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A carbonylative cross-coupling strategy to the total synthesis of the sarcodictyins: preliminary studies and synthesis of a cyclization precursor

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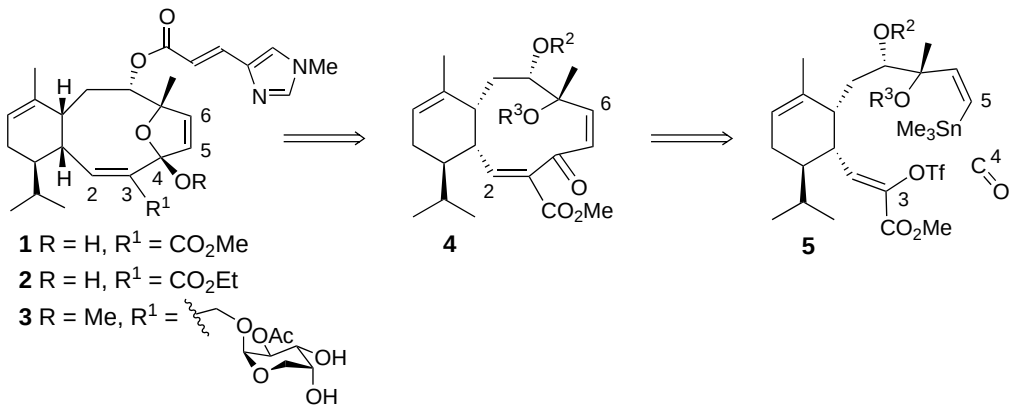
Abstract—Preliminary studies were conducted on the implementation of a new strategy to the total synthesis of the common diterpenoid tricyclic skeleton of sarcodictyins and eleutherobin. According to the approach presented, a key retrosynthetic disconnection is devised at the C3–C5 position, identifying a carbonylative cross-coupling reaction as the medium-sized ring forming step. The synthesis of a fully functionalized cyclization precursor, comprising a *Z* vinylstannane and a carboalkoxy-substituted *Z* enol triflate as reactive centres, is described.

The limitations inherent in the use of the chemoterapeutic agent Taxol® (paclitaxel) in clinical applications have raised interest in the identification of compounds of comparable cytotoxicity that share the same mode of action at the subcellular level.[1] Among these are the marine diterpenoids sarcodictyin A (**1**) and B (**2**)[2] and eleutherobin (**3**)[3] (Scheme 1). Both sarcodictyins and eleutherobin are characterized by an activity profile different from that of paclitaxel; in particular, they are active against paclitaxel resistant tumour cell lines and therefore hold potential as second generation microtubule-stabilizing anticancer agents.[4–6]

The challenging molecular architecture and potent biological activity of sarcodictyins and eleutherobin have immediately elicited the interest of the synthetic community. To date, sarcodictyins A and B have been synthesized successfully by Nicolaou et al.,[7] who have also exploited a similar route for accessing eleutherobin.[8] A subsequent report by Danishefsky and co-



Scheme 1. Key retrosynthetic disconnections.

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workers details an alternative access to eleutherobin.[9] A number of partial syntheses and alternative strategies have also been described.[10]

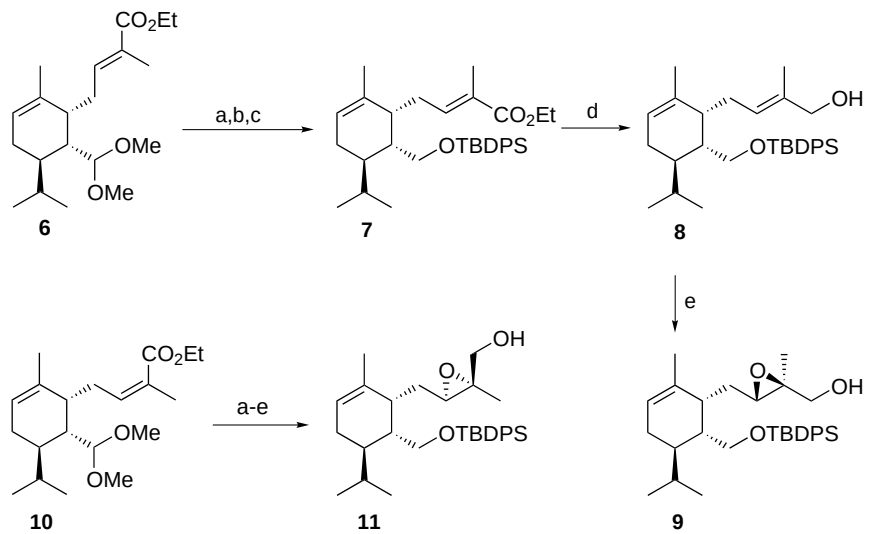
All members of the sarcodictyin family are characterized by a fused tricyclic skeleton of terpenoid origin comprising a six-, nine- and five-membered ring, in which the five-membered ring is an internal hemiacetal (or acetal in the case of eleutherobin). The most obvious retrosynthetic move is to convert the acetal into its parent ketone, thus revealing, after removal of the urocanic chain appendage, a bicyclic skeleton **4** (Scheme 1) featuring a six- and ten-membered ring.

