Synthesis of the Tricyclic Core of Eleutherobin and Sarcodictyins and Total Synthesis of Sarcodictyin A

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Eleutherobin (**1**, Figure 1)[1,2] and sarcodictyins A (**2**)[3,4] and B (**3**),[3,4] are three marine-derived diterpenoids which share similar molecular architecture and exciting biological activity. Eleutherobin (**1**) was recently isolated by Fenical *et al.*[1,2] from an *Eleutherobia species* of soft corals (possibly *E. albiflora* Alcynoacea, Alcyoniidea) found in the Indian Ocean near Bennett's shoal in Western Australia, while sarcodictyins A (**2**) and B (**3**) were found by Pietra and his group in the Mediterranean stoloniferan coral *Sarcodictyon roseum* and first reported in 1987.[3] Faulkner[5] and Kashman[6] have reported the isolation of similar structures, valdivones[5] and eleuthosides.[6] Eleutherobin (**1**) and sarcodictyins A (**2**) and B (**3**) exhibit potent antitumor activities[1,2,4] against a variety of tumor cells. Moreover, these compounds exert their cytotoxic action via the paclitaxel-like mechanism[7] of inducing tubulin polymerization and microtubule stabilization. The success enjoyed by paclitaxel as an anticancer agent[8] and the recent excitement generated by the epothilones[9] bode well for the potential of these similarly behaving molecules in cancer chemotherapy. The novel molecular structures of eleutherobin and sarcodictyins, coupled with their natural scarcity and exciting biological actions, prompted us to undertake their total synthesis. In this communication, we report the construction of the tricyclic core structure (**I**, Figure 2) of these substances and the total synthesis of sarcodictyin A (**2**).

Structurally, eleutherobin (**1**) and sarcodictyins A (**2**) and B (**3**) consist of a synthetically challenging tricyclic skeleton and a *N*(6′)-methylurocanic acid side chain linked to the main frame through an ester bond of the C-8 hydroxyl group. While the sarcodictyins feature a free OH at C-4 and an ester at C-15, eleutherobin includes a methoxy group at C-4 and is β-glycosylated at C-15 with D-2-acetylarabinose. A major challenge of these natural products is the construction of their common tricyclic core. Figure 2 outlines, retrosynthetically, the present strategy toward this skeleton. Thus, it was anticipated that **I** could be derived by spontaneous ring closure of hydroxy ketone **II**, upon the generation of the latter compound from the corresponding 5,6-acetylenic system. The 10-membered ring of these structures was envisioned to arise from an intramolecular acetylide-aldehyde addition causing ring closure at C4−C5.

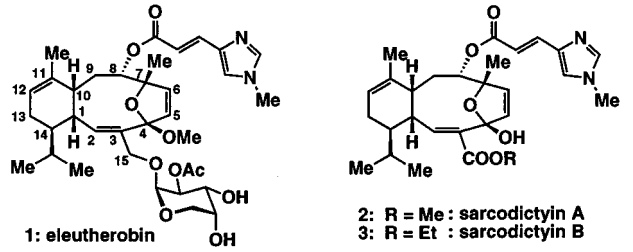

Figure 1. Structures of eleutherobin (**1**) and sarcodictyins A (**2**) and B (**3**).

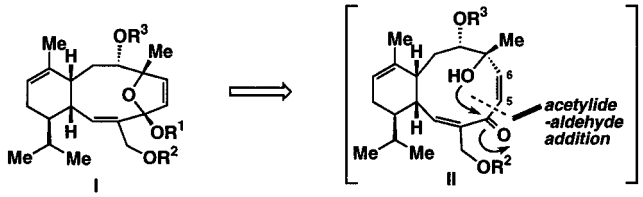

Figure 2. Retrosynthetic analysis of the core structure **1**.

