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Arjunolic Acid in Molecular Recognition: First Synthesis and Cation Binding Studies of a novel Arjuna-18-crown-6

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Arjunolic acid, a functionally rich chiral triterpenoid with a rigid pentacyclic backbone, has the potential to be used as a structural framework for the design of molecular receptors and supramolecular architectures. The design and synthesis of the first arjunolic acid-derived 18-crown-6 and its binding studies with metal and *tert*-butylammonium ions are reported.

Keywords: Crown ethers; Molecular recognition; Terpenes and terpenoids; Complexation

INTRODUCTION

During the past two decades a variety of molecular frameworks, including natural products, have been used for the design of molecular receptors, biomimetic systems and supramolecular systems capable of reproducing themselves or storing and processing information at a molecular level [1–8]. Rigid frameworks with spatially well-separated functional groups not only help the target molecule to attain a well-defined geometry in three dimensions but also help in positioning the required functional elements as necessary. Among various natural products, steroids have been used extensively [9–12] for the construction of molecular receptors [13–16], organogelators [17–18], dendrimers [19] and combinatorial chemistry [20–21]. Although many functionally rich chiral terpenoids having well-defined structural frameworks are naturally abundant, there is little activity in the use of those in the design of molecular receptors and as architectural components in supramolecular architectures [22–23].

In 1954, King et al. reported the extraction of arjunolic acid (**1**), a terpenoid from the heavy wood powder of *Terminalia arjuna* [24]. This chiral, pentacyclic, triterpenic acid has a rigid backbone with two equatorial hydroxyl groups and one equatorial hydroxymethyl group attached to the 'A' ring and one carboxyl group at the ring junction of the *cis*-fused 'D' and 'E' rings [25]. The geometry of the hydroxyl and the hydroxymethyl groups attached to C_2—C_4 of arjunolic acid has a mirror image resemblance to the C_3—C_5 carbons of D-glucopyranose (Fig. 1). Medicinal activities of arjunolic acid and other extraneous constituents of *T. arjuna* have been reported [26–27]. However, no attempt has so far been made to use this naturally occurring chiral triterpenoid, with its uniquely positioned functional groups, in molecular recognition and supramolecular chemistry. Herein we communicate the design and synthesis of a novel chiral 18-crown-6 based upon arjunolic acid, with a built-in handle for the attachment of additional functional groups, and the results of its binding studies with monovalent cations [28–29].

RESULTS AND DISCUSSION

Arjunolic acid **1** was extracted from the heavy wood powder of *T. arjuna* in the form of a colorless crystalline solid using an improved method developed in our laboratory. For the design of a molecular receptor using arjunolic acid, it occurred to us that a crown ether could be constructed using its 2 and 3 hydroxyl groups. Such a design should maintain a gauche disposition of the 'O—C—C—O' unit of the crown ether ring at the ring junction. Molecular mechanics calculations using the Hyperchem program indicated that the *gauche* disposition of the 'O—C—C—O' unit at the ring junction and the *gauche* conformation of the other 'O—C—C—O' units in the

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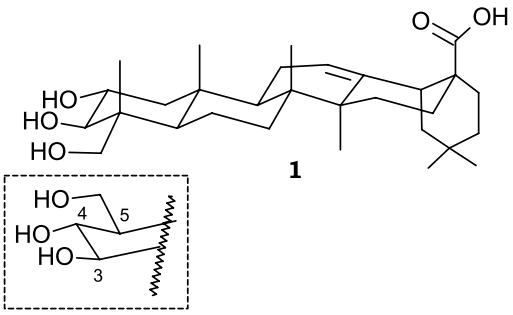


FIGURE 1 Arjunolic acid **1** (inset: corresponding enantiomorphic array of hydroxy groups in the D-glucopyranose scaffold).

crown ether ring preorganize the arjuna-crown ether for cation binding (see Fig. 2 for an energy-minimized structure) [30]. The proximate 23-OH and the distal 28-COOH groups could then be modified to create various functionalized crown ethers. The arjuna-18-crown-6 derivative **6** with an attached benzoate chromophore (for easy identification and purification purposes) became the first target compound to be synthesized for complexation studies.