The presence in the C2–C6 portion of target structure **4** of a substituted α-carboalkoxy-α,α′-dienone suggests the possible use of a Stille carbonylative cross-coupling reaction.[11] Application of this reaction to the key cyclization precursor **5**, bearing a *Z* vinylstannane and a carboalkoxy-substituted *Z* enol triflate as reactive centres, would directly introduce the desired substructural element. The present communication describes a synthetic approach to such a cyclization precursor.

The starting point of the synthetic pathway is ester **6**, available from our previous work on sarcodictyin synthesis (Scheme 2).[10a] From previous experience,[10a,d] as well as from model studies, we were aware that the dimethylacetal group of **6** would interfere in reactions featuring Lewis acids as promoters or catalysts, e.g. the Sharpless' asymmetric epoxidation[12] or Ti(O*i*-Pr)$_4$-promoted epoxide opening protocols.[13,14] We decided therefore to convert the dimethyl acetal to a less sensitive functionality. The C2‡ aldehyde in **6** was set free by acidic cleavage (99%), and subsequently reduced to a primary alcohol with $NaBH_4$ (93%). Protection with TBDPSCl yielded intermediate **7** (86%), in which the stability of the 'south' chain is secured. At this stage, reduction of the ester to the allylic alcohol **8** (99%) and Sharpless' asymmetric epoxidation[12] (87%; 90% considering recovered starting material) were straightforward. The *cis* epoxide **11** could also be accessed via the same route starting from the corresponding ester **10**.[10a] By means of a S_N2 opening at the secondary position, oxirane **11** would give the stereochemical arrangement present in the target molecule.

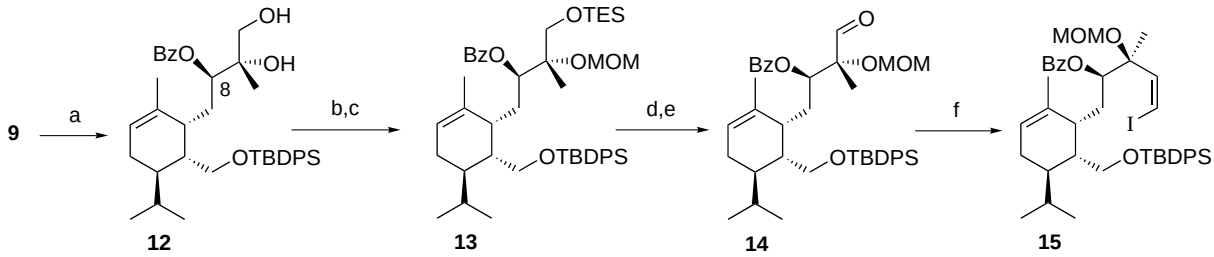
Application of the regio- and stereoselective epoxide opening procedure developed by Sharpless and coworkers [carboxylic acid, Ti(O*i*-Pr)$_4$, CH_2Cl_2],[13] did not lead to the desired opened products. A variant to this protocol, which involved preforming the titanium–nucleophile complex before addition of the substrate in chloroform,[14] proved more effective, though a sharp difference in the reactivity of the *cis* and *trans* oxiranes was observed. In the case of *cis* oxirane **11**, no opened product could be detected and/or isolated in satisfying yield, whereas epoxide **9** could be opened efficiently with the preformed titanium complex of benzoic acid to give **12** (66%; 86% considering recovered starting material) (Scheme 3). In the resulting diol **12**, the configuration of the secondary C8‡ position is opposite to that of the natural product, and must be redeemed at a later stage with an inversion step.

