SYNTHESIS OF 2α,3α-EPOXY-9β-BENZOYLOXY-β-AGAROFURAN AND 2,3-DEHYDRO-4β,12-EPOXY-9β-BENZOYLOXY-β-DIHYDROAGAROFURAN

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The first stereoselective synthesis of 2α,3α-epoxy-9β-benzoyloxy-β-agarofuran (**3**) and 2,3-dehydro-4β,12-epoxy-9β-benzoyloxy-β-dihydroagarofuran (**4**) from (–)-carvone in 13 steps, respectively, has been described. In addition, the synthesis of 2,3-dehydro-4β,9β-dihydroxy-β-dihydroagarofuran (**13**) has also been reported. By the reduction of **4** to give **13**, the 4β,12-epoxy configuration of **4** was established.

Key words: 2α,3α-Epoxy-9β-benzoyloxy-β-agarofuran; 2,3-Dehydro-4β,12-epoxy-9β-benzoyloxy-β-dihydroagarofuran; 2,3-Dehydro-4β,9β-dihydroxy-β-dihydroagarofuran.

The plant of the *Celastraceae* family have proven to be a rich source of chemically and biologically interesting natural products. Although the tumor inhibitory compounds of the maytansine[1] and triptolide[2] groups have attracted a great deal of attention, the most characteristic class of compounds in these plants are polyhydroxy sesquiterpenes based on the agarofuran skeleton.

Triptogelin G-2 (**1**, ref.[3]) and 1α,9β-dibenzoyloxy-2β,3β,4β-trihydroxy-β-dihydroagarofuran[4] (**2**) are two of the structurally complex β-dihydroagarofuran polyol esters. In this paper, we wish to describe the synthesis of 2α,3α-epoxy-9β-benzoyloxy-β-agarofuran (**3**) and 2,3-dehydro-4β,12-epoxy-9β-benzoyloxy-β-dihydroagarofuran (**4**), as unexpected products in the synthesis of compound **1** and **2**.

We employed 9β-benzoyloxy-2-oxo-α-agarofuran (**5**), which was prepared in ten steps from (–)-carvone[5,6] as the starting material.

Our synthetic design of target molecule **1** required 1-bromo-2-oxo-9β-benzoyloxy-α-agarofuran as a key intermediate. Contrary to our expectation, bromination[7] of **5** with Br_2 in CCl_4 gave 12-bromo-2-oxo-9β-benzoyloxy-α-agarofuran (**6**), which was reduced

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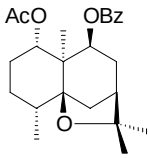
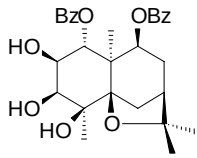
with sodium borohydride in the presence of cerium(III) chloride[8] to give 12-bromo-2α-hydroxy-9β-benzoyloxy-α-agarofuran (**7**). According to the reported method[9], treatment of α-bromohydrin with sodium hydride would give a 1,2-epoxide. In the bromohydrin **7**, however, the group is not in the *ortho*-position of the bromine atom.

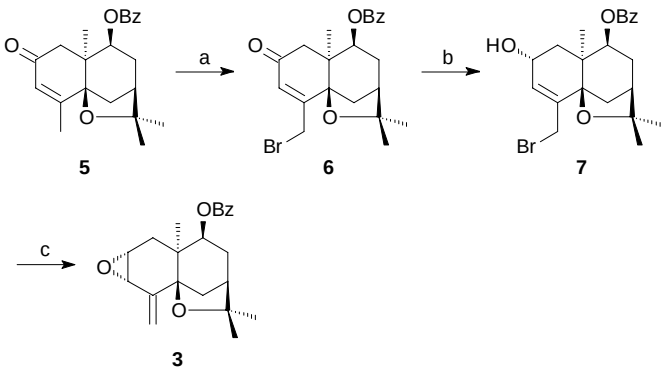


1



2

When **7** was stirred therefore with NaH in THF at ambient temperature for 1 h, a debrominated product 2α,3α-epoxy-9β-benzoyloxy-β-agarofuran (**3**) was obtained in 90% yield (Scheme 1). The structure of **3** was confirmed by ^{1}H NMR, ^{13}C NMR (DEPT) and mass spectra. The stereochemistry of 2,3-epoxy group was determined by its ^{1}H NMR spectrum which showed 3-H at δ 3.56 ppm (d, J = 4.5 Hz), and 2-H at δ 3.34 ppm (dd, J = 5.2 and 4.5 Hz). This is consistent with a slightly flattened half-chair conformation for ring A in which the dihedral angle between 2β-H and 1α-H is close to 90° (J = 0 Hz), and the angle between 1β-H and 2β-H is 35–40°, giving rise to a coupling constant in the range of 5.0–5.5 Hz.



