Synthesis of functionalized C ring equivalent of Eleutherobin

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Dedicated to Dr. A.V. Rama Rao on the occasion of his 70th birthday

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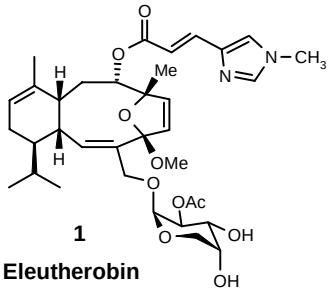
Abstract

A practical synthesis of fully functionalized 'C' ring equivalent of cytotoxic marine natural product Eleutherobin is described starting from simple and easily accessible chemicals.

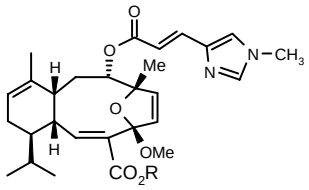
Keywords: Eleutherobin, cytotoxic, Tubulin polymerization, asymmetric dihydroxylation, Lindlar's catalyst

Introduction

The Eleuthesides comprise a family of marine derived natural products that exhibit cytotoxic activity.[1] Most intriguing of these is Eleutherobin **1**, which was isolated in 1995 by Fenical *et al.,* from an Eleutherobia species of marine soft corals (*Eleutherobia albiflora* Alcynacea, Alcyoniidea) collected in the Indian Ocean near Bennett's Shoal in Western Australia.[2] The soft corals have tentacles, which are surrounded by needle tipped poison sacs called nematocysts. By injecting this nerve toxin into passing prey, they paralyze the creatures they intend to devour.



1
Eleutherobin



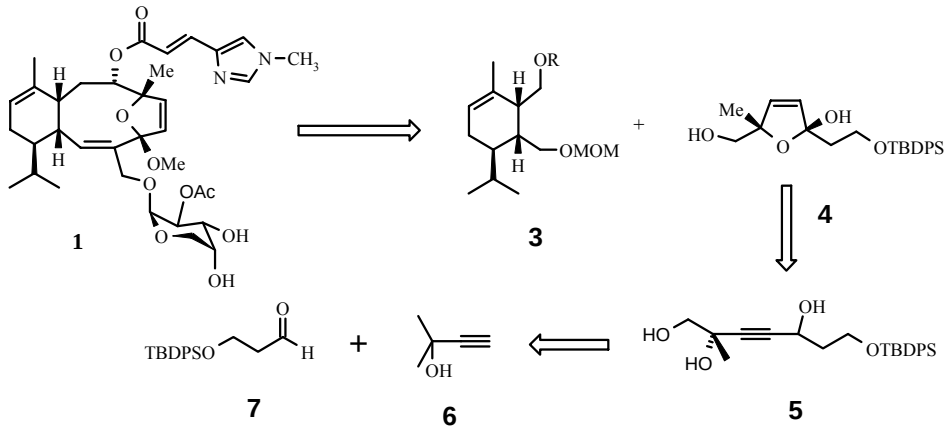
2
R=Me: Sarcodictyin A
R=Et : Sarcodictyin B

Eleutherobin is a diterpene glycoside[3] (means it has a 20 carbon core) and belongs to the family of 1,4-oxacladiellanes. Due to its complex architecture, it is easier to look at it as a composition of three different parts. The carbon skeleton (the eleutherobin core) which contains

a cyclohexene ring that is *cis*-fused to cyclodecane ring, an ester and a sugar. Unfortunately this soft coral is a very rare species and produces only extremely small amounts of the toxin, therefore in order to obtain sufficient amounts for use as an anti-cancer drug it must be produced synthetically.

