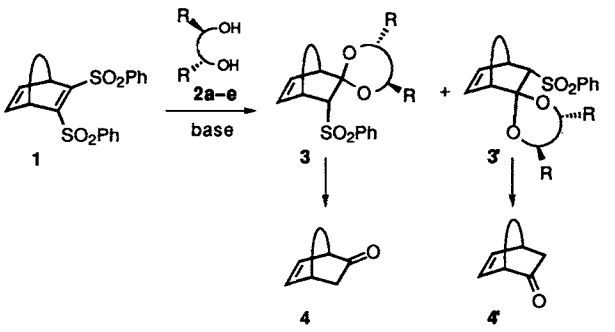
Total Enantiotopic Discrimination between Carbon Atoms of a Double Bond in the Reaction of Diolates with *meso*-Bis(phenylsulfonyl)alkenes—Synthesis of Enantiopure Ketones**

Sergio Cossu,* Ottorino De Lucchi,* and Paolo Pasetto

Dedicated to Professor Waldemar Adam on the occasion of his 60th birthday

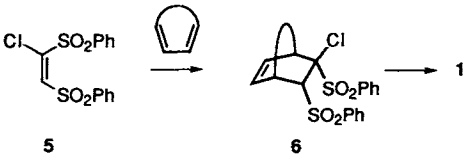
Enantiotopic discrimination of two functional groups in a *meso* compound is a well-established and convenient procedure for preparing enantiopure compounds, which avoids separation and disposal of the unwanted enantiomer.[1] This method, sometimes referred to as the "*meso* trick", is usually applied to diesters or other pairs of enantiotopic functional groups, and is often performed with enzymes.[2] The enantiotopic discrimination of two adjacent carbon atoms is very rare, and, other than the alkyllithium-based rearrangement of *meso* epoxides,[3] there are almost no cases in which such an extreme case of the *meso* trick was applied to an alkene.[4] Here we show that alkenes that are doubly substituted with phenylsulfonyl groups in *meso* compounds undergo reaction with the salts of alcohols and diols to afford totally dissymmetrical compounds in quantitative yields. This represents an enantiotopic discrimination[4] of the carbon atoms of a double bond. The reaction affords diastereo- and enantiopure ketones that are difficult to prepare by conventional routes, and can be utilized in the synthesis of numerous natural products,[5] antibiotics,[6] and drugs used in cancer[7] and AIDS therapy.[8]

The synthetic sequence consists of the reaction of a bis(phenylsulfonyl)alkene **1** with a chiral diol **2** followed by hydrolysis and reductive desulfonylation [Eq. (1)]. Since the reaction is totally stereoselective and affords one only of the possible diastereoisomers (**3**), a single enantiomeric ketone **4** is obtained.



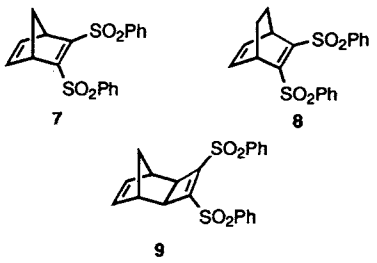
(1)

Starting **1** are readily prepared by cycloaddition of bis(phenylsulfonyl)acetylene with dienes.[9] Because this acetylene is not very stable, (*Z*)-1-chloro-1,2-bis(phenylsulfonyl)ethylene (**5**) may be used as its synthetic equivalent in the Diels–Alder reaction [Eq. (2)].[10] There are also several other routes available for preparing **1**.[11] The derivatives of **1** used in the present study

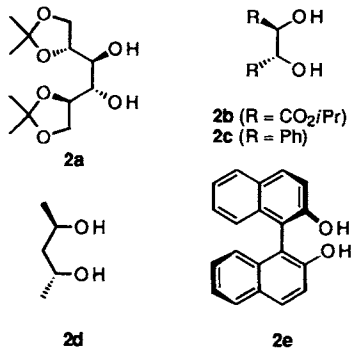


(2)

are the polycycles **7**–**9**,[12] which were chosen as representatives of the [2.2.1], [2.2.2], and cyclobutene systems.



The diols used represent the classes of 1,2- (**2a**–**c**) and 1,3-diols (**2d**) with substituents of different size as well as the atropisomers 1,1'-binaphthalene-2,2'-diol (**2e**). They all possess a C_2-symmetry axis, which avoids partition of the products into further diastereoisomers. Reaction of the sodium salts of **2a**–**e** (prepared by treatment with NaH in THF) with **7**–**9** leads to the ketals **10**–**12** (Table 1).



