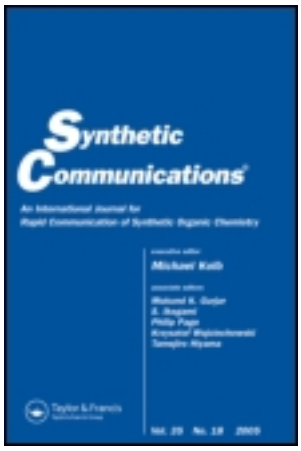

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AN IMPROVED PREPARATION OF 2-AZABICYCLO[2.2.2]OCTANE

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AN IMPROVED PREPARATION OF 2-AZABICYCLO[2.2.2]OCTANE

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ABSTRACT

An improved preparative four-step synthesis to isoquinuclidine tosylate salt **4** has been demonstrated in 70% overall yield from *p*-aminobenzoic acid (PABA) **1**. Hydrogenation of PABA **1** affords 4-aminocyclohexane carboxylic acid **2** as an 80 : 20 mixture of *cis*- and *trans*-isomers. Heating the mixture at 250°C effected epimerization and cyclization to provide the bicyclic lactam **3**. Subsequent Red-Al reduction and treatment with tosic acid furnished the desired bicyclic amine, tosylate salt **4**.

Key Words: Bicyclic aza compounds; Hydrogenation; Lactamisation; Reduction

Recently, we had need of multi-kilogram quantities of 2-azabicyclo[2.2.2]octane. A literature survey revealed very few procedures suitable for large scale preparation of this deceptively simple compound, most resulting in low yields. Imino Diels-Alder approaches,

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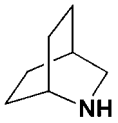
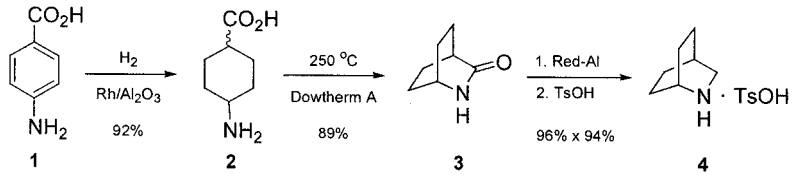
such as Grieco's aqueous method[1] employing 1,3-cyclohexadiene (CHD)/benzylamine/formaldehyde, and Cava's approach[2] employing CHD and $CH_2{=}NCO_2Et$ are low yielding (30–35%) and require chromatographic purification. Addition of water-soluble lanthanide Lewis acids[3] did not improve the yield in our hands. Malpass's Diels-Alder type reaction[4] between CHD and chlorosulfonylisocyanate followed by de-chlorosulfonylation was also a low yielding sequence (~10%) in our hands. Similarly, Diels-Alder reactions of dihydropyridine[5] gave low yields (~40%). The approach[6] via an intramolecular cyclization of *cis*-4-aminocyclohexanecarboxylic acid (ACHA) is attractive, but lacks an efficient method to prepare pure *cis*-ACHA, since hydrogenation of *p*-aminobenzoic acid gave a mixture of *cis*- and *trans*-ACHA. However, an Org. Syn. preparation[7] of bicyclic lactam **3** from a mixture of *cis*- and trans-ACHA via a high temperature (250°C) induced epimerization-cyclization protocol, avoids the need for separating the *cis*- and *trans*-isomers. Although there is one known method that avoids the high temperature reaction, it suffers from having two additional steps.[8]



2-Azabicyclo[2.2.2]octane

We therefore focused on this high temperature route based on its simplicity, and addressed several issues before this route could be useful for large scale preparation: 1) the hydrogenation conditions[7] for the preparation of ACHA, **2**, require long reaction time and is difficult to reproduce; 2) the bicyclic lactam **3** is obtained by concentrating the aqueous solution; 3) the reduction of lactam **3** to amine **4** is generally carried out using highly hazardous lithium aluminum hydride,[9] which is not safe for large scale preparation; and finally, 4) the development of a suitable salt form of the amine, possessing well-behaved physical properties and providing good impurity rejection, is preferred. Here we report that we have addressed these issues and developed an improved preparative procedure to the title compound as the tosylate salt and have successfully demonstrated the procedure on multi-kilogram scale. The synthetic route to **4** is depicted in Scheme 1.



Scheme 1.

