Tandem Reactions

Enantiospecific Strategy Towards Oxygen-Bridged Terpenoids: Tandem Transannular-Cyclization and Ring-Contraction Processes**

*Antonio Rosales, Rosa E. Estévez, Juan M. Cuerva, and J. Enrique Oltra**

The transannular cyclization of medium-sized rings contributes to the enhancement of molecular rigidity and structural complexity, two properties often associated with biological activity in small molecules.[1] In fact, there are several naturally occurring terpenoids with a transannular oxygen

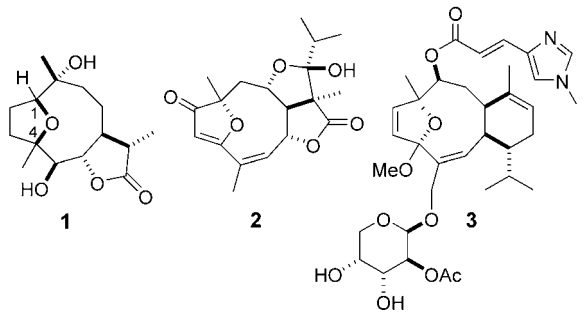
[*] Dr. A. Rosales, R. E. Estévez, Dr. J. M. Cuerva, Dr. J. E. Oltra
Department of Organic Chemistry
Faculty of Sciences
Campus Fuentenueva s/n
University of Granada
18071 Granada (Spain)
Fax: (+34) 958-248-437
E-mail: joltra@ugr.es

[**] This work was supported by the "Junta de Andalucía" (PAI group FQM339). We also thank Dr. A. F. Barrero for his collaboration during the early stage of the work as well as our English colleague Dr. J. Trout for revising our text.

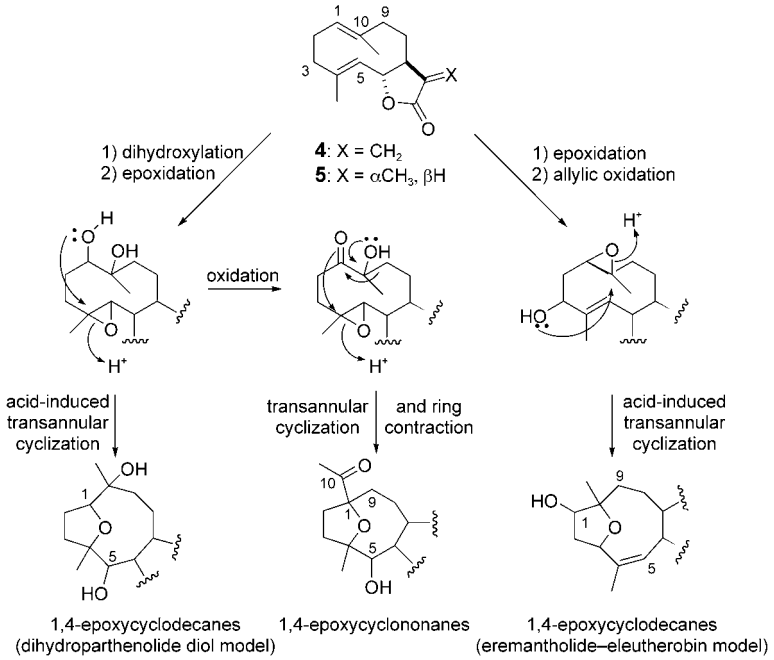
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

 DOI: 10.1002/ange.200461210

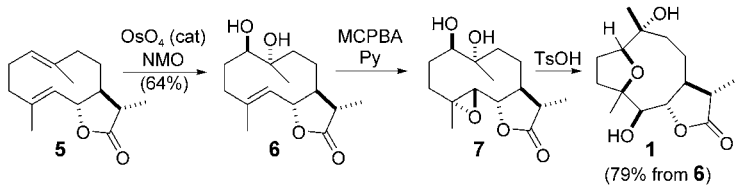
bridge in their 1,4-epoxycyclodecane system, such as dihydroparthenolide diol (**1**),[2] eremantholide A (**2**),[3] and eleutherobin (**3**),[4] all of which show interesting pharmacological properties. The 1,4-epoxycyclononane system, however, is considerably less widespread among natural products, although some examples have been reported.[5] Bioactive terpenoids with the 1,4-epoxycyclodecane motif have attracted the attention of chemists, and different total syntheses of **2**[6] and **3**[7] have been described. Moreover, some procedures for the synthesis of 1,4-epoxycyclononanes have been developed,[8] and other tetrahydrofuran derivatives have recently been prepared by radical tandem reactions.[9] These total syntheses, however, are generally restricted to the preparation of only one or a few specific compounds, require numerous steps and generally give low overall yields.



