thank the Orscheln foundation of Moberly Missouri for the purchase of the Hewlett-Packard 5890 GCMS with a computer work station.

Registry No. 1, 123381-63-5; Na-*p*-ClNMBHA, 123381-62-4; Sanger's reagent, 70-34-8; *O*-phenylhydroxylamine hydrochloride, 6092-80-4; *O*-phenylbenzohydroxamic acid, 4380-77-2.

Supplementary Material Available: Tables of positional and thermal parameters, hydrogen atom positions, and anisotropic thermal parameters (3 pages). Ordering information is given on any current masthead page.

Synthesis of Chiral 2,6-Dithiabicyclo[3.1.1]heptane. The Dithia Parent Analogue of the TXA_2 Nucleus[1]

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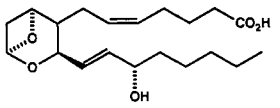
Thromboxane A_2 (TXA_2), a potent blood platelet aggregating component of the arachidonic acid cascade, is thought to play a central role in many pulmonary–cardiovascular disorders.[2] Until recently,[3] the chemical

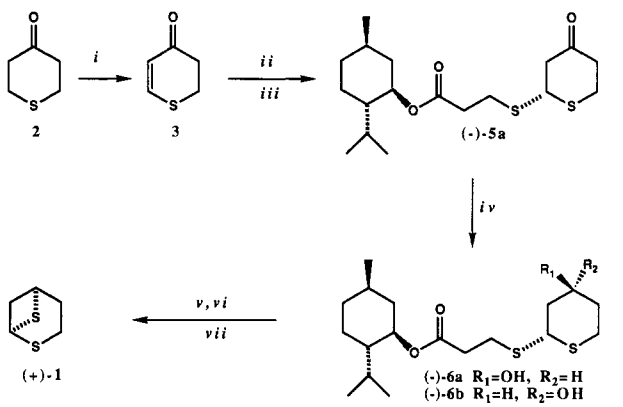


TXA_2

1

structure of this labile natural product remained uncertain, and in order to further the understanding of its biochemical and chemical properties, efforts have been made to synthesize more stable analogues or derivatives.[4] Although computer calculations have been carried out on the parent and on sulfur-substituted model analogues of the bicyclic oxetane ring system,[5] the synthesis of these unadorned heterocyclic compounds has not been described. Since ring substitution on heterocycles greatly adds stability toward ring opening and polymerization,[6] the synthesis of TXA_2[3] itself and, as well as, other ring-substituted heteroatom analogues have been published.[4] Since the bicyclic ring moiety is reported to be a prerequisite for the biochemical activity in TXA_2,[3] we felt it useful to try to prepare, by Ohuchida et al.[4a] methodology, the (less strained by 10.5 kcal/mol; MMX[7] calculation) parent nucleus 1 to see if

Scheme I[a]



[a] (i) NCS/pyridine/CH_2Cl_2/0 °C; (ii) (–)-4/*i*-$PrNEt_2$/DMF; (iii) hexanes/–10 °C; (iv) LS-Selectride/THF/–78 °C; (v) chromat (silica); (vi) MsCl/Et_3N/CH_2Cl_2/0 °C; (vii) $(Me_3Si)_2NLi$/THF/reflux 2 h.

any of the reported properties of the more fully elaborated sulfurated derivative of TXA_2[4] are retained in this simple system.

Thus, the synthesis of (+)- or (–)-1 was accomplished in seven steps, from commercially available 4-thiapyrone 2 (Scheme I).[4a,8b] Conversion of 2 into the unsaturated derivative 3 by treatment with 1 equiv of NCS and pyridine in CH_2Cl_2 at 0 °C followed by base-catalyzed (*i*-$PrNEt_2$)[4a,8a] Michael type addition of optically pure menthol mercapto ester (–)-4[8b] ($[\alpha]^{23}_D$ –70.4° (*c* = 1.0, MeOH)), prepared from *l*-menthol esterification of 3-mercapto propionic acid, in DMF quantitatively afforded the diastereomeric mixture (–)-**5a** and (–)-**5b** with the anticipated anomeric selectivity in excess of 95% (determined by 400-MHz ^1H NMR spectroscopy).[8b]