Step 1—Hydrogenation

Hydrogenation conditions for the conversion of PABA **1** to ACHA **2** were investigated, and 5% Rh/Al_2O_3 was found to be an excellent hydrogenation catalyst in terms of reactivity. As in Windhorst et al's procedure[10] the solvent is 30% ethanol in water plus 3% AcOH, which provides solubility for both the starting material and the product. Hydrogenation of PABA **1** at 700 psi and 65°C for 2 h afforded ACHA **2** in 90–95% yield as a mixture of 80 : 20 *cis*- and *trans*-isomers (Table 1). The hydrogenation could also be carried out at 40 psi/65°C with 5 wt% catalyst, but it required 24 h to reach completion. The rate of reaction was also significantly slower in the absence of acetic acid. For scale up, we chose to run at 300 psi/65°C with 10 wt% catalyst for speed and reliability. Under these conditions the reaction consistently gave >99.7% completion within 2 h on 1.5 kg scale in 5-gal. vessels. Hydrogenation with PtO_2 (10 wt%) at 50 psi/22°C in water for 15 h also afforded the product in 90–95% yield, but the ratio of *cis*- and *trans*-isomers is 60 : 40.

Table 1. Hydrogenation of 4-Aminobenzoic Acid to 4-Aminocyclohexanecarboxylic Acid

Entry	Catalyst	Solvent(s)	Hydrogenation	Time	Yield* of **2** (*cis* : *trans*)
1	5% Rh/Al_2O_3 (10% wt)	30% EtOH/H_2O + 3% AcOH	700 psi, 65°C	2 h	90–95% (80 : 20)
2	”	”	300 psi, 65°C	2–5 h	90–95% (80 : 20)
3	”	”	100 psi, 65°C	5 h	90–95% (83 : 17)
4	”	”	40 psi, 65°C	15 h	90–95% (82 : 18)
5	”(5 wt%)	”	100 psi, 65°C	24 h	90–95% (80 : 20)◆
6	”(3 wt%)	”(no AcOH)	100 psi, 65°C	24 h	25% (84 : 16)◆
7	PtO_2 (10 wt%)	H_2O	50 psi, 22°C	15 h	90–95% (60 : 40)

*Uncorrected isolated yield, starting from 10–40 g of 4-aminobenzoic acid.
◆200 g scale.

After removal of catalyst from the reaction mixture, the filtrate is concentrated and ACHA **2** is precipitated from acetone/water as a 80 : 20 mixture of *cis*- and *trans*-isomers in 90–95% yield with ~5% loss to the mother liquor. The purity of the solid is 90–95 wt%.

Step 2—Epimerization–Cyclization

Conversion ACHA **2** to isoquinuclidone **3** is accomplished by heating a slurry of the substrate in Dowtherm® A at 250–260°C for 20–30 min with simultaneous removal of water.[7] The product is directly crystallized out of the reaction mixture by heptane (5 × vol) addition, thereby avoiding the water extractions and concentration as described in the original Org. Syn. preparation.[7] Initially, the reaction was carried out at a concentration of 5–6 mL/g, followed by dilution with heptane (5 × vol) to provide a slurry of product for filtration/isolation. Under this protocol, the typical isolated yield is 80–85% with loss to mother liquor at 6–10% due to high solubility of the lactam in Dowtherm®A. In order to minimize product loss to mother liquor, the reaction mixture was concentrated (170°C/24 in) to half original volume before heptane dilution. Unfortunately, lactam **3** co-distilled with Dowtherm®A during the concentration resulting in 26% loss to the distillate and an isolated yield is only 66%. Fortunately, the distillate could be recycled in the subsequent run without any problem. Finally, by conducting the lactamization at a concentration of 3 mL Dowtherm®A per gram of substrate with a Dean–Stark trap, the reaction afforded the bicyclic lactam in 89% isolated yield with 91 wt% purity containing 9 wt% Dowtherm®A with 4% product loss to mother liquor. The reaction is air sensitive and should be kept under nitrogen at all time to prevent the reaction from turning into a dark brown mixture. This high temperature-induced-epimerization results in the same yield whether starting from an 80 : 20 or a 60 : 40 mixture of *cis*/*trans*-ACHA.

