## Total synthesis of (+)-pramanicin and stereochemical elucidation of the natural product

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## Total synthesis of (+)-pramanicin is achieved through a 'one pot' Michael addition of an aminosilyl zincate species to an $\alpha$ , $\beta$ -unsaturated lactam and quenching of the resultant enolate with an $\alpha$ , $\beta$ -unsaturated $\gamma$ , $\delta$ -epoxy aldehyde.

(–)-Pramanicin 1, recently isolated from a fungus belonging to the *Stagonospora* species, contains a highly functionalised  $\gamma$ lactam-based head group with a functionalised lipophilic side chain.<sup>1</sup> The isolated compound shows antifungal activity towards various fungal pathogens including *Candida albicans*, *Candida parapsilosis* and *Cryptococcus neoformans*. The latter micro-organism is responsible for meningitis infection in AIDS patients and therefore pramanicin 1 poses an interesting target for synthesis. Recently, Harrison and co-workers have elucidated the biosynthesis of pramanicin and showed that the carbon skeleton derives from eight acetate units and a serine residue.<sup>2†</sup> Herein we report the total synthesis of (+)-pramanicin 9 which unequivocally establishes the full relative and absolute stereochemistry of the natural product.

Retrosynthetically, pramanicin can be divided into two fragments, the suitably protected lactam 2 derived from L-glutamic acid and the side chain epoxy aldehyde  $3.\ddagger$  We envisaged that these two components could be joined *via* the

addition of a silyl entity (masked hydroxy group) in a conjugate fashion to **2** and trapping of the resultant enolate with the aldehyde **3**. The addition of this silyl group should occur in an *anti* fashion to the TBDMS protected hydroxymethyl pendant, thus establishing the correct stereochemistry of the secondary alcohol following Tamao oxidation<sup>4</sup> (Scheme 1).

Thus, reaction of lactam 2 with a 1:1 mixture of (diethylamino)diphenylsilyllithium and diethylzinc at -78 °C and trapping of the resulting enolate with the aldehyde 3 followed by ethanolysis of the sensitive silylamine furnished compound 4 (60%). This reaction clearly establishes the complete carbon backbone of pramanicin with a readily oxidisable alkoxysilyl appendage. Confirmation of the stereochemical outcome of the silyl zincate addition has been made *via* addition of the phenyldimethylsilyl<sup>5</sup> group to lactam 2 under identical conditions and removal of the protecting groups to afford 11 for single crystal X-ray analysis¶ (Scheme 2).

Oxidation of the  $\beta$ -hydroxy lactam 4 to the corresponding diketone 5 could only be accomplished using Dess-Martin periodinane as oxidant. Chromium based reagents led to extensive decomposition and no reaction was observed using manganese dioxide. The diketone 5 proved to be unstable to prolonged exposure to air and to chromatography thus preclud-



Scheme 1 *Reagents and conditions*: i,  $(Et_2N)Ph_2SiLi$ ,  $Et_2Zn$ , -78 °C, then 3, THF, -78 °C, then EtOH, NH<sub>4</sub>Cl, 24 h, 60%; ii, Dess–Martin periodinane, CH<sub>2</sub>Cl<sub>2</sub>, 0 to 25 °C; iii, dimethyldioxirane, Ni(acac)<sub>2</sub> (cat.), acetone, H<sub>2</sub>O, 0 °C, 60% from 4; iv, MCPBA (3 equiv.), KHF<sub>2</sub> (2.5 equiv.), DMF, 0 °C, 53%; v, SiO<sub>2</sub>,45 °C, 0.1 mmHg, 84%; vi, H<sub>2</sub>SiF<sub>6</sub> (20–25% aq.), THF, 0 to 25 °C, 53%; vii, Dess–Martin periodinane, CH<sub>2</sub>Cl<sub>2</sub>, 0 to 25 °C; viii, dimethyldioxirane, Ni(acac)<sub>2</sub> (cat.), acetone, H<sub>2</sub>O, 0 °C, 53%; vii, Dess–Martin periodinane, CH<sub>2</sub>Cl<sub>2</sub>, 0 to 25 °C; viii, dimethyldioxirane, Ni(acac)<sub>2</sub> (cat.), acetone, H<sub>2</sub>O, 0 °C, 59% from 8; ix, MCPBA (3 equiv.), KHF<sub>2</sub> (2.5 equiv.), DMF, 0 °C, 70%; x, TFA, CH<sub>2</sub>Cl<sub>2</sub>, 0 to 25 °C, 78%; xi, H<sub>2</sub>SiF<sub>6</sub> (20–25% aq.), THF, 0 to 25 °C, 55%.



