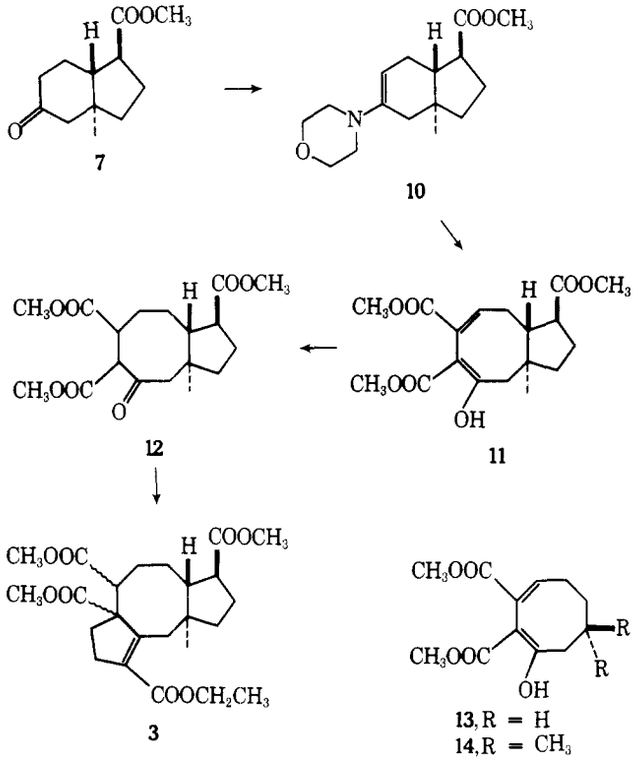
sulting *N*-acyl sulfonamide **6** [mp 185–188 °C; NMR ($CDCl_3$) δ 0.85 (s, 3), 1.1–2.5 (m, 12), 3.87 (m, 4), 7.63 (d, 2, J = 9 Hz), 7.91 (d, 2, J = 9 Hz), 8.55 (br s, 1)] was hydrolyzed with concommitant loss of the ketal and the resulting crude keto acid was esterified to give the trans-fused hydrindan **7** in overall yield of 42% from enone **4**.[12] The structure and stereochemistry of **7** was firmly established by converting it to the known ester **9**[13] via the crystalline thioketal **8** (mp 54–57 °C). The ester **9** produced from **7** was identical (IR, ^1H NMR, ^{13}C NMR, VPC, TLC) with a sample of **9** prepared by an established route.[13,14]

Having established the crucial trans BC ring juncture, attention was turned to expanding the six-membered ring to an eight-membered ring via the well-known reaction between enamines and acetylenic esters.[15] It had been suggested that a trans-fused hydrindanone such as **7** should enolize predominantly away from the ring juncture.[16] This suggestion was primarily an extrapolation from results obtained with trans-fused decalones and steroidal ketones. Thus, when a mixture of keto ester **7** and morpholine was heated in refluxing tetrahydrofuran over 4A molecular sieves, crude enamino ester **10** was obtained in a 90% yield. The appearance of the vinyl proton as a doublet (J = 4.5 Hz) at δ 4.50 (benzene-d_6) in the ^1H NMR spectrum of **10** confirmed that enamine formation had occurred predominantly, if not exclusively, away from the ring juncture. When crude **10** was allowed to react with dimethyl acetylenedicarboxylate and the crude mixture of products was hydrolyzed with aqueous acidic methanol, a 40% yield of a mixture of 1:1 adducts between **7** and dimethyl acetylenedicarboxylate was obtained. Keto ester **7** was also obtained in an 8% yield. The mixture of adducts was 75–80% dienol **11** which was obtained in pure form by crystallization from petroleum ether [mp 114–117 °C; IR (CCl_4) 1730, 1658, 1610 cm^{-1}; UV max (MeOH) 220 nm (ε 7200), 264 (9100); NMR ($CDCl_3$) δ 0.93 (s, 3), 1.3–2.9 (m, 10), 3.78 (sharp m, 9), 7.08 (t, 1, J = 9 Hz), 13.0 (br s, 1); mass spectrum (70 eV) m/e 352 (M^+)].[17] The similarity between the spectral properties of **11** and those of the related cyclooctadienols **13**[18] and **14**[19] support the assigned structure.



