Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 47 (2006) 771–774
Tetrahedron Letters

Synthesis of *trans*-1,8,12,13-tetraoxadispiro[4.1.4.2]-tridecanes—a new class of peroxides☆

D. Naveen Kumar,[a] N. Sudhakar,[a] B. Venkateswara Rao,[a,*] K. Hara Kishore[b] and U. Suryanarayana Murty[b]

[a]*Organic Division III, Indian Institute of Chemical Technology, Hyderabad 500 007, India*
[b]*Biology Division, Indian Institute of Chemical Technology, Hyderabad 500 007, India*

Received 10 October 2005; revised 11 November 2005; accepted 18 November 2005

Abstract—The synthesis of *trans*-1,8,12,13-tetraoxadispiro[4.1.4.2]tridecanes, a new class of peroxide skeletons using Birch reduction of aromatic compounds followed by ozonolysis and acid catalysed cyclisation is described.

Cyclic peroxides are important chemical frameworks in many pharmacologically active compounds, for example, artemisinin[1] and yingzhaosu[2] which are potent antimalarial compounds and chondrillin[3] which shows significant antitumour activity. Many cyclic peroxides, which exhibit antifungal, antibacterial and antitumour activities have been reported previously from a number of marine organisms, especially from sponges of the family *Plakinidae*,[4] among which, plakinic acids contain a rare 1,2-dioxolane-ring systems.[5] Owing to the promising pharmacological activities of peroxide-containing compounds, the design and synthesis of new peroxides and the development of new approaches has become a burgeoning field in organic chemistry.[6]

The preparation of 1,2-dioxolanes from 1,3-diketones was known in the early 1960s[7] and recently, Zvilichovsky and co-workers[8] reported the formation of mixtures of 1,2-dioxolane intermediates via ozonolysis of simple alkyl derivatives of 1,4-cyclohexadienes. Based on this information, we envisaged the synthesis of new tricyclic bis-spiroperoxyketals by internal trapping of carbonyl oxides during ozonolysis of products from Birch reduction of aromatic compounds. Earlier, this protocol was utilised in our laboratory for the synthesis of biologically active compounds.[9] Although the significance of tricyclic bis-spiroketals is well known, as these compounds exist in nature as sub-structures of many polyether antibiotics,[10] tricyclic bis-spiroperoxyketals are novel skeletons. Herein, we report for the first time the synthesis of *trans*-1,8,12,13-tetraoxadispiro[4.1.4.2]tridecane **1** and its 2,9-dimethyl derivatives **2** and **3** (Fig. 1) and the evaluation of their antimicrobial activity.

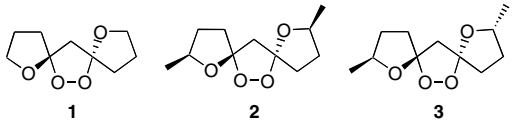


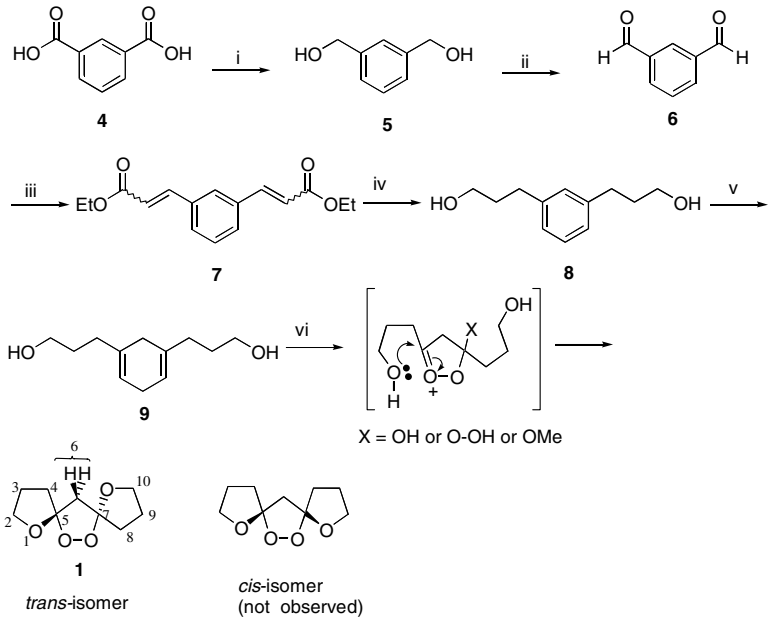
Figure 1.

