Antitumor Agents

A Formal Total Synthesis of Eleutherobin Through an Unprecedented Kinetically Controlled Ring-Closing-Metathesis Reaction of a Densely Functionalized Diene**

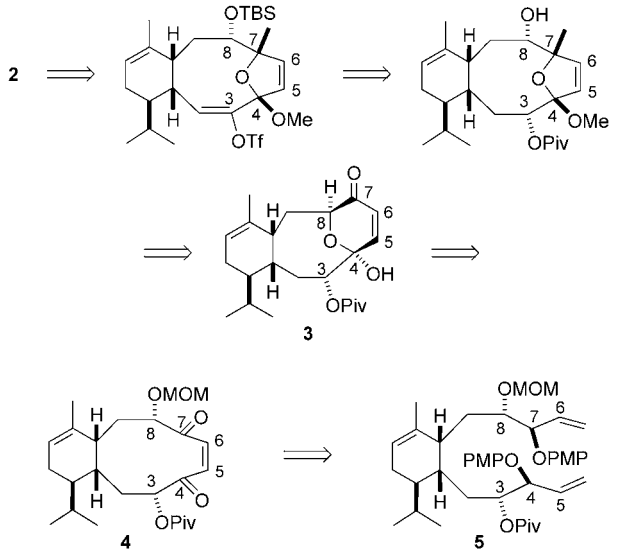
*Damiano Castoldi, Lorenzo Caggiano, Laura Panigada, Ofer Sharon, Anna M. Costa, and Cesare Gennari**

Sarcodictyins A (**1a**) and B (**1b**) were isolated in 1987 by Pietra and co-workers from the Mediterranean stoloniferan coral *Sarcodictyon roseum*.[1] Their antitumor activity was recognized about a decade later, and their taxol-like mechanism of action was discovered in 1996.[2] In the meantime, the diterpene glycoside eleutherobin (**2**) was reported by Fenical et al. from an *Eleutherobia* species of Australian soft coral, accompanied by disclosure of its potent cytotoxicity in 1995.[3] Two years later, eleutherobin was shown to act similarly to the sarcodictyins, effecting mitotic arrest through tubulin polymerization.[4] Both sarcodictyins and eleutherobin (the "eleutheside" family of microtubule-stabilizing drugs) are characterized by an activity profile different from that of taxol; they are active against taxol-resistant tumor cell lines and therefore hold potential as second-generation microtubule-stabilizing anticancer agents.[4,5] The scarce availability of **1** and **2** from natural sources makes their total syntheses vital for further biological investigations.[5] To date, sarcodictyin A and B have been synthesized successfully by Nicolaou et al.,[6] who have also exploited a similar route to eleutherobin.[7] A subsequent report by Danishefsky and co-workers details an elegant alternative access to eleutherobin.[8] A number of synthetic approaches to the eleutheside natural products and syntheses of simplified analogues have also been described.[9]

1a: R = Me
1b: R = Et

2

Herein we report the preparation of **3**, a key intermediate in the synthesis reported by Danishefsky and co-workers,[8] and thus a formal total synthesis of eleutherobin (**2**) (Scheme 1). The main step of our strategy, used for obtaining the [8.4.0] fused bicyclic ring system **4**, is a ring-closing metathesis (RCM)[10] reaction of the densely functionalized diene **5**.



Scheme 1. Retrosynthetic analysis of eleutherobin (**2**).

Diene **5** was synthesized from aldehyde **6** (prepared in six steps on a multigram scale from *R*-(−)-carvone in 30% overall yield)[9a,g] through multiple stereoselective Hafner–Duthaler oxyallylations (Scheme 2).[11] The first oxyallylation, in the presence of the [(*S*,*S*)-taddolCpTiCl] complex **7**, proceeded with complete stereocontrol to give the desired stereoisomer **8** in 73% yield. After standard protection of the alcohol as the methoxymethyl ether **9** in 95% yield, cleavage of the dimethylacetal group and reduction with $NaBH_4$ to give **10** in 75% yield, an efficient and well-established sequence of steps[8c,9n] led to the homologated aldehyde **11** (95%). The same oxyallylation procedure described above was applied, this time in the presence of the [(*R*,*R*)-taddolCpTiCl] complex **7**, to give the desired alcohol **12** in 83% yield with

[*] D. Castoldi, Dr. L. Caggiano,[+] L. Panigada, Dr. O. Sharon, Prof. Dr. C. Gennari
Dipartimento di Chimica Organica e Industriale
Centro di Eccellenza C.I.S.I., Università degli Studi di Milano
Istituto di Scienze e Tecnologie Molecolari (ISTM) del CNR
Via G. Venezian 21, 20133 Milano (Italy)
Fax: (+39) 02-5031-4072
E-mail: cesare.gennari@unimi.it
Dr. A. M. Costa
Departamento de Química Orgànica
Universitat de Barcelona
Av. Diagonal 647, 08028 Barcelona (Spain)
[+] Current address: Department of Chemistry
University of Sheffield
Dainton Building, Brook Hill, Sheffield, S3 7HF (UK)

