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A DIASTEREOSELECTIVE SILVER(I) PROMOTED *GEM*-DIBROMOCYCLOPROPANE RING OPENING REACTION *VIA* AN ANCHIMERIC ASSISTED TRANSANNULAR BENZOATE MIGRATION[1]

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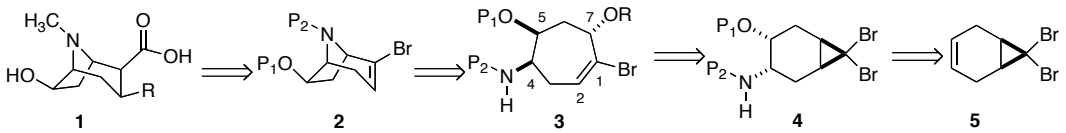
Abstract – A highly diastereoselective synthesis of a protected 4-amino-5,7-dihydroxy-1-bromocyclohept-1-ene was achieved by a silver tosylate promoted *gem*-dibromocyclopropane ring opening reaction. The target molecule was prepared in only six steps from benzene or four steps from 7,7-dibromo-3-norcarene. The key to this approach was the discovery of a stereoselective transannular benzoate migration, which occurred *via* tandem anchimeric assistance in a silver(I) promoted *gem*-dibromocyclopropane ring opening reaction.

INTRODUCTION

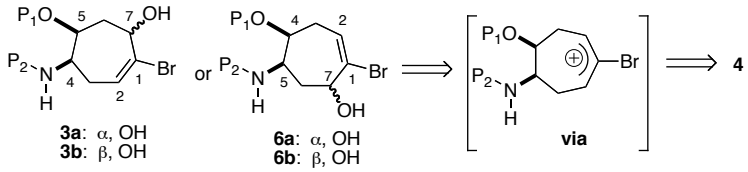
Various substituted tropanes are extremely potent and selective in their interactions with the central nervous system. They interact with the dopamine neurotransmitter, and are potential medications for cocaine addiction. In addition, they interact with the serotonin neurotransmitter and have generated interest as potential antidepressants.[3] Recently, Kozikowski has shown that 6- and 7-hydroxy-substituted cocaine[4] and WIN-analogues are capable of blocking dopamine reuptake[5] and attenuating cocaine's locomotor activity (AD_{50} = 94 mg/Kg).[6] There have been several approaches to the 2,3-disubstituted tropane ring system of cocaine that derive their asymmetry *via* a desymmetrization of tropanones.[7]

As part of a project directed toward the synthesis of a substituted cocaine ring system, we hoped to synthesize either the endo- or exo-6-hydroxy-substituted tropane (**1**) from the corresponding aza-bicyclovinyl bromide (**2**) (Scheme 1). We envisioned preparing **2** *via* an intramolecular palladium catalyzed allylation reaction from cycloheptene (**3**) or a stereoisomer of **3**. The cycloheptene (**3**) and/or its isomers were envisioned as being derived by a silver(I) promoted *gem*-dibromocyclopropane ring opening reaction of the various stereoisomers of **4**.[8] Finally, the dibromonorcarane (**4**) should easily be derived by an aminohydroxylation of *gem*-dibromonorcarene (**5**) *via* an aminohydroxylation reaction.



Scheme 1. Retrosynthesis of substituted tropane **1**

While this route has the advantage of a rapid entry into the tropane ring system, it does suffer from the potential problem of a lack of regio- and stereocontrol in the silver-promoted ring opening reaction. A key aspect of this sequence will be the reliance upon the palladium-catalyzed allylation reaction to convert any regioisomer of **3a/b** (**6a/b**) into a common intermediate.



Scheme 2. Either **3a/b** or **6a/b** are potentially derived from **4** by ring-opening

However, what remains to be controlled is the relative *cis*/*trans* stereochemistry between C-4 and C-7 in **3** and C-5 and C-7 in **6**. We hoped this stereochemical problem would be solved by a transannular participation of the amide carbonyl (Figure 1). Reported herein is our stereochemical study of this silver promoted reaction sequence and the serendipitous discovery of a practical solution to this problem.

