allowed to stir at 0 °C for 15 min. The cold bath was then removed and the solution stirred at room temperature for another 12 h. The reaction was quenched by the addition of 3 mL of saturated NH_4Cl. The aqueous layer was extracted three times with Et_2O. The combined organic layers were washed twice with saturated aqueous $NaHCO_3$, once with brine, filtered, and dried and the solvent removed in vacuo. The crude reaction mixture was then chromatographed on silica and eluted first with 100% hexanes to remove naphthalene. Further elution with hexane–EtOAc (95:5) afforded cannabidiol dimethyl ether (6) as an impure fraction. This fraction was further separated by HPLC, eluting with hexane–EtOAc (97:3) to yield 0.143 g (71%) of cannabidiol dimethyl ether (6): $\alpha^{29}_D = -123.0$ (c = 1.02 g/100 mL, EtOH) (lit.[15] $\alpha^{29}_D = -133$ (c = 1.04, EtOH); ^1H NMR ($CDCl_3$) δ 0.90 (t, J = 7 Hz, 3 H), 1.25–1.40 (m, 4 H), 1.58–1.63 (overlapping multiplet, 5 H), 1.66 (s, 3 H), 1.73 (m, 2 H), 1.92–2.04 (bm, 1 H), 2.11–2.26 (bm, 1 H), 2.53 (t, J = 8 Hz, 2 H), 2.89 (dt, J = 5, 11 Hz, 2 H), 3.73 (s, 6 H), 3.96–4.01 (bm, 1 H), 4.32 (m, 2 H), 5.20 (s, 1 H), 6.33 (s, 2 H); ^{13}C NMR δ 14.0, 19.0, 22.5, 23.4, 29.7, 30.7, 31.0, 31.7, 36.1, 36.4, 45.2, 55.9, 105.0, 109.6, 118.9, 125.9, 131.2, 141.9, 149.5, 158.6; IR (neat) 3071, 2960, 2929, 2857, 1641, 1607, 1583, 1452, 1420, 1235, 1116 cm^{-1}; HRMS exact mass calcd for $C_{24}H_{34}O_2$ 342.2559, found 342.2561.

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Acknowledgment. We gratefully thank Dr. Raj Razdan for ^1H NMR spectra of an authentic sample of cannabidiol. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

Registry No. **5**, 13956-29-1; **6**, 1242-67-7; **7**, 591-51-5; *exo*-**8**, 140695-30-3; *endo*-**8**, 140633-44-9; **9**, 2785-97-9; **10**, 140633-45-0; **11**, 67895-00-5; **12**, 140633-46-1; **13**, 2786-02-9; *exo*-**14**, 140695-29-0; *endo*-**14**, 140633-47-2; **15**, 140633-48-3; **16**, 1972-05-0; **17**, 23050-49-9; **18**, 10293-10-4; **19**, 140633-49-4; **19** alcohol, 140633-50-7; olivetol dimethyl ether, 22976-40-5.

Supplementary Material Available: ^1H and ^{13}C NMR spectra (21 pages). This material is contained in many 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.

Thermostable Enzymes in Organic Synthesis. 7. Total Synthesis of the Western Corn Rootworm Sex Pheromone 8-Methyldec-2-yl Propanoate Using a TBADH-Generated C_2-Bifunctional Chiron

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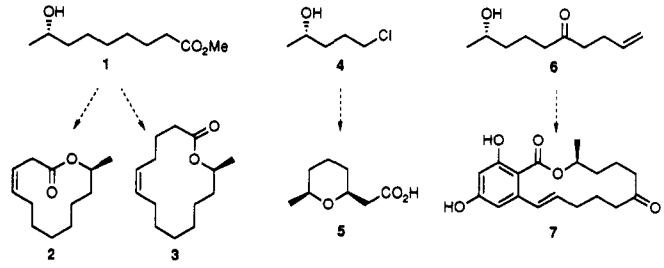
Received February 12, 1992

Enantiomerically pure alcohols produced by *Thermoanaerobium brockii* alcohol dehydrogenase (TBADH)-catalyzed asymmetric reduction of polyfunctional ketones are useful building blocks for natural products synthesis. This advantage has been demonstrated by a total synthesis of all four isomers of 8-methyldec-2-yl propanoate, the sex pheromone emitted by the female western corn rootworm, *Diabrotica virgifera virgifera* LeConte. These four isomers were obtained in a very short procedure (either three or five steps) with an enantiomeric purity that exceeds 99% using a single chiral building block, (2*S*,8*S*)-(+)-2,8-dihydroxynonane. The latter diol, characterized by a synthetically useful C_2 symmetry, was obtained by TBADH-catalyzed reduction of nonane-2,8-dione.

Introduction

Thermoanaerobium brockii alcohol dehydrogenase (TBADH) is a very useful biocatalyst that affects the reduction of a broad range of aliphatic ketones to the corresponding secondary alcohols with excellent enantioselectivity. In our previous work we have produced a broad variety of chiral mono-, bi-, and trifunctional secondary alcohols by TBADH-catalyzed reduction of the corresponding ketones.[1-3] These alcohols may be conveniently employed as chiral building blocks (chirons[4]) for total synthesis of natural products containing chiral carbinol centers. We have demonstrated this advantage (Scheme I) by employing (*S*)-(+)-methyl 8-hydroxynonanoate (**1**) in the total synthesis of (*S*)-(+)-(*Z*)-dodec-3-en-11-olide (ferrulactone II) (**2**)[5] and (*S*)-(+)-(*Z*)-tetradec-5-en-13-olide (**3**).[3] Similarly, (*S*)-(+)-5-chloropentan-2-ol (**4**) was employed in the total synthesis of (+)-(*S*,*S*)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid (**5**).[2,6] More recently we completed the total synthesis of (*S*)-(−)-zearalenone (**7**) using (*S*)-2-hydroxydec-9-en-6-one (**6**).[7] All of these

