From D-Arabinose to the Marine Natural Product Eleutherobin

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In 1994 the soft coral *Eleutherobia* sp. was discovered as the source of a marine natural product with outstanding biological activity. In a bioassay-guided fractionation of its extract, Fenical et al. were able to attribute the cytotoxic activity to the glycosylated diterpenoid eleutherobin (**1**). The structure of **1** was elucidated by extensive 2D NMR spectroscopy and mass spectrometry (Figure 1).[1] The eunicellane carbon

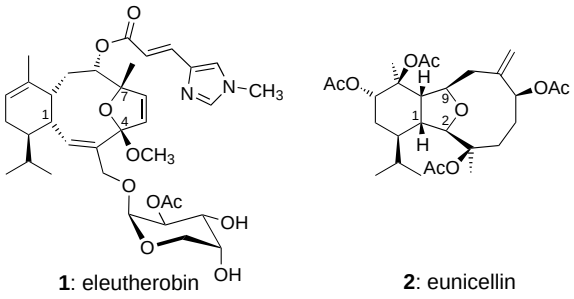


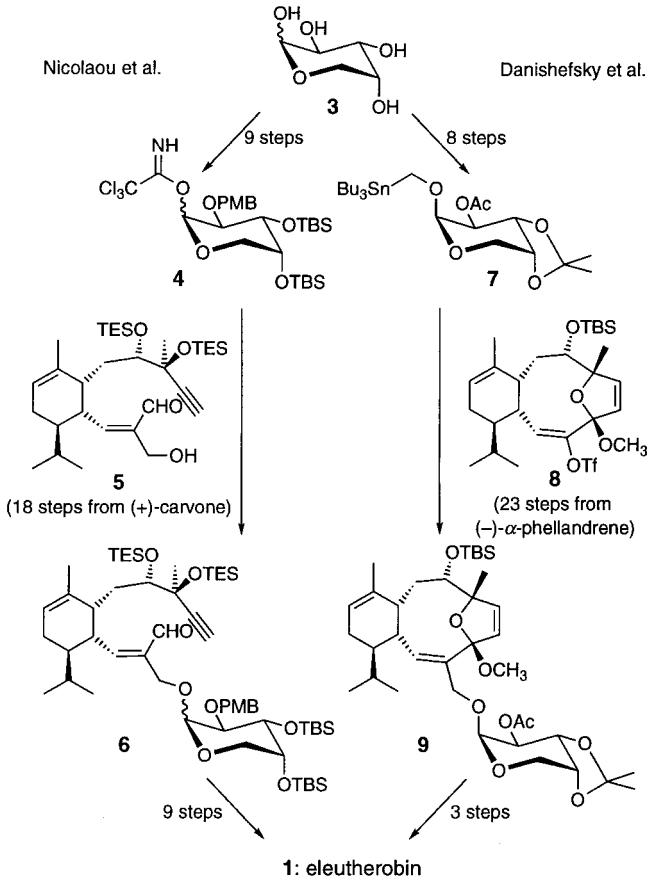
Figure 1. The marine natural products eleutherobin (**1**) and eunicellin (**2**).

skeleton of **1** is exclusive to natural products from gorgonians and alcyonaceans and it was observed for the first time in eunicellin (**2**) from *Eunicella stricta* in 1968.[2] Compounds **1** and **2** differ with respect to the position of their oxygen bridges, namely between C-2 and C-9 in **1** and between C-4 and C-7 in **2**. Other members of the small group of natural products with a 4,7-oxaeunicellane skeleton include the eleuthosides[3] and the nonglycosylated sarcodictyins[4] and valdivones[5] from related soft corals.

Eleutherobin (**1**) competes with paclitaxel (formerly known as taxol) for its binding at the microtubuli, inhibits their depolymerization, and thereby prevents the division of cancer cells.[6] Until 1994, paclitaxel had remained the only compound showing that mode of action, despite intense efforts.[7] Since then, additional natural products, the epothilones[8] and discodermolide[9], have shown the same effect. Eleutherobin (**1**) showed an in vitro cytotoxicity of about 10 – 15 nM (IC_{50}) against a diverse panel of tumor tissue cell lines with an approximate 100-fold increased potency toward selected breast, renal, ovarian, and lung cancer cell lines (National Cancer Institute (NCI)). It exhibited a similar tumor-type selectivity as paclitaxel (correlation coefficient 84%, COMPARE protocol[10], NCI).