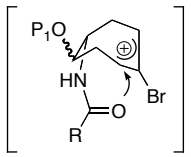
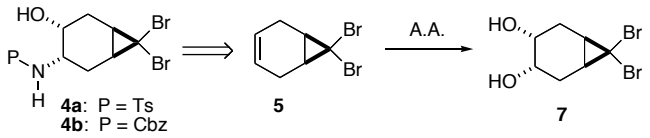


Figure 1. Desired advantageous participation by amide carbonyl

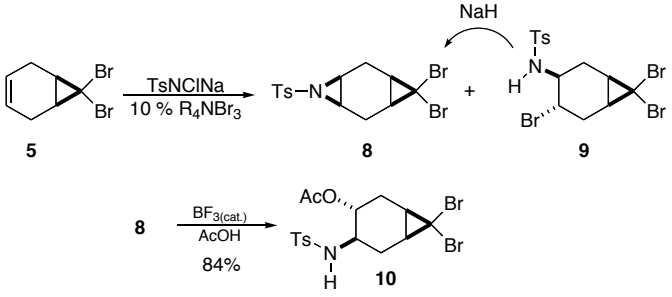
RESULTS AND DISCUSSION

Because of the potential for the rapid and enantioselective introduction of the amino and hydroxyl groups in **5**, we initially studied the Sharpless asymmetric aminohydroxylation (A.A.) of **5** to form either the *N*-Ts or the *N*-Cbz protected *cis*-amino alcohols (**4a**) and (**4b**) (Scheme 3).[9] Unfortunately all of our efforts in this regard were fruitless. For instance, neither **4a** or **4b** was observed upon exposure of a *t*-BuOH/H_2O solution of dibromide (**5**) to either chloramine-T or the sodium salt of *N*-chlorobenzylcarbamate in the presence of 1 mol% of OsO_4, and 1.2 mol% of $(DHQ)_2PHAL$. In fact, the only isolable product detected was diol (**7**).



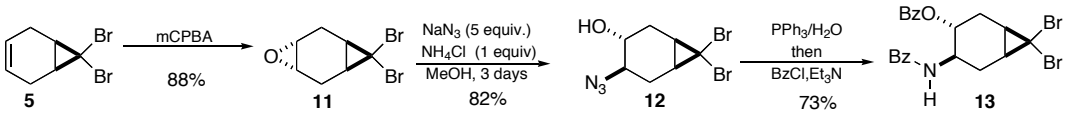
Scheme 3. Failed aminohydroxylation of **5**

Because of our lack of success with the *cis*-aminohydroxylation of **5**, we turned our attention to preparing *trans*-amino alcohols with either *N*-Ts or the *N*-Bz protecting groups *via* a nucleophilic opening of aziridine (**8**) or epoxide (**11**). We have previously shown that 7,7-dibromo-3-norcarene (**5**) could be easily converted into *endo*-aziridene (**8**) by a bromonium-catalyzed aziridination.[10-12] The aziridene in turn could be cleanly opened by treatment with catalytic BF_3 in acetic acid providing a good yield of *trans*-β-acetoxysulfonamide (**10**).



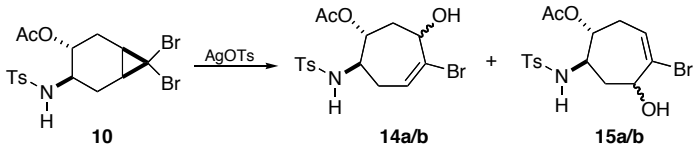
Scheme 4. Preparation of *N*-Ts *trans*-aminoalcohols

The known epoxide (**11**)[13] was easily prepared by epoxidation with mCPBA, and then opened with NaN_3 and NH_4Cl in MeOH to provide the known *trans*-azido alcohol (**12**).[10] The azide group in **12** was reduced with PPh_3 and the resulting aminoalcohol was per-protected with benzoyl chloride to give the *trans*-β-benzoyloxysulfonamide **(13)** in 73% yield.



