Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 975–978

TETRAHEDRON: *ASYMMETRY*

Rational resolution of the isosteric enantiomers of 6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol and conversion to the two isosteric diastereoisomers of the calcium channel blocker UK-74,756

John E. G. Kemp,[a,*] Robert A. Bass,[a] Jon Bordner,[b] Peter E. Cross,[a] Roger F. Gammon[a] and Jennifer A. Price[a]

[a]*Discovery Chemistry, Pfizer Global Research and Development, Sandwich, Kent CT13 9NJ, UK*
[b]*Structural Chemistry and Computational Chemistry, Pfizer Global Research and Development, Groton, CT, USA*

Received 13 March 2001; accepted 5 April 2001

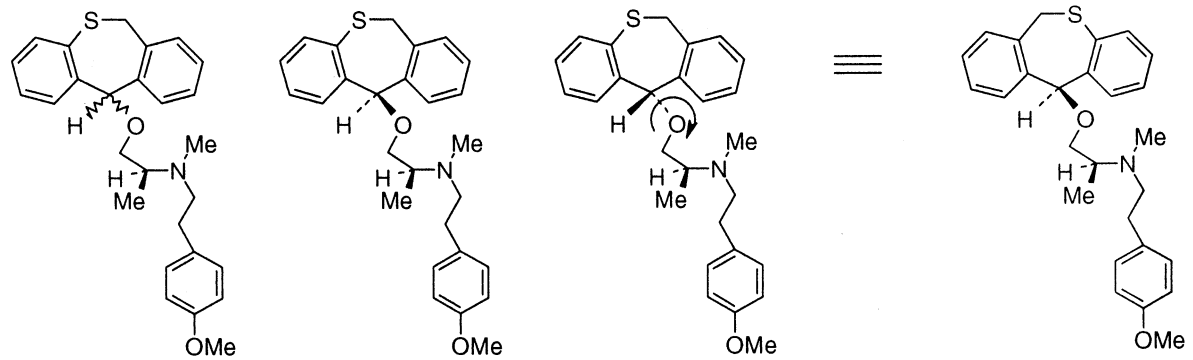
Abstract—Sulfoxidation of the (+)-Noe-lactol derivative of racemic 6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol broke the isosterism and converted an inseparable mixture of two compounds into a separable mixture of four. X-Ray structural determination on one of these and subsequent manipulation provided resolved 6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol and all four sulfoxides in known configurations, and enabled the resolution by synthesis of the two isosteric diastereoisomers of the calcium channel blocker UK-74,756. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

The calcium channel blocker UK-74,756 was synthesised from racemic 6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol by procedures in our patent[1] and is thus a mixture of the diastereoisomers **i** and **ii** which we were keen to separate. The separation of the diastereoisomeric mixture is hampered by the fact that they are isosteres of each other by virtue of an exchange of an -SCH_2- group for -CH_2S-. A second structural feature of UK-74,756 also disfavours conventional separations: the two stereocentres are not closely coupled. We decided to tackle the problem by resolving the thiepinol.

2. Results and discussion

Preparation of the (+)-Noe-lactol derivatives[2–4] of the racemic thiepinol **1** provides two close-coupled stereocentres, but compounds **3** and **4** (Scheme 1) are still isosteric and were not preparatively separable.



