Asymmetric 1,3-Dipolar Cycloaddition of a (*Z*)-Alkene Dipolarophile. Synthesis of (3*S*,4*R*) Ethyl 1-Azabicyclo[2.2.1]heptane-3-carboxylate

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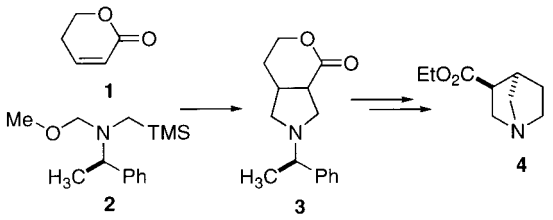
Introduction

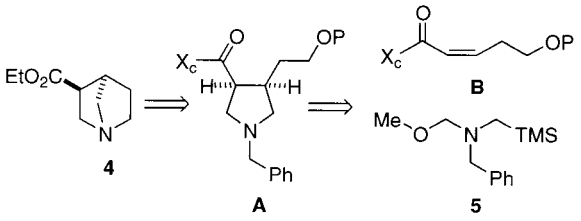
Versatile syntheses of the stereoisomers of 3-carboxy-1-azabicyclo[2.2.1]heptane derivatives represent a significant challenge because of the important physiological properties of this class of compounds.[1] Many methods have been reported for the preparation of completely racemic material,[2] the racemic *endo* (3*S**,4*R**) diastereoisomers[3] or the racemic *exo* (3*R**,4*R**) diastereoisomers.[3] Our particular interest was in the synthesis of the enantiomerically pure (3*S*,4*R*) stereoisomer **4**. The reported[4] preparation of **4** involves the 1,3-dipolar addition of a chiral azomethine ylide derived from **2** with 5,6-dihydro-2*H*-pyran-2-one **1** (Scheme 1). This results in a 1:1 mixture of diastereoisomers **3**, which are separated at a later stage by fractional recrystallization and the appropriate diastereoisomer converted through to **4**.

Scheme 1



We potenially had the requirement for multi-kilogram amounts of **4**; therefore, the development of new, more stereoselective methods for the preparation of 3-carboxy-1-aza-bicyclo[2.2.1]heptane derivatives was warranted. Although the 1,3-dipolar addition of a chiral azomethine ylide with an achiral dipolarophile did not lead to any observed asymmetric induction,[4] there are reports indicating that a chiral auxiliary located within the dipolarophile can lead to useful levels of asymmetric induction.[5] Our retrosynthesis based upon this type of approach is outlined (Scheme 2). The key disconnection was envisaged as the diastereoselective addition of the achiral azomethine ylide derived from **5** to the (*Z*)-alkene **B**. The (*Z*)-alkene geometry is required to set the relative stereochemistry at C-3 and C-4 required in the final product. Precedent for the use of (*Z*)-crotonic acid derivatives in the Lewis acid promoted Diels−Alder reaction suggested alkene isomerization prior to [4 + 2] cycloaddition could be a problem.[6] However, it was hoped that the milder conditions required for the [3 + 2] dipolar cycloaddition the alkene geometry would be retained. With regard to the choice of chiral auxiliary (X_c), we opted for the bornane-2,10-sultam derivative because it has been reported to give good levels of asymmetric induction in nonchelation-controlled processes.[7] It was planned to protect the hydroxyl group as a *tert*-butyldimethylsilyl ether (P = TBS), this would allow selective hydroxyl deprotection of intermediate **A** and hence allow conversion to **4** by standard chemistry.[3,4]

Scheme 2



Results and Discussion

Alkyne **6** was prepared from 3-butyn-1-ol (97%) according to the published procedure[8] (Scheme 3). Treatment of **6** with butyllithium and the quenching with solid carbon dioxide[9] gave a quantitative yield of the unstable acid **7**. Although **7** could be isolated, it was not stable to column chromatography nor could it be stored for longer than 2 or 3 days and therefore was used directly in subsequent reactions. Bornane-2,10-sultam derivative **8** was prepared from acid **7** (63%) by nucleophilic attack of the lithium salt of the chiral auxiliary on an intermediate pivaloyl mixed anhydride.[10] Controlled hydrogenation of alkyne **8** over Lindlar's catalyst in toluene gave