Similar to sarcodictyins **2**,[4] initial reports of eleutherobin's structure in a 1995 patent were accompanied by disclosures of its potent cytotoxicity albeit in the absence of a supporting mechanistic rationale. Three years after this patent disclosure, Fenical *et al*., and their collaborators at Bristol-Myers Squibb revealed more detailed biological studies of eleutherobin including evidence that it acted by mitotic arrest through tubulin polymerization.[5] Specifically, eleutherobin was shown to be cytotoxic to HCT116 human colon carcinoma cells (IC_{50} = 10.7 nM *versus* taxol: IC_{50} = 4.6 nM) and human ovarian carcinoma cells A2780 (IC_{50} = 13.7 nM *versus* taxol: IC_{50} = 6.7 nM).[6] Because of this excellent properties in various cell lines coupled with structural complexity and scarce availability, several synthetic efforts were put up by reputed schools of organic synthesis. The total synthesis was achieved by groups of Nicolaou,[7] Danishefsky[8] and several partial syntheses are reported.[9]

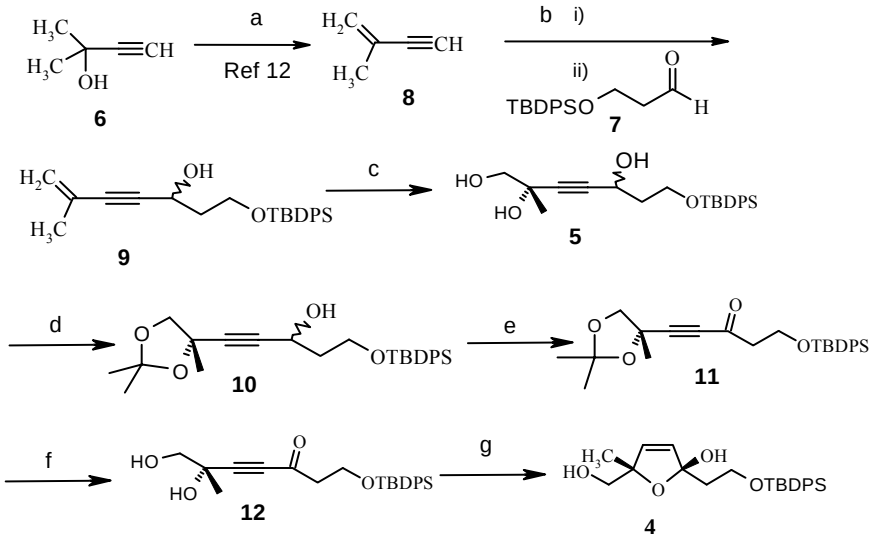
A programme was initiated in our group to synthesize structurally simplified analogs of Eleutherobin for understanding SAR.[10] In this context, we required an easy and flexible approach for "C" ring fragment of Eleutherobin which was believed to be essential for the potent activity. The logical disconnection (**Scheme 1**) revealed simple starting materials derived from 1,3–propane diol and acetylene.



Scheme 1

Results and Discussion

The 3-O-*tert*-butylsilyl propanaldehyde **7** (obtained from mono protection of 1,3-propane diol followed by oxidation)[11] was added to 3-methyl-3-buten-1-yne **8** (prepared from 2-methyl-3-butyn-2-ol **6** by dehydration following a literature procedure)[12] in the presence of ^{n}BuLi to furnish enynol **9** in 56% over all yield from **6**.



Scheme 2. Reagents, Conditions and yields: (a) Ac_2O, H_2SO_4 (cat), 50°C, 60%; (b) ^{n}BuLi, -20°C, THF, 94%; (c) AD mix-alpha, ^{t}BuOH:H_2O (1:1), 0°C; (d) 2,2-DMP, CSA, CH_2Cl_2, r.t., 95%; (e) MnO_2, CH_2Cl_2, r.t., 92% (f) 80% AcOH, r.t., 82%; (g) Pd;$CaCO_3$, H_2, Ethylacetate, r.t., 93%.

