Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 1211–1213

TETRAHEDRON LETTERS

(+)-*syn*-Benzotriborneol: the first functionalised enantiopure C_3-symmetric benzocyclotrimer

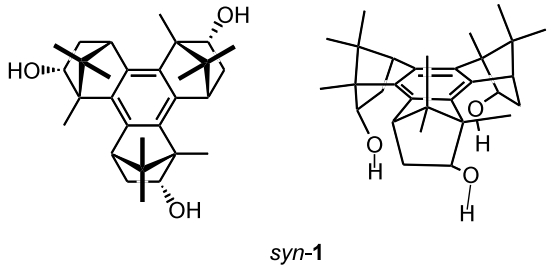
Fabrizio Fabris,* Luca Bellotto and Ottorino De Lucchi

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

Received 18 September 2002; revised 31 October 2002; accepted 9 December 2002

Abstract—Copper(I) thiophencarboxylate readily and effectively cyclotrimerises protected 5-bromo-6-trimethylstannylborn-5-en-2-ols, leading to oxygen-functionalised benzocyclotrimers. The remarkably high *syn* to *anti* ratio is driven by relative displacement of the halide and metal on the alkene moiety and depends on the steric hindrance of the protecting group of the hydroxy function. The less hindered methyl derivative affords exclusively *syn*-benzocyclotrimer. The readily removable methoxymethyl derivative gives enantiopure *syn*-tribenzoborneol in high yields.

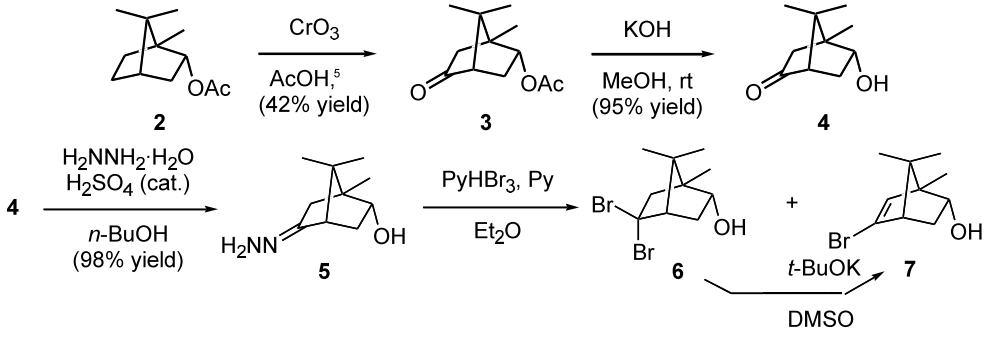
C_3-Symmetric chiral triols can be effectively used as ligands for metal ions,[1] which can be used in asymmetric synthesis.[2] Furthermore, the corresponding ethers are related to crown ethers, with relevant interest on ion transportation.[3] Our research group has been involved for a long time in the cyclotrimerisation reaction of polycyclic molecules which affords benzocyclotrimers of cup-shaped geometry with potential host–guest properties.[4] Recently we have focused our efforts on the achievement of the following goals: (a) to obtain selectively *syn* cyclotrimers (usually the cyclotrimerisation reactions afford mixtures of *syn* and *anti* diastereomers, where the *anti* isomer prevails the *syn*); (b) to obtain cyclotrimers functionalised at the outer rim; (c) to obtain enantiopure structures. In this paper we report the achievement of these goals by selective synthesis of the enantiopure trimer of born-5-en-2-ol *syn*-**1** (Fig. 1).



syn-**1**

Figure 1. Flat and perspective representation of *syn*-**1**.

The starting material for the synthesis of *syn*-**1** is commercially available (−)-bornyl acetate **2**, that was oxidised to ketone **3** as reported by Meinwald and co-workers.[5] The hydrolysis of the acetyl group was accomplished with potassium hydroxide in methanol giving **4** in high yield.[6]

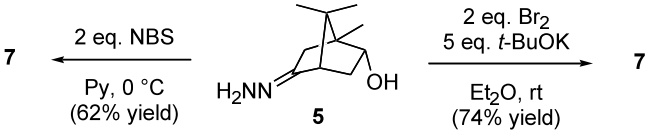


Keywords: asymmetry; copper and compounds; cyclotrimerisation; cyclotrimers; diastereoselection; stereochemistry; terpenes; triols.
* Corresponding author. Tel.: +39-41-2348908; fax: +39-41-2348517; e-mail: fabrisfa@unive.it

0040-4039/03/$ - see front matter
PII: S0040-4039(02)02789-2

The ketoalcohol was reacted with excess of hydrazine monohydrate to afford hydrazone **5** quantitatively.[7] The latter was converted into the bromide **7** using different methods. The reaction with piridinium perbromate[8] underwent with difficulty, producing an unseparable mixture of **6** and **7**. The former was converted into the olefin **7** in a further step with an overall yield of 58%.[9]

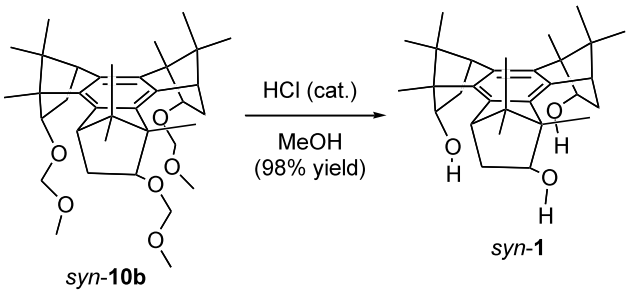
Better results were obtained with NBS in pyridine,[10] or with bromine in the presence of potassium *tert*-butoxide. The latter reaction was conveniently carried out under sonication. 5-Bromoborn-5-en-2-ol was easily purified by sublimation.