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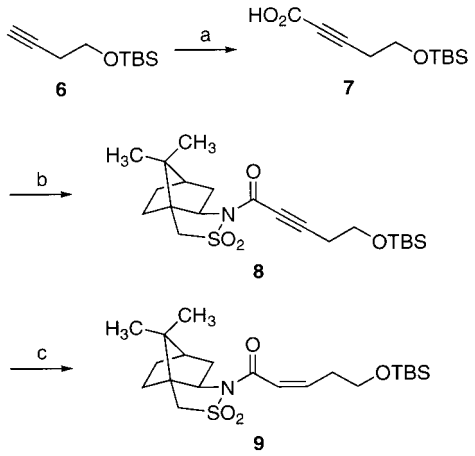
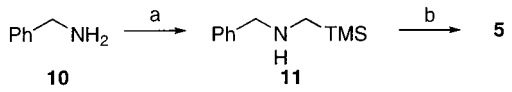
Scheme 3[a]



[a] Reagents and conditions: (a) n-BuLi, $CO_{2(s)}$, THF, −75 °C; (b) *t*-BuCOCl, NEt_3, THF, −75 °C and then 2(*R*)-(−)-bornane-2,10-sultam, n-BuLi, THF, −75 °C; (c) H_2, 5% Pd/$CaCO_3$+Pb, toluene, rt.

Scheme 4[a]



[a] Reagents and conditions: (a) $TMSCH_2Cl$, CH_3CN, 82 °C; (b) ref 12.

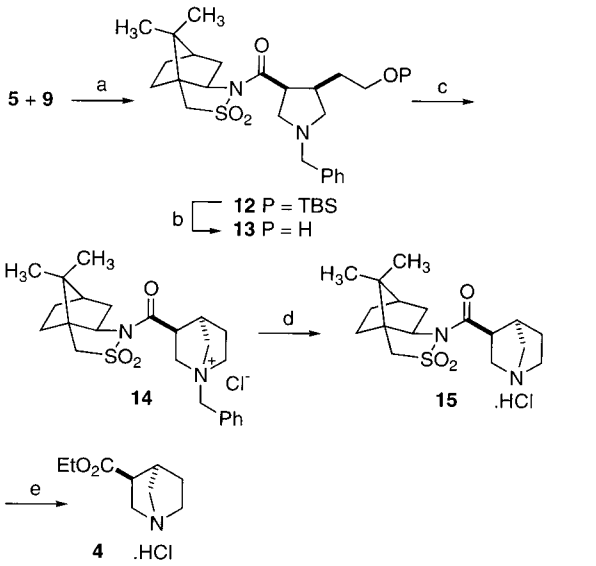
the (*Z*)-alkene **9** (100%).[11] Extended reaction time or high catalyst loading led to the partial formation of the unwanted corresponding (*E*)-alkene and the fully saturated alkane.

It was felt that the published procedure[12] for the preparation of **5** would not be suitable for scale-up to a large scale (Scheme 4), the main limitations being the high temperature (220 °C) required for the formation of **11**, the absence of solvent in this reaction which would lead to handling difficulties upon cooling, and finally the requirement to purify **11** by distillation.

Initial studies on the reaction of **10** with chloromethyltrimethylsilane in high boiling solvents such as *o*-xylene or 1,2-dichlorobenzene were unsuccessful. However it was found that acetonitrile was a suitable solvent and gave an 82% yield of **11** after 16 h at reflux (82 °C). The material obtained was of suitable purity, and no distillation was required. Conversion of **11** to **5** was carried out by the published procedure.[12]

