Summer Scholar Report

Method Development for Synthesis of Allylic and Alkyl Tosylates

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Abstract:

A method for synthesis of allylic tosylates from allylic alcohols was developed that does not require metal catalysis or harsh conditions. The method was also utilized to produce secondary tosylates from their parent alcohols. Sodium hydride was used to generate the alkoxide, which can then be treated with p-toluenesulfonyl anhydride to give the corresponding tosylate without generating nucleophilic anions. Synthetic parameters were developed by considering each reaction step separately. Reaction conditions for the formation of the alkoxide from sodium hydride and the alcohol were followed by quenching the alkoxide with methyl iodide and measuring the formation of the methyl ether. Optimized reaction parameters for the second step were established by working with a stable cyclohexyl tosylate. Application of these conditions to the preparation of an allylic tosylate successfully resulted in product, which could be characterized by NMR and mass spectroscopy, although high yield was never achieved due to the sensitivity of the product to elimination.

Introduction:

Addition of the *p*-toluenesulfonyl group to alcohols is a useful synthetic tool to prepare tosylates as precursors to other organic compounds and as substrates in studies of organic mechanisms. Their utility derives chiefly from the properties of the tosylate group as an excellent leaving group in nucleophilic and other reactions. Methods for synthesis of primary and secondary tosylates from alcohols are very generally and widely applicable. These include the Tipson method and variants[1,2,3], which are not without problems, and metal-catalyzed reactions[4,5], some of which utilize expensive metals that are difficult to regenerate. The usual method, dissolving equivalent amounts of alcohol and *p*-toluenesulfonyl chloride in pyridine followed by slow quenching with water,[1] does not work well for allylic tosylates. These compounds are difficult to synthesize and isolate because of the nature of the tosylate group as a great leaving group and its allylic proximity to the CC π-bond.[6] Attempts to synthesize allylic tosylates in the presence of good nucleophiles like chloride in the reaction mixture, as generated when using *p*-toluenesulfonyl chloride, lead instead to isolation of the allylic chlorides in S_N2 reactions (Scheme 1) [7,8] and also to possible rearrangements in S_N2'

processes. Use of bases like pyridine to facilitate the preparation of the tosylate leads instead to 1,2- and 1,4-elimination of tosylate giving dienes (Scheme 2).[8]

Allylic tosylates and their synthesis are relatively unexplored in the literature. The main impediment to synthesis of these compounds is the ease of ionization of the *p*-toluenesulfonate ion leaving a very stable allylic carbocation, leaving them prone to degradation and elimination to diene products (Scheme 2). Unfortunately, reaction conditions for the formation of the tosylate also promote unwanted side products.
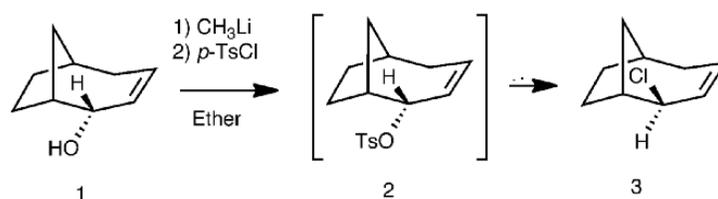
Scheme 1. *SN2 displacement of tosylate by chloride ions*
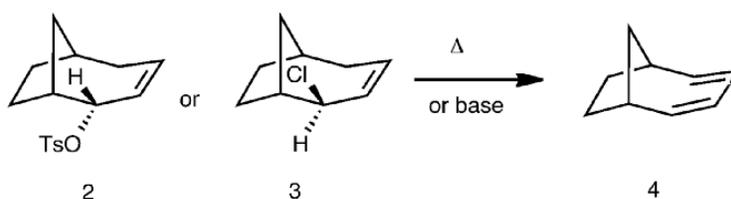
Scheme 2. *Example of thermal or base degradation of allylic tosylates and chlorides.*

