Pergamon

Tetrahedron Letters 42 (2001) 9187–9190

TETRAHEDRON LETTERS

Synthesis of a simplified sarcodictyin analogue which retains microtubule stabilising properties

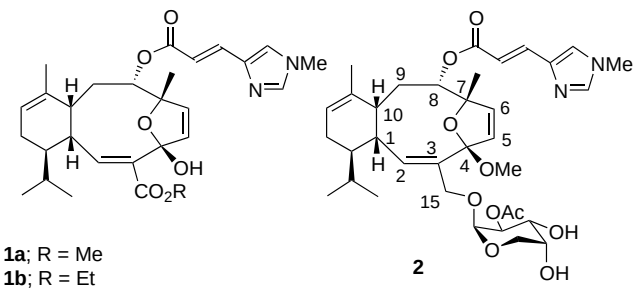
Joachim Telser,[a] Raphael Beumer,[a] Andrew A. Bell,[a] Simona M. Ceccarelli,[a] Diego Monti[b] and Cesare Gennari[a,b,*]

[a]*Dipartimento di Chimica Organica e Industriale, Università di Milano, via G. Venezian 21, I-20133 Milan, Italy*
[b]*Centro CNR per lo Studio delle Sostanze Organiche Naturali, via G. Venezian 21, I-20133 Milan, Italy*

Received 9 October 2001; accepted 23 October 2001

Abstract—A strategy featuring ring-closing metathesis as key reaction is applied to the synthesis of the sarcodictyin analogue **15**. The precursor diene is accessed via a brief and efficient protocol, employing multiple stereoselective allylations. Simplified analogue **15** retains microtubule stabilising properties.

Sarcodictyins A (**1a**) and B (**1b**) (Fig. 1) were isolated in 1987 by Pietra et al. from the Mediterranean stoloniferan coral *Sarcodictyon roseum*,[1] while their antitumour activity was recognised about a decade later, and their paclitaxel-like mechanism of action uncovered (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 (1995).[3] Two years later, in 1997, it was shown that eleutherobin, similarly to sarcodictyins, acted by mitotic arrest through induced tubulin polymerisation.[4]



1a; R = Me
1b; R = Et

2

Figure 1. Marine diterpenoids sarcodictyin A (**1a**), B (**1b**) and eleutherobin (**2**).

Both sarcodictyins and eleutherobin (the 'eleutheside' family of microtubule-stabilising drugs) are characterised 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-stabilising anticancer agents.[4,5] The scarce availability of **1** and **2** from natural sources (e.g. eleutherobin amounts to 0.01–0.02% of dry weight of the rare alcyonaceans of the *Eleutherobia* species) makes their total synthesis vital for further biological investigations.[5] To date, sarcodictyins A and B have been synthesised successfully by Nicolaou et al.,[6] who have also exploited a similar route for accessing eleutherobin.[7] A subsequent report by Danishefsky and co-workers details an elegant alternative access to eleutherobin.[8] A number of partial syntheses and alternative strategies have also been described.[9] The total syntheses of eleuthesides have generated very limited diversity in the diterpenoid core, with major variations reported only in the C-15 functionality.[5–8] However, there is a general agreement that the (*E*)-*N*-methylurocanic side chain, the C-4/C-7 ether bridge, and the cyclohexene ring are important determinants of antimitotic activity.[5]

As a part of our ongoing programme aimed at the synthesis of simplified analogues of the eleutheside natural products, ideally showing improved synthetic accessibility and retaining microtubule stabilising properties, we describe in this letter a brief and efficient synthesis of the 6–10 fused-ring system of the eleuthesides via a ring-closing metathesis (RCM) reaction.[10]

Keywords: allylation; antitumour compounds; metathesis; stereocontrol.

* Corresponding author. Tel.: +39-025835.4091; fax: +39-025835.4072; e-mail: cesare.gennari@unimi.it