Hemisynthesis can be a valuable alternative to total synthesis, especially when nature provides sufficient quantities of homochiral raw materials that can easily be isolated from renewable sources. This is true of germacrolides (+)-costunolide (**4**) and (+)-11β,13-dihydrocostunolide (**5**, see Scheme 1), which can be obtained in (multi)-gram quantities from the commercially available extract Costus Resinoid.[10] Additional amounts of these compounds can also be obtained by chemical synthesis.[11] We therefore deemed that accessible germacrolides might well be a suitable starting material for the enantiospecific synthesis of both 1,4-epoxycyclodecanes and 1,4-epoxycyclononanes as they require relatively simple but selective chemical transformations based on the different reactivity shown by the double bonds located at $\Delta^{1(10)}$ and Δ^{4} of the cyclodecadiene ring (Scheme 1).[12]



Scheme 1. Hypothetical strategy for the synthesis of oxygen-bridged terpenoids from accessible germacrolides.



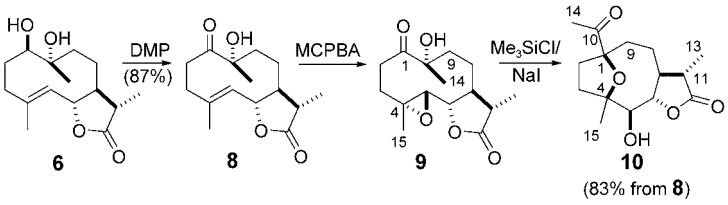
Scheme 2. Enantiospecific synthesis of **1** from **5**. NMO = *N*-methylmorpholine *N*-oxide, MCPBA = *m*-chloroperbenzoic acid, Py = pyridine, Ts = *p*-toluenesulfonyl.

To prove our hypothesis, we selected (+)-dihydroparthenolide diol (**1**) as the first synthetic target. To determine the absolute stereochemistry of natural **1**, we started the synthesis with homochiral (+)-11β,13-dihydrocostunolide (**5**), which was obtained from commercial Costus Resinoid.[10b] Selective dihydroxylation of **5** by using the Upjohn procedure[13] allowed us to obtain diol **6**[14] with a yield of 64%. Treatment of **6** with MCPBA (*m*-chloroperbenzoic acid) in the presence of pyridine furnished epoxide **7**, which was submitted to the next step without further purification. Thus the acid-induced transannular cyclization of crude **7** provided (+)-dihydroparthenolide diol (**1**) in 79% yield (from **6**). The spectroscopic data for synthetic **1** as well as optical rotation measurements[15] agreed with those reported for natural (+)-dihydroparthenolide diol, thus confirming the chemical structure of this metabolite. As the absolute stereochemistry of (+)-11β,13-dihydrocostunolide (**5**) is known,[16] the chemical synthesis of **1** from **5** suggests that the absolute configuration of natural **1** is that as depicted in Scheme 2.

We subsequently approached the second part of our hypothesis, that is, a tandem reaction combining transannular-cyclization and ring-contraction processes that we hoped would lead to 1,4-epoxycyclononanes. Owing to both entropy and enthalpy factors, the synthesis of nine-membered carbocycles by ring-closing procedures is rendered quite difficult.[8a,17] Nine- and ten-membered rings, however, have similar total strain levels,[18] and therefore ring-contraction processes from cyclodecanes to cyclononanes should not be

seriously hindered by thermodynamic phenomena. Surprisingly, synthetic chemists have not yet exploited this procedure probably owing to the lack of a suitable technique.[19] Within this context we considered that with the anchimeric assistance provided by an OH group located at C-10, an epoxyketone such as **9** might undergo acid-induced transannular cyclization followed by a ring-contraction process that leads to 1,4-epoxycyclononanes (see Scheme 1), and thus open a novel synthetic way towards nine-membered carbocycles.

