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Studies on the Total Synthesis of Paraherquamide A. Stereocontrolled, Asymmetric Synthesis of α-Alkyl-β-Hydroxyproline Derivatives

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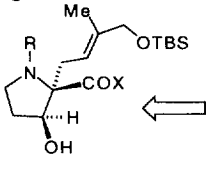
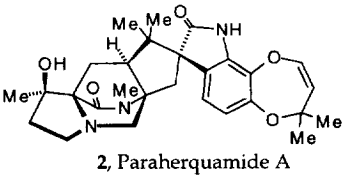
Summary: The dianion formed from 3(S),2(R)-3-hydroxyproline ethyl ester (**5**) with LDA, can be alkylated with a variety of alkyl halides with net retention of configuration to give the corresponding α-alkylated-β-hydroxyproline esters (**6**) in good yield. Copyright © 1996 Elsevier Science Ltd

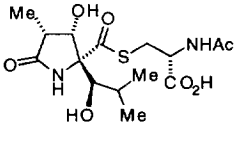
Substituted proline derivatives are widely found as constituents of natural products.[1] For example, the microbial products paraherquamide A (**1**)[2] and lactacystin (**2**)[3] contain densely functionalized α-substituted-β-hydroxyproline moieties. As part of a general program[4] aimed at developing new methods to access α-substituted amino acids in high optical purity, we have examined the enolate alkylation of 3(S), 2(R)-3-hydroxyproline ethyl ester (**5**) which is readily available from racemic 3-ketoproline by Baker's yeast reduction as described by Cooper, Gallagher and Knight.[5] More specifically, ongoing work in these laboratories on the total synthesis of paraherquamide A,[6a] mandated access to a β-functionalized α-prenylated proline derivative corresponding to **1**.



1



2, Paraherquamide A



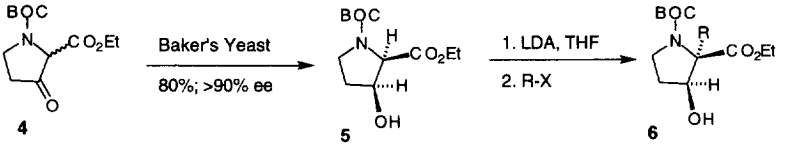
3, Lactacystin

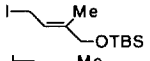
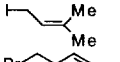
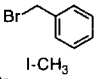
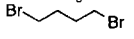
There are no general synthetic methods available for the synthesis of optically active α-substituted-β-hydroxyproline derivatives. Seebach[7] has developed a useful method to α-alkylate proline via formation of the corresponding bicyclic pivaldehyde aminal, followed by enolate alkylation which, proceeds with net retention of configuration; subsequent vigorous hydrolysis of the hindered, α-alkylated bicyclic aminal, provides the corresponding α-substituted proline derivatives in high enantiomeric excess.

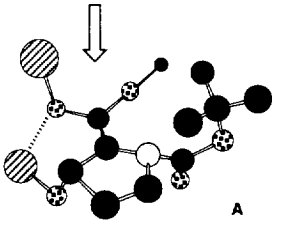
N-Boc-3(S), 2(R)-3-Hydroxyproline ethyl ester (**5**),[5] made by Baker's yeast reduction of N-Boc-3-ketoproline ethyl ester (**4**) in >90% ee, was treated with 3 equivalents of LDA at -10°C in THF to form the corresponding alkoxy enolate dianion. The subsequent alkylation was performed by cooling the mixture to -30°C and a mixture of alkyl halide (1.5 eq) and HMPA (1.4 eq) was added. The reaction was allowed to warm to 0 °C and then to 25 °C for 4 hours up to 1-2 days depending on the specific alkyl halide. Following

standard work-up and extraction of the organic-soluble product, the α-alkylated products **6a-e** (Scheme 1) were purified by silica gel chromatography and were obtained in moderate-good yields. In each case, only one diastereomer was formed, and little or no O-mono-alkylated or O-,C-dialkylated by-products were produced.

Scheme 1



Entry	RX	% YIELD of 6
a		70%
b		73%
c		53%
d	I-CH_3	57%
e		49% (X-RAY)



For **6c**, **6d**, and **6e**, only the desired C-alkylation product was obtained, and there was no evidence for the production of O-alkylation products. For **6a** and **6b**, there was less than 1-2% of the corresponding O-alkylation products which, were easily removed by chromatography.

These highly stereoselective alkylation reactions all proceeded with net retention of configuration giving single diastereoisomers as evidenced by ^1H nmr. The relative stereochemistry of alkylation was rigorously secured through a single crystal X-ray analysis for **6e** (Figure 1). The absolute and relative stereochemistry of **6a** was secured by chemical correlation.[6] The relative and thus, absolute stereochemistry for all alkylation products **6a-e** was assigned based on similarities in nmr spectroscopic characteristics and optical rotation.

