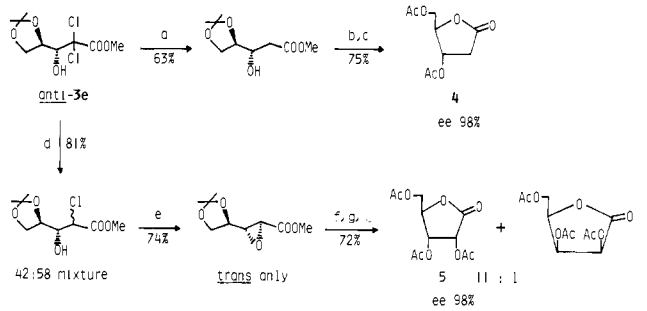
Scheme I[a]



[a] (a) +e, 0.3 A, 6F/mol, 0.2 M Me_4NCl/90% MeOH; (b) TFA, room temperature, 2 h; (c) Ac_2O/pyridine, room temperature, 3 h; (d) +e, 0.3 A, 3F/mol, 0.2 M NH_4NO_3/90% MeOH; (e) MeONa/MeOH, room temperature, 2 h; (f) KOH/H_2O-dioxane, reflux, 6 h; (g) dilute HCl, room temperature, 2 h.

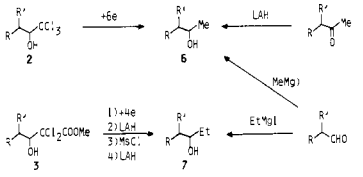
common chemical methods, the stereochemistry of the addition of this anion to aldehydes is hitherto unknown.[10] The easy electroreductive generation of dichloro(methoxycarbonyl)methyl anion and the almost exclusive formation of anti isomers from **1e**,**f**[12] are highly useful for the stereoselective synthesis of carbohydrates as exemplified by the syntheses of di-*O*-acetyl-2-deoxy-D-ribono-1,4-lactone (**4**) and tri-*O*-acetyl-D-ribono-1,4-lactone (**5**) from *anti*-**3e** (Scheme I).

(10) The addition of a zinc enolate to **1e** has been shown to be less selective than our results.[11]

(11) Murakami, M.; Mukaiyama, T. *Chem. Lett.* **1982**, 1271.

(12) (a) Fischer, H.; Baer, E. *J. Biol. Chem.* **1939**, *128*, 463. (b) English, J., Jr.; Griswold, P. H., Jr. *J. Am. Chem. Soc.* **1948**, *70*, 1390.

(13) The ratio was determined by ^1H NMR. In the compounds **2a-d** and **3a,b,d**, the chemical shifts of protons located on the carbon atom having a hydroxy group were as follows: **2a**, δ(syn) 3.96 (d, J = 2 Hz), δ(anti) 3.88 (d, J = 3 Hz); **2b**, δ(syn) 3.96 (br s), δ(anti) 3.85 (d, J = 6 Hz); **2c**, δ(syn) 4.15 (br s); **2d**, δ(syn) 4.21 (d, J = 2.5 Hz), δ(anti) 4.13 (d, J = 3 Hz); **3a**, δ(syn) 4.21 (d, J = 3 Hz), δ(anti) 4.10 (d, J = 6 Hz); **3b**, δ(syn) 4.30 (d, J = 6 Hz); **3d**, δ(syn) 4.47 (d, J = 6 Hz). The stereoconfiguration was determined by GLC analysis according to the reported methods.[14] Thus, **2** and **3** were transformed to alcohols **6** and **7**, respectively, and the retention time

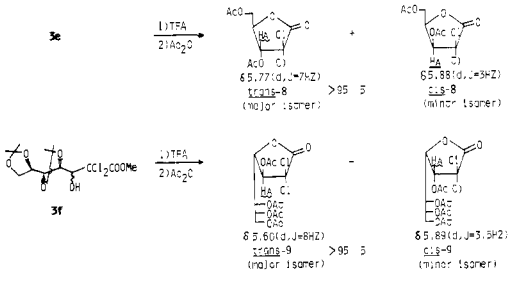


of each of these alcohols was compared with that of the authentic samples prepared by LAH reduction of ketones and the Grignard reaction of aldehydes. Since syn and anti isomers of each of the alcohols clearly showed different retention time, the stereoconfiguration could easily be identified.

(14) (a) Gault, Y.; Felkin, H. *Bull. Soc. Chim. Fr.* **1964**, 742. (b) Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828.

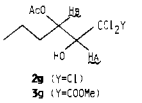
(15) The ratio was determined by isolation of each isomer with column chromatography on silica gel. The stereoconfiguration was confirmed by conversion of the products to known sugar compounds. Major isomers of **2e** and **2f** were identified to be anti isomers through their transformation to erythrose and mannose, respectively, by our previously reported method.[8] On the other hand, minor isomers gave threose and glucose suggesting that their configurations were syn.

(16) The ratio was determined by ^1H NMR of *O*-acetylated γ-lactones **8** and **9**, which were derived from **3e** and **3f**, respectively. The proton (H_A)

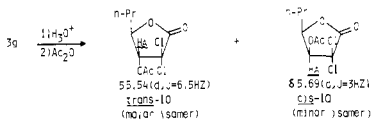


located on C-3 carbon of **8** and **9** showed two sets of doublets in the ratio of >95:5. The formation of di-*O*-acetyl-2-deoxy-D-ribono-1,4-lactone (**4**) from the major isomer of **3e** clearly showed that it was the anti isomer. The high similarity of the ^1H NMR of H_A of **8** with **9** suggested that the major isomer of **9** had a trans configuration at C-3 and C-4 positions. Hence, the major isomer of **3f** was assigned to be anti.

(17) The ratio was determined by ^1H NMR: **2g**, δ(syn, minor) 3.93 (br s, H_A), 5.55 (t, H_B, J = 7 Hz), δ(anti, major) 4.14 (d, H_A, J = 5 Hz), 5.29 (d t, H_B, J = 5, 8 Hz); **3g**, δ(syn, minor) 4.30 (br s, H_A), 5.49 (t, H_B, J = 7 Hz), δ(anti, major) 4.45 (d, H_A, J = 7 Hz), 4.95-5.22 (m, H_B). The fact



that the major isomer of **3g** was anti was suggested by comparing the ^1H NMR of H_A of *O*-acetylated γ-lactone **10** derived from **3g** with that of **8**. The



reasonable correlation of the ^1H NMR of **2g** with that of **3g** supported that the major isomer of **2g** was anti.

Synthesis of Macrocyclic Trichothecanoids: Baccharin B5 and Roridin E

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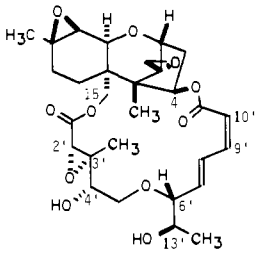
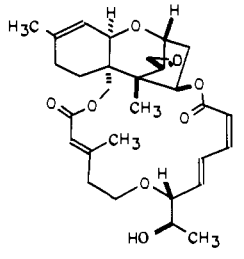
Received August 1, 1983

For the past few years, we have been investigating the synthetic opportunities afforded by the conformational preferences of macrocyclic compounds. One of the natural products under study in this context is the highly oxygenated trichlothecanoid baccharin B5 (**I**).[1] This stereochemically interesting compound is a potent antileukemic (T/C > 200) and is now being isolated in large quantities from a Brazilian shrub, *Baccharis megapotamica*, by NIH for evaluation as a chemotherapeutic agent. Baccharin is among the most complex of the roridin class of macrocyclic trichothecanoids whose simpler members include compounds such as roridin E (**2**).[2] Described here are the first[3] syntheses of



1



2

naturally occurring roridins in the form of syntheses of **1** and **2** starting from verrucarol and D-xylose. Of particular interest is the use of an achiral C1′-C5′ precursor and the establishment

(1) Kupchan, S. M.; Jarvis, B. B.; Dailey, R. G.; Bright, W.; Bryan, R. F.; Shizuri, Y. *J. Am. Chem. Soc.* **1976**, **98**, 7092. Kupchan, S. M.; Streelman, D. R.; Jarvis, B. B.; Dailey, R. G.; Sneeden, A. T. *J. Org. Chem.* **1977**, *42*, 4221. Jarvis, B. B.; Stahly, G. P.; Pavanasasivam, G.; Mazzola, E. P. *J. Med. Chem.* **1980**, *23*, 1054.