Diol **12** was protected with a TES group at the primary position, a methoxymethyl ether was introduced at the tertiary alcohol and then the primary alcohol was deprotected (TAS-F, 81% over three steps)[15] and oxidized (DMP)[16] to aldehyde **14** (99%). Application of Stork's ylide[17] led to isolation of the desired *Z* vinyl iodide **15** (61%).



Scheme 2. *Reagents and conditions*: (a) AcOH, THF, H_2O, rt, 17 h, 99%; (b) $NaBH_4$, EtOH, rt, 15 min, 93% (compound *E*), 98% (compound *Z*); (c) TBDPSCl, Im, CH_2Cl_2, rt, 2 h, 86% (compound *E*), 88% (compound *Z*); (d) $LiAlH_4$, Et_2O, rt, 30 min, 99% (compound *E*), 97% (compound *Z*); (e) TBHP, Ti(O*i*-Pr)$_4$ (10%), (+)-DET (12%), 4 Å MS, CH_2Cl_2, –20°C, 20 h, 87% (compound *E*), 55% (compound *Z*).

‡ Sarcodictyin numbering.



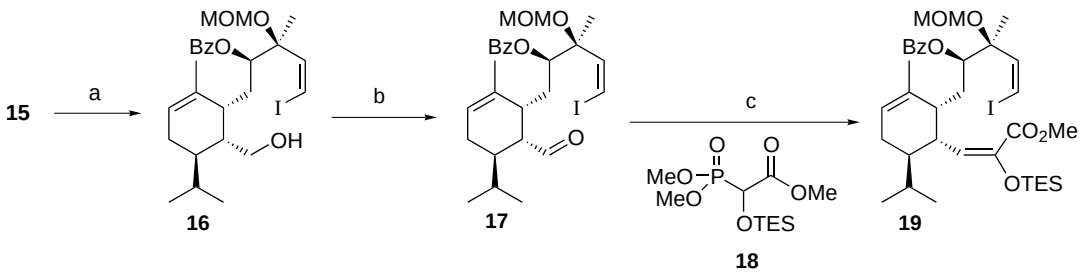
Scheme 3. *Reagents and conditions*: (a) $Ti(Oi\text{-}Pr)_4$, BzOH, then **9**, $CHCl_3$, rt, 8 h, 66% (+23% recovered starting material); (b) TESCl, Im, CH_2Cl_2, rt, 2 min; (c) MOMCl, DIPEA, CH_2Cl_2, 50°C, 8 h; (d) TAS-F, DMF, H_2O, rt, 40 min, 81% over three steps (b, c, d); (e) DMP, CH_2Cl_2, rt, 1 h, 99%; (f) Ph_3PCHI, $NaN(TMS)_2$, then **14**, −78°C, 3 h, 61%.

At this stage, we turned our attention to elaboration of the 'south' chain. Deprotection of the silyl ether at the C2‡ position with the HF·Py complex[18] led to the primary alcohol **16** (97%) (Scheme 4).

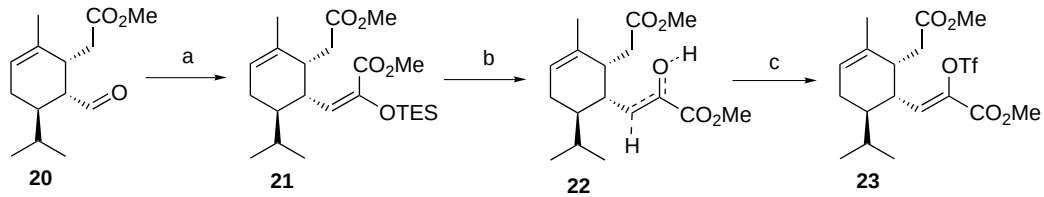
This was oxidized (DMP)[16] to aldehyde **17** (99%), which was homologated to silyl enol ether **19** in good yield (87%) by application of the phosphonate reagent **18**, bearing a silyl protected alkoxy group in the α-position. This reagent was developed by a minor modification of other known α-alkoxyphosphonate reagents.[19]