Scheme I



(1) (a) Keinan, E.; Hafeli, E. K.; Seth, K. K.; Lamed, R. *J. Am. Chem. Soc.* **1986**, *108*, 162. (b) Lamed, R.; Keinan, E.; Zeikus, J. G. *Enzyme Microb. Technol.* **1981**, *3*, 144.
(2) Keinan, E.; Seth, K. K.; Lamed, R. *J. Am. Chem. Soc.* **1986**, *108*, 3474.
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(4) Hanessian, S. *Total synthesis of natural products: the chiron approach*, Pergamon Press: Oxford, 1983.
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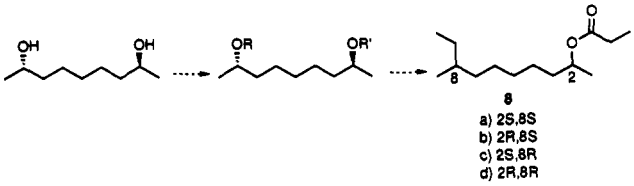
Scheme II



compounds were obtained with essentially quantitative enantiomeric purity.

The outstanding ability of TBADH to discriminate between two carbonyl groups having similar chemical reactivity is demonstrated by the direct synthesis of enantiomerically pure **6** via enzymatic reduction of dec-9-ene-2,6-dione.[7] These results raise an obvious question concerning the outcome of TBADH-catalyzed reduction of a symmetrical diketone. Preferential reduction of one carbonyl would produce a bifunctional chiral building block having one asymmetric carbinol center. However, if both carbonyls are reduced, and with the same stereoselectivity, then one could obtain an extremely useful chiron, having C_2 symmetry. Such bifunctional chirons are very attractive intermediates, as they do not require selective identification of either group. Modification of any one of the two functions would cause asymmetrization, yielding a single diastereomer that may be specifically manipulated and used in the synthesis of enantiomerically active compounds.

In this paper we show that such chirons can indeed be produced by the above-mentioned enzymatic system. Moreover, we demonstrate the advantage of using such a C_2 chiron in synthesis. In particular, we present a short and efficient entry to all four isomers of the sex pheromone emitted by the female western corn rootworm (WCR), *Diabrotica virgifera virgifera* LeConte. This pheromone was isolated and identified as 8-methyldec-2-yl propanoate (**8**).[8] Although racemic **8** may be easily prepared,[8,9] the synthesis of any of the four stereoisomers **8a–d** has been reported to involve many steps, including difficult separation procedures. As is usually the case with aliphatic carbon skeletons which contain essentially noninteracting asymmetric carbon atoms, synthesis of these isomers requires the preparation and cross-coupling of two different chiral building blocks, each containing an appropriate asymmetric center. For example, in Mori's synthesis of **8c** and **8d** the hydrocarbon center (8*R*) was prepared by degradation of (*R*)-(+)-citronellol and the (2*R*) and (2*S*) carbinol centers were obtained from the two microbially generated enantiomers of β-hydroxybutyrate.[10] Sonnet et al. have employed four different chiral building blocks for the same purpose, three of which were obtained by HPLC resolution of diastereomeric derivatives and one by degradation of D-isoleucine.[11] A recent attempt to prepare these compounds from a single chiral source, (*S*)-(+)-β-hydroxybutyrate via cyclic intermediates, afforded **8a** and **8c** with apparently poor enantiomeric purity.[12]

Results and Discussion

Retrosynthetic analysis of compounds **8a–d** suggests that these isomers could be prepared from a single chiral building block, 2,8-dihydroxynonane, which possesses the two required asymmetric centers (Scheme II). Monofunctionalization (e.g., by esterification) of this diol would break its C_2 symmetry and produce a single diastereomer in which the two previously identical chiral centers are now differentiated. This modified chiron represents a key intermediate in the synthesis of all four compounds **8a–d**, as each of its asymmetric centers can be easily manipulated with appropriate use of copper-mediated cross-coupling methods and alcohol inversion techniques.

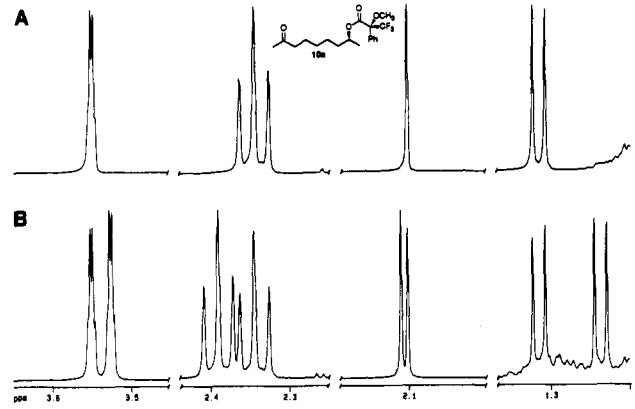


Figure 1. Determination of diastereomeric purity of the (8*S*)-8-hydroxynonan-2-one ester **10a** by ^{1}H NMR spectroscopy. (A) Partial NMR spectrum of **10a** in $CDCl_3$. (B) Partial spectrum of 1:1 mixture of **10a** and **10b** (prepared from racemic **10**) under the same conditions.

