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The Synthesis of Chiral 3-Oxo-6-[(phenylmethoxy)-carbonyl]-2-piperazineacetic Acid Esters Designed for the Presentation of an Aspartic Acid Side Chain. A Subsequent Novel Friedel Crafts Reaction

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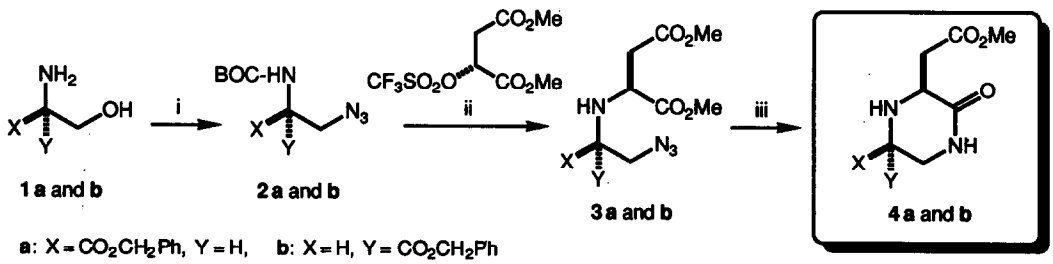
Abstract: *The syntheses of (2S, 6R)-, and (2S, 6S)-3-oxo-6-[(phenylmethoxy)carbonyl]-2-piperazineacetic acid methyl esters from* L- *or* D-*serine and dimethyl-D-malate are described. Acylation of the (2S, 6S) isomer with 3-methoxyphenylacetyl chloride, hydrogenolysis of the benzyl ester, followed by treatment with oxalyl chloride then aluminum chloride led to an unexpected tricyclic product into which a C_2O_2 unit had been incorporated.*

The stereo controlled syntheses of unnatural amino acids,[2] tight turn mimics,[3] and compounds capable of displaying natural amino acid side chains in novel ways,[4] have all received considerable interest recently. In this regard we desired a synthesis of each diastereoisomer of the 3-oxopiperazines (**4a** and **b**), which were designed as cyclic templates bearing an aspartic acid side chain. Related compounds have been shown to have activity as transcarbamoylase inhibitors.[5] Several synthetic approaches to 2-substituted-3-oxopiperazines have been reported in the literature, including reaction of ethylenediamines with α-haloesters, maleates and fumarates; however, these methods did not permit control of absolute stereochemistry in the products.[5, 6] Our initial work in this area, based on the obvious synthetic disconnection to aspartic acid and ethyl bromopyruvate, or an equivalent, met with failure. Subsequently, we investigated an alternate synthetic disconnection to the units of malic acid, and a differentiated α,β-diaminopropionic acid equivalent, the results of which are presented in this communication.



Scheme 1: (i) $(t\text{-BuOCO})_2O$ / H_2O / dioxane, then HN_3 / $(NCO_2iPr)_2$ / Ph_3P, -78 °C to rt, 18 h; yields (unoptimized): 67% **2a**, 39% **2b**. (ii) 1:1 TFA / CH_2Cl_2, 0 °C to rt, 30 min., and the amine isolated from EtOAc / $NaHCO_3$. $(CF_3SO_2)_2O$ was added to dimethyl-*D*-malate in CH_2Cl_2 at -78 °C; after 5 min., 2 equivalents of 2,6-lutidine was added, and after 5 min. the amine and 1 equivalent of 2,6-lutidine in CH_2Cl_2 were added at -78 °C, and allowed to warm to rt for 18 h; yields : 61% **3a**, 73% **3b**. (iii) Ph_3P / THF, 1% H_2O, rt, 3 d; yields : 85% **4a**, 49% **4b**.

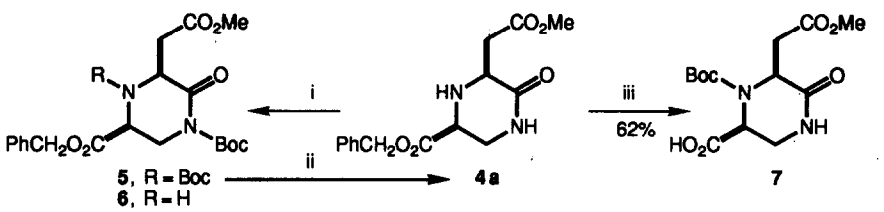
We considered the key approach to assembling a N-substituted aspartic acid derivative of the type (3) (Scheme 1) would involve S_N2 displacement of the triflate derived from dimethyl-*D*-malate with a suitable β-

protected α,β-diaminopropionic acid equivalent. Although many routes to differentially protected α,β-diaminopropionic acids have been reported,[7] we decided to utilize benzyl (*S*)- or (*R*)-3-azido-2-*tert*-butoxycarbonylaminopropionate (**2a** or **b**), where the azide functions as a latent amine. These compounds were readily derived from *L*- or *D*-serine benzyl ester (**1a** or **b**) respectively by the method previously described by Otsuka *et al.* for the methyl ester.[8] The benzyl ester was desired for our purposes to provide orthogonal protection to the other carboxylate in (**4**).

