## A stereocontrolled enantiospecific route to tirandamycin B

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The enal 15 was synthesized in enantiomerically pure form starting from (S)-3-benzyloxy-2-methylpropanol 3 *via* highly regio- and stereo-selective methylation of the  $\gamma$ , $\delta$ -epoxy acrylate 5 with trimethylaluminium in the presence of water, developing an enantiospecific route to tirandamycin B.

Tirandamycin B 1 was isolated together with tirandamycin A 2 from a culture broth of Streptomyces flaveolus.<sup>1</sup> Both are representative members of the dienoyl tetramic acid family of antibiotics and possess potent antimicrobial activity as well as inhibitory activity against bacterial DNA-directed RNA polymerase.<sup>2</sup> In 1991, DeShong and coworkers succeeded in the first synthesis of tirandamycin B in racemic form.<sup>3</sup> This is the only complete synthesis of this antibiotic reported so far although there have been several reports concerning the synthesis of racemic and optically active tirandamycin A.4-6 Recently, we have developed a novel regio- and stereo-selective methylation reaction of  $\gamma$ ,  $\delta$ -epoxy acrylates with trimethylaluminium in the presence of water,7 which provides a useful route to polypropionate chains.8 We report here a stereocontrolled enantiospecific synthesis of enal 15, DeShong's key intermediate for the synthesis of tirandamycin B, from (S)-3-benzyloxy-2methylpropanol 3 employing this methodology for the assembly of its polypropionate chain structure.

The known epoxy alcohol 4,9 readily available from (S)-3-benzyloxy-2-methylpropanol 3, was subjