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FACIAL SELECTIVITY OF THE SHARPLESS BROMINE CATALYZED AZIRIDINATION[1]

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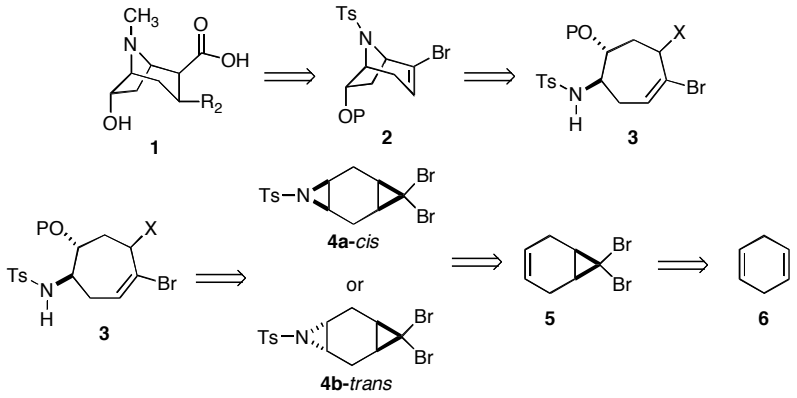
Abstract – A bromine catalyzed aziridination reaction has been applied to 7,7-dibromo-3-norcarene, which resulted in a highly stereoselective route to *cis*-4,4-dibromo-8-(toluene-4-sulfonyl)-8-azatricyclo[5.1.0.0]octane in a 46% yield. In order to confirm the stereochemistry of the aziridination reaction *trans*-4,4-dibromo-8-(toluene-4-sulfonyl)-8-azatricyclo[5.1.0.0]octane and its diastereoisomer *cis*-4,4-dibromo-8-(toluene-4-sulfonyl)-8-aza-tricyclo[5.1.0.0]octane were prepared in a stereoselective manner from the corresponding *cis*- and *trans*-7,7-dibromo-3-norcarene epoxides (61 and 9.2% yields, respectively). These three routes offer stereochemical proof for the stereospecificity of the bromine-catalyzed aziridination of hindered alkenes.

INTRODUCTION

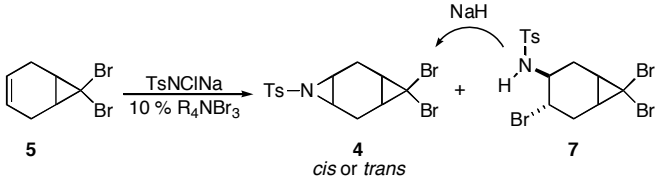
As part of a project directed toward the synthesis of a substituted cocaine ring system, we hoped to synthesize the 6-substituted tropane (**1**) from cycloheptane (**3**) (Scheme 1). In turn we envisioned preparing **3** from either *cis*- or *trans*-aziridine (**4a**) and (**4b**) by two ring opening reactions.[3,4] In the course of our synthetic investigations of this route to the tropane ring system, we desired diastereoselective access to both the *cis*- and *trans*-aziridines (**4a**) and (**4b**). Thus we decided to investigate the various methods for the aziridination of cyclohexene (**5**). Herein, we describe two diastereoselective approaches for the selective synthesis of both *cis*- and *trans*-tosylaziridines (**4a**) and (**4b**). These results show the stereoselectivity of the bromine-catalyzed aziridination reaction and in turn lend credence to the mechanism proposed by Sharpless.[5,6]



