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Biocatalytic-Based Synthesis of Optically Pure (C-6)-Functionalized 1-(tert-Butyldimethylsilyloxy) 2-Methyl-(E)-2-heptenes

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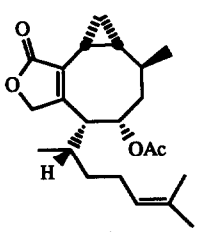
Abstract: Controlled lipase hydrolysis of sulcatol chloroacetate at pH 7.2 to 55% completion gives (*R*)-(-)-sulcatol of 89% ee. Alkaline hydrolysis of the unreacted ester provides the (*S*)-(+) enantiomer efficiently and in an optically pure state. The latter is protected at its hydroxyl group, oxidized at its less sterically hindered terminal methyl group, and transformed into useful bifunctional reagents possessing 100% ee.

INTRODUCTION

Many bioactive natural products contain as a component of their structure sidechains formally derived from 2-methyl-2-heptene. Since the interconnective bond to the structural core is invariably made at C-6 of this pendant group, the covalent attachment necessarily involves at least one stereogenic center. While this sidechain is known to occur in unoxidized form as in acetoxycrenulatin (1),[1] it is more often present in a higher state of oxidation. Ceroplastol I (2) exemplifies the usual pattern of hydroxyl



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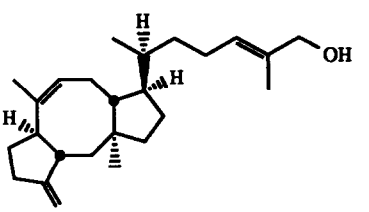

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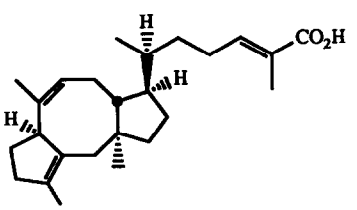

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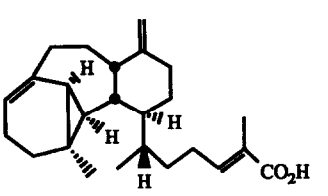

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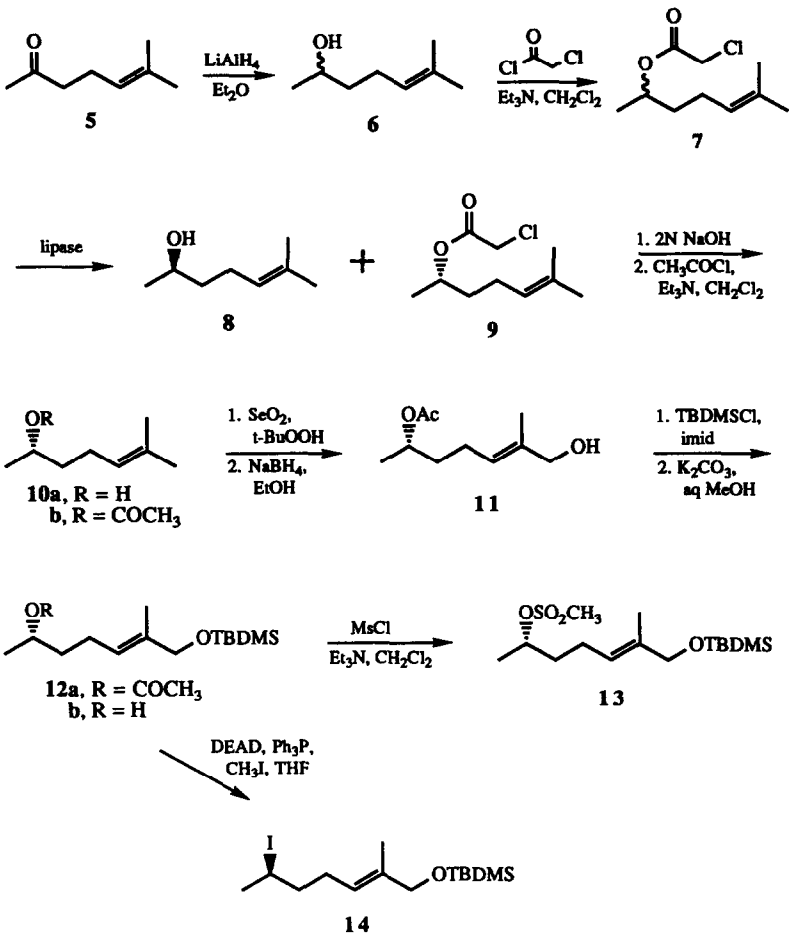
substitution.[2] The sesterterpenoids albolic acid (3)[3] and cerorubenic acid-III (4)[4] typify the state of more advanced oxygenation. To the extent that the attachment of such groups by nucleophilic means, *viz.*, S_N2 chemistry, might be attractive, the ready accessibility of optically pure bifunctional building blocks could greatly facilitate the asymmetric synthesis of such molecules.