The primary 23-OH group of methyl arjunolate **2** was protected by tritylation with trityl chloride/triethylamine to afford the trityl derivative **3** in 90% yield (Scheme 1). High-dilution macrocyclization of **3** with pentaethylene glycol ditosylate/NaH in THF produced the crown ether derivative **4** (Scheme 1) in 65% yield. Detritylation of **4** was carried out by treatment with dichloroacetic acid to produce the arjuna-18-crown-6 **5** in 68% yield. Benzoylation of **5** was carried out by heating with benzoyl chloride/triethylamine/DMAP in benzene to produce the arjuna-crown ether **6** (Fig. 3) in 80% yield. It was purified by HPLC before characterization and complexation studies.

Complexation of compound **6** with cations was carried out in chloroform at 25°C using Cram's picrate extraction method [31]. Values of $\log K_a$ were: $[M^+]$ Na^+, 5.6; K^+, 7.1; Rb^+, 5.7; Cs^+, 5.3; ^{t}Bu—NH_3^+, 3.4 (Fig. 4). Structural preorganization enhances the binding both enthalpically and entropically [32–33]. The '*gauche*' disposition of the 'O—C—C—O' unit has been observed in the complexed structure of '18-crown-6', which binds the K^+ ion selectively [22–23]. The stronger binding of the arjuna-crown ether **6** to K^+ might be due to the preservation of the '*gauche*' disposition of the 'O—C—C—O' unit (Fig. 2).

CONCLUSIONS

We have designed and synthesized the first arjunolic acid-derived 18-crown-6 and studied its binding with monovalent cations. The prediction, based upon force field calculations [30], that the preorganized structure of the arjuna-18-crown-6 (Fig. 2) will have an identical selectivity trend to monovalent cations as 18-crown-6 has been supported by the experimental results (Fig. 4). The current set of data does not reflect the role of the rigid triterpenoid framework on complexation. Nevertheless, the facile synthesis of the chiral arjuna-18-crown-6, with two additional functional groups at the 23 and 28 positions, and its high association constants make it very attractive for the design of molecular receptors [34], biomimetic systems [2,4,35,36] and supramolecular systems capable of performing specific tasks.

EXPERIMENTAL

General

Analytical thin layer chromatography (TLC) was performed using precoated aluminum-backed plates (Merck Kieselgel 60 F254) visualized by ultraviolet irradiation or in an I_2 chamber. HPLC was carried out using a JASCO 2000 + double-pump system using commercial HPLC-grade solvents. A gradient of 90–100% methanol/water during 0–15 min and then 100% methanol was