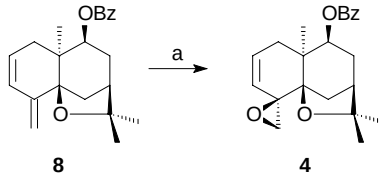
5 **6** **7** **3**

a) Br_2, CCl_4, 0 °C, 4 h; b) $NaBH_4$, $CeCl_3.7\ H_2O$, MeOH, 0 °C, 30 min; c) NaH, THF, 25 °C, 1 h

SCHEME 1

In our previous work[10], diene **8** was obtained by reduction of enone **5** and dehydration of the resulted enol with anhydrous copper sulfate dispersed on silica gel[11]. Epoxidation of **8** with dimethyldioxirane[12] at room temperature stereoselectively gave

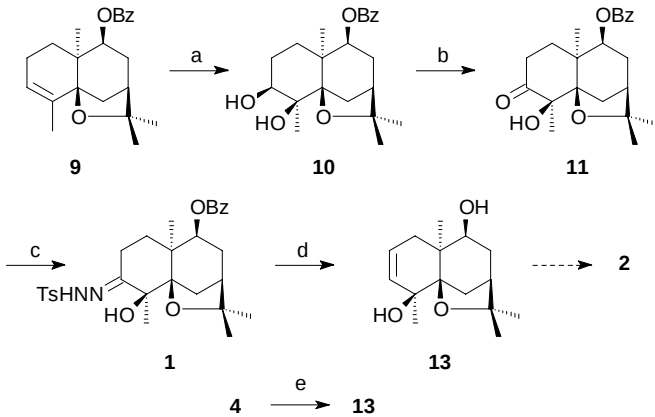
epoxide **4** in 95% yield (Scheme 2). Steric effects might be responsible for this result. The determination of the configuration of 4β,12-epoxy in compound **4** is discussed below.



a) dimethyldioxirane, acetone, 25 °C, 10 min

SCHEME 2

In our alternative synthetic route to target compound **2**, 2,3-dehydro-4β,9β-dihydroxy-β-dihydroagarofuran (**13**) was obtained as a possible precursor of **2** in four step from 9β-benzoyloxy-α-agarofuran[5,6] (**9**) (Scheme 3).



a) OsO_4/ pyridine, r.t., 16 h; b) DMSO, $(CF_3CO)_2O/Et_3N$, -78 °C, 2 h;
c) $TsNHNH_2$, EtOH, r.t., 10 h;
d) LDA, THF, -50 °C → r.t., 2 h; e) $LiAlH_4/Et_2O$, 0 °C, 15 h

SCHEME 3

Hydroxylation of **9** with OsO_4 in pyridine gave stereoselectively diol **10** stoichiometrically. The ^1H NMR spectrum indicated that diol **10** is 3β,4β-dihydroxy-9β-benzoyloxy-β-dihydroagarofuran on the base of the observation that 3-H appeared at δ 3.64 ppm as a triplet (J = 8 Hz). With conventional oxidants, such as pyridinium dichromate (PDC), PCC, compound **10** could not be oxidized to ketone **11**. Employing, DMSO activated by trifluoroacetic anhydride in triethylamine[13], **10** was converted to **11** at –78 °C in 75% yield. Ketone **11** was stirred with 4-toluenesulfonylhydrazide in anhydrous ethanol at r.t. to give hydrazone **12** stoichiometrically. Without further purification, **12** was treated[14] with excess LDA to afford the allylic alcohol **13**. As the reactions from **10** to **13** did not involve C-4, its configuration was retained.

Reduction of epoxide **4** with $LiAlH_4$ gave the alcohol whose spectral data were identical with those of **13**. All these results show that epoxide **4** is 2,3-dehydro-4β,12-epoxy-9β-benzoyloxy-β-dihydroagarofuran.

The conversions of **4** and **13** to the target molecule **2** are in progress.

