Enantioselective Total Synthesis and Absolute Configuration of the Natural Norsesquiterpene 7-Demethyl-2-methoxycalamenene by a Silane-Terminated Intramolecular Heck Reaction

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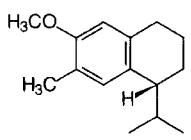
The total synthesis of the norsesquiterpene 7-demethyl-2-methoxycalamenene (**1**) by a newly developed enantioselective silane-terminated Heck reaction is described. The Pd^0-catalyzed transformation of the allylsilane **7**, obtained from 3-(3-methoxyphenyl)propanol (**2**) in 7 steps, provides the tetralin **8** in 91% yield and with 92% *ee* in the presence of (*R*)-BINAP. Transformation of **8** *via* **14** *and* **15** gives **1**. The absolute configuration of **1** which has previously not been known was deduced from a single-crystal X-ray analysis of **10**, obtained from the cyclization product **8** by hydroboration and acylation with camphanic acid chloride.

The palladium-catalyzed arylation and alkenylation of alkenes, known as the Heck reaction[1], is one of the most versatile and efficient methods for C–C bond formation. The broad application of this reaction is attributed to its excellent functional group tolerance and the possibility of using chiral ligands for the synthesis of enantiopure compounds[2], which is of great use especially for the preparation of natural products[3]. Thus, the Heck reaction is not only an excellent method for the formation of substituted carbocyclic but also for heterocyclic[4] systems.

However, a major limitation of the Heck reaction is the usually low selectivity of the double-bond formation in the β-hydride elimination step, which leads to a mixture of double-bond isomers. A recent approach to solve this problem is the application of allylsilanes as the alkene component in the intramolecular Heck reactions[5]. Following this strategy, we are able to generate vinyl- or (*E*)-trimethylsilylvinyl-substituted hetero- and carbocycles. In the presence of a chiral ligand such as (*R*)- or (*S*)-BINAP enantioselectivities up to 90% *ee* were obtained.

In this paper we report on the application of the enantioselective silane-terminated Heck reaction for the synthesis of 7-demethyl-2-methoxycalamenene (**1**), a natural cadinene-type norsesquiterpene[6]. By X-ray analysis[7] of a camphanic acid derivative of an intermediate in the synthesis we were able to determine the absolute configuration of **1** which has not been known so far.

Scheme 1



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For the synthesis of **1** the 2-iodo-5-methoxy-4-methylbenzene derivative **7** containing an allylsilane moiety was the key intermediate (Scheme 2). It was obtained from 3-(3-methoxyphenyl)propanol (**2**) in seven steps by protection of the hydroxy group, selective deprotonation of the less hindered *ortho*-position of the methoxy group with *tert*-butyllithium, quenching with an excess of iodomethane and subsequent deprotection of the alcohol to give **3** in 77% overall yield. The following iodination of **3** by a modified protocol of Königstein et al.[8] using I_2/HIO_3 in methanol gave **4** selectively, which was converted into the *p*-toluenesulfonate **5** by standard methods in 94% yield. Finally, the allylsilane moiety was introduced by nucleophilic substitution reaction of the *p*-toluenesulfonate in **5** with 3-(trimethylsilyl)propynyllithium, generated from trimethylpropargylsilane and *n*-butyllithium followed by selective hydrogenation of the alkyne moiety. The substitution reaction in the presence of catalytic amounts of NaI and tetrabutylammonium iodide (TBAI) afforded **6** in 71% yield. It can be assumed that in the transformation the *p*-toluenesulfonate is converted into the more reactive iodide at first. For the hydrogenation of the propargylsilane **6** a nickel catalyst was used to give **7** in 67% yield. Other attempts for a selective *cis*-hydrogenation employing $Pd/BaSO_4$, H_2 or KOOCN=NCOOK, CH_3COOH, MeOH or $Pd_2(dba)_3$, NEt_3, HCOOH, PBu_3 failed. The described sequence allows the preparation of the allylsilane **7** in seven steps in an overall yield of 41% starting from the known **2** which can easily be obtained from 3-methoxycinnamic acid in one step.

The intramolecular Heck reaction of the allylsilane **7** was best accomplished with a catalyst system containing 2.5 mol-% of $Pd_2(dba)_3 \cdot CHCl_3$ (dba = dibenzylideneacetone), 7.0 mol-% (*R*)-BINAP and 1.1 equivalents of Ag_3PO_4 in DMF at 80°C to give the vinyl-substituted tetraline **8** in

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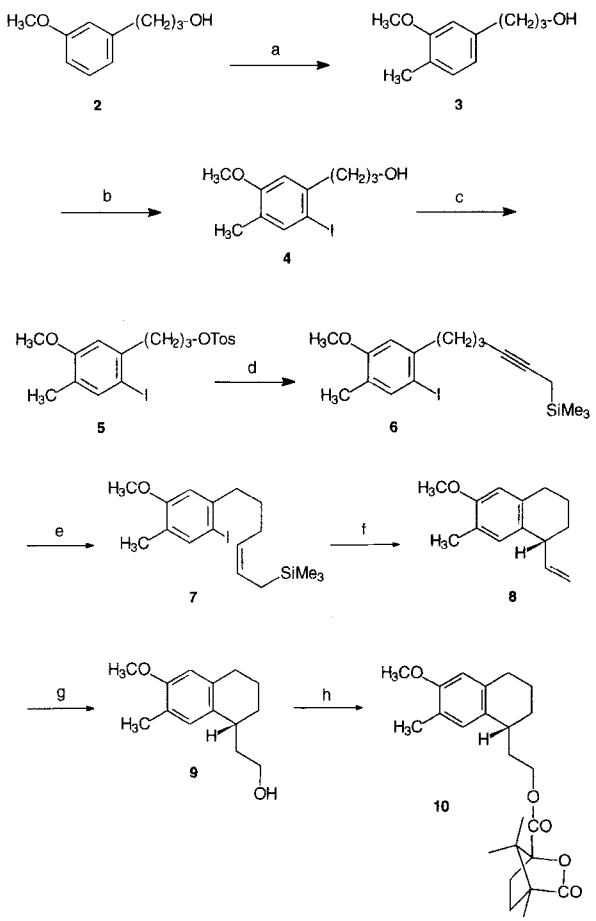
Scheme 2



