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SYNTHESIS OF 1-AZABICYCLO[3.1.0]HEXANE SYSTEMS

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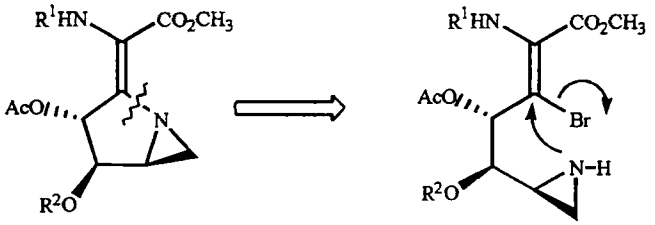
The synthesis of aziridino[1,2-*a*]pyrrolidine systems related to the azinomycin family of antitumor agents is reported and was based on an intramolecular addition-elimination reaction sequence.

In our previous work [1-4] we have detailed an effective cyclization reaction between an aziridine and β-bromoacrylate system to form the aziridino[1,2-*a*]-pyrrolidine ring system of the antitumor agents azinomycins A and B [5-7]. This cyclization reaction allows access to the tetrasubstituted olefins with complete control of stereochemistry.



Since we demonstrated that the cyclization reaction is stereospecific and occurs with apparently complete stereoselection, control of stereochemistry of the precursory vinyl bromide is vital. The vinyl bromide necessary for pyrrolidine formation containing C(12) ethers was introduced by the treatment of Ib with N-bromosuccinimide (NBS) to initially form the α-bromoimines IIb. Base promoted tautomerization using bulky amine bases resulted in formation of vinyl bromides (*E*)-IIIb with high levels of stereoselection (typically 10:1 *E*/*Z*). However, olefin Ia needed to be warmed ($CDCl_3$, 40°C) overnight in the presence of N-bromosuccinimide to produce IIa. This was a noticeable difference from the C(12) ethers that were completed after 2 h at room temperature. We also found that the intermediate α-bromoimine IIa produced from either (*E*)- or (*Z*)-Ia underwent only a modestly stereoselective base-promoted tautomerization with *t*-BuOK in THF. Treatment of the α-bromoimine IIa with sterically bulky amine bases resulted in exclusive formation of (*Z*)-vinyl bromide IIIa. This is a reversal from results of C(12) ether systems that resulted in predominately (*E*)-vinyl bromides (*E*)-IIIb. The configuration of the vinyl bromides were correlated with spectral data of related compounds by the distinctive difference of the C(13)-H, C(12)-H, and NH proton chemical shifts (Table 1).

Treatment of vinyl bromides III (Scheme 2) with Et_3SiH in the presence of $Pd(OAc)_2$ and Et_3N accomplished removal of the N-benzoxycarbonyl protecting group to afford the corresponding free aziridines IV [8]. Cyclization of (*E*)-IVb in the presence of an amine base afforded (*E*)-Vb in good yields. On the other hand, cyclization of free aziridine IVa using amine bases resulted in low yields of the desired intact aziridino[1,2-*a*]pyrrolidine ring system. The product isolated in this case resulted from aziridine opening by the bromide ion following cyclization of the free aziridine onto the β-bromoacrylate. Formation of the ring-opened aziridine product was prevented by warming

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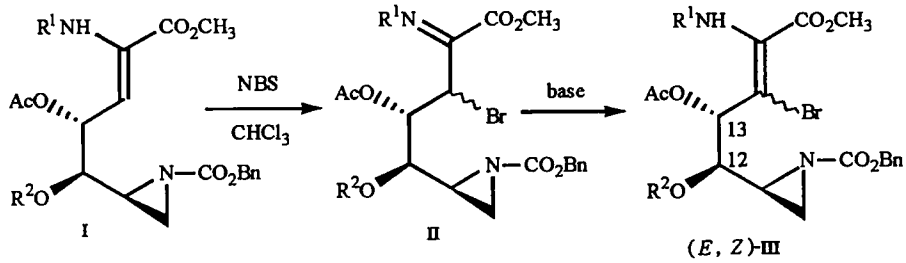
TABLE 1. Proton Chemical Shift Correlation ($CDCl_3$, ppm)

Compound	C(13)-H	C(12)-H	NH	Compound	C(13)-H	C(12)-H
(*E*)-IIIa	5.71	5.52	8.39	(*E*)-Va	5.53	5.28
(*Z*)-IIIa	6.02	5.10	6.62	(*Z*)-Va	6.07	5.25
(*E*)-IIIb	5.70	3.75	9.00	(*E*)-Vb	5.39	4.30
(*Z*)-IIIb	5.98	3.42	7.10	(*Z*)-Vb	5.95	4.30

Scheme 1

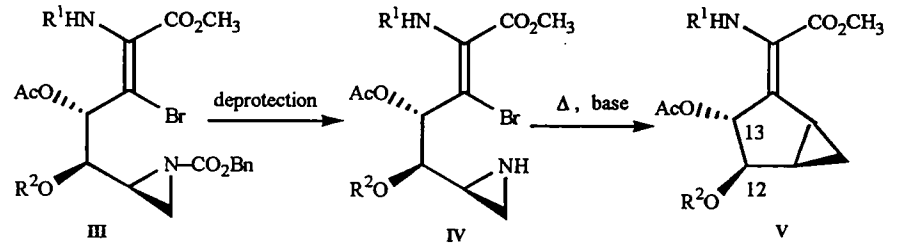


(a) $R^1 = CO_2CH_3$, $R^2 = COCH_2Ph$
(b) $R^1 = COCH_3$, $R^2 = p\text{-}CH_3OC_6H_4CH_2$

the free aziridine in the presence of Dowex anion-exchange resin (carbonate form) to afford the aziridino[1,2-*a*]pyrrolidine without competing aziridine opening. The cyclization reaction IV to V was found to be stereospecific, and was observed to occur with complete stereoselectivity within the limits of detection by ^1H NMR.

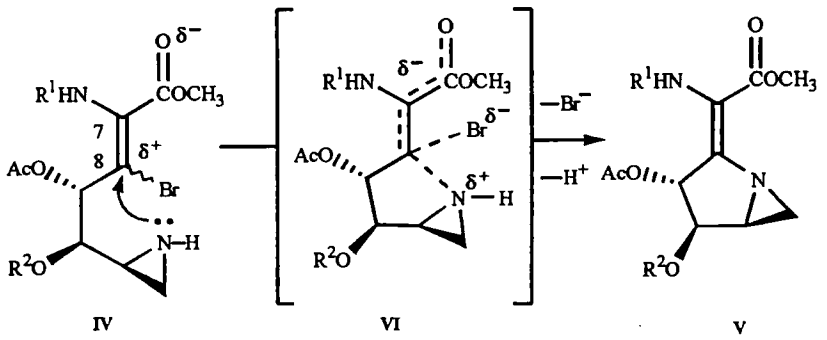
While we have viewed this reaction as a Michael addition-retro Michael sequence, it seems unlikely that this is the case in view of the stereochemical outcomes of the cyclization reactions of the *E*- and *Z*-vinyl bromides [9]. We view this process to be much closer to a direct displacement reaction [10, 11] where the structure VI is either a short-lived intermediate between starting material IV and product V. In any case, it is clear that the C(7)-C(8) olefin never exists in a state such that the barrier to rotation about this bond is low enough to allow isomerization, as we have never detected any stereochemical leakage during the cyclization reactions.

Scheme 2



(a) $R^1 = CO_2CH_3$, $R^2 = COCH_2Ph$
(b) $R^1 = COCH_3$, $R^2 = p\text{-}CH_3OC_6H_4CH_2$

The work presented here shows results of an effective intramolecular Michael addition-elimination cyclization between an aziridine and β-bromoacrylate system to afford an aziridino[1,2-*a*]pyrrolidine ring system containing various C(12)-protected alcohol systems. The reaction was found to be stereospecific and occurred with complete stereoselectivity.



