JOC The Journal of Organic Chemistry

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Two Scalable Syntheses of (*S*)-2-Methylazetidine

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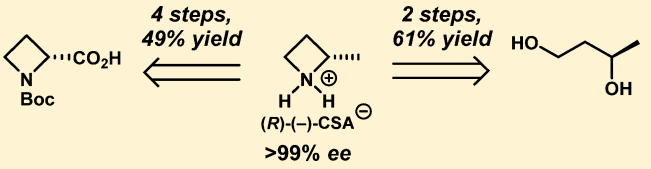
Supporting Information

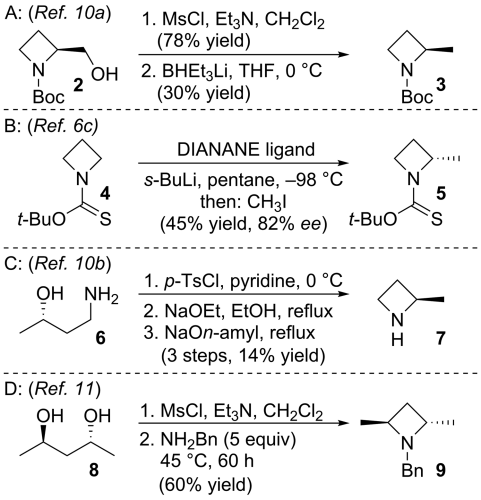
ABSTRACT: Two orthogonal routes for preparing (*S*)-2-methylazetidine as a bench stable, crystalline (*R*)-(−)-CSA salt are presented. One route features the in situ generation and cyclization of a 1,3-bis-triflate to form the azetidine ring, while the second route involves chemoselective reduction of *N*-Boc azetidine-2-carboxylic acid. Both sequences afford the desired product in good overall yields (61% and 49%) and high enantiomeric excess (>99% *ee*), avoid column chromatography, and are suitable for the large-scale production of this material.



There is a growing recognition that substituted azetidines are a privileged class of compounds in medicinal chemistry. This four-membered azaheterocycle tends to exhibit defined, rigid conformations and often displays superior metabolic stability, ligand efficiency, and physicochemical profiles relative to its higher homologues.[1] Several recently approved drugs (Melagatran, Exanta, Azelnidipine)[2] and phase 3 clinical assets (Baricitinib, Cobimetinib, Delafloxacin)[3] that incorporate substituted azetidines have been disclosed. Substituted azetidines have also found applications in the field of chiral ligand design.[4] Interestingly, more method development has focused on preparing piperidines and pyrrolidines than azetidines, likely due to the challenge associated with forming the strained four-membered ring[5a] and the relative prevalence of piperidines and pyrrolidines in natural products. While a variety of methods to prepare substituted azetidines have been reported in the past decade,[5] general approaches for the preparation of enantioenriched 2-substituted azetidines are relatively rare.[6]

An efficient method to prepare (*S*)-2-methylazetidine (**1**) on multihundred gram scale with >98% *ee* was desired. Despite the simplicity of this compound, there is limited commercial availability of this material,[7] and few procedures for preparing it in either racemic[7−9] or enantioenriched form[6,10,11] (including protected derivatives) have been reported. None of these procedures were deemed suitable for large-scale application without significant process improvements. For example, Cowart et al. have described a two-step synthesis of *N*-Boc-2-methylazetidine (**3**) from *N*-Boc-2-hydroxymethyl azetidine (**2**) via mesylation and subsequent Super-Hydride reduction on 1 g scale (Scheme 1A).[10a] Although this approach is direct, the final step employs column chromatography and only gives a 30% yield. Hodgson et al. have reported a concise approach for preparing enantiomerically enriched 2-substituted azetidines that features alkylation of a C2-lithiated azetidine (Scheme 1B).[6c] However, this chemistry requires cryogenic conditions (−98 °C) and superstoichiometric amounts of an enantioenriched diamine ligand and gives the product in 45% yield with 82% *ee*. Among known routes to 2-methylazetidine that involve de novo azetidine ring synthesis, a three-step synthesis of (*R*)-2-methylazetidine **7** from amine **6** in 14% yield was reported in 1999 (Scheme 1C);[10b] yet neither amine **6** nor its antipode are readily available. Marinetti demonstrated that treatment of the bis-mesylate derived from **8** with neat benzylamine affords azetidine **9** in 60% yield without erosion of enantiopurity (Scheme 1D).[11] However, column chromatography using basic alumina was required in order to separate the desired azetidine from excess benzylamine.