The [3 + 2] dipolar cycloaddition of alkene **9** with azomethine ylide precursor **5** in the presence of a catalytic quantity of TFA[5a−c] provided a 4:1 mixture of diastereoisomers, as determined by HPLC analysis (Scheme 5). The major component **12** was readily isolated by column chromatography in 73% yield. Stereochemical assignment of **12** was not possible at this stage, vide infra, the structure of the minor component is assumed to be the corresponding (3*R*,4*S*) stereoisomer. The stereochemistry observed in **12** is consistent with the cycloaddition proceeding via the accepted[7] transition state structure for the reactions of acryoyl bornane-2,10-sultam derivatives. Silyl ether **12** was readily deprotected with aq HCl to give alcohol **13** (84%). Treatment of **13** with NEt_3 and

Scheme 5[a]



[a] Reagents and conditions (a) cat. TFA, toluene, rt; (b) 2 M aq HCl, THF, rt; (c) NEt_3, MsCl, CH_2Cl_2, −20 °C to room temperature; (d), H_2, Pd/C, EtOH, 80 °C; (e) LiOH, H_2O, THF, rt and then $HCl_{(g)}$ EtOH, 80 °C.

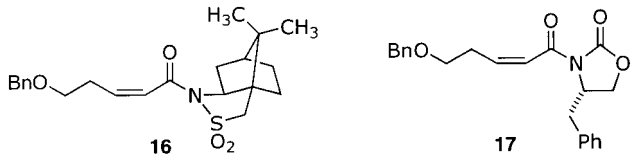


Figure 1.

MsCl[13] gave rise directly to the quaternary ammonium salt **14** (85%). Hydrogenolysis of **14** over palladium on carbon resulted in *N*-benzyl deprotection, and tertiary amine **15** was isolated as the hydrochloride salt (77%). Conversion of **15** to ethyl ester **4** could be achieved by a two-step procedure. LiOH hydrolysis[14] of **15** gave the carboxylate salt, which was not isolated but converted into the ethyl ester **4** by treatment with HCl in ethanol. Ethyl ester **4** was isolated in 92%, and the chiral auxiliary could be recovered in 95%. A one-step procedure involving the treatment of **15** with $Ti(O^iPr)_4$ in ethanol[15] resulted in the formation of **4**, but the product could not be separated from the titanium salts due to its water solubility and highly polar nature. The relative and absolute stereochemistry of **4** was determined by chiral HPLC. Authentic samples of all four stereoisomers of ethyl 1-aza-bicyclo[2.2.1]heptane-3-carboxylate were prepared by published literature methods[3,4] to enable chiral HPLC comparison.

During the course of the work, exploratory trials on two other (*Z*)-alkene dipolarophiles was undertaken, the substrates were prepared using similar chemistry, and a brief study of [3 + 2] dipolar cycloadditions performed. *O*-Benzyl ether **16** (Figure 1) generated a 3.5:1 mixture of diastereoisomers when reacted with the dipole derived from **5**, where as **17**, which contained the 4(*S*)-phenylmethyloxazolidinone auxiliary, generated a 2.6:1 mixture of diastereoisomers. In neither example could the ster-

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eochemistry of the pyrrolidine products be determined nor were they taken through to final products due to the nonorthogonal nature of the nitrogen and oxygen protecting groups. From these studies it is apparent that the nature of the auxiliary can have a significant effect on the process where as the effect of the O-protecting group is relatively minor.

In conclusion, an efficient synthesis of (3*S*,4*R*) ethyl 1-aza-bicyclo[2.2.1]heptane-3-carboxylate **4** using a stereoselective [3 + 2] dipolar cycloaddition of a chiral (*Z*)-alkene dipolarophile has been demonstrated. The absolute stereochemistry was controlled by the use of 2(*R*)-(−)-bornane-2,10-sultam chiral auxiliary and the relative C-3, C-4 stereochemistry by the (*Z*)-alkene geometry. Using the same methodology it should be possible to prepare the corresponding (3*R*,4*S*) enantiomer simply by using the readily available 2(*S*)-(+)-enantiomer of the sultam chiral auxiliary.

