derivation of eq 1 is greatly simplified.

Low-valence transition-metal compounds have been shown to be effective in the photosensitized isomerization of NBD to Q (e.g., CuCl[12] and copper(I) phosphine complexes[6]). The results of this study indicate that the presence of higher valence states of the metal may inhibit the production of quadricyclane; therefore, oxygen and other oxidizing agents would have to be rigorously excluded in the photosensitized conversion of NBD to Q by transition-metal compounds.

Acknowledgment. We gratefully acknowledge financial support from Frank J. Seiler Research Lab (Air Force Systems Command), Utah Consortium for Energy Research and Education, and the Utah State University Research Office.

Registry No. $CuCl_2$, 7447-39-4; $CuSO_4$, 7758-98-7; $SnCl_2$, 7772-99-8; $CuBr_2$, 7789-45-9; quadricyclane, 278-06-8; norbornadiene, 121-46-0.

Diastereoselective Benzyloxymercuration/Demercuration of Derivatives of γ-Alkyl-δ-hydroxy-α,β-unsaturated Esters. A New Strategy for the Synthesis of Aldol-Type Products

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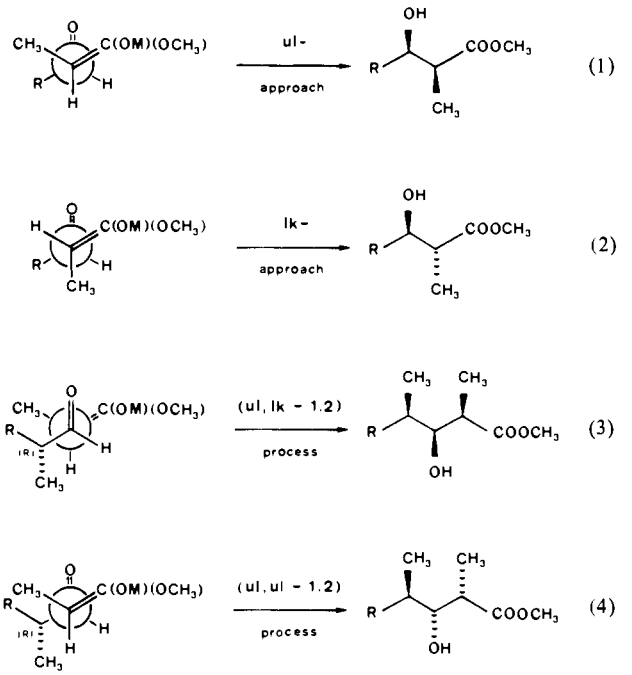
Abstract: The diastereoselective construction of open-chain carbon skeletons with three or more consecutive asymmetric centers—bearing alternating oxygen (RO) and alkyl (R) substituents—by the aldol addition reaction still poses considerable problems (eq 3 and 4). An alternative route to some products with this substitution pattern and with certain relative configurations is the α-alkylation of β-hydroxy esters followed by two-carbon chain extension via Wittig olefination and benzyloxylation via the title reaction (Scheme I and Chart I; cf. **5** → **12** → **21**). Readily available enantiomerically pure starting materials can be employed. It is demonstrated by the examples described here that the addition of benzyloxy groups to the β-position of unsaturated esters and of enones with δ-RO groups is mainly directed by the γ-substituent. With conversions of 60–85%, the chemical yields are in the order of 85–95%, and the major diastereomers of certain configuration prevail to the extent of >90% with γ-methyl and >95% with γ-ethyl groups (Chart I). The configuration of the products is assigned by conversion to cyclic acetals or hemiacetals (Chart II) and 300-MHz ^1H NMR spectroscopy. From this assignment, the relative topicity of benzyloxylation is specified as *ul*-1,2 (eq 8).

There has been a keen interest in acyclic stereoselection due largely to the determination of synthetic chemists to construct acyclic or macrocyclic target molecules that contain a large number of centers of chirality. Some of these natural products, such as macrolide and ionophore antibiotics, have attracted considerable attention, which led to a renaissance of the aldol reaction as a highly desirable method for stereochemical control in syntheses of conformationally flexible compounds. In fact, advances in the enantioselective and diastereoselective execution of aldol additions have been impressive and culminated in the total syntheses of many structurally intriguing molecules.[1-3] As exemplified in 1 and 2 for the addition of a methyl propionate metal enolate to an aldehyde, each component has two enantiotopic faces, and the two possible relative topicities give rise to two diastereomers.[4] Many ingenious procedures now exist that provide one of the adducts directly or indirectly with high diastereoselectivity.[1-3]

However, a more difficult problem arises if the aldehyde contains one or more centers of chirality. In addition to the relative topicity, with which the two trigonal centers combine, the process must also secure a preference for one of the two possible relative topicities within the aldehyde; i.e., the attacking enolate must exhibit diastereoface selection.[5] This is demonstrated with an



(1)

(2)

(3)

(4)

α-methyl-branched aldehyde in eq 3 and 4. In this case, the relative configuration on *three* consecutive centers is to be established in a *single* step. There are more or less useful solutions to fulfill this task.[1-3,6]

(1) Heathcock, C. H. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, Chapter 2. Heathcock, C. H. In "Comprehensive Carbantion Chemistry"; Durst, T., Buncel, E., Eds.; in preparation. Heathcock, C. H. *Pure Appl. Chem.* **1983**, in press. Heathcock, C. H. In "Asymmetric Reactions and Processes in Chemistry"; Eliel, E. L., Otsuka, S., Eds.; American Chemical Society, Washington, D.C., 1982; ACS Symp. Ser. No. 185, p 55. Heathcock, C. H. *Science* (Washington, D.C.) **1981**, *214*, 395.

(2) Evans, D. A.; Nelson, J. V.; Taber, T. R. "Topics in Stereochemistry"; Wiley-Interscience: New York, 1982; Vol. 13, p 1.

(3) Masamune, S. In "Organic Synthesis Today and Tomorrow"; Trost, B. M., Hutchinson, R., Eds.; Pergamon Press: New York, 1981; p 197.

(4) Seebach, D.; Goliński, J. *Helv. Chim. Acta* **1981**, *64*, 1413.

(5) Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828; Cram, D. J.; Wilson, D. R. *Ibid.* **1963**, *85*, 1245.

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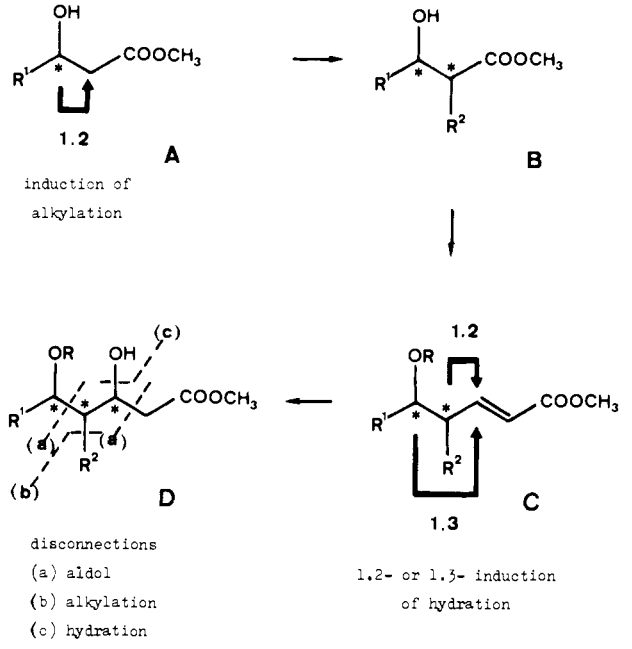
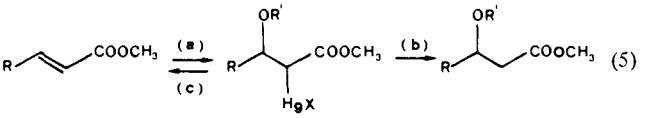
Scheme I



We would like to present here a totally different strategy of assembling consecutive asymmetric carbon atoms along an open-chain skeleton stepwise. It has the added advantage of using starting materials that are readily available in both enantiomeric forms, such as β-hydroxybutanoic[7] and malic acid;[8] see A, R^1 = CH_3 and R^1 = $COOCH_3$, respectively, in Scheme I. The first step, A → B in Scheme I, is a diastereoselective alkylation of alkoxide enolates and has been described in detail by us[9] and by others.[10,11] The second operation, also well-known, is the reduction of the ester to the aldehyde and a Wittig olefination, which in this case is synthetically equivalent with an aldol *condensation*. It produces the α,β-unsaturated ester C of trans configuration. In the third step, we hoped to add an oxygen function diastereoselectivity with 1,2- and/or 1,3-asymmetric induction, C → D. This particular step is the subject of the present publication.

