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Concise syntheses of enantiomerically pure protected 4-hydroxypyroglutamic acid and 4-hydroxyproline from a nitroso-cyclopentadiene cycloadduct

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ABSTRACT

O-TBS-protected methyl *trans*-4-hydroxypyroglutamate and methyl *trans*-4-hydroxyproline ester were synthesized from nitroso-cyclopentadiene Diels–Alder cycloadducts. Enzymatic resolution of the key intermediate, 4-amino-cyclopent-2-enol, provides access to both L- and D-amino acids.

1. Introduction

Syntheses and studies of both non-proteinogenic natural and unnatural amino acids continue to be of considerable interest, often because of their enzyme inhibitory and antimetabolite properties. Among these amino acids, substituted glutamic acids attract particular attention because of their interaction with glutamate receptors in the central nervous system (CNS) and their involvement in many other biological processes.[1] Proline and its derivatives are of considerable interest because their cyclic structures play a critical role in forming protein and peptide secondary structures such as β-turns and α-helices.[2] 4-Substituted prolines are particularly interesting because the C-4 substituents can influence not only the conformation of the pyrrolidine ring, but also the rate of *cis–trans* isomerization about the amide bond. In the investigation of collagenous peptides that have repeating units of Gly-X–Y (X is often occupied by proline residues, and Y is frequently occupied by hydroxyproline residues), hydroxylation of proline at the 4-position is found to affect greatly the conformational stability of the collagen triple helix.[3] In addition, many biologically active natural products including kainic acid have a 4-substituted proline framework.[4] Due to the biological importance of substituted glutamic acids and 4-substituted prolines, extensive efforts have focused on development of their syntheses. Among these studies, 4-hydroxypyroglutamates have received particular interest[5] because they are able to be transformed to both 4-substituted glutamic acids and prolines. In addition, they also have been employed as key intermediates in the syntheses of many biologically interesting heterocycles.[6] Herein, we report asymmetric syntheses of substituted pyroglutamate and proline derivatives from oxazines that are readily derived from nitroso cycloaddition reactions.

2. Results and discussion

Nitroso Diels–Alder reactions with 1,3-cycloalkadienes afford cycloadducts **2**. These versatile compounds have been used to synthesize many natural products and other biologically interesting compounds.[7] The same scaffolds are readily converted to novel amino acids. Oxidative cleavage of the double bond of **2** gives cyclic oxyamino acids **3**. Subsequent N–O bond reduction provides the corresponding acyclic hydroxy α-amino acids **5** (Route A). Alternatively, N–O reduction of **2** gives amino hydroxy cycloalkenes **4** that can also be oxidatively converted to amino acids **5** (Route B). We anticipated that these intermediates could also serve as precursors of substituted pyroglutamates **6** and prolines **7**. Thus, we became interested in developing asymmetric syntheses of these useful amino acids.

Using generalized route A (Scheme 1), we previously reported specific examples of the syntheses of dipeptides such as **12** that contain carboxy proline analogs and conformationally restricted glutamate analogs **3**. The method involved oxidation of amino acid hydroxamates **9** in the presence of dienes, to trap the transient nitroso agent **10** giving adduct **11** and subsequent alkene oxidation to generate **12**.[7a] Diastereoselectivity of the cycloaddition (**10**→**11**) depended on the size of the starting amino acid side chain (R of **8**) and, using route B, enantiomerically enriched forms of **4** could be obtained by removal of the starting amino acid either hydrolytically or under Edman degradation conditions.[7f] Addition of appropriate side chains, such as a phenylacetyl group (penicillin G side chain), imparted antibiotic activity, similar to that of β-lactam antibiotics, to amino acid **3**-containing peptides such as **13**.[8] Heinz also used nitroso cycloaddition chemistry and a variant of route A to synthesize racemic 4-hydroxypyroglutamate **14** in a sequence that also included high pressure N–O bond reduction[5a] (Scheme 2).