Scheme 1. Representative Precedent for the Synthesis of Enantioenriched 2-Methylazetidines

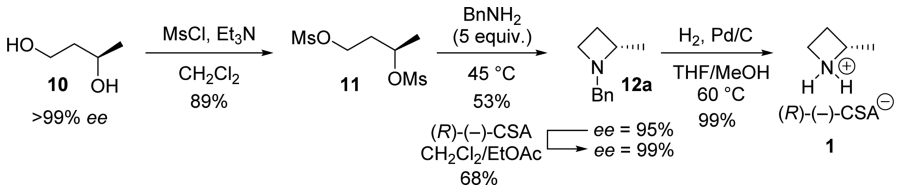


In response to the limitations associated with previous approaches toward enantioenriched 2-methylazetidine, the development of a new, scalable route was pursued. Herein we describe our efforts, which culminated in the development of

Received: January 22, 2016
Published: February 19, 2016

DOI: 10.1021/acs.joc.6b00149
J. Org. Chem. 2016, 81, 3031−3036

Scheme 2. Synthesis of (*S*)-2-Methylazetidine 1 via Bis-mesylate 11



Scheme 3. Precedent for the Synthesis of 1,3-Substituted Azetidines via One-Pot Bis-Triflation/Cyclization

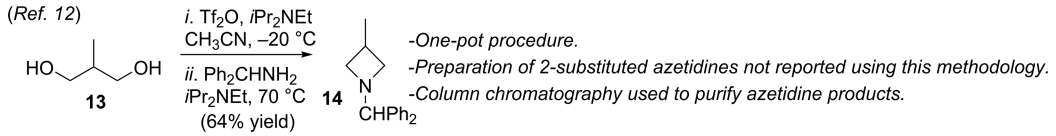
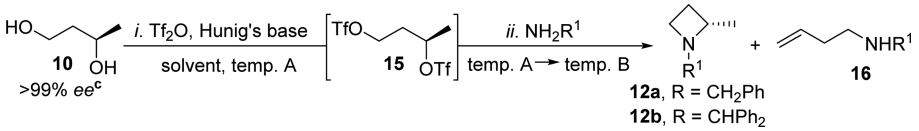


Table 1. Optimization of the Synthesis of 12a, 12b



entry	R^1	method[a]	solvent	temp A (°C)	temp B (°C)	% yield **12**[b] [%*ee*][c]	% yield **16**[b]
1	$CHPh_2$	A	CH_3CN	−25	70	62 [90]	5
2	$CHPh_2$	A	CH_3CN	−25	22	59 [92]	3
3	CH_2Ph	A	CH_3CN	−25	22	53 [98]	3
4	$CHPh_2$	A	CH_3CN	−35	22	63 [89]	4
5	$CHPh_2$	B	CH_3CN	−35	22	74 [89]	4
6	$CHPh_2$	B	CH_2Cl_2	−35	reflux	45	4

[a]Generation of bis-triflate **15**: (Method A) Tf_2O (2.1 equiv) is added to a precooled solution of **10** (11.1 mmol). Hünig's base (5 equiv) is added followed by the indicated primary amine (1.05 equiv). (Method B) Tf_2O (2.2 equiv) is added to a precooled solution of diol **10** (11.1 mmol) and Hünig's base (2.62 equiv). Additional Hünig's base (2.62 equiv) is added followed by the indicated primary amine (1.05 equiv). [b]Determined by analysis of crude ^1H NMR spectra using 2,6-dimethoxytoluene as an internal standard. [c]Determined by chiral GC analysis of a purified sample.

two orthogonal approaches for preparing this material as a bench-stable, crystalline, (*R*)-(−)-CSA salt. Both syntheses avoid the use of column chromatography, proceed in good yields, provide analytically pure material with >99% *ee*, and utilize readily available starting materials.

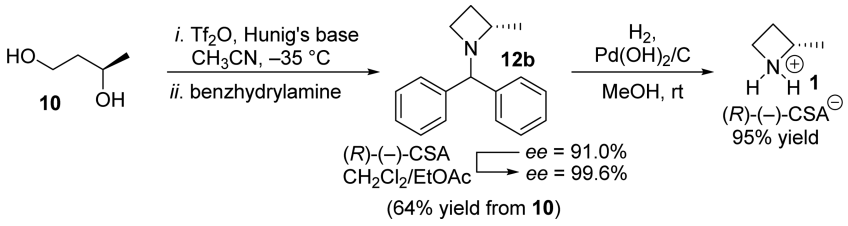
Given the wide commercial availability of (*R*)-(−)-1,3-butanediol **10**, initial efforts focused on applying Marinetti's chemistry[11] to the preparation of *N*-benzyl-2-methyl azetidine (Scheme 2). Treatment of the bis-mesylate **11** with neat benzylamine (5 equiv) afforded the desired azetidine **12a** in 53% yield with 95% *ee*; however, this cyclization was plagued by the formation of dimeric and polymeric side products. Removal of these byproducts and excess benzylamine necessitated tedious column chromatograpy, which was not suitable for large scale applications. Several attempts were made to render the cyclization step more scalable by replacing benzylamine with benzhydrylamine, reducing the number of equivalents of benzylamine, conducting the reaction at elevated temperature, and using solvents (DMF, CH_3CN) and/or bases (Cs_2CO_3, $NaHCO_3$, Et_3N). Unfortunately, none of these changes led to any significant improvements in the process. During the course of this work, it was discovered that recrystallization of the (*R*)-(−)-CSA salt of azetidine **12a** in a solvent mixture of ethyl acetate and dichloromethane improved the enantiopurity from 95% to >99% *ee*. Subsequent hydrogenolysis of **12a** proceeded smoothly to give **1** as a crystalline solid.

