Pergamon

Tetrahedron Letters 43 (2002) 6521–6524

TETRAHEDRON LETTERS

Suitable entry to a 10-membered ring with eleutheside functionality through Nozaki–Hiyama condensation

Celso Sandoval, Elena Redero, Miguel A. Mateos-Timoneda and Francisco A. Bermejo*

Departamento de Química Orgánica, Universidad de Salamanca, Pza de la Merced sn, E-37008 Salamanca, Spain

Received 8 July 2002; accepted 17 July 2002

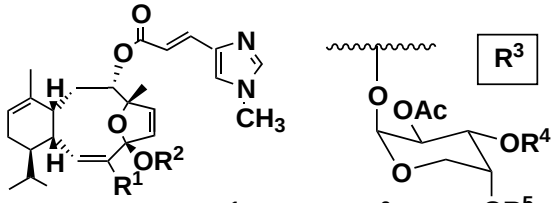
Abstract—Access to a medium-sized unit of 15-*seco*-eleutheside analog **19** has been opened through the $NiCl_2/CrCl_2$-mediated intramolecular condensation of iodoaldehyde **8** with excellent yields. Transformation of the phenylcyclononanol **15** into the tetracyclic analog **19** was achieved in a four-step sequence with 65% overall yield.

Gorgonian and soft corals are a rich source of oxacyclic diterpenes.[1] Sarcodictyns **1**–**2**[2,3] and eleutheside **3**–**5**[4–6] (Fig. 1) are derived from cembrane precursors by C2–C11 bond formation and have in common the oxatricyclic ring system of the 4,7-oxaeunicellane skeleton, composed of the oxacyclononane and dihydrofurane units containing six stereogenic centers, five of them inside the medium-sized oxacyclic moiety. It has been shown that eleutherobin **3**, similarly to sarcodictyns **1**–**2**, induces tubulin polymerization, causing mitotic arrest.[7] Both types of compound are active against paclitaxel-resistant tumor cell lines and have thus been included within the second generation of microtubule-stabilizing antimitotic agents.[8,9]

The limited availability of these diterpenes from natural sources means that their total synthesis is necessary to characterize their activity profile. To date, sarcodictyns **1**–**2** have been successfully synthesized by Nicolaou et al.,[10] while eleutherobin **3** has been prepared by the groups of Nicolaou[11] and Danishefsky.[12] Several synthetic approaches have also been published concerning alternative strategies to the above mentioned main synthetic contributions.[13]

In the course of studies directed toward the total synthesis of eleuthesides, we have undertaken a model study of the intramolecular cyclization leading to a 10-membered ring eleutheside analog, **6**, of the fused oxacyclononane–dihydrofurane system present in all types of these target antimitotic diterpenes (Fig. 2).

Planning to use the Nozaki–Hiyama[14,15] condensation to close the 10-membered ring, starting from the appropriate iodoaldehyde **8**, we identified alcohol **7** as a key intermediate. Preparation of the latter required the



1: Sarcodictyn A : R^1= COOMe; R^2= H

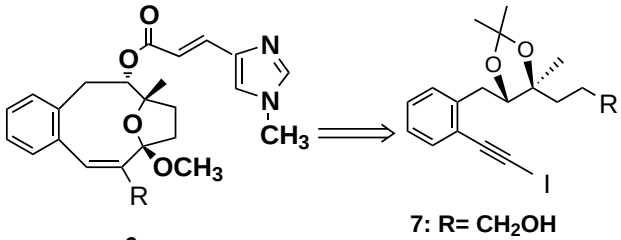
2: Sarcodictyn B : R^1= COOEt; R^2= H

3: Eleutherobin: R^1= CH_2R^3; R^2= Me; R^4= R^5= H

4: Eleuteside A: R^1= CH_2R^3; R^2= R^5= H; R^4= Ac

5: Eleuteside B: R^1= CH_2R^3; R^2= R^4= H; R^5= Ac

Figure 1.



6

7: R= CH_2OH

8: R= CHO

Figure 2.

Keywords: anticancer agents; antimitotic; eleuthesides; sarcodictyns; eleutherobin; Nozaki–Hiyama condensation.