The bis(phenylsulfonyl)alkene **7** was considered as the standard substrate for testing the behavior of the different diols. Best results were obtained with (*R*,*R*)-(+)-1,2-diphenyl-1,2-ethanediol (**2c**) and **2e**, which both gave a single diastereoisomer (entries 3 and 5 in Table 1). Diol **2c** was used for desymmetrization of **8** and **9** because of the higher crystallinity of the adducts and simplicity in detecting the two diastereoisomers by NMR spectropscopy. With no exceptions **2c** gave the single diastereoisomers **11c** and **12c** (entries 7 and 9); that is, total C=C discrimination was accomplished in all cases. Diols derived from mannitol and tartaric acid **2a** and **2b** gave poorer results (entries 1, 2, and 6) with formation of both diastereoisomers. However, no attempts were made to separate the diastereoisomers. (2*R*,4*R*)-(−)-Pentanediol (**2d**) also showed little selectivity with substrates **7** and **8** (entries 4 and 8).

[*] Dr. S. Cossu, Prof. Dr. O. De Lucchi, Dr. P. Pasetto
Dipartimento di Chimica, Università Ca' Foscari di Venezia
Dorsoduro 2137, I-30123 Venezia (Italy)
Fax: Int. code +(41)529-8517
e-mail: delucchi@unive.it

[**] This work was supported by C. N. R. (Rome). We thank Prof. R. Ballini (Universitá Camerino, Italy) for helpful suggestions.

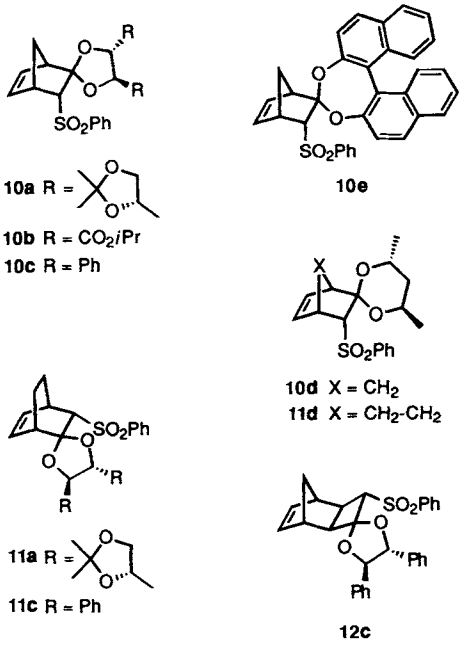
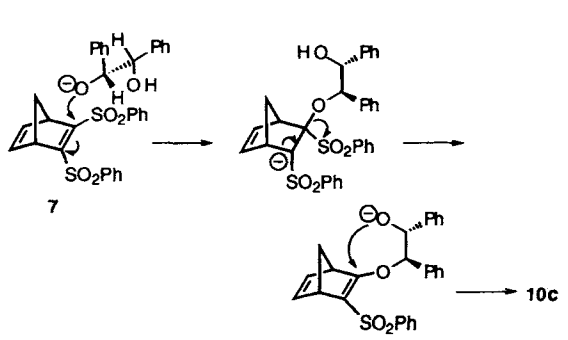


Table 1. Yields, diastereomeric ratios, and optical activity for the products of the reaction of **7**–**9** with diols **2a**–**e**.

Entry	Substrate	Diol	Product	Yield [%]	Diastereomeric ratio [a]	Optical activity [d]
1	**7**	**2a**	**10a**	97	85:15	
2		**2b**	**10b**	93	70:30	
3		**2c**	**10c**	88	[c]	+112.9 (1.7)
4		**2d**	**10d**	92	60:40	
5		**2e** [b]	**10e**	92	[c]	
6	**8**	**2a**	**11a**	72	50:50	
7		**2c**	**11c**	96	[c]	+87.9 (1.6)
8		**2d**	**11d**	90	50:50	
9	**9**	**2c**	**12c**	92	[c]	+82.2 (1.4)

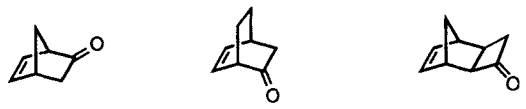
[a] Determined by ^{1}H NMR spectroscopy at 200 MHz. [b] Used as a racemic mixture. [c] Only one diastereomer was obtained. [d] The concentration c is given in parentheses; the measurements were conducted in $CHCl_3$.

