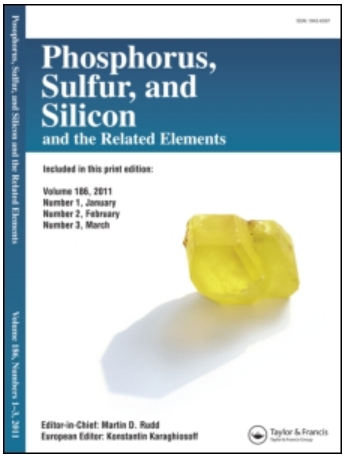

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Annulation Reactions of Chiral Vinylsulfonium Salts with 2-Indolecarboxaldehyde

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ANNULATION REACTIONS OF CHIRAL VINYLSULFONIUM SALTS WITH 2-INDOLECARBOXALDEHYDE

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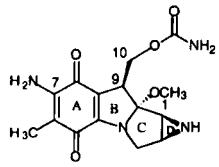
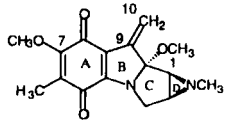
The preparation of the chiral vinylsulfonium salts **4**, **5**, *and* **6** *is described. Their use in an annulation with 2-indolecarboxaldehyde and sodium azide proceeds to form the azido alcohol* **2** *with low asymmetic induction. These results represent an initial investigation of the asymmetric induction obtained from enantiomerically pure vinylsulfonium salts.*

Keywords: Asymmetric induction; bicyclic heterocyclic compounds; sulfonium salts

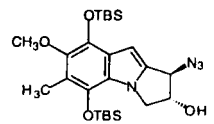
Our interest in developing an efficient synthesis of the tetracyclic ring system of the antitumor antibiotic, mitomycin C, led to the discovery that reaction of dimethylvinylsulfonium iodide with the sodium salt of indole-2-carboxaldehyde gave the formation of the tetracyclic oxirane **1**, which upon treatment with sodium azide forms the azido alcohol **2** in a 72% yield (Scheme 1).[1] The fully substituted azido alcohol **3** has proven to be a useful intermediate in the racemic syntheses of mitomycin K and aziridinomitosenes.[2–4] Therefore we undertook the preparation of the enantiomerically pure vinylsulfonium salts **4**, **5**, and **6** in an attempt to develop an asymmetric synthesis of **2** as a model for **3**. This article constitutes the first investigation of chiral, nonracemic vinylsulfonium salts in asymmetric syntheses.



Mitomycin C



Mitomycin K



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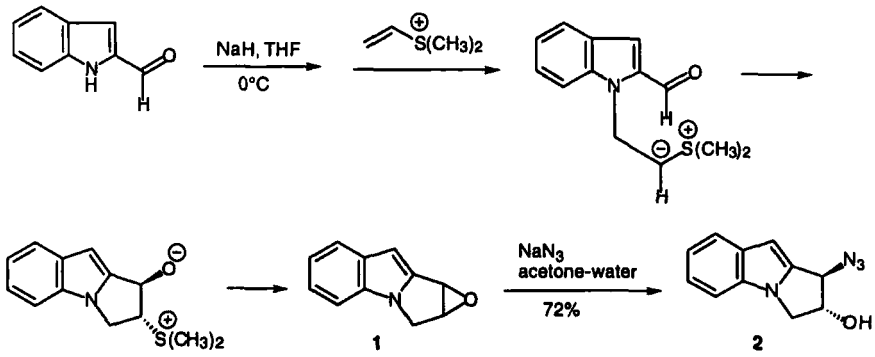
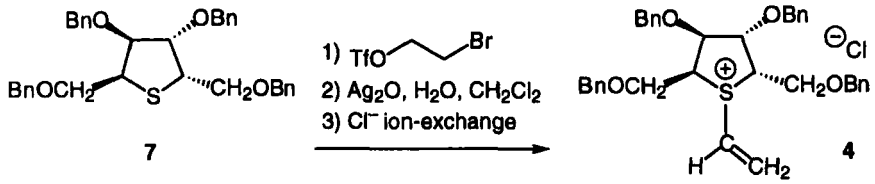


SCHEME 1

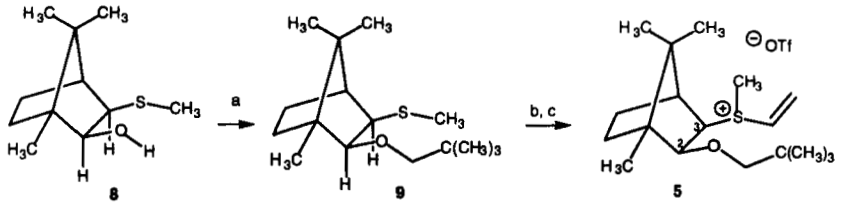
Vinylsulfonium salt **4** was synthesized from the known C2 symmetric sulfide **7**[5] by alkylation with 2-bromoethyl trifluoromethanesulfonate, followed by elimination of HBr with silver (I) oxide and then ion exchange (Scheme 2). The ease of synthesis and the fact that **7** is C2 symmetric (alkylation gives only one possible diastereomer) made **4** an attractive initial target.



SCHEME 2

The rigid relationship between the two exo-oriented 2,3-functionalities of **5** causes the vinyl group to be blocked on one side with the sterically bulky neopentyloxy group at the 2 position. Vinylsulfonium salt **5** was synthesized from the known sulfide **8**[7,8] by alkylation with 1-iodo-2,2-dimethylpropane[9] to give the sulfide **9**. However, alkylation with 2-bromoethyl trifluoromethanesulfonate resulted in a mixture of diastereomeric salts, which were not readily separated. Elimination of HBr was accomplished with silver (I) oxide to give **5** as a mixture of diastereomers (Scheme 3).

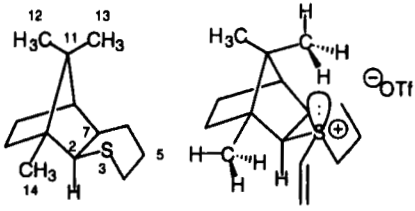
A more promising candidate appeared to be the cyclic sulfide **10**. The same rigid relationship between the 2 and 7 substitutents (corresponding to the 2 and 3 positions in the camphor skeleton) is maintained and since the sulfide can no longer rotate freely about a carbon-sulfur single bond in **10** as is the case with the sulfide group in **9**, it was expected that alkylation would produce only one diastereomeric salt product.



a) NaH, NMP; then $ICH_2C(CH_3)_3$;130°C, 18 h, 44%. b) $BrCH_2CH_2OTf$, CH_2Cl_2, 75%. c) Ag_2O, CH_2Cl_2, H_2O, 7 d, 49%.

