Synthesis and Acylation of Salts of L-Threonine β-Lactone: A Route to β-Lactone Antibiotics

Yunlong Pu, Fionna M. Martin, and John C. Vederas*

Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2

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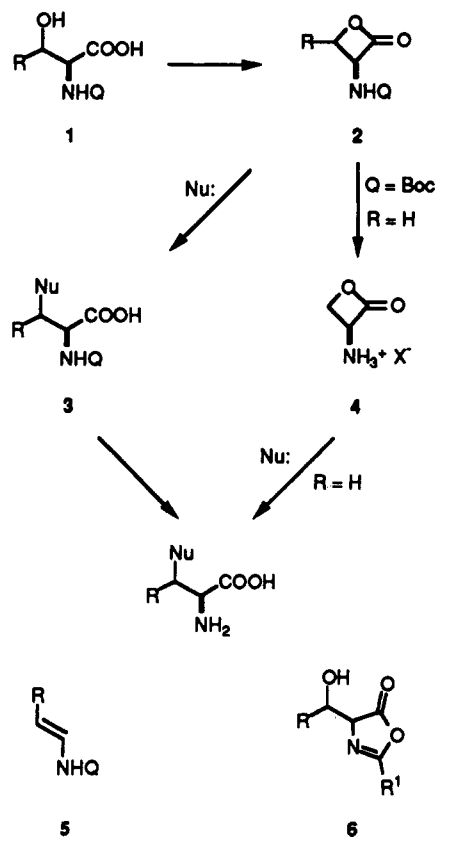
The synthesis and N-acylation of β-lactones derived from L-threonine and L-*allo*-threonine were investigated. Treatment of *N*-[(*o*-nitrophenyl)sulfenyl]-L-threonine (**7a**) and *N*-[(*o*-nitrophenyl)sulfenyl]-L-*allo*-threonine (**7b**) with 4-bromobenzenesulfonyl chloride in pyridine at −43 to −0 °C gives the corresponding β-lactones **8a** and **8b**, respectively, in 45–56% yields. These can be deprotected with thiophenol or *p*-thiocresol in the presence of *p*-toluenesulfonic acid to produce optically pure salts of L-threonine β-lactone (**9a**) and its *allo* isomer **9b** (65–92%). Compound **9a** is readily acylated by reagents such as acid chlorides (e.g., acetyl, benzoyl) and mixed anhydrides to afford *N*-acyl β-substituted β-lactones such as **10** (antibiotic SQ 26,517), **14**, **15**, and **16** in good yield (84–92%). Reaction of β-lactones **8a**, **8b**, and **9a** with HBr in acetic acid results in nucleophilic ring opening by bromide at the β-position to give pure isomers of 2-amino-3-bromobutanoic acid.

The biological importance and synthetic utility of optically pure α-amino acids continue to spur efforts to develop efficient syntheses of this class of compounds.[1] One approach that affords rapid access to unusual α-amino acids (Scheme I) involves cyclization of N-protected serine derivatives **1** (R = H) to corresponding β-lactones **2** followed by ring opening with various carbon or heteroatom nucleophiles to produce **3**.[2] If the protecting group Q is *tert*-butoxycarbonyl (Boc), treatment with nonnucleophilic acids (e.g., *p*-toluenesulfonic acid) provides salts of α-amino-β-propiolactone **4** that react with many nucleophiles to allow direct access to sensitive unprotected α-amino acids.[2d] The serine lactone ring formation relies on hydroxyl group activation under Mitsunobu conditions at low temperature (Ph_3P, dialkyl azodicarboxylate, −78 °C).[2b] Unfortunately, such cyclization conditions cannot be generally applied to other β-hydroxy amino acid derivatives, which bear a β alkyl substituent, because rapid decarboxylative elimination to **5** intervenes.[3] Although this problem can be overcome by carboxyl group activation, previous work has shown that reasonable yields of **2** (R = alkyl) are usually achieved only if the protecting group is incapable of forming azlactones **6**.[3] The sulfonamide group used in earlier studies[3] (Q = SO_2Ph) must be removed under harsh hydrolytic or reductive conditions[4,5] that are incompatible with the β-lactone functionality as well as with many β-substituents in **3**.

