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Synthesis and Enantiomeric Purity Determination of the Optically Active Epoxide Disparlure, Sex Pheromone of the Gypsy Moth

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Enantiomerically pure (+)-*cis*-7(*R*),8(*S*)-epoxy-2-methyloctadecane (disparlure, **1a**), the sex pheromone of *Porthetria dispar* (L.), has been synthesized in 12% yield by a five-step sequence of reactions. By the same technique, (−)-*trans*-**1** has been prepared in similar yield, $[\alpha]^{24}_D$ −23.6°. The sequence can be used to prepare *cis*- and/or *trans*-**1** in racemic or enantiomerically pure form. ^{13}C NMR of the immediate precursor to **1**, in the presence of chiral lanthanide shift reagent, allows the determination of its enantiomeric purity.

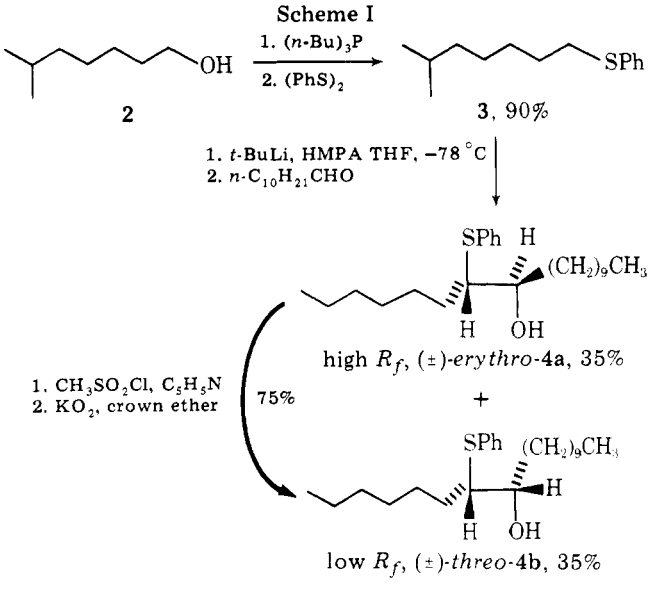
Disparlure (*cis*-7,8-epoxy-2-methyloctadecane, **1a**) has been identified as the sex pheromone of the gypsy moth, *Porthetria dispar* (L.),[1] a serious hardwood pest in the Northeast United States. Active investigation of chemical and biological means of controlling this insect have prompted several groups to devise syntheses for the racemate[2] and for optically active **1a**.[3,4] The dextro enantiomer (*cis*-7(*R*),-8(*S*)-epoxy-2-methyloctadecane) is significantly more active than is the racemate.[3a] Syntheses of optically active **1a** have either utilized optically pure natural products as starting materials[3] or have involved fractional crystallization-based resolutions of key chemical intermediates.[4] While some of the previously reported syntheses of optically active **1a** have proven to be long and have proceeded in low overall yield,[3] the approach used by Farnum et al.[4] is a considerable improvement in these regards.[5]

We have recently reported a procedure for the preparation of optically active epoxides[6] and herein demonstrate its applicability to the convenient preparation of disparlure of high enantiomeric purity from readily available starting materials.

Method of Synthesis. Scheme I illustrates the synthesis of disparlure precursor **4**. Initially, 6-methylheptanol (**2**) is converted in one high-yield step to 6-methylheptyl phenyl sulfide (**3**) using tri-*n*-butylphosphine and phenyl disulfide.[7] The α-thiolithio anion of **3** is added to undecanal to provide a 1:1 mixture of *erythro*- and *threo*-β-hydroxy sulfides, **4a** and **4b**. Although the chemical yield is less than quantitative (~70%), the unreacted portion of sulfide **3** is easily recovered during the chromatographic isolation of **4a** and **4b** and may be recycled. A certain amount of the inexpensive undecanal is lost to side reactions. Synthesis of alternate intermediates similar to **4** can be achieved using undecyl phenyl sulfide and 6-methylheptanal. While the yields are comparable, this alternative is less efficient, since now it is the less readily available 6-methylheptanal that is lost to side reactions.

