

Synthesis and Cycloaddition Reactions of 1,1'-Dimenthene

Fabrizio Fabris, Lucia Leoni and Ottorino De Lucchi*

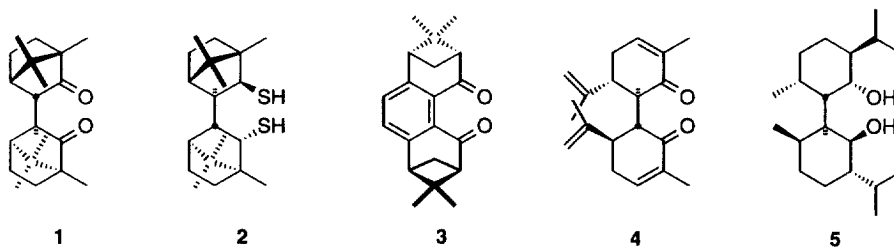
Dipartimento di Chimica, Università Ca' Foscari di Venezia, Dorsoduro 2137, I-30123 Venezia, Italy

Received 2 November 1998; accepted 30 November 1998

Abstract: The synthesis of the hitherto unknown 1,1'-dimenthene **11** from menthone has been studied in detail. The most convenient procedure entails conversion of menthone **6** into its tosylhydrazone **7**, Shapiro transformation into the iodide **9** and copper-mediated homocoupling to **11**. Under optimised reaction conditions a ca. 55% overall yield of dimenthene **11** was obtained from menthone. The reactivity of dimenthene towards Diels-Alder cycloaddition reactions proved expectedly poor, as result of the difficulty of the diene to adopt a planar conformation. 4-Phenyltriazoline-3,5-dione (PTAD), tetracyanoethylene (TCNE) and singlet oxygen afford fair to good yields of the non-symmetrical cycloadducts **13a-c**. In the case of PTAD, the C_2 symmetrical adduct **13a'** is also formed but it converts into the non-symmetrical adduct **13a** on standing. The endoperoxide **13c** obtained in the photooxygenation reaction is transformed into furan **14**, possibly via the unstable *syn*-diepoxide **15**. In contrast, the *anti* diepoxide **15**, obtained from *m*-CPBA oxidation of dimenthene **11** is stable towards heating and it is not transformed into the furan.

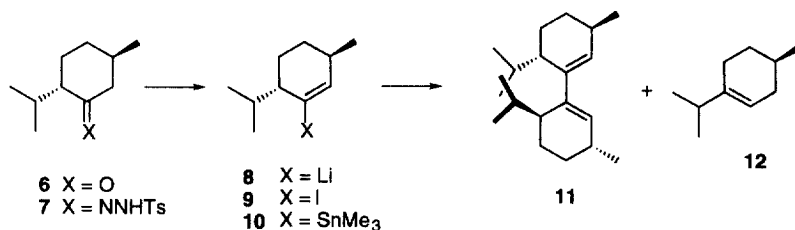
© 1999 Published by Elsevier Science Ltd. All rights reserved.

The positive features exhibited by C_2 -symmetric compounds are largely recognised and discussed in several instances.¹ Besides standard procedures,¹ another convenient access to enantiopure C_2 -symmetric molecules is the homocoupling of monofunctionalized simple natural products as, for example, monoterpenes. Scattered reports in the literature witness this approach even though the strategy has not yet been fully recognised as standard practice for the preparation of chiral auxiliaries for asymmetric synthesis. Examples of molecules falling into this category are **1-5** derived from camphor (**1^{2a}** and **2^{2b}**), verbenone³ (**3**), carvone^{4a} (**4**) and menthol^{4b} (**5**). Other examples of C_2 molecules derived from monoterpenes are known but in these cases the structures of interest have been obtained as a components of complex reaction mixtures.