Fractional crystallization (hexanes, –10 °C) afforded pure (–)-**5a** in 25% overall yield from 2. Reduction (LS-Selectride in THF at –78 °C) of (–)-**5a** gave no better than a 2:1 mixture of the epimeric alcohols (–)-**6a**[8b] and (–)-**6b**[8b] in 80% yield. Chromatographic separation of (–)-**6a** from (–)-**6b** on silica and mesylation of the free hydroxy group followed by treatment with $(Me_3Si)_2NLi$ in THF (at reflux for 2 h) afforded, after workup and sublimation of the resulting crude residue, (+)-2,6-dithiabicyclo[3.1.1]heptane [mp 44–45 °C, $[\alpha]^{23}_D$ +84.8° (*c* = 0.24, $CHCl_3$)] in 40% yield. Similarly, using *d*-menthol, the (–) enantiomer[8b] [mp 42–43 °C, $[\alpha]^{23}_D$ –101.5° (*c* = 2.64, $CHCl_3$)] was also obtained in 40% yield.

The chemistry of 1, as expected, is dominated by the strain in the bicyclic thietane moiety. For example, in the presence of a nucleophile such as a catalytic amount of benzyl mercaptan, the four-membered ring readily transsulfurates to the benzyl thiolated derivative 7. Loss of benzyl mercaptan then gives dihydrothiapyran, 8, which can also participate in the further addition–elimination processes that ultimately lead to the complex mixture of unsaturated thiapyran derivatives observed (^1H NMR, eq

(1) Dedicated to Prof. E. C. Taylor on the occasion of his 65th birthday.

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(7) Obtained from Serena Software, P.O. Box 3076, Bloomington, IN 47402-3076.

(8) (a) Casy, G.; Lane, S.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1397. (b) All new compounds had satisfactory combustion analyses and or high-resolution mass spectra. Optical purity is based on successive fractional crystallizations and comparison of the rotations to the enantiomers. The variance of the optical rotation between (+)-1 and (–)-1 is due to the polymerization and decomposition of the compound during recrystallization. (+)-4: R_f (20% ether/pentane) 0.50; mp 34 °C; $[\alpha]^{23}_D$ +70.8° (*c* = 1.0, EtOH); ^1H NMR ($CDCl_3$) δ 0.7–1.7 (19 H, m), 2.6–2.8 (4 H, m), 4.7 (1 H, dt, J_1 = 10.6 and J_2 = 4.4 Hz); ^{13}C NMR ($CDCl_3$) δ 170.6, 74.2, 46.6, 40.6, 38.5, 33.9, 31.0, 25.9, 23.1, 21.6, 20.4, 19.5, 16.0. (–)-4: mp 34 °C; $[\alpha]^{23}_D$ –70.3° (*c* = 1.0, EtOH).

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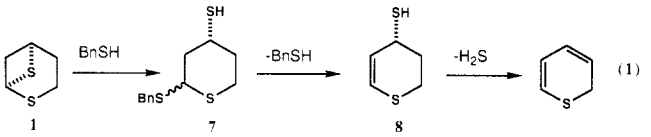
1). The ease by which this type of trans-sulfurization occurs may be an important contributing factor to the



(1)

antimicrobial activity that we have observed with certain strained disulfides.[9a] Even though **1** is not an S–S bonded disulfide, the strained dithiaketal functionality, nonetheless, permits trans-sulfurization to occur. Unfortunately, no antimicrobial activity against several of the common bacterial or viral strains could be noted.[9b] Further, the compound is also void of any platelet aggregating properties as well as lipoxygenase inhibition.[9b] Since the fully elaborated congener[4a] is active, it suggests that the side chains of TXA_2 are also important for biochemical activity.