In searching for a more robust method for producing bulk quantities of (*S*)-2-methylazetidine, a recent report from Hillier et al. describing the one-pot synthesis of 3-substituted azetidines from 1,3-diols using a bis-triflation/cyclization protocol (Scheme 3) was identified.[12] This work demonstrated that 1,3-bis-triflates react with primary amines faster and generally in higher yields than 1,3-bis-tosylates to give the corresponding azetidines. However, Hillier et al. only reported the synthesis of 2,4-unsubstituted azetidines derived from 1,3-unsubstituted primary alcohols; the use of secondary, chiral alcohols was not reported. While there are literature precedents for the synthesis of 2-substituted azetidines through displacement of secondary alkyl triflates with primary amines without loss of stereochemical integrity,[13] these transformations typically employ conformationally preorganized sugar-derived substrates that often lack α-hydrogens capable of opening up undesired elimination pathways. Based on these precedents, several concerns were identified in the potential application of this chemistry to a scalable synthesis of enantioenriched 2-methylazetidine: (1) secondary alkyl triflates may not be viable electrophiles in this context or may not proceed with clean inversion of stereochemistry;[14] (2) excess Hünig's base (ca. 5 equiv) must be separated from the tertiary amine product; and (3) alternatives to column chromatography need to be identified in order to enable practical isolation and purification on a large scale.[15]

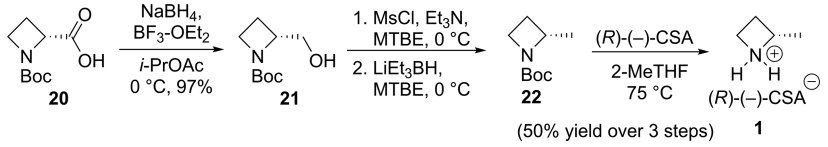
The feasibility of preparing enantioenriched 2-methylazetidine **12** through the one-pot generation and cyclization of a bis-triflate was evaluated under several sets of conditions (Table 1). Treatment of a cold (−25 °C) solution of (*R*)-1,3-butanediol

DOI: 10.1021/acs.joc.6b00149
J. Org. Chem. 2016, 81, 3031−3036

Scheme 4. Scalable Synthesis of (*S*)-2-Methylazetidine (1) from Diol 10



Scheme 5. Scalable Synthesis of (*S*)-2-Methylazetidine (1) from Azetidine-2-carboxylic Acid (20)



10 with triflic anhydride followed by Hünig's base (method A) cleanly generated the putative bis-triflate **15**, as monitored by TLC. Subsequent treatment with benzhydrylamine followed by warming to 70 °C generated the desired 2-methylazetidine product **12b** in 62% yield and 90% *ee* (Table 1, entry 1). Only minor quantities of the elimination byproduct **16** were observed in the crude ^{1}H NMR.[16] Conducting the cyclization step at room temperature afforded a comparable yield to heating at 70 °C (entry 2). Benzylamine was also viable in this transformation and afforded the corresponding product in excellent enantiopurity (98% *ee*) but lower yield compared to benzhydrylamine (entry 3). The highest yield was obtained by dropwise addition of Tf_2O to a premixed solution of (*R*)-1,3-butanediol and Hünig's base at −35 °C followed by treatment with benzhydrylamine and warming to room temperature (Method B, entry 5).

The optimized conditions from Table 1, entry 5 were applied to a 20-g-scale preparation of **1** (Scheme 4). After generation of crude **12b** from **10**, it was discovered that the desired azetidine could be separated from excess Hünig's base by dissolving the crude reaction mixture in toluene and washing the obtained solution with water.[15] This procedure is uniquely effective for separating the desired azetidine from excess Hünig's base; employing ethyl acetate or dichloromethane as the extraction solvent led to contamination of the product with significant quantities of Hünig's base. Filtration through a short plug of silica gel[17] followed by formation of the (*R*)-(−)-CSA salt and two successive recrystallizations from a mixture of dichloromethane and ethyl acetate afforded **12b** in 64% isolated yield as a crystalline white solid. In addition to removing trace impurities, the recrystallization step improves the enantiopurity from 91% *ee* to >99.6% *ee*.[18] Hydrogenolysis in the presence of palladium hydroxide afforded (*S*)-2-methylazetidine (**1**) as a bench stable, crystalline (*R*)-(−)-CSA salt. To date, this general approach has been used to produce over 200 g of **1**. The absolute stereochemistry of **1** was confirmed through single-crystal X-ray diffraction studies; see the Supporting Information for details.

Concurrent to the efforts involving azetidine ring synthesis, an orthogonal route beginning from (*R*)-azetidine-2-carboxylic acid (**20**) to prepare **1** was also developed. Inspired by a process chemistry route reported to synthesize enantiopure 2-methylpyrrolidine from Boc-proline,[19] we sought to improve upon the disconnection first reported by Cowart et al.[10a] using an analogous sequence of (1) reduction, (2) activation of the hydroxyl, and (3) reduction to the methyl group, followed by a concomitant deprotection and isolation step.