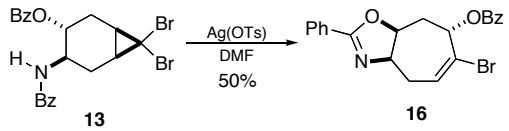
Scheme 5. Preparation of *N*-Bz *trans*-aminoalcohols

We next examined the silver-promoted ring opening reaction of the *trans*-β-acetoxysulfonamide (**10**) (Scheme 6). Unfortunately, treatment of **10** with AgOTs in anhydrous DMF gave a mixture of all four possible products (i.e. both diastereomers of the two possible regioisomers **14** and **15**). Not surprising we found it near impossible to separate the mixtures of **14a/b** and **15a/b**. Unfortunately neither changing the silver reagent (AgOAc, AgOTf, $AgNO_3$) or the amount of the reagent did not improve the situation.



Scheme 6. Unselective ring-opening of *N*-Ts *trans*-amino alcohol

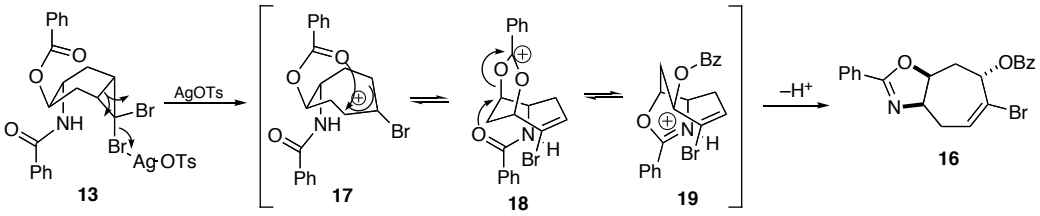
To our surprise simply switching both the nitrogen and oxygen protecting groups to benzoyl groups had a remarkable affect on the ring opening reaction. Thus, treating the bis-benzoate (**13**) to the identical silver tosylate conditions gave a single compound, albeit in a low yield (30%). Our initial analysis of the ^{1}H NMR spectrum was quite encouraging for the formation of a bicyclic intermediate (**16**), in that the product contained no N-H functional group. Other aspects of the ^{1}H NMR spectrum were not consistent with a [3.2.1]azabicyclo intermediate. Recrystallization of **16** from benzene/water gave crystals suitable for X-Ray analysis. The X-Ray analysis of **16** showed the formation of a bicyclic product, which was not a [3.2.1]bicyclic structure but instead the *cis*-fused [5.3.0] bicyclic ring system (Figure 2).



Scheme 7. Ring-opening of **13** provided single diastereomer

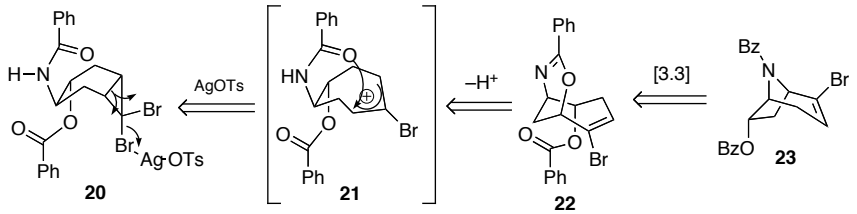
With the realization that the structure contained an oxazoline ring system, the yield of the silver promoted rearrangement was easily increased by the use of base in the work-up (50%). Thus, use of the base prevented any acid-catalyzed hydrolysis. For the same reason triethylamine was used as a co-solvent for

the silica gel chromatography. Knowing the structure of **16**, also allowed us to propose a mechanism of the rearrangement for the formation of **16** (Scheme 8).



