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General strategy for a short and efficient synthesis of 3-hydroxy-4-methylprolines (HMP)

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Abstract—The non-proteinogenic amino acid 3-hydroxy-4-methylproline (HMP) is an active constituent of some potent antimicrobials including echinocandins, nostopeptins, pneumocandins, sporiofungin and mulundocandins. A synthesis has been achieved in 10 steps with 29% overall yield; the Evans' aldol reaction using Crimmins' modified method was pivotal to the success of the strategy.

Several substituted pyrrolidine alkaloids found in plants and microorganisms have aroused considerable interest as potential therapeutic agents and as tools for understanding biological recognition processes. Some microbial cyclic peptides,[1] containing a pyrrolidine or proline moiety observed in Nature such as mulundocandins[2] (isolated from *Aspergillus sydowi*), aculeacin A[3] (from *Aspergillus aculeatus*), echinocandins[4] (from *Aspergillus ruglosus* and *Aspergillus nidulans*), sporiofungin A,[5] nostopeptins[6] and some pneumocandins[7–9] were found to have therapeutic activity as anticancer, antifungal, antibiotic, antiviral and immune stimulating agents.[10] (2*S*,3*S*,4*S*)-3-Hydroxy-4-methylproline (HMP) (**1a**) has emerged as one of the most common modules of all these cyclic peptides (Fig. 1).

It is likely that this component would itself manifest activity and could potentiate activity in analogues. For the elucidation of defined structure activity relationships and for the preparation of analogues of these cyclic peptide antibiotics, it is essential to develop a short and efficient synthesis of **1a** and its stereoisomers. Different strategies have been reported in the literature for the synthesis of the naturally occurring active constituent (2*S*,3*S*,4*S*)-HMP (**1a**), present in echinocandins, and its antipode (2*R*,3*R*,4*R*)-HMP (**1c**).[11] Our earlier report[12] on the synthesis of the spiro fused β-lactone-γ-lactam segment of oxazolomycin using Evans' aldol reaction following Crimmins' modified method as the key reaction, formed the basis of our strategy to develop a short and efficient synthesis of (2*S*,3*S*,4*S*)-HMP and its stereoisomers.

Retrosynthetically, HMP could be obtained from an Evans' aldol adduct which in turn could be derived from commercially available Garner's aldehyde and oxazolidin-2-one (Scheme 1).

Our primary focus was on the Evans' aldol[13a] reaction between the (*S*)-oxazolidinone derivative **3** and (*R*)-Garner's aldehyde **4** using Crimmins' modified method. Since higher diastereomeric excess are known to be obtained in aldol reactions with $TiCl_4$,[13b] the outcome of this reaction would be fascinating because both substrates **3** and **4** would have independent (complementary or opposing) influences on the course of the aldol reaction. Execution of this reaction in the presence of $TiCl_4$ (1.0 equiv) and DIEA (2.5 equiv) at 0 °C gave two isomers **2** (non-Evans' *anti*) and **5** (non-Evans' *syn*) in a 2:3 ratio as liquids whose stereochemical assignments were confirmed on later stage. Similarly, (*R*)-oxazolidinone derivative **6** and (*S*)-Garner's aldehyde **7** were subjected to aldol reaction with $TiCl_4$, two isomers were obtained maintaining the same ratio (2:3). Much to

