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Cyclopropyl aziridines: solvolytic reactions of the *N*-tosylaziridines of (+)-2-carene and (+)-3-carene

Abstract: The *N*-tosylaziridine **4** of (+)-2-carene **1** was prepared and subjected to solvolytic reactions with weak protic acids. For comparison, the solvolytic reactions of *cis*-3-carene-*N*-tosylaziridine **8** were also studied. The solvolyses of **4** were more rapid than those of **8**, and both rings were opened in **4**, whereas only the aziridine was opened in **8**. This leads to the conclusion that the aziridine and cyclopropane rings in **4** can achieve a conjugated transition state.

Keywords: aziridines; conjugation; cyclopropanes; solvolysis.

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Introduction

(+)-2-Carene **1** is a naturally occurring chiral terpene and an important starting material for asymmetric synthesis [1]. Although it contains a vinylcyclopropane [2, 3], **1** has been shown that the two functions are non-conjugated [4–6], and they react accordingly, for example, giving products from a Prins reaction in which the cyclopropane remains intact [6].

By contrast, it has been shown previously that (+)-2-carene epoxide **2**, in which the epoxide is apparently conjugated to the cyclopropane [7–13], shows heightened reactivity compared to typical epoxides when reacted solvolytically with weak protic acids including water [14] (Scheme 1). Unconjugated (+)-3-carene epoxide **3** does not react in the same manner [14, 15]. The epoxide and cyclopropane in compound **2**, being in close proximity, are clearly much more reactive than the molecular combination of **3**.

Aziridines are nitrogen analogs of epoxides and generally undergo similar nucleophilic ring opening reactions [16–19]. One difference, of course, is that the nitrogen is trivalent, and thus the third group attached to the nitrogen affects the reactivity of the aziridine towards nucleophilic opening. Nitrogen is less electronegative than oxygen, but an electron withdrawing *p*-toluenesulfonyl group on the nitrogen atom serves as a group that makes the reactivity of the aziridine similar to that of an epoxide [16].

A number of groups have reported syntheses of compounds containing an aziridine adjacent to a cyclopropane ring [20–65]; however, the reactivity of only a few derivatives has been studied [20–28]. In particular, it has been shown that the aziridine can be hydrogenated without affecting the cyclopropane moiety in the molecule [29, 30].

Aziridines are known to undergo solvolytic opening by treatment with carboxylic acids, including acetic acid [17]. However, Yadav et al. have reported that *N*-tosylaziridines are inert in the presence of carboxylic acids in dichloromethane under non-solvolytic conditions in the absence of a catalyst [66].

Besbes has reported a solvolysis of *N*-acylaziridines by water [67] and suggested a concerted mechanism that involves hydrogen bonding of one molecule of water to the *N*-acyl group with a second molecule of water attacking a gem-dimethyl carbon atom (Scheme 2). His work has been based on the earlier work by Buchholz and Stamm [68].

To our knowledge, there have been no studies on solvolysis of any cyclopropyl aziridine. In this article, we report the first preparation of the *N*-tosylaziridine **4** of (+)-2-carene **1** and our initial findings regarding the solvolytic reactions of **4** [69, 70]. We also report solvolysis of (+)-3-carene *N*-tosylaziridine **8**.

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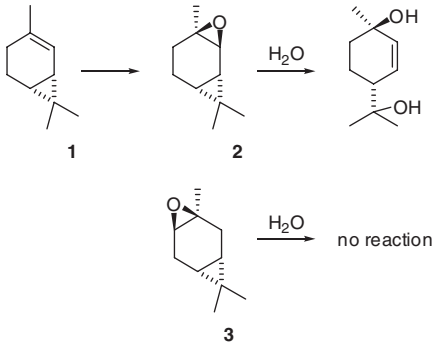
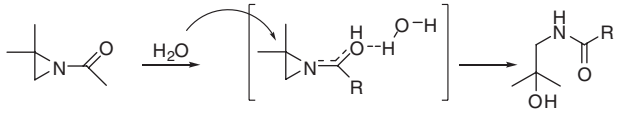
Results and discussion

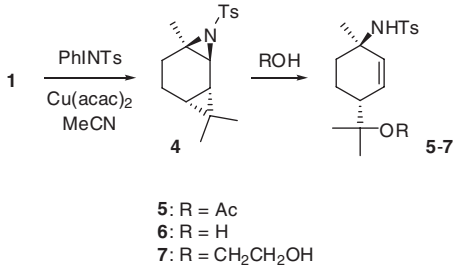
The desired *N*-tosylaziridine **4** was successfully synthesized from **1** by the Evans copper-catalyzed method, which involves a concerted mechanism (Scheme 3) [31] without possible complications of ionic or radical mechanisms



Scheme 1 Solvolytic reactions of carene epoxides with water [14].



