Antitumor Agents

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

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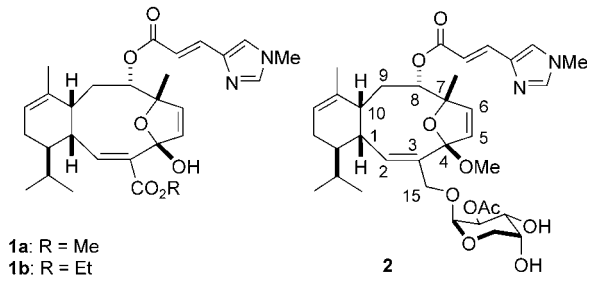
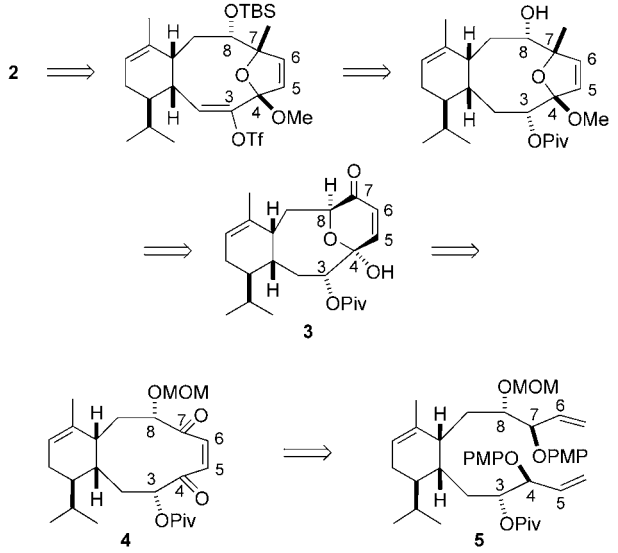
Sarcodictyins A (**1a**) and B (**1b**) were isolated in 1987 by Pietra and co-workers from the Mediterranean stoloniferan



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]

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



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

the [8.4.0] fused bicyclic ring system **4**, is a ring-closing metathesis (RCM)[10] reaction of the densely functionalized diene **5**.

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

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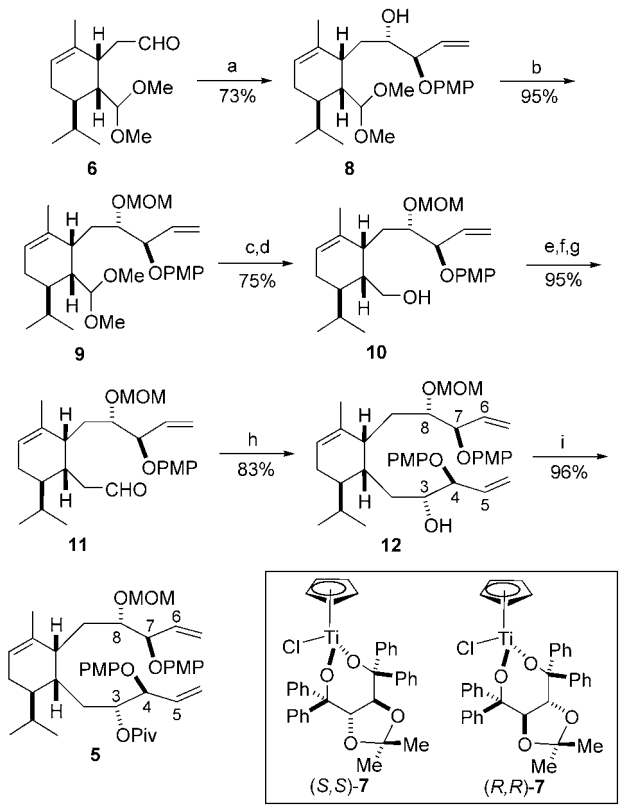
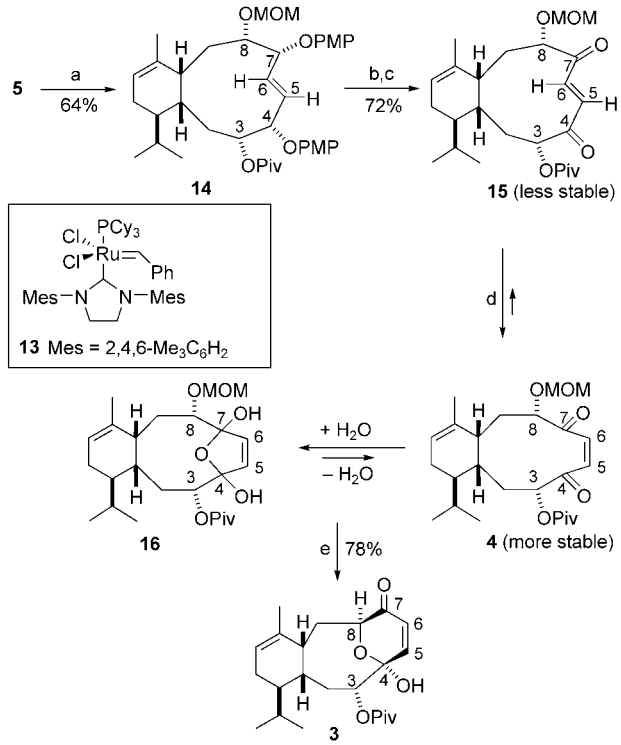


