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Rearrangement Reactions of Aromadendrane Derivatives. The Synthesis of (+)-Maaliol, Starting from Natural (+)-Aromadendrene-IV[1]

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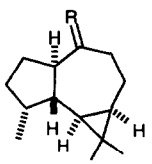
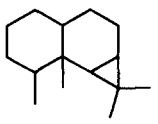
Abstract: *Starting from the hydroazulene α-ketol 6, which can easily be prepared from (+)-aromadendrene (1), two different routes to hydronaphthalene compounds with a maaliane skeleton have been developed, both proceeding in high overall yield. The first route leads to cis-fused maaliane derivatives; the second one offers access to trans-fused maaliane sesquiterpenes, as demonstrated in this paper in the synthesis of (+)-maaliol (5).*

(+)-Aromadendrene (1), structurally characterized by a dimethyl cyclopropane ring, fused to a hydroazulene ring system, is the main constituent in a commercially available distillation tail of the oil of *Eucalyptus globulus*[2]. Treatment of this distillation tail with ozone followed by crystallization of the crude ozonolysis product has proven to be a simple and efficient route to large quantities of pure (+)-apoaromadendrone (2)[3]. This chiral compound is a suitable starting material for the synthesis of sesquiterpenes with a hydroazulene skeleton, as demonstrated previously in the synthesis of (−)-kessane[4], and a number of mono- and dihydroxy-aromadendranes[5].



1: R = CH_2
2: R = O



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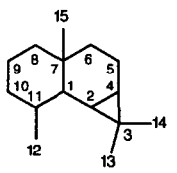

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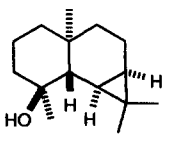

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We now wish to report on the rearrangement reactions of derivatives of **2** to hydronaphthalene ring systems with a fused dimethyl cyclopropane ring. Examples of such hydronaphthalene sesquiterpenes are the aristolanes (**3**) and maalianes (**4**). (+)-Maaliol (**5**), a representative of the maaliane sesquiterpenes, has been found in several plant species[6,7], and has been synthesized from (–)-epi-α-cyperone[8]. In this paper the synthesis of **5** starting from (+)-aromadendrene (**1**) is described.

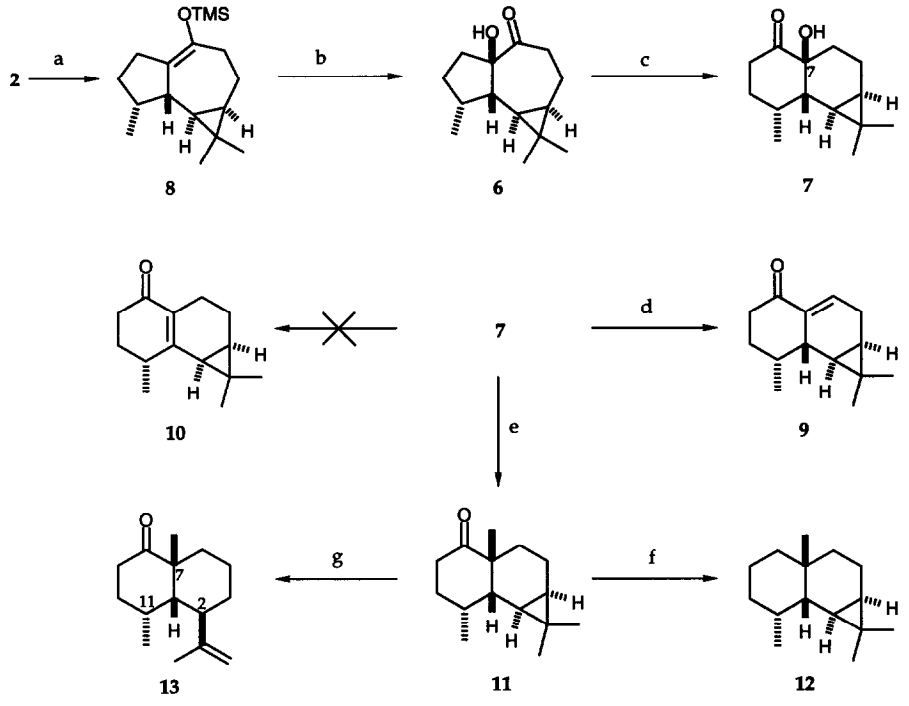
In the literature the rearrangement of a hydronaphthalene- to a hydrazulene skeleton is frequently seen[9]. Only a few examples are known of the reversed rearrangement reaction[10]. For aromadendrane derivatives the α-ketol rearrangement[11] of hydroazulenic α-ketol **6** to the hydronaphthalenic α-ketol **7** was investigated first.

This α-ketol **6** was easily prepared from **2** via its thermodynamically controlled silyl enol ether **8**[5] (Scheme I). Epoxidation with in situ generated dimethyldioxirane[12] and subsequent treatment with silica gel gave the α-ketol **6** in almost quantitative yield. The selective formation of the *cis*-fused ketol **6** must be the result of an attack from the sterically less hindered β side of the molecule[13]. Ketol **6** appeared to be unstable under gas chromatographic conditions and was partly converted into another product with, according to GC-MS analysis, the same molecular weight as **6**. This process could be imitated and improved by stirring a solution of **6** in EtOAc with neutral or basic Al_2O_3. In this way, the rearranged α-ketol **7** was obtained in 98% yield. The stereochemistry of the hydroxyl group at C7 in **7** was confirmed by a crystal structure determination[14].

Acid-catalyzed dehydration of **7** gave the unsaturated ketone **9** as the sole product. Unfortunately, its C1-C7 double bond isomer **10** was not formed at all. Several other attempts to synthesize this compound were unsuccesful as well. Compound **10** was thought to be very useful in the synthesis of aristolanes (**3**), because introduction of an angular methyl group via a conjugate addition should give the aristolane skeleton.

