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Auxiliary Mediated Synthesis of Aziridine-2-carboxylic Acid Derivatives

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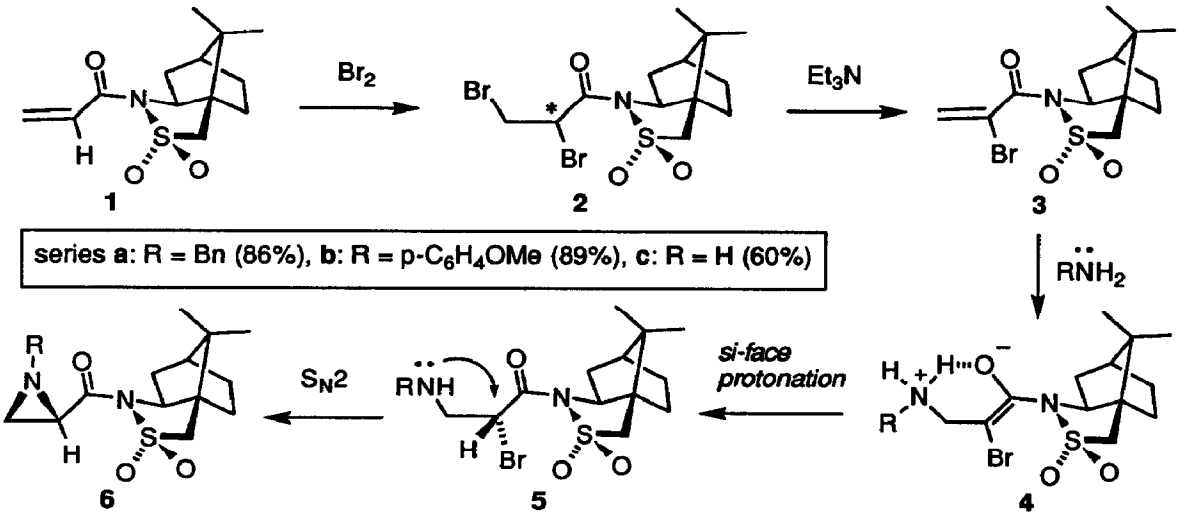
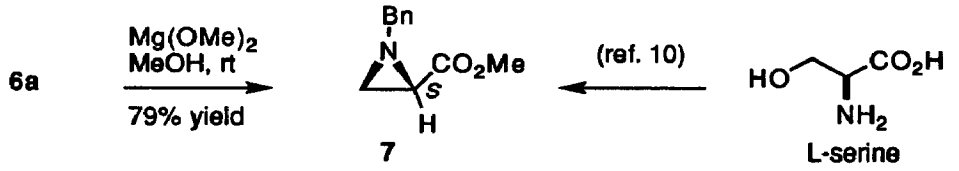
Abstract: *A convenient protocol for the asymmetric synthesis of stereodefined aziridine-2-carboxylic acid derivatives from α,β-unsaturated acryloyl- and crotonoyl camphor sultams is reported.*

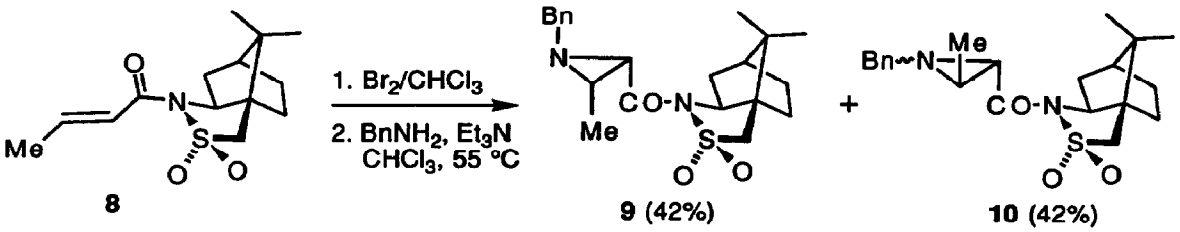
Aziridine-2-carboxylates are useful chiral building blocks for the asymmetric synthesis of modified amino acids and related compounds (via nucleophilic ring opening)[1] as well as targets that incorporate the intact aziridine ring (via peripheral functional group manipulation).[2] A commonly used strategy for the synthesis of aziridine-2-carboxylates involves the so-called Gabriel-Cromwell reaction of 2,3-dihalopropionic (or 2-bromo acrylic) acid derivitives with primary amines.[3] Enantiomerically pure aziridine-2-carboxylates can be obtained by this route via physical resolution of diastereomers[4] or kinetic resolution of racemic aziridine-2-carboxylates using hydrolases.[5] However, stereocontrolled synthetic access to this class of compounds is generally restricted to dehydrative ring closure of β-hydroxy-α-aminoacid derivatives[6] or double S_N2 displacement of oxirane-2-carboxylates with an ammonia equivalent.[7] We now report an expedient G-C route to this class of compounds wherein the asymmetric induction is controlled using Oppolzer's camphor-derived sultam as a chiral auxiliary.[8]