IV VI V

EXPERIMENTAL

Methyl (2*E*,4*R*,5*R*)-4-Acetoxy-5-[(2*S*)-N-(benzyloxycarbonyl)aziridin-2-yl]-3-bromo-5-phenylacetoxy-2-[N-methoxycarbonylamino]-2-pentenoate ((E)-IIIa). A solution of olefin IIa (137 mg, 0.25 mmol) in $CHCl_3$ (1.25 ml) was treated with N-bromosuccinimide (44 mg, 0.25 mmol, 1.0 equiv) under N_2 and the reaction mixture was warmed at 40°C shielded from light for 12 h. Potassium *tert*-butoxide (28 mg, 0.25 mmol, 1.0 equiv) was added to the reaction at 25°C and the mixture was stirred an additional 2 h. The reaction mixture was concentrated under a stream of N_2 and the residue was directly purified by flash chromatography (silica, 30% ethyl acetate/hexanes) to afford a separable 1:1 mixture of vinyl bromides (*E*)-IIIa and (*Z*)-IIIa (122 mg combined, 77%) as white foams.

The (*Z*)-vinyl bromide was characterized: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.2-7.35 (m, 10H, ArH); 6.62 (bs, 1H, NH); 6.02 (d, *J* = 8.7 Hz, 1H, C(13)-H); 5.1-5.02 (m, 3H, C(12)-H and OCH_2Ph); 3.87 (s, 3H, OCH_3); 3.74 (s, 3H, OCH_3); 3.57 (s, 2H, O_2CCH_2Ph); 2.85 (ddd, *J* = 8.4, 6.2, 3.5 Hz, 1H, C11-H); 2.40 (d, *J* = 6.3 Hz, 1H, C10-H); 2.22 (d, *J* = 3.5 Hz, 1H, C10-H); 1.74 (s, 3H, CH_3CO). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.8, 169.4, 152.9, 135.4, 133.1, 129.1, 128.6, 128.5, 128.4, 128.2, 128.0, 127.2, 73.3, 70.9, 68.3, 53.3, 41.1, 36.7, 29.9, 20.3. IR (neat) 3297, 3031, 2953, 1731, 1636, 1494 cm^{-1}. FABMS, *m/z* (relative intensity) 633/635 (M^+ + H, 9/9).

The (*E*)-vinyl bromide was characterized: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.39 (br. s, 1H, NH), 7.22-7.35 (m, 10H, ArH); 5.71 (d, *J* = 9.1 Hz, 1H, C(13)-H); 5.55 (dd, *J* = 9.1, 3.9 Hz, 1H, C(12)-H); 5.11 (s, 3H, OCH_2Ph); 3.85 (s, 3H, OCH_3); 3.65 (s, 3H, OCH_3); 3.63 (s, 2H, O_2CCH_2Ph); 2.66 (m, 1H, C11-H); 2.31 (d, *J* = 6.2 Hz, 1H, C10-H); 2.11 (d, *J* = 3.5 Hz, 1H, C10-H); 1.67 (s, 3H, CH_3CO). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.2, 163.5, 162.4, 153.5, 135.5, 132.7, 129.1, 128.6, 128.5, 128.4, 128.3, 128.0, 127.4, 71.7, 69.6, 68.5, 52.9, 52.7, 41.0, 35.4, 28.6, 20.0. IR (neat) 3297, 3031, 2953, 1731, 1636, 1494 cm^{-1}. FABMS, *m/z* (relative intensity) 633/635 (M^+ + H, 4/4).

