

## Surprising obtention of an enantiopure eight-membered cyclic ether from camphor

Antonio García Martínez,<sup>a,\*</sup> Enrique Teso Vilar,<sup>b</sup> Amelia García Fraile,<sup>b</sup>  
Santiago de la Moya Cerero<sup>a,\*</sup> and Cristina Díaz Morillo<sup>b</sup>

<sup>a</sup>*Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, Ciudad Universitaria s/n, 28040 Madrid, Spain*

<sup>b</sup>*Instituto Universitario de Investigación, Facultad de Ciencias, UNED, Senda del Rey 9, 28040 Madrid, Spain*

Received 12 April 2007; revised 18 May 2007; accepted 25 May 2007

Available online 31 May 2007

Dedicated to Professor Miguel Yus on the occasion of his 60th birthday

**Abstract**—A highly-functionalized eight-membered cyclic ether, with an additional interesting trans-fusion to a cyclobutane ring, is enantiospecifically obtained in high yield from a camphor-derived di(spiroepoxide)-substituted 1-norbornyl triflate, via a regio- and stereocontrolled domino process. The described process could constitute a novel model procedure for the preparation of eight-membered cyclic ethers from  $\alpha,\alpha'$ -bis(spiroepoxide) cyclopentyl derivatives.

© 2007 Elsevier Ltd. All rights reserved.

Polyfunctionalized medium-sized cyclic ethers are common structural features of a wide range of biologically-active marine natural products, such as the well-known strong toxins brevetoxins and ciguatoxins (e.g., **1** in Fig. 1).<sup>1</sup> Among those, eight-membered cyclic ethers are distinctive constituents of marine products, such as the interesting ones produced by the red algae of the genus *Laurencia* (e.g., **2** in Fig. 1), whose abundance and structural features have allowed their classification in two subclasses, the lauthisan type and the laureane one, in view of a common biogenetic origin.<sup>2</sup>

The biological interest and structural complexity of marine medium-sized cyclic ethers have made these compounds to be the subject of a significant synthetic effort within the last decade. In this sense, the work carried out by authors as Masamune, Kocienski, Overman, Nicolaou, Schreiber, Moody, Kotsuki, Hiramama or Paquette, among others, must be emphasized.<sup>3</sup> These synthetic efforts have been mainly focused on the construction of eight-membered cycles, due to their special synthetic difficulties, arising from conformational entropy factors and developing transannular repulsions as the ring is formed from acyclic precursors.<sup>4</sup>

So far, many approaches to eight-membered cyclic ethers,<sup>5</sup> mainly involving condensations,<sup>5a-d</sup> rearrangements,<sup>5e,f</sup> ring-expansions,<sup>5g-i</sup> radical cyclizations,<sup>5j</sup> or, more recently, ring-closing metatheses,<sup>5k-o</sup> have been developed. Nevertheless, problems related with precursor preparations, overall yields, general scope, and stereoselectivity (carbohydrates are standard chiral starting materials for stereoselective preparations),<sup>6</sup> still keep alive the interest in developing new approaches to such interesting medium-sized cyclic ethers.

Continuing with our preliminary studies on the solvolysis of spiroepoxide 1-norbornyl triflates,<sup>7</sup> we have serendipity discovered a regio- and stereocontrolled domino process from camphor-derived bis(spiroepoxide) 1-norbornyl triflate **3** to the interesting cyclobutane-fused<sup>8</sup> eight-membered cyclic ether **4** (Scheme 1).<sup>9</sup> The reaction was carried out under the standard conditions used previously for the solvolysis of related triflates (i.e., refluxing aqueous ethanol buffered with triethylamine).<sup>7,10</sup> The obtained result has an important synthetic interest, since it constitutes the first example for the stereoselective construction of a highly-functionalized eight-membered cyclic ether from a chiral terpene. In this sense, it could be used as synthetic model for the construction of enantiopure eight-membered cyclic ethers.