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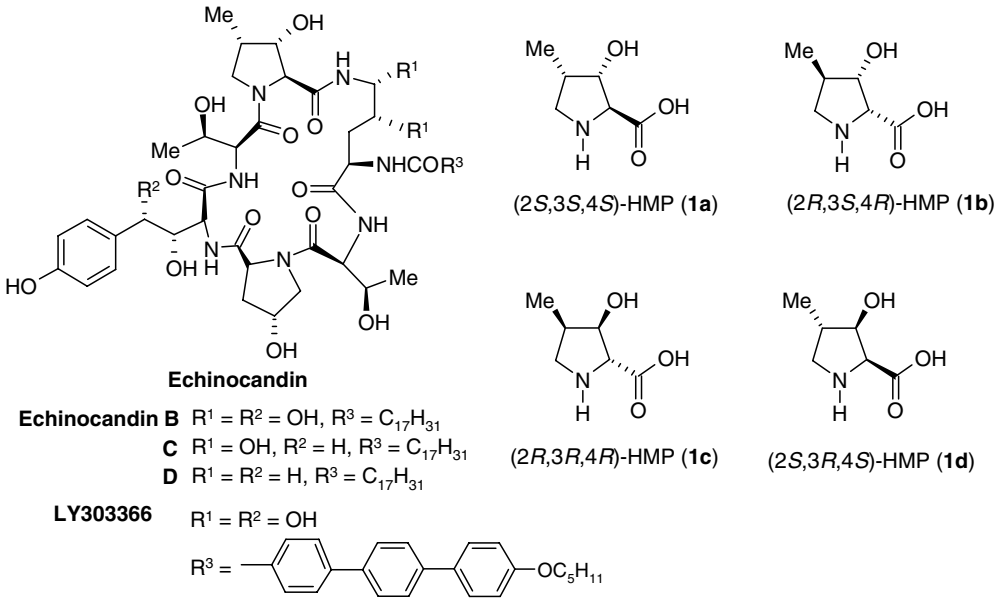
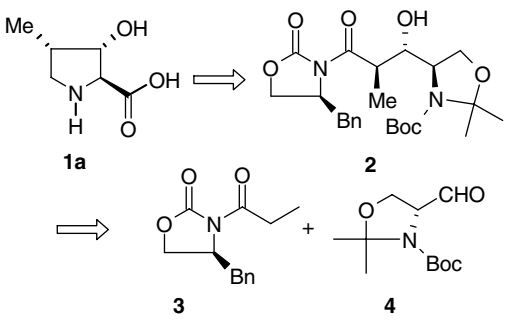


Figure 1. Echinocandins and HMPs.



Scheme 1. Retrosynthetic strategy.

our delight, isomer **8** crystallized out in 40% yield after column purification of the crude material. Spectroscopic and elemental data supported the structure of **8**;[14] a single crystal X-ray diffraction study (CCDC 615731)[15] conclusively proved the stereochemical assignments as non-Evans *anti–anti* (Scheme 2). This stereochemical outcome was in fact unexpected though we were aware of some prior literature precedents of such double stereodifferentiating reactions.[16] We also performed the aldol reaction between (*S*)-oxazolidinone derivative **3** and (*S*)-Garner's aldehyde **7** and observed the formation of **10**, exclusively. The X-ray crystallographic analysis (Fig. 2) confirmed the structure of **10** (CCDC 615732).[15] (*R*)-Oxazolidin-2-one derivative **6** and (*R*)-Garner's aldehydes **4**/**12** under identical conditions gave exclusively one isomer **11**/**13**, the structures of which were confirmed by X-ray crystallography.[12] In summary, the combination of **3** and **4** or **6** and **7** were mismatched favouring both *syn–anti* (non-Evans' *anti*) and *syn–syn* (non-Evans' *syn*) isomers, while that of **3** and **7** or **6** and **4** were matched leading to only the *syn–syn* (Evans' *syn*) isomer (Scheme 2).

Our next task was to demonstrate the novel use of these intermediates in the synthesis of 3-hydroxy-4-methyl-

