= 8.1 Hz), 8.36 (d, 1 H, J = 8.1 Hz), and 11.59 (s, 1 H exchanged with D_2O); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.2, 55.6, 100.2, 104.2, 121.9, 123.7, 125.5, 126.4, 128.9, 129.8, 147.6, 155.6, and 171.3; MS m/e 232, 200, 129, 102, and 101. Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.27; H, 5.22.

The last component isolated from the silica gel plate (45 mg) was assigned as methyl 5-methoxy-2-oxo-3-benzoxocine-6-carboxylate (**43**) (20%): mp 120–121 °C; IR (KBr) 1765, 1720, 1620, 1240, 805, and 785 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 3.56 (s, 3 H), 3.79 (s, 3 H), 5.89 (d, 1 H, J = 6.3 Hz), 6.37 (d, 1 H, J = 6.3 Hz), 7.33–7.38 (m, 1 H), and 7.47–7.60 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.7, 59.2, 107.0, 117.7, 126.8, 127.3, 130.4, 131.1, 132.2, 140.1, 161.8, 164.5, and 168.2; MS m/e 260, 231, 229, 217, 201 (base), 157, and 101; HRMS calcd for $C_{14}H_{12}O_5$ 260.0684, found 260.0676.

Photochemical Rearrangement of Spiro[5-carbomethoxy-4-methyl-7-oxabicyclo[2.2.1]hept-5-en-2-one-3,1′-cyclopropane] (48). Irradiation of a 0.05 M solution of spirocyclopropane **48**[45] (210 mg) in benzene through a Pyrex filter sleeve for 1 h gave rise to a mixture of three products. Chromatography of the mixture on a silica gel column using an ethyl acetate–hexane mixture as the eluent afforded 52 mg (45% yield) of spiro[5-carbomethoxy-1-methyl-2-oxabicyclo[3.2.0]hept-3-en-6-one-7,1′-cyclopropane] (**49**): NMR (300 MHz, $CDCl_3$) δ 1.31–1.55 (m, 4 H), 1.55 (s, 3 H), 3.79 (s, 3 H), 5.17 (d, 1 H, J = 2.8 Hz), and 6.57 (d, 1 H, J = 2.8 Hz), ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.7, 16.2, 16.9, 48.5, 52.3, 87.4, 99.9, 141.3, 149.4, 166.9, and 203.7. Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.27; H, 5.62.

One of the two other minor photoproducts was identified on the basis of its spectral properties as dispiro[2.1.2.1]octane-4,8-dione (**52**)[54] (50%): mp 180–181 °C; IR (KBr) 1740, 1350, 1080, 1020, and 790 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 1.94 (s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 50.5, and 209.6; HRMS calcd for $C_8H_8O_2$ 136.0524, found 136.0524.

The other compound (71 mg) was assigned as methyl 2-methylfuran-3-carboxylate (**50**) (50%): NMR (300 MHz, $CDCl_3$) δ 2.57 (s, 3 H), 3.82 (s, 3 H), 6.63 (d, 1 H, J = 1.9 Hz), and 7.22 (d, 1 H, J = 1.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 51.1, 110.5, 113.1, 140.2, 159.2, and 164.4. Anal. Calcd for $C_7H_8O_3$: C, 59.98; H, 5.76. Found: C, 59.97; H, 5.62.

Photochemical Rearrangement of Spiro[5,6-dicarbomethoxy-4-methyl-7-oxabicyclo[2.2.1]hept-5-en-2-one-3,1′-cyclopropane] (53). Photolysis of a 0.05 M solution of spirocyclopropane **53**[45] (270 mg) in benzene for 2 h using a Pyrex filter sleeve afforded a mixture of three products which were separated by silica gel chromatography. The first fraction isolated from the column contained 110 mg (65%) and was assigned as dimethyl 2-methylfuran-3,4-dicarboxylate (**54**): IR (neat) 1735, 1450, 1310, 1210, 1095, and 1040 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 2.51 (s, 3 H), 3.83 (s, 3 H), 3.86 (s, 3 H), and 7.75 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.4, 51.7, 51.8, 112.7, 118.6, 145.4, 159.2, 162.4, and 163.4. Anal. Calcd for $C_9H_{10}O_5$: C, 54.55; H, 5.09. Found: C, 54.37; H, 5.02.

The second component isolated from the column was assigned as dispiro[2.1.2.1]octane-4,8-dione (**52**)[54] by comparison of its spectral properties with a sample obtained from the photolysis of **48**. The last material isolated from the column was assigned as dimethyl 7-methyl-2-oxospiro[2.4]hept-6-ene-5,6-dicarboxylate (**55**) (30%): IR (neat) 1765, 1735, 1370, 1225, 1160, and 1100 cm^{-1}, NMR (300 MHz, $CDCl_3$) δ 4.27 (q, 1 H, J = 1.7 Hz), 3.76 (s, 6 H), 2.04 (d, 3 H, J = 1.7 Hz), and 1.35–1.57 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.6, 18.0, 18.6, 40.1, 51.4, 52.7, 59.3, 122.3, 157.5, 163.7, 167.4, and 206.9. Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.39; H, 5.78.

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Supplementary Material Available: ^1H NMR and ^{13}C NMR spectra (75 MHz) for all compounds with high-resolution mass spectra (18 pages). Ordering information is given on any current masthead page.

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Enantioselective Formation of Functionalized 1,3-Disubstituted Allenes: Synthesis of α-Allenic ω-Carbomethoxy Alcohols of High Optical Purity[1]

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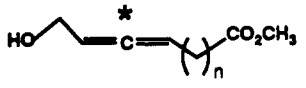
A general, high yield synthesis of multigram quantities of the title allenic alcohols is described. Intermediate **5**, derived from D-mannitol, was elaborated to both enantiomers (**10** and **11**) of the antifungal constituent (**11**) of *Sapium japonicum* and the lower homologue (**16**) useful for the synthesis of allenyl prostaglandins. The natural material was thus shown to possess the *R* configuration. The product allenes were formed in >94% ee as determined by ^{13}C NMR spectral analysis of the corresponding Mosher esters.