(2) Traxler, P.; Zurcher, W.; Tamm, Ch. *Helv. Chim. Acta* **1970**, *53*, 207. Matsumoto, M.; Minato, H.; Tori, K.; Ueyama, M. *Tetrahedron Lett.* **1977**, 4093.

(3) Previous synthetic work on the roridins: Tulshian, D. B.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1981**, *103*, 474. Roush, W. R.; Spada, A. P. *Tetrahedron Lett.* **1982**, 3773. Esmond, R.; Fraser-Reid, B.; Jarvis, B. B. *J. Org. Chem.* **1982**, *47*, 3358.

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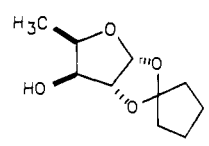
of chiral centers on that segment using the conformational structure of an 18-membered roridin-like macrocycle for stereochemical control.

Our basic approach to the macrocycle entailed the use of D-xylose as a source of the C6′,C13′ asymmetric centers and then the use of the conformational properties of an intermediate macrolide (**7**) to control the remaining centers at C2′–C4′.

D-Xylose was first treated with cyclopentanone ($CuSO_4$, catalytic H_2SO_4), and resulting crystalline diketal was selectively hydrolyzed (0.2% HCl, THF–H_2O), monotosylated (*p*-TsCl, C_5H_5N), and reduced ($LiAlH_4$) to give the required C6′,C13′ synthon **3** (65% overall).[4]

The achiral C1′–C5′ segment was prepared from the *t*-BuMe_2Si ether of 3-butyn-1-ol by ethoxycarboxylation (a, *n*-BuLi; b, ClCOOEt), conjugate methylation (Me_2CuLi, Et_2O),[5] and reduction ($LiAlH_4$) in 45% overall yield. Conversion to the chloride (NCS, Me_2S)[6] and coupling with the sodium salt of **3** (THF–HMPA, catalyst Bu_4NI) was followed by desilylation (Bu_4NF, THF) and Jones oxidation to give the required acid **4** (70–75% overall).



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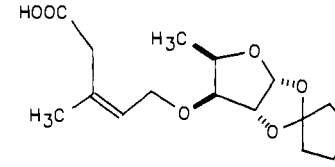

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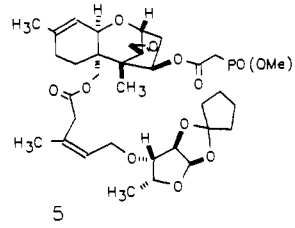
The primary C15 hydroxyl of verrucarol[8] was esterified selectively (95% yield at 55% conversion) by use of 1 equiv of **4** with dicyclohexylcarbodiimide (DCC) and 0.1 mol % 4-pyrrolidinopyridine (4-pp).[7] The C4 appendage was then added as (dimethoxyphosphinyl)acetic acid (2 equiv, DCC and 4-pp) under more vigorous conditions to yield the desired phosphono ester **5** quantitatively. Removal of the cyclopentylidene group (0.1 M TsOH, 1:3 H_2O–HOAc) produced a diol, which was cleaved ($NaIO_4$, THF–H_2O), deformylated (Et_3N, MeOH), and treated with excess (formylmethylene)triphenylphosphorane (toluene, 25 °C, 40 h). The resulting α,β-unsaturated aldehyde was formed in 60–65% overall yield as a 4:1 *E*:*Z* mixture. Although we were unable to increase the selectivity for the desired *E* isomer **6**, the contaminating *Z*-unsaturated aldehyde was readily removed by flash chromatography.



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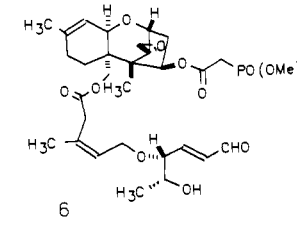

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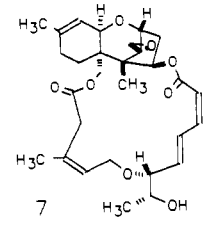

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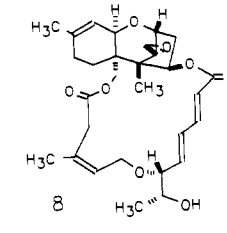
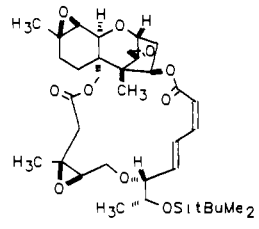


