Cuparene Sesquiterpenes: Synthesis of (+)-3-Hydroxycuparene and (+)-Cuparene

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Introduction

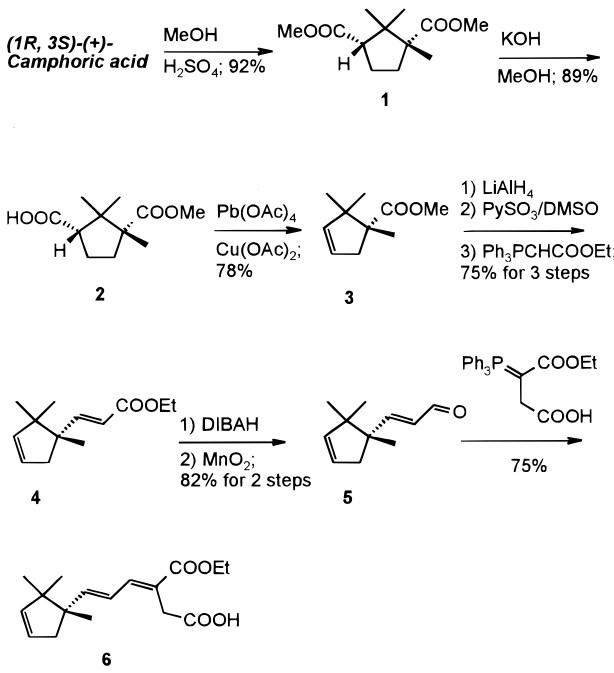
Many cuparene-type sesquiterpenes have been isolated from natural sources,[1] and their biological activities[2] prompted the study in this field. Since the cuparene skeleton has significant steric crowding around a benzylic quaternary center, its stereoselective synthesis is very difficult. Several different basic approaches have been developed to this end. The reported strategies involved either enantioselective construction of the quaternary center starting from a framework which contains the aromatic ring[3] or enantiocontrolled addition of the *p*-tolyl moiety to a chiral cyclopentane derivative.[4] Other methods which build up the aromatic ring starting from an enantiopure cyclopentane have been developed only recently.[5]

We have previously shown that the benzoannulation reaction of 3-(alkoxycarbonyl)-3,5-hexadienoic acids[6] is a useful and efficient procedure for the enantioselective synthesis of phenols bearing a benzylic stereocenter[7] starting from γ-chiral-α,β-unsaturated aldehydes. Now we report a further development of this method in construction of an aromatic ring bearing a highly sterically congested quaternary stereocenter. Using the benzoannulation reaction we synthesized the cuparane sesquiterpenes (+)-3-hydroxycuparene and (+)-cuparene in enantiomerically pure form starting from the aldehyde **5** as a chiral synthon which is prepared from commercially available (+)-camphoric acid.

Results and Discussion

To obtain an enantiopure and easily available 1,2,2-trimethylcyclopentane building block for our synthesis, we selected (+)-camphoric acid as starting material. In the literature[8] it is known that the dimethyl ester of camphoric acid **1** can be hydrolyzed regioselectivity by methanolic KOH to give acid **2** (Scheme 1). Oxidative decarboxylation effected using lead tetraacetate and copper acetate[9] afforded the cyclopentene ester **3**, which was converted to the related aldehyde by $LiAlH_4$ reduction and $PySO_3$ oxidation.[10] The latter C9 aldehyde was homologated to C15 3-(ethoxycarbonyl)-3,5-hexadienoic acid (**6**) following a straightforward and efficient four step process. The C2 homologation with (carbethoxymethylene)triphenylphosphonium betaine gave the ester **4** which was converted to aldehyde **5** through DIBAH reduction followed by MnO_2 oxidation. Wittig reaction using triphenyl(α-carbethoxy-β-carboxyethyl)phosphonium betaine[11] afforded the chiral acid **6** which can be converted in the phenol derivative **7** through the benzoannulation protocol developed by us.[6,7]