We have previously suggested[3] that the active site of TBADH has an open structure that puts limits on the size of the small alkyl group attached to the carbonyl group but allows considerable flexibility with regard to the size and functional groups on the second alkyl chain. This hypothesis is based on the general features of TBADH-catalyzed reduction of a broad sample of ω-substituted ketones.[1-3] Very similar reaction rates and consistent enantioselectivity are observed with various methyl ketones bearing an additional functional group at the terminal position, including methyl ester, cyano, ethyl ether, olefin, acetylene, phenyl, and chloride. Also, linear chain substrates are reduced faster than their branched isomers, particularly when the branch point is positioned close to the carbonyl. Thus, for example, substrates having a linear backbone of six–nine carbon atoms are generally reduced at similar rates (0.1–0.4 of that of 2-hexanone) and with very high stereoselectivity, affording alcohols with an *S* configuration.

On the basis of this experience, we predicted that TBADH-catalyzed reduction of nonane-2,8-dione (**9**) would produce (*S*)-(+)-8-hydroxynonan-2-one (**10**) and (2*S*,8*S*)-(+)-2,8-dihydroxynonane (**11**). Indeed, experiments with this diketone confirmed that (a) compound **9** is a substrate of TBADH; (b) it is reduced stepwise to produce hydroxy ketone **10** first and then diol **11**; (c) both carbinol centers are obtained with an *S* configuration and with very high enantioselectivity (>99% ee) as determined by NMR (Figures 1–3); and (d) compound **9** is a quite reactive substrate, as reflected by its relative rate of TBADH-catalyzed reduction (0.55 and 0.15 for the first and second reduction steps, respectively, on a relative scale where reduction rate of 2-hexanone is 1.00).

Diketone **9**, which has two reactive sites, was expected to be at least twice as reactive as the monoketone **10**. The observation that **9** is actually 3.6 times more reactive than **10** indeed reflects this prediction as well as a minor difference in structure of the two substrates. Enantiomeric purity of **10** and **11** was determined by NMR, using the

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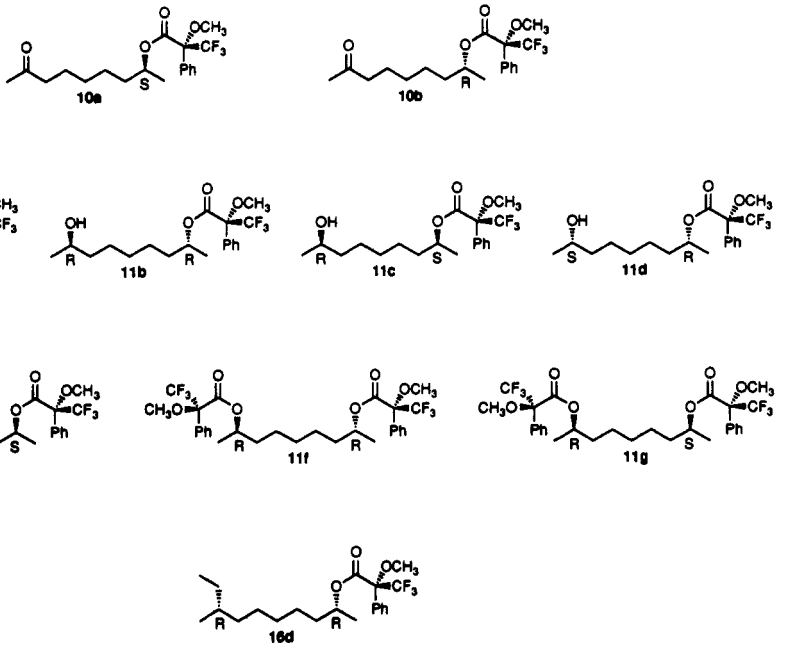
Scheme III. Mosher Esters of 10, 11, and 8d



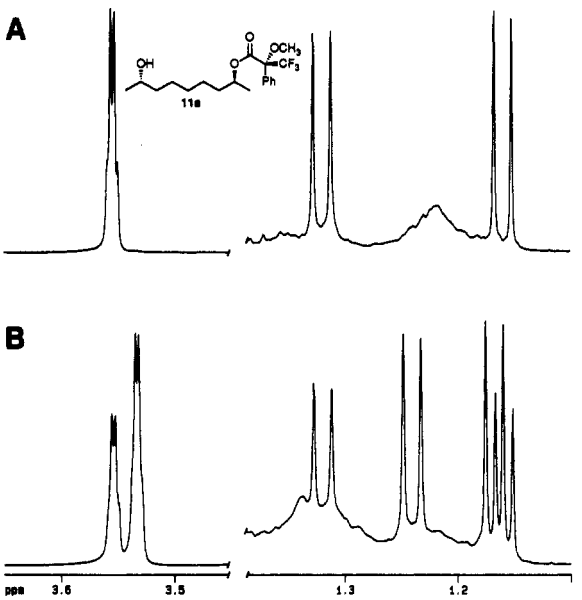


Figure 2. Determination of diastereomeric purity of the (2*S*,8*S*)-dihydroxynonane monoester **11a** by ^{1}H NMR spectroscopy. (A) Partial NMR spectrum of **11a** in $CDCl_3$. (B) Partial spectrum of mixture of **11a**, **11b**, **11c**, and **11d** under the same conditions. This mixture was obtained via reduction of **9** with $NaBH_4$ followed by monoesterification with Mosher's reagent.