Methyl (2*E*,4*S*,5*R*)-4-Acetoxy-2-(N-acetylamino)-5-((2*S*)-N-(benzoxycarbonyl)aziridin-2-yl)-3-bromo-5-(*p*-methoxybenzyloxy)-2-pentenoate ((*E*)-IIIb). A solution of olefin (*Z*)-IIb (162 mg, 0.3 mmol) in CH_2Cl_2 (2.5 ml) was treated with N-bromosuccinimide (55 mg, 0.3 mmol) at 0°C and the reaction mixture was allowed to stir at 25°C for 4 h. 2,2,6,6-Tetramethylpiperidine (101 µl, 0.6 mmol, 2 equiv) was added at 0°C, and the reaction mixture was stirred 8 h at 25°C. The mixture was diluted with EtOAc (50 mL), washed with NaCl (2×5 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was purified by flash chromatography (30% EtOAc/hexanes) to afford (*E*)-IIIb (117 mg, 63%) and (*Z*)-XX (24 mg, 13%).

The E-isomer was characterized: $[\alpha]_D^{20}$ +84.1° (c 0.39, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.03 (br. s, 1H); 7.32 (s, 5H); 7.20 (d, *J* = 8.6 Hz, 2H); 6.81 (d, *J* = 8.6 Hz, 2H); 5.70 (d, *J* = 6.8 Hz, 1H); 5.10 (ABq, *J* = 12.2 Hz, Δν = 32.4, 2H); 4.66 (ABq, *J* = 10.6 Hz, Δν = 90.6 Hz, 2H); 3.81 (s, 3H); 3.78-3.79 (m, 1H); 3.77 (s, 3H); 2.59-2.61 (m, 1H); 2.35 (d, *J* = 5.2 Hz, 1H); 2.08 (s, 3H); 1.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.9, 168.3, 163.9, 162.9, 159.6, 135.4, 133.2, 130.0, 129.8, 128.6, 128.5, 128.4, 113.9, 111.0, 78.3, 74.0, 73.6, 68.7, 55.4, 52.6, 36.9, 27.9, 22.2, 20.6. IR (neat) 3254, 1775, 1710, 1509, 1429, 1294, 1179 cm^{-1}. HR-FABMS, *m/z* 619.1307 ($C_{28}H_{31}N_2O_9{}^{79}Br$ + H requires 619.1291).

Methyl (2*E*,3*R*,4*R*,5*S*)-3-acetoxy-α-methoxycarbonylamino-4-phenylacetoxy-1-azabicyclo-[3.1.0]hexene-$\Delta^{2\alpha}$-acetate ((*E*)-Va). A mixture of IIIa (48 mg, 0.08 mmol), Et_3SiH (120 µl, 0.76 mmol, 10 equiv) and Et_3N (1.9 µl, 0.16 equiv) in CH_2Cl_2 (0.8 ml, 0.2 M) was treated with $Pd(OAc)_2$ (2 mg, catalytic) at 25°C under N_2. Gas evolution

was observed as the clear reaction mixture turned black while stirring at 25°C for 20 min. Direct purification of the reaction mixture by flash chromatography (silica, 20% ethyl acetate/hexanes followed by 10% CH_3OH/CH_2Cl_2) afforded free aziridine IVa (28 mg) as a yellow oil. A solution of the free aziridine IVa in $CHCl_3$ (0.3 ml, 0.2 M) was treated with Dowex 1X8-400 (ion-exchange resin, strongly basic anion, 8% cross-linking, 200-400 mesh, carbonate form) (35 mg, 1.3 w/w equiv) and the reaction mixture was warmed at 35°C for 18 h. Direct purification of the reaction mixture by flash chromatography (silica, 60% ethyl acetate/hexanes) afforded (*E*)-Va (12 mg, 52%) as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.34-7.24 (m, 11H, NH and ArH); 5.53 (s, 1H, C(13)-H); 5.28 (d, J = 5.0 Hz, 1H, C(12)-H); 3.83 (s, 3H, OCH_3); 3.70 (s, 2H, PhCH_2); 3.67 (s, 3H, OCH_3); 3.40-3.30 (m, 1H, C11-H); 2.66 (d, J = 5.2 Hz, 1H, C10-H); 2.36 (d, J = 3.7 Hz, C10-H); 2.08 (s, 3H, CH_3CO). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.2, 169.4, 163.4, 154.3, 132.5, 129.1, 129.0, 128.5, 128.4, 128.3, 127.3, 119.8, 127.3, 119.8, 83.4, 75.5, 52.4, 52.1, 46.2, 41.6, 40.6, 20.4. HR-FABMS, *m/z* 418.1393 ($C_{20}H_{22}N_2O_8$ + H requires: 418.1376).