Replacement of the hydroxyl group of **7** by a methyl group via reaction with Li in NH_3, followed by addition of MeI[15], gave selectively the *cis*-fused ketone **11** in 72% yield. A Wolff-Kishner reduction gave the *cis*-fused maaliane **12** in 84% yield. The stereochemistry of the angular methyl group at C7 was difficult to establish. Due to overlap of the four methyl groups in the ^1H NMR spectrum of **11** and **12**, NOE measurements could not give a definite answer. After opening of the cyclopropane ring of **11** with concentrated aqueous HCl in refluxing EtOH, this problem could be solved. In the obtained product **13** the position of the isopropenyl group at C2 was determined with ^1H-^{13}C HETCOR and COSY experiments. NOE measurements on **13** showed the complete absence of a NOE between the angular methyl group at C7 and the methyl group at C11, indicating a β position for the angular methyl group in compound **13**. From this it can be concluded that in the compounds **11** and **12** the angular methyl group also has the β position. As a consequence, this route could not be used in the synthesis of the *trans*-fused (+)-maaliol (**5**).

Scheme I[a]

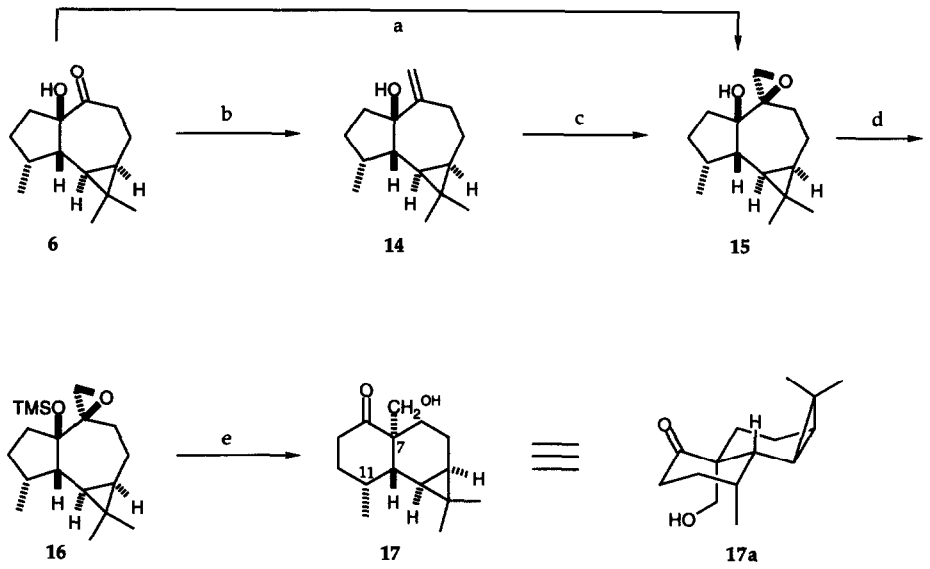


[a] (a) TMSCl, Et_3N, DMF, 130°C; (b) dimethyldioxirane; SiO_2; (c) Al_2O_3; (d);TsOH, benzene, Δ; (e) Li, NH_3, *t*BuOH; MeI; (f) N_2H_4, diethylene glycol, 100→200°C; (g) HCl, EtOH, Δ.

In a second approach the C15 carbon atom was introduced before rearrangement of the hydroazulene skeleton. This approach is based on a recently reported reaction in which silylated 2,3-epoxy alcohols were rearranged to β-hydroxy ketones under the influence of Lewis acids[16]. The application of this method to our system required the synthesis of the epoxide **16**. This compound possesses the proper stereochemistry for the synthesis of *trans*-fused maaliane derivatives and should give the rearranged β-hydroxy ketone **17** upon treatment with a Lewis acid (Scheme II).

The readily available α-ketol **6** was also the starting material in this approach. Treatment of **6** with trimethylsulfonium iodide[17] gave the epoxide **15** in a moderate yield (56%). A much better yield of **15** was obtained when **6** was subjected to a Wittig olefination followed by a Sharpless epoxidation. The Wittig reaction required the protection of the hydroxyl group of **6** as its trimethylsilylether. Using lithium free conditions, i.e. potassium disilazide as a base[18], a high yield of the olefination product was obtained. After deprotection of the hydroxyl group with TBAF, the olefinic alcohol **14** was isolated in 96% overall yield from **6**.

Scheme II[a]



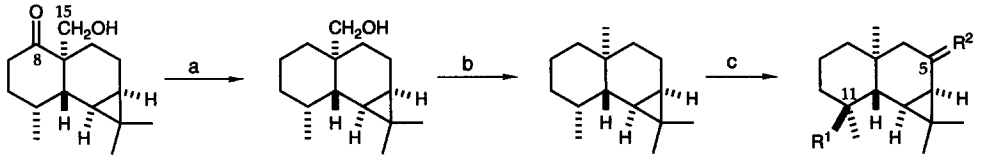
[a] (a) trimethylsulfonium iodide, KO*t*Bu, DMSO; (b) TMSCl, HMDS, pyridine; $Ph_3P{=}CH_2$; TBAF; (c) *t*BuOOH, $VO(Acac)_2$; (d) TMSCl, HMDS, pyridine; (e) $TiCl_4$, CH_2Cl_2, -78°C.

The compound **14** (8-hydroxy-alloaromadendrene) has been isolated from *Cassinia subtropica*[19] and has been synthesized previously in low yield via allylic oxidation[20] and microbial oxidation[21] of (–)-alloaromadendrene. Comparison of the spectral data of our synthetic **14** with those of the natural product shows that these compounds are identical, thus supporting our stereochemical assignments of the α-ketol **6** (vide supra). Sharpless epoxidation of **14** with *t*BuOOH/$VO(Acac)_2$[22] gave exclusively the β-epoxide **15**. Subsequent trimethylsilylation of the hydroxyl group gave **16** in 96% overall yield from **14**. Treatment of **16** with 1.1 equivalent of $TiCl_4$ in CH_2Cl_2 at -78°C afforded the rearranged product **17** in excellent yield (94%). NOE measurements on **17** showed a clear NOE between the angular hydroxymethyl group at C7 and the methyl group at C11, indicating the α-position of the angular hydroxymethyl group and a *trans*-fused ringsystem (formula **17a**).

Having established the *trans* ring junction in compound **17**, the next steps in our synthetic route towards (+)-maaliol (**5**) were the removal of the oxygen functions at C8 and C15, and the introduction of a β-hydroxyl group at C11. Our first attempt to remove the oxygen functions in **17** via reduction of the carbonyl group to a hydroxyl group, mesylation of both hydroxyl groups and finally reduction of the mesylates failed. More successful was a stepwise removal of the oxygen functions. Conversion of **17** into its tosylhydrazone followed by reduction with $NaBH_3CN$ in the presence of $ZnCl_2$[23] afforded the alcohol **18** in 69% yield (Scheme III).