* Corresponding author. Tel.: +34-923-294481; fax: +34-923-294574; e-mail: fcobmjo@usal.es

0040-4039/02/$ - see front matter
PII: S0040-4039(02)01475-2

application of a four-step sequence to the dihydroxy bromo ester **9**, previously prepared by our group through a stereocontrolled route starting from *o*-bromo-phenethyl alcohol (Scheme 1).[15]

Glycol protection followed by reduction of the ester group with diisobutylaluminum hydride in toluene at 0°C led to the bromo alcohol **11** with excellent yield.

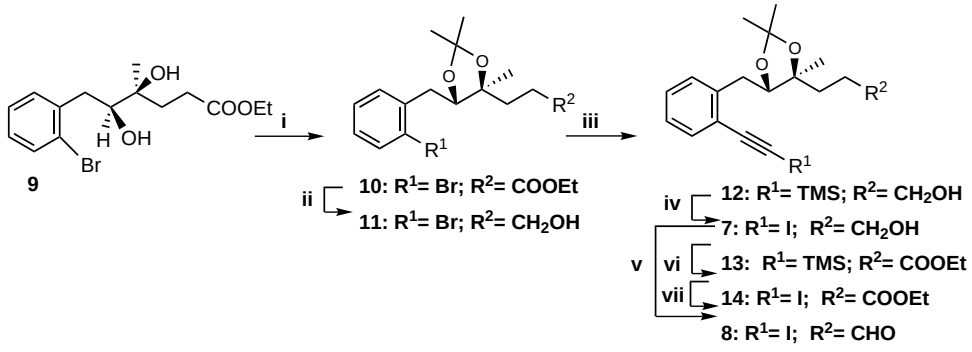
Intermediate **11** was converted into iodoaldehyde **8** by a four-step sequence involving a Stille coupling, followed by desilylation, iodination and oxidation of the alcohol.

Palladium-catalyzed cross-coupling reaction of the bromoalcohol **11** with [(trimethylsilyl)ethynyl]tributyl stannane[16] led to the trimethysilylacetylene **12**, with 93% yield under the conditions described by Stille.[17] Similarly, the bromo ester **10** led to the trimethylsilylacetylene **13**, with 95% yield under the same conditions. Other attempts to obtain either **12** or **13** by Sonogashira–Hagihara coupling[18] through treatment of bromo derivatives **10** or **11** with trimethylsilyl acetylene and diethylamine, under the catalytic effect of $(Et_3P)_2PdCl_2$ in the presence of copper(I) iodide, led to the recovery of the starting materials.

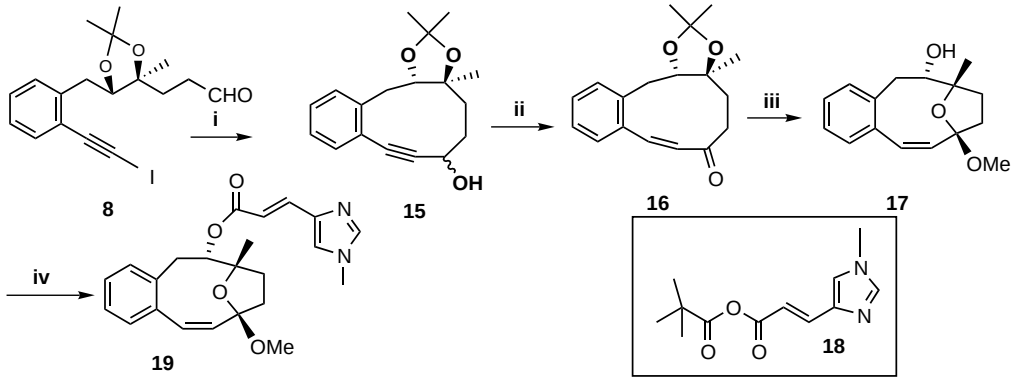
Substitution of the trimethylsilyl group of **12** with iodine was accomplished by the action of $AgNO_3$ and *N*-iodosuccinimide. Flash chromatography of the reaction product led to the isolation of **7**, with 75% yield.[19] Alternative transformation of **12** into **7** by removal of the TMS substituent by treatment of **12** with $AgNO_3$ and KCN, followed by treatment of the acetylene intermediate with iodine and morpholine in benzene at room temperature, afforded the iodoacetylene **7**, but with lower yields (58%).[20] Finally, Dess–Martin oxidation of the iodoalcohol **7** led to the precursor iodoaldehyde **8**, with excellent yield. Similarly, conversion of trimethylsilylacetylene ester **13** into iodoaldehyde **8** was achieved by iodination followed by diisobutylaluminumhydride reduction of **14** in toluene at −78°C, with 54% overall yield.