An isolated report in which L-threonine derivative **7c** bearing an (*o*-nitrophenyl)sulfenyl group was inadvertently cyclized to β-lactone **8a** in 23% yield[6] prompted us to investigate this protecting group (Scheme II). In the present study we describe (1) the cyclizations of *N*-[(*o*-nitrophenyl)sulfenyl]-L-threonine (**7a**) and its diastereomer **7b** to the corresponding β-lactones **8a** and **8b**; (2) the deprotection of these products to form stable β-lactone salts **9a** and **9b**; and (3) the N-acylation of these salts with various reagents. A number of such N-acylated α-amino β-lactones are microbial metabolites with antibiotic activity.[7] Examples include *N*-acetyl-L-threonine β-lactone (SQ 26,517) (**10**)[7a,b] and obafluorin (**11**).[7c,d,g] The present

Scheme I



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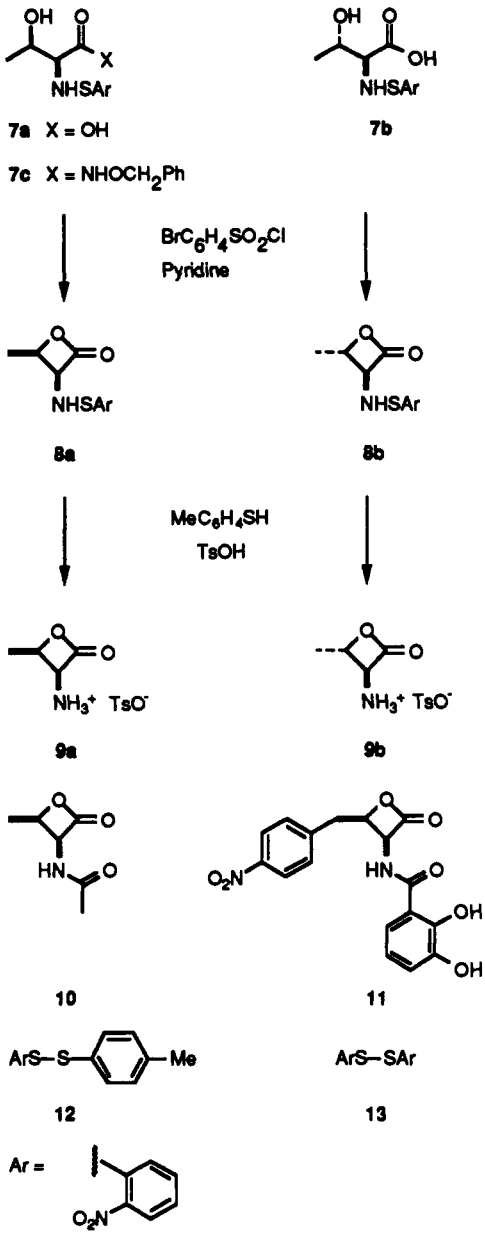
Scheme II

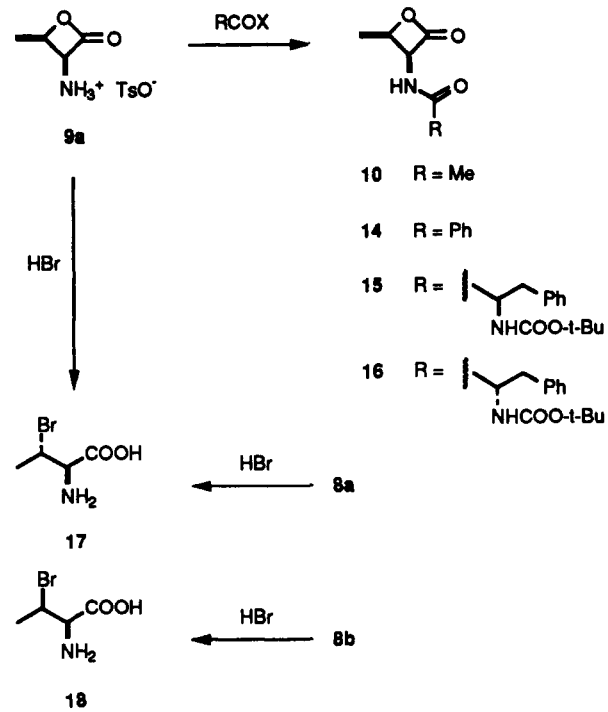


approach provides efficient access to this class compounds.