The initial attempts to oxidize the 2°-propargylic alcohol in **9** to ketone followed by dihydroxylation and acetonation to realize the key fragment **11** were futile. Alternatively, the asymmetric dihydroxylation followed by acetonation and oxidation was more straightforward. Unfortunately this was not more efficient in enantiomeric exess due to pre existence of racemic 2° alcohol group. As no alternative route worked to circumvent this problem, we proceeded with the synthesis as it is. Thus the initial dihydroxylation of enynol **9** to triol **5** was successfully achieved under Sharpless asymmetric dihydroxylation conditions and subsequent acetonation of 1°, 3° diol was pleasingly successful to obtain ynol **10** in over 95% yield. The oxidation of ynol **10** to ynone **11** was achieved in over 92 % yield using MnO_2 (5 eq.) in CH_2Cl_2 for 5 h. At this juncture, the optical purity of **11** was determined using chiral HPLC (Chiralcel OB-H column) and found to be slightly over 75%. This relatively modest *ee* may be attributed to the pre existence of racemic 2° alcohol in enynol **9**. No attempt to enrich the ee was attempted, as the objective was to initially synthesize only structural analogs for SAR. Deprotection of acetonide with 80% acetic acid afforded alkyne keto diol **12**. The next task of selective and partial reduction of triple bond to *cis* olefin under Pd–$CaCO_3$, H_2 also triggered the intramolecular lactalization to furnish the desired 'C' ring intermediate **4** of Eleutherobin in 93% yield. This fully functionalized 'C' ring equivalent of eleutherobin will be further utilized in synthesis of Eleutherobin analogs.

Conclusions

In conclusion, this manuscript describes the practical synthesis of the 'C' ring equivalent of Eleutherobin which is compatable to scale up to multigram quantities to be used in making structural analogs.

Experimental Section

General Procedures. Crude products were purified by column chromatography on silica gel (60-120 mesh). ^{1}H NMR spectra were obtained in $CDCl_3$ at 200 and 300 MHz. Chemical shifts are given in ppm, with respect to internal TMS, *J* values are quoted in Hz. Infrared spectra were obtained neat, only the most significant absorptions in cm^{-1} are indicated. The optical rotations were recorded on JASCO DIP-370 digital polarimeter. All reactions were carried out under nitrogen atmosphere using dry glassware.

1-[2-(*tert*-Butyldiphenylsilyloxy)-ethyl]-4-methyl-4-penten-2-ynyl alcohol (9). To a stirred solution of enyne **8** (0.88 g, 13.3 mmol)[12] in THF (40 mL) under nitrogen atmosphere at –20 ^{o}C, was added drop wise a 1.6 M solution of ^{n}BuLi in hexane (8.3mL, 13.3 mmol) over a period of 15 minutes. The reaction mixture was stirred at the same temperature for 10 minutes and the aldehyde **7** (5.00 g, 16 mmol) in THF (30 mL) was added. The stirring was continued for 1 h at – 20 ^{o}C, and the reaction was quenched by the addition of saturated NH_4Cl (50 mL) while being vigorously stirred and allowing the temperature to rise slowly to room temperature. The resulting solution was diluted with water and extracted with ether (3x100 mL), and the combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent and purification by column chromatography furnished the enynol **9** (5.69 g, 94%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (t, 4H, *J* = 7.4 Hz), 7.43-7.32 (m, 6H), 5.25 (s, 1H), 5.20 (s, 1H), 4.79-4.72 (m, 1H), 4.07-4.00 (m, 1H) 3.84-3.78, (m, 1H), 2.99 (bs, 1H), 2.08-1.98 (m, 1H), 1.88 (s, 4H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.82, 134.06, 132.28, 129.08, 127.05, 121.26, 87.98, 85.48, 61.10, 38.26, 26.07, 25.84, 22.67 and 18.34; IR (KBr): 3418, 2859, 1428, 1108 and 704 cm^{-1}; MS (EI): *m/z* 321 (M-57, -^{t}Bu), 294, 247, 229, 199, 105, 77 and 57; Anal. Calcd for $C_{24}H_{30}O_2Si$: C, 76.14; H, 7.99 Found: C, 76.35; H, 8.02.