Introduction

During work directed toward the synthesis of medicinally important allenyl prostanoic acid derivatives,[2] we required optically active α-allenic alcohols **1** containing the ω ester functionality. It is known that various organometallic reagents react with chiral propargylic derivatives to form optically active allenes[3] (eq 1). The reaction has been successfully applied to acetates,[4] carbamates,[5] sulfinates,[6,7a] sulfonates,[6,7b] halides,[8] and ethers.[9] It is gen-



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(1) Contribution No. 809 from the Institute of Organic Chemistry, Syntex Research.

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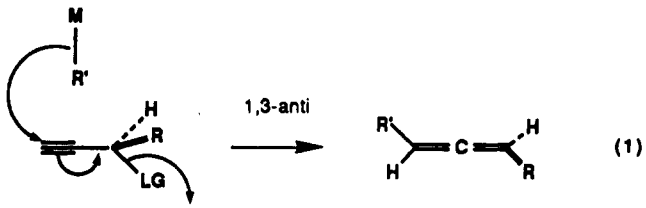


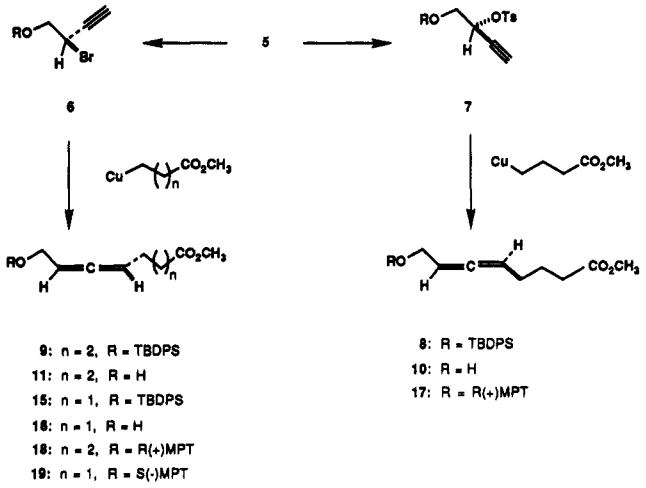
(1)

erally recognized that organocopper-mediated formations of allenes from acyclic propargylic precursors proceed with overall anti 1,3-displacement.[4-6,10-12] A plausible mechanism has recently been proposed.[6] The enantiomeric purity of allenes formed by this method vary according to substrate, organometallic reagent,[11] and leaving group[12] employed. Olsson and Claesson[12] found that higher optical yields were obtained with better leaving groups, i.e., acetates and mesylates. Stereochemical studies are complicated by the fact that organocuprates have been shown to racemize the product allenes under normal reaction conditions.[13] Highest enantiomeric excesses (ee's) are obtained when the reaction time is kept to a minimum (<15 min).[12] Vermeer et al.[13b] found that the rate of isomerization is greater with lithium dialkylcuprates and Grignard reagents in the presence of catalytic copper(I) halides than with the monoalkyl copper(I) reagent MeCu. Acyclic, 1,3-disubstituted allenes have been prepared in as much as 88% ee using monoalkyl cuprates of the type [(RCuX)M].[10a] Elsevier and Vermeer recently reported optical yields of allenic hydrocarbons approaching 100% using this type of reagent on a series of enantiomerically pure or enriched substrates.[6] We report here a novel, highly enantioselective synthesis of allenes of general structure 1 by the addition of *functionalized* stoichiometric organocopper(I) reagents **14** to optically active acetylenic bromide **6** and tosylate **7** (Scheme I). Both enantiomers (**10** and **11**) of the antifungal constituent **11** of *Sapium japonicum*,[14] possessing approximately the same rotatory power as the natural material, were prepared from the same intermediate **5**. A racemic synthesis[15a] and an enantioselective synthesis[15b] have appeared previously. Multigram quantities of the lower homologue **16**, potentially useful in the synthesis of allenyl prostaglandins, was also prepared by this method.

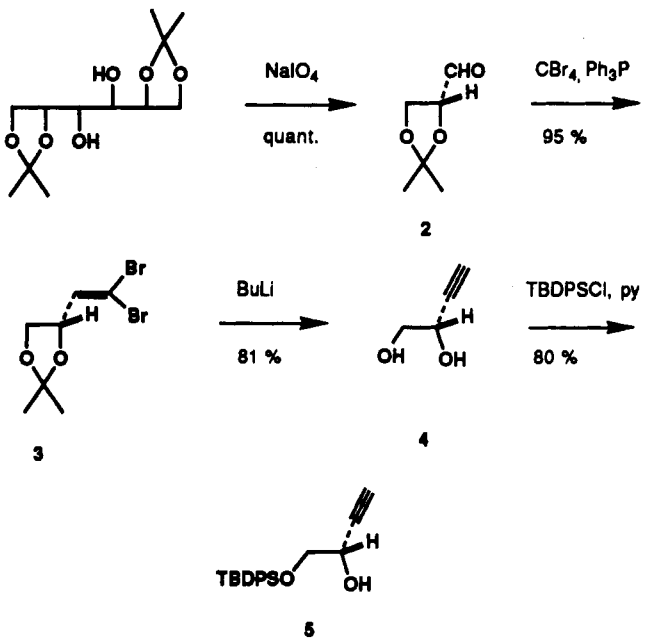
Results and Discussion

Substrate Synthesis. The functionalized acetylenes

Scheme I



Scheme II



6 and 7 used in the allene forming reactions were prepared as shown in Scheme II. Anhydrous (+)-2,3-*O*-isopropylidene-D-glyceraldehyde **2** was prepared in quantitative yield by oxidative cleavage of 1,2:5,6-di-*O*-isopropylidene-D-mannitol in a three-phase system as previously reported.[16] Chain extension of the aldehyde **2** by one carbon to form the dibromoolefin **3**[17] was accomplished in 95% yield by reaction with carbon tetrabromide–triphenylphosphine reagent[18] in dichloromethane. Treatment of **3** with 2 equiv of *n*-butyllithium in tetrahydrofuran (THF) gave the lithium salt of the corresponding terminal acetylene acetonide, which was immediately hydrolyzed to the diol **4** without isolation[19] using *p*-toluenesulfonic acid monohydrate in methanol (81%). This completed the formyl to ethynyl conversion[18] in 77% overall yield. Diol **4** was isolated as a crystalline solid having $[\alpha]^{25}_{D}$ +36° (*c*