To this end, (*R*)-Boc azetidine-2-carboxylic acid **20** was reduced to 2-hydroxylmethyl azetidine **21** using in situ generated borane; **21** was then converted to the corresponding mesylate (Scheme 5). Due to the chemical instability of the analogous pyrrolidine intermediate reported in literature,[19] the mesylate was carried forward to the next reaction as a solution. Reduction with Super-Hydride then produced the desired (*S*)-Boc-2-methylazetidine **22**. Due to the volatility of this intermediate, isolation at this stage was not practical. Boc-deprotection was first attempted using benzenesulfonic acid, which was reported to be uniquely useful in both effecting Boc deprotection and forming a bench stable crystalline salt with 2-methylpyrrolidine.[19] When applied to azetidine **22**, deprotection with benzenesulfonic acid was successful, but crystallization and isolation of the salt could not be achieved as the product either stayed in solution or persisted as an oil. With the knowledge that (*R*)-(−)-CSA forms a stable crystalline salt with (*S*)-2-methylazetidine, direct treatment with (*R*)-(−)-CSA was evaluated. Deprotection of **22** in the presence of (*R*)-(−)-CSA was slow in refluxing MTBE/THF. However, by changing solvent from MTBE/THF (present from the previous two reactions) to the higher-boiling 2-methyltetrahydrofuran, a higher reaction temperature (75 °C) could be attained and Boc-deprotection went to completion. Upon cooling, (*S*)-2-methyl azetidinium (*R*)-camphorsulfonate crystallized out of the reaction. Reslurrying, filtration, and washing led to isolation of the desired material as a white solid in four overall steps (three of which were telescoped) and 49% overall yield without the need for chromatographic separation.

■ CONCLUSIONS

In summary, we have described two scalable routes that are effective in producing hundreds of grams of (*S*)-2-methylazetidine as a stable, crystalline, nonhygroscopic (*R*)-(−)-CSA salt in >99% *ee* from readily available starting materials without the need for column chromatography.

■ EXPERIMENTAL SECTION

General. *R*-(−)-1,3-Butanediol was purchased from a commercial vendor (>99% *ee*) and used without further purification. (*R*)-1-(*tert*-butoxycarbonyl)azetidine-2-carboxylic acid was prepared from (*R*)-azetidine-2-carboxylic acid using a literature procedure.[20] All other chemicals and reagents were purchased from commercial sources and used without further purification. Anhydrous acetonitrile and

DOI: 10.1021/acs.joc.6b00149
J. Org. Chem. 2016, 81, 3031−3036

tetrahydrofuran were purchased from a commercial vendor and used without further purification. All air- and/or moisture-sensitive reactions were performed under an atmosphere of nitrogen. Reactions were monitored by thin layer chromatography (TLC) using precoated 250 μm silica gel plates and visualized by fluorescence quenching under UV light or staining with iodine, *p*-anisaldehyde, or potassium permanganate. Unless otherwise indicated, yields refer to isolated compounds. ^{1}H NMR spectra were recorded at 25 °C with a spectrometer equipped with an AutoX ID 600-5 probe at 600 MHz. ^{13}C NMR spectra were recorded at 25 °C with a spectrometer equipped with a 5 mm BBO cryoprobe equipped with a *Z*-axis gradient at 100 MHz. Chemical shifts are reported in part per million (PPM) using the internal solvent residual of CD_3OD or $CDCl_3$ as an internal standard. Signals are listed as follows: chemical shift in ppm (multiplicity identified as s = singlet, br = broad, d = doublet, t = triplet, q = quartet, p = pentet, sx = sextet, m = multiplet; integration; coupling constants in Hz). The HRMS analysis was conducted on a TOF mass spectrometer in positive electrospray mode. The sample was separated on a UHPLC system prior to mass spectrometric analysis. The resulting spectra were automatically lockmass corrected, and the target mass ions and the confirming adduct (Na^+) were extracted and combined as a chromatogram. The mass accuracy was calculated for all observed isotopes against the theoretical mass ions derived from the chemical formula. Elemental analyses are within 0.4% of theory. Melting points were uncorrected.

*(2R)-4-[(Methylsulfonyl)oxy]butan-2-yl Methanesulfonate (**11**).*[21] A solution of *R*-(−)-1,3-butanediol (3 g, 30 mmol) and triethylamine (10.1 g, 99.9 mmol) in dichloromethane (60 mL) was cooled to 0 °C in an ice water bath and treated with methanesulfonyl chloride (11.4 g, 99.9 mmol) in a dropwise manner at 0 °C. After 15 min the ice water bath was removed and the mixture was stirred at rt for 2 h. The mixture was diluted with aqueous saturated ammonium chloride (80 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated to give a residue. The residue was purified using column chromatography eluting with ethyl acetate/petroleum ether (1:4 to 3:2) to give **11** (7.3 g, 89%) as a colorless oil. ^{1}H NMR (600 MHz, CD_3OD) δ 4.98 (sx, 1H, J = 6.0 Hz), 4.40 (t, 2H, J = 5.8 Hz), 3.16 (s, 3H), 3.15 (s, 3H), 2.15 (q, 2H, J = 6.0 Hz), 1.52 (d, 3H, J = 6.5 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 77.5, 67.6, 38.6, 37.3, 37.1, 21.7; $[\alpha]_D^{24}$ = −47.5° (c = 1, CH_3OH).