Experimental Section

5-(*tert*-Butyldimethylsiloxy)pent-2-ynoic Acid (7). To a stirred solution of **6**[8] (5.00 g, 27.17 mmol) in THF (50 mL) at −75 °C was added n-BuLi (2.5 M in hexanes, 11.4 mL, 28.5 mmol) at such a rate to maintain an internal temperature <−60 °C. After 20 min at −75 °C, $CO_{2(s)}$ (5 g, 110 mmol) was added. The reaction was stirred at −75 °C for 45 min and then allowed to warm to 10 °C before being added to 5% citric acid solution (50 mL). The layers were separated, and the aqueous phase was acidified to pH 5 by the addition of 2 M HCl solution (5 mL) and then extracted with EtOAc (3 × 50 mL). The combined organic phase was washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo to give **7** as a colorless liquid (6.50 g, 100%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (t, 2 H, J = 11.7 Hz), 2.57 (t, 2 H, J = 11.7 Hz), 0.89 (s, 9 H), 0.08 (s, 6 H); IR (neat, cm^{-1}) 2240, 1690; LRMS (EI -ve) m/z 227 (M − H)$^-$.

2(*R*)-[*N*-5-(*tert*-Butyldimethylsiloxy)pent-2-ynoyl]bornane-2,10-sultam (8). To a stirred solution of **7** (5.30 g, 23.25 mmol) in THF (175 mL) at −75 °C was added pivaloyl chloride (3.00 mL, 24.36 mmol) at such a rate to maintain an internal temperature <−70 °C. Triethylamine (3.41 mL, 24.51 mmol) was added at such a rate to maintain an internal temperature <−60 °C. After stirring at −75 °C for 15 min, the mixture was stirred at 0 °C for 30 min and then recooled to −75 °C, to give a solution of the pivaloyl mixed anhydride. Concomitantly, to a stirred solution of 2(*R*)-(−)-bornane-2, 10-sultam (5.00 g, 23.22 mmol) in THF (40 mL) at −75 °C was added n-BuLi (2.5 M in hexanes, 9.8 mL, 24.50 mmol). After 15 min at −75 °C, the solution was added to pivaloyl mixed anhydride solution at −75 °C by cannula at such a rate to maintain the internal temperature <−65 °C. After 45 min at −75 °C, the reaction was allowed to warm to room temperature and 5% citric acid solution (150 mL) added. The solution was extracted with EtOAc (2 × 200 mL), and the combined organic phase was washed with saturated $NaHCO_3$ solution (200 mL) and brine (200 mL), dried over $MgSO_4$, and concentrated in vacuo to give the crude product. Purification by flash column chromatography on SiO_2 (petroleum ether 40−60/EtOAc, 4:1) gave **8** as a white solid (6.22 g, 63%): mp 117−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (dd, 1 H, J = 7.5, 5.0 Hz), 3.82 (t, 2 H, J = 7.1 Hz), 3.50 (d, 1 H, J = 13.8 Hz), 3.43 (d, 1 H, J = 13.8 Hz), 2.63 (t, 2 H, J = 6.9 Hz), 2.27−2.18 (m, 1 H), 2.08 (dd, 1 H, J = 13.8, 7.9 Hz), 1.98−1.84 (m, 3 H), 1.44−1.31 (m, 2 H), 1.17 (s, 3 H), 0.97 (s, 3 H), 0.89 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 93.3, 74.3, 64.9, 60.5, 53.0, 48.5, 47.8, 44.8, 38.4, 32.9, 26.5, 25.8, 23.5, 20.9, 19.9, 18.2, −5.4; $[\alpha]^{25}_D$ −84.5 (c = 1.03, MeOH); IR (neat, cm^{-1}) 2230, 1661, 1297; HRMS calcd for $C_{21}H_{35}NO_4SSi$; 425.2056, found 425.2044; LRMS (CI +ve) m/z 443 (M^+ + NH_4). Anal. Calcd for $C_{21}H_{35}NO_4SSi$: C, 59.26; H, 8.29; N, 3.29. Found: C, 59.26; H, 8.74; N, 3.20.

