SYNTHESIS AND ALLYLIC OXIDATION OF 2,3-DEHYDRO-9β-BENZOYLOXY-β-AGAROFURAN

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2,3-Dehydro-9β-benzoyloxy-β-agarofuran (*VI*), possible precursor of (±)-triptogelin G-2 (*I*), has been synthesized through a twelve-step procedure, allylic oxidation of which with various oxidative reagents has also been investigated, and three unusual oxidized products, ketoaldehyde *X*, peroxide *XI*, and ketone *XII*, were isolated.

A large number of β-dihydroagarofuran polyol esters have been isolated[1–4] from the plants of family *Celastraceae*. Some of them exhibit insecticidal properties[5,6], insect antifeedant effect[7,8] and antitumor activity[9]. Recently, Takaishi et al. isolated[10] triptogelin G-2 (*I*) from the achenes of *Tripterygium wilfordii* J. D. HOOK.

Although triptogelin G-2 (*I*) is one of the least structurally complex β-dihydroagarofuran polyol esters, it still presents a considerable synthetic challenge, due primarily to the presence of five axial substituents appended to a *trans*-decahydronaphthalene skeleton. In the present paper, we wish to describe the synthesis of 2,3-dehydro-9β-benzoyloxy-β-agarofuran (*VI*), the possible precursor of compound *I*. We also investigated the allylic oxidation of compound *VI* with various oxidative reagents and obtained three unusual oxidized products *X* – *XII*.

Our synthetic design (Scheme 1) was to employ 9-oxo-α-agarofuran (*II*), which was easily prepared in seven steps from carvone[11], as starting material. According to the published method[12,13], compound *II* was converted to 3β-hydroxy-9-oxo-β-agarofuran (*III*) with an overall yield of 50%. Dehydration of alcohol *III* to 2,3-dehydro-9-oxo-β-agarofuran (*IV*) could be effected by using phosphorus oxychloride/pyridine system;

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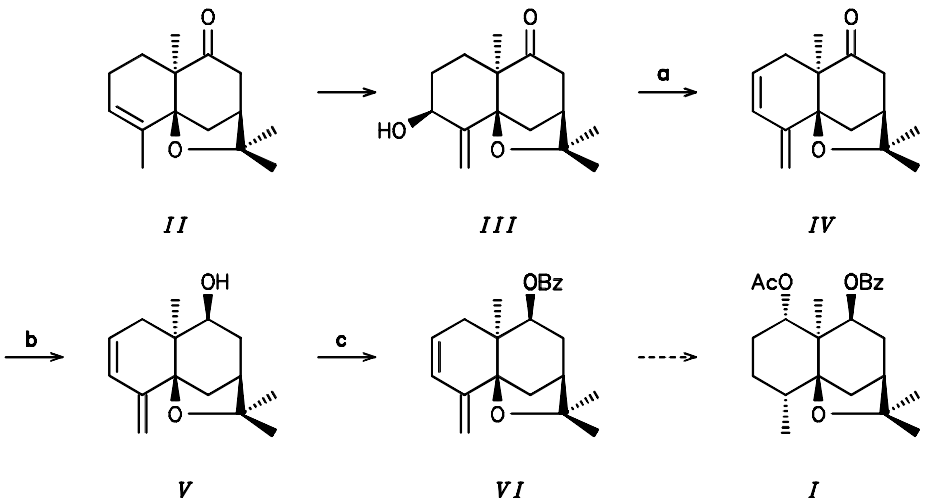
however, a better yield (87%) with no trace of by-products was obtained by using anhydrous copper sulfate dispersed on silica gel[14].

The carbonyl group of *IV* was stereoselectively reduced with lithium aluminum hydride at −50 °C to give exclusively the required 9β-hydroxy group[12,13]. Since the 9β-hydroxy group was sterically hindered and strongly hydrogen-bonded, the alcohol *V* was completely resistant to esterification under normal conditions. In the presence of the strong base butyl lithium, the hydroxy group could be transformed to benzoate ester *VI*.

