Novel Family of Heterocyclic Strained Helices. Cesium-Assisted Syntheses and Conformational and Chiroptical Properties and Geometries

Kurt Meurer,† Fritz Vögtle,*,† Albrecht Mannschreck,‡ Georgine Stühler,‡ Heinrich Puff,§ and Albrecht Roloff§

Institut für Organische Chemie and Biochemie der Universität Bonn, Gerhard-Domagk-Strasse 1, D-5300 Bonn 1, Federal Republic of Germany, Institut für Organische Chemie der Universität Regensburg, Universitätstrasse 32, D-8400 Regensburg, Federal Republic of Germany, and Anorganisch-Chemisches Institut der Universität Bonn, Gerhard-Domagk-Strasse 1, D-5300 Bonn 1, Federal Republic of Germany

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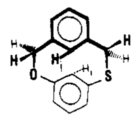
The syntheses of 1-oxa-10-thia[2.2]metacyclophane (1) and 1-thia-10-(*p*-tolylsulfonyl)-10-aza[2.2]metacyclophane (2) have been achieved for the first time by cesium-assisted high-dilution methods. Prior to application of the cesium effect, 1 and 2 were not available. In the NMR spectra, the intraannular hydrogens H_i of both 10-membered rings (Figure 1) are strongly shifted upfield. Both molecular helices 1 and 2 can be resolved (1) or enantiomerically enriched (2) by inclusion chromatography with triacetyl cellulose. The optical rotations are high, i.e., $[\alpha]^{RT}_{365} = 1545$, $\Delta\epsilon_{242} = 81$ for (−)-1 (in 1,4-dioxane). The absorption spectra and the circular dichroisms of 1 and 2 (Figures 2 and 3), as well as the comparison with exocyclic-substituted [2.2]metacyclophanes like 6–11, give insight into the dependence between structure and helicity of these 10-membered rings. The absolute configurations of 1 and 2 can be presumed from circular dichroic correlations (Figure 4). The kinetic parameters for the ring inversions of 1 and 2, accessible by measuring the rates of racemization or interconversion, were determined to be $\Delta G^{\ddagger}_{INT} = 123.3$ kJ mol^{-1}, $k_{INT} = 4.87 \times 10^{-5}$ s^{-1} (100 °C) for 1 and $\Delta G^{\ddagger}_{INT} = 130.7$ kJ mol^{-1}, $k_{INT} = 5.40 \times 10^{-6}$ s^{-1} (102 °C) for 2. The high barrier of racemization of 2 is discussed. X-ray analyses of 1 and 2 disclose for the first time exact data about the C–N, C–O, and C–S bond lengths as well as the transannular distances *d* between C(H_i) and C′(H_i) and the bond angles in this new type of two-bladed propellers. The geometries and helicities of 1 and 2 are illustrated and compared by using the torsion angles α–δ (Figure 7).

Introduction

Small and rigid screw-shaped molecules are valuable models for systematic investigations of helicity, especially if they also lack centers of chirality. We have previously reported on hydrocarbon helices consisting of five,[1] four,[2] and three aromatic rings.[3,4] The helical structure of these large ring compounds is more or less fixed conformationally through an ethano bridge. If one of the sulfur atoms within the planar chiral skeleton of 1,10-dithia[2.2]metacyclophane (**3a–e**)[5-8] is formally substituted by an oxygen or a nitrogen atom, the new 1-oxa-10-thia[2.2]metacyclophanes **1** and the 1-thia-10-aza[2.2]metacyclophanes **2**, as well as derivatives like **4** and **5**, will be obtained. Thus helicity should be the consequence of the asymmetric propeller arrangement of the aromatic rings in **1**, **2**, **4**, and **5** connected through nonequivalent two-membered bridges.



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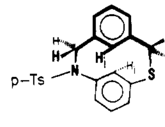

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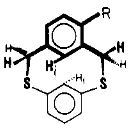

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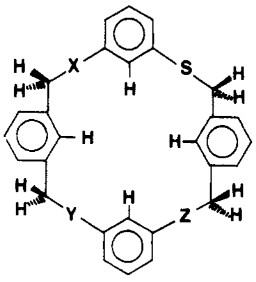
a: R = -H
b: = -COOH
c: = -COOCH$_3$
d: = -COOCH$_2$CH$_3$
e: = -COOC$_6$H$_{11}$

Results and Discussion

Cesium-Assisted Syntheses. Previous attempts, started as early as 1972, to synthesize dihetera[2.2]metacyclophanes,[9] such as **1** and **2** containing two *different* heteroatoms in the bridges failed because of the strongly favored formation of dimeric products like **Ia,b** and **IIa,b**.[10] In the meantime, the syntheses of 1,10-dithia[2.2]metacyclophanes (maximum yield then of **3a**, 21–29%[5]) were optimized by applying appropriate high dilution techniques[7] (maximum yield of **3a**, 68–90%).



I a : X = O , Y = S , Z = O
I b : X = O , Y = O , Z = S
II a : X = N-Ts , Y = S , Z = N-Ts
II b : X = N-Ts , Y = N-Ts , Z = S

Stimulated by studies on the selective steering of the formation of oligomers of medio- and macrocyclic compounds in diluted solutions by use of cesium carbonate in dimethylformamide,[11] we found that the combined application of the cesium effect[12,13] and high-dilution meth-

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‡ Institut für Organische Chemie der Universität Regensburg.

§ Anorganisch-Chemisches Institut der Universität Bonn.

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(13) Kliesser, B.; Rossa, L.; Vögtle, F. *Kontakte* **1984**, *1*, 3. By applying high-dilution cyclization conditions to synthesize strained and rigid molecules, the use of cesium bases (cesium hydroxide) led to higher yields compared to other alkali metal bases (hydroxides). The large cesium ion possibly is better suited to form a nonstrained bridge between intramolecularly approaching reaction centers than smaller alkali metal cations. Similar arguments may hold for other C–C, C–S, C–O, and C–N bond formations: Vögtle, F.; Mayenfels, P.; Luppertz, F. *Synthesis* **1984**, in press. Meurer, K.; Duchene, K.-H.; Vögtle, F., unpublished results. See also ref 12.