Results and Discussion

Initial investigations on cyclization of optically pure **7a** and **7b** to the corresponding β-lactones **8a** and **8b** indicated that the best conditions (45–56% yield) are similar to those employed earlier for the *N*-phenylsulfonyl analogues,[3] namely, carboxyl group activation at −43 to −0 °C by 4-bromobenzenesulfonyl chloride in pyridine. No epimerization could be detected by NMR analysis (≥98% one isomer). Change of the reaction conditions (e.g., base, solvent composition) or the activating reagent (e.g., use of other para-substituted benzenesulfonyl chlorides) drastically reduces the yield of β-lactone. The (*o*-nitrophenyl)sulfenyl protecting group can be removed from **8a** and **8b** by aromatic thiols such as thiophenol or *p*-thiocresol in the presence of anhydrous *p*-toluenesulfonic acid under carefully controlled conditions to afford the tosylate salts of the previously unknown parent oxetanones **9a** and **9b** (65–92% yield), respectively. Isolation of the mixed disulfide **12** from the *p*-thiocresol reaction supports the previously proposed deprotection mechanism[8] involving nucleophilic attack by the aromatic thiol group on the sulfenyl sulfur atom. However, the overall process may be considerably more complicated because reagent concentration appears to be a critical factor for the success of this reaction. Modest dilution of the mixture hinders the transformation and leads to recovery of starting material. The symmetrical disulfide **13** is also produced and may play an important role in the completion of the deprotection.[8] The β-substituted salts **9a** and **9b** are much more stable under acidic or neutral aqueous conditions than the corresponding unsubstituted β-lactone salt **4** derived from serine,[2d] but dilute aqueous base destroys these compounds instantly.

Scheme III



Since a number of N-acylated β-substituted α-amino β-lactones are naturally occurring antibiotics,[7] attachment of acyl groups to the nitrogen of **9a** was investigated. Treatment of **9a** with acetyl chloride and pyridine produces the antibiotic SQ 26,517 (**10**)[7a,b] in 84% yield without detectable epimerization (Scheme III). The unoptimized overall yield of 28% over four steps from L-threonine compares favorably to the previously reported[7b] overall yield of 1.6% for a five-step synthesis of racemic SQ 26,517 from DL-*allo*-threonine. Direct cyclization of *N*-acetylthreonine to **10** with dicyclohexylcarbodiimide has been reported to proceed in ca. 0.8% yield (product not isolated).[7b] Benzoylation of **9a** with benzoyl chloride occurs analogously to give the corresponding *N*-benzoyl derivative **14** in 85% yield. Interestingly, N-protected α-amino acids, and thus presumably peptides, can be attached to β-lactone salt **9a** without epimerization. Coupling of the *N*-*tert*-butoxycarbonyl (Boc) derivative of D-phenylalanine via the mixed anhydride with ethyl chloroformate to **9a** affords a 92% yield of **15**. Boc-L-phenylalanine reacts similarly with **9a** to give the other pure diastereomer **16** (92%). In such reactions it appears to be advantageous to avoid prolonged exposure of the lactone salt to base unless acylating agent is present in order to avoid complications due to lactone decomposition and/or polymerization.

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Preliminary experiments suggest that attack of nucleophiles at the β-position of the threonine and *allo*-threonine β-lactones is often disfavored, in contrast to the facile ring openings at the methylene of the serine-derived β-lactones (e.g., **2** (R = H), **4**)[2] and in accord with observations on *N*-(phenylsulfonyl)threonine β-lactone.[3] For example, attempts to open the *N*-benzoylthreonine β-lactone (**14**) with pyrazole, acetate, or copper-catalyzed Grignard reagents (e.g., EtMgCl with CuBr·SMe_2) fail to produce significant amounts of β-substituted products. However, treatment of *N*-(*o*-nitrophenyl)sulfenyl protected β-lactones **8a** or **8b** with concentrated HBr in acetic acid cleaves the ring with inversion of configuration at C-3 and concomitant removal of the protecting group to give the optically pure 2-amino-3-bromobutanoic acids **17**[9] (68%) and **18** (69%), respectively. The stereochemical assignment relies upon comparison of chemical shifts and coupling constants for the C-2 and C-3 hydrogens for a series of *allo*-threonine and threonine derivatives.[3,10] Similar conditions also transform the lactone salt **9a** to **17** in 92% yield. The *N*-benzoyl β-lactone **14** is converted in high yield (94%) to the corresponding β-bromo compound **19** by anhydrous magnesium bromide, but this product is unstable at room temperature and appears to lose bromine through elimination, as shown by the appearance of signals at 5.45 (q) and 1.42 (d) in the ^{1}H NMR spectrum.

