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# Synthesis and Diels-Alder Reactions of Enantiopure (-)-*trans*-Benzo[*d*]-dithiine-*S,S'*-dioxide

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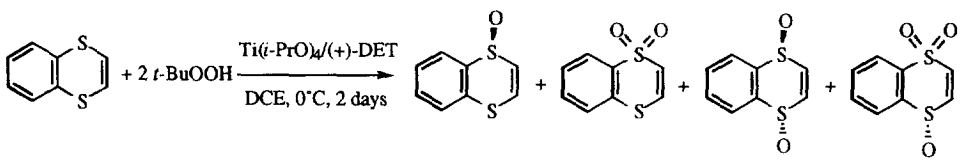
***Abstract:*** Enantiopure (-)-*trans*-benzo[*d*]dithiine-*S,S'*-dioxide **4** was obtained by enantioselective oxidation of the parent benzo[*d*]dithiine. The reaction of the *bis*-sulfoxide with a series of cyclic dienes affords the corresponding Diels-Alder cycloadducts with diastereoselectivities ranging from fair to high and good chemical yields.

Dienophiles bearing an α-sulfinyl group are efficient reagents in asymmetric cycloadditions, particularly when a second EWG is present in the ethylenic system. The ability of the sulfoxide moiety to activate the double bond and to direct the stereochemistry of the cycloaddition, together with its facile removal by reduction or β-elimination, render such a functionality a useful and powerful chiral auxiliary.[1]

In this communication we report on the asymmetric synthesis and on the reactivity as a dienophile of (-)-*trans*-benzo[*d*]dithiine-*S,S'*-dioxide **4**,[2] obtained in its almost enantiopure form and as a single diastereomer by direct asymmetric oxidation of the parent benzo[*d*]dithiine **1**[3] with the modified Sharpless reagent [Ti(IV)/(+)-diethyltartrate/*t*-butyl hydroperoxide= 1:4:2] developed in our laboratories a few years ago[4] (eq. 1).

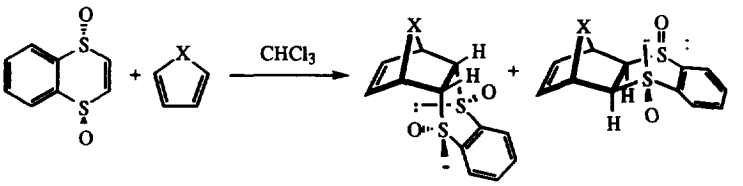



**1** (-)**2** (8%) **3** (37%) (-)**4** (25%) (-)**5** (30%)

The enantioselective oxidation of compound **1** by two eq. of *t*-butylhydroperoxide affords the sulfoxide (-)-**2**, [8%, mp 110-111°C, e.e.>98%,[5] $[\alpha]_D^{25}$= -383 (c=1.0, chloroform)], the achiral sulfone **3** [37%, mp 109-111°C], the *trans-bis*-sulfoxide (-)-**4** [25%, mp 206-208°C, e.e.>98%,[5,6] $[\alpha]_D^{25}$=-365 (c=0.8, chloroform)] and the sulfone-sulfoxide (-)-**5** [30%, mp 130-136°C, e.e.=80%[5], $[\alpha]_D^{25}$= -207 (c=1.0, chloroform)]. No *meso-bis*-sulfoxide is detected in the reaction mixture.

After chromatographic separation (flash chromatography over silica gel, ethyl acetate/petroleum ether), the reactivity of (-)-**4** with cyclic dienes has been examined. The results are reported in Table 1.

**Table 1.**

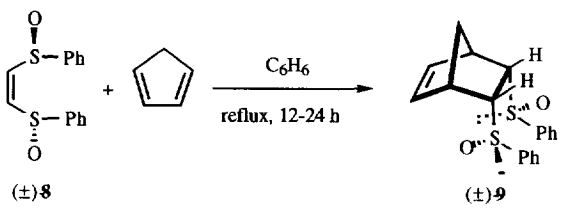



(-)-4 *endo*-6[7] *exo*-7[7]

| Diene | $AlEt_2Cl$ (eq) | Temperature (°C) | Time (hrs) | Yield (%) | Diast. Ratio[8] *endo*-6/*exo*-7 |
|---|---|---|---|---|---|
| Cyclopentadiene | 0 | 25 | 15 | 95 | >99:1 |
| | 0 | 60 | 0.5 | 95 | >99:1 |
| 1,3-Cyclohexadiene | 0 | 25 | 120 | 97 | >99:1 |
| | 0 | 80 | 24 | 92 | >99:1 |
| Furan | 0 | 60 | 15 | 60 | 28:72 |
| | 0.5 | 0 | 0.25 | 73 | 71:29 |