Scheme 2. Reagents and conditions: a) *s*-BuLi (1.3 M in cyclohexane), PMPOAllyl, [(*S*,*S*)-taddolCpTiCl] **7**, THF/Et_2O (57:43), −78→0 °C, 73%; b) DIPEA, TBAI, MOMCl, CH_2Cl_2, 25 °C, 95%; c) $LiBF_4$, CH_3CN/H_2O (98:2), 25 °C; d) $NaBH_4$, EtOH, 25 °C, 75% over two steps; e) MsCl, TEA, CH_2Cl_2, 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

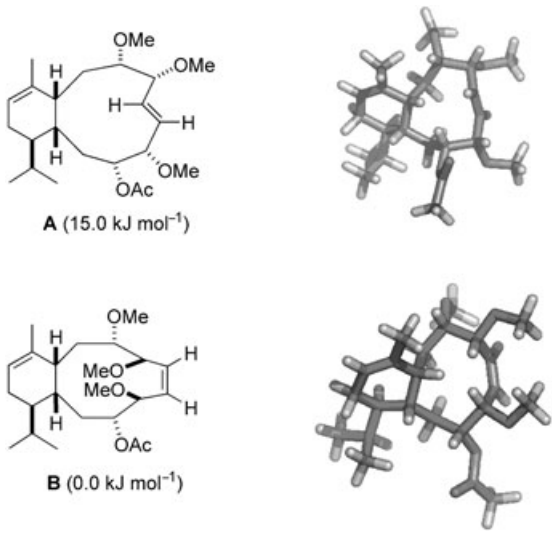


Figure 1. Lowest energy conformers and relative energies of the *E* stereoisomer **A** (corresponding to **14**) and of the *Z* stereoisomer **B**, obtained at the PM3 level.[16,17]

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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[1] a) M. D'Ambrosio, A. Guerriero, F. Pietra, *Helv. Chim. Acta* **1987**, *70*, 2019–2027; b) M. D'Ambrosio, A. Guerriero, F. Pietra, *Helv. Chim. Acta* **1988**, *71*, 964–976.

[2] a) M. Ciomei, C. Albanese, W. Pastori, M. Grandi, F. Pietra, M. D'Ambrosio, A. Guerriero, C. Battistini, *Proc. Am. Assoc. Cancer Res.* **1997**, *38*, 5 ; b) C. Battistini, M. Ciomei, F. Pietra, M. D'Ambrosio, A. Guerriero (Pharmacia S.p.A.), PCT Int. Appl. WO 9636335, **1996** [*Chem. Abstr.* **1997**, *126*, P54863x].

[3] W. Fenical, P. R. Jensen, T. Lindel (University of California), US 5473057, **1995** [*Chem. Abstr.* **1996**, *124*, P194297z].

[4] a) T. Lindel, P. R. Jensen, W. Fenical, B. H. Long, A. M. Casazza, J. Carboni, C. R. Fairchild, *J. Am. Chem. Soc.* **1997**, *119*, 8744–8745; b) B. H. Long, J. M. Carboni, A. J. Wasserman, L. A. Cornell, A. M. Casazza, P. R. Jensen, T. Lindel, W. Fenical, C. R. Fairchild, *Cancer Res.* **1998**, *58*, 1111–1115.

[5] For a comprehensive review on the chemistry and biology of the eleuthesides, see: K. C. Nicolaou, J. Pfefferkorn, J. Y. Xu, N. Winssinger, T. Ohshima, S. Kim, S. Hosokawa, D. Vourloumis, F. van Delft, T. Li, *Chem. Pharm. Bull.* **1999**, *47*, 1199–1213. See also: a) K. C. Nicolaou, N. Winssinger, D. Vourloumis, T. Ohshima, S. Kim, J. Pfefferkorn, J. Y. Xu, T. Li, *J. Am. Chem. Soc.* **1998**, *120*, 10814–10826; b) R. Britton, E. D. de Silva, C. M. Bigg, L. M. McHardy, M. Roberge, R. J. Andersen, *J. Am. Chem. Soc.* **2001**, *123*, 8632–8633, and references therein.