2(*R*)-[(*Z*)-*N*-5-(*tert*-Butyldimethylsiloxy)pent-2-enoyl]bornane-2,10-sultam (9). A solution of **8** (5.18 g, 12.19 mmol) and palladium on calcium carbonate, poisoned with lead (Lindlar's catalyst, Pd 5%, 78 mg), in toluene (100 mL) was stirred at room temperature under a H_2 atmosphere for 3 h. The catalyst was removed by filtration through Celite and the filtercake washed with toluene (2 × 20 mL). The filtrate was concentrated in vacuo to give **9** as a white solid (5.30 g, 100%): mp 62−63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.52 (d, 1 H, J = 11.3 Hz), 6.45 (dt, 1 H, J = 11.2, 6.7 Hz), 3.92 (dd, 1 H, J = 7.5, 5.4 Hz), 3.72 (t, 2 H, J = 6.25 Hz), 3.51 (d, 1 H, J = 13.7 Hz), 3.43 (d, 1 H, J = 13.7 Hz), 2.89−2.81 (m, 2 H), 2.16−2.06 (m, 2 H), 1.95−1.88 (m, 3 H), 1.45−1.33 (m, 2 H), 1.18 (s, 3 H), 0.97 (s, 3 H), 0.88 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 149.4, 120.7, 65.5, 62.4, 53.6, 48.8, 48.3, 45.2, 39.1, 33.9, 33.4, 27.0, 26.5, 21.3, 20.4, 18.8, −4.9; $[\alpha]^{25}_D$ −72.7 (c = 1.07, MeOH); IR (neat, cm^{-1}) 1681, 1331, 834; HRMS calcd for $C_{21}H_{37}NO_4SSi$; 427.2213, found 427.2220; LRMS (CI +ve) m/z 428 (M^+ + H). Anal. Calcd for $C_{21}H_{37}NO_4SSi$; C, 58.98; H, 8.72; N, 3.28. Found: C, 58.98; H, 8.72; N, 3.02.

Trimethylsilylmethylbenzylamine (11).[12] A stirred solution of benzylamine **10** (17.8 mL, 163 mmol) and chloromethyltrimethylsilane (10.0 g, 81.5 mmol) in acetonitrile (200 mL) was heated at reflux for 16 h. Upon cooling to room temperature the solution was filtered and the filtrate concentrated in vacuo to 100 mL. Water (100 mL) was added and the solution extracted with hexane (2 × 100 mL). The combined organic phase was washed with brine (100 mL), dried over $MgSO_4$, and concentrated in vacuo to give **11** as a colorless liquid (12.95 g. 82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.17 (m, 5 H), 3.79 (s, 2 H), 2.00 (s, 2 H), 0.04 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 128.5, 128.3, 126.7, 58.1, 39.5, −2.6; IR (neat, cm^{-1}) 2953, 1453, 1246; HRMS calcd for $C_{11}H_{19}NSi$: 193.1282. Found: 193.1285; LRMS (CI +ve) m/z 194 (M^+ + H). Anal. Calcd for $C_{11}H_{19}NSi$; C, 68.33; H, 9.90; N, 7.24. Found: C, 68.22; H, 9.86; N, 7.11.