The crucial step in our strategy, the cyclization of iodoaldehyde **8** mediated by $CrCl_2$ and $NiCl_2$ (Nozaki–Hiyama[21] coupling), proceeded smoothly, affording the 10-membered acetylene alcohol **15** with 85% yield (Scheme 2).

Transformation of the alkynol **15** into the α,β-unsaturated ketone **16** was accomplished by hydrogenation with Pd on $BaSO_4$ and quinolein followed by Dess–Martin oxidation with 88% overall yield. The use of hydrogen with palladium on $CaCO_3$ either with lead or quinolein led to the recovery of the starting material, while oxidation of the intermediate allylic alcohol with



Scheme 1. *Reagents and conditions*: (i) 2,2-dimethoxypropane, pTsOH, CH_2Cl_2, 98%; (ii) dibaH, toluene, 0°C, 90%; (iii) Bu_3SnCC/TMS, $Pd(PPh_3)_4$, toluene, reflux, **12** (93%), **13** (95%); (iv) NIS, $AgNO_3$, DMF, 75%; (v) Dess Martin, 98%; (vi) NIS, $AgNO_3$, DMF, 72%; (vii) dibaH, toluene, −78°C, 75%.



Scheme 2. *Reagents and conditions*: (i) $CrCl_2$, $NiCl_2$, THF, 85%; (ii) (a) $Pd/BaSO_4$, quinolein, 90%; (b) Dess Martin, 98%; (iii) PPTS, MeOH, reflux, 75%; (iv) **18**, Et_3N, DMAP, 85%.

manganese dioxide afforded the unsaturated ketone **16**, with somewhat lower yields (60%).

Access to the oxatricyclic ring system was enabled by treatment of **16** with pyridinium *p*-toluenesulfonate in refluxing methanol. Complete spectroscopic analysis of the reaction product revealed the presence of a single product: namely, the thermodynamically controlled cyclization product **17**.[11]

Structural assignment of the macrocyclic carbinol **17** was based on mechanistic reasoning and NOE correlations, whose results are represented by double arrows in Fig. 3. Thus, sizeable NOE effects (4% each) at the methyl group (δ: 1.52 ppm) and at the benzyl β-proton (δ: 2.86 ppm) were seen upon irradiation at the proton geminal to the hydroxy function (δ: 3.65 ppm). However, by irradiation at the methyl group (δ: 1.52 ppm) an increase in intensity corresponding to the signal at the proton geminal to the hydroxy function (δ: 3.65 ppm) was remarkable (6%) but no NOE effect was observed at the methoxy group. By irradiation at the methoxy function (δ: 3.05 ppm) we observed NOE effects (2% each) at both olefinic protons α and β positions (δ: 5.37 and 5.71 ppm) to the tetrahydrofurane moiety. The spatial proximity of the proton geminal to the hydroxy function (δ: 3.65 ppm), the methyl (δ: 1.52 ppm) and the methoxy groups (δ: 3.05 ppm) lying at the tetrahydrofurane unit was demonstrated by a *Rotating frame NOESY* experiment (mixing time: 350 ms).

Acylation of **17** with the rather unstable mixed anhydride **18**[10c,11] in the presence of triethylamine and dimethylaminopyridine led to the eleutheside analog **19** (**6**, R = H) with 85% yield.[22]

Conclusion. Intramolecular condensation of iodoaldehyde **8** mediated by $NiCl_2$ and $CrCl_2$ opened the access to the medium-sized bicyclic system present in the phenylcyclononyne carbinol **15**, with excellent yields. The easy transformation of **15** into the oxatricyclic analog **19** confirms the viability of our synthetic strategy to access the eleutheside functionality present in our synthetic model (**6**, R = H). Transformation of **9** into **19** was accomplished by application of a 10-step sequence with 28% overall yield.

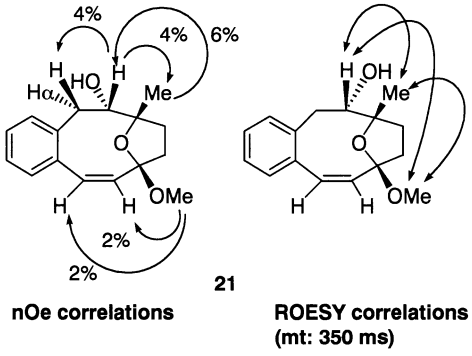


Figure 3.

