Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 999–1005

TETRAHEDRON: *ASYMMETRY*

A camphor-derived vinylsulfonium salt as a reagent for a cycloannulation

Kyung-hee Kim and Leslie S. Jimenez*

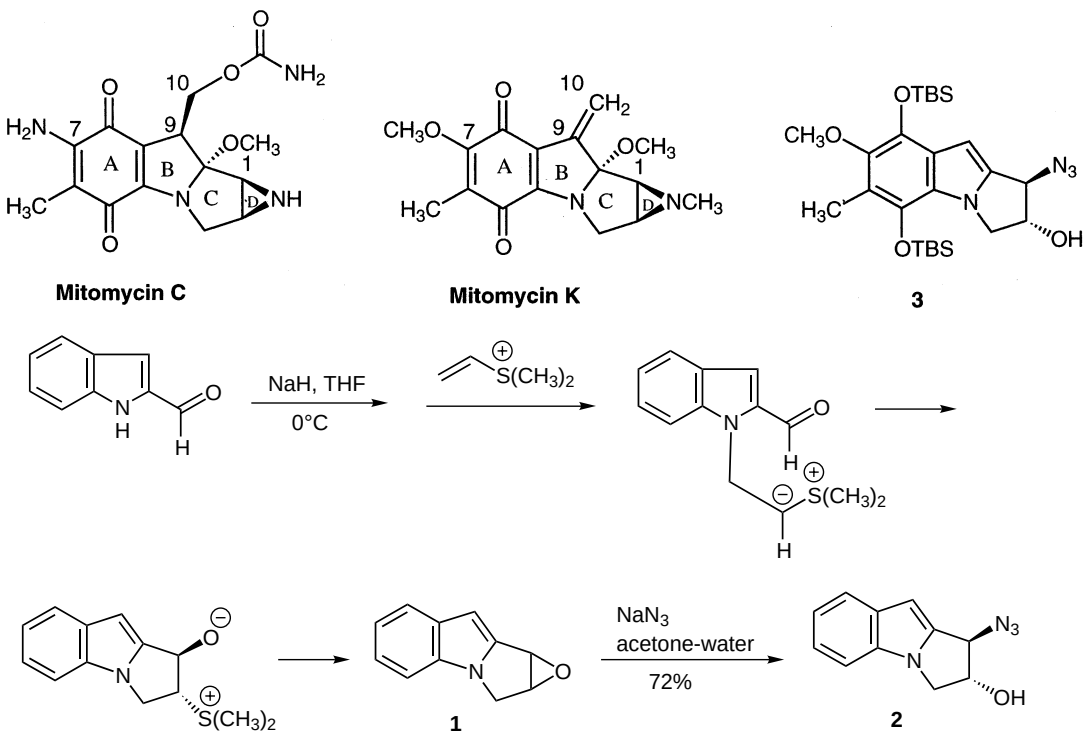
Department of Chemistry, Rutgers University, Piscataway, NJ 08854-8087, USA

Received 29 January 2001; accepted 27 March 2001

Abstract—A chiral, non-racemic vinylsulfonium salt **6** was prepared from camphorquinone in seven steps and reacted with indole-2-carboxaldehyde to give a tricyclic azido alcohol **2** in a 35% yield and 43% e.e. and a 40% recovery of the chiral sulfide.

1. Introduction

We previously discovered a method for the formation of the tetracyclic ring system of the antitumor antibiotic, mitomycin C, by reaction of dimethylvinylsulfonium iodide with the sodium salt of indole-2-carboxaldehyde to give the tetracyclic oxirane **1**, which upon treatment with sodium azide formed 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] Therefore we were interested in chiral, non-racemic vinylsulfonium salts to attempt an asymmetric synthesis of this key intermediate.

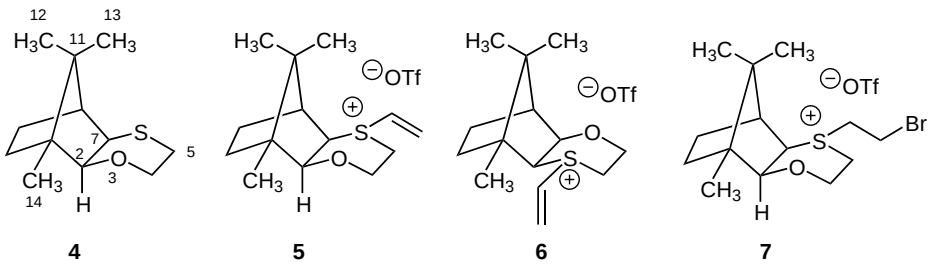


Scheme 1.

* Corresponding author. E-mail: jimenez@rutchem.rutgers.edu

0957-4166/01/$ - see front matter
PII: S0957-4166(01)00170-7

The five-step synthesis of the 1,4-oxathiane **4** from camphor has been previously reported by Aggarwal et al. for use as a reagent in the enantioselective synthesis of stilbene oxides.[3] There are a number of chiral, non-racemic, cyclic or bicyclic sulfides reported in the literature which have been studied as reactants in asymmetric epoxidation with aryl aldehydes.[4] The advantage of rigid, cyclic versus acyclic sulfides is that alkylation of the former almost always results in the formation of a single diastereomeric sulfonium salt. Thus we set out to synthesize vinylsulfonium salt **5** and the related **6** to determine their efficacy in the asymmetric version of the annulation outlined in Scheme 1. It was expected that **6** would prove to be the better reagent since it was thought that the C-(14) methyl group would help to block one side of the vinyl group, adding to the blocking effect of the C-(13) methyl group. In practice, this prediction turned out to be correct.