\* Corresponding authors. E-mail: [santmoya@quim.ucm.es](mailto:santmoya@quim.ucm.es)

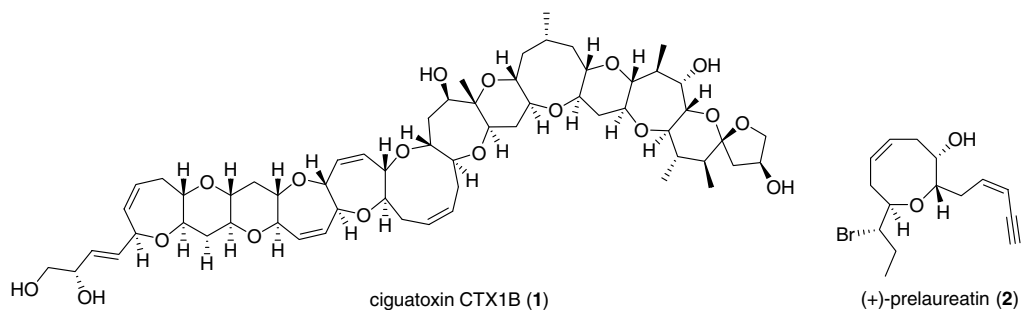
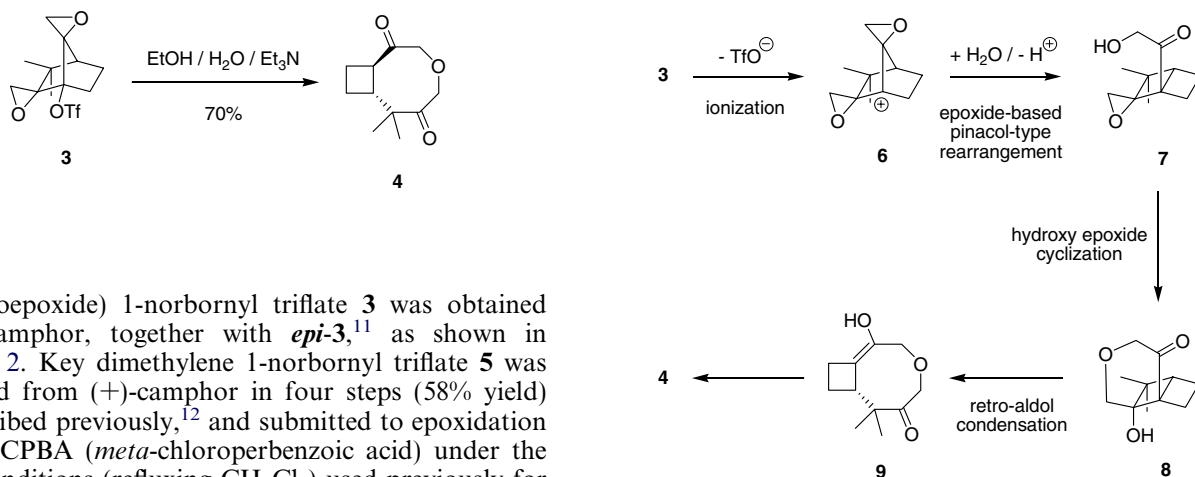


Figure 1.

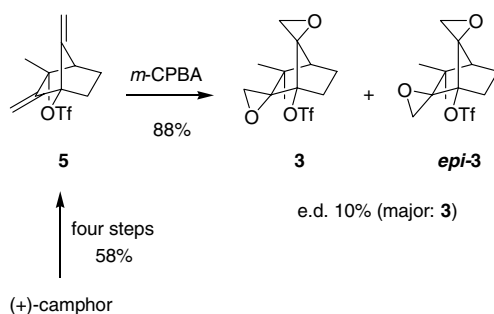


Scheme 1.