The stereochemistry of **10c**, **11c**, and **12c** was determined by X-ray crystallography.[13] The mechanism of formation for **10c** from **7** and **2c** requires attack of the alcoholate functionality at the vinyl carbon atom α to the sulfonyl group, elimination, and addition [Eq. (3)]. Assuming that the approach of the reagent occurs from the *exo* face of the alkene, as is usually observed in norbornenes,[14] the least encumbered trajectory is the one shown in which the phenyl group points upwards, and the alkyl chain to the side. After elimination of the phenylsulfinate anion, a second nucleophilic addition takes place to provide the observed product. The sulfonyl group in **10c** is in the *endo* position, which is in accordance with the *exo* rule of attack of the proton onto the anion.[14] The latter stereoisomer appears to be the kinetic product, because if an excess of base is present epimerization occurs with formation of only the *exo* phenylsulfonyl isomer. Similar reasoning also accounts for the stereochemistry observed for **11c** and **12c**. However, in these cases attack of the alcoholate on **8** and **9** occurs from the *endo* face, as generally observed for these systems.[15]



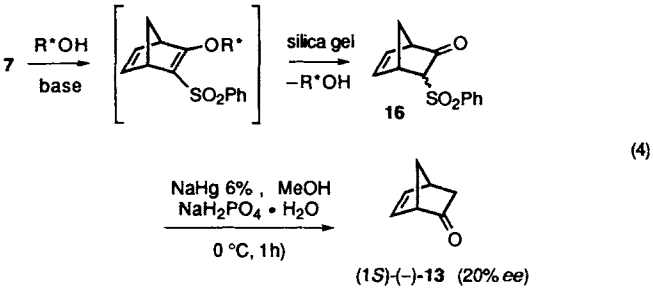
(3)

Diastereopure **10c**, **11c**, and **12c** can be hydrolyzed (Nafion H in toluene at reflux, 5 h) and desulfonylated (NaHg 6% in MeOH/$NaH_2PO_4 \cdot H_2O$, 0 °C, 2 h) to give the enantiomerically pure ketones **13**–**15**[16] in 75-90% yields with the absolute configuration shown. Deacetalization of **10c** affords



mixtures of epimers at the carbon atom α to the sulfonyl group in **16**. This scrambling apparently does not affect the enantiopurity of **13**–**15**. The α-sulfonyl ketones are also of synthetic interest and can be subjected to alkylation and further selective operations that are not dependent on the sterochemistry of the sulfone.[17] The deacetalization–desulfonylation sequence can be reversed to accomplish reductive desulfonylation[18] before hydrolysis. However, desulfonylation of α-sulfonyl ketones is easier and can be carried out with milder reducing agents.[19]

The step that is relevant for the stereochemistry of the products is the initial attack by the diolate ion on **1**. Once the alkene carbon has been chosen by the chiral diol, desymmetrization is virtually accomplished. On this basis, any monofunctionalized chiral alcoholate ion can provide desymmetrization through the enolether and, thus, the ketone. Indeed, reaction of **7** with the lithium salt of (1*R*,2*S*,5*R*)-(−)-menthol (obtained from *n*BuLi and menthol in THF) directly gives **16** in 80% yield [Eq. (4)]



(4)

after column chromatography on silica gel. The sufonyl ketone **16** is reduced to (1*S*)-(−)-**13** with NaHg (6% in MeOH/$NaH_2PO_4 \cdot H_2O$, 0 °C, 1 h, 20% *ee*, 80% yield). This reduces the entire operation to just two steps and allows easy recovery of the chiral auxiliary.

Although this latter protocol is rapid and effective, it produces ketones with lower optical purity since it does not allow a check of the enantiomeric purity of the ketone at the diasteromeric level. We are presently defining other enantiopure alcohols capable of maximum selectivity and studying other stereoselective transformations of these and other bis(phenylsulfonyl)alkenes.