Methyl (2*Z*,3*R*,4*R*,5*S*)-3-Acetoxy-α-methoxycarbonylamino—4-phenylacetoxy-1-azabicyclo-[3.1.0]hexene-$\Delta^{2\alpha}$-acetate ((*Z*)-Vb). Following the procedure for the preparation of (*E*)-Va, the reaction of IIIa (40 mg, 0.06 mmol), Et_3SiH (101 μl, 0.06 mmol, 10 equiv), Et_3N (1.5 μl, 0.01 mmol, 0.16 equiv), and $Pd(OAc)_2$ (2 mg, catalytic) at 25°C under N_2 afforded free aziridine IVa (29 mg), which was cyclized at 35°C to afford (*Z*)-Va (10 mg, 48%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.31-7.25 (m, 10H, ArH); 6.44 (br s, 1H, NH); 6.07 (d, J = 1. Hz, 1H, C(13)-H); 5.25 (dd, J = 5.2, 1.2 Hz, 1H, C(12)-H); 3.74 (s, 3H, OCH_3); 3.62, (s, 2H, OCH_2Ph); 3.55 (s, 3H, OCH_3); 3.31-3.28 (m, 1H, C11-H); 2.47 (d, J = 6.0 Hz, 1H, C10-H); 2.07-2.06 (m, 4H, C10-H and CH_3CO). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.9, 169.8, 163.3, 154.1, 150.4, 133.1, 129.2, 128.6, 127.3, 120.5, 80.3, 78.5, 52.8, 52.3, 45.0, 40.9, 37.6, 29.7, 20.6.

Methyl (2*E*,3*R*,4*R*,5*S*)-α-Acetamido-3-acetoxy-4-*p*-methoxybenzoxy-1-azabicyclo[3.1.0]-hexane-$\Delta^{2\alpha}$-acetate ((*E*)-Vb). Following the procedure for the preparation of (*E*)-Va, deprotection and cyclization of IIIb afforded (*E*)-Vb (48%): $[\alpha]_D^{20}$ +81.6° (c 0.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.38 (s, NH); 7.21 (d, J = 8.6 Hz, 2H); 6.89 (d, J = 8.6 Hz, 2H); 5.39 (d, J = 1.3 Hz, 1H); 4.43 (ABq, J = 11.4 Hz, Δν = 74.6 Hz, 2H); 4.30 (d, J = 4.5 Hz, 1H); 3.82 (s, 3H); 3.81 (s, 3H); 3.11 (m, 1H); 2.70 (m, 1H); 2.60 (d, J = 3.8 Hz, 1H); 2.11 (s, 3 H); 2.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.5, 168.5, 164.0, 159.7, 149.2, 129.7, 128.8, 120.2, 114.0, 84.9, 79.6, 70.8, 52.1, 55.3, 52.2, 45.8, 42.8, 22.9, 21.0. IR (neat) ν_{max} 3318, 2959, 1740, 1684, 1514, 1435, 1247, 1222, 1031 cm^{-1}. HR-EIMS, *m/z* 404.1556 ($C_{20}H_{24}N_2O_7$ requires 404.1584).

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