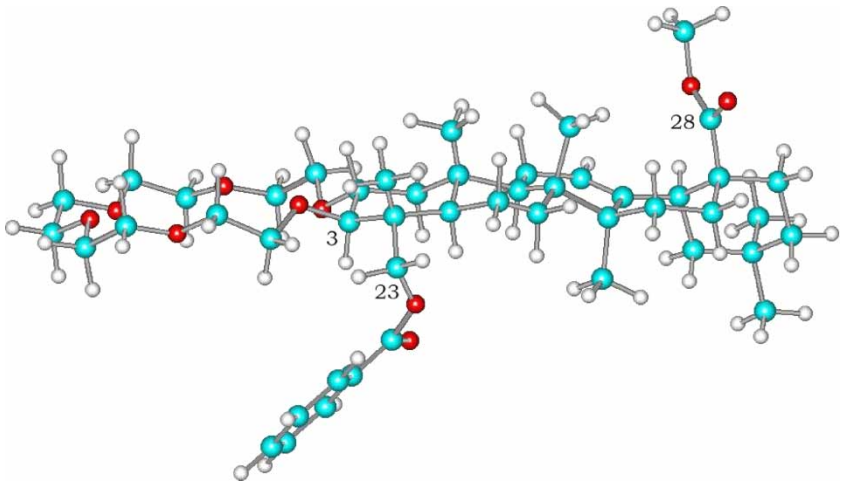
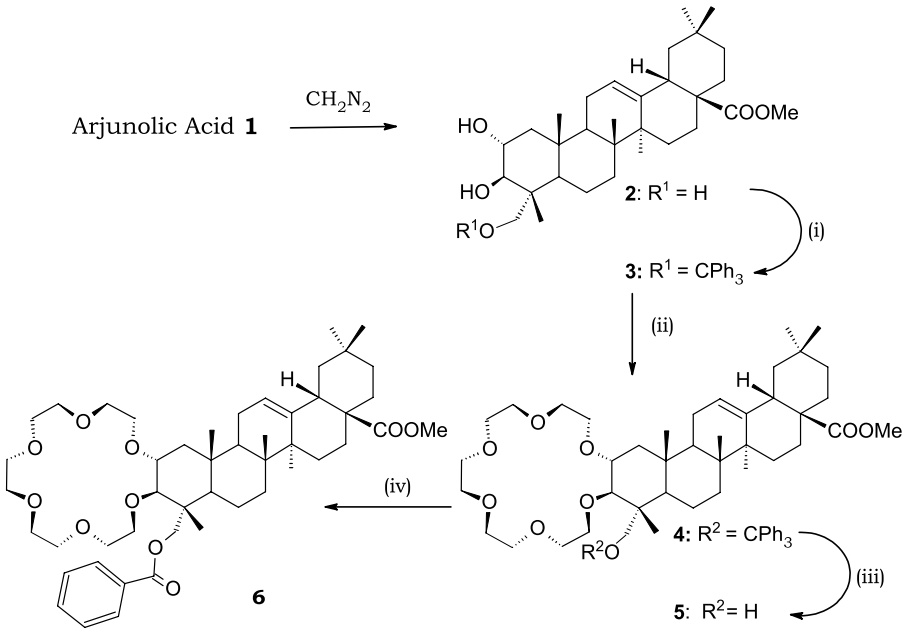


FIGURE 2 Energy-minimized structure [30] of compound **6**.



SCHEME 1 (i) Ph_3CCl/Et_3N/RT, (ii) $PEGTs_2$/NaH/THF/reflux, (iii) $Cl_2CHCOOH$/RT, (iv) PhCOCl/ Et_3N/DMAP/RT.

used as mobile phase in all cases, using an HiQ sil C18V analytical HPLC column of dimensions 4.6 × 250 mm. A UV detector monitoring at 254 nm was used. Column chromatography was carried out using Si-gel (100–200 mesh). $[\alpha]_D$ values are given in $10^\circ\,cm^2\,g^{-1}$. NMR spectra were acquired on a Bruker DRX 500 spectrometer, operating at 500 (^1H) or 125 MHz (^{13}C). Chemical shifts (δ) are reported in ppm relative to the residual solvent signal. The multiplicities of the ^1H signals are designated by: s = singlet; d = doublet; t = triplet; br = broad; m = multiplet, app = apparent. All coupling constants, *J*, are reported in Hertz. ^{13}C NMR spectra were acquired on a broad band decoupled mode. Mass spectra were recorded on an electronspray mass spectrometer [TOF MS, ES(+) using acetonitrile/water/formic acid (50:50:0.05)]. All the solvents used for extraction and purification purposes were distilled before use.

Extraction of Arjunolic Acid (1) [24]

Fine heavy-wood powder of *T. arjuna* (1 kg) was initially extracted with petroleum ether (20 h) to remove greasy nonpolar material. Subsequent extraction with diethylether (40 h) yielded a white, crystalline solid (12–15 g) that was recrystallized from