The dianion derived from **5** (see structure **A**[8]) is expected to have a concave shape due to the Li-coordinated bicyclo[4.3.0] ring system geometry; alkylation from the convex face opposite the alkoxy substituent is the expected (and observed) diastereofacial bias.

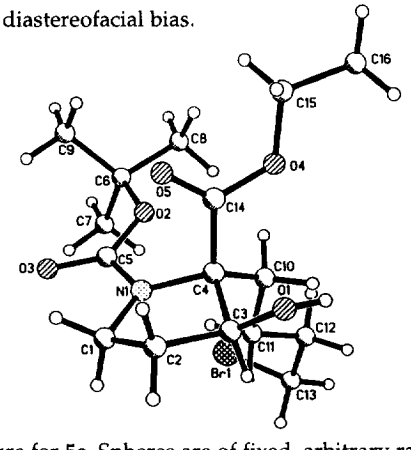


Figure 1. X-ray Structure for **5e**. Spheres are of fixed, arbitrary radius.

General experimental procedure: A solution of **5** (104 mg, 0.4 mmol) in THF (0.4 mL) was cannulated over a period of 2 min. to a magnetically stirred solution of LDA (1.2 mmol, 0.8M solution in THF) at -50°C. The reaction mixture was stirred at -10 °C for 25 min., and then at 0 °C for 5 min. followed by the dropwise addition of a solution of alkylating reagent (0.6 mmol) in HMPA (0.56 mmol) at -30 °C over a period of 2 min. The mixture was stirred at 0°C for about 1 h; the ice bath was then removed and the mixture was allowed to continue stirring at room temperature for 4 h (**6a** and **6b**) or 48h (**6c-e**). The reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with EtOAc (3 x 15 mL), washed with brine (5 x 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (eluted with hexane:EtOAc:MeOH, 5:3:0.5) to afford **6a-e**.[9-13]

It is noteworthy that, neither β-elimination nor significant O-alkylation attended these transformations. Further, the convenience and simplicity of performing the alkylations directly on substrate **5** without the need for additional protection[6,7] or manipulation should render this approach a highly attractive and general method for synthesizing functionalized pyrrolidine derivatives. The application of this methodology to the total synthesis of paraherquamide A (*via* **6a**), lactacystin and related substituted proline derivatives and pyrrolizidine alkaloids is under active investigation in these laboratories.

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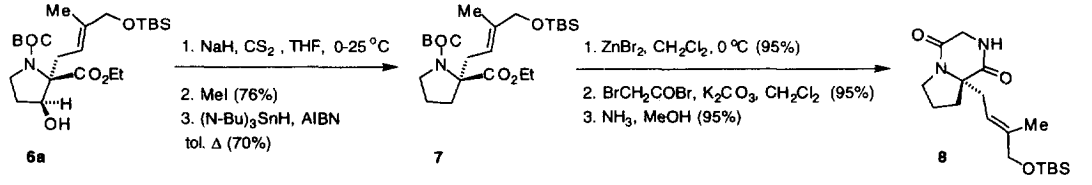
6. (a) Cushing, T.D.; Sanz-Cervera, J.F.; Williams, R.M., *J.Am.Chem.Soc.* **1996**, *118*, 557; The absolute stereochemistry of the overall process was further corroborated by the conversion of **6a** into the bicyclic substance **8** which (as the enantiomer) was previously converted into (+)-paraherquamide B, a substance whose absolute stereochemistry has been confirmed (see ref. 6a); see also: (b) Williams, R.M.; Glinka, T.; Kwast, E.; Coffman, H.; Stille, J.K., *J.Am.Chem.Soc.* **1990**, *112*, 808:



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8. Structure **A** was minimized and rendered on CSC Chem 3D Plus™.

9. Data for **6a**, colorless oil, yield (70%), $[\alpha]_D^{25}$ -32.2 (C, 0.74, EtOAc). IR(neat): 3449, 2977, 2955, 2928, 2857, 1739, 1703, 1391, 1367, 1251, 837, 774. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01-0.02(6H, m), 0.83-0.84(9H, m), 1.17-1.26(3H, m), 1.32-1.41(9H, m), 1.37-1.70(3H, m), 1.898-1.98(2H, m), 2.74-2.88(2H, m), 3.14-3.19(1H, m), 3.60-3.77(1H, m), 3.94(2H, s), 4.02-4.22(3H, m), 5.25-5.29(1H, m). ^{13}C NMR (75.47MHz, $CDCl_3$) δ -5.1, 14.0, 14.1, 14.3, 14.4, 18.5, 22.0, 26.0, 28.4, 28.5, 30.2, 30.4, 31.1, 31.4, 44.9, 45.4, 61.3, 68.1, 68.4, 71.2, 71.7, 76.5, 76.8, 79.6, 80.4, 117.7, 118.1, 138.2, 138.6, 153.8, 172.3. Anal. Calcd. for $C_{23}H_{43}NO_6Si$: C, 60.36; H, 9.47; N, 3.06. Found: C, 60.17; H, 9.30; N, 3.05. (reaction scale: 1.67 g of **5**).