Although the β-substituted α-amino β-lactones presently appear to be more limited for synthesis of α-amino acids than the corresponding unsubstituted derivatives **2** (R = H) and **4** derived from serine, the present approach clearly promises to provide ready access to a large number of natural β-lactone antibiotics and their analogues. Further investigations on the synthesis and biological activity of such compounds (e.g., obafluorin (**11**)) are in progress.

Experimental Section

General procedures and instrumentation have been described previously.[2a-d]

***N*-[(*o*-Nitrophenyl)sulfenyl]-L-threonine (7a).** Conversion of L-threonine by the literature procedure[6] afforded **7a** in 79% yield with the following properties: mp 141–144 °C (lit.[6] mp 145–148 °C); IR (KBr) 2900–3000 (br), 1741, 1330, 1285, 737 cm^{-1}; ^{1}H NMR (CD_3OD, 360 MHz) δ 8.25 (m, 2 H, Ar H), 7.68 (m, 1 H, Ar H), 7.30 (m, 1 H, Ar H), 4.20 (m, 1 H, MeC*H*OH), 3.38 (d, 1 H, *J* = 4 Hz, C*H*NH), 1.40 (d, 3 H, *J* = 6 Hz, CH_3); exact mass 272.0468 (272.0467 calcd for $C_{10}H_{12}N_2O_5S$). Anal. Calcd for $C_{10}H_{12}N_2O_5S$: C, 44.11; H, 4.44; N, 10.29; S, 11.77. Found: C, 44.12; H, 4.45; N, 9.99; S, 11.96.

***N*-[(*o*-Nitrophenyl)sulfenyl]-L-*allo*-threonine (7b).** Conversion of L-*allo*-threonine by the procedure[6] used to generate **7a** gave **7b** in 51–76% yield: mp 139–141 °C; IR (KBr) 3300, 1714, 1333, 739 cm^{-1}; ^{1}H NMR (CD_3OD, 200 MHz) δ 8.16 (m, 2 H, Ar H), 7.72 (m, 1 H, Ar H), 7.31 (m, 1 H, Ar H), 4.18 (m, 1 H, CH_3CHOH), 3.42 (d, 1 H, *J* = 4 Hz, C*H*NH), 1.30 (d, 3 H, *J* = 7.6 Hz, CH_3); exact mass 272.0464 (272.0467 calcd for $C_{10}H_{12}N_2O_5S$). Anal. Calcd for $C_{10}H_{12}N_2O_5S$; C, 44.11; H, 4.44; N, 10.29; S, 11.77. Found: C, 43.85; H, 4.35; N, 9.99; S, 11.46.

(3*S*,4*R*)-3-[[(*o*-Nitrophenyl)sulfenyl]amino]-4-methyl-2-oxetanone (8a). A solution of 4-bromobenzenesulfonyl chloride (2.00 g, 8.0 mmol) in dry pyridine (14 mL) at 0 °C was added dropwise over 10 min to a solution of **7a** (1.00 g, 3.9 mmol) in pyridine (14 mL) at −43 °C. After 1 h at −43 °C the mixture was warmed to 0 °C for 3 h. Ice water (50 mL) was added and the solution was acidified to pH 2. The mixture was extracted with EtOAc (5 × 50 mL), and the combined extracts were dried (Na_2SO_4) and concentrated. Purification by flash chromatography (hexane/EtOAc, 6/4) gave 550. mg (56%) of **8a**: mp 123–127 °C (lit.[6] mp 134–135 °C); IR ($CHCl_3$ cast) 1816, 1512, 1337, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.34 (m, 1 H, Ar H), 8.10 (m, 1 H, Ar H), 7.80 (m, 1 H, Ar H), 7.38 (m, 1 H, Ar H), 4.92 (quint, 1 H, *J* = 6 Hz, CH_3CH), 4.75 (dd, 1 H, *J* = 8, 6 Hz, C*H*NH), 3.52 (d, 1 H, *J* = 8 Hz, N*H*), 1.6 (d, 3 H, *J* = 6 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 169.5 (s), 134.5 (d), 127.0 (d), 126.3 (d), 125.9 (d), 125.4 (d), 123.9 (d), 75.7 (d), 70.8 (d), 15.2 (q); exact mass 254.0358 (254.0361 calcd for $C_{10}H_{10}N_2O_4S$). Anal. Calcd for $C_{10}H_{10}N_2O_4S$: C, 47.24; H, 3.96; N, 11.02; S, 12.61. Found: C, 46.97; H, 3.82; N, 10.77; S, 12.56.