UK-74,756 - mixture of two isosteric diastereoisomers

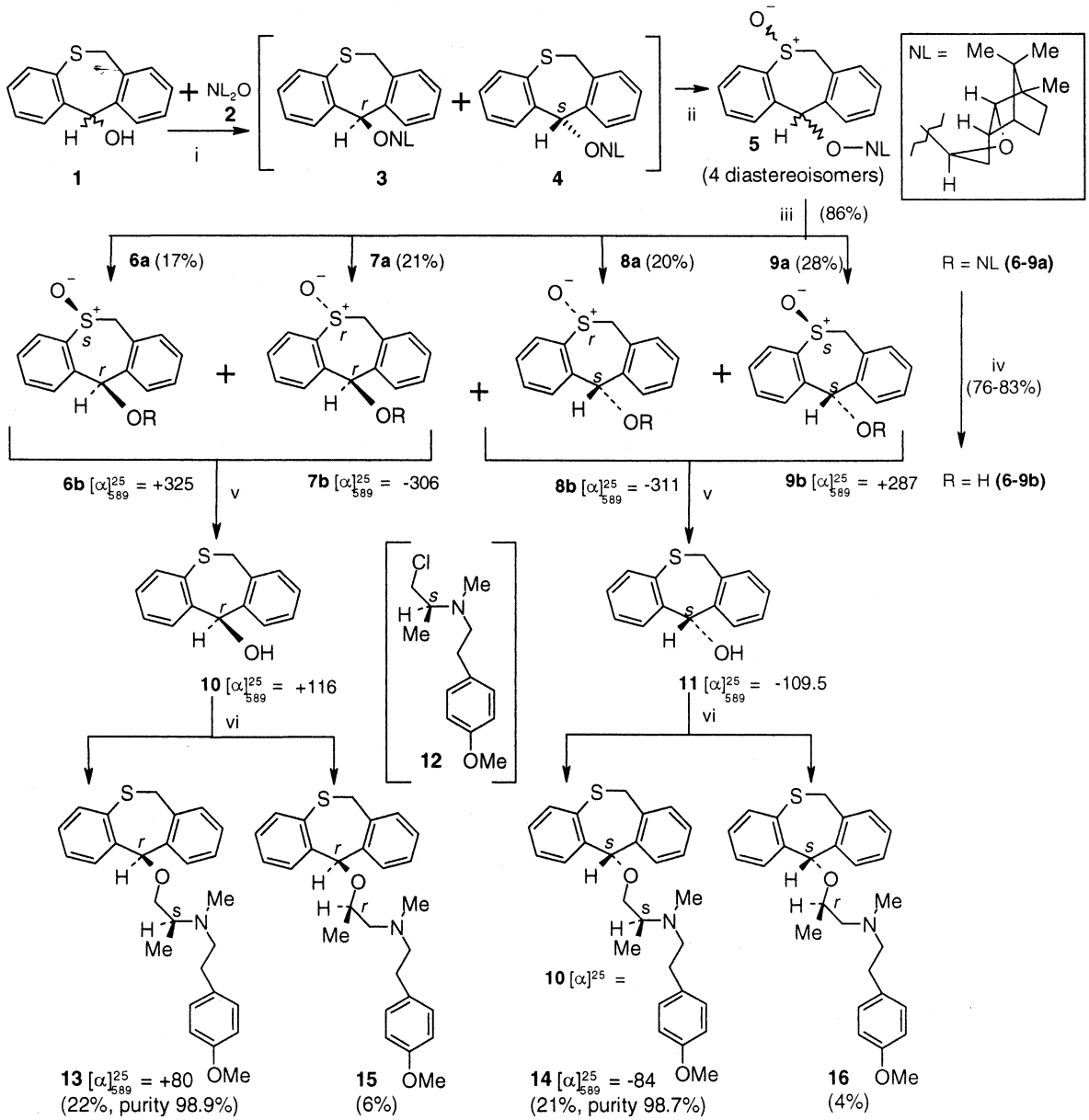
Isomer **i**

Isomer **ii**

Isomer **ii**

* Corresponding author.

PII: S0957-4166(01)00168-9



Scheme 1. (i) TsOH (53%); (ii) *m*-CPBA (55%); (iii) flash chromatography or HPLC (17–28%); (iv) TsOH, aq. THF, 20°C, 18 h (76–83%); (v) $NaBH_4$, $CoCl_2$, 15°C, 2 h (49–82%); (vi) **12**, CsOH, CH_2Cl_2, H_2O, reflux 2.5 h (4–22%).

In approaching the problem of resolving the thiepinol, we regarded it as essential to circumvent the isosterism inherent in the -CH_2S- group, and the simplest way of doing this was to oxidise the sulfur. Of the two options, the sulfone would have had the apparent advantage of introducing no new chiral centres, so restricting the number of isomers to two. However, although it is possible to reduce sulfones back to sulfides this remains a difficult transformation[5] and there are few mild procedures.[6] Accordingly, we opted for the sulfoxides. Oxidation of the mixture of the two sulfides **3** and **4** led to a mixture of four diastereoisomeric sulfoxides **5**, which proved to be readily separable analytically by TLC or HPLC. Preparative separation was achieved readily by flash chromatography on silica, eluting with 2:1 ether/pentane. The Noe lactol was cleaved from sulfoxides **6a**–**9a** with aqueous toluenesulfonic acid, yielding two pairs (**6b**/**8b** and **7b**/**9b**) of enantiomeric sulfoxide alcohols, and we reduced[7] each with $CoCl_2$/$NaBH_4$ to one or other of the resolved enantiomeric thiepinols **10** or **11**.