While route A does provide access to novel amino acids and the use of amino acid hydroxamates **9** gives diastereoselectively

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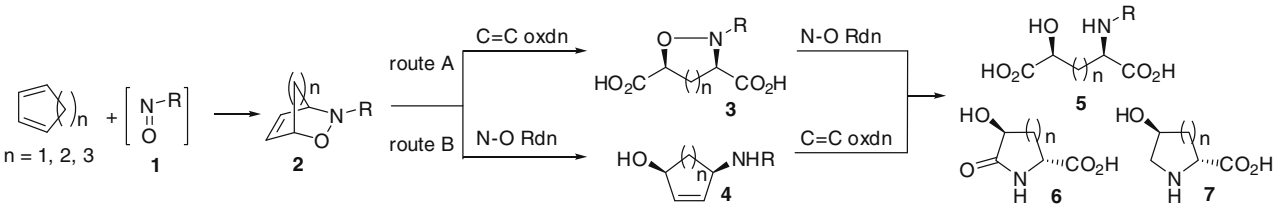
enriched cycloadducts and eventual peptides, we sought alternative methods that would provide access to substituted glutamates, prolines and analogs in enantiomerically pure form. No catalytic asymmetric intermolecular acylnitroso cycloaddition reaction has yet been developed despite considerable effort[9] although a moderately successful intramolecular example has been described.[10] Yamamoto has reported very effective catalytic asymmetric cycloadditions using pyridyl nitroso agents, but removal of the pyridyl moiety requires several steps and is often low yielding.[7c,7d] Consequently, with a renewed focus on the potential of route B, we sought to capitalize on our previously reported enzymatic resolution of amino cyclopentenols **4**[11] to allow access to either enantiomer of the targeted glutamate and proline analogs. Thus, $NaIO_4$-mediated oxidation of Boc-hydroxylamine **15** in the presence of cyclopentadiene afforded cycloadduct **16**. Then, N–O reduction with 20 mol % of molybdenumhexacarbonyl in the presence of excess $NaBH_4$ gave (±)-aminocyclopentenol **17** in 60% overall yield from *N*-hydroxycarbamate **15**. Multigram kinetic resolution of **17** with immobilized *Candida antartica* lipase B (CALB) provided acetate (−)-**18** in 92–98% ee after 43% conversion (98% after one recrystallization) as well as (−)-**17** in 46% (98% ee after one recrystallization). Methanolysis of acetate **18** gave alcohol (+)-**17** (Scheme 3).

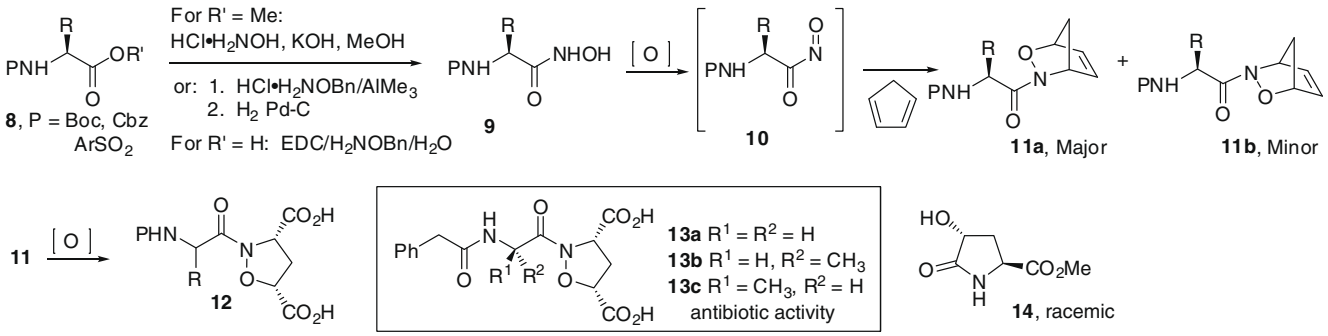
Reaction of **(+)-17** with TBSCl gave silyl ether **19**, which was oxidized to the diacid with $RuCl_3/NaIO_4$ which upon treatment with excess diazomethane provided protected methyl *trans*-*N*-Boc-4-hydroxypyroglutamate **20** in moderate yield. The *R*-configuration of the α-amino acid carbon (C-2) in **20** was confirmed to correspond with that of D-glutamate by comparison to reported specific rotation data[5b] (Scheme 4).

Reduction of pyroglutamates to proline derivatives has been effected with $BH_3{\cdot}Me_2S$[12] or $NaBH(OMe)_3$.[13] While subjection of **20** to these conditions resulted in decomposition or no desired product, we did find that a two-step process that proceeded through a hemiaminal intermediate was effective.[14] Thus, treatment of **20** with $LiEt_3BH$ at −78 °C gave isolable hemiaminal **21**, which upon reaction with $BF_3{\cdot}OEt_2$ and Et_3SiH provided protected 4-hydroxyproline **22**.[15] The NMR spectrum of **22** was consistent with that reported by Gellman[16] (Scheme 5).