Benzyloxymercuration/Demercuration of α,β-Unsaturated δ-Hydroxy Ester and Ketone Derivatives

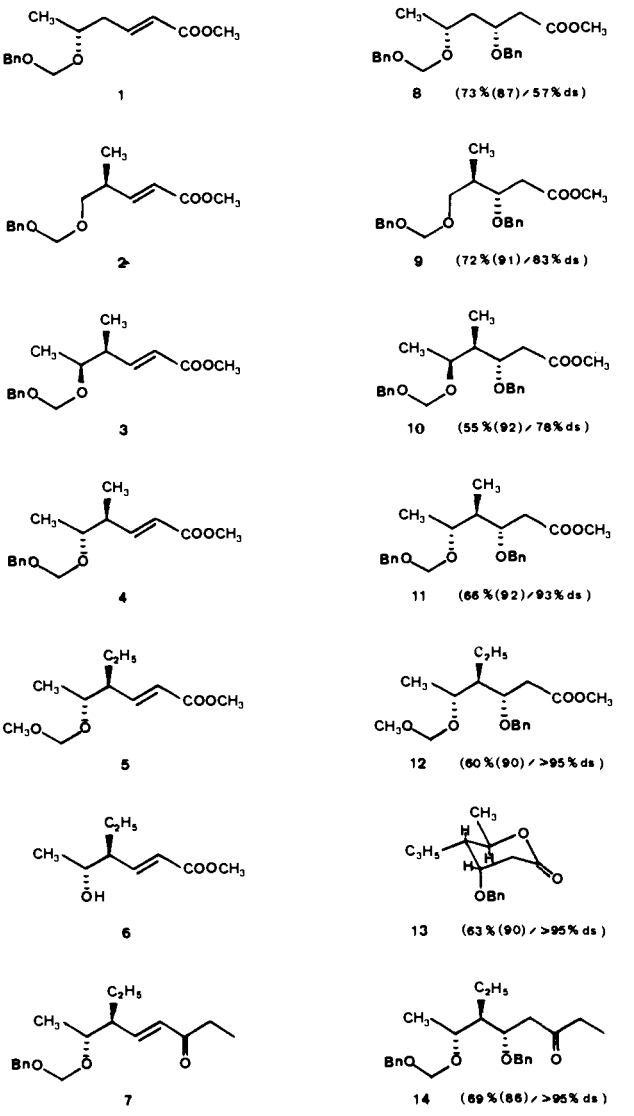
The alkoxymercuration of α,β-unsaturated carbonyl compounds has been documented[12] to proceed with high regioselectivity, the RO group being added in the β-position and the mercury atom in the α-position, (a) in eq 5. The subsequent reductive dem-



(5)

ercuration (b) is usually accompanied by elimination (c), which regenerates starting material.[12b] There have also been numerous examples of "mercury-assisted" intramolecular addition of heteroatoms to various alkenes and alkynes with excellent regio- and diastereoselectivity.[12c] We set out to study the alkoxymercuration of derivatives of δ-hydroxy-α,β-unsaturated esters which should be subject to induction by asymmetric centers in the γ- and/or δ-position. Benzyl alcohol was chosen as the nucelophile for the alkoxymercuration process, so that the resulting benzyl ethers would serve as readily removable protecting groups for the derived hydroxyl function. The (benzyloxy)methoxy esters **1–4**, the methoxymethoxy ester **5**, the hydroxy ester **6**, and the (benzyloxy)methoxy ketone **7** were used as racemic or enantiomerically pure substrates (see Experimental Section) for the benzyloxymercuration process. The reaction was carried out by stirring a solution of the α,β-unsaturated carbonyl derivative in methylene chloride/10% benzyl alcohol with ca. 20% excess mercuric acetate for 24 h in the presence of perchloric acid, working up to isolate the crude mercuration product, and immediately reducing with sodium borohydride in tetrahydrofuran (THF). Unreacted or

Chart I



(6) Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *104*, 5526.
(7) Lemieux, R. U.; Giguere, J. *Can. J. Chem.* **1951**, *29*, 678. Deol, D. S.; Ridley, D. D.; Simpson, G. W. *Aust. J. Chem.* **1976**, *29*, 2459. Seuring, B.; Seebach, D. *Helv. Chim. Acta* **1977**, *60*, 1175.
(8) Seebach, D.; Hungerbühler, E. In "Modern Synthetic Methods 1980"; Scheffold, R., Ed.; Salle + Sauerländer: Aarau, Switz., 1980.
(9) Seebach, D.; Wasmuth, D. *Helv. Chim. Acta* **1980**, *63*, 197; *Angew Chem.* **1981**, *93*, 1007; *Angew Chem., Int. Ed. Engl.* **1981**, *20*, 971. Züger, M.; Weller, Th.; Seebach, D. *Helv. Chim. Acta* **1980**, *63*, 2005. Wasmuth, D.; Arigoni, D.; Seebach, D. *Ibid.* **1982**, *65*, 344.
(10) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825; *Ibid.* **1980**, *63*, 1383; *Tetrahedron Lett.* **1981**, 425.
(11) Shieh, H.-M.; Prestwich, G. D. *J. Org. Chem.* **1981**, *46*, 4319; *Tetrahedron Lett.* **1982**, 4643. Chamberin, A. R.; Dezube, M. *Ibid.* **1982**, 3055.
(12) (a) Chaudhuri, A. K.; Mallik, K. L.; Das, M. N. *Tetrahedron* **1963**, *19*, 1981. Bloodworth, A. J.; Bunce, R. J. *J. Chem. Soc., Chem. Commun.* **1970**, 753; *J. Chem. Soc. C* **1971**, 1453. Cabaleiro, M. C.; Ayala, A. D.; Johnson, M. D. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1207. Maskens, K.; Polgar, N. *J. Chem. Soc., Perkin Trans. 1* **1973**, 109. Larock, R. C. *Angew. Chem.* **1978**, *90*, 28; *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 27 and references cited therein. (b) Oda, J.; Nakagawa, T.; Inouye, Y. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 373. Barluenga, J.; Villamana, J.; Yus, M. *Synthesis* **1981**, 375. Butler, R. N. In "Synthetic Reagents"; Pizey, J. S., Ed.; Ellis Horwood: Chichester, England, 1981; Vol. 4, Chapter 1. (c) See for instance: Hoye, T. R.; Kurth, M. J. *J. Am. Chem. Soc.* **1979**, *101*, 5065. Bartlett, P. A.; Adams, J. L. *Ibid.* **1980**, *102*, 337. Hoye, T. R.; Caruso, A. J.; Kurth, M. J. *J. Org. Chem.* **1981**, *46*, 3550. White, J. D.; Nishiguchi, T.; Skeean, R. W. *J. Am. Chem. Soc.* **1982**, *104*, 3923. Riediker, M.; Swartz, J. *Ibid.* **1982**, *104*, 5842.

regenerated unsaturated ester and the diasteromeric products were separated chromatographically, and the ratios were determined by a combination of capillary gas–liquid chromatography (CGC) and ^{13}C NMR spectroscopy. The major diastereomers **8–14** formed are shown in Chart I. (The values in parentheses are isolated chemical yields of the products, yields calculated from unrecovered starting materials, and percentages of the major diastereomers.[13] In the case of the conversion of the ketone **7** to the aldol derivative **14**, the yield includes an oxidation step, because the demercuration with borohydride was accompanied by reduction of the keto group. The assignment of configuration of the main products is described in the next section. The diastereoselectivities are generally high, and the yields are satisfactory.

Comparison of the first two examples (**1** → **8** vs. **2** → **9**) and of the third and fourth reactions (**3** → **10** vs. **4** → **11**) in Chart I indicates that for useful diastereoselectivity a γ-substituent must be present and that its directing effect overrides that of the RO-bearing center. The preferred relative topicity of attack of the benzyloxy group is specified *ul*-1,2,[14] independent of the nature of the α,β-unsaturated carbonyl system (ester or ketone) and of the type of protection of the hydroxy group (free OH, OCH_2OMe, or OCH_2OBn).

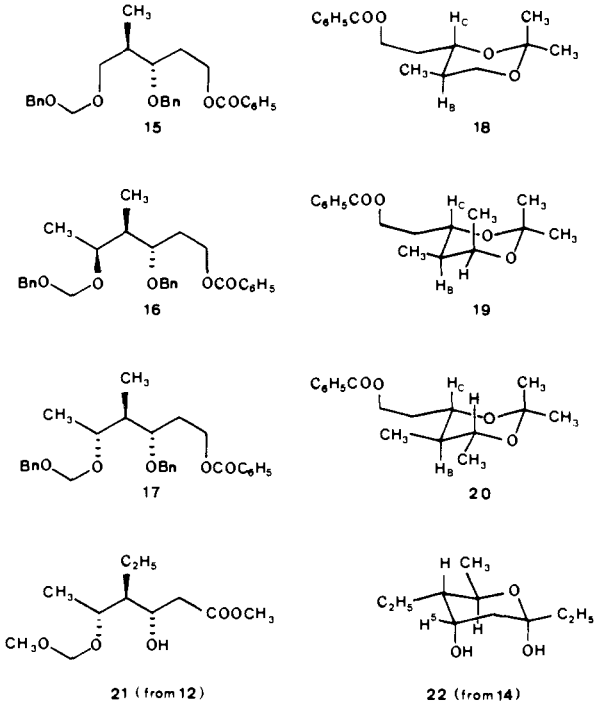
Debenzylations and Configurational Assignments

Of the products **8–14** only the lactone **13** is subject to direct NMR analysis for assignment of configuration. As in all other cases, the 300-MHz proton NMR spectrum was used for this purpose. The two α-carbonyl hydrogens of **13** both exhibit a small coupling constant (2 and 3 Hz) from the vicinal BnOCH hydrogen, indicating the axial position of the benzyloxy group as shown in Chart I.