Scheme 1 summarizes the construction of the required cyclization precursor **15**. Thus, **4** was obtained from (+)-carvone by a modification of Trost's method[10] and converted to ester **5** via a Claisen rearrangement [$(EtO)_3CCH_3$, EtCOOH, 170 °C, 74% yield]. DIBAL reduction (−78 °C) of **5** resulted in the formation of **6** in 97% yield, whereas condensation of the latter with the appropriate ketophosphonate anion gave ester **7** in 100% yield. Reduction of **7** with DIBAL (−78 → 0 °C) afforded **8** in 91%. Sharpless asymmetric epoxidation[11] of **8** gave the expected hydroxy epoxide (87%), which was mesylated (MsCl-Et_3N) and converted to alcohol **9** by the action of sodium naphthalenide[12] (90% for two steps). Alcohol **9** was then transformed to its PMB ether **10** by exposure to PMBOC(=NH)-CCl_3-PPTS[13] (89% based on *ca.* 50% conversion) and, thence, to ketone **11** by oxymercuration ($Hg(OAc)_2$; then Li_2PdCl_4−$CuCl_2$)[14] in 65% yield. The chelation-controlled addition[15] of HC≡CMgBr to **11** proceeded in CH_2Cl_2−THF (3:1) at −78 → 25 °C to afford, after desilylation (TBAF, 72% for two steps), acetylenic diol **12** (*ca.* 7:1 ds). The stereochemistry of this intermediate and its precursors was proven by an X-ray crystallographic analysis (see Supporting Information) of lactone A (Scheme 1), which was obtained by oxidation of **12** with excess of Dess−Martin reagent.[16] Careful oxidation of **12**, however, produced the desired aldehyde, which underwent Knoevenagel condensation with ethyl cyanoacetate[17] in the presence of β-alanine, furnishing, after silylation with TMSOTf-*i*Pr_2NEt, the (*E*)-cyanoester **13** exclusively (71% for three steps). The stereochemical outcome of this reaction was attributed to steric reasons and was confirmed by the successful ring closure to a 10-membered ring (*vide infra*). Finally, DIBAL reduction of **13** (74%), followed by protection of the resulting hydroxy alehyde (**14**) as a silyl ether (TIPSOTf), gave aldehyde **15** as a single isomer and in 91% yield.

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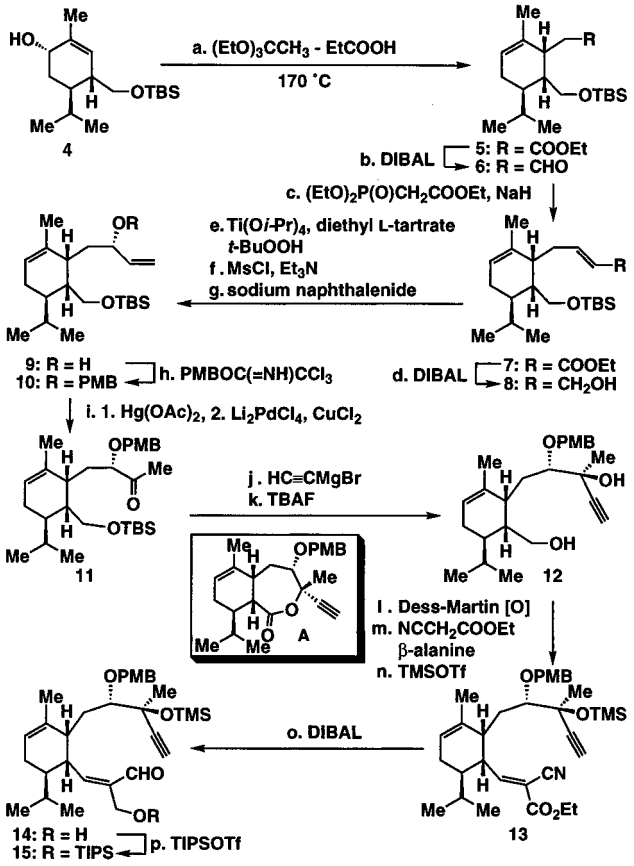
Scheme 1. Synthesis of Acetylene−Aldehyde Compound **15**[a]