Initially, we carried out the synthesis of **1**, as shown in Scheme 1. Our synthesis commenced with the reduction of commercially available *m*-phthalic acid **4** using LAH in THF to give diol **5**. Oxidation of **5** using TEMPO free radicals afforded dialdehyde **6**, which upon Wittig reaction with $PPh_3CHCOOEt$ in DCM resulted in compound **7**, the major product being the bis-trans-diastereomer. Compound **7** upon hydrogenation using H_2–Pd/C in MeOH followed by reduction with LAH in THF gave compound **8**. Birch reduction of compound **8** using Li/liq. NH_3 and EtOH in THF gave 1,4-dihydro compound **9** and this was without further purification, subjected to ozonolysis in 10% MeOH in DCM (compound **9** was partly soluble in neat DCM at −78 °C) followed by treatment with catalytic TsOH to give compound **1** as a solid (mp 50–52 °C). The overall yield of compound **1** was 27% from **8** and the average

☆ IICT Communication No.: 050904.

* Corresponding author. Tel.: +91 40 27160123x2614; fax: +91 40 27160512; e-mail: venky@iict.res.in

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.11.107



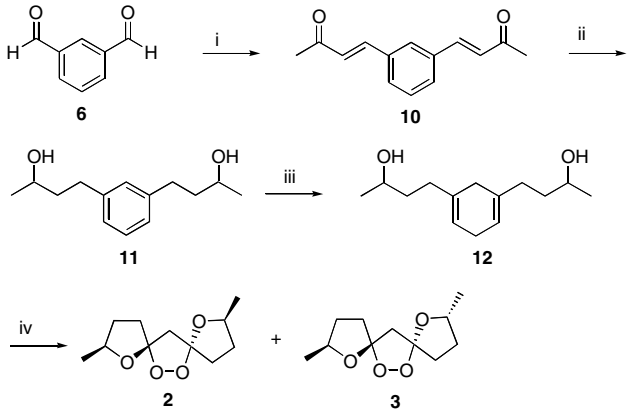
Scheme 1. Reagents and conditions: (i) LAH, THF reflux, 75%; (ii) TEMPO, EtOAc/toluene, 0 °C, 83%; (iii) Ph_3PCHCO_2Et, DCM 93%; (iv) (a) Pd/C–H_2, MeOH; (b) LAH, THF, 0 °C–rt, 79% overall yield for two steps; (v) Li–liq. NH_3–EtOH, THF; (vi) (a) O_3, 10% MeOH in DCM; (b) catalytic TsOH, the combined overall yield from **8** is 27%.

yield for each stage was calculated as 67%.[11] Interestingly, we isolated only the trans compound **1** and did not observe formation of the corresponding cis-isomer. The trans-stereochemistry of **1** was confirmed by its ^1H NMR spectrum in which the geminal protons of the C-6 carbon appeared as a singlet at δ 2.86. The C_2 symmetry of the molecule was evident from its ^1H and ^{13}C NMR spectra. In addition to this, we confirmed the structure by mass and elemental analysis.[12]

According to computational studies[13] the trans-isomer of **1** is more stable than the cis-isomer by 1.86 kcal/mol.

With this result in hand, next we carried out the synthesis of compounds **2** and **3** (Scheme 2). Dialdehyde **6** upon treatment with the phosphorane $PPh_3CHCOCH_3$ in DCM afforded compound **10** exclusively as the bis-trans-diastereomer, which upon hydrogenation using H_2–Pd/C in MeOH followed by reduction with LAH in THF gave **11**. Using the same procedure as described earlier, compound **11** was subjected to Birch reduction followed by ozonolysis and treatment with a catalytic amount of TsOH gave a mixture of diastereomers **2** and **3** (1:1 ratio). These diastereomers were separated using silica gel column chromatography to afford pure compounds **2** (solid mp 53 °C) and **3** (colorless syrup). The combined yield of compounds **2** and **3** was 37% from compound **11** and the average yield for each stage was 72%.[14]