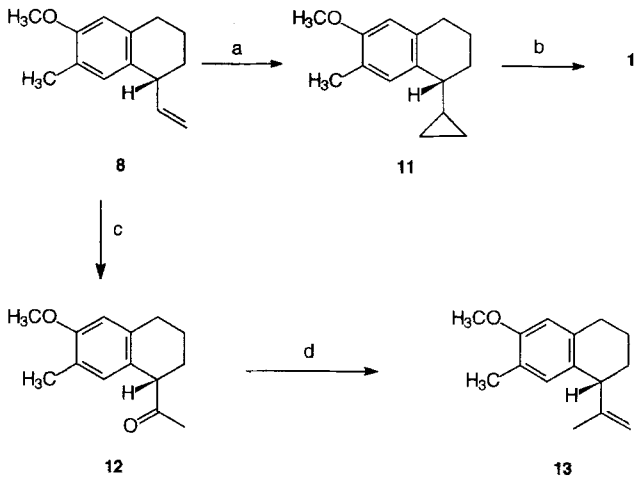
(a) i) $ClSiMe_2tBu$, imidazole, CH_2Cl_2, 2, ii) *t*BuLi, 0 °C, THF, 4 h, then CH_3I, 4 h, room temp., iii) TBAF, THF, 4 h, 77%. – (b) I_2, HIO_3, MeOH/H_2O (4:1), 24 h, reflux, 91%. – (c) TosCl, NEt_3, cat. DMAP, CH_2Cl_2, 95% (94% from **3**). – (d) Trimethylpropargylsilane, *n*BuLi,THF, –70 °C, 1 h, then **5**, cat. NaI, cat. TBAI, 9 h, 65 °C, 71%. – (e) Ni, H_2, EtOH, 67%, (57% from **5**). – (f) Cat. $Pd_2(dba)_3 \cdot CHCl_3$, cat. (*R*)-BINAP, Ag_3PO_4, DMF, 48 h, 91%. – (g) $BH_3 \cdot SMe_2$, THF, 0 °C, 6 h; H_2O, aq. NaOH, aq. H_2O_2, 50 °C, 45 min then room temp. 20 h, 78%. – (h) (1*S*)-(–)-Camphanoyl chloride, pyridine/CH_2Cl_2 (1:2), room temp., 18 h, 74%.

91% yield with 92% *ee*. This result clearly demonstrates the great advantage of the allylsilane-terminated Heck reactions[5] for the stereo- and regioselective construction of sp^3-carbon centers. (*R*)- and (*S*)-BINAP as chiral ligands were found to provide the highest enantiomeric excesses and yields. The use of other chiral ligands such as DIOP, MeO-BIPHEP[9] and a biferrocenylamine ligand[10] gave less satisfactory results. The addition of a silver salt[11] has a benefical effect on the reaction rate of the Heck reaction. We assume that this arises from a silver-mediated iodide abstraction from the primarily formed arylpalladium iodide species to give a more electrophilic cationic palladium complex.

In order to determine the absolute configuration of the non-crystalline **8** by X-ray analysis and its enantiomeric purity by HPLC analysis using a chiral column[12], the vinyl group in **8** was converted into **9** by hydroboration with $BH_3 \cdot SMe_2$. Furthermore, by use of (1*S*)-(–)-camphanic acid chloride, **9** could be transformed into the crystalline camphane derivative **10** (Scheme 2) the structure of which was determined by X-ray analysis, clearly demonstrating that the stereogenic center in **8** must have the (*R*) configuration, since in the tranformation of **8** into **9** and **10** a change of the configuration at the stereogenic center can be excluded[13].

Conversion of **8** into the isopropyl derivative **1** was initially performed according to a cyclopropanation/hydrogenolysis route (Scheme 3). Cyclopropanation of **8** applying a modification of Furukawa's procedure[14] provided **11** in only 27% yield, which can be explained by steric hindrance. In comparison, the cyclopropanation of vinylcyclohexane under the same conditions provided the cyclopropylcyclohexane in quantitative yield. Hydrogenolytic ring opening of **11** gave the desired norsesquiterpene **1** in 45% yield. Unfortunately, **1** contains about 20% of a byproduct, which could not be removed by chromatography or distillation. The moderate yields of this sequence and the difficulties in obtaining pure **1** encouraged us to look for other suitable strategies for the transformation of **8** into **1**. Thus, we converted the vinyl group of **8** into the corresponding ketone **12** in 46% yield via a Wacker oxidation[15] using O_2 in DMF/H_2O in the presence of CuCl and a catalytic amount of $PdCl_2$. Wittig reaction of the ketone with Ph_3PCH_3I/*n*BuLi gave the isopropenyl-substituted tetrahydronaphthalene system **13** in 32% yield. The moderate yields prompted us again to look for new alternatives.

Scheme 3

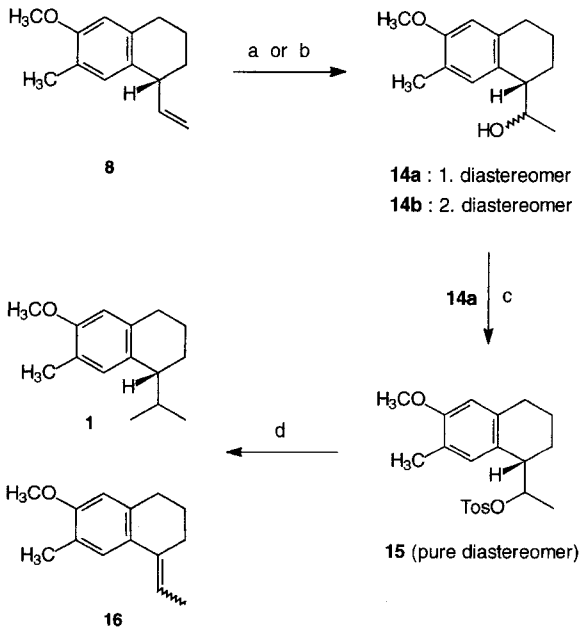


(a) $ZnEt_2$, $ClCH_2I$, CH_2Cl_2, 27%. – (b) Cat. PtO_2, CH_3CO_2H, H_2, 45 °C, 45%. – (c) Cat. $PdCl_2$, CuCl, O_2, DMF/H_2O (6:1), 46%. – (d) Ph_3PCH_3I, *n*BuLi, THF, 32%.