7-(*tert*-Butyldiphenylsilyloxy)-2-methyl-(2*R*)-3-heptyne-1,2,5-triol (5). To a 250 mL round bottom flask was added 72.5 mL of ^{t}BuOH, 72.5 mL of water and AD mix-α (20.30 g, 1.4 g/mmol). The mixture was stirred at room temperature for about 5 minutes and then cooled to 0 ^{o}C. To this solution was added enynol **9** (5.0 g, 13.2 mmol) and the reaction was stirred vigorously at 0 ^{o}C for 24 h. The reaction was quenched with saturated aqueous sodium sulfite (20.50 g) at room temperature. Ethyl acetate (100 mL) was added to the reaction mixture, and after separation of the layers, the aqueous phase was further extracted with the ethylacetate (2x50 mL). The combined organic layers were washed with brine, and dried over anhydrous Na_2SO_4. The

purification of the crude residue gave triol **5** (4.90 g, 90% yield) as a viscous liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.72-7.52 (m, 4H), 7.48-7.24 (m, 6H), 4.64 (q, 1H, J = 5.2 Hz), 3.96-3.64 (m, 2H,) 3.58 (dd, 1H, $J_{1,2}$ = 3.7, $J_{1,3}$ = 11.1), 3.42 (d, 1H, J = 11.1 Hz), 1.98-180 (m, 2H), 1.34 (s, 3H), 1.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.49, 133.20, 129.76, 127.73, 86.88, 84.86, 70.65, 68.45, 61.25, 60.55, 39.36, 26.82, 25.13, and 19.09; IR (KBr): 3330, 2931, 1427, 1061 and 761 cm^{-1}; MS (FAB): *m/z* 412 (M^+), 391, 307, 269, 229, 199, 167, 154, 135, 107, 91, 69 and 47; Anal. Calcd for $C_{24}H_{32}O_4Si$: C, 69.87; H, 7.82 Found: C, 69.62; H, 7.95.

1-[2-(*tert*-Butyldiphenylsilyloxy)-ethyl]-3-[2,2,4-trimethyl-(4*R*)-1,3-dioxolan-4-yl]-2-propynyl alcohol (10). To a solution of 2,2-dimethoxypropane (2.22 mL, 21.3 mmol) and camphorsulfonic acid (0.24 g, 1.06 mmol) in CH_2Cl_2 (50 mL) was added drop wise to a solution of the triol **5** (4.40 g, 10.6 mmol) in CH_2Cl_2 (30 mL) at 25 ^{o} C. After stirring for 30 minutes, the reaction mixture was quenched by adding a few drops of triethylamine. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography to give the corresponding acetonide **10** (4.58 g, 95% yield) as colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.77-7.48 (m, 4H), 7.44-7.20 (m, 6H), 4.64 (q, 1H, $J_{1,2}$ = 5.9, $J_{1,3}$ = 11.1), 4.12-3.86 (m, 2H), 3.84-3.60 (m, 2H), 3.01 (d, 1H, J = 5.9 Hz), 2.08-174 (m, 2H), 1.48 (s, 3H), 1.40 (s, 3H), 1.34 (s, 3H), 1.01 (s, 9H); IR (KBr): 3471, 2935, 1107 and 771 cm^{-1}; MS (FAB): *m/z* 437 (M-CH_3), 319, 269, 229, 199, 165, 138, 135, 105, 77 and 57; Anal. Calcd for $C_{27}H_{36}O_4Si$: C, 71.64; H, 8.02 Found: C, 71.76; H, 8.15.