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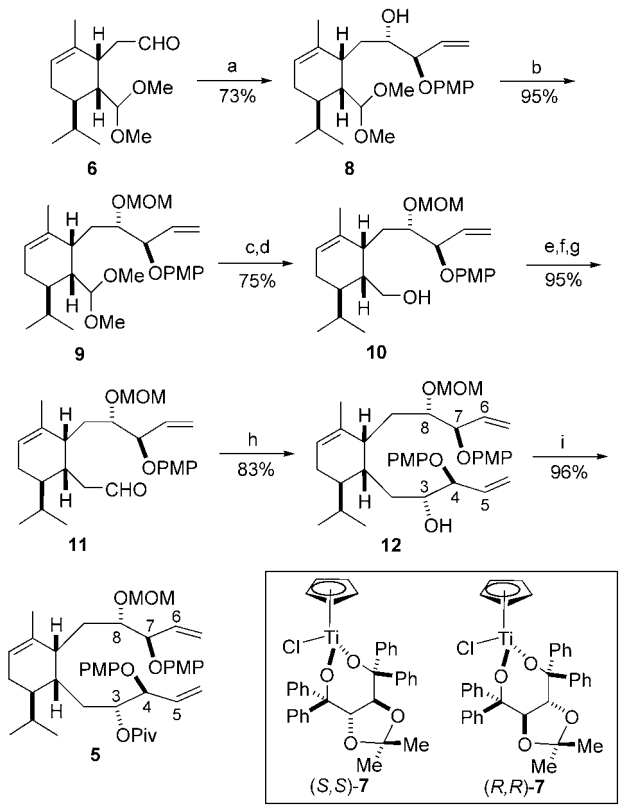
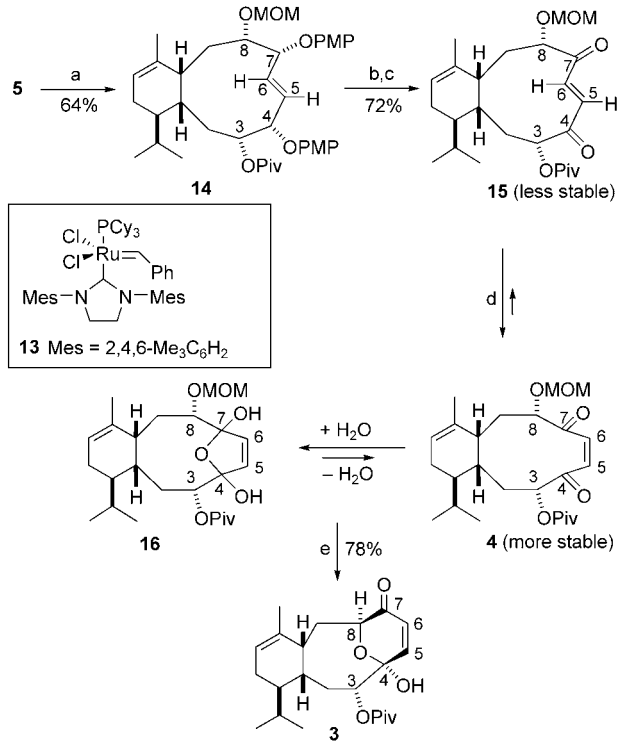


Scheme 2. Reagents and conditions: a) *s*-BuLi (1.3 M in cyclohexane), PMPOAllyl, [(*S*,*S*)-taddolCpTiCl] **7**, THF/Et_2O (57:43), −78→0 °C, 73 %; b) DIPEA, TBAI, MOMCl, CH_2Cl_2, 25 °C, 95 %; c) $LiBF_4$, CH_3CN/H_2O (98:2), 25 °C; d) $NaBH_4$, EtOH, 25 °C, 75 % over two steps; e) MsCl, TEA, CH_2Cl_2, 0→25 °C, 95 %; f) KCN, [18]crown-6, CH_3CN, 80 °C, quant.; g) DIBAL-H, toluene/hexane (1:2), −78 °C, quant.; h) *s*-BuLi (1.4 M in cyclohexane), PMPOAllyl, [(*R*,*R*)-taddolCpTiCl] **7**, Et_2O/THF (81:19), −78→25 °C, 83 %; i) PivCl, DMAP, DIPEA, CH_2Cl_2, 25 °C, 96 %. PMP = *p*-methoxyphenyl; DIPEA = diisopropylethylamine; TBAI = tetrabutylammonium iodide; MOM = methoxymethyl; Ms = methanesulfonyl; TEA = triethylamine; DIBAL-H = diisobutylaluminum hydride; Piv = *tert*-BuCO; DMAP = 4-(dimethylamino)pyridine; taddol = 1,1,4,4-tetraphenyl-2,3-O-isopropylidene-threitol.