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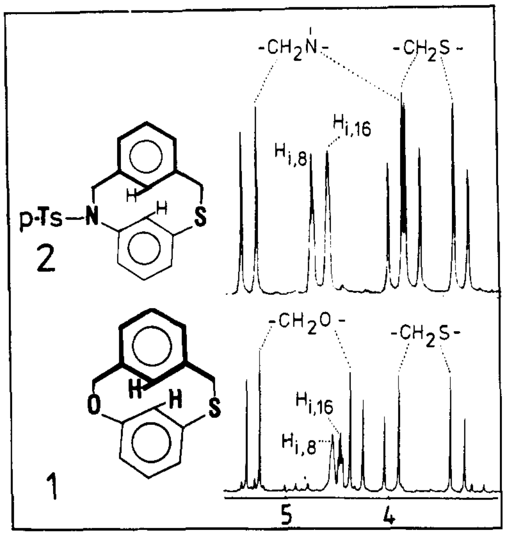

Figure 1. ^1H NMR spectra (sections) of **1** and **2** (same δ scale).

ods[14] allowed for the first time access to the heterocycles **1** and **2**, respectively. **1** was isolated after reacting 1,3-bis(bromomethyl)benzene and 1-hydroxy-3-benzenethiol under assistance of cesium hydroxide and application of high-dilution conditions[14] inside a solvent mixture of ethanol/benzene. To date, we have obtained **1** in a maximum yield of no more than 1.9% after a series of experiments aimed at optimization. Reaction of 1-(*p*-toluenesulfonyl)amino-3-benzenethiol and 1,3-bis(bromomethyl)benzene led to **2** in a higher yield of 9% using a procedure analogous to **1**.

Experiments to prepare **1** using the more common cesium carbonate route in dimethylformamide[11,15] led to very low yields (maximum 0.3%). We were not able to isolate any of **1** and **2** without application of the "cesium effect".[13]

Analogous experiments aimed at optimizing the syntheses of the strained planar chiral dithiaphane **3** by using the different alkali hydroxides (LiOH, NaOH, KOH, RbOH, CsOH)[8,13] again demonstrated the yield increasing effect of the *cesium* compound. A change of solvent (*tert*-butyl alcohol, *n*-butanol, benzene, toluene, ethanol/toluene, or acetonitrile instead of ethanol/benzene or dimethylformamide) or a change of bases (F^-[16] or Br^- instead of OH^- or CO_3^{2-}) led, in spite of high-dilution methods, only to macrocyclic or open-chained oligomeric products. When utilizing the above mentioned cesium effect without application of high dilution, the yields of higher molecular weight oligomers increase. Therefore, parameters such as the cesium effect and high-dilution conditions should in general be varied in order to obtain a selective steering of products especially in the case of strained cyclophanes or of special crown compounds.[13,16,17]

Oxidation of **1** and **2** using 37% H_2O_2 solution in acetic acid leads to the sulfones **4** and **5** which exhibit low solubility and high melting points.

^{1}H NMR Spectroscopic Properties. The NMR absorption spectra of **1** and **2** are comparable. The intraannular aromatic protons H_i appear at high fields as triplets: **1** $H_i(8) = 4.52$, $H_i(16) = 4.44$, $J_m = 2$ Hz; **2** $H_i(8) = 4.76$, $H_i(16) = 4.57$, $J_m = 2$ Hz. Both the deshielding effect of the *p*-toluenesulfonyl group and the longer C–N distance within the skeleton of **2** compared to **1** seem to provoke the additional upfield shift of the intraannular hydrogens $H_i(8)$ and $H_i(16)$ ($\Delta\delta = 0.2$–0.3 ppm) in going from **2** to **1** (Figure 1).

The AB patterns of the bridging methylene segments ($-CH_2S$) of **1** and **2** exhibit similar coupling constants ($J_{AB} = 12$ Hz) and shifts (**1**, 3.35, 3.96 ppm; **2**, 3.30, 3.91 ppm). The $-CH_2O$ methylene group with $J_{AB} = 11$ Hz and $-CH_2N$ with $J_{AB} = 12$ Hz give rise to the following shifts for **1** (4.31, 5.29 ppm) and **2** (3.75, 5.35 ppm). The high-temperature NMR spectra (signals unchanged up to 150 °C) disclose that the *p*-toluenesulfonyl group rotation in **2** does not seem to be appreciably hindered.

Enantiomer Separation and Interconversion. **1** was totally resolved and **2** enantiomerically enriched by inclusion chromatographic techniques with a triacetyl cellulose[24] column (TAC 20–30 $\mu m^{3,4,8}$). The optical rotations at several wavelengths were determined for (–)-**1** only, because the available amounts of (+)-**1** were limited. It was not possible to determine the enantiomeric purity of (–)-**2** or (+)-**2**. The racemization and interconversion of (–)-**1** was studied in 1,4-dioxane solution at 92 and 100 °C. At 92 °C the racemization proceeds slowly, and at 100 °C a barrier of interconversion of $\Delta G^{\ddagger}_{INT} = 123.3$ kJ mol^{-1} is found and the interconversion is $k_{INT} = 4.87 \times 10^{-5}$ s^{-1}. The half-life was determined to be 2 h at that temperature.

The racemization or interconversion of (+)-**2** or (–)-**2** was carried out in distilled mesitylene at temperatures of 102, 123.5, and 132 °C. At 102 °C the following data were obtained: $\Delta G^{\ddagger}_{INT} = 130.7$ kJ mol^{-1}, $k_{INT} = 5.40 \times 10^{-6}$ s^{-1}, $t_{1/2} = 17.8$ h; at 123.5 °C, $\Delta G^{\ddagger}_{INT} = 130.5$ kJ mol^{-1}, $k_{INT} = 5.44 \times 10^{-5}$ s^{-1}, $t_{1/2} = 1.8$ h; at 132 °C, $\Delta G^{\ddagger}_{INT} = 129.0$ kJ mol^{-1}, $k_{INT} = 1.943 \times 10^{-4}$ s^{-1}, $t_{1/2} = 0.5$ h. The racemizations of (+)-**2**, (–)-**2**, and (–)-**1** were studied at wavelengths of $\lambda_1 = 365$ nm and $\lambda_2 = 436$ nm. Hence, the enantiomers of **2** show higher stability toward racemization than those of **1**.

The higher racemization barrier of **2** compared to **1** calls for an explanation. At first sight this result does not appear to be plausible when taking into account the longer C–N bonds in **2** vs. the C–O bonds in **1** (vide infra). The angles at the nitrogen atom were determined to be 117.7°, 123.0°, and 119.2°.[32] They hint at approximate sp^2 hybridization. Besides nitrogen inversion, other electronic and steric effects (an influence of the mass of the *p*-tosyl group, its rotation) could be responsible for the unexpected barrier difference between **1** and **2**. The (enantiomeric) stability of **1** and **2** is underlined by the fact that during the racemization experiments we found no indication of transannular C–C bond formation yielding biphenyl-type compounds.[25a]

Chiroptical Properties and Absolute Configuration. The absorption and circular dichroic curves (Figures 2 and 3) were measured in 1,4-dioxane. The intensive Cotton effects of $(-)_D$-**1** ($\Delta\epsilon = -80.64$) and of (+)-**1** (qualitative measurement) at the wavelength $\lambda = 222$ nm are equivalent to the π–π^* absorption (^1L_a) of **1** ($\epsilon = 27500$). A further Cotton effect is found at $\lambda = 242$ nm [$(-)_D$-**1**, $\Delta\epsilon = -60.48$, UV $\epsilon = 5200$]. Most likely, the absorption at 242 nm can be attributed to a bathochromic effect of the phenol ether segment in **1**. For $(-)_{365}$-**2** and (+)-**2** intensive circular dichroisms at $\lambda = 224$ nm [$\Delta\epsilon = -7.88$ for $(-)_{365}$-**2**, $\Delta\epsilon = +4.08$ for $(+)_{365}$-**2**, $\epsilon = 33000$] are observed. A Cotton effect of analogous positive sign at $\lambda = 231$ nm ($[\Theta]_{max} = +63.1$) is observed for $(-)_D$-**10**.[18] A CD correlation of **1** and

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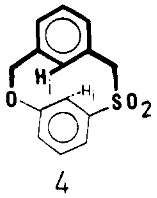

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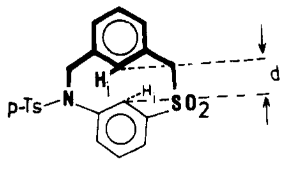

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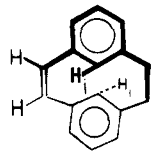

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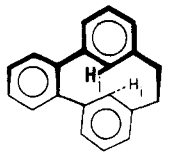

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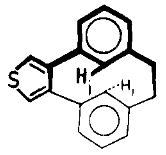

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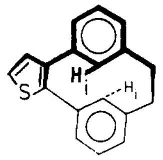

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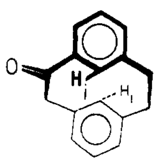

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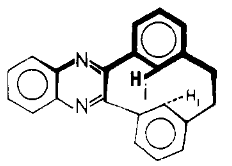

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2 to the already known absolute configuration of (−)-**10** can be presumed (Figure 4). Consequently, the M configuration of $(-)_D$-**10** would correspond to a M configuration of $(+)_D$-**1** and $(+)_{365}$-**2**; hence, it is $(+)_D$-**10** (P) and $(-)_D$-**1** (P) and $(-)_D$-**2** (P). The absorption spectra and CD curves of $(+)_{546}$-**8** (λ = 220 nm), $(+)_{436}$-**11** (λ = 224 nm), $(+)_{365}$-**7** (λ = 228 nm) seem to support this supposition.[3,4] The M configuration of $(+)_{540}$-**8** has been determined by the Bijvoet method. A slightly increasing bathochromic effect can be observed at the ^1L_a band of $(+)_D$-**1**, $(+)_{365}$-**2**, $(+)_{365}$-**7**, and $(-)_D$-**10**. The effect is most pronounced in the case of $(-)_D$-**10** because of the carbonyl chromophor. The π–π^* absorption of $(+)_{365}$-**7** (λ = 228 nm) is found at shorter wavelength compared to $(-)_D$-**10** (λ = 231 nm). The Cotton effect of $(+)_{365}$-**7** at λ = 245 nm is most likely a conjugation band of the benzene ring inside the bridging segments of three-nucleic helices. The CD absorptions at 220–228 nm (**8**, **11**, **7**) [$\Delta\epsilon$ = +22 (**8**), $\Delta\epsilon$ = +82 (**11**), $\Delta\epsilon$ = +90 (**7**)] support this assumption.[4]

Geometries of 1 and 2.[28-32] The X-ray determination of (±)-**1** and (±)-**2** gives a detailed picture of the stair-stepped helical skeleton of the heterocyclic [2.2]metacyclophanes **1** and **2** (Figures 5 and 6). A projection of