Notable advances have recently been made in the acquisition of the enantiomers of sulcatol (6), the aggregation pheromone of the ambrosia beetles *Gnathotricus sulcatus*[5] and *Gnathotricus retucus*.[6] The *S* isomer has been arrived at from *L*-fucose,[7] (*S*)-(-)-lactate,[8] and (*S*)-(+)-ethyl 3-hydroxybutyrate,[9] but these routes are lengthy and not conveniently amenable to scale-up. Nor is classic resolution of the brucine salt of the phthalic hemiester of (±)-6 practical.[10] Baker's yeast reduction of 5 appears to be a risky process. Under ordinary conditions, no reduction occurs;[9] suitable improvisation can, however, result in the formation of (*S*)-6 (94% ee).[11] Heightened workability has been demonstrated for the pig pancreatic lipase-catalyzed transesterification of trichloroethanol butyrate and (*R*)-sulcatol in anhydrous ester.[11]

As our starting point, we sought to develop a simple method for the preparation of both sulcatol enantiomers in good chemical and optical yields and with full control over the stereochemical outcome. To this end, racemic 6 was converted to its chloroacetate ester 7,[12] lipase-catalyzed hydrolysis of which was carried out at pH 7.2 to 55% completion (based on the amount of NaOH added). Although extensive experimentation was not carried out, the available evidence suggests that the specificity of the microbial lipase toward the enantiomers of 7 is very high. As a consequence, fine-tuning of the product distribution appears to be entirely feasible. Saponification of the (*S*)-(+)-chloroacetate (9) provided (*S*)-(+)-sulcatol (10a) in 99% yield and at a quality level of 100% ee.

Once this optimally useful route to 10a was developed, acetate 10b was prepared and subjected to selenium dioxide-promoted allylic oxidation in the presence of *tert*-butylhydroperoxide.[13,14] This procedure gives rise to a mixture of 11 and the corresponding aldehyde in an approximate ratio of 3:1. Reduction of the latter with sodium borohydride permits the convenient isolation of 11 in 75% combined yield. The *E* stereochemical assignment follows from extensive precedent. More specifically, the trans geometry is clearly reflected in the diagnostic chemical shift of the -C<u>H</u>O proton in the aldehyde (δ 9.4)[15] and the downfield shift of the ^{13}C NMR signal for the -<u>C</u>H_2O- carbon in 11. In cis isomers, steric interactions are known to induce enhanced shielding of these resonances.[16]

Following protection of the terminal hydroxyl as its *tert*-butyldimethylsilyl ether, the secondary hydroxyl group was unmasked via mild hydrolysis to give 12b. Conventional mesylation delivered 13 in 98% yield. Here the stereogenic center is of the *S* configuration. Alternatively, we have adopted the triphenylphosphine/diethyl azodicarboxylate/methyl iodide reagent[17,18] for formation of the (*R*)-iodide 14. This



5 6 7 8 9 10a, R = H b, R = $COCH_3$ 11 12a, R = $COCH_3$ b, R = H 13 14

Mitsunobu-like inversion occurs with an overall efficiency of 84% (based on the recovery of some unreacted 12b) and was preferred to the Oshikawa modification[19] where N-methyltriazolinedione replaces DEAD. The important advantage offered by these reactions resides in their mechanistic character. As halogenation proceeds, iodide ion is liberated (and consumed) only in direct proportion to chemical change involving the alcohol and is never present in excess. Consequently, possible product racemization by S_N2 displacement of iodide ion by I^- [20] does not gain importance.