Bis(spriopoxide) 1-norbornyl triflate **3** was obtained from camphor, together with *epi-3*,<sup>11</sup> as shown in Scheme 2. Key dimethylene 1-norbornyl triflate **5** was prepared from (+)-camphor in four steps (58% yield) as described previously,<sup>12</sup> and submitted to epoxidation with *m*-CPBA (*meta*-chloroperbenzoic acid) under the same conditions (refluxing CH<sub>2</sub>Cl<sub>2</sub>) used previously for related methylene 1-norbornyl triflates.<sup>7</sup>

From a mechanistic point of view, formation of an oxabicyclo[6.2.0]decane, such as the eight-membered cyclic ether **4**, by the solvolysis of a 1-norbornyl triflate is unknown.<sup>13</sup> This unprecedented result can be explained according to the coincidence of a series of key structural factors in reacting triflate **3**, which makes possible the amazing domino process shown in Scheme 3.

After initial ionization,<sup>14</sup> the formed 1-norbornyl cation **6** should undergo an epoxide-based pinacol-type rearrangement of its C2–C7 bond,<sup>15</sup> to generate hydroxy epoxide **7** after hydrolysis. The special conformational restriction of **7**,<sup>16</sup> as well as an adequate disposition of its epoxidic ring, makes possible a highly efficient 6-*exo*-tet hydroxy-epoxide cyclization,<sup>17</sup> to generate tricyclic β-hydroxy ketone **8**, which should undergo a



Scheme 2.

Scheme 3.

favorable retro-aldol reaction (note strain releasing) to bicyclic enol **9**.<sup>18</sup> Final keto–enol equilibration of **9** with its more-stable *trans*-fused tautomer explains the detection of **4** as the unique solvolysis final product.

Geometry factors are really crucial in this reaction. Thus, solvolysis of *epi-3*, under the same reaction conditions that those used for **3** (see Scheme 1), gives place to bicyclo[2.1.1]heptane-based ketone **10**<sup>19</sup> (Fig. 2), via the expected pinacol-type rearrangement of its C2–C3 bond.<sup>20,21</sup>

From a synthetic point of view, the discovered process could constitute a useful synthetic methodology for planning the preparation of β,β'-dioxooxocanes (note the synthetic utility of the carbonyl groups for possible subsequent functionalizations) from α,α'-bis(spriopoxide) cyclopentyl-carbocation precursors, as retrosynthetic Scheme 4 shows.

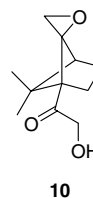
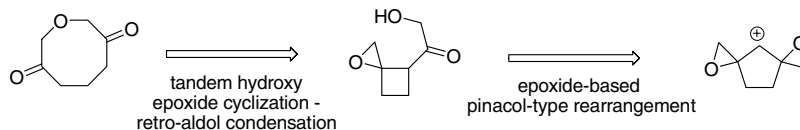


Figure 2.



Scheme 4.

In conclusion, the stereocontrolled formation of a highly-functionalized and synthetically-interesting eight-membered cyclic ether from an enantiopure camphor-derived bis(spiroepoxide) 1-norbornyl triflate is described. It constitutes the first example for the construction of such valuable rings from a chiral terpene. In relation to the last, the described process could constitute a novel model procedure for the preparation of eight-membered cyclic ethers.

### Acknowledgments

This work was financially supported by the Ministry of Education and Science, Spain (Research project CTQ2004-07244-C02-02) and UCM-CM (Research project CCG06-UCM/PPQ-1174). C.D.M. thanks UNED for a postgraduate grant.