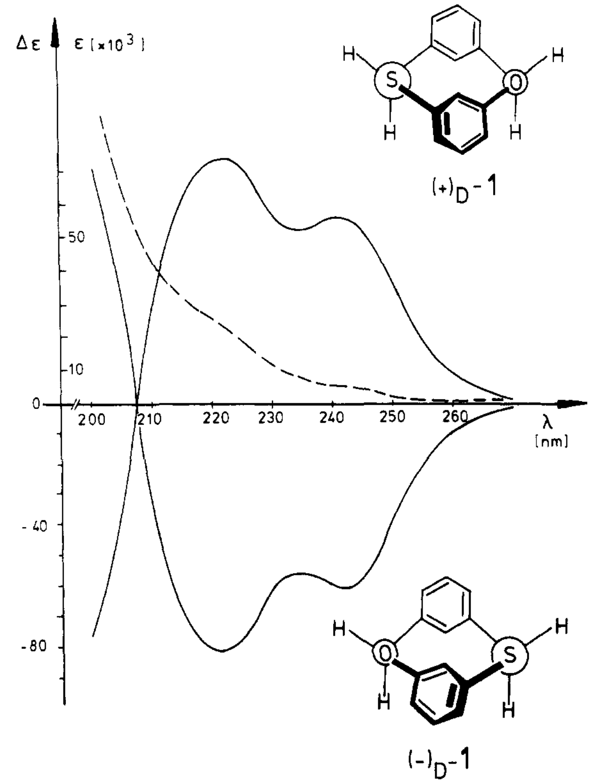

Figure 2. Spectral properties of (−)-1 and (+)-1. Absorption spectrum (ordinate scale on the left inside) (– –); circular dichroisms of (−)-1 and (+)-1 (qualitative measurement) (—).

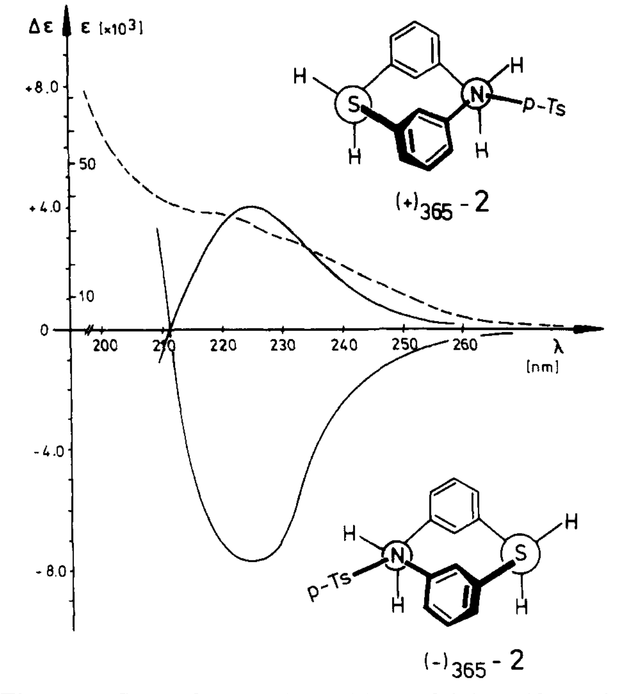

Figure 3. Spectral properties of (−)-2 and (+)-2. Absorption spectrum (ordinate scale on the left inside) (– –) circular dichroisms of (−)-2 and (+)-2 (—).

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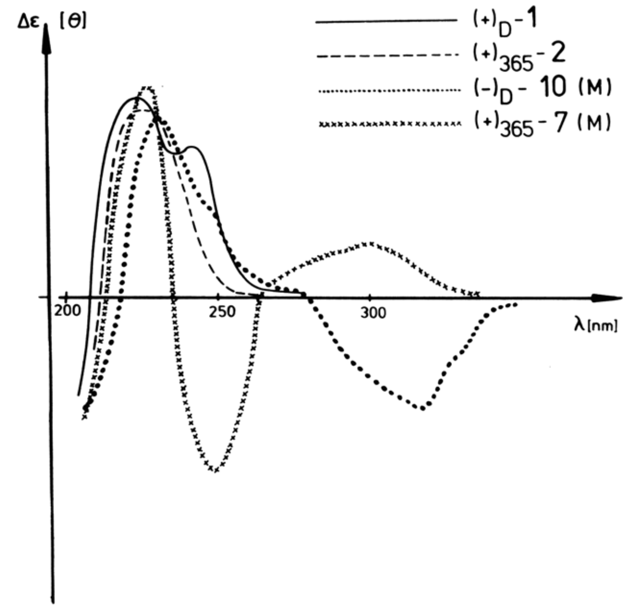

Figure 4. Comparison of the CD curves of (+)$_D$-**1**, (+)$_{365}$-**2**, (−)$_D$-**10**, and (+)$_{365}$-**7** and attempted correlation of the absolute configuration of (+)$_D$-**1** and (+)$_{365}$-**2** to be M.

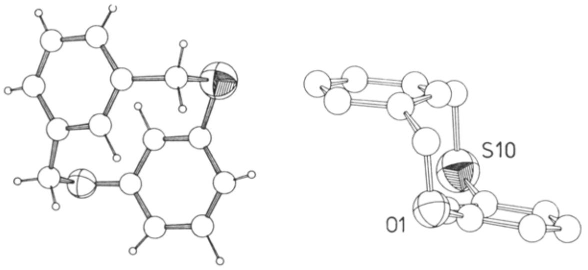

Figure 5. X-ray structure of **1** and terraced arrangement of **1**.

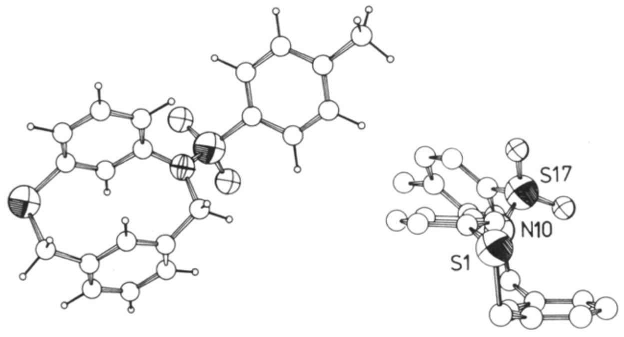

Figure 6. X-ray structure of **2** and terraced arrangement of **2**.

the terraced asymmetric structure of both aromatic rings (Figures 5 and 6) and the perspective presentation of the heterocyclic, ten-membered ring between the hindered benzene rings[32] exhibit a typical "anti" conformation of the skeleton of these [2.2]metacyclophanes.

