyl acetate afforded the optically active half ester **5a** in quantitative yield, $[\alpha]^{28}_D$ +15.1° (*c* 0.53, $CHCl_3$).

As can be seen in Table I, the reactions are highly stereoselective and in both cases the (−) enantiomer of the mixed diester is formed.[9] The high stereoselectivity of the enzymatic reactions is reflected by the fact that only insignificant quantitites of the byproduct dibenzyl ester are formed (less than 2%) even during the 18.5-h experiment. Most importantly, in spite of the notorious lability of the malonate hydrogen, the chiral centers of **4** and **5** are virtually unaffected during prolonged storage or when dissolved in hydrophobic organic solvents, such as hexane or chloroform, where in the case of **4a** less than 5% racemization was observed over a period of 6 days. This is of course in marked contrast to their behavior in aqueous solutions. Not surprisingly, both **4** and **5** underwent almost instant racemization in a dilute solution of phosphate buffer at pH 7.1.

For both substrates a considerable slowdown in reaction rate was observed toward 70% conversion. As the recovered enzyme was shown to retain most of its activity, the retardation could not be due to enzyme inactivation, but rather to incursion of the reverse reaction. As the reaction with benzyl alcohol proceeds and more methanol is formed, this reverse reaction becomes increasingly important until equilibrium is attained at approximately 70% conversion. The existence of this equilibrium was con-

(1) Kitazume, T.; Sato, T.; Kobayashi, T.; Lin, J. T. *J. Org. Chem.* **1986**, *51*, 1003. Luyten, M.; Muller, S.; Herzog, B.; Keese, R. *Helv. Chim. Acta* **1987**, *70*, 1250. De Jeso, B.; Belair, N.; Deleuze, H.; Rascle, M. C.; Maillard, B. *Tetrahedron Lett.* **1990**, *31*, 653.

(2) Thomas, N. R.; Rose, J. E.; Gani, D. *J. Chem. Soc., Chem. Commun.* **1991**, 908.

(3) Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 114. Margolin, A. L. CHEMTECH **1991**, 160.

(4) Zaks, A.; Klibanov, A. M. *J. Am. Chem. Soc.* **1986**, *108*, 2767. Fitzpatrick, P. A.; Klibanov, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 3166.

(5) For example see: Holdgrun, X. K.; Sih, C. J. *Tetrahedron Lett.* **1991**, 3465. Goergens, U.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1991**, 1064.

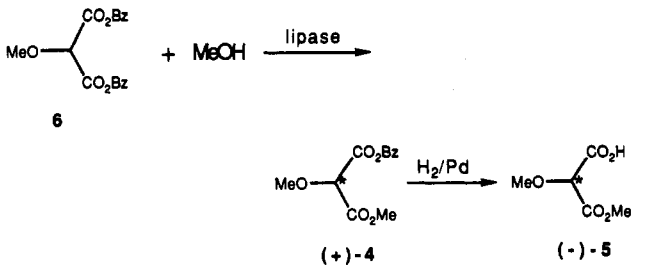
(6) Gutman, A. L.; Bravdo, T. *J. Org. Chem.* **1989**, *54*, 4263. Gutman, A. L.; Bravdo, T. *J. Org. Chem.* **1989**, *54*, 5645. Gutman, A. L.; Zuobi, K.; Bravdo, T. *J. Org. Chem.* **1990**, *55*, 3546.

(7) Lipase from *Candida cylindracea* was purchased from Sigma Chemical Co. as a crude powder with a specific activity of 700 units/mg of solid. It has been recently redefined as lipase from *Candida cepacia*.

(8) To avoid temperature induced racemization, distillations were carried out within 1–2 h at relatively low oven temperature (50–70 °C) and high vacuum (0.05 mmHg).

(9) Determination of absolute configurations of **4** and **5** by correlation to structures of known chiral compounds is currently underway.

Scheme II



firmed by carrying out the reaction with benzyl alcohol in the presence of an equimolar amount of methanol, in which case the reaction reached equilibrium at 20% conversion.

In a further preparative experiment, we showed that it is possible to carry out a stereoselective enzymatic transesterification with methanol as well. Thus, when the corresponding methoxy-substituted dibenzyl malonate 6 was subjected to the lipase from *Candida cylindracea* and methanol, under similar conditions, transesterification occured at a similar rate and the mixed methyl benzyl ester was formed. Determination of optical purity by polarimetry and HPLC on a chiral column revealed that in this case the opposite (+)-4 enantiomer was formed with an ee value of 90–95%.[10] Hydrogenolysis of this material would give the respective (-) enantiomer of the half ester 5 (Scheme II). The prochiral specificity of the enzyme thus allows the preparation of either the (+) or (-) enantiomer of the mixed diesters of monosubstituted malonates by following one of the two complementary routes.