The next step was the protection of the alcoholic moiety with different protecting groups, able to resist to the strongly basic and nucleophilic conditions of the metallation step. Methyl,[11] methoxymethyl[12] and methoxyethoxymethyl[13] derivatives have been produced. Metallation with lithium diisopropylamide followed by quenching with trimethyltin chloride gave the precursors for the cyclotrimerisation in high yields.[4a,b,h,g]

The cyclotrimerisation reactions mediated by copper(I) thiophenecarboxylate[4a,b] (CuTc) were carried out in NMP at −20°C and afforded benzocyclotrimers high yields (R = Me: 82%, R = MOM: 86%, R = MEM: 93% yields). Remarkably, high *syn* to *anti* ratios were obtained in for **9b** (5.5:1) and **9c** (5:1) and complete *syn*-diastereoselectivity for **9a**. These stereochemical results are in accordance with other experiments carried out with (+)-camphor and (−)-epicamphor derivatives aimed at the determination of the mechanism of the cyclotrimerisation reaction.[14]

The cleavage of methoxymethyl moiety of *syn*-**10b** with hydrochloric acid in methanol[15] led to the isolation of the enantiopure triol *syn*-**1** in high yield.[16]



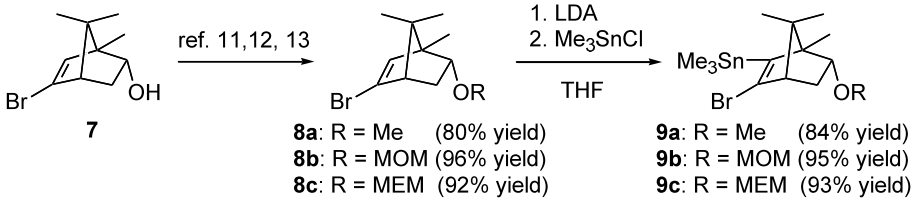
In conclusion, we have successfully synthesised for the first time a enantiopure functionalised *syn*-benzocyclotrimer. The high *syn* selectivity of the cyclotrimerisation reaction, the high yields obtained in every step and the ready availability of the substrate allow the preparation of large amounts of the triol, which will be implemented in several applications of asymmetric synthesis.

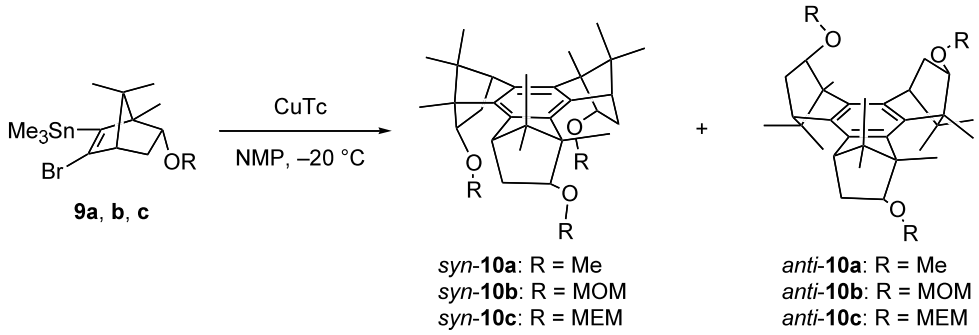
Acknowledgements

This work was co-funded by MURST (Rome) within the national project 'Stereoselezione in Sintesi Organica. Metodologie e Applicazioni'.

References

1. (a) Moberg, C. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 248; (b) Tse, B.; Kishi, Y. *J. Org. Chem.* **1994**, *59*, 7807; (c) Nugent, W. A.; Rajanbabu, T. V.; Burk, M. J. *Science* **1993**, *259*, 479.