From natural sources, eleutherobin (**1**) as well as the eleuthosides are available only in scarce amounts (0.01 – 0.02% of the dry weight of the rare alcyonacean *Eleutherobia* sp.). These are insufficient to explore their biochemical properties. This bottleneck was recently overcome by two total syntheses of eleutherobin (**1**) by Nicolaou et al.[11] and by Danishefsky et al.[12] Nicolaou et al. also synthesized the less cytotoxic sarcodictyin A.[11b]

Both research groups take advantage of the chiral pool and start from D-arabinose to synthesize their glycosylation building blocks **4** and **7**, respectively (Scheme 1). The two



Scheme 1. The synthetic strategies by Nicolaou et al. (left) and Danishefsky et al. (right). PMB = 4-methoxybenzyl; TBS = *tert*-butyldimethylsilyl; TES = triethylsilyl.

approaches differ strategically with regard to the order of the glycosylation step and the construction of the oxygen-bridged, ten-membered ring. While Nicolaou et al. make use of Schmidt's method and employ a trichloroacetimidate to glycosylate the monocyclic allylic alcohol **5**,[13] Danishefsky et al. first generate the norterpenoid tricycle **8**, which is then subjected to a modified Stille coupling to simultaneously introduce the missing carbon atom and the arabinose moiety.[14]

In both approaches, the required diastereomeric purity of the glycosylated intermediates **6** and **9**, respectively, is reached in a laborious way. Nicolaou et al. obtain **6** as a mixture of

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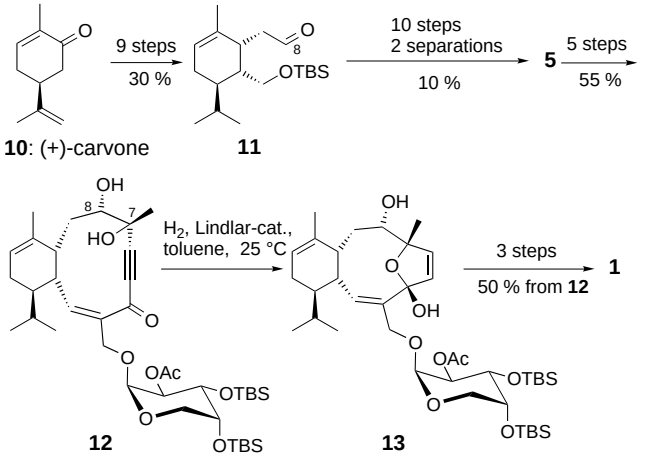
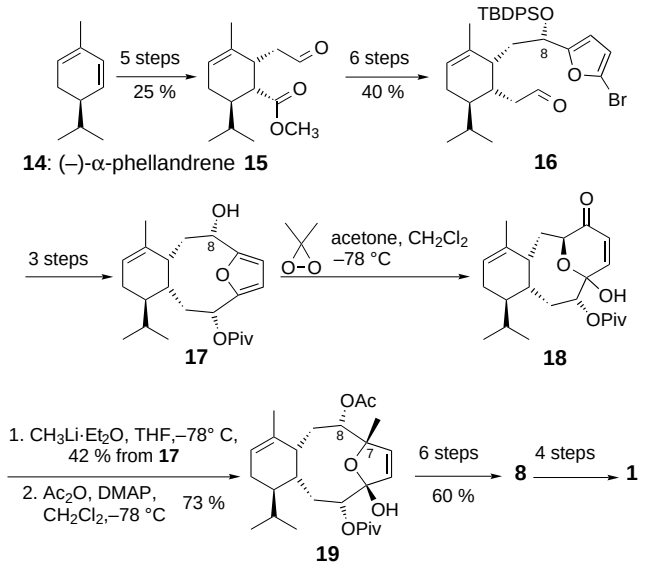
anomers from which the desired β-form is separated by column chromatography (α: 28%, β: 54%). Danishefsky et al. stereospecifically couple the anomerically pure arabinosyloxymethyl stannane **7** to the vinyl triflate **8**, but they obtain a yield of only 40–50%. In addition, **7** has to be separated from its α-anomer before use.

The monoterpenes (+)-carvone (**10**; Scheme 2) and (−)-α-phellandrene (**14**; Scheme 3) were chosen as the starting materials for the synthesis of the diterpenoid skeleton of eleutherobin (**1**) by Nicolaou et al. and Danishefsky et al., respectively. Again, both routes require the separation of



Scheme 2. Outline of the total synthesis of eleutherobin (**1**) by Nicolaou et al. TBS = *tert*-butyldimethylsilyl.