The A ring was grafted onto dienol **11** in the following manner. The mixture of adducts from the ring expansion was hydrogenated at 45 psi over 5% palladium on alumina to give a 90% yield of β-keto ester **12** after chromatography over silica gel. Sequential treatment of **12** with sodium hydride and 1-carbethoxycyclopropyltriphenylphosphonium tetrafluoroborate[20] gave a 30% yield of a *single* α,β-unsaturated ester **3** after chromatography over silica gel and recrystallization from petroleum ether [mp 120–121 °C; UV max (MeOH) 237 nm (ε 8700); NMR ($CDCl_3$) δ 0.82 (s, 3), 1.29 (t, 3, J = 7 Hz), 1.3–3.6 (m, 17), 3.70 (s, 3), 3.71 (s, 3), 3.74 (s, 3), 4.21 (q, 2, J = 7 Hz); exact mass calcd for $C_{24}H_{34}O_8$ 450.2254, found 450.2296].[21]

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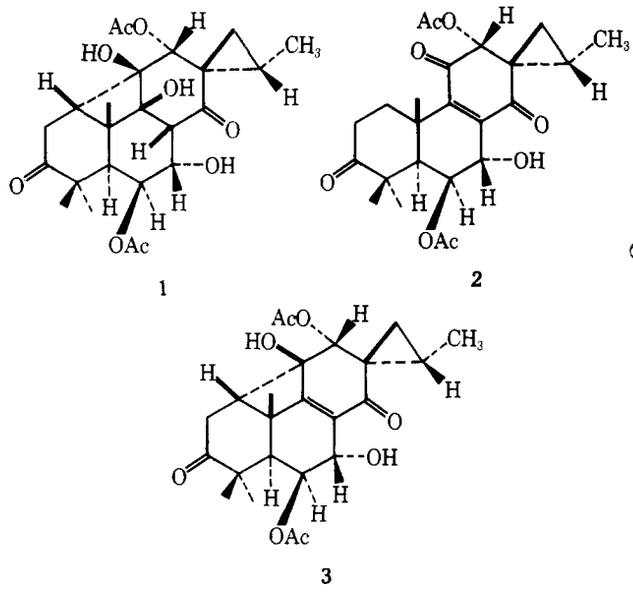
Synthesis and Structural Determination of Dehydrocyclobutatusin, a Diterpenoid with a Four-Membered Ring

Summary: Irradiation of the diterpenoid, barbatusin (**2**), produces dehydrocyclobutatusin (**3**), which contains a new four-membered ring; the structure of **3** was determined by x-ray methods.

Sir: Cyclobutatusin (**1**), a diterpenoid isolated from *Coleus barbatus*,[1,2] retains the basic spiro[2,5]octane system of bar-



1 2 3

batusin (2)[2,3] but in addition has a four-membered ring formed by a bond between C(1) and C(11). These findings suggested that cyclobutatusin might be the product of a photochemically induced reaction involving a barbatusin-type precursor.[1,2] The formation of cyclobutanol derivatives upon UV irradiation of diterpenoids,[4] steroids,[5] and triterpenoids[6] has been extensively studied and this fact prompted us to examine the irradiation of barbatusin. We now wish to report the photosynthesis of a 1,11-cyclo species, dehydrocyclobutatusin (3), a probable precursor in the biogenesis of cyclobutatusin.

Irradiation of a benzene solution of barbatusin in the n–π^* band gave **3**, mp 176–180 °C, $C_{24}H_{30}O_8$ (M^+ 446), in 40% yield. The IR spectrum indicated the presence of hydroxyl, ester, keto, α,β-unsaturated keto, and acetyl functions (ν 3450, 1735, 1705, 1660, 1240 cm^{-1}). The NMR spectrum ($CDCl_3$, ppm) revealed the presence of three tertiary methyl groups at 4α, 4β (1.17, 1.18), and 10β (1.65), and also one secondary *C*-methyl group in the spiro side chain, d at δ 1.05 (J = 4 Hz), two acetyl functions at 2.02 (3 H, s) and 2.03 (3 H, s), two CHOAc protons at 5.75 (d of d, J_{5-6} = 4 Hz, J_{6-7} = 2 Hz) for the 6α and at 4.8 for the 12β-H, one proton at 4.62 assigned to the 7β-H (d, J_{6-7} = 2 Hz), and two hydroxyl groups (br signals at 3.40 and 3.66 with $W_{1/2}$ = 16 and 12 Hz). The two latter signal patterns collapsed following deuterium exchange (with D_2O). The UV spectrum showed an absorption maximum at 230 nm (ϵ 8475) reminiscent of that due to the α,β-unsaturated keto chromophore of barbatusin (**2**). This absorption had one half of its intensity, thus indicating the presence of one chromophore, and can thus be associated with the structural feature present in the BC ring system of structure **3**.

Dehydrocyclobutatusin which is isomeric with barbatusin readily formed an acetylated derivative, $C_{26}H_{32}O_9$, mp 127–129 °C. The presence of a hydroxyl group which resisted acetylation was indicated by examination of the NMR spectrum: the complex signal pattern at δ 3.08 ($W_{1/2}$ = 16 Hz) was assigned to that OH group and collapsed following deuterium exchange; the additional acetyl group could be observed at 2.18 (3 H, s, 7α-OAc) and the geminal CHOAc proton at 5.08 (d, J_{6-7} = 2 Hz).