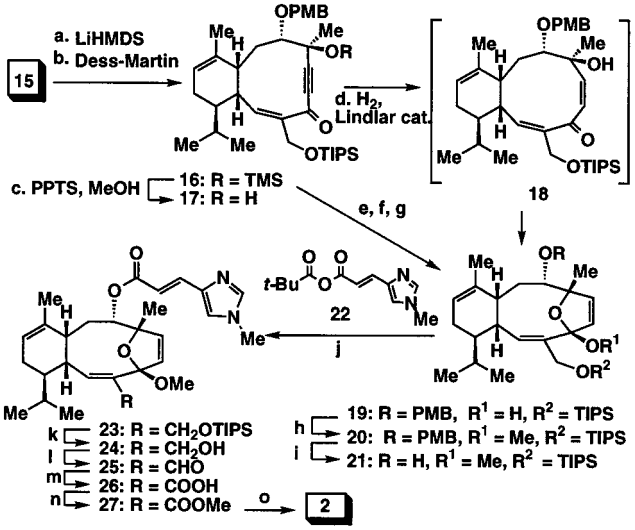


[a] a. 40 equiv of $(EtO)_3CCH_3$, 0.1 equiv of EtCOOH, 170 °C, 72 h, 74%; b. 1.0 equiv of DIBAL, CH_2Cl_2, −78 °C, 0.5 h, 97%; c. 1.5 equiv of $(EtO)_2P(O)CH_2CO_2Et$, 2.0 equiv of NaH, THF, 0 → 25 °C, 100%; d. 4.0 equiv of DIBAL, CH_2Cl_2, −78 → 0 °C, 2 h, 91%; e. 0.1 equiv of Ti(O*i*-Pr)$_4$, 0.12 equiv of diethyl L-tartrate, 1.5 equiv of *t*-BuOOH, CH_2Cl_2, −20 °C, 8 h, 87%; f. 5.0 equiv of MsCl, 6.0 equiv of Et_3N, CH_2Cl_2, −78 °C, 1 h; g. 5.0 equiv of sodium naphthalenide, THF, 0 °C, 10 min, 90% for two steps; h. 5.0 equiv of PMBOC(=NH)CCl_3, 1.0 equiv of PPTS, CH_2Cl_2, 25 °C, 48 h, 89%, *ca.* 50% conversion; i. 1.1 equiv of $Hg(OAc)_2$, MeOH, 25 °C, 12 h; then 1.0 equiv of Li_2PdCl_4, 3.0 equiv of $CuCl_2$, MeOH, 55 °C, 3 h, 65%; j. 15 equiv of HC≡CMgBr, CH_2Cl_2:THF, −78 → 25 °C, 12 h; k. 4.0 equiv of TBAF, THF, 25 °C, 1 h, 72% for two steps, ds ratio *ca.* 7:1; l. 1.5 equiv of Dess−Martin periodinate, 20 equiv of pyr, 20 equiv of $NaHCO_3$, CH_2Cl_2, 0 → 25 °C, 4 h; m. 30 equiv of $NCCH_2COOEt$, 4.0 equiv of *β*-alanine, 95% EtOH, 25 °C, 72 h; n. 5.0 equiv of TMSOTf, 10 equiv of *i*-Pr_2NEt, CH_2Cl_2, −78 °C, 10 min, 71% for three steps; o. 4.0 equiv of DIBAL, CH_2Cl_2, −78 °C, 2 h, 74%; p. 10 equiv of TIPSOTf, 20 equiv of *i*-Pr_2NEt, CH_2Cl_2, −78 °C, 1 h, 91%.

The ring closure of acetylenic aldehyde **15** was smoothly realized with LiHMDS in THF (0 → 25 °C), and the resulting alcohol was oxidized with Dess−Martin periodinate to afford the 10-membered ring ketone **16** (85% for two steps). Removal of the TMS group from **16** was achieved with PPTS in MeOH, leading to compound **17** (94%). Careful semireduction of the acetylene moiety was performed with H_2 and Lindlar's cat. in toluene, yielding directly the desired tricyclic compound **19** (75%), presumably via the intermediacy of **18**. With PPTS in MeOH, lactol **19** was converted to **20**.