Steps 3 and 4—Red-Al Reduction and Tosylate Formation

BH_3 reduction of the bicyclic lactam **3** was met with difficulty in breaking the amine borane complex, even with refluxing 0.5 M aqueous sulfuric acid. We therefore investigated the thermally stable *bis*-(2-methoxyethoxy)aluminum hydride (Red-Al® or Vitride®).[11–14]. Reduction of the bicyclic lactam to the bicyclic amine was carried out with 2.5 eq of Red-Al (3.4 M in toluene, KF $< 500\,\mu g/mL$) at 80°C. The reaction is quenched with 1.4 M NaOH solution (1.02 eq relative to Red-Al®) to furnish a slightly cloudy

organic phase and a heterogeneous aqueous phase. The aqueous phase was extracted with toluene, which gave an emulsion, but most of the aqueous phase could be separated. Celite® was added to the mixture and filtered to remove the gummy aluminum salts. The filtrate now separated into two clear layers. After drying the organic phase with sodium sulfate, the free base solution is used directly in the tosylate salt formation without concentration because of the volatility of the product. The concentration of the product in each of the three organic extracts were: ~90 g/L, ~19 g/L and ~3 g/L, which translates to about 84%, 12% and 3% of product recovered respectively. It is noteworthy to mention that the Celite® treatment not only made the cuts easier, but also removed some colored impurities and minimized product loss to the mother liquor.

The average assay yield of the bicyclic amine in toluene for the three 27 mol batches was 95% as determined by titration. Treatment of the solution with one equivalent of toluenesulfonic acid monohydrate, followed by azeotropic removal of water afforded the crystalline tosylate salt. A total of 20.5 kg of the material was isolated with an average wt% purity of 90.6%. The corrected yield for the salt formation is 85% and the overall yield for the two steps was 80%.

Further Optimization

In theory, the reduction of the bicyclic lactam requires only three hydrides. The above preparation used 2.5 mole of Red-Al® per mole of **3**, which corresponds to five hydride equivalents. The employment of excess hydride is not only unnecessary but also unsafe due to large hydrogen release during quenching of these reactions as observed in the multi-kilogram runs. Therefore employment of $\leq$2 mole of Red-Al® per mole of **3** or **4** hydride equivalent was investigated. Laboratory scale reaction using 36 g of the lactam and 1.84 eq of Red-Al® (3.7 hydride equivalents) gave an excellent yield of 96.6% of the amine. The subsequent tosylate salt formation step was also improved to 92.8% yield by reducing the crystallization volume. These changes are detailed in the experimental section.

In summary, an improved procedure to provide preparative quantities of bicyclic amine isoquinuclidine has been successfully demonstrated. The described procedures have been used for the preparation of 20 + kg (66 mol) of the bicyclic amine as the tosylate salt in 62% overall yield from *p*-aminobenzoic acid (PABA, **1**). The four-step synthesis begins with the hydrogenation of PABA using Rh/Al_2O_3 to furnish a 92% yield of 4-aminocyclohexane carboxylic acid, **2,** as an 80 : 20 *cis* and *trans* mixture. Subsequent heating at 250°C in Dowtherm® A to effect epimerization and

cyclization afforded the bicyclic lactam **3** in 84% yield. Red-Al reduction furnished the desired 2-azabicyclo[2.2.2]octane in 95% yield, which was converted to the tosylate salt **4** in 85% yield. The employment of a more concentrated Dowtherm® mixture and reduced amounts of Red-Al® led to yield improvements for the cyclization step from 84 to 89% and the tosylate salt step from 85 to 91%. These improvements raised the overall yield of the bicyclic amine to as high as 70%.

EXPERIMENTAL

General

All reactions were conducted under an atmosphere of dry N_2. As necessary, most of the solvents and reagents were dried over 3 or 4 Å molecular sieves and residual water was determined by Karl Fisher titration. Melting points were uncorrected. ^1H and ^{13}C NMR spectra were collected at 500 and 125 MHz, respectively, from samples in the specified deuterated solvent. Assay yields of products were determined by HPLC analysis using the corresponding pure products as standards. Dowtherm® A was purchased from Fluka.

***Cis*- and *Trans*-4-Aminocyclohexanecarboxylic Acid (2):** Prior to the actual run, a conditioning run in the 5-gallon vessel is carried out using 25 g of the catalyst with 10 L of 30% EtOH/H_2O, and 300 mL acetic acid at 300 psi hydrogen and 65°C for 3 h. A general procedure is as follows: A mixture of 4-aminobenzoic acid (PABA, **1**) (1500 g, 10.9 mol), 30% EtOH/H_2O (15 L), acetic acid (450 mL) and 5% Rh/Al_2O_4 (150 g) is hydrogenated at 300 psi and 65°C. When 3 eq of hydrogen has been absorbed ($\leq$2 h, $<$0.3% starting material relative to product by ^1H NMR analysis in D_2O), the mixture is cooled to 20°C and transferred to a storage bottle.