### References and notes

- (a) Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2004**, *21*, 1; (b) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1; (c) Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1; (d) Yasumoto, T. *Chem. Rec.* **2001**, *3*, 228; (e) Yasumoto, T.; Murata, M. *Nat. Prod. Rep.* **2000**, *17*, 293; (f) Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 1; (g) Scheuer, P. J. *Tetrahedron* **1994**, *50*, 3; (h) Shimizu, Y. *Chem. Rev.* **1993**, *93*, 1897; (i) Erikson, K. L. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1983; Vol. 5, pp 131–257; (j) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897.
- (a) Ishihara, J.; Shimada, Y.; Kanoh, N.; Tagasugi, Y.; Fukuzawa, A.; Murai, A. *Tetrahedron* **1997**, *53*, 8371; (b) Ishihara, J.; Kanoh, N.; Murai, A. *Tetrahedron Lett.* **1995**, *36*, 737; (c) Fukuzawa, A.; Tagasugi, Y.; Murai, A. *Tetrahedron Lett.* **1991**, *32*, 5597.
- Some interesting reviews on the synthesis of medium-sized cyclic ethers are: (a) Fujiwara, K. In *Topics in Heterocyclic Chemistry*; Kiyota, H., Ed.; Springer: Berlin, 2006; Vol. 5, pp 97–148; (b) Nakamuro, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127; (c) Elliot, M. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2301; (d) Elliot, M. C.; Williams, E. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2303; (e) Yet, L. *Chem. Rev.* **2000**, *100*, 2963; (f) Hoberg, J. O. *Tetrahedron* **1998**, *54*, 12631; (g) Álvarez, E.; Cándenas, M. L.; Pérez, R.; Ravelo, J. L.; Martín, J. D. *Chem. Rev.* **1995**, *95*, 1953.
- (a) Rhee, H. J.; Beom, H. Y.; Kim, H.-D. *Tetrahedron Lett.* **2004**, *45*, 8019; (b) Linderman, R. J.; Siedlecki, J.; O'Neill, S.; Sun, H. *J. Am. Chem. Soc.* **1997**, *119*, 6919, and references cited therein; (c) Kreiter, C. G.; Lehr, K.; Leyendecker, M.; Sheldrik, W. S.; Exner, R. *Chem. Ber.* **1991**, *124*, 3; (d) Iluminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 102.
- For instance see: (a) Sugimoto, M.; Suzuki, T.; Hagiwara, H.; Hoshi, T. *Tetrahedron Lett.* **2007**, *48*, 1109; (b) Kim, H.; Choi, W. J.; Jung, W. J.; Kim, S.; Kim, D. *J. Am. Chem. Soc.* **2003**, *125*, 10238; (c) Nicolaou, K. C.; Yang, Z.; Shi, G.-Q.; Gunzner, J. L.; Agrios, K. A.; Gärtner, P. *Nature* **1998**, *392*, 264; (d) Cockterill, G. S.; Kocienski, P.; Treadgold, R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2093; (e) Boeckman, R. K., Jr.; Zhang, J.; Reeder, M. R. *Org. Lett.* **2002**, *4*, 3891; (f) Sudha, A. V. R. L.; Nagarajan, M. *Chem. Commun.* **1996**, 1359; (g) Ghosh, S.; Tuhina, K.; Bhowmik, D. R.; Venkateswaran, R. V. *Tetrahedron* **2007**, *63*, 644; (h) Tanaka, S.; Hayashi, K.; Sano, S.; Shiro, M. *Synlett* **2004**, 481; (i) Carling, R. W.; Clark, J. S.; Holmes, A. B. *J. Chem. Soc., Perkin Trans. 