The enantiomeric serine benzyl esters (**1a** or **b**) were N-protected with a Boc group and subjected to Mitsunobu displacement using hydrazoic acid and diisopropylazodicarboxylate to give the azides (**2a** and **b**).[8,9] Removal of the N-protecting group and alkylation with the triflate generated from dimethyl-*D*-malate *in situ*[10] gave the diastereomeric N-substituted *L*-aspartic acid derivatives (**3a** and **b**). That the reaction proceeded by a S_N2 mechanism, rather than elimination to the fumarate (or maleate) followed by conjugate addition, is evidenced by the lack of detectable diastereomeric cross contamination in either the azides (**3**) or the 3-oxopiperazines (**4**). Reduction of the azides (**3a** and **b**) with triphenylphosphine in wet THF resulted in the anticipated spontaneous lactamization to the 3-oxo-6-[(phenylmethoxy)carbonyl]-2-piperazineacetic acid methyl esters (**4a** and **b**).[11] None of the other diastereoisomer, or any of the 7-membered lactam from condensation with the β-carboxylate were detected in the product. The relatively low yield (unoptimized) of **4b** appears to result from either relatively slow hydrolysis of the iminophosphorane Staudinger product[12] in step (iii), or slow lactamization resulting in polar products.

Since chiral α-hydroxy acids are generally available by diazotization of the corresponding α-amino acids,[13] this methodology should be generally applicable to the synthesis of 3-oxopiperazines of the type (**4**) bearing the side chain of any α-amino acid, with control of absolute stereochemistry at each stereocenter.

We sought to utilize this 3-oxopiperazine for the synthesis of a series of N-acylated derivatives, including a series of polycyclic condensed compounds. Our first indication of unanticipated reactivity with this system came from attempted Boc protection of the secondary amine of (**4a**), resulting in a mixture of the *bis*-Boc derivative (**5**) and the imide (**6**), evincing facile acylation of the lactam nitrogen (Scheme 2). Acid deprotection of (**5**) gave back the 3-oxopiperazine (**4a**). This problem was circumvented by hydrogenolysis of the benzyl ester of (**4a**) to give the zwitterionic α-amino acid, and reaction of this latter compound with di-*tert*-butyl dicarbonate in aqueous bicarbonate to provide the desired Boc protected amino acid (**7**).

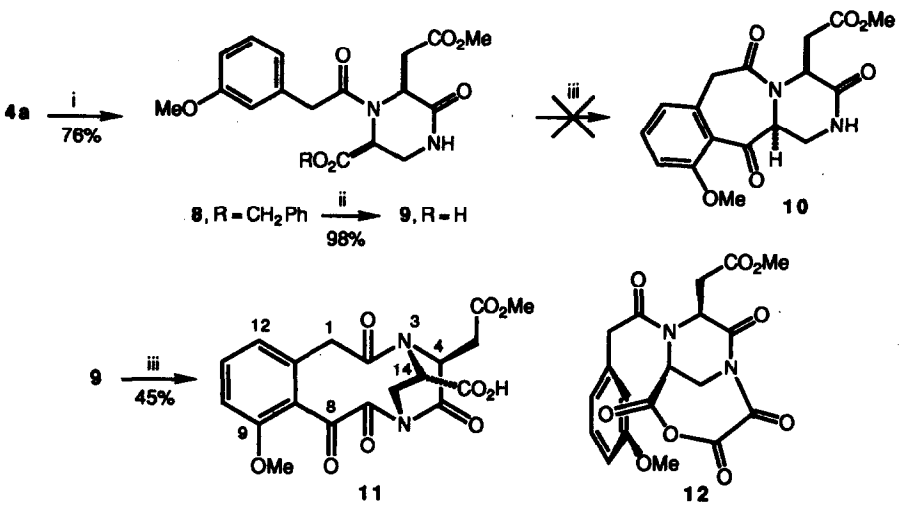


Scheme 2: (i) (t-BuOCO)2O / DMAP / CH_2Cl_2, rt, 24 h; yields: 31% **5**, 41% **6**. (ii) TFA / CH_2Cl_2, rt, 0.5 h. (iii) H_2 / 10% Pd / C, then (t-BuOCO)2O / aqueous bicarbonate / dioxane.