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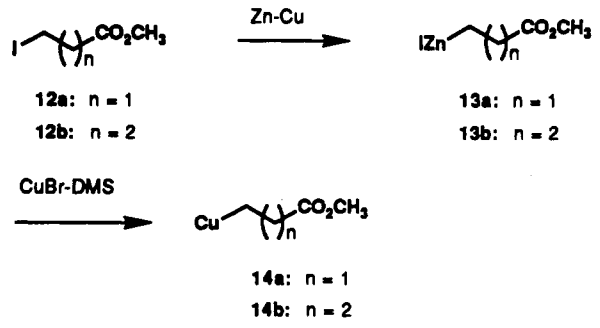
Scheme III



1, $CHCl_3$), which compared favorably with the rotation of its antipode recently prepared by a different route[20] ($[\alpha]_D$ −38° (*c* 1, $CHCl_3$)). Selective protection of the primary alcohol function using *tert*-butylchlorodiphenylsilane in pyridine gave the desired monoprotected alcohol **5** in 80% yield along with diprotected material (5%). The enantiomeric purity of **5** was determined to be >97% ee by proton NMR (500 MHz) of the corresponding Mosher ester[21] using the methoxyl proton integrals. Alcohol **5** served as the common intermediate for the stereoselective synthesis of **10**, **11**, and **16**. To prepare levorotatory forms **11** and **16** it was necessary to invert the stereochemistry at C2 and introduce a suitable leaving group prior to the allene-forming reaction. This was accomplished in one step by bromination of **5** using carbon tetrabromide–triphenylphosphine[22] in THF containing pyridine. This reaction occurred with complete inversion of stereochemistry[23] in contrast to the moderate stereoselectivity observed in other systems.[24] The bromide **6** was isolated in 97% yield as an unstable oil, $[\alpha]^{25}_D$ +5.70° (*c* 0.42, MeOH). To prepare the dextrorotatory allene **10** the alcohol **5** was converted into a leaving group by treatment with *p*-toluenesulfonyl chloride and triethylamine in dichloromethane giving tosylate **7** in 99% yield, $[\alpha]^{25}_D$ +20.7° (*c* 0.61, MeOH).

Allene-Forming Reactions. The required copper(I) species **14a** and **14b** were prepared by transmetalation of the corresponding zinc homoenolate[25] **13a** or zinc bishomoenolate[25] **13b**, which in turn were prepared from methyl 3-iodopropionate[26] (**12a**) or methyl 4-iodobutyrate[26] (**12b**) (Scheme III). Reaction of iodide **12b** with zinc–copper couple in toluene containing *N*,*N*-dimethylacetamide cosolvent at 60 °C gave **13b** as previously described.[27] Subsequent treatment with a stoichiometric amount of copper(I) bromide dimethyl sulfide complex and stoichiometric hexamethylphosphoramide (HMPA) gave the desired functionalized organocopper(I) reagent **14b**. This reagent was stable at room temperature under nitrogen for at least 3 days but was usually used immediately. Treatment of this reagent with the bromide **6** or the tosylate **7** at room temperature led to complete reaction within 10 min. Allene **8**, from reaction with **7**, was isolated in 96% yield, $[\alpha]^{25}_D$ +65.0° (*c* 0.34, MeOH). Allene **9**, from reaction with **6**, was isolated in 88% yield, $[\alpha]^{25}_D$ −63.8° (*c* 0.43, MeOH). Both enantiomers **8** and **9** displayed identical IR, HNMR, and MS and differed only in the sign of their optical rotations. Deprotection of **9** with tetrabutylammonium fluoride in THF gave **11**, the antifungal constituent of *Sapium japonicum*,[14] in 98% yield, $[\alpha]^{25}_D$ −77.3° (*c* 0.31, MeOH), −53.4° (*c* 0.31, $CHCl_3$). Similarly, deprotection of **8** gave the antipode **10**, $[\alpha]^{25}_D$ +82.5° (*c* 0.53, MeOH), +53.7° (*c* 0.99, $CHCl_3$). Except for the sign and magnitude of optical rotation, these allenes had identical spectral and physical properties which were consistent with those reported for natural material, $[\alpha]^{12}_D$ −51.3° (*c* 0.94, $CHCl_3$).

In an analogous manner the iodide **12a** was converted to the zinc homoenolate **13a** and then to the organocopper(I) reagent **14a**. Treatment of **14a** with bromide **6** in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1*H*)-pyrimidinone (DMPU) cosolvent gave allene **15**, which was deprotected without purification, affording **16** in 78% yield from bromide **6**, $[\alpha]^{25}_D$ −77.9° (*c* 0.43, MeOH), −5.95° (*c* 1.0, $CHCl_3$).

Stereochemistry. The use of the chiron **2** allows unambiguous stereochemical assignment of the product allenes. Because the allene-forming reaction occurs with overall anti 1,3-displacement, and the absolute configuration of the substrate **6** is known by relation to D-mannitol, the stereochemistry of the natural material **11** must be *R*.[28] The absolute configurations of allenes **10**, **11**, and **16** also conform to the Lowe–Brewster rule[29] which relates the sign of optical rotation to the screw pattern of the polarizabilities of the substituents.

In spite of the vast amount of accumulated information about chiral allenes, methods for determination of enantiomeric purity are scant.[30] It has been common practice to report enantiomeric purities based on chiroptical measurements. A semiempirical quantitative treatment of optical rotation has been developed by Runge and Kresze.[31,32] Application of this method to **11** gave $[\alpha]_D$ −55.1° ($CHCl_3$). This was in good agreement with the reported value for the natural material, −51.3° ($CHCl_3$) and with the observed value for the synthetic material, −53.4° ($CHCl_3$). However, when solvent corrections were made for methanol, the calculated (−51.9°) and the observed (−77.3°) values were not in agreement.[33]

Chiral lanthanide shift reagents generally have more fundamental applicability as an absolute method for chiral recognition; however, only a few successful applications to allenes have been reported.[34,35] The most appropriate

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method is that of Mannschreck et al.[35] which used a mixture of the achiral salt Ag(fod) and the optically active complex (+)-Yb(hfbc)$_3$ as an additive. Application of this method to a mixture of **10** and **11** gave only line broadening at high concentrations of additive with no differentiation of enantiomeric shifts.

The Mosher esters[21] **17**, **18**, and **19** were prepared and analyzed by NMR spectroscopy. The ^{19}F (282 MHz) and the ^{1}H (500 MHz) NMR spectra did not show separation of signals in mixtures of the diastereomeric esters **17** and **18** or in the ester prepared from racemic **16**.[36] The ^{13}C NMR (125 MHz) spectra of these mixtures did show separation of signals originating from carbons 1, 2, 3, and 4.[37] In pure samples of **17**, **18**, and **19**, signals originating from the minor diastereoisomers could not be detected. To estimate the enantiomeric purity of the allene axes, several mixtures of **17** and **18** were accurately weighed and the weight ratios compared to the ratio obtained by averaging the ^{13}C NMR line intensities for each mixture. Good agreement of these ratios confirmed that the enantiomeric purity of **5** (>97% ee) was conserved during the chemical transformations leading to **17** and **18**. In a sample containing 97:3 (wt/wt) of **17** and **18**, respectively, signals originating from **18** were clearly resolved for three of the four carbons of interest showing the diastereomeric purity of each component was at least 94%.[38]

In summary, we have described a highly enantioselective synthesis of the title allenic alcohols in multigram quantities. Either enantiomer is now available in >94% ee through a single intermediate of known absolute configuration. A ^{13}C NMR based analytical method capable of differentiating diastereoisomers of the corresponding Mosher esters has been demonstrated. The difficulty of this enantiomeric purity determination is underscored by the failure of three other widely used NMR-based methods.

Experimental Section

Melting points are uncorrected. IR spectral data are reported in wavenumbers (cm^{-1}). Optical rotations were measured on a Perkin-Elmer 141 polarimeter. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded in ppm on Bruker WM 300 or AM-500 spectrometers in $CDCl_3$ (J values in hertz). Radial chromatography was performed as a Harrison Research Chromatotron 7924 using silica gel plates (No. 7749, Kieselgel 60 PF_{254}, Merck). Silica gel thin-layer chromatography (TLC) plates were purchased from Analtech and the Kieselgel 60 silica gel used for column chromatography was purchased from Merck. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. Toluene was distilled from sodium and stored over molecular sieves. All other reagents were used as received. 1,2:5,6-Di-*O*-isopropylidene-D-mannitol and anhydrous *N*,*N*-dimethylacetamide were purchased from Aldrich. Zinc–copper couple was purchased from Morton Thiokol (Alfa).

(*R*)-(+)-2,3-*O*-Isopropylidene-D-glyceraldehyde (2) was prepared as previously described:[16] $[\alpha]^{25}_D$ +63.3° (*c* 1.25, C_6H_6).

(*S*)-4-(2,2-Dibromoethenyl)-2,2-dimethyl-1,3-dioxolane (3).[17] A solution of 200 g (763 mmol) of triphenylphosphine in 1000 mL of CH_2Cl_2 was vacuum-purged with nitrogen and cooled to 4 °C in an ice bath. To this mechanically stirred solution was added 15 g (190 mmol) of pyridine and 127 g (383 mmol) of carbon tetrabromide, which caused the temperature to rise to 24 °C. Stirring continued for 0.50 h, during which time the mixture cooled to 3 °C. A solution of **2** (25.0 g, 192 mmol) in 50 mL of CH_2Cl_2 was added, and the ice bath was removed. Stirring was continued for 1.5 h when the reaction was judged complete by TLC (25:75 ethyl acetate–hexanes, R_f(**2**) 0.10, R_f(**3**) = 0.70). The mixture was filtered, and the entire process was repeated on the same scale (25.0 g of **2**) and again on a smaller scale (14.2 g of **2**). When judged complete by TLC, each reaction was filtered for a combined workup. The crude mixture was concentrated in vacuo at 30 °C, 1-L of diethyl ether was added, and the mixture was mechanically stirred at 0 °C for 0.25 h. The ether was decanted, and the operation was repeated. The combined organic solutions were concentrated, 500 mL of hexane was added, and the mixture was stirred mechanically at 0 °C for 0.25 h. The hexane solution was decanted, and the operation was repeated. The combined organic solutions were concentrated to 220 g of red oil. Silica gel (500 g) chromatography using ethyl acetate–hexanes (0:100 → 10:90) as eluants gave 134.4 g of **3** as a colorless liquid (95%): $[\alpha]^{25}_D$ −3.56° (*c* 3.8, MeOH); IR (neat) 2983, 1372, 1215, 1058; ^{1}H NMR (300 MHz) 6.53 (d, J = 7.6, 1 H), 4.73 (dt, J = 6.4, 7.6, 1 H), 4.19 (dd, J = 6.3, 8.4, 1 H), 3.68 (dd, J = 6.5, 8.4, 1 H), 1.42 (d, J = 0.5, 3 H),, 1.38 (d, J = 0.6, 3 H); MS *m*/*e* (relative intensity) 288 (1.5), 286 (2.4), 284 (M$^+$, 2.0), 271 (15), 256 (12), 175 (3), 96 (9), 72 (42), 43 (100). Anal. Calcd for $Br_2C_7H_{10}O_2$: C, 29.40; H, 3.52. Found: C, 29.67; H, 3.63.

(*S*)-3-Butyne-1,2-diol (4). Two identical reactions were performed as follows: A solution of 31.8 g (111 mmol) of **3** in 300 mL of anhydrous THF was vacuum purged with nitrogen, cooled to −78 °C, and stirred mechanically as 153 mL (245 mmol) of *n*-butyllithium (1.6 M in hexane) was added dropwise over 1.5 h. The mixture was allowed to warm to 10 °C over 1 h, 500 mL of diethyl ether and 250 mL of deionized water were added, and stirring was continued for 0.25 h. The aqueous layer was extracted with 100 mL of diethyl ether, and the combined organic solutions were washed with 3 × 250 mL of deionized water. The yellow solution obtained was stirred as 25.3 g (133 mmol) of *p*-toluenesulfonic acid monohydrate and 500 mL of methanol were added. After 2 h the reaction was judged complete by TLC (65:35 ethyl acetate–hexanes, R_f(**4**) = 0.40). Triethylamine (13.6 g, 135 mmol) was added, the mixture was concentrated at 30 °C, and the residue was taken up into 500 mL of ethyl ether and dried ($MgSO_4$). Concentration at 30 °C gave a yellow oil, which was purified by silica gel (400 g) chromatography, eluting with ethyl acetate–hexanes (40:60 → 60:40). Further purification was achieved by trituration in hot hexanes, leaving 15.5 g of **4** as a white crystalline solid (81%). Note: this material is subject to sublimation under vacuum: mp 34–35 °C; $[\alpha]^{25}_D$ +35.5° (*c* 1.07, $CHCl_3$); IR (film) 3300 (br), 2116, 1075; ^{1}H NMR (500 MHz) 4.47 (s, 1 H), 3.76–3.69 (m, 2 H), 2.76 (br s, 1 H exchanges with D_2O), 2.51 (d, J = 1.8, 1 H), 1.77 (br s, 1 H exchanges with D_2O); MS *m*/*e* (relative intensity) 86 (M$^+$, 3), 85 (3), 84 (3), 56 (100), 55 (95). Anal. Calcd for $C_4H_6O_2$: C, 55.80; H, 7.03. Found: C, 55.53; H, 7.24.

(*S*)-1-[(*tert*-Butyldiphenylsilyl)oxy]-3-butyn-2-ol (5). A magnetically stirred solution of 26.5 g (308 mmol) of **4** and 225 mL of pyridine was vacuum purged with nitrogen, cooled to −7 °C (ice–salt), and treated with 82.5 g (300 mmol) of *tert*-butylchlorodiphenylsilane added via syringe over 0.75 h. Stirring was continued for 1 h, an additional 8.5 g (31 mmol) of silane was added, and stirring was continued at ambient temperature for 3 h when complete disappearance of **4** by TLC (15:85 ethyl acetate–hexanes, R_f(**4**) = 0.05, R_f(**5**) = 0.60) was observed. Diethyl ether (750 mL) was added, and the mixture was filtered and washed with 3 × 400 mL of deionized water, dried ($MgSO_4$), and concentrated under reduced pressure at 40 °C. Toluene (100 mL) was added and removed under vacuum to azeotrope remaining pyridine. The residue was percolated through 750 g of silica gel, eluting first with 2:98 ethyl acetate–hexanes, giving diprotected material (5%), and then with 5:95 ethyl acetate–hexanes, giving 78.5 g of **4** as a yellow oil (80%): $[\alpha]^{25}_D$ +0.65° (*c* 0.11, MeOH); IR (neat) 3303, 1464, 1113; ^{1}H NMR (500 MHz) 7.72–7.65 (m, 4 H), 7.46–7.36 (m, 6 H), 4.45 (m, 1 H), 3.78 (ddd, J = 3.8, 6.6, 10.2, 2 H), 2.65 (d, J = 5.5, 1 H exchanges with D_2O), 2.41 (d, J = 2.4, 1 H), 1.08 (m, 9 H); MS *m*/*e* (relative intensity) 324 (M$^+$, 6), 255 (57), 199 (100), 183 (16), 77 (21). Anal. Calcd for $C_{20}H_{24}O_2Si$: C, 74.03; H, 7.45. Found: C, 74.04; H, 7.70.

The optical purity of **5** was analyzed by ^{1}H NMR of the corresponding Mosher ester[21] using the racemic compound for

(36) Prepared from racemic **5**.

(37) Numbering is based on the parent allenes with the carbon bearing the alcohol function being C1.

(38) The enantiomeric purity of the allene axis is probably significantly higher than 94%, as no signals from the minor diastereoisomer were detected in pure samples. However, due to the inherent uncertainty of ^{13}C NMR integration we have provided this experimentally determined lower limit for ee.

comparison. ^{1}H NMR (500 MHz): methoxyl proton integrals 3.57 ppm (J = 0.8, 3 H), 3.54 (d, J = 0.8, 3 H), ratio of methoxyl peaks 98.5:1.5 (97% ee). ^{13}C NMR (125 MHz): Signals originating from the minor diastereoisomer were not detected.