Scheme 1

RESULTS AND DISCUSSION

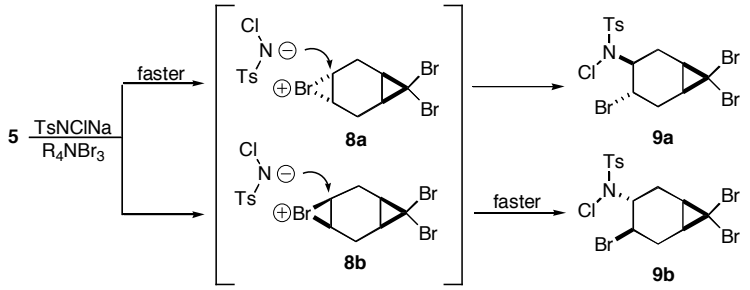
The starting 7,7-dibromo-3-norcarene (**5**) was prepared by the dibromocyclopropanation procedure of cyclohexa-1,4-diene reported by Winstein.[7] Treatment of **5** with 1 equiv. chloramine-T and 10 mol % phenyltrimethylammonium perbromide[8] provided a 3:1 mixture of oxidized products, the *N*-tosylaziridine (**4**) (35 %) and bromo sulfonamide (**7**) (11.3 %) (Scheme 2). The bromo sulfonamide (**7**) was cleanly converted into the aziridine (**4**) upon treatment with NaH under anhydrous conditions (98 %). The mixture of **4** and **7** could similarly be converted into **4** with NaH, which greatly simplified the chromatographic purification of **4**. While the ^{1}H NMR and ^{13}C NMR spectra clearly indicated the formation of **4** as a single diastereoisomer, we were unable to determine whether the *cis* or *trans* stereoisomer was formed.[9]



Scheme 2

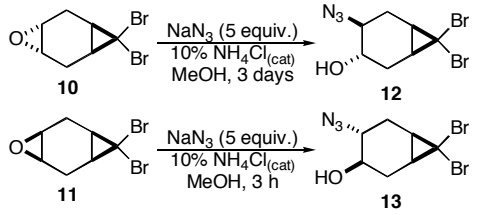
Sharpless has suggested that the perbromide-catalyzed aziridination of alkenes occurs through a bromonium ion (**8a**) or (**8b**) that is subsequently trapped by chloramine-T (forming **9a** or **9b**) (Scheme 3). The intermediate *N*-chlorosulfonamide (**9**) is then reduced by a halide ion and cyclized to form the corresponding tosylaziridine (**4**). In terms of the stereochemistry of aziridination, two mechanistic questions still remained unanswered. Are the two diastereotopic bromonium ions (**8a**) and (**8b**) rapidly inter-converting? Which of the two diastereotopic bromonium ions reacts faster with chloramine-T? Thus, at the outset it was not clear to us whether a facially biased alkene would react under these conditions to form the sterically more hindered *cis*-aziridine (**4a**) or sterically less hindered *trans*-aziridine (**4b**). Therefore, we decided to stereospecifically synthesize both the *cis*- and *trans*-*N*-

tosylaziridines (**4a**) and (**4b**) from stereo-defined starting materials and compare them to the material made from the Sharpless procedure.



Scheme 3

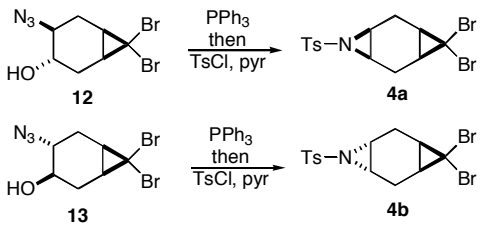
Following virtually identical conditions, the known *trans*-epoxide (**10**)[10] and *cis*-epoxide (**11**)[11] were converted into diastereomeric azido-alcohols (**12**) and (**13**) (scheme 4).[12] Exposing the *trans*-epoxide (**10**) to excess NaN_3 (5 equiv.) and NH_4Cl (1 equiv.) in refluxing methanol for 3 days produced the azido-alcohol (**12**) in an 82 % yield. Not surprisingly the diastereomeric epoxide (**11**) reacted more quickly with NaN_3 requiring only 3 h to give the corresponding azide (**13**) in the same yield (82 %).



Scheme 4

Once again under similar conditions the diastereomeric azido-alcohols (**12**) and (**13**) were transformed to the corresponding *cis*- and *trans N*-tosylaziridines (**4a**) and (**4b**), respectively (Scheme 5).[13] Exposure of **12** with triphenylphosphine in hot toluene (80 °C, 2 h) reductively cyclized **12** to an aziridine, which was protected *in situ* (TsCl/pyr, 0 °C) to form the *cis*-tosylaziridine (**4a**) (22 % yield). The low yield of **4a** is presumably due to the steric hindrance of the *endo*-azide in **12**. This is supported by the observation that exposure of the diastereomeric *exo*-azide (**13**) to the same PPh_3/TsCl conditions provided the corresponding *trans*-tosylaziridine (**4b**) in a much higher 84 % yield. With authentic samples of **4a** and **4b** in hand it was evident that the *N*-tosylaziridine prepared from the bromine-catalyzed aziridination of **5** gives exclusively the *cis*-aziridine (**4a**). The ^{1}H NMR and ^{13}C NMR of **4a** and **4b** were clearly distinguishable and the crude ^{1}H NMR spectra from the bromine-catalyzed aziridination showed no evidence of the *trans*-aziridine (**4b**).