Starting from the readily accessible N-acryloyl camphor sultam **1**,[9] the overall reaction sequence proceeds through five distinct mechanistic steps: bromination (**1** → **2**), β-elimination (**2** → **3**), conjugate addition (**3** → **4**), proton transfer (**4** → **5**), and S_N2 ring closure (**5** → **6**). Good to excellent yields of the aziridines **6a-c** are obtained after simple flash chromatography. In only one case (**6b**), could a minor diastereomer even be detected (ds = 9:1). The configuration of the newly formed chiral center in **6a** was determined to be "S" after (nondestructive) removal of the sultam auxiliary using methanolic magnesium methoxide. The resulting aziridine ester **7** had an $[\alpha]_D$ = -83.5 ° (*c* 1.14, EtOH) which compared well with $[\alpha]_D$ = -85.3 ° (*c* 1.03) reported for the same compound derived from L-serine (reference 3a). This result implies that the key stereodifferentiating step involves face-selective α-protonation of enolate **4** with the sense of asymmetric induction following from the model proposed by Curran and Oppolzer (cf. reference 8). Note that the pseudo C_2 symmetry of the auxiliary predicts si-attack on **4** for both the E- and Z-amide conformations. Interestingly, the initial bromination step was also found to be diastereoselective producing dibromides corresponding to **2** in ratios up to 5:1 (configuration at the α-center not determined).



Repetition of our aziridination protocol with the N-crotonoyl camphor sultam **8** resulted in the clean formation of a 1:1 mixture of chromatographically separable aziridines **9** and **10** in 84% combined yield. The production of two isomeric aziridines is consistent with the mechanism presented above *but with the conjugate addition step being nonselective.* Similar lack of facial selectivity has been observed with the β-addition of nucleophilic radicals to analogous α,β-unsaturated acylsultams (reference 8). Evidence that **9** and **10** possess the 2,3-trans and 2,3-cis disubstituted aziridine stereochemistry comes from their respective ^1H NMR spectra with **9** exhibiting a $J_{2,3}$ = 6.8 Hz and **10** existing as a mixture of slowly interconverting N-invertomers that only become averaged-out upon heating to 150 °C (cf. reference 3). In spite of the apparent limitations with β-substituted systems, the described aziridination procedure may turn out to be the method of choice for the synthesis of stereodefined aziridine carboxylic acid derivatives with more complex β-subtitution patterns and/or the "unnatural" 2R stereochemistry via the readily accessible antipodal camphor sultams.[10]



Representative Experimental Procedure: Liquid bromine (0.050 mL, 0.970 mmol) was added to a stirred solution of (+)-N-propenoylbornane-2,10-sultam (**1**) (250 mg, 0.929 mmol) in $CHCl_3$ (2.0 mL, spectroscopic grade) under an Ar atmosphere. After stirring at room temperature for 1 h, the reaction was judged to be complete by ^1H NMR analysis of an aliquot (**1** and **2** have very similar Rf values precluding TLC monitoring). Benzylamine (150 mg, 1.39 mmol) and triethylamine (188 mg, 1.86 mmol) were added to the reaction flask and stirring was continued at room temperature overnight. (This step may also be run at 55 °C if shorter reaction times are desired.) At this time, TLC analysis (2:1 hexanes-EtOAc) showed the clean formation of aziridine **6a**, Rf 0.23, at the expense of dibromide **2**, Rf 0.45. The reaction mixture was diluted with $CHCl_3$ (50 mL) and washed successively with 10 mL each of 0.1 N HCl, sat. $NaHCO_3$ soln., and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated to give the crude product, which was purified by flash chromatography (2:1 hexs-EtOAc) to give 300 mg (86% yield) of **6a** as a white solid.[11]