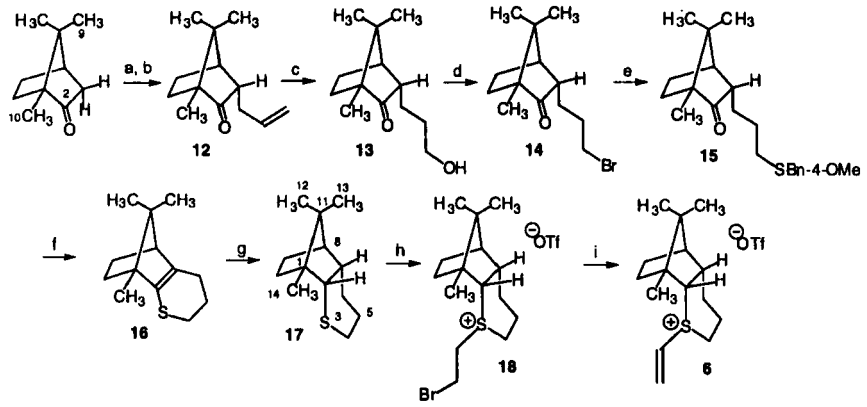
SCHEME 3

With the additional geometrical constraints in the vinylsulfonium salt **11**, it was expected that the annulation between the vinylsulfonium salt and a 2-indolecarboxaldehyde would take place from only one side of the vinyl group. The 14-methyl group of **11** blocks access to one side of the vinyl group's α-carbon.



10 **11**

The first step in the proposed synthesis of **10** was the alkylation of camphor with allyl iodide. Alkylation with allyl iodide at 0°C gave a mixture of exo and endo diastereomers. Alkylation at −22°C or lower did not occur at an appreciable rate. Separation of the exo and endo isomers of 3-allylcamphor or of later intermediates proved to be extremely difficult. Treatment of the endo and exo mixture with potassium *t*-butoxide in *t*-butanol gave the thermodynamically more stable endo isomer 12.[10,11] Therefore the synthetically more accessible endo vinylsulfonium salt **6** (Scheme 4) was synthesized instead of the exo analog **11**. Hydroboration-oxidation of **12** resulted in the alcohol **13** in a 60% yield.[12] Conversion into the bromide **14** was accomplished with PBr_3 in CH_2Cl_2 in an 80% yield. Nucleophilic displacement of the bromide with the sodium salt of 4-methoxy-α-toluenethiol produced sulfide **15** in a 75% yield. Unexpectedly, removal of the 4-methoxybenzyl group in refluxing trifluoroacetic acid gave the sulfide **16** in a quantitative yield.[13] Reduction with $BF_3 \cdot 2H_2O$ and Et_3SiH in CH_2Cl_2 resulted in the sulfide **17** in a 97% yield.[14] NOESY spectra of **17** showed small enhancements of the 13-methyl (1.0%), 14-methyl (0.33%), and C_7-H (0.44%) when C_2-H was irradiated. This indicates that the thermodynamically

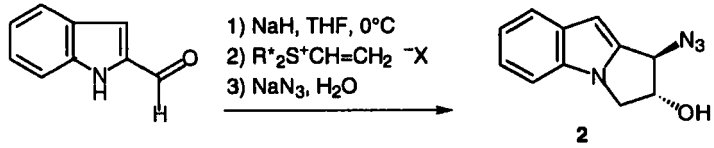


a) LDA, TMEDA, THF, $ICH_2CH=CH_2$, 0°C, 65%. b) tBuOK, tBuOH, 12 h, 90%. c)$(C_6H_{11})_2BH$, THF, 0°C, 1 h; then $NaBO_3 \cdot 4H_2O$, H_2O, 60%. d) PBr_3, CH_2Cl_2, 80%. e) $NaSCH_2C_6H_4$-4-OMe, EtOH, 4 h, 75%. f) TFA, reflux, 2 h, ~100%. g) $BF_3 \cdot 2H_2O$, CH_2Cl_2, Et_3SiH, 0°C, 97%. h) $BrCH_2CH_2OTf$, CH_2Cl_2, 92%. i) Ag_2O, CH_2Cl_2, H_2O, 7 d, 42%.

SCHEME 4

more stable endo isomer is formed under these conditions (see Scheme 1 for numbering). Alkylation of **17** with 2-bromoethyl trifluoromethanesulfonate gives only one diastereomer **18** (92%). Treatment with silver (I) oxide produces vinylsulfonium salt **6** (42%). Irradiation of **6**'s C_2-H resulted in enhancements of the C_7-H (5.1%), 13-methyl (1.8%), 14-methyl (0.62%), and the hydrogen attached to the α-carbon of the vinyl group (5.2%). When the C_7-H was irradiated, enhancements of the C_2-H (4.6%), 13-methyl (1.1%), and C_8-H (4.6%) were observed.

Vinylsulfonium salts **4–6** were reacted with the sodium salt of 2-indolecarboxaldehyde to form **1** in situ, then sodium azide was added and the azido alcohol **2** was isolated[1] (Scheme 5). Enantiomeric excesses were determined by preparing the Mosher's esters of **2** and integrating the peak areas of two different diastereomeric hydrogens in the ^1H NMR spectra.[16] This allowed for the approximate determination of enantiomeric excesses using various solvents and temperatures for this cycloannulation (Table I).



SCHEME 5

A number of optically active epoxides have been prepared from chiral, nonracemic ylides under various conditions with 10–95% ee.[5,7] In the annulation leading to **2**, the sulfur ylide is formed in situ after conjugate

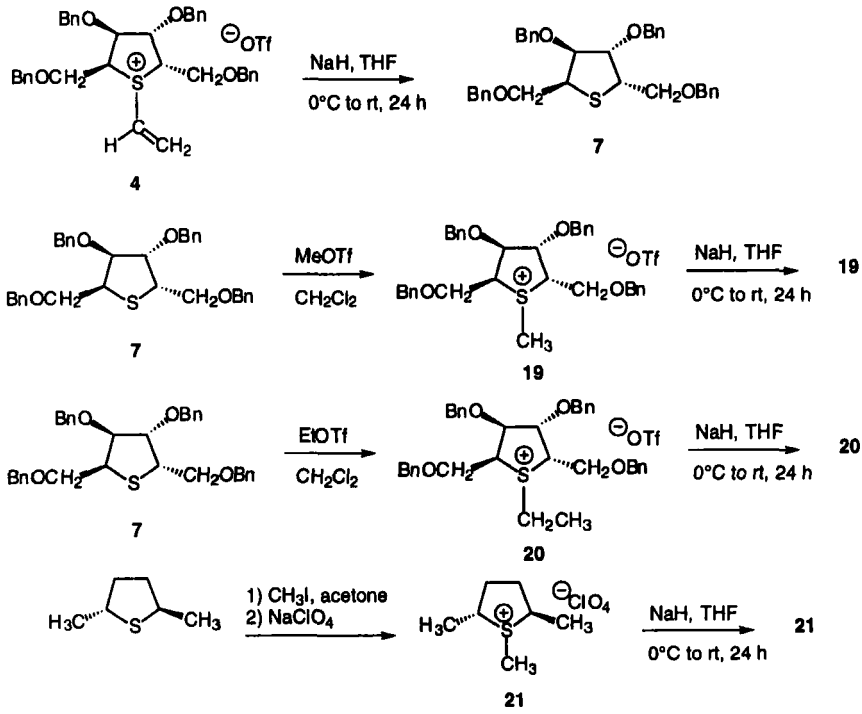
TABLE I Chemical Yields and % ee of **2** Formed from Vinylsulfonium Salts **4–6**

Entry	Salt	Solvent	Temp (°C)	Yield (%)	% ee	Recovery (%) of sulfide
1	**4**	THF	0	54	30	58
2	**4**	THF/DMSO	0	48	30	57
3	**4**	THF	−22	49	24	48
4	**4**	THF/DMSO	−22	48	17	51
5	**4**	THF	−78	44	18	49
6	**4**	THF/DMSO	−78	46	21	48
7	**5**	THF	20	46	10	73
8	**5**	THF	0		10	50
9	**6**	THF	20	93	30	95
10	**6**	THF	0		30	50
11	**6**	THF	−20		30	50
12	**6**	THF	−45			43
13	**6**	THF	−78			50
14	**6**	THF/DMSO	0		20	50

addition of the indole anion to the vinylsulfonium salt (Scheme 1). From the results shown in Table I, it would appear that the benzyloxymethyl groups of **4** do not have enough steric bulk to enforce approach of the aldehydic group from only one face of the sulfur ylide. Lowering the temperature did not have an ameliorating effect on the enantioselectivity of this reaction with **4** nor did using the more polar 1:1 THF:DMSO as solvent in place of pure THF. The low enantioselectivity observed with **5** is not surprising since this vinylsulfonium salt exists as a mixture of diastereomers.

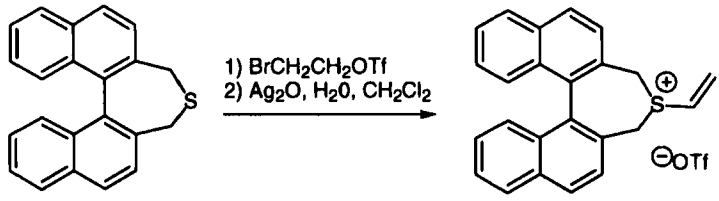
Varying the temperature from +20 to −20°C in THF did not affect the enantioselectivity of the annulation with vinylsulfonium salt **6** significantly. At −45°C, the yield of **2** is quite low with **6** and none is detected at −78°C, although in both cases the sulfide **17** is recovered. Use of the more polar 1:1 DMSO:THF at 0°C caused a decrease in enantiomeric excess. The C_{14} methyl group of **6** is not as ideally placed to block one side of a sulfur ylide formed in situ as might be expected of the exo vinylsulfonium salt **11**. The low enantioselectivity obtained with **6** was somewhat disappointing, but not entirely unexpected. More effective vinylsulfonium salts such as **11** (or an analog which retains the exo-exo geometry at the 2 and 7 positions) may result in better asymmetric induction in the formation of the azido alcohol **2**.

It was possible that the modest enantioselectivities observed for the cycloannulation were due to epimerization of the sulfonium salts under the basic reaction conditions. The effect of base on vinylsulfonium salt **4** was studied by stirring it in THF in the presence of NaH for 24 h



SCHEME 6

(Scheme 6). The sulfide **7** was the only product recovered, presumably because of the loss of acetylene under the basic conditions. Therefore the *S*-methyl and *S*-ethylsulfonium salts of **7** were synthesized by reacting **7** with methyl trifluoromethanesulfonate and ethyl trifluoromethanesulfonate respectively. These sulfonium salts were then reacted with NaH in THF for 24 h. Their respective NMR spectra indicated no clear differences between the starting materials and the product obtained after the basic treatment. However the sulfonium salts **19** and **20** show a complicated pattern of peaks in their ^{1}H NMR spectra even after purification (the *S*-alkyl group is cis to the 2- and 3-substituents and trans to the 4- and 5-substituents or vice versa). For this reason, the simpler trimethylthiophenium salt **21** was synthesized by methylating (2*R*,5*R*)-dimethylthiolane.[12] This salt was then treated with NaH in THF as before. The ^{1}H NMR spectra showed that the C_2 symmetry of the starting compound was retained; no sign of other stereoisomers was present. From these experiments we conclude that epimerization of the sulfonium salt during the annulation reaction to form azido alcohol **2** is unlikely to be the cause of the moderate asymmetric induction observed for this reaction.



22 **23**

SCHEME 7

The racemic sulfide **22** was also synthesized in three steps from 1-bromo-2-methylnaphthalene.[13] Conversion to the vinylsulfonium salt **23** was accomplished in the usual way by alkylation with 2-bromoethyl trifluoromethanesulfonate, followed by treatment with silver (I) oxide (Scheme 7). Compound **23** is markedly unstable, decomposing within 1 h at rt. Preparing **23** and using it immediately in the annulation with the sodium salt of 2-indolecarboxaldehyde and sodium azide results only in the recovery of unreacted 2-indolecarboxaldehyde and the sulfide **22**. Dissolving **23** in dry THF in the presence of NaH resulted in a 70% isolated yield of **22**. From these results we conclude that **23** loses acetylene quite readily making it unsuitable for our purposes.

EXPERIMENTAL

Nuclear magnetic resonance (NMR) spectra were acquired using a Varian-Gemini 200 MHz or a Varian Unity 400 MHz spectrometer. Melting points were determined on a Thomas Hoover melting point apparatus. NMR chemical shifts are given in parts per million (ppm) downfield from tetramethylsilane (TMS) or relative to internal $CHCl_3$. Infrared spectra were recorded by using a Genesis Series FT-IR instrument. Elemental analyses were obtained from Quantitative Technologies, Inc. (Whitehouse, NJ). Mass spectra were obtained either from University of California, Riverside Mass Spectrometry Facility or Rutgers University, Food Science Mass Spectrometry Facility. Unless otherwise noted, materials were obtained from commercially available sources and used without further purification. Tetrahydrofuran (THF) and dichloromethane were distilled from calcium hydride under a nitrogen atmosphere. Chromatographic purification was performed with EM Science 230–400 mesh silica gel. Reactions and chromatography fractions were monitored and analyzed by thin layer chromatography (TLC) using EM Science 250-μm 60 F_{254} silica plates. EtOAc = ethyl acetate, PE = petroleum ether, 30–60°C.