In conclusion, two diastereoselective routes to the *cis-N*-tosylaziridines (**4a**) (46 and 9.2 % yields) and one diastereoselective route to the *trans-N*-tosylaziridines (**4b**) (61 % yield) have been developed. These three routes help establish the stereospecificity of the bromine-catalyzed aziridination of hindered alkenes. In particular, this heavily biased substrate demonstrates the high degree that the initially formed bromonium ion can be trapped. Further use of these *N*-tosylaziridines for the synthesis of the tropane ring system will be reported in due course.



Scheme 5

EXPERIMENTAL

General Methods: Unless otherwise stated, all reactions were carried out under an atmosphere of nitrogen using oven-dried glassware and standard syringe/septa techniques. Analytical TLC was performed using precoated glass-backed plates (Whatman K6F 60A, F_{254}) that were analyzed by fluorescence upon 254 nm irradiation or by staining with *p*-anisaldehyde, potassium permanganate, or phosphomolybdic acid stains. Liquid chromatography was performed using (flash chromatography) of the indicated solvent system on ICN reagent silica gel 60 (60-200 mesh). Ether and tetrahydrofuran were distilled from benzophenone and sodium metal. Dichloromethane and triethylamine were distilled from calcium hydride. Hexanes refers to the petroleum fraction bp 40-60 ºC. Commercial reagents were used without purification unless otherwise noted. ^{1}H and ^{13}C NMR spectra were recorded on Varian 300 and 500 MHz spectrometers. Chemical shifts are reported relative to $CDCl_3$ (7.26 ppm) or internal tetramethylsilane (0.00 ppm) for ^{1}H spectrum and $CDCl_3$ (77.0 ppm) for ^{13}C spectrum. Melting points are uncorrected. IR spectra were obtained on a Prospect MIDAC FT-IR spectrometer. HRMS spectrometric data was performed by the University of Minnesota Mass Spectrometry Laboratory. Combustion analyses were performed by M-H-W Laboratories, Phoenix, AZ.

***cis*-4,4-Dibromo-8-(toluene-4-sulfonyl)-8-azatricyclo[5.1.0.0^{3,5}]octane (4a) Method A:** To a solution of dibromide (**5**) (1.00 g, 3.96 mmol) dissolved in 20 mL of CH_3CN were added

phenyltrimethylammonium tribromide (PTAB) (0.142 g, 0.377 mmol) and Chloramine-T•$3H_2O$ (1.23 g, 4.35 mmol) at rt. The reaction was stired for 16 h, then diluted with CH_2Cl_2 (20 mL) and saturated $NaHCO_3$ solution (20 mL). The organic layer was separated, and the aqueous layer extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried using Na_2SO_4 and the solvent was removed in vacuo. The crude material was first run through a plug of silica gel using 0 - 50 % ether/hexanes to remove starting material and excess tosylamine, and then a column was run using 5-20 % EtOAc/hexanes. Isolated were 0.204 g (20 %) of dibromide (**5**), 0.476 g (28 %) of aziridine as a white crystalline solid, and 0.182 g (9.1 %) of open tribromide (**7**) as an off-white crystalline solid. R_f 0.37 (20 % EtOAc/hexanes). mp 177 - 179 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) 7.77 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H), 2.96 (m, 2H), 2.63 (m, 2H), 2.44 (s, 3H), 1.79 (m, 2H), 1.12 (ddd, *J* =17.0, 5.0, 4.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) 144.5, 135.1, 129.7, 127.7, 39.8, 37.0, 26.4, 21.7, 20.6. IR (neat): 3044, 2996, 2922, 1596, 1547, 1494, 1393, 1163 cm^{-1}. HRMS (CI) calcd for $C_{14}H_{15}NO_2\ Br_2S$ [M+H$^+$] 419.9269, obsd 419.9279. Anal. Calcd for $C_{14}H_{15}NO_2Br_2S$: C, 39.93, H, 3.59. Found: C, 40.04, H, 3.77.