(3*S*,4*R*)-1-Benzyl-3-[(2*R*)-*N*-bornane-2,10-sultam]carbonyl-4-(2-*tert*-butyldimethylsiloxyethyl)pyrrolidine (12). To a stirred solution of **9** (1.93 g, 4.52 mmol) and **5** (1.60 g, 6.75 mmol) in toluene (20 mL) at room temperature was added TFA (35 μL, 0.45 mmol). After 1 h, EtOAc (50 mL) was added, and the solution was washed with saturated $NaHCO_3$ solution (40 mL) and brine (40 mL), dried over $MgSO_4$, and concentrated in vacuo to give the crude products. Purification by flash column chromatography on SiO_2 (petroleum ether 40−60/EtOAc, 4:1 and then 2:1) gave **12** as a white solid (1.84 g, 73%) and the minor diastereoisomer as a white solid (370 mg, 15%). **12**: mp 89−91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.22 (m, 5 H), 3.90−3.86 (m, 1 H), 3.79−3.57 (m, 3 H), 3.53 (t, 2 H, J = 6.7 Hz), 3.49 (d, 1 H, J = 13.8 Hz), 3.41 (d, 1 H, J = 13.8 Hz), 3.13−3.08 (m, 2 H), 2.68−2.60 (m, 1 H), 2.57 (t, 1 H, J = 8.5 Hz), 2.24−2.20 (m, 1 H), 2.10−2.05 (m, 2 H), 1.93−1.85 (m, 2 H), 1.70−1.56 (m, 3 H), 1.42−1.34 (m, 2 H), 1.10 (s, 3 H), 0.95 (s, 3 H), 0.85 (s, 9 H), 0.00 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 139.0, 128.8, 128.2, 127.0, 68.0, 62.4, 60.6, 60.2, 57.9, 53.2, 48.2, 47.7, 46.4, 44.8, 38.7, 38.6, 33.8, 33.0, 26.4, 26.0, 21.1, 19.9, 18.3, −5.3, −5.4; $[\alpha]^{25}_D$ −51.2 (c = 0.25, MeOH); IR (neat, cm^{-1}) 1690, 1333; HRMS Calc'd for $C_{30}H_{48}N_2O_4SSi$: 560.3104, found 560.3100; LRMS (CI +ve) m/z 561 (M^+ + H). **Minor diastereoisomer**: mp 83−85 °C; ^{1}H NMR (400 MHz, $CDCl_3$ δ 7.33−7.21 (m, 5 H), 3.87 (t, 1 H, J = 6.3 Hz), 3.83−3.76 (m, 1 H), 3.66−3.64 (m, 2 H), 3.56−3.48 (m, 3 H), 3.42 (d, 1 H, J = 13.8 Hz), 3.20−3.16 (m, 1 H), 3.05−3.01 (m, 1 H), 2.74−2.67 (m, 2 H), 2.26−2.22 (m, 1 H), 2.10−2.08 (m, 2 H), 1.93−1.87 (m, 2 H), 1.79−1.64 (m, 2 H), 1.55−1.47 (m, 1 H), 1.42−1.32 (m, 2 H), 1.17 (s, 3 H), 0.97 (s, 3 H), 0.84 (s, 9H), −0.02 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 139.1, 128.8, 128.3, 126.9, 65.4, 61.8, 60.3, 59.6, 56.5, 53.2, 47.8, 47.7, 46.4, 44.7, 39.5, 38.8, 33.0, 32.9, 26.5, 26.0, 21.0, 19.9, 18.2, −5.4; $[\alpha]^{25}_D$ −60.8 (c = 1.01, MeOH); IR (neat, cm^{-1}) 1689, 1331; HRMS calcd for $C_{30}H_{48}N_2O_4SSi$: 560.3104, found 560.3108; LRMS (CI +ve) m/z 561 (M^+ + H). Anal. Calcd for $C_{30}H_{48}N_2O_4$ SSi: C, 64.25; H, 8.63; N, 4.99. Found: C, 64.15; H, 8.97; N, 5.04.

(3*S*,4*R*)-1-Benzyl-3-[(2*R*)-*N*-bornane-2,10-sultam]carbonyl-4-(2-hydroxyethyl)pyrrolidine (13). To a stirred solution of **12** (1.69 g, 3.02 mmol) in acetone (25 mL) at 0 °C was added 2 M HCl solution (3.0 mL, 6.00 mmol). After 10 min, the solution was allowed to warm to room temperature. After 30 min at room temperature, saturated $NaHCO_3$ solution (25 mL) was added and the solution stirred for 30 min. Water (20 mL) was added and the solution extracted with EtOAc (4 × 20 mL). The combined organic phase was washed with brine (40 mL), dried