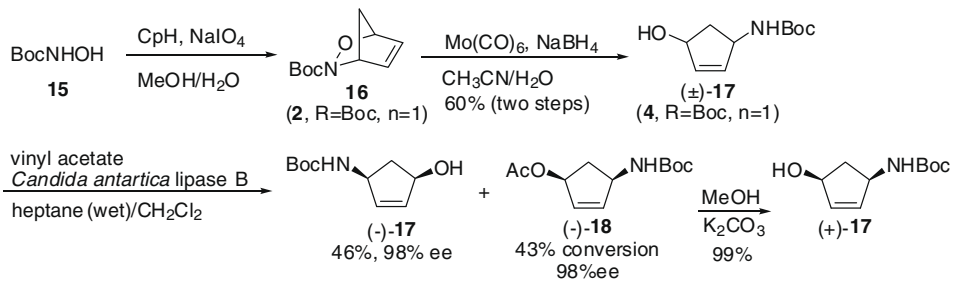
The methodology described here provides access to 4-substituted pyroglutamates and prolines from readily prepared 4-aminocyclopent-2-enols in two to three steps. The availability of both enantiomers of 4-aminocyclopent-2-enol via enzymatic resolution makes it feasible to synthesize both the L- and D-amino acids. Use of homologous or other dienes in the initial cycloaddition will allow syntheses of numerous analogs of potential interest.



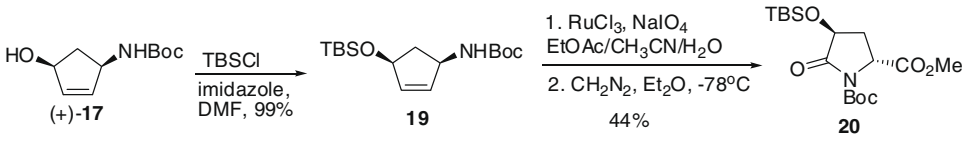
Scheme 1. Generalized nitroso cycloaddition followed by elaboration to novel amino acids.



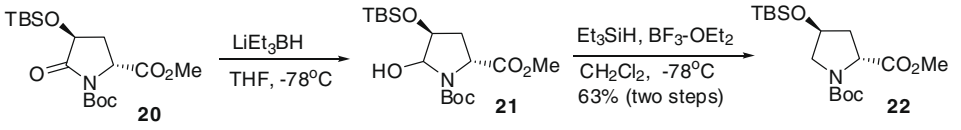
Scheme 2. Cycloadditions of amino acid-based acylnitroso agents gives precursors to novel peptides and antibiotics.



Scheme 3. Enzymatic resolution of racemic aminoalcohols obtained from nitroso cycloadducts provides enantiomerically pure amino cyclopentols.



Scheme 4. Conversion of aminocyclopentenol, **17**, to pyroglutamate **20**.



Scheme 5. Conversion of pyroglutamate, **20**, to proline derivative, **22**.

3. Experimental

3.1. General

Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl, and methylene chloride was distilled from calcium hydride. All other solvents and chemicals were purchased from Acros or Aldrich and used as is. Silica gel flash column chromatography was performed using Silica Gel 60 (30–70 μm irregular particles). All specific rotations were measured using a Perkin Elmer model 343 polarimeter at 589 nm and 20 °C. Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on a Varian UnityPlus 300 NMR at 300 MHz and 75 MHz, respectively. High resolution mass spectra were recorded on a JEOL JMS-AX505 HA Double Sector Mass Spectrometer.

3.1.1. 4-(*tert*-Butyl-dimethyl-silanyloxy)-cyclopent-2-enyl]-carbamic acid *tert*-butyl ester 19

To a solution of (+)-**17**[11] (243 mg, 1.22 mmol) in DMF (3 mL) were added TBDMSCl (276 mg, 1.83 mmol) and imidazole (249 mg, 3.66 mmol), and the mixture was stirred overnight at rt under N_2. DMF was removed in vacuo, and 20 mL of EtOAc was added to dissolve the residue. The EtOAc solution was washed with 5% Na_2CO_3 solution and brine, and then dried over Na_2SO_4. Removal of the Na_2SO_4 and solvent gave the title product as a light yellow oil (380 mg, 99%). $[\alpha]_D^{20} - 0.3$ (*c* 1.0, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.80 (m, 2H), 4.69 (m, 2H), 4.57 (br, 1H), 2.70 (dt, J_1 = 13.5 Hz, J_2 = 8.4 Hz, 1H), 1.43 (s, 9H), 1.34 (dt, J_1 = 13.5 Hz, J_2 = 5.1 Hz, 1H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.4, 136.7, 133.9, 79.5, 75.6, 54.5, 42.9, 28.6, 26.1, 18.4, −3.4, −4.5. HRMS Calcd for $C_{16}H_{32}NO_3Si$ $(M+H)^+$: 314.2151, found: 314.2144.