The challenge is to find conditions, which produce maximum yields of tosylate without elimination or rearrangement. Our approach was to use *p*-toluenesulfonyl anhydride instead of the corresponding sulfonyl chloride since this would produce *p*-toluenesulfonate anion, a much weaker nucleophile than the chloride ion. This would hinder any possible S_N2 or S_N2' reaction that could occur and reduce the presence of ions that could facilitate elimination. Sodium hydride, as opposed to methyl lithium, was utilized for the first step of the reaction because quantities of this solid reagent are more easily measured. Unlike methyl lithium solutions whose concentrations are variable and decrease over time, sodium hydride is stable as long as it is desiccated. Use of sodium hydride also obviates the presence of nucleophilic ions whereas methyl lithium solutions contain halide from manufacturing. Furthermore, sodium hydride

only produces sodium ions and hydrogen gas during the formation of the alkoxide intermediate. Thus, these putative side products are not expected.

The goal of this research is to elucidate better reaction conditions than current methods for the tosylation of alcohols that will be applicable to allylic tosylates. In order to develop a method for allylic tosylates we first needed to determine the feasibility of the synthetic methods on similar alkyl compounds that are not allylic. Working with the secondary alcohols provides solid information about the kinetics and reactivity of the synthesis as a whole without the degradation possible in the synthesis with the allylic compounds.

Results and Discussion:

The methodology for allylic tosylation was developed by using isophorol **6** (3,5,5-trimethyl-2-cyclohexenol) as the prototype alcohol for this reaction. Isophorol **6** can be easily synthesized by lithium aluminum hydride reduction from the readily available ketone isophorone **5** (3,5,5-trimethyl-2-cyclohexenone) (Scheme 3). Our early reactions of p-toluenesulfonyl anhydride with isophoryl alkoxide generated from isophorol and sodium hydride in diethyl ether were promising, but it became evident that a number of factors needed to be worked out to optimize yield. Since this was ostensibly a twostep process, first the formation of the alkoxide intermediate, then, the addition of the p-toluenesulfonyl group (Scheme 3), each step was focused on individually to determine which synthetic conditions were more effective in increasing yield of product.
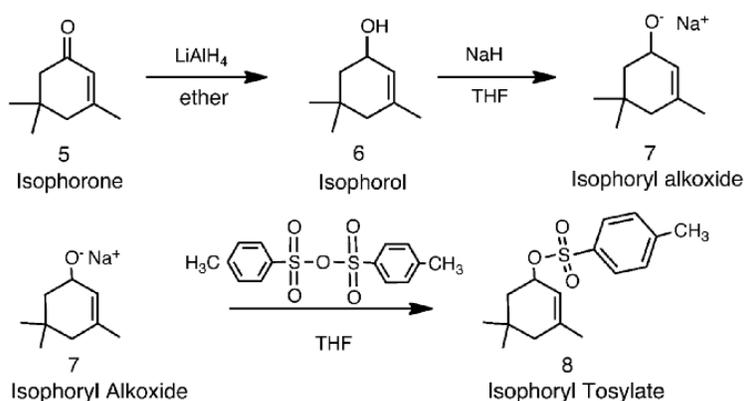
Scheme 3. *Outline of allylic tosylate synthesis from isophorone.*

Elucidation of the First Step Reaction Parameters for Alkoxide Formation:

To determine the ideal conditions for the formation of the alkoxide, it was necessary to find a way to either measure the rate of formation of the alkoxide intermediate or find a way to isolate it. The approach taken was to measure the alkoxide formed over periods of time to determine the optimum contact time for sodium hydride with isophorol **6**. Alkoxide concentration was then determined by quenching with methyl iodide, which served as a reactive alkylating agent (Scheme 4).
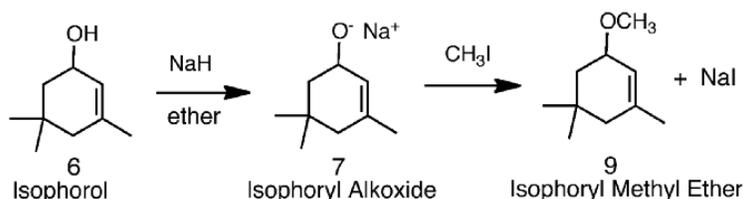
**Scheme 4.** *Reaction of synthesis intermediate with methyl iodide.*