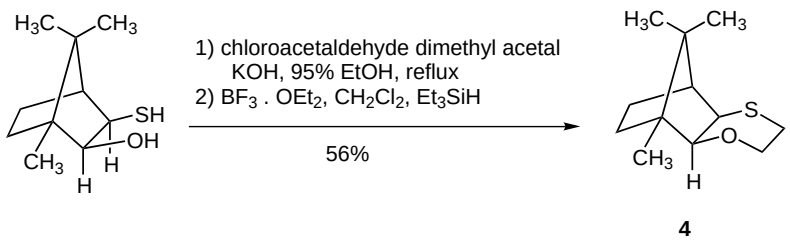
4 **5** **6** **7**

2. Results and discussion

The vinylsulfonium salt **5** was prepared from 1,4-oxathiane **4** in two steps. Alkylation with 2-bromoethyl triflate then afforded bromide **7** as a single diastereomer in an 80% yield. Treatment of **7** with silver(I) oxide in a biphasic dichloromethane/water solvent system resulted in a 50% yield of **5**. Vinylsulfonium salt **5** was then used in the cyclization with indole-2-carboxaldehyde and sodium azide to form the azido alcohol **2** in 40% yield. The chiral sulfide **4** was recovered after the reaction (25% recovery). The e.e.s were calculated by forming the diastereomeric Mosher's esters of **2** and integrating the peak areas of two separate diastereomeric hydrogens in the ^{1}H NMR spectra and averaging the results. Vinylsulfonium salt **5** induced a $\sim$10% e.e. for the annulation reaction. This was not entirely unexpected since **5** has only a hydrogen at the C-(8) position which would not block that face of the vinyl group. However, vinylsulfonium salt **6**, which has a methyl group at the C-(14) position to block one face of the vinyl group, was expected to transfer chirality more effectively than **5**.

The synthesis of cyclic sulfide **8** was more problematic. Originally a synthesis similar to that of **4** was envisaged (Scheme 2).[3] *exo*-3-Hydroxycamphor was prepared by the reduction of (1*R*)-(−)-camphorquinone with LS-Selectride® at 0°C in a 47% yield.[5] The source of the LS-Selectride® proved to be critical. Our first bottle of LS-Selectride® was obtained from Aldrich and gave reduction exclusively at the 3-position of camphorquinone. However, two later batches of LS-Selectride® purchased from the same company were much more active and gave reduction indiscriminately at both the 2- and 3-positions.[6] Fortunately, LS-Selectride® purchased from Acros again resulted in a selective reduction at the 3-position.

Benzyl sulfide **9** has been previously prepared by the reaction of camphor and benzylthiol in the presence of the Lewis acid $BF_3{\cdot}OEt_2{\cdot}H_2O$.[7] *exo*-3-Hydroxycamphor was therefore reacted with benzylthiol in the presence of boron trifluoride diethyl etherate and triethylsilane to produce a compound which was assigned structure **10**. The mass spectrum of this compound gave a parent ion at m/z 186 as expected for **10**. In addition the ^{1}H and ^{13}C NMR spectra in $CDCl_3$ for this compound differed markedly from that reported previously for the 2-*exo*, 3-*exo* diol **11**.[8] The thiol **10** was reacted with chloroacetaldehyde dimethyl acetal under basic conditions in an attempt to form **12**. After numerous reactions to form **12** failed under various conditions, the structural assignment for **10** was re-examined. The reaction of *exo*-3-hydroxycamphor with boron trifluoride diethyl etherate and triethylsilane in the absence of benzylthiol produced an identical product as had been formed previously in its presence. Therefore, it was



4

Scheme 2.

clear that the 2-*exo*, 3-*exo* diol **11** was being formed. The ^1H and ^{13}C NMR spectra in $CDCl_3/CD_3OD$ of **11** have been previously reported and were nearly identical to the spectra we obtained in $CDCl_3$.[9]

exo-3-Hydroxycamphor was converted into the corresponding methyl ether **13** by treatment with methyl triflate and 2,6-di-*tert*-butylpyridine in dichloromethane.[10] Reaction of **13** with triethylsilane and either boron trifluoride diethyl etherate or $BF_3{\cdot}OEt_2{\cdot}H_2O$[11] gave **14** with or without benzylthiol. Thus, it appears that a substituent at the 3-position disfavors hemithioacetal formation at the 2-position even in the presence of a Lewis acid.

