Stereoselective Entry to Bicyclic β-Lactams via Free Radical Cyclization of 2-Azetidinone-Tethered Bromohomoallylic Alcohols

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Abstract: Triphenyltin hydride-promoted reaction of β -lactamtethered bromodienes gave six-, seven-, or eight-membered bicyclic ring structures through intramolecular free radical cyclization. The cyclization precursors were synthesized by stereoselective tin-mediated carbonyl bromoallylation of 4-oxoazetidine-2-carbaldehydes in an aqueous environment.

Key words: carbonyl additions, cyclizations, lactams, radical reactions, tin

The stereodivergent synthesis of chiral β-lactams remains a worthwhile goal for synthetic organic chemists. The development of new derivatives of β -lactam antibiotics and inhibitors of β-lactamases, as well as structure-activity relationship studies, this has resulted in the synthesis of a new structural type having the 2-azetidinone ring as a common feature.¹ In contrast to the diastereoselective addition of propenylmetal compounds to chiral aldehydes, which is one of the most important reactions for the construction of a carbon skeleton,² the analogous reaction involving bromoallylmetals has been scarcely investigated,³ despite the synthetic utility of the bromovinyl moiety in bromohomoallylic alcohols.⁴ In view of our interest in the synthesis of β-lactams and other nitrogenated compounds of biological interest,5 efforts were directed towards exploring the metal-mediated bromoallylation of 4-oxoazetidine-2-carbaldehydes/free radical reaction sequence, as a novel stereocontrolled access to bicyclic β -lactams.

Isomerically pure aldehydes **1a**–**f** were obtained following our previously reported procedures.^{5,6} Enantiopure 2azetidinones **1a**–**d** were obtained as single *cis*-enantiomers from imines [(R)-2,3-O-isopropylideneglyceraldehyde], through a Staudinger reaction with the appropriate alkoxyacetyl chloride in the presence of triethylamine, followed by sequential acidic acetonide hydrolysis, and oxidative cleavage.⁵ Racemic compounds (±)-**1d** and (±)-**1e** were obtained as single *cis*-diastereoisomers, following our one-pot method from *N*,*N*-di(*p*-methoxyphenyl)glyoxal diimine.⁶

Recently, we have developed protocols for coupling between 2,3-dibromopropene and 4-oxoazetidine-2-carbaldehydes.⁷ It was found that the Barbier-type bromoallylation reaction of β-lactam aldehydes promoted by tin in the presence of catalytic amounts of different Lewis or Brønsted acids in aqueous media was efficient. For the current work, bismuth(III) chloride was found to be the additive of choice. Under the optimized conditions, the carbonyl bromoallylation of aldehydes 1 gave the corresponding bromohomoallylic alcohols 2 in good yields with high diastereoselectivities (Scheme 1). Additionally, α,β -unsaturated esters were found to be completely unreactive under these conditions, and the chemoselective bromoallylation of 4-oxoazetidine-2-carbaldehydes (+)-1c and (+)-1d bearing an α , β -unsaturated ester moiety was possible. None of the 1,4-addition product was obtained, giving exclusively the alcohols (+)-2c and (+)-2d by stereoselective addition to the aldehyde moiety. Sometimes, bromohomoallylic alcohols anti-2 were obtained as a minor component from the metal-mediated bromoallylation of aldehydes 1. Fortunately, in all cases the diastereomeric alcohols 2 and *anti-2* could be easily separated by gravity flow chromatography.

Since their introduction in 1982,8 vinyl radical cyclizations have proved to be extremely popular in organic synthesis for the synthesis of five- or six-membered rings.⁹ The formation of rings with seven or more atoms results in unfavorable reaction rates because the addition step is often too slow to allow it to compete successfully with other pathways open to the radical intermediate. Although construction of medium-sized rings using free radical methodology is difficult to achieve,¹⁰ we and others were able to prepare medium-sized rings fused to 2-azetidinones.¹¹ In this context, it was planned to investigate this closure strategy on some bromohomoallylic alcohols 2 bearing an extra alkene tether (Scheme 2). The tin-promoted radical reaction of bromodienic alcohol (+)-2a gave the eight-membered ring fused- β -lactam (+)-3 together with the homoallylic alcohol (+)-4. While the free radical cyclization proceeded elegantly in bromodiene (+)-2c to provide the desired non-conventional bicyclic β lactam (+)-5 as single isomer, bromodienes (+)-2b and (+)-2d did not afford the desired bicycles. The 1-vinyl-3hydroxy-6-hexenyl radical (radical numbering) derived from bromide (\pm) -2e afforded the seven-membered ring fused bicycle (\pm) -6 which prevailed over the isomeric product (\pm) -7 containing a six-membered ring. Triphenyltin hydride-promoted cyclization of bromodiene (\pm) -2f af-

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Scheme 1 Stereoselective preparation of bromohomoallylic alcohols 2 in aqueous media. Reagents and conditions: a) Sn, BiCl₃, THF–H₂O, r.t.

forded the expected fused 2-azetidinone (\pm) -8 as a single isomer in fair yield.