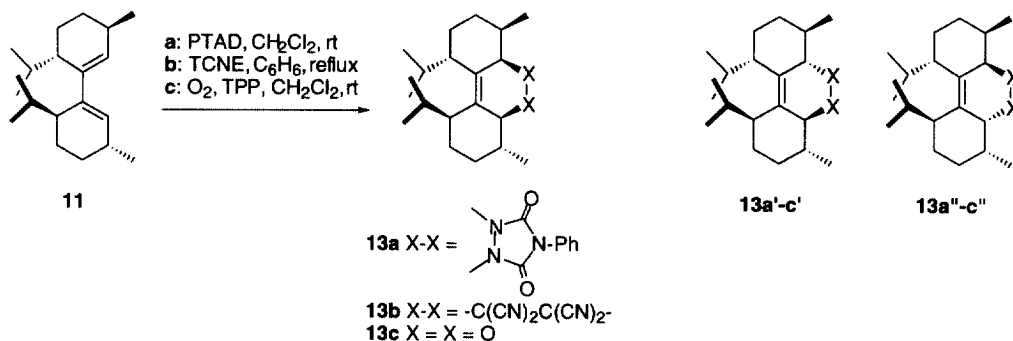


Here we wish to present research aimed at the synthesis of a diene derived from menthone belonging to this class of compound and the study of its chemistry. Menthone was easily converted into the vinyl lithium derivative **8** by the Shapiro reaction described by Garner and co-workers⁵ but it was not possible to use it directly for the coupling reaction because of the presence of lithium sulfonates in the reaction mixture. The lithium compound **8** was hence transformed into the iodide **9⁵** in 70% yield using a large excess of iodine (4 eq) or into the trimethyltin derivative⁶ **10** with trimethyltin chloride (4 eq). The homocoupled product **11** was thus obtained from **9** using *t*-BuLi and anhydrous CuI (1 eq) in 90% yields.⁷ Important is the use of stoichiometric amounts of THF as coordinating the cuprate allows the coupling but the use of THF as solvent lowers the yields, leading to large amounts of decomposition products. Alternatively, one equivalent of TMEDA can be used in place of THF. In this case low temperatures are necessary to control reactivity, as TMEDA ensures an exothermic reaction. In another coupling procedure, the tin compound **10** was coupled

with $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ to give **11** in 40% yield.⁸ The former procedure was however adopted as the method of choice and it was used for the synthesis of several grams of dimenthene **11**. In all cases, the alkene **12** is formed as a side product but it is easily removed from the desired diene **11** because of its high volatility.



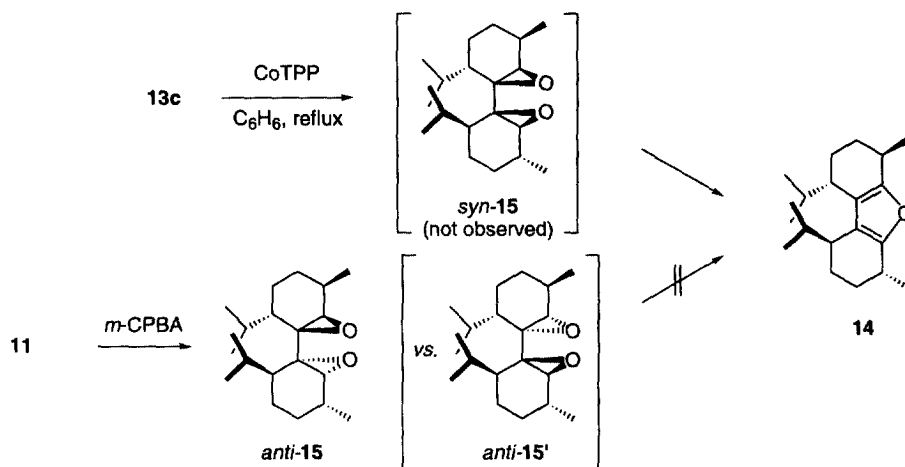
Simple calculations (MM3 level) on the conformational behaviour of **11** highlight its peculiar geometry and the difficulty of the diene to become planar, especially in view of the steric hindrance of the isopropyl groups. As was experienced in a similar case,⁹ the Diels-Alder reactivity of **11** is of interest because it may exhibit a *supra-supra* or *antara-antara* mode of addition. Cycloaddition reactions of **11** were tested with the most common dienophiles and its reactivity proved to be rather poor. While maleic anhydride and (*E*)-bis(phenylsulfonyl)ethylene did not lead to any adduct even at pressures as high as 15 Kbar, 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD), tetracyanoethylene (TCNE) and singlet oxygen led to Diels-Alder products whose spectroscopic data were consistent with the non-symmetrical adducts **13a** (65%), **13b** (40%) and **13c** (30%).



The stereochemistry of the cycloadducts **13a-c** was deduced by the number of lines in their NMR spectra. Significantly, the non-symmetrical (*C*₁-symmetric) nature of **13a-c** reflects in 20 distinct signals in the ¹³C NMR spectrum. The other possible configurations **13a'-c'** or **13a''-c''** would exhibit half this number of signals because of their *C*₂-molecular symmetry.