To this end we prepared crude **9** (Scheme 3) and treated it without further purification with a substoichiometric quantity of Me_3SiCl/NaI. In this manner, we obtained oxygen-bridged cyclononane **10** with a yield of 83% (from **8**).[20] Analysis of HRMS and ^{13}C NMR spectra of **10** supported the tricyclic nature of this product, and the IR spectrum showed bands assignable to alcohol, ketone, and γ-lactone groups. Moreover, in the ^{1}H NMR spectrum, signals at $\delta = 3.75$ (d, $J = 8.9$ Hz, H-5) and 4.30 (t, $J = 9.0$ Hz, H-6) indicated that the



Scheme 3. Enantiospecific synthesis of **10** from **6**. DMP = Dess–Martin periodinane.

OH group was equatorially juxtaposed to the *trans*-fused γ-lactone. The signal for the hydrogen atoms of a methyl ketone unit also appeared in this spectrum at $\delta = 2.19$ (s, 3H, H-14) together with those of two other methyl groups at $\delta = 1.36$ (s, 3H, H-15) and 1.20 (d, $J = 6.9$ Hz, 3H, H-13). The chemical shifts and multiplicities of the protons of these two methyl groups indicate that the former ($\delta = 1.36$) is attached to an oxygenated quaternary carbon center and that the latter ($\delta = 1.20$) is coupled to H-11 ($\delta = 2.32$, dq, $J = 6.9$, 12.0 Hz). The ^{13}C NMR spectrum showed signals for quaternary oxygenated carbon centers at $\delta = 86.0$ (C-4) and 89.0 (C-1), which correspond to the heads of the oxygenated bridge. Furthermore, the HMBC (heteronuclear multiple-bond correlation) spectrum showed correlations between H-5 and C-4, between H-15 and C-4, and between H-14 and C-1, and firmly support structure **10**. Finally, the NOE observed between H-15 and H-6 may be explained by assuming a 1*S*,4*S*,6*S* stereochemistry in which H-6 and the oxygen bridge are situated on the same side of the cyclononane ring (see Figure 1).[21]

The chemical transformation of **9** into **10** represents an unprecedented tandem reaction that provides a straightforward synthetic means of obtaining the otherwise elusive nine-membered carbocycles. This method works well at room temperature under mild conditions, needs only catalytic proportions of Me_3SiCl/NaI, and conforms to the principles of selectivity and atom- and step-economy required in contemporary chemistry.[22] The reaction also produces a substantial increase in molecular rigidity and structural

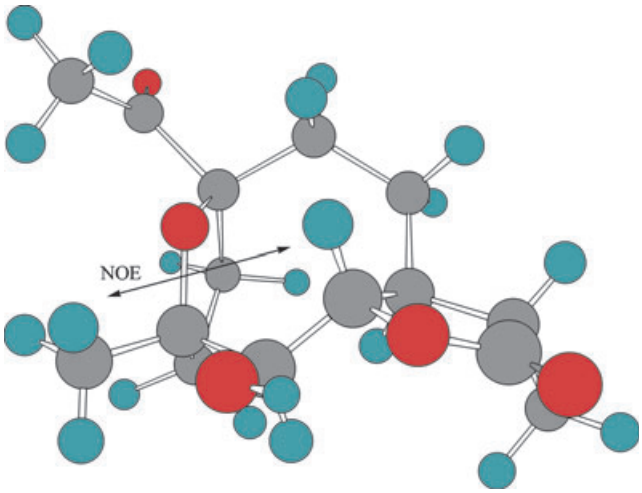


Figure 1. Minimized energy conformation of **10.** NOE between H-6 and H-15. O = red, C = gray, H = blue.

complexity in only one step, thus proving itself to be a potentially useful tool for diversity-oriented synthesis.[1]

Finally, we embarked upon the preparation of (−)-1β,10α-epoxy-11β,13-dihydrocostunolide (**11**) by the selective epoxidation of **5**.[10b] The results obtained in the synthesis of **1** (Scheme 2) suggest that the allylic oxidation at C-3 of **11** followed by the acid-induced transannular cyclization of the corresponding epoxy-alcohol (see Scheme 1) will give the 1,4-epoxycyclodecane model shown by eremantholide A (**2**) and eleutherobin (**3**), a task we are currently engaged on.