0040-4039/01/$ - see front matter
PII: S0040-4039(01)02045-7

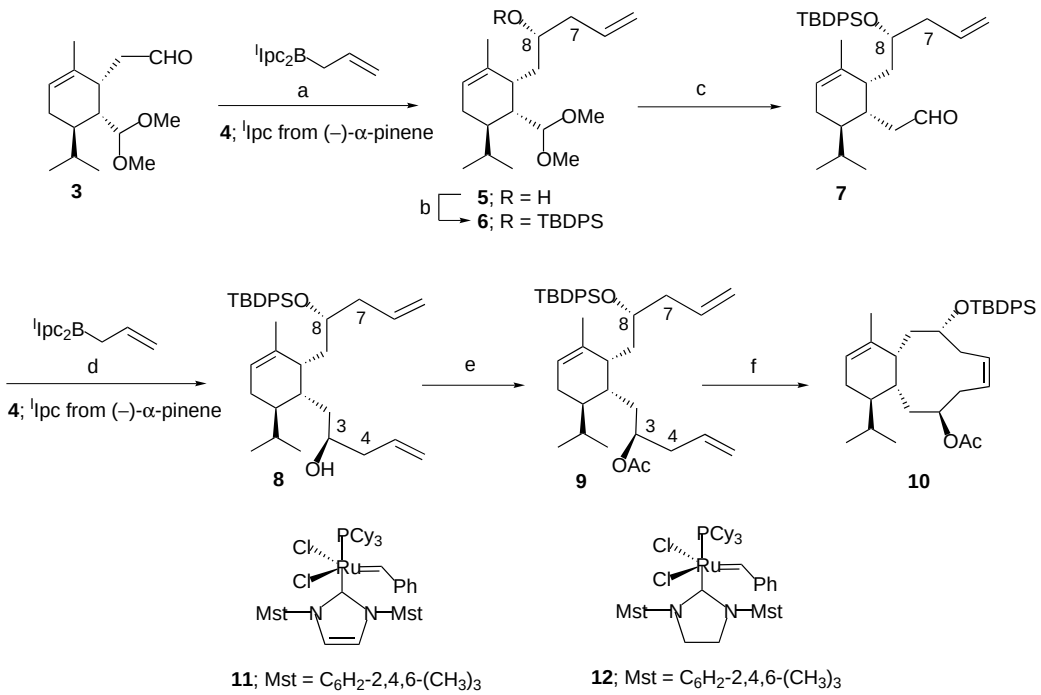
Despite its effectiveness in the synthesis of rings of all sizes, two factors still limit the scope of the RCM reaction: (a) in ring sizes ≥ 8, no control over the E/Z stereochemistry of the double bond generated is possible. Stereochemical control is mostly determined by the substrate structure and is probably of thermodynamic origin;[11] (b) the reports that describe application of the RCM to medium sized—particularly 10-membered—rings, are still very rare, especially when dense functionality close to the reaction centre is involved.[12]

Aldehyde **3**, previously synthesised in our laboratory,[9a,g] was prepared on a multigram scale and submitted to the allyl borane derived from (–)-α-pinene,[13] generating the C-8 oxygenated stereocentre (Scheme 1).

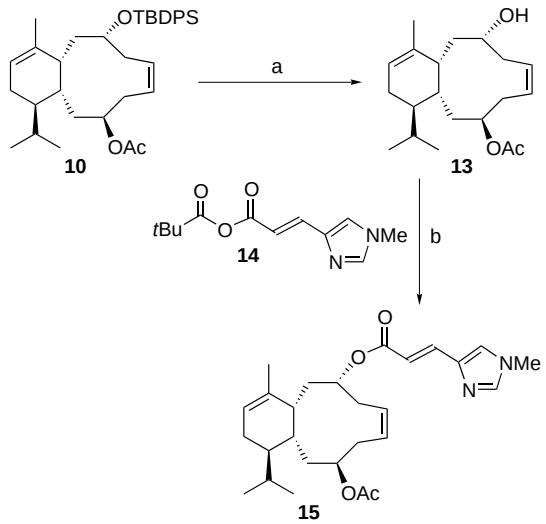
The allylation reaction proceeded with complete stereocontrol in favour of the desired stereoisomer (diastereomeric purity >95% by ^{1}H and ^{13}C NMR). After standard alcohol protection, an efficient and well established sequence of steps[8c] led to the homologated aldehyde **7**, on which the same allylation procedure described above was applied. Addition of the allyl borane derived from (–)-α-pinene to aldehyde **7** was again completely stereoselective (diastereomeric purity of **8** >95%). Homoallylic alcohol **8** was acetylated to **9**, and this compound was subjected to RCM using a variety of catalysts. After a number of attempts, the recently developed Nolan and Grubbs' catalysts **11**[14] and **12**[15] gave the desired ring-closed product **10** as a single Z stereoisomer in $\geq 80\%$ yield. As expected, entropic support (by virtue of the *cis* fusion to the cyclohexyl ring) made ring closure of diene **9** extremely smooth. Luckily, and delightfully, the stereochemistry of the double bond created by the RCM reaction was fully controlled in the desired sense (100% Z) by the structure of the new 10-membered ring.[11] The Z stereochemistry of the double bond was unequivocally assigned by detection of the olefinic $^3J_{cis}$ coupling constant (11.5 Hz between the protons at δ 5.51 and 5.86 ppm, respectively) by a 400 MHz H,H-COSY experiment, and by detection of a NOE contact between these protons in a 400 MHz NOESY experiment.