^1H NMR spectroscopy of both isomers **2** and **3** revealed the existence of the intrinsic trans-stereochemistry at the spiro centres. The geminal protons at the C-6 carbon resonated at δ 2.84 and 2.81 for **2** and **3**, respectively, as singlets. Other analytical data were in agreement with the proposed structures.[12] Compounds **2** and **3** are



Scheme 2. Reagents and conditions: (i) $Ph_3PCHCOCH_3$, DCM 96%; (ii) (a) Pd/C–H_2, MeOH; (b) LAH, THF, 0 °C–rt, 82% overall yield for two steps; (iii) Li–liq. NH_3–EtOH, THF; (iv) (a) O_3, 10% MeOH–DCM; (b) catalytic TsOH, overall yield from **11** is 37%.

formed from racemic-**12** and meso-**12**, respectively. Of the two C_2-symmetric compounds possible from racemic-**12**, we observed only one isomer with trans–trans–trans-stereochemistry (compound **2**) and this was confirmed by the observation of NOE's between the C-6 protons and C-2 and C-9 methyls (Fig. 2).

Antimicrobial evaluation of the above three compounds against six bacterial organisms[15] and two fungal strains[16] was investigated (Tables 1 and 2). The minimum inhibitory concentrations (MIC) of the compounds **1**, **2** and **3** against six test organisms were determined by the broth dilution method.[17] Results showed moderate antibacterial activity whilst none were active against *Pseudomonas aeruginosa*. The agar cup bioassay was employed for testing the antifungal activity

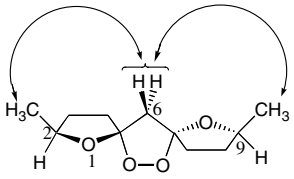


Figure 2. NOE's between the C-6 geminal protons and C-2 and C-9 methyls in compound **2**.

Table 1. Antibacterial activity of compounds **1**, **2** and **3** (MIC, μg/mL)

Microorganism	**1**	**2**	**3**	Ciprofloxacin[a]
(Gram +ve)				
Bacillus subtilis	50	25	25	0.78
Bacillus sphaericus	25	12.5	25	0.78
Staphylococcus aureus	50	50	25	0.39
(Gram −ve)				
Klebsiella aerogenes	50	50	25	0.78
Chromobacterium violaceum	25	25	12.5	0.39
Pseudomonas aeruginosa	—	—	—	0.78

[a] Ciprofloxacin is used as positive control (standard).

Table 2. Antifungal activity levels of compounds **1**, **2** and **3**

Microorganism	**1**		**2**		**3**		Clotrimazole[a]
	A	B	A	B	A	B	
Aspergillus niger	7	11	6	9	8	12	26
Rhizopus oryzae	8	12	6	8	8	11	23

($A = 30$ μg/mL, $B = 100$ μg/mL); inhibitory zone diameters are in millimetre.

[a] Clotrimazole is used as positive control (standard).

of **1**, **2** and **3** following the standard procedure[18] and this revealed moderate inhibition against *Aspergillus niger* and *Rhizopus oryzae*.

In conclusion, we have demonstrated the synthesis of new *trans*-1,8,12,13-tetraoxadispiro[4.1.4.2]tridecanes and established the stereochemical outcome of the reaction by NMR spectroscopy of each compound. Currently, studies are in progress to improve the yields, to synthesise other analogues and to complete the evaluation of their biological activity.

Acknowledgements

D.N.K. and N.S. thank the UGC, New Delhi, for financial assistance (S.R.F.). The authors thank Dr. K. Bhanu Prakash, for helping with the energy calculations and Dr. J. S. Yadav and Dr. A. C. Kunwar, for their support and encouragement.