The bicyclic structures (by DEPT, HMQC, HMBC, and COSY) and the stereochemistry (by vicinal proton couplings and qualitative homonuclear NOE difference spectra) of fused β -lactams 3 and 5–8 were established by oneand two-dimensional NMR techniques. Taking into account that optically pure bromohomoallylic alcohols 2 could be obtained and cyclized, the stereochemistry for adducts 2 was immediately deduced by comparison with the NOE results of the bicyclic systems. The *cis*-stereochemistry of the four-membered ring is set during the cyclization step to form the 2-azetidinone ring, and it is transferred unaltered during further synthetic steps.

In conclusion, we have shown that a combination of metal-mediated carbonyl-bromoallylation reaction and free radical cyclization constitutes a novel stereocontrolled access to fused bicyclic β -lactams of non-conventional structure. These results open up the possibility of future application to chiral building blocks other than 2-azetidinones.

All commercially available compounds were used without further purification. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker AMX-500, Bruker Avance-300, Varian VRX-300S, or Bruker AC-200. NMR spectra were recorded in CDCl₃ solutions, except where otherwise stated. Chemical shifts are given in ppm relative to TMS (¹H, 0.0 ppm), or CDCl₃ (¹³C, 76.9 ppm). Elemental

M a) Ó PMP **PMF** (±)-2e (±)-6 (37%) (±)-7 (29%) Me a) 0 PMP PMP O (±)-8 (40%) (±)-2f

(+)-2a

PMF

(+)-2c

CO₂Me

Scheme 2 Preparation of bicyclic β-lactams 3–7 via free radical cyclization of bromodienes 1. Reagents and conditions: a) Ph₃SnH, AIBN, C_6H_6 , reflux (*p*-MeOPh = PMP).

Me

OH

Ó

٩H

PMP

(+)-5 (46%)

(+)-4 (17%)

OH

PMP

(+)-3 (57%)

O

MeO₂C

a)

analyses were obtained at the UCM Microanalysis Service (Facultad de Farmacia, UCM, Madrid). Low and high resolution mass spectra were taken on a HP5989A spectrometer using CI modes unless otherwise stated. Electrospray ionization (ESI) was performed on a Bruker ESQUIRE LC at 400 eV. Specific rotation [α]_D is given in deg cm² g⁻¹ at 20 °C, and the concentration (*c*) is expressed in g per 100 mL.

Bromohomoallylic Alcohols; General Procedure

2,3-Dibromopropene (600 mg, 3 mmol) was added to a well stirred suspension of the appropriate aldehyde **1** (1.0 mmol), Sn powder (178 mg, 1.5 mmol), and BiCl₃ (63 mg, 0.2 mmol) in THF–H₂O (1:1, 10 mL) at r.t. After disappearance of the starting material (TLC), sat aq NaHCO₃ (10 mL) was added at 0 °C, and the mixture was allowed to warm to r.t., before being extracted with EtOAc (3×10 mL). The organic extract was washed with brine, dried (MgSO₄), and concentrated under reduced pressure. Chromatography of the residue (hexanes–EtOAc) gave analytically pure compounds **2**.

(3R,4S)-1-Allyl-4-[(R)-3-bromo-1-hydroxybut-3-enyl]-3-methoxyazetidin-2-one [(+)-2a]

Prepared from (+)-**1a** (106 mg, 0.63 mmol); 128 mg (70%) of compound (+)-**2a** was obtained as a colorless oil after purification by flash chromatography (hexanes–ethyl acetate, 1:1).

 $[\alpha]_{\rm D}$ +44.9 (*c* 1.0, CHCl₃).

IR (CHCl₃): 3430, 1741 cm⁻¹.

¹H NMR (300 MHz): $\delta = 2.60$ (br s, 1 H), 2.64 (s, 1 H), 2.67 (d, 1 H, J = 1.0 Hz), 3.63 (s, 3 H), 3.76 (t, 1 H, J = 4.5 Hz), 3.83 (dt, 1 H, J = 6.8, 1.1 Hz), 4.10 (dt, 1 H, J = 5.4, 1.6 Hz), 4.21 (m, 1 H), 4.52 (d, 1 H, J = 5.1 Hz), 5.22 (d, 1 H, J = 1.0 Hz), 5.29 (dq, 1 H, J = 7.6, 1.2 Hz), 5.56 (d, 1 H, J = 1.7 Hz), 5.72 (d, 1 H, J = 1.2 Hz), 5.79 (m, 1 H).