Scheme 2 Reagents and conditions: i, PhMe<sub>2</sub>SiLi, Et<sub>2</sub>Zn, THF, -78 °C, 99%; ii, TBAF, THF, 80%; iii, TFA, CH<sub>2</sub>Cl<sub>2</sub>, 85%.

ing its purification. Therefore immediate oxidation of the diketone unit with dimethyldioxirane and a nickel(II) acetvlacetonate<sup>6</sup> catalyst gave hydroxy dione 6 as a single diastereoisomer in excellent overall yield (60%). The ethoxy-(diphenvl)silvl group blocked the top face of the diketone directing reaction to the opposite face and thus setting the configuration of the tertiary alcohol as required. Tamao oxidation of silane 6 proceeded smoothly at low temperature with MCPBA as oxidant to produce the secondary alcohol with retention of configuration as desired. The use of peracetic acid or hydrogen peroxide as alternative oxidants gave only intractable mixtures of products. Removal of the Boc group via thermolysis on silica under vacuum<sup>7</sup> followed by deprotection of the TBDMS moiety using fluorosilicic acid<sup>8</sup> furnished compound 7 (Scheme 1). Comparison of 7 with authentic pramanicin by NMR analysis revealed very slight differences in the chemical shift of the protons associated with the alkene and the epoxide ring system. Alternatively, synthesis of diastereoisomer 8 using ent-3 as the enolate quench (62%) and elaboration as before yielded isomer 9. This diastereoisomer 9 was identical by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy with authentic pramanicin (see Fig. 1). Whilst the Merck group<sup>1</sup> established the relative stereochemistry of the  $\gamma$ -lactam ring of the natural



**Fig. 1** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) spectra showing olefinic resonance's (left) and protons  $\alpha$  to epoxide ( $\delta \sim 1.6$ , right); top: diastereoisomer **7**; middle: diastereoisomer **9**; bottom: authentic pramanicin.

product and that the side chain epoxide was *trans*, they did not establish the stereochemistry of the side chain relative to the lactam entity. In their paper, pramanicin was depicted (arbitrarily) as *ent*-7. This work clearly establishes the relative stereochemistry to be as in isomer 9. However, the optical rotation of isomer 9 ( $[\alpha]_D^{25}$  +28.8, *c* 0.21 in MeOH) is of opposite sign to that reported for authentic pramanicin ( $[\alpha]_D^{25}$  -31.5, *c* 0.21 in MeOH) and thus indicates the absolute stereochemistry of pramanicin to be that of 1.

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## Notes and references

<sup>†</sup> Harrison and co-workers have also published a biomimetic synthesis of the fatty acid side chain of pramanicin in racemic form; see ref. 3.

‡ Aldehyde **3** was prepared from (*E*)-dodec-2-enol *via* Sharpless asymmetric epoxidation, oxidation to the aldehyde using Dess–Martin periodinane, Horner–Emmons homologation under standard conditions and reduction of the  $\alpha$ , $\beta$ -unsaturated ester using DIBAL-H followed by oxidation to give aldehyde **3**, again employing Dess–Martin periodinane as oxidant (55% overall)

§ Lactam 2 was prepared from pyroglutamic acid methyl ester *via* NaBH<sub>4</sub> reduction to the alcohol, protection of the alcohol as the TBDMS ether and Boc protection of the amide under standard conditions.  $\alpha$ -Selenation employing LDA and phenylselenyl bromide followed by *syn* elimination using hydrogen peroxide and pyridine afforded lactam 2 (46% overall).

 $\P$  Full details of the X-ray crystallographic studies on lactam 11 will be reported elsewhere.

Note added at proof: Harrison and co-workers have recently determined the absolute stereochemisty of the lactam entity of pramanicin from biosynthetic considerations; see ref. 9.

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