EXPERIMENTAL

(±)-6-Chloroacetoxy-2-methyl-2-heptene (7). To a mechanically stirred suspension of lithium aluminum hydride (9.5 g, 0.25 mol) in anhydrous ether (1000 mL) cooled to 0 °C was added dropwise a solution of commercial 5 (63.1 g, 0.5 mol) in dry ether (250

mL) under nitrogen during 1 h. The reaction mixture was stirred at this temperature for 1 h and quenched carefully with saturated sodium sulfate solution (250 mL). The organic phase was separated and the aqueous layer was acidified to pH 3 with 10% HCl prior to extraction with ether (3x). The combined ethereal layers were washed with saturated $NaHCO_3$ and NaCl solutions, dried, and evaporated to give 64.9 g (99%) of racemic sulcatol (6) as a colorless oil.

A sample of alcohol 6 (50.74 g, 396 mmol) in dichloromethane (200 mL) was treated with triethylamine (80.20 g, 792 mmol) and cooled to 0 °C. A solution of chloroacetyl chloride (89.40 g, 792 mmol) in dichloromethane (100 mL) was introduced during 40 min and mechanical stirring was continued for 30 min before the mixture was poured into ice water and extracted with dichloromethane (4 x 200 mL). The combined organic phases were washed with water, saturated $NaHCO_3$ solution, and brine prior to drying and solvent evaporation. The brown oil was filtered through silica gel (100 g, elution with 2.5% ethyl acetate in petroleum ether) and distilled to give 75.81 g (94%) of 7 as a colorless oil, bp 80 °C at 0.7 Torr; IR (neat, cm^{-1}) 2980, 2930, 2860, 1750, 1730, 1450, 1410, 1380, 1310, 1290, 1190, 1130, 1065, 960, 780; ^1H NMR (300 MHz, $CDCl_3$) δ 5.15-5.03 (m, 1 H), 5.03-5.91 (m, 1 H), 4.01 (s, 2 H), 2.08-1.94 (m, 2 H), 1.80-1.44 (m, 2 H), 1.67 (d, J = 0.9 Hz, 3 H), 2.57 (s, 3 H), 1.25 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 166.85, 132.34, 123.10, 73.08, 41.13, 35.72, 25.60, 23.85, 19.76, 17.54; MS m/z (M^+) calcd 204.0917, obsd 204.0948.

Anal. Calcd for $C_{10}H_{17}ClO_2$: C, 58.68; H, 8.37. Found: C, 58.72; H, 8.37.

Lipase-Catalyzed Hydrolysis of (±)-7. Into a 500 mL three-necked RB flask fitted with a mechanical stirrer, pH electrode, and septum was added water (200 mL), pH 7 buffer (100 mL), and chloroacetate 7 (75.81 g, 0.37 mol). A 50 mL syringe charged with 1 N NaOH solution was connected to a syringe pump controlled by a pH meter set for 7.2-7.4. To the vigorously stirred suspension was added lipase (0.89 g of Pseudomonas derived lipase P30 purchased from Amano International Enzyme Company, Troy, VA 22974). The consumption of NaOH was quite rapid at the outset. After 2 h, an additional 1.33 g of lipase was introduced. After a reaction time of 21 h, the hydrolysis was deemed to be 55% complete (based on the 204 mL of NaOH consumed). The reaction mixture was extracted with ether (5 x 150 mL) and the combined ethereal phases were dried and evaporated. The residue was subjected to silica gel chromatography (elution with 2.5% ethyl acetate in petroleum ether) to return 34.36 g of unreacted (*S*)-(+)-9, $[\alpha]_D^{23}$ +13.43 (*c* 0.03, EtOH) as a colorless oil. An increase in solvent polarity to 40% ethyl acetate provided 25.04 g (52.7%) of (*R*)-(-)-sulcatol (8) of 89% ee, $[\alpha]_D^{23}$ -13.01 (*c* 0.03, EtOH), lit[21] $[\alpha]_D^{23}$ -14.5 .