Data for **(+/-)-(1S*,3R*,4R*,6R*)-4-Methyl-*N*-(4,7,7-tribromobicyclo[4.1.0]hept-3-yl)-benzenesulfonamide (7)**. R_f 0.49 (20 % EtOAc/hexanes) ^{1}H NMR (300 MHz, $CDCl_3$), 7.76 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 4.76 (d, *J* = 5.1 Hz, 1H), 3.94 (ddd, *J* = 16.2, 9.9, 6.0 Hz, 1H), 3.15 (m, 1H), 2.85 (ddd, *J* =15.6, 9.9, 6.0 Hz, 1H), 2.56 (ddd, *J* = 15.3, 6.0, 1.8 Hz, 1H), 2.43 (s, 3H), 1.92 (m, 2H), 1.42 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) 143.9, 137.0, 129.8, 127.4, 54.1, 50.3, 36.8, 32.9, 29.0, 28.8, 26.9, 21.7. IR (neat): 3268, 3087, 2921, 1597, 1514, 1438, 1328, 1160, 1092 cm^{-1}. HRMS (CI) calcd for $C_{14}H_{16}NO_2Br_3S$ [M+H$^+$] 499.8530, obsd 499.8559, calcd for [M+NH_4^+] 516.8796, obsd 516.8772.

***cis*-4,4-Dibromo-8-(toluene-4-sulfonyl)-8-azatricyclo[5.1.0.0^{3,5}]octane (4a) Method B:** To a solution of tribromide (**7**) (143 mg, 0.286 mmol) in THF (2.8 mL) under nitrogen there was added 60 % NaH/mineral oil (24.3 mg, 0.632 mmol). After two hours the reaction was worked up by adding 10 % $NaHCO_3$ solution (10 mL) and was extracted with ethyl acetate (3 x 10 mL), The organic layers were combined and dried using Na_2SO_4, and the solvent was removed in vacuo. The crude product required no further purification, yielding 117 mg (98 %).

(+/-) -(1R*,3R*,4R*,6S*)-4-Azido-7,7-dibromobicyclo[4.1.0]heptan-3-ol (12): To a solution of epoxide (**10**) (302 mg, 1.12 mmol) in methanol (3 mL) there were added NaN_3 (366 mg, 5.63 mmol) and ammonium chloride (69.7 mg, 1.30 mmol). The mixture was then heated to 70°C for 3 days. The reaction

was then diluted with ether (10 mL) and brine (10 mL). The layers were separated, and the aqueous layer was extracted with ether (3 x 10 mL). The organic layers were combined and dried over Na_2SO_4 and concentrated in vacuo. The remaining solid was purified by column chromatography (10 - 20 % EtOAc/hexanes) to yield 286 mg (82 %) of azido alcohol as a white solid, and 50 mg of epoxide starting material (17 %). R_f 0.49 (20 % EtOAc/hexanes) mp 57-59 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) □ 3.63 (ddd, *J* = 9.9, 9.9, 6.9 Hz, 1H), 3.23 (ddd, *J* = 12.5, 10.5, 5.4 Hz, 1H), 2.64 (ddd, *J* = 15.0, 9.6, 5.7 Hz, 1H), 2.45 (m, 1H), 2.25 (br s,1H), 2.09-1.81 (m, 3H), 1.49 (ddd, *J* = 15.0, 12.6, 4.2, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) □ 69.4, 63.5, 37.5, 30.0, 29.3, 27.6, 26.9. HRMS calcd for $C_7H_9N_3OBr_2$ [M+NH_4^+] 326.9456, obsd 326.9453. IR (neat): □ 3386, 3024, 2924, 2865, 2108, 1636, 1439, 1321, 1291, 1253, 1047 cm^{-1}. Anal. Calcd for $C_7H_9N_3OBr_2$: C, 27.04, H, 2.92. Found: C, 27.30, H, 3.12.