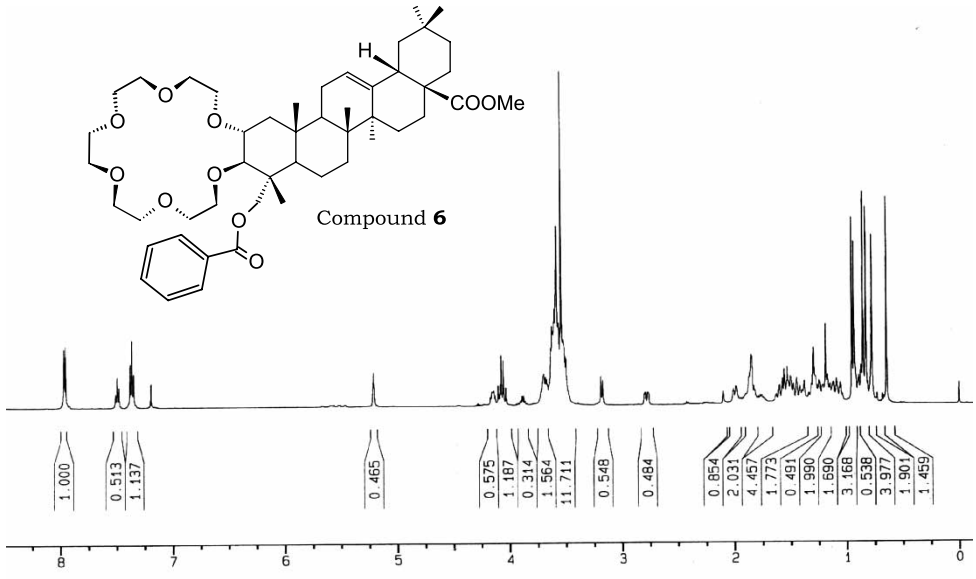


FIGURE 3 500 MHz ^1H NMR of compound **6**.

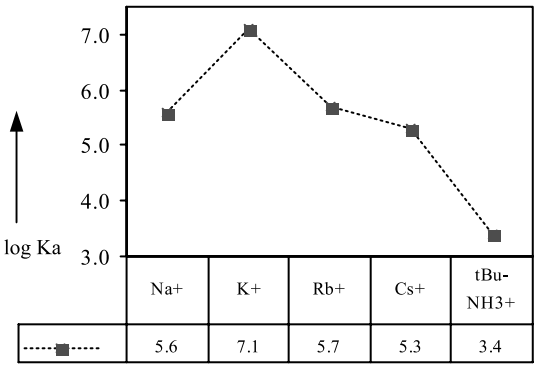


FIGURE 4 Plot of log K_a vs. cations.

methanol to obtain arjunolic acid as a colorless, crystalline solid (9 g as the first crop).

Methyl Arjunolate (2) [24]

Arjunolic acid **1** (0.53 g, 1.08 mmol) suspended in methanol (2 cm^3) was treated with a solution of diazomethane (5.4 mmol) in ether (20 cm^3) at room temperature. After 15 h the volatiles were removed under reduced pressure and the crude product was purified by column chromatography (Si-gel, 100–200 mesh) using 50–90% ethyl acetate/petroleum ether as eluant to afford a white foamy solid of methyl arjunolate **2** (0.53 g, 97%). $[\alpha]_D^{298} = +31.5$ (c 0.046, $CHCl_3$); FTIR: ν_{max} (neat, cm^{-1}) 3391 (s), 2946 (s), 2863 (s), 1725 (s), 1658 (w), 1462 (m), 1455 (m), 1433 (m); δ_H (500 MHz, $CDCl_3$): 5.28 (br, app, t, 1H, 12-H), 3.76 (br, m, 1H), 3.68 (br, m, 1H), 3.62 (s, 3H, —CO—O—CH_3), 3.45 (m, 2H), 2.86 (dd, 1H, $J_1 = 13.7$ Hz, $J_2 = 3.8$ Hz), 2.0–0.80 (terpenoid protons, 20H), 1.12 (s, 3H), 1.02 (s, 3H), 0.92 (s, 3H), 0.90 (s, 6H), 0.72 (s, 3H). δ_C (125 MHz, $CDCl_3$): 178.7, 144.2, 122.5, 51.9, 49.8, 48.0, 46.2, 42.1, 41.6, 39.7, 38.7, 34.3, 33.5, 32.8, 32.7, 31.1, 30.1, 28.0, 26.4, 24.0, 23.9, 23.4, 18.8, 17.4, 17.3, 13.1. *m/e* 502 (M^+, 15%), HRMS (ESI): *m/z* calcd ($C_{31}H_{50}O_5Na$) 525.3556, found 525.3538 $[M + Na]^+$.