Although the conversion of the primary neopentyl-type hydroxyl group of **18** into its sulfonate esters (mesylate, tosylate or isopropylsulfonate[24]) proceeded smoothly, the subsequent reduction with Super-Hydride® gave only (tosylate, mesylate) or mainly (isopropylsulfonate) O-S bond cleavage. However, removal of this hydroxyl group could be achieved via reduction of its phosphordiamidate with Li in $EtNH_2/tBuOH$[25]. In this way the *trans*-fused maaliane **19** was obtained in 64% yield, together with 18% of **18**. Comparison of the spectral data of the maalianes **12** and **19** showed that these compounds are not identical, thus giving further evidence for our stereochemical assignments.

Scheme III[a]



17 **18** **19**

5: R^1=OH; R^2=2H
20: R^1=H; R^2=O
21: R^1=OH; R^2=O

[a] (a) tosylhydrazine, $NaBH_3CN$, $ZnCl_2$, MeOH, Δ; (b) n-butyllithium, bis(dimethylamino)chlorophosphoramidate; Li, $EtNH_2$, $tBuOH$; (c) RuO_2, $NaIO_4$, 50°C.

To complete the synthesis of (+)-maaliol **5**, a β-hydroxyl group had to be introduced at C11 in compound **19**. It is known that tertiary C-atoms can be hydroxylated using a catalytic amount of ruthenium(IV)oxide (RuO_2) in combination with an excess of sodium periodate ($NaIO_4$)[5,26]. The application of this method to **19** afforded a mixture of three products, which was easily separated with column chromatography. GC-MS and NMR analysis of these products showed the formation of (+)-maaliol **5**, the ketone **20**, and the hydroxy ketone **21**. Thus, oxidation had taken place at C11 as well as at C5 next to the dimethyl cyclopropane ring[27]. When the oxidation reaction was allowed to continue long enough, the hydroxy ketone **21** was isolated as the sole product in 81% yield. Reductive removal of the carbonyl group would lead to (+)-maaliol, but this possibility has not been investigated further. Instead, the oxidation of **19** with $RuO_2/NaIO_4$ was performed with three equivalents of $NaIO_4$. In this way, an optimum yield (25%) of (+)-maaliol (**5**) was obtained, together with the starting material **19** (17%), the ketone **20** (28%), and the hydroxy ketone **21** (10%). Physical and spectroscopic data of our synthetic **5** are in agreement with those reported in the literature[7].

Starting from the readily available (+)-apoaromadendrone (**2**), two different routes to hydronaphthalene compounds with a maaliane skeleton have been developed, both in high overall yield. The first route leads to *cis*-fused maaliane derivatives; the other offers access to *trans*-fused maaliane sesquiterpenes, as demonstrated in this paper in the synthesis of (+)-maaliol (**5**).

EXPERIMENTAL SECTION

Melting points were determined on a Mettler FP80 HT. Optical rotations were obtained from $CHCl_3$ solutions on a Perkin-Elmer 241 polarimeter. ^1H and ^{13}C NMR spectra were recorded at 200 MHz and 50 MHz, respectively, on a Bruker AC-E 200 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0) as an internal standard in $CDCl_3$ as the solvent. Mass spectral data were determined on either an AEI MS 902 spectrometer or a Hewlett Packard 5970 B series MSD coupled with a Hewlett Packard 5890 A gas chromatograph with a DB-17 fused silica capillary column. Elemental analyses were determined on a Carlo Erba elemental analyzer 1106. GC analyses were carried out on a Varian Vista 6000 gas chromatograph with a flame ionization detector and a DB-17 fused silica capillary column, 30 m x 0.25 mm i.d., film thickness 0.25 μm. Peak areas were integrated electronically with a Spectra-Physics integrator SP 4290. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh). Solvents were dried and distilled fresh by common practice. For all dry reactions, flasks were dried at 150°C and flushed with dry nitrogen just before use, and reactions were carried out under an atmosphere of dry nitrogen. Product solutions were dried over anhydrous $MgSO_4$, unless otherwise noted, prior to evaporation of the solvent under reduced pressure by using a rotary evaporator.

(–)-8-Hydroxy-alloaromadendrone (6). To a mixture of 400 mL of CH_2Cl_2, 400 mL of acetone, 400 mL of water, 1.0 g of 18-Crown-6, and 45 g of $NaHCO_3$ was added 300 mL of 0.29 M Oxone (87 mmol of $KHSO_5$) in water at 0°C. The mixture was stirred vigorously and 16.68 g (60 mmol) of **8**[5] was added at 0°C. Stirring was continued for 1 h, after which time 250 mL of saturated aqueous $NaHCO_3$ was added. The aqueous layer was extracted with three 250-mL portions of CH_2Cl_2. The combined organic layers were washed with 400 mL of 10% aqueous $Na_2S_2O_3$ and 400 mL of saturated aqueous $NaHCO_3$, and then dried. After evaporation of the solvent under reduced pressure, the residue was taken up in 200 mL of EtOAc and 50 g of silica gel was added. The mixture was stirred at room temperature for 18 h, filtered, and then the solvent was evaporated under reduced pressure to yield 13.19 g (99%) of α-ketol **6**: mp 95°C (from methanol); $[\alpha]_D$ -76.7° (c 2.1); ^1H NMR δ 0.21 (dd, J = 9.1, 10.6 Hz, 1H), 0.72 (ddd, J = 5.2, 9.1, 12.0 Hz, 1H), 0.94 (d, J = 6.6 Hz, 3H), 0.96 (s, 3H), 0.99 (s, 3H), 1.24-1.51 (m, 3H), 1.68-2.01 (m, 3H), 2.36-2.63 (m, 3H), 2.95 (br s, 1H), 3.01 (ddd, J = 3.7, 5.1, 13.6 Hz, 1H); ^{13}C NMR δ 15.04 (q), 15.44 (q), 18.82 (s), 19.04 (t), 22.97(d), 26.93 (d), 27.96 (q), 30.50 (t), 35.93 (d), 35.93 (t) , 40.32 (t), 48.99 (d), 90.30 (s), 212.42 (s); mass spectrum, *m/e* (relative intensity) 222 (M^+, 46), 204 (32), 179 (39), 165 (85), 161 (100), 137 (79), 123 (62), 109 (71), 95 (58); calcd for $C_{14}H_{22}O_2$ (M^+) *m/e* 222.1620, found *m/e* 222.1622. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.62; H, 9.97. Found: C, 75.33; H, 9.92.