The α-alkoxy-α,β-unsaturated ester **21**, prepared in an analogous way (78%) from aldehyde **20**,[10a] was initially used as a model compound for the conversion of the silyl enol ether moiety to a *Z* enol triflate (Scheme 5). Deprotection of the triethylsilyl group with HF·Py[18] proceeded smoothly to give product **22** (70%), which was isolated as a mixture of tautomeric forms, comprising the keto form and the two isomeric enol forms. The stereoselective conversion of α-keto ester **22** to the *Z* enol triflate, which would serve as the coupling partner of the 'north' chain vinylstannane in the synthetic plan, was best achieved with Comins' reagent.[20] Selective formation of the *Z* enol triflate **23** from the model ketone could be achieved (50%) by employing a slightly substoichiometric amount (0.95 equiv.) of base, an expedient reported to favour formation of the thermodynamic enolate.[21]

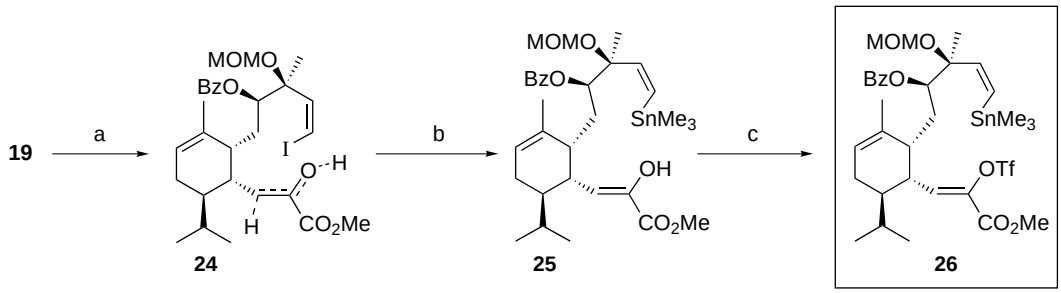
Removal of the silicon group from **19** with HF·Py[18] afforded, as before for the model compound, a mixture of tautomers **24** (72%) (Scheme 6). We decided to perform iodine to tin exchange before the triflate forming step, to avoid exposure of the delicate vinyl iodide to the strong base required for enolate formation. Treatment with Pd_2dba_3 and hexamethylditin gave *Z* vinylstannane **25** in disappointingly low yield (26%, 63% considering recovered starting material) for such a late stage transformation, which could not be improved by any variation of the experimental protocol.[22] The α-enol ester mojety of **25** (a single enol form was detected) could be converted with Comin's reagent[20] to the carboalkoxy-substituted enol triflate, which was isolated as a single *Z* isomer **26** (75%).



Scheme 4. *Reagents and conditions*: (a) HF·Py, THF/Py, 55°C, 8 h, 97%; (b) DMP, CH_2Cl_2, rt, 1 h, 99%; (c) **18**, $LiN(TMS)_2$, then **17**, THF, −78°C to rt, 1.5 h, 87%.



Scheme 5. *Reagents and conditions*: (a) **18**, $LiN(TMS)_2$, then **20**, THF, −78°C to rt, 1 h, 78%; (b) HF·Py, THF/Py, rt, 5 min, 70%, mixture of keto and enol tautomers; (c) $NaN(TMS)_2$ (0.95 equiv.), 2-bis-trifluoromethanesulfonyl-amino pyridine, THF, −78°C, 20 min–2 h, 50%, *Z*-isomer only.



Scheme 6. *Reagents and conditions*: (a) HF·Py, THF/Py, rt, 4.5 h, 72%; (b) Pd_2dba_3, hexamethylditin, NMP, 50°C, 6 h, 26%; (c) $NaN(TMS)_2$, 2-bis-trifluoromethanesulfonyl-amino pyridine, THF, −78°C, 1.5 h, 75%, *Z*-isomer only.

Previous studies from our group explored the behaviour of simple carboalkoxy-substituted enol triflates, such as that present in **26**, towards the palladium-catalyzed Stille carbonylative coupling with vinylic stannanes, resulting in the identification of optimal reaction conditions [CO (1 atm), Pd_2dba_3 (5%), CuI (20%), $As(Ph)_3$ (40%), LiCl (3 equiv.), NMP, rt].[11d] Preliminary attempts to use this protocol for the ten-membered ring closure of cyclization precursor **26** were not rewarding. Work is in progress in our laboratories to complete the synthetic sequence.

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