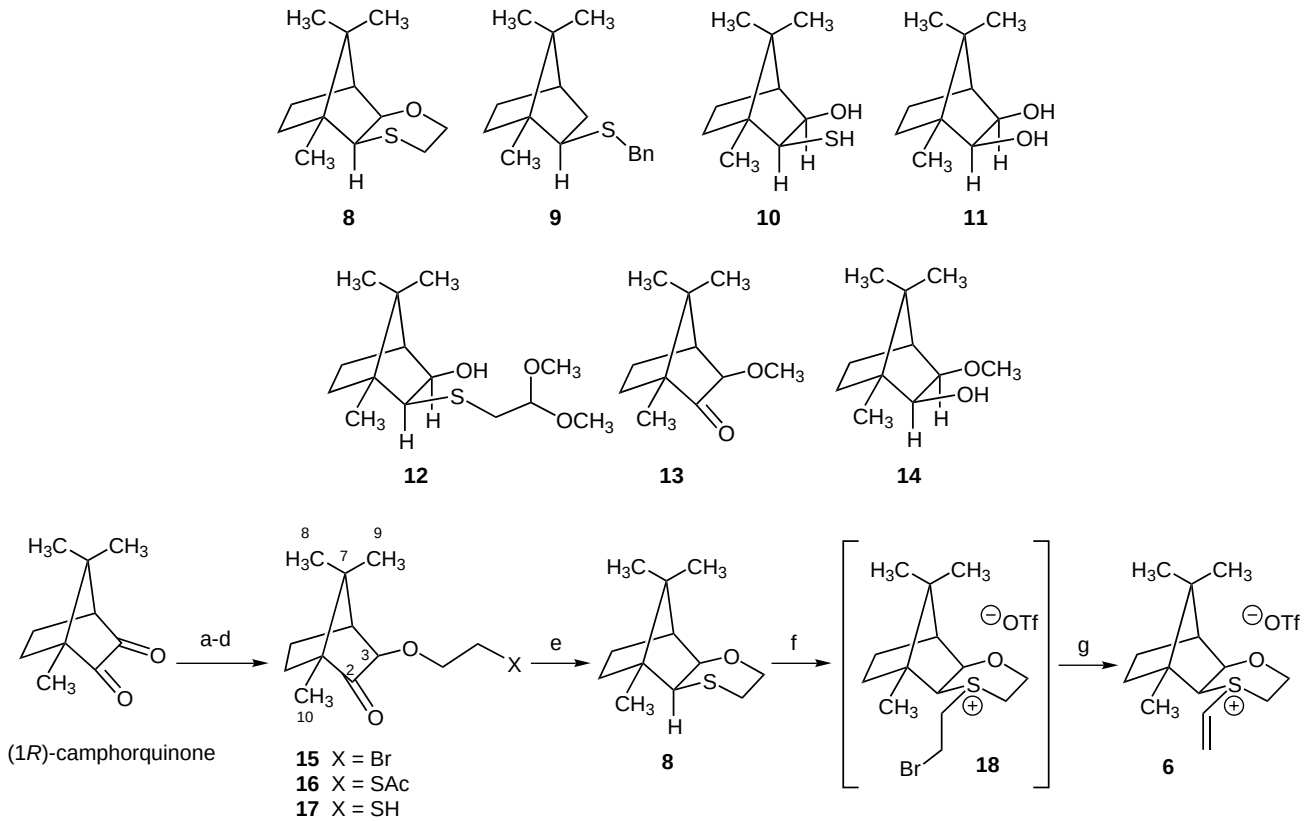
Therefore, we turned to keto thiol **17**, as an intermediate that might undergo intramolecular cyclization more readily under reductive conditions to form the sulfide **8** (Scheme 3). *exo*-3-Hydroxycamphor was converted into the bromide **15** by reaction with 2-bromoethyl triflate and 2,6-di-*tert*-butylpyridine in dichloromethane in a 55% yield. The reaction of **15** with potassium thioacetate in refluxing acetone produced **16** in a 98% yield. Deprotection of the acetyl group of **16** using sodium thiomethoxide in methanol produced **17** in a quantitative yield;[12] however, the yield after purification by flash column chromatography was only 15%. Therefore the crude compound **17** was used directly in the next reaction to avoid the loss of yield during the purification. The cyclic sulfide **8** was then obtained by the intramolecular cyclization of thiol **17** using $BF_3{\cdot}OEt_2{\cdot}H_2O$ and triethylsilane (Scheme 3).[3]

Alkylation of **8** with 2-bromoethyl trifluoromethanesulfonate gave sulfonium salt **18**.[13] On purification of compound **18** by flash chromatography vinylsulfonium salt **6** was formed as a mixture with **18**. The mixture was treated with silver(I) oxide in water/dichloromethane to obtain **6** in a 30% yield from **8**.

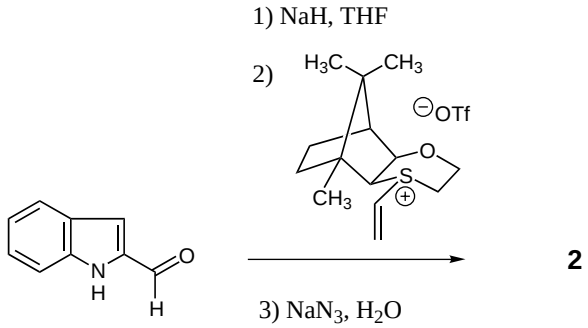
Vinylsulfonium salt **6** was reacted with the sodium salt of indole-2-carboxaldehyde to form the tetracyclic oxirane **1** in situ, sodium azide was then added and the azido alcohol **2** (Scheme 4) was isolated in a 35% yield. The chiral auxiliary sulfide **8** was recovered after the annulation reaction (40% recovery). E.e.s were determined by preparing the Mosher's ester of **2** and integrating the peak areas of two different diastereomeric hydrogens in the ^1H NMR spectra.[5] Vinylsulfonium salt **6** gave 43% e.e. for this annulation reaction. The absolute stereochemistry of the major enantiomer of azido alcohol **2** was not determined.