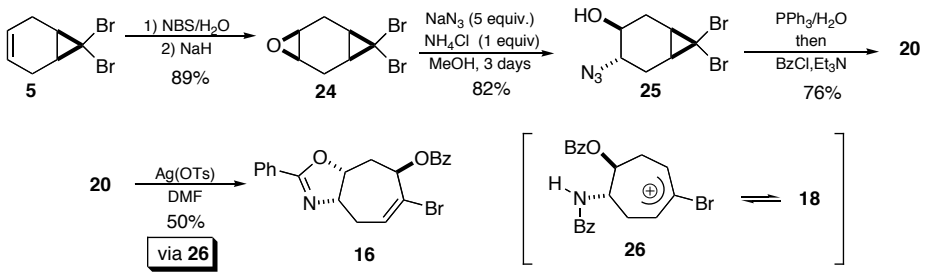
Scheme 8. Possible mechanism for the formation of **16**

As outlined in Scheme 8, we hypothesized that the benzoate migration was initiated by concerted involvement of the benzoate group, which due the stereoelectronic requirements of the ring opening reactions is preorganized to react with the allyl-cation intermediate. We proposed that the diastereomeric benzoate (**20**) would trap the benzamide instead; thus, the benzamide-trapped-intermediate (**21**) would lose a proton and form **22** or its [3,3]-sigmatropic rearrangement product (**23**) (Scheme 9).



Scheme 9. Possible route to a [3.2.1]bicyclic structure via the diastereomer (**20**)

To test this hypothesis, we synthesized the diastereomeric benzoate protected amino alcohol (**20**), *via* the route outlined in Scheme 10. To our surprise when the diastereomer (**20**) was exposed to the identical AgOTs ring opening conditions a similar yield (50%) of **16** was isolated as the sole product. This result suggests that the benzoate participation in this rearrangement is not concerted and that the silver promoted ring opening of both **13** and **20** occurs through the same allylic cation intermediate (**26**).



Scheme 10.

In conclusion, two diastereo-convergent routes to the *cis*-fused [5.3.0] bicyclic ring system (**16**) have been established (26 and 28 % yields). Both routes take advantage of an anchimeric assisted transannular benzoate migration reaction for the high diastereocontrol. Further work toward the use of this route for the preparation of the tropane ring system is ongoing and will be reported in due course.

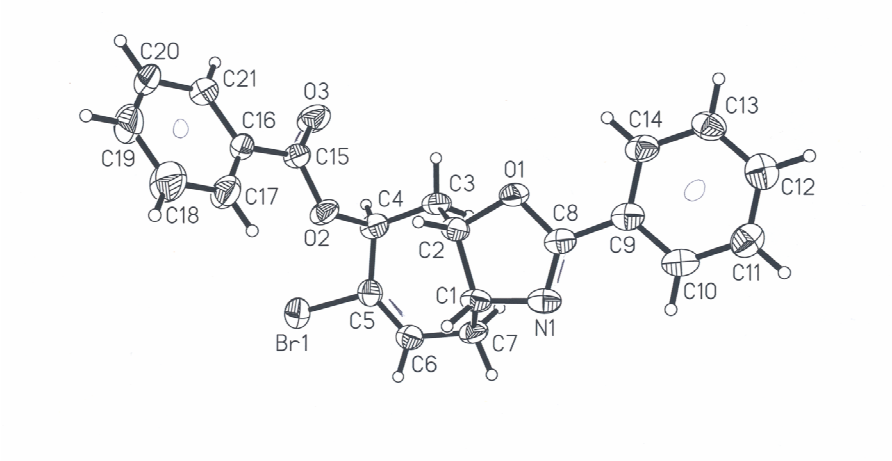


Figure 2. X-Ray crystal structure of compound (**16**)

EXPERIMENTAL[14]

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 °C. 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 $CDCl_3$ (δ 7.26 ppm) or internal tetramethylsilane (δ 0.00 ppm) for ^{1}H spectrum and $CDCl_3$ (δ 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.