¹³C NMR (75 MHz): δ = 167.4, 132.0, 129.5, 120.0, 118.7, 83.3, 68.4, 59.9, 59.5, 45.7, 44.2.

MS (EI): $m/z = 291 [M(^{81}Br)^+, 98], 289 [M(^{79}Br)^+, 100].$

Anal. Calcd for $C_{11}H_{16}NO_3Br$: C, 45.53; H, 5.56; N, 4.83. Found: C, 45.62; H, 5.54; N, 4.80.

Bromohomoallyl Alcohol (+)-2b

Prepared from (+)-**1b** (145 mg, 0.73 mmol); 143 mg (61%) of the less polar compound (+)-**2b** and 12 mg (5%) of the more polar compound, its *anti*-epimer were obtained after purification by column chromatography (hexanes–EtOAc, 2:1).

(3R,4S)-4-[(R)-3-Bromo-1-hydroxybut-3-enyl]-3-methoxy-1-(3-methylbut-2-enyl)azetidin-2-one [(+)-2b]

Colorless oil; $[\alpha]_D$ +41.8 (*c* 1.0, CHCl₃).

IR (CHCl₃): 3434, 1740 cm⁻¹.

¹H NMR (300 MHz): $\delta = 1.67$ (s, 3 H), 1.74 (s, 3 H), 2.64 (d, 2 H, J = 6.3 Hz), 3.61 (s, 3 H), 3.72 (t, 1 H, J = 4.5 Hz), 3.76 (dd, 1 H, J = 15.4, 7.6 Hz), 4.09 (dd, 1 H, J = 15.4, 6.1 Hz), 4.18 (td, 1 H, J = 6.5, 4.0 Hz), 4.47 (d, 1 H, J = 4.9 Hz), 5.15 (m, 1 H), 5.56 (d, 1 H, J = 1.5 Hz), 5.70 (d, 1 H, J = 1.5 Hz).

 ^{13}C NMR (75 MHz): δ = 167.0, 137.3, 129.6, 119.7, 117.8, 83.2, 68.2, 59.4, 59.3, 45.5, 38.3, 25.5, 17.9.

MS (EI): $m/z = 320 [M(^{81}Br)^+, 98], 318 [M(^{79}Br)^+, 100].$

Anal. Calcd for $C_{13}H_{20}NO_3Br$: C, 49.07; H, 6.34; N, 4.40. Found: C, 49.17; H, 6.38; N, 4.37.

(3*R*,4*S*)-4-[(*S*)-3-Bromo-1-hydroxybut-3-enyl]-3-methoxy-1-(3-methylbut-2-enyl)azetidin-2-one [*anti*-(+)-2b] Colorless oil; $[a]_D$ +61.5 (*c* 1.3, CHCl₃). IR (CHCl₃): 3432, 1742 cm⁻¹.

¹H NMR (300 MHz): $\delta = 1.69$ (s, 3 H), 1.74 (s, 3 H), 2.61 (dd, 1 H, J = 14.4, 5.6 Hz), 2.74 (dd, 1 H, J = 14.4, 8.1 Hz), 3.64 (s, 3 H), 3.65 (dd, 1 H, J = 8.7, 5.0 Hz), 3.71 (dd, 1 H, J = 16.6, 8.3 Hz), 4.04 (dd, 1 H, J = 14.9, 5.9 Hz), 4.19 (dt, 1 H, J = 7.6, 4.9 Hz), 4.55 (d, 1 H, J = 4.9 Hz), 5.14 (m, 1 H), 5.54 (d, 1 H, J = 1.5 Hz), 5.72 (d, 1 H, J = 1.5 Hz).

 ^{13}C NMR (75 MHz): δ = 166.4, 137.8, 129.6, 119.2, 116.9, 83.8, 67.7, 59.2, 58.3, 45.7, 38.1, 25.5, 17.7.

MS (EI): $m/z = 320 [M(^{81}Br)^+, 98], 318 [M(^{79}Br)^+, 100].$

Anal. Calcd for $C_{13}H_{20}NO_3Br$: C, 49.07; H, 6.34; N, 4.40. Found: C, 48.95; H, 6.30; N, 4.38.

3-[2-(3-Bromo-(*R*)-1-hydroxybut-3-enyl)-1-(4-methoxyphenyl)-(2*S*,3*R*)-4-oxoazetidin-3-yloxy]acrylic Acid Methyl Ester [(+)-2c]

From (+)-1c (168 mg, 0.55 mmol); 183 mg (78%) of compound (+)-2d was obtained as a colorless oil after purification by flash chromatography (hexanes–EtOAc, 2:1).