Experimental Section[8b]

2-[[2-[(Menthyloxy)carbonyl]ethyl]thio]thiacyclohexan-4-one [(−)-5a]. To a solution of dihydrothiin-4-one (0.627 g, 5.5 mmol) and *l*-3-menthyl mercaptopropionate (4.026 g, 16.5 mmol) in dry DMF (18 mL) was added 0.19 mL (1.1 equiv) of *i*-$PrNEt_2$ under an atmosphere of argon. After stirring for 15 h, the solvent was removed under reduced pressure, and the residue was chromatographed on silica (1:5 EtOAc/hexanes) to give 1.8 g of a colorless oil. The oil was dissolved in hexanes and placed in the freezer (−20 °C). After 2 days, the crystals formed were collected and recrystallized to give 0.23 g (25% yield) of (−)-**5a**: R_f (13% EtOAc/hexanes) 0.18; mp 49–50 °C; $[\alpha]^{23}_D$ −225.16° (*c* = 0.89, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.7–0.9 (18 H, m), 2.1–3.0 (10 H, m), 4.4 (1 H, dd, *J* = 5.0 Hz), 4.7 (1 H, dt, J_1 = 10.56 and J_2 = 4.4 Hz); ^{13}C NMR ($CDCl_3$) δ 204.9, 170.7, 74.3, 49.1, 48.0, 46.6, 42.8, 40.6, 34.5, 33.9, 31.0, 27.0, 26.0, 25.8, 23.2, 21.7, 20.4, 16.1. Enantiomer (+)-**5a** was similarly obtained from *d*-menthol: mp 50–51 °C; $[\alpha]^{23}_D$ +223.58° (*c* = 1.0, EtOH).

2-[[2-[(Menthyloxy)carbonyl]ethyl]thio]thiacyclohexan-4-ol [(−)-6a]. To a solution of (−)-**5a** (0.25 g, 0.7 mmol) in dry THF (20 mL) kept at −78 °C under an atmosphere of argon was added dropwise 1.3 equiv of a 1 M THF solution of LS-Selectride. The mixture was stirred at −78 °C for 2 h and then quenched with 10 mL of a saturated aqueous solution of NH_4Cl. Ethyl acetate (30 mL) was added at ambient temperature, and the mixture was transferred to a separatory funnel. The organic phase was separated, washed with 2 × 20 mL of brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica (1:6 EtOAc/toluene) to give an 80% overall yield of the two isomeric alcohols, (−)-**6a** and (−)-**6b**. (−)-**6a**: R_f (1:7 EtOAc/benzene) 0.18; mp 66–67 °C; $[\alpha]^{23}_D$ −213.56° (*c* = 0.5, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.7–2.20 (23 H, m), 2.63–3.08 (6 H, m), 4.0–4.15 (1 H, m), 4.18–4.30 (1 H, dd, *J* = 4.84 Hz), 4.50–4.80 (1 H, dt, J_1 = 10.56 and J_2 = 4.4 Hz). (−)-**6b**: R_f (1:7 EtOAc/benzene) 0.11; mp 81–82 °C; $[\alpha]^{23}_D$ −95.4° (*c* = 0.50, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.72–2.20 (23 H, m), 2.63–2.99 (6 H, m), 3.6–3.79 (1 H, m), 3.83–3.98 (1 H, dd, *J* = 10.27 Hz), 4.68–4.83 (1 H, dt, J_1 = 10.56 and J_2 = 4.4 Hz). Similarly, using the *d*-menthol mercapto ester ((+)-4),[8b] (+)-**6a** [mp 66–67 °C; $[\alpha]^{23}_D$ −211.40° (*c* = 0.50, EtOH)] and (+)-**6b** [mp 79–80 °C; $[\alpha]^{23}_D$ +92.74° (*c* = 0.5, EtOH)] were obtained.