(+)-[1aR-(1aα,3aβ,7α,7aβ,7bα)]-Decahydro-3a-hydroxy-1,1,7-trimethyl-1*H*-cyclopropa[a]naphthalen-4-one (7). To a solution of 7.70 g (35 mmol) of **6** in 100 mL of EtOAc was added 16 g of Al_2O_3. The resulting mixture was stirred at room temperature for 18 h, and then filtered. After evaporation of the solvent under reduced pressure, 7.56 g (98%) of **7** was obtained as a white solid: mp 104-105°C (from petroleum ether (bp 80-100°C)); $[\alpha]_D$ +9.9° (c 0.81); ^1H NMR δ 0.28 (dd, J = 6.1, 9.2 Hz, 1H), 0.51-0.62 (m, 1H), 0.92 (s, 3H), 0.94 (d, J = 7.8 Hz, 3H), 0.99 (s, 3H), 0.99-1.14 (m, 1H), 1.34-1.54 (m, 2H), 1.67-2.13 (m, 4H), 2.10 (br s, 1H), 2.26 (ddd, J = 3.6, 5.7, 14.3 Hz, 1H), 2.44-2.66 (m, 1H), 2.78 (ddd, J = 8.0, 10.8, 14.2 Hz, 1H); ^{13}C NMR (C_6D_6) δ 15.03 (q), 16.92 (s), 16.92 (t), 17.53 (q), 18.95 (d), 19.99 (d), 27.99 (d), 27.99 (q), 29.44 (t), 32.12 (t), 36.19 (t), 44.59 (d), 75.55 (s), 210.73

(s); mass spectrum, *m/e* (relative intensity) 222 (M^+, 62), 204 (33), 179 (43), 165 (75), 161 (100), 137 (84), 123 (66), 109 (71), 95 (58); calcd for $C_{14}H_{22}O_2$ (M^+) *m/e* 222.1620, found *m/e* 222.1623. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.62; H, 9.97. Found: C, 75.47; H, 9.92.

(–)-[1aR-(1aα,7α,7aβ,7bα)]-1a,2,4,5,6,7,7a,7b-Octahydro-1,1,7-trimethyl-1*H*-cyclopropa[a]naphthalen-4-one (9). To a solution of 1.10 g (5.0 mmol) of **7** in 75 mL of benzene was added 40 mg of *p*-toluenesulfonic acid. The mixture was heated at reflux for 2 h, allowed to come to room temperature, and then diluted with 40 mL of petroleum ether (bp 40-60°C). The organic layer was washed with two 50-mL portions of water, dried, and then evaporated under reduced pressure. The resulting residue was flash chromatographed [17:1 petroleum ether (bp 40-60°C)/EtOAc] to give 866 mg (85%) of **9**: $[\alpha]_D$ -71° (c 2.07); ^1H NMR δ 0.44 (d, J = 8.9 Hz, 1H), 0.65 (s, 3H), 0.67 (br t, J = 8.9 Hz, 1H), 0.90 (d, J = 6.9 Hz, 3H), 0.99 (s, 3H), 1.68-1.82 (m, 1H), 1.94-2.29 (m, 3H), 2.32-2.59 (m, 4H), 6.52 (dd, J = 4.1, 6.8 Hz, 1H); ^{13}C NMR δ 12.51 (q), 13.56 (q), 16.48 (s), 16.48 (d), 21.03 (t), 22.77 (d), 27.93 (q), 29.26 (t), 33.35 (d), 35.14 (d), 35.22 (t), 134.33 (d), 136.44 (s), 201.58 (s); mass spectrum, *m/e* (relative intensity) 204 (M^+, 17), 189 (8), 161 (46), 147 (25), 133 (25), 119 (22), 105 (100), 91 (68), 77 (43), 41 (63); calcd for $C_{14}H_{20}O$ (M^+) *m/e* 204.1514, found *m/e* 204.1513.

(+)-*cis*-Maali-8-one (11). To a mixture containing 630 mg (90 mmol) of lithium in 200 mL of dry NH_3 was added dropwise a solution of 4.44 g (20 mmol) of **7** and 1.88 mL (20 mmol) of dry *t*BuOH in 60 mL of dry ether over 5 min at -78°C. After stirring for an additional 5 min, 4.4 mL (70 mmol) MeI was added. The mixture was stirred at -78°C for 2.5 h, solid ammonium chloride was added, and NH_3 was evaporated overnight at room temperature. Then, 150 mL of water was added, and the aqueous layer was extracted with four 100-mL portions of ether. The combined organic layers were washed with 150 mL of brine, dried, and then evaporated under reduced pressure. The resulting residue was flash chromatographed [3:1 to 2:1 petroleum ether (bp 40-60°C)/CH_2Cl_2] to give 3.18 g (72%) of **11**: mp 63-64°C (from methanol); $[\alpha]_D$ +42.5° (c 1.7); ^1H NMR δ 0.25 (dd, J = 5.7, 9.3 Hz, 1H), 0.43-0.55 (m, 1H), 0.62-0.86 (m, 1H), 0.86 (s, 3H), 0.94 (s, 3H), 0.95 (d, J = 6.1 Hz, 3H), 1.13 (s, 3H), 1.20-1.37 (m, 2H), 1.68-2.04 (m, 4H), 2.16 (dt, J = 3.7, 15.4 Hz, 1H), 2.44-2.64 (m, 2H); ^{13}C NMR δ 15.13 (q), 15.45 (t), 16.48 (s), 18.25 (q), 19.38 (d), 20.04 (d), 26.53 (q), 28.58 (q), 28.73 (d), 29.51 (t), 32.22 (t), 37.15 (t), 44.36 (d), 46.50 (s), 216.05 (s); mass spectrum, *m/e* (relative intensity) 220 (M^+, 16), 205 (11), 177 (13), 159 (18), 151 (29), 125 (68), 107 (38), 93 (41), 82 (57), 41 (100); calcd for $C_{15}H_{24}O$ (M^+) *m/e* 220.1827, found *m/e* 220.1823. Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.97. Found: C, 81.49; H, 11.14.