 $[\alpha]_{\rm D}$ +145.7 (*c* 1.0, CHCl₃).

IR (CHCl₃): 3430, 1742, 1715 cm⁻¹.

¹H NMR (300 MHz): δ = 2.36 (br s, 1 H), 2.64 (m, 2 H), 3.71 (s, 3 H), 3.78 (s, 3 H), 4.39 (m, 2 H), 5.18 (d, 1 H, *J* = 4.6 Hz), 5.56 (d, 1 H, *J* = 1.9 Hz), 5.59 (d, 1 H, *J* = 13.2 Hz), 5.69 (d, 1 H, *J* = 1.2 Hz), 6.86 (d, 2 H, *J* = 9.0 Hz), 7.45 (d, 2 H, *J* = 9.0 Hz), 7.59 (d, 1 H, *J* = 12.2 Hz).

¹³C NMR (75 MHz): δ = 167.1, 161.5, 159.7, 157.0, 130.1, 128.7, 120.5, 120.3, 114.1, 100.5, 80.7, 68.9, 60.1, 55.4, 51.3, 45.5.

MS (EI): m/z = 427 [M(⁸¹Br)⁺, 18], 425 [M(⁷⁹Br)⁺, 18], 149 [100].

Anal. Calcd for $C_{18}H_{20}NO_6Br$: C, 50.72; H, 4.73; N, 3.29. Found: C, 50.80; H, 4.80; N, 3.26.

Bromohomoallyl Alcohol (+)-2d

Prepared from (+)-1d (155 mg, 0.73 mmol); 156 mg (64%) of the less polar compound (+)-2d and 14 mg (6%) of the more polar compound, its *anti*-epimer were obtained after purification by column chromatography (hexanes–EtOAc, 2:1).

2-[2-(3-Bromo-(*R*)-1-hydroxybut-3-enyl)-3-methoxy-(2*S*,3*R*)-4-oxoazetidin-1-yl]acrylic Acid Methyl Ester [(+)-2d] Colorless oil; $[\alpha]_D$ +75.1 (*c* 0.9, CHCl₃).

IR (CHCl₃): 3429, 1741, 1648 cm⁻¹.

¹H NMR (300 MHz): δ = 2.53 (m, 3 H), 3.65 (s, 3 H), 3.80 (s, 3 H), 4.22 (m, 1 H), 4.51 (t, 1 H, *J* = 5.0 Hz), 4.64 (d, 1 H, *J* = 5.4 Hz), 5.53 (d, 1 H, *J* = 1.7 Hz), 5.67 (d, 1 H, *J* = 1.2 Hz), 6.05 (s, 1 H), 6.15 (s, 1 H).

¹³C NMR (75 MHz): δ = 166.7, 163.5, 131.6, 129.5, 120.0, 117.8, 83.6, 68.5, 61.9, 59.9, 52.7, 45.6.

MS (EI): $m/z = 358 [M(^{81}Br)^+, 98], 356 [M(^{79}Br)^+, 100].$

Anal. Calcd for $C_{12}H_{16}NO_5Br$: C, 43.13; H, 4.83; N, 4.19. Found: C, 43.20; H, 4.80; N, 4.17.

2-[2-(3-Bromo-(S)-1-hydroxybut-3-enyl)-3-methoxy-(2*S***,3***R***)-4-oxoazetidin-1-yl]acrylic Acid Methyl Ester** [*anti-*(+)-2d] Colorless oil; $[\alpha]_{\rm D}$ +80.6 (*c* 1.1, CHCl₃).

IR (CHCl₃): 3430, 1741, 1647 cm⁻¹.

¹H NMR (300 MHz): δ = 2.68 (m, 3 H), 3.69 (s, 3 H), 3.82 (s, 3 H), 4.24 (m, 1 H), 4.53 (dd, 1 H, *J* = 5.1, 3.7 Hz), 4.71 (d, 1 H, *J* = 5.4 Hz), 5.55 (d, 1 H, *J* = 1.7 Hz), 5.72 (d, 1 H, *J* = 1.2 Hz), 6.11 (s, 1 H), 6.26 (s, 1 H).

¹³C NMR (75 MHz): δ = 166.3, 163.1, 130.7, 129.6, 119.7, 117.6, 84.4, 68.8, 61.7, 59.9, 52.8, 45.7.