2-[[2-[(Menthyloxy)carbonyl]ethyl]thio]-4-thiacyclohexane Mesylate. A mixture of 1.0 g (2.77 mmol) of (−)-**6a**, 1.2 mL (3 equiv) of Et_3N, and freshly distilled mesyl chloride (0.45 mL, 2 equiv) was stirred in 25 mL of dry CH_2Cl_2 under an atmosphere of argon at 0 °C. After 1 h, the mixture was transferred to a separatory funnel and washed with brine. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. The resulting residue was chromatographed on silica (1:6 EtOAc/toluene) to give the mesylate (95% yield) as a colorless oil: R_f (1:6 EtOAc/toluene) 0.43; $[\alpha]^{23}_D$ −95.40° (*c* = 0.50, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.72–2.17 (18 H, m), 2.63–2.99 (10 H, m), 3.03 (3 H, s), 4.21–4.32 (1 H, q), and 4.95–5.08 (1 H, m). From *d*-menthol, the corresponding (+) enantiomer was similarly obtained.

2,6-Dithiabicyclo[3.1.1]heptane [(+)-1].[4a] To a solution of the above mesylate (0.6 g, 1.8 mmol) in dry THF (20 mL) kept under an atmosphere of argon and at 60 °C was added dropwise 3.75 mL (3.75 mmol) of a 1 M THF solution of lithium hexamethyldisilazane. The reaction mixture was then refluxed for 2 h and allowed to reach ambient temperature, and the solvent was removed by rotary evaporation. The resulting residue was chromatographed on silica (1:9 ether/pentane) to give 0.09 g (37% yield) of a white solid, which was further purified by sublimation on to a cold finger (40 °C, 24 mmHg): R_f (10% ether/pentane) 0.42; mp 44–45 °C; $[\alpha]^{23}_D$ +84.8° (*c* = 0.24, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.24 (1 H, dd, *J* = 5.9 Hz), 4.03 (1 H, m), 3.84 (1 H, dt, J_1 = 9.6 and J_2 = 6.6 Hz), 3.45 (1 H, m), 2.93 (1 H, dd, *J* = 12.6 Hz), 2.52 (1 H, m), 2.3–2.4 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 23.06, 30.92, 44.65, 49.75, 50.56. The corresponding enantiomer was similarly obtained from *d*-menthol: mp 42–43 °C; $[\alpha]^{23}_D$ −101.5° (*c* = 2.64, $CHCl_3$).

Acknowledgment. We are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the Natural Sciences and Engineering Research Council of Canada for support of this work.

(9) (a) Stinson, S. *Chem. Eng. News* **1987**, February 9th, 23. (b) Racemic material was used. We would like to thank Drs. David Thomson and Geoffrey K. Richards of The Montreal General Hospital and Dr. Roy Johnson (Upjohn) for these results.

Renieramycins E and F from the Sponge *Reniera* sp.: Reassignment of the Stereochemistry of the Renieramycins

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A bright blue sponge of the genus *Reniera*, which has been found both at Isla Grande, Mexico, and some 14 200 km distant, in an obscure marine lake in Palau, Western Caroline Islands, was shown to contain a series of alkaloids that included renierone (**1**), mimosamycin (**2**), *N*-formyl-1,2-dihydrorenierone (**3**), the isoindole **4**, and renieramycins A-D (**5–8**).[1] A similar suite of metabolites that include mimosamycin (**2**), mimocin (**9**), and saframycins A (**10**), B (**11**), C (**12**), and S (**13**) were isolated after treatment of the culture medium of a streptothricin-producing strain of *Streptomyces lavendulae* no. 314 with sodium cyanide.[2] Striking similarities between renierone (**1**) and mimocin (**9**) and between the renieramycins **5–8** and saframycins **10–13** were noted. However, the stereochemistry assigned to the renieramycins **5–8**[1b] differed from that determined by X-ray analysis[2c] of saframycin C (**12**) at C-1, the point of attachment of the side chain.[3] In this paper we report

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(3) The absolute configuration of the renieramycins is unknown: they have been redrawn with the opposite absolute configuration to that in ref 1b in order to correspond with the saframycins.

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