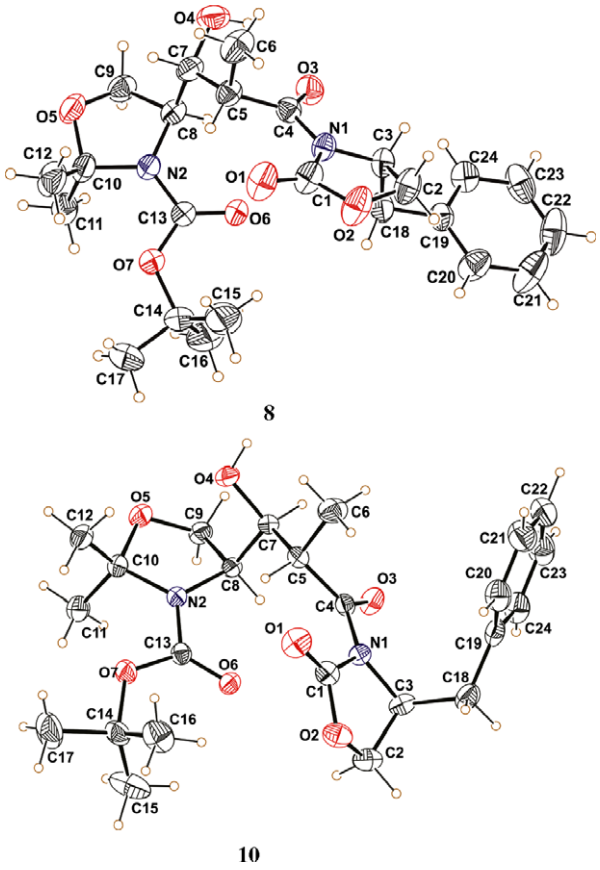
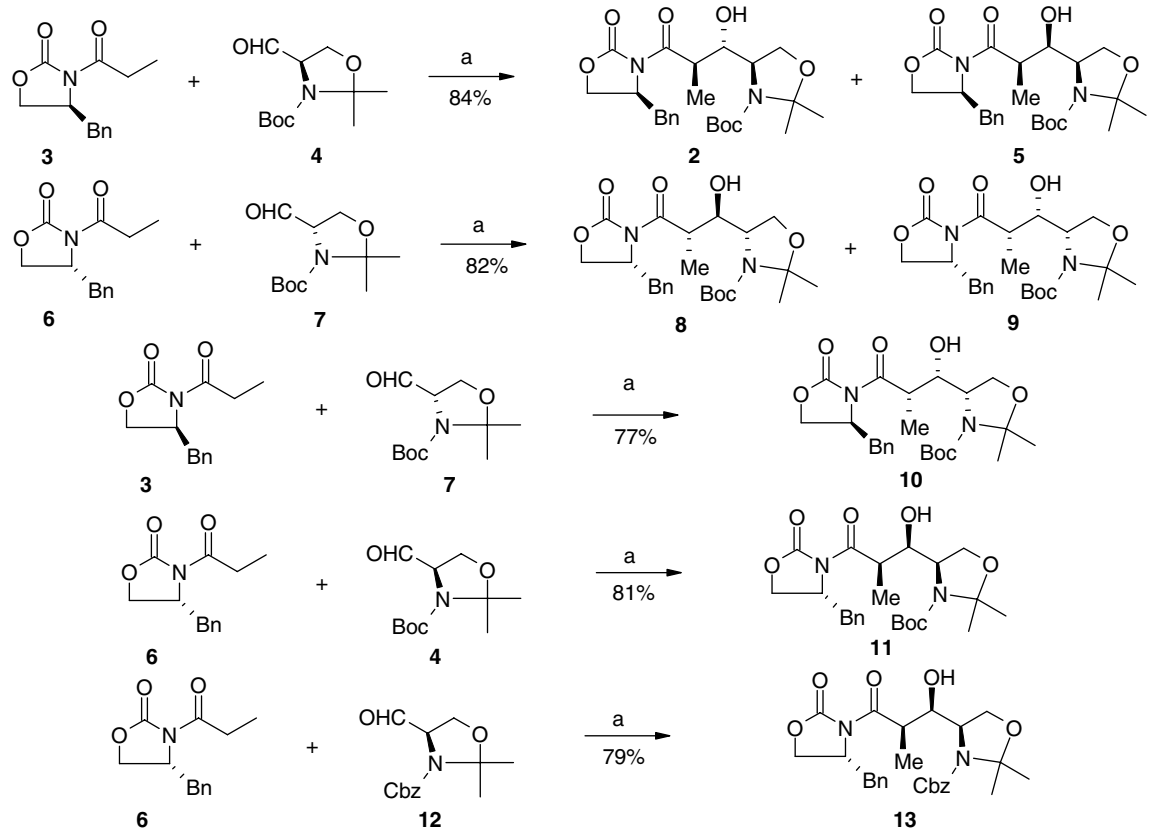
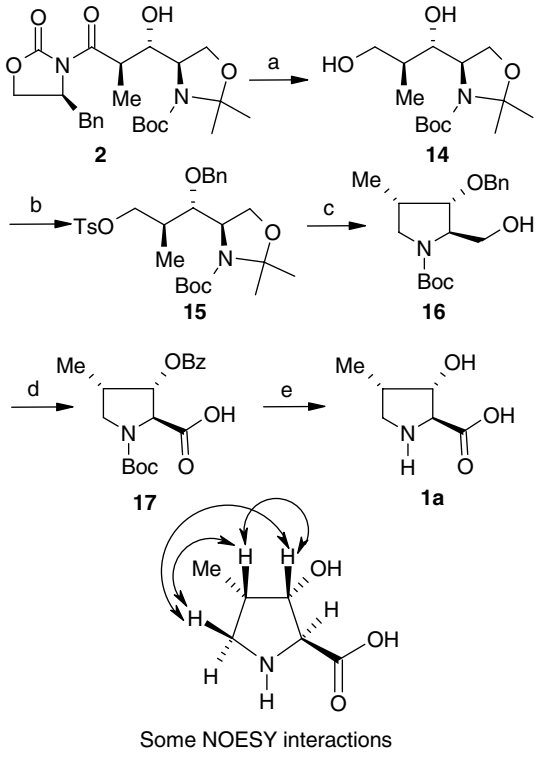