The natural norsesquiterpene **1** was finally synthesized from **8** in a three-step sequence via the secondary alcohols **14a/b** (Scheme 4). For the hydroxylation of **8** two different methods were applied. Thus, the hydroxymercuration[16] and subsequent reduction with sodium borohydride provided the secondary alcohols **14a/b** in 80% yield as a 2:1 mixture of the two diastereomers. Alternatively, alcohols **14a/b** were obtained in 43% yield in a ratio of 1:2, when

alkene **8** was treated with the system $PhSiH_3$, cat. $Co(acac)_2$, O_2 according to a protocol of Mukaiyama et al.[17] The main diastereomer of **14a/b** obtained in the hydroxymercuration could be separated by chromatography on silica gel followed by crystallization allowing the preparation of the diastereopure and nearly enantiopure alcohol **14a**. We were not able to determine the relative configuration of this compound. Tosylation of **14a** with 2.5 equiv. of *p*-toluenesulfonic acid chloride in pyridine/dichloromethane and catalytic amounts of DMAP gave **15** in 81% yield. In the last step the *p*-toluenesulfonate **15** was treated with an excess of Me_2CuLi in Et_2O to give the desired norsesquiterpene **1** in 56% yield. Unfortunately, even under optimized conditions[18], in addition to **1** the alkene **16** was formed as a byproduct in 40% yield by simple elimination under the slightly basic conditions. Since the obtained mixture of **1** and **16** was difficult to separate it was treated with $BH_3{\cdot}SMe_2$ and subsequently with H_2O_2. Thus **16** was transformed into the more polar secondary alcohol *rac*-**14** while **1** remained unchanged. *rac*-**14** could now easily be removed by chromatography on silica gel allowing the isolation of pure **1**.

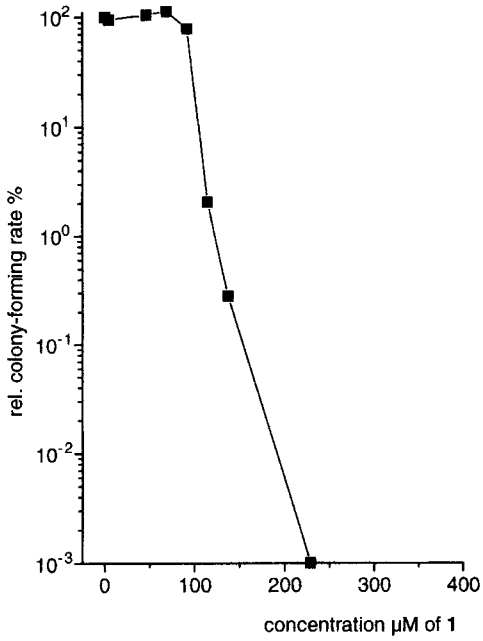
Scheme 4



(a) $Hg(OAc)_2$, THF/H_2O, room temp.; aqueous NaOH, $NaBH_4$, 80% (91%), 2 diastereomers (2:1). – (b) $PhSiH_3$, cat. $Co(acac)_2$, O_2, THF, 8 h, room temp., 43%, 2 diastereomers (1:2). – (c) **14a**: TosCl, cat. DMAP, pyridine/CH_2Cl_2 (1:2), 81% (15% of **14a** recovered). (d) Me_2CuLi, Et_2O, −35°C to −23°C, 31 h, 56% **1** and 40% **16**.

The cytotoxicity of 7-demethyl-2-methoxycalamenene (**1**) to human tumor cells was determined by a colony-forming assay[19]. Figure 1 shows the cytocide effect of norsesquiterpene **1** on A 549 cells of a bronchial adenocarcinoma after a drug exposure of 24 h. There was a decrease in colony formation of 50% (ED_{50}) using a concentration of **1** of 95.1 μM. The cyclization product **8** displays a similar cytotoxicity under the same conditions with an ED_{50} of 125.2 μM.

Figure 1. Cytotoxicity of 7-demethyl-2-methoxycalamenene (**1**)



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Experimental

^1H and ^{13}C NMR: Varian XL-200, Bruker AMX-300, Varian XL-500; multiplicities were determined with APT pulse sequence. – MS: Varian MAT 311A, high resolution: Varian MAT 731. – IR: Bruker IFS 25. – UV: Perkin-Elmer Lambda 9. – Melting points were determined by using a Mettler FP 61 melting point apparatus and are uncorrected. – Optical rotations: Perkin-Elmer 241 polarimeter. – Elemental analyses were carried out in the analytical laboratory of the university. – All solvents were distilled prior to use. Reagents and materials were obtained from commercial suppliers and were used without further purification. All reactions were carried out under a positive pressure of argon and monitored by TLC (Macherey-Nagel & Co., Alugram SIL G/UV_{254}). Products were isolated by column chromatography on silica gel (Silica gel 60, particle size 0.04–0.063 mm, Merck). The acetonitrile for the HPLC analysis was of HPLC quality (J. T. Baker or Merck). Water was bidistilled in quartz vessels. The solvents were automatically mixed and filtered through a membrane filter (0.2 μm) prior to use.

Cell Culture and Colony-Forming Assay: The cell line A 549 of a human bronchial adenocarcinoma (American Type Culture Collection, Rockville, MD) used in this study was a gift from the Institut für Zellbiologie der Universität Essen. Cells were cultured in Dulbecco's modified eagle's medium DMEM supplemented with 10% fetal calf serum, 44 mM of $NaHCO_3$ and 4 mM of L-glutamine in an incubator under humidified atmosphere of 7.5% CO_2 and 92.5% air. Colony-forming assay was performed by seeding cells in 6-well multiplates at densities of 10^2, 10^3, 10^4, and 10^5 cells/well. After cell attachment the desired concentration of the freshly di-

luted drug in DMSO (1% final concentration in the culture wells) was added and incubated for 24 h. After drug removal, cells were refed with fresh culture medium. Following a cultivation period of 12 days for colony formation, cells were fixed and stained with Löffler's methylene blue. Colonies of more than 1 mm in diameter were counted. The relative colony-forming rates of drug-treated cells relative to non-treated cells could be determined. All survival points were done in triplicate, and experiments were conducted twice.