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10. We recently demonstrated that the aziridines **6a** and **6b** can serve as effective precursors to chiral azomethine ylides which undergo auxiliary-controlled 1,3-dipolar cycloadditions. Garner, P.; Dogan, O. *J. Org. Chem.* **1994**, *59*, 0000.

11. Characterization data for compound **6a:** Rf 0.21, 2:1 hexanes/EtOAc; mp: 117-119 °C; $[\alpha]^{22}_D$ = +18.8° (*c* 2. 08, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.22 (m, 5 H, Ph), 3.89 (dd, J = 7.2 & 4.8 Hz, 1 H, H-2'), 3.75 (d, J = 13.3 Hz, 1 H, 1/2 CH_2Ph), 3.52 (d, J = 13.8, Hz, 1 H, 1/2 CH_2SO_2), 3.46 (d, J = 13.3 Hz, 1/2 CH_2Ph, 1 H), 3.43 (d, J = 13.8 Hz 1 H, 1/2 CH_2SO_2), 2.88 (dd, J = 6.4 & 3.1 Hz, 1 H, H-2), 2.31 (d, J = 3.3 Hz, 1 H, H-3), 2.19-2.00 (m, 2 H), 1.93-1.82 (m, 4 H), 1.45-1.30 (m, 2 H), 1.13 (s, 3 H, CH_3), 0.97 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 168.5 (C=O), 138.1 128.5, 127.1 (6C, aromat.), 65.53, 64.00, 53.50, 49.01, 48.02, 52.34, 45.00, 38.63, 38.02, 36.00, 33.03, 26.76, 21.13, 19.90; IR ($CHCl_3$) 3660 (w), 3010 (m), 2950 (m), 2380 (w), 1690 (s, C=O), 1410 (s), 1325 (s), 1260 (s), (1215 (s), 1225 (s), 1125 (s), 1050 (w); HRMS *m/z* calcd. for $C_{20}H_{27}N_2O_3S$ (M+1) 375.1742, obsd. 375.1736.

6b: Rf 0.30, 2:1 hexanes/EtOAc; $[\alpha]^{22}_D$ = -29.2° (*c* 2.10, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.95 (d, J = 9.0 Hz, 2 H, Ph), 6.77 (d, J = 8.8 Hz, 2 H, Ph), 3.93 (dd, J = 7.8 & 4.9 Hz, H-2'), 3.74 (s, 3 H, OCH_3), 3.57 (d, J = 13.9 Hz, 1 H, 1/2 CH_2SO_2), 3.48 (d, J = 13.9 Hz, 1 H, 1/2 CH_2SO_2), 3.42 (dd, J = 6.1 & 3.1 Hz, 1 H, H-2), 2.69 (t, J = 2.4 Hz, 1 H, H-3), 2.34 (dd, J = 6.2 & 1.7 Hz, 1 H, H-3), 2.30-2.20 (m, 1 H), 2.11 (dd, J = 7.7 & 6.2 Hz, 1 H), 1.96-1.83 (m, 3 H), 1.46-1.30 (m, 2 H), 1.25 (s, 3 H, CH_3), 1.00 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 168.1 (C=O), 155.7, 128.4, 121.6, 114.3 (6 C, aromat.), 65.54, 5.54, 53.13, 49.06, 47.95, 44.72, 38.39, 37.91, 35.57, 32.93, 26.49, 21.00, 19.97; IR ($CHCl_3$) 3660 (w), 3000 (m), 2950 (m), 2380 (w), 1700 (s, C=O), 1500 (s), 1410 (m), 1330 (s), (1270 (s), 1220 (s), 1130 (m), 1060 (w), 1030 (w); HRMS *m/z* calcd. for $C_{20}H_{26}N_2O_4S$ (M) 390.1613, obsd. 390.1612.