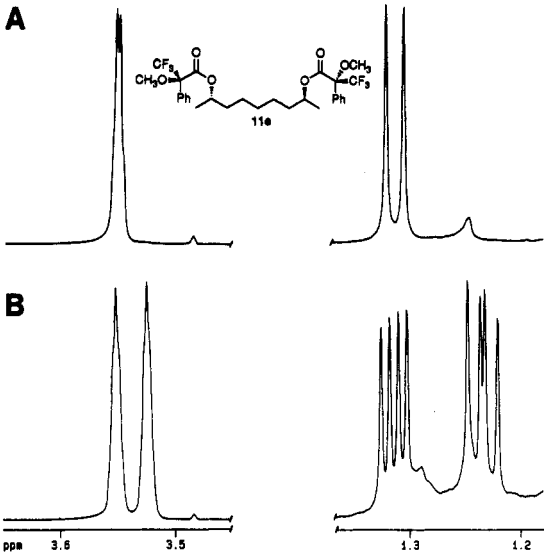


Figure 3. Determination of diastereomeric purity of the (2*S*,8*S*)-dihydroxynonane diester **11b** by ^{1}H NMR spectroscopy. (A) Partial NMR spectrum of **11e** in $CDCl_3$. (B) Partial spectrum of **11e**, **11f**, and **11g** (in a 1:1:2 ratio) under the same conditions. This mixture was obtained via reduction of **9** with $NaBH_4$ followed by diesterification with Mosher's reagent.

Mosher esters **10a**, **11a**, and **11e**[13] (Figures 1–3 and Scheme III). Considering the fact that no traces of the opposite diastereomers could be observed in these NMR spectra, we conclude that the enantiomeric purities of both **10** and **11** exceed 99% ee. A remarkable observation is the long range influence of the Mosher ester chirality on remote atoms in the molecule. In the diastereomeric compounds **10a** and **10b**, for example, the signals of the methylene hydrogens at position α to the carbonyl, and even those of the methyl group at the end of the chain (seven atoms away from the asymmetric carbinol center), are well separated in the NMR spectrum (Figure 1B). The same phenomenon is observed in the spectra of the monoesters **11a–d** (Figure 2B). This effect cannot be attributed to an intramolecular interaction between the chiral centers and the remote oxygen functionality because the same phenomenon is observed in the case of compounds **16d** and its diastereomers (vide infra, Figure 4) where a saturated hydrocarbon tail is affected by a chiral center, positioned eight atoms away. The four, equally intense, methyl doublets shown in the spectrum of diesters **11e–g**, (Figure 3B) reflect a statistical distribution of three diol diastereomers obtained by $NaBH_4$ reduction of **9**: *RR*, *SS*, and *RS* (meso) at a 1:1:2 ratio. While each of the diesters of first two diols is represented by one signal, the diester of the *RS* diol is represented by two methyl signals. In the case of the monoesters **11a–d**, however, the two sets of NMR signals appear in unequal proportions (Figure 2B). Expectedly, this reflects the fact that the asymmetric

(13) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

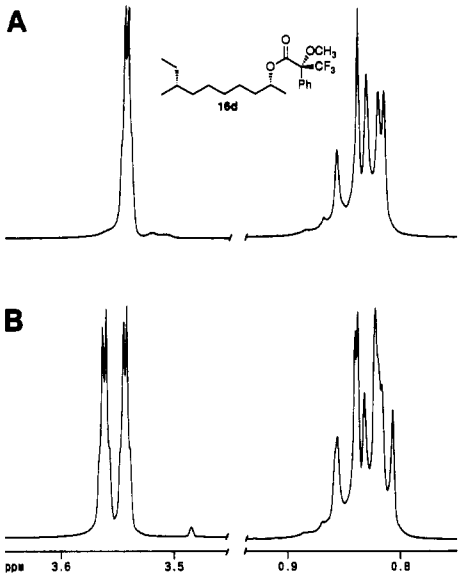
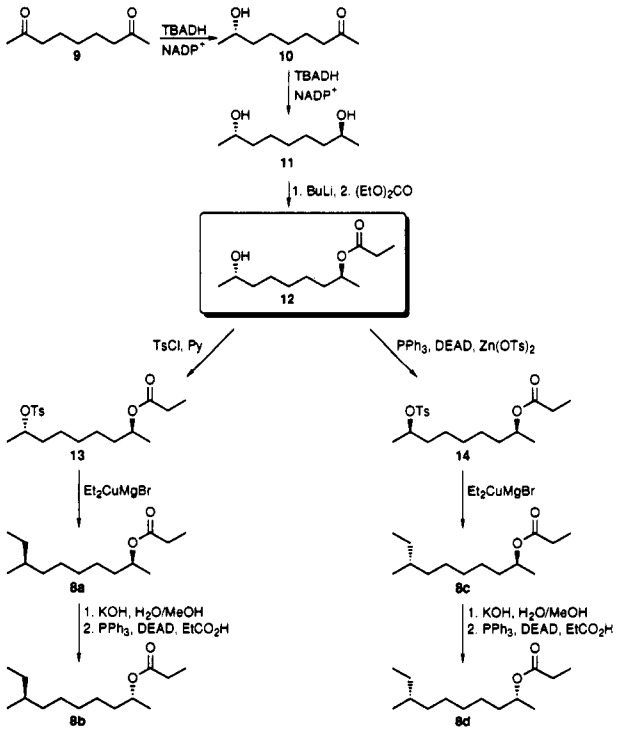


Figure 4. Determination of diastereomeric purity of the (2*R*,8*R*)-8-methyldec-2-yl ester **16d** by ^{1}H NMR spectroscopy. (A) Partial NMR spectrum of **16d** in $CDCl_3$. (B) Partial spectrum of a mixture containing all four Mosher esters of **8a–d** under the same conditions.