MS (ES): $m/z = 358 [M(^{81}Br)^+, 98], 356 [M(^{79}Br)^+, 100].$

Anal. Calcd for $C_{12}H_{16}NO_5Br$: C, 43.13; H, 4.83; N, 4.19. Found: C, 43.22; H, 4.81; N, 4.21.

Bromohomoallyl Alcohol [(±)-2e]

Prepared from (\pm)-**1e** (230 mg, 0.996 mmol); 309 mg (88%) of the less polar compound (\pm)-**2e** and 27 mg (8%) of the more polar compound, its *anti*-epimer were obtained after purification by column chromatography (CH₂Cl₂-EtOAc, 20:1),

(3RS,4SR)-4-[(RS)-3-Bromo-1-hydroxybut-3-enyl]-1-(4-meth-oxyphenyl)-3-vinylazetidin-2-one [(±)-2e]

Colorless solid; mp 119-120 °C (hexanes-EtOAc).

IR (KBr): 3431, 1741 cm⁻¹.

¹H NMR (300 MHz): $\delta = 2.26$ (d, 1 H, J = 3.9 Hz), 2.53 (dd, 1 H, J = 14.5, 8.9 Hz), 2.69 (d, 1 H, J = 14.4 Hz), 3.78 (s, 3 H), 4.00 (dd, 1 H, J = 8.8, 5.6 Hz), 4.21 (m, 2 H), 5.43 (ddd, 1 H, J = 10.0, 1.5, 0.5 Hz), 5.47 (dt, 1 H, J = 17.1, 1.5 Hz), 5.55 (d, 1 H, J = 1.5 Hz), 5.69 (s, 1 H), 5.99 (ddd, 1 H, J = 17.1, 10.0, 8.8 Hz), 6.85 (d, 2 H, J = 9.0 Hz), 7.47 (d, 2 H, J = 9.0 Hz).

 ^{13}C NMR (75 MHz): $\delta = 165.8,\,156.7,\,131.2,\,129.0,\,128.8,\,122.8,\,120.7,\,120.6,\,114.1,\,70.3,\,59.2,\,55.6,\,55.1,\,45.9.$

MS (EI): $m/z = 353 [M(^{81}Br)^+, 22], 351 [M(^{79}Br)^+, 22], 149 [100].$

Anal. Calcd for $C_{16}H_{18}NO_3Br$: C, 54.56; H, 5.15; N, 3.98. Found: C, 54.65; H, 5.11; N, 4.00.

(3RS,4SR)-4-[(SR)-3-Bromo-1-hydroxybut-3-enyl]-1-(4-methoxyphenyl)-3-vinylazetidin-2-one, [anti-(±)-2e] Colorless oil.

IR (CHCl₃): 427, 1739 cm⁻¹.

¹H NMR (300 MHz): $\delta = 2.17$ (d, 1 H, J = 5.7 Hz), 2.68 (m, 2 H), 3.80 (s, 3 H), 4.09 (dd, 1 H, J = 8.5, 5.9 Hz), 4.28 (dd, 1 H, J = 5.9, 2.9 Hz), 4.53 (m, 2 H), 5.38 (dd, 1 H, J = 11.0, 1.0 Hz), 5.45 (dt, 1 H, J = 18.3, 1.3 Hz), 5.56 (d, 1 H, J = 1.7 Hz), 5.70 (d, 1 H, J = 1.7Hz), 6.25 (ddd, 1 H, J = 17.1, 10.2, 8.9 Hz), 6.90 (d, 2 H, J = 9.0Hz), 7.41 (d, 2 H, J = 9.0 Hz).

¹³C NMR (75 MHz): δ = 165.4, 156.6, 130.7, 130.0, 129.4, 121.8, 120.5, 119.3, 114.6, 66.9, 58.7, 55.8, 55.6, 44.9.

MS (EI): $m/z = 353 [M(^{81}Br)^+, 26], 351 [M(^{79}Br)^+, 26], 149 [100].$

Anal. Calcd for $C_{16}H_{18}NO_3Br$: C, 54.56; H, 5.15; N, 3.98. Found: C, 54.46; H, 5.12; N, 3.95.

Bromohomoallyl Alcohol (±)-2f

Prepared from (\pm)-**1f** (150 mg, 0.612 mmol); 153 mg (67%) of the more polar compound (\pm)-**2f** and 18 mg (8%) of the less polar compound, its *anti*-epimer, were obtained after purification by column chromatography (hexanes–EtOAc,5:1).

(3RS,4SR)-4-[(RS)-3-Bromo-1-hydroxybut-3-enyl]-3-isopropenyl-1-(4-methoxyphenyl)azetidin-2-one [(±)-2f] Colorless oil.

IR (CHCl₃): 3434, 1744 cm⁻¹.