(3*S*,4*S*)-3-[[(*o*-Nitrophenyl)sulfenyl]amino]-4-methyl-2-oxetanone (8b). The procedure used to convert **7a** to **8a** was employed to transform **7b** (200 mg, 0.73 mmol) to **8b** in 45% yield: mp 107–110 °C; IR (KBr) 3300 (br), 1800, 1512, 1338, 1138, 736 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.30 (m, 1 H, Ar H), 8.07 (m, 1 H, Ar H), 7.74 (1 H, m, Ar H), 7.34 (m, 1 H, Ar H), 4.70 (m, 1 H, $CHCH_3$), 4.41 (dd, 1 H, *J* = 7, 4 Hz, C*H*NH), 3.72 (d, 1 H, *J* = 7 Hz, N*H*), 1.61 (d, 3 H, *J* = 7 Hz, CH_3); exact mass 254.0357 (254.0361 calcd for $C_{10}H_{10}N_2O_4S$). Anal. Calcd for $C_{10}H_{10}N_2O_4S$: C, 47.24; H, 3.96; N, 11.02; S, 12.61. Found: C, 47.43; H, 3.89; N, 10.88; S, 12.60.

Deprotection of 8a to (3*S*,4*R*)-3-Amino-4-methyl-2-oxetanone *p*-Toluenesulfonate Salt (9a), 4-Methylphenyl 2-Nitrophenyl Disulfide (12), and 2-Nitrophenyl Disulfide (13). To a stirred suspension of **8a** (100 mg, 0.40 mmol) in 1 mL of CH_2Cl_2 (concentration important) under an argon atmosphere was added anhydrous *p*-toluenesulfonic acid (74 mg, 0.43 mmol) followed by *p*-thiocresol (100 mg, 0.80 mmol). The mixture was kept 5 h at 20 °C, the solvent was evaporated, and the resulting yellow solid was triturated with diethyl ether until it was colorless. Recrystallization from EtOAc/hexane yielded **9a** (81 mg, 75%): mp ca. 120 °C dec; IR (KBr) 3100 (br), 1841, 1204 cm^{-1}; ^{1}H NMR (DMF-d_7, 360 MHz) δ 7.59 (d, 2 H, *J* = 7 Hz, Ar H), 7.08 (d, 2 H, *J* = 7 Hz, Ar H), 5.45 (d, 1 H, *J* = 7 Hz, C*H*NH_3), 5.10 (quint, 1 H, *J* = 7 Hz, CH_3CH), 2.25 (s, 3 H, ArCH_3), 1.65 (d, 3 H, *J* = 7 Hz, CH_3); FAB MS (glycerol) 274 (MH^+). Anal. Calcd for $C_{11}H_{15}NO_5S$: C, 48.35; H, 5.49; N, 5.12; S, 11.72. Found: C, 48.17; H, 5.36; N, 4.90; S, 11.34.

Thiophenol could be used in the above procedure in place of *p*-thiocresol to afford variable yields (65–92%) of **9a** with identical properties.

Evaporation of the combined ether layers from the trituration procedure and purification of the residue by repeated preparative TLC (hexane/EtOAc, 9/1) gave unsymmetrical disulfide **12** (13.9 mg, 13% based on **8a**) and symmetrical disulfide **13** (2.7 mg, 2%). For **12**: IR ($CHCl_3$ cast) 1590, 1565, 1489, 1337, 1305, 799 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.20 (m, 2 H, Ar H), 7.60 (m, 1 H, Ar H), 7.35 (m, 3 H, Ar H), 7.08 (d, 2 H, *J* = 8 Hz, Ar H), 2.25 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 137.9 (d), 137.3 (s), 134.1 (d), 130.0 (d), 129.7 (d), 128.5 (s), 128.3 (s), 127.0 (d), 126.3 (d), 126.0 (s), 21.0 (q); exact mass 277.0230 (277.0230 calcd for $C_{13}H_{11}NO_2S_2$).