Originally, reactions were carried out in diethyl ether since the solvent could be easily removed, but under several different conditions our yield remained low. It became clear that the sodium hydride was not sufficiently soluble in diethyl ether. Replacing diethyl ether with tetrahydrofuran (THF) significantly improved product yields. These experiments established that within 4-6 hours of reaction, essentially all the alcohol was converted to the alkoxide.

Using the purity of the ether product, determined by NMR, we could gauge which parameters maximized yield. The parameters adjusted for this step were temperature, reaction time, concentration, and solvent. The temperature of the reaction was increased from room temperature to 40°C, resulting in a visible change in the solution color after about 4 hours, suggesting that alkoxide formation was complete. The reaction with methyl iodide was slow in refluxing diethyl ether, but in refluxing THF 100% conversion was achieved. Conversion from isophorol to its methyl ether **9** could be easily followed by development of the methyl peak at 3.35 ppm and disappearance of any alcohol peak in the NMR.

Elucidation of the Second Step Reaction Parameters for Tosylate Formation:

Because of the known sensitivity of allylic tosylates to elimination, the second step parameters were determined by working with a secondary alcohol without the possibility of allylic interference. The alcohol chosen was 4-methylcyclohexanol, a symmetric,

secondary alcohol, which is also a cyclic alcohol like isophorol with similar steric requirements at the reaction site and an uncomplicated NMR spectrum for product analysis. Utilizing the conditions previously established for alkoxide formation, the second tosylation step was carried out with *p*-toluenesulfonyl anhydride (Table 1). During the tosylation of the secondary alcohol, it was determined that the reaction with sodium hydride could be heated to 60°C to speed up the reaction without degradation. Although heat can be applied in the first step in the allylic tosylation, the reaction temperature must be reduced for the second step of the reaction to avoid elimination. While experimenting with the secondary alcohols to fine tune reaction parameters, it was found that reactions produced pure crystalline product suitable for x-ray diffraction analysis. The secondary tosylate from *trans*-4-methylcyclohexanol **10** (Scheme 5) was synthesized in 24% pure crystalline yield and characterized by NMR spectroscopy. Tosylates of other secondary alcohols, l-menthol and l-borneol, (**11** and **12**) were successfully synthesized using the same method, producing very pure crystalline product in 42% and 57% yield, respectively, which were characterized by NMR.
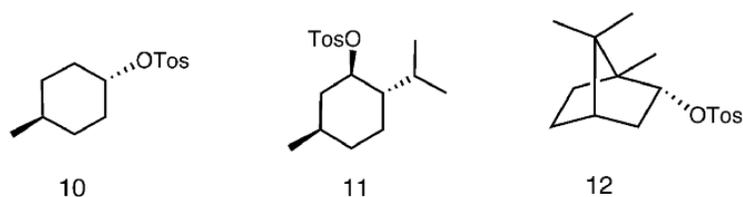
Scheme 5. *Alkyl tosylate structures*

The pure crystals of 11 and 12 were suitable for characterization by x-ray crystallography.[9] X-ray crystal structures for these tosylates appear in Figures 1 and 2.