2. (a) Bonchio, M.; Licini, G.; Di Furia, F.; Mantovani, S.; Modena, G.; Nugent, W. A. *J. Org. Chem.* **1999**, *64*, 1326; (b) Bonchio, M.; Calloni, S.; Di Furia, F.; Licini, G.; Modena, G.; Moro, S.; Nugent, W. A. *J. Am. Chem. Soc.* **1997**, *119*, 6935; (c) Kaufman, D.; Boese, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 545.
3. (a) Paquette, L. A.; Ra, C. S.; Gallucci, J. C.; Kang, H.-J.; Ohmori, N.; Arrington, M.; David, W.; Brodbelt, J. S. *J. Org. Chem.* **2001**, *66*, 8629; (b) Paquette, L. A.; Tae, J.; Hickey, E. R.; Trego, W. E.; Rogers, R. D. *J. Org. Chem.* **2000**, *65*, 9160; (c) Paquette, L. A.; Tae, J.; Gallucci, J. C. *Org. Lett.* **2000**, *2*, 143; (d) Tae, J.; Rogers, R. D.; Paquette, L. A. *Org. Lett.* **2000**, *2*, 139.
4. (a) Borsato, G.; De Lucchi, O.; Fabris, F.; Lucchini, V.; Pasqualotti, M.; Zambon, A. *Tetrahedron Lett.* **2003**, *44*, 561; (b) Borsato, G.; De Lucchi, O.; Fabris, F.; Groppo, L.; Lucchini, V.; Zambon, A. *J. Org. Chem.* **2002**, *67*, 7894; (c) Cossu, S.; Cimenti, C.; Peluso, P.; Paulon, A.; De Lucchi, O. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 4086; (d) Zambrini, L.; Fabris, F.; De Lucchi, O.; Gardenal, G.; Visentin, F.; Canovese, L. *Tetrahedron* **2001**, *57*, 8719; (e) Cossu, S.; De Lucchi, O.; Paulon, A.; Peluso, P.; Zonta, C. *Tetrahedron Lett.* **2001**, *42*, 3515; (f) Paulon, A.; Cossu, S.; De Lucchi, O.; Zonta, C. *J. Chem. Soc., Chem. Commun.* **2000**, 1837; (g) Zonta, C.; Cossu, S.; De Lucchi, O. *Eur. J. Org. Chem.* **2000**, 1965; (h) Fabris, F.; De Martin, A.; De Lucchi, O. *Tetrahedron Lett.* **1999**, *40*, 9121; (i) Zonta, C.; Cossu, S.; Peluso, P.; De Lucchi, O. *Tetrahedron Lett.* **1999**, *40*, 8185; (j) Durr, R.; Cossu, S.; Lucchini, V.; De Lucchi, O. *Angew. Chem., Int. Ed. Engl.* **1998**, *36*, 2805; (k) Cossu, S.; De Lucchi, O.; Lucchini, V.; Valle, G.; Balci, M.; Dastan, A.; Demirci, B. *Tetrahedron Lett.* **1997**, *38*, 5319; (l) Durr, R.; De Lucchi, O.; Cossu, S.; Lucchini, V. *J. Chem. Soc., Chem. Commun.* **1996**, 2447.
5. Meinwald, J.; Shelton, J. S.; Buchanan, G. L.; Courtin, A. *J. Org. Chem.* **1968**, *33*, 99.
6. (a) Robillard, R.; Ingold, K. U. *Tetrahedron Lett.* **1986**, *27*, 2817; (b) Allen, S. A.; Darby, N.; Salisbury, P.; Sigurdson, E. R.; Money, T. *Can. J. Chem.* **1979**, *57*, 773.
7. Cremlyn, R.; Bartlet, M.; Lloyd, J. *Phosphorus and Sulfur* **1988**, *40*, 91.
8. Pross, A.; Sternhell, S. *Aust. J. Chem.* **1971**, *24*, 1437.
9. Frank, N. L.; Baldrige, V. V.; Siegel, J. S. *J. Am. Chem. Soc.* **1995**, *117*, 2102.
10. Bourgeoius, D.; Lallemand, J.-Y.; Pancrazi, A.; Prunet, J. *Synlett* **1999**, 1555.
11. Johnstone, R. A. W.; Rose, M. E. *Tetrahedron* **1979**, *35*, 2169.
12. Stork, G.; Takahashi, T. *J. Am. Chem. Soc.* **1977**, *99*, 1275.
13. Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, *11*, 809.
14. Fabris, F.; De Martin, A.; Zambrini, L.; Rosso, E.; De Lucchi, O., in preparation.
15. Auerbach, J.; Weinreb, S. M. *J. Chem. Soc., Chem. Commun.* **1974**, 298.
16. Analytical data for (1*R*,2*R*,4*S*,5*R*,6*R*,8*S*,9*R*,10*R*,12*S*)-3,4,7,8,11,12-hexahydro-2,6,10-trihydroxy-1,5,9,13,13′,14,14′,15,15′-nonamethyl-1,4:5,8:9,12-trimethanotriphenylene *syn*-**1**: mp 250–252°C. $[\alpha]_D^{22}=+105$ (*c* 0.8, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 4.20 (3H, d, $J=7.6$ Hz), 3.02 (3H, d, $J=3.5$ Hz), 2.55 (3H, m), 1.97 (3H, bs), 1.33 (9H, s), 1.01 (3H, d, $J=12.6$ Hz), 0.94 (9H, s), 0.56 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 141.9, 134.1, 77.7, 58.1, 57.7, 48.8, 38.0, 21.2, 19.2, 12.0. IR (KBr) ν 3387, 2956, 1455, 1389, 1051 cm^{-1}. Anal. calcd for $C_{30}H_{42}O_3$: C, 79.96; H, 9.39. Found: C, 79.94; H, 9.38%.