The vessel is rinsed with 30% EtOH/H_2O (7.5 L). The mixture and the rinse are filtered through Celite® 545 (Aldrich; 1–2 inch pad; wet-packed with H_2O), then washed with H_2O (3.75 L). The filtrate is concentrated under reduced pressure at 30–60°C to ~3.75 L. The mixture is diluted with acetone (33.75 L) and aged at 20°C for 2–15 h. The resulting slurry is filtered, washed with acetone (5.63 L) and vacuum dried under a nitrogen sweep to give 1.6 kg (91 wt%, 91% yield) of 4-aminocyclohexanecarboxylic acid, **2**, as a 80 : 20 *cis*- and *trans*-isomer mixture based on NMR. The wt% of the material is determined based on $HClO_4$ titration, thermogravimetric and Karl Fisher measurements.

In one preparative campaign, 14.85 kg of PABA **1** were hydrogenated in 11 batches using 5-gallon autoclaves (stainless steel and Hasteloy).

Isolation was performed in four batches with a total of 15.66 kg of crystalline solid isolated. The material had an average wt% purity of 91.1%, which was 14.27 kg of pure product. The overall yield for the step was 92%. **2**: m.p. 234–236°C; ^{1}H NMR (D_2O) δ 3.32 (m, *cis* NH_2–C*H*), 3.17 (m, *trans* NH_2–C*H*), 2.42 (m, *cis* CO_2H–C*H*), 2.14 (m, *trans* CO_2H–C*H*), 2.09 (m, *trans* H3,5 eq), 1.90–2.00 (m, H2,6 eq), 1.87 (m, *cis* H3,5 eq), 1.56–1.70 (m, H2,6 ax, *cis* H3,5 ax), 1.43 (m, *trans* H3,5 ax); ^{13}C NMR (D_2O) δ 185.5 (*trans* *C*O_2H), 184.3 (*cis* *C*O_2H), 50.7 (*trans* C4), 49.9 (*cis* C4), 46.0 (*trans* C1), 42.2 (*cis* C1), 30.5 (*trans* C3,5), 28.5 (*trans* C2,6), 28.1 (*cis* C3,5), 25.7 (*cis* C2,6). Anal. Calcd for $C_7H_{13}NO_2 \cdot 0.5\ H_2O$: C, 55.24; H, 9.27; N, 9.20. Found: C, 55.09; H, 9.21; N, 8.81.

3-Isoquinuclidinone (3). Method A: In a 72-L round bottomed flask equipped with a mechanical stir, and a distillation apparatus, a mixture of *cis*- and *trans*-4-aminocyclohexanecarboxylic acid **2** (3.83 kg, 92.6 wt%, 24.8 mol) and Dowtherm® A (23.5 L) is heated as a slurry to reflux temperature (250–260°C) under a slight nitrogen sweep using two 220-volt heating mantles. Heating is continued for 30 min during which time water formed is allowed to distill away (~3–4 L of Dowtherm® A and water is collected). A homogeneous solution is formed by the end of the reaction. The solution is allowed to cool to 22°C. The mixture is concentrated under reduced pressure (b.p. 165–175°C/25–27 Hg in) to about half volume (~12 L). The mixture is cooled to 20°C and then diluted with heptane (55 L). After aging at −5 to 0°C for 1–2 h, the mixture is filtered and washed with cold heptane (3 × 6.3 L). The wet cake is dried under vacuum/nitrogen sweep at 20°C, yielding 2.55 kg of 3-isoquinuclidone **3** as a beige solid. The product is 80 wt% pure along with ~19 wt% Dowtherm®A based on LC assay. This corresponds to a yield of 2.05 kg (66%) pure. Product loss to the mother liquor is ~150 g (5%). About 800 g (26%) of product is lost to the distillate (14.4 L), which is recycled the subsequent runs as follows.