3-(3-Methoxy-4-methylphenyl)propan-1-ol (**3**): Alcohol **2** (3.00 g, 18.1 mmol), which was obtained from commercially available 3-methoxycinnamic acid by reduction with $LiAlH_4$ according to known procedures, was added to a cooled (0 °C) suspension of imidazole (1.90 g, 28.0 mmol) and tBuMe$_2$SiCl (3.07 g, 20.4 mmol) in dry dichloromethane (40 ml). After stirring for 3 h at room temp., the mixture was poured into water and extracted with dichloromethane (3 × 20 ml). The combined organic extracts were washed with brine, dried with Na_2SO_4, filtered through silica gel, and the solvent was evaporated in vacuo. 5.06 g (18.0 mmol, 100%) of the tBuMe$_2$Si-protected alcohol was obtained which was dissolved in dry THF (50 ml). After addition of molecular sieves (4 Å) the solution was cooled to −78 °C and *tert*-butyllithium (19.4 ml, 36.1 mmol; 1.86 M solution in hexane) was added dropwise over a period of 15 min. The reaction mixture was stirred for 4 h under argon at 0 °C and then the reaction was quenched by addition of iodomethane (7.69 g, 54.2 mmol) in THF (5 ml). After stirring of the reaction mixture for 4 h at room temp., water was added, the phases were separated and the aqueous layer was extracted with diethyl ether (3 × 25 ml). The combined organic phases were washed with brine, dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/diethyl ether, 120:1). The obtained product was again dissolved in THF (50 ml), and tetrabutylammonium fluoride (TBAF·3 H_2O) (8.10 g, 25.7 mmol) was added. After stirring for 3 h at room temp. the reaction mixture was partitioned between diethyl ether and subsequently between water and brine. The combined organic layers were dried (Na_2SO_4), concentrated, and the residue was chromatographed on silica gel (petroleum ether/EtOAc, 4:1) to give **3** as a colorless oil (2.51 g, 13.9 mmol, 77%). R_f = 0.10. – IR (film): $\tilde{\nu}$ = 3354 cm^{-1} (OH), 2998, 2864 (C–H), 1614 (C=C). – ^{1}H NMR ($CDCl_3$): δ = 1.48 (br s, 1H, OH), 1.88 (m, 2H, 2-H), 2.17 (s, 3H, CH_3), 2.67 (t, J = 6.5 Hz, 2H, 3-H), 3.68 (t, J = 6.5 Hz, 2H, 1-H), 3.81 (s, 3H, OCH_3), 6.67 (s, 1H, 2′-H), 6.70 (d, J = 7.5 Hz, 1H, 6′-H), 7.03 (d, J = 7.5 Hz, 1H, 5′-H). – ^{13}C NMR ($CDCl_3$): δ = 15.82 (CH_3), 32.13 (C-2), 34.36 (C-3), 55.19 (OCH_3), 62.18 (C-1), 110.3 (C-2′), 120.1 (C-6′), 123.9 (C-4′), 130.4 (C-5′), 140.7 (C-1′), 157.6 (C-3′). – MS (70 eV), *m/z* (%): 180 (36) [M$^+$], 136 (100) [M$^+$ – C_2H_4O], 121 (19) [M$^+$ – C_3H_7O]. – $C_{11}H_{16}O_2$ (180.2): calcd. C 73.30, H 8.95; found C 73.46, H 9.09.

3-(2-Iodo-5-methoxy-4-methylphenyl)propan-1-ol (**4**): A solution of iodine (2.24 g, 8.82 mmol) in methanol (100 ml) was added to a stirred solution of alcohol **3** (3.97 g, 22.1 mmol) in methanol (20 ml). A solution of HIO_3 (0.82 g, 4.6 mmol) in water (30 ml) was added and the mixture refluxed for 28 h. The mixture was concentrated in vacuo and the residue dissolved in dichloromethane and the solution washed with aqueous Na_2SO_3 solution. The separated organic layer was subsequently washed with water and brine, all washings were extracted with dichloromethane, and the combined organic solutions were dried and concentrated. The crude product was purified by flash chromatography on silica gel (acetone/CH_2Cl_2/petroleum ether, 1:1:6) to give **4** (6.14 g, 20.1 mmol, 91%). R_f = 0.26, m.p. 58 °C. – IR (film): $\tilde{\nu}$ = 3354 cm^{-1}, 3342 (OH), 2996, 2866, 2844 (C–H). – ^{1}H NMR ($CDCl_3$): δ = 1.47 (br s, 1H, OH), 1.80–1.91 (m, 2H, 2-H), 2.13 (s, 3H, CH_3), 2.77 (br t, J = 7.5 Hz, 2H, 3-H), 3.72 (t, J = 6.5 Hz, 2H, 1-H), 6.70 (s, 1H, 6′-H), 7.52 (s, 1H, 3′-H). – ^{13}C NMR ($CDCl_3$): δ = 15.29 (CH_3), 33.27 (C-2), 37.00 (C-3), 55.31 (OCH_3), 62.02 (C-1), 88.43 (C-2′), 111.2 (C-6′), 126.8 (C-4′), 140.3 (C-3′), 142.6 (C-1′), 158.1 (C-5′). – MS (70 eV), *m/z* (%): 306 (4) [M$^+$], 135 (37) [$C_9H_{11}O^+$], 55 (72), 43 (100) [$C_2H_3O^+$]. – $C_{11}H_{15}IO_2$ (306.1): calcd. C 43.16, H 4.94; found C 43.00, H 4.99.

3-(2-Iodo-5-methoxy-4-methylphenyl)propyl p-Toluene-4-sulfonate (**5**): To a stirred solution of alcohol **4** (4.27 g, 14.0 mmol) in dichloromethane (30 ml) at 0 °C, NEt_3 (1.69 g, 16.7 mmol), 4-dimethylaminopyridine (DMAP) (0.17 g, 1.4 mmol), and *p*-toluenesulfonic acid chloride (2.93 g, 15.3 mmol) were added. After stirring for 3 h at room temp., the mixture was poured into 10 ml of water and extracted with dichloromethane (2 × 20 ml). The combined organic extracts were washed with brine and dried with Na_2SO_4. Flash chromatography (silica gel, petroleum ether/EtOAc, 5:1) afforded **5** (6.09 g, 13.2 mmol, 95%) as colorless crystals. R_f = 0.35, m.p. 76 °C (CH_2Cl_2). – IR (KBr): $\tilde{\nu}$ = 2958 cm^{-1}, 2918, 2892, 2848 (C–H), 1382, 1350, 1172 (R–SO_2–OR′). – ^{1}H NMR ($CDCl_3$): δ = 1.88–1.98 (m, 2H, 2′-H), 2.12 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 2.72 (br t, J = 7.5 Hz, 2H, 3′-H), 3.79 (s, 3H, OCH_3), 4.08 (t, J = 6.0 Hz, 2H, 1′-H), 6.68 (s, 1H, 6″-H), 7.34 (d, J = 8.0 Hz, 2H, 3-H), 7.49 (s, 1H, 3″-H), 7.80 (d, J = 8.0 Hz, 2H, 2-H). – ^{13}C NMR ($CDCl_3$): δ = 15.28 (CH_3), 21.57 (CH_3), 29.09 (C-2′), 36.36 (C-3′), 55.30 (OCH_3), 69.43 (C-1′), 88.06 (C-2″), 111.6 (C-6″), 127.1 (C-4″), 127.8 (C-3), 129.8 (C-2), 132.9 (C-4), 140.4 (C-3″), 141.1 (C-1″), 144.7 (C-1), 158.0 (C-5″). – MS (70 eV), *m/z* (%): 460 (100) [M$^+$], 288 (74) [M$^+$ – $C_7H_8SO_3$], 161 (37) [M$^+$ – $C_7H_8SO_3$ – I]. – $C_{18}H_{21}IO_4S$ (460.3): calcd. C 46.97, H 4.60; found C 46.87, H 4.60.

6-(2-Iodo-5-methoxy-4-methylphenyl)-1-trimethylsilylhex-2-yne (**6**): A 2.36 M solution of *n*-butyllithium in hexane (1.3 ml, 3.0 mmol) was added via syringe to a stirred solution of propargylsilane (0.34 g, 3.0 mmol) in 6 ml of THF at −78 °C under argon. After stirring for 1 h at this temp., the 3-(trimethylsilyl)propynyllithium was transferred via syringe to a solution of **5** (1.20 g, 2.61 mmol), Bu_4NI (96 mg, 0.26 mmol) and NaI (39 mg, 0.26 mmol) in 20 ml of THF at room temp. under argon. The reaction mixture was stirred for 9 h at 65 °C and then the reaction was quenched by addition of water (15 ml). The crude product was extracted with diethyl ether (2 × 20 ml), the combined organic phases were washed with brine, dried, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/diethyl ether, 100:1) to give **6** (0.74 mg, 1.85 mmol, 71%). R_f = 0.20, m.p. 54 °C (hexane). – IR (KBr): $\tilde{\nu}$ = 3030 cm^{-1}, 2996, 2958, 2940, 2906 (C–H), 2256, 2216, 2182 (C≡C). – ^{1}H NMR ($CDCl_3$): δ = 0.10 (s, 9H, $SiMe_3$), 1.44 (t, J = 2.5 Hz, 2H, 1-H), 1.68–1.78 (m, 2H, 5-H), 2.11 (s, 3H, CH_3), 2.20 (tt, J = 7.0, 2.5 Hz, 2H, 4-H), 2.75 (br t, J = 7.5 Hz, 2H, 6-H), 3.77 (s, 3H, OCH_3), 6.68 (s, 1H, 6′-H), 7.49 (br s, 1H, 3′-H). – ^{13}C NMR: δ = −1.98 ($SiMe_3$), 7.01 (C-1), 15.31 (CH_3), 18.51 (C-4), 29.87 (C-5), 39.77 (C-6), 55.27 (OCH_3), 78.09 (C-2), 78.22 (C-3), 88.46 (C-2′), 111.4 (C-6′), 126.7 (C-4′), 140.4 (C-3′), 142.8 (C-1′), 158.0 (C-5′). – MS (70 eV), *m/z* (%): 400 (1) [M$^+$], 273 (47) [M$^+$ – I], 258 (100) [M$^+$ – CH_3 – I], 199 (21) [M$^+$ – I – SiC_3H_{10}], 73 (74) [$SiMe_3^+$]. – $C_{17}H_{25}IOSi$ (400.4): calcd. C 51.00, H 6.29; found C 50.89, H 6.45.

(Z)-6-(2-Iodo-5-methoxy-4-methylphenyl)-1-trimethylsilylhex-2-ene (**7**): Under hydrogen (1 atm) nickel(II) acetate tetrahydrate (0.13 g, 0.53 mmol) was suspended in 10 ml of degassed ethanol and a solution of sodium borohydride (20 mg, 0.53 mmol) in 5 ml of degassed ethanol was added to the suspension with vigorous

stirring, whereupon the color of the mixture changed spontaneously from light green to black. After stirring for 5 min, ethylenediamine (64 mg, 1.1 mmol) and 10 min later alkyne **6** (0.68 g, 1.70 mmol) were added successively. The reaction mixture was stirred under hydrogen (1 atm) for 8 h (TLC), then diluted with dichloromethane and filtered through silica gel. It was then washed with water and brine, dried with Na_2SO_4, and concentrated in vacuo. Purification of the residue by column chromatography (petroleum ether/diethyl ether 150:1) gave allylsilane **7** (0.46 g, 1.14 mmol, 67%) as a colorless oil. $R_f = 0.36$. – IR (film): $\tilde{\nu} = 3004$ cm^{-1}, 2950, 2858 (C–H), 1644, 1600 (C=C). – ^1H NMR ($CDCl_3$): $\delta = -0.05$ (s, 9H, $SiMe_3$), 1.47 (d, $J = 8.0$ Hz, 2H, 1-H), 1.56–1.66 (m, 2H, 5-H), 2.07 (br q, $J = 7.5$ Hz, 2H, 4-H), 2.11 (s, 3H, CH_3), 2.65 (br t, $J = 7.5$ Hz, 2H, 6-H), 3.78 (s, 3H, OCH_3), 5.27–5.49 (m, 2H, 2-H, 3-H), 6.65 (s, 1H, 6′-H), 7.50 (s, 1H, 3′-H). – ^{13}C NMR ($CDCl_3$): $\delta = -1.71$ ($SiMe_3$), 15.31 (CH_3), 18.56 (C-1), 26.77 (C-5), 30.56 (C-4), 40.61 (C-6), 55.28 (OCH_3), 88.56 (C-2′), 111.2 (C-6′), 126.0 (C-3), 126.5 (C-4′), 126.9 (C-2), 140.3 (C-3′), 143.5 (C-1′), 158.0 (C-5′). – MS (70 eV), *m/z* (%): 402 (1) [M^+], 290 (100) [$M^+ - C_3H_{12}Si$], 261 (94) [$M^+ - C_8H_{17}Si$], 135 (82) [$C_9H_{11}O^+$], 73 (85) [$SiMe_3^+$]. – $C_{17}H_{27}IOSi$ (402.4): calcd. C 50.74, H 6.76; found C 50.89, H 6.73.