Application to the Synthesis of Allylic Tosylates:

Reaction conditions for the synthesis of secondary alkyl tosylates were now applied to the prototypical allylic system. The alkoxide of isophorol **7** was generated with sodium hydride in THF. Although heat can be applied in the first step in the allylic tosylation (alkoxide formation), the reaction temperature must be reduced for the second (tosylation) step of the reaction to minimize elimination reactions. Addition of *p*-toluenesulfonic anhydride led to reaction mixtures, which were analyzed by GC/MS. It was found that the most efficient work-up procedure was to evaporate the solvent in vacuo and to then add cold (0° C) pentane, followed immediately by filtration, which removed all of the insoluble p -toluenesulfonic anhydride and the sodium p -toluenesulfonate salt. Table 1 provides details on synthetic results under different reaction conditions.

Table 1. Preparative Conditions and Yields for Various Tosylate Syntheses.

| Starting Alcohol	Temperature	Moles of Alcohol	Moles NaH	Hours Reacted Step 1	Moles of Ts₂O	Hours Reacted Step 2	Tosylate Yield
Isophorol	40C	0.01	0.025	5	0.0125	4	33%[†]
Isophorol	40C	0.01	0.025	5	0.0125	8	30%[†]
Isophorol	40C	0.01	0.025	5	0.0125	20	18%[†]
Isophorol	50C	0.01	0.025	4	0.0125	1	17%[†]
Isophorol	50C	0.01	0.025	4	0.0125	2	15%[†]
Isophorol	50C	0.01	0.025	4	0.0125	3	14%[†]
Isophorol	60C*	0.0025	0.004	5	0.00275	4	31%[†]
Isophorol	60C*	0.0025	0.004	5	0.00275	6	54%[†]
Isophorol	60C*	0.0025	0.004	5	0.00275	22	26%[†]
4-methyl-cy-clohexanol	60C	0.01	0.022	5	0.0125	4	24%[‡]
l-(-)-menthol	60C	0.01	0.011	4	0.011	4	42%
l-(-)-borneol	60C	0.01	0.011	4	0.011	4	50%

*= Temperature was lowered to 40°C before addition of the tosyl anhydride
†= Yield determined from NMR analysis of product mix
‡= Pure crystal yield
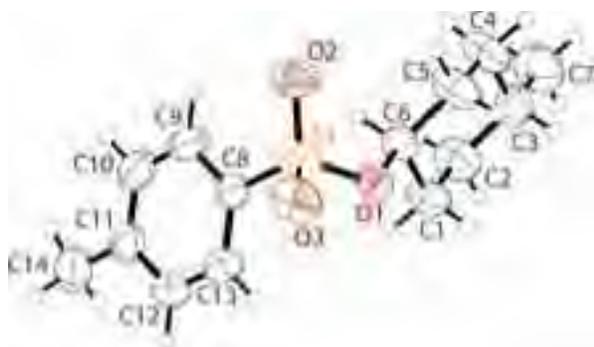
**Figure 1.** *Crystal Structure of trans-4-methylcyclohexyl ptoluenesulfonate 10*
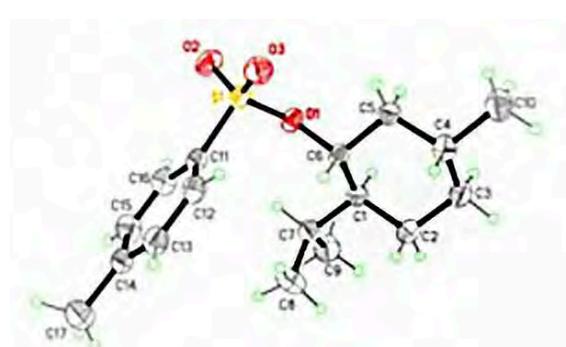
Figure 2. *Crystal Structure of (1R, 2S, 5R)-2-isopropyl-5-methylcyclohexyl p-toluenesulfonate 11*