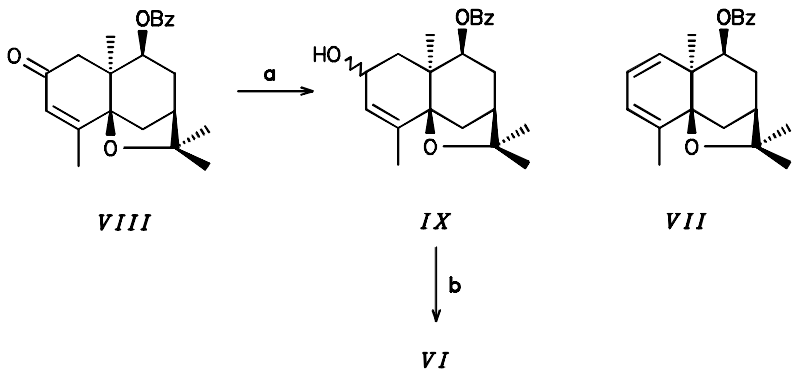
In the course of alternative synthetic work, we required 1,2-dehydro-9β-benzoyloxy-α-agarofuran (*VII*) as the key intermediate. Quite unexpectedly, dehydration of alcohol *IX*, prepared from 2-oxo-9β-benzoyloxy-α-agarofuran[15] (*VIII*), under identical reaction conditions as used for dehydration of *III* afforded β-agarofuran *VI* as the exclusive product (Scheme 2). This result also confirmed the stereostructure of *VI* described in Scheme 1, because the desired stereochemistry of the 9-benzoyloxy group in compound *VIII* was assigned by Huffman[15].

The initial strategy for the introduction of an oxygen substituent at C-1 was the allylic oxidation of conjugated diene *VI* with 10% chromium trioxide supported on silica gel, but the only product which could be isolated was the rearranged unsaturated dicarbonyl compound *X* (Scheme 3). With a catalytic amount of chromium trioxide and *tert*-butyl hydroperoxide, the product was the unsaturated peroxide *XI* (77% yield). Selenium dioxide oxidation of *VI* resulted in a complex mixture of products. Employing the chromium trioxide/pyridine complex generated in situ[16] as the oxidative agent, the exocyclic double bond of diene *VI* was cleaved to produce 4-nor-agarofuranone *XII* in



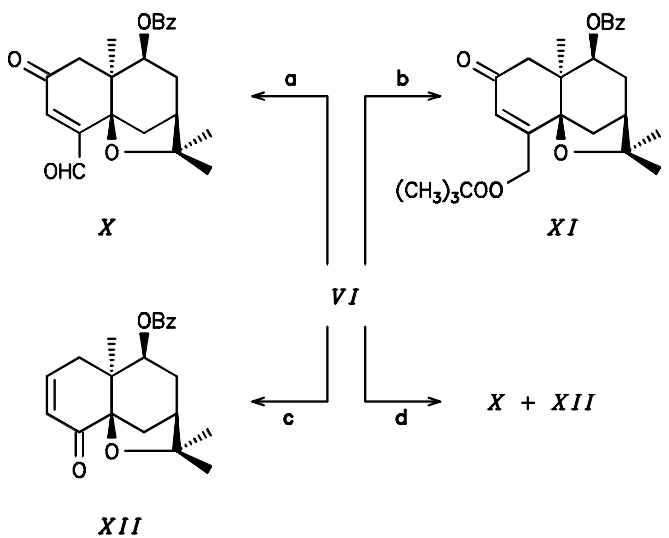
a) $CuSO_4$ on silica gel, CCl_4, reflux; b) $LiAlH_4$, ether, −50 °C; c) 1. n−BuLi, THF, 25 °C; 2. C_6H_5COCl, 25 °C

SCHEME 1



a) $NaBH_4$, $CeCl_3.7H_2O$, CH_3OH, 25 °C; b) $CuSO_4$ on silica gel, CCl_4, reflux

SCHEME 2



a) 10% CrO_3 on silica gel, CH_2Cl_2, 25 °C; b) CrO_3, 75% $(CH_3)_3COOH$, CH_2Cl_2, 25 °C; c) CrO_3/pyridine, CH_2Cl_2, 0 °C; d) CrO_3/3,5–dimethylpyrazole, CH_2Cl_2, −20 °C;

SCHEME 3

40% yield. Using the chromium trioxide/3,5-dimethylpyrazole complex[12,13] the isolated products were *X* and *XII* (Scheme 3). The structures of compounds *X*, *XI* and *XII* were determined by their IR, ^{1}H NMR, ^{13}C NMR (DEPT) and high-resolution mass spectra.

It was apparent that allylic oxidation of *VI* was not a viable approach to *I*, but might be convenient for preparation of 12-oxo-β-dihydroagarofuran polyol esters.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on a Nicolet FT-170SX spectrophotometer as liquid films (wavenumbers in cm^{-1}). ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker AM-400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) in deuteriochloroform with tetramethyl- silane as internal standard. Chemical shifts are given in ppm (δ-scale) and coupling constants (*J*) in Hz. Mass spectra were determined on a VG ZAB-HS spectrometer (energy of ionizing electrons 70 eV). For column chromatography, silica gel (200 – 300 mesh) and petroleum ether (b.p. 60 – 90 °C) were used.