Scheme 1



This cyclization step was performed at room temperature using ethyl chloroformate or trifluoroacetic anhydride as activating agent followed by the addition of an excess of triethylamine. The so-formed mixed anhydride is unstable in base and decomposes to a divinylketene intermediate (Scheme 2), which cyclized through a 1,6-electrocyclic reaction to give **7** (or its (carboxyethyl)-

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(11) For the preparation of this betaine, see: Hudson, R. F.; Chopard, P. A. *Helv. Chim. Acta* **1963**, *46*, 2178. (b) Compound **6** was obtained as a single stereoisomer. Since the Wittig reaction of this betaine with the aldehydes affords the 3-(*E*)-alkylidenesuccinic acid monomethyl esters in highly stereoselective fashion, we assigned the *E* stereochemistry at the new formed double bond of the compound **6**. For previous studies on the stereoselectivity of this reaction, see: Röder, E.; Krauss, H. *Liebigs Ann. Chem.* **1992**, 177. Paquette, L. A.; Schulze, M. M.; Bolin, D. *J. Org. Chem.* **1994**, *59*, 2043.

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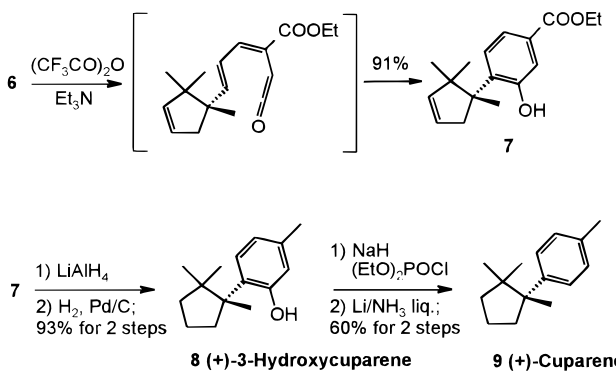
Scheme 2



trifluoroacetyl derivative). The procedure works under very mild conditions, and both the rates of convertion and the yields of product are dependent upon the activating agent.

When ethyl chloroformate was used, the reaction was very fast (a few minutes at 0−20 °C) and the phenolic derivative[12] (70%) was obtained together with a small amount of the diethyl ester of acid **6** (15%). We assumed that ethanol, derived from the decomposition of the mixed anhydride, reacts in competitive behavior with the divinylketene to give the ethyl ester.[13] The same procedure performed by using trifluoroacetic anhydride as the activating agent with prolonged reaction time (2 h) gave the phenolic derivative **7** in 91% yield.

Compound **7** is a key intermediate for the synthesis of cuparene sesquiterpenes since it has the whole C15 framework of this kind of natural product. Elaboration of the C5 aliphatic and C6 aromatic rings can afford different members of the cuparene family. Reduction of the ester group using $LiAlH_4$ gave the benzylic alcohol which was easily reduced by hydrogenation to enantiopure (+)-3-hydroxycuparene (**8**). The latter phenol was first detected in the liverworts of *Herbertus subdentatus*,[14] but its absolute configuration was not established. Only recently, the (−)-enantiomer was isolated from *Lejeunea aquatica*[15] during a chemosystematic study. While the structure of the isomeric *δ*-cuparenol has been assigned both by chemical correlation and enantioselective synthesis,[5a] no enantioselective preparation of 3-hydroxycuparene has been reported in the literature until now.

Deoxygenation of **8** afforded (+)-cuparene, which is a natural sesquiterpene found in higher plants.[16] To this end, different methods of reduction were attempted. Hydrogenolysis of the phenyltetrazolyl[17a] derivative of **8** gave unsatisfactory results, but cleavage of the diethyl phosphate ester by lithium in liquid ammonia[17b] smoothly afforded enantiopure (+)-cuparene (**9**) in good chemical yield.

In conclusion, we have demonstrated that the benzoannulation previously developed by us is very flexible and may be adapted to the synthesis of phenols bearing sterically congested quaternary stereocenters. Herein, we have reported the first synthesis of (+)-3-hydroxycuparene and its conversion into (+)-cuparene. Moreover our approach to cuparene-type sesquiterpenes starts from commercially available (+)-camphoric acid. Since (−)-camphoric acid is also available, a formal synthesis of the opposite enantiomers of the above-mentioned natural products is thus defined.