3. Conclusion

Vinylsulfonium salt **6**, which has a methyl group at C-(14) to block one face of the vinyl group, transfers chirality more efficiently than **5** as expected. However, the moderate enantioselectivity observed for **6** indicates



Scheme 3. (a) LS-Selectride®, THF, −5°C; then 50% NaOH, 30% H_2O_2 (47%); (b) $BrCH_2CH_2OTf$, 2,6-di-*t*-butylpyridine, CH_2Cl_2, 7 days (55%); (c) KSAc, acetone, rt, 1 h (98%); (d) NaSMe, MeOH, rt, 1 h; (e) $BF_3{\cdot}OEt_2{\cdot}H_2O$, CH_2Cl_2, Et_3SiH (56%); (f) 3.0 equiv. $BrCH_2CH_2OTf$, CH_2Cl_2, 1 day; (g) Ag_2O; 1:1 H_2O:CH_2Cl_2 (30%).



Scheme 4.

that the methyl group is not a large enough blocking group to effect complete facial selectivity. In the future, vinylsulfonium salts with larger, bulkier groups at the C-(13) and C-(14) positions will be designed and synthesized.

4. 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 residual $CHCl_3$. 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.

4.1. 1-Azido-2,3-dihydro-2-[(*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyloxy]-1*H*-pyrrolo[1,2-*a*]indole. Mosher's ester of 2

Into a 10 mL flask CCl_4 (150 μL), pyridine (150 μL, 1.89 mmol), and Mosher's reagent, (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (13 μL, 0.07 mmol) were added via syringe. The alcohol **2** (5 mg, 0.023 mmol) in CCl_4 (2 mL) was added. The reaction mixture was then stirred at rt for 3 h. Excess of 3-dimethylaminopropylamine (12 μL, 0.10 mmol) was added and stirred for 30 min. The reaction mixture was diluted with ether (30 mL) and washed with cold aqueous HCl (1N, 10 mL), sat. aqueous $NaHCO_3$ (10 mL), and NaCl (10 mL) solution. The organic layer was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give a bright yellow paste (7 mg, 0.016 mmol, 72%). Approximate e.e.s were determined by integrating the signal areas of two of the diasteromeric hydrogens and averaging the results.

One diastereomer: ^{1}H NMR ($CDCl_3$): δ 3.48 (q, J = 1.2, 3H, OMe), 4.16 (dd, J = 2.4, 11.8, 1H, H-3), 4.64 (dd, J = 5.8, 11.8, 1H, H-3), 5.04 (dd, J = 0.8, 2.2, 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 = 7.8, 1H).

The other diastereomer: ^{1}H NMR ($CDCl_3$): δ 3.51 (q, J = 1.2, 3H, OMe), 4.02 (dd, J = 2.8, 11.7, 1H, H-3), 4.64 (dd, J = 5.8, 11.7, 1H, H-3), 5.13 (dd, J = 0.7, 2.5, 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 = 7.8, 1H).

4.2. [(1*R*,2*S*,7*R*,8*S*)-*exo*]-6-(2-Bromoethyl)-1,11,11-trimethyl-3-oxa-6-thiatricyclo[6.2.1.0^{2,7}]undecanium trifluoromethanesulfonate 7

Compound **4** (0.125 g, 1.58 mmol) was placed in a 50 mL one-necked flask and CH_2Cl_2 (3 mL) was added. A solution of (0.92 g, 3.60 mmol) of 2-bromoethyl trifluoromethanesulfonate in CH_2Cl_2 (2 mL) was added. The resulting mixture was stirred for 2 days. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (CH_2Cl_2:methanol 95:5) to give a brown solid (0.215 g, 80%). Mp 107–109°C; ^{1}H NMR ($CDCl_3$): δ 0.94 (s, 3H), 0.96 (s, 3H), 1.24 (s, 3H), 1.25–1.45 (m, 2H), 1.55–1.65 (m, 1H), 1.85–2.00 (m, 1H), 2.20 (d, J = 4.5 Hz, 1H), 3.75–3.90 (m, 4H), 3.95–4.10 (m, 1H), 4.12–4.20 (m, 4H), 4.20–4.55 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 11.2, 20.9, 21.7, 25.0, 27.8, 32.9, 37.6, 45.8, 48.9, 49.2, 49.9, 60.6, 61.3, 85.5; IR: 2964, 1265, 1163, 1030 cm^{-1}; MS (FAB): m/z 319 (M^+), 321 (M^++2); HRMS(CI): m/z (M^+, $C_{14}H_{24}BrOS^+$) calcd 319.07312, obsd 319.07315.