The distillate (~800 g lactam/14.4 L) is combined with 24.8 mol of a mixture of *cis*- and *trans*-4-aminocyclohexanecarboxylic acid **2** and Dowtherm®A (10 L) and heated to reflux temperature (250–260°C) under a slight nitrogen sweep as before and processed as described above to provide 3.38 kg of 3-isoquinuclidone **3** as a light beige solid. The product is 76.4 wt% along with ~20 wt% Dowtherm®A based on LC assay. This gives a yield of 2.58 kg (83%) pure. Product loss to the mother liquor is ~100 g (3%). About 920 g (30%) of product is lost to the distillate (17.7 L).

The distillate (~920 g lactam/17.7 L) is again combined with 24.8 mol of a mixture of *cis*- and *trans*-4-aminocyclohexanecarboxylic acid and Dowtherm® A (7 L) and processed as before to provide 3.06 kg of 3-isoquinuclidone **3** as an off-white solid. The product is 87.6 wt% along with

~15 wt% Dowtherm® A based on LC assay. This gives a yield of 2.68 kg (86%) pure. Product loss to the mother liquor is ~120 g (4%). About 1 kg (32%) of product is loss to the distillate (18.1 L).

Again, the distillate (~1 kg lactam/18.1 L) is combined with 24.8 mol of a mixture of *cis*- and *trans*-4-aminocyclohexanecarboxylic acid **2**, but no additional Dowtherm® A is added and processed the same way as before but without concentration to provide 4.1 kg of 3-isoquinuclidone **3** as a white solid. The product is 78 wt% along with ~15 wt% Dowtherm® A based on LC assay. This gives a yield of 3.2 kg (103%) pure. Product loss to the mother liquor is ~200 g (6%). About 7 g (0.2%) of product is lost to the distillate (2 L).

All four batches of product (~10.5 kg pure) from above are combined and stirred in heptane (50 L) at +50°C for 10 min under nitrogen. After cooling to 20°C, and aging at −5 to 0°C for 1–2 h, it is filtered and washed with cold heptane (3 × 9 L). The wet cake is dried under vacuum/nitrogen at 22°C, to afford 12.3 kg of 3-isoquinuclidone **3** as a light tan solid. The product is 84 wt% pure and contains ~15 wt% Dowtherm® A based on LC assay. This give a yield of 10.33 kg (98%) pure. Product loss to the mother liquor is ~12 g (0.1%).

Method B: In a round bottom flask equipped with a mechanical stirrer, and a Dean–Stark trap, a mixture of *cis*- and *trans*-4-aminocyclohexanecarboxylic acid **2** (50 g, 94.8 wt%, 0.331 mol), and Dowtherm®A (142 mL) is heated to reflux temperature (250–260°C) under a slight nitrogen sweep. Heating is continued for 30 min during which time a total of ~15 mL of a water/Dowtherm®A mixture is collected. The mixture becomes a homogeneous solution at the end of reaction. The solution is allowed to cool to 20°C and then diluted with heptane (635 mL). After stirring at −5 to 0°C for 1–2 h, it is filtered and washed with cold heptane (2 × 100 mL). The wet cake is dried under vacuum/nitrogen sweep at 22°C overnight, yielding 40.7 g of 3-isoquinuclidone **3** as an off-white solid. The product is 91 wt% containing 9 wt% Dowtherm®A based on LC assay. This corresponds to a yield of 37 g (89%) pure. Product loss to the mother liquor is ~1.7 g (4%). An analytical sample is obtained by recrystallization from cyclohexane: m.p. 168–170°C; ^{1}H NMR (D_2O) δ 3.72 (br s, 1H), 2.50 (br s, 1H), 1.85–1.65 (m, 8H); ^{13}C NMR (D_2O) δ 182.5, 48.3, 37.8, 27.2, 24.0. Anal. Calcd for $C_7H_{11}NO \cdot 0.25\ H_2O$: C, 64.84; H, 8.94; N, 10.80. Found: C, 64.85; H, 8.82; N, 10.41.