(+)-*cis*-Maaliane (12). A solution of 730 mg (3.3 mmol) of **11**, 4.2 g (75 mmol) of KOH and 2.69 mL (55 mmol) of hydrazine monohydrate in 25 mL of diethylene glycol was stirred at 100-110°C for 2.5 h. Water and hydrazine were then distilled off, and the mixture was stirred at 200°C for 4.5 h. After cooling, 100 mL of ice-water was added and the aqueous mixture extracted with three 75-mL portions of ether. The combined organic layers were washed with 75 mL of 0.4 N aqueous HCl solution, 75 mL of saturated aqueous $NaHCO_3$, 75 mL of brine, dried, and then evaporated under reduced pressure. The resulting product was flash chromatographed (n-pentane) to give 571 mg (84%) of **12**: $[\alpha]_D$ +83.1° (c 1.8); ^1H NMR δ 0.27 (dd, J = 5.0, 9.4 Hz, 1H), 0.52 (ddd, J = 1.7, 7.7, 9.4 Hz, 1H), 0.84 (d, J = 6.8 Hz, 3H), 0.87 (s, 3H), 0.89 (s, 3H), 0.98 (s, 3H), 0.91-1.65 (m, 10H), 1.65-1.87 (m, 1H), 1.90-2.12 (m, 1H); ^{13}C NMR δ 15.46 (t), 16.39 (s), 19.29 (q), 19.53 (d), 19.64 (d), 21.69 (t), 26.01 (q), 29.03 (t), 29.03 (2·q), 29.59 (d), 30.52 (t), 31.42 (s), 37.78 (t), 40.63 (d); mass spectrum, *m/e* (relative intensity) 206 (M^+, 12), 191 (8), 163 (29), 135 (14), 123 (18), 109 (76), 95 (32), 93 (32), 81 (100); calcd for $C_{15}H_{26}$ (M^+) *m/e* 206.2034, found *m/e* 206.2034.

(+)-[1R-(1β,4aβ,8α,8aβ)]-Decahydro-1,4a-dimethyl-8-(1-methylethenyl)-4(2*H*)-naphthalenone (13). To a solution of 179 mg (0.80 mmol) of **11** in 4.5 mL of ethanol was added 0.85 mL of concentrated aqueous HCl solution. The mixture was heated at reflux for 45 min, allowed to come to room temperature, and then diluted with 20 mL of ice-water. The aqueous solution was extracted with four 15-mL portions of CH_2Cl_2. The combined organic layers were washed with 20 mL of saturated aqueous $NaHCO_3$ solution followed by 20 mL of brine, dried, and then evaporated under reduced pressure. The resulting residue was flash chromatographed [20:1 petroleum ether (bp 40-60°C)/EtOAc] to give 120 mg (67%) of pure **13**: mp 65-65.5°C (from methanol); $[\alpha]_D$ +114° (c 0.47); ^1H NMR δ 0.79-0.96 (m, 1H), 1.06 (d, J = 7.3 Hz, 3H), 1.63 (s, 3H), 1.23-2.21 (m, 9H), 2.25 (ddd, J = 1.6, 5.7, 16.5 Hz, 1H), 2.41-2.68 (m, 2H), 4.58 (br s, 1H), 4.68 (br s, 1H); ^{13}C NMR δ 18.44 (q), 19.73 (q), 22.30 (t), 27.49 (t), 28.21 (q), 30.52 (d), 34.60 (t), 35.75 (t), 37.58 (t), 45.56 (d), 50.47 (s), 50.85 (d), 111.00 (t), 150.27 (s), 215.41 (s); mass spectrum, *m/e* (relative intensity) 220 (M^+, 11), 205 (4), 177 (5), 149 (11), 135 (11), 125 (100), 107 (29), 93 (34), 67 (39), 41 (72); calcd for $C_{15}H_{24}O$ (M^+) *m/e* 220.1827, found *m/e* 220.1827. Anal. Calcd for $C_{14}H_{22}O_2$: C, 81.76; H, 10.98. Found: C, 81.46; H, 10.95.

(–)-8-Hydroxy-alloaromadendrene (14). To a stirred solution of 5.55 g (25 mmol) of **6** in 80 ml of dry pyridine was added 18.7 mL of hexamethyldisilazane (HMDS) and 9.4 mL of TMSCl. The reaction mixture was stirred at room temperature for 15 min, and then concentrated under reduced pressure. The resulting residue was flash chromatographed [40:1 petroleum ether (bp 40-60°C)/EtOAc] to give 7.29 g (100%) of the trimethylsilylether of **6**.[^1H NMR δ 0.04 (s, 9H), 0.15 (dd, J = 8.9, 11.5 Hz, 1H), 0.66 (ddd, J = 5.4, 8.9, 11.4 Hz, 1H), 0.86 (d, J = 7.0 Hz, 3H), 0.92 (s, 3H), 0.97 (s, 3H), 1.15-1.93 (m, 6H), 2.20-2.43 (m, 2H), 2.61 (ddd, J = 3.2, 8.2, 13.2 Hz, 1H), 3.10 (ddd, J = 2.4, 6.8, 13.2 Hz, 1H); ^{13}C NMR δ 1.49 (3·q), 14.83 (q), 15.22 (q), 18.73 (s), 18.99 (t), 23.36 (d), 26.13 (d), 27.92 (q), 32.32 (t), 34.03 (t), 35.74 (d), 40.52 (t), 51.70 (d), 93.11 (s), 211.80 (s); mass spectrum, *m/e* (relative intensity) 294 (M^+, 38), 251 (33), 237 (81), 209 (8), 169 (10), 155 (19), 119 (12), 105 (19), 73 (100), 41 (31)] as a colourless oil which was used immediately for the next reaction:

To a suspension of 8.75 g (24.5 mmol) of methyltriphenylphosphonium bromide in 80 mL of dry THF was added dropwise 37 mL of 0.66 M (26 mmol) potassium hexamethyldisilazide in toluene at -78°C. Then a solution of 3.86 g (13.2 mmol) of the trimethylsilylether of **6** in 45 mL of dry THF and 5 mL of dry N,N'-dimethylpropyleneurea (DMPU) was added slowly at -78°C. The reaction mixture was allowed to warm to room temperature over a 3-h period and poured into 200 mL of ice water. The aqueous solution was extracted with four 80-mL portions of petroleum ether (bp 40-60°C). The combined organic layers were washed with 100mL of brine, dried, and then evaporated under reduced pressure. The remaining residue was flash chromatographed [20:1 petroleum ether (bp 40-60°C)/EtOAc] to give 3.205 g (83%) of the trimethylsilylether of **14** [^1H NMR δ 0.04 (s, 9H), 0.08 (dd, J = 9.1, 11.8 Hz, 1H), 0.64 (br dt, J = 6.8, 9.6 Hz, 1H), 0.90 (d, J = 7.1 Hz, 3H), 0.93 (s, 3H), 0.96 (s, 3H), 1.16-2.00 (m, 6H), 2.10-2.30 (m, 2H), 2.35-2.60 (m, 2H), 4.83 (br s, 1H), 4.91 (d, J = 1.7 Hz, 1H); ^{13}C NMR δ 1.73 (3·q), 15.75 (q), 16.41 (q), 17.56 (s), 20.97 (t), 23.03 (d), 25.05 (d), 28.36 (q), 30.03 (t), 32.09 (t), 33.57 (d), 34.89 (t), 50.87 (d), 90.65 (s), 111.73 (t), 152.41 (s); mass spectrum, *m/e* (relative intensity) 292 (M^+, 6), 277 (16), 251 (8), 223 (33), 202 (8), 187 (10), 159 (17), 117 (14), 91 (24), 73 (100)] and 0.379 g (13%) of **14**. The trimethylsilylether of **14** was dissolved in 35 mL of THF and 20 mL of 1.1 M TBAF in THF was added. After stirring at room temperature for 10 min, 75 mL of water and 60 mL of petroleum ether (bp 40-60°C) were added. The two-phase mixture was separated, and the aqueous layer was extracted with two 60-mL portions of petroleum ether (bp 40-60°C). The combined organic layers were washed with 75 mL of brine, dried, and then evaporated under reduced pressure. The resulting residue was flash chromatographed [10:1 petroleum ether (bp 40-60°C)/EtOAc] to give another 2.410 g (total yield from **6**: 96%) of **14**: mp 55.5°C (from CH_3CN); $[\alpha]_D$ -153° (c 1.3)

(lit.[19]:-105°); ^{1}H NMR data were identical to those reported in the literature[18-20]; ^{13}C NMR δ 15.58 (q), 16.33 (q), 17.81 (s), 20.94 (t), 22.99 (d), 25.05 (d), 28.28 (q), 30.27 (t), 31.75 (t), 33.97 (d), 36.17 (t), 48.71 (d), 88.23 (s), 111.41 (t), 152.61 (s); the mass spectrum was consistent with that reported in the literature[18]. Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.97. Found: C, 81.44; H, 11.02.

(–)-8-Hydroxy-alloaromadendrene-β-epoxide (15). To a solution of 2.22 g (10 mmol) of **6** in 20 mL of dry DMSO was added subsequently 3.06 g (15 mmol) of trimethylsulfonium iodide and 1.40 g of KO*t*Bu. The reaction mixture was stirred at room temperature for 1.5 h, poured into 100mL of ice-water,and extracted with four 50-mL portions of CH_2Cl_2. The combined organic layers were washed with 75 mL of water, dried, and then evaporated under reduced pressure. The resulting residue was flash chromatographed [8:1 to 5:1 petroleum ether (bp 40-60°C)/EtOAc] to give 1.336 g (56%) of **15**: mp 104-105°C (from petroleum ether (bp 80-100°C)); $[\alpha]_D$ -57.7° (c 0.8); ^{1}H NMR δ 0.20 (dd, J = 9.1, 11.5 Hz, 1H), 0.61 (ddd, J = 5.5, 9.1, 11.5 Hz, 1H), 0.91 (d, J = 6.8 Hz, 3H), 0.97 (s, 3H), 1.00 (s, 3H), 1.07-1.46 (m, 4H), 1.67-1.87 (m, 4H), 1.88 (s, 1H), 2.33-2.57 (m, 2H), 2.65 (d, J = 4.4 Hz, 1H), 2.8 (dd, J = 2.1, 4.4 Hz, 1H); ^{13}C NMR δ 15.08 (2 x q), 18.92 (s), 19.28 (t), 24.10 (d), 25.31 (d), 28.28 (q), 31.98 (t), 32.20 (t), 35.65 (d), 35.65 (t), 49.26 (d), 54.27 (t), 61.47 (s), 87.00 (s); mass spectrum, *m/e* (relative intensity) 236 (M^+, 6), 218 (13), 205 (43), 193 (28), 175 (55), 163 (100), 121 (69) 107 (64), 93 (71); calcd for $C_{15}H_{24}O_2$ (M^+) *m/e* 236.1776, found *m/e* 236.1778. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.23. Found: C, 76.27; H, 10.39.

To a solution of 2.20 g (10.0 mmol) of **14** in 80 mL of benzene was added 150 mg of $VO(Acac)_2$ and 5.0 mL of 3.0 M (15 mmol) *t*BuOOH in isooctane. The reaction mixture was stirred for 2.5 h at room temperature and 100 mL of 10% aqueous $Na_2S_2O_3$ was added. The two-phase mixture was separated, and the aqueous layer was extracted with two 50-mL portions of EtOAc. The combined organic layers were washed with 60 mL of brine, dried, and then evaporated under reduced pressure to give 2.32 g (98%) of crude **15**.