Scheme 3. Reagents and conditions: a) cat. **13** (30 mol %), toluene, 110 °C, 6.5 h, 64 %; b) CAN, CH_3CN/H_2O (4:1), 0 °C, 80 %; c) DMP, CH_2Cl_2, 25 °C, 90 %; d) $CDCl_3$, 25 °C; e) $BF_3{\cdot}Et_2O$, Me_2S, CH_2Cl_2, −78→−20 °C, 78 %. CAN = ceric ammonium nitrate; DMP = Dess–Martin periodinane.

complete stereocontrol. Homoallylic alcohol **12** was then transformed into the pivalate **5** (96 %), and this diene was subjected to ring-closing metathesis.

The RCM reaction of a number of densely functionalized diene cyclization precursors of type **5** (bearing protected and/or free alcohol functionalities at both the allylic and the homoallylic positions) had previously been investigated with a variety of catalysts, but no desired cyclized frameworks were obtained.[9o] However, none of the previously examined diene precursors had the allylic alcohols protected as *p*-methoxyphenyl (PMP) ethers, which were discovered to facilitate the RCM reaction in comparison with other protective groups and with the free alcohols.[9o]

Based on these premises, diene **5** was treated with the second-generation Grubbs RCM catalyst[12] **13** (Scheme 3). Under forcing conditions[13] (slow addition by syringe pump (over 2.5 h) of a solution of RCM catalyst **13** (30 mol %) in toluene to a boiling solution of **5** in toluene, and additional stirring for 4 h at 110 °C), the *E* stereoisomer **14**[14] was formed and isolated in 64 % yield. This result contrasts sharply with many other *Z*-selective RCM reactions of diene cyclization precursors less-densely functionalized than diene **5**, that is, bearing protected and/or free alcohol functionalities at both the homoallylic positions and at only one allylic position.[9-h,m,n,o] In the presence of a second-generation Grubbs catalyst, these dienes lead to the more stable *Z*-cyclized products under thermodynamic control.[15] Preliminary molecular-mechanics calculations[16] show that the *E* stereoisomer **A** (corresponding to **14**) is less stable than the *Z* stereoisomer **B** by ≈ 6.6 kJ mol^{-1} (Figure 1). This energy difference increases to approximately 15.0 kJ mol^{-1} when the lowest-energy conformers are optimized at the PM3 level.[17] The reasons why the less stable *E* stereoisomer **14** was formed on this occasion (under kinetic control) and no trace of the more stable *Z* stereoisomer could be identified in the reaction mixture are not completely clear and will be investigated in detail. At the moment we can offer a tentative explanation as follows: the *trans* ruthenium-cyclobutane intermediate might be more stable than the *cis* species, leading to the *E* stereoisomer under kinetic control. Once formed, the *E* double bond of **14**, flanked by two bulky OPMP groups, might be too sterically hindered to react again with the ruthenium methylidene via cycloaddition and cycloreversion, thus arresting the equilibrium between the ring-closed and ring-opened products and inhibiting thermodynamic control.[18]

Confident that the greater stability of the *Z* 10-membered carbocycle would eventually prevail, we continued our

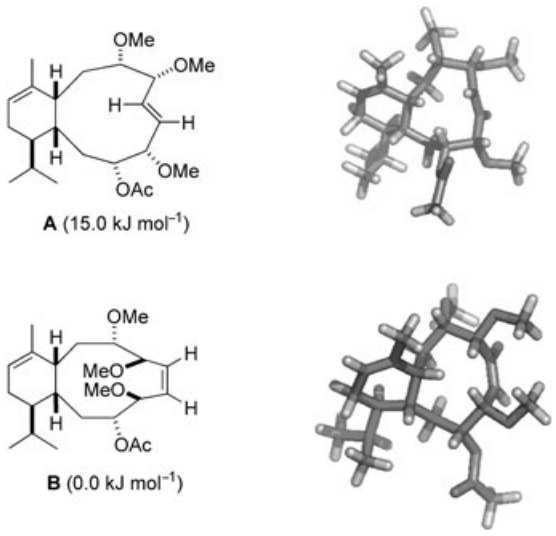


Figure 1. Lowest energy conformers and relative energies of the *E* stereoisomer **A** (corresponding to **14**) and of the *Z* stereoisomer **B**, obtained at the PM3 level.[16,17]