GC/MS analysis was used to identify compounds in the product mixture (Figure 3). The target tosylate product **8** was detected at a retention time of 16.5 minutes in the gas chromatogram. The starting alcohol **6** normally appears around 8.1 minutes, but it is frequently absent confirming the conversion of the alcohol to either product or degradation/rearrangement. Peaks for dienes **13** and **14**, formed by 1,2- and 1,4-elimination (Scheme 6) appear at 3.8 and 4.1 minutes. Under certain reaction conditions two peaks appear around 15.3 min with molecular masses twice those of the dienes from

possible Diels-Alder dimerization of the diene degradation products in the injection port of the gas chromatograph. Finally a peak at 20.0 minutes gave a non-allylic rearrangement of the target product.
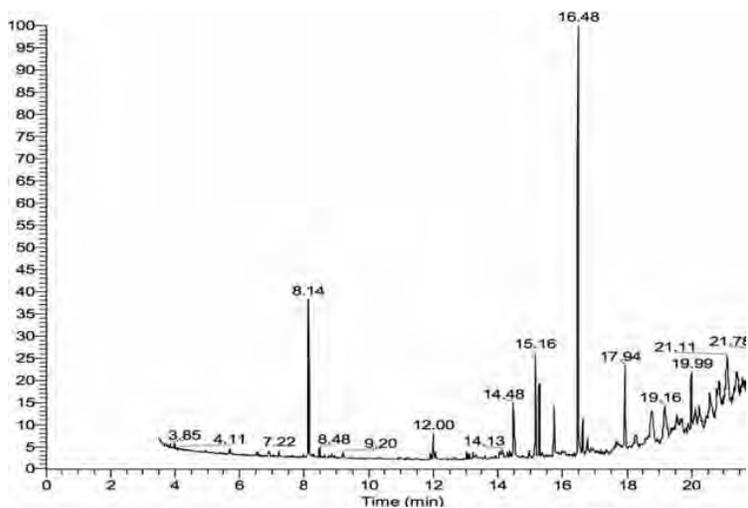
Figure 3. *Typical GC/MS chromatogram of isophoryl tosylate reaction mixture.*
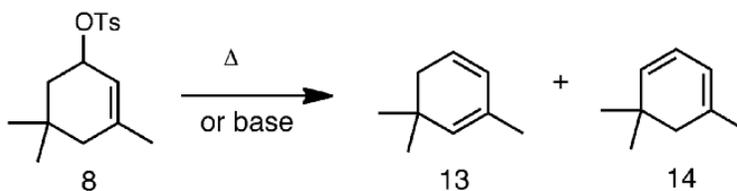
Scheme 6. *Formation of dienes by elimination from isophoryl tosylate.*

The fragmentation pattern for our product was unusual because there was no parent ion close to the molecular mass of the product. The highest mass observed corresponded to that of the carbocation formed by loss of the tosylate group. A similar situation occurred with our secondary tosylates, **10**, **11**, and **12** , which gave GC peaks from 13 - 22 min. in the chromatogram. None of these showed parent molecular ions. Apparently the tosylate group is immediately eliminated from these compounds when ionized in the electron beam. Both the allylic tosylation product and the secondary tosylates show no molecular ions but do show peaks related to their molecular mass minus the mass of the tosylate anion. However, in electrospray LC/MS analysis at ambient temperature, the molecular ion does appear.

Preparative high-pressure liquid chromatography (HPLC) was used to separate and isolate the compounds in the product mixture. Samples of the fractions were collected as each of the major constituents emerged from the detector. These HPLC cuts were analyzed using GC/MS to confirm the identity of each compound. Sufficient samples were obtained by combining HPLC fractions through several runs of the chromatographic method. Solvent was removed in vacuo at 30° C to produce NMR samples for analysis. The fraction for **8** appeared to be pure tosylate under GC/MS analysis.

Conclusions:

A straightforward, alternative method has been developed for the tosylation of alcohols, which involves relatively mild conditions, does not require metal catalysis, and does not generate strong nucleophiles. In this research secondary alkyl and allylic tosylates were successfully prepared, isolated, and characterized. Although yields of the allylic tosylate were not great, further optimization of the reaction conditions is possible. The synthesis of secondary alkyl tosylates occurs in moderate yield and high purity. Since the tosylates retain the stereochemistry of the starting alcohol and serve as excellent leaving groups, these alkyl tosylates make good candidates as intermediates for S_N2 stereo-inversion to alcohols of opposite configuration. The potential for this stereo-inversion to take place with high stereospecificity could provide a very synthetically useful method, especially if it could be carried out as a one-pot synthesis.