Experimental Section

(*R*)-1,2,2-Trimethylcyclopent-3-enecarboxylic Acid Methyl Ester (3). Commercially available (1*R*,3*S*)-(+)-camphoric acid (45 g, 0.225 mol) in methanol (300 mL) was treated with concentrated (96%) H_2SO_4 (100 mL). After 4 h the mixture was poured onto crushed ice and extracted with diethyl ether (3 × 200 mL). The combined organic portions were washed with brine (2 × 100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. Distillation of the residue (146−148 °C/20 mmHg) afforded pure diester **1** (47 g, 0.206 mol, 92%). The latter was treated with methanolic (250 mL) KOH (12.7 g, 0.227 mol) at reflux for 3 days and then acidified with 5% HCl(aq) (250 mL). The reaction was extracted with ethyl acetate (3 × 100 mL), and the combined organic portions were washed with brine (100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column using 8:2 hexane/ethyl acetate as eluant to afford the starting diester (4 g, 0.017 mol) and the monoacid monoester **2** (40 g, 0.183 mol, 89%). The obtained acid was dissolved in benzene (500 mL) and heated at reflux in the presence of lead tetraacetate[9] (128.6 g, 0.29 mol), pyridine (17.4 g, 0.22 mol), and cupric acetate monohydrate (6.79 g, 34 mmol). When the evolution of carbon dioxide ceased (2 h), the mixture was cooled to room temperature and diluted with water (800 mL). The organic phase was separated, and the aqueous phase was extracted with benzene (2 × 80 mL). The combined organic portions were washed with 5% HCl(aq) (300 mL), washed with brine (100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. Distillation of the residue gave pure ester **3** (24 g, 0.143 mol, 78%) as a colorless oil: bp 92−94 °C (20 mmHg); $[\alpha]^{20}_D$ +102° (*c* 4.5, $CHCl_3$); FT-IR (film) 1734, 1458, 717 cm^{-1}; EI-MS *m*/*z* 168 (M^+, 7), 109 (M^+ − COOMe, 33), 99 (100); ^1H NMR (250 MHz, $CDCl_3$) *δ* 5.53 (1H, m), 5.32 (1H, m), 3.69 (3H, s), 3.17 (1H, dt, *J* = 16.5, 2.2 Hz), 2.03 (1H, ddd, *J* = 16.5, 3, 1.1 Hz), 1.22 (3H, s), 1.13 (3H, s), 0.9 (3H, s). Anal. Calcd for $C_{10}H_{16}O_2$ (168.24): C, 71.39; H, 9.59. Found: C, 71.18; H, 9.66.

3-[(1*R*)-1,2,2-Trimethylcyclopent-3-enyl]prop-2-enecarboxylic Acid Ethyl Ester (4). $LiAlH_4$ (5 g, 0.132 mol) was added to a 0 °C solution of ester **3** (21 g, 0.125 mol) in dry diethyl ether (200 mL). The reaction mixture was stirred for 1 h and then quenched by dropwise addition of ethyl acetate (100 mL) followed by addition of 5% aqueous HCl (200 mL). The organic phase was separated, and the aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic phases were washed with brine (100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The obtained alcohol (17 g, 0.121 mol) was dissolved in dry DMSO (100 mL) and oxidized to aldehyde by mean of $PySO_3$ (45 g, 0.283 mol) using Et_3N (100 g, 0.99 mol) as base. The reaction mixture was diluted with water (300 mL) and extracted with diethyl ether (3 × 100 mL). The combined organic phases were washed with brine (100 mL), dried over sodium sulfate, filtered, and concentrated by distillation of the solvent at atmospheric pressure. The crude aldehyde was not purified but treated directly with Ph_3PCHCO_2-Et (50 g, 0.144 mol) in $CHCl_3$ at reflux for 30 h. The solvent was evaporated under reduced pressure and the residue chromatographed on a silica gel column using 95:5 hexane/ethyl

(12) With the term phenolic derivative we mean the mixture of phenol **7** and its (carboxyethyl)trifluoroacetyl derivative. Phenol **7** and the related phenol ester are separable by chromatography, and their distribution depends on experimental conditions (80/20, 90/10 in our hands). Treatment with ethanolic NaOH or $NaBH_4$ converts directly the phenolic esters in the phenol **7** to give a crude product which was easily purified (see Experimental Section).