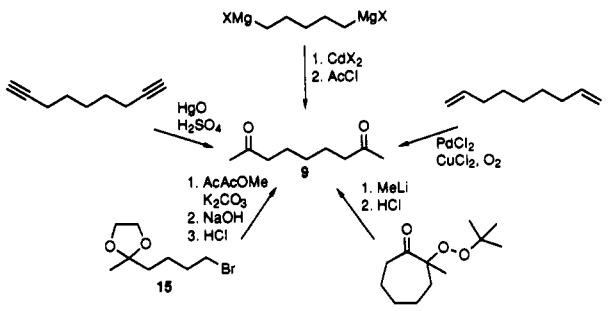
Scheme IV. Total Synthesis of All Four Isomers of 8-Methyldec-2-yl Propanoate



Mosher reagent reacts with either (*R*)- or (*S*)-alcohol with a different reaction rate.

With enantiomerically pure diol **11** at our disposal, we synthesized all four isomers **8a–d**, as outlined in Scheme IV. Esterification with 1 equiv of propanoic anhydride afforded the statistically expected mixture of diol **11**, hydroxy ester **12**, and diester **12a** in approximately 1:2:1 ratio, respectively. Compound **12**, our key chiral building block, was easily separated from the mixture by column chromatography. The other two components, **11** and **12a**, were quantitatively recovered and recycled for further preparation of **12**. In principle, **12** could be prepared via an alternative, three-step procedure involving enzymic reduction of **9** to **10**, esterification of the latter, and a second enzyme-catalyzed reduction of the resultant keto ester.

Scheme V. Alternative Synthetic Approaches to Nonane-2,8-dione (9)



Tosylation of **12** was carried out either with retention of configuration at the carbinol center to produce **13** or with inversion of that configuration[14] to yield the epimeric tosylate **14**. Both of these tosylates were alkylated with diethylcuprate that was prepared from ethylmagnesium bromide.[15] This highly stereospecific cross-coupling reaction is known to proceed with inversion of configuration at the carbinol carbon.[16] Thus, ethylation of tosylates **13** and **14** afforded two of our target molecules, **8a** and **8c**, respectively. The other two pheromone isomers were obtained by epimerizing **8a** and **8c** at their carbinol centers using Mitsunobu's method.[17] Compounds **8a** and **8c** were first hydrolyzed with wet methanolic KOH and the resulting alcohols were reacted with diethyl azodicarboxylate, triphenylphosphine, and propanoic acid in benzene to give isomers **8b** and **8d**, respectively. Physical properties (^{1}H NMR, ^{13}C NMR, IR, MS, and optical rotation) of all four compounds **8a–d** were found to be in satisfactory agreement with the reported data of these compounds.[8-12,18]

ee values of **8a–d** were determined by optical rotation measurements and, more reliably, by NMR, using Mosher's esters (one example is given in Figure 4).[13] It may be concluded from these spectra that the very high level of enantiomeric purity (>99%) of the enzymatic reduction products **10** and **11** has been maintained throughout the chemical steps of the synthesis. This is particularly noteworthy in the case of **8d** (Figure 4) where the synthesis involves three steps of inversion of configuration at the asymmetric carbons.

The bifunctional substrate nonane-2,8-dione (**9**) is readily available via a number of alternative approaches (Scheme V), including (a) mercury(II)-catalyzed hydration of a monosubstituted alkyne,[19] (b) addition of alkylcadmium to acetyl chloride,[20] (c) palladium-catalyzed Wacker oxidation of monosubstituted olefin,[21] and (d) oxidative cleavage of 2-methylcycloheptanone.[22] Alternatively, we prepared this compound from the bromo ketal **15** and methyl acetoacetate (e). Although the latter approach is somewhat less efficient than most of the

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(17) Mitsunobu, O. *Synthesis* **1981**, 1.
(18) Naoshima, Y.; Manakata, Y.; Yoshida, S.; Funai, A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 549.
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above-mentioned methods, its main advantage lays in the opportunity to obtain substrate **9** with selective isotopic labeling at one side of the molecule.

In conclusion, in this paper we have shown once again that chiral alcohols produced by TBADH-catalyzed asymmetric reduction of polyfunctional ketones are useful building blocks for natural products syntheses. This advantage has been demonstrated by the total synthesis of all four isomers of the sex pheromone emitted by the female western corn rootworm (WCR), **8a–d**, with enantiomeric purity that exceeds 99% using a single chiral building block, (2*S*,8*S*)-(+)-2,8-dihydroxynonane (**11**). The latter diol, having a synthetically useful C_2 symmetry, is obtained by TBADH-catalyzed reduction of the corresponding diketone. The total syntheses of other naturally occurring compounds using enzyme-generated chirons are currently under way in our laboratories.

Experimental Section

General Methods. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ at 400 and 100 MHz, respectively. Infrared spectra were measured neat with a Perkin-Elmer 1600 series FTIR spectrometer. GC analyses were carried out with a Heliflex 0.25-mm × 30-m capillary column (Altech AT-35 no. 13642). Positive ion mass spectra using the fast ion bombardment (FIB) technique were obtained on a VG ZAB-VSE double focusing, high resolution mass spectrometer equipped with a cesium ion gun. Optical rotations were measured in a 1-dm (1 mL) cell. TLC was performed on glass sheets precoated with silica gel (Merck, Kieselgel 60, F254, art. 5715). Column chromatographic separations were performed on silica gel (Merck, Kieselgel 60, 230–400 mesh, art. 9385) under pressure of 0.4 atm (flash chromatography). THF was dried by distillation over sodium benzophenone ketyl. (*R*)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid (Mosher's acid) was purchased from Aldrich. $NADP^+$ was purchased from Sigma. TBADH (37 units/mg) was obtained from Sigma (no. A9287).