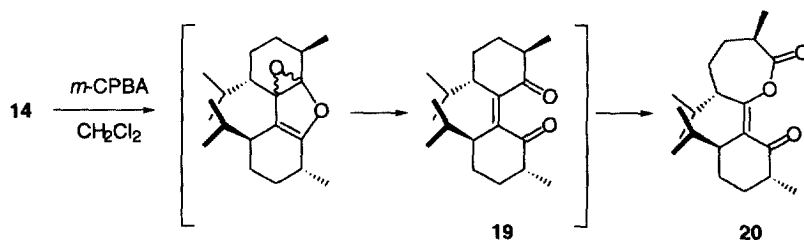
Interestingly, on performing the reaction of **11** with PTAD within an NMR tube with continuous monitoring of the reaction, the transient formation of the *C*₂-symmetric adduct **13a'** (preferred on steric grounds and on the size of the coupling constants over **13a''**) could be recorded. This observation points to a dipolar mechanism kinetically leading to **13a'** and thermodynamically to **13a**. Because PTAD, TCNE and singlet oxygen are known to proceed occasionally with mechanisms involving dipolar intermediates, the poor reactivity exhibited by other dienophiles is ascribed to the inability of the diene to become planar and thus not allow sufficient orbital overlap for concerted cycloaddition.⁹

Upon heating with catalytic CoTPP in refluxing benzene, the endoperoxide **13c** rapidly and cleanly converts into furan **14**. The expected bis-epoxide *syn*-**15** could not be observed.^{9b} The structure of the furan **14** was deduced from its spectroscopic data, including MS. The MS spectrum of **13c** is identical to that of **14** indicating a rapid and clean loss of a water molecule from the endoperoxide or the derived bis-epoxide. Such a possibility prompted us to investigate the reactivity of diene **11** with *m*-CPBA.^{9b} The reaction proceeds at rt in dichloromethane to afford one product only out of the three possible ones. Because of the presence of only one half of signals in the ¹H and ¹³C NMR spectra, the C₂-symmetric structure *anti*-**15** was assigned to the diepoxide, preferred over the alternative C₂-symmetric structure *anti*-**15'** because of indications given by the structures minimised at the MM3 level and because of the size of the coupling constants observed in the ¹H NMR spectrum between the proton of the epoxide ring and the adjacent proton at the ring carbon substituted with the methyl group.



Indeed, the minimised structure *anti*-**15'** shows a dihedral angle between the two hydrogens of *ca.* 80°. The expected coupling constant of 0.3 Hz is in contrast with $J = 1.3$ Hz that was observed, while in structure *anti*-**15** the angle of 67° is in agreement with that observed (1.3 Hz).

Bisepoxide *anti*-**15** was submitted to both Brønsted and Lewis acids treatment to obtain furan **14** but the only result was the complete decomposition of the substrate into complex reaction mixtures. Also CoTPP was used with the same aim but it proved to be ineffective even after several hours at reflux. Several reducing agents¹⁰ were also employed to effect the reductive cleavage of endoperoxide **13c** such as thiourea, LAH, Red-Al® but the sole product was the furan **14**. On the other hand, the reaction of **14** with *m*-CPBA was expected to give the enedione **19** according to the reactivity observed in 2,5-substituted alicyclic furans.¹¹



The reaction performed at 0° C produced mainly a compound lacking C₂ symmetry, as shown by the presence of at least six methyl doublets in its ¹H NMR spectrum. Other spectroscopic data (MS, IR etc.) support the hypothesis that a Baeyer-Villiger reaction occurred in the enedione **19** to produce **20** by analogy to the reactivity of the unsubstituted octahydrodibenzofuran.¹²

In conclusion, we have prepared for the first time the enantiopure diene derived from menthone **11**, showed that it reacts in Diels-Alder reactions to afford the non-symmetric adducts **13** and transformed the endoperoxide derived from the photooxygenation into furan **14**. Because the only adducts to dimenthene were obtained from dienophiles that are known occasionally to proceed through dipolar intermediates¹³ it is supposed that the cycloaddition reactions with these substrates do not follow concerted pathways.

Acknowledgements. This work was co-funded by MURST (Rome) within the national project "Stereo-selezione in Sintesi Organica. Metodologie e Applicazioni".