Methyl 23-[(Triphenylmethyl)oxy]arjunolate (3)

Compound **2** (7.6 g, 15.12 mmol) dissolved in dry dichloromethane (75 cm^3) was treated successively with triethylamine (4.2 cm^3, 30.1 mmol) and trityl chloride (4.64 g, 16.66 mmol). The reaction mixture was stirred at room temperature for 2.5 h. Volatiles were removed under reduced pressure and the crude product was purified by column chromatography (Si-gel, 100–200 mesh) using 5–15% ethyl acetate/chloroform (containing 1 drop of triethylamine per 100 cm^3 of the eluant) to obtain the desired product (10.15 g, 90%) as a foamy solid. HPLC (254 nm) $t_R = 17.3$ min (100%); $[\alpha]_D^{298} = +37.0$ (c 0.30, $CHCl_3$). UV (10% $CHCl_3$/MeOH, log ϵ) $\lambda_{max} = 259.2$ nm (3.11); FTIR: ν_{max} (neat, cm^{-1}) 3430 (s), 3086 (w), 3058 (w), 2947 (s), 2882 (s), 1724 (s), 1658 (w), 1598 (w), 1548 (w), 1490 (m), 1462 (s), 1448 (s), 1388 (s), 1364 (m), 1345 (m), 1319 (w), 1303 (w) cm^{-1}. δ_H (500 MHz, $CDCl_3$) 7.46 (d, 6H, $J = 8.5$ Hz), 7.31(t, 6H, 7.2 Hz), 7.25 (t, 3H, $J = 7.2$ Hz), 5.30 (br, app, t, 1H, 12-H), 3.76–3.68 (m, 1H), 3.61 (s, 3H, —CO—O—CH_3), 3.42 (d, 1H, $J = 9.3$ Hz), 3.13 (d, 1H, $J = 9.3$ Hz, 23-H_a), 2.87 (dd, $J_1 = 13.7$ Hz, $J_2 = 3.9$ Hz, 1H), 2.86 (d, $J = 9.3$ Hz, 1H, 23-H_b), 2.1-0.80 (m, terpenoid Hs, 20H), 1.19 (s, 3H), 0.98 (s, 3H), 0.94 (s, 3H), 0.92 (s, 3H), 0.71 (s, 3H), 0.68 (s, 3H). δ_C (125 MHz, $CDCl_3$) 178.7, 144.3, 144.2, 129.1, 128.3, 127.5, 122.7, 86.9, 79.6, 68.7, 66.9, 51.9, 48.9, 48.4, 47.2, 46.4, 46.2, 43.4, 42.1, 41.8, 39.8, 38.3, 34.3, 33.5, 32.8, 32.7, 31.1, 28.0, 26.2, 24.0, 23.9, 23.5, 18.6, 17.4, 17.3, 13.8. HRMS (ESI): *m/z* calcd ($C_{50}H_{64}O_5Na$) 767.4651, found 767.4612 $[M + Na]^+$.

23-[(Triphenylmethyl)oxy], 28-(methoxycarbonyl) -arjuna-18-crown-6 (4)