Scheme 2 Hydrolysis of *N*-acylaziridines reported by Besbes [67].



Scheme 3 Preparation of **4** and its solvolysis to **5–7**.

[71]. Under optimized conditions, the yields using $Cu(acac)_2$ as the catalyst were low (8% based on **1**, 16% based on limiting reagent PhINTs), but not surprisingly so. For aziridination of 1-methylcyclohexene using $Cu(acac)_2$ as the catalyst, Evans and colleagues have reported a 32% yield based on PhINTs as the limiting reagent using five equivalents of the alkene [31, 72]. Other catalysts used by Evans et al. may have given a somewhat higher yield [31, 72], but we chose $Cu(acac)_2$ because it is commercially available, inexpensive, and air stable. Methods using rhenium [73] and rhodium [74] catalysts were also briefly explored but their use did not give any appreciable yield of **4**. Thus, although an improved preparation of **4** remains a future goal, it can be stated that the current low yields are a function of the structure of **1** and the limitations of present aziridination technologies.

The ^{1}H NMR spectrum of aziridine **4** is very similar to that of the epoxide **2**. The singlet at 3.03 ppm for N-C-H indicates that the aziridine is *trans* to the cyclopropane because there is no splitting in the signals of the adjacent protons. *Trans* stereochemistry is also expected based on the precedent of the methyl trioxorhenium epoxidation of (+)-2-carene **1**, in which the cyclopropane ring blocks one face of the cyclohexane ring, causing the heteroatom to be delivered to the opposite face. No diastereomers were observed.

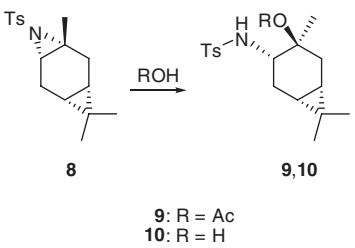
Aziridine **4** was initially subjected to two solvolytic reactions with acetic acid and water (Scheme 3). Solvolysis of **4** with acetic acid occurred rapidly (judging by TLC analysis) at room temperature but the mixture was stirred overnight to ensure completion. The reaction gave the desired 1,4-addition product **5** as the major product. On a 12.7 mg scale reaction, 67% yield of **5** was realized, but subsequent larger runs were less clean. For example, with a 54.4 mg of the starting material **4** the yield of **5** was only 24%. We do not at this point have a good explanation for this variability. Solvolysis of **4** with water was heterogeneous and occurred slowly at room temperature, but reaction at 80°C for 17 h gave **6** as the major product in 53% yield.

There was no apparent solvolytic reaction of **4** with methanol. After 1 day at room temperature, NMR of the crude mixture showed only unreacted **4**. An attempted reaction for 1 day under reflux conditions also failed, as shown by TLC analysis. We then tried ethylene glycol, which has a higher boiling point and had worked well with **2** [14]. At 100°C for 18 h, the heterogeneous reaction gave the expected product **7**.

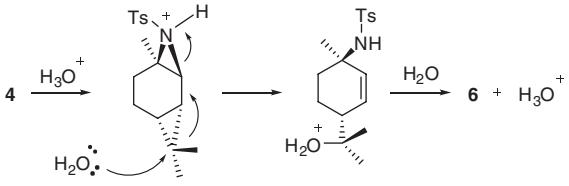
For comparison, the *trans-N*-tosylaziridine of (+)-3-carene was desired, but surprisingly, the use of the Evans method did not give the expected aziridine. Instead, analysis of the ^{1}H NMR of the crude mixture suggested the presence of allylic amines.

Therefore, we turned to the Sharpless method [75], which has been used by the Chandresekaran group to make the *cis-N*-tosylaziridine **8** [76]. Aziridine **8** was allowed to react with acetic acid and with water (Scheme 4). Solvolytic reactions of **8** did occur in both cases to give the respective products **9** and **10**, but much more slowly than with **4**.