For **13**: IR ($CHCl_3$ cast) 1587, 1566, 1505, 1333, 777 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.33 (dd, 2 H, *J* = 8.2, 1.5 Hz), 7.79 (dd, 2 H, *J* = 8.2, 1.4 Hz), 7.55 (dd, 1 H, *J* = 8.2, 1.4 Hz), 7.50 (dd, 1 H, *J* = 8.2, 1.5 Hz), 7.36 (dd, 1 H, *J* = 8.3, 1.4 Hz), 7.33 (dd, 1 H, *J* = 8.3, 1.4 Hz); exact mass 307.9926 (307.9926 calcd for $C_{12}H_8N_2O_4S_2$).

(3*S*,4*S*)-3-Amino-4-methyl-2-oxetanone *p*-Toluenesulfonate Salt (9b). The procedure described to form **9a** was used to transform **8b** to **9b** in 76% yield: mp ca. 120 °C dec; IR (KBr) 3000–2800, 1831, 1219, 1172 cm^{-1}; ^{1}H NMR (d_7-DMF, 200 MHz) δ 7.65 (d, 2 H, *J* = 8 Hz, Ar H), 7.13 (d, 2 H, *J* = 8 Hz, Ar H), 5.10 (m, 2 H, C*H*NH_3, CH_3CH), 2.30 (s, 3 H, ArCH_3), 1.65 (d, 3 H, *J* = 8 Hz, CH_3); FAB MS (glycerol) 274 (MH^+).

(3*S*,4*R*)-3-(Acetylamino)-4-methyl-2-oxetanone (10). A mixture of **9a** (54.0 mg, 0.200 mmol) in CH_2Cl_2 (5 mL) at −10 °C was treated with pyridine (0.040 mL, 0.50 mmol) and acetyl chloride (19.0 mg, 0.24 mmol). The mixture was kept at −10 °C for 1 h, allowed to warm to 0 °C over 2 h, and then kept at 20 °C for 7 h. The solvent was removed in vacuo to give an oily residue that was then partitioned between EtOAc and aqueous $KHSO_4$. The organic layer was dried over Na_2SO_4 and concentrated to a liquid that crystallized upon standing to pure **10** (24 mg, 84%): mp 94–96 °C (lit.[7b] mp 105.5–107 °C); IR ($CHCl_3$ cast), 3280 (br), 1839, 1817, 1743, 1664, 1541 cm^{-1}; ^{1}H NMR ($CDCl_3$,

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200 MHz) δ 6.51 (br, 1 H, NH), 5.63 (dd, 1 H, J = 8, 6 Hz, CHNH), 4.90 (dq, 1 H, J = 6, 8 Hz, CH_3CH), 2.09 (s, 3 H, CH_3CO), 1.44 (d, 3 H, J = 6 Hz, CH_3CH); FAB MS 144 (MH^+).

(3S,4R)-3-(Benzoylamino)-4-methyl-2-oxetanone (14). A suspension of **9a** (110 mg, 0.39 mmol) in 3 mL of CH_2Cl_2 at 0 °C under argon was treated with benzoyl chloride (0.07 mL, 0.60 mmol) followed by pyridine (0.06 mL, 0.74 mmol). The solution was stirred at 0 °C for 1 h and then warmed to 20 °C overnight. EtOAc was added and the solution was washed with water (3 × 10 mL). The organic extract was dried (Na_2SO_4) and evaporated. The resulting residue was triturated with diethyl ether to yield solid **14** (68 mg, 85%): mp 157–159 °C; IR (KBr) 3261, 1839, 1808, 1641, 1596, 1289, 720, 680 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.82 (m, 2 H, Ar H), 7.58 (m, 3 H, Ar H); 5.44 (dd, 1 H, J = 6, 8 Hz, CHNH), 5.00 (quint, 1 H, J = 6 Hz, CH_3CH), 1.45 (d, 3 H, J = 6 Hz, CH_3); MS (CI, NH_3) 223 (M + NH_4^+, 8.7), 206 (M + H^+, 100).