over $MgSO_4$, and concentrated in vacuo to give the crude product. Purification by flash column chromatography on SiO_2 (EtOAc) gave **13** as a white solid (1.13 g, 84%): mp 144−145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.24 (m, 5 H), 3.89−3.86 (m, 1 H), 3.81−3.75 (m, 1 H), 3.66 (d, 1 H, J = 12.9 Hz), 3.60 (d, 1 H, J = 12.5 Hz), 3.58 (t, 2 H, J = 6.5 Hz), 3.51 (d, 1 H, J = 13.7 Hz), 3.44 (d, 1 H, J = 13.7 Hz), 3.13−3.06 (m, 2 H), 2.77−2.72 (m, 1 H), 2.65 (dd, 1 H, J = 9.2, 8.3 Hz), 2.27 (t, 1 H, J = 9.0 Hz), 2.12−2.04 (m, 2 H), 1.95−1.86 (m, 3 H), 1.81−1.60 (m, 3 H), 1.43−1.34 (m, 2 H), 1.11 (s, 3 H), 0.96 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 138.9, 128.7, 128.3, 127.2, 65.5, 61.6, 60.6, 60.1, 57.8, 53.2, 48.2, 47.7, 46.0, 44.7, 38.7, 38.0, 33.6, 33.0, 26.4, 21.0, 19.9; $[\alpha]^{25}_D$ −65.2 (c = 0.49, MeOH); IR (neat, cm^{-1}) 1689, 1329; HRMS, calcd for $C_{24}H_{34}N_2O_4S$; 446.2239, found 446.2232; LRMS (CI +ve) m/z 447 (M^+ + H). Anal. Calcd for $C_{24}H_{34}N_2O_4S$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.29; H, 7.65; N, 5.98.

(3*S*,4*R*)-1-Benzyl-3-[(2*R*)-*N*-bornane-2,10-sultam]carbonyl-1-azonia-bicyclo[2.2.1]heptane Chloride (14). To a stirred solution of **13** (860 mg, 1.93 mmol) in CH_2Cl_2 (20 mL) at −20 °C were added triethylamine (670 μL, 4.82 mmol) and methanesulfonyl chloride (180 μL, 2.33 mmol). After 20 min, the solution was allowed to warm to room temperature, diluted with CH_2Cl_2 (12 mL), and washed with saturated $NaHCO_3$ solution (6 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 12 mL), and the combined organic phase was washed with brine (6 mL), 2 M HCl solution (6 mL), and brine (6 mL), dried over $MgSO_4$, and concentrated in vacuo to give **14** as a hydrated white solid (761 mg, 85%): mp 160 °C (dec); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.65 (m, 2 H), 7.47−7.36 (m, 3 H), 5.31 (d, 1 H, J = 12.6 Hz), 5.18 (d, 1 H, J = 12.6 Hz), 4.41−4.35 (m, 1 H), 4.25−4.20 (m, 1 H), 4.10−4.05 (m, 3 H), 3.87−3.84 (m, 1 H), 3.56−3.43 (m, 4 H), 3.30−3.24 (m, 1 H), 2.29−2.23 (m, 1 H), 2.09−1.98 (m, 2 H), 1.94−1.80 (m, 4 H), 1.46−1.31 (m, 2 H), 1.07 (s, 3 H), 0.95 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 132.0, 130.2, 129.2, 128.9, 67.3, 65.5, 61.9, 60.6, 59.6, 52.8, 48.8, 47.9, 44.7, 44.3, 39.6, 38.2, 32.7, 26.3, 24.4, 20.7, 19.7; $[\alpha]^{25}_D$ −40.7 (c = 1.00, MeOH); IR (neat, cm^{-1}) 1678, 1328, 1133; HRMS calcd for $C_{24}H_{33}N_2O_3S$; 429.2212, found 429.2208; LRMS (CI +ve) m/z 429 (M^+ − Cl). Anal. Calcd for $C_{24}H_{33}ClN_2O_3S\cdot 2.5\ H_2O$: C, 56.51; H, 7.51; N, 5.49. Found: C, 56.74; H, 7.14; N, 5.40; Karl Fisher Titrimetry (K_F) = 8.83% w/w H_2O.