The *erythro*- and *threo*-β-hydroxy sulfides (**4a** and **4b**, respectively) can be separated readily by liquid chromatography (neutral alumina, CH_2Cl_2–hexane 1:5),[8] the chromatogram (280 nm detection) providing visual evidence for the quality of the separation. The threo isomer **4b** is the precursor of the desired *cis*-epoxide.

Scheme I



Resolution of **4b** is also achieved by liquid chromatographic separation of the diastereomeric (*R*)-1-(1-naphthyl)ethyl isocyanate derived carbamates (**5a** and **5b**, Scheme II).[6] Again, the chromatogram provides visual evidence of the completeness of this facile separation, a matter relevant to the ultimate enantiomeric purity of the pheromone. Silanolysis[9] of the low R_f diastereomer, **5b**, provides (−)-**4b**. The silanolysis reaction is known to preserve the stereochemical integrity of the alcohol being retrieved from a diastereomerically pure carbamate.[9] After retrieval, (−)-**4b** was stereospecifically converted to disparlure by methylation followed by treatment with base (Scheme II). In this manner, (+)-**1a**, $[\alpha]^{24}_D$ +0.8°, was ob-

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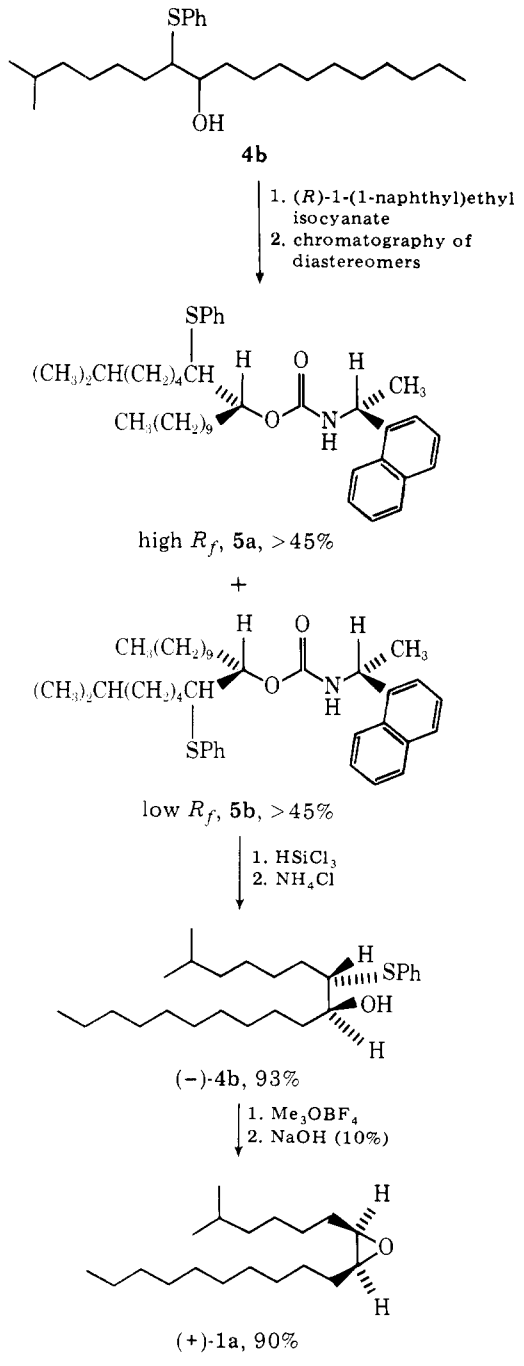
Scheme II



tained in 12% overall yield (from **2**).[10] The amount of disparlure afforded by the sequence can be further increased by inversion of *erythro*-**4a** to *threo*-**4b** using a sequence described by Corey et al.[11] In this instance, the inversion was found to proceed in 75% yield.