(1*R,3*R**,4*R**,6*S**)-7,7-Dibromo-4-tosylaminobicyclo[4.1.0]heptan-3-yl acetate (10):** In a 10 mL RBF was placed aziridene **(8)** (500 mg, 1.19 mmol) and acetic acid (1.2 mL) and the reaction mixture was cooled to 5 °C. In a separate vial was mixed acetic acid (1. 2 mL) and boron trifluoride etherate (19 mg,

0.129 mmol). The contents of the vial were also cooled to 5ºC and then added to the flask *via* syringe. The reaction was allowed to stir for 2.5 h. The reaction mixture was then quenched by the addition of sat. aqueous K_2CO_3. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL). The combined organic layers were then dried over anhyd. Na_2SO_4, and concentrated *en vacuo*. The crude material was purified by flash column chromatography on silica gel (10-80% Et_2O/Hexanes) yielding *trans*-β-acetoxy-sulfonamide **(10)** (481 mg, 84%). R_f 0.24 (20% EtOAc/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 4.74 (ddd, *J* = 15.0, 9.0, 2.1 Hz, 1H), 4.62 (d, *J* = 5.4 Hz, 1H), 3.27-3.15 (m, 1H), 2.60 (ddd, *J* = 15.9, 9.9, 5.4 Hz, 1H), 2.42 (s, 3H), 2.34-2.37 (m, 1H), 2.00-1.83 (m, 2H), 1.74 (s, 3H), 1.47-1.37 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 144.0, 138.0, 129.7(2C), 126.8(2C), 70.0, 53.5, 36.9, 30.5, 28.6, 28.1, 27.1, 21.5, 20.8 IR (thin film): ν 3272, 3028, 2922, 1722, 1627, 1597, 1569, 1495, 1442, 1372, 1331, 1305, 1288, 1249, 1184, 1161, 1092, 1039. HRMS Calcd for $C_{16}H_{19}NO_4Br_2S$ $[M+H]^+$: 479.9474 Found: 479.9497.

(1*R,3*R**,4*R**,6*S**)-4-Benzamido-7,7-dibromobicyclo[4.1.0]heptan-3-yl benzoate (13):** Azido alcohol **(12)** (550 mg, 1.78 mmol) was dissolved in wet THF (1.5 mL, 1.2 M) at rt and triphenylphosphine (700 mg, 2.67 mmol) was added all in one portion. The reaction was allowed to stir overnight at rt after which it was determined complete by TLC (anisaldehyde stain, UV). The volatiles were removed by rotovap and high vacuum overnight after which the crude material was dissolved in CH_2Cl_2 (1.5 mL, 1.2 M) and cooled to 0ºC (ice bath temp). Triethylamine (0.620 mL, 4.45 mmol) was added *via* syringe and after 5 min BzCl (0.455 mL, 3.92 mmol) was added and the reaction was allowed to warm to rt. The reaction was allowed to stir overnight at rt until determined complete by TLC ($KMnO_4$ stain, UV). The reaction was then quenched by adding aqueous sat. $NaHSO_4$ (1 mL) followed by dilution with Et_2O (4 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 0.5 mL). The organic layers were then washed with aqueous sat. $NaHCO_3$ (1 mL), and brine (1 mL). The organic layer was then dried over anhyd. Na_2SO_4, and concentrated *en vacuo*. The crude material was purified by flash column chromatography on silica gel (20% EtOAc/Hexanes) yielding bis-benzoate **(13)** as a crystalline white solid (643 mg, 73%). R_f 0.16 (20% EtOAc/Hexanes) mp 124-127 ºC. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.64 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.63-7.31 (m, 6H), 6.56 (d, *J* = 8.4 Hz, 1H), 5.28 (ddd, *J* = 11.1, 9.3, 7.2 Hz, 1H), 4.23-4.17 (m, 1H), 2.91 (ddd, *J* = 14.7, 9.3, 5.4 Hz, 1H), 2.56 (dd, *J* = 14.7, 7.2 Hz, 1H), 2.36-2.09 (m, 3H), 1.59 (ddd, *J* = 14.7, 12.3, 4.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 167.9, 167.4, 134.1, 133.6, 131.5, 130.2, 129.8, 129.6, 128.5, 126.9, 72.6, 60.5, 50.6, 32.3, 27.6, 27.3, 21.1, 15.0, 14.2, 12.5 IR (thin film): ν 2295, 1810, 1750, 1685, 1510, 1290, 1240, 1100, 890, 743, 667. Anal. Calcd for $C_{21}H_{19}NO_3Br_2$: C, 51.14; H. 3.88. Found: C, 51.36; H, 4.06.