Of the other benzyloxylation products, the esters **9**, **10**, and **11** were reduced with lithium alanate (LAH) in ether, followed by benzoylation in methylene chloride in the presence of 4-(dimethylamino)pyridine (Steglich base[15]) to give the derivatives **15**, **16**, and **17**, respectively, of 1,3,5-triols with three differently protected OH groups. Debenzylation ($Pd/C/H_2/EtOH$) and acetalization with 2,2-dimethoxypropane under acid catalysis produced the 1,3-dioxanes **18**, **19**, and **20**; only the major stereoisomers are shown. Their relative configurations could be deduced from the 300-MHz NMR spectra. The most informative signals are those from the H_C hydrogens as marked in the formulas **18** (δ 3.65), **19** (δ 3.46), and **20** (δ 3.65), which appear as multiplets from one small (2.5–3.0 Hz) and two large couplings (9.0–9.5 Hz). This is only compatible with a 1,2-diaxial relationship between H_B and H_C, since there must be one small gauche coupling between H_C and one of the diastereotopic CH_2 hydrogens on the side chain.[16]

Debenzylation of the adduct **12** of benzyl alcohol furnished compound **21** with a free OH group in the β-carbonyl position, formally the product of hydration (with *ul*-1,2-induction) of the unsaturated ester **5**, but formally also the product of aldol-type addition (with *ul*-1,2- or *ul*-1,3-induction) of methyl acetate to

Chart II



MEM-protected 2-ethyl-3-hydroxybutanal; cf. Scheme I. The diastereoselective formation of **14** proves that the new method is also applicable to ketones. For assignment of its configuration, **14** was debenzylated by hydrogenolysis, which led to the isolation of the cyclic hemiacetal **22** of the corresponding dihydroxy ketone. The proton H^5 of **22** appears as a quartet in the 300-MHz NMR spectrum ($D_2O/CDCl_3$) with a coupling constant of 3 Hz, indicating that the hydroxy group at C-5 is in an axial position, so that H^5 has three vicinal coupling partners in a gauche relationship.

Discussion of the Results

In their study of oxymercuration of 4-substituted cyclohexenes, Henbest and co-workers[17] demonstrated that Lewis-base groups (OH, OCH_3, OBn, OAc, CO_2CH_3, CH_2OH, CN) in the substrates strongly direct the addition to the olefinic double bond. For example, four diastereomeric adducts could be expected from the methoxymercuration of 3-cyclohexen-1-ol by trans addition of the HgOAc and OCH_3 groups. However, a single mercurial compound was obtained in 95% yield. It was suggested that the hydroxy group assisted the formation of the mercuronium ion complex as shown in eq 6 and that the axial attack by methanol led to the observed adduct. The acyclic analogue, (*Z*)-3-hexen-1-ol, gave only one isomer upon methoxymercuration. This could also be rationalized, as shown in equation 7, by assuming a mercuronium ion intermediate similar to that derived from 3-cyclohexen-1-ol.

The diastereoselectivity observed in this report might be due to a mercuronium ion similar to those derived from the homoallylic alcohols in eq 6 and 7. This is shown in eq 8 for the substrate **4** (Chart I): the more stable mercuronium ion is the one in which the γ-methyl group occupies a position opposite to the acetoxymercuro group, relative to the plane of the olefin. Addition of benzyl alcohol to the β-position then leads to the observed predominant diastereomer with relative topicity *ul*-1,2. It can also be readily seen that the δ-methyl group exerts smaller steric influence. It should be noted that the β-attack of the nucleophile on the mercuronium ion derived from the α,β-unsaturated carbonyl compound overrides the preferred mode of opening of the mercuronium ions from the simple homoallylic alcohols as shown in eq 6 and 7.

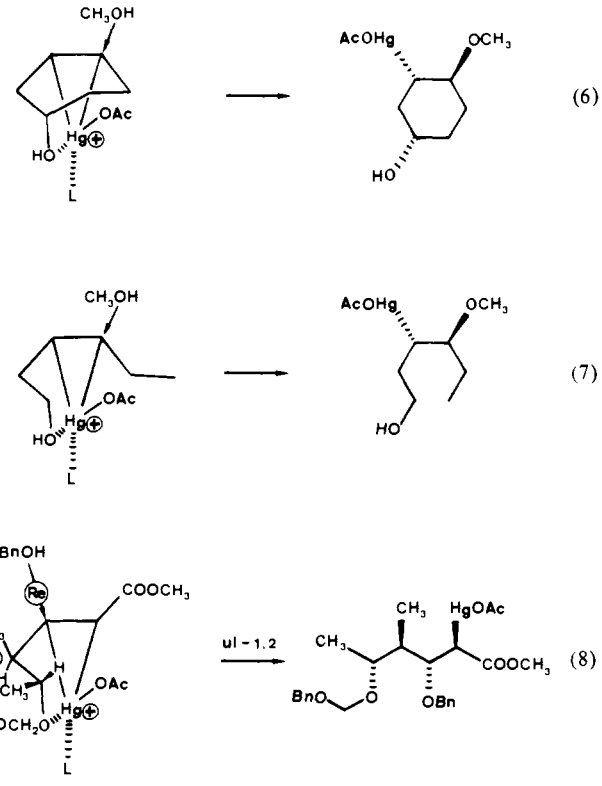
(13) We have previously indicated the diastereoselectivities of transformations by the percentages of the major diastereomers (% ds) [Seebach, D.; Naef, R. *Helv. Chim. Acta* **1981**, *64*, 2704]. A referee pointed out that with this definition a totally nonselective transformation furnishing a 1:1 ratio of diastereomers would be 50% diastereoselective. This point is well taken. We therefore propose to define the indicator, % ds, as the percentage of a given diastereomer in a mixture of diastereomeric products. We feel that the commonly used % de is not a useful number because it is applicable to mixtures of two and only two diastereomers and because one has to convert it back to a diastereomer ratio to arrive at a meaningful number. Thus, the statement "the diastereomer A was formed in 50% de" does not immediately tell us that a simple crystallization or chromatography of the product mixture will lead to the isolation of that diastereomer in 75% yield, a physically meaningful number which was measured in the first place.

(14) Seebach, D.; Prelog, V. *Angew. Chem.* **1982**, *94*, 696; *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654.

(15) Höfle, V. G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem.* **1978**, *90*, 602; *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.

(16) The configurations of the major isomers in compounds **8** and **12** were assumed to be as shown, in analogy with the other proven cases, with due consideration of the proposed mechanistic picture in eq 8.

(17) Henbest, H. B.; Nicholls, B. *J. Chem. Soc.* **1959**, 227; Henbest, H. B.; McElhinney, R. S. *Ibid.* **1959**, 1834.



Subsequent to this work, it was found that sodium borohydride reduction of the organomercurials in dichloromethane/water biphasic system significantly minimized the undesired elimination side reaction, which regenerated starting materials. Work is in progress to prove the scope of the reaction and thus also to test the validity of the mechanistic picture of eq 8.

Experimental Section

Thin-layer chromatography used commercial plates coated with silica gel 60 F_{254} and column chromatography used silica gel 60 with particle size 0.040–0.063 mm from Merck, Darmstadt, West Germany. Gas–liquid chromatography used glass capillary column (19.6 m with Pluronic L 64 and 13.5 m with SE-54) with hydrogen (1.35 atm) as carrier gas in a Carlo-Erba-4160 HRGC. ^{1}H NMR spectra were recorded on a Varian EM-390 and Bruker WM-300, whereas ^{13}C NMR spectra were recorded on a Varian CFT-20. All NMR spectra were determined in deuterated chloroform and chemical shifts are reported as δ values in ppm with tetramethylsilane as an internal standard ($\delta = 0$). Coupling constants (J) are given in hertz. Signals in the ^{1}H NMR spectra are characterized as s (singlet), d (doublet), t (triplet), qa (quadruplet), qi (quintuplet), sx (sextet), sp (septet), m (multiplet), and b (broad). Signals in the ^{13}C NMR spectra due to the minor isomers are given in italics. Infrared spectra were determined in chloroform on a Perkin-Elmer 297 infrared spectrometer and the absorption maxima are reported in cm^{-1}. Optical rotations were determined in chloroform in a 1-mL cell with 1-dm path length on a Perkin-Elmer 241 polarimeter.

Tetrahydrofuran was predistilled from KOH and then distilled from K/benzophenone under argon. Dichloromethane was distilled from P_2O_5, diethyl ether was distilled from $LiAlH_4$, and pentane and toluene were distilled from NaH. Benzyl alcohol was washed with aqueous base and then distilled at reduced pressure. Dimethyl sulfoxide, oxalyl chloride, and triethylamine were distilled from CaH_2. Mercuric acetate was purchased from Fluka (Buchs, Switzerland) and 70% perchloric acid from Riedel-De Haën (Seelze-Hannover, West Germany).

Aqueous pH 7 solution refers to a 100-mL solution containing 1.45 g NaOH and 8.5 g KH_2PO_4, and pH 8 to a 100-mL solution containing 1.87 g of NaOH and 6.8 g of KH_2PO_4.

The (benzyloxy)methoxy-protected aldehydes that were used in the preparation of the racemic α,β-unsaturated esters **1** through **4** have been described previously.[18] The corresponding alcohols were accessible in three steps from commerical β-keto esters; cf. also the preparation of the corresponding optically active analogues **5** through **7** described in detail below.

(18) Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, 1035.

(2*S*,3*R*)-(−)-2-Ethyl-3-(methoxymethoxy)-1-butanol. Ethyl (2*R*,3*R*)-(−)-2-ethyl-3-hydroxybutanoate[19] ($[\alpha]^{RT}_D$ −11.1° (*c* 1.44, $CHCl_3$)) was prepared following the procedures for alkylation of β-hydroxybutanoates[10] and of malates.[9]

To a stirred solution of 474 mg (2.96 mmol) of this ester in 6 mL of dichloromethane was added 1.1 mL (6.4 mmol) of ethyldiisopropylamine, followed by 0.45 mL (5.9 mmol) of chloromethyl methyl ether. After stirring at room temperature for 21 h, the reaction mixture was diluted with 60 mL of pentane and washed with 20 mL of saturated aqueous NaCl and then 20 mL of saturated aqueous $NaHCO_3$. The aqueous phases were extracted with two 50-mL portions of pentane. The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated. The resulting residue was passed through 10 g of silica gel with 100 mL of 20% ether in pentane. The filtrate was then concentrated to an oil. To a stirred solution of this residue in 10 mL of ether at 0 °C was added 100 mg (2.6 mmol) of lithium tetrahydridoaluminate. After stirring at room temperature for 1 h, 0.1 mL of water, 0,1 mL of 15% aqueous NaOH, and 0.3 mL of water were added successively. After 30 min, the reaction mixture was filtered and concentrated. Chromatography of the resulting residue on silica gel with 1:1 ether:pentane afforded 447 mg (2.76 mmol, 93%) of the alcohol: IR ($CHCl_3$) 3680, 3520; ^{1}H NMR ($CDCl_3$) 0.93 (t, J = 7, 3 H, CH_3CH_2), 1.23 (d, J = 7, 3 H, CH_3CH), 2.67 (t, J = 6, 1 H, OH), 3.37 (s, 3 H, OCH_3), 4.60 (d, J = 7, 1 H, OC*H*HO), 4.73 (d, J = 7, 1 H, OCH*H*O); $[\alpha]^{RT}_D$ −65.0° (*c* 1.23, $CHCl_3$). Anal. Calcd for $C_8H_{18}O_3$: C, 59.23; H, 11.18. Found: C, 59.18; H, 11.04.

(2*S*,3*R*)-3-(1-Ethoxyethoxy)-2-ethyl-1-butanol. To a stirred solution of 10 g (62.4 mmol) of ethyl (2*R*,3*R*)-(−)-2-ethyl-3-hydroxybutanoate in 90 mL of freshly distilled ethyl vinyl ether was added 1 mL of trifluoroacetic acid. After stirring at room temperature for 12 h, the reaction mixture was diluted with 250 mL of ether and then washed with 100 mL of saturated aqueous $NaHCO_3$. The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated. To a stirred solution of this residue in 200 mL of ether at 0 °C was added 3.7 g (98 mmol) of lithium tetrahydridoaluminate. After stirring at room temperature for 12 h, the reaction mixture was cooled to 0 °C and 2 mL of water, 2 mL of 15% aqueous KOH, and 4 mL of water were added successively. After 30 min, the reaction mixture was filtered through Celite. The solid residue was extracted with two 50-mL portions of hot ether. The combined ethereal solution was dried over anhydrous Na_2SO_4, filtered, and concentrated. Distillation of the resulting residue at 60 °C (0.75 mmHg) afforded 9.8 g (51.5 mmol, 83%) of the alcohol: IR ($CHCl_3$) 3620, 3500; ^{1}H NMR ($CDCl_3$) 0.93, 1.27 (2 × t, J = 7, 2 × 3 H, CH_3CH_2), 1.25, 1.30 (2 × d, J = 7, 2 × 3 H, CH_3CH), 2.70 and 3.12 (d × d, J = 5.6 and 5.7, 1 H), 4.70 (qa, J = 5, 1 H, OCHO). Anal. Calcd for $C_{10}H_{22}O_3$: C, 63.12; H, 11.65. Found: C, 62.99; H, 11.63.

(2*S*,3*R*)-(−)-3-((Benzyloxy)methoxy)-2-ethyl-1-butanol. By the procedure described for the preparation of (2*S*,3*R*)-3-(methoxymethoxy)-2-ethyl-1-butanol, 722 mg (4.5 mmol) of ethyl (2*R*,3*R*)-(−)-2-ethyl-3-hydroxybutanoate, 1.7 mL (9.9 mmol) of ethyldiisopropylamine, 1.25 mL (9.0 mmol) of chloromethyl benzyl ether, and 150 mg (3.95 mmol) of tetrahydridoaluminate gave 965 mg (4.05 mmol, 90%) of the alcohol: IR ($CHCl_3$) 3670, 3520; ^{1}H NMR ($CDCl_3$) 0.93 (t, J = 7, 3 H, CH_3CH_2), 1.23 (d, J = 7, 3 H, CH_3CH), 2.62 (t, J = 5, 1 H, OH), 4.62 (bs, 2 H, $C_6H_5CH_2$), 4.70 (d, J = 7, 1 H, OC*H*HO), 4.83 (d, J = 7, 1 H, OCH*H*O), 7.35 (bs, 5 H, C_6H_5); $[\alpha]^{RT}_D$ −57.1° (*c* 1.77, $CHCl_3$). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.50; H, 9.28.

Methyl (*E*)-5-((Benzyloxy)methoxy)-2-hexenoate (1) (General Procedure A). To a stirred solution of 0.90 mL (10.5 mmol) of oxalyl chloride in 20 mL of dichloromethane at −78 °C under argon was added 1.50 mL (21.1 mmol) of dimethyl sulfoxide in a dropwise manner. After complete addition, the resulting mixture was allowed to stir for an additional 10 min, and then 1.96 g (9.32 mmol) of 3-((benzyloxy)methoxy)-1-butanol in 10 mL of dichloromethane was slowly added. After 20 min, 5.80 mL (41.6 mmol) of triethylamine was added and cooling was discontinued. After the reaction mixture had warmed to room temperature, it was added to 200 mL of ether and washed successively with two 100-mL portions of cold 10% aqueous HCl and 100 mL of saturated aqueous $NaHCO_3$. Each aqueous phase was extracted with one 100-mL portion of ether. The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated to give an oily residue.

To a stirred solution of the above crude aldehyde in 27 mL of toluene was added 4.50 g (13.5 mmol) of triphenylcarbomethoxymethylene-

(19) Sutter, M., projected Ph.D. thesis, ETH, Zürich.

(20) For specification of configuration of racemic diastereomers, we use the like/unlike nomenclature (see ref 15), according to which $R^*,R^* = l$ and $R^*,S^* = u$; for compounds with more than two asymmetric carbon atoms, the relative configurations are specificed pairwise, following the numbering of the IUPAC name.

phosphorane and the resulting mixture was stirred in an oil bath at 80 °C for 14 h. The cooled reaction mixture was passed through a short column of silica gel with 20% ether in pentane, and the filtrate was concentrated. Chromatography of the resulting residue on silica gel with 20% ether in pentane afforded 2.13 g (8.06 mmol, 86%) of the ester **1**: IR ($CHCl_3$) 1720, 1660; ^1H NMR ($CDCl_3$) 1.22 (d, J = 7, 3 H, CH_3), 2.40 (bt, J = 7, 2 H, $CH_2CH{=}C$), 3.72 (s, 3 H, CO_2CH_3), 3.92 (sx, J = 7, 1 H, $CHOCH_2$), 4.62 (s, 2 H, $C_6H_5CH_2$), 4.80 (s, 2 H, OCH_2O), 5.88 (bd, J = 16, 1 H, $HCCO_2CH_3$), 7.0 (d × t, J = 16, 7.5, 1 H, $CH_2CH{=}C$), 7.38 (bs, 5 H, C_6H_5). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.06; H, 7.72.

Methyl (*E*)-5-((Benzyloxy)methoxy)-4-methyl-2-pentenoate (2). By the general procedure A, 205 mg (0.97 mmole of 3-((benzyloxy)methoxy)-2-methyl-1-propanol, 0.1 mL (1.17 mmol) of oxalyl chloride, 0.17 mL (2.4 mmol) of dimethyl sulfoxide, 0.67 mL (4.8 mmol) of triethylamine, and 0.5 g (1.5 mmol) of the phosphorane gave 220 mg (0.83 mmol, 86%) of the ester **2**: IR ($CHCl_3$) 1720, 1660; ^1H NMR ($CDCl_3$) 1.08 (d, J = 7, 3 H, CH_3), 2.62 (bqi, J = 7, 1 H, $CHCH{=}C$), 3.73 (s, 3 H, CO_2CH_3), 3.85 (d, J = 7, 2 H, OCH_2CH), 4.58 (s, 2 H, $C_6H_5CH_2$), 4.75 (s, 2 H, OCH_2O), 5.88 (bd, J = 16, 1 H, $HCCO_2CH_3$), 6.98 (d × d, J = 16, 7, 1 H, $CHCH{=}C$), 7.37 (bs, 5 H, C_6H_5). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C 86.27; H, 7.69.

Methyl (*l*)-(*E*)-5-((Benzyloxy)methoxy)-4-methyl-2-hexenoate (3).[20] By the general procedure A, 128 mg (0.57 mmol) of (*l*)-3-((benzyloxy)methoxy)-2-methyl-1-butanol, 0.06 mL (0.7 mmol) of oxalyl chloride, 0.1 mL (1.4 mmol) of dimethyl sulfoxide, 0.4 mL (2.8 mmol) of triethylamine, and 0.25 g (0.75 mmol) of the phosphorane gave 145 mg (0.52 mmol, 91%) of the ester **3**: IR ($CHCl_3$) 1720, 1660; ^1H NMR ($CDCl_3$) 1.07 (d, J = 7, 3 H, CH_3), 1.13 (d, J = 7, 3 H, CH_3), 2.50 (m, 1 H, $CHCH{=}C$), 3.70 (s, 3 H, CO_2CH_3), 4.60 (s, 2 H, $C_6H_5CH_2$), 4.75 (d, J = 7.5 1 H, $OCHHO$), 4.80 (d, J = 7.5, 1 H, $OCHHO$), 5.85 (bd, J = 16, 1 H, $HCCO_2CH_3$), 7.03 (d × d, J = 16, 7.5, 1 H, $CHCH{=}C$), 7.33 (bs, 5 H, C_6H_5). Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.16; H, 8.07.