(*R*)-2-Bromo-1-[(*tert*-butyldiphenylsilyl)oxy]-3-butyne (6). A dry 100-mL, 3-necked flask equipped with a magnetic stirring bar, a nitrogen inlet, and a 25-mL addition funnel was charged with 1.30 g (4.00 mmol) of **5**, 2.52 g (9.60 mmol) of triphenylphosphine, 30 mL of anhydrous tetrahydrofuran, and 0.36 g (4.56 mmol) of pyridine. To the addition funnel was added 1.53 g (4.60 mmol) of carbon tetrabromide and 10 mL of anhydrous tetrahydrofuran, and the system was vacuum purged with nitrogen and placed in a room temperature water bath. The contents of the addition funnel was added to the stirred solution over 5 min and stirring continued for 45 min until complete reaction as judged by TLC (10:90 ethyl acetate–hexanes, R_f(**5**) = 0.43, R_f(**6**) = 0.74). Hexanes (50 mL) was added, and the mixture was filtered and concentrated. The residue was taken into 50 mL of hexanes, washed with 2 × 20 mL of 1 M HCl, 1 × 20 mL of saturated aqueous Na_2SO_4, and 2 × 20 mL of brine, and dried ($MgSO_4$). Concentration gave an oil which was purified by silica gel (50 g) chromatography using hexanes as eluant. Fractions containing **6** were combined to give 1.50 g of **6** (97%) as a clear colorless oil which rapidly decomposes to a red oil upon standing. Note: this material is unstable and should be stored at low temperatures or used immediately. $[\alpha]^{25}_D$ +5.70° (*c* 0.42, MeOH); IR (neat) 3308, 1437, 1112, 701; ^{1}H NMR (300 MHz) 7.70 (m, 4 H), 7.42 (m, 6 H), 4.46 (dt, J = 2.36, 6.66, 1 H), 3.91 (ddd, J = 3.78, 6.32, 10.7, 2 H), 2.59 (d, J = 2.4, 1 H), 1.08 (m, 9 H); ^{13}C NMR 19.3, 26.8 (3 C), 36.2, 67.5, 75.6, 80.3, 127.6 (4 C), 129.6 (2 C), 132.8 (2 C), 135.8 (4 C); MS *m/e* (relative intensity) 333 (2), 331 (45), 329 (46), 263 (97), 261 (100), 181 (36), 167 (32). Satisfactory combustion analysis could not be obtained for this compound.

(*S*)-1-[(*tert*-Butyldiphenylsilyl)oxy]-3-butyn-2-ol *p*-Toluenesulfonate (7). A solution of 1.62 g (5.00 mmol) of alcohol **5**, 1.14 g (6.00 mmol) of *p*-toluenesulfonyl chloride, 0.631 g (6.25 mmol) of triethylamine, and 20 mL of CH_2Cl_2 was vacuum purged with nitrogen and stirred for 17 h, at which time the reaction was judged complete by TLC (7:93 diethyl ether–hexanes, R_f(**5**) = 0.25, R_f(**7**) = 0.34). The mixture was diluted with 100 mL of diethyl ether, washed with 2 × 40 mL of saturated aqueous $NaHCO_3$ and 1 × 40 mL brine, and dried ($MgSO_4$). Concentration gave an oil, which was purified by silica gel (100 g) chromatography using 8:92 ethyl ether–hexanes as eluant, giving 2.36 g of **7** (99%) as a colorless oil: $[\alpha]^{25}_D$ +20.7° (*c* 0.61, MeOH); IR (neat) 3145, 2135, 1371, 1113; ^{1}H NMR (500 MHz) 7.81 (m, 2 H) 7.62 (m, 4 H), 7.44–7.25 (m, 8 H), 5.15 (m, 1 H), 3.83 (ddd, J = 4.5, 7.2, 11.3, 2 H), 2.42 (s, 3 H), 2.40 (d, J = 2.3, 1 H), 1.02 (m, 9 H); MS *m/e* (relative intensity) 496 ((M + NH_4)$^+$, 35), 342 (15), 274 (100), 196 (33). Anal. Calcd for $C_{27}H_{30}O_4SSi$: C, 67.75; H, 6.32. Found: C, 67.71; H, 5.99.

Allene-Forming Reactions. General Synthesis of Organocopper Reagent (14b). A dry 50-mL, three-necked flask fitted with a thermometer, nitrogen inlet, septum cap, and magnetic stirring bar was charged with 0.55 g (8.42 mmol) of zinc–copper couple, 15 mL of 16:84 (v/v) *N,N*-dimethylacetamide (DMAC)–toluene, and 1.20 g (5.26 mmol) of methyl 4-iodobutyrate **12b**.[26] The system was vacuum purged with nitrogen and heated to an internal temperature of 60 °C in an oil bath with stirring. The reaction was monitored by following the disappearance of the iodide by gas chromatography (3% SE-30 on Gas Chrom Q, 100/120, 8 ft × $^1/_8$ in., column temperature 90 °C, t_R = 4.17 min). When the iodide was completely consumed (usually within 5 h) the heating bath was removed and 1.08 g (5.26 mmol) of copper(I) bromide–dimethyl sulfide complex was added followed by 0.94 g (5.26 mmol) of hexamethylphosphoramide. Stirring was continued for 15 min, during which time the internal temperature reached 25 °C.

(*S*)-(+)-Methyl 8-[(*tert*-Butyldiphenylsilyl)oxy]-5,6-octadienoate (8). To the freshly prepared organocopper reagent **14b** at 25 °C was added a solution of 0.95 g (1.98 mmol) of tosylate **7** in 2 mL of 16:84 DMAC–toluene over 3 min. The temperature rose to 30 °C during the addition. Stirring was continued for 12 min, and the reaction was quenched by the addition of 10 mL of saturated aqueous NH_4Cl and 30 mL of diethyl ether. After being stirred for 15 min the mixture was diluted with 100 mL of diethyl ether, filtered, and washed sequentially with 2 × 40 mL of saturated aqueous $NaHCO_3$, 2 × 40 mL of water, and 1 × 40 mL of brine and dried ($MgSO_4$). The solution was concentrated in vacuo, and the residue was purified by radial chromatography using 12:88 diethyl ether–hexanes, giving 0.78 g of **8** (96%) as a colorless oil: $[\alpha]^{25}_D$ +65.0° (*c* 0.34, MeOH); IR (neat) 1960, 1740, 1103; ^{1}H NMR (500 MHz) 7.68 (m, 4 H), 7.43–7.35 (m, 6 H), 5.25 (m, 1 H), 5.12 (m, 1 H), 4.20 (dd, J = 2.7, 6.0, 2 H), 3.64 (s, 3 H), 2.31 (t, J = 7.5, 2 H) 2.01 (dq, J = 2.9, 7.1, 2 H), 1.71 (quin, J = 7.5, 2 H), 1.04 (m, 9 H); MS *m/e* (relative intensity) 4.08 (M$^+$, 5), 351 (84), 319 (46), 273 (56), 213 (100). Anal. Calcd for $C_{25}H_{32}O_3Si$: C, 73.49; H, 7.89. Found: C, 73.71; H, 7.93.