The (*S*)-(+)-chloroacetate (9) was dissolved in methanol (75 mL), treated with 2 N NaOH (150 mL), and stirred at room temperature for 0.5 h. The reaction mixture was poured into ice water, extracted into ether (4 x 100 mL), and purified as above to give

21.25 g (99%) of (*S*)-(+)-sulcatol (**10a**) having 100% ee, $[\alpha]_D^{23}$ +14.57 (*c* 0.03, EtOH), lit[23] $[\alpha]_D$ +14.4 .

(*S*)-(+)-Sulcatol Acetate (10b). A solution of **10a** (21.25 g, 165.7 mmol) and triethylamine (33.54 g, 331.5 mmol) in dry dichloromethane (200 mL) was cooled to 0 °C and treated dropwise with acetyl chloride (26.0 g, 331.5 mmol) while being mechanically stirred. The reaction mixture was stirred at room temperature for 1 h, poured into ice water, and extracted with dichloromethane (4 x 50 mL). The combined organic phases were washed with water, 10% $NaHCO_3$ solution, and brine prior to drying and evaporation. Distillation of the residue gave pure **10b**, bp 45 °C at 1 Torr, as a colorless oil (23.99 g, 85%), $[\alpha]_D^{23}$ +7.70° (*c* 0.03, EtOH); IR (neat, cm^{-1}) 2980, 2940, 2880, 2860, 1740, 1450, 1375, 1250, 1135, 1070, 1025, 960, 950, 845; ^1H NMR (300 MHz, $CDCl_3$) δ 5.15-4.98 (m, 1 H), 4.95-4.75 (m, 1 H), 2.10-1.90 (m, 2 H), 2.00 (s, 3 H), 1.66 (d, J = 0.95 Hz, 3 H), 1.65-1.40 (m, 2 H), 1.57 (s, 3 H), 1.19 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 170.63, 132.01, 123.46, 70.61, 35.93, 25.60, 23.97, 21.27, 19.92, 17.51; MS *m/z* (M^+-CH_3CO_2H) calcd 110.1096, obsd 110.1118.

Allylic Oxidation of 10b. To a solution of selenium dioxide (333 mg, 3.0 mmol) and salicyclic acid (1.45 g, 10.5 mmol) in dry dichloromethane (35 mL) at 0 °C was added *tert*-butyl hydroperoxide (30.04 g of 90%, 0.30 mol) followed by a solution of **10b** (17.03 g, 0.10 mmol) in the same solvent (35 mL). After being stirred at room temperature for 38 h, the reaction mixture was diluted with benzene (60 mL) and the solvent was evaporated under reduced pressure. The residue was taken up in ether and washed with saturated $NaHCO_3$ solution. The bicarbonate washes were back-extracted with ether and the combined organic layers were dried and concentrated. Flash chromatographic purification on silica gel (elution with 5% ethyl acetate in petroleum ether) gave 5.6 g of the (*S*)-(+)-aldehyde. An increase in solvent polarity (to 40% ethyl acetate) provided 10.4 g of (*S*)-(+)-alcohol (**11**).

For the aldehyde: pale yellow oil; IR (neat, cm^{-1}) 2980, 2940, 2880, 2820, 2720, 1735, 1690, 1640, 1500, 1375, 1250, 1135, 1060, 1025, 950, 850, 820; ^1H NMR (300 MHz, $CDCl_3$) δ 9.39 (s, 1 H), 6.55-6.40 (m, 1 H), 5.05-4.80 (m, 1 H), 2.50-2.30 (m, 2 H), 2.03 (s, 3 H), 1.90-1.60 (m, 2 H), 1.74 (d, J = 0.9 Hz, 3 H), 1.25 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 195.00, 170.59, 153.08, 139.78, 70.16, 34.47, 25.05, 21.25, 19.93, 9.14; MS *m/z* (M^+) calcd 184.1129, obsd 184.1110; $[\alpha]_D^{23}$ +1.16 (*c* 0.03, EtOH).

For **11**: colorless oil; IR (neat, cm^{-1}) 3440, 2980, 2940, 2860, 1740, 1450, 1375, 1250, 1135, 1070, 1020, 955, 850; ^1H NMR (300 MHz, $CDCl_3$) δ 5.38-5.30 (m, 1 H), 4.89-4.81 (m, 1 H), 3.94 (s, 2 H), 2.10-1.85 (m, 2 H), 1.99 (d, J = 1.4 Hz, 3 H), 1.70-1.35 (m, 2 H), 1.61 (s, 3 H), 1.18 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 170.74, 135.45, 124.66, 70.42, 68.53, 35.48, 23.46, 21.24, 19.87, 13.47; MS *m/z* (M^+) calcd 186.1256, obsd 186.1284; $[\alpha]_D^{23}$ +4.97 (*c* 0.03, EtOH).