Received: December 27, 1996 [Z9936IE]
German version: *Angew. Chem.* **1997**, *109*, 1598–1601

  0570-0833/97/3613-1505 $ 17.50+.50/0

Keywords: asymmetric synthesis · chirality · ketones · synthetic methods

[1] E. L. Eliel, S. H. Wilen, L. N. Mander, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**, pp. 962–963.
[2] E. Schoffers, A. Golebiowski, C. R. Johnson, *Tetrahedron* **1996**, *52*, 3769–3826; L. A. Paquette, H.-C. Tsui, *J. Org. Chem.* **1996**, *61*, 142–145.
[3] N. S. Simpkins in *Advanced Asymmetric Synthesis* (Ed.: G. R. Stephenson), Chapman & Hall, London, **1996**, pp. 111–125; D. M. Hodgson, A. R. Gibbs, G. P. Lee, *Tetrahedron* **1996**, *52*, 14361–14384.
[4] Hydroboration: K. Burgess, W. A. van der Donk in *Advanced Asymmetric Synthesis* (Ed.: G. R. Stephenson), Chapman & Hall, London, **1996**, pp. 181–211; hydrosilylation: E. Campi, P. Perlmutter, *ibid.*, pp. 212–221.
[5] O. De Lucchi, W. Adam in *Comprehensive Organic Synthesis, Vol. 5* (Eds.: B. M. Trost, I. Fleming, L. A. Paquette), Pergamon, **1991**, pp. 193–214.
[6] G. Helmchen, A. Krotz, H.-P. Neumann, M. L. Ziegler, *Liebigs Ann. Chem.* **1993**, 1313–1317.
[7] M. Hono in *Anticancer Agents Based on Natural Product Models*, Academic Press, London, **1980**, p. 73.
[8] C. A. Flechter, H. Hilper, P. L. Myers, S. M. Roberts, R. J. Storer, *J. Chem. Soc. Chem. Commun.* **1989**, 1707–1709.
[9] L. Pasquato, O. De Lucchi, L. Krotz, *Tetrahedron Lett.* **1991**, *32*, 2177–2178.
[10] S. Cossu, O. De Lucchi, *Gazz. Chim. It.* **1990**, *120*, 569–576.
[11] T. Cohen, R. H. Ritter, D. Ouelette, *J. Am. Chem. Soc.* **1982**, *104*, 7142–7148; O. De Lucchi, G. Marchioro, *Phosphorus Sulfur Relat. Elem.* **1985**, *24*, 305–309; H. Landen, H.-D. Martin, A. Steigel, *Chem. Ber.* **1987**, *120*, 171–175; K. A. Herbert, M. G. Banwell, *Synth. Commun.* **1989**, *19*, 327–337; S. Cossu, O. De Lucchi, D. Fabbri, G. Licini, L. Pasquato, *Org. Prep. Proc. Int.* **1991**, *23*, 573–592; G. O'Doherty, R. D. Rogers, L. A. Paquefte, *J. Am. Chem. Soc.* **1994**, *116*, 10883–10894.
[12] Preliminary experiments on several other polycyclic bis(phenylsulfonyl)-alkenes [10] show that the reaction is general.
[13] The X-ray structure analyses were carried out by Dr. Giovanni Valle (C. N. R., Centro Studi Biopolimeri, via Marzolo 1, I-35131 Padova, Italy).
[14] J. Spanget-Larsen, R. Gleiter, *Tetrahedron* **1983**, *39*, 3345–3350, and references therein.
[15] E. Müller, *Chem. Ber.* **1976**, *109*, 3793–3803; U. Azzena, S. Cossu, O. De Lucchi, G. Melloni, *Gazz. Chim. It.* **1989**, *119*, 357–358.
[16] Enantiopure **13**: J. Martynow, M. Dimitroff, A. G. Fallis, *Tetrahedron Lett.* **1993**, *34*, 8201–8204, see also ref. [6]; enantiopure **14**: M. Demuth, S. Chandrasekhar, K. Schaffner *J. Am. Chem. Soc.* **1984**, *106*, 1092–1095; D. A. Lightner, J. K. Gawronski, T. D. Bouman, *ibid.* **1980**, *102*, 5749–5754; **15**: +388.0 (*c* 3.2, in pentane).
[17] B. M. Trost, N. R. Schmuff, *J. Am. Chem. Soc.* **1985**, *107*, 396–405.
[18] N. S. Simpkins, *Sulphones in Organic Synthesis*, Pergamon, Oxford, **1993**, pp. 334–372; B. M. Trost, H. C. Arndt, P. E. Strege, T. R. Verhoeven, *Tetrahedron Lett.* **1976**, 3477–3480; H. Künzer, M. Stahnke, G. Sauer, R. Wiechert, *ibid.* **1991**, *32*, 1949–1952; G. H. Lee, E. B. Choi, E. Lee, C. S. Pak, *ibid.* **1993**, *34*, 4541–4544; E. Alonso, D. Guijarro, M. Yus, *Tetrahedron* **1995**, *51*, 2699–2708; R. Giovannini, M. Petrini, *Synlett* **1995**, 973–974.
[19] R. A. Holton, D. J. Crouse, A. D. Williams, R. M. Kennedy, *J. Org. Chem.* **1987**, *52*, 2317–2318; M. Fujii, K. Nakamura, H. Mekata, S. Oka, A. Ohno, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 495–500; A. B. Smith III, K. J. Hale, J. P. McCauley, Jr., *Tetrahedron Lett.* **1989**, *30*, 5579–5582; A. R. Harris, T. J. Mason, G. R. Hannah, *J. Chem. Res. Synop.* **1990**, *7*, 218–219.