(*R*)-(−)-Methyl 8-[(*tert*-Butyldiphenylsilyl)oxy]-5,6-octadienoate (9). Prepared in the same manner as **8** above except that 0.60 g (1.55 mmol) of the bromide **6** was substituted for the tosylate **7**. Chromatography gave 0.56 g of **9** (88.4%): $[\alpha]^{25}_D$ −63.8° (*c* 0.43, MeOH); IR, ^{1}H NMR, MS were all identical with those of **8**. Anal. Calcd for $C_{25}H_{32}O_3Si$: C, 73.49; H, 7.89. Found: C, 73.61; H, 7.91.

(*S*)-(+)-Methyl 8-Hydroxy-5,6-octadienoate (10). To a solution of 0.400 g (0.980 mmol) of **8** in 10 mL of THF was added 1.50 mL (1.50 mmol) of tetrabutylammonium fluoride (1 M in THF) with stirring. After 1 h the reaction was judged complete by TLC (25:75 ethyl acetate–hexanes, R_f(**8**) = 0.62, R_f(**10**) = 0.17). The mixture was concentrated, and the residue was taken up into 40 mL of CH_2Cl_2 and washed with 10 mL of water. The aqueous layer was back-extracted with 10 mL of CH_2Cl_2 and the combined organic solutions were dried ($MgSO_4$) and concentrated. The residue was purified by radial chromatography using 10:90 → 100:0 diethyl ether–hexanes as eluants. Fractions containing **10** were combined and concentrated giving 0.167 g of **10** as a colorless oil (100%): $[\alpha]^{25}_D$ +82.5° (*c* 0.53, MeOH), +53.7° (*c* 0.99, $CHCl_3$); IR (neat) 3413 (br), 1964, 1736, 1420, 1246, 1154, 1057; ^{1}H NMR (500 MHz) 5.35 (m, 1 H), 5.25 (m, 1 H), 4.12 (dd, J = 5.8, 3.2, 2H), 3.68 (s, 3 H), 2.38 (t, J = 6.0, 2 H), 2.15 (br s, 1 H exchanges with D_2O), 2.07 (m, 2 H), 1.78 (m, 2 H); ^{13}C NMR 24.0, 27.8, 33.2 (each t), 51.6 (q), 60.6 (t), 92.4 (d, 2 C), 174.1, 203.4 (each s); MS *m/e* (relative intensity) 170 (M$^+$, 5), 152 (38), 124 (20), 110 (100), 91 (29), 79 (35). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.58; H, 8.29.

(*R*)-(−)-Methyl 8-Hydroxy-5,6-octadienoate (11). The synthesis, isolation, and purification were performed as described above for compound **10** (98%): $[\alpha]^{25}_D$ −77.3° (*c* 0.31, MeOH), −53.4° (*c* 0.31, $CHCl_3$); IR, ^{1}H NMR, ^{13}C NMR, and MS were all identical with those of **10** above. Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.25; H, 8.36.

(*R*)-(−)-Methyl 7-Hydroxy-4,5-heptadienoate (16). A dry 1-L, 3-necked Morton flask fitted with a mechanical stirrer, thermometer, and nitrogen inlet was charged with 14.0 g (200 mmol) of zinc–copper couple, 28.7 g (134 mmol) of methyl 3-iodopropionate **12a**,[26] and 300 mL of 16:84 *N,N*-dimethylacetamide (DMAC)–toluene. The system was carefully vacuum purged with nitrogen and placed in a 60 °C oil bath under stirring. When the internal temperature reached 50 °C, an exotherm caused the temperature to rise to 84 °C. Stirring continued for 1 h when the reaction was judged complete by GC analysis of the iodide (3% SE-30 on Gac Chrom Q, 100/120, 8 ft × $^1/_8$ in., column temperature 80 °C, t_R = 3.62 min). The oil bath was removed and 27.6 g (134 mmol) of copper(I) bromide–dimethyl sulfide complex and 17.2 g (134 mmol) of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) were added, and stirring was continued for 40 min. A solution of 26.0 g (65.9 mmol) of bromide **6** in 30 mL of 16:84 DMAC–toluene was added over 5 min, and stirring was continued for 15 min when the reaction was judged complete by TLC (10:90 ethyl acetate–hexanes, R_f(**6**) = 0.80, R_f(**15**) = 0.68). The mixture was quenched by the addition of 150 mL of saturated aqueous NH_4Cl solution with stirring for 15 min. The mixture was diluted with 500 mL of diethyl ether and filtered, and the organic phase was washed with 150 mL of saturated aqueous $NaHCO_3$ and 150 mL of brine and dried ($MgSO_4$). The entire operation was then repeated using 30.0 g (76.1 mmol) of bromide **6** and the appropriate amounts of the other reagents. The combined organic solutions were concentrated to give 47.8 g (85.3%) as a yellow oil which was pure by TLC. This material was dissolved in 300 mL of tetrahydrofuran, and 145 mL (145 mmol) of tetrabutylammonium fluoride (1 M in tetrahydrofuran)