More specifically, the reaction of **8** with acetic acid for 21 days at room temperature gave 25% yield of **9**, along



Scheme 4 Solvolysis of **8**.



Scheme 5 Possible mechanism of hydrolysis of aziridine **4**.

with 22% recovery of unreacted **8**. No regioisomers or diastereomers of **9** were observed. In a similar way, heterogeneous solvolysis of **8** in water at room temperature for 21 days gave **10** in 12% yield, and 23% of unreacted **8** was recovered. No regioisomers or diastereomers of **10** were observed. Solvolysis of **8** in water at 80°C for 17 h was less clean by TLC than at room temperature and produced 15% of **10**. *p*-Toluenesulfonamide (37%) was also obtained, indicating that significant detosylation occurs at the higher temperature, which was not observed with **4**. Substrate **8** was fully consumed and no regioisomers or diastereomers of **10** were observed.

As already mentioned, the aziridine system in **4** is more reactive than the aziridine in **8**. A mechanism for the solvolytic openings of **4** may involve a delocalized full or partial positive charge stemming from protonation of the ring nitrogen (Scheme 5). The cyclopropane and aziridine rings in **4** are *trans* to each other. This stereochemistry is favorable for a transition state with an *anti*-periplanar relationship between the two bonds that must break, allowing the system to produce the double bond in a concerted E_2 manner.

Conclusions

The solvolytic reactions of the conjugated cyclopropyl *N*-tosylaziridine **4** are similar to that of the conjugated cyclopropyl epoxide **2**. Both rings are opened in **4**, whereas only the aziridine is opened in the non-conjugated cyclopropyl *N*-tosylaziridine **8**. Reaction rates are significantly faster in the reactions of **4** than in the reactions of **8**. Both **4** and **2** behave in a manner suggesting that the two rings in both compounds are conjugated which enables a positive charge to be delocalized through both three-membered rings.

Experimental

(+)-2-Carene **1** was purchased from TCI America (Portland, OR, USA) and Aldrich Chemical Company (Milwaukee, WI, USA). (+)-3-Carene was purchased from Aldrich Chemical Company. [*N*-(*p*-Toluenesulfonyl)imino]phenyliodinane was prepared according to the Yamada et al. method [77] or by the method we recently developed [78]. *cis*-*N*-Tosylaziridine **8** was prepared according to the method of Chandresekaran et al. [76]. Copper(II) acetylacetonate and anhydrous acetonitrile were purchased from Aldrich. Ethylene glycol was purchased from Fisher Scientific (Fair Lawn, NJ, USA). TLC plates (silica gel GF, 250 μ, 10 × 20 cm, catalog no. 21521) were purchased from Analtech (Newark, DE, USA). TLC plates were visualized under short-wave UV, with I_2 or by spraying with ceric ammonium nitrate/sulfuric acid and heating. Column chromatography was carried out using flash silica gel from Aldrich (catalog no. 60737). Infrared spectra (neat) were run on a Nicolet 380 FT-IR (Penn State University Park). ^{1}H NMR spectra (400 MHz) and ^{13}C NMR spectra (100 MHz) were obtained on a Bruker DRX-400 instrument (Penn State University Park) for solutions in $CDCl_3$. High resolution mass spectrometry was performed on a Waters Synapt G2-S Q-TOF instrument (Penn State University Park).