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: 64.29; H, 9.71.

The (*S*)-(+)-aldehyde (5.6 g, 27.47 mmol) was dissolved in absolute ethanol (25 mL) and treated slowly with sodium borohydride (732 mg, 19.2 mmol) at 0 °C, and stirred at this temperature for 1 h. The reaction mixture was acidified to pH 5 and extracted with ether. The combined ethereal layers were washed with 10% $NaHCO_3$ solution and brine, dried, and evaporated. Purification by flash silica gel chromatography (elution with 40% ethyl acetate in petroleum ether) gave 3.60 g (70%) of **11**. When these reactions were performed in tandem, the yield of **11** was 75%.

(*S*)-(+)-6-Acetoxy-1-(*tert*-Butyldimethylsilyloxy)-2-methyl-(*E*)-2-heptene (12a). To a solution of **11** (13.50 g, 72.5 mmol) in DMF (100 mL) was added imidazole (14.81 g, 217.4 mmol), *tert*-butyldimethylsilyl chloride (21.85 g, 145 mmol), and 4-(dimethylamino)pyridine (88.5 mg, 0.73 mmol). The resulting mixture was stirred at room temperature for 2 days before being poured into a 1:1 mixture of ether and saturated $NaHCO_3$ solution. The aqueous phase was extracted with ether and the combined organic phases were washed with water and brine, dried, and evaporated. Purification of the residual oil by chromatography on silica gel (elution with 2.5% ethyl acetate in petroleum ether) gave **12a** (18.36 g, 84%) as a colorless oil; IR (neat, cm^{-1}) 2960, 2940, 2865, 1740, 1465, 1380, 1250, 1120, 1075, 1030, 845, 780; ^1H NMR (300 MHz, $CDCl_3$) δ 5.38-5.32 (m, 1 H), 4.93-4.82 (m, 1 H), 3.98 (s, 2 H), 2.15-1.95 (m, 2 H), 2.01 (s, 3 H), 1.70-1.40 (m, 2 H), 1.57 (s, 3 H), 1.20 (d, J = 6.3 Hz, 3 H), 0.89 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 170.63, 135.04, 123.35, 70.62, 68.45, 35.68, 25.92, 23.49, 21.30, 19.92, 18.38, 13.30, -5.31; MS *m/z* (M^+-C_4H_9) calcd 243.1416, obsd 243.1416, $[\alpha]_D^{23}$ +3.42 (*c* 0.03, EtOH).

Anal. Calcd for $C_{16}H_{32}O_3Si$: C, 63.95; H, 10.73. Found: C, 63.99; H, 10.74.

(*S*)-(+)-1-(*tert*-Butyldimethylsilyloxy)-2-methyl-(*E*)-2-hepten-6-ol (12b). A solution of **12a** (6.01 g, 20 mmol) in methanol (100 mL) was treated with a solution of potassium carbonate (3.04 g, 22 mmol) in water (30 mL) and stirred at room temperature for 3 days. The methanol was removed under reduced pressure, the residue was extracted with ether, and this solution was dried and evaporated. Purification by chromatography (silica gel, elution with 20% ethyl acetate in petroleum ether furnished **12b** (4.92 g, 95%) as a colorless oil; IR (neat, cm^{-1}) 3350, 2960, 2940, 2900, 2860, 1470, 1465, 1390, 1375, 1360, 1260, 1120, 1075, 1010, 840, 780, 670; ^1H NMR (300 MHz, $CDCl_3$) δ 5.50-5.30 (m, 1 H), 3.99 (s, 2 H), 3.85-3.70 (m, 1 H), 2.23-2.00 (m, 2 H), 1.62 (br s, 1 H), 1.59 (s, 3 H), 1.57-1.35 (m, 2 H), 1.17 (d, J = 6.2 Hz, 3 H), 0.89 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 134.84, 123.92, 68.49, 67.74, 38.94, 25.91, 23.88, 23.42, 18.36, 13.35, -5.31; MS *m/z* (M^+-OH) calcd 241.1987, obsd 241.1958; $[\alpha]_D^{23}$ +8.16 (*c* 0.03, EtOH).