Methyl (*u*)-(*E*)-5-((Benzyloxy)methoxy)-4-methyl-2-hexenoate (4). By the general procedure A, 225 mg (1.0 mmol) of *u*-3-((benzyloxy)-methoxy)-2-methyl-1-butanol, 0.10 mL (1.17 mmol) of oxalyl chloride, 0.16 mL (2.25 mmol) of dimethyl sulfoxide, 0.6 mL (4.3 mmol) of triethylamine, and 0.45 g (1.3 mmol) of the phosphorane gave 251 mg (0.9 mmol, 90%) of the ester **4**: IR ($CHCl_3$) 1720, 1660; ^1H NMR ($CDCl_3$) 1.08 (d, J = 7, 3 H, CH_3), 1.13 (d, J = 7, 3 H, CH_3), 2.47 (m, 1 H, $CHCH{=}C$), 3.72 (s, 3 H, CO_2CH_3), 4.60 (s, 2 H, $C_6H_5CH_2$), 4.73 (d, J = 6, 1 H, $OCHHO$), 4.80 (d, J = 6, 1 H, $OCHHO$), 5.85 (bd, J = 16, 1 H, $HCCO_2CH_3$), 7.02 (d × d, J = 16, 7.5, 1 H, $CHCH{=}C$), 7.38 (bs, 5 H, C_6H_5). Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.04; H, 8.10.

Methyl (4*S*,5*R*)-(*E*)-(+)-4-Ethyl-5-(methoxymethoxy)-2-hexenoate (5). By the general procedure A, 292 mg (1.8 mmol) of (2*S*,3*R*)-(−)-2-ethyl-3-(methoxymethoxy)-1-butanol, 0.17 mL (2.0 mmol) of oxalyl chloride, 0.28 mL (4.0 mmol) of dimethyl sulfoxide, 1.1 mL (7.9 mmol) of triethylamine, and 0.9 g (2.7 mmol) of the phosphorane gave 338 mg (1.56 mmol, 87%) of the ester **5**: IR ($CHCl_3$) 1720, 1660; ^1H NMR ($CDCl_3$) 0.87 (t, J = 7, 3 H, CH_2CH_3), 1.13 (d, J = 7, 3 H, CH_3), 2.13 (sp, J = 5, 1 H, $CHCH{=}C$), 3.37 (s, 3 H, OCH_3), 3.73 (s, 3 H, CO_2CH_3), 4.58 (d, J = 6, 1 H, $OCHHO$), 4.69 (d, J = 6, 1 H, $OCHHO$), 5.85 (d, J = 16, 1 H, $HCCO_2CH_3$), 6.88 (d × d, J = 16, 10, 1 H, $CHCH{=}C$). $[\alpha]^{RT}_D$ +6.1° (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.29; H, 9.35.

Methyl (4*S*,5*R*)-(*E*)-(+)-4-Ethyl-5-hydroxy-2-hexenoate (6). By the general procedure A, 205 mg (1.08 mmol) of (2*S*,3*R*)-3-(1-ethoxyethoxy)-2-ethyl-1-butanol, 0.11 mL (1.3 mmol) of oxalyl chloride, 0.19 mL (2.7 mmol) of dimethyl sulfoxide, 0.76 mL (5.5 mmol) of triethylamine, and 0.54 g (1.6 mmol) of the phosphorane gave an unsaturated ester, which was dissolved in a mixture of 4 mL of tetrahydrofuran and 1 mL of 10% aqueous HCl. After stirring at room temperature for 2 h, the reaction mixture was diluted with 60 mL of ether and then washed successively with 20 mL of saturated aqueous NaCl and 20 mL of saturated aqueous $NaHCO_3$. Each aqueous phase was extracted with one 20-mL portion of ether. The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated. Chromatography of the resulting residue on silica gel with 60% ether in pentane afforded 130 mg (0.75 mmol, 70%) of the ester 6: IR ($CHCl_3$) 3620, 3480, 1720, 1660; ^1H NMR ($CDCl_3$) 0.88 (t, J = 7, 3 H, CH_2CH_3), 1.18 (d, J = 7, 3 H, CH_3), 2.05 (sp, J = 5, 1 H, $CHCH{=}C$), 3.73 (s, 3 H, CO_2CH_3), 5.88 (d, J = 16, 1 H, $HCCO_2CH_3$), 6.87 (d × d, J = 16, 10, 1 H, $CHCH{=}C$); $[\alpha]^{RT}_D$ +21.8° (*c* 1.03, $CHCl_3$). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.92; H, 9.37.

(6*S*,7*R*)-(*E*)-(+)-7-((Benzyloxy)methoxy)-6-ethyl-4-octen-3-one(7). By the oxidation step of general procedure A, 1.04 g (4.29 mmol) of (2*S*,3*R*)-(−)-3-((benzyloxy)methoxy)-2-ethyl-1-butanol, 0.42 mL (4.9 mmol) of oxalyl chloride, 0.70 mL (9.8 mmol) of dimethyl sulfoxide, and 2.7 mL (19 mmol) of triethylamine gave the corresponding aldehyde. To a stirred suspension of 145 mg (6.0 mmol) of sodium hydride in 10 mL of tetrahydrofuran at 0 °C was added 1.1 g (6.1 mmol) of dimethyl(2-oxobutyl)phosphonate in 5 mL of tetrahydrofuran. After 30 min, a solution of the crude aldehyde in 10 mL of tetrahydrofuran was added and cooling was discontinued. After stirring at room temperature for 16 h, the reaction mixture was diluted with 100 mL of ether and then washed with 50 mL of saturated aqueous $NaHCO_3$. The aqueous phase was extracted with two 50-mL portions of ether. The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated. Chromatography of the resulting residue on silica gel with 20% ether in pentane afforded 1.20 g (4.13 mmol, 96%) of the ketone **7**: IR($CHCl_3$) 1690, 1670, 1630; ^1H NMR ($CDCl_3$) 0.70 (t, J = 7, 3 H, $CHCH_2CH_3$), 1.10 (t, J = 7, 3 H, $COCH_2CH_3$), 1.15 (d, J = 7, 3, H, CH_3), 2.13 (sp, J = 5, 1 H, $HCCH{=}C$), 2.57 (qa, J = 7, 2 H, $COCH_2CH_3$), 3.83 (m, 1 H, HCO), 4.62 (s, 2 H, $C_6H_5CH_2$), 4.73 (d, J = 7.5, 1 H, $OCHHO$), 4.81 (d, J = 7.5, 1 H, $OCHHO$), 6.10 (d, J = 16, 1 H, =CHCO), 6.73 (d × d, J = 16, 9, 1 H, $HCCH{=}C$), 7.38 (bs, 5 H, C_6H_5). $[\alpha]^{RT}_D$ +14.0° (*c* 1.18, $CHCl_3$). Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.26; H, 9.15.

Methyl (*l*)- and (*u*)-3-Benzyloxy-5-((benzyloxy)methoxy)hexanoate (8) (General Procedure B). To a stirred solution of 175 mg (0.66 mmol) of methyl (*E*)-5-((benzyloxy)methoxy)-2-hexenoate(**1**) in 1.3 mL of dichloromethane were added, successively, 0.17 mL (1.64 mmol) of benzyl alcohol, 263 mg (0.82 mmol) of mercuric acetate, and 2 μL of 70% perchloric acid. The resulting mixture was stirred at room temperature for 24 h and then added to 60 mL of cold dichloromethane. It was washed with 40 mL of cold aqueous pH 7 solution and the aqueous phase was extracted with 40 mL of dichloromethane. The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated. To a vigorously stirred mixture of 6 mL of tetrahydrofuran 6 mL of aqueous pH 8 solution and 25 mg (0.66 mmol) of sodium borohydride in an ice water bath was added the above residue in 2 mL of tetrahydrofuran. After a few minutes, the reaction mixture was filtered through Celite with 60 mL of dichloromethane. The filtrate was washed with 40 mL of cold aqueous pH 7 solution. The aqueous phase was extracted with 40 mL of dichloromethane. The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated. Chromatography of the resulting residue on silica gel with 20% ether in pentane afforded 28 mg (0.11 mmol, 16%) of starting material **1** and 180 mg (0.48 mmol, 73%) of the adduct **8**. Capillary gas–liquid chromatography (13.5 m SE-54, 250 °C, 1.35 atm H_2) indicated a 57:43 mixture of diastereomers (retention time 192 and 199 s): IR ($CHCl_3$) 1730; ^1H NMR ($CDCl_3$) 1.20 and 1.22 (d, J = 7, 3 H, CH_3), 2.58 and 2.60 (d, J = 6, 2 H, $CH_2CO_2CH_3$), 3.67 and 3.68 (s, 3 H, CO_2CH_3), 4.55 (s, 2 H, $C_6H_5CH_2$), 4.57 (d, J = 9, 1 H, $OCHHC_6H_5$), 4.68 (d, J = 9, 1 H, $OCHHC_6H_5$), 4.75 (d, J = 6, 1 H, $OCHHO$), 4.82 (d, J = 6, 1 H, $OCHHO$), 7.33 (bs, 5 H, C_6H_5), 7.37 (bs, 5 H, C_6H_5). Anal. Calcd for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 71.01; H, 7.67.

