ECLIPSE Computer. All crystallographic calculations were carried out on this system.
(8) See paragraph at end of paper regarding supplementary material.
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Raymond Zelnik*
Department of Organic Chemistry
Institute Butantan, São Paulo, Brazil

Joyce A. McMillan, Iain C. Paul*
Department of Chemistry
University of Illinois, Urbana, Illinois 61801

David Lavie*
Department of Organic Chemistry
The Weizmann Institute of Science, Rehovot, Israel

Vicente G. Toscano, Roberto R. DaSilva
Institute of Chemistry
University of São Paulo, São Paulo, Brazil

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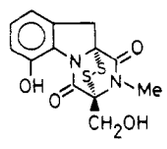
Approaches to the Resolution of Racemic Cyclic Disulfides. Application to an Epidithiodioxopiperazine

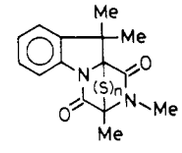
Summary: The chemical resolution of **2** has been performed via diastereomer formation (**9** and **10**) as well as via a kinetically controlled transformation; the enantiomers **11** and **12** have the same anti-reverse transcriptase activity.

Sir: Chemical resolution of racemic cyclic disulfides, devoid of convenient handles for conversion into diastereomers, has not been reported. We wish to report a method developed for the resolution of a racemic epidithiodioxopiperazine which might be of general applicability to other chiral cyclic disulfides.

Dehydrogliotoxin **1**, the sporidesmins,[1] and chaetocin[2] belong to the class of fungal metabolites containing an epi-



1

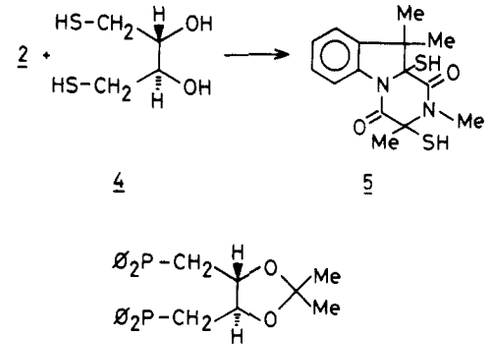


2: n = 2
3: n = 1

dithiodioxopiperazine ring system. The first two compounds have the *R* configuration at the bridgehead carbons and exhibit selective antiviral properties, whereas the antipodal chaetocin does not show this activity. Recently we reported a synthesis[3] of a racemic dehydrogliotoxin analogue **2**, which inhibits reverse transcriptase,[4] the RNA-dependent DNA polymerase of RNA tumor viruses, and whose activity is of the same order as that of gliotoxin. Separate examination of the enantiomers of **2** might indicate whether the antiviral activity of epidithiodioxopiperazines is related to their bridgehead configurations.

In general, resolution of **2**, which lacks a reactive handle, might be achieved[5] by crystallization, chromatographic,[6] or kinetic methods. Initially we attempted a kinetic asymmetric transformation by two routes, viz., reduction of **2** to **5** with the optically active dimercapto compound **4** (Scheme I) and partial desulfurization of **2** to **3** with the chiral phosphine **6**. When **2** was treated with 0.5 equiv of the optically active

Scheme I

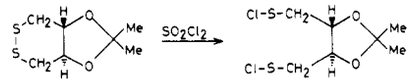


4 **5**

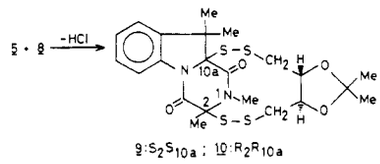
6

Cleland's reagent **4**,[7] racemic mixtures of **2** and the dithiol **5** were isolated. However, when **2** was reacted with 0.25 equiv of the diphosphine **6** [(−)-Diop[8]], a 19% enrichment[9] in one enantiomer in the isolated starting material was observed. As this enrichment was too small for our needs, we turned to resolution via covalent formation of diastereomers. The reaction scheme for the synthesis[3] of **2** proceeds via the stable intermediate **5**.[10] This could be converted into diastereomers and each transformed into **2** without racemization as will be shown below. The resolving agent was selected on the basis of the following considerations: (i) a bifunctional agent was selected, as diastereomers with a high rigidity would allow an optimal separation;[11] (ii) the minimum number of diastereomers (two) would result if this bifunctional reagent possessed an axis of symmetry. These features were present in a derivative of (−)-Diop (**6**), viz., the disulfenyl chloride **8**. This was prepared quantitatively from **7**[12] with SO_2Cl_2 and a trace of pyridine in CCl_4 (Scheme II).

