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Malic Acid: A Convenient Precursor for the Synthesis of Peptide Secondary Structure Mimetics

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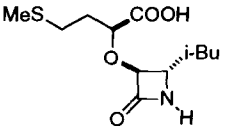
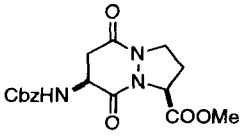
Abstract: Syntheses of optically active ether-linked β-lactams and aza-proline analogues via 4-bromo-2-hydroxybutanoic acid esters derived from (S)- or (R)-malic acid are described. From these intermediates peptide secondary structure mimetics can be synthesized.

As a part of our continuing efforts in the synthesis of peptide secondary structure mimetics,[1] we desired the β-lactam **1**, a key intermediate in our reverse turn synthesis[1b] and β-turn mimetic template **2**. While there are no published synthetic methods available for the preparation of these compounds,[2] we envisioned that optically active 4-bromo-2-hydroxybutanoic acid derived from malic acid could be a suitable precursor.



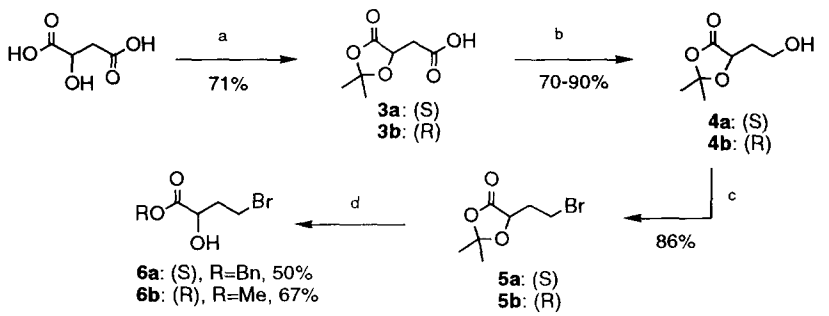
1



2

To this end, protection[3] and reduction of (S)- or (R)-malic acid afforded the hydroxy acetonides **4a** and **4b** respectively. Reaction of hydroxy acetonide **4** with Ph_3P/CBr_4, followed by transesterification smoothly produced the corresponding 4-bromo-2-hydroxybutanoate **6a** or **6b**[4](Scheme 1).

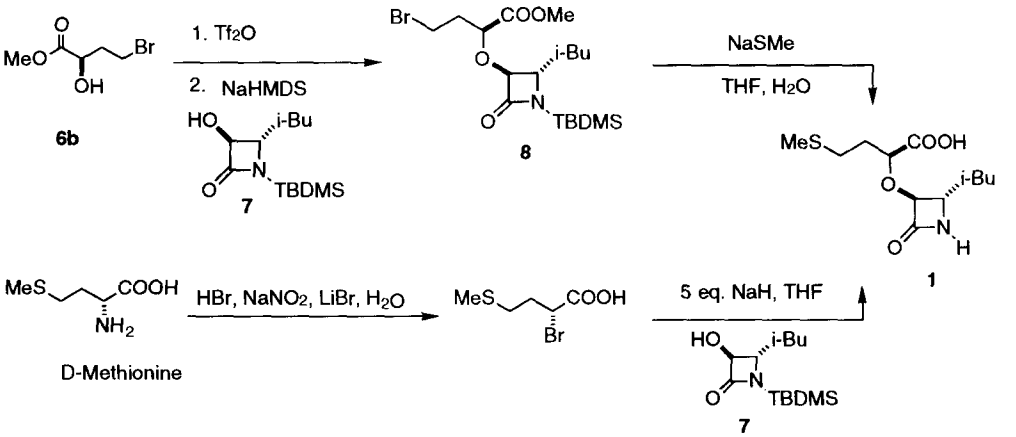
Scheme 1



Conditions: a. 2,2-dimethoxypropane, cat. p-TsOH, acetone b. i) BH_3, THF, 0 oC ii) MeOH
c. PPh_3, CBr_4, THF d. ROH, p-TsOH