Anal. Calcd for $C_{14}H_{30}O_2Si$: C, 65.05; H, 11.70. Found: C, 65.04; H, 11.64.

(*S*)-(+)-1-(*tert*-Butyldimethylsilyloxy)-6-(methanesulfonyloxy)-2-methyl-(*E*)-2-heptene (13). To a cold (0 °C), nitrogen-blanketed solution of **12b** (2.20 g, 8.5 mmol) in dry tetrahydrofuran (25 mL) was added triethylamine (1.04 g, 10.2 mmol) followed by methanesulfonyl chloride (1.17 g, 10.2 mmol). The resulting mixture was stirred at 0 °C for 5 min, then poured into ice water and extracted with ether (4 x 25 mL). The combined organic phases were dried and concentrated to leave a residue that was purified by column chromatography (silica gel, elution with 10% ethyl acetate in petroleum ether). There was isolated 2.80 g (98%) of **13** as a colorless oil; IR (neat, cm^{-1}) 3120, 2960, 2940, 2900, 2860, 1473, 1463, 1360, 1255, 1180, 1115, 1075, 1010, 975, 920, 840, 780, 670; ^1H NMR (300 MHz, $CDCl_3$) δ 5.38-5.32 (m, 1 H), 4.85-4.70 (m, 1 H), 3.98 (s, 2 H), 2.97 (s, 3 H), 2.25-2.00 (m, 2 H), 1.85-1.60 (m, 2 H), 1.58 (s, 3 H), 1.41 (d, J = 6.3 Hz, 3 H), 0.89 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 135.69, 122.32, 79.80, 68.20, 38.57, 36.43, 25.87, 23.16, 21.12, 18.32, 13.40, -5.36; MS (M^+-C_4H_9) calcd 279.1086, obsd 279.1064; $[\alpha]_D^{23}$ +8.46 (*c* 0.03 EtOH).

(*R*)-(-)-1-(*tert*-Butyldimethylsilyloxy)-6-iodo-2-methyl-(*E*)-2-heptene (14). To a solution of triphenylphosphine (803 mg, 3.06 mmol) in dry tetrahydrofuran (20 mL) was added a solution of diethyl azodcarboxylate (533 mg, 3.06 mmol) in the same medium (5 mL) at 0 °C under nitrogen. After 30 min of stirring, a solution of **12b** (720 mg, 2.78 mmol) in dry tetrahydrofuran (10 mL) was introduced and stirring was continued for 30 min whereupon methyl iodide (434 mg, 3.06 mmol - filtered through alumina before use) dissolved in 10 mL of THF was added dropwise over a period of 20 min. This mixture was stirred at 0 °C for 2 h and at room temperature for 16 h. After solvent removal under reduced pressure, the residue was subjected to silica gel chromatography (elution with 1% ethyl acetate in petroleum ether) to give 522 mg (51%) of **14**. Recovery of **12b** (280 mg, 39%) was achieved by increasing solvent polarity to 10% ethyl acetate. The yield of iodide based on unreacted alcohol is 84%; IR (neat, cm^{-1}) 2960, 2930, 2890, 2860, 1470, 1460, 1440, 1390, 1380, 1360, 1255, 1140, 1115, 1070, 1010, 860, 840, 820, 780, 670; ^1H NMR (300 MHz, $CDCl_3$) δ 5.39-5.32 (m, 1 H), 4.24-4.14 (m, 1 H), 4.01 (s, 2 H), 2.24-2.05 (m, 2 H), 2.02-1.85 (m, 1 H), 1.93 (d, J = 6.8 Hz, 3 H), 1.75-1.55 (m, 1 H), 1.64 (s, 3 H), 0.91 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 135.81, 122.28, 68.37, 42.73, 29.98, 28.94, 27.79, 25.96, 18.41, 13.63, -5.27; MS *m/z* (M^+-C_4H_9) calcd 311.0328, obsd 311.0359; $[\alpha]_D^{23}$ -2.59 (*c* 0.03, EtOH).

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