(13) In the same way (see ref 7) the ClCOOEt-mediated benzoannulation of 3-(ethoxycarbonyl)-3,5-hexadienoic acids bearing a tertiary stereogenic center gives the related phenols in higher yields. The different behavior for compound **6** can be explained in term of major steric hindrance around the position 6 of the hexadienoic system.

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acetate as eluant to afford pure **4** (19 g, 0.091 mol, 75%) as a colorless oil: $[\alpha]^{20}_D$ +12° (*c* 1.5, $CHCl_3$); FT-IR (film) 1720, 1651, 1456, 723 cm^{-1}; EI-MS *m*/*z* 209 ($M^+ + 1$, 19), 208 (M^+, 5), 193 ($M^+ - Me$, 8), 163 ($M^+ - OEt$, 20), 135 ($M^+ - COOEt$, 100); ^1H NMR (250 MHz, $CDCl_3$) δ 7.15 (1H, d, J = 15.6 Hz); 5.80 (1H, d, J = 15.6 Hz); 5.68−5.57 (1H, m); 5.57−5.48 (1H, m); 4.20 (2H, q, J = 6.7 Hz); 2.76−2.10 (2H, m), 1.30 (3H, t, J = 6.7 Hz), 1.08 (3H, s), 0.97 (3H, s), 0.85 (3H, s). Anal. Calcd for $C_{13}H_{20}O_2$ (208.30): C, 74.96; H, 9.68. Found: C, 75.10; H, 9.65.

3-[(1*R*)-1,2,2-Trimethylcyclopent-3-enyl]prop-2-enal (5). DIBAH (0.17 mol, 1 M solution in THF) was added dropwise to a 0 °C solution of ester **4** (16 g, 77 mmol) in dry THF (100 mL), and the solution was stirred for 1 h. The reaction mixture was quenched with 5% aqueous HCl solution (80 mL). The separated aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic phases were washed with brine (60 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The obtained allylic alcohol was treated under stirring with MnO_2 (35 g, 400 mmol) in CH_2Cl_2 at reflux for 24 h. After filtration of the oxidant the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel column using 95:5 hexane/ethyl acetate as eluant to afford pure aldehyde **5** (10.4 g, 63 mmol, 82%) as a colorless oil: $[\alpha]^{20}_D$ + 16.7° (*c* 1.7, $CHCl_3$); FT-IR (film) 1694, 1629, 1456, 717 cm^{-1}; EI-MS *m*/*z* 165 ($M^+ + 1$, 57), 164 (M^+, 25), 135 ($M^+ -$ COH, 59), 82 (100); ^1H NMR (250 MHz, $CDCl_3$) δ 9.55 (1H, d, J = 7.7 Hz), 7.02 (1H, d, J = 15.8 Hz), 6.10 (1H, dd, J = 15.8, 8 Hz), 5.62 (1H, m), 5.54 (1H, m), 2.49 (1H, dt, J = 16.2, 2.3 Hz), 2.26 (1H, dt, J = 16.2, 2.3 Hz), 1.13 (3H, s), 1.00 (3H, s), 0.88 (3H, s). Anal. Calcd for $C_{11}H_{16}O$ (164.25): C, 80.44; H, 9.82. Found: C, 80.50; H, 9.79.