The C(8)–C′(16) distances in **1** and **2** are remarkably similar and comparable to **6** and **7**. They differ only about ±2.4 pm. This gives information on the distribution of steric compression in the skeleton of strained [2.2]metacyclophanes because it seems to be a C(H_i)–C′(H_i) contact (257–263 pm) generally observed in cyclophanes.[3,4,25b]

Figure 7 and Table I give the data suitable for a comparison of the different torsion angles in **1**, **2**, **6**, and **7**. The angle α formed by the planes of the two metaphenylene rings and the twist angle δ increase in proceeding from **2** to **1** and from **7** to **6**. This correlates to the bond lengths inside the aliphatic bridges. According to these data, **6** shows the strongest distortion regarding the angles α and δ. It is $\alpha = 9.1°$ and $\delta = 8.3°$ for **6**. Similar but less pronounced deviations are found for **7** ($\alpha = 7.2°$, $\delta = 7.2°$) as is to be expected. For **2** and **1** there are only found the angles $\alpha = 4.4°$ (**1**), $\alpha = 2.4°$ (**2**), $\delta = 6.9°$ (**1**), and $\delta = 5.4°$ (**2**). The influence of the sp^2 hybridization inside the bridge between the aromatic planes of **6** and **7** leads to increased angles of $\gamma = 31.0°$ (**6**) and $\gamma = 33.8°$ (**7**) compared to those of **1** and **2** [$\gamma = 5.6°$ (**1**), $\gamma = 6.9°$ (**2**)]. Principally, it may be supposed that the helical distortion of these strained heterocycles increases generally from **2** to **1**, from **2** to **7** and from **7** to **6**. This correlates with the increased strain of **2**, **1**, **7**, and **6**.

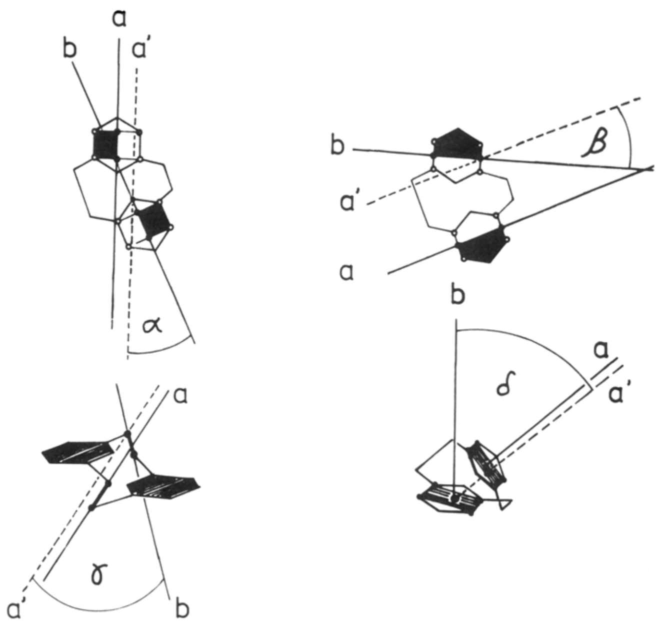

Figure 7. Comparison of the angles α, β, γ, and δ in **1**, **2**, **6**, and **7** and the intraannular distances d. Definition of the angles α, β, γ, and δ: a, b, strictly defined lines; a′; projected line parallel to a (a//a′); a′ and b, cross in a well defined point. α, β, γ, and δ are angles formed by the lines a′ and b.

Table I. Torsion Angles α, β, γ, and δ and Transannular C(H_i)–C′(H_i) Distances d of 1, 2, 6, and 7

	1	2	6^{25b}	7^{3}
d, pm	262	257	259	258
α, deg	4.4	2.4	9.1	7.2
β, deg	6.3	4.9	7.3	10.1
γ, deg	5.6	6.9	31.0	33.8
δ, deg	6.9	5.4	8.3	7.2

Experimental Section

General Methods. Melting points are uncorrected and were taken on a Reichert melting point apparatus. NMR spectra were recorded on a Varian EM-360 and Varian EM-390 instrument unless otherwise specified. In the description of the ^1H NMR data, s represents singlet, d doublet, t triplet, m multiplet. Optical rotations are uncorrected and were determined with a Perkin Elmer 241 polarimeter and a 1-dm thermostated cell. CD spectra were recorded on a CNRS Roussel-Jouan Dichrographe III in 1,4-dioxane, UV data were determined with a Varian Cary 17 instrument.