(R)-6-Methoxy-7-methyl-1-vinyl-1,2,3,4-tetrahydronaphthalene (**8**): A mixture of $Pd_2(dba)_3 \cdot CHCl_3$ (56 mg, 0.054 mmol, 2.5 mol%) and (*R*)-BINAP (94 mg, 0.15 mmol, 7.0 mol%) in degassed DMF (15 ml) was slowly heated at 55°C under argon with vigorous stirring to achieve a homogeneous system (10 min). Ag_3PO_4 (1.0 g, 2.4 mmol, 1.1 eq) and the allylsilane **7** (0.87 g, 2.16 mmol) were added, and the reaction mixture was then heated at 80°C for 48 h. After completion of the reaction (TLC), the resulting mixture was diluted with diethyl ether, filtered through silica gel, and washed with water. The organic phase was separated and the aqueous phase extracted with diethyl ether (2 × 20 ml). The combined organic phases were extracted with brine, dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography using petroleum ether/diethyl ether (150:1) to afford the cyclization product **8** (400 mg, 1.98 mmol, 91%) as a colorless oil. $R_f = 0.26$, $[\alpha]_D^{20} = -88.2$ ($c = 1$ in $CHCl_3$), 92% *ee*. – IR (film): $\tilde{\nu} = 2996$ cm^{-1}, 2856 (C–H), 1638, 1616, 1582 (C=C). – ^1H NMR ($CDCl_3$): $\delta = 1.60–1.95$ (m, 4H, 2-H, 3-H), 2.15 (s, 3H, CH_3), 2.74 (br m, 2H, 4-H), 3.34 (br dt, $J = 7.5$, 6.5 Hz, 1H, 1-H), 3.79 (s, 3H, OCH_3), 5.02 (ddd, $J = 17.0$, 2.0, 2.0 Hz, 1H, *trans* $=CH_2$), 5.06 (ddd, $J = 10.0$, 2.0, 1.0 Hz, 1H, *cis* $=CH_2$), 5.85 (ddd, $J = 17.0$, 10.0, 7.5 Hz, 1H, –CH=), 6.51 (s, 1H, 5-H), 6.90 (s, 1H, 8-H). – ^{13}C NMR ($CDCl_3$): $\delta = 15.80$ (CH_3), 20.91 (C-3), 29.82 (C-2), 30.32 (C-4), 42.95 (C-1), 55.19 (OCH_3), 110.1 (C-5), 114.5 ($=CH_2$), 123.9 (C-7), 129.5 (C-8a), 131.4 (C-8), 135.1 (C-4a), 143.5 (–CH=), 155.9 (C-6). – MS (70 eV), *m/z* (%): 202 (100) [M^+], 187 (68) [$M^+ - CH_3$], 175 (24) [$M^+ - C_2H_3$], 171 (25) [$M^+ - OCH_3$]. – $C_{14}H_{18}O$ (202.3): calcd. C 83.12, H 8.97; found C 82.98, H 9.03.

(R)-2-(6-Methoxy-7-methyl-1,2,3,4-tetrahydronaphthalene-1-yl)-ethanol (**9**): A solution of alkene **8** (60 mg, 0.30 mmol) in THF (10 ml) was treated dropwise at 0°C with $BH_3 \cdot SMe_2$ (56 mg, 0.74 mmol). The mixture was stirred for 6 h under argon at room temp. After cooling to 0°C, water (0.40 ml), 2 N NaOH (0.40 ml), and 30% aqueous H_2O_2 (0.25 ml) were added. The reaction mixture was heated at 45°C for 45 min and then stirred at room temp. for 20 h. It was diluted with brine and extracted with diethyl ether (2 × 10 ml). The combined extracts were washed with water and brine, and the aqueous layers were back-washed with diethyl ether (2 × 10 ml). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc, 7:1) gave the primary alcohol **9** (51 mg, 0.23 mol, 78%) as a colorless oil. – $R_f = 0.14$, $[\alpha]_D^{20} = -7.2$ ($c = 1.4$ in $CHCl_3$), 92% *ee*[12]. – ^1H NMR ($CDCl_3$): $\delta = 1.32$ (br s, 1H, OH), 1.55–1.88 (m, 5H, 3′-H, 2′-H, 2-H), 1.95–2.02 (m, 1H, 2-H), 2.17 (s, 1H, CH_3), 2.72 (m, 2H, 4′-H), 2.87 (m_c, 1H, 1′-H), 3.77 (t, $J = 7.0$ Hz, 2H, 1-H), 3.79 (s, 3H, OCH_3), 6.52 (s, 1H, 5′-H), 6.94 (s, 1H, 8′-H). – ^{13}C NMR ($CDCl_3$): $\delta = 15.91$ (CH_3), 19.76 (C-3′), 27.91 (C-2′), 29.72 (C-4′), 33.29 (C-1′), 39.85 (C-2), 55.25 (OCH_3), 61.12 (C-1), 110.2 (C-5′), 124.0 (C-7′), 130.7 (C-8′), 132.1 (C-8a′), 135.2 (C-4a′), 155.6 (C-6′). – MS (70 eV), *m/z* (%): 220 (24) [M^+], 175 (100) [$M^+ - C_2H_5O$]. – $C_{14}H_{20}O_2$: calcd. 220.1463; found 220.1463 (HRMS).