Compound **3** (0.351 g, 0.47 mmol) was dissolved in dry THF (5 cm^3) and sodium hydride (0.39 g, 9.95 mmol) was added. The reaction mixture was stirred at room temperature for 5 min and then at 60°C for 5 min and then cooled to room temperature and treated with a solution of pentaethyleneglycol ditosylate (0.40 g, 0.73 mmol) in dry THF (3 cm^3). Then the reaction mixture was diluted with dry THF (5 cm^3) and heated with continuous stirring at 60°C for 72 h. After concentrating to one-third of its original volume under reduced pressure, the reaction mixture was poured into a mixture of 50 g of crushed ice containing chloroform (25 cm^3). The chloroform layer was separated and the aqueous layer was extracted with chloroform (3 × 25 cm^3). The combined organic layer was washed with distilled water (3 × 20 cm^3) and dried over anhydrous magnesium sulfate. Volatiles were removed under reduced pressure and the crude product was purified by column chromatography (Si-gel, 100–200 mesh) using 10–30% ethyl acetate/chloroform adding one drop of triethylamine per 25 cm^3 solvent as the eluant. The desired product was obtained as a white foamy solid (0.29 g, 65%). HPLC (254 nm) $t_R = 30.9$ min (100%); $[\alpha]_D^{298} = +13.1$ (c 0.24, $CHCl_3$), λ_{max} (10% $CHCl_3$/MeOH, log ϵ) = 259.2 nm (3.17); FTIR: ν_{max} (neat, cm^{-1}) 3056 (w), 2922 (s), 2863 (s), 1726 (s), 1598 (w), 1488 (m), 1461 (m), 1449 (m), 1387 (m), 1349 (w), 1319 (w), 1303 (w). δ_H (500 MHz, $CDCl_3$): 7.41 (d, 6H, $J = 7.5$ Hz), 7.26 (t, 6H, $J = 7.1$ Hz), 7.22 (t, 3H, $J = 7.1$ Hz), 5.32 (br, app, t, 1H, 12-H), 4.10–4.05 (m, 1H), 3.81–3.75 (m, 1H), 3.62, (s, 3H, —CO—O—CH_3), 3.75–3.55 (m, 15H), 3.55–3.46 (m, 2H), 3.43 (d, 2H, $J = 9.5$ Hz), 3.21 (t, 2H, $J = 5.0$ Hz), 3.05 (d, 1H, $J = 8.9$ Hz), 2.91–2.84 (m, 2H), 2.80 (d, 1H, $J = 8.8$ Hz), 2.06 (dd, 1H, $J_1 = 14.0$ Hz, $J_2 = 3.9$ Hz), 2.02–0.88 (m, terpenoid Hs, 17 H), 1.19 (s, 3H), 0.95 (s, 3H), 0.94 (s, 3H), 0.93 (s, 3H), 0.72 (s, 3H), 0.56

(s, 3H). δ_C (125 MHz, $CDCl_3$): 178.7, 144.3, 144.2, 129.5, 128.0, 127.3, 122.7, 86.3, 84.5, 79.4, 72.9, 71.4, 71.3, 71.0, 70.9, 70.8, 69.4, 64.5, 51.9, 48.5, 47.8, 47.2, 44.6, 44.5, 42.1, 41.8, 39.8, 38.0, 34.3, 33.5, 32.6, 31.1, 28.0, 26.2, 24.1, 18.5, 17.5, 17.3, 15.0. HRMS (ESI): m/z calcd ($C_{60}H_{82}O_9Na$) 969.5857, found 969.5877 $[M + Na]^+$.

23-Hydroxy, 28-(methoxycarbonyl)-arjuna-18-crown-6 (5)

Compound **4** (0.84 g, 0.88 mmol) was treated with of a solution of dichloroacetic acid (20%) in chloroform (4.5 cm^3) and stirred at room temperature for 3 h. Then the reaction mixture was diluted with chloroform (40 cm^3), washed with distilled water (4 × 10 cm^3) and dried over anhydrous magnesium sulfate. Volatiles were removed under reduced pressure and the crude product was purified by Si-gel (100–200 mesh) using 50–90% ethyl acetate/chloroform as the eluant. The desired product was obtained as a foamy solid (0.427 g, 68%). $[\alpha]_D^{298} = +18.9$ (c 0.24, $CHCl_3$). FTIR: ν_{max} (neat, cm^{-1}) 3453 (m), 2920 (s), 2864 (s), 1726 (s), 1658 (w), 1462 (m), 1386 (m), 1363 (m). δ_H (500 MHz, $CDCl_3$): 5.27 (br, app, t, 1H, 12-H), 4.15–4.07 (m, 1H), 4.0–3.93 (m, 1H), 3.87–3.80 (m, 1H), 3.78–3.57 (m, 22 Hs), 3.62 (s, 3H, —CO—O—CH_3), 3.57–3.47 (m, 2H), 3.34 (d, $J = 10.3$ Hz, 1H), 3.32 (d, $J = 8.8$ Hz, 1H), 2.86 (dd, 1H, $J_1 = 13.7$ Hz, $J_2 = 3.5$ Hz), 2.10–0.78 (m, terpenoid Hs, 15 H), 1.12 (s, 3H), 0.97 (s, 3H), 0.92 (s, 3H), 0.89 (s, 3H), 0.72 (s, 3H), 0.69 (s, 3H). δ_C (125 MHz, $CDCl_3$): 178.7, 144.3, 122.5, 85.2, 78.9, 73.1, 73.0, 71.9, 71.4, 71.2, 71.1, 71.0, 70.9, 70.6, 69.3, 66.8, 65.3, 51.9, 48.0, 47.8, 47.1, 46.2, 44.7, 44.1, 42.1, 41.7, 39.7, 38.1, 34.3, 33.5, 32.8, 32.6, 31.1, 30.1, 26.4, 24.0, 23.9, 18.4, 17.6, 17.2, 14.1. HRMS (ESI): m/z calcd ($C_{41}H_{68}O_9Na$) 727.4761, found 727.4767 $[M + Na]^+$.