2,3-Dehydro-9-oxo-β-agarofuran (*IV*)

A mixture of *III* (0.75 g, 3.0 mmol) dissolved in dry carbon tetrachloride (30 ml) and anhydrous $CuSO_4$ absorbed on silica gel (3.0 g, 3.9 mmol $CuSO_4$) was refluxed under stirring for 3 h. After cooling, the catalyst was removed by filtration, washed with acetone (10 ml) and the filtrate was evaporated. The crude product was purified by chromatography eluting with petroleum ether–ether (4 : 1) to give 0.61 g, (87%) of *IV* as colorless needles, m.p. 98 – 100 °C. IR spectrum: 2 975, 1 702 (C=O), 1 639, 1 603. ^{1}H NMR spectrum: 0.95 s, 3 H (CH_3-10); 1.19 s, 3 H (CH_3-11); 1.24 s, 3 H (CH_3-11); 5.04 and 5.25 2 × bs, 2 H (H-12); 5.82 m, 1 H (H-2); 6.19 dd, 1 H, J = 9.7, J' = 2.8 (H-3). Mass spectrum, *m*/*z* (%): 232 (M^+, 40), 217 (56), 214 (100), 199 (72). For $C_{15}H_{20}O_2$ (232.3) calculated: 77.55% C, 8.68% H; found: 77.56% C, 8.66% H.

2,3-Dehydro-9β-hydroxy-β-agarofuran (*V*)

To a stirred suspension of $LiAlH_4$ (0.14 g, 3.7 mmol) in ether (20 ml) at –50 °C under argon was added dropwise a solution of *IV* (0.66 g, 2.8 mmol) in ether (20 ml). The mixture was stirred at the same temperature for 5.5 h, then warmed to room temperature and stirred for additional 18 h. The resulting suspension was cooled to –10 °C, and to this water (1 ml) and 10% aqueous NaOH (1 ml) were added cautiously to destroy the excess reagent. The reaction mixture was filtered and the white residue was washed with hot tetrahydrofuran (15 ml), the combined filtrates were dried with anhydrous $MgSO_4$. Removal of the solvents under reduced pressure and purification by chromatography (petroleum ether–ether, 1 : 2) afforded 0.63 g (95%) of *V* as colorless needles, m.p. 114 – 116 °C. IR spectrum: 3 460 (OH), 2 924, 1 642, 1 601, 1 454. ^{1}H NMR spectrum: 0.90 s, 3 H (CH_3-10); 1.30 s, 3 H (CH_3-11); 1.53 s, 3 H (CH_3-11); 3.60 m, 1 H (H-9); 5.10 and 5.28 2 × bs, 2 H (2 × H-12); 5.83 m, 1 H (H-2); 6.16 dd, 1H, J = 9.8, J' = 3.1 (H-3). Mass spectrum, *m*/*z* (%): 234 (M^+, 54), 219 (42), 216 (100). For $C_{15}H_{22}O_2$ (234.3) calculated: 76.88% C, 9.46% H; found: 76.70% C, 9.52% H.

2,3-Dehydro-9β-benzoyloxy-β-agarofuran (*VI*)

A) To a stirred solution of *V* (1.4 g, 6.0 mmol) and a few crystals of 2,2′-bipyridyl in tetrahydrofuran (20 ml) at room temperature 1.5 M solution of butyl lithium in ether (ca 4 ml) was added dropwise until excess base appeared (red color). After 10 min a solution of benzoyl chloride (0.93 g, 6.6 mmol) in tetrahydrofuran (4 ml) was added. The mixture was stirred at room temperature for 15 min and then was refluxed for 1 h, resulting in a yellow solution. The cooled reaction mixture was poured