3.1.2. 4-(*tert*-Butyl-dimethyl-silanyloxy)-5-oxo-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester 20

To a solution of **19** (157 mg, 0.5 mmol) in EtOAc/CH_3CN (1:1, 2.8 mL) at 0 °C was added $NaIO_4$ (481 mg, 2.25 mmol) in H_2O (5.5 mL) followed by $RuCl_3$ (18.4 mg, 0.0885 mmol). The mixture was stirred at 0 °C open to the air for 15 min and then at room temperature for 2 h. The reaction mixture was suction filtered through a short pad of Celite®. The layers were separated, and the aqueous layer was saturated with NaCl and was extracted with EtOAc (3 × 3 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to give the crude diacid as a brown oil.

The brown oil was dissolved in Et_2O (8.0 mL) and treated with excess CH_2N_2 in Et_2O at −78 °C. After 30 min, the excess CH_2N_2 was quenched with AcOH in Et_2O. The reaction mixture was washed with saturated $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O (1 × 8 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated to give a brown oil that was chromatographed on silica gel eluting with EtOAc/hexanes (1:6–1:3) to give compound **20** (82 mg, 44%) as a clear oil. $[\alpha]_D^{20} = -34.7$ (*c* 1.0, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$), δ: 4.59 (dd, J_1 = 9.6 Hz, J_2 = 1.5 Hz, 1H), 4.42 (dd, J_1 = 10.2 Hz, J_2 = 8.1 Hz, 1H), 3.79 (s, 3H), 2.37 (ddd, J_1 = 13.2 Hz, J_2 = 8.4 Hz, J_3 = 1.5 Hz, 1H), 2.21 (dt, J_1 = 13.2 Hz, J_2 = 10.2 Hz, 1H), 1.50 (s, 9H), 0.89 (s, 9H), 0.18 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.2, 171.9, 149.7, 84.0, 69.8, 55.1, 52.9, 32.0, 28.0, 25.8, 18.4, -4.3, -5.1. HRMS Calcd for $C_{17}H_{32}NO_6Si$ $(M+H)^+$: 374.1999, found: 374.1972.

3.1.3. 4-(*tert*-Butyl-dimethyl-silanyloxy)-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester 22

A 1.0 M solution of lithium triethylborohydride in THF (0.225 mL, 0.225 mmol) was added to a solution of **20** (70 mg, 0.187 mmol) in THF (4 mL) at −78 °C under a nitrogen atmosphere. After 30 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (0.35 mL) and warmed to 0 °C. H_2O_2 (30%) (1 drop) was added, and the mixture was stirred at 0 °C for 20 min. The organic solvent was removed in vacuo, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product **21** (78 mg) was used without further purification.

A solution of **21** and triethylsilane (0.030 mL, 0.187 mmol) in CH_2Cl_2 (3 mL) was cooled to −78 °C, and boron trifluoride etherate (0.026 mL, 0.206 mmol) was then added dropwise under a nitrogen atmosphere. After 30 min, 0.030 mL of triethylsilane and 0.026 mL of boron trifluoride etherate were added. The resulting mixture was stirred for 2 h at −78 °C, and was then quenched with saturated aqueous $NaHCO_3$ (0.3 mL). The mixture was extracted with CH_2C1_2 (3 × 5 mL), dried over Na_2SO_4, and filtered. Evaporation of the solvent and purification by flash chromatography (EtOAc/hexanes: 10–30%) gave 42 mg (63%) of product **22** as a clear oil. $[\alpha]_D^{20} = +39.2$ (*c* 1.0, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$), δ: 4.41 (m, 1H), 4.33 (t, J = 7.8 Hz, 1H), 3.73 (s, 3H), 3.59 (td, J_1 = 10.5 Hz, J_2 = 4.8 Hz, 1H), 3.34 (m, 1H), 2.17 (m, 1H), 2.02 (m, 1H), 1.46–1.41 (d, 9H), 0.87 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) mixture of rotamers δ: 174.0, 173.8, 154.8, 154.1, 80.3, 70.6, 69.9, 58.3, 57.8, 55.1, 54.8, 52.4, 52.2, 40.0, 39.1, 28.6, 28.5, 25.9, 18.2, 1.22, −4.6, −4.7. HRMS Calcd for $C_{17}H_{34}NO_5Si$ $(M+H)^+$: 360.2206, found: 360.2203.

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