Experimental Section:

Instrumentation. A Bruker AVANCE III 400 MHz FT-NMR spectrometer was used to confirm the structure of products and used to determined product mixture proportions. NMR samples were dissolved in deuterated chloroform with TMS reference; the proton, ^{13}C, and COSY NMR spectra were then analyzed. Varian Dynamax UV-1 HPLC and Agilent liquid Chromatography driver were used to separate product mixtures. A normal phase silica preparatory column (Agilent Dynamax Microsorb 60-8 SI) of 250 x 10.0 mm length and diameter was used at a flow rate of 2 mL/min. Samples were analyzed over a 67-minute period with a gradient of hexane-THF. The HPLC solvents transitioned from 100% hexane to 99% hexane/1 % THF over the first 60 minutes, then to 100% THF over 2 minutes and was held at 100% THF for 5 minutes before returning to 100% hexane in 3 minutes. A Thermo-Fisher FOCUS/ITQ-700 GC-MS was used to determine proportions of product mixture and confirm purity of the collected HPLC fractions. All samples were dissolved in hexane and analyzed on a GC temperature gradient over 22 minutes with the initial temperature of 50°C transitioning to a final temperature of 250°C the GC was then followed by subsequent positive ion mass spectral analysis with an MS transfer line temperature of 300°C and a helium gas flow of 1.5 mL/min.

3,5,5-Trimethyl-2-cyclohexenol (Isophorol) (6). All glassware was dried and flushed with nitrogen. 3.037 g (0.080 moles about 10% excess) of LiAlH4 was added to 150 mL of diethyl ether in a 250 mL three-neck round bottom flask, equipped with a condenser. 10.514 g (0.072 moles) of isophorone **5** was diluted with 50 mL diethyl ether and added to a dropping funnel attached to the reaction flask. The reaction was stirred while the isophorone solution was added slowly, dropwise, over about an hour, the reaction was stirred for another 2-3 hours. The reaction was heated to reflux at a constant rate. Once this was achieved, the solution was kept refluxing overnight. Any lost solvent was replaced, 20 mL of cold distilled water was added slowly dropwise, followed by dropwise addition of 30 mL of 15% NaOH. The solution was filter, and the solvent was rotary evaporated off leaving 8.760 g of **6** in 82.1% yield. ^{1}H NMR (CDCl$_3$) (ppm) 0.88 (3H, s), 0.99 (3H, s), 1.23 (1H, d of d), 1.61 (1H, d), 1.68 (3H, s), 1.76(1H, d of d), 1.85 (1H, d), 1.87 (1H, s), 4.24 (1H, d of d), 5.43 (1H, s). MS(EI), 38.9, 52.9, 53.9, 67.0, 77.1, 81.9, 95.0, 96.0, 110.0, 123.0, 137.9. [reported[10] ^{1}H NMR (CDCl$_3$) (ppm) 0.88 (3H, s), 0.99 (3H, s), 1.23 (1H, d of d, J=9.1, 12.4 Hz), 1.68 (3H, s), 1.64–1.88 (4H, m), 4.20-4.27 (1H, m), 5.43 (1H, s)].