A Typical Procedure for the Formation of 1-Azido-2,3-dihydro-2-hydroxy-1*H*-pyrrolo[1,2-a]indole (2)[1]

In a 5-ml round-bottom flask, a total of 14 mg (0.10 mmol) of 2-indolecarboxaldehyde and 4 mg (0.10 mmol) of NaH (60% dispersion in mineral oil) was stirred in 2 mL of dry THF under N_2 at 0°C (ice bath). A total of 40 mg (0.10 mmol) of dialkylvinylsulfonium salt **6** was added after 20 min, and then the reaction mixture was stirred for 5 h. A total of 20 mg (0.30 mmol) of NaN_3 dissolved in 0.5 mL deionized water was added to the reaction mixture, and then the reaction mixture was stirred at rt for about 12 h. The solvent was removed under reduced pressure, and then the residue was extracted with dichloromethane. The organic layer was dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The crude compound was purfied by flash chromatography (4:1 petroleum ether:ethyl acetate). A yellow oil was obtained (35–93% depends on vinylsulfonium salts used).

^{1}H NMR ($CDCl_3$): δ 2.42 (br s, 1H), 3.88 (dd, J = 2.9, J = 11, 1H), 4.31 (dd, J = 5.5, J = 11, 1H), 4.60–4.75 (m, 1H), 4.75–4.80 (m, 1H), 6.52 (s, 1H), 7.00–7.30 (m, 3H), 7.63 (d, J = 7.7, 1H).

^{13}C NMR ($CDCl_3$): 50.4, 64.7, 80.1, 96.7, 109.8, 120.0, 121.6, 122.3, 132.0, 133.0, 137.0.

IR: 3414, 3054, 2950, 2886, 2099, 1463, 1310, 1222, 1084 cm^{-1}.

1-Azido-2,3-dihydro-2-[(*R*)-α-methoxy-α-(trifluoromethyl) phenylacetyloxy]-1*H*-pyrrolo[1,2-a]indole (Mosher's Ester of 2)

The azido alcohol **2** (17.0 mg, 0.079 mmol) was added to 2 ml of dichloromethane in a 10 mL flask. Pyridine (6.45 ul, 0.079 mmol) and Mosher's reagent, (*S*)-(+)-α-methoxy-α-(trifluoromethyl) phenylacetyl chloride (18 ul, 0.099 mmol) were added via syringe. The reaction was then stirred at rt for 24 h before adding 10 ml of dichloromethane and 10 ml of 1N HCl. The phases were separated and the organic layer was dried over $MgSO_4$, filtered, and the solvent removed in vacuo to give a bright yellow paste. The yield is 72% (25 mg, 0.059 mmol). Approximate enantiomeric excesses were determined by integrating the signal areas of two of the diastereomeric hydrogens and averaging the results.

One diastereomer: ^{1}H NMR ($CDCl_3$): δ 3.48 (q, J = 1.2 Hz, 3H, OMe), 4.16 (dd, J = 2.4, 11.9 Hz, 1H, H-3), 4.64 (dd, J = 5.8, 11.7 Hz, 1H, H-3), 5.04 (dd, J = 0.8, 2.2 Hz, 1H, H-1), 5.75–5.85 (m, 1H, H-2), 6.56 (s, 1H), 7.10–7.50 (m, 8H), 7.65 (d, J = 7.77 Hz, 1H). The other diastereomer: ^{1}H NMR ($CDCl_3$): δ 3.51 (q, J = 1.2 Hz, 3H, OMe), 4.02 (dd, J = 2.8, 11.7 Hz,

1H, H-3), 4.64 (dd, J = 5.8, 11.7 Hz, 1H, H-3), 5.13 (dd, J = 0.7, 2.5 Hz, 1H, H-1), 5.75–5.85 (m, 1H, H-2), 6.56 (s, 1H), 7.10–7.50 (m, 8H), 7.65 (d, J = 7.7 Hz, 1H).

One diastereomer: ^{19}F NMR 400 MHz ($CDCl_3$): δ 37675 Hz.

The other diastereomer: ^{19}F NMR 400 MHz ($CDCl_3$): δ 37693 Hz.

2-Bromoethyl Trifluoromethanesulfonate[14]

In a 100-mL round-bottomed flask, 1.62 mL (20.0 mmol) of pyridine in 30 mL CH_2Cl_2 was cooled to −22°C (dryice/ethylene glycol) bath and 3.36 mL (20.0 mmol) of trifluoromethanesulfonic anhydride was added. After 0.5 h, 1.4 mL (20.0 mmol) of 2-bromoethanol was added and the reaction mixture was warmed to rt. The mixture was stirred for 2 h and then filtered, the solvent removed under reduced pressure, and the residue passed through a silica gel column with hexane. The solvent was then removed under reduced pressure. Yield: 3.36 g (65%). ^1H NMR ($CDCl_3$): δ 3.62 (t, 2H, J = 6.4), 4.75 (t, 2H, J = 6.4).

(2*S*,3*S*,4*S*,5*S*)-3,4-Dibenzyloxy-2,5-dibenzyloxymethyl-1-ethenyl-2,3,4,5-tetrahydrothiophenium Chloride (4)

Sulfide **7** (600 mg, 1.1 mmol) was dissolved in 10 mL of anhydrous CH_2Cl_2, followed by the addition of 2-bromoethyl trifluoromethanesulfonate (1.71 g, 6.67 mmol). The flask was capped and allowed to stir at rt for 48 h. The solvent was removed under reduced pressure and then the residue was loaded onto a silica gel column and eluted with 85:15 PE:EtOAc (100 mL), followed by 9:1 CH_2Cl_2: MeOH in which the polar salt was recovered. A light brown oil was obtained after removal of the solvent, to which 5 mL CH_2Cl_2 and 5 mL of deionized water were added. A total of 154 mg of Ag_2O (0.66 mmol) was added to the flask which was then capped and allowed to stir vigorously overnight at room temperature. The reaction mixture was then filtered and the filtrate was extracted with CH_2Cl_2 (2 × 10 mL), dried over $MgSO_4$, filtered, and the solvent removed in vacuo. It was then purified by flash chromatography with 97:3 CH_2Cl_2:MeOH. Anion exchange was then carried out using Dowex 1-X4, 50–100 mesh, chloride form, in a 2 cm diameter column. The column was first prepared by initially rinsing the resin with fresh deionized water (10 mL × 4). It was then treated with 10 mL of 1N KOH, followed by water (10 mL × 2). The resin was then acidified by 1N HCl (10 mL) and again rinsed with water until neutral. The sulfonium salt (300 mg, 0.42 mmol) was dissolved in a 3:1 H_2O:CH_3CN mixture (2 mL) and loaded onto the column. The fractions containing **4** were combined and the solvent removed under reduced pressure. The sample was dried in a vacuum oven at 40°C over P_2O_5 for 24 h. A total of 204 mg

of an oil was obtained (81%). ^{1}H NMR ($CDCl_3$): δ 3.20–3.30 (m, 1H), 3.45–85 (m, 3H), 3.91 (dd, J = 5.4, 10.4 Hz, 1H), 4.20–4.80 (m, 11H), 5.19 (d, J = 9.9 Hz, 1H), 5.24 (d, J = 16.8 Hz, 1H), 6.39 (dd, J = 9.9, 16.8 Hz, 1H), 7.20–7.45 (m, 20H). ^{13}C NMR ($CDCl_3$): δ 48.6, 60.4, 70.8, 73.4, 73.8, 75.6, 75.9, 79.2, 83.1, 113.7, 128.0, 128.1, 128.3, 128.4, 128.6, 128.66, 128.74, 128.8, 132.3, 138.2, 138.5, 138.8, 138.9.