References and notes

1. (a) Jefford, W.; Vicente, M. G. H.; Jacquier, Y.; Favarger, F.; Marenda, J.; Millason-Schmidt, P.; Brunner, G.; Burger, U. *Helv. Chim. Acta* **1996**, *79*, 1475–1487; (b) Cummings, J. N.; Polypradith, P.; Posner, G. H. *Adv. Pharmacol.* **1997**, *37*, 253; (c) Haynes, R. K.; Vonwiller, S. *Acc. Chem. Res.* **1997**, *30*, 73; (d) Robert, A.; Meunier, B. *Chem. Soc. Rev.* **1998**, *27*, 273–279.
2. O'Neill, P. M.; Searle, N. L.; Raynes, K. J.; Maggs, J. L.; Ward, S. A.; Storr, R. C.; Park, B. K.; Posner, G. H. *Tetrahedron Lett.* **1998**, *39*, 6065–6068.
3. Snider, B. B.; Shi, Z. *J. Org. Chem.* **1990**, *55*, 5669–5671.
4. (a) Sandler, J. S.; Colin, P. L.; Hooper, J. N. A.; Faulkner, D. J. *J. Nat. Prod.* **2002**, *65*, 1258–1261; (b) Chen, Y.; McCarthy, P. J.; Harmody, D. K.; O'Rourke, R. S.; Chilson, K.; Selitrennikoff, C.; Pomponi, S. A.; Wright, A. E. *J. Nat. Prod.* **2002**, *65*, 1509–1512; (c) Faulkner, D. *Nat. Prod. Rep.* **2001**, *18*, 1–49; (d) Casteel, D. A. *Nat. Prod. Rep.* **1999**, *16*, 55–73.
5. (a) Davidson, B. S. *J. Org. Chem.* **1991**, *56*, 6722–6724; (b) Qureshi, A.; Salva, J.; Harper, M. K.; Faulkner, D. J. *J. Nat. Prod.* **1998**, *61*, 1539–1542; (c) Horton, P. A.; Longley, R. E.; Kelly Borges, M. K.; McConnel, O. J.; Ballas, L. M. *J. Nat. Prod.* **1994**, *57*, 1374–1381.
6. (a) Jin, H.-X.; Liu; Zhang, Q.; Wu, Y. *Tetrahedron Lett.* **2005**, *46*, 5767–5769; (b) Wasserman, H. H.; Wiberg, K. B.; Larsen, D. L.; Parr, J. *J. Org. Chem.* **2005**, *70*, 105–109; (c) Tang, Y.; Dong, Y.; Vennerstrom, J. L. *Med. Res. Rev.* **2004**, *24*, 425–448; (d) Yang, Y.-K.; Lee, S.; Tae, J. *Bull. Korean Chem. Soc.* **2004**, *25*, 1307–1308; (e) Dussault, P. H.; Trullinger, T. K.; Noor-e-Ain, F. *Org. Lett.* **2002**, *4*, 4591–4593; (f) Jefford, C. W. *Curr. Med. Chem.* **2001**, *8*, 1803–1826; (g) Murakami, N.; Kawanishi, M.; Itagaki, S.; Horii, T.; Kobayashi, M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 69–72; (h) Murakami, N.; Kawanishi, M.; Itagaki, S.; Horii, T.; Kobayashi, M. *Tetrahedron Lett.* **2001**, *42*, 7281–7285; (i) McCullough, K. J.; Nojima, M. *Curr. Org. Chem.* **2001**, *5*, 601–636; (j) Dussault, P. H.; Eary, C. T.; Lee, R. J.; Zope, U. R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2189; (k) Dussalut, P. H.; Eary, C. T. *J. Am. Chem. Soc.* **1998**, *120*, 7133.
7. (a) Rieche, A.; Bischoff, C. *Chem. Ber.* **1962**, *95*, 77–82; (b) Milas, N. A.; Mageli, O. L.; Golubovic, A.; Arndt, R. W.; Ho, J. C. J. *J. Am. Chem. Soc.* **1963**, *85*, 222–226.
8. Gbara-Haj-Yahia, I.; Zvilichovsky, G.; Seri, N. *J. Org. Chem.* **2004**, *69*, 4135.
9. (a) Shashidhar Kumar, A.; Bhaket, P.; Rao, B. V. *ARKIVOC* **2005**, 74–81; (b) Kumar, A. S.; Haritha, B.; Rao, B. V. *Tetrahedron Lett.* **2003**, *44*, 4261; (c) Rao, B. V.; Rao, A. S. *Synth. Commun.* **1995**, 1531. For the Birch reduction of 2-picoline followed by hydrolysis, see: (d) Kumar, D. N.; Rao, B. V. *Tetrahedron Lett.* **2004**, *10*, 2227.
10. (a) Allen, P. R.; Brimble, M. A.; Prabaharan, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 379; (b) Brimble, M. A.; Fares, F. A. *Tetrahedron* **1999**, *55*, 7661–7706.
11. In most cases nearly 60% of **8** was recovered and the yields quoted are calculated on the basis of starting material recovery.
12. Analytical data for compounds **1**, **2** and **3**.
Compound **1**: White solid: mp 50–52 °C; IR (KBr, cm^{-1}): 2965, 2930, 2865, 1725, 1460, 1435, 1340, 1190, 1110, 1065, 1010, 925, 900; ^1H NMR (300 MHz, $CDCl_3$): δ 4.00–3.87 (m, 4H), 2.86 (s, 2H), 2.32–1.82 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 114.89, 67.83, 51.43, 31.78, 24.42; FAB-MS *m/z*: 187 $[M+1]^+$; accurate mass calcd for $[M+1]^+$ ($C_9H_{17}O_4$) = 187.0970, found: 187.0976.
Compound **2**: White solid: mp 53 °C; IR ($CHCl_3$, cm^{-1}): 2972, 2932, 1736, 1698, 1457, 1386, 1322, 1257, 1206, 1180, 1142, 1120, 1062, 939, 892; ^1H NMR (200 MHz, $CDCl_3$): δ 4.23–4.10 (m, 2H), 2.84 (s, 2H), 2.30–1.97 (m, 6H), 1.54–1.33 (m, 2H), 1.27 (d, 6H, $J = 6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 114.92, 75.29, 53.10, 32.21, 32.07, 20.46; ES-MS