Although compound **10** does not possess the correct functionality for accessing the eleuthesides, it represents the first successful synthesis of the 6–10 fused-ring system via a 100% Z selective RCM, and can be exploited for accessing analogues and mimetics of the natural products, e.g. **15** (Scheme 2).[16]

Within the framework of a European collaboration (research training network: 'Design and synthesis of microtubule stabilising anticancer agents'), the drug-like compound **15** was investigated by the Botta group (Siena, Italy) using the tubulin minireceptor binding-site model described by Snyder and co-workers in 1999.[17] The model predicts for **15** a tubulin affinity (predicted dissociation constant $K_{\text{pred.}} = 24$ μM) only slightly weaker than paclitaxel ($K_{\text{pred.}} = 11$ μM, $K_{\text{expt.}} =$



Scheme 1. *Reagents and conditions*: (a) (i) THF, −78°C to rt, 6 h, (ii) H_2O_2, 6N NaOH, rt, 15 h, 77% (>95% diastereomeric purity); (b) TBDPS-Cl, excess imidazole, CH_2Cl_2, rt, 16 h, 98%; (c) (i) AcOH:THF:H_2O (3:1:1), rt, 16 h, 99%, (ii) $NaBH_4$, EtOH, rt, 15 min, 98%, (iii) Ms-Cl, Et_3N, CH_2Cl_2, 0°C to rt, 1 h, 98%, (iv) KCN, 18-crown-6, MeCN, 80°C, 5 h, 95%, (v) DIBAl-H, hexane–toluene (2:1), −78°C, 40 min, 98%; (d) (i) THF, −78°C, 2 h, (ii) H_2O_2, 6N NaOH, rt, 15 h, 55% (>95% diastereomeric purity); (e) Ac_2O, cat. DMAP, Py, rt, 90%; (f) **11** (20% mol), CH_2Cl_2, rt, 24 h, 80% (100% Z), or **12** (7% mol), CH_2Cl_2, rt, 168 h, 88% (95% after recovering starting material, 100% Z).



Scheme 2. *Reagents and conditions*: (a) TBAF, THF, rt, 94%; (b) **14** (Ref. 6b), Et_3N, DMAP, CH_2Cl_2, 59% (87% after recovering starting material).

15 μM) and sarcodictyin B ($K_{pred.} = 11$ μM, $K_{expt.} = 11$ μM).[18] The experimental tubulin polymerising ability was tested at Pharmacia (Nerviano, Italy): although **15** was shown to be less potent ($ED_{90} = 10$ μM) than paclitaxel ($ED_{90} = 0.5$ μM), which was used as a reference,[19] it is interesting to note that this simplified analogue of the natural product (lacking inter alia the C-4/C-7 ether bridge) retains microtubule stabilising properties.

Using Brown's oxyallylation methodology [(*Z*)-γ-(methoxymethoxy)allyldiisopinocampheylborane from either (−)- or (+)-α-pinene][13d] in one or both the allylation steps, we were able to synthesise in high yield and good stereoselectivity all possible compounds with *R*,*R* or *S*,*S* relative stereochemistry at the two oxygenated stereocentres formed in the reaction (7*S*,8*S*; 7*R*,8*R*; 3*S*,4*S*; 3*R*,4*R*). We are actively pursuing the use of these new substrates for the synthesis of structurally more related sarcodictyin analogues and for a total synthesis of the natural products (starting from 3*S*,4*S*,7*S*,8*S* or 3*R*,4*R*,7*S*,8*S*).

Acknowledgements

A graduate fellowship is gratefully acknowledged by S. Ceccarelli (Pharmacia, Nerviano, Italy). We thank the European Commission for financial support (IHP Network grant 'Design and synthesis of microtubule stabilising anticancer agents' HPRN-CT-2000-00018) and for postdoctoral fellowships to R. Beumer (IHP Network HPRN-CT-2000-00018), A. A. Bell ('Marie Curie' fellowship ERB FMB ICT 98 2891) and J. Telser ('Marie Curie' fellowship HPMFCT 1999 00001). We would also like to thank Merck (Merck's Academic Development Program Award to C. Gennari, 2001), and MURST COFIN 2000 (MM03155477) for financial support.