1* **1992**, 83; (j) Nandi, A.; Chattopadhyay, P. *Tetrahedron Lett.* **2002**, *43*, 5977; (k) Ortega, N.; Martín, T.; Martín, V. S. *Org. Lett.* **2006**, *8*, 871; (l) Takemura, A.; Fujiwara, K.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2004**, *45*, 7565; (m) Kadota, I.; Uyehara, H.; Yamamoto, Y. *Tetrahedron* **2004**, *60*, 7361; (n) Clark, J. S.; Freeman, R. P.; Cacho, M.; Thomas, A. W.; Swallow, S.; Wilson, C. *Tetrahedron Lett.* **2004**, *45*, 8639; (o) Maruyama, M.; Inoue, M.; Oishi, T.; Oguri, H.; Ogasawara, Y.; Shindo, Y.; Hiramata, M. *Tetrahedron* **2002**, *58*, 1835.
- For instance see Refs. 5c,f,j.
- García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Lora Maroto, B.; Díaz Morillo, C. *Tetrahedron Lett.* **2001**, *42*, 8293, and references cited therein.
- Cyclobutanes are frequent key structural units in biologically important compounds: For instance see: (a) Ortuño, R. M.; Moglioni, G. Y.; Moltrasio, G. Y. *Curr. Org. Chem.* **2005**, *9*, 237; (b) Meek, S. J.; Pradaux, F.; Demont, E. H.; Harrity, J. P. A. *Org. Lett.* **2006**, *8*, 5597; (c) Xu, F.; Morikawa, T.; Matsuda, H.; Ninomiya, K.; Yoshikawa, M. *J. Nat. Prod.* **2004**, *67*, 569.
- Std. react. conditions: see Ref. 7. React. time: 30 days. Yield: 70%. Purification: flash chromatography (silica gel, CH<sub>2</sub>Cl<sub>2</sub>). **4**: Colorless oil.  $[\alpha]_D^{20}$  -4.7 (0.70, CH<sub>2</sub>Cl<sub>2</sub>). HRMS: 196.1091 (calcd for C<sub>11</sub>H<sub>16</sub>O<sub>3</sub>, 196.1099). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz),  $\delta$ : 4.58 (d, *J* = 16.7 Hz, 1H), 4.38 (d, *J* = 18.1 Hz, 1H), 3.79 (d, *J* = 16.7 Hz, 1H), 3.77–3.69 (several m, 1H), 3.72 (d, *J* = 18.1 Hz, 1H), 2.23–2.15 (m, 2H), 1.82–1.69 (several m, 3H), 1.49 (s, 3H), 0.95 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz),  $\delta$ : 214.1, 211.5, 79.3, 78.0, 48.6, 46.8, 45.9, 21.7, 19.4, 17.6, 16.1 ppm. IR (CCl<sub>4</sub>),  $\nu$ : 2972, 1705 (str.), 1387, 1364 cm<sup>-1</sup>. EM, *m/z*: 196 (M<sup>+</sup>, 9), 167 (12), 166 (91), 151 (5), 138 (23), 124 (24), 123 (98), 109 (21), 99 (37), 96 (38), 95 (100), 81 (62), 79 (18), 69 (73), 67 (42), 55 (66). The structural assignment was strongly supported by <sup>1</sup>H–<sup>1</sup>H HMBC, and <sup>1</sup>H–<sup>13</sup>C HMQC NMR experiments. The presence of the cyclobutane ring was additionally confirmed by the values for the measured cyclobutane <sup>1</sup>J(C–H) coupling constants (132–134 Hz).
- The rate for the solvolysis of triflates via carbocationic processes can be improved using dimethyl sulfoxide as the solvent: Creary, X.; Burtch, E. A. *J. Org. Chem.* **2004**, *69*, 1227.
- Std. react. conditions: see Ref. 7. React. time: 24 h. Yield: 88% (e.d. 10%). Purification: flash chromatography (silica gel, hexane/CH<sub>2</sub>Cl<sub>2</sub>: 4/1). Spectroscopic data for both