Acknowledgements

We thank the 'Dirección General de Investigación de Ciencia y Tecnologia', Spain (CICYT, Grant 1FD1997-1640) for financial support. We gratefully acknowledge Professor Luca Banfi (University of Genova, Italy) for very useful correspondence concerning the Nozaki–Hiyama condensation. Thanks are given to Dr. Jesus Angel de la Fuente, Instituto Biomar S.A., Polígono Industrial de Onzonilla, Edificio CEI, 24231 Onzonilla, León, Spain, for technical assistance.

References

1. (a) Coll, J. C. *Chem. Rev.* **1992**, *92*, 613–631; (b) Wahlberg, I.; Eklund, A.-M. In *Progress in the Chemistry of Organic Natural Products*; Herz, W.; Kirby, G. W.; Moore, R. E.; Steglich, W.; Tamm, Ch., Eds.; Springer-Verlag: New York, 1992; Vol. 60, pp. 1–141; (c) Bernardelli, P.; Paquette, L. A. *Heterocycles* **1998**, *49*, 531–556.
2. D'Ambrossio, M.; Guerriero, A.; Pietra, F. *Helv. Chim. Acta* **1987**, *70*, 2019–2027.
3. D'Ambrossio, M.; Guerriero, A.; Pietra, F. *Helv. Chim. Acta* **1988**, *71*, 964–976.
4. Fenical, W. H.; Jensen, P. R.; Lindel, T. US Patent No 5473057, 1995; *Chem. Abstr.* **1996**, *102*, 194297z.
5. Lindel, T.; Fenical, W. H.; Jensen, P. R.; Long, B. H.; Casazza, A. M.; Carboni, J.; Fairchild, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 8744–8745.
6. Ketzinel, S.; Rudi, A.; Schleyer, M.; Benayahu, Y.; Kashman, Y. *J. Nat. Prod.* **1996**, *59*, 873–875.
7. 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.
8. 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*, 1199–1213.
9. Britton, R.; de Silva, D. E.; Bigg, C. M.; McHardy, L. M.; Roberge, M.; Andersen, R. *J. Am. Chem. Soc.* **2001**, *123*, 8632–8633.
10. (a) Nicolaou, K. C.; Xu, J.-Y.; Kim, S.; Ohshima, T.; Hosokawa, S.; Pfefferkorn, J. *J. Am. Chem. Soc.* **1997**, *119*, 11353–11354; (b) Nicolaou, K. C.; Kim, S.; Pfefferkorn, J.; Xu, J.; Ohshima, T.; Hosokawa, S.; Vourloumis, D.; Li, T. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1418–1421; (c) Nicolaou, K. C.; Xu, J. Y.; Kim, S.; Pfefferkorn, J.; Ohshima, T.; Vourloumis, D.; Hosokawa, S. *J. Am. Chem. Soc.* **1998**, *120*, 8661–8673 (see also Ref. 8).
11. 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*, 2520–2524 (see also Ref. 10a).
12. (a) Chen, X.-T.; Gutteridge, C. E.; Bhattacharya, S. K.; Zhou, B.; Pettus, T. R.; Hascall, T.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 185–187; (b) Chen, X.-T.; Zhou, B.; Bhattacharya, S. K.; Gutteridge, C. E.; Pettus, T. R.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 789–792; (c) Bhattacharya, S. K.; Chen, X.-T.; Gutteridge, C. E.; Danishefsky, S. *Tetrahedron*

Lett. **1999**, *40*, 3313–3316; (d) Chen, X.-T.; Bhattacharya, S. K.; Zhou, B.; Gutteridge, C. E.; Pettus, T. R.; Danishefsky, S. *J. Am. Chem. Soc*. **1999**, *121*, 6563–6579.