EXPERIMENTAL

Melting points were uncorrected. For column chromatography, 200–300 mesh silica gel was used. IR spectra were recorded on a Nicolet FT-170SX spectrophotometer as liquid films or KBr discs. ^{1}H NMR and ^{13}C NMR spectra were measured on Varian FT-80A or Bruker AM-400 spectrometers with TMS as internal standard and $CDCl_3$ as solvent. Chemical shifts are given in ppm (δ-scale) and coupling constants (*J*) in Hz. Mass spectra were determined on a V.G. ZAB-HS spectrometer (EI, 70 eV). Dimethyldioxirane was prepared by the literature method[12]. Elemental analyses were performed on a German Vario EL elementar.

12-Bromo-2-oxo-9β-benzoyloxy-α-agarofuran (**6**)

A solution of **5** (400 mg, 1.1 mmol) in CCl_4 (10 ml) was treated with Br_2 (200 mg, 1.2 mmol) in CCl_4 (5 ml) at 0 °C. The mixture was stirred at r.t. until the orange color disappeared. After removal of solvent, the red oil was purified by silica gel chromatography (petroleum ether–ether, 7 : 1) offered **6** (300 mg, 63%) as a pale yellow oil. IR spectrum: 1 713, 1 679, 1 276. ^{1}H NMR spectrum (80 MHz): 1.33 s, 3 H (10-CH_3); 1.48 s, 3 H (11-CH_3); 1.67 s, 3 H (11-CH_3); 4.18 s, 2 H (12-H); 5.20 d, 1 H, *J* = 6.0 (9-H); 6.35 brs, 1 H (3-H); 7.36–8.26 m, 5 H (Ar-H). Mass spectrum, *m/z* (%): 434 (M + 2, 13), 432 (M, 13), 353 (15), 231 (27), 173 (13), 122 (35), 105 (100).

12-Bromo-2α-hydroxy-9β-benzoyloxy-α-agarofuran (**7**)

To an ice-cooled mixture of **6** (200 mg, 0.45 mmol) and $CeCl_3 . 7 H_2O$ (250 mg, 0.53 mmol) in MeOH (10 ml) was added $NaBH_4$ (60 mg, 1.5 mmol) in portions. The reaction mixture was stirred at 0 °C for 30 min. The excess $NaBH_4$ was destroyed by addition of 5% aqueous NaOH (5 ml) at 0 °C and stirring was continued for 10 min. The MeOH was removed *in vacuo*, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 ml). The combined extracts were washed with 5% aqueous HCl (3 × 10 ml) and brine (10 ml) and dried over $MgSO_4$. After removal of solvent, **7** (200 mg, 100%) was obtained as a white solid. IR spectrum: 3 371 (OH), 1 712, 1 280. ^{1}H NMR spectrum (80 MHz): 1.12 s, 3 H (10-CH_3); 1.34 s, 3 H (11-CH_3); 1.49 s, 3 H (11-CH_3); 4.05 s, 2 H (12-H); 4.25 m, 1 H (2-H); 5.06 dd, 1 H, *J* = 5.3 (9-H); 6.15 brs, 1 H (3-H); 7.39–8.14 m, 5 H (Ar-H). Mass spectrum, *m/z* (%): 436 (M + 2, 2), 434 (M), 355 (26), 233 (21), 157 (20), 105 (100).

2α,3α-Epoxy-9β-benzoyloxy-β-agarofuran (**3**)

To a solution of **7** (44 mg, 0.10 mmol) in dry THF (4 ml) was added NaH (10 mg, 0.4 mmol) and the mixture was stirred at r.t. for 1 h. The precipitate was removed by filtration through a layer of silica gel and washed with ether. Evaporation of the filtrates and silica gel chromatography of the residue gave **3** (32 mg, 90%) as a colorless oil. IR spectrum: 1 711, 1 278. ^{1}H NMR spectrum (400 MHz): 1.06 s, 3 H (10-CH_3); 1.27 s, 3 H (11-CH_3); 1.51 s, 3 H (11-CH_3); 3.34 dd, 1 H, *J* = 5.2, *J*″ = 4.5 (2-H); 3.56 d, 1 H, *J* = 4.5 (3-H); 5.14 d, 1 H, *J* = 7.9 (9-H); 5.58 s, 1 H (12-H); 5.60 s, 1 H (12-H); 7.45–8.14 m, 5 H (Ar-H). ^{13}C NMR spectrum (100 MHz): 25.59 (C-15), 25.75 (C-13), 30.35 (C-14), 30.35 (C-8), 32.63 (C-6), 34.30 (C-1), 42.09 (C-7), 44.49 (C-10), 51.65 (C-2), 55.32 (C-3), 73.54

(C-9), 83.08 (C-11), 83.15 (C-5), 119.93 (C-12), 143.47 (C-4), 166.14 (C=O), 128.51, 129.78, 130.53, 133.06 (6 Ar-C). Mass spectrum, *m/z* (%): 354 (M, 18), 339 (19), 293 (4), 249 (100), 232 (18), 188 (24), 105 (100). For $C_{22}H_{26}O_4$ (354.2) calculated: 74.54% C, 7.40% H; found: 74.25% C, 7.21% H.