6c: Rf 0.31, 1:1 hexanes/EtOAc; mp: 129-131 °C; $[\alpha]^{22}_D$ = +65.1° (*c* 7.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 3.90 (dd, J = 7.6 & 5.1 Hz, 1 H, H-2'), 3.55 (d, J = 13.8, Hz, 1 H, 1/2 CH_2SO_2), 3.47 (d, J = 13.8 Hz, 1 H, 1/2 CH_2SO_2), 3.15 (bs, 1 H, N-H), 2.20-1.80 (m, 7 H), 1.55-1.30 (m, 3 H), 1.21 (s, 3 H, CH_3), 0.99 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 128.4 (C=O), 65.25, 53.00, 47.91, 44.74, 38.32, 32.88, 29.69, 29.21, 26.49, 26.43, 20.89, 19.94; IR ($CHCl_3$) 3660 (w), 3280 (w), 2950 (s), 2450 (w), 1680 (s, C=O), 1500 (s), 1400 (s), 1330 (s), 1265 (s), 1215 (s), 1160 (s), 1130 (s), 1050 (s) 970 (w).

9: Rf 0.35, 2:1 hexanes/EtOAc; $[\alpha]^{22}_D$ = +1.74° (*c* 2.88, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.27 (m, 5 H, aromat.), 3.94 (dd, J = 6.6 & 6.0 Hz, 1 H, H-2'), 3.88 (d, J = 13.7 Hz, 1 H, 1/2 CH_2Ph), 3.55 (d, J = 13.8, Hz, 1 H, 1/2 CH_2SO_2), 3.48 (d, J = 13.7 Hz, 1 H, 1/2 CH_2Ph), 3.45 (d, J = 13.7 Hz, 1 H, 1/2 CH_2SO_2), 2.93 (d, J = 6.8 Hz, 1 H, H-2), 2.24 (m, 1 H, H-3), 2.13 (m, 2 H), 1.91 (m, 3 H), 1.49-1.32 (m, 2 H), 1.26 (d, J = 5.5 Hz, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 1.00 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 167.9 (C=O), 138.2 128.5, 127.9, 127.1, (6 C, aromat.), 65.51, 63.82, 53.20, 49.02, 48.01, 45.01, 44.51, 43.89, 38.45, 32.88, 26.46, 21.10, 20.02, 13.30; IR ($CHCl_3$) 3660 (w), 3010 (m), 2950 (m), 2380 (w), 1690 (s, C=O), 1410 (s), 1325 (s), 1260 (s), 1215 (s), 1225 (s), 1125 (s), 1050 (w); HRMS *m/z* calcd. for $C_{21}H_{28}N_2O_3S$ (M) 388.1821, obsd. 388.1835.

10: Rf 0.44, 2:1 hexanes/EtOAc; mp 129-130 °C; $[\alpha]^{23}_D$ = +48.2° (*c* 3.60, $CHCl_3$); ^1H NMR (200 MHz, 150 °C, DMSO-d_6) δ 7.50-7.20 (m, 5 H, aromat.), 3.85 (s, 2 H, CH_2SO_2), 3.72 (m, 1 H, H-2'), 3.71 (d, J = 14.2 Hz, 1 H, 1/2 CH_2Ph), 3.57 (d, J = 14.1 Hz, 1 H, 1/2 CH_2Ph)) 2.78 (br s, 1H, H-2), 2.42 (m, 1 H, H-3), 2.09-1.85 (m, 5 H), 1.50-1.35 (m, 2 H), 1.25 (dd, J = 5.6 & 1.8 Hz, 3 H, CH_3), 1.03 (s, 3 H, CH_3), 0.97 (s, 3 H, CH_3); IR ($CHCl_3$) 3680 9w), 3015 (m), 2960 (m), 2495 (w), 1690 (s, C=O), 1420 (m), 1330 (s), 1260 (s), 1210 (s), 1160 (m), 1125 (s), 1110 (m), 1050 (m); HRMS *m/z* calcd. for $C_{21}H_{28}N_2O_3S$ (M) 388.1821, obsd. 388.1843.

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