Isoquinuclidine Tosylate (4). Method A: To a 100-L round bottomed flask equipped with a mechanical stir, and a condenser, is charged 3-isoquinuclidone **3** (4.02 kg, 84%, 26.97 mol) and toluene (19 L, KF 6 μg/mL) under a nitrogen atmosphere. The resulting suspension (KF 470 μg/mL) is cooled

to 10–15°C and 3.4 M Red-Al®/toluene (20.13 L, 68.45 mol) was slowly added, while keeping the internal temperature ≤50°C (Caution: vigorous hydrogen gas evolution). The resulting mixture is heated at 80–90°C for 2 h and then cooled to 20°C. After cooling to 10–15°C, it is carefully quenched with a 1.4 M NaOH (50 L, 70 mol) over 2 h, while maintaining the internal temperature ≤60°C. The quenched mixture is gradually heated to 70°C, aged for 10 min, then cooled to 22°C. Celite® 545 (Aldrich, 3 kg) is added and the emulsified mixture is filtered via a centrifuge through a 5 μm bag coated with 0.5 kg of wet Celite in order to remove the pasty aluminum salts. The filter cake is washed with toluene (2 L). The filtrate was allowed to settle and the layers were separated. The aqueous layer is extracted with toluene (2 × 19 L). The combined organic phases are dried with Na_2SO_4 (2 kg), filtered, and washed with toluene (6 L). The bicyclic amine in the filtered organic phase (~71.5 L 0.3 wt% H_2O) is assayed by titration to have a concentration of 39.6 mg/mL. This corresponds to 25.46 mol or 94% yield. To the filtrate is added *p*-toluenesulfonic acid monohydrate (4.9 kg, 25.46 mol) at 20°C over 20 min. A slight exotherm is observed (19→32°C). The mixture is heated to 70–75°C and then distilled under reduced pressure (65–75°C/15–20 in) to remove ~15 L (~20 vol%) of toluene/water (until KF < 0.4 mg/mL). The solution is seeded (~0.1 g) at ~50°C, and allow to cool to 20°C under nitrogen. After stirring at 20°C overnight, the product is filtered and washed with toluene (2 × 5 L) and heptane (2 × 5 L). The wet cake is dried under vacuum/nitrogen at 20°C to furnish 6.9 kg of 2-azabicyclo[2.2.2]octane tosylate, **4**, as a light brown clumpy solid. The wt% is 89.83 wt% based on GC, TG, and KF. This corresponds to 6.20 kg pure or 86% yield from the free base.

Method B (Recommended Procedure): To a 1-L round bottomed flask equipped with a mechanical stir, and a condenser, is charged 3-isoquinuclidone **3** (36 g, 91 wt%, 0.26 mol) and toluene (171 mL, KF 50 μg/mL) under a nitrogen atmosphere. The suspension (KF 380 μg/mL) was cooled to 0–5°C and then slowly added 3.4 M Red-Al/toluene (153 mL, 0.52 mol), while keeping the internal temperature ≤40°C (Caution: vigorous hydrogen gas evolution). The resulting mixture is heated at 80–90°C for 2 h, cooled to 20°C and stirred overnight. After cooling to 10–15°C, it is carefully quenched with a 1.1 M NaOH (480 mL, 0.525 mol) over 2 h, while maintaining the internal temperature ≤60°C. The quenched mixture is gradually heated to 70°C, aged for 10 min, then cooled to 22°C. Celite® 545 (Aldrich, 36 g) is added to the emulsified mixture and then filtered through a pad of Celite (20 g) to remove the pasty aluminum salts. The filtrate is now in two clear layers. After separating the layers, the aqueous layer is extracted with toluene (2 × 171 mL). The combined organic phases are dried with Na_2SO_4 (20 g), filtered and washed with toluene (90 mL). The filtrate is

assayed by titration to contain 27.93 g (0.251 mol) of the bicyclic amine free base (96.6%).

To the filtrate is added *p*-toluenesulfonic acid monohydrate (48.8 g, 0.251 mol) at 20°C over 20 min. A slight exotherm is observed (20→32°C). The mixture is heated to 70–75°C and then distilled under reduced pressure (65–75°C/15–20 in) to remove ~170 mL (~25 vol%) of toluene/water (until KF < 0.4 mg/mL). The solution is allowed to cool to 20°C under nitrogen during which time solid crystallized. After stirring at 20°C overnight, the product is filtered and washed with toluene (2 × 50 mL) and heptane (100 mL). The wet cake is dried under vacuum/nitrogen at 20°C to furnish 68.4 g of 2-azabicyclo[2.2.2]octane tosylate, **4**, as an off-white solid. The purity is 96.55 wt% based on GC, TG, and KF measurements. This corresponds to 66 g pure or 94.3% yield from the free base. The overall yield is 91% from lactam **3**. Product loss to the mother liquor is 0.1 g (0.2%). **4**: m.p. 131–133°C; ^{1}H NMR (D_2O) δ 7.70 (d, $J = 8.3$ Hz, 2H), 7.38 (d, $J = 8.3$ Hz, 2H), 3.42 (br s, 1H), 3.20 (br s, 2H), 2.40 (s, 3H), 2.00–1.90 (m, 3H), 1.82–1.68 (m, 6H); ^{13}C NMR (D_2O) δ 143.3, 140.3, 130.3, 126.2, 45.9, 45.7, 22.8, 22.62, 22.58, 21.3. Anal. Calcd for $C_{14}H_{21}NO_3S$: C, 59.34; H, 7.47; N, 4.94; S, 11.32. Found: C, 59.32; H, 7.42; N, 4.83; S, 11.29.