In contrast, acylation of the 3-oxopiperazine (**4a**) with 3-methoxyphenylacetyl chloride proceeded to give the amide (**8**), (Scheme 3). We have since found that acylation of this secondary amine proceeds optimally under Schotten-Baumann conditions. Hydrogenolytic removal of the benzyl ester of (**8**) afforded the carboxylic acid (**9**). Attempted intramolecular Friedel-Crafts acylation by treatment of (**9**) with oxalyl chloride followed by aluminum trichloride to generate the fused tricyclic compound (**10**) led to a single major new product, and first inspection of the sharp NMR spectrum revealed the presence of a 1,2,3-trisubstituted aromatic, possibly associated with a rigid structure. However, the ^{13}C NMR spectrum, which showed six carbonyl carbons, six aromatic carbons and seven aliphatic carbons, and the mass spectrum [$(MH)^+ = 418$], were consistent with a molecular formula into which a C_2O_2 unit from oxalic acid had been incorporated, and clearly eliminated (**10**)

from consideration as the reaction product.[14] These data, along with the infrared spectrum (carbonyl absorbances at 1824, 1750, 1729, 1689 and 1669 cm^{-1}), lack of an amide proton in the ^1H NMR spectrum, the observation that chromatography required the addition of acetic acid to the eluent, and the broad absorbance at 3512 cm^{-1} in the infrared spectrum consistent with the presence of a carboxylic acid, prompted assignment of the structure as the novel bicyclo[6.2.2] compound (**11**).[15] Interestingly, in the ^1H NMR spectrum, both ring methine protons resonate at unusual chemical shifts. The methine proton of carbon-4 is at δ 5.75, and appears from molecular modeling studies to be in the deshielding zone of carbonyl groups,[16] whereas the methine of carbon-14, bearing the carboxylic acid resonates at δ 3.10, and appears to be in the shielding zone of the carbonyl of carbon-2.

We propose that the mechanism of this transformation involves intramolecular trapping of the initially generated chloroglyoxylic anhydride to give the intermediate (**12**). The presence of absorbances at 1855 and 1821 cm^{-1} in the crude product from treatment of (**9**) with oxalyl chloride are consistent with the anhydride within (**12**), but not with an acid chloride. Furthermore, the mass spectrum of this intermediate revealed the presence of the correct molecular mass for (**12**), while suitable masses for the chloride isomers of the anticipated acid chloride were not observed.[17] While the molecular formula of (**12**) is identical to the tricyclic product (**11**), thin layer chromatography does not show the presence of any detectable quantity of (**11**) until after treatment of this intermediate with aluminum chloride. The observation that Friedel-Crafts acylation had occurred *ortho* to the methoxy group exclusively (none of the *para* isomer could be detected) could be rationalized by chelation of the methoxy substituent and a carbonyl of the glyoxylic anhydride in (**12**) to aluminum during the Friedel-Crafts acylation.



Scheme 3: (i) 3-$MeOC_6H_4CH_2COCl$ / Et_3N / DMAP (1 equiv.) / CH_2Cl_2, rt, 24 h. (ii) H_2 / 10% Pd / C. (iii) See note.[14]

Although the Friedel-Crafts product (**11**) is highly crystalline, X-ray quality crystals have not been obtained. If successful, these results will be reported elsewhere in due course.