5-(*tert*-Butyldiphenylsilyloxy)-1-[2,2,4-trimethyl-(4*R*)-1,3-dioxolan-4-yl]-1-pentyn-3-one (11). A mixture of acetonide **10** (4.00 g, 8.8 mmol) and MnO_2 (3.84 g, 44.2 mmol) in CH_2Cl_2 (60 mL) was stirred at room temperature for 5 h. Then, it was filtered through a pad of celite, the solvent was evaporated and the residue was purified by column chromatography to afford the ketone **11** (3.66 g, 92% yield). $[\alpha]_D^{25}$: -4.86° (*c* 1.2, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.68-7.58 (m, 4H), 7.52-7.26 (m, 6H), 4.15 (d, 1H, J = 8.1 Hz), 3.96 (t, 2H, J = 5.9 Hz), 3.74 (d, 1H, J = 8.1 Hz), 2.74 (t, 2H, J = 5.9 Hz), 1.54 (s, 3H), 1.44 (s, 3H), 1.38 (s, 3H), 1.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.05, 136.77, 135.95, 130.13, 128.12, 111.79, 93.51, 82.38, 75.70, 73.84, 59.63, 48.57, 27.15, 26.99, 26.59, 26.24, and 19.58; IR (KBr): 2934, 1681, 1108, 772 and 704 cm^{-1}; MS (FAB): *m/z* 393 (M-^{t}Bu), 315, 199, 165, 135, 91 and 57; Anal. Calcd for $C_{27}H_{34}O_4Si$: C, 71.96; H, 7.60 Found: C, 71.49; H, 7.72.

6,7-Dihydroxy-1-(*tert*-butyldiphenylsilyloxy)-6-methyl-4-heptyn-3-one (12). A solution of **11** (3.30 g, 7.3 mmol) in 80% aq. AcOH (100 ml) was stirred at room temperature for 24 h. The reaction mixture was concentrated under vacuum and the residue was diluted with CH_2Cl_2 (100 ml) cooled to 0 ^{o}C and was neutralized to pH-7 by adding saturated aq. $NaHCO_3$ solution in small portions. The layers were then separated, aqueous layer extracted with CH_2Cl_2 (2x50 mL) and the combined organic extracts were washed sequentially with water and brine. After drying Na_2SO_4 and removing solvent under vacuum, purification of the crude residue gave keto diol alkyne **12** (2.46 g, 82% yield). $[\alpha]_D^{25}$: -6.24^0 (*c* 0.6, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.62 (d, 4H, J = 6.8 Hz), 7.42-7.32 (m, 6H), 3.97 (d, 2H, J = 5.2 Hz), 3.63 (d, 1H, J = 11.3 Hz) 3.45 (d, 1H, J = 11.3 Hz), 2.75 (t, J = 5.2 Hz), 1.42 (s, 3H), 1.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$):

δ 185.50, 135.65, 133.40, 129.81, 128.01, 94.88, 82.64, 74.25, 71.62, 59.45, 46.40, 27.15, 26.42, and 19.82; IR (KBr): 3330, 2931, 1670, 1427, 1061 and 761 cm^{-1}; HRMS (FAB) Calcd for $C_{24}H_{30}O_4Si$ (M^+) 410.1913 Found: 410.1909.

5-Hydroxy-5-[2-(*tert*-butyldiphenylsilyloxy)-ethyl)-2-methyl-(2*R*,5*R*)-2,5-dihydro-2-furanyl methanol (4). A suspension of Lindlar's catalyst (0.3 mol %) in toluene (50 ml) was treated with H_2 at room temperature for 10 minutes. A solution of **12** (2.20 g, 5.3 mmol) in toluene (15 ml) was then added. After 20 minutes the reaction mixture was filtered through celite and concentrated by evaporation. The crude product was purified by flash chromatography to give **4** (2.05 g, 93 % yield). $[\alpha]_D^{25}$: -5.4° (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, 4H, *J* = 6.8), 7.42-7.32 (m, 6H), 5.80-5.50 (m, 2H), 3.97 (d, 2H, *J* = 5.2 Hz), 3.63 (d, 1H, *J* = 11.3 Hz), 3.45 (d, 1H, *J* = 11.3 Hz), 2.75 (t, 2H, *J* = 6.09 Hz), 1.42 (s, 3H), 1.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.72, 132.92, 130.28, 129.75, 128.50, 126.62, 98.22, 75.82, 74.56, 53.62, 46.32, 21.75, 20.52, and 19.02; IR (KBr): 3330, 2431, 1670, 1427, 1051 and 761 cm^{-1}; HRMS (FAB) Calcd for $C_{24}H_{32}O_4Si$ (M^+) 412.2069 Found: 412.2062.

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