MS (FAB): *m/z* 567 (M^+), 477 ($M^+ + H^+ - CH_2C_6H_5$). Anal. Calcd. for $C_{36}H_{39}ClO_4S$: C, 71.33; H, 6.91. Found: C, 71.41; H, 6.60.

(1*R*,2*S*,3*R*,4*S*)-3-(2-Bromoethyl)-1,7,7-trimethyl-2-(2,2 dimethylpropoxy)-3-(methylthio)bicyclo[2.2.1]-heptanium Trifluoromethanesulfonate

A total of 0.50 g (1.82 mmol) of **9** was placed in a 50 mL, one necked flask and 10 mL CH_2Cl_2 was added. A total of 2.34 g (9.10 mmol) of 2-bromoethyl trifluoromethanesulfonate was added to the reaction mixture. The resulting mixture was stirred for 1 day. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (95:5 CH_2Cl_2:methanol). Yield: 0.73 g (75%), mp, 120°C (decomp.). ^{1}H NMR ($CDCl_3$): δ 0.88 (s, 3H, both diastereomers), 0.95 (s, 9H, one diastereomer), 0.96 (s, 9H, one diastereomer), 1.05 (s, 3H, both diastereomers), 1.24 (s, 3H, both diastereomers), 1.10–2.30 (m, 5H, both diastereomers), 3.02 (s, 3H, both diastereomers), 3.20–4.50 (m, 6H, both diastereomers). IR: 2961, 1163, 1031 cm^{-1}. MS (EI): *m/z* 377 (M^+), 379 ($M^+ + 2$), 297 ($M^+ - HBr$). HRMS, *m/z* (M^+, $C_{28}H_{34}BrOS^+$) calcd. 377.1514, obsd. 377.1514.

(1*R*,2*S*,3*R*,4*S*)-3- Ethenyl-1,7,7-trimethyl-2-(2,2-dimethylpropoxy)-3-(methylthio)bicyclo[2.2.1]heptanium Trifluoromethanesulfonate (5)

A total of 0.246 g (0.47 mmol) of the 2-bromoethyl salt was placed in a 25 mL, one-necked flask and 3 mL of CH_2Cl_2 was added. After the salt was dissolved in CH_2Cl_2, 3 mL of deionized water was added (biphasic system). A total of 0.054 g (0.23 mmol) of Ag_2O was added and the resulting mixture was stirred at room temperature for a week. The resulting mixture was diluted with CH_2Cl_2 and the organic layer was washed with water (2 × 50 mL), and then dried over Na_2SO_4. The solution was filtered through Celite and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (98:2 CH_2Cl_2:methanol) to give an oil, which after a day was transformed into a solid. Yield: 0.10 g (49%), mp, 105–106°C. ^{1}H NMR ($CDCl_3$): δ 0.87 (s, 3H, one diastereomer), 0.89 (s, 9H, one diastereomer),

0.94 (s, 3H, one diastereomer), 0.96 (s, 9H, one diastereomer), 0.99 (s, 3H, one diastereomer), 1.03 (s, 3H, both diastereomers), 1.22 (s, 3H, one diastereomer), 1.20–2.20 (m, 5H, both diastereomers), 2.92 (s, 3H, one diastereomer), 3.06 (s, 3H, one diastereomer), 3.10–3.45 (m, 2H, both diastereomers), 3.74 (dd, J = 7.6, 13.4 Hz, 1H, one diastereomer), 4.00 (ddd, J = 2.0, 9.1, 14,8 Hz, one diastereomer), 4.65 (dd, J = 2.6, 7.6 Hz, 1H, one diastereomer), 5.05–5.15 (m, 1H, one diastereomer), 6.25–6.45 (m, 2H, one diastereomer), 7.00–7.20 (m, 1H, one diastereomer). IR: 2960, 1479, 1162, 1081, 1031 cm^{-1}. MS (FAB): *m/z* 297 (M^+). HRMS, *m/z* (M^+, $C_{28}H_{33}OS^+$) calcd. 297.2252, obsd. 297.2251.

(1*R*,2*S*,7*S*,8*S*)-3-Ethenyl-1,11,11-trimethyl-3-thiatricyclo [6.2.1.$0^{2,7}$] undecanium Trifluoromethanesulfonate (6)

A total of 0.548 g (1.17 mmol) of **18** was placed in a 25 mL, one-necked flask and 5 mL of CH_2Cl_2 was added. After the salt was dissolved in CH_2Cl_2, 5 mL of deionized water was added (biphasic system). A total of 0.136 g (0.58 mmol) of Ag_2O was added and the reaction mixture was stirred for a week. The reaction mixture was then diluted with CH_2Cl_2 and the organic layer was washed with water (2 × 50 mL), and then dried over Na_2SO_4. The solution was filtered through Celite and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (98:2 CH_2Cl_2:methanol) to give a oil, which transformed into a solid after 1 d. Yield: 0.19 g (42%), mp, 98–100°C. ^1H NMR ($CDCl_3$): δ 0.92 (s, 3H), 0.97 (s, 3H), 1.06 (s, 3H), 1.50–1.80 (m, 5H), 1.80–1.88 (m, 1H), 1.92–2.00 (m, 1H), 2.05–2.40 (m, 2H), 2.65–2.90 (m, 1H), 3.54 (ddd, J = 3.8, 10.1, 12.4 Hz, 1H), 4.11 (ddd, J = 7.3, 9.8, 12.4 Hz, 1H), 4.40 (d, J = 11.3 Hz, 1H), 6.39 (dd, J = 1.6, 8.8 Hz, 1H), 6.45 (dd, J = 1.6, 16.3 Hz, 1H), 6.99 (dd, J = 8.8, 16.3 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 15.7, 18.4, 19.2, 19.9, 21.6, 22.8, 31.7, 37.6, 39.7, 48.6, 49.3, 51.0, 65.4, 124.6, 137.9. IR: 3048, 2961, 1463, 1384, 1159, 1031, 976 cm^{-1}. MS (EI): *m/z* 236 (M^+), 210 ($M^+ - CH{=}CH_2$). HRMS, *m/z* (M^+, $C_{25}H_{24}S^+$) calcd. 236.1599, obsd. 236.1597.