The *bis*-sulfoxide (-)-**4** reacts with the three dienes under relatively mild conditions affording the corresponding cycloadducts. The yields range from fair to good. The reaction with cyclopentadiene and 1,3-cyclohexadiene affords quantitatively only one product. The expected *endo* selectivity[9] was unumbigously determined for the norbornene cycloadduct **6a** via $^1H$ NOE experiments and X-ray diffractometric analysis.[10]

It is worthy of note that the cycloaddition of *bis*-sulfoxide (-)-**4** with cyclopentadiene requires milder reaction conditions and shorter reaction times than that of the linear analogue, *i.e. bis*-benzensulfinylethylene (±)-**8** (eq. 2).[9]




(±)-8 (±)-9 (2)

A similar enhanced reactivity of cyclic dienophiles compared with the linear analogues has already been observed for the corresponding sulfones, *i.e.* benzo[*d*]dithiine-*S,S,S',S'*-tetraoxide *versus* (Z)-*bis*-benzensolfonyl-ethylene[11] and also in the case of cyclic alkenyl-*bis*-sulfoxides.[12]

The lowest diastereoselectivity is obtained with furan. Both *endo* and *exo* diastereomers are formed in different ratios depending on the reaction conditions.[13] Thermal reaction affords mainly the *exo* adduct, while the Lewis acid catalyzed reaction is much faster and preferentially leads to the *endo* product. The determination of the relative stereochemistry of *endo* **6c** and *exo* **7c** cycloadducts could not be carried out directly on the two

products. The $^1$H NMR spectra of **6c** and **7c** adducts are rather different (figure 1 and 2 respectively) and, in particular, the $^1$H NMR signals of adduct **(+)-7c** are broad.[14]

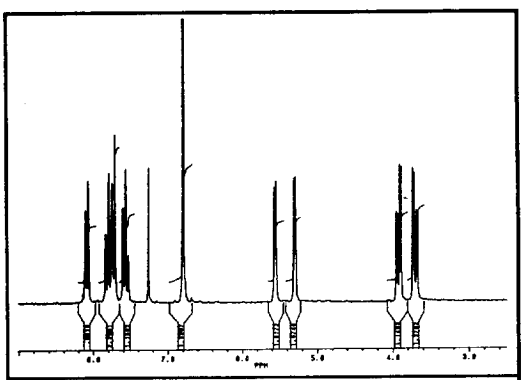


**Figure 1.** (+)-**6c** (200 MHz $^1$H NMR)

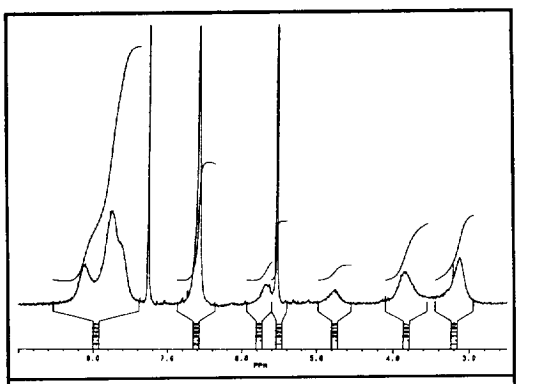
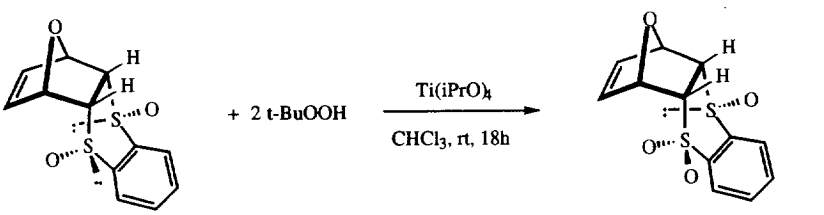
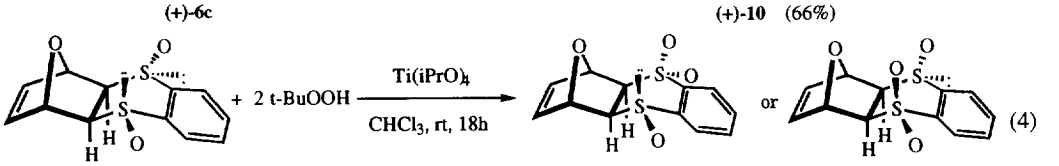


**Figure 2.** (+)-**7c** (200 MHz $^1$H NMR)

In the aim of determining the relative configurations, both cycloadducts were further oxidized to the corresponding solfones (eqs 3 and 4).