2-(R)-(6-Methoxy-7-methyl-1,2,3,4-tetrahydronaphthalene-1-yl)-ethyl (1S,4R)-4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate (**10**): To a solution of the primary alcohol **9** (105 mg, 0.48 mmol) in 8 ml of a mixture of dichloromethane and pyridine (2:1) (1*S*)-(–)-camphanic acid chloride (124 mg, 0.57 mmol) was added at 0°C. After stirring for 18 h at room temp., the reaction mixture was diluted with dichloromethane (10 ml) and treated with 2 N HCl (→ pH = 3). The separated aqueous phase was extracted with dichloromethane (2 × 10 ml), the combined organic layers were extracted with water and brine, dried with Na_2SO_4, and concentrated in vacuo. Flash chromatography of the residue on silica gel gave **10** (141 mg, 0.35 mmol, 74%). Crystallization from diethyl ether/dichloromethane/hexane provided suitable crystals for an X-ray analysis[7] of **10**. $R_f = 0.36$ (petroleum ether/EtOAc, 5:1), m.p. 124°C (hexane), $[\alpha]_D^{20} = -28.0$ ($c = 1$ in $CHCl_3$). – IR (KBr): $\tilde{\nu} = 2952$ cm^{-1}, 2934, 2870, 2838 (C–H), 1786 (C=O), 1726 (C=O). – ^1H NMR ($CDCl_3$): $\delta = 0.99$ (s, 3H, 7-CH_3), 1.07 (s, 3H, 7-CH_3), 1.12 (s, 3H, 4-CH_3), 1.65–1.92 (m, 7H, 2″-H, 3″-H, 5-H, 2′-H), 2.00–2.13 (m, 2H, 2′-H, 6-H), 2.16 (s, 3H, Ar-CH_3), 2.43 (ddd, $J = 13.5$, 10.5, 4.0 Hz, 1H, 6-H), 2.72 (br m, 2H, 4″-H), 2.83 (m_c, 1H, 1″-H), 3.79 (s, 3H, OCH_3), 4.35 (t, $J = 7.0$ Hz, 2H, 1′-H), 6.51 (s, 1H, 5″-H), 6.87 (s, 1H, 8″-H). – ^{13}C NMR ($CDCl_3$): $\delta = 9.71$ (4-CH_3), 15.91 (Ar-CH_3), 16.81 (7-CH_3), 16.83 (7-CH_3), 19.70 (C-3″), 27.79 (C-2″), 28.98 (C-5), 29.62 (C-4″), 30.71 (C-6), 33.64 (C-1″), 35.52 (C-2′), 54.10 (C-7), 54.79 (C-4), 55.28 (OCH_3), 64.17 (C-1′), 91.16 (C-1), 110.4 (C-5″), 124.2 (C-7″), 130.5 (C-8″), 131.1 (C-8a″), 135.2 (C-4a″), 155.9 (C-6″), 167.6 (C=O), 178.1 (C=O). – MS (70 eV), *m/z* (%): 400 (32) [M^+], 201 (13) [$C_{14}H_{17}O^+$], 175 (100) [$C_{12}H_{15}O^+$]. – $C_{24}H_{32}O_5$ (400.2): calcd. C 71.97, H 8.05; found C 71.87, H 7.97.

(R)-1-Cyclopropyl-6-methoxy-7-methyl-1,2,3,4-tetrahydronaphthalene (**11**): $ZnEt_2$ (2.3 ml, 2.3 mmol, 1 M solution in hexane) was added dropwise to a stirred solution of **8** (0.23 g, 1.16 mmol) in dry 1,2-dichloroethane under argon atmosphere at 0°C. To this solution $ClCH_2I$ (0.82 g, 4.65 mmol) was added over a period of 1 h via syringe. The reaction mixture was stirred for 30 min at 0°C and then for 5 h at room temp. A saturated NH_4Cl solution was added to the reaction mixture which was vigorously stirred for 10 min and then extracted with diethyl ether (2 × 15 ml). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography of the residue on silica gel (petroleum ether/diethyl ether, 180:1) afforded **11** (69 mg, 0.32 mmol, 27%) as a colorless oil. **11** contained 10% of the alkene **8** which could not be separated by column chromatography. $R_f = 0.28$, $[\alpha]_D^{20} = -80.3$ (c in 1 in $CHCl_3$). – ^1H NMR ($CDCl_3$): $\delta = 0.12–0.21$ (m, 1H, cyclopropyl-H), 0.40–0.50 (m, 2H, cyclopropyl-H), 0.64–0.72 (m, 1H, cyclopropyl-H), 0.77–0.89 (m, 1H, cyclopropyl-H), 1.63–1.72 (m, 2H, 3-H), 1.77–1.84 (m, 1H, 1-H), 1.85–1.95 (m, 2H, 2-H), 2.19 (s, 3H, CH_3), 2.70–2.76 (m, 2H, 4-H), 3.79 (s, 3H, OCH_3), 6.52 (s, 1H, 5-H), 7.27 (s, 1H, 8-H). – ^{13}C NMR ($CDCl_3$): $\delta = 2.63$ (C-2′), 6.60 (C-2′), 16.01

(CH_3), 18.12 (C-1'), 21.26 (C-3), 29.91 (C-2), 30.11 (C-4), 42.60 (C-1), 55.24 (OCH_3), 110.1 (C-5), 123.7 (C-7), 130.2 (C-8), 132.5 (C-8a), 135.0 (C-4a), 155.8 (C-6). – MS (70 eV), *m/z* (%): 216 (76) [M^+], 201 (85) [$M^+ - CH_3$], 188 [$M^+ - C_2H_4$], 175 (100) [$M^+ - C_3H_5$].

(S)-1-(6-Methoxy-7-methyl-1,2,3,4-tetrahydronaphthalene-1-yl)-ethanol (**14**): A solution of $Hg(OAc)_2$ (374 mg, 1.17 mmol) in water (2 ml) was treated dropwise with THF (3 ml) whereupon a yellow product precipitated. The mixture was cooled to 0°C and a solution of the alkene **8** (0.21 g, 1.04 mmol) in THF (2 ml) was introduced. After stirring for 20 h at room temp., the reaction mixture was treated with 3 N NaOH (3 ml) and sodium borohydride (26 mg, 0.69 mmol), then stirred for additional 2 h. The mixture was partitioned between brine and diethyl ether, the organic phase separated and the aqueous layer extracted with diethyl ether (2 × 15 ml). The combined organic phases were dried, concentrated in vacuo, and the residue was purified by chromatography on silica gel (petroleum ehter/diethyl ether, 7:1) to give the secondary alcohols **14a/b** (183 mg, 0.83 mmol, 80%, 91% based on conversion) as two single diastereomers in the ratio of 2:1. An additional purification by recrystallization from hexane gave the main diastereomer **14a** as colorless needles: R_f = 0.19 (petroleum ether/diethyl ether, 7:1), $[\alpha]_D^{20}$ = −30.7 (*c* = 1 in $CHCl_3$), m.p. 69°C (hexane). – IR (KBr): $\tilde{\nu}$ = 3352 cm^{-1} (OH), 2928, 2868, 2830 (C–H). – ^1H NMR ($CDCl_3$): δ = 1.20 (d, *J* = 6.5 Hz, 3H, 2-H), 1.54 (d, *J* = 3.5 Hz, 1H, OH), 1.77–1.86 (m, 4H, 2'-H, 3'-H), 2.17 (s, 3H, CH_3), 2.64–2.78 (m, 3H, 4'-H, 1'-H), 3.80 (s, 3H, OCH_3), 3.96 (dquint, *J* = 6.5, 3.5 Hz, 1H, 1-H), 6.56 (s, 1H, 5'-H), 6.98 (s, 1H, 8'-H). – ^{13}C NMR ($CDCl_3$): δ = 15.92 (CH_3), 19.96 (C-2), 20.07 (C-3'), 24.61 (C-2'), 29.52 (C-4'), 44.16 (C-1'), 55.22 (OCH_3), 70.83 (C-1), 110.6 (C-5'), 123.7 (C-7'), 128.6 (C-8a'), 131.5 (C-8'), 136.2 (C-4a'), 156.1 (C-6'). – MS (70 eV), *m/z* (%): 202 (9) [M^+], 175 (100) [$M^+ - C_2H_5O$]. – $C_{14}H_{20}O_2$ (220.3): calcd. C 76.33, H 9.15; found C 76.19, H 9.27.