Methyl (*u*)- and (*l*)-3-Benzyloxy-5-((benzyloxy)methoxy)-4-methylpentanoate(9). By the general procedure B, 153 mg (0.58 mmol) of methyl (*E*)-5-((benzyloxy)methoxy)-4-methyl-2-pentenoate (**2**), 0.15 mL (1.45 mmol) of benzyl alcohol, 230 mg (0.72 mmol) of mercuric acetate, and 2 μL of 70% perchloric acid gave 33 mg (0.12 mmol, 21%) of starting material **2** and 155 mg (0.42 mmol, 72%) of the adduct **9** ^{13}C NMR spectrum indicated a 83:17 mixture of diastereomers: IR ($CHCl_3$) 1730; ^1H NMR ($CDCl_3$) 0.97 (d, J = 7, 3 H, CH_3), 2.13 (m, 1 H, CH_3CH), 2.55 (d, J = 6, 2 H, $CH_2CO_2CH_3$), 3.55 (d, J = 6, 2 H, $CHCH_2O$), 3.62 (s, 3 H, CO_2CH_3), 4.0 (m, 1 H, $CHOCH_2C_6H_5$), 4.55 (s, 2 H, $CH_2C_6H_5$), 4.58 (s, 2 H, $CH_2C_6H_5$), 4.72 (s, 2 H, OCH_2O), 7.30 (bs, 5 H, C_6H_5), 7.33 (bs, 5 H, C_6H_5); ^{13}C NMR ($CDCl_3$) *11.91*, 12.84, 36.81, 36.95, *37.52*, 51.51, 69.39, 69.87, *70.05*, 72.25, *72.56*. *76.89*, 77.68, 94.81, 127.48, 127.64, 127.81, 128.26, 128.37, 137.97, 138.62, 172.44. Anal. Calcd for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.85; H, 7.75.

Methyl (*u*,*u*)- and (*l*,*u*)-3-(Benzyloxy)-5-((benzyloxy)methoxy)-4-methylhexanoate (10). By the general procedure B, 128 mg (0.46 mmol) of methyl (*l*)-(*E*)-5-((benzyloxy)methoxy)-4-methyl-2-hexenoate (**3**), 0.12 mL (1.16 mmol) of benzyl alcohol, 180 mg (0.56 mmol) of mercuric acetate, and 1.5 μL of 70% perchloric acid gave 51 mg (0.18 mmol, 39%) of starting material **3** and 99 mg (0.26 mmol, 55%) of the adduct **10**. The ^{13}C NMR spectrum and capillary gas–liquid chromatography (13.5 m SE-54, 250 °C, 1.35 atm H_2) indicated a 78:22 mixture of diastereomers (retention time 297 and 304 s): IR ($CHCl_3$) 1730; ^1H NMR ($CDCl_3$) 0.97 and 1.03 (d, J = 7, 3 H, CH_3), 1.18 and 1.20 (d, J = 7, 3 H, CH_3), 1.82 (m, 1 H, CH_3CH), 2.58 (m, 2 H, $CH_2CO_2CH_3$), 3.62 (s, 3 H, CO_2CH_3), 4.50 and 4.53 (s, 2 H, $CH_2C_6H_5$), 4.60 and 4.62 (s, 2 H, $CH_2C_6H_5$), 4.64 (d, J = 9, 1 H, $OCHHO$), 4.73 (d, J = 9, 1 H, $OCHHO$), 7.30 (bs, 5 H, C_6H_5), 7.33 (bs, 5 H, C_6H_5); ^{13}C NMR ($CDCl_3$) 9.27, *10.41*, *18.06*, 18.69, 36.98, *37.54*, 42.57, 51.50, 69.63, 71.74,

72.07, 74.07, *77.48*, 77.93, *93.31*, 93.70, 127.50, 127.58, 127.74, 128.01, 128.27, 128.36, 138.02, 138.53, 172.46. Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.52; H, 7.91.

Methyl (*u*,*l*)- and (*l*,*l*)-3-(Benzyloxy)-5-((benzyloxy)methoxy)-4-methylhexanoate (11). By the general procedure B, 137 mg (0.49 mmol) of methyl (*u*)-(*E*)-5-((benzyloxy)methoxy)-4-methyl-2-hexenoate (**4**), 0.13 mL (1.26 mmol) of benzyl alcohol, 200 mg (0.63 mmol) of mercuric acetate, and 1.5 μL of 70% perchloric acid gave 39 mg (0.14 mmol, 28%) of starting material **4** and 125 mg (0.32 mmol, 66%) of the adduct **11**. The ^{13}C NMR spectrum and capillary gas–liquid chromatography (13.5 m SE-54, 250 °C, 1.35 atm H_2) indicated a 93:7 mixture of diastereomers (retention time 316 and 322 s): IR ($CHCl_3$) 1730; ^1H NMR ($CDCl_3$) 0.92 (d, J = 7, 3 H, CH_3), 1.17 (d, J = 7, 3 H, CH_3), 2.07 (m, 1 H, CH_3CH), 2.55 (bd, J = 6, 2 H, $CH_2CO_2CH_3$), 3.62 (s, 3 H, CO_2CH_3), 4.53 (s, 2 H, $CH_2C_6H_5$), 4.63 (s, 2 H, $CH_2C_6H_5$), 4.73 (d, J = 7.5, 1 H, OC*H*HO), 4.81 (d, J = 7.5, 1 H, OCH*H*O), 7.33 (bs, 5 H, C_6H_5), 7.35 (bs, 5 H, C_6H_5); ^{13}C NMR ($CDCl_3$) *9.76*, 10.53, 17.36, *18.00*, 36.37, *38.17*, 41.31, *43.55*, 51.46, 69.63, *69.89*, 71.67, *72.12*, 74.22, *76.12*, 76.71, 92.97, *93.74*, 126.95, 127.44, 127.54, 127.62, 127.73, 127.96, 128.26, 128.35, 128.63, 138.07, 138.67, 172.58. Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.41; H, 7.79.

Methyl (3*S*,4*R*,5*R*)-(−)-3-(Benzyloxy)-4-ethyl-5-(methoxymethoxy)hexanoate (12). By the general procedure B, 94 mg (0.43 mmol) of methyl (4*S*,5*R*)-(E)-(+)-4-ethyl-5-(methoxymethoxy)-2-hexenoate (**5**), 0.11 mL (1.0 mmol) of benzyl alcohol, 170 mg (0.53 mmol) of mercuric acetate, and 1.5 μL of 70% perchloric acid gave 28 mg (0.13 mmol, 30%) of starting material **5** and 87 mg (0.27 mmol, 63%) of the adduct **12**. The 300-MHz ^1H NMR spectrum indicated diastereomeric purity in excess of 95%: IR ($CHCl_3$) 1730; ^1H NMR ($CDCl_3$) 0.95 (t, J = 7, 3 H, CH_2CH_3), 1.22 (d, J = 7, 3 H, CH_3), 2.57 (d × d, J = 9.5, 15.5, 1 H, $CHHCO_2CH_3$), 2.73 (d × d, J = 3.5, 15.5, 1 H, $CHHCO_2CH_3$), 3.33 (s, 3 H, OCH_3), 3.65 (s, 3 H, CO_2CH_3), 4.52 (s, 2 H, $CH_2C_6H_5$), 4.54 (d, J = 7, 1 H, OC*H*HO); 4.65 (d, J = 7, 1 H, OCH*H*O), 7.32 (bs, 5 H, C_6H_5); $[\alpha]^{RT}_D$ −34.4° (*c* 1.60, $CHCl_3$). Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.39; H, 8.54.

(4*S*,5*R*,6*R*)-(+)-4-(Benzyloxy)-5-ethyl-6-methyltetrahydro-α-pyrone (13). By the general procedure B, 30 mg (0.18 mmol) of methyl (4*S*,5*R*)-(*E*)-(+)-4-ethyl-5-hydroxy-2-hexenoate (6), 0.2 mL (1.9 mmol) of benzyl alcohol, 63 mg (0.2 mmol) of mercuric acetate, and 1 μL of 70% perchloric acid gave 10 mg (0.06 mmol, 32%) of starting material 6 and 27 mg (0.11 mmol, 60%) of the adduct **13**. The 300-MHz ^1H NMR spectrum indicated diastereomeric purity in excess of 95%: IR ($CHCl_3$) 1725; ^1H NMR ($CDCl_3$) 0.87 (t, J = 7, 3 H, CH_2CH_3), 1.37 (d, J = 7, 3 H, CH_3); 2.43 (d × d, J = 18, 4, 1 H, $CHHC{=}O$), 2.97 (d × d, J = 18, 3, 1 H, $CHHC{=}O$), 3.88 (m, 1 H, $CHOCH_2$), 4.40 (d, J = 12, 1 H, OC*H*HC_6H_5), 4.67 (d, J = 12, 1 H, OCH*H*C_6H_5), 7.37 (bs, 5 H, C_6H_5); $[\alpha]^{RT}_D$ +88.7° (*c* 0.93, $CHCl_3$). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.49; H, 8.19.