In a similar manner, *erythro*-**4a** was resolved via diastereomeric (*R*)-1-(1-naphthyl)ethyl isocyanate derived carbamates. The low R_f carbamate, after silanolysis,[9] methylation, and ring closure, yields (−)-*trans*-7(*S*),8(*S*)-epoxy-2-methyloctadecane, $[\alpha]^{24}_D$ −23.6°, in essentially the same overall yield as noted for the cis isomer. Rotations of −26.6 ± 0.8°,[3a] 27.6 ± 1.0°,[3a] and 22.2°[4] have been reported previously for this epoxide.

Enantiomeric Purity Determination. Since the alkyl substituents of disparlure are very similar, the molecule is effectively meso from most experimental viewpoints. Disparlure's optical rotation is extremely small (estimates from +0.2 to +0.7° have been cited for the optically pure material)[3,4] and it is hence difficult to determine the optical purity of synthetic samples by optical rotation. Likewise, our attempts to determine enantiomeric purity by utilizing chiral solvating agents and optically active lanthanide shift reagents in conjunction with ^1H and ^{13}C NMR were unsuccessful. However, we have been successful in estimating the enantiomeric purity of our synthetic disparlure from the enantiomeric composition of its immediate precursor, **4b**.

Table I. ^{13}C NMR Resonance Assignments of 4a, 4b, and 1a

carbon	δ (4 calcd)[b]	δ (4a)[c]	δ (4b)[c]	Δδ (4a−4b)[d]	δ (1 calcd)[b]	δ (1)
1	22.1	22.72	22.72		22.1	22.79
2	27.9	27.98	28.00		27.9	28.02
3	39.4	38.89	38.94		39.4	39.08
4	27.0	28.98	27.71	+0.27	27.0	27.01
5	27.7	27.31	27.31	+0.24	27.5	27.48
6		31.98	31.74	−0.41		28.02
7		57.45	57.86	−0.97		57.41
8		72.39	73.36	−1.08		57.41
9	35.5	33.28	34.36			28.02
10	26.5	26.26	26.00		29.2	29.72
11	30.2	29.65	29.67		30.0	29.72
12	30.0	29.65	29.67		30.0	29.72
13	30.0	29.65	29.67		30.0	29.72
14	30.0	29.65	29.67		30.0	29.72
15	29.8	29.41	29.43		29.7	29.72
16	32.2	31.98	31.98		32.2	32.08
17	22.7	22.72	22.72		22.7	22.79
18	13.9	14.13	14.15		13.9	14.16
1′		135.69	135.45	+0.24		
2′		132.15	132.52	−0.37		
3′		129.22	129.18			
4′		127.18	127.26			

[a] δ ($CDCl_3$) ± 0.02 ppm from Me_4Si, 100 mg/2 mL. [b] Calculated using formula described by L. P. Lindeman and J. Q. Adams, *Anal. Chem.*, **43**, 1245 (1971). [c] Assignments based on comparison with predicted chemical shift values, peak intensities, and in some instances SFORD. [d] Observed chemical shift nonequivalence (δ (**4a**) − δ (**4b**)) for a mixture of 80% **4b** and 20% **4a**.

The ^{13}C NMR resonances of **4a** and **4b** are presented in Table I. Although overlapping signals prevent accurate measurement of diastereomeric purity for **4a** and **4b** with ^1H NMR, ^{13}C spectra unambiguously provide this information. The ortho and ipso ^{13}C resonances of diastereomers **4a** and **4b** (as well as C-7 and C-8 resonances) show enough chemical shift difference to permit determination of diastereomeric purity. Thus, the completeness of the chromatographic separation of **4a** and **4b** can be gauged not only by the appearance of the chromatogram but also by ^{13}C NMR.