(3S,4R)-3-[[(N-(tert-Butoxycarbonyl)-D-phenylalaninyl]amino]-4-methyl-2-oxetanone (15). A solution of N-(tert-butoxycarbonyl)-D-phenylalanine (26.5 mg, 0.10 mmol) in CH_2Cl_2 (3.0 mL) at −5 °C was treated with triethylamine (10 mg, 0.10 mmol) and ethyl chloroformate (11 mg, 0.10 mmol). The solution was stirred for 20 min and **9a** (27.3 mg, 0.10 mmol) and pyridine (0.02 mL, 0.20 mmol) were added. After 30 min at −5 °C, the solution was allowed to warm to 20 °C overnight. The solvent was removed and the residue was triturated with EtOAc (3 × 5 mL). The combined organic extracts were washed with water, dried (Na_2SO_4), and concentrated to afford a solid. This was triturated with hexane and 10:1 hexane/ether (ca. 2 mL) to afford pure **15** (32.0 mg, 92%): mp 156–157 °C; IR ($CHCl_3$ cast), 3328, 2979, 1825, 1686, 1665 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.24 (m, 5 H, Ar H), 7.01 (d, 1 H, J = 8 Hz, NH), 5.57 (dd, 1 H, J = 8, 6 Hz, CHNH), 4.92 (d, 1 H, J = 8 Hz, NH), 4.80 (quint, 1 H, J = 6 Hz, CH_3CH), 4.38 (dd, 1 H, J = 8, 8 Hz, CHNHBoc), 3.06 (m, 2 H, $PhCH_2CH$), 1.40 (s, 9 H, $NHCOOC(CH_3)_3$), 1.22 (d, 3 H, J = 6 Hz, CH_3CH); FAB MS m/z 349 (MH^+). Anal. Calcd for $C_{18}H_{24}N_2O_5$: C, 62.05; H, 6.94; N, 8.04. Found: C, 62.13; H, 6.72; N, 8.06.

(3S,4R)-3-[[N-(tert-Butoxycarbonyl)-L-phenylalaninyl]amino]-4-methyl-2-oxetanone (16). The procedure used to prepare **15** was employed to condense N-(tert-butoxycarbonyl)-L-phenylalanine with **9a** to afford a 92% yield of **16**: mp 144–145 °C; IR ($CHCl_3$ cast), 3334, 1827, 1677 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.25 (m, 6 H, Ar H and NH), 5.52 (dd, 1 H, J = 8, 6 Hz, CHNH), 5.11 (d, 1 H, J = 8 Hz, NH), 4.85 (quint, 1 H, J = 6 Hz, CH_3CH), 4.39 (dd, 1 H, J = 8, 6 Hz, CHNHBoc), 3.07 (m, 2 H, $PhCH_2CH$), 1.40 (s, 9 H, $NHCOOC(CH_3)_3$), 1.33 (d, 3 H, J = 6 Hz, CH_3CH); FAB MS m/z 349 (MH^+). Anal. Calcd for $C_{18}H_{24}N_2O_5$: C, 62.05; H, 6.94; N, 8.04. Found: C, 61.73; H, 6.74; N, 7.92.

(2R,3S)-2-Amino-3-bromobutanoic Acid (17) from 8a. A 30% solution of HBr in acetic acid (0.11 mL, 1.70 mmol) was added to **8a** (86 mg, 0.34 mmol), and the mixture was stirred at 20 °C for 15 min. The acetic acid was evaporated and EtOAc (25 mL) was added. This solution was extracted with water (3 × 20 mL) and concentrated to yield solid **17** (42 mg, 68%): mp 179–183 °C dec (lit.[9] mp 198 °C); IR (KBr) 3067 (br), 1733, 1482, 1201 cm^{-1}; ^1H NMR (D_2O, 200 MHz) δ 4.60 (dq, 1 H, J = 8, 4 Hz, CH_3CH), 4.31 (d, 1 H, J = 4 Hz, $CHNH_3$), 1.72 (d, 3 H, J = 8 Hz, CH_3); FAB (glycerol) 181.96, 183.97 ($MH^+(^{79}Br)(^{81}Br)$).