References

1. (a) D'Ambrosio, M.; Guerriero, A.; Pietra, F. *Helv. Chim. Acta* **1987**, *70*, 2019; (b) D'Ambrosio, M.; Guerriero, A.; Pietra, F. *Helv. Chim. Acta* **1988**, *71*, 965.
2. (a) Ciomei, M.; Albanese, C.; Pastori, W.; Grandi, M.; Pietra, F.; D'Ambrosio, M.; Guerriero, A.; Battistini, C. *Proc. Am. Assoc. Cancer Res.* **1997**, *38*, 5 (Abstract 30); (b) Battistini, C.; Ciomei, M.; Pietra, F.; D'Ambrosio, M.; Guerriero, A. Pharmacia S.p.A., PCT Int. Appl. WO 9,636,335, 1996 (*Chem. Abstr.* **1997**, *126*, P54863x).
3. Fenical, W.; Jensen, P. R.; Lindel, T. University of California, USA, 5,473,057, 1995 (*Chem. Abstr.* **1996**, *124*, P194297z).
4. (a) Lindel, T.; Jensen, P. R.; Fenical, W.; Long, B. H.; Casazza, A. M.; Carboni, J.; Fairchild, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 8744; (b) Long, B. H.; Carboni, J. M.; Wasserman, A. J.; Cornell, L. A.; Casazza, A. M.; Jensen, P. R.; Lindel, T.; Fenical, W.; Fairchild, C. R. *Cancer Res.* **1998**, *58*, 1111.
5. (a) For a comprehensive review on the chemistry and biology of the sarcodictyins, see: Nicolaou, K. C.; Pfefferkorn, J.; Xu, J.; Winssinger, N.; Ohshima, T.; Kim, S.; Hosokawa, S.; Vourloumis, D.; van Delft, F.; Li, T. *Chem. Pharm. Bull.* **1999**, *47*, 1199; (b) See also: Britton, R.; de Silva, D. E.; Bigg, C. M.; McHardy, L. M.; Roberge, M.; Andersen, R. *J. Am. Chem. Soc.* **2001**, *123*, 8632 and references cited therein.
6. (a) Nicolaou, K. C.; Xu, J.-Y.; Kim, S.; Ohshima, T.; Hosokawa, S.; Pfefferkorn, J. *J. Am. Chem. Soc.* **1997**, *119*, 11353; (b) Nicolaou, K. C.; Xu, J. Y.; Kim, S.; Pfefferkorn, J.; Ohshima, T.; Vourloumis, D.; Hosokawa, S. *J. Am. Chem. Soc.* **1998**, *120*, 8661; (c) Nicolaou, K. C.; Kim, S.; Pfefferkorn, J.; Xu, J.; Ohshima, T.; Hosokawa, S.; Vourloumis, D.; Li, T. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1418; (d) Nicolaou, K. C.; Winssinger, N.; Xu, J. Y.; Kim, S.; Pfefferkorn, J.; Ohshima, T.; Vorloumis, D.; Li, T. *J. Am. Chem. Soc.* **1998**, *120*, 10814.
7. (a) Nicolaou, K. C.; van Delft, F.; Ohshima, T.; Vourloumis, D.; Xu, J.; Hosokawa, S.; Pfefferkorn, J.; Kim, S.; Li, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2520; (b) Nicolaou, K. C.; Ohshima, T.; Hosokawa, S.; van Delft, F. L.; Vourloumis, D.; Xu, J. Y.; Pfefferkorn, J.; Kim, S. *J. Am. Chem. Soc.* **1998**, *120*, 8674.
8. (a) Chen, X.-T.; Gutteridge, C. E.; Bhattacharya, S. K.; Zhou, B.; Pettus, T. R. R.; Hascall, T.; Danishewsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 185; (b) Chen, X.-T.; Zhou, B.; Bhattacharya, S. K.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 789; (c) Chen, X.-T.; Bhattacharya, S. K.; Zhou, B.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 6563.
9. (a) Ceccarelli, S.; Piarulli, U.; Gennari, C. *Tetrahedron Lett.* **1999**, *40*, 153; (b) Rainier, J. D.; Xu, Q. *Org. Lett.* **1999**, *1*, 27; (c) Baron, A.; Caprio, V.; Mann, J. *Tetrahedron Lett.* **1999**, *40*, 9321; (d) Carter, R.; Hodgetts, K.; McKenna, J.; Magnus, P.; Wren, S. *Tetrahedron* **2000**, *56*, 4367; (e) Ceccarelli, S.; Piarulli, U.; Gennari, C. *J. Org. Chem.* **2000**, *65*, 6254; (f) Ceccarelli, S.; Piarulli, U.; Telser, J.; Gennari, C. *Tetrahedron Lett.* **2001**, *42*, 7421; (g) Ceccarelli, S.; Piarulli, U.; Gennari, C. *Tetrahedron* **2001**, *57*, 8531.