(5*S*,6*R*,7*R*)-(−)-5-(Benzyloxy)-7-((benzyloxy)methoxy)-6-ethyl-3-octanone (14). By the general procedure B, 80 mg (0.26 mmol) of (6*S*,7*R*)-(*E*)-(+)-7-((benzyloxy)methoxy)-6-ethyl-4-octen-3-one (**7**), 0.3 mL (2.9 mmol) of benzyl alcohol, 100 mg (0.31 mmol) of mercuric acetate, and 1 μL of 70% perchloric acid yielded a residue that was oxidized with 0.35 mL (0.49 mmol) of dimethyl sulfoxide, 0.02 mL (0.23 mmol) of oxalyl chloride, and 0.14 mL (1.0 mmol) of triethylamine according to the oxidation step of general procedure A to give 20 mg (0.07 mmol, 25%) of the starting material **7** and 72 mg (0.18 mmol, 69%) of the adduct **14**. The ^{13}C NMR spectrum indicated diastereomeric purity in excess of 95%: IR ($CHCl_3$) 1710; ^1H NMR ($CDCl_3$) 0.95 (t, J = 7, 3 H, $CHCH_2CH_3$), 1.0 (t, J = 7, 3 H, $COCH_2CH_3$), 1.23 (d, J = 7, 3 H, CH_3), 2.38 (qa, J = 7, 2 H, $COCH_2CH_3$), 2.68 (bd, J = 7, 2 H, $CHCH_2CO$), 3.88 (m, 1 H, CH_3CHO), 4.32 (7, 1 H, $CHOCH_2C_6H_5$), 4.47 (s, 2 H, $CH_2C_6H_5$), 4.58 (s, 2 H, $CH_2C_6H_5$), 4.69 (d, J = 7.5, 1 H, OC*H*HO), 4.77 (d, J = 7.5, 1 H, OCH*H*O), 7.30 (bs, 5 H, C_6H_5), 7.33 (bs, 5 H, C_6H_5); ^{13}C NMR: 7.65, 13.09, 18.27, 18.77, 37.08, 45.14, 48.33, 69.67, 72.00, 73.06, 93.30, 127.42, 127.71, 128.27, 128.42, 138.90, 139.01, 210.40; $[\alpha]^{RT}_D$ −41.2° (*c* 1.11, $CHCl_3$). Anal. Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 75.39; H, 8.78.

(*u*)- and (*l*)-3-(Benzyloxy)-5-((benzyloxy)methoxy)-4-methylpentyl Benzoate (15) (General Procedure C). To a stirred solution of 106 mg (0.28 mmol) of methyl (*u*)- and (*l*)-3-(benzyloxy)-5-((benzyloxy)methoxy)-4-methylpentanoate (**9**) in 3 mL of ether was added 20 mg (0.5 mmol) of lithium tetrahydridoaluminate. After stirring at room temperature for 2 h, the reaction mixture was treated successively with 0.02 mL of water, 0.02 mL of 15% aqueous NaOH, and 0.06 mL of water. After 15 min, $MgSO_4$ was added and the resulting mixture was filtered. Concentration of the filtrate gave a residue, which was dissolved in 1.5 mL of dichloromethane, and then 60 mg (0.49 mmol) of *N*,*N*-dimethylaminopyridine and 0.05 mL (0.43 mmol) of benzoyl chloride were added. After stirring at room temperature for 2 h, the reaction mixture was diluted with 60 mL of ether and washed with 30 mL of saturated aqueous $NaHCO_3$. The organic phase was dried over anhydrous $MgSO_4$, filtered, and then concentrated. Chromatography of the resulting residue on silica gel with 20% ether in pentane afforded 109 mg (0.24 mmol, 86%) of the ester **15**: IR ($CHCl_3$) 1710; ^1H NMR ($CDCl_3$) 1.0 (d, J = 7, 3 H, CH_3), 3.57 (d, J = 6, 2 H, $CHCH_2O$), 4.73 (s, 2 H, $CH_2C_6H_5$), 7.35 (bs, 2 × 5 H, 2 × C_6H_5). Anal. Calcd for $C_{28}H_{32}O_5$: C, 74.97; H, 7.19. Found: C, 74.93; H, 7.17.

(*l*,*l*)- and (*u*,*l*)-3-(Benzyloxy)-5-((benzyloxy)methoxy)-4-methylhexyl Benzoate(16). By the general procedure C, 83 mg (0.21 mmol) of methyl (*u*,*u*)- and (*l*,*u*)-3-(benzyloxy)-5-((benzyloxy)methoxy)-4-methylhexanoate (**10**), 20 mg (0.5 mmol) of lithium tetrahydridoaluminate, 60 mg (0.49 mmol) of *N*,*N*-dimethylaminopyridine, and 0.05 mL (0.43 mmol) of benzoyl chloride gave 87 mg (0.19 mmol, 90%) of the ester **16**: IR ($CHCl_3$) 1710; ^1H NMR ($CDCl_3$) 1.02 and 1.08 (d, J = 7, 3 H, CH_3), 1.22 (d, J = 7, 3 H, CH_3), 4.53 (s, 2 H, $CH_2C_6H_5$), 4.63 (s, 2 H, $CH_2C_6H_5$), 4.74 (d, J = 6, 1 H, OC*H*HO), 4.84 (d, J = 6, 1 H, OCH*H*O), 7.35 (bs, 2 × 5 H, 2 × C_6H_5). Anal. Calcd for $C_{29}H_{34}O_5$: C, 75.30; H, 7.41. Found: C, 75.43; H, 7.38.

(*l*,*u*)- and (*u*,*u*)-3-(Benzyloxy)-5-((benzyloxy)methoxy)-4-methylhexyl Benzoate (17). By the general procedure C, 104 mg (0.27 mmol) of methyl (*u*,*l*)- and (*l*,*l*)-3-(benzyloxy)-5-((benzyloxy)methoxy)-4-methylhexanoate (**11**), 20 mg (0.5 mmol) of lithium tetrahydridoaluminate, 60 mg (0.49 mmol) of *N*,*N*-dimethylaminopyridine, and 0.05 mL (0.43 mmol) of benzoyl chloride gave 100 mg (0.22 mmol, 82%) of the ester **17**: IR ($CHCl_3$) 1710; ^1H NMR ($CDCl_3$) 0.93 (d, J = 7, 3 H, CH_3), 1.20 (d, J = 7, 3 H, CH_3), 4.50 (d, J = 6, 1 H, $CHHC_6H_5$), 4.55 (d, J = 6, 1 H, $CHHC_6H_5$), 4.58 (s, 2 H, $CH_2C_6H_5$), 4.71 (d, J = 6, 1 H, OC*H*HO), 4.74 (d, J = 6, 1 H, OCH*H*O), 7.32 (bs, 2 × 5 H, 2 × C_6H_5). Anal. Calcd for $C_{29}H_{34}O_5$: C, 75.30; H, 7.41. Found: C, 75.20; H, 7.39.

(2-(*u*)- and (*l*)-2,2,5-Trimethyl-1,3-dioxan-4-yl)ethyl Benzoate (18) (General Procedure D). A suspension of 5 mg of 10% palladium on activated charcoal and 64 mg (0.14 mmol) of (*u*)- and (*l*)-3-(benzyloxy)-5((benzyloxy)methoxy)-4-methylpentyl benzoate (**15**) in 3 mL of ethanol was stirred vigorously under hydrogen for 10 h. The mixture was then filtered through Celite with ethyl acetate washings. The filtrate was concentrated to a residue, which was dissolved in 3 mL of 2,2-dimethoxypropane containg 3 mg of *p*-toluene sulfonic acid monohydrate. After stirring at room temperature for 1 h, solid Na_2CO_3 was added, and after an additional 15 min, the reaction mixture was filtered with ether washing. Concentration of the filtrate gave a residue that was chromatographed on silica gel with 15% ether in pentane to afford 36 mg (0.13 mmol, 91%) of the dioxane **18**: IR ($CHCl_3$) 1710; ^1H NMR ($CDCl_3$) 0.79 (d, J = 7, 3 H, CH_3), 1.37 (s, 3 H, CH_3CCH_3), 1.42 (s, 3 H, CH_3CCH_3), 3.52 (d × d, J = 11.5, 11.5, 1 H, $CHCHHO$), 3.65 (d × d × d, J = 2.5, 9.5, 9.5, 1 H, CHOC), 3.71 (d × d, J = 5, 11.5, 1 H, $CHCHHO$). Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.87; H, 8.12.

2-[(*u*,*u*)- and (*l*,*u*)-2,2,5,6-Tetramethyl-1,3-dioxan-4-yl]ethyl Benzoate (19). By the general procedure D, 44 mg (0.095 mmol) of (*l*,*l*)- and (*u*,*l*)-3-(benzyloxy)-5-((benzyloxy)methoxy)-4-methylhexyl benzoate (**16**), 5 mg of 10% palladium on activated charcoal in 3 mL of ethanol, and then 3 mg of *p*-toluenesulfonic acid monohydrate in 3 mL of 2,2-dimethoxypropane gave 26 mg (0.089 mmol, 94%) of the dioxane **19**: IR ($CHCl_3$) 1710; ^1H NMR ($CDCl_3$): δ 0.86 and 0.91 (d, J = 7, 3 H, CH_3), 1.10 and 1.13 (d, J = 7, 3 H, CH_3), 1.32 and 1.39 (s, 3 H, CH_3CCH_3), 1.34 and 1.43 (s, 3 H, CH_3CCH_3), 3.46 (d × d × d, J = 3, 9, 9, 1 H, CHOC). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 69.79; H, 8.35.

2-[(*u*,*l*)- and -(*l*,*l*)-2,2,5,6-Tetramethyl-1,3-dioxan-4-yl]ethyl Benzoate (20). By the general procedure D, 68 mg (0.15 mmol) of (*l*,*u*)- and (*u*,*u*)-3-(benzyloxy)-5-((benzyloxy)methoxy)-4-methylhexyl benzoate (**17**), 5 mg of 10% palldium on activated charcoal in 3 mL of ethanol, and then 3 mg of *p*-toluenesulfonic acid monohydrate in 3 mL of 2,2-dimethoxypropane gave 41 mg (0.14 mmol, 93%) of the dioxane **20**: IR ($CHCl_3$) 1710; ^1H NMR ($CDCl_3$) 0.83 (d, J = 7, 3 H, CH_3), 1.20 (d, J = 7, 3 H, CH_3), 1.37 (s, 3 H, CH_3CCH_3), 1.43 (s, 3 H, CH_3CCH_3), 3.60 (d × qa, J = 10, 7, 1 H, CH_3CHOC), 3.65 (d × d × d, J = 2.5, 9.5, 9.5, 1 H, CHOC). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 69.64; H, 8.22.