Trimethylsilylether 16. To a stirred solution of 2.32 g of crude **15** in 20 mL of dry pyridine was added 3.8 mL of hexamethyldisilazane (HMDS) and 1.9 mL of TMSCl. The reaction mixture was stirred at room temperature for 20 min, and then concentrated under reduced pressure. The resulting residue was flash chromatographed [50:1 petroleum ether (bp 40-60°C)/EtOAc] to give 2.97 g (96% from **14**) of pure **16**: ^{1}H NMR δ 0.10 (s,9H), 0.16 (dd, J = 9.0, 11.6 Hz, 1H), 0.57 (ddd, J = 4.6, 9.0, 12.1 Hz, 1H), 0.88 (d, J = 6.8 Hz, 3H), 0.96 (s, 3H), 0.98 (s, 3H), 1.01-1.54 (m, 4H), 1.61-1.83 (m, 4H), 2.15-2.40 (m, 1H), 2.47-2.63 (m, 3H); ^{13}C NMR δ 2.11 (3·q), 14.84 (q), 15.03 (q), 18.74 (s), 19.54 (t), 24.70 (d), 25.66 (d), 28.31 (q), 33.11 (t), 33.40 (t), 34.85 (t), 35.73 (d), 52.42 (d), 53.23 (t), 60.73 (s), 89.94 (s); mass spectrum, *m/e* (relative intensity) 308 (M^+, 6), 278 (23), 235 (100), 209 (39), 193 (27), 183 (24), 157 (16), 131 (16), 73 (73); calcd for $C_{15}H_{32}O_2Si$ (M^+) *m/e* 308.2171, found *m/e* 308.2171.

(–)-15-Hydroxy-*trans*-maali-9-one (17). To a solution of 2.002 g (6.5 mmol) of **16** in 28 mL of dry CH_2Cl_2 was added 7.15 mL of 1.0 M (7.15 mmol) $TiCl_4$ in CH_2Cl_2 at -78°C. The reaction mixture was stirred at -78°C for 15 min, and then 40 mL of 1N aqueous HCl solution was added. After dilution with 40 mL of water, the two-phase mixture was separated, and the aqueous layer was extracted with three 40-mL portions of CH_2Cl_2. The combined organic layers were washed with 50 mL of brine, dried, and then evaporated under reduced pressure. The resulting residue was flash chromatographed [2:1 petroleum ether (bp 40-60°C)/EtOAc] to give 1.448 g (94%) of **17**: mp 137-138°C (from petroleum ether (bp 80-100°C)); $[\alpha]_D$ -75.1° (c 0.7); ^{1}H NMR δ 0.52-0.86 (m, 2H), 0.90 (s, 3H), 0.99 (s, 3H), 1.17 (d, J = 7.3 Hz, 3H), 1.47-1.67 (m, 3H), 1.72-2.13 (m, 6H), 2.22 (dt, J = 4.0, 14.5 Hz, 1H), 2.78 (ddd, J = 6.4, 12.5, 14.5 Hz, 1H), 3.89 (br d, J = 11.4 Hz, 1H), 4.07 (br d, J = 11.4 Hz, 1H); ^{13}C NMR δ 14.88 (q), 15.26 (t), 15.37 (q), 18.35 (s), 19.39 (d),

21.67 (d), 25.30 (t), 28.96 (q), 31.08 (d), 32.64 (t), 34.38 (t), 42.74 (d), 53.69 (s), 62.85 (t), 215.65 (s); mass spectrum, *m/e* (relative intensity) 236 (M^+, 4), 220 (13), 206 (42), 189 (40), 163 (75), 147 (51), 145 (51), 137 (45), 111 (56), 83 (100); calcd for $C_{15}H_{24}O_2$ (M^+) *m/e* 236.1776, found *m/e* 236.1776. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.33; H, 10.41.

(–)-15-Hydroxy-*trans*-maaliane (18). To a solution of 1.18 g (5.0 mmol) of **17** in 5 mL of MeOH was added 1.07 g (5.75 mmol) of tosylhydrazine. The mixture was heated at reflux for 2h, and 15 mL of MeOH was added followed by a solution of 419 mg (6.67 mmol) of $NaBH_3CN$ and 467 mg (3.33 mmol) of $ZnCl_2$ in 13 mL of MeOH. After stirring at reflux temperature for 3h, 100 mL of 0.1N aqueous NaOH solution was added. The resulting mixture was filtered over Celite, and extracted with four 60-mL portions of EtOAc. The combined organic layers were washed with 75 mL of brine, dried, and then evaporated under reduced pressure. The resulting residue was flash chromatographed [10:1 petroleum ether (bp 40-60°C)/EtOAc] to give 767 mg (69%) of **18**: mp 127-128°C (from n-heptane); $[\alpha]_D$ -21° (c 1.2); ^1H NMR d 0.40 (dd, J = 6.5, 9.1 Hz, 1H), 0.51 (dt, J = 7.2, 13.2 Hz, 1H), 0.61 (t, J = 8.4 Hz, 1H), 0.64-0.83 (m, 1H), 0.94 (d, J = 7.4 Hz, 3H), 0.95 (s, 3H), 0.99 (s, 3H), 1.05 (br s, 1H), 1.17 (dd, J = 5.2, 6.4 Hz, 1H), 1.30-1.92 (m, 9H), 3.70 (br d, J = 11.0 Hz, 1H), 3.83 (br d, J = 11.0 Hz, 1H); ^{13}C NMR δ 15.10 (q), 15.60 (q), 16.00 (t), 16.94 (t), 18.03 (s), 19.76 (d), 22.04 (d), 29.31 (q), 32.10 (d), 33.54 (t), 33.62 (t), 34.06 (t), 37.20 (s), 41.93 (d), 62.09 (t); mass spectrum, *m/e* (relative intensity) 222 (M^+, 1), 204 (2), 191 (81), 161 (10), 135 (79), 121 (20), 109 (56), 91 (49), 67 (59), 41 (100); calcd for $C_{15}H_{26}O$ (M^+) *m/e* 222.1983, found *m/e* 222.1983. Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.72; H, 11.84.

(–)-*trans*-Maaliane (19). To a solution of 666 mg (3.0 mmol) of **18** in 20 mL of dry THF and 5 mL of TMEDA was added dropwise a solution of 3.0 mL of 1.5 M n-butyllithium in hexane at 0°C. The mixture was stirred for 30 min at 0°C, and 2 h at room temperature. The resulting solution was then cooled to 0°C, 3 mL (20 mmol) of bis(dimethylamino)chlorophosphoramidate added, and the solution allowed to warm to room temperature overnight. Then 40 mL of a saturated aqueous $NaHCO_3$ solution was added at 0°C, and the mixture was extracted with four 30-mL portions of EtOAc. The combined organic layers were washed with 40 mL of brine, dried on K_2CO_3, and then evaporated under reduced pressure. The resulting residue was used immediately for the next reaction.