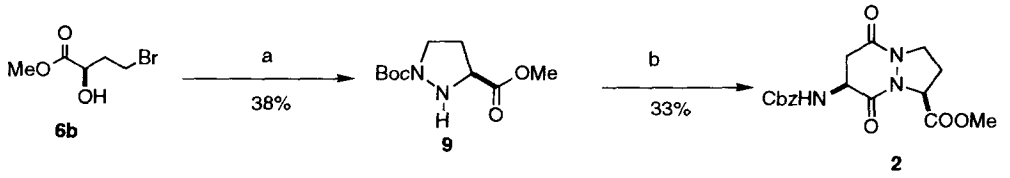
Conversion of **6b** to its triflyloxy ester[5] by reaction with triflic anhydride followed by alkoxy β-lactam **7**[6] provided ether linked β-lactam **8** in moderate yield (30%). Reaction of **8** with sodium thiomethoxide gave the desired product **1** in 38% yield (Scheme 2)[7]. The stereochemistry of **1** was determined by unequivocal synthesis from D-methionine (second reaction in Scheme 2) and NMR. The enantiomeric benzyl ester **6a** was also converted to the β-lactam **1** (with inverted stereochemistry) by the same reaction sequence.

Scheme 2



In the case of mimetic **2**, reaction of **6b** with trifluoromethanesulfonic anhydride and *t*-butylcarbazate, followed by base-mediated cyclization gave aza-proline[8] **9** with inversion of stereochemistry in acceptable yield.[9] Finally, the acylation of **9** with Cbz-Asp(O-*t*-Bu)-OH in the presence of HATU[10], subsequent deprotection of the *t*-Boc group and cyclization provided the desired bicyclic compound **2** in 35 % chemical yield[11] over the two steps (Scheme 3).

Scheme 3



Conditions: a. i) Tf_2O, 2,6-lutidine ii) $BocNHNH_2$ iii) NaHMDS, THF. b. i) Cbz-Asp(O-*t*-Bu)-OH, HATU, DIEA ii) TFA iii) toluene, heat

In summary, we have demonstrated an efficient synthetic route to optically pure 4-bromo-2-hydroxybutanoic acid esters from L- or D-malic acid and their application toward the synthesis of peptide secondary structure mimetic templates.

Acknowledgment: The authors thank Dr. Michael Kahn for encouragement and Dr. Tomas Vaisar for obtaining the mass spectra. We are grateful to Richard Shen and Brian Carroll for the HPLC analysis and the preparation of **7** respectively.

References and Notes:

1. a) Gardner, B.; Nakanishi, H.; Kahn, M. *Tetrahedron* **1993**, *49*, 3433. (b) Kahn, M. *Synlett.* **1993**, 821. (c) Chen, S.; Chrusciel, R. A.; Nakanishi, H.; Raktabutr, A.; Johnson, M. E.; Sato, A.; Weiner, D.; Hoxie, J.; Saragovi, H. U.; Greene, M. I.; Kahn, M. *Proc. Natl. Acad. Sci. USA*, **1992**, *89*, 5872.
2. Lombart, H.-G.; Lubell, W. *J. Org. Chem.* **1994**, *59*, 6147 and references cited therein.
3. Collum, D. B.; McDonald, J. H. III; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2118.
4. Bromo ester **6a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.18 and 2.35 (set of m, 2H, $BrCH_2CH_2$-), 2.82 (d, 1H, OH), 3.55 (m, 2H, $BrCH_2CH_2$-), 4.40 (m, 1H, CHOH), 5.25 (s, 2H, CH_2Ph), 7.38 (m, 5H, phenyl). MS CI(NH_3) m/z 290, 292. **6b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.14 (m, 1H), 2.33 (m, 1H), 2.87 (d, 1H, *J*=5Hz, OH), 3.55 (m, 2H), 3.81 (s, 3H), 4.37 (quintet, 1H, *J*=4.5Hz): ^{13}C NMR (125MHz, $CDCl_3$) δ 28.7, 37.0, 52.8, 68.3.