Examination of the ^{13}C NMR spectrum of racemic disparlure precursor **4b** in the presence of a chiral lanthanide shift reagent (CLSR) revealed nonequivalent resonances for the aromatic ipso and ortho carbons of the enantiomers (Figure 1). Similarly, nonequivalence can be observed for the ipso and ortho carbon resonances of **4a**. Since the ring closure sequence has been noted to be totally stereospecific, the enantiomeric composition of the product should correspond to that of the precursor **4b**. By this ^{13}C-CLSR criterion, the precursor **4b** was of such enantiomeric purity that the minor enantiomer could not be detected. We reiterate that the chromatographic separation of the diastereomers provides evidence of complete separation and that the subsequent steps are known to preserve stereochemical integrity. Thus, the presumption is that our synthetic disparlure is of essentially complete enantiomeric purity.

In conclusion, this route offers an alternative approach to

that of Farnum et al.[4] for the synthesis of disparlure in high yield and enantiomeric purity. The reactions in the short sequence seem suitable for large-scale operation although such an operation has not been undertaken. Starting materials are readily available and inexpensive and the chromatographic separations required are so straightforward that they should be readily and conveniently attainable on a large scale. The reaction sequence can be modified to afford either the cis or trans isomers of **1** as the racemates or the enantiomerically pure materials. The enantiomeric composition of the immediate precursor of disparlure can be determined directly.

Experimental Section

General. Melting points were determined on a Büchi apparatus and are uncorrected. ^{1}H NMR spectra were recorded using Varian EM-390 or HR-220 spectrometers at 30 °C. ^{13}C NMR spectra were obtained using a Jeolco JNM-FX-60 operating in the FT mode (spectral width 2250 Hz, 16K data points, corresponding to a data point resolution of 0.28 Hz) at 30 °C. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Mass spectra were obtained on a Varian MAT CH-5 spectrometer, and IR were obtained using a Beckmann IR-12 instrument. Rotations were taken on a Zeiss visual polarimeter with a 1-dm cell. Elemental analyses were performed by Mr. J. Nemeth and associates, University of Illinois. Unless otherwise stated, chromatographic separations were obtained using apparatus previously described.[5]

6-Methylheptyl Phenyl Sulfide (3). This compound was obtained from 6-methylheptanol (**2**)[9] using a procedure similar to that described in the literature.[6] To a stirred solution of phenyl disulfide (14.3 g, 0.066 mol) and tri-*n*-butylphosphine (13.3 g, 0.066 mol) in 50 mL of dry benzene was added **2** (8.0 g, 0.062 mol). The mixture was stirred for 1 h, then passed through a column of silica gel (30 mm × 25 cm), eluting with CH_2Cl_2–hexane 1:7 (500 mL). The solvent was removed at reduced pressure, and the residue was distilled to afford 13.4 g (96%) of a clear, colorless liquid: bp 154–157 °C (0.3 mm); NMR (CCl_4) δ 6.6–7.2 (m, 5 H, Ar), 2.67 (t, 2H, SCH_2), 1.0–1.7 (m, 9 H, $(CH_2)_4CH$), 0.79 (d, 6 H, $CH(CH_3)_2$); MS (70 eV), *m/e* (rel intensity) 222 (44.3), 123 (25.2), 110 (100), 57 (15.1), 43 (27.6), 41 (35.2); IR (neat) 2920–2980, 2880, 1590, 1480, 1390, 1370, 1270–1300, 1100, 1030, 740, and 700 cm^{-1}.

Anal. Calcd for $C_{14}H_{22}S$: C, 75.61; H, 9.97; S, 14.42. Found: C, 75.41; H, 9.74; S, 14.58.