To a mixture containing 300 mg (43 mmol) of lithium in 40 mL of dry ethylamine was added dropwise a solution of the crude phosphordiamidate in 20 mL of dry THF and 0.75 mL of dry *tert*-butyl alcohol over 30 min under argon atmosphere. After stirring for an additional 10 min, sufficient solid ammonium chloride was added to destroy the excess lithium. Then, 50 mL of water was added, and the aqueous layer was extracted with four 30-mL portions of pentane. The combined organic layers were washed with 40 mL of 1N aqueous HCl solution, 40 mL of brine, dried on K_2CO_3, and then carefully concentrated under atmospheric pressure. The resulting residue was flash chromatographed [pentane to 10:1 petroleum ether (bp 40-60°C)/EtOAc] to give 120 mg (18%) of **18** and 397 mg (64%) of **19** as a colourless oil: $[\alpha]_D$ -11.1° (c 0.57); ^1H NMR δ 0.40- 1.03 (m, 4H), 0.88 (s, 3H), 0.91 (s, 3H), 0.99 (s, 3H, 1.01 (d, J = 8.7 Hz, 3H), 1.22-1.93 (m, 10H); ^{13}C NMR δ 14.94 (q), 15.17 (q), 15.76 (t), 17.02 (s), 17.27 (t), 19.12 (q), 19.74 (d), 22.68 (d), 29.42 (q), 31.82 (s), 32.61 (d), 33.95 (t), 40.34 (t), 41.18 (t), 41.27 (d); mass spectrum, *m/e* (relative intensity) 206 (M^+, 8), 191 (41), 163 (21), 150 (28), 135 (34), 123 (31), 109 (70), 82 (90), 81 (100), 41 (99); calcd for $C_{15}H_{26}$ (M^+) *m/e* 206.2034, found *m/e* 206.2034.

(+)-Maaliol (5). To a bottle containing 4 mL of CCl_4, 4 mL of CH_3CN, 6 mL of H_2O, and 600 mg (2.8 mmol) of $NaIO_4$ was added 192 mg (0.93 mmol) of **19** and 10 mg of $RuO_2 \cdot xH_2O$. The bottle was closed air-tight and rotated around its axis in a waterbath of 50°C until the colour of the mixture had turned from yellow to black (5 h). The reaction mixture was filtered through

celite, and the filter cake was washed with 25 mL of H_2O and 20 mL of CH_2Cl_2. The combined filtrates were separated, and the aqueous layer was extracted with three 15-mL portions of CH_2Cl_2. The combined organic layers were washed with 20 mL of aqueous 10% $Na_2S_2O_3$ and 20 mL of brine, dried, and then evaporated under reduced pressure. The resulting residue was flash chromatographed [20:1 to 3:1 petroleum ether (bp 40-60°C)/EtOAc] to give, in order of elution, 33 mg (17%) of **19**, 58 mg (28%) of **20**, 52 mg (25%) of **5**, and 23 mg of **21**.

5: mp 101.5-102.5°C (from n-heptane) (lit.[7]: 103°C); $[\alpha]_D$ +35.1° (c 0.57), (lit.[7]: +32.6°), +20° (c 0.33 in ethanol) (lit.[8]: +18.4 in ethanol); ^1H NMR δ 0.47 (dd, J = 6.1, 9.2 Hz, 1H), 0.55-0.82 (m, 2H), 0.83 (s, 3H), 0.91 (s, 3H), 1.01 (s, 3H), 1.22 (s, 3H), 0.85-1.61 (m, 9H), 1.66-1.88 (m, 2H); ^{13}C NMR δ 15.29 (q), 15.29 (t), 17.31 (s), 18.55 (q), 18.96 (d), 19.58 (d), 19.93 (t), 22.81 (q), 28.94 (q), 32.81 (s), 39.41 (t), 41.04 (t), 42.50 (t), 49.42 (d), 72.58 (s); the mass spectrum was consistent with that reported in the literature[7]. Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.89; H, 11.82.

20: $[\alpha]_D$ +220° (c 0.73); ^1H NMR δ 0.95 (s, 3H), 1.06 (d, J = 7.4 Hz, 3H), 1.14 (s, 3H), 1.17 (s, 3H), 1.13-1.74 (m, 10H), 1.88 (dd, J = 1.2, 16.5 Hz, 1H), 1.96-2.14 (m, 1H); ^{13}C NMR δ 14.90 (q), 16.24 (t), 16.49 (q), 20.66 (q), 28.63 (s), 29.45 (q), 31.65 (d), 32.57 (d), 33.20 (t), 36.32 (d), 39.67 (s), 39.68 (t), 41.71 (d), 58.26 (t), 209.64 (s); mass spectrum, *m/e* (relative intensity) 220 (M^+, 20), 205 (12), 177 (51) 161 (31), 149 (36), 121 (33), 109 (52), 107 (64), 96 (66), 81 (53), 67 (54), 41 (100); calcd for $C_{15}H_{24}O$ (M^+) *m/e* 220.1827, found *m/e* 220.1827.

21: mp 130-130.5°C (from n-heptane); $[\alpha]_D$ +17° (c 1.1); ^1H NMR δ 0.93 (s, 3H), 1.15 (s, 3H), 1.19 (br t, J = 10.8 Hz, 1H), 1.20 (s, 3H), 1.30 (s, 3H), 1.32-1.68 (m, 8H), 1.74 (d, J = 16.5 Hz, 1H), 1.82-1.93 (m, 1H), 1.99 (dd, J = 1.5, 16.5 Hz, 1H) ; ^{13}C NMR δ 16.59 (q), 19.56 (q), 19.92 (t), 22.89 (q), 28.86 (s), 29.03 (q), 30.07 (d), 35.68 (d), 38.82 (t), 40.64 (s), 42.58 (t), 49.59 (d), 57.90 (t), 72.53 (s), 208.93 (s); mass spectrum, *m/e* (relative intensity) 236 (M^+, 2), 218 (68), 203 (33), 178 (50), 161 (65), 121 (46), 107 (66), 85 (63), 83 (100), 59 (89); calcd for $C_{15}H_{24}O_2$ (M^+) *m/e* 236.1776, found *m/e* 236.1776. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 75.96; H, 10.54.

In a similar experiment 171 mg (0.83 mmol) of **19** was treated with 2.14 g (10 mmol) of $NaIO_4$ for 96 h to yield, after workup and flash chromatography, 159 mg (81%) of **21**.

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