2,3-Dehydro-4β,12-epoxy-9β-benzoyloxy-β-dihydroagarofuran (**4**)

Under stirring, a 0.099 N solution of dimethyldioxirane[12] in acetone (3 ml, 0.3 mmol) was added to **8** (40 mg, 0.12 mmol) in acetone (0.5 ml) at r.t. and then the mixture was stirred for 10 min. After removal of the solvent under reduced pressure, the crude product was purified by silica gel chromatography (petroleum ether–ether, 3 : 1) to give **4** (40 mg, 95%) as a white solid. IR spectrum: 1 705, 1 278. ^{1}H NMR spectrum (400 MHz): 1.25 s, 3 H (10-CH_3); 1.28 s, 3 H (11-CH_3); 1.56 s, 3 H (11-CH_3); 1.69 m, 2 H; 1.91 ddd, 1 H, J = 13.1, J' = 4.60, J'' = 2.9; 2.03 m, 1 H; 2.12 m, 1 H (8-H); 2.33 ddd, 1 H, J = 16.1, J' = 7.5, J'' = 3.8 (8-H); 2.77 d, 1 H, J = 4.4 (12-H); 2.88 d, 1 H, J = 17.2 (6-H); 3.11 d, 1 H, J = 4.4 (12-H); 5.22 d, 1 H, J = 7.5 (9-H); 5.24 dd, 1 H, J = 10.0, J'' = 3.0 (3-H); 6.07 ddd, 1 H, J = 9.9, 6.8, 2.5 (2-H); 7.33–8.11 m, 5 H (Ar-H). Mass spectrum, *m/z* (%): 354 (M, 1), 339 (2), 202 (10), 143 (20), 105 (100), 77 (50). For $C_{22}H_{26}O_4$ (354.2) calculated: 74.54% C, 7.40% H; found: 74.38% C, 7.42% H.

3β,4β-Dihydroxy-9β-benzoyloxy-β-dihydroagarofuran (**10**)

To a solution of **9** (340 mg, 1.0 mmol) in pyridine (20 ml) was added OsO_4 crystal (270 mg, 1.05 mmol) and the mixture was stirred for 16 h at r.t. To the resulted solution was added $NaHSO_3$ (500 mg), pyridine (2 ml) and H_2O (6 ml). After stirring for an additional 5 h, the reaction mixture was extracted with CH_2Cl_2 (3 × 20 ml), washed with saturated aqueous solution of $NaHCO_3$ (2 × 10 ml), brine (3 × 10 ml), dried over $MgSO_4$ and concentrated *in vacuo*. After purification by silica gel chromatography (petroleum ether–ether, 1 : 2), **10** (370 mg, 99%) was obtained as a white solid, m.p. 208–210 °C. IR spectrum: 3 490 (OH), 1 710. ^{1}H NMR spectrum (80 MHz): 1.28 s, 3 H (10-CH_3); 1.37 s, 3 H (11-CH_3); 1.42 s, 3 H (11-CH_3); 1.49 s, 3 H (4-CH_3); 3.64 t, 1 H, J = 8 (3-H); 4.98 d, 1 H, J = 4.8 (9-H); 7.38–8.11 m, 5 H (Ar-H). Mass spectrum, *m/z* (%): 374 (M, 5), 359 (6), 298 (2), 122 (13), 105 (100). For $C_{22}H_{30}O_5$ (374.2) calculated: 70.55% C, 8.08% H; found: 70.48% C, 8.01% H.