The known side chain synthon **12**[8] from (*S*)-(+)-1-amino-2-propanol was coupled to these newly resolved thiepinols under basic conditions, giving the two resolved isosteric diastereoisomers **13** and **14** of UK-74,756. This final stage required some development but was achieved in acceptable yields using a rapidly stirred two phase system (aq. CsOH/CH_2Cl_2) under reflux. Regioisomers **15** and **16**, and *only* these isomers, were formed as by-products via stereospecific ring opening of aziridinium ion intermediates,[9–13] and the stereochemistry of the methyl groups in **13**–**16** follows from this mechanism.

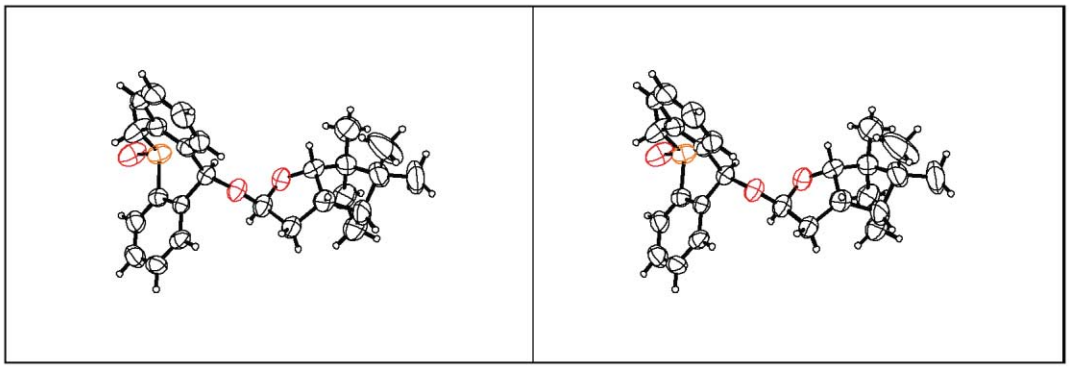


Figure 1. X-Ray structure of compound **6a**.

The integrity of the stereocentres was conserved throughout the sequence, as was confirmed by the high diastereoisomeric purity of **13** and **14**, by HPLC and by the NMR signals for the *N*-Me group in C_5D_5N. It was particularly gratifying that the toluenesulfonic acid cleavage did not epimerise the benzhydrylic centre: one explanation is that the partial positive charge on the sulfoxide sulfur inhibits formation of the carbocation necessary for epimerisation. Any epimerisation of compounds **6b**–**9b** would have revealed itself in the loss of *cis–trans* integrity in whichever is the thermodynamically less stable epimer (or both if they have very similar stability); however, both were epimerically stable to the cleavage conditions.

The stereochemical assignments presented an interesting challenge. The X-ray structure[†14–16] material of compound **6a** established its relative stereochemistry, and the absolute configuration was established by the known configuration of the Noe-lactol fragment. The crystal of **6a** belonged to the orthorhombic space group $P2_12_12_1$. The unit cell dimensions were as follows: $a=8.236(2)$, $b=11.090(4)$, $c=25.35(1)$ Å. The structure was solved by direct methods and routinely refined to an *R*-index of 0.037. Details of the X-ray analysis are available as supplementary material. Knowledge of the absolute stereochemistry of all stereocentres in **6a** led to a detailed argument enabling a rigorous assignment of the configurations of all 22 stereocentres in all 14 related compounds made.

The structures of compounds **6b**, **10**, **13** and **15** follow directly as compounds prepared from **6a** itself. The third lactol **8a** gave with tosic acid a sulfoxide alcohol **8b** enantiomeric with **6b**; the structures of **8a**, **8b**, **11**, **14** and **16** follow directly. Thiepinol **10** was also made from sulfoxide **7b**, which must therefore share the (*R*)-alcohol stereochemistry of **6b** and be epimeric with **6b** at sulfur (i.e. *trans*). The structure of **7a** follows. Compounds **7b** and **9b** were enantiomers, establishing the structures of **9b** and **9a**. None of the homochiral thiepinols and their sulfoxides have been previously reported; however, the spectral and chromatographic properties of the *trans*-isomers **7b** and **9b** are identical with Šindelář and Protiva's[17] racemic, hitherto unassigned, 'higher-melting sulfoxide'; their 'lower-melting sulfoxide' was the *cis*-isomer.