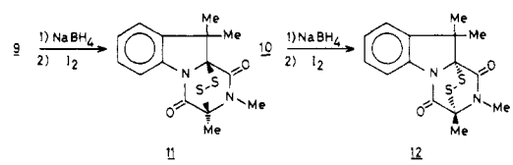
Scheme II



7 **8**



9: S_2S_{10a} ; **10**: R_2R_{10a}



11 **12**

Reaction of **8** (2.1 mmol) in CCl_4 with **5** (2.1 mmol) in the presence of 2 equiv of pyridine gave, besides **2**, the diastereomeric[13] disulfides **9** and **10**. Separation by column chromatography on silica gel[14] (Merck 60 PF254) using CH_2Cl_2/CCl_4 (1:1 v/v) as eluent gave **9** and **10** (28% yield of each) whose ^1H NMR spectra were nearly identical (for the ketalic CH_3 groups: broad singlet at δ 1.40 for **9**; two singlets at 1.3 and 1.4 for **10**). Reduction of **9** or **10** with $NaBH_4$ in ethanol followed by reoxidation with I_2/pyridine in CH_2Cl_2[3] gave the enantiomers **11** {$[\alpha]^{22}D$ +477° (*c* 0.65 in $CHCl_3$)} or **12** {$[\alpha]^{22}D$ −484° (*c* 0.64 in $CHCl_3$)}, respectively, in 82% yield as well as the precursor **7** of the resolving agent. Compound

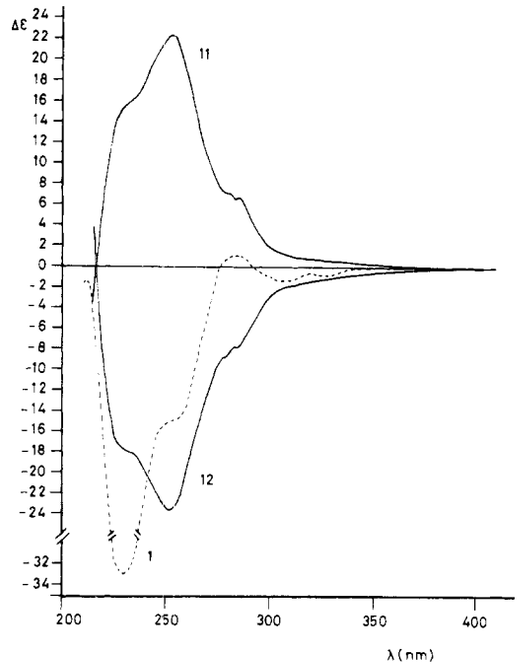


Figure 1. Circular dichroism curves of 1, 11, and 12.

11 or 12 could not yet be brought to crystallization; their ^1H NMR spectra in the presence of a chiral shift reagent showed that the optical purity is higher than 90%.[9] The absolute configurations were derived from CD spectra (Figure 1). Dehydrogliotoxin (1) shows a negative Cotton effect at 230 nm.[15] From this the tentative conclusion is drawn that 11 possesses the *S* configuration, while **12** has the *R* configuration.[16] Surprisingly, both enantiomers were found to have the same anti-reverse transcriptase activity,[17] indicating that there is no relation between this property of epidithiodioxopiperazines and their bridgehead configurations.

Applications of this method of resolution[18] to other racemic, cyclic disulfides and to chiral compounds having two reactive functional groups is under investigation.

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References and Notes

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(6) Conformational enantiomers of cyclic disulfides have been resolved by chromatography, followed by crystallization: A. Lüttringhaus, U. Hess, and H. J. Rosenbaum, *Z. Naturforsch., B*, **22**, 1296 (1967).
(7) M. Carmack and C. J. Kelley, *J. Org. Chem.*, **33**, 2171 (1968).
(8) H. B. Kagan and T. P. Dang, *J. Am. Chem. Soc.*, **94**, 6429 (1972).
(9) The ^1H NMR spectrum of racemic **2** showed two signals for the *N*-methyl as well as for the C_2-methyl group when tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III) was used as chiral shift reagent; enantiomeric purity could be determined easily by integration.
(10) Dithiol **5** can also be obtained quantitatively by reduction of **2** with $NaBH_4$; see, e.g., ref 3.
(11) A possible relation between rigidity in diastereomers and their ease of separation can be deducted from Woodward's statement that separation of diastereomeric salts is more likely to succeed when the chiral centers are as close as possible in space: R. B. Woodward et al., *Tetrahedron*, **19**, 247 (1963), and footnotes on p 259.
(12) This compound is prepared in 50% overall yield from L-(+)-tartaric acid; see ref 7.
(13) In thin layer chromatography on silica gel (Merck precoated F-254 plates) compounds **2**, **9**, and **10** had R_f values of 0.35, 0.29, and 0.23, respectively, when CH_2Cl_2 was used as eluent.
(14) A layer of Na_2CO_3 was placed on top of the column to prevent acid-catalyzed deketalization of **9** and **10**.
(15) S. Safe and A. Taylor, *J. Chem. Soc. C*, 1189 (1971).
(16) The Cotton effect at 230 nm is due to an n, π^* transition of a peptide bond; see, e.g., R. Nagarajan and R. W. Woody, *J. Am. Chem. Soc.*, **95**, 7212 (1973).
(17) Details on these tests will be published elsewhere.
(18) The method outlined here meets all of the principal desirable features of resolution via diastereomeric formation as formulated by S. H. Wilen, ref 5, p 111.

Henricus C. J. Ottenheijm*
Jacobus D. M. Herscheid, Rutger J. F. Nivard
Department of Organic Chemistry
Catholic University of Nijmegen
Toernooiveld, Nijmegen, The Netherlands
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