References and Notes

- (1) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581
- (2) a) Ito, Y.; Konoike, T.; Harada, T.; Saegusa, T. *J. Am. Chem. Soc.* **1977**, *99*, 1487. b) Schroth, W.; Hintzsche, E.; Spitzner, R.; Ströhl, D.; Sieler, J. *Tetrahedron* **1995**, *51*, 13247. Schroth, W.; Hintzsche, E.; Spitzner, R.; Ströhl, D.; Schmeiß, K.; Sieler, J. *Tetrahedron* **1995**, *51*, 13261. Bonnat, M.; Durand, J.-O.; Le Corre, M. *Tetrahedron: Asymmetry* **1996**, *7*, 559. Salama, P.; Poirier, M. *Ibid.* **1997**, *8*, 2757 and references cited herein.
- (3) Paquette, L. A.; Bzowej, E. I.; Branan, B. M.; Stanton, K. J. *J. Org. Chem.* **1995**, *60*, 7277.
- (4) a) Frazier, R. H., Jr.; Harlow, R. L. *J. Org. Chem.* **1980**, *45*, 5408. Mazzega, M.; Fabris, F.; Cossu, S.; De Lucchi, O.; Lucchini, V.; Valle, G. *Tetrahedron* in press. b) McNulty, J.; Millar, M. J. communicated at the ICOS-12, Venezia (Italy) 1998, Book of Abstract PB13 page 219.
- (5) Garner, C. M.; Mossman, B. C.; Prince, M. E. *Tetrahedron Lett.* **1993**, *34*, 4273.
- (6) Seyferth, D.; Vaughan, L. G. *J. Organomet. Chem.* **1963**, 138.
- (7) A 1.7 M solution of *t*-BuLi in hexanes (8.9 mL, 17.0 mmol) was added to iodomenthene (3.0 g, 11.4 mmol) under argon atmosphere at -20 °C. The temperature was left to rise to 0 °C within 30 min (the mixture sometimes reacts violently at that temperature, forming a white solid but the yields are not lowered). CuI (2.17 g, 11.4 mmol), dry *n*-hexane (12 mL) and dry THF (1 mL) was added in the order, the suspension rapidly darkened and was vigorously stirred for 3 days. The resulting black mixture was filtered through silica gel, washing the pad with hexanes (5 x 10 mL). The volatile materials were removed to afford a colorless solid that was recrystallized from MeOH to obtain 2.88 g (92% overall yield) of colorless needles mp: 86-87 °C. [α]_D²² = +61 (CHCl₃, *c* 1.5). ¹H-NMR (CDCl₃, 200 MHz) δ 5.39 (2 H, q, *J* = 1.8 Hz), 2.24-0.80 (14 H, series of m), 0.94 (6 H, d, *J* = 6.7 Hz), 0.91 (6 H, d, *J* = 6.8 Hz), 0.67 (6 H, d, *J* = 6.7). ¹³C-NMR (CDCl₃, 50 MHz) δ 143.47, 131.32, 40.61, 31.12, 30.74, 28.95, 22.23, 21.10, 20.86, 15.77. IR (KBr) ν 2971, 2930, 2853, 1719, 1462, 1364, 1279, 858 cm⁻¹.
- (8) Ghosal, S.; Luke, G. P.; Kyler, K. S. *J. Org. Chem.* **1987**, *52*, 4296.
- (9) a) Delogu, G.; Fabbri, D.; Fabris, F.; Sbrogiò, F.; Valle, G.; De Lucchi, O. *J. Chem. Soc., Chem. Commun.* **1995**, 1887. b) Fabris, F.; Sbrogiò, F.; De Lucchi, O.; Delogu, G.; Fabbri, D.; Valle, G. *Gazz. Chim. Ital.* **1997**, *127*, 393.
- (10) Adam, W.; Cueto, O.; De Lucchi, O.; Peters, K.; Peters, E. M.; Von Schnering, H. G. *J. Am. Chem. Soc.* **1981**, *103*, 5822.
- (11) Cattalini, M.; Cossu, S.; Fabris, F.; De Lucchi, O. *Synth. Commun.* **1996**, *26*, 637.
- (12) Gingerich, S. B.; Jennings, P. W. *J. Org. Chem.* **1984**, *49*, 1284.
- (13) Adam, W.; Carballera, N. *J. Am. Chem. Soc.* **1984**, *106*, 2874. Cheng, C.-C.; Seymour, C. A.; Petti, M. A.; Greene, F. D.; Blount, J. F. *J. Org. Chem.* **1984**, *49*, 2910. Hofman, P.; Gleiter, R. *Tetrahedron Lett.* **1975**, 159. Fatiadi, A. J. *Synthesis* **1986**, 249. Adam, W. *Angew. Chem.* **1974**, *86*, 683; *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 619. Adam, W.; Balci, M. *J. Am. Chem. Soc.* **1979**, *101*, 7537. Clennan, E. L.; Nagraba, K. *Ibid.* **1988**, *110*, 4312. O'Shea, K. E.; Foote, C. S. *Ibid.* **1988**, *110*, 7167.