Figure 2. ORTEP diagrams of **8** and **10**.

proline. Reductive hydrolysis[17] of the oxazolidinone ring of **2** with lithium borohydride generated primary alcohol **14**. A protection–deprotection sequence shown in Scheme 3 furnished the tosyl derivative **15** which was subjected to cyclization in the presence of *p*-TSA-MeOH to give the appropriately substituted pyrrolidine deriva-



Scheme 2. Reagents and conditions: (a) $TiCl_4$ (1.1 equiv), DIEA (2.5 equiv), CH_2Cl_2, 0 °C, 2 h.



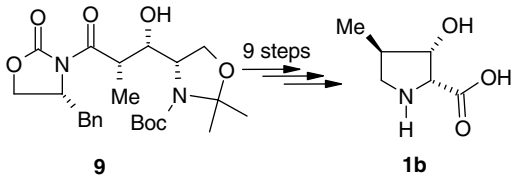
Some NOESY interactions

Scheme 3. Reagents and conditions: (a) LiCl, $NaBH_4$, EtOH/THF (2:1), 0 °C, 4 h, 92%; (b) (i) TBDMSCl, Et_3N, DMAP (cat.), CH_2Cl_2, 0 °C, 6 h, 90%; (ii) NaH, BnBr, DMF, 0 °C to rt, 1 h, 91%; (iii) TBAF, THF, 0 °C to rt, 3 h, 89%; (iv) TsCl, Et_3N, CH_2Cl_2, 0 °C, 6 h, 97%; (c) *p*-TSA, MeOH, rt, 3 h, 76%; (d) $RuCl_3$, $NaIO_4$ (aq), EtOAc, rt, 1 h, 86%; (e) (i) 6 N HCl, 80 °C, 40 h; (ii) Dowex 50 × 4 (H^+ form), 82%.

tive **16**. The structure was confirmed from spectral and analytical data.[18] RuO_4 oxidation of **16** afforded the 3-benzoyloxy-4-methylproline derivative **17** where benzyl ether had been oxidized to a benzoate ester during the oxidation of hydroxymethyl functionally to a carboxyl group, which on heating with 6 N HCl produced 3-hydroxy-4-methylproline as its hydrochloride salt. The crude product was passed through a column of Dowex 50W × 4 (H^+ form) resin to secure 3-hydroxy-4-methylproline (**1a**) as a white solid whose ^1H, ^{13}C NMR and IR data[19] were in excellent agreement with reported values.[11k] The specific rotation of **1a** was $[\alpha]_D^{25}$ −26.6 (*c* 1.0, H_2O) {lit.[11k] for **1a** $[\alpha]_D^{25}$ −27.0 (*c* 0.8, H_2O)} (Scheme 3). The stereochemistry of HMP **1a** was assigned on the basis of the vicinal coupling constants ($J_{3,4} = 3.8$ Hz for the *cis* relationship) and the singlet at 4.14 ppm indicating a *trans* relationship with respect to H-2 and H-3. Further, a *cis* relationship between the substituents at C-3 and C-4 in **1a** was supported by the strong *n*Oe interaction between H-3 and H-4.

Similarly, compound **9** was taken through all nine steps described above leading to the formation of (2*R*,3*S*,4*R*)-HMP (**1b**) (Scheme 4). The structure of **1b** was confirmed from spectral and analytical data;[20] the absolute configuration was ascertained from the NOESY experiment.

In summary, we have comprehensively studied the outcome of the Evans' aldol reaction with both isomers of oxazolidin-2-one and Garner's aldehyde and achieved the synthesis of (2*S*,3*S*,4*S*)-HMP (**1a**) (from



Scheme 4. Synthesis of **1b**.

commercially available (*S*)-oxazolidin-2-one and (*R*)-Garner's aldehyde) in 10 steps with 29% overall yield better than that of Takeya's method,[11a] one of the shortest procedure in the literature (12 steps, 22% overall yield). We have also demonstrated a short and efficient stereoselective route to all stereoisomers of 3-hydroxy-4-methylproline (HMP) starting from the aldol products. Different analogues of this class of cyclic peptides are the focus of our ongoing work in order to study the effect of this segment (HMP stereoisomers) on their biological activity. Studies on the synthesis of other biologically active natural products from Evans' aldol adducts are in progress and will be reported in due course.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.10.137.