[6] a) K. C. Nicolaou, J. Y. Xu, S. Kim, T. Ohshima, S. Hosokawa, J. Pfefferkorn, *J. Am. Chem. Soc.* **1997**, *119*, 11353–11354; b) K. C. Nicolaou, J. Y. Xu, S. Kim, J. Pfefferkorn, T. Ohshima, D. Vourloumis, S. Hosokawa, *J. Am. Chem. Soc.* **1998**, *120*, 8661–8673; c) K. C. Nicolaou, S. Kim, J. Pfefferkorn, J. Y. Xu, T. Ohshima, S. Hosokawa, D. Vourloumis, T. Li, *Angew. Chem.* **1998**, *110*, 1484–1487; *Angew. Chem. Int. Ed.* **1998**, *37*, 1418–1421.

[7] a) K. C. Nicolaou, F. van Delft, T. Ohshima, D. Vourloumis, J. Y. Xu, S. Hosokawa, J. Pfefferkorn, S. Kim, T. Li, *Angew. Chem.* **1997**, *109*, 2631–2634; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2520–2524; b) K. C. Nicolaou, T. Ohshima, S. Hosokawa, F. L. van Delft, D. Vourloumis, J. Y. Xu, J. Pfefferkorn, S. Kim, *J. Am. Chem. Soc.* **1998**, *120*, 8674–8680.

[8] a) X.-T. Chen, C. E. Gutteridge, S. K. Bhattacharya, B. Zhou, T. R. R. Pettus, T. Hascall, S. J. Danishefsky, *Angew. Chem.* **1998**, *110*, 195–197; *Angew. Chem. Int. Ed.* **1998**, *37*, 185–187; b) X.-T. Chen, B. Zhou, S. K. Bhattacharya, C. E. Gutteridge, T. R. R. Pettus, S. J. Danishefsky, *Angew. Chem.* **1998**, *110*, 835–838; *Angew. Chem. Int. Ed.* **1998**, *37*, 789–792; c) X.-T. Chen, S. K. Bhattacharya, B. Zhou, C. E. Gutteridge, T. R. R. Pettus, S. J. Danishefsky, *J. Am. Chem. Soc.* **1999**, *121*, 6563–6579.

[9] a) S. Ceccarelli, U. Piarulli, C. Gennari, *Tetrahedron Lett.* **1999**, *40*, 153–156; b) A. Baron, V. Caprio, J. Mann, *Tetrahedron Lett.* **1999**, *40*, 9321–9324; c) R. Carter, K. Hodgetts, J. McKenna, P. Magnus, S. Wren, *Tetrahedron* **2000**, *56*, 4367–4382; d) S. Ceccarelli, U. Piarulli, C. Gennari, *J. Org. Chem.* **2000**, *65*, 6254–6256; e) Q. Xu, M. Weeresakare, J. D. Rainier, *Tetrahedron* **2001**, *57*, 8029–8037; f) S. Ceccarelli, U. Piarulli, J. Telser, C. Gennari, *Tetrahedron Lett.* **2001**, *42*, 7421–7425; g) S. Ceccarelli, U. Piarulli, C. Gennari, *Tetrahedron* **2001**, *57*, 8531–8542; h) J. Telser, R. Beumer, A. A. Bell, S. M. Ceccarelli, D. Monti, C. Gennari, *Tetrahedron Lett.* **2001**, *42*, 9187–9190; i) C. Sandoval, E. Redero, M. A. Mateos-Timoneda, F. A. Bermejo, *Tetrahedron Lett.* **2002**, *43*, 6521–6524; j) K. P. Kaliappan, N. Kumar, *Tetrahedron Lett.* **2003**, *44*, 379–381; k) J. D. Winkler, K. J. Quinn, C. H. MacKinnon, S. D. Hiscock, E. C. McLaughlin, *Org. Lett.* **2003**, *5*, 1805–1808; l) G. Scalabrino, X.-W. Sun, J. Mann, A. Baron, *Org. Biomol. Chem.* **2003**, *1*, 318–327; m) R. Beumer, P. Bayón, P. Bugada, S. Ducki, N. Mongelli, F. Riccardi Sirtori, J. Telser, C. Gennari, *Tetrahedron Lett.* **2003**, *44*, 681–684; n) R. Beumer, P. Bayón, P. Bugada, S. Ducki, N. Mongelli, F. Riccardi Sirtori, J. Telser, C. Gennari, *Tetrahedron* **2003**, *59*, 8803–8820; o) L. Caggiano, D. Castoldi, R. Beumer, P. Bayón, J. Telser, C. Gennari, *Tetrahedron Lett.* **2003**, *44*, 7913–7919; p) N. Ritter, P. Metz, *Synlett* **2003**, 2422–2424.