8

Macrocylization was accomplished using finely ground K_2CO_3 and 18-crown-6 in toluene (−20 to >0 °C) and led to a 1.5:1 mixture of (*E*,*Z*)- and (*E*,*E*)-macrolides (**7** and **8**) in 75% yield.[9] Prolonged reaction times or more vigorous cyclization conditions gave higher **7**:**8** ratios, but the improved stereoselectivity resulted only from selective destruction of **8**. Alternative cyclization of an analogous triphenylphosphonium ylide led largely to the undesired isomer **8**. Macrolides **7** and **8** were widely separated on TLC and the *E*,*E* byproduct was readily removed by flash chromatography to give the desired (*E*,*Z*)-dienoate **7** in 45% isolated yield. While selectivity for the required *E*,*Z* isomer was low, it may be compared to an analogous acyclic Horner–Emmons reaction which shows a 3.5:1 preference for the *E*,*E* product when (*E*)-hexenal is reacted with cyclohexyl (dimethoxyphosphinyl)-acetate under our macrocylclization conditions.

Conversion of **8** to roridin *E* (**2**) was effected by treatment with potassium *tert*-butoxide in isopropyl alcohol. These conditions resulted in smooth conjugation of the C3′=C4′ olefin to yield a single product (70%) that was indistinguishable from a sample of natural roridin E kindly provided by Professor Bruce Jarvis of the University of Maryland. This conversion establishes the disputed configuration of C13′ as *R*.[10] While the high stereoselectivity of this olefin isomerization is also noteworthy, it is likely to be a result of a local steric interactions rather than of conformational perturbations by the macrocycle.

After protection of the C13′ hydroxyl as the *t*-BuMe_2Si ether (*t*-BuMe_2SiOTf, lutidine; >95%), silyl-**8** was treated with *m*-chloroperbenzoic acid in benzene (25 °C, 4 h) and a single triepoxide, **9**, was formed (70%). The stereoselection measured by



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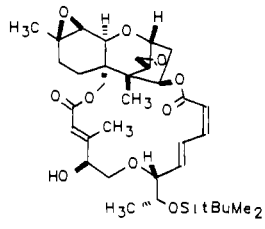

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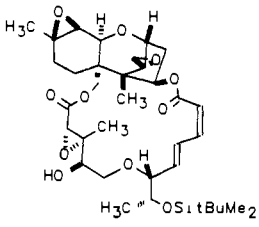

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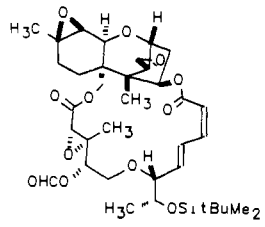

response-calibrated HPLC was >15:1 both for both the nuclear epoxide and for the macrocyclic C3′–C4′ epoxide. The reaction is notable in that it cleanly establishes four new asymmetric centers of which two appear to be controlled by the conformation of the macrocycle.

Elimination of the C3′–C4′ epoxide using potassium *tert*-butoxide in isopropyl alcohol (−25 °C, 2 h) provided a 90% yield of the desired *E*-2′,3′-unsaturated lactone **10** as the sole product. Allylic alcohol epoxidation (*t*-BuOOH, $VO(acac)_2$, CH_2Cl_2, 25 °C)[11] then produced a single epoxide **11** in 90% yield having the natural stereochemistry at C2′ and C3′. The final operation of C4′ inversion was conducted by a Mitsunobu reaction[12] using