into saturated aqueous $NaHCO_3$ (15 ml), and extracted with ether (3 × 20 ml). The combined ether extracts were washed with saturated aqueous $NaHCO_3$ (2 × 10 ml) and brine (2 × 10 ml), and dried over anhydrous Na_2SO_4. Chromatographic purification using petroleum ether–ether (8 : 1) as eluent gave 1.95 g (96%) of *VI* as colorless needles, m.p. 129 – 130 °C. IR spectrum: 2 972, 1 712 (C_6H_5COO), 1 641, 1 602, 1 452. ^{1}H NMR spectrum: 1.02 s, 3 H (CH_3-10); 1.30 s, 3 H (CH_3-11); 1.53 s, 3 H (CH_3-11); 2.70 m, 1 H (H-7); 5.05 and 5.27 2 × s, 2 H (2 × H-12); 5.21 d, 1 H, J = 7.8 (H-9), 5.72 m, 1 H (H-2); 6.17 dd, 1 H, J = 9.9, J' = 2.7 (H-3); 7.44 – 8.10 m, 5 H (5 × Ar-H). ^{13}C NMR spectrum: 24.67 (C-15), 25.09 (C-13), 30.41 (C-14), 31.73 (C-8), 32.81 (C-6), 33.15 (C-1), 42.94 (C-7), 44.25 (C-10), 73.91 (C-9), 82.78 (C-11), 83.35 (C-5), 112.74 (C-12), 127.50 (C-2), 128.05 (C-3), 114.36 (C-4), 166.10 (C=O), 128.47, 129.77, 130.51, 132.92 (6 × Ar-C). High resolution mass spectrum, *m*/*z*: for $C_{22}H_{26}O_3$ (M^+) calculated 338.1882, found 338.1890.

B) To an ice-cooled mixture of *VIII* (0.30 g, 0.85 mmol) and cerium(III) chloride heptahydrate (0.45 g, 1.0 mmol) dissolved in methanol–ether (5 : 1, 24 ml) sodium borohydride (0.090 g, 2.4 mmol) was added in several portions. The reaction mixture was stirred at room temperature for 3 h. Then the excess hydride was destroyed by addition of 5% aqueous HCl (2 ml) at 0 °C and stirring continued for additional 10 min. The solvents were removed in vacuo and the aqueous layer was extracted with dichloromethane (2 × 10 ml). After washing with brine and drying over anhydrous $MgSO_4$, the solvent was evaporated. The crude product was purified by chromatography (petroleum ether–ether, 2 : 1) to give 0.26 g (88%) of *IX* as a white solid. IR spectrum: 3 540 (OH); 1 709 (C_6H_5COO). ^{1}H NMR spectrum: 1.08 s, 3 H (CH_3-10); 1.33 s, 3 H (CH_3-11); 1.48 s, 3 H (CH_3-11); 1.83 d, 3 H, J = 1.5 (CH_3-4); 4.21 br, 1 H (H-2); 5.08 d, 1 H, J = 5.4 (H-9); 5.73 bs, 1 H (H-3); 7.31 – 8.09 m, 5 H (5 × Ar-H). A stirred mixture of *IX* (0.24 g, 0.70 mmol) in carbon tetrachloride (10 ml) and anhydrous $CuSO_4$ supported on silica gel (1.0 g, 1.3 mmol $CuSO_4$) was refluxed for 10 min. After usual working up 0.21 g (91%) of compound *VI* was obtained, identical with the product prepared by procedure *A*).

Allylic Oxidation of 2,3-Dehydro-9β-benzoyloxy-β-agarofuran (*VI*)

A) With 10% CrO_3 dispersed on silica gel. Chromium trioxide (1.0 g) was dissolved in minimum quantity of water (ca 2 ml), and diluted by addition of methanol (10 ml). This solution was mixed with silica gel (10 g, 200 – 300 mesh), resulting in a fine slurry. Evaporation of the solvents under reduced pressure afforded a free-flowing powder of reagent.

A mixture of *VI* (0.2 g, 0.60 mmol) in dry dichloromethane (25 ml) and freshly prepared reagent (1.8 g, 1.8 mmol) was stirred at room temperature for 1 h. The reaction mixture was filtered and the solid was washed with ether (20 ml). Evaporation of the combined filtrates followed by chromatography (petroleum ether–ether, 6 : 1) gave 0.15 g (68%) of dicarbonyl compound *X* as colorless needles, m.p. 190 – 192 °C. IR spectrum: 1 712 (C_6H_5COO), 1 686 (C=O), 1 660 (CHO). ^{1}H NMR spectrum: 1.19 s, 3 H (CH_3-10); 1.26 s, 3 H (CH_3-11); 1.47 s, 3 H (CH_3-11); 5.17 d, 1 H, J = 7.8 (H-9); 6.56 s, 1 H (H-3); 7.45 – 8.07 m, 5 H (5 × Ar-H); 9.86 s, 1 H (CHO). ^{13}C NMR spectrum: 24.38 (C-15), 25.12 (C-13), 30.02 (C-14), 30.59 (C-8), 32.94 (C-6), 43.86 (C-7), 44.67 (C-1), 45.85 (C-10), 73.16 (C-9), 81.18 (C-11), 84.87 (C-5), 141.99 (C-3), 148.06 (C-4), 165.72 (C=O), 194.21 (C-12), 199.84 (C-2), 128.58, 129.74, 133.31 (6 × Ar-C). High-resolution mass spectrum, *m*/*z*: for $C_{21}H_{21}O_5$ ($M^+ - CH_3$) calculated 353.1389, found 353.1389.