[10] For reviews, see: a) R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413–4450; b) S. K. Armstrong, *J. Chem. Soc. Perkin Trans. 1* **1998**, 371–388; c) M. E. Maier, *Angew. Chem.* **2000**, *112*, 2153–

2157; *Angew. Chem. Int. Ed.* **2000**, *39*, 2073 – 2077; d) A. Fürstner, *Angew. Chem.* **2000**, *112*, 3140 – 3172; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012 – 3043.

[11] A. Hafner, R. O. Duthaler, R. Marti, G. Rhis, P. Rothe-Streit, F. Schwarzenbach, *J. Am. Chem. Soc.* **1992**, *114*, 2321 – 2336, and references therein.

[12] a) J. Huang, E. D. Stevens, S. P. Nolan, J. L. Petersen, *J. Am. Chem. Soc.* **1999**, *121*, 2674 – 2678; b) M. Scholl, T. M. Trnka, J. P. Morgan, R. H. Grubbs, *Tetrahedron Lett.* **1999**, *40*, 2247 – 2250; c) J. Huang, H.-J. Schanz, E. D. Stevens, S. P. Nolan, *Organometallics* **1999**, *18*, 5375 – 5380; d) M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953 – 956; e) T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18 – 29.

[13] For a discussion of these optimized RCM conditions, see: K. Yamamoto, K. Biswas, C. Gaul, S. J. Danishefsky, *Tetrahedron Lett.* **2003**, *44*, 3297 – 3299.

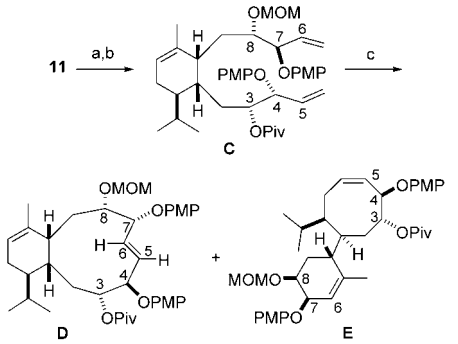
[14] The 5-H/6-H coupling constant was determined from a decoupled ^{1}H NMR spectrum acquired by irradiation at $\delta = 5.04$ ppm, which corresponds to the frequency of protons 4-H and 7-H. The signals of the olefinic protons (at $\delta = 5.96$ and 5.71 ppm, assigned to protons 5-H and 6-H) became two doublets whose coupling constant, typical of an *E* double bond, was easily determined: $^3J_{5,6\text{-H}} = 16.5$ Hz. The NOESY spectrum showed two positive cross peaks due to scalar coupling (*E* double bond), instead of two negative cross peaks due to NOE (*Z* double bond).

[15] The use of second-generation metathesis catalysts usually results in the selective formation of the thermodynamically favored stereoisomeric products in RCM reactions, which furnish medium-sized rings: a) C. W. Lee, R. H. Grubbs, *Org. Lett.* **2000**, *2*, 2145 – 2147; b) A. Fürstner, K. Radkowski, C. Wirtz, R. Goddard, C. W. Lehmann, R. Mynott, *J. Am. Chem. Soc.* **2002**, *124*, 7061 – 7069; c) J. Murga, E. Falomir, J. Garcìa-Fortanet, M. Carda, J. A. Marco, *Org. Lett.* **2002**, *4*, 3447 – 3449; d) J. Prunet, *Angew. Chem.* **2003**, *115*, 2932 – 2936; *Angew. Chem. Int. Ed.* **2003**, *42*, 2826 – 2830.

[16] The calculations were performed at the University of Barcelona. Lowest-energy conformers of structures **A** and **B** were calculated by performing Monte Carlo conformational searches (50000 steps for each isomer) with MacroModel 8.5 (MM2*, $CHCl_3$ GB/SA): a) F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson, W. C. Still, *J. Comput. Chem.* **1990**, *11*, 440 – 467; b) G. Chang, W. C. Guida, W. C. Still, *J. Am. Chem. Soc.* **1989**, *111*, 4379 – 4386; c) W. C. Still, A. Tempczyk, R. C. Hawley, T. Hendrickson, *J. Am. Chem. Soc.* **1990**, *112*, 6127 – 6129.

[17] The lowest-energy conformers obtained with MacroModel for isomers **A** and **B** (180 and 97 conformers respectively, using a 20.0 kJ mol^{-1} energy window from the global minima) were optimized at the PM3 level using the Gaussian 03 package (Gaussian 03 (Revision B.04), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **2003**).

[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.