Methyl (3*S*,4*S*,5*R*)-(−)-4-Ethyl-3-hydroxy-5-(methoxymethoxy)hexanoate (21). By the hydrogenolysis step of general procedure D, 17.3 mg (0.053 mmol) of methyl (3*S*,4*R*,5*R*)-(−)-3-(benzyloxy)-4-ethyl-5-(methoxymethoxy)hexanoate (**12**) and 5 mg of 10% palladium on activated charcoal in 1 mL of ethanol gave 11.6 mg (0.05 mmol, 93%) of the ester **21**: IR ($CHCl_3$) 3680, 3500, 1730; ^1H NMR ($CDCl_3$) 0.93 (t, J = 7, 3 H, CH_3CH_2), 1.23 (d, J = 7, 3 H, CH_3), 2.57 (d × d, J = 6, 16, $CHCHCO_2CH_3$), 2.62 (d × d, J = 2, 16, 1 H, $CHHCO_2CH_3$), 3.37 (s, 3 H, OCH_3), 3.72 (s, 3 H, CO_2CH_3), 3.92 (m, 1 H, CH_3CHO), 4.20 (m,

1 H, CHOH), 4.61 (d, J = 6, 1 H, OCHHO), 4.69 (d, J = 6, 1 H, OCHHO); $[\alpha]^{RT}_D$ −49.6° (c 0.70, $CHCl_3$). Anal. Calcd for $C_{11}H_{22}O_5$: C, 56.39; H, 9.46. Found: C, 56.42; H, 9.50.

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Registry No. (±)-**1**, 87518-81-8; (±)-**2**, 87518-82-9; (±)-**3**, 87518-83-0; (±)-**4**, 87518-84-1; (+)-**5**, 87518-85-2; (+)-6, 87518-86-3; (+)-**7**, 87518-87-4; (±)-*l*-**8**, 87518-88-5; (±)-*u*-**8**, 87518-89-6; (±)-*l*-**9**, 87518-90-9; (±)-*l*-**9**, 87518-91-0; (±)-*u*,*u*-**10**, 87518-92-1; (±)-*l*,*u*-**10**, 87583-28-6; (±)-*u*,*l*-**11**, 87583-29-7; (±)-*l*,*l*-**11**, 87583-30-0; (−)-**12**, 87518-93-2; (+)-**13**, 87518-94-3; (−)-**14**, 87518-95-4; (±)-*u*-**15**, 87518-96-5; (±)-*l*-**15**, 87518-97-6; (±)-*u*,*u*-**16**, 87518-98-7; (±)-*l*,*u*-**16**, 87583-31-1; (±)-*u*,*l*-**17**, 87583-32-2; (±)-*l*,*l*-**17**, 87583-33-3; (±)-*u*-**18**, 87518-99-8; (±)-*l*-**18**, 87519-00-4; (±)-*u*,*u*-**19**, 87519-01-5; (±)-*l*,*u*-**19**, 87583-34-4; (±)-*u*,*l*-**20**, 87583-35-5; (±)-*l*,*l*-**20**, 87583-36-6; (−)-**21**, 87519-02-6; **22**, 87519-03-7; chloromethyl methyl ether, 107-30-2; ethyl vinyl ether, 109-92-2; (2*S*,3*R*)-(−)-2-ethyl-3-methoxymethoxy-1-butanol, 87519-04-8; ethyl (2*R*,3*R*)-(−)-2-ethyl-3-hydroxybutanoate, 87519-05-9; ethyl (2*R*,3*R*)-2-ethyl-3-(methoxymethoxy)butanoate, 87519-06-0; 3-(1-ethoxyethoxy)-2-ethyl-1-butanol, 87519-07-1; ethyl 3-(1-ethoxyethoxy)-2-ethylbutanoate, 87519-08-2; (2*S*,3*R*)-(−)-3-benzyloxymethoxy-2-ethyl-1-butanol, 87519-09-3; chloromethyl benzyl ether, 3587-60-8; ethyl (2*R*,3*R*)-3-benzyloxymethoxy-2-ethylbutanoate, 87519-10-6; (±)-3-benzyloxymethoxy-1-butanol, 87519-11-7; (±)-3-benzyloxymethoxy-1-butanal, 87519-12-8; triphenylcarbomethoxymethylenephosphorane, 2605-67-6; (±)-3-benzyloxymethoxy-2-methyl-1-propanol, 87519-13-9; (±)-3-benzyloxymethoxy-2-methyl-1-propanal, 79027-30-8; (±)-*l*-3-benzyloxymethoxy-2-methyl-1-butanol, 87519-14-0; (±)-*u*-3-benzyloxymethoxy-2-methyl-1-butanol, 87519-15-1; (±)-*u*-3-benzyloxymethoxy-2-methyl-1-butanal, 87519-16-2; (±)-*l*-3-benzyloxymethoxy-2-methyl-1-butanal, 87519-17-3; (2*R*,3*R*)-2-ethyl-3-methoxymethyl-1-butanal, 87519-18-4; 3-(1-ethoxyethoxy)-2-ethyl-1-butanal, 87519-19-5; (2*R*,3*R*)-3-benzyloxymethoxy-2-ethyl-1-butanal, 87519-20-8; dimethyl (2-oxobutyl)phosphonate, 41162-15-6; benzyl alcohol, 100-51-6; benzoyl chloride, 98-88-4; 2,2-dimethoxypropane, 77-76-9.

The Denticulatins, Two Polypropionate Metabolites from the Pulmonate *Siphonaria denticulata*

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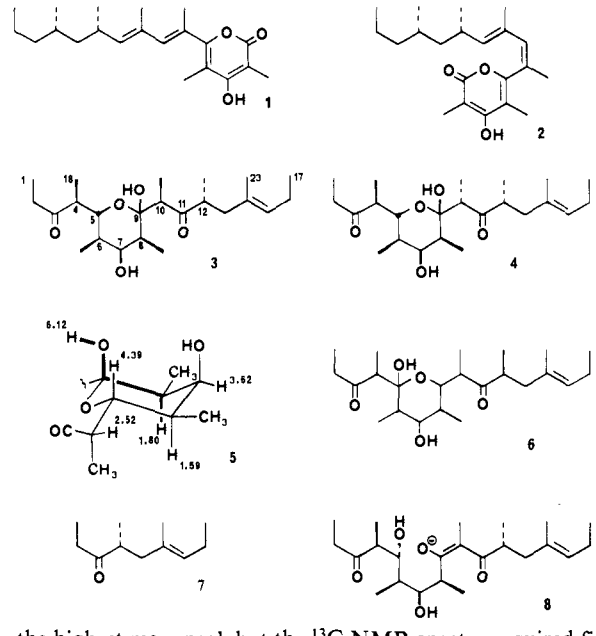
Abstract: Two isomeric polypropionate metabolites, denticulatin A (**3**) and denticulatin B (**4**), were isolated from the marine pulmonate mollusk *Siphonaria denticulata*. The structures were elucidated by interpretation of spectral data and a single-crystal X-ray diffraction study. Denticulatin A was ichthyotoxic at 10 μg/mL while denticulatin B was toxic at 30 μg/mL.

Siphonaria denticulata Quoy and Gaimard, 1833,[1] is an air-breathing marine mollusk of the subclass Pulmonata. This pulmonate mollusk is commonly found in the intertidal zone along the coast of New South Wales, Australia. The siphonariids, commonly known as false limpets, resemble limpets in both appearance and behavior. When submerged, siphonariids remain firmly clamped in crevices on rocks. Shortly after they are exposed by the retreating tide they move about the rocks to feed on encrusting algae and microorganisms, returning to their crevices when threatened by the heat of the sun or the incoming tide.[2] Thus, siphonariids are exposed to both marine and terrestrial predators and may employ chemical defense mechanisms. We have recently reported the isolation of two antimicrobial pyrones, diemenesin A (**1**) and diemenensin B (**2**) from *Siphonaria diemenensis*.[3] In this paper we describe the structural elucidation of denticulatin A (**3**) and denticulatin B (**4**), further examples of *Siphonaria* metabolites having a polypropionate carbon skelton.

Specimens of *S. denticulata* were collected at Coledale and Eden, New South Wales, Australia, in March 1982 and stored in acetone until needed. The ethyl acetate soluble material from the acetone extracts was chromatographed by HPLC on Partisil using ether–hexane (1:1) as the eluant to obtain denticulatin A (**3**, 0.06–0.12 mg/animal) and denticulatin B (**4**, 0.04–0.10 mg/animal). Initial examination of spectral data revealed that **3** and **4** were isomeric, had the same carbon skeleton, and probably differed in stereochemistry at a single center.

Both denticulatin A (**3**), $[\alpha]_D$ −30.7°, and denticulatin B (**4**), $[\alpha]_D$ −26.4°, had the molecular formula $C_{28}H_{40}O_5$. The high-resolution mass spectra indicated a molecular formula of $C_{28}H_{38}O_4$ for the highest mass peak but the ^{13}C NMR spectra required five oxygen atoms, two of which were incorporated into a hemiketal group that would be expected to eliminate water in the mass spectrometer. Since the compounds are so similar, we will describe



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