*(2S)-1-Benzyl-2-methylazetidine (**12a**).*[22] (2*R*)-4-[(Methylsulfonyl)oxy]butan-2-yl methanesulfonate (**11**) (7.20 g, 29.2 mmol) was dissolved in benzylamine (19.2 mL, 175 mmol) and stirred at 45 °C for 16 h. The reaction mixture was cooled to rt and a mixture of cyclohexane/methyl *tert*-butyl ether (1:1, 200 mL) was added, resulting in the precipitation of white solids. The precipitates were removed by filtration, and the filtrate was evaporated under reduced pressure and purified using column chromatography eluting with dichloromethane (with 1% ammonium hydroxide)/methanol (100:0 to 99.5:0.5) to give **12a** (2.5 g, 53%, *ee* = 94.8% by chiral GC) as a pale yellow oil. ^{1}H NMR (600 MHz, CD_3OD) δ 7.21−7.34 (m, 5H), 3.65 (d, 1H, J = 12.5 Hz), 3.56 (d, 1H, J = 12.5 Hz), 3.33−3.42 (m, 1H), 3.25−3.32 (m, 1H), 2.98 (q, 1H, J = 8.5 Hz), 2.07−2.14 (m, 1H), 1.79 (p, 1H, J = 9.4 Hz), 1.02 (d, 3H, J = 6.2 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 138.4, 130.6, 129.5, 128.6, 64.1, 63.4, 52.5, 26.7, 21.3; $[\alpha]^D_{24}$ = +32.4° (c = 0.5, CH_3OH).

*(2S)-1-Benzyl-2-methylazetidinium-[(1R,4S)-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl]methanesulfonate (**12a-CSA salt**).* To a solution of *R*-(−)-CSA (3.60 g, 15.4 mmol) in EtOH (15 mL) was added a solution of (2*S*)-1-benzyl-2-methylazetidine **12a** (2.50 g, 15.5 mmol) in EtOH (10 mL). The mixture was stirred at rt for 15 h. The resulting solution was evaporated to remove EtOH. The residue was suspended in MTBE (60 mL) and evaporated to remove MTBE. The residue was suspended in MTBE (60 mL), and the solids were collected by filtration. The filter cake was dried under reduced pressure to give a light yellow solid (3.5 g, 95.6%), which was dissolved in dichloromethane (5 mL), and then ethyl acetate (8 mL) was added. The mixture was stirred at rt for 30 min, during which time substantial solids precipitated from solution. The solids were collected by filtration, and the filter cake was suspended in dichloromethane (3 mL), stirred at rt for 10 min, and then diluted with ethyl acetate (5 mL). The mixture was stirred at rt for 30 min, and the solids were then collected by filtration. The solids were dried under reduced pressure to give **12a-CSA salt** (2.5 g, 68%, *ee* = >99% by chiral GC) as a white crystalline solid. Mp = 158−160 °C; ^{1}H NMR (600 MHz, CD_3OD) δ 7.44−7.55 (m, 5H), 4.56−4.66 (m, 1H), 4.37 (s, 2H), 4.07 (q, 1H, J = 9.7 Hz), 3.99 (td, 1H, J = 9.4, 3.5 Hz), 3.33 (d, 1H, J = 15.0 Hz), 2.79 (d, 1H, J = 15.2 Hz), 2.64−2.73 (m, 1H), 2.52−2.62 (m, 1H), 2.36 (dt, 1H, J = 17.5, 4.3 Hz), 2.23−2.33 (m, 1H), 2.00−2.10 (m, 2H), 1.90 (d, 1H, J = 18.3 Hz), 1.58−1.68 (m, 1H), 1.39−1.47 (m, 1H), 1.29 (d, 3H, J = 6.6 Hz), 1.14 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 218.3, 131.5, 131.4, 131.1, 130.6, 67.6, 59.7, 58.9, 52.2, 48.9, 48.3, 44.2, 43.8, 27.9, 25.9, 25.5, 20.6, 20.3, 19.0; $[\alpha]_D^{24}$ = −10.0° (c = 1, CH_3OH). Elemental analysis: Anal. Calcd for $C_{21}H_{31}NO_4S$: C = 64.09%, H = 7.94%, N = 3.56%. Found: C = 64.07%, H = 8.01%, N = 3.45%.