(1*S*,2*S*,4*R*,7*R*)-4,8,8-trimethyl-3-[(4-methylphenyl)sulfonyl]-3-azatricyclo[5.1.0.02,4]octane (4) A two-necked 50 mL pear flask was oven-dried, fitted with septa, cooled under nitrogen, and charged with a stir bar, (+)-2-carene (**1**, 2.3 mL, 14.7 mmol, 2.0 eq.), and anhydrous acetonitrile (14.7 mL). The solution was cooled in an ice bath, treated with copper(II) acetylacetonate (0.192 g, 0.1 eq.) and [*N*-(*p*-toluenesulfonyl)imino]phenyliodinane (2.74 g, 1.0 eq.), and the heterogeneous mixture was stirred in ice for 17 min, then allowed to warm to room temperature. After 35 min, the now transparent green solution was treated with 10 mL of 1 M sodium hydroxide. The mixture was poured into a separatory funnel and extracted three times with methyl *t*-butyl ether. The organic solutions were combined and washed successively with 1 M NaOH (5 mL), water, and saturated sodium chloride. The solution was dried over sodium sulfate, filtered, and concentrated to a dark green liquid. Chromatography eluting with 5% ethyl acetate/hexanes, followed by 15% ethyl acetate/hexanes yielded 0.363 g of **4** (8% based on **1**, 16% based on PhINTs) as an oil. Compound **4** solidified after 8 days in the freezer. R_f (30% ethyl acetate/hexanes): 0.54; ^{1}H NMR: δ 7.84 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.5 Hz, 2H), 3.03, (s, 1H), 2.43 (s, 3H), 1.84, (m, 1H), 1.65 (s, 3H), 1.61 (m, 2H), 1.27 (m, 1H), 1.00 (s, 6H), 0.70 (d, J = 9 Hz, 1H); ^{13}C NMR: δ 143.5, 138.8, 129.6, 127.1, 51.5, 46.3, 31.0, 30.1, 28.5, 21.7, 21.1, 20.2, 19.8, 16.34, 16.32; IR: 3270 (br), 2935 (br), 1449, 1375, 1317, 1150, 1091, 1022, 990, 903, 814, 708, 650 cm^{-1}. HRMS. Calcd for $[C_{17}H_{24}NO_2S]^+$, m/z 306.1528. Found: m/z 306.1527.

***N*-[(1*R*,4*R*)-4-(2-acetoxypropan-2-yl)-1-methylcyclohex-2-en-1-yl]-4-methylbenzenesulfonamide (5)** A 10 mL round-bottom flask with a stir bar was oven-dried, fitted with septa, cooled under nitrogen, and treated with aziridine **4** (61.0 mg) and glacial acetic acid (2.44 mL). The mixture was stirred for 2 min, after which time a clear solution was formed. After 22.5 h at room temperature, flash silica gel and ethyl acetate were added and the mixture was concentrated to a powder. This material was added to the top of a silica gel column, and product **5** was eluted with a gradient of ethyl acetate/hexanes (5%, 15%, 25%, 40%, 100% ethyl acetate) to yield **5** (25.9 mg, 40%) as an oil; R_f (30% ethyl acetate/hexanes): 0.32; ^{1}H NMR: δ 7.76 (d, J = 8.3 Hz, 2H), 7.27, (d, J could not be determined because of $CDCl_3$ peak overlap, 2H), 5.62 (dd, J = 10.5 Hz and 2.3 Hz, 1H), 5.55 (d, J = 10.5 Hz, 1H), 4.50 (s, 1H), 2.69 (m, 1H), 2.42 (s, 3H), 1.96 (s, 3H), 1.80 (m, 2H), 1.66 (m, 1H), 1.56 (s, 1H), 1.38 (s, 3H), 1.36 (s, 3H), 1.29 (s, 3H); ^{13}C NMR:

δ 170.5, 143.1, 140.5, 133.8, 129.6, 128.2, 127.2, 84.2, 56.6, 43.7, 36.2, 27.2, 23.5, 23.1, 22.6, 21.7, 21.5; IR: 3268 (br), 2970, 1724, 1429, 1386, 1368, 1321, 1254, 1215, 1156, 1132, 1091, 1018, 815, 735, 661, 576 cm^{-1}. HRMS. Calcd for $[C_{19}H_{27}NO_4SNa]^+$, *m/z* 388.1558. Found: *m/z* 388.1556.