13. (a) Baron, A.; Caprio, V.; Mann, J. *Tetrahedron Lett*. **1999**, *40*, 9321–9324; (b) Jung, M. E.; Huang, A.; Johnson, T. W. *Org. Lett*. **2000**, *2*, 1835–1837; (c) Carter, R.; Hodgetts, K.; McKenna, J.; Magnus, P.; Wren, S. *Tetrahedron* **2000**, *56*, 4367–4382; (d) Kim, P.; Nantz, M. H.; Kurth, M. J.; Olmstead, M. M. *Org. Lett*. **2000**, *2*, 1831–1834; (e) Kim, P.; Olmstead, M. M.; Nantz, M. H.; Kurth, M. J. *Tetrahedron Lett*. **2000**, *41*, 4029–4032; (f) By, K.; Kelly, P. A.; Kurth, M. J.; Olmstead, M. M.; Nantz, M. H. *Tetrahedron* **2001**, *57*, 1183–1187; (g) Xu, Q.; Weeresakare, M.; Rainier, J. D. *Tetrahedron* **2001**, *57*, 8029–8037; (h) Ceccarelli, S.; Piarulli, U.; Gennari, C. *Tetrahedron Lett*. **1999**, *40*, 153–156; (i) Ceccarelli, S.; Piarulli, U.; Gennari, C. *J. Org. Chem*. **2000**, *65*, 6254–6256; (j) Ceccarelli, S.; Piarulli, U.; Gennari, C. *Tetrahedron* **2001**, *57*, 8531–8542; (k) Ceccarelli, S.; Piarulli, U.; Telser, J.; Gennari, C. *Tetrahedron Lett*. **2001**, *42*, 7421–7425; (l) Telser, J.; Beumer, R.; Bell, A. A.; Ceccarelli, S. M.; Monti, D.; Gennari, C. *Tetrahedron Lett*. **2001**, *42*, 9187–9190.
14. (a) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc*. **1986**, *108*, 6048–6050; (b) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett*. **1983**, *24*, 5281.
15. Redero, E.; Sandoval, C.; Bermejo, F. *Tetrahedron* **2001**, *57*, 9597–9605.
16. Logue, M. W.; Teng, K. *J. Org. Chem*. **1982**, *47*, 2549–2553.
17. Krolski, M. E.; Renaldo, A. F.; Rudisill, D. E.; Stille, J. K. *J. Org. Chem*. **1988**, *53*, 1170–1176.
18. Takahashi, S.; Kuroyama, K.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627–630.
19. Nishikawa, T.; Shibuya, S.; Hosokawa, S.; Isobe, M. *Synlett* **1994**, 485–486.
20. Schmidt, H. M.; Arens, J. F. *Recueil Chim. Pays-Bas* **1967**, *86*, 1138–1142.
21. Banfi, L.; Guanti, G. *Tetrahedron Lett*. **2000**, *41*, 6523–6526 and references cited therein. See also Ref. 14.
22. All compounds described in this paper exhibited spectroscopic data completely in accordance with their assigned structures. Details will be provided in a subsequent full paper. Compound **19** was obtained as a colorless oil R_f: 0.4 ($CHCl_3$:MeOH = 95:5); IR (film) ν 3180, 2862, 1705, 1638, 1458, 1271, 1167, 1123 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.21 (s, 3H); 1.65 (dt, $J = 1.2$ Hz, $J = 4$ Hz, $J = 13$ Hz, 1H); 1.95 (m, 2H); 2.20 (m, 1H); 2.71 (dd, $J = 5$ Hz; $J = 13$ Hz, 1H); 3.04 (s, 3H); 3.22 (t, $J = 13$ Hz, 1H); 3.70 (s, 3H); 4.22 (ddd, $J = 1.2$ Hz; $J = 5$ Hz; $J = 13$ Hz, 1H); 5.37 (d, $J = 13$ Hz, 1H); 6.54 (d, $J = 15.5$ Hz, 1H); 6.72 (d, $J = 13$ Hz, 1H); 7.08 (s, 1H); 7.20 (m, 4H); 7.25 (d, $J = 15.5$ Hz, 1H); 7.49 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 26.81 (q); 28.00 (t); 33.58 (q); 33.68 (t); 34.85 (t); 49.60 (q); 79.40 (d); 80.56 (s); 98.80 (s); 117.18 (d); 122.38 (d); 126.15 (d); 126.89 (d); 126.98 (d); 128.89 (d); 131.97 (d); 132.58 (d); 135.67 (d); 138.00 (s); 138.15 (s); 138.28 (s); 139.09 (d); 166.50 (s) ppm; MS (EI): (m/z, %): 394 (3); 369 (2); 266 (10); 207 (5); 166 (5); 135 (100); 108 (25); 57 (25) ppm.