***threo*- and *erythro*-2-Methyl-7-phenylthio-8-octadecanols (4a and 4b).** These compounds were prepared by a method similar to that of Dolak and Bryson.[13] To a solution of **3** (6.70 g, 0.03 mol) and hexamethylphosphoric triamide (13.6 g, 0.075 mol) in 75 mL of tetrahydrofuran at −78 °C was added dropwise *tert*-butyllithium (22 mL, 1.84 M in pentane). The orange solution thus obtained was stirred at −78 °C for 2 h, and 5.61 g (0.033 mol) of *n*-undecanal in 150 mL of tetrahydrofuran was added dropwise to the reaction mixture over a period of 1 h. The mixture was then allowed to warm slowly to room temperature and was poured over 50 g of ice; the organic layer was isolated and the aqueous layer was extracted twice with 50-mL portions of diethyl ether. The organic layers were combined and dried ($MgSO_4$) and the solvent removed at reduced pressure. The residue was chromatographed (neutral alumina, hexane–CH_2Cl_2 3:1) to provide two components. The high R_f material was identified as unreacted **3**; the low R_f material was found to be a 1:1 mixture of **4a** and **4b** (8.2 g, 70%).

Chromatography of the erythro–threo mixture (neutral alumina, hexane–CH_2Cl 5:1) separated the diastereomers (α = 1.3). In order to insure complete diastereomeric purity, a fraction comprised of the trailing edge of the first band and the leading edge of the second band (ca. 15% of the total) was rechromatographed.

The erythro isomer, **4a**, was eluted first and was isolated as a clear, pale yellow oil: NMR ($CDCl_3$) δ 7.2–7.8 (m, 5 H, Ar), 3.57 (m, 1 H, OC**H**), 3.16 (m, 1 H, SC**H**), 2.43 (broad s, 1 H, O**H**), 1.1–1.8 (m, 27 H, CH_2's and $CH(CH_3)_2$), 0.87 and 0.84 (t and d, 9 H, CH_2CH_3 and $CH(CH_3)_2$); MS (10 eV), *m/e* (rel intensity) 392 (1.0), 222 (14.9), 171 (63.6), 110 (21.4), 97 (100), 83 (76.9), 71 (25.3), 69 (41.9), 57 (41.9), 43 (5.5); IR (neat) 3200–3600, 2960, 2880, 1470, 1390, 1370, 1050–1100, 1025, 750, and 690 cm^{-1}.

The threo isomer, **4b**, was eluted second and was isolated as a clear, pale yellow oil: NMR ($CDCl_3$) δ 7.2–7.8 (m, 5 H, Ar), 3.64 (m, 1 H, OC**H**), 3.02 (m, 1 H, SC**H**), 2.34 (broad s, 1 H, O**H**), 1.1–1.8 (m, 27 H, CH_2's and $CH(CH_3)_2$), 0.89 and 0.88 (t and d, 9 H, CH_2CH_3 and $CH(CH_3)_2$); MS (10 eV), *m/e* (rel intensity) 392 (12.4), 222 (86.6), 171 (54.8), 110 (63.4), 97 (100), 83 (90.4), 71 (98.4), 69 (58.3), 57 (91.6), 43 (11.3); IR (neat) 3200–3600, 2960, 2880, 1470, 1390, 1370, 1050–1100, 1030, 1010, 750, and 690 cm^{-1}.