In summary, we present an enantiospecific strategy for the synthesis of oxygen-bridged terpenoids from accessible germacrolides. This method has proved to be useful for obtaining antimycobacterial (+)-dihydroparthenolide diol (**1**) and 1,4-epoxycyclononane **10**. The synthesis of **10** employs a novel tandem reaction that combines a transannular cyclization with a ring-contraction process and opens up a new approach to nine-membered carbocycles.

Received: July 6, 2004

Keywords: carbocycles · cyclization · epoxidation · ring contraction · synthetic methods

[1] S. L. Schreiber, *Science* **2000**, *287*, 1964–1969.
[2] Dihydroparthenolide diol, a scarce metabolite from the Chinese plant *Carpesium longifolium*, has antimycobacterial activity: a) C. Yang, C. Yuan, Z. Jia, *J. Nat. Prod.* **2003**, *66*, 1554–1557; b) J. K. Rugutt, F. R. Fronczek, S. G Franzblau, I. M. Warner, *Acta Crystallogr. Sect. E* **2001**, *57*, 323–325.
[3] For an exhaustive review on furanoheliangolides, including eremantholide A and other bioactive oxygen-bridged sesquiterpenoids, see: D. S. Brown, L. A. Paquette, *Heterocycles* **1992**, *34*, 807–834.
[4] Eleutherobin, isolated from an Australian soft coral of the genus *Eleutherobia*, showed antitumor properties closely related to

those of Taxol; see: a) I. Ojima, S. Chakravarty, T. Inoue, S. Lin, L. He, S. B. Horwitz, S. D. Kuduk, S. J. Danishefsky, *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 4256 – 4261; b) T. Lindel, *Angew. Chem.* **1998**, *110*, 806 – 808; *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 774 – 776; c) 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.

[5] a) R. Durán-Patrón, J. Aleu, R. Hernández-Galán, I. G. Collado, *J. Nat. Prod.* **2000**, *63*, 44 – 47; b) J. Jakupovic, F. Jeske, T. Morgenstern, F. Tsichritzis, J. A. Marco, W. Berendsohn, *Phytochemistry* **1998**, *47*, 1583 – 1600.

[6] Total synthesis of eremantholide A: a) K. Takao, H. Ochiai, K. Yoshida, T. Hashizuka, H. Koshimura, K. Tadano, S. Ogawa, *J. Org. Chem.* **1995**, *60*, 8179 – 8193; b) J. R. Boeckman Jr., S. K. Yoon, D. K. Heckendorn, *J. Am. Chem. Soc.* **1991**, *113*, 9682 – 9684; Other synthetic studies on furanoheliangolides: c) D. S. Brown, L. A. Paquette, *J. Org. Chem.* **1992**, *57*, 4512 – 4521.

[7] Total synthesis of eleutherobin: a) 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; b) S. K. Bhattacharya, X. T. Chen, C. E. Gutteridge, S. J. Danishefsky, *Tetrahedron Lett.* **1999**, *40*, 3313 – 3316; c) 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; d) 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. Engl.* **1998**, *37*, 789 – 792; e) K. C. Nicolaou, F. van Delft, T. Ohshima, D. Vourloumis, J. Xu, S. Hosokawa, J. Pfefferkorn, S. Kim, T. Li, *Angew. Chem.* **1997**, *109*, 2630 – 2634; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2520 – 2524; More recent approaches: f) R. Beumer, P. Bayón, P. Bugada, S. Ducki, N. Mongelli, F. R. Sirtori, J. Telser, C. Gennari, *Tetrahedron* **2003**, *59*, 8803 – 8820; g) K. P. Kaliappan, N. Kumar, *Tetrahedron Lett.* **2003**, *44*, 379 – 381; h) C. Sandoval, E. Redero, M. A. Mateos-Timoneda, F. A. Bermejo, *Tetrahedron Lett.* **2002**, *43*, 6521 – 6524.