4.3. [(1*R*,2*S*,7*R*,8*S*)-*exo*]-6-Ethenyl-1,11,11-trimethyl-3-oxa-6-thiatricyclo[6.2.1.0^{2,7}]undecanium trifluoromethanesulfonate 5

Compound **7** (0.127 g, 0.27 mmol) was placed in a 25 mL one-necked flask and CH_2Cl_2 (2 mL) was added. After the salt was dissolved in CH_2Cl_2, deionized water (2 mL) was added (biphasic system), followed by Ag_2O (0.035 g, 0.15 mmol) and the resulting mixture was stirred for 5 days. 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® to give a clear solution and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2:methanol 95:5) to give a brown solid (0.052 g, 50%). Mp 115–117°C; ^{1}H NMR ($CDCl_3$): δ 0.93 (s, 3H), 0.96 (s, 3H), 1.24 (s, 3H), 1.30–1.50 (m, 3H), 1.85–2.00 (m, 1H), 2.01 (d, J = 4.8, 1H), 3.55–3.70 (m, 1H), 3.92 (d, J = 6.5 Hz, 1H), 4.00–4.15 (m, 1H), 4.20–4.40 (m, 1H), 4.48 (d, J = 6.5 Hz, 1H), 4.50–4.60 (m, 1H), 6.47 (dd, J = 8.8, 1.5 Hz, 1H), 6.49 (dd, J = 16, 1.5 Hz, 1H), 7.15 (dd, J = 8.8, 16 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 11.3, 21.3, 21.8, 27.7,

32.9, 39.2, 47.8, 49.1, 50.3, 61.2, 62.6, 85.3, 122.3, 138.9; IR: 3054, 2962, 1258, 1159, 1030 cm^{-1}; MS (EI): m/z 239 (M^+); HRMS(CI): m/z (M^+, $C_{14}H_{23}OS^+$) calcd 239.14696, obsd 239.14705.

4.4. [(1*R*,3*R*,4*S*)-*exo*]-3-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one

Into a 100 mL, three-necked flask, LS-Selectride® (1.0 M, 6.0 mL, 6.0 mmol) in THF and anhydrous THF (15 mL) were added via a syringe at −5°C (ice–salt bath). (1*R*)-(−)-camphorquinone (1.0 g, 6.0 mmol) was then added to the mixture under a nitrogen atmosphere. The mixture was stirred for 1 h at 0°C. The reaction was quenched by adding water (2 mL) and ethanol (10 mL) at 0°C. The mixture was stirred for 30 min. Aqueous NaOH solution (50% by wt, 3 mL) and H_2O_2 (30%, 5 mL) was added to the reaction mixture. The aqueous phase was saturated with anhydrous K_2CO_3. The organic layer was separated, the aqueous layer was extracted with ether (2×50 mL), and the ether layer was washed with water (3×50 mL). The organic layer was dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give a yellow oil. The crude compound was purified by flash chromatography (petroleum ether:ethyl acetate:85:15) to give a white solid (0.47 g, 47%). Mp, 211–213°C (lit.[14] 209–211°C); ^{1}H NMR ($CDCl_3$): δ 0.93 (s, 3H). 0.94 (s, 3H), 0.99 (s, 3H), 1.20–1.50 (m, 2H), 1.60–1.70 (m, 1H), 1.90–2.05 (m, 1H), 2.08–2.10 (m, 1H), 2.30–2.50 (bs, 1H), 3.73 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 9.4, 20.4, 21.4, 25.5, 28.9, 47.1, 49.6, 57.4, 77.6, 220.4; IR: 3458, 2961, 1746, 1454, 1393, 1374, 1267, 1014 cm^{-1}; MS (CH_4/CI): m/z 169 ($M+H^+$), 186 ($M+NH_4^+$).

4.5. [(1*R*,3*R*,4*S*)-*exo*]-3-Methoxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one[15] 13

Into a 50 mL, three-necked flask, 3-*exo*-hydroxycamphor (0.050 g, 0.30 mmol) and CH_2Cl_2 (2 mL) were placed under a nitrogen atmosphere. 2,6-Di-*tert*-butylpyridine (0.13 mL, 0.60 mmol) and methyl triflate (0.10 g, 0.60 mmol) were added to the reaction flask. The mixture was stirred at rt for 2 days. The reaction was quenched by addition of water (2 mL). The mixture was diluted with CH_2Cl_2, then washed sequentially with 1N HCl, sat. $NaHCO_3$, sat. NaCl solution, and then dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure to give a brown oil. The crude compound was purified by flash chromatography (a gradient of 98:2, 95:5, 90:10, 80:20, 50:50 petroleum ether:ethyl acetate was used) to give a colorless oil (0.050 g, 91%); ^{1}H NMR ($CDCl_3$): δ 0.86 (s, 3H), 0.87 (s, 3H), 0.91 (s, 3H), 1.30–1.40 (m, 2H), 1.60–1.80 (m, 1H), 1.85–2.15 (m, 2H), 3.20 (s, 1H), 3.45 (s, 3H); lit.[15] ^{1}H NMR (CCl_4): δ 0.86 (s, 3H), 0.90 (s, 3H), 0.93 (s, 3H), 1.31 (m, 1H), 1.35 (m, 1H), 1.77 (m, 1H), 1.96 (m, 1H), 1.98 (d, 1H), 3.12 (s, 1H), 3.48 (s, 3H).

