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Synthetic Studies on Sarcodictyins and Eleutherobin: Synthesis of Fully Functionalized Cyclization Precursors

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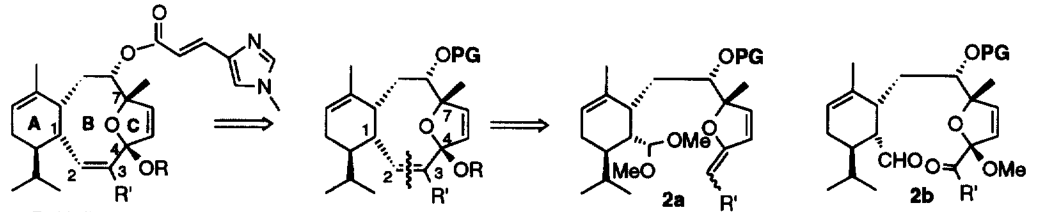
Abstract: Unprecedented synthetic transformations were demonstrated during the preparation of fully functionalized cyclization precursors of type **2**, in a synthetic approach to sarcodictyin A and B (**1a,b**) and eleutherobin (**1c**).

Keywords: antitumour compounds; asymmetric synthesis; marine metabolites; Wittig reactions

The marine diterpenoids sarcodictyins A and B (**1a,b**) [1] and eleutherobin (**1c**) [2] (Scheme 1), extracted in minute quantities from the soft corals *Sarcodictyon roseum* and *Eleutherobia albiflora*, have shown outstanding biological activity. Both eleutherobin and sarcodictyins show potent *in vitro* cytotoxicity against diverse tumor cell lines [2b, 3] and compete with paclitaxel for its binding at the microtubuli, inhibiting their depolymerisation [3b, 4]. This tubulin stabilizing activity adds sarcodictyins and eleutherobin to the restricted family of taxol®-like cytotoxic agents (together with the epothilones [5] and discodermolide [6]).



1a: R=H, R'=CO_2Me
1b: R=H, R'=CO_2Et
1c: R=Me, R'=CH_2O(2-O-acetyl-β-D-arabinopiranosyl)

R'=CO_2Et
PG=Protective group

R'=CH_2OPG
PG=Protective group

Scheme 1

The extremely interesting biological activity and limited availability of sarcodictyins and eleutherobin from natural sources has elicited a rapid solution to the problem of their synthesis. Two total syntheses of eleutherobin have been accomplished recently [7], and Nicolaou *et al.* also synthesized sarcodictyin A and B [3b, 8], making use of a known elaboration of (+)-carvone to assemble the six-membered ring [9].

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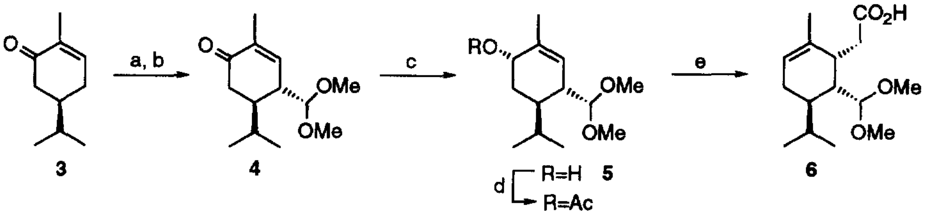
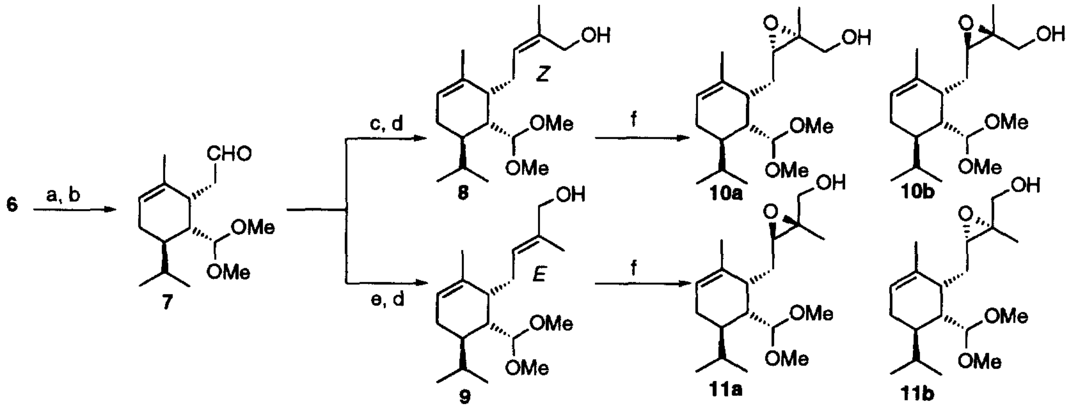
On approaching the synthesis of the common tricyclic skeleton of sarcodictyins and eleutherobin *via* a C_2-C_3 disconnection, intermediates of type **2a** and **2b** were identified as fully functionalized precursors to the closure of the B ring *via* an aldol type reaction (**2a**) or a McMurry reaction (**2b**). Their synthesis was achieved *via* a brief and convergent route, making use of some new synthetic transformations.

Intermediate **6** (Scheme 2), possessing the correct stereochemistry and appropriate functionality for the synthesis, was accessed through an unprecedented route, starting from the readily available natural product (-)-carvone. (-)-Carvone was subjected to selective hydrogenation to afford **3** [10]. Electrophilic formylation occurred from the less hindered face of the intermediate dienoxysilane [11], yielding **4** as the only diastereoisomer. Diastereoselective reduction from the equatorial direction with L-selectride® [12] gave alcohol **5** as the main product (9:1 diastereoisomeric ratio),[2] which was subjected to acetylation followed by an Ireland-Claisen rearrangement.



Scheme 2. Reagents and Conditions: a) MeMgBr (3M in Et_2O), $FeCl_3$, Et_2O, TMSCl, TEA, DMPU, -20 °C, RT, 81%; b) $BF_3{\cdot}Et_2O$, $(MeO)_3CH$, CH_2Cl_2, -70 °C, 45%; c) L-selectride®, THF, -78 °C, 91%, 9:1 d.r.; d) Ac_2O, TEA, DMAP, CH_2Cl_2, 95%; e) i. $LiN(TMS)_2$, TBDMSCl, THF, DMPU, -78 °C, RT; ii. Xylene, 190 °C, 5h; iii. NaOH, THF, 70%.

The acid appendage was elongated through either a *trans*- or a *cis*-selective Horner-Wittig reaction [13] with propionate derivatives on aldehyde **7** (Scheme 3). Following unsuccessful attempts with asymmetric dihydroxylation,[3] oxidation of the double bond was obtained *via* Sharpless asymmetric epoxidation (SAE) of



Scheme 3. Reagents and Conditions: a) $LiAlH_4$, Et_2O, RT, 91%; b) Dess-Martin periodinane, CH_2Cl_2, RT, 100%; c) $(CF_3CH_2O)_2P(O)CH(CH_3)CO_2Et$, 18-crown-6·$CH_3CN$, $KN(TMS)_2$, THF, -78 °C, 85%, Z only; d) $LiAlH_4$, Et_2O, RT, 96%; e) i. $(EtO)_2P(O)CH(CH_3)CO_2Et$, NaH, DME, RT, 85%, 9:1 E/Z; ii. separation of major E isomer by flash-chromatography; f) (+)- or (-)-DET (12%), $Ti(O{\it i}Pr)_4$ (10%), *t*BuOOH (5.5 M in nonane) (2 eq), CH_2Cl_2, -20 °C, 50-95%, see text for diastereoselectivities.

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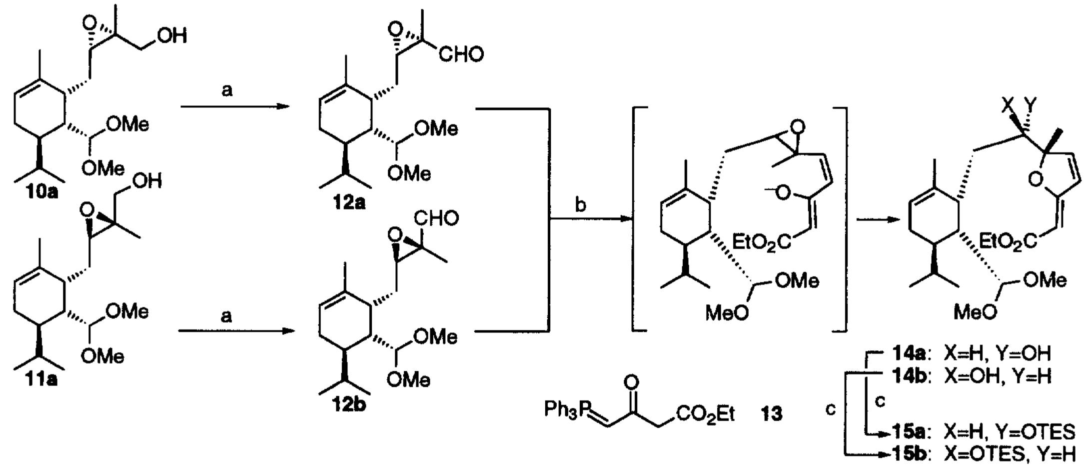
[2] The complementary ratio (1:9) was obtained by reduction from the axial direction with $LiAlH_4$.

[3] Although *p*-methoxybenzoyl protected allylic alcohols are reported to undergo regioselective dihydroxylation [14], the *p*-methoxybenzoyl derivative of **8** furnished the product corresponding to dihydroxylation of the endocyclic double bond when subjected to standard AD conditions.