23-(Benzoyloxy), 28-(methoxycarbonyl)-arjuna-18-crown-6 (6)

Compound **5** (0.095 g, 0.135 mmol) was dissolved in dry dichloromethane (1 cm^3) and the solution was treated successively with triethylamine (0.070 cm^3, 0.50 mmol), benzoyl chloride (0.032 cm^3, 0.28 mmol) and DMAP (0.012 g, 0.098 mmol). The mixture was stirred at room temperature for 15 h. The reaction mixture was diluted with chloroform (50 cm^3), washed with distilled water (3 × 15 cm^3) and dried over anhydrous magnesium sulfate. Volatiles were removed under reduced pressure and the crude product was purified by column chromatography (Si-gel, 100–200 mesh) using 10–40% ethyl acetate/chloroform as the eluant. The desired product was obtained as a foamy solid (0.087 g) in 80% yield. HPLC (254 nm) $t_R = 21.33$ min (100%); $[\alpha]_D^{298} = +22.5$ (c 0.28, $CHCl_3$), UV (10% $CHCl_3$/MeOH, $\log \epsilon$) $\lambda_{max} = 273.5$ nm (3.11); FTIR: ν_{max} (neat, cm^{-1}) 2944 (s), 2865 (s), 1722 (s), 1659 (w), 1601 (w), 1462 (m), 1452 (m) cm^{-1}. δ_H (500 MHz, $CDCl_3$) 8.03 (d, 2H, $J = 7.2$ Hz), 7.56 (t, 1H, $J = 7.4$ Hz), 7.43 (t, 2H, $J = 7.8$ Hz), 5.28 (br, app, t, 1H, 12-H), 4.24–4.19 (m, 1H), 4.15 (d, 1H, $J = 11.3$ Hz), 4.11 (d, 1H, $J = 11.3$ Hz), 3.80–3.49 (m, 24 H), 3.62 (s, 3H, —CO—O—CH_3), 3.25 (d, 1H, $J = 9.3$ Hz), 2.85 (dd, 1H, $J_1 = 13.7$ Hz, $J_2 = 3.9$ Hz), 2.17–0.80 (m, terpenoid Hs, 16 H), 1.02 (s, 3H), 1.00 (s, 3H), 0.92 (s, 3H), 0.89 (s, 3H), 0.84 (s, 3H), 0.71 (s, 3H). δ_C (125 MHz, $CDCl_3$), δ 178.7, 166.6, 144.2, 133.4, 130.7, 129.9, 128.9, 122.5, 84.9, 78.5, 73.7, 71.4, 71.3, 71.2, 71.1, 71.0, 70.9, 70.8, 69.8, 66.4, 51.9, 48.5, 48.3, 47.1, 46.2, 45.0, 43.8, 41.9, 41.8, 39.7, 37.9, 34.3, 33.5, 32.7, 31.1, 30.1, 27.9, 25.8, 24.0, 23.9, 23.4, 18.5, 17.3, 17.2, 14.3. HRMS (ESI): m/z calcd ($C_{48}H_{73}O_{10}$) 809.5204, found 809.5214 $[M + H]^+$.

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