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PREPARATION OF HETEROCYCLIC AMINO ACIDS VIA INTRAMOLECULAR MUKAIYAMA ALDOL CONDENSATION: SYNTHESIS OF A NOVEL CYCLOLEUCINE ANALOGUE

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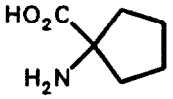
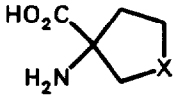
Summary: A novel 5-*endo*$_t$*exo*$_n$ intramolecular Mukaiyama aldol condensation was employed in a simple synthesis of 3-amino-3-tetrahydrofurancarboxylic acid, an oxygenated cycloleucine analogue.

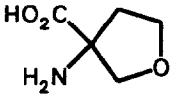
The non-protein amino acids[1] are of growing importance on account of their intrinsic biological activities, as well as for the unique properties they impart when incorporated into peptide chains. Cyclic amino acids are of particular interest, as exemplified by cycloleucine **1**, which possesses diverse physiological activities,[2] and which has been utilized in the synthesis of conformationally restricted peptide sweeteners.[3] The corresponding tetrahydrothiophene analogue **2a** is an inhibitor of S-adenosylmethionine transferase,[4] while the naturally occuring plant metabolite cucurbitine **2b** has been isolated from several species of Cucurbitaceae,[5] and displays anthelminthic activity.[6] We were interested in preparing the previously unknown tetrahydrofuran analogue **3**, as part of a program to synthesize novel, biologically active amino acids.[7] We report herein a direct and concise synthesis of **3** via a novel application of the intramolecular Mukaiyama aldol condensation.



1



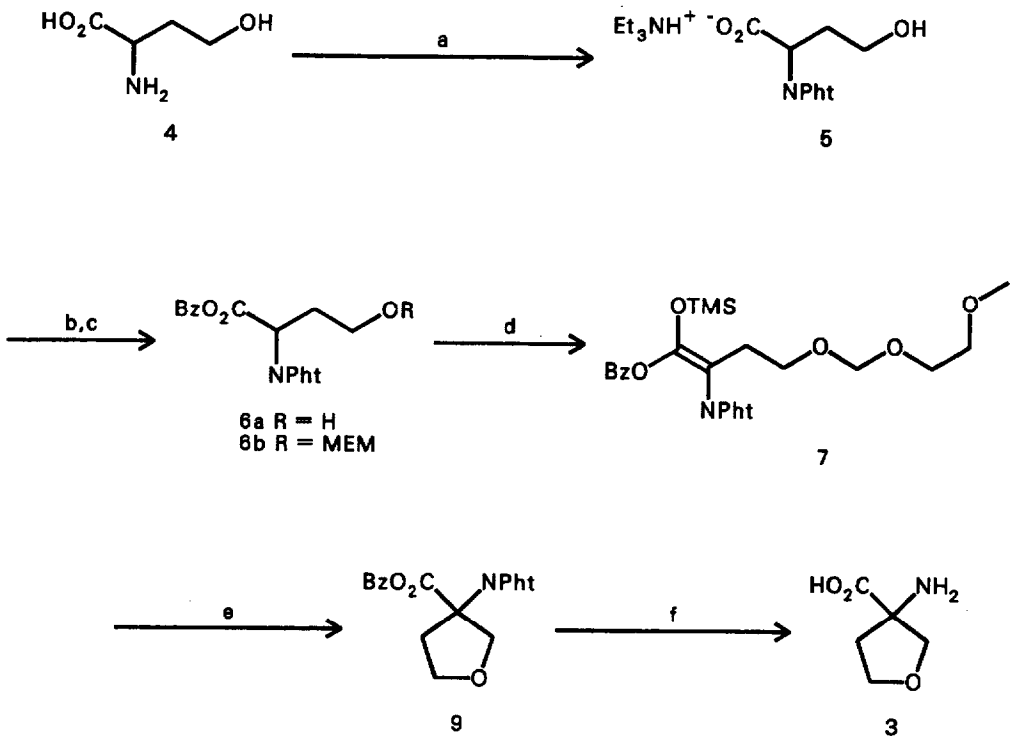
2a X = S
2b X = NH



3

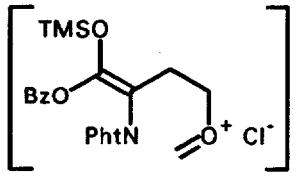
The proximity of an oxygen atom β to the carboxyl group of **3** suggested the use of an intramolecular Mukaiyama aldol condensation,[8] a reaction of some utility as a method for the synthesis of 6, 7, and 8-membered oxacyclic rings.[9] As illustrated in Scheme 1, selective functionalization of D,L-homoserine **4**