(+)-6c (+)-10 (66%) (3)




(+)-7c (+)-11 (75%) (4)

Surprisingly, neither (+)-**6c** nor (+)-**7c** derivatives afforded the corresponding *bis*-sulfones, but only one of the two possible diastereomeric sulfone-sulfoxides. Both products (+)-**10** [66%, mp 170-172°C, $[\alpha]_D^{25}$= +67 (c=0.2, chloroform)] and (+)-**11** [75%, mp 208-210°C, $[\alpha]_D^{25}$= +20 (c=0.2, chloroform] exhibit sharp $^1$H NMR spectra. The *endo* stereochemistry of derivative (+)-**10** has been determined by X-ray crystallographic analysis.[10] A rationale of the overall oxidation pattern, at least for compound (+)-**10**, can be obtained by looking at its X-ray structure. It may been seen that the equatorial unreacted electron pair on the sulfur atom is in a rather inaccessible position compared with the axial one. The highly selective oxidation of the adduct (+)-**7c** cannot be explained at the moment by simple molecular model analysis. In fact, because of the flexibility of the molecule, both electron pairs seem available, depending on the geometry adopted by the system.

The facile and completely enantioselective synthesis of (-)-*trans*-benzo[*d*]dithiine-*S,S'*-dioxide **4** and the preliminary promising results concerning its reactivity in Diels-Alder cycloadditions suggest that such a compound may be an intersting chiral dienophile. Work is now in progress to determine its reactivity as chiral acetylene and ethylene equivalents.

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## References and Notes

1. "The Chemistry of Sulphones and Sulphoxides" Patai, S.; Rappoport, Z. and Stirling, C. Eds., John Wiley & Sons Inc., Colchester, Essex, Great Britain (1988); De Lucchi, O.; Pasquato, L. *Tetrahedron* **1988**, *44*, 6755; Arai, Y; Koizumi, T *Sulfur Reports* **1993**, *15*, 41.
2. Part of this work has been presented at the EUCHEM Conference "Cycloadditions and Related Reactions: Theory and Practice", Vulcano Island, Italy, 21-24 June 1995.
3. Benzo[*d*]dithiine **1** was obtained *via* reaction of the disodium salt of the benzene-1,2-dithiol (Fluka) with *cis*-1,2-dichloroethylene in *ca.* 70% yield.
4. Di Furia, F.; Modena, G.; Seraglia, R. *Synthesis* **1984**, 325.
5. The e.e. values were determined by $^1$H NMR in the presence of (*S*)-(+) or (*R*)-(-)-1-(9-anthryl)-2,2,2-trifluoroethanol.
6. Enantiomeric excesses of *bis*-sulfoxide (-)-**4** cannot be directly determined since no splitting of signals after addition of Pirkle alcohol is obtained on the racemic derivative. At any rate an e.e.>98% was determined after further oxidation to sulfone-sulfoxide (-)-**5** by *m*-CPBA [mp 140-142°C, $[\alpha]_D^{25}$= -257 (c=1.1, chloroform)].
7. Data for: **(+)-6a**: mp 254-255°C, $[\alpha]_D^{25}$= +207 (c=0.5, chloroform); **(+)-6b**: mp 218-220°C with dec., $[\alpha]_D^{25}$= +217 (c=0.5, chloroform); **(+)-6c**: mp 185-188 $[\alpha]_D^{25}$=+148 (c=0.2, chloroform) ; **(+)-7c**: mp 208-210°C, $[\alpha]_D^{25}$=+50 (c=0.1, chloroform).
8. Determined via $^1$H NMR.
9. Bertotti, E.; Luciani, G.; Montanari, F. *Gazzetta Chim. It.* **1959**, 89, 1564; Cinquini, M.; Colonna, S.; Montanari, F. *J. Chem. Soc. C*, **1970**, 572.
10. Valle, G. unpublished.
11. Cossu, S.; De Lucchi, O.; Fabbri, D.; Licini, G.; Pasquato, L. *Org. Prep. Proced. Int.* **1991**, *23*, 573.
12. Aggarwal V., Drabowicz J., Grainger R.S., Gultekin Z., Lightowler M., Spargo, P.L. *J. Org. Chem.* **1995**, *60*, 4962.
13. The reduced and variable diastereoselection obtained with furan may be due to the reversibility of the cycloaddition reaction.
14. $^1$H NMR spectra of cycloadduct (+)-**7c** are modified by changing the temperature (20-65°C), thus indicating the presence of an equilibrium between conformers. Unfortunately, some of the signals are still broad at high temperature.

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