This study significantly extends the synthetic utility of lipases in organic solvents. It provided the first synthetic route to chiral monosubstituted malonates and points the way to the synthesis of other analogues of this important class of compounds. Further work in this field is currently underway in our laboratory.

Acknowledgment. We thank Dr. A. Kirby for useful discussions and the Israel Academy of Sciences and Humanities for financial support.

Supplementary Material Available: Experimental details and ^{1}H NMR for obtained compounds (12 pages). Ordering information is given on any current masthead page.

(10) This ee value was obtained when the reaction proceeded to 50%. In this case the slowdown toward 70% conversion was accompanied by significant formation of the byproduct dimethyl ester with a concomittant lower optical purity for (+)-4.

Pyranose α-Enones Provide Ready Access to Functionalized *trans*-Decalins via Bis-Annulated Pyranosides Obtained by Intramolecular Diels–Alder Reactions. A Key Intermediate for Forskolin[1]

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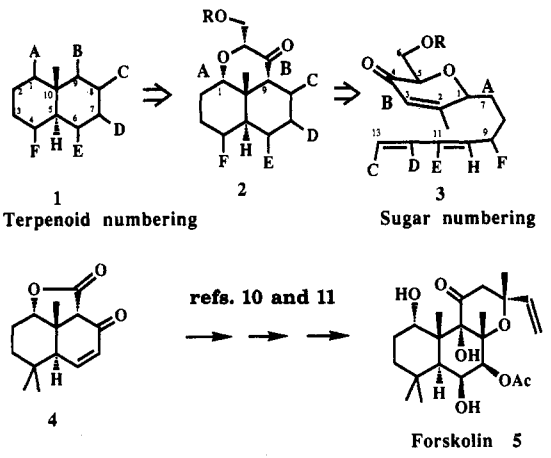
Summary: Intramolecular Diels–Alder routes for the preparation of bis-annulated pyranosides, as chiral precursors of functionalized *trans*-decalin rings of terpenoid natural products, have been investigated.

Strategies for the use of carbohydrate derivatives to synthesize carbocyclic natural products in our laboratory have exploited the sugar ring both for its stereodirecting properties and reactivity as well as for the variety of latent functional groups that it masks.[2] The sugar therefore serves as more than a source of chirality, and for maximum utility, the integrity of the ring needs to be maintained as far into the synthesis as possible. This approach was illustrated in the synthesis of *N*-acetyl actinobolamine[3] where the enhanced Diels–Alder reactivity of a carbohydrate-derived α-enone vis-a-vis its carbocyclic counterpart[4] was used to furnish the molecular framework. Our recent successes with tricothecanes,[5] pipitzol,[6] polyquinanes,[7] and phyllantocin[8] have encouraged us to consider other carbocyclic targets, and *trans*-decalin core 1, common to many terpenoids, is the topic of this manuscript.

Scheme I



The labels A → F in 1 (Scheme I) represent sites at which functional groups and/or other rings are frequently located on the bicyclic core. In view of the aforementioned high reactivity of carbohydrate derived α-enones, an intramolecular Diels–Alder (IMDA) reaction[9] seemed an attractive avenue to 1. Accordingly retrosynthetic analysis led to the bis-annulated pyranose 2 and thence to the hex-2-en-4-ulopyrano intermediate 3. In this manuscript we demonstrate the validity of this approach with a syn-

(1) This work was supported by grants from NIH (GM 37380) and NSF (8920033).

(2) Fraser-Reid, B.; Tsang, R. In *Strategies and Tactics in Organic Synthesis*; Lindberg, T., Ed.; Academic Press: New York, 1989; Vol. 2, pp 123–162.

(3) Rahman, M. A.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1985**, *107*, 5576.

(4) Fraser-Reid, B.; Underwood, R.; Osterhout, M.; Grossman, J. A.; Liotta, D. *J. Org. Chem.* **1986**, *51*, 2152.

(5) Tsang, R.; Fraser-Reid, B. *J. Org. Chem.* **1985**, *50*, 4659.

(6) Yeung, B. A.; Alonso, R.; Vite, G. D.; Fraser-Reid, B. *J. Carbohyd. Chem.* **1989**, *8*, 413.

(7) Dickson, J. K., Jr.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1990**, 1440.

(8) Bik-Wah, A.; Contelles, J. L. M.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1989**, 1160.

(9) After this work was completed a paper describing IMDA reactions of hex-2-enopyranosiduloses was published: Herscovici, J.; Delatre, S.; Antonakis, K. *Tetrahedron Lett.* **1991**, *32*, 1183.

0022-3263/92/1957-1065$03.00/0