[8] a) G. A. Molander, C. Köllner, *J. Org. Chem.* **2000**, *65*, 8333 – 8339; b) J. L. Mascareñas, A. Rumbo, L. Castedo, *J. Org. Chem.* **1997**, *62*, 8620 – 8621.

[9] a) A. Gansäuer, B. Rinker, N. Ndene-Schiffer, M. Pierobon, S. Grimme, M. Gerenkamp, C. Mück-Lichtenfeld, *Eur. J. Org. Chem.* **2004**, 2337 – 2351; b) A. Gansäuer, B. Rinker, M. Pierobon, S. Grimme, M. Gerenkamp, C. Mück-Lichtenfeld, *Angew. Chem.* **2003**, *115*, 3815 – 3818; *Angew. Chem. Int. Ed.* **2003**, *42*, 3687 – 3690.

[10] a) A. F. Barrero, A. Rosales, J. M. Cuerva, J. E. Oltra, *Org. Lett.* **2003**, *5*, 1935 – 1938; b) A. F. Barrero, J. E. Oltra, J. M. Cuerva, A. Rosales, *J. Org. Chem.* **2002**, *67*, 2566 – 2571; c) A. F. Barrero, J. E. Oltra, M. Álvarez, A. Rosales, *J. Org. Chem.* **2002**, *67*, 5461 – 5469.

[11] For a review on the synthesis of costunolide, 11β,13-dihydrocostunolide, and other germacrane sesquiterpenoids, see: A. J. Minnaard, B. P. A. W. Joannes, A. de Groot, *Tetrahedron* **1999**, *55*, 2115 – 2146.

[12] Owing to both steric and electronic factors, the double bond at Δ^4 is considerably less reactive than that at $\Delta^{1(10)}$. Carbon-atom numbering corresponds to the germacrane system.

[13] a) K. Bergstad, S. Jonson, J. E. Bäckvall, *J. Am. Chem. Soc.* **1999**, *121*, 10424 – 10425; b) V. VanRheenen, R. C. Kelly, D. Y. Cha, *Tetrahedron Lett.* **1976**, 1973 – 1976.

[14] All of the products obtained, except **7** and **9**, were isolated by flash chromatography and characterized by spectroscopic techniques including high resolution mass spectrometry and NMR spectroscopy.

[15] Data for synthetic **1**: gold-colored syrup; $[\alpha]_D^{20} = +9.1$ ($c = 0.90$, CH_2Cl_2); HR(FAB)MS: m/z: calcd. for $C_{15}H_{24}O_5Na$: 307.1521; found: 307.1516 $[M+Na]^+$; ^1H and ^{13}C NMR spectra matched those reported for the natural product.[2a]

[16] The absolute stereochemistry of (+)-11β,13-dihydrocostunolide (**5**) was established by chemical correlation with (+)-costunolide (**4**).[10b]

[17] A. Deiters, R. Fröhlich, D. Hoppe, *Angew. Chem.* **2000**, *112*, 2189 – 2192; *Angew. Chem. Int. Ed.* **2000**, *39*, 2105 – 2107.

[18] E. L. Eliel, S. H. Wilen, M. P. Doyle, *Basic Organic Stereochemistry*, Wiley, New York, **2001**, pp. 429 – 433.

[19] For a rare example of ring contraction reactions from ten- to nine-membered carbocycles, see: X. Lei, C. Doubleday, Jr., N. J. Turro, *Tetrahedron Lett.* **1986**, *27*, 4675 – 4678.

[20] For experimental details, see Supporting Information.

[21] The interatomic distance between H-6 and H-15 of **10** is 3.789 Å in the minimized energy conformation shown in Figure 1 (CS Chem3D Pro, MOPAC).

[22] a) B. M. Trost, *Angew. Chem.* **1995**, *107*, 285 – 307; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259 – 281; b) B. M. Trost, *Science* **1991**, *254*, 1471 – 1477.