***N*-[(1*R*,4*R*)-4-(2-hydroxypropan-2-yl)-1-methylcyclohex-2-en-1-yl]-4-methylbenzenesulfonamide (6)** Aziridine **4** (50.1 mg) was weighed directly into a 5 mL round-bottom flask and treated with distilled water (2.0 mL). The heterogeneous mixture was stirred at 80°C for 17 h, then cooled, poured into a separatory funnel, treated with saturated sodium chloride, and extracted three times with ethyl acetate. The organic solutions were combined, washed with water and then saturated sodium chloride, dried over sodium sulfate, filtered, and concentrated to an oil/solid. Chromatography on flash silica gel, eluting with a gradient of ethyl acetate/hexanes (20%, 50%, 100% ethyl acetate) yielded **6** (27.9 mg, 53%) as a solid. The solid was crystallized from a mixture of ethyl acetate and hexanes to yield 12.2 mg (44% recovery); mp 142°C sharp; R_f (60% ethyl acetate/hexanes): 0.42; ^{1}H NMR: δ 7.80 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 5.71 (d, *J* = 10.4 Hz, 1H), 5.61 (dd, *J* = 10.4 Hz and 2.4 Hz, 1H), 4.51 (s, 1H), 2.41 (s, 3H), 2.07 (m, 1H), 1.64 (m, 2H), 1.84 (m, 1H), 1.76 (m, 1H), 1.72 (s, 1H), 1.57 (m, 1H), 1.34 (s, 3H), 1.17 (s, 3H), 1.12 (s, 3H); ^{13}C NMR: δ 143.1, 140.5, 134.0, 129.6, 128.9, 127.2, 72.7, 56.6, 46.3, 36.4, 28.0, 27.3, 26.2, 21.9, 21.7. IR: 3500 (br), 3272 (br), 2971, 1456, 1369, 1319, 1156, 1092, 815, 664, 556 cm^{-1}. HRMS. Calcd for $[C_{17}H_{24}NO_3S]^-$, *m/z* 322.1477. Found: *m/z* 322.1489.

***N*-[(1*R*,4*R*)-4-(2-(2-hydroxyethoxy)propan-2-yl)-1-methylcyclohex-2-en-1-yl]-4-methylbenzenesulfonamide (7)** A 10 mL round-bottom flask was oven-dried, fitted with septa, and cooled under N_2. Aziridine **4** (53.8 mg) was weighed directly into the flask. A stir bar, a condenser, a two-neck adaptor, and a temperature probe were added. Ethylene glycol (2.14 mL) was added. The heterogeneous mixture was stirred and warmed to 100°C with a heating mantle. The mixture was stirred at 100°C for 18 h. The yellow solution was allowed to cool and then poured into a separatory funnel. Saturated sodium chloride was added and the mixture was extracted three times with ethyl acetate. The organic solutions were combined and washed with saturated sodium chloride. The solution was dried over sodium sulfate, filtered, and concentrated to an oil. This was chromatographed on flash silica gel, eluting with a gradient of ethyl acetate/hexanes (20%, 40%, 60%, 100% ethyl acetate) to yield **8** (24.8 mg, 38%) as a solid. The solid was crystallized from a mixture of ethyl acetate and hexanes to yield white crystals (11.5 mg, 46% recovery); mp 137–138°C. R_f (60% ethyl acetate/hexanes): 0.49; ^{1}H NMR: δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 10 Hz, 2H), 5.64 (d, *J* = 10 Hz, 1H), 5.54 (dd, *J* = 10 Hz and 2.5 Hz, 1H), 4.46 (s, 1H), 3.67 (s, 2H), 3.42 (t, *J* = 4.8 Hz, 2H), 2.43 (s, 3H), 2.24 (m, 1H), 1.84 (m, 2H), 1.67 (m, 1H), 1.56 (s, 1H), 1.35 (m, 1H), 1.27 (s, 3H), 1.09 (s, 3H), 1.06 (s, 3H); ^{13}C NMR: δ 140.8, 133.6, 129.9, 129.5, 127.5, 77.7, 62.7, 62.3, 57.0, 43.9, 36.9, 27.6, 23.3, 22.9, 22.1, 22.0; IR: 3407 (br), 3186 (br), 2933, 1672, 1380, 1357, 1178, 1052 963, 735 cm^{-1}. HRMS. Calcd for $[C_{19}H_{28}NO_4S]^-$, *m/z* 366.1739. Found: *m/z* 366.1739.