A Straightforward Solid-Phase Synthesis of Cyclic Oligodeoxyribonucleotides**

ElMostafa Alazzouzi, Nuria Escaja, Anna Grandas, and Enrique Pedroso*

Nuclease-resistant oligonucleotides have received much attention due to their potential use in antisense or antigene therapeutics.[1] Cyclic oligonucleotides (CONs) have an intrinsic resistance to degradation by exonucleases, the most active nucleases. CONs can be used as efficient templates for DNA and T7-RNA polymerases to obtain multiple copies of their sequences by the rolling-circle mechanism[2] and are excellent models for studying structures of nucleic acids.[3] In addition, some CON sequences show interesting biological properties.[4]

The synthesis of CONs is a challenging case of macrocycle formation, since each nucleotide unit contributes six atoms to the cyclic backbone. Owing to the competition between inter- and intramolecular reactions, only relatively small sequences (2- to 8-mer) have been obtained by chemical ligation of partially protected oligonucleotides in dilute solutions.[5] Larger cyclic structures (24-mer or more) have only been successfully prepared by template-directed cyclization, chemically or enzymatically, of unprotected oligonucleotides.[6] The template sequence may be either a segment of the CON, as in the ligation of nicked dumbbells,[6a] or a second oligonucleotide molecule that forms a duplex[6b] or a triplex[6c] with the linear precursor of the CON. The main drawbacks of most of these template-assisted procedures[6a,c] are that the sequence of the affordable CONs is restricted and that a lower limit is imposed on their size by the need for efficient hybridization and adequate base pairing with the template sequences.

To our knowledge, the advantages of automated solid-phase methods have been successfully used by only one group for preparing CONs.[7] In their approach, the exocyclic amino group of cytosine is attached to the solid support, where both chain elongation and cyclization are carried out. The largest sequence obtained, which of course has to contain at least one cytosine residue, is a hexadecamer in 1% yield. This shows the difficulty of the synthetic goal.

The solid-phase synthesis described here allows facile obtention of small to medium-sized CONs with no restrictions on sequence. The procedure takes advantage of two main characteristics of the solid-phase methodology: pseudo-dilution conditions for cyclization [8] and ready elimination of by-products by simple filtration.

The synthesis starts with the anchoring of the 3′-terminal nucleotide to the solid matrix through the new bifunctional linker 3-chloro-4-hydroxyphenylacetic acid (**1**, Figure 1). To obtain a homogeneously derivatized resin it is advisable to couple the nucleotide to the linker and then to anchor the resulting product to the support. Thus, the reaction between the 2,4,5-trichlorophenyl ester derivative of linker **2** and a nucleoside phosphoramidite in the presence of tetrazole followed by oxidation gives the nucleotide-linker **3** (B = T, C^{Bz}, A^{Bz}, G^{iBu}). Aminomethyl-polystyrene-*co*-1%-divinylbenzene or a poly-

[*] Prof. Dr. E. Pedroso, E. Alazzouzi, N. Escaja, Prof. Dr. A. Grandas
Departament de Química Orgànica, Facultat de Química
Universitat de Barcelona
Martí i Franquès 1–11, E-08028 Barcelona (Spain)
Fax: Int. code +(3)339-7878
e-mail: pedroso@mafalda.qui.ub.es

[**] This work was supported by funds from the DGICYT (grant nos. PB91-270 and PB94-844) and the Generalitat de Catalunya (Centre de Referència de Biotecnologia and GRQ93-1094).

  0570-0833/97/3613-1506 $ 17.50+.50/0