B) With CrO_3/tert-butyl hydroperoxide. *tert*-Butyl hydroperoxide (75%, 1 ml) was added dropwise at room temperature to a stirred solution of CrO_3 (0.03 g, 0.30 mmol) in dichloromethane (15 ml), yielding a brown solution. Then, compound *VI* (0.34 g, 1.0 mmol) was introduced. Stirring was continued for 2 h, during which time the brown reaction solution turned gray. The resulting solution was diluted with ether (50 ml), and washed successively with saturated aqueous $NaHCO_3$ (2 × 20 ml), H_2O (2 × 20 ml) and brine (20 ml) prior to drying over anhydrous Na_2SO_4. Chromatography using

petroleum ether–ether (6 : 1) as eluent afforded 0.34 g (77%) of peroxide *XI* as a white solid, m.p. 161 – 163 °C. IR spectrum: 1 715 (C_6H_5COO); 1 679 (C=O). ^{1}H NMR spectrum: 1.21 s, 3 H (CH_3-10); 1.26 s, 9 H ($(CH_3)_3CO$); 1.38 s, 3 H (CH_3-11); 1.57 s, 3 H (CH_3-11); 4.63 and 4.74 AB system, *J*(AB) = 14.3 (2 × H-12); 5.15 d, 1 H, *J* = 6.9 (H-9); 6.18 s, 1 H (H-3); 7.44 – 8.07 m, 5 H (5 × Ar-H). ^{13}C NMR spectrum: 24.25 (C-15), 25.29 (C-13), 26.36 ($(CH_3)_3C$), 30.32 (C-14), 30.89 (C-8), 32.99 (C-6), 43.57 (C-7), 44.20 (C-1), 45.71 (C-10), 73.09 (C-12), 73.24 (C-9), 80.79 ($(CH_3)_3C$), 82.50 (C-11), 83.49 (C-5), 128.99 (C-3), 151.99 (C-4), 165.81 (C=O), 199.10 (C-2), 128.53, 129.78, 133.20 (6 × Ar-C). High-resolution mass spectrum, *m/z*: for $C_{26}H_{34}O_6$ (M^+) calculated 442.2355, found 442.2323.

C) With CrO_3/pyridine complex. To an ice-cooled stirred solution of pyridine (5 ml) in dry dichloromethane (30 ml) CrO_3 (2.6 g, 26 mmol) was added over a period of 5 min. After 15 min a dark red slurry was formed. This mixture was combined with a solution of compound *VI* (0.10 g, 0.30 mmol) in dichloromethane (10 ml). The mixture was warmed to room temperature, and stirring was continued for additional 4 h. The reaction mixture was decanted from the brown tarry residue which was washed with ether (60 ml). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (2 × 20 ml), H_2O (2 × 20 ml) and brine (2 × 20 ml), and dried over anhydrous Na_2SO_4. The products were separated by chromatography (petroleum ether–ether, 6 : 1) to afford 0.04 g (40%) of ketone *XII* as a white solid: m.p. 155 – 157 °C. IR spectrum: 1 714 (C_6H_5COO), 1 683 (C=O). ^{1}H NMR spectrum: 1.16 s, 3 H (CH_3-10); 1.28 s, 3 H, (CH_3-11); 1.57 s, 3 H (CH_3-11); 5.20 d, 1 H, *J* = 7.5 (H-9); 6.11 dd, 1 H, *J* = 10.1, *J′* = 2.7 (H-3); 6.91 m, 1 H (H-2); 7.47 – 8.11 m, 5 H (5 × Ar-H). ^{13}C NMR spectrum: 23.95 (C-15), 24.31 (C-13), 29.68 (C-14), 30.64 (C-8), 32.41 (C-1, C-6), 43.22 (C-7), 46.49 (C-10), 73.51 (C-9), 84.15 (C-11), 84.13 (C-5), 127.11 (C-3), 149.27 (C-2), 166.01 (C=O), 194.70 (C-4), 128.58, 129.72, 130.50, 133.20 (6 × Ar-C). High-resolution mass spectrum, *m/z*: for $C_{20}H_{21}O_4$ ($M^+ - CH_3$) 325.1440, found 325.1420.

D) With CrO_3/3,5-dimethylpyrazole complex. Following a published procedure[15], compound *VI* was converted to ketoaldehyde *X* and ketone *XII* in yields of 21% and 17%, respectively.

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