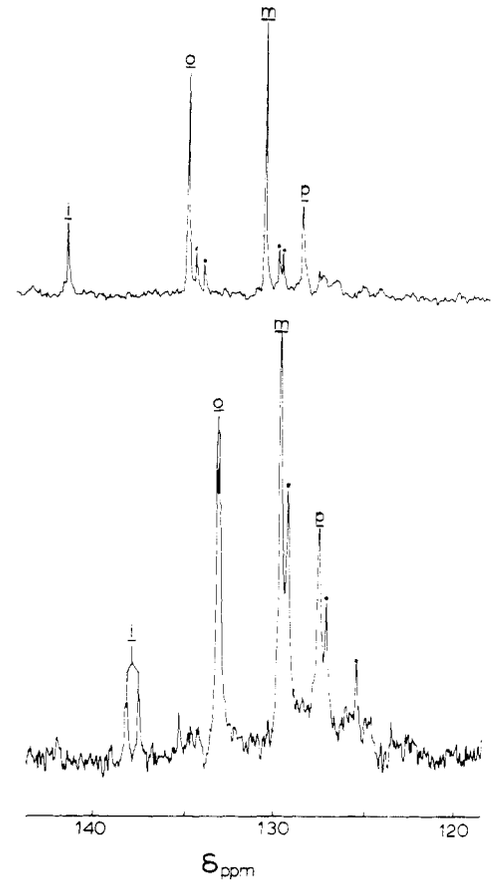


Figure 1. ^{13}C NMR spectrum of the aromatic region of **4a** in the presence of tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III): (bottom) racemate, (top) resolved precursor to (+)-**1a**. The starred peaks are those of the optically active lanthanide shift reagent. Induced shifts are not as great in the racemate as in the pure enantiomer, even though the two sets of experimental conditions were roughly comparable. This may be due in part to the fact that the enantiomers may have different equilibrium constants for coordination to the CLSR or that traces of moisture may have dissimilarly influenced the experiments. Doubling of the ipso carbon resonance in the spectrum of the racemate was observed in a series of spectra obtained after incremental addition of CLSR.

1-Decyl-2-phenylthio-6-methylheptyl *N*-[1-(1-Naphthyl)-ethyl]carbamates (5a and 5b). These carbamates were synthesized from **4b** (1.00 g, 2.6 mmol) by the method previously described for similar compounds.[5] Chromatography of the diastereomers (neutral alumina, hexane–CH_2Cl_2 5:1) separated (α = 1.6) two major UV adsorbing (280 nm) components. As a precaution to insure diastereomeric purity, an intermediate fraction consisting of the tailing edge of peak one and the leading edge of peak two was isolated and rechromatographed.

The high R_f fraction yielded 570 mg of a clear colorless oil: NMR ($CDCl_3$) δ 7.2–7.8 (m, 12 H, Ar), 5.63 (quintet, 1 H, NC**H**), 4.90 (d, 1 H, N**H**), 4.7 (m, 1 H, OC**H**), 3.25 (m, 1 H, SC**H**), 1.54 (d, 3 H, $NCHCH_3$), 1.25 (m, 27 H, CH_2's and $CH(CH_3)_2$), 0.83 and 0.85 (d and t, 9 H, $CH(CH_3)_2$ and CH_2CH_3); IR (neat) 3300–3400, 3060, 2900–3000, 2880, 1720, 1450–1550, 1390, 1320, 1200–1280, 1000–1120, 800, and 780 cm^{-1}; MS (70 eV), *m/e* (rel intensity) 589 (0.1), 222 (3.3), 215 (100), 214 (54.6), 200 (64.3), 170 (13.3), 155 (79.8), 141 (1.0), 127 (5.0), 113 (0.8), 99 (1.3), 85 (5.8), 71 (10.6), 57 (31.4), 43 (25.9).

The low R_f fraction yielded 500 mg of a clear, colorless oil: NMR ($CDCl_3$) δ 7.2–8.2 (m, 12 H, Ar), 5.63 (quintet, 1 H, NC**H**), 4.90 (d, 1 H, N**H**), 4.7 (m, 1 H, OC**H**), 3.2 (m, 1 H, SC**H**), 1.63 (d, 3 H, $NCCH_3$), 1.27 (m, 27 H, CH_2's and $CH(CH_3)_2$), 0.83 and 0.83 (d and t, 9 H, $CH(CH_3)_2$ and CH_2CH_3); IR (neat) 3200–3400, 3060, 2900–3000, 2860, 1720, 1450–1550, 1390, 1380, 1320, 1200–1280, 1000–1120, 800, and 780 cm^{-1}; MS (70 eV), *m/e* (rel intensity) 589 (0.2), 215 (100), 214 (63.1), 170 (16.4), 155 (79.5), 129 (11.1), 127 (6.4), 97 (8.3), 85 (5.2), 83 (12.3), 71 (9.3), 69 (12.4), 57 (13.1), 55 (11.1), 43 (14.8), 41 (8.0).