Hydrobromide Salt of (2R,3S)-2-Amino-3-bromobutanoic Acid (17) from 9a. A 30% solution of HBr in acetic acid (0.13 mL, 1.90 mmol) was added to **9a** (100 mg, 0.37 mmol), and the mixture was stirred at 20 °C for 15 min. The solvent was evaporated to yield a solid, which after trituration with diethyl ether yielded **17** as its bromide salt (90 mg, 92%): mp 180–195 °C dec (lit.[9] mp 198 °C); IR (KBr), 3016–2800 (br), 1734, 1482, 1200; ^1H NMR (DMF-d_7, 360 MHz) δ 9.20 (br s, 1 H, CO_2H), 5.05 (dq, 1 H, J = 6, 5 Hz, CH_3CH), 4.75 (d, 1 H, J = 6 Hz, $CHNH_3$), 2.00 (d, 3 H, J = 6 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 90.5 MHz) δ 169.1, 60.2, 48.3, 24.4; FAB MS (HCOOH/glycerol) 181.98, 183.99 ($MH^+(^{79}Br)(^{81}Br)$).

(2R,3R)-2-Amino-3-bromobutanoic Acid (18). The procedure described above for preparation of **17** from **8a** was used to convert **8b** to **18** in 69% yield except that an 18-h reaction time was required: mp 165 °C dec; IR (CH_3CN cast) 3000–2800 (br), 1737, 1488, 1211 cm^{-1}; ^1H NMR (D_2O, 200 MHz) δ 4.75 (m, 1 H, CH_3CH), 4.20 (d, 1 H, J = 4 Hz, $CHNH_3$), 1.75 (d, 3 H, J = 7 Hz, CH_3); FAB MS 181.96, 183.96 ($MH^+(^{79}Br)(^{81}Br)$).

(2R,3S)-3-Bromo-2-(benzoylamino)butanoic Acid (19). A solution of **14** (65 mg, 0.32 mmol) in freshly distilled THF (5.0 mL) was added dropwise at 20 °C to a suspension of anhydrous $MgBr_2 \cdot OEt_2$ (1.30 mmol) (prepared by addition of freshly distilled 1,2-dibromoethane (0.12 mL, 1.3 mmol) to Mg metal (32 mg, 1.30 mmol) in diethyl ether (5.0 mL)). After 10 min, the mixture was cooled to 4 °C and acidified with 1 M H_3PO_4 (6 mL). The phases were separated and the aqueous phase was extracted with ether (3 × 10 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated to yield a colorless oil (**19**) (86 mg, 94%). This material could be purified by preparative TLC (formic acid/methanol/$CHCl_3$, 1:9:90) but was unstable and decomposed rapidly at room temperature: ^1H NMR ($CDCl_3$, 200 MHz) δ 8.80 (br s, 1 H, CO_2H), 7.85 (m, 2 H, Ar H), 7.52 (m, 3 H, Ar H), 7.00 (d, 1 H, J = 8 Hz, NH), 5.08 (dd, 1 H, J = 8, 4 Hz, CHNH), 4.55 (quint, 1 H, J = 4 Hz, CH_3CH), 1.95 (d, 3 H, J = 8 Hz, CH_3).

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The Synthesis of 1*H*-, 3*H*-, and 5*H*-2-Benzazepine Derivatives in the Reaction of Bicyclic Aromatic Nitro Compounds with Dimethyl Phosphite and Amines in the Basic Conditions[1]

Witold Danikiewicz and Mieczysław Mąkosza*

Institute of Organic Chemistry, Polish Academy of Sciences, ul. Kasprzaka 44/52, PL-01-224 Warszawa, Poland

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1- and 2-nitronaphthalenes and 5-, 6-, and 8-nitroquinolines react with dimethyl phosphite and various primary and secondary amines in the presence of NaOMe in MeOH to give 1*H*-, 3*H*, and 5*H*-2-benzazepine or pyridazepine derivatives. Some structural features of these compounds deduced from the NMR spectra and molecular mechanics calculations are discussed.

In our preliminary communication we have reported that 1-nitronaphthalene (**1a**) reacts with dimethyl phosphite in the presence of NaOMe in MeOH yielding three main products (**2**, **3**, and **4**) in a ratio depending on the reaction

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