*(2S)-2-Methylazetidinium-[(1R,4S)-7,7-dimethyl-2-oxobicyclo-[2.2.1]hept-1-yl]methanesulfonate (**1** from **12a-CSA salt**).* A solution of **12a-CSA salt** (2.5 g, 6.4 mmol) in methanol (25 mL) and THF (25 mL) was treated with 10% palladium hydroxide on carbon (450 mg). The suspension was heated to 60 °C, filled with H_2 (30 psi), and stirred for 20 h. The cooled reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give **1** (1.9 g, 99%) as a white crystalline solid. Spectral data match those reported below.

*(2S)-1-(Diphenylmethyl)-2-methylazetidinium-[(1R,4S)-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl]methanesulfonate (**12b-CSA salt**).* Method B, 20 g scale. A solution of *R*-(−)-1,3-butanediol (20.0 g, 222 mmol, >99% *ee* by chiral GC) and Hünig's base (101.5 mL, 583 mmol) in acetonitrile (444 mL) was cooled to −30 °C and treated with neat trifluoromethanesulfonic anhydride (81.2 mL, 480 mmol, 2.18 equiv) dropwise via addition funnel over 90 min, maintaining the internal reaction temperature between −30 and −35 °C. After the addition was complete, the reaction mixture was stirred for 10 min at −30 °C and then treated with additional trifluoromethanesulfonic anhydride (1.5 mL) dropwise and then stirred at −30 °C for an additional 15 min. The reaction mixture was treated with additional Hünig's base (101.5 mL, 583 mmol) over the course of 15 min while maintaining the internal temperature below −30 °C. After an additional 10 min at −30 °C the reaction mixture was treated with a solution of benzhydrylamine (38.4 mL, 222 mmol) in acetonitrile (40 mL) dropwise over 30 min via an addition funnel, maintaining the internal reaction temperature below −30 °C. The reaction mixture was stirred at −30 °C for 20 min then placed in an ice water bath for 30 min. The reaction was then stirred at rt for 30 min, followed by heating at 45 °C for 30 min. The reaction mixture was cooled to rt, poured into deionized water (900 mL), and extracted with toluene (1 L). The aqueous phase was back-extracted with toluene (300 mL), and the combined organic layers were washed with water (2 × 250 mL), dried over sodium sulfate, filtered, and evaporated. The crude product was dissolved in dichloromethane (300 mL) and loaded onto a plug of silica gel (300 mL, preflushed with 1:1 heptane/ethyl acetate). The plug was flushed with 1:1 heptane/ethyl acetate (1.2 L), and the filtrate was evaporated to give a red oil (50.2 g). The crude product was dissolved in methanol (200 mL), placed in a water bath at 10 °C, and treated with *R*-(−)-camphorsulfonic acid (49 g) in batches over 5 min. The solution was stirred at rt for 2 h, and the solvent was evaporated; the solids were dried under high vacuum for 15 h to give crude product (99.2 g, *ee* = 91.8% by chiral SFC analysis). The salt was dissolved in dichloromethane (100 mL) and stirred at rt for 10 min to give a dark solution. Ethyl acetate (850 mL) was added slowly with stirring, and solids precipitated from solution after ∼5 min. The suspension was stirred at rt for 2 h, and the solids were collected by filtration and washed with ethyl acetate (50 mL) to give white solids (72.1 g). These solids were dissolved in dichloromethane (100 mL) and treated with ethyl acetate (700 mL). The mixture was stirred at rt, and solids immediately precipitated from solution. The suspension was stirred at rt for 15 h, and then the solids were collected by filtration, washed with ethyl acetate (50 mL), and dried under reduced pressure

DOI: 10.1021/acs.joc.6b00149
J. Org. Chem. 2016, 81, 3031−3036

to give **12b-CSA salt** (66.7 g, 64% yield, *ee* = 99.6% by chiral SFC) as a white crystalline solid. Mp = 199−201 °C; ^{1}H NMR (600 MHz, CD_3OD) δ 7.54−7.59 (m, 4H), 7.43−7.53 (m, 6H), 5.67 (s, 1H), 4.69−4.76 (m, 1H), 3.92−4.06 (m, 2H), 3.36 (d, 1H, J = 14.6 Hz), 2.81 (d, 1H, J = 15.2 Hz), 2.70−2.75 (m, 1H), 2.58−2.64 (m, 1H), 2.31−2.39 (m, 2H), 2.03−2.09 (m, 2H), 1.91 (d, 1H, J = 18.9 Hz), 1.62−1.66 (m, 1H), 1.41−1.47 (m, 1H), 1.16 (s, 3H), 1.11 (d, 3H, J = 6.4 Hz), 0.88 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 218.2, 136.1, 136.0, 131.1, 130.74, 130.71, 130.4, 129.7, 128.6, 74.8, 69.0, 59.7, 52.4, 48.9, 48.5, 44.2, 43.8, 27.9, 26.0, 24.9, 20.6, 20.3, 19.4; $[\alpha]_D^{24}$ = −42.6° (c = 1, CH_3OH). Elemental analysis: Anal. Calcd for $C_{27}H_{35}NO_4S$: C = 69.05%, H = 7.51%, N = 2.98%. Found: C = 68.90%, H = 7.59%, N = 2.91%.