The chiral sulfoxide group is increasingly recognised[18] as a useful stereocontrolling moiety; however, the current work shows that its utility is not wholly dependent on homochiral sulfoxidation.[19,20] The separability of a mixture of stereoisomers can depend more on their intrinsic properties than on the number of components in the mixture, and the principle employed in this work, removing isosterism to impart separability—even at the cost of an increase in the number of components of a mixture—should be widely applicable.[21]

[†] **Single crystal X-ray analysis**. A representative crystal was surveyed and a 1 Å data set (maximum sin $\Theta/\lambda=0.5$) was collected on a Nicolet R3m/μ diffractometer. Atomic scattering factors were taken from the International Tables for X-Ray Crystallography.[14] All crystallographic calculations were facilitated by the SHELXTL[15] system. All diffractometer data were collected at room temperature. Pertinent crystal, data collection and refinement are summarised in the supplementary material.[16]

A trial structure was obtained by direct methods. This trial structure refined routinely. Hydrogen positions were calculated wherever possible. The methyl hydrogens were located by difference Fourier techniques. The hydrogen parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycles of least squares refinement were all less than 0.1 of the corresponding standard deviations. The final *R*-index was 3.70%. A final difference Fourier revealed no missing or misplaced electron density.

The refined structure was plotted using the SHELXTL plotting package (Fig. 1). Coordinates, anisotropic temperature factors, distances and angles are available as supplementary material.[16]

References

1. Alker, D.; Cross, P. E.; Bass, R. J. EP 365093, April 25, 1990.
2. Noe, C. R. *Chem. Ber.* **1982**, *115*, 1576–1590.
3. Noe, C. R. *Chem. Ber.* **1982**, *115*, 1591–1606.
4. Noe, C. R. *Chem. Ber.* **1982**, *115*, 1607–1616.
5. Grossert, J. S. In *The Chemistry of Sulphones and Sulphoxides*; Patai, S.; Rappoport, Z.; Stirling, C., Eds. Reduction of Sulphoxides and Sulphones. Wiley: Chichester, 1988; pp. 925–968.
6. Gašić, M. J.; Putniković, B. *J. Serb. Chem. Soc.* **1997**, *62*, 117–119.
7. Chasar, D. W. *J. Org. Chem.* **1971**, *36*, 613–614.
8. Alker, D.; Kemp, J. E. G.; Cross, P. E. WO 9110648,

July 25, 1991.
9. Barnett, C. R.; Smirz, J. C. *J. Org. Chem.* **1976**, *41*, 710–711.
10. Miocque, M.; Duclos, J. P. *Chim. Ther.* **1969**, *4*, 363–380.
11. Gladych, J. M. Z.; Hartley, D. In *Comprehensive Organic Chemistry*; Barton, D.; Ollis, W. D.; Sutherland, I. O., Eds. Polyfunctional Amines. Pergamon Press: Oxford, 1979; Vol. 2; pp. 61–130.
12. De Sousa, S. E.; O'Brien, P.; Poumelec, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1483–1492.
13. Liu, Q.; Marchington, A. P.; Rayner, C. M. *Tetrahedron* **1997**, *53*, 15729–15742.
14. International Tables for X-Ray Crystallography, Kynoch Press: Birmingham, 1974; Vol. IV, pp. 55, 99, 149.
15. Sheldrick, G. M. SHELXTL. User Manual, Nicolet Instrument Co., 1981.
16. Full details for **6a** have been deposited at the Cambridge Crystallographic Data Centre, reference No. CCDC 163982. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.
17. Šindelář, K.; Protiva, M. *Coll. Czech. Chem. Commun.* **1970**, *35*, 3328–3334.
18. Allin, S. M.; Shuttleworth, S. J.; Bulman Page, P. C. *Organosulfur Chem.* **1998**, *2*, 97–155.
19. Kagan, H. B.; Diter, P. *Organosulfur Chem.* **1998**, *2*, 1–39.
20. Matsuyama, H. *Sulfur Rep.* **1999**, *22*, 85–121.
21. Subsequent to the completion of this work, an effective chiral sulfoxidation of aryl benzyl sulfides was reported, though dibenzthiepins were not exemplified: Donnoli, M.; Superchi, S.; Rosini, C. *J. Org. Chem.* **1998**, *63*, 9392–9395.