3-Oxo-4β-hydroxy-9β-benzoyloxy-β-dihydroagarofuran (**11**)

To a mixture of CH_2Cl_2 (3 ml) and DMSO (0.6 ml) was added trifluoroacetic anhydride (0.6 ml) at –60 °C and stirred for 10 min at –78 °C. Then a solution of **10** (410 mg, 1.1 mmol) in CH_2Cl_2 (10 ml) was added dropwise at this temperature. After stirring for 1 h at –78 °C and 45 min at –60 °C, to the mixture was added Et_3N (0.6 ml) at –60 °C. The mixture was allowed to warm to r.t. and stirring was continued for 4 h. The reaction mixture was washed with ice-cooled 1% aqueous HCl (2 × 10 ml), brine (2 × 10 ml), dried over Na_2SO_4, concentrated *in vacuo*. The residue was purified by silica gel chromatography (petroleum ether–ether, 1 : 2) to afford **11** (310 mg, 75%) as a white solid, m.p. 174–176 °C. IR spectrum: 3 467 (OH), 1 711. ^{1}H NMR spectrum (80 MHz): 1.33 s, 3 H (10-CH_3); 1.38 s, 3 H (11-CH_3); 1.40 s, 3 H (11-CH_3); 1.51 s, 3 H (4-CH_3); 5.11 d, 1 H, J = 6 (9-H); 7.40–8.11 m, 5 H (Ar-H). Mass spectrum, *m/z* (%): 372 (M, 2), 181 (9), 105 (100), 77 (47).

3-(4-Toluenesulfonylhydrazono)-4β-hydroxy-9β-benzoyloxy-β-dihydroagarofuran (**12**)

To a solution of **11** (250 mg, 0.65 mmol) in EtOH (15 ml) was added 4-toluenesulfonylhydrazide (120 mg, 0.65 mmol) and the mixture was stirred at r.t. for 10 h. After removal of the solvent, **12** (350 mg, 100%) was obtained as a colorless solid without further purification. IR spectrum: 3 425 (NH), 3 205

(OH), 1 709. ^{1}H NMR spectrum (80 MHz): 1.20 s, 3 H (10-CH_3); 1.30 s, 3 H (11-CH_3); 1.39 s, 6 H (11-CH_3 and 4-CH_3); 2.40 s, 3 H (Ar-CH_3); 4.98 d, 1 H, J = 5.0 (9-H); 7.3–8.5 m, 9 H (Ar-H). Mass spectrum, *m/z* (%): 356 (M – 184, 3), 339 (2), 234 (3), 201 (4), 105 (100), 91 (33), 77 (53), 57 (40).

2,3-Dehydro-4β,9β-dihydroxy-β-dihydroagarofuran (**13**)

A) To 1.2 M solution of LDA in hexane (5 ml) was added a solution of **12** (120 mg, 0.22 mmol) in dry THF (10 ml) dropwise at –50 °C. After stirring for 2 h at this temperature, to the mixture was added saturated aqueous solution of NH_4Cl (5 ml) and the stirring was continued till the reaction mixture turned to light yellow. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 10 ml). The combined organic layer was washed with brine (2 × 10 ml), dried over $MgSO_4$, concentrated *in vacuo*. The residue was purified by silica gel chromatography (petroleum ether–ether, 1 : 1) to offer **13** (40 mg, 73%) as a white solid, m.p. 110–112 °C. IR spectrum: 3 435 (OH), 2 963, 1 454, 1 161, 1 016. ^{1}H NMR spectrum (400 MHz): 1.23 s, 3 H (10-CH_3); 1.30 s, 6 H (11-CH_3); 1.57 s, 3 H (4-CH_3); 3.51 m, 1 H (9-H); 5.57 dd, 1 H, J = 10.4, J' = 3.2 (3-H); 5.24 ddd, 1 H, J = 10.2, J' = 5.9, J'' = 2.0 (2-H). Mass spectrum, *m/z* (%): 252 (M, 1), 250 (2), 237 (3), 234 (5), 201 (6), 191 (6), 181 (14), 173 (43), 140 (43), 111 (73), 91 (65), 43 (100). For $C_{15}H_{24}O_3$ (252.2) calculated: 71.38% C, 9.59% H; found: 71.15% C, 9.42% H.

B) To a suspension of $LiAlH_4$ (20 mg) in dry Et_2O (2 ml) was added a solution of **4** (15 mg) in dry Et_2O (3 ml) and the mixture was stirred at 0 °C under argon for 15 h. Then 10% aqueous NaOH (0.1 ml) and H_2O (0.3 ml) was added and stiring was continued for an additional 5 h. The reaction mixture was filtered and the white slurry was washed with Et_2O. The combined organic layer was washed with brine (2 ml), concentrated *in vacuo* and purified by silica gel chromatography (petroleum ether–ether, 3 : 1) to give **13** (7 mg, 66%), whose spectral data were identical with those of the sample prepared by method *A*.

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