was added with stirring at room temperature. After 1.5 h the reaction was judged complete by TLC (25:75 ethyl acetate-hexanes, R_f(15) = 0.62, R_f(16) = 0.17). The mixture was concentrated, taken into 300 mL of dichloromethane, and washed with 200 mL of water. The aqueous layer was back-extracted with 2 × 100 mL of dichloromethane, and the combined organic solutions were dried ($MgSO_4$) and concentrated to a dark oil. This residue was subjected to silica gel chromatography (500 g) made up in 20:80 ethyl acetate-hexanes and eluted with 30:70 of the same to give 17.2 g of 16 (93%) as a clear oil: $[\alpha]^{25}_D$ -77.9° (c 0.43, MeOH), -5.95 (c 1.0, $CHCl_3$); IR (neat) 3413 (br), 1964, 1736, 1420, 1246, 1154, 1057. ^{1}H NMR (500 MHz) 5.37 (m, 2 H), 4.09 (dd, J = 5.7, 3.1, 2 H), 3.69 (s, 3 H), 2.47 (m, 2 H), 2.35 (m, 2 H), 1.88 (br s, 1 H exchanges with D_2O); ^{13}C NMR 23.4, 32.6 (each t), 51.9 (q), 60.3 (T), 92.4, 93.5 (each d), 173.4, 202.9 (each s); MS m/e (relative intensity) 156 (M^+, 6), 138 (18), 110 (100), 97 (22), 79 (43). Anal. Calcd for $C_8H_{12}O_3$: c, 61.53; H, 7.75. Found: C, 61.28; H, 7.82.

Mosher esters 17, 18, and 19 were prepared using the standard procedure[21] and were carefully[39] purified by radial chromatography (15:85 ethyl acetate-hexanes) prior to analysis.

(39) Although no separation of diastereoisomers was observed on TLC, care was taken to avoid discarding any early or late fractions which could have been diastereomerically enriched.

17: ^{13}C NMR (125 MHz) 24.0, 27.5, 33.2 (each t, CH_2), 51.5 (q, CO_2CH_3), 55.5 (q, OCH_3), 64.65 (t, OCH_2, C1),[35] 86.38 (d, HC=, C2), 92.39 (d, =CH, C4), 166.3 (s, CO_2CH_2), 173.8 (s, CO_2CH_3), 206.42 (s, =C=, C3).

18: unlisted data were identical with that of compound 17; ^{13}C NMR (125 MHz) 64.61 (t, OCH_2, C1), 86.42 (d, HC=, C2), 92.47 (d, =CH, C4), 206.29 (s, =C=, C3).

Mosher ester of racemic 16.[36] ^{13}C NMR (125 MHz) 23.2, 32.8 (both t, CH_2), 51.6 (q, CO_2CH_3), 55.5 (q, OCH_3), 64.40 (t, OCH_2, C1), 64.45 (t, OCH_2, C1), 87.34 (d, HC=, C2), 87.37 (d, HC=, C2), 92.13 (d, =CH, C4), 92.20 (d, =CH, C4), 166.3 (s, CO_2CH_2), 173.1 (s, CO_2CH_3), 205.94 (s, =C=, C3), 206.06 (s, =C=, C3).

19: unlisted data were identical with that of the ester of racemic 16 above; ^{13}C NMR (125 MHz) 64.45 (t, OCH_2, C1), 87.31 (d, HC=, C2), 92.11 (d, =CH, C4), 206.03 (s, =C=, C3).

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Supplementary Material Available: ^{1}H NMR spectra for compound 6 and ^{13}C NMR spectra for compounds 6, 17, 18, 19, a mixture of 17 and 18, and the Mosher ester of racemic 16 (7 pages). Ordering information is given on any current masthead page.

Enantiomerically Pure Acetals in Organic Synthesis. 1. Chromatographic Separability of Furanoside and Pyranoside Acetals Derived from α-Hydroxy Esters[1]

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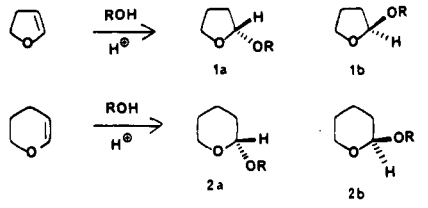
A general chromatographic separation of diastereomeric furanoside and pyranoside acetals derived from α-hydroxy esters is described. Application of this separation methodology is made to rapid syntheses of the diastereomers of (S)-methyl lactyl 4-deoxy-β-*erythro*-pentopyranoside.

Most enantioselective syntheses of uncommon sugars begin with an inexpensive carbohydrate available from the chiral pool.[2] Synthetic routes from such starting materials sometimes require many steps. Routes to carbohydrates from non-carbohydrate precursors have been employed,[3] but normally lead to racemic products. A general and reliable method by which enantiomerically pure carbohydrates might be prepared from achiral or racemic non-carbohydrate precursors could provide a valuable alternative approach, particularly for deoxy and heteroatom-containing carbohydrates.

Tetrahydrofuranyl (THF) and tetrahydropyranyl (THP) ethers such as 1 and 2 represent the simple parent ring systems for carbohydrate furanosides and pyranosides. The anomeric center, a mixed acetal, is stereogenic and usually stereorandom. When R is achiral, **1a** and **1b**, or **2a** and **2b**, are enantiomers. However, if R is chiral, then **1a** and **1b** are diastereomers, as are **2a** and **2b**. Diastereomers are sometimes separable,[4] and so an examination of the chromatographic separability of the diastereomeric THF and THP ethers derived from several commercially available enantiomerically pure alcohols was undertaken.



Separation Studies

Pairs of diastereomeric THP ethers 3-8, derived from the terpenic alcohols (-)-menthol, (+)-isomenthol, (-)-borneol, (-)-isopinocampheol, (-)-nopol, and (-)-myrtenol, respectively, were examined initially. None of these diastereomeric pairs were separable on analytical TLC plates

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