(1*R,3*S**,4*S**,6*S**)-4-Benzamido-7,7-dibromobicyclo[4.1.0]heptan-3-yl benzoate (20):** Azido alcohol

(25) (460 mg, 1.49 mmol) was dissolved in wet THF (1.5 mL, 1.2 M) at rt and triphenylphosphine (585 mg, 2.23 mmol) was added all in one portion. The reaction was allowed to stir overnight at rt after which it was determined complete by TLC (anisaldehyde stain, UV). The volatiles were removed by rotovap and high vacuum overnight after which the crude material was dissolved in CH_2Cl_2 (1.5 mL, 1.2 M) and cooled to 0ºC (ice bath temp). Triethylamine (0.623 mL, 4.47 mmol) was added *via* syringe and after 5 min BzCl (0.380 mL, 3.28 mmol) was added and the reaction was allowed to warm to rt. The reaction was allowed to stir overnight at rt until determined complete by TLC ($KMnO_4$ stain, UV). The reaction was then quenched by adding aqueous sat. $NaHSO_4$ (1 mL) followed by dilution with Et_2O (4 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 0.5 mL). The organic layers were then washed with aqueous sat. $NaHCO_3$ (1 mL), and brine (1 mL). The organic layer was then dried over anhyd. Na_2SO_4, and concentrated *en vacuo*. The crude material was purified by flash column chromatography on silica gel (20% EtOAc/Hexanes) yielding bis-benzoate **(20)** as a crystalline white solid (562 mg, 76%). R_f 0.18 (20% EtOAc/Hexanes). mp 131-134 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 8.4, 1.5 Hz, 2H), 7.59 (dd, *J* = 8.4, 1.5 Hz, 2H), 7.58-7.31 (m, 6H), 6.27 (d, *J* = 8.4 Hz, 1H), 5.08 (ddd, *J* = 11.4, 11.4, 5.4 Hz, 1H), 4.57-4.51 (m, 1H), 2.75 (dd, *J* = 14.2, 7.2 Hz, 2H), 2.09-1.88 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 167.7, 167.2, 134.4, 133.4, 131.3, 130.1, 129.6, 128.5, 126.8, 125.5, 72.7, 60.4, 49.6, 31.5, 29.1, 26.2, 21.1, 15.3, 14.2, 12.2 IR (thin film): ν 2295, 1810, 1750, 1685, 1510, 1290, 1240, 1100, 890, 743, 667. Anal. Calcd for $C_{21}H_{19}NO_3Br_2$: C, 51.14; H. 3.88. Found: C, 51.41; H, 4.01.

(3a*R,5*E*,7*S**,8a*S**)-6-Bromo-4,7,8,8a-tetrahydro-2-phenyl-3aH-cyclohepta[d]oxazol-7-yl benzoate (16):** Bis-benzoate (**13 or 20**, 50 mg, 0.10 mmol) was dissolved in DMF (0.50 mL) in a 5 mL RBF. Silver tosylate (285 mg, 1.0 mmol) was added all in one portion and the reaction was brought to reflux. The reaction was allowed to stir at reflux for three days with the progress monitored by ^{1}H NMR spectroscopy *via* aliquots. After this time, the reaction mixture was diluted with EtOAc (2 mL) and washed thoroughly with sat. aqueous $NaHCO_3$ (3 x 2 mL). The organics were then immediately subjected to silica gel flash column chromatography (18% EtOAc/2% Et_3N/hexanes) making sure to sufficiently pre-condition the column with Et_3N. The bicyclic oxazoline was obtained as a white solid (21 mg, 51%). R_f 0.24 (20% EtOAc/hexanes). mp 135-137ºC (decomp.)(recrystallized from benzene/water). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.2 Hz, 2H), 7.89 (d, *J* = 7.2 Hz, 2H), 7.72 (s, 1H), 7.63-7.37 (m, 5H), 6.48 (dd, *J* = 9.3, 4.2 Hz. 1H), 6.04 (dd, *J* = 3.9, 1.8 Hz, 1H), 5.07 (ddd, *J* = 13.2, 11.1, 3.6, 1H), 4.68 (ddd, *J* = 13.5, 11.1, 3.6 Hz, 1H), 2.74 (ddd, *J* = 17.7, 6.0, 3.6 Hz, 1H), 2.65-2.39 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 163.4, 133.3, 131.4, 129.7, 129.3, 128.4(2C), 128.2(2C), 128.1(2C), 127.1(2C), 123.5, 76.4, 74.2, 68.3, 31.8, 30.1, 29.6 IR (thin film): ν 2929, 1720, 1647, 1601, 1449, 1264,