4.6. [(1*R*,2*S*,3*R*,4*S*)-2-*exo*-3-*exo*]-3-Methoxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol 14

Into a 50 mL flask, the ketone **13** (0.030 g, 0.16 mmol) and dichloromethane (1 mL) were added under a nitrogen atmosphere at 0°C. $BF_3{\cdot}OEt_2{\cdot}H_2O$ (0.15 mL, 0.94 mmol) was added and after 5 min triethylsilane (0.03 mL, 0.30 mmol) was added at 0°C. The resulting mixture was stirred overnight while the reaction temperature warmed to rt. The reaction was quenched by adding ice-water and the resulting mixture was extracted into dichloromethane (2×50 mL). The organic layer was washed with aqueous $NaHCO_3$ (1N, 30 mL), and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography (4:1 petroleum ether:ethyl acetate) to give a white solid (0.024 g, 80%); ^{1}H NMR ($CDCl_3$): δ 0.79 (s, 3H), 0.94 (s, 3H), 0.80–0.95 (m, 2H), 1.04 (s, 3H), 1.40–1.50 (m, 1H), 1.60–1.70 (m, 1H), 1.80 (d, $J=5.1$, 1H), 2.60–2.80 (bs, 1H), 3.36 (d, $J=6.9$ Hz, 1H), 3.43 (s, 3H), 3.61 (d, $J=6.9$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 11.3, 21.0, 22.2, 24.5, 33.4, 46.8, 47.7, 49.0, 58.6, 80.0, 85.8.

4.7. [(1*R*,3*R*,4*S*)-*exo*]-3-(2-Bromoethoxy)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 15

Into a 100 mL, three-necked flask, 3-*exo*-hydroxycamphor (0.80 g, 4.7 mmol) and CH_2Cl_2 (7 mL) were placed under a nitrogen atmosphere. 2,6-Di-*t*-butylpyridine (2.12 mL, 9.4 mmol) and a solution of 2-bromoethyl triflate (2.42 g, 9.4 mmol) in CH_2Cl_2 (2 mL) was added to the reaction flask. The mixture was stirred at rt. After 2 and 4 days, more di-*tert*-butylpyridine (2.12 mL, 9.4 mmol) and 2-bromoethyl triflate (2.41 g, 9.4 mmol) were added to the reaction mixture each time. The resulting mixture was stirred for another 3 days. The reaction was quenched by addition of water (5 mL). The mixture was diluted with CH_2Cl_2, then washed sequentially with 1N HCl, sat. $NaHCO_3$, brine, and then dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure to give a brown oil. The crude compound was purified by flash chromatography (a gradient of 98:2, 95:5, 90:10, 80:20, 60:40 petroleum ether:ethyl acetate was used) to give an oily compound (0.75 g, 55%) and some starting material. ^{1}H NMR ($CDCl_3$): δ 0.92 (s, 3H), 0.93 (s, 3H), 1.00 (s, 3H), 1.30–1.40 (m, 2H), 1.60–1.70 (m, 1H), 1.90–2.00 (m, 1H), 2.10–2.20 (m, 1H), 3.44 (s, 1H), 3.40–3.50 (m, 2H), 3.80–3.90 (m, 1H), 4.00–4.20 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 9.4, 20.2, 21.4, 25.3, 29.3, 30.7, 46.9, 48.3, 57.5, 71.3, 84.8, 217.5; IR: 2962, 1747, 1275, 1131 cm^{-1}; MS (DCI/NH_3): m/z 292 ($M+NH_4^+$), 294 ($M+NH_4^+$+2). Anal. calcd for $C_{12}H_{19}BrO_2$: C, 52.38; H, 6.96. Found: C, 52.32; H, 6.97%.

4.8. [(1*R*,3*R*,4*S*)-*exo*]-3-(2-Thioacetylethoxy)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 16

Into a 50 mL flask, potassium thioacetate (0.45 g, 3.8 mmol) was placed, and acetone (5 mL) was added. Into this heterogeneous solution, the bromide **15** (0.70 g, 2.5 mmol) in acetone (3 mL) was then added. The resulting mixture was stirred for 1 h at rt. The solvent was removed under reduced pressure and the residue was diluted with CH_2Cl_2. The solution was washed with $NaHCO_3$ (2×50 mL) and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure to give a brown oil. The crude compound was purified by flash chromatography (96:4 petroleum ether:ethyl acetate) to give a color-

less oily compound (0.65 g, 98%). ^{1}H NMR ($CDCl_3$): δ 0.90 (s, 3H), 0.92 (s, 3H), 0.97 (s, 3H), 1.20–1.40 (m, 2H), 1.55–1.65 (m, 1H), 1.90–2.00 (m, 1H), 2.08–2.10 (m, 1H), 2.32 (s, 3H), 3.00–3.10 (m, 2H), 3.40 (s, 1H), 3.60–3.70 (m, 1H), 3.80–3.90 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 9.4, 20.2, 21.3, 25.2, 29.3, 29.4, 30.8, 46.9, 48.2, 57.4, 69.9, 84.6, 195.5, 217.5; IR: 2959, 2873, 1749, 1692, 1129, 1015 cm^{-1}; MS (DCI/NH_3): m/z 271 ($M+H^+$), 288 ($M+NH_4^+$). Anal. calcd for $C_{14}H_{22}O_3S$: C, 62.19; H, 8.20. Found: C, 62.13; H, 8.11%.