The presence in **3** of the groupings shown in ring C, in association with a spirocyclopropane ring at C(13), would account for much of the above data. Furthermore the location of a tertiary OH group at C(11) was in accord with this information.

At this stage, the three-dimensional structure of dehydrocyclobutatusin was determined by the x-ray structure analysis

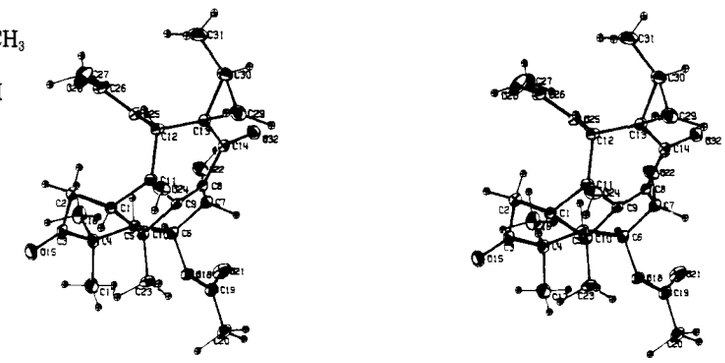


Figure 1. Stereoscopic view of a single molecule of **3**.

of the crystals obtained from benzene solution. The colorless crystals appear to react with moisture forming a white surface coating. A single crystal ~0.4 × 0.2 × 0.2 mm was used to collect 1976 reflections on a Syntex $P2_1$ diffractometer (CuKα radiation). The space group is monoclinic, $P2_1$, with two molecules per unit cell: a = 8.242 (9), b = 10.816 (9), c = 12.810 (9) Å, β = 94.27 (7) °. The structure was solved by direct methods[7] and refined by full-matrix least-squares methods (for all nonzero reflections) to an R factor of 0.042.[8] Anisotropic temperature factors were used for all nonhydrogen atoms. A stereoscopic drawing of a single molecule is shown in Figure 1. The bond lengths are close to accepted values with the C(1)–C(11) distance in the four-membered ring being 1.602 (6) Å. The crystal packing is stabilized by extensive hydrogen bonding between hydroxyl oxygens O(24) and O(22) and carbonyl oxygens O(28) and O(21), respectively, in symmetry-related molecules.

The molecular mechanism responsible for the photoisomerization of barbatusin into dehydrocyclobutatusin is obviously an intramolecular γ-hydrogen transfer from C(1) to the electron deficient n–π^* excited carbonyl group at C(11) (Norrish type II process).[9] The relative ease whereby the new 1,11-cyclo species (**3**) is obtained strongly supports the assumption of a biogenetic pathway leading to cyclobutatusin (**1**) through its dehydro compound (**3**) whose double bond at C(8)–C(9) would add the elements of water from the less hindered upper side of the molecule.

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Supplementary Material Available. Tables of coordinates, temperature factors, bond lengths, bond angles, and structure factors for **3**, and the experimental details of the preparation of **3** (9 pages). Ordering information is given on any current masthead page.

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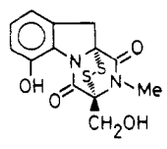
Approaches to the Resolution of Racemic Cyclic Disulfides. Application to an Epidithiodioxopiperazine

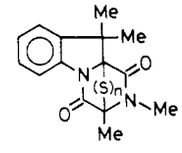
Summary: The chemical resolution of **2** has been performed via diastereomer formation (**9** and **10**) as well as via a kinetically controlled transformation; the enantiomers **11** and **12** have the same anti-reverse transcriptase activity.

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

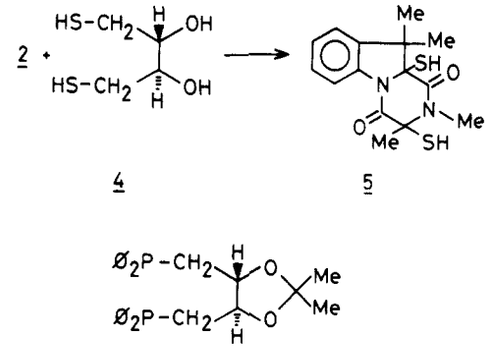


2: n = 2
3: n = 1

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

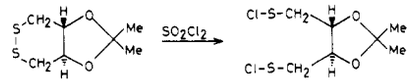


4 **5**

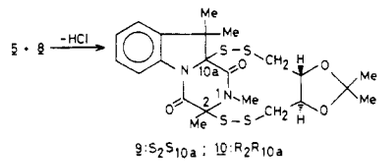
6

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).

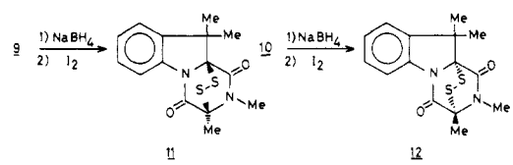
Scheme II



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