(+/-)-(1R*,3S*,4S*,6S*)-4-Azido-7,7-dibromobicyclo[4.1.0]heptan-3-ol (13): To a solution of epoxide (**11**) (302 mg, 1.12 mmol) in methanol (2.2 mL) were added NaN_3 (363 mg, 5.58 mmol) and ammonium chloride (59.8 mg, 1.12 mmol). The mixture was then heated to 70 ºC and allowed to stir for 3 h. The reaction was then diluted with ether (5 mL) and brine (10 mL). The aqueous layer was extracted with ether (3 x 10 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (10 - 20 % EtOAc/hexanes) to yield 286 mg (82 %) of azide as a white solid. R_f 0.49 (20 % EtOAc/hexanes) mp 84 - 86 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) □ 3.37-3.52 (m, 2H), 2.57 (ddd, *J* = 15.6, 9.9, 5.4 Hz, 1H), 2.47 (dd, *J* = 13.8, 6.3 Hz, 1H), 2.21 (br s, 1H), 1.85-2.04 (m, 2H), 1.50 (ddd, *J* = 14.7, 11.4, 3.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) □ 70.0, 62.4, 37.3, 29.5, 28.0, 27.8, 27.1. IR (neat): □ 3387, 2924, 2865, 2108, 1290, 1047 cm^{-1}. HRMS calcd for $C_7H_9N_3OBr_2$ [M + NH_4^+] 326.9456, obsd 326.9435. Anal. Calcd for $C_7H_9N_3OBr_2$: C, 27.04, H, 2.92. Found: C, 27.25, H, 3.17.

***cis*-4,4-Dibromo-8-(toluene-4-sulfonyl)-8-azatricyclo[5.1.0.0^{3,5}]octane (4a) Method C:** To a solution of azide (**12**) (20.0 mg, 64.3 □mol) in toluene (2 mL) was added triphenylphosphine (20.1 mg, 76.6 □mol). The reaction was heated at 80 ºC for 2 h until complete as judged by TLC analysis. The reaction was cooled to 0 ºC and pyridine (10 □L, 0.13 mmol) then tosyl chloride (18.6 mg, 97.5 □mol) were added. The reaction was stirred overnight, then quenched with 10 % $NaHCO_3$ and extracted 3 times with CH_2Cl_2. The organic layers were dried using Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified using column chromatography (10 - 20 % EtOAc/hexane). A white solid was isolated which had identical spectral data to compound (**4a**) yielding 6.0 mg of product (22 %).

***trans*-4,4-Dibromo-8-(toluene-4-sulfonyl)-8-azatricyclo[5.1.0.0^{3,5}]octane (4b):** To a solution of azide (**13**) (15.0 mg, 48.2 μmol) in toluene (2 mL) was added triphenylphosphine (15.2 mg, 58.0 μmol). The reaction was heated at 80 ºC for 2 h until complete as judged by TLC analysis. The reaction was cooled to 0 ºC and pyridine (10 μL, 0.13 mmol) then tosyl chloride (18.4 mg, 96.5 μmol) were added. The reaction was stirred overnight, then quenched with 10 % $NaHCO_3$ and extracted 3 times with CH_2Cl_2. The organic layers were dried using Na_2SO_4 and solvent was removed in vacuo. The crude product was purified using column chromatography (10 - 20 % EtOAc/hexane), yielding 17.0 mg of product as a white crystalline solid (84 %). R_f 0.50 (20 % EtOAc/hexanes). mp 165 -167 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 2.88 (s, 2H), 2.46 (s, 3H), 2.33 (ddd, *J* = 16.5, 6.0, 2.5 Hz, 2H), 1.79 (dd, *J* = 16.0, 1.0 Hz, 2H), 1.70 (ddd, J = 5.0, 3.0, 1.0 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.5, 135.3, 129.8, 127.7, 38.5, 36.9, 22.8, 21.7, 18.8. IR (film): ν 2920, 1596, 1428, 1323, 1159, 1091 cm^{-1}. HRMS calcd for $C_{14}H_{15}NO_2Br_2S$ $[M+H]^+$ 419.9269, obsd 419.9290.

ACKNOWLEDGMENTS

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REFERENCES AND NOTES

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