m/z: 215 $[M+1]^+$; accurate mass calcd for $[M+1]^+$ ($C_{11}H_{19}O_4$) = 215.1283, found: 215.1286.
Compound **3**: Colourless syrup; IR ($CHCl_3$, cm^{-1}): 2971, 2930, 1736, 1456, 1382, 1338, 1209, 1174, 1138, 1069, 936, 888; ^1H NMR (200 MHz, $CDCl_3$): δ 4.33–4.09 (m, 2H), 2.81 (s, 2H), 2.35–1.93 (m, 6H), 1.67 (m, 1H), 1.44 (m, 1H), 1.33 (d, 3H, $J = 5.9$ Hz), 1.26 (d, 3H, $J = 5.9$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 114.97, 114.76, 77.21, 75.27, 52.54, 33.81, 32.40, 32.08, 32.01, 22.72, 20.49; ES-MS *m/z*: 215$[M+1]^+$; accurate mass calcd for $[M+1]^+$ ($C_{11}H_{19}O_4$) = 215.1283, found: 215.1281.

13. Computational studies were carried out on MOPAC 6 software using the Austin Model 1 (AM1) method.
14. In this case, we recovered 65% of the starting material **11** and the combined yields of **2** and **3** are based on this recovery.
15. Six test organisms: *Bacillus subtilis* (MTCC 441), *B. sphaericus* (MTCC 511), *Staphylococcus aureus* (MTCC 96), *Klebsiella aerogenes* (MTCC 39), *Chromobacterium violaceum* (MTCC 2656) and *Pseudomonas aeruginosa* (MTCC 741) were obtained from the Institute of Microbial Technology, Chandigarh. Cultures of the test organisms were maintained on nutrient agar slants and were sub-cultured in petri dishes prior to testing. The nutrient agar and nutrient broth were procured from M/S Himeda, Mumbai, India.
16. Two test organisms: *Aspergillus niger* (MTCC 281) and *Rhizopus oryzae* (MTCC 262) were obtained from the Institute of Microbial Technology, Chandigarh. Cultures of test organisms were maintained on potato dextrose agar slants and were sub-cultured in petri dishes prior to testing. The nutrient agar and the potato dextrose agar media were procured from M/S Himeda, Mumbai, India.
17. National Committee for Clinical Laboratory Standard (NCCLS) method for dilution antimicrobial susceptibility tests for bacteria, which grow aerobically. *Nat. Comm. Clin. Lab. Stands,* Villanova; 1982; p 242.
18. Linday, M. E. *Practical Introduction to Microbiology*; E & F.N. Spon Ltd, 1962; p 177.