The total synthesis of sarcodictyin A (**2**) was accomplished as shown in Scheme 2. Treatment of **20** with Na-liqNH_3 furnished the rather labile alcohol **21**, together with its 5,6-dihydro derivative (95%, *ca.* 2:1 ratio). This mixture was immediately esterified using mixed anhydride **22** (prepared from *N*(6′)-methylurocanic acid ethyl ester[18] by hydrolysis and reaction with *t*-BuCOCl) in the presence of Et_3N and 4-DMAP,

Scheme 2. Synthesis of Sarcodictyin **A** (**2**)[a]



[a] a. 2.0 equiv of LiHMDS, THF, 25 °C, 10 min; b. 2.5 equiv of Dess−Martin periodinane, 20 equiv of $NaHCO_3$, CH_2Cl_2, 0 → 25 °C, 4.5 h, 85% for two steps; c. 1.0 equiv of PPTS, MeOH, 25 °C, 30 min, 94%; d. 0.3 equiv of Lindlar's catalyst, H_2, PhMe, 25 °C, 20 min, 75%; e. 2.0 equiv of DDQ, CH_2Cl_2:H_2O, 25 °C, 0.5 h, 80%; f. 1.0 equiv of PPTS, MeOH, 25 °C, 1 h, 80%; g. 0.5 equiv of Lindlar's catalyst, H_2, PhMe, 25 °C, 20 min; h. 5.0 equiv of CSA, MeOH, 25 °C, 8 h, 76%; i. 5.0 equiv of Na-liquid NH_3, −78 °C; then 20 in THF−EtOH, 5 min, 95%; *ca.* 2:1 mixture of **21** and 5,6-dihydro-**21**; j. 5.0 equiv of **22**, 20 equiv of Et_3N, 2.0 equiv of 4-DMAP, CH_2Cl_2, 25 °C, 48 h, 83%; k. 4.0 equiv of TBAF, THF, 25 °C, 2 h, 100%; l. 2.5 equiv of Dess−Martin periodinane, 10 equiv of $NaHCO_3$, CH_2Cl_2, 25 °C, 0.5 h; m. 6.0 equiv of $NaClO_2$, 3.0 equiv of NaH_2PO_4, 50 equiv of 2-methyl-2-butene, THF, *t*-BuOH, H_2O; n. CH_2N_2, Et_2O, 88% for three steps; o. 2.0 equiv of CSA, $CHCl_3$:H_2O (10:1), 25 °C, 6 h, 80%.

furnishing, after purification, **23** in 60% overall yield from **20**. The same compound was obtained from **16** via a sequence involving: (i) DDQ deprotection of the PMP group (80%); (ii) removal of the TMS group with PPTS in MeOH (80%); (iii) H_2-Lindlar's catalyst; (iv) PPTS-MeOH to give **21** (52% for 2 steps); and (v) esterification with **22** (83%). Desilylation (TBAF, 100%) of **23**, followed by stepwise oxidation and esterification (CH_2N_2, 88% for three steps) as indicated in Scheme 2, gave methoxy sarcodictyin A (**27**) via intermediates **24**−**26**. Finally, exposure of **27** to CSA in $CHCl_3$:H_2O (10:1) furnished sarcodictyin A (**2**) in 90% yield. Synthetic sarcodictyin (**2**) exhibited identical properties to those reported[3] for the natural substance (^1H and ^{13}C NMR, MS, $[\alpha]^{25}_D$, IR and UV).

The described chemistry renders sarcodictyin A (**2**) readily available and paves the way for the construction of other members of the sarcodictyin family for chemical biology studies.

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Supporting Information Available: Physical data and procedures for selected compounds (34 pages). See any current masthead page for ordering and Internet access instructions.

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