(4) Cf.: Baker, B. R.; Schaub, R. E. *J. Am. Chem. Soc.* **1955**, *77*, 5900.
(5) Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851.
(6) Corey, E. J.; Kim, C. U.; Takeda, M. *Tetrahedron Lett.* **1972**, 4339.
(7) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522. Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, 4475.
(8) From anguidine (Tulshian, D. B.; Fraser-Reid, B. *Tetrahedron Lett.* **1980**, 4549) or by fermentation of *M. verrucaria* (ATCC 24751, Strain UV-2) (fermentation/isolation procedure by: Jarvis, B. B. University of Maryland, private communication).
(9) Cf.: Burri, K. F.; Cardone, R. A.; Chen, W. Y.; Rosen, P. *J. Am. Chem. Soc.* **1978**, *100*, 7069. Stork, G.; Nakamura, E. *J. Org. Chem.* **1979**, *44*, 4010. Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A.; *Ibid.* **1979**, *44*, 4011. Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2030. Horner-Emmons with K_2CO_3/crown: Aristoff, P. A. *J. Org. Chem.* **1981**, *46*, 1954. Aristoff, P. A. *Synth. Commun.* **1983**, *13*, 145.
(10) Jarvis, B. B.; Midiwo, J. O.; Flippen-Anderson, J. L.; Mazzola, E. P. *J. Nat. Prod.* **1982**, *45*, 440.
(11) Rossiter, B. E.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett.* **1979**, 4733.

formic acid (Ph_3P, DEAD, C_6H_6; >90% yield based on consumed starting material), although the reaction could not be pressed beyond 40% conversion. The product was quantitatively converted to baccharin B5 (**1**) by deformylation/desilylation with Bu_4NF/THF. Our synthetic material was identical by all the usual criteria including ^{13}C NMR with a sample of the natural **1** generously supplied by Dr. Matthew Suffness of NIH and Dr. Fred Boettner of Polysciences.

The synthesis of baccharin described here is an application of macrocyclically controlled remote asymmetric induction to complex natural product synthesis. It not only provides a simple route to the baccharinoids but also illustrates that potential of remote asymmetric induction strategies in organic synthesis.[13]

Supplementary Material Available: Full NMR, IR, and mass spectral data for compounds **3**–**11** (7 pages). Ordering information is given on any current masthead page.

(12) Review: Mitsunobu, O. *Synthesis* **1981**, *1*.
(13) This work was supported by NIH Grant GM32598.

Crystal Structures of Azoarene-Capped Analogues of 1,10-Diaza-4,7,14,17-tetraoxa- and 1,10-Diaza-4,7,14,17-tetrathiacyclooctadecane. Comparison of C–O and C–S Bond Conformations in Capped Crown Analogues

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Seiji Shinkai,*[2] and Yoshihiro Honda[2]

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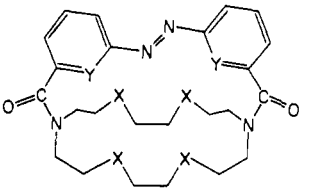
Received July 18, 1983

Macropolycyclic polyethers contain intramolecular cavities lined with molecular segments capable of binding cations in three-dimensional cagelike structures. The Azoarene-capped O and S crown ethers (e.g., **1**–**3**) undergo photoinduced reversible inter-



1, X = O; Y = N
2, X = S; Y = N
3, X = S; Y = CH

conversion between the trans and cis azo linkages, resulting in substantial changes in their cation binding properties.[3] The X-ray structures of the azopyridine-capped analogue of 1,10-diaza-18-crown-6 (**1**) and the azobenzene-capped sulfur analogue (**3**) have been determined as a step in understanding how ion selectivity and binding are controlled by the cavity structure. The conformations of the crown rings in **1** and **3** are substantially different from those of the "free" analogues, the latter containing the first example of the C–S anti conformation in a thiacrown macrocycle.

X-ray quality crystals of **2** could not be obtained. X-ray data: Picker FACS-I diffractometer, graphite monochromator, Cu Kα λ = 1.5418 Å; 2θ–θ intensity scan, 10-s backgrounds, 2θ = 126°.