¹H NMR (300 MHz): δ = 1.94 (s, 3 H), 2.19 (br s, 1 H), 2.59 (m, 2 H), 3.78 (s, 3 H), 4.00 (d, 1 H, *J* = 5.1 Hz), 4.28 (m, 2 H), 5.21 (d, 1 H, *J* = 0.7 Hz), 5.25 (t, 1 H, *J* = 1.5 Hz), 5.54 (dd, 1 H, *J* = 1.7, 0.5 Hz), 5.67 (m, 1 H), 6.86 (d, 2 H, *J* = 9.0 Hz), 7.46 (d, 2 H, *J* = 9.0 Hz).

¹³C NMR (75 MHz): δ = 165.9, 156.9, 137.4, 131.2, 129.3, 121.1, 120.6, 118.9, 114.2, 69.7, 59.7, 57.7, 55.6, 46.1, 22.9.

MS (EI): $m/z = 368 [M(^{81}Br)^+, 35], 366 [M(^{79}Br)^+, 35], 149 [100].$ Anal. Calcd for $C_{17}H_{20}NO_3Br: C, 55.75; H, 5.50; N, 3.82.$ Found: C, 55.89; H, 5.47; N, 3.80.

(*3RS*, *4SR*)-4-[(*SR*)-3-Bromo-1-hydroxybut-3-enyl]-3-isopropenyl-1-(4-methoxyphenyl)azetidin-2-one [*anti*-(±)-2f] Colorless oil.

IR (CHCl₃): 3430, 1745 cm⁻¹.

¹H NMR (300 MHz): δ = 1.93 (s, 3 H), 2.15 (br s, 1 H), 2.47 (dd, 1 H, *J* = 14.4, 9.8 Hz), 2.71 (d, 1 H, *J* = 14.1 Hz), 3.80 (s, 3 H), 4.10 (d, 1 H, *J* = 5.9 Hz), 4.29 (m, 1 H), 4.40 (dd, 1 H, *J* = 6.2, 3.8 Hz), 5.25 (t, 1 H, *J* = 1.3 Hz), 5.28 (d, 1 H, *J* = 1.0 Hz), 5.53 (dd, 1 H, *J* = 1.7, 0.5 Hz), 5.64 (m, 1 H), 6.89 (d, 2 H, *J* = 9.0 Hz), 7.50 (d, 2 H, *J* = 9.0 Hz).

 ^{13}C NMR (75 MHz): δ = 165.6, 156.6, 136.9, 131.3, 129.7, 120.7, 119.9, 117.7, 114.2, 68.3, 59.6, 57.7, 55.6, 46.0, 23.3.

MS (EI): $m/z = 368 [M(^{81}Br)^+, 27], 366 [M(^{79}Br)^+, 27], 149 [100].$

Anal. Calcd for $C_{17}H_{20}NO_3Br$: C, 55.75; H, 5.50; N, 3.82. Found: C, 55.62; H, 5.47; N, 3.84.

Free Radical Cyclization of Bromohomoallylic Alcohols 2; General Procedure

A solution of the appropriate vinyl bromide 2 (0.40 mmol), triphenyltin hydride (0.60 mmol) and AIBN (cat.) in benzene (35 mL) was heated at reflux until the starting material had completely disappeared (TLC). The reaction mixture was allowed to cool to r.t., the solvent was removed under reduced pressure, and bicycles **3** and **5–8** were obtained after purification by flash chromatography on silica gel (hexanes–EtOAc–Et₃N).

Bicycle (+)-3

Prepared from (+)-2a (51 mg, 0.18 mmol); 8 mg (17%) of the less polar compound (+)-4 and 16 mg (57%) of the more polar compound (+)-3 were obtained after purification by column chromatography (hexanes–EtOAc, 1:1; 1% Et₃N).

(7R,8S,9R)-7-Hydroxy-9-methoxy-5-methylene-1-azabicyclo[6.2.0]decan-10-one [(+)-3]

Colorless oil; $[\alpha]_D$ +113.4 (*c* 0.5, CHCl₃).

IR (CHCl₃): 3434, 1744 cm⁻¹.

¹H NMR (300 MHz): $\delta = 2.03$ (m, 1 H), 2.22 (m, 1 H), 2.35 (m, 1 H), 2.45 (ddd, 1 H, J = 14.3, 5.1, 0.8 Hz), 2.60 (dd, 1 H, J = 14.3, 6.2 Hz), 3.02 (br s, 1 H), 3.13 (ddd, 1 H, J = 14.8, 9.1, 1.7 Hz), 3.63 (s, 3 H), 3.64 (m, 2 H), 3.89 (dd, 1 H, J = 4.8, 1.3 Hz), 4.18 (t, 1 H, J = 5.4 Hz), 4.50 (dd, 1 H, J = 4.8, 0.6 Hz), 4.93 (s, 1 H), 4.95 (s, 1 H).