(−)-*threo*-2-Methyl-7-phenylthio-8-octadecanol (4b). This

compound was prepared by silanolysis of the low R_f carbamate **5b** as previously described.[5] The (−)-**4b** was obtained as a clear, colorless oil (93% yield): $[\alpha]^{24}_D$ −6.7° (*c* 3.5, $CHCl_3$); NMR and IR spectra were identical to those of racemic **4b**.

(+)-*cis*-7(*R*),8(*S*)-Epoxy-2-methyloctadecane (1a). This compound was prepared by methylation of (−)-**4b** (200 mg, 0.5 mmol) with $(CH_3)_3OBF_4$ (80 mg, 0.54 mmol) in dry CH_2Cl_2, followed by treatment with NaOH (10%, aqueous). The crude product was purified by GLC (3% SE-30 on Chromosorb W, ⅛ in. × 12 in. column, 170 °C).

A clear colorless liquid was obtained (129 mg, 90%): $[\alpha]^{24}_D$ +0.8 ± 0.1° (*c* 10, CCl_4); NMR (CCl_4) δ 2.65 (m, 1 H, $\overline{CHCHO}$), 1.1–1.6 (m, 27 H, CH_2's and $CH(CH_3)_2$), 0.86 (d and t, 9 H, CH_2CH_3 and $CH(CH_3)_2$); IR (CCl_4) 2960, 2940, 2860, 1470, 1385, 1370, and 1250 cm^{-1}; MS, *m/e* 282.

1-Decyl-2-phenylthio-6-methylheptyl *N*-[1-(1-Naphthyl)-ethyl]carbamates Derived from 4a. These carbamates were prepared from *erythro*-**4a** and resolved in a manner identical to that used for the preparation of the threo derived **5a** and **5b**. After chromatographic separation of the two diastereomeric carbamates (α = 1.5), the NMR, IR, and MS of these erythro compounds were found to be essentially indistinguishable from those of the threo analogues, **5a** and **5b**.

(−)-*erythro*-2-Methyl-7-phenylthio-8-octadecanol (4a). This compound was obtained by a procedure identical to the one used for the resolution of **4b**. It was obtained by silanolysis of the low R_f carbamate derived from (*R*)-(+)-1-(1-naphthyl)ethylamine: NMR, IR, MS, identical to those of racemic **4a**; $[\alpha]^{24}_D$ −7.5° (*c* 3.5, $CHCl_3$).

(−)-*trans*-7(*S*),8(*S*)-Epoxy-2-methyloctadecane (1b). This compound was prepared from (−)-**4a** by a procedure identical to that used to obtain **1a**.

A clear colorless liquid was obtained: $[\alpha]^{24}_D$ −23.6 (*c* 1, CCl_4); NMR (CCl_4) δ 2.43 (t, 2 H, $\overline{CHCHO}$), 1.1–1.6 (m, 27 H, CH_2's and $CH(CH_3)_2$), 0.86 (d and t, 9 H, $CH(CH_3)_2$ and CH_3); IR (CCl_4) 2960, 2930, 2860, 1470, 1390, 1370, 1250, 860, and 800 cm^{-1}; MS, *m/e* 282.

Preparation of 4a from 4b. Methanesulfonyl chloride (0.03 mL, 0.5 mmol) was added to a solution of **4b** (137 mg, 0.35 mmol) in CH_2Cl_2 and pyridine (0.04 mL, 0.5 mmol) at −20 °C. The mixture was stirred for 1 h; the organic solution was extracted with dilute HCl and 5% $NaHCO_3$ and then dried (K_2CO_3). Solvent removal at reduced pressure afforded crude mesylate which was used without further purification.