6-[(1*R*)-1,2,2-Trimethylcyclopent-3-enyl]-3-(ethoxycarbonyl)-3,5-hexadienoic Acid (6). The aldehyde **5** (5.5 g, 33.6 mmol) in $CHCl_3$ (80 mL) was treated with triphenyl(carbethoxycarboxyethyl)phosphonium betaine (15 g, 37 mmol) at reflux for 36 h. Removal of the solvent under reduced pressure and purification of the residue on a silica gel column using 8:2 hexane/ethyl acetate as eluant afford the acid **6** (7.5 g, 25.7 mmol, 75%): $[\alpha]^{20}_D$ +13.7° (*c* 1.2, $CHCl_3$); FT-IR (film) 3270, 1713, 1637, 985, 947, 773, 717 cm^{-1}; EI-MS *m*/*z* 293 ($M^+ + 1$, 37), 292 (M^+, 100), 275 ($M^+ - OH$, 46); ^1H NMR (250 MHz, $CDCl_3$) δ 7.38 (1H, d, J = 10.5 Hz), 6.40 (1H, d, J = 14 Hz), 6.23 (1H, dd, J = 14, 10.5 Hz), 5.64−5.57 (1H, m), 5.53−5.47 (1H, m), 4.23 (2H, q, J = 7 Hz), 3.50 (2H, s), 2.47 (1H, dt, J = 16, 2.2 Hz), 2.16 (1H, bd, J = 16 Hz), 1.28 (3H, t, J = 7 Hz), 1.07 (3H, s), 0.94 (3H, s), 0.82 (3H, s). Anal. Calcd for $C_{17}H_{24}O_4$ (292.38): C, 69.84; H, 8.27. Found: C, 69.73; H, 8.19.

4-[(1*R*)-1,2,2-Trimethylcyclopent-3-enyl]-3-hydroxybenzoic Acid Ethyl Ester (7).

(a) ClCOOEt as Activating Agent. ClCOOEt (0.8 g, 7.2 mmol) was added in one portion to a solution of acid **6** (1 g, 3.4 mmol) in dry THF (20 mL), and then Et_3N (1 g, 10 mmol) was added dropwise keeping the temperature under 20 °C. The mixture was stirred for 10 min and then acidified with an excess of 5% aqueous HCl and extracted with ethyl acetate. Concentration of the organic phase gave a residue which was treated with ethanolic (40 mL) NaOH (0.4 g, 10 mmol) at room temperature for 10 min. The reaction was diluted with ethyl acetate (60 mL) and 5% aqueous HCl solution (50 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic portions were washed with brine (40 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was chromatographed on a silica gel column eluting with 9:1 hexane/ethyl acetate to obtain the diethyl ester of acid **6** (160 mg, 0.5 mmol) and phenol **7** (655 mg, 2.4 mmol, 70%).

(b) $(CF_3CO)_2O$ as Activating Agent. $(CF_3CO)_2O$ (3.8 g, 18 mmol) was added in one portion to a solution of acid **6** (2.5 g, 8.6 mmol) in dry THF (25 mL), and then Et_3N (2.6 g, 25.7 mmol) was added dropwise. The mixture was stirred at room temperature for 2 h and then acidified with an excess of 5% aqueous HCl and extracted with ethyl acetate. The organic phase was concentrated under reduced pressure and the residue dissolved in ethanol (50 mL). The latter mixture was cooled to 0 °C and treated with $NaBH_4$ (760 mg, 20 mmol), stirring for 1 h. The reaction was diluted with ethyl acetate (60 mL) and 5% aqueous HCl solution (60 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic portions were washed with brine (40 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column eluting with 9:1 hexane/ethyl acetate to obtain phenol **7** (2.15 g, 7.8 mmol, 91%) as white crystals: $[\alpha]^{20}_D$ +77.6° (*c* 1, $CHCl_3$); FT-IR (film) 3343, 1682, 1608, 882, 772, 710 cm^{-1}; EI-MS *m*/*z* 275 ($M^+ + 1$, 66), 274 (M^+, 100), 229 ($M^+ - OEt$, 37); ^1H NMR (250 MHz, $CDCl_3$) δ 7.52 (2H, m), 7.38 (1H, d, J = 8 Hz), 6.20 (1H, bs), 5.81 (1H, m), 5.63 (1H, m), 4.35 (2H, q, J = 6.9 Hz), 3.17 (1H, d, J = 17 Hz), 2.48 (1H, d, J = 17 Hz), 1.48 (3H, s), 1.37 (3H, t, J = 6.9 Hz), 1.26 (3H, s), 0.73 (3H, s). Anal. Calcd for $C_{17}H_{22}O_3$ (274.36): C, 74.42; H, 8.08. Found: C, 74.45; H, 8.10.