***N*-[(1*R*,3*S*,4*S*,6*S*)-4-acetoxy-4,7,7-trimethylbicyclo[4.1.0]hept-3-yl]-4-methylbenzenesulfonamide (9)** A 10 mL pear-shaped flask was oven-dried, fitted with septa, and cooled under N_2. Aziridine **8** (0.1022 g) was weighed directly into the flask. A stir bar and glacial acetic acid (4 mL) were added. The solution was stirred at room temperature for 21 days. The solvent was removed *in vacuo* and the crude material was chromatographed on flash silica gel, eluting with a gradient of ethyl acetate/hexanes (5%, 15%, 30%, 50% ethyl acetate) to yield **9** (30.8 mg, 25%) as a solid. Unreacted **8** (22.9 mg, 22%) was also recovered. Compound **9**: R_f (30% ethyl acetate/hexanes): 0.35; ^{1}H NMR: δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 4.76 (d, *J* = 8.3 Hz, 1H), 3.54 (q, *J* = 8.3 Hz, 1H), 2.48 (m, 1H), 2.41 (s, 3H), 1.92 (s, 3H), 1.73 (m, 1H), 1.40 (s, 6H), 0.95 (s, 3H), 0.91–1.00 (m, 2H), 0.78 (t, *J* = 4.6 Hz, 1H), 0.23 (t, *J* = 6.4 Hz, 1H); ^{13}C NMR: δ 170.6, 143.4, 138.1, 129.7, 127.2, 83.8, 59.6, 46.5, 30.0, 25.2, 24.1, 24.0, 23.7, 22.6, 21.7, 18.7, 10.1; IR: 3269 (br), 2925, 1727, 1446, 1258, 1157, 1081, 1018, 911, 814, 714, 663 cm^{-1}. HRMS. Calcd for $[C_{19}H_{27}NO_4SNa]^+$ *m/z* 388.1558. Found: *m/z* 388.1552.

Preparation of *N*-[(1*R*,3*S*,4*S*,6*S*)-4-hydroxy-4,7,7-trimethylbicyclo-[4.1.0]hept-3-yl]-4-methylbenzenesulfonamide (10) at room temperature Aziridine **8** (0.105 g) was weighed directly into a 10 mL pear-shaped flask. A stir bar and distilled water (4 mL) were added. The heterogeneous mixture was stirred at room temperature for 21 days, then poured into a separatory funnel, and extracted three times with dichloromethane. The organic solutions were combined and washed with saturated sodium chloride. The solution was dried over sodium sulfate, filtered, and concentrated to an oil. The crude material was chromatographed on flash silica gel, eluting with a gradient of ethyl acetate/hexanes (5%, 30%, 50%, 100% ethyl acetate) to yield **10** (11.2 mg, 12%) as an oil that solidified on standing for 1 day. Unreacted **8** (24.2 mg, 23%) was also recovered. Compound **10**: mp 125–128°C; R_f (30% ethyl acetate/hexanes): 0.13; ^{1}H NMR: δ 7.76 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 4.54 (d, *J* = 8.5 Hz, 1H), 3.60 (q, *J* = 8.5 Hz, 1H), 2.41 (s, 3H), 2.08 (m, 1H), 1.72 (m, 1H), 1.6 (bs, 1H), 1.19 (s, 3H), 1.10 (s, 3H), 1.08 (s, 3H), 0.96–1.02 (m, 2H), 0.78 (t, *J* = 4.5 Hz, 1H), 0.22 (m, 1H); ^{13}C NMR: δ 143.3, 138.2, 129.7, 127.2, 72.3, 59.8, 47.7, 29.9, 29.0, 27.6, 25.2, 23.4, 21.7, 18.8, 9.5; IR: 3450 (br), 3272 (br), 2967, 1446, 1303, 1155, 1080, 1017, 917, 814, 734, 663 cm^{-1}. HRMS. Calcd for $[C_{17}H_{25}NO_3SNa]^+$, *m/z* 346.1453. Found: *m/z* 346.1454.

Preparation of 10 at 80°C Aziridine **8** (0.100 g) was weighed directly into a 10 mL round-bottom flask and treated with distilled water (4 mL). The heterogeneous mixture was stirred at 80°C for 17 h, then cooled, poured into a separatory funnel, and extracted three times with ethyl acetate. The organic solutions were combined, washed with saturated sodium chloride, dried over sodium sulfate, filtered, and concentrated to an oil. The crude material was chromatographed on flash silica gel, eluting with a gradient of ethyl acetate/hexanes (5%, 30%, 50%, 100% ethyl acetate) to yield **10** (15.8 mg, 15%) as an oil that solidified on standing for 1 day. Also separated was *p*-toluenesulfonamide (17.7 mg, 37%).

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