The mesylate from **4b** was dissolved in a mixture of dry solvents (DMF–DME–Me_2SO 1:1:1) and 18-crown-6 (100 mg). The mixture was cooled (0 °C) and KO_2 (170 mg) was added in small portions over 5 min. The mixture was stirred for 30 min, then extracted with 10% Na_2SO_3, and dried (K_2CO_3). Solvent removal at reduced pressure afforded a clear oil, the NMR and IR of which were identical to those of authentic **4a**; yield 100 mg (73%).

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Registry No.—**1a,** 54910-51-9; **1b,** 54910-54-2; **2,** 1653-40-3; **3,** 68900-43-6; **4a,** 68900-44-7; (−)-**4a,** 68927-72-7; **4b,** 68900-45-8; (−)-**4b,** 68926-73-8; **4b** mesylate, 68900-47-0; **5a,** 68900-46-9; **5b,** 68926-74-9; undecanal, 112-44-7.

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(8) The initial elution of *erythro*-hydroxy sulfide, **4a,** is not expected on the basis of the model previously proposed for such separations.[6] Possibly, the large alkyl chains do not permit the weak OH–S hydrogen bonding interaction to determine the conformation about the C_7–C_8 bond.
(9) W. H. Pirkle and J. R. Hauske, *J. Org. Chem.*, **42,** 2779 (1977).
(10) The overall yield of 12% (including the resolution step; i.e., yield is actually 24% of theoretical) is to be compared to the overall yield of 13.8% (excluding resolution) attained by Farnum et al.[4] If allowance is made for the recovery of 30% of **3**, the yield is raised to 17.2% (or 34.4% theory). Epimerization of **4a** to **4b** (a refinement that could be similarly applied to Farnum's sequence)[4] further raises the overall yield to 29.8% (or 58.6% of theory). However, the recycling of **2** and the epimerization of **4a** would be of significance only during production of large quantities of disparlure.
(11) E. J. Corey, K. C. Nicolaou, M. Shibasaki, Y. Machida, and C. S. Shiner, *Tetrahedron Lett.*, 3183 (1975).
(12) Although numerous procedures for the synthesis of **2** have been reported, we have found it convenient to prepare **2** by conjugate addition of lithium diisoamyl cuprate to methyl acrylate (75%),[11,12] followed by $LiAlH_4$ reduction of the product ester (95%).[12]
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Synthesis of *C*-Nucleosides. 17.[1] *s*-Triazolo[4,3-*a*]pyrazines[2]

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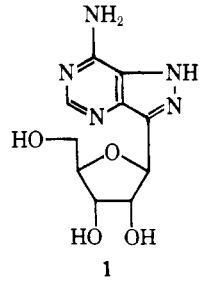
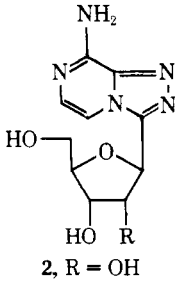
8-Substituted-3-alkyl- and -glycosyl-*s*-triazolo[4,3-*a*]pyrazines, closely related to the *C*-nucleoside formycin, have been prepared from 3-chloro-2-hydrazinopyrazine and thioimidates. Their spectroscopic properties, especially ^1H and ^{13}C NMR, are discussed.

We report further development of synthetic routes to *C*-nucleosides containing a nitrogen bridgehead atom such as the *s*-triazolo[4,3-*a*]pyrazine cycle. A nucleoside of type **2** or **3** is of special interest since it has a structure closely related to that of adenosine and formycin **1**. Such fused heterocycles are not well known; although some substituted *s*-triazolo[4,3-*a*]pyrazines have been obtained by Nelson and Potts[4] and Mallet and Rose[5] by reaction of 2-hydrazinopyrazines with ortho esters or carboxylic acid derivatives, no *s*-triazolo[4,3-*a*]pyrazine functionalized on carbon 8 (i.e., atom 6 of the purine ring) has been described to our best knowledge.



1



2, R = OH
3, R = H

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