5. Hoffman, R. V.; Kim, H. -O. *Tetrahedron Lett.* **1990**, *31*, 2953.
6. We acknowledge Dr. M. Qabar in this laboratory for the preliminary study. Qabar, M; Kahn, M unpublished results.
7. Ether-linked β-lactam **1**. ^{1}H NMR(CD_3OD, 500 MHz) δ 0.95 (d, 6H, *J* = 6Hz, -$CH_2CH(CH_3)_2$), 1.45 (m, 1H), 1.60 (m, 2H), 1.95 - 2.1 (set of m, 2H), 2.08 (s, 3H, -CH_2SCH_3), 2.62 (m, 2H, -CH_2SCH_3), 3.73 (m, 1H), 4.14 (dd, 1H, *J* = 4, 8Hz, OC*H*COOH), 4.27 (d, 1H, *J* = 2Hz). MS CI (isobutane) m/z 275.9.
8. De Nardo, M. *Farmaco, Ed. Sci.* **1977**, *32*, 522; *Chem. Abstr.* **1977**, *87*, 118063.
9. Aza-proline **9**: 38 % yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47 (s, 9H, $(CH_3)_3$), 2.07-2.15 (m, 1H, C-4 H), 2.34-2.41 (m, 1H, C-4 H), 3.46 (ddd, 1H, *J* =6.0, 9.5, 11.0 Hz, C-3 H), 3.61 (ddd, 1H, *J* =7.0, 9.0, 10.5 Hz, C-3 H), 3.74 (s, 3H), 3.88 (t, 1H, *J* =7.5 Hz, CH), 4.51 (bs, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.31 ($(CH_3)_3$), 31.89 (C-4 CH_2), 45.60 (C-3 CH_2), 52.39 (C-5 CH_2), 59.55 (OCH_3), 80.50 ($C(CH_3)_3$), 155.15 (CO_2CH_3), 172.07 (OC(=O)N); IR (neat) 3470, 1740, 1697, 1437, 1366, 1170, 1128 cm^{-1}; MS (ES^+) m/z 231.
10. Kim, H.-O, Gardner, B.; Kahn, M. *Tetrahedron Lett.* **1995**, *34*, 6013.
11. Experimental Procedure of Bicyclic Ester **2**: To a stirred solution of Cbz-Asp(O-*t*-Bu)-OH (190 mg, 0.6 mmol) with aza-proline methyl ester **9** (46 mg, 0.2 mmol) in dichloromethane (1 mL) was added HATU (250 mg), followed by diisoproylethylamine (0.1 mL) at rt. After stirring at rt for 11h, to this stirred solution was added additional Cbz-Asp(O-*t*-Bu)-OH (190 mg), HATU (250 mg) and diisopropylethylamine (0.1 mL). The resulting solution was stirred for 16h. After dilution with EtOAc (20 mL), the solution was washed with 1N HCl (10 mL), sat. $NaHCO_3$ (15 mL), brine (10 mL), dried (Na_2SO_4), and concentrated to provide a brown oil. The crude product was purified by flash chromatography (hexane: EtOAc = 80:20 to 70:30 to 60:40) to provide an oil (62 mg, 58%).

The above oil (60 mg) was treated with TFA (2 mL) at room temperature overnight. After concentration, the oily residue was taken up in toluene (10 mL) and heated at reflux overnight. After concentration, the oily residue was taken up in EtOAc (20 mL), washed with sat. $NaHCO_3$ (10 mL), dried (Na_2SO_4), and concentrated to give an oil. Crude product was purified by preparative TLC (hexane:EtOAc:MeOH = 60:30:10) to provide an oil. (24 mg, 60%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.3 -2.5 (set of m, 2H), 2.5 -2.7 (set of m, 2H), 3.22 (dd, 1H, (O=)CNCH_2), 3.50 (m, 0.4H), 3.78 and 3.79 (two s, 3H, OMe, ratio 2:1), 3.93 (m, 0.6H), 4.38 and 4.64 (m, 1H, CH), 4.90 (dd, 1H, *J*= 2.5, 9 Hz, CH), 5.13 (s, 2H, CH_2Ph), 5.66 (d, 1H, *J*= 5.5 Hz, NH), 7.35 (m, 5H, phenyl); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.03, 35.99(35.60), 43.54(43.02), 48.90(49.31), 53.47, 56.98(57.81), 67.48, 128.26, 128.47, 128.79, 136.17, 155.96, 163.58(164.60), 166.25, 169.49(169.30). Based upon ^{1}H and ^{13}C NMR, the product consisted of a 2:1 ratio of diastereomers. MS CI(NH_3) m/z 362 ($M+H^+$), 379 ($M+NH4^+$).

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