1-Oxa-10-thia[2.2]metacyclophane (1). Solution 1: 1,3-bis(bromomethyl)benzene[21] (1.31 g, 5 mmol) was dissolved in 250 mL of dry benzene free from thiophene. Solution 2: cesium hydroxide (1.49 g, 10 mmol, mp 272.3 °C, $d = 3.675$) was dissolved in water (0.8 mL) by gently warming. 3-Hydroxybenzenethiol[19,20] (0.64 g, 5 mmol) was added to 200 mL of absolute ethanol. The latter two solutions were combined and filled with absolute ethanol to a total volume of 250 mL. Solution 1 and solution 2, then, were simultaneously and separately dropped into 2.5 L of boiling stirred ethanol in the reaction flask. Two precision dropping funnels and a two-component high-dilution apparatus (2C-VP)[22] were used which were protected from light and held under an argon atmosphere. The velocity of dropping was 25 mL/h and the resulting dropping time was 10 h. After the mixture had been refluxed for additional 5 h, the solvent was evaporated in vacuo and the residue dissolved in CH_2Cl_2. The solid products were filtered off and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, concentrated, and chromatographed (silica gel Woelm, 02824/32–63 μ; $CHCl_3$/toluene/light petroleum bp 40–60 °C, 2:1:1) to give 5.7–21.7 mg (0.5–1.9%) of 1: mp 93–94 °C (ethanol/water), R_f ($CHCl_3$/toluene/light petroleum bp 40–60 °C, 2:1:1, DC silica gel F_{160} Merck) 0.47; IR (KBr, cm^{-1}) 1595, 1575, 1470, 1430, 810; ^1H NMR ($CDCl_3/Me_4Si$, δ) 3.35, 3.96 (AB, 2 H, J_{AB} = 12 Hz), 4.31, 5.29 (AB, 2 H, J_{AB} = 11 Hz), 4.44 (t, 1 H, J_m = 2 Hz), 4.52 (t, J_m = 2 Hz), 7.08–7.58 (m, 6 H); exact mass for $C_{14}H_{12}OS$, *m/e* (calcd) 228.0609, *m/e* (obsd) 228.0655. Anal. Calcd for $C_{14}H_{12}OS$ ($+0.5H_2O$): C, 73.65 (70.74); H, 5.30 (5.39). Found: C, 70.77; H, 5.31. The amount of dimeric products (Ia,b) was 183 mg (16%): mp 196 °C (ethanol); R_f ($CHCl_3$/toluene/light petroleum bp 40–60 °C, 2:1:1, DC silica gel F_{160}, Merck) 0.52; ^1H NMR ($CDCl_3/Me_4Si$, δ) 4.00 (s, 4 H), 5.14 (s, 4 H), 6.75–7.60 (m, 16 H); mass for $C_{28}H_{24}O_2S_2$, *m/e* (calcd) 456, *m/e* (obsd) 456. Anal. Calcd for $C_{28}H_{24}O_2S_2$: S, 14.04. Found: S, 14.24.[10]

Cyclization experiments of **11** and **12** in dimethylformamide-/cesium carbonate[13,15] under high-dilution conditions[14] gave 1 in less than 0.3% yield. Other procedures to synthesize 1 (K_2CO_3/*i*-amyl alcohol; K_2CO_3 or Na_2CO_3, dimethylformamide; KOH, NaOH/*tert*-butyl alcohol; KOH, ethanol/butanol; KOH, *n*-butanol/toluene) failed; **Ia** and **Ib** were formed mainly.

1-((*p*-Tolylsulfonyl)amino)-3-benzenethiol (15). Bis(3-amino-*p*-tolylsulfonyl) disulfide[23] (**14**) (2.22 g, 40 mmol) was dissolved in 150 mL of acetic acid by gentle heating. Powdered alumina (0.52 g, 40 mmol) was added to this solution. After 50 mL of 37% hydrochloric acid was dropped slowly into the mixture, it was refluxed for 3 h. Unreacted alumina was filtered and the filtrate, while warm, was poured into a saturated solution of NaOH. The mixture was then acidified with concentrated H_2SO_4 (pH of 8, phenolphthalein). A colorless, foul-smelling product was crystallized overnight. Recrystallization from ethanol/water gave 11.2 g (52%) of **15**: mp 104–105 °C (ethanol/water); ^1H NMR ($CDCl_3/Me_4Si$, δ) 2.37 (s, 3 H), 3.45 (s, 1 H), 6.80–7.20 (m, 4 H), 7.52 (s, 1 H), 7.72, 7.21 (AA′BB′, 4 H, $J_{AA'BB'}$ = 8 Hz); mass for $C_{13}H_{13}NO_2S_2$, *m/e* (calcd) 279, m/e (obsd) 279. Anal. Calcd for $C_{13}H_{13}NO_2S_2$: C, 55.89; H, 4.69; N, 5.01. Found: C, 55.97; H, 4.92; N, 4.76.

1-Thia-10-(*p*-tolylsulfonyl)-10-aza[2.2]metacyclophane (2). Solution 1: 1,3-bis(bromomethyl)benzene (**12**, 1.31 g, 5 mmol) was dissolved in 250 mL of absolute, thiophene-free benzene. Solution 2: cesium hydroxide (1.49 g, 10 mmol) was dissolved in water (0.8 mL) under gentle warming. 3-((*p*-Tolylsulfonyl)-amino)benzenethiol (**15**) was added to 200 mL of absolute ethanol. Both latter solutions were combined and filled to a total volume of 250 mL by addition of absolute ethanol. Solutions 1 and 2 were added simultaneously to 2.5 L of ethanol similar to the procedure used for the synthesis of 1. The velocity of dropping was 8 mL/h and the resulting dropping time ca. 30 h. Column chromatography (glass column, Θ = 30 cm, J = 150 cm) on silica gel (Woelm, 02824, 63–100) with distilled chloroform and toluene (proportion 20:1) gave 0.17 g (9%) of **2**: mp 215–217 °C; R_f ($CHCl_3$/toluene 20:1, silica gel F_{160}, Merck) = 0.26; ^1H NMR ($CDCl_3/Me_4Si$, δ) 2.40 (s, 3 H), 3.91, 3.30 (AB, 2 H, J_{AB} = 1.6 Hz), 4.57 (t, 1 H, J_m = 1.6 Hz), 4.76 (t, 1 H, J_m = 13 Hz), 5.35, 3.75 (AB, 2 H, J_{AB} = 12 Hz), 7.72, 7.26 (AA′BB′, $J_{AA'BB'}$ = 8 Hz), 7.10–7.60 (m, 6 H); IR (KBr, cm^{-1}) 1605, 1575, 1500, 1350, 1340, 1160, 1100, 1050, 900, 815, 760; exact mass for $C_{21}H_{19}NO_2S_2$, *m/e* (calcd) 381.0857, *m/e* (obsd) 381.0858. Anal. Calcd for $C_{21}H_{19}NO_2S_2$: C, 66.11; H, 5.01; N, 3.67. Found: C, 65.94; H, 5.01; N, 3.74. The excess of dimer products IIa,b: 0.34 g (18%); ^1H NMR ($CDCl_3/Me_4Si$, δ) 2.38 (s, 6 H), 4.38 (s, 4 H), 5.05 (s, 4 H), 6.75–7.75 (m, 24 H); $C_{42}H_{38}N_2O_4S_4$, *m/e* 762.