Nonane-2,8-dione (9). 2-(4-Bromobutyl)-2-methyl-1,3-dioxolane (**15**)[23] (11.15 g, 50 mmol), ethyl acetoacetate (13.01 g, 100 mmol), and K_2CO_3 (13.8 g, 100 mmol) were mixed in acetone (200 mL) and DMF (20 mL), and the mixture was refluxed for 24 h. Most of the acetone was removed under reduced pressure and the residue was worked up with water and diethyl ether. The solvent was removed again and the residue was refluxed for 2 h in a mixture of 4% aqueous NaOH (150 mL) and methanol (100 mL). The mixture was cooled with an ice bath, acidified with HCl (6 N, 50 mL), and stirred at rt for 1 h. Most of the methanol was removed under reduced pressure and the residue was extracted with CH_2Cl_2. Removal of solvents and distillation afforded **9** (3.6 g, 46%). Spectral properties of this product were found to be identical to the literature data.[19-22]

Enzymatic Reduction of Nonane-2,8-dione. Nonane-2,8-dione (**9**) (1.289 g, 8.26 mmol) was added to 75 mL of an aqueous solution containing TBADH (15 mg, 555 units), $NADP^+$ (26 mg, 0.031 mmol), TRIS buffer (0.05 M, pH 8.0), 2-propanol (15 mL), and mercaptoethanol (20 mg). The mixture was gently stirred at 40–50 °C for 2 days under Ar, more $NADP^+$ (15 mg, 0.018 mmol) was added, and the mixture was stirred for additional 2 days. Excess NaCl was added and the mixture was extracted with diethyl ether. Solvent was removed under reduced pressure and the residue was subjected to column chromatography (silica gel, hexane:ethyl acetate 4:1–1:3) to give recovered starting material **9** (50 mg, 3.9%), (2*S*)-(+)-hydroxynonan-8-one (**10**) (650 mg, 50%), and (2*S*,8*S*)-(+)-dihydroxynonane (**11**) (309 mg, 23.4%). Data for **10**: MS (FIB) 159 (M + H$^+$). $[\alpha]^{23}_D$ = +7.92° (*c* = 8.18, $CHCl_3$). ^1H NMR: 3.72–3.66 (m, 1 H), 2.35 (t, *J* = 7.4, 2 H), 2.04 (s, 3 H), 1.51–1.16 (m, 8 H), 1.09 (d, *J* = 7.4, 3 H). ^{13}C NMR ($CDCl_3$): 209.47, 67.59, 43.53, 38.29, 29.74, 29.01, 25.41, 23.63, 23.34 ppm. IR (neat): 3410, 2931, 2858, 1709, 1459, 1409, 1369, 1163, 1129, 1054 cm^{-1}. Data for **11**: $[\alpha]^{23}_D$ = +14.48° (*c* = 2.63, $CHCl_3$). ^1H NMR: 3.84–3.75 (m, 2 H), 1.60–1.25 (m, 10 H), 1.19 (d, *J* = 6.2, 6 H). ^{13}C NMR: 68.09, 39.20, 29.58, 25.68, 23.48 ppm. IR (neat): 3343, 2957, 2929, 2857, 1462, 1413, 1373, 1330, 1129, 1074, 1013, 991, 933, 853, 810 cm^{-1}.

Determination of Relative Rate of TBADH-Catalyzed Reduction of 9 and 10. Solutions of nonane-2,8-dione (**9**) (78 mg, 0.5 mmol), 8-hydroxynonan-2-one (**10**) (79 mg, 0.5 mmol), and hexanone (50 mg, 0.5 mmol) were placed in three reaction flasks together with 2-propanol (3 mL each). An aqueous solution (12 mL) containing TBADH (0.7 mg, 28 units), $NADP^+$ (1 mg, 0.0012 mmol), mercaptoethanol (2 mg), and aqueous phosphate buffer (pH 8.0, 50 mM) was added to each of these flasks, and the mixtures were stirred at 40 °C. Progress of the reaction was monitored by withdrawing 1-mL samples and working them up with $(NH_4)_2SO_4$ and ethyl acetate, followed by GC analyses. Reduction of all three substrates was found to proceed linearly within the first 4 h: hexanone was reduced at a rate of 12.7%/h and compounds **9** and **10** at rates of 7%/h and 1.9%/h, respectively.

General Procedure for Preparation of Mosher's Esters. The appropriate chiral alcohol (2 mg) was dissolved in THF (0.5 mL) together with *N*,*N*-dimethyl-4-aminopyridine (20 mg). (*R*)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride (20 mg) was added, and the mixture was stirred at rt for 2 h, worked up with water and CH_2Cl_2, and filtered through a short silica gel column using CH_2Cl_2. Removal of the solvent under reduced pressure afforded the desired Mosher's ester in essentially quantitative yield.