4.9. [(1*R*,3*R*,4*S*)-*exo*]-3-(2-Mercaptoethoxy)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 17

Into a 50 mL flask was placed compound **16** (0.64 g, 2.4 mmol), and anhydrous methanol (10 mL) was added. Sodium thiomethoxide (0.165 g, 2.4 mmol) was added to this solution. The resulting mixture was stirred at rt for 1 h. An aqueous HCl solution (0.6N, 10 mL) was added to the reaction flask. The solution was extracted with CH_2Cl_2 (2×30 mL). The organic layer was washed with brine (2×50 mL) and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure to give a yellow oil (0.57 g). The crude compound was purified by flash chromatography (96:4 petroleum ether:ethyl acetate) to give a colorless oil in 15% yield. The crude compound was used directly for the next reaction to avoid the loss of mass by purification. ^{1}H NMR ($CDCl_3$): δ 0.94 (s, 3H), 0.95 (s, 3H), 1.00 (s, 3H), 1.20–1.50 (m, 2H), 1.55–1.70 (m, 1H), 1.90–2.05 (m, 2H), 2.10–2.15 (m, 1H), 2.80–2.90 (m, 2H), 3.46 (s, 1H), 3.80–3.90 (m, 1H), 4.00–4.10 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 9.5, 20.4, 21.5, 25.5, 29.5, 38.4, 39.2, 47.1, 48.4, 70.1, 85.1, 217.5; IR: 2962, 1748 cm^{-1}; MS (DCI/NH_3): m/z 229 ($M+H^+$), 246 ($M+NH_4^+$).

4.10. [(1*R*,2*S*,7*R*,8*S*)-*exo*]-1,11,11-Trimethyl-6-oxa-3-thiatricyclo[6.2.1.0^{2,7}]undecane 8

Into a 100 mL flask was placed crude compound **17** (0.57 g, 2.5 mmol), and CH_2Cl_2 (20 mL) was added. $BF_3{\cdot}OEt_2{\cdot}H_2O$ (0.40 mL, 2.5 mmol), was added and after 5 min triethylsilane (1.34 mL, 12.5 mmol) was added at 0°C. The resulting mixture was stirred for 4 h allowing the reaction to warm to rt. The reaction was quenched by adding ice-water and the resulting mixture was extracted into dichloromethane (2×50 mL). The organic layer was washed with $NaHCO_3$ (1N, 30 mL), and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography (98:2 petroleum ether:ethyl acetate) to give a colorless oil (0.30 g, 56%); ^{1}H NMR ($CDCl_3$): δ 0.83 (s, 3H), 0.94 (s, 3H), 1.00–1.20 (m, 2H), 1.40 (s, 3H), 1.55–1.65 (m, 1H), 1.70–1.80 (m, 1H), 1.88 (d, J=4.9, 1H), 2.60–2.80 (m, 2H), 3.08 (d, J=6.8, 1H), 3.37 (d, J=6.8, 1H), 3.55 (ddd, J=10.4, 6.8, 3.8, 1H), 3.88 (ddd, J=10.4, 8.5, 8.5, 1H); ^{13}C NMR ($CDCl_3$): δ 12.6, 21.8, 22.1, 24.6, 26.4, 37.9, 48.4, 49.2, 51.3, 56.2, 62.8, 81.2; IR: 2956, 1479, 1391, 1096 cm^{-1}; MS (CI): m/z 213 ($M+H^+$). Anal. calcd for $C_{12}H_{20}OS$: C, 67.87; H, 9.49. Found: C, 67.67; H, 9.42%.

4.11. [(1*R*,2*S*,7*R*,8*S*)-*exo*]-3-Ethenyl-1,11,11-trimethyl-6-oxa-3-thiatricyclo[6.2.1.0^{2,7}]undecanium trifluoromethanesulfonate 6

Compound **8** (0.30 g, 1.42 mmol) was placed in a 100 mL one-necked flask and CH_2Cl_2 (2 mL) was added. A solution of 2-bromoethyl trifluoromethanesulfonate (1.10 g, 4.24 mmol) in CH_2Cl_2 (2 mL) was added. The resulting mixture was stirred for 1 day. Excess 2-bromoethyl trifluoromethanesulfonate was removed by flash chromatography (100% CH_2Cl_2). On purification some of the crude compound **18** formed **6** spontaneously. The mixture of **18** and **6** was placed in a 50 mL, one-necked flask, CH_2Cl_2 (3 mL) was added to dissolve the compounds and deionized water (3 mL) was added. Ag_2O (0.18 g, 0.75 mmol) was added and the resulting mixture was stirred for 1 day. 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® to give a clear solution and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (9:1 CH_2Cl_2:methanol) to give a brown oil (0.16 g, 30%); ^{1}H NMR ($CDCl_3$): δ 0.91 (s, 3H), 1.00 (s, 3H), 1.23 (s, 3H), 1.20–1.30 (m, 1H), 1.40–1.60 (m, 1H), 1.60–1.75 (m, 1H), 1.75–1.80 (m, 1H), 2.00–2.05 (m, 1H), 3.60–3.80 (m, 1H), 4.08 (d, J=6.3, 1H), 4.00–4.05 (m, 1H), 4.20–4.40 (m, 1H), 4.43 (d, J=6.3, 1H), 4.40–4.50 (m, 1H), 6.44 (dd, J=9.0, 1.9, 1H), 6.51 (dd, J=16.2, 1.9, 1H), 7.02 (dd, J=9.0, 16.2, 1H); ^{13}C NMR ($CDCl_3$): δ 13.2, 20.8, 21.5, 23.6, 36.1, 39.8, 49.5, 50.3, 50.8, 60.9, 67.7, 82.1, 123.8, 138.3; IR: 3046, 2961, 1258, 1159, 1030 cm^{-1}; MS (CI): m/z 239 (M^+), 213 (M^+–CH=CH_2+H^+); HRMS(CI): m/z (M^+, $C_{14}H_{23}OS^+$) calcd 239.14696, obsd 239.14681.