1-Oxa-10-thia[2.2]metacyclophane 10,10-Dioxide (4) and 1-Thia-10-(*p*-tolylsulfonyl)-10-aza[2.2]metacyclophane 1,1-Dioxide (5). 1 (10 mg, 2.62×10^{-2} mmol) or **2** (10 mg, 4.39×10^{-2} mmol) is dissolved in 0.2–0.4 mL of benzene under weakly heating conditions. The mixture was diluted with 1 mL of acetic acid (99%) and filtered. To the filtrate was added excess 35% H_2O_2 the reaction temperature was held at 60 °C without stirring for 1 h, and then it was cooled to room temperature. The solvents were carefully concentrated and the resulting mixture was cooled in the refrigerator for 10 h. In both cases, we got colorless, insoluble, amorphous material with yields of 5.51 mg (51%) of **4** and 3.65 mg (32%) of **5**. Both melting points were higher than 310 °C. Mass for $C_{14}H_{12}O_3S$ (**4**), *m/e* (calcd) 260, *m/e* (obsd) 260; IR (KBr, cm^{-1}) 1350, 1310, 1150, 1100, 900, 780; exact mass for $C_{21}H_{19}NO_4S_2$ (**5**), *m/e* (calcd) 413.0755, *m/e* (obsd) 413.0740; IR (KBr, cm^{-1}) 1610, 1490, 1370, 1350, 1330, 1310, 1175, 1165, 1150, 1110, 900, 850, 830, 790.

Resolution of (±)-1-Oxa-10-thia[2.2]metacyclophane [(±)-1]. Racemic (±)-1 was resolved by semipreparative liquid chromatography (LC)[24] on triacetyl cellulose in 96% ethanol. The flow was 4–5 mL/min at room temperature and the pressure was 2 bar. After collection of several fractions we got (–)-1: $[\alpha]^{RT}{}_{365} = -1545 \pm 96$; $[\alpha]^{RT}{}_{436} = -750 \pm 25$; $[\alpha]^{RT}{}_{546} = -355 \pm 30$; $[\alpha]^{RT}{}_{578} = -300 \pm 35$; $[\alpha]^{RT}{}_{D} = -280 \pm 35$; mp 113–115 °C. The specific rotations were measured in 1,4-dioxane (J. T. Baker Chem., 8031). The resolution of (±)-1 by LC is complete, but the chromatographic determination of the enantiomeric purity was not possible because of the little amount of obtained material: $\Delta\epsilon_{222} = -80.64$; $\Delta\epsilon_{242}$ nm = –60.48 for (–)-1 (1,4-dioxane); exact mass for (–)-$C_{14}H_{12}OS$, *m/e* (calcd) 228.0609, *m/e* (obsd) 228.0601; exact mass for (+)-$C_{14}H_{12}OS$, *m/e* (calcd) 228.0609, *m/e* (obsd) 228.0609.

Resolution of (±)-1-Thia-10-(*p*-tolylsulfonyl)-10-aza[2.2]metacyclophane [(±)-2]. Racemic (±)-**2** was enantiomerically enriched by the same procedure as above in 96% ethanol. After collection of several fractions we got (+)-**2**: $[\alpha]^{RT}{}_{365} = +40 \pm 4$; $[\alpha]^{RT}{}_{436} = -20 \pm 3$ (1.2 g/L); mp 214–218 °C (ethanol). (–)-**2**: $[\alpha]^{RT}{}_{365} = -57 \pm 4$; $[\alpha]^{RT}{}_{436} = -31 \pm 3$ (1.2 g/L); mp 213–217 °C (ethanol). The specific rotations are determined in acetone. The chromatographic determination of the enantiomeric purity was not possible: $\Delta\epsilon_{224} = -7.88$ (1,4-dioxane); exact mass for (–)-$C_{21}H_{19}NO_2S_2$, *m/e* (calcd) 381.0857, *m/e* (obsd) 381.0857; $\Delta\epsilon_{224} = +4.08$; exact mass for (+)-$C_{21}H_{19}NO_2S_2$, *m/e* (calcd) 381.0857, *m/e* (obsd) 381.0853.

Rate of Racemization (Interconversion) of (–)-1. (–)-1, 0.40 mg, 2.1×10^{-3} mmol, was dissolved in 2.0 mL of 1,4-dioxane (spectrograde). In a typical run 1 mL of this solution was immersed in a constant temperature silicone oil bath (T = 92, 100 °C). The temperatures recorded inside the tube were constant within ±0.4 °C during the runs. At several intervals a 1-mL sample of this solution was taken and chilled in an ice bath. The optical rotations of such a sample were then recorded at 22 °C (room temperature) without further dilution. The measurements at 22 °C were directly carried out on a solution of (–)-1 in dioxane in a thermostated (10-cm path length) polarimeter cell. The optical rotations $[\alpha]^{22}$ were observed at 589, 546, 436, and 365 nm over a period of 2 h (100 °C) and 4 h (92 °C). After each racemization (interconversion) experiment, mainly, because of the long heating times, the racemized (–)-1 was compared with the racemic (±)-1 and identified by analytical thin-layer chromatography (silica gel F_{160}, Merck, $CHCl_3$/toluene/light petroleum 40–60 °C, 2:1:1).