(2*S*,8*S*)-(+)-2-(Propanoyloxy)-8-hydroxynonane (12). A solution of diol **11** (309 mg, 1.93 mmol) in THF (4 mL) was stirred and cooled at 0 °C as BuLi (1.6 M in hexane, 1.33 mL, 2.12 mmol) was added. The mixture was allowed to warm to rt. Propanoic anhydride (273 mg, 2.1 mmol) was added, and the mixture was stirred at rt for 20 min and then worked up with diethyl ether and water. Solvent was removed under reduced pressure and the residue was subjected to column chromatography (silica gel, hexane:ethyl acetate 4:1), affording (+)-**12** (200 mg, 48%), (2*S*,8*S*)-(+)-2,8-bis(propanoyloxy)nonane (130 mg, 25%), and unreacted **11** (50 mg, 16%). Data for (+)-**12**: $[\alpha]^{23}_D$ = +7.74° (*c* = 4.78, $CHCl_3$). MS (FIB): 217 (M + H$^+$). ^1H NMR: 4.92–4.83 (m, 1 H), 3.82–3.73 (m, 1 H), 2.27 (q, *J* = 7.2, 2 H), 1.62–1.24 (m, 10 H), 1.18 (d, *J* = 6.0, 3 H), 1.16 (d, *J* = 5.6, 3 H), 1.11 (t, *J* = 7.2, 3 H). ^{13}C NMR: 174.19, 70.68, 67.91, 39.10, 35.80, 29.37, 27.88, 25.62, 25.26, 23.43, 19.93, 9.17 ppm. IR (neat): 3412, 2974, 2933, 2859, 1735, 1463, 1375, 1277, 1196, 1125, 1081, 1011 cm^{-1}. Data for diester: MS (FIB) 273 (M + H$^+$). ^1H NMR: 4.92–4.83 (m, 2 H), 2.27 (q, *J* = 7.2, 4 H), 1.62–1.24 (m, 10 H), 1.18 (d, *J* = 6.0, 6 H), 1.11 (t, *J* = 7.2, 6 H). ^{13}C NMR ($CDCl_3$): 174.16, 70.66, 35.83, 29.28, 27.91, 25.28, 19.97, 9.20. IR (neat): 2977, 2938, 2860, 1734, 1463, 1425, 1377, 1336, 1275, 1194, 1125, 1082, 1012, 924, 877, 807 cm^{-1}.

(2*S*,8*S*)-(+)-2-(Propanoyloxy)non-8-yl *p*-Toluenesulfonate (13). A solution of compound **12** (100 mg, 0.46 mmol) in pyridine (2 mL) was stirred and cooled at 0 °C as tosyl chloride (130 mg, 0.56 mmol) was slowly added. The mixture was stirred at rt for 24 h and then worked up with CH_2Cl_2 and dilute aqueous HCl. Solvent was removed under reduced pressure and the residue was washed with CH_2Cl_2 through a short silica gel column. Removal of solvent afforded compound **13** (145 mg, 85%) in the form of a colorless oil: $[\alpha]^{23}_D$ = +0.35° (*c* = 3.47, $CHCl_3$). MS (FIB): 371 (M + H$^+$). ^1H NMR: 7.78 (d, *J* = 8.0, 2 H), 7.31 (d, *J* = 8.0, 2 H), 4.88–4.80 (m, 1 H), 4.62–4.54 (m, 1 H), 2.43 (s, 3 H), 2.28 (q, *J* = 7.6, 2 H), 1.22 (d, *J* = 6.3, 3 H), 1.17 (d, *J* = 6.3, 3 H), 1.11 (t, *J* = 7.6, 3 H). ^{13}C NMR: 174.10, 144.38, 134.52, 129.63, 127.70, 80.48, 70.57, 36.30, 35.71, 28.89, 27.88, 25.17, 24.70, 21.57, 20.77, 19.95, 9.19 ppm. IR (neat): 2978, 2938, 2861, 1731, 1598, 1496, 1462, 1364, 1275, 1177, 1124, 1082, 1018, 916, 816, 664 cm^{-1}.

(2*S*,8*R*)-(+)-2-(Propanoyloxy)non-8-yl *p*-Toluenesulfonate (14). Compound **12** (100 mg, 0.46 mmol) was dissolved in benzene (10 mL) together with triphenylphosphine (606 mg, 2.31 mmol) and $Zn(OTs)_2$ (111 mg, 0.28 mmol). Diethyl azodicarboxylate (DEAD) (0.38 mL, 2.3 mmol) was added dropwise, and the mixture was stirred at rt for 24 h and then washed through a short silica gel column using hexane:ethyl acetate 9:1. Removal of solvent under reduced pressure afforded compound **14** (106 mg, 62%) in the form of a colorless oil. All the spectral data (^1H NMR, ^{13}C

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NMR, IR, MS) were identical to those of 13: $[\alpha]^{23}_D$ = +1.12° (c = 2.68, $CHCl_3$).

(2S,8S)-(+)-8-Methyldec-2-yl Propanoate (8a). Ethylmagnesium cuprate was prepared by dropwise addition of ethylmagnesium bromide (3.92 mL of 1 M solution in THF, 3.92 mmol) to a heterogeneous mixture of CuI (373 mg, 1.96 mmol) in THF (8 mL) at -40 °C followed by stirring at the same temperature for 30 min. The mixture was cooled to -78 °C, compound 13 was slowly added, and the mixture was stirred for 5 days at -35 °C. A saturated aqueous solution of ammonium chloride was added, and the mixture was stirred for 5 min at the same temperature and then extracted with diethyl ether. Solvent was removed under reduced pressure and the residue was subjected to column chromatography (silica gel, hexane:ethyl acetate 50:1) to give 8a (66 mg, 74%) in the form of a colorless oil: $[\alpha]^{23}_D$ = +8.58° (c = 1.2, $CHCl_3$) [lit.[11] +8.5972° (c = 12.7, $CHCl_3$)]. ^1H NMR: 4.92-4.84 (m, 1 H), 2.28 (q, J = 7.6, 2 H), 1.94-1.06 (m, 13 H), 1.18 (d, J = 6.4, 3 H), 1.12 (t, J = 7.6, 3 H), 0.83 (t, J = 7.1, 3 H), 0.82 (d, J = 6.4, 3 H).