Acknowledgements

We thank the National Science Foundation (CHE-0074836) and Schering-Plough Research Institute, Kenilworth, NJ for financial support.

References

1. Wang, Z.; Jimenez, L. *J. Am. Chem. Soc.* **1994**, *116*, 4977–4978.
2. (a) Wang, Z.; Jimenez, L. *Tetrahedron Lett* **1996**, *37*, 6049–6052; (b) Wang, Z.; Jimenez, L. *J. Org. Chem.* **1996**, *61*, 816–818; (c) Dong, W.; Jimenez, L. *J. Org. Chem.* **1999**, *64*, 2520–2523.
3. Aggarwal, V. K.; Ford, J. G.; Jones, R. V. H.; Fieldhouse, R. *Tetrahedron: Asymmetry* **1998**, *9*, 1801–1807.
4. (a) Breau, L.; Ogilvie, W. W.; Durst, T. *Tetrahedron Lett.* **1990**, *31*, 35–38; (b) Breau, L.; Durst, T. *Tetrahedron: Asymmetry* **1991**, *2*, 367–370; (c) Solladie-Cavallo, A.; Adib, A. *Tetrahedron* **1992**, *48*, 2453–2464; (d) Solladie-Cavallo, A.; Adib, A.; Schmitt, M.; Fischer, J.; DeCian, A. *Tetrahedron: Asymmetry* **1992**, *3*, 1597–1602; (e) Aggarwal, V. K.; Kalomiri, M.; Thomas, A. P. *Tetrahedron: Asymmetry* **1994**, *5*, 723–730; (f) Aggarwal, V. K.;

Ford, J. G.; Thompson, A.; Jones, R. V. H.; Standen, M. C. H. *J. Am. Chem. Soc.* **1996**, *118*, 7004–7005.
5. Krishnamurthy, S.; Brown, H. C. *J. Am. Chem. Soc.* **1976**, *98*, 3383–3384.
6. (a) Anet, F. A. L. *Can. J. Chem.* **1961**, *39*, 789–794; (b) Angyal, S. J.; Craig, D. C.; Tran, T. Q. *Aust. J. Chem.* **1984**, *37*, 661–666.
7. (a) Archer, N. J.; Rayner, C. M.; Bell, D.; Miller, D. *Synlett* **1994**, 617–619; (b) Olah, G. A.; Wang, Q.; Nirupam, J. T.; Prakash, G. K. S. *Synthesis* **1992**, 465–466.
8. Brisdon, B. J.; England, R.; Mahon, M. F.; Reza, K.; Sainsbury, M. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1909–1914.
9. (a) Partanen, T.; Malkonen, P.; Vainiotalo, P.; Vepsalainen, J. *J. Chem. Soc., Perkin Trans. 2* **1990**, 777–782; (b) We cannot readily account for the discrepancy between the NMR data (solvent = $CDCl_3$ in both cases) reported for **11** in Ref. 8 and our own. Equally puzzling is the original mass spectrum we obtained with what appeared to be the parent ion for **10** at $m/z = 186$. We can only conclude that a minor impurity was present although the ^1H NMR data indicated that the compound was >95% pure. We later obtained a mass spectrum with a small peak at $m/z = 169$ (M^+–H) and a considerably larger signal at $m/z = 153$ (M^+–OH). There was no sign of the peak at $m/z = 186$.
10. Paquette, L.; Bulman-Page, P.; Pansegrau, P.; Wiedeman, P. *J. Org. Chem.* **1988**, *53*, 1450–1460.
11. Prepared by adding 1 equiv. of water to boron trifluoride diethyl etherate.
12. Wallace, O.; Springer, D. *Tetrahedron Lett.* **1998**, *39*, 2693–2694.
13. Wang, Y.; Zhang, W.; Colandrea, V.; Jimenez, L. *Tetrahedron* **1999**, *55*, 10659–10672.
14. Pfrunder, B.; Tamm, C. *Helv. Chim. Acta* **1969**, *53*, 1630–1643.
15. Kaiser, C.; Rittner, R.; Basso, E. *Magn. Reson. Chem.* **1997**, *35*, 609–613.