(+)-3-Hydroxycuparene (8). The phenolic ester **7** (1.2 g, 4.4 mmol) in dry THF (30 mL) was reduced with $LiAlH_4$ (170 mg, 4.5 mmol) at 0 °C, stirring for 2 h. Methanol (10 mL) was slowly added, and then 5% aqueous HCl solution (50 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic portions were washed with brine (50 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude benzylic alcohol was dissolved in ethyl acetate (100 mL) and hydrogenated at atmospheric pressure (36 h) using 10% Pd/C (100 mg) as catalyst. After removal of the catalyst by filtration, the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica gel column using 9:1 hexane/ethyl acetate as eluant to afford pure (+)-3-hydroxycuparene (**8**) (900 mg, 4.1 mmol, 93%): $[\alpha]^{20}_D$ +61° (*c* 1, $CHCl_3$); FT-IR (film) 3527, 1617, 1462, 1411, 949, 809 cm^{-1}; EI-MS *m*/*z* 217 ($M^+ + 1$, 83), 216 (M^+, 5), 215 ($M^+ - 1$, 24), 148 (100); ^1H NMR (250 MHz, $CDCl_3$) δ 7.19 (1H, d, J = 8 Hz), 6.69 (1H, bd, J = 8 Hz), 6.49 (1H, s), 4.70 (1H, bs), 2.68−2.50 (1H, m), 2.27 (3H, s), 2.00−1.48 (5H, m), 1.42 (3H, s), 1.19 (3H, s), 0.77 (3H, s). Anal. Calcd for $C_{15}H_{22}O$ (218.34): C, 82.52; H, 10.16. Found: C, 82.71; H, 10.23.

(+)-Cuparene (9). (+)-3-Hydroxycuparene (**8**) (400 mg, 1.83 mmol) in dry THF (20 mL) with stirring was treated with NaH (85 mg of 60% dispersion in oil, 2 mmol) and diethyl phosphorochloridate (350 mg, 2 mmol) keeping the temperature under 20 °C. After 2 h the mixture was poured onto crushed ice and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated under reduced pressure. The obtained crude phosphate ester was dissolved in diethyl ether (10 mL) and added to cooled liquid ammonia (−78 °C) under nitrogen. Lithium powder (100 mg, 14 mmol) was added and the mixture stirred for 20 min. The reaction was quenched by adding solid NH_4Cl (3.2 g, 60 mmol), and the ammonia was then removed by warming at room temperature. The residue was treated with water (50 mL) and extracted with diethyl ether (100 mL). The organic phase was concentrated under reduced pressure and the crude product purified on a silica gel column eluting with 95:5 hexane/ethyl acetate. Bulb to bulb distillation afforded pure (+)-cuparene (**9**) (220 mg, 1.09 mmol, 60%) as a colorless oil: $[\alpha]^{20}_D$ +66.4° (*c* 1.5, $CHCl_3$), lit.[16] $[\alpha]^{20}_D$ +65° (*c* 5.9, $CHCl_3$); FT-IR (film) 1516, 1460, 812 cm^{-1}; EI-MS *m*/*z* 203 ($M^+ + 1$, 6), 202 (M^+, 25), 132 (100); ^1H NMR (250 MHz, $CDCl_3$) δ 7.23 (2H, d, J = 8.1 Hz), 7.08 (2H, d, J = 8.1 Hz), 2.48 (1H, m), 2.31 (3H, s), 1.84−1.45 (5H, m), 1.24 (3H, s), 1.05 (3H, s), 0.56 (3H, s). Anal. Calcd for $C_{15}H_{22}$ (202.34): C, 89.04; H, 10.96. Found: C, 89.13; H, 10.92.

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Supporting Information Available: NMR spectra of compounds **3**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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