¹³C NMR (75 MHz): δ = 167.4, 144.8, 117.8, 84.2, 68.1, 60.4, 60.0, 42.1, 40.1, 36.0, 25.3.

MS (EI): m/z = 211 [M⁺, 100].

Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.65; H, 8.14; N, 6.60.

(3*R*,4*S*)-1-Allyl-4-[(*R*)-1-hydroxybut-3-enyl]-3-methoxyazetidin-2-one, [(+)-4]

Colorless oil; $[\alpha]_D$ +52.1 (*c* 0.8, CHCl₃).

IR (CHCl₃): 3428, 1740 cm⁻¹.

¹H NMR (300 MHz): δ = 2.29 (m, 2 H), 2.46 (br s, 1 H), 3.62 (s, 3 H), 3.72 (t, 1 H, *J* = 4.8 Hz), 3.87 (m, 2 H), 4.16 (ddt, 1 H, *J* = 15.7, 5.0, 1.6 Hz), 4.49 (d, 1 H, *J* = 4.9 Hz), 5.20 (m, 4 H), 5.83 (m, 2 H).

 ^{13}C NMR (75 MHz): δ = 167.9, 134.5, 132.4, 118.9, 118.7, 83.7, 70.3, 60.5, 59.9, 44.6, 39.0.

MS (EI): m/z = 211 [M⁺, 100].

Anal. Calcd for $C_{11}H_{17}NO_3{:}$ C, 62.54; H, 8.11; N, 6.63. Found: C, 62.66; H, 8.08; N, 6.61.

(2R,6R,7S)-[6-Hydroxy-8-(4-methoxyphenyl)-4-methylene-9oxo-2-oxa-8-azabicyclo[5.2.0]non-3-yl]acetic Acid Methyl Ester [(+)-5]

Prepared from (+)-2c (57 mg, 0.134 mmol); 21 mg (46%) of compound (+)-5 was obtained as a colorless oil after purification by flash chromatography (hexanes–EtOAc, 3:2; 1% Et₃N).

 $[\alpha]_{\rm D}$ +58.2 (*c* 0.8, CHCl₃).

IR (CHCl₃): 3432, 1744, 1730 cm⁻¹.

¹H NMR (300 MHz): $\delta = 2.07$ (br s, 1 H), 2.42 (dd, 1 H, J = 14.3, 8.8 Hz), 2.60 (dd, 1 H, J = 15.2, 6.3 Hz), 2.84 (dd, 1 H, J = 15.2, 7.2 Hz), 2.98 (dd, 1 H, J = 14.5, 6.4 Hz), 3.70 (s, 3 H), 3.79 (s, 3 H), 4.16 (dd, 1 H, J = 8.6, 3.5 Hz), 4.49 (q, 1 H, J = 8.0 Hz), 4.55 (t, 1 H, J = 3.9 Hz), 4.78 (d, 1 H, J = 3.9 Hz), 5.17 (s, 1 H), 5.20 (s, 1 H), 6.85 (d, 2 H, J = 9.0 Hz), 7.58 (d, 2 H, J = 9.0 Hz).

¹³C NMR (75 MHz): δ = 170.4, 162.5, 156.6, 143.0, 131.2, 119.5, 118.5, 114.2, 80.2, 79.8, 72.0, 62.6, 55.5, 52.0, 40.2, 38.9.

MS (ES): $m/z = 360 [M^+ + 1, 11], 347 [100].$

Anal. Calcd for C₁₈H₂₁NO₆: C, 62.24; H, 6.09; N, 4.03. Found: C, 62.36; H, 6.12; N, 4.02.

Bicycles (±)-6 and (±)-7

Prepared from (\pm)-**2e** (45 mg, 0.13 mmol); 13 mg (37%) of the more polar compound (\pm)-**6** and 10 mg (29%) of the less polar compound (\pm)-**7** were obtained after purification by column chromatography (hexanes–EtOAc, 2:1; 1% Et₃N).

(1R,6R,7S)-6-Hydroxy-8-(4-methoxyphenyl)-4-methylene-8azabicyclo[5.2.0]nonan-9-one [(±)-6] Colorless oil.

IR (CHCl₃): 3433, 1745 cm⁻¹.