10. For reviews, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413; (b) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2037; (c) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371; (d) Fürstner, A. *Synlett* **1999**, 1523; (e) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073.
11. (a) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792; (b) Bourgeois, D.; Mahuteau, J.; Pancrazi, A.; Nolan, S. P.; Prunet, J. *Synthesis* **2000**, 869.
12. (a) Fürstner, A.; Müller, T. *Synlett* **1997**, 1010; (b) Chang, S.; Grubbs, R. H. *Tetrahedron Lett.* **1997**, *38*, 4757; (c) Gerlach, K.; Quitschalle, M.; Kalesse, M. *Synlett* **1998**, 1108; (d) Barrett, A. G. M.; Baugh, S. P. D.; Braddock, C.; Flack, K.; Gibson, V. C.; Giles, M. R.; Marshall, E. L.; Procopiou, P. A.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1998**, *63*, 7893; (e) Oishi, T.; Nagumo, Y.; Hirama, M. *Chem. Commun.* **1998**, 1041; (f) Quitschalle, M.; Kalesse, M. *Tetrahedron Lett.* **1999**, *40*, 7765.
13. (a) Brown, H. C.; Desai, M. C.; Jadhav, P. K. *J. Org. Chem.* **1982**, *47*, 5065; (b) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092; (c) Brown, H. C.; Jadhav, P. K.; Bhat, K. S.; Perumal, P. T. *J. Org. Chem.* **1986**, *51*, 432; (d) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 1535; (e) Brown, H. C.; Racherla, U. S.; Liao, Y.; Khanna, V. V. *J. Org. Chem.* **1992**, *57*, 6608.
14. (a) Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674; (b) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247; (c) Huang, J.; Schanz, H.-J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **1999**, *18*, 5375.
15. (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953; (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *43*, 18.
16. All compounds described in the present paper gave spectroscopic data completely in accordance with their assigned structures. Details will be provided in a subsequent full paper. Final compound **15** was obtained as a clear oil; $R_f = 0.25$ (hexane/EtOAc 1:4); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.70 (d, $J = 6.7$ Hz, 3H), 0.87 (d, $J = 6.7$ Hz, 3H), 1.26–2.05 (m, 12H), 2.07 (s, 3H), 2.18–2.23 (m, 1H), 2.25–2.40 (m, 2H), 2.77–2.88 (m, 2H), 3.72 (s, 3H), 5.18–5.24 (m, 1H), 5.34 (br s, 1H), 5.39–5.45 (m, 1H), 5.55–5.62 (m, 1H), 5.66–5.74 (m, 1H), 6.54 (d, $J = 15.6$ Hz, 1H), 7.09 (s, 1H), 7.47 (s, 1H), 7.55 (d, $J = 15.6$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 15.11, 20.88, 21.17, 24.22, 24.34, 26.22, 26.88, 29.18, 29.59, 31.61, 32.71, 33.49, 34.60, 37.31, 37.49, 72.51, 73.57, 116.35, 121.02, 122.20, 126.39, 127.92, 135.85, 137.93, 138.41, 166.72, 170.37; IR (CCl_4): ν 2960, 2850, 1745, 1705, 1640, 1450, 1440, 1380, 1345, 1295, 905 cm^{-1}; $[\alpha]_D^{20} = -29$ (c 0.7, EtOAc); HRMS [EI (30 eV)] calcd for $[C_{27}H_{38}N_2O_4]^+$: 454.2832. Found: 454.2802.
17. Wang, M.; Xia, X.; Kim, Y.; Hwang, D.; Jansen, J. M.; Botta, M.; Liotta, D. C.; Snyder, J. P. *Org. Lett.* **1999**, *1*, 43.
18. The tubulin minireceptor binding-site model was recently improved by inclusion of the sarcodictyins and eleutherobin in the training set (unpublished results and personal communication by Professor M. Botta, University of Siena).
19. ED_{90} = effective dose that induces 90% tubulin polymerisation (see Ref. 2b). These data were kindly provided by Dr. Nicola Mongelli and Dr. Sylvie Ducki (Pharmacia, Nerviano).