(1*R*,2*S*,3*R*,4*S*)-1,7,7-Trimethyl-2-(2,2-dimethylpropoxy)-3-(methylthio)-bicyclo[2.2.1]-heptane (9)

A total of 2.0 g of NaH (50 mmol, 60% mineral oil dispersion) was placed in a 50 mL, three-necked, round-bottomed flask at room temperature under a nitrogen atmosphere and washed with petroleum ether (3 × 30 mL) by stirring, allowing the hydride to settle, and withdrawing the liquid via syringe. One neck of the reaction flask was connected to a water aspirator and the trace of petroleum ether was removed. The

aspirator hose was removed and a reflux condenser was connected, and then 2.0 g (30 mmol) of **8** in 30 mL 1-methyl-2-pyrrolidinone (NMP) was added to the flask. The reaction mixture was stirred for 0.5 h and 6.0 mL (45 mmol) of neopentyl iodide was syringed into the flask. The resulting mixture was heated to 130°C for 18 h and then 20 mL water was added. The mixture was extracted with ether (3 × 50 mL). The extracted ether was washed with 1N HCl (2 × 30 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL), water (3 × 50 mL), and then dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (petroleum ether) to give 1.18 g of a colorless oil (44%). ^1H NMR ($CDCl_3$): δ 0.79 (s, 3H), 0.91 (s, 3H), 0.93 (s, 9H), 1.20 (s, 3H), 0.85–1.15 (m, 2H), 1.45–1.55 (m, 1H), 1.65–1.80 (m, 2H), 2.10 (s, 3H), 2.90 (d, J = 7.8, 1H), 3.00 (d, J = 7.8, 1H), 3.28 (d, J = 7.8, 1H), 3.42 (d, J = 7.8, 1H). ^{13}C NMR ($CDCl_3$): δ 12.5, 17.2, 21.6, 22.1, 27.4, 29.2, 33.3, 34.0, 47.6, 50.8, 51.0, 59.7, 84.3, 89.3. IR: 2952, 1476, 1390, 1362, 1118, 1083 cm^{-1}. MS (EI): *m/z* 270 (M^+), 255 (M^+—CH_3), 222 (M^+—CH_3SH). Anal. Calcd. for $C_{16}H_{30}SO$: C, 71.05; H, 11.18. Found: C, 71.32; H, 11.15.

(1*R*,4*S*)-3-Allyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one

(+)-Camphor (6.1 g, 40 mmol) was added to a solution of lithium diisopropylamine (LDA), prepared from *n*-butyl lithium (18.0 mL, 2.5 M in hexane) and diisopropylamine (5.90 mL, 45 mmol) in THF (40 mL) at 0°C under a nitrogen atmosphere. The reaction mixture was stirred for 0.5 h. Tetramethylethylenediamine (TMEDA, 18.1 mL, 120 mmol) and allyl iodide (4.39 mL, 70 mmol) was added to the reaction mixture at 0°C. The resulting reaction mixture was stirred at 0°C for 2 h. It was quenched at 0°C with 1N HCl (50 mL) and extracted with ether (3 × 50 mL). The extracted ether was washed with saturated aqueous $NaHCO_3$ (2 × 50 mL), water (2 × 50 mL) and then dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography (2:98 ether:petroleum ether) to give 5.0 g (65%) of a colorless oil. The product is a mixture of exo and endo isomers and is used directly in the next reaction.

[(1*R*,3*S*,4*S*)-Endo]-3-allyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (12)

A total of 2.0 g (10.4 mmol) of allyl camphor (mixture of endo and exo isomers) and K*t*OBu (20.8 mL, 1.0 M in 2-methyl-2-propanol) was placed in a 100 mL, round bottomed flask at room temperature. The

resulting reaction mixture was stirred for 12 h and then 50 mL of 1 N HCl solution were added. The reaction mixture was extracted with ether (2 × 50 mL). The ether layer was washed with saturated aqueous $NaHCO_3$ (3 × 50 mL), water (2 × 50 mL), and then dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure to give 1.8 g of a colorless oil (90%). ^1H NMR ($CDCl_3$): δ 0.87 (s, 3H), 0.90 (s, 3H), 0.99 (s, 3H), 1.20–1.35 (m, 1H), 1.50–1.80 (m, 3H), 1.80–2.10 (m, 2H), 2.40–2.65 (m, 2H), 4.95–5.30 (m, 2H), 5.69–5.90 (m, 1H). ^{13}C NMR ($CDCl_3$): × 10.0, 19.8, 20.0, 20.4, 31.5, 31.8, 46,2, 46,5, 49,8, 59.1, 116.2, 136.9, 221.1. IR: 3077, 2963, 1738, 1640, 1447, 1373, 994, 912 cm^{-1}. MS (EI): *m/z* 192 (M^+), 177 (M^+–CH_3). Anal. Calcd. for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 80.84; H, 10.44.

[(1*R*,3*S*,4*S*)-Endo]-3-(3-hydroxypropyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (13)

Borane in tetrahydrofuran (19.3 mL, 1.0 M, 19.3 mmol) was placed in a dry, nitrogen-flushed, round-bottomed flask at 0°C. Cyclohexene (3.92 mL, 38.7 mmol) was added dropwise and the resulting mixture was stirred at 0°C for 1 h. A total of 2.48 g (12.9 mmol) of **12** was added to the slurry of dicyclohexylborane in THF. The cooling bath was removed and the mixture was stirred for 2 h at room temperature. For oxidation, $NaBO_3 \cdot 4H_2O$ (8.91 g, 57.9 mmol) and water (10 mL) was added and the mixture was stirred at room temperature for 2 h. The product was extracted into ether (3 × 50 mL) and the organic layer was washed with water (2 × 50 mL), and then dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography (1:4 ethyl acetate:petroleum ether) to give 1.3 g of a colorless oil (60%). ^1H NMR ($CDCl_3$): δ 0.87 (s, 3H), 0.90 (s, 3H), 1.00 (s, 3H), 1.20–1.45 (m, 3H), 1.50–1.90 (m, 6H), 2.05–2.20 (m, 1H), 2.30–2.40 (m, 1H), 3.50–3.60 (m, 2H). ^{13}C NMR ($CDCl_3$): δ10.0, 19.7, 20.0, 20.5, 24.0, 31.6, 46.3, 46.9, 49.7, 59.2, 62.8, 222.8. IR: 3431, 2937, 1737, 1449, 1374, 1061 cm^{-1}. MS (EI): *m/z* 210/(M^+), 192 (M^+–H_2O), 164 (M^+–H_2O–CH_2=CH_2). Anal. Calcd. for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 73.75; H, 10.46.