¹H NMR (300 MHz): δ = 1.87 (m, 2 H), 2.06 (m, 1 H), 2.32 (m, 2 H), 2.48 (m, 2 H), 3.57 (m, 1 H), 3.80 (s, 3 H), 4.35 (m, 2 H), 4.86 (d, 1 H, *J* = 2.2 Hz), 4.96 (d, 1 H, *J* = 2.2 Hz), 6.88 (d, 2 H, *J* = 9.0 Hz), 7.44 (d, 2 H, *J* = 9.0 Hz).

¹³C NMR (75 MHz): δ = 167.2, 156.3, 144.9, 131.0, 119.3, 116.2, 114.4, 69.6, 59.6, 55.5, 51.6, 41.8, 35.4, 25.5.

MS (EI): m/z = 273 [M⁺, 100].

Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.22; H, 7.04; N, 5.15.

(1RS,2RS,5RS,6SR)-5-Hydroxy-7-(4-methoxyphenyl)-2-methyl-3-methylene-7-azabicyclo[4.2.0]octan-8-one [(±)-7] Colorless oil.

IR (CHCl₃): 3432, 1743 cm⁻¹.

¹H NMR (300 MHz): δ = 1.31 (d, 3 H, *J* = 6.6 Hz), 2.03 (d, 1 H, *J* = 5.4 Hz), 2.38 (ddd, 1 H, *J* = 16.1, 9.0, 1.2 Hz), 2.55 (m, 2 H), 3.10 (dd, 1 H, *J* = 7.4, 6.0 Hz), 3.79 (s, 3 H), 4.07 (t, 1 H, *J* = 5.4 Hz), 4.27 (m, 1 H), 4.94 (s, 1H), 4.97 (s, 1 H), 6.88 (d, 2 H, *J* = 9.0 Hz), 7.53 (d, 2 H, *J* = 9.0 Hz).

 ^{13}C NMR (75 MHz): $\delta = 167.1,\,156.1,\,145.4,\,131.3,\,118.6,\,114.4,\,111.3,\,68.6,\,56.8,\,55.5,\,54.2,\,37.1,\,32.9,\,19.1.$

MS (ES): *m*/*z* = 296 [M⁺ + 23, 100], 273 [M⁺, 12].

Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.42; H, 7.05; N, 5.10.

$(1RS,2RS,6RS,7SR)\mbox{-}6\mbox{-}Hydroxy\mbox{-}8\mbox{-}(4\mbox{-}methoxy\mbox{-}heny\mbox{-})\mbox{-}2\mbox{-}methy\mbox{-}y\mbox{-}2\mbox{-}methy\mbox{-}y\mbox{-}2\mbox{-}methy\mbox{-}y\mbox{-}2\mbox{-}methy\mbox{-}y\mbox{-}2\mbox{-}methy\mbox{-}y\mbox{-}2\mbox{-}methy\mbox{-}y\mbox{-}2\mbox{-}methy\mbox{-}y\mbox{-}2\mbox{-}methy\mbox{-}y\mbox{-}2\mbox{-}methy\mbox{-}y\mbox{-}2\mbox{-}methy\mbox{-}y\mbox{-}2\mbox{-}methy\mbox{-}y\mbox{-}2\mbox{-}methy\mbox{-}y\mbox{-}2\mbox{-}methy\mbox{-}y\mbox{-}2\mbox{-}2\mbox{-}methy\mbox{-}y\mbox{-}2\mbox{-}methy\mbox{-}y\mbox{-}2\mbox{-$

Prepared from (±)-**2f** (57 mg, 0.134 mmol); 15 mg (40%) of compound (±)-**8** was obtained as a colorless oil after purification by flash chromatography (CH₂Cl₂–EtOAc, 20:1, 1% Et₃N).

IR (CHCl₃): 3436, 1741 cm⁻¹.

¹H NMR (300 MHz): δ = 1.22 (d, 3 H, *J* = 6.4 Hz), 1.94 (d, 1 H, *J* = 5.9 Hz), 2.37 (m, 5 H), 3.10 (dd, 1 H, *J* = 7.3, 4.6 Hz), 3.78 (s, 3 H), 4.08 (m, 1 H), 4.25 (dd, 1 H, *J* = 13.7, 5.9 Hz), 4.84 (s, 1 H), 5.58 (s, 1H), 6.86 (d, 2 H, *J* = 9.0 Hz), 7.52 (d, 2 H, *J* = 9.0 Hz).

¹³C NMR (75 MHz): δ = 168.1, 154.4, 133.4, 131.2, 125.5, 120.1, 114.1, 63.9, 60.8, 57.8, 55.5, 53.0, 45.2, 40.1, 8.1.

MS (ES): $m/z = 288 [M^+ + 1, 100], 287 [M^+, 22].$

Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 71.17; H, 7.33; N, 4.90.

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