Rate of Racemization (Interconversion) of (+)-2 and (–)-2. (+)-**2** (0.64 mg, 1.68×10^{-3} mmol) (–)-**2** (0.32 mg, 0.42×10^{-3} mmol) was dissolved in 2.0 mL of mesitylene. In a typical run 1 mL of these solutions was immersed in a constant temperature silicone oil bath [T = 102.5 °C for (–)-**2**, 132.0 °C for (–)-**2**, 123.5 °C for (+)-**2**]. The temperature recorded inside the tube was constant within ±0.5 °C during the runs. At several intervals a 1-mL sample of these solutions was taken and chilled in an ice bath. The optical rotations of such a sample were then recorded at 22 °C (room temperature) without any further dilution. The measurements at 22 °C were directly carried out on a solution of (–)-**2** or (+)-**2** in mesitylene in a thermostated (10-cm path length) polarimeter cell. The optical rotations $[\alpha]^{22}$ were observed at 589, 546, 436, and 365 nm over a period of 3 h [(–)-**2**, 102.5 °C], 31 min [(–)-**2**, 132.0 °C], and 42 min [(+)-**2** 123.5 °C]. All racemization (interconversion) experiments were controlled at the end of the racemization with a racemic reference sample (±)-**2** in addition to analytical thin-layer chromatography (silica gel F_{160}, Merck, $CHCl_3$/toluene, 20:1).

Registry No. (±)-1, 90970-18-6; (−)-1, 91049-37-5; (+)-1, 91049-38-6; (±)-2, 90970-19-7; (+)-2, 91049-39-7; (−)-2, 91049-40-0; (±)-4, 90970-20-0; (±)-5, 90970-21-1; 14, 90970-22-2; 15, 90970-23-3; Ia, 90970-24-4; Ib, 90970-25-5; IIa, 90970-26-6; IIb, 90970-27-7; *m*-$(CH_2Br)_2C_6H_4$, 626-15-3; *m*-HOC_6H_4SH, 40248-84-8; CsOH, 21351-79-1.

Supplementary Material Available: X-ray data for 1 and 2 (11 pages). Ordering information is given on any current masthead page.

Total Synthesis of (±)-Dysidin, a Marine Metabolite Containing an *N*-Acyl-*O*-methyltetramic Acid

Paul G. Williard* and Stephen E. de Laszlo

Department of Chemistry, Brown University, Providence, Rhode Island 02912

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The total synthesis of racemic dysidin (3), a unique halogenated marine natural product, is described. This compound along with its diastereomer was prepared by N-acylation of the (±)-5-isopropyl-4-*O*-methyltetramic acid (5) with (±)-(*E*)-5-methyl-3-methoxy-6,6,6-trichloro-2-hexenoic acid (4). Separation of the diastereomers 3 and 18 was effected by fractional crystallization.

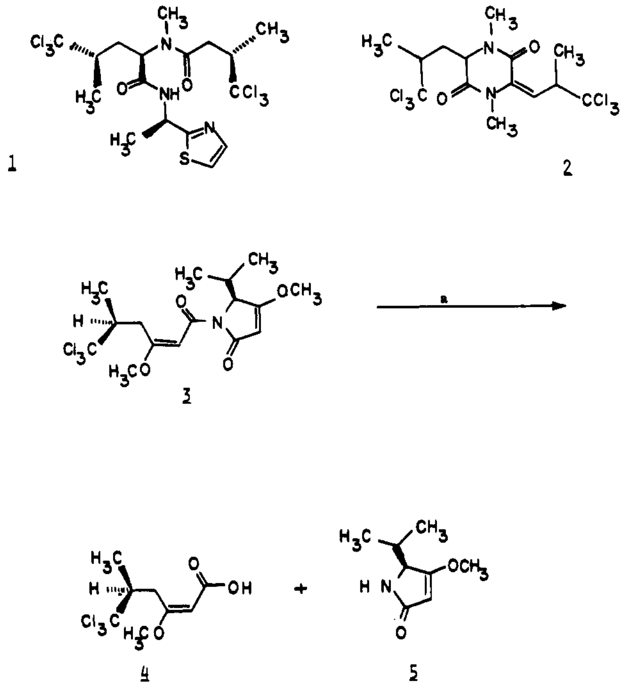
Introduction

At least 15 secondary metabolites have been isolated from the Indopacific sponge, *Dysidea herbacea*.[1] These metabolites belong to a wide variety of structural types including polybrominated diphenyl ethers,[2] nonhalogenated terpenes,[3] and a series of unique polychlorinated metabolites derived from amino acid precursors.[4] Examples of compounds belonging to this latter category are dysidenin (1),[3a] the diketopiperazine 2,[3b] and dysidin (3).[4b] Compounds 1, 2, and 3 pose an interesting synthetic challenge because of the inclusion of a trichloromethyl group in their skeletons. As far as we know, the three natural products 1–3, along with some desmethyl analogues and a diastereomer of 1, are the only naturally occurring compounds which contain the trichloromethyl functionality. In the present study we wish to report the first total synthesis of one of these natural products, namely dysidin (3).

Results and Discussion

During the structure elucidation, it had been shown that basic hydrolysis of dysidin (3) leads to compounds 4 and 5 via scission of the *N*-acyl bond of 3.[4b] This is also a convenient retrosynthetic dissection. A convergent synthesis of 3 from the two fragments 4 and 5 was completed by us.

Scheme I[a]



[a] (a) NaOH.

Preparation of 4. The trichloromethyl group is introduced as early as possible in our synthesis because this group is relatively inert. Thus a convenient starting material is the diastereomeric mixture of 2-bromo-3-methyl-4,4,4-trichlorobutyric acids (6) formed by the radical chain addition of bromotrichloromethane to crotonic acid. The regiochemistry of this addition is similar to the addition of bromotrichloromethane to ethyl crotonate.[5] Treatment of the diastereomeric acids (6) with activated zinc leads to a vigorous, spontaneous reaction. This zinc reduction gave 3-methyl-4,4,4-trichlorobutyric acid (7) in 65% overall yield from crotonic acid.

When the acid chloride 8 was dissolved in methylene chloride and treated with slightly less than 1 equiv of Meldrum's acid[6] and pyridine, the formation of 9 occurred

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(1) For a discussion of the difficulties associated with the chemotaxonomy associated with marine sponges and in particular with the variation of metabolites obtained from *D. herbacea*, see: Bergquist, P. R.; Wells, R. J. In "Marine Natural Products, Chemical and Biological Perspectives"; Scheuer, P. J., Ed.; Academic Press: New York, 1983; Vol. V, pp 1–50.

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