(2S,8R)-(-)-8-Methyldec-2-yl Propanoate (8c). The reaction was carried out as described above using tosylate 14 (104 mg, 0.28 mmol) and ethylmagnesium cuprate that was prepared from ethylmagnesium bromide (2.8 mL, 2.8 mmol) and cuprous iodide (267 mg, 2.8 mmol) in THF (8 mL) to produce 8c (46 mg, 72%). All the spectral data (^1H NMR, ^{13}C NMR, IR, MS) were identical to those of 8a: $[\alpha]^{23}_D$ = -4.12° (c = 1.62, $CHCl_3$) [lit.[11] -3.77° (c = 15, $CHCl_3$)]; [lit.[10] -4.25° (c = 1.11, $CHCl_3$)].

(2R,8S)-(+)-8-Methyldec-2-yl Propanoate (8b). Compound 8a (66 mg, 0.29 mmol) was dissolved in methanol (1 mL) and mixed with 3 N aqueous KOH (1 mL). The mixture was stirred at rt for 24 h and then worked up with CH_2Cl_2 and water. Solvent was removed under reduced pressure and the residue was filtered through a short silica gel column using hexane:ethyl acetate: 4:1, affording (2R,8S)-(+)-8-methyldecan-2-ol (42 mg, 84%): $[\alpha]^{23}_D$ = +15.64° (c = 1.0, $CHCl_3$) [lit.[11] +15.782° (neat, d = 0.8307)]. ^1H NMR: 3.80-3.71 (m, 1 H), 1.63-1.07 (m, 13 H), 1.15 (d, J = 6.0, 3 H), 0.82 (t, J = 7.1, 3 H), 0.81 (d, J = 6.4, 3 H). ^{13}C NMR: 68.11, 39.34, 36.55, 34.33, 29.96, 29.43, 27.02, 25.78, 23.41, 19.15, 11.36.

The above-mentioned alcohol (40 mg, 0.23 mmol) was dissolved in benzene (1 mL) together with triphenylphosphine (73 mg, 0.28 mmol) and propanoic acid (21 mg, 0.28 mmol). Diethyl azodicarboxylate (DEAD) was added at rt, and the mixture was stirred at the same temperature for 24 h and then worked up with CH_2Cl_2 and water. Solvent was removed under reduced pressure and the residue was filtered through a short silica gel column using hexane:ethyl acetate: 49:1, affording 8b (32 mg, 57%). All the spectral data (^1H NMR, ^{13}C NMR, IR, MS) were identical to those of 8a: $[\alpha]^{23}_D$ = +4.02° (c = 1.57, $CHCl_3$) [lit.[11] -4.054° (c = 21, $CHCl_3$)].

(2R,8R)-(-)-8-Methyldec-2-yl Propanoate (8d). Hydrolysis of 8c (46 mg, 0.2 mmol) in MeOH was carried out with 3 N KOH as described above for 8a to give (2R,8R)-(-)-8-methyldecan-2-ol (30 mg, 87%). All the spectral data (^1H NMR, ^{13}C NMR, IR, MS) were identical to those of the alcohol obtained by hydrolysis of 8a: $[\alpha]^{23}_D$ = -1.32° (c = 1.41, $CHCl_3$) [lit.[11] +0.925° (c = 12, $CHCl_3$)]; [lit.[10] -1.32° (c = 1.19, $CHCl_3$)].

The above-mentioned alcohol (30 mg, 0.17 mmol) was dissolved in benzene (1 mL) together with triphenylphosphine (52 mg, 0.2 mmol) and propanoic acid (15 mg, 0.2 mmol) and reacted with DEAD (32 mL, 0.2 mmol) as described above, affording 8d (28 mg, 72%). All the spectral data (^1H NMR, ^{13}C NMR, IR, MS) were identical to those of 8a: $[\alpha]^{23}_D$ = -8.43° (c = 1.74, $CHCl_3$) [lit.[11] -7.967° (c = 15, $CHCl_3$)]; [lit.[10] -7.57° (c = 1.05, $CHCl_3$)]; [lit.[17] -8.02° (c = 1.18, $CHCl_3$)].

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Supplementary Material Available: ^1H NMR and ^{13}C NMR spectra of compounds 10, 11, 12, 12a, and 13 and ^1H NMR spectrum of 8d (11 pages). Ordering information is given on any current masthead page.

Total Syntheses of the Marine Sponge Pigments Fascaplysin and Homofascaplysin B and C

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The *Fascaplysinopsis* spp. marine sponge pigments fascaplysin (1), homofascaplysin B (4), and homofascaplysin C (5) have been synthesized by peracid oxidation, reaction with oxalyl chloride/methanol, or Vilsmeier formylation, respectively, of the keystone intermediate 12*H*-pyrido[1,2-*a*:3,4-*b*']diindole (7). The versatile 7 was prepared from indole (17) in six steps (78% yield), a sequence in which the key reaction is the trifluoroacetic acid-induced ring closure of diindole 15, followed by Pd/C-catalyzed dehydrogenation of the crude mixture of cyclized products 25, 26, to give 7 in 93% yield from 15.

The red pigment, fascaplysin (1), was isolated in 1988 from the marine sponge *Fascaplysinopsis* Bergquist sp., collected in the South Pacific near the Fiji islands.[1] Fascaplysin has anti-microbial activity and is cytotoxic against L-1210 mouse leukemia.[1] More recently, this pigment, with the counterion dehydroluffariellolide diacid monoanion (2), was extracted from the Fijian sponge *F. reticulata*, along with the other novel β-carbolines homofascaplysin A (3) (accompanied by counterion 2), homofascaplysin B (4), homofascaplysin C (5), and secofascaplysin A (6).[2]

The fascaplysins possess the novel 12*H*-pyrido[1,2-*a*:3,4-*b*']diindole (7) ring system, unprecedented amongst natural products,[3] but related to the relatively small group of natural products having two indoles interconnected at their respective C-2 positions. Well-known examples of

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