[(1*R*,3*S*,4*S*)-Endo]-3-(3-bromopropyl)-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-one (14)

In a dry, round-bottomed flask under a nitrogen atmosphere, **13** (1.21 g, 5.8 mmol) and PBr_3 (6.0 mL, 1.0 M in CH_2Cl_2) were added dropwise at 0°C. The resulting mixture was stirred for 15 min at 0°and for 1 h at room temperature. The reaction was quenched by adding 5 g of ice. The

reaction mixture was diluted with saturated NaCl and extracted with ether (2 × 50 mL). The ether layer was washed with saturated NaCl (2 × 50 mL), water (2 × 50 mL), and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure to give 1.24 g of a colorless oil (80%). ^1H NMR ($CDCl_3$): δ 0.87 (s, 3H), 0.90 (s, 3H), 1.00 (s, 3H), 1.20–1.95 (m, 8H), 2.00–2.06 (m, 1H), 2.30–2.40 (m, 1H), 3.30–3.50 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 10.0, 19.8, 20.0, 20.5, 26.6, 31.5, 31.8, 33.9, 46.3, 46.7, 49.3, 59.0, 221.8. IR: 2960, 1738, 1449, 1250 cm^{-1}. MS (EI): *m/z* 272 (M^+), 274 ($M^+ + 2$), 257 ($M^+ - CH_3$), 259 ($M^+ + 2 - CH_3$), 193 (M^+—Br), 165 (M^+—Br—CH_2=CH_2). Anal. Calcd. for $C_{13}H_{21}BrO$: C, 57.15; H, 7.75. Found: C, 57.69; H, 7.78.

[(1*R*,3*S*,4*S*)-Endo]-3-[3-(4-methoxyphenylmethylthio)-propyl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (15)

In a 100 mL, three-necked, round-bottomed flask, equipped with condensor, nitrogen inlet tube, and funnel, ethanol (2 mL), and sodium (0.105 g, 4.54 mmol) were placed. After sodium was dissolved in ethanol, 4-methoxy-α-toluenethiol (0.64 mL, 4.54 mmol) was added dropwise through the funnel. The resulting mixture was turned to a clear yellow solution. A total of 1.24 g (4.54 mmol) of **14** in 2 mL of ethanol was added and the resulting mixture was stirred for 4 h. The product was extracted with ether (2 × 50 mL) and the ether layer was washed with saturated aqueous $NaHCO_3$ (2 × 50 mL), water (2 × 50 mL), and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography (2:98 ethyl acetate:petroleum ether) to give 1.18 g of a colorless oil (75%). ^1H NMR ($CDCl_3$): δ0.84 (s, 3H), 0.88 (s, 3H), 0.99 (s, 3H), 1.20–1.40 (m, 2H), 1.40–1.80 (m, 6H), 1.95–2.00 (m, 1H), 2.25–2.45 (m, 3H), 3.67 (s, 2H), 3.80 (s, 3H), 6.84 (d, J = 8.6, 2H), 7.23 (d, J = 8.6, 2H). ^{13}C NMR ($CDCl_3$): δ 10.0, 19.8, 20.0, 20.5, 27.0, 28.2, 31.4, 31.5, 36.1, 46.2, 46.6, 49.6, 55.7, 59.0, 114.3, 130.3, 130.9, 159.0, 221.8. IR: 2956, 1737, 1610, 1511, 1455, 1301, 1249, 1175, 1036 cm^{-1}. MS (EI): *m/z* 346 (M^+). Anal. Calcd. for $C_{21}H_{30}O_2S$: C, 72.79; H, 8.73. Found: C, 72.68; H, 8.72.

(5*S*,8*R*)-3,4,5,6,7,8-Hexahydro-8,9,9-trimethyl-5,8-methano-2*H*-1-benzothiopyran (16)

Into a 100 mL, one-necked, round-bottomed flask equipped with a condensor, **15** (0.83 g, 2.40 mmol) was placed and 15 mL of trifluoroacetic acid and 1 mL of anisole was added. The resulting mixture was heated under reflux for 2 h. The excess of trifluoroacetic

acid was removed under reduced pressure and iodine solution (20 mL, 0.05 M in water) was added. The resulting mixture was stirred for 2 h. The product was extracted with ether (2 × 50 mL) and the extracted ether was washed with 5% $Na_2S_2O_3$ (20 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL), water (2 × 50 mL), and then dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography (100% petroleum ether) to give a 0.53 g of a colorless oil (100%). ^1H NMR ($CDCl_3$): δ 0.77 (s, 3H), 0.83 (s, 3H), 0.94 (s, 3H), 0.95–1.25 (m, 2H), 1.45–1.60 (m, 1H), 1.75–2.00 (m, 3H), 2.05–2.15 (m, 3H), 2.70–2.80 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 11.4, 19.7, 19.8, 24.0, 24.1, 26.4, 27.5, 33.6, 54.9, 56.4, 56.9, 132.7, 134.1. IR: 2928, 1751, 1282 cm^{-1}. MS (CI): *m/z* 209 ($M + H^+$), 193 (M^+-CH_3).

(1*R*,2*S*,7*S*,8*S*)-1,11,11-Trimethyl-3-thiatricyclo[6.2.1.$0^{2,7}$]undecane (17)

A total of 0.53 g (2.5 mmol) of **16** was dissolved in 20 mL of CH_2Cl_2 and 0.76 mL (12.0 mmol) of $BF_3 \cdot 2H_2O$ was added at 0°C. The resulting reaction mixture was stirred for 1 min at 0°C and 0.74 mL (4.6 mmol) of Et_3SiH was added. The reaction mixture was stirred for 2 days at room temperature. The mixture was poured into 50 mL of ice water and extracted with ether (2 × 50 mL). The extracted ether layer was washed with saturated aqueous $NaHCO_3$ (2 × 50 mL), water (2 × 50 mL), and then dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography (2:98 ethyl acetate:petroleum ether) to give 0.48 g of a colorless oil (90%). ^1H NMR ($CDCl_3$): δ 0.86 (s, 3H), 0.92 (s, 3H), 0.95 (s, 3H), 1.15–1.60 (m, 7H), 1.75–2.00 (m, 3H), 2.60–2.75 (m, 2H), 3.20–3.28 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 15.7, 18.8, 20.3, 21.8, 22.4, 26.2, 30.6, 37.6, 48.1, 49.7, 49.8, 53.6. IR: 2950, 2921, 1482, 1451, 1389, 1260 cm^{-1}. MS (EI): *m/z* 210 (M^+), 100 ($C_6H_8S^+$). Anal. Calcd. for $C_{13}H_{22}S$: C, 74.22; H, 10.54. Found: C, 73.76; H, 10.56.

(1*R*,2*S*,7*S*,8*S*)-3-(2-Bromoethyl)-1,11,11-trimethyl-3-thiatricyclo[6.2.1.$0^{2,7}$]undecanium Trifluoromethanesulfonate (18)

A total of 0.37 g (1.7 mmol) of **17** was placed in a 50 mL, one-necked flask and 5 mL of CH_2Cl_2 was added. A total of 1.35 g (5.30 mmol) of 2-bromoethyl trifluoromethanesulfonate was added and the resulting reaction mixture was stirred for 1 day at room temperature. The

solvent was removed under reduced pressure and the residue was purified by flash chromatography (95:5 CH_2Cl_2:methanol) to give an oil, which transformed into a solid after 1 day. Yield: 0.73 g (92%), mp, 84°C (decomp.). ^1H NMR ($CDCl_3$): δ 0.97 (s, 3H), 1.04 (s, 6H), 1.50–1.84 (m, 7H), 1.95–2.35 (m, 2H), 2.70–2.90 (m, 1H), 3.60–3.90 (m, 5H), 4.15–4.30 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 16.1, 18.4, 19.1, 20.1, 21.7, 22.9, 24.9, 31.4, 36.6, 37.4, 46.2, 48.8, 49.2, 51.0, 64.0, IR: 2955, 1162, 1031 cm^{-1}. MS (EI): *m/z* 316 (M^+), 318 ($M^+ + 2$), 237 (M^+—Br). HRMS, *m/z* (M^+, $C_{25}H_{25}BrS^+$) calcd. 316.0860, obsd. 316.0859.