An alternative procedure for preparing **12b-CSA salt** that avoids the use of silica gel plug filtration is as follows (Method A, 10 g scale):

A solution of *R*-(−)-1,3-butanediol (10.0 g, 111 mmol) in acetonitrile (222 mL) in a three-neck 1 L flask was cooled to −25 °C. The solution was then treated with neat trifluoromethanesulfonic anhydride (37.9 mL, 224 mmol) dropwise over 30 min while maintaining the internal reaction temperature between −25 to −30 °C. The reaction mixture was stirred for an additional 40 min between −25 to −30 °C and then treated with Hünig's base (48.3 mL, 266 mmol) dropwise over 30 min while maintaining the internal temperature between −25 to −30 °C. The resulting slurry was stirred for 60 min at −25 °C and treated with additional Hünig's base (48.3 mL, 266 mmol) over 10 min, followed by benzhydrylamine (19.6 g, 107 mmol) dropwise over 15 min while maintaining the internal temperature below −20 °C. The reaction is then warmed to rt and stirred for 30 min, then heated to 45 °C, and stirred for 20 min. The cooled reaction mixture was diluted with toluene (750 mL) and deionized water (500 mL). The layers were separated, and the organic layer was washed with water (500 mL), dried over sodium sulfate, filtered through paper, and evaporated to give an off-white solid (26.9 g). The solid was dissolved in methanol (25 mL) and treated with *R*-(−)-camphorsulfonic acid (24.8 g) dissolved in methanol (50 mL) at rt. The solution was evaporated to dryness, and residual methanol was removed by suspending the solids in ethyl acetate (25 mL) and evaporating. The solids were dried under high vacuum for 18 h. The solids were dissolved in dichloromethane (75 mL), and ethyl acetate (300 mL) was added slowly with stirring. After stirring at rt for 1 h, additional ethyl acetate (200 mL) was added. The suspension was cooled to 0 °C with stirring, and additional ethyl acetate (100 mL) was added. The solids were collected by filtration and dried under reduced pressure to afford **12b-CSA salt** (30.5 g, 58% yield, *ee* = 99.6% by chiral SFC). Spectral data were consistent with those obtained using Method B.

*(2S)-2-Methylazetidinium-[(1R,4S)-7,7-dimethyl-2-oxobicyclo-[2.2.1]hept-1-yl]methanesulfonate (**1** from **12b-CSA salt**).* A 300 mL stainless steel reactor was charged with a solution of **12b-CSA salt** (29.4 g, 62.6 mmol) in methanol (125 mL) and 20% palladium hydroxide on carbon (1.78 g). The reactor was flushed with nitrogen three times and hydrogen three times, then pressurized to 60 psi of hydrogen, and stirred at rt for 16 h. The hydrogen was released, and the reaction mixture was filtered through a pad of Celite, eluting with methanol (100 mL). The filtrate was concentrated in vacuo to give a white solid. The white solid is suspended in a mixture of ethyl acetate/MTBE (1:1, 200 mL) and stirred for 1 h at 60 °C. After cooling to rt, the slurry was stirred for an additional 1 h and then the solids are collected by filtration. The solids are suspended in MTBE (100 mL) and stirred at rt for 16 h. The solids are collected by filtration, washed with MTBE (25 mL), and dried under reduced pressure to give **1** (18.1 g, 95%, *ee* > 99%[23]) as a white crystalline solid. Mp = 144−146 °C; ^{1}H NMR (600 MHz, CD_3OD) δ 4.63 (sx, 1H, J = 7.0 Hz), 4.05 (q, 1H, J = 9.4 Hz), 3.92 (td, 1H, J = 10.0, 5.0 Hz), 3.32 (d, 1H, J = 14.8), 2.78 (d, 1H, J = 14.8 Hz), 2.57−2.67 (m, 2H), 2.36 (dt, 1H, J = 18.1, 4.1 Hz), 2.24−2.32 (m, 1H), 1.99−2.10 (m, 2H), 1.92 (d, 1H, J = 18.7 Hz), 1.62−1.68 (m, 1H), 1.55 (d, 3H, J = 7.0 Hz), 1.41−1.47 (m, 1H), 1.11 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 218.4, 59.7, 59.1, 49.2, 48.5, 44.1, 43.8, 43.7, 27.9, 27.5, 25.9, 20.4, 20.3, 20.0; $[\alpha]_D^{24}$ = −26.5° (c = 1, CH_3OH). Elemental analysis: Anal. Calcd for $C_{14}H_{25}NO_4S$: C = 55.42%, H = 8.31%, N = 4.62%. Found: C = 55.59%, H = 8.41%, N = 4.49%.

Azetidine **1** (25 mg) was dissolved in dichloromethane/toluene (1:1, 1 mL) in an open vial and allowed to sit for 48 h. Single crystals suitable for X-ray diffraction studies were obtained.