10. Data for **6b**, colorless oil, yield (73%), $[\alpha]_D^{25}$ -48.2 (C, 0.98, EtOAc). IR(neat): 3447, 2972, 2930, 2873, 1743, 1699, 1668, 1391, 1170, 1137. ^{1}H NMR(300 MHz, $CDCl_3$) δ 1.22-1.29(3H, m), 1.34-1.37(9H, m), 1.53-1.65(6H, m), 1.84-2.01(2H, m), 2.70-2.91(3H, m), 3.10-3.19(1H, m), 3.57-3.77(1H, m), 4.03-4.19(3H, m), 4.92-4.94(1H, m). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 18.3, 18.5, 26.3, 26.4, 28.5, 28.6, 30.6, 30.9, 31.3, 31.8, 45.0, 45.6, 61.4, 71.4, 71.9, 76.5, 79.7, 80.5, 118.4, 118.7, 135.8, 135.9, 154.0, 154.1, 172.3, 172.4. Anal. Calcd. for $C_{17}H_{29}NO_5$: C, 62.36; H, 8.93; N, 4.28. Found: C, 62.19; H, 9.03; N, 4.27. (reaction scale: 312 mg of **5**).

11. Data for **6c**, colorless oil, yield (53%), $[\alpha]_D^{25}$ -77.6 (C, 0.59, EtOAc). IR(neat): 3446, 3085, 3062, 3030, 2979, 2881, 1732, 1693, 1681, 1392, 1367, 1167. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26-1.31(3H, m), 1.38-1.46(1H, m), 1.48(9H, s), 2.66(1H, broad), 2.70-2.80(1H, m), 3.22-3.27(1H, m), 3.54-3.81(2H, m), 4.11-4.19(1H, m), 4.23-4.31(2H, m), 7.11-7.27(5H, m). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 14.41, 14.46, 28.6, 30.5, 30.9, 36.8, 37.8, 45.0, 45.3, 60.6, 61.6, 72.2, 72.5, 75.9, 79.9, 80.8, 126.7, 126.9, 128.3, 128.5, 130.8, 130.9, 136.5, 136.8, 153.9, 154.2, 169.5, 172.1. Anal. Calcd. for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.15; H, 7.69; N, 3.87. (reaction scale: 104 mg of **5**).

12. Data for **6d**, colorless oil, yield (57%), $[\alpha]_D^{25}$ -3.9 (C, 0.54, EtOAc). IR(neat): 3443, 2980, 2936, 1746, 1731, 1698, 1391, 1167, 1094. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18-1.26(3H, m), 1.36-1.41(9H, m), 1.52-1.56(3H, m), 1.89-1.96(1H, m), 2.00-2.08(1H, m), 2.83(1H, broad), 3.33-3.14(1H, m), 3.65-3.71(1H, m), 4.05-4.21(3H, m). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 14.4, 21.6, 22.6, 28.5, 28.6, 30.8, 31.4, 61.5, 69.1, 79.8, 80.0, 80.4, 81.1, 154.1, 172.3. Anal. Calcd. for $C_{13}H_{23}NO_5$: C, 57.13; H, 8.48; N, 5.12. Found: C, 56.92; H, 8.28; N, 5.05. (reaction scale: 104 mg of **5**).

13. Data for **6e**, white powder, yield (49%), $[\alpha]_D^{25}$ -22.8 (C, 0.54, EtOAc). IR(neat): 3438, 2973, 2934, 2875, 1735, 1696, 1672, 1383, 1366, 1246, 1168, 772. ^{1}H NMR(300 MHz, $CDCl_3$) δ 1.21-1.24(3H, m), 1.28-1.40(2H, m), 1.32-1.40(9H, m), 1.83-2.18(6H, m), 2.62(1H, broad), 3.22-3.28(1H, m), 3.36-3.41(1H, t, J=6.5Hz), 3.65-3.75(1H, m), 4.06-4.22(2H, m), 4.24-4.30(1H, m). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 14.4, 21.9, 22.1, 28.5, 30.6, 31.2, 32.4, 32.7, 32.9, 33.6, 34.0, 45.0, 45.5, 61.4, 71.0, 76.6, 76.8, 79.9, 80.5, 154.0, 172.3. Anal. Calcd. for $C_{16}H_{28}BrNO_5$: C, 48.74; H, 7.16; N, 3.55. Found: C, 48.90; H, 7.31; N,3.60. (reaction scale: 104 mg of **5**).

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