- epimers agree with the corresponding structures. Relative configurations at both C2 and C7 norbornane positions for both epimers were unambiguously established on the basis of  $^1\text{H}$ – $^{13}\text{C}$  HMQC and selective 1D NOESY NMR experiments. Key distinctive dipolar interactions are related with the C3-*exo* methyl and the C2 and C7 epoxidic methylene groups.
- García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Lora Maroto, B. *Eur. J. Org. Chem.* **2002**, 3731.
  - Norbornane, bicyclo[2.1.1]heptane, cyclopentane, and cyclohexane are the common frameworks for products obtained by solvolysis of 1-norbornyl triflates. For instance, see: (a) Müller, P.; Mareda, J.; Milin, D. *J. Phys. Org. Chem.* **1995**, 8, 507; (b) Müller, P.; Mareda, J. In *Cage Hydrocarbons*; Olah, G. A., Ed.; Wiley: New York, 1991, Chapter 6; Also see: (c) García Martínez, A.; Osío Barcina, J.; Rodríguez Herrero, M. E.; Iglesias de Dios, M.; Teso Vilar, E.; Subramanian, L. R. *Tetrahedron Lett.* **1994**, 35, 7285; (d) García Martínez, A.; Osío Barcina, J.; Teso Vilar, E. *Tetrahedron* **1996**, 52, 14041; (e) García Martínez, A.; Teso Vilar, E.; de la Moya Cerero, S.; Osío Barcina, J.; Gómez, P. C. *J. Org. Chem.* **1999**, 64, 5611. Also see Ref. 7.
  - Ionization has been also proposed as the first step for the solvolysis of related spiroepoxide 1-norbornyl triflates (i.e., Ref. 7).
  - To the best of our knowledge no precedents have been reported for the formation of the interesting bicyclo[2.2.0]hexane system by rearrangement of 1-norbornyl cations. In this sense, see an unfortunate attempt in: Applequist, D. E.; Klieman, J. P. *J. Org. Chem.* **1961**, 26, 2178.
  - Several reports have revealed that eight-membered rings are better formed if conformational restrictions imposed by an existing ring or other functional groups are present in the precursor (e.g., see Ref. 4b and references cited therein).
  - Suzuki et al. have taken advantage of 8-*exo*-tet hydroxy epoxide cyclizations for the total syntheses of several interesting natural eight-membered cyclic ethers. For instance see Ref. 5a and references cited therein.
  - Acid catalysis is probably acting in the process. A synchronous 7-to-9 step cannot be discarded.
  - Std. react. conditions: see Ref. 7. React. time: 30 days. Yield: 60%. Purification: flash chromatography (silica gel,  $\text{CH}_2\text{Cl}_2$ ). Compound **10**: Colorless oil.  $[\alpha]_{\text{D}}^{20} +17.4$  (1.30,  $\text{CHCl}_3$ ). HRMS: 196.1106 (calcd for  $\text{C}_{11}\text{H}_{16}\text{O}_3$ , 196.1099).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz),  $\delta$ : 3.89 (d,  $J = 12.1$  Hz, 1H), 3.76 (d,  $J = 12.1$  Hz, 1H), 3.27 (d,  $J = 6.2$  Hz, 1H), 3.08 (d,  $J = 6.2$  Hz, 1H), 2.24 (br s, 1H), 2.02–1.94 (several m, 2H), 1.92–1.84 (several m, 2H), 1.75 (dd,  $J = 9.1$  Hz,  $J = 9.1$  Hz, 1H), 1.13 (s, 3H), 1.11 (s, 3H) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz),  $\delta$ : 216.5, 64.1, 63.2, 60.0, 53.8, 48.4, 44.4, 27.3, 21.5, 21.5, 18.6 ppm. IR ( $\text{CHCl}_3$ ),  $\nu$ : 3020, 1747 (str.), 1396, 1338  $\text{cm}^{-1}$ . EM,  $m/z$ : 197 ( $\text{M}^{+\cdot} + 1$ , 6), 196 ( $\text{M}^+$ , 20), 181 (5), 165 (13), 150 (13), 137 (23), 123 (24), 109 (29), 107 (31), 95 (100), 81 (48), 67 (48), 55 (36).
  - C2–C3 rearrangement is the common observed process for related spiroepoxide 1-norbornyl triflates (Ref. 7).
  - Note the undetected 6-*exo*-tet hydroxy-epoxide cyclization of **10**, under the used reaction conditions, probably due to the unfavorable, and conformationally-restricted, disposition of both reacting groups.