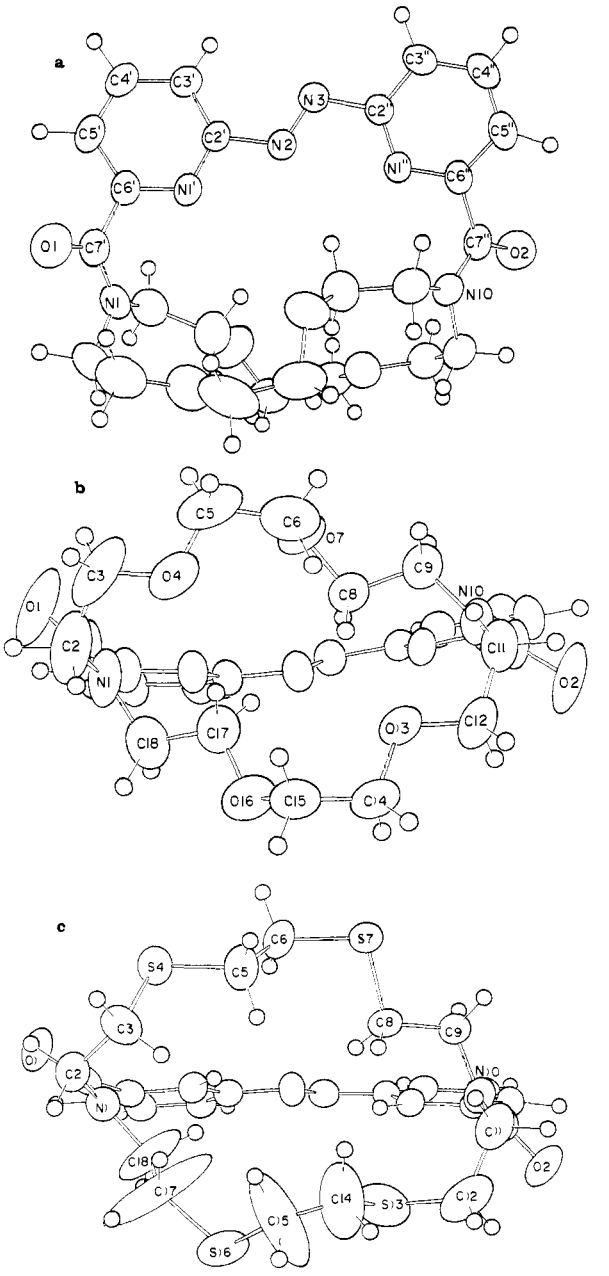


Figure 1. ORTEP drawings of **1** and **3**. The C, N, O, and S atoms are illustrated as 50% probability ellipses, and the H atoms are 0.1-Å radius circles. (a) **1** viewed perpendicular to the azopyridine moiety. (b) **1** viewed parallel to the azopyridine moiety. (c) **3** viewed parallel to the azobenzene moiety.

Crystal data: **1**, $C_{24}H_{30}N_6O_6$, M_r 498, 0.033 × 0.26 × 0.41 mm crystal (toluene), $C2/c$, a = 43.126 (4) Å, b = 7.9747 (4) Å, c = 14.367 (1) Å, β = 93.45 (2)°, Z = 8, ρ_{Xray} = 1.341 g cm^{-3}, 3995 unique reflections, 2936 with $I > 3\sigma(I)$; **3**, $C_{26}H_{32}N_4O_2S_4$, M_r = 560, 0.3 × 0.20 × 0.25 mm crystal (methylene chloride–chlorobenzene), $P2_1/a$, a = 10.766 (1) Å, b = 23.552 (2) Å, c = 11.569 (1) Å, β = 111.057 (4), Z = 4, ρ_{Xray} = 1.361 g cm^{-3}, 4431 unique reflections, 2873 with $I > 3\sigma(I)$. Block-diagonal, least-squares refinement of $\sum w(F_o - F_c)^2$, $w = 1/\sigma^2(F)$. Final $R(\sum|F_o - F_c|/\sum F_o)$ and weighted R ($[\sum w(F_o - F_c)^2/\sum wF_o^2]^{1/2}$) values are 0.052 and 0.051 for **1** and 0.076 and 0.057 for **3**[4] (atomic coordinates and temperature factors are given in the supplementary material).

(1) University of Maryland.
(2) Nagasaki University.
(3) Shinkai, S.; Nakaji, T.; Nishida, Y.; Ogawa, T.; Manabe, O. *J. Am. Chem. Soc.* **1980**, *102*, 5860–5865. Shinkai, S.; Kouno, T.; Kusano, Y.; Manabe, O. *J. Chem. Soc., Perkin Trans. 2* **1982**, 2741–2747.
(4) UNIVAC 1100/82 computer. Crystallographic programs: Stewart, J. M.; Machin, P. A.; Dickinson, C.; Ammon, H. L.; Heck, H. S.; Flack, H. The X-ray 76 System of Crystallographic Programs, Tecnical Report 446, 1976, Computer Science Center, University of Maryland, College Park, MD.

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