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REFERENCES

1. Larsen, S.D.; Grieco, P.A. Aza Diels-Alder Reactions in Aqueous Solution: Cyclocondensation of Dienes with Simple Iminium Salts Generated Under Mannich Conditions. J. Am. Chem. Soc. **1985**, *107*, 1768–1769.
2. (a) Cava, M.P.; Wilkins, C.K., Jr. A New Isoquinuclidine Synthesis. Chem. Ind. **1964**, 1422–1423; (b) Cava, M.P.; Wilkins, C.K.; Dalton, D.R.; Bessho, K. A New Isoquinuclidine Synthesis, A New Route to *dl*-Dioscorone. J. Org. Chem. **1965**, *30*, 3772–3775.
3. Yu, L.; Chen, D.; Wang, P.G. Aqueous Aza Diels-Alder Reactions Catalyzed by Lanthanide (III) Trifluoromethanesulfonates. Tet. Lett. **1996**, *37*, 2169–2172.

4. Malpass, J.R.; Tweddle, N.J. Reaction of Chlorosulphonyl Isocyanate with 1,3-Dienes. Control of 1,2- and 1,4-Addition Pathways and the Synthesis of Aza- and Oxa-Bicyclic Systems. J. Chem. Soc. Perkin Trans. I **1977**, *8*, 874–887.
5. Tomisawa, H.; Hongo, H. Studies on 1-Alkyl-2(1H)-pyridone Derivatives. X. The Diels-Alder Reaction of 1-Methyl-2(1H)-pyridone with Maleic Anhydride. Chem. Pharm. Bull. **1970**, *18*, 925–931.
6. Wendt, G. Ein gutes Losungsmittel fur die Molekular-gewichtsbestimmung nach Rast. Chem. Ber. **1942**, *75*, 425–429.
7. Pearlman, W.M. 3-Isoquinuclidone. Org. Syn. **1969**, *49*, 75–77.
8. Dryden, H.L.; Scaros, M.G. Synthesis of Isoquinuclidine. GB Patent 2,096,997, October 27, 1982.
9. Yokota, M.; Takizawa, E.; Ohkura, Y.; Fukai, C.; Tomiyama, T. Isoquinuclidine-based Expectorants. Synthesis and Biological Activities of N-Alkoxybenzylisoquinuclidines. Eur. J. Med. Chem. **1997**, *32*, 377–384.
10. Windhorst, A.D.; Bechger, L.; Visser, G.W.M.; Menge, W.P.M.B.; Leurs, R.; Timmerman, H.; Herscheid, J.D.M. Approaches Towards the Synthesis of Fluoro(cyclo)alkylamines. J. Fluorine Chem. **1996**, *80*, 35–40.
11. Cerny, M.; Malek, J.; Capka, M.; Chvalovsky, V. Properties of Sodium bis(2-methoxyethoxy)aluminum Hydride IV. Reduction of Oximes, Amides, Lactams, Imides, and Nitriles. Collect. Czech. Chem. Commun. **1969**, *34*, 1033–1041.
12. Bazant, V.; Capka, M.; Cerny, M.; Chvalovsky, V.; Kochloefl, K.; Kraus, M.; Malek, J. Properties of Sodium bis(2-methoxyethoxy)aluminum Hydride. I. Reduction of some organic functional groups. Tet. Lett. **1968**, *29*, 3303–3306.
13. Vit, J; Papaionnou, C.; Cohen, H.; Batesky, D. Reductions with VITRIDE® Reducing Agent. Eastman Org. Chem. Bull. **1974**, *46*, 1–7.
14. Vit, J. VITRIDE® Reducing Agent. Eastman Org. Chem. Bull. **1970**, *42*, 1–10.

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