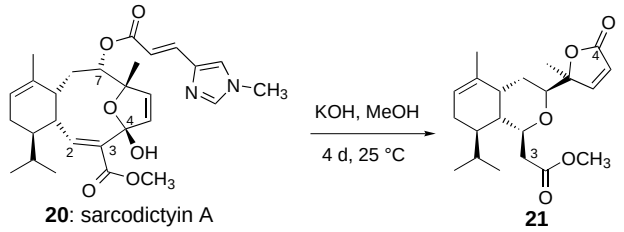
Scheme 3. Outline of the total synthesis of eleutherobin (**1**) by Danishefsky et al. DMAP = 4-dimethylaminopyridine; Piv = pivaloyl (CO*t*Bu); TBDPS = *tert*-butyldiphenylsilyl.

diastereomers by chromatography. The addition of 1-ethoxyvinyllithium to the TBS-protected aldehyde **11** (Scheme 2) leads to a mixture of diastereomeric alcohols (5:4 ratio in favor of the desired configuration at C-8), which is separated by Nicolaou et al. in a later step. Danishefsky et al. have to separate a mixture of diastereomeric alcohols after addition of 2-bromo-5-lithiofuran to their aldehyde **15** (Scheme 3), obtaining the desired diastereomer in a yield of 57%.

The key step of the synthesis by Nicolaou et al. is the stereoselective hydrogenation of the unsaturated cyclododecanone **12,** which was obtained through intramolecular acetylide–aldehyde condensation of **5**. The intermediate (*Z*)-olefin immediately rearranges to the tricyclic dihydrofuran **13** (Scheme 2). Solely the hydroxy group at the quaternary carbon atom C-7 takes part in the intramolecular formation of the hemiacetal. It can be concluded from the synthesis by Danishefsky et al. that the participation of the hydroxy group at C-8 could have been possible in that acetalization. Oxidation of the furan **17** (Scheme 3) by dimethyldioxirane at −78 °C gives the dihydropyranone **18**, because there appears to be no intermediate with a free hydroxy group at C-7. After nucleophilic methylation of **18**, the great preference of the cyclic system for the formation of a dihydrofuran ring becomes clearly visible. Treatment with acetic anhydride/DMAP leads to the selective acetylation of the ring oxygen atom of the dihydropyranone, and in the subsequent ring contraction to give **19**, it is substituted by the oxygen connected to C-7.

Both total syntheses of eleutherobin (**1**) are completed by the introduction of the (*E*)-*N*(6′)-methylurocanic acid moiety through acylation of the free hydroxy function at C-8, followed by the removal of the TBS- or isopropylidene protecting groups, respectively, in the arabinose side chain. The longest linear sequences are 28 steps in the case of the synthesis by Nicolaou et al. and 27 steps for that by Danishefsky et al.

The reactivity of the strained, tricyclic skeleton of the 4,7-oxaeunicellanes was previously studied by Pietra et al. in 1988, and their results could be of importance for an understanding of the chemical properties of these compounds.[4b] Treatment of sarcodictyin A (**20**) with methanolic potassium hydroxide led to the formation of the butenolide **21** (Scheme 4). The Michael acceptor property of the carbon



Scheme 4. The rearrangement of sarcodictyin A (**20**) observed by Pietra et al.

atom C-2 favors this rearrangement, leading to a relaxation of the strained ring system. After methanolysis of the *N*-methylurocanate, the newly formed hydroxy group attacks at C-2, and the fragmentation of the carbon–carbon bond between C-3 and C-4 by retro-Claisen condensation follows immediately thereafter.

The absolute stereochemistry of eleutherobin (**1**) had not been determined when the compound was first isolated, because priority was given to biological testing.[1] However,

results obtained by Pietra et al. strongly suggested the proposed absolute configuration of the diterpenoid 4,7-oxaeunicellane skeleton.[4] Of the enantiomeric arabinoses, the L-enantiomer appears to be favored in nature.[15] Therefore, it is remarkable that Nicolaou et al. and Danishefsky et al. could unambiguously identify the sugar unit of **1** as D-arabinose. In addition to a comparison of optical rotations, Danishefsky et al. even synthesized the L-arabinosyl diastereomer *neo*-eleutherobin.

In the tubulin depolymerization assay, synthetic eleutherobin (**1**) and two closely related analogues proved to be about as active as paclitaxel.[11a] It will be interesting to see whether the marine natural products containing a 4,7-oxaeunicellane skeleton will fulfill their promise.

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