SCHEME 1



(a) $PhtNCO_2Et$, Et_3N, THF, reflux, 24h, 71%. (b) BzBr, DMF, 23°C, Et_3N, 44h, 92%. (c) $(iPr)_2EtN$, MEMCl, CH_2Cl_2, 23°C, 19 h, 97% . (d) 1.2 eq. LDA, THF, -78°C, 30 min; TMSCl, CH_2Cl_2, -78°C→ 23°C, 1.5h. (e) 1.0 eq $TiCl_4$, CH_2Cl_2, 1h, 0°C, 32% from **6b**. *(f) 6N HCl/HOAc (1:1), 100°C, 3h; EtOH, propylene oxide, 58% .*

provided a convenient route to the desired cyclization precursor. Phthalimide formation, followed by benzylation of the amine salt **5**, afforded the benzyl ester **6a** in 65% overall yield. The alcohol **6a** was smoothly converted to the corresponding (methoxyethoxy)methyl (MEM) ether **6b** in 97% yield after chromatography, by treatment with MEM chloride in CH_2Cl_2 in the presence of N,N-diisopropylethylamine. The MEM ether group was chosen as the cyclization initiator since previous work has shown that in the presence of Lewis acids, regioselective C-O bond cleavage of the unsymmetrical acetal occurrs with elimination of the 2-methoxyethoxy group, followed by intra- or intermolecular nucleophilic attack on the resulting methylene oxonium ion.[10] Formation of the ester enolate of **6b** with lithium diisopropylamide in THF at -78°C followed by quenching with trimethylsilyl chloride and evaporation of solvent, gave the crude silyl ketene acetal **7**. Exposure of **7** for one hour to titanium tetrachloride (1.0 equiv.) in dichloromethane at 0°C followed by aqueous workup and chromatography on silica gel, afforded the tetrahydrofuran **9** in 32% yield, presumably through the intermediacy of methylene oxonium ion **8**.



8

Acidic hydrolysis of **9**, followed by evaporation and treatment of the hydrochloride salt with propylene oxide in ethanol, furnished the desired 3-amino-3-tetrahydrofurancarboxylic acid **3** in 58% yield, mp 244-247°C . Using the terminology of Kocienski,[9] the Mukaiyama cyclization of **7** represents a 5-*endo*$_t$*exo*$_n$ ring closure, and is nominally disfavored under Baldwin's rules.[11] Interestingly, one other example of a 5-*endo*$_t$*exo*$_n$ tetrahydrofuran cyclization has been reported previously.[12]

In conclusion, the simple and direct preparation of **3** outlined here demonstrates the applicability of the intramolecular Mukaiyama aldol condensation for the synthesis of tetrahydrofuran-substituted amino acids. This methodology can provide a useful approach for the synthesis of heterocyclic amino acids which would be difficult to obtain by more conventional methods.[13]

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13. All compounds isolated gave satisfactory spectral (^{1}H NMR) and analytical data (± 0.3% for C,H,N). Selected physical data are as follows:

9: ^{1}H NMR(400 Mhz, CDCl3) δ 2.89 (ddd, 1, J=5.5, 7.5, 13.0 Hz), 3.00 (dt, 1, J=7.3, 14.6 Hz), 4.03 (dt, 1, J=5.2, 8.4 Hz), 4.10 (q, 1, J=7.7 Hz), 4.44 (d, 1, J=9.6 Hz), 4.65 (d, 1, J=10.4 Hz), 5.19 (s, 2), 7.26 (m, 5), 7.73 (m, 2), 7.84 (m, 2); ^{13}C NMR(100.6 MHz, $CDCl_3$) δ 35.48, 67.54, 67.66, 67.73, 74.69, 123.37 (2C), 127.72 (2C), 128.27 (2C), 128.51 (2C), 131.68, 134.30 (2C), 135.11, 168.52 (2C), 170.73; CI MS (MH^+) 352; Anal. ($C_{20}H_{17}N_{10}O_5$) C,H,N.

3: ^{1}H NMR(400 MHz, D_2O) δ 2.24 (dt, 1, J=7.1, 13.8 Hz), 2.60 (ddd, 1, J=5.8,8.6,13.8 Hz), 4.00 (m, 1), 4.01, 4.05 (AB quartet, 2, J=10.5 Hz), 4.12 (ddd, 1, J=6.2, 8.5, 17.2); ^{13}C NMR(100.6 MHz, D_2O) δ 38.69, 68.86, 70.44, 77.44, 176.72; FAB MS (glycerol matrix) (MH^+) 132; Anal. ($C_5H_9N_1O_3 \cdot 0.2\ H_2O$) C,H,N.

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