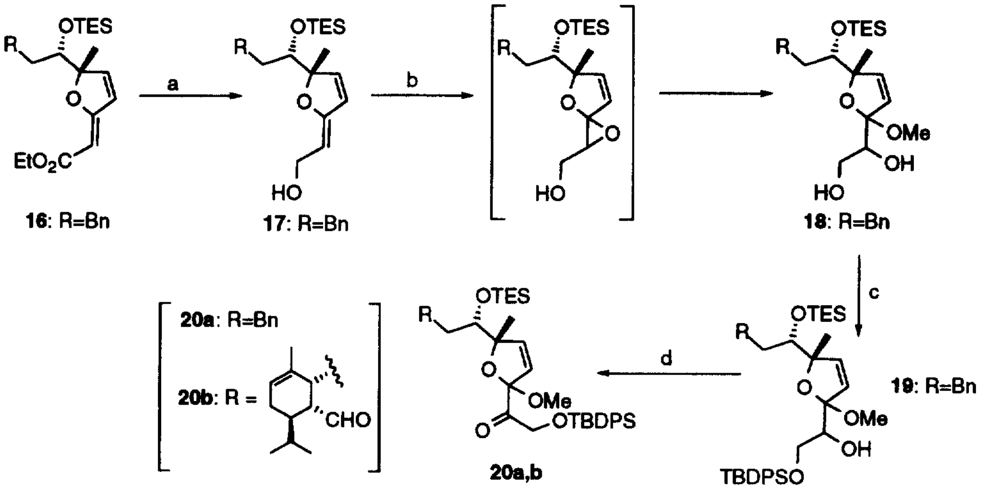
allylic alcohols **8** and **9**, prepared *via* reduction of the corresponding esters. Both (+)- and (-)-diethyl tartrate (DET) were employed, so that all possible diastereoisomeric epoxy-alcohols (**10a,b**, **11a,b**) were accessed. Reaction of **8** with (+)-DET gave a 1:9 mixture of **10a** and **10b**, while the reaction with (-)-DET proved to be a mismatched case, yielding a 1:1 ratio of the two diastereoisomers. On the contrary, excellent stereocontrol was obtained for **9**, which afforded either **11a** or **11b** upon reaction in the presence of (-)- and (+)-DET respectively (≥ 98:2 diastereoisomeric ratios). All epoxy-alcohols were cleanly oxidized to the corresponding aldehydes (e.g. **12a,b**, Scheme 4) with buffered Dess-Martin periodinane.

Although the anion of ethyl 4-(triphenylphosphoranylidene)acetacetate (**13**) is known to perform a Wittig reaction with aldehydes [15], no reaction was obtained with **12a,b** under the reported conditions (NaH, THF, H_2O). However, when **12a** was exposed to the anion of **13**, preformed with sodium bis-trimethylsilylamide in THF, a rapid and Z-selective Wittig reaction ensued; the intermediate enolate performed a conformationally biased intramolecular attack on the epoxide ring at the more substituted carbon, and **14a** was isolated in 60% overall yeld. This unprecedented transformation allowed the introduction of all the remaining carbon atoms and of the dihydrofuran ring C of the target molecules in a single highly convergent step. Alternatively, since **10a** represents a mismatched case product of the SAE, we examined **11a** as an alternative: the Wittig reaction of **12b** with **13** affords **14b**, from which the correct stereochemistry can be accessed *via* simple inversion of the secondary alcohol. Both alcohols were easily protected with triethylsilyl chloride.



Scheme 4. Reagents and Conditions: a) Dess-Martin periodinane, Py, CH_2Cl_2, RT, 98%; b) **13**, $NaN(TMS)_2$, THF, 0 °C, RT, 70%, 85:15 Z/E; c) TESCl, Imidazole, CH_2Cl_2, RT, 75%.

In view of employing an intramolecular McMurry reaction for the formation of ring B, we examined elaboration of the dihydrofuran side chain on model compound **16** (Scheme 5), which was obtained *via* an analogous route from hydrocinnamic aldehyde. Reduction of the ester moiety with lithium aluminium hydride afforded allylic alcohol **17**, an electron rich enol ether. It is known that the directive effect of hydroxy groups in dimethyldioxirane (DMDO) oxidations is diminished in protic solvent mixtures [16]. However, by treating **17** with DMDO in MeOH/acetone, exclusive oxidation of the exocyclic double bond was obtained, and the intermediate epoxide was smoothly converted to the desired diol **18** (mixture of diastereoisomers) by regioselective solvolysis in 92% overall yield. Ketone **20a** (1.8:1 acetal epimeric ratio) was easily obtained by selective protection of the primary hydroxy group and oxidation with Dess-Martin periodinane.



Scheme 5. Reagents and Conditions: a) $LiAlH_4$, Et_2O, 0 °C; b) DMDO, Acetone, MeOH, 0 °C, 92% (overall yield for a and b); c) TBDPSCl, Imidazole, CH_2Cl_2, RT, 80%; d) Dess-Martin periodinane, Py, CH_2Cl_2, RT, 83%.

The cyclization reactions of compounds **15b** and **20b** are currently under study, as well as new synthetic approaches to the tricyclic skeleton of sarcodictyins and eleutherobin.

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