planned synthesis by removal of the PMP groups (CAN, 80%) and oxidation of the allylic diol (DMP, 90%). Enedione **15** (5-H, 6-H: $\delta = 7.02$, 6.64 ppm; $^3J_{5,6\text{-H}} = 17.3$ Hz) showed remarkable properties: while recording its ^{1}H NMR spectrum in $CDCl_3$ it cleanly isomerized to the more stable *Z* stereoisomer **4** (5-H, 6-H: $\delta = 7.20$, 6.13 ppm; $^3J_{5,6\text{-H}} = 14.0$ Hz; $t_{1/2} =$ 63 h). Bis-hemiacetal **16** (5-H, 6-H: $\delta = 6.29$, 6.18 ppm; $^3J_{5,6\text{-H}} = 5.8$ Hz) was obtained as the only product after flash chromatography of the *Z* enedione **4**, showing the propensity of **4** to add water and equilibrate with its hydrated form.[19] Finally, the MOM protecting group of the **15**/**4**/**16** mixture was removed ($BF_3{\cdot}Et_2O$, Me_2S)[20] to give compound **3** (78%), which produced analytical data identical to those previously reported by Danishefsky and co-workers (^{1}H NMR, ^{13}C NMR, IR spectroscopy, HRMS, R_f, $[\alpha]_D$).[8c]

In summary, we have completed a formal total synthesis of eleutherobin (**2**) through: 1) multiple stereoselective titanium-mediated oxyallylations, 2) an unprecedented kinetically controlled RCM reaction of a densely functionalized diene bearing two allylic alcohols protected as PMP ethers in the presence of a second-generation Grubbs catalyst, and 3) the isomerization of an *E* 10-membered enedione to the more stable *Z* 10-membered enedione.

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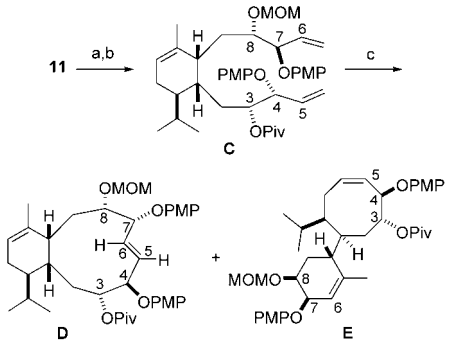
[18] The RCM reaction of a diastereoisomer of **5** (**C**) was also investigated. The *E* stereoisomer **D** ($^3J_{5,6\text{-H}} = 17.0$ Hz) was obtained (27%) together with the rearranged product **E** (15%), which originates from a ring-opening metathesis/ring-closing metathesis (ROM/RCM) process involving the trisubstituted double bond of the cyclohexene ring and the two terminal alkenes. Compound **D** was transformed into the target molecule **3** through the same sequence of reactions described in Scheme 3. Reagents and conditions: a) PMPOAllyl, *s*-BuLi (1.4 M in cyclohexane), (+)-Ipc_2BOMe, $BF_3{\cdot}Et_2O$, THF, −78 °C → 25 °C, 40%; b) PivCl, DMAP, DIPEA, CH_2Cl_2, 25 °C, 83%; c) cat. **13** (30 mol%), toluene, 110 °C, 6.5 h, 27% **D**, 15% **E**. PMP = *p*-methoxyphenyl; Piv = *tert*-BuCO; DMAP = 4-(dimethylamino)pyridine; DIPEA = diisopropylethylamine; (+)-Ipc_2BOMe = (+)-*B*-methoxydiisopinocampheylborane. For *syn*-selective boron-mediated oxyallylation reactions, see: H. C. Brown, P. K. Jadhav, K. S. Bhat, *J. Am. Chem. Soc.* **1988**, *110*, 1535 – 1538.



[19] ESI HRMS (resolution: 25800) of the *Z* enedione **4**, from a MeOH/H_2O (98:2) solution, gave the exact molecular ions $[M+Na]^+$ for **4** (calcd for $C_{25}H_{38}NaO_6$: 457.25606; found: 457.25582; error = 0.52 ppm), the hydrated form **16** (calculated for $C_{25}H_{40}NaO_7$: 475.26662; found: 475.26681; error = 0.40 ppm), and the hemiacetal-methylacetal corresponding to the addition of MeOH (calcd for $C_{26}H_{42}NaO_7$: 489.28227; found: 489.28031; error = 4.00 ppm).

[20] a) K. Fuji, T. Kawabata, E. Kujita, *Chem. Pharm. Bull.* **1980**, *28*, 3662 – 3664; b) M. Sasaki, T. Noguchi, K. Tachibana, *J. Org. Chem.* **2002**, *67*, 3301 – 3310.