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9. **CAUTION:** Hydrazoic acid is both extremely toxic and can decompose explosively. This reaction should only be carried out in a well ventilated hood behind a blast shield. We have run this reaction on 120 mmol scale without incident.
10. Feenstra, R. W.; Stokkingreef, E. H. M.; Nivard, R. J. F.; Ottenheijm, H. C. J. *Tetrahedron Lett.*, **1987**, *28*, 1215-1218.
11. All new compounds gave spectral and analytical data consistent with the structures assigned.
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14. Oxalyl chloride (38 mg, 0.30 mmol) and DMF (10 mg) were added to a solution of the acid (**9**, 100 mg, 0.27 mmol) in CH_2Cl_2 (5 mL), and stirred at room temperature for 1 h. Nitrobenzene (4 mL) was added, and the CH_2Cl_2 removed by evaporation. The resulting solution was added *via* syringe pump over 12 h to a stirred solution of 1 M aluminum chloride in nitrobenzene (0.7 mL). After stirring for an additional 6 h, the mixture was subjected to a normal extractive work-up. The resulting nitrobenzene solution was applied to a silica column and eluted with CH_2Cl_2 to remove nitrobenzene, and then 90:10:1 CH_2Cl_2 / MeOH / AcOH to give (4*S*, 14*S*)-14-carboxy-1,2,4,5,7,8-hexahydro-9-methoxy-2,5,7,8-tetraoxo-3,6-ethano-3,6-benzodiazecine-4-acetic acid, α-methyl ester (**11**), (40 mg, 45%): mp 245-247 °C; $[\alpha]^{20}_D$ = +55.36° (c = 1.16, MeOH); μ_{max} (KBr) 3512, 2955, 1824, 1750, 1729, 1689, 1669, 1598, 1578, 1470, 1439, 1358, 1311, 1270, 1210, 1179, 1054, 990, 943, 916, 804, 791, 771, 754, 659 cm^{-1}; δ_H (CD_3COCD_3, 300 MHz) 2.94 (2H, d, *J* = 7.5 Hz, CH_2CO_2), 3.10 (1H, dd, *J* = 13.7 and 11.3 Hz, $CHCO_2H$), 3.55 (1H, d, *J* = 15.6 Hz, *CH*HAr), 3.68 (3H, s, CH_3), 3.705 (3H, s, CH_3), 4.22 (1H, dd, *J* = 13.8 and 3.3 Hz, *CH*HN), 4.33 (1H, dd, *J* = 11.1 and 3.3 Hz, CH*H*N), 4.94 (1H, d, *J* = 15.0 Hz, CH*H*Ar), 5.75, (1H, t, *J* = 6.9 Hz, $CHCH_2CO_2$), 7.02 (1H, d, *J* = 7.8 Hz, 10-CH), 7.10 (1H, d, *J* = 8.7 Hz, 12-CH), 7.45 ppm (1H, t, *J* = 8.3 Hz, 11-CH). The connection of the spin systems in the ^1H NMR spectrum were confirmed by a 2D COSY experiment. δ_C (CD_3COCD_3, 75 MHz), 32.2, 40.2, 43.6, 52.2, 52.5, 56.2, 57.3, 88.3, 113.0, 119.7, 125.1, 132.6, 136.1, 152.1, 159.2, 161.0, 167.7, 169.8, 174.2 ppm. Found (FAB ms): 419.1096, calc. for $C_{19}H_{19}N_2O_9$ $(MH)^+$ requires 419.1091.
15. Although bicyclo[6.2.2] systems are well known, we are not aware of any previous examples of the 1,2,4,5,7,8-hexahydro-3,6-ethano-3,6-benzodiazecine ring system, the closest analogy being an alkaloid-derived bicyclo[6.2.2] lactam resulting from an acetic anhydride / sodium acetate induced C-D ring cleavage of dihydrocorynantheic acid (Dolby, L. J.; Sakai, S. *Tetrahedron*, **1967**, *23*, 1-9). Pyroergotamine, an N-pyruvoyldiketopiperazine, has been reported and the structure determined by X-ray crystallography (Day, R. O.; Day, V. W.; Wheeler, D. M. S.; Stadler, P. A.; Loosli, H.-R. *Helv. Chim. Acta*, **1985**, *68*, 724-733, and Calcagni, A.; Mazza, F.; Pochetti, G.; Rossi, D.; Lucente, G. *Int. J. Pept. Protein Res.*, **1985**, *26*, 166-173). The diketopiperazine ring exists in a boat conformation, and the ketone is at 79.7° to the planar imide; modeling of the bicyclo[6.2.2] product (**11**) suggests that a similar conformation is adopted by the α-keto imide portion of (**11**). A cyclic anhydride resulting from the treatment of proline with excess oxalyl chloride has previously been reported (Hearn, W. R.; Worthington, R. E. *J. Org. Chem.*, **1967**, *32*, 4072-4074). While this compound contains a six rather than seven membered ring, and incorporates a lactam rather than imide functionality, it represents the closest analogy in the literature for the proposed intermediate (**12**), particularly since the facile acylation of the lactam nitrogen in (**4a**) has been demonstrated. Although the infrared spectrum of this cyclic anhydride was not reported, the synthesis was repeated under modified conditions (trichloroethylene / $NaHCO_3$, 3 d / rt, filtered and the solvent evaporated; after 2 d / rt crystals formed.) The infrared spectrum showed carbonyl absorbances at 1841, 1821, 1775, and 1695 cm^{-1}, consistent with the proposed intermediate (**12**).
16. Modeling of compound (**11**) was accomplished using Sybyl 5.5 software (Tripos Associates, Inc.). Geometry optimization was performed using a combination of MM2 and MAXIMIN2 force fields.
17. Found (FAB ms): 419.1093, calc. for $C_{19}H_{19}N_2O_9$ $(MH)^+$ requires 419.1091.

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