An alternative route for the synthesis of the secondary alcohols **14a/b** employs a catalytic methodology according to the general procedure of Mukaiyama et al.[17]: $PhSiH_3$ (0.13 g, 1.18 mmol, 2.2 equiv.) was added to a solution of alkene **8** (110 mg, 0.54 mmol) in dry THF (10 ml) at room temp. $Co(acac)_2$ (9.7 mg, 0.03 mmol, 5 mol-%) was added and oxygen was then passed through the reaction mixture continuously for 8 h whereupon a dark green solution formed. The solution was diluted with diethyl ether and washed with water. The separated organic layer was then washed with brine, dried, and concentrated in vacuo. Purification of the residue by chromatography on silica gel using petroleum ether/diethyl ether (7:1) gave the diastereomers **14a/b** (51 mg, 0.23 mmol, 43%) in a ratio of 1:2, the main diastereomer being the minor component in the hydroxymercuration of **8**.

(S)-1-(6-Methoxy-7-methyl-1,2,3,4-tetrahydronaphthalene-1-yl)-ethyl p-Toluene-4-sulfonate (**15**): To a magnetically stirred solution of the secondary alcohol **14a** (133 mg, 0.60 mmol) in 6 ml of a mixture of pyridine and dichloromethane (1:2) *p*-toluenesulfonic acid chloride (288 mg, 1.51 mmol) and 4-dimethylaminopyridine (7 mg, 0.06 mmol) were added. After stirring for 44 h at 4°C, the reaction mixture was allowed to warm to room temp. and neutralized with 1 N HCl. The separated aqueous phase was extracted with dichloromethane (2 × 20 ml), the combined organic layers were washed with water and brine, dried with Na_2SO_4 and concentrated in vacuo. Flash filtration of the residue through silica gel provided **15** (184 mg, 0.49 mmol, 81%) as an inseparable mixture with about 15% of **14a** (20 mg, 0.09 mmol, 15%). This mixture was used in the following cuprate reaction without further purification.

(R)-7-Demethyl-2-methoxycalamenene[6a] (**1**): A mixture of CuI (620 mg, 3.26 mmol) in dry diethyl ether (3 ml) was treated dropwise with methyllithium (4.0 ml, 6.4 mmol of a 1.6 M solution in diethyl ether) with vigorous stirring at −8°C under argon until the yellow precipitate disappeared and a colorless solution appeared. The solution was cooled to −60°C and a solution of *p*-toluenesulfonate **15** (184 mg, 0.49 mmol) in 4 ml of dry diethyl ether was added dropwise via syringe. The mixture was stirred at −35°C to −23°C for 31 h. The reaction was quenched with saturated aqueous NH_4Cl/NH_3 (3:1) and the mixture was extracted with diethyl ether (3 × 10 ml). The combined organic phases were washed with brine, dried with Na_2SO_4 and concentrated in vacuo. Flash chromatography of the residue on silica gel gave an inseparable mixture of **1** and the alkene **16**. This mixture was dissolved in THF, then treated with 0.3 ml (3.2 mmol) of $BH_3 \cdot SMe_2$ and stirred for 18 h at room temp. The reaction was quenched by successive addition of water (0.6 ml), 3 N NaOH (0.6 ml) and 30% aqueous H_2O_2 (0.35 ml) at 0°C and the mixture was stirred for 20 h at room temp. It was then diluted with brine and extracted with diethyl ether (3 × 10 ml). The combined organic layers were washed with water and brine and the aqueous layers were again washed with diethyl ether (2 × 10 ml). The combined organic layers were dried and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel with petroleum ether/diethyl ether (150:1) followed by petroleum ether/EtOAc (7:1) gave the norsesquiterpene **1** (60 mg, 0.27 mmol, 56%) with 90% purity and *rac*-**14** (43 mg, 0.20 mmol, 40%). – R_f of **1** = 0.24 (petroleum ether/diethyl ether, 180:1), $[\alpha]_D^{20}$ = +51.0 (*c* = 0.9 in $CHCl_3$) {ref.[6a]: $[\alpha]_D^{20}$ = +53.9 (*c* = 1.3 in $CHCl_3$)}. – ^1H NMR ($CDCl_3$): δ = 0.72 (d, *J* = 7.0 Hz, 3H, CH_3), 1.00 (d, *J* = 7.0 Hz, 3H, CH_3), 1.50–1.61 (m, 2H, 8-H, 9-H), 1.71–1.95 (m, 2H, 8-H, 9-H), 2.17 (br s, 3H, CH_3), 2.22 (dqq, *J* = 7.0, 7.0, 7.0 Hz, 1H, 11-H), 2.61 (ddd, *J* = 6.0, 6.0, 7.0 Hz, 1H, 10-H), 2.64–2.72 (m, 2H, 7-H), 3.79 (s, 3H, OCH_3), 6.50 (s, 1H, 1-H), 6.96 (s, 1H, 4-H). – ^{13}C NMR ($CDCl_3$): δ = 16.03 (CH_3), 17.36 (CH_3), 21.30 (CH_3), 21.66 (C-8), 23.38 (C-9), 30.16 (C-7), 31.41 (C-11), 42.70 (C-10), 55.22 (OCH_3), 110.1 (C-1), 123.5 (C-3), 130.4 (C-4), 131.8 (C-5), 136.3 (C-6), 155.3 (C-2). – MS (70 eV), *m/z* (%): 218 (11) [M^+], 175 (100) [$M^+ - C_3H_7$]. – $C_{15}H_{22}O$: calcd. 218.1671; found 218.1670 (HRMS).

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