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14. *Analytical and spectral data of compound* **8**. $[\alpha]_D^{25}$ −37.7 (*c* 1.5, $CHCl_3$); IR ($CHCl_3$): 1688, 1781 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.40 (d, 3H, $J = 7.2$ Hz), 1.48 (s, 9H), 1.50 (s, 3H), 1.60 (s, 3H), 2.73 (dd, 1H, $J = 11.2$, 13.8 Hz), 3.48 (dt, 1H, $J = 2.8$, 11.2 Hz), 3.67 (dd, 1H, $J = 2.8$, 13.8 Hz), 3.83 (dq, 1H, $J = 2.8$, 7.2 Hz), 3.94 (dd, 1H, $J = 5.6$, 9.0 Hz), 4.0 (d, 1H, $J = 10.9$ Hz), 4.09 (dd, 1H, $J = 5.6$, 9.0 Hz), 4.13–4.18 (m, 2H), 4.29 (d, 1H, $J = 9.0$ Hz), 4.57–4.63 (m, 1H), 7.26–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 15.8, 24.0, 27.9, 28.4, 37.1, 37.8, 55.7, 59.9, 65.1, 65.8, 75.4, 80.2, 93.7, 126.9, 128.7,

129.1, 136.5, 152.2, 153.2, 177.8; Anal. Calcd for $C_{24}H_{34}N_2O_7$: C, 62.32; H, 7.41; N, 6.06; Found: C, 62.20; H, 7.45; N, 6.10.

15. Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 615731 for **8** and CCDC 615732 for **10**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 0 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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18. *Analytical and spectral data of compound* **16**. $[\alpha]_D^{25}$ −53.7 (*c* 1.75, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 1.07 (d, 3H, $J = 6.4$ Hz); 1.46 (s, 9H), 2.20–2.38 (m, 1H), 3.17 (t, 1H, $J = 10.3$ Hz), 3.46 (dd, 1H, $J = 7.3$, 10.3 Hz), 3.58–3.84 (m, 3H), 4.05 (t, 1H, $J = 5.4$ Hz), 4.45 (d, 1H, $J = 11.9$ Hz), 4.65 (d, 1H, $J = 11.9$ Hz), 7.23–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 11.3, 28.4, 35.7, 52.1, 64.7, 65.5, 71.1, 80.2, 81.7, 127.6, 127.7, 128.4, 138.0, 156.9; Anal. Calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.22; H, 8.39; N, 4.31.
19. *Analytical and spectral data of compound* **1a**. Mp 259–260 °C (decomp.); $[\alpha]_D^{25}$ −26.6 (*c* 1.0, H_2O); IR (Nujol): 1377, 1460, 1620, 3059, 3311 cm^{-1}; ^1H NMR (D_2O, 400 MHz): δ 1.11 (d, 3H, $J = 6.8$ Hz), 2.25–2.36 (m, 1H), 3.11 (t, 1H, $J = 11.5$ Hz), 3.66 (dd, 1H, $J = 7.8$, 11.5 Hz), 4.14 (s, 1H), 4.48 (d, 1H, $J = 3.8$ Hz); ^{13}C NMR (D_2O + acetone-d_6, 100 MHz): 11.8, 39.0, 51.6, 71.8, 78.2, 174.1.
20. *Analytical and spectral data of compound* **1b**. Mp 218–219 °C (decomp.); $[\alpha]_D^{25}$ +21.1 (*c* 1.0, H_2O); IR (Nujol): 1377, 1454, 1461, 1604, 3062, 3363 cm^{-1}; ^1H NMR (D_2O, 400 MHz): δ 1.10 (d, 3H, $J = 7.3$ Hz), 2.32–2.42 (m, 1H), 3.18 (dd, 1H, $J = 7.5$, 11.8 Hz), 3.66 (dd, 1H, $J = 7.0$, 11.8 Hz), 3.98 (d, 1H, $J = 4.3$ Hz), 4.21 (t, 1H, $J = 4.8$ Hz); ^{13}C NMR (D_2O + acetone-d_6, 100 MHz): 16.5, 42.8, 52.3, 69.4, 82.0, 174.6.