(3*S*,4*R*)-3-[(2*R*)-*N*-Bornane-2,10-sultam]carbonyl-1-azabicyclo[2.2.1]heptane Hydrochloride (15). EtOH (30 mL) was added to a flask containing 10% Pd/C (250 mg) and **14** (1.98 g, 4.26 mmol). The mixture was placed under an atmosphere of H_2 and heated to 80 °C. After 5 h, it was allowed to cool to room temperature and water (30 mL) added. The catalyst was removed by filtration through Celite, and the filtercake was washed with a 1:1 EtOH/H_2O solution (100 mL). Concentration of the filtrate in vacuo gave **15** as a hydrated white solid (1.23 g, 77%): mp >230 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 4.03−3.94 (m, 2 H), 3.75 (d, 1 H, J = 13.7 Hz), 3.78−3.56 (m, 3 H), 3.55−3.45 (m, 3 H), 3.39−3.28 (m, 2 H), 2.22−1.94 (m, 1 H), 2.10−1.83 (m, 6 H), 1.53−1.47 (m, 1 H), 1.44−1.36 (m, 1 H), 1.15 (s, 3 H), 1.03 (s, 3 H); ^{13}C NMR (100 MHz, d_6DMSO) δ 170.1, 66.9, 61.6, 56.9, 53.6, 53.5, 50.1, 48.9, 46.6, 45.9, 41.4, 39.4, 33.5, 27.3, 23.8, 20.7, 19.7; $[\alpha]^{25}_D$ −59.0 (c = 0.70, H_2O); IR (neat, cm^{-1}) 1698, 1331, 1211; HRMS calcd for $C_{17}H_{27}N_2O_3S$; 339.1742, found 339.1733; LRMS (CI +ve) m/z 339 (M^+ − Cl). Anal. Calcd for $C_{17}H_{27}ClN_2O_3S\cdot 0.2\ H_2O$: C, 53.94; H, 7.30; N, 7.40. Found: C, 53.86; H, 7.24; N, 7.31; Karl Fisher Titrimetry (K_F) = 1.01% w/w H_2O.

(3*S*,4*R*)-Ethyl 1-Azabicyclo[2.2.1]heptane-3-carboxylate (4).[4] Lithium hydroxide monohydrate (280 mg, 6.68 mmol) was added to a suspension of amide **15** (500 mg, 1.34 mmol) in water (10 mL) and THF (2 mL) and then stirred at room temperature for 18 h. The solution was then extracted with CH_2Cl_2 (5 × 20 mL) followed by Et_2O (2 × 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to give 2(*R*)-(−)-bornane-2,10-sultam (272 mg, 95%). The aqueous phase was concentrated in vacuo and then azeotroped with EtOH (2 × 20 mL). The residue was then dissolved in EtOH (20 mL) which had been saturated with dry $HCl_{(g)}$. The mixture was then heated at reflux for 1h before being allowed to cool to room temperature. The solvent was removed in vacuo and the residue azeotroped with CH_2Cl_2 (2 × 20 mL). CH_2Cl_2 (20 mL) was added and the suspension stirred for 15 min and then filtered. The filtercake was washed with CH_2Cl_2 (2 × 20 mL), and the filtrate was concentrated in vacuo to give **4** as a hygroscopic white solid (253 mg, 92%); ^{1}H NMR (400 MHz, CD_3OD) δ 4.27−4.22 (m, 2 H), 3.68−3.50 (m, 5 H), 3.44 (d, 1 H, J = 8.8 Hz), 3.36−3.26 (m, 2 H), 2.17−2.07 (m, 1 H), 1.77−1.71 (m, 1 H), 1.31 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 171.7, 62.6, 61.4, 55.5, 53.5, 45.0, 40.4, 24.4, 14.4; $[\alpha]^{25}_D$ +28.9 (c = 0.96, MeOH); IR (neat, cm^{-1}) 1725, 1196; LRMS (CI +ve) m/z 170 (M^+ − Cl).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of selected compounds and compounds for which no elemental analysis was obtained as well as chiral HPLC for compound **4**.

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