*tert-Butyl (2R)-2-(Hydroxymethyl)azetidine-1-carboxylate (**21**).*[24] A round bottomed flask was charged with (2*R*)-1-(*tert*-butoxycarbonyl)azetidine-2-carboxylic acid (42.3 g, 210 mmol) and isopropyl acetate (100 mL) and stirred at rt for 10 min. The internal reaction temperature was then cooled to 0 °C, and sodium borohydride (13.0 g, 336 mmol) was added in one portion. The reaction was then stirred for 5 min at 0 °C, and boron trifluoride diethyl etherate (51.7 mL, 420 mmol) was added dropwise over 1 h, while the internal reaction temperature was maintained between 0 and 10 °C. The reaction was then continued for 3 h at 0 °C. The reaction was then quenched through dropwise addition of 0.5 M NaOH solution (270 mL) over 30 min, maintaining the internal temperature between 0 and 10 °C. After the addition was complete, the reaction mixture was heated to 50 °C for 20 min with vigorous stirring, which caused both layers to appear clear. The layers were separated, and the aqueous layer was back-extracted with isopropyl acetate (40 mL). The combined organic layers were then washed with brine (50 mL), dried over sodium sulfate, filtered, and concentrated in vacuo overnight to provide **21** (38.2 g, 97%) as a colorless, clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42−4.49 (m, 1H), 3.88 (q, 1H, J = 8.0 Hz), 3.69−3.81 (m, 3H), 2.13−2.22 (m, 1H), 1.89−1.98 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 157.3, 80.1, 66.7, 63.5, 46.7, 28.2, 17.9; HRMS (m/z): Calcd for $C_9H_{17}NO_3$ $[M + Na]^+$ 210.1101; found 210.1095.

*(2S)-2-Methylazetidinium-[(1R,4S)-7,7-dimethyl-2-oxobicyclo-[2.2.1]hept-1-yl]methanesulfonate (**1**).* A solution of **21** (38.2 g, 204 mmol) in MTBE (400 mL) was cooled to 0 °C and treated with triethylamine (26.2 mL, 189 mmol) followed by DMAP (582 mg, 4.72 mmol). Methanesulfonyl chloride (20.7 mL, 265 mmol) was then added dropwise over 15−30 min while the reaction temperature was maintained between 0 and 5 °C. The reaction was then stirred at 0 °C for 3 h. The reaction was then treated with 1 M aqueous phosphoric acid (175 mL) over the course of 10 min with vigorous stirring, while the reaction temperature was maintained between 5 and 15 °C. The layers were separated, and the organic layer was washed with sat. sodium bicarbonate solution (75 mL) followed by brine (75 mL). The organic layer was dried over sodium sulfate and then filtered. The filtrate was concentrated in vacuo to a volume of ∼300 mL to azetropically remove any residual water and used directly in the next reaction as a solution. This solution was cooled to 0 °C and treated with a solution of lithium triethylborohydride (400 mL, 400 mmol, 1 M in THF) dropwise over 1 h, while the temperature was maintained between 0 and 7 °C. After the addition was complete, the ice bath was removed and the reaction was warmed to rt and stirred for 72 h. The reaction was then cooled to 0 °C, and a separate flask was charged with MTBE (150 mL) and water (150 mL) and also cooled to 0 °C with stirring. The reaction was then poured slowly into the water/MTBE mixture, while the temperature was maintained below 10 °C. After the addition was complete, the mixture was transferred to a separatory funnel and the layers were separated. The organic layer was then washed sequentially with 1 M phosphoric acid solution (300 mL), saturated sodium bicarbonate (100 mL) solution, and brine (100 mL). The organic layer was dried over sodium sulfate and filtered to provide the desired stock solution of product. The reaction mixture was concentrated to ca. 1/4 the volume, and 2-methyltetrahydrofuran (200 mL) was added. The mixture was concentrated to ca. 1/4 the volume again, and additional 2-methyltetrahydrofuran (300 mL) was added. The mixture was treated with (*R*)-(−)-camphorsulfonic acid (49.7 g, 214 mmol) and heated to 75 °C for 15 h. The reaction mixture was cooled to rt, and crystalline material formed. The mixture was heated at 55 °C for 2 h and cooled to 45 °C for 1 h and then rt for 6 h. The solids were collected by filtration, washed with 2-methyltetrahydrofuran (100 mL), and then dried in a vacuum oven for 15 h to give **1** as a crystalline white solid (30.8 g, 50%, *ee* = >99%[23]). Spectral data matched those for **1** above. $[\alpha]_D^{24}$ = −23.0° (c = 1, CH_3OH).

DOI: 10.1021/acs.joc.6b00149
J. Org. Chem. 2016, 81, 3031−3036

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00149.

Crystallographic data for **1** (CIF)

^{1}H and ^{13}C NMR spectra for all new compounds; SFC traces establishing the enantiopurity of **12b** and **1** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Brian Samas for X-ray crystallography determination. We thank Jim Bradow, Jason Smith, Laurence Philippe, and Chao Li for performing chiral SFC and chiral GC analyses. We thank Andre Shavnya and Ping Han for experimental assistance. We thank Vincent Mascitti for helpful discussions.

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DOI: 10.1021/acs.joc.6b00149
J. Org. Chem. 2016, 81, 3031−3036