(2*S*,3*S*,4*S*,5*S*)-2,5- Dibenzyloxymethyl-3,4-dibenzyloxy-1-methyltetrahydrothiophenium Trifluoromethanesulfonate (19)

The sulfide **7** (20 mg, 0.037 mmol) was dissolved in 2 ml of CH_2Cl_2. Methyl trifluoromethanesulfonate (17 μL, 0.15 mmol) was added and the reaction mixture was stirred for 36 h at rt under a nitrogen atmosphere. Flash chromatography (99:1 CH_2Cl_2:MeOH) gave an 85% yield of a brown oil (27 mg, 0.031 mmol). ^1H NMR ($CDCl_3$): δ 2.82 (s, 3H), 3.75–4.25 (m, 6H), 4.20–4.30 (m, 2H), 4.35–4.80 (m, 8H), 7.15–7.65 (m, 20H).

(2*S*,3*S*,4*S*,5*S*)-2,5-Dibenzyloxymethyl-3,4-dibenzyloxy-1-ethyltetrahydrothiophenium Trifluoromethanesulfonate (20)

The sulfide **7** (27 mg, 0.050 mmol) was dissolved in 2 ml of CH_2Cl_2. Ethyl trifluoromethanesulfonate (26 μL, 0.20 mmol) was added and the reaction mixture was stirred for 36 h at rt under a nitrogen atmosphere. Flash chromatography (99:1 CH_2Cl_2:MeOH) gave a 65% yield of a brown liquid (23 mg, 0.030 mmol). ^1H NMR ($CDCl_3$): δ 1.36 (t, J = 2.4 Hz, 3H), 3.35 (t, J = 2.4 Hz, 2H), 3.65–4.12 (m, 4H), 4.45–4.85 (m, 12H), 7.15–7.65 (m, 20H).

(2*R*,5*R*)-1,2,5-Trimethyltetrahydrothiophenium Perchlorate (21)

A total of 55 mg (0.47 mmol) of (2*R*,5*R*)-dimethylthiolane[12] was dissolved in acetone (2 mL). Iodomethane (178 ml, 2.83 mmol) was added and the reaction flask was capped and stirred for 24 h. Sodium perchlorate (63 mg, 0.52 mmol) was then added and the mixture was allowed to stir for another 4 h. The precipitate was then filtered off and the filtrate was concentrated in vacuo before being purified on a short silica gel column using 9:1 CH_2Cl_2:MeOH to obtain a white solid in a 40% yield

(44 mg, 0.19 mmol). ^{1}H NMR (D_2O): δ 1.55 (dd, J = 6.9, 0.9 Hz, 3H), 1.68 (dd, J = 6.9, 0.9 Hz, 3H), 1.75–2.35 (m, 2H), 2.45–2.60 (m, 2H), 2.85 (d, J = 0.9 Hz, 3H), 3.95–4.35 (m, 2H). ^{13}C NMR (CD_3OD): δ 13.9, 19.1, 19.9, 36.5, 36.9, 46.2, 64.0. IR: 3055, 1597, 1556, 1421, 1264 cm^{-1}.

Typical Base-Catalyzed Epimerization Study of Sulfonium Salts

The sulfonium salt **21** (18 mg, 0.025 mmol) was dissolved in THF (4 mL). At 0°C, NaH (60%, 1.5 mg, 0.0056 mmol) was added and the mixture was allowed to stir for 24 h while gradually reaching rt. A total of 5 mL of water was then added to the mixture and it was extracted with ether (2 × 5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to a brown liquid (90% yield). The ^{1}H NMR spectrum showed the starting material to be unchanged.

4-Ethenyl-4,5-dihydro-3*H*-dinaphtho[2,1-c:1′,2′-*e*] thiepinium Trifluoromethanesulfonate (23)

A mixture of **22** (244 mg., 0.78 mmol) and 2-bromoethyl trifluoromethanesulfonate (804 mg, 3.12 mmol) was stirred in distilled CH_2Cl_2 (10 mL) for 36 h at room temperature in a flask covered in aluminum foil and under a nitrogen atmosphere. Following removal of solvent in vacuo, the mixture was then purified by column chromatography (98:2 PE:EtOAc) to recover unreacted **22** and then 95:5 CH_2Cl_2:MeOH to obtain 108 mg of **23** as a clear oil (53%). ^{1}H NMR ($CDCl_3$): δ 3.69 (d, J = 11.4 Hz, 1H), 4.11 (d, J = 14.4 Hz, 1H), 4.75 (d, J = 14.4 Hz, 1H), 5.09 (d, J = 11.4 Hz, 1H), 6.38 (dd, J = 9, 16 Hz, 1H), 6.47 (d, J = 9 Hz, 1H), 6.70 (d, J = 16 Hz, 1H), 7.20–7.40 (m, 4H), 7.55–7.65 (m, 3H), 7.88 (d, J = 8.4 Hz, 1H), 8.0–8.15 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 44.1, 44.8, 118.7, 120.6, 122.9, 123.4, 124.3, 127.1, 127.2, 127.6, 127.7, 127.9, 128.9, 130.6, 130.9, 131.7, 131.8, 134.6, 134.8, 135.9, 136.0, 137.2. IR ($CDCl_3$): 3057, 2958, 1723, 1509, 1280, 1030 cm^{-1}. MS (EI): *m/z* 339 (M^+), 313 (M^+–C_2H_2), 280 (M^+–C_2H_2S). HRMS, *m/z* (M^+, $C_{24}H_{19}S^+$) calcd. 339.1207, obsd. 339.1207.

Dealkylation of 23

A total of 5 mL of distilled THF was added to a 25 mL, 2-necked flask containing **23** (56 mg, 0.11 mmol). The solution was cooled to 0°C with an ice bath before NaH (60% in mineral oil, 3.2 mg, 0.12 mmol) was added. The reaction was monitored by tlc and showed the presence

of **22** within 30 min. The solution was allowed to stir for another 3 h at 0°C before allowing it to warm to room temperature and stirring it overnight. The solvent was then removed under reduced pressure and the paste redissolved in water (15 mL) and extracted with CH_2Cl_2 (2×15 mL). The organic layer was dried over $MgSO_4$, filtered, and the solvent removed in vacuo before purifying by flash chromatography (98:2 P:/EtOAc) to recover 24.7 mg (69%) of **22**.

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