3,5,5-Trimethyl-1-methoxycyclohex-2-ene (Isophorol Methyl Ether) (9). All glassware was dried and flushed with nitrogen. 1.407 g (0.010 moles) of isophorol **6** in 15 mL of freshly dried THF was added to a 100 mL three-neck round bottom flask equipped with a condenser. 0.549 g (0.023 moles, double excess) of sodium hydride was then added with 30 mL of THF. The reaction was stirred for 4 hours at 40°C, 1.5 mL (3.42 g, 0.024 moles, double excess) of methyl iodide was added to the reaction and then the reaction was stirred for 2 hours. Once the reaction was complete the reaction solution transferred to a separatory funnel and washed thrice with 15 mL cold brine solution. The THF solution was transferred to a beaker containing anhydrous magnesium sulfate and then filtered, the THF was then rotary evaporated off leaving an oil, which was 100% **9** by NMR. ^{1}H NMR (CDCl$_3$) (ppm) 0.87 (3H, s), 0.99 (3H, s), 1.26 (1H, t), 1.68 (3 H, s), 1.70 (1H, d of d), 1.74(2H, q), 3.35 (3H, s), 3.80 (1H, br s), 5.49 (1H, s), values found agree with literature.[11]

trans-4-Methylcyclohexyl p-toluenesulfonate (10). All glassware was dried and flushed with nitrogen. 1.179 g (0.010 moles) of *trans*-4-methylcyclohexanol in 15 mL of freshly dried THF was added to a 100 mL three-neck round bottom flask equipped with a condenser. 0.578 g (0.024 moles, double excess) of sodium hydride was then added with 30 mL of THF, the reaction was heated to 60°C via an oil bath. After stirring for 5 hours, 4.104 g (0.0126 moles, excess) of *p*-toluenesulfonic anhydride was added to the reaction, and then the reaction was stirred for 4 hours. Once the reaction was complete, the reaction solution was filtered using a fritted glass filter. The reaction vessel was rinsed with an additional 10 mL of THF. 40 mL of dry pentane was added to the flask, which

was left in the freezer, whereupon product crystallized out from the bi-layer system in 24% yield. ^{1}H NMR (CDCl$_3$) (ppm) 0.85 (3H, d), 0.93 (2H, q), 1.32 (1H, broad m), 1.47 (2H), 1.70 (2H, d), 1.91 (2H, d), 2.45 (3H, t), 4.38 (1H, sep), 7.33 (2H, d), 7.79 (2H, d). MS(EI), 38.9, 55.0, 65.0, 79.0, 81.0, 91.0, 95.9, 96.9, 108.1.

(1R, 2S, 5R)-2-Isopropyl-5-methylcyclohexyl p-toluenesulfonate (Menthyl tosylate) (11). All glassware was dried and flushed with nitrogen. 1.558 g (0.010 moles) of *l*-menthol in 15 mL freshly dried THF was added to a 100 mL three-neck round bottom flask equipped with a condenser. 0.273 g (0.011 moles, excess) of sodium hydride was then added with 30 mL of THF, the reaction was heated to 60°C via an oil bath. After stirring for 5 hours, 3.633 g (0.011 moles, excess) of *p*-toluenesulfonic anhydride was added to the reaction and then the reaction mixture was stirred for 4 hours. Once the reaction was complete, the reaction solution was filtered using a fritted glass filter. The reaction vessel was rinsed with an additional 10 mL of THF. The solvent from the filter solution was removed through rotary evaporation, 25 mL of dry pentane was added to the flask, and the pentane solution was filtered. While under vacuum and low temperature 1.300 g of pure product **11** solidified out (42% yield). The solid was recrystallized in pentane, producing crystals suitable for x-ray diffraction. ^{1}H NMR (CDCl$_3$) (ppm) 0.52 (3H, d), 0.83 (3H, d), 0.88 (3H, d), 0.95 (1H, t of d), 1.18 (1H, quin), 1.37 (2H, m), 1.63 (2H, m), 1.69 (2H, s), 1.89 (1H, quin of d), 2.14 (1H, d), 2.44 (3H, s), 4.40 (1H, t of d), 7.33 (2H, d), 7.81 (2H, d), values agree with those found in the literature[12] . MS(EI), 27.9, 39.0, 43.0, 67.0, 79.0, 81.0, 91.1, 95.0, 107.0, 109.0, 125.0, 137.0, 152.9.