1103, 706, 691. HRMS Calcd for $C_{21}H_{18}NO_3Br$ $[M+H]^+$: 412.0542 Found: 412.0544. Confirmed by X-Ray Crystallography.

X-Ray Crystal-Structure Determination of 16 (see *Table 1* and *Figure 2*): A crystal of the compound was attached to a glass fiber and mounted on the Siemens SMART system for a data collection at 193 (2) K. An initial set of cell constants was calculated from reflections harvested from three sets of 20 frames. The initial sets of frames are oriented such that orthogonal wedges of reciprocal space were surveyed. This produces orientation matrices determined from 70 reflections. Final cell constants are calculated form a set of 4941 strong reflections from the actual data collection.

Table 1. Crystallographic data of compound **(16)**

Empirical formula	$C_{21}H_{18}NO_3Br_2$	**θ range for data collection**	1.22 to 25.02°
Crystal Habit, color	Plate, colorless	**Index ranges**	$-20 < h < 19,\ 0 < k < 7,\ 0 < l < 20$
Crystal size	0.8 x 0.3 x 0.04 mm	**Reflections collected**	9139
Crystal system	Monoclinic	**Independent reflections**	3153 (R_{int} = 0.0216)
Space group	$P2_1/n$ a = 17.3174(3) Å α = 90° b = 6.2468(2) Å β = 105.274(1)° c = 17.2575(5) Å γ = 90°	**System Used**	SHELXTL-V5.0
		Solution	Direct methods
		Refining method	Full-matrix least-squares on F^2
Volume	1800.94(8) $Å^3$	**Weighting scheme**	Weighting scheme
Z	4	**Absorption correction**	SADABS (Sheldrick, 1996)
Formula weight	412.27	**Max. and min. transmission**	1.000 and 0.836
Density (calculated)	1.521 Mg/m^3	**Data / restraints / parameters**	3152 / 0 / 235
Absorption coefficient	2.303 mm^{-1}	**R indices (I>2σ(I) = 2523)**	R1 = 0.0356, wR2 = 0.0763
F(000)	840	**R indices (all data)**	R1 = 0.0507, wR2 = 0.0871
Diffractometer	Siemens SMART Platform CCD	**Goodness-of-fit on F^2**	1.014
Wavelength	0.71073 Å	**Largest diff. peak and hole**	0.263 and -0.417 $eÅ^{-3}$
Temperature	193(2) K		

ACKNOWLEDGEMENTS

We would like to thank V. G. Young Jr. and the X-Ray Crystallography Laboratory at the University of Minnesota for determining the structure of **16**. We thank the Arnold and Mabel Beckman Foundation, the American Cancer Society for an Institutional Research Grant (IRG-58-001-40-IRG-19), the American Chemical Society-Petroleum Research Fund (ACS-PRF#33953-G1) and the National Institute of General Medical Sciences (GM63150) for their generous support of our program. Funding by the National Science Foundation (NSF-EPSCoR award #0314742) for a Varian 600 MHz Inova Spectrometer and NMR facility is gratefully acknowledged.

REFERENCES AND NOTES

1. This paper is dedicated to Professor Barry M. Trost on the occasion of his 65th birthday.
2. University of Minnesota Undergraduate Research Opportunity Program (UROP) Participant.
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