endo-(1S)-1,7,7-Trimethyl-bicyclo[2.2.1]heptan-2-yl *p*-toluenesulfonate (Bornyl tosylate) (12). All glassware was dried and flushed with nitrogen. 1.527 g (0.0099 moles) of *l*-borneol in 15 mL of freshly dried THF was added to a 100 mL three-neck round bottom flask equipped with a condenser. 0.277 g (0.012 moles, excess) of sodium hydride was then added with 30 mL of THF, the reaction was heated to 60°C via an oil bath. After the reaction was stirred for 4 hours, 3.633 g (0.011 moles, excess) of *p*-toluenesulfonic anhydride was added to the reaction, and then the reaction was stirred for 4 additional hours. Once the reaction was complete the reaction solution was filtered using a fritted glass filter. The reaction vessel was rinsed with an additional 10 mL of THF. The solvent from the filter solution was removed through rotary evaporation, 25 mL of dry pentane was added to the flask, and the pentane solution was filtered. While under vacuum and low temperature 1.557 g of pure product **12** solidified out (50.3% yield). The solid was recrystallized in pentane, producing crystalline solid, which gave an NMR of the pure product but was not suitable for x-ray diffraction. ^{1}H NMR (CDCl$_3$) (ppm) 0.73 (3H, s), 0.80 (3H, s), 0.84 (3H, s), 1.14 (1H, d of d), 1.26 (2H, q), 1.63 (1H, t), 1.71 (1H, m), 1.90 (1H, m), 2.11 (1H, m), 2.45 (3H, s), 4.62 (1H, d of t), 7.33 (2H, d),

7.79 (2H, d), values agree with those found in the literature.[13] MS(EI), 38.9, 43.0, 51.0, 55.1, 65.0, 67.1, 77.0, 79.0, 91.0,93.0, 95.0, 107.0, 121.0, 136.0.

3,5,5-Trimethyl-2-cyclohexenyl *p*-toluenesulfonate (Isophoryl Tosylate) (8). All glassware was dried and flushed with nitrogen. 0.3487 g (0.0025 moles) of isophorol in 15 mL of freshly dried THF was added to a 100 mL threeneck round bottom flask equipped with a condenser. 0.0911 g (0.0038 moles, 10% excess) of sodium hydride was then added with 30 mL of dry THF, and the reaction was heated to 60°C via an oil bath. The reaction was stirred for 5 hours; then the oil bath was reduced to 40°C. 0.9158 g (0.0028 moles) of *p*-toluenesulfonic anhydride was added to the reaction, and the reaction mixture was stirred for 6 hours. Once the reaction was complete, the reaction solution was filtered using a fritted glass filter. The reaction vessel was rinsed with an additional 10 mL of THF. The effluent was collected and the THF solvent was rotary evaporated off, 40 mL of prechilled dry pentane was added, and the solution was refiltered. The pentane was then rotary evaporated off from the filtered solution leaving crude **8**. NMR analysis showed a 54% yield of **8**. A normal phase silica semi-preparatory column with a 100% hexane to 99:1 hexane-THF gradient was used to analyze, separate, and purify components of the product mixture. The final product was stored at -20° C.. ^{1}H NMR (CDCl$_3$) (ppm) 0.94 (3H, s), 0.99 (3H, s), 1.25 (1H, d of d), 1.57 (1H, d), 1.61 (1H, d), 1.89 (3H, s), 2.21 (1H, d), 2.46 (3H, s), 3.83 (1H, d of d), 5.41 (1H, s), 7.36 (2H, d), 7.81 (2H, d). MS(EI), 38.9, 40.9, 42.9, 51.0, 55.9, 57.0, 67.1, 79.0, 81.1, 91.1, 93.0, 95.0, 105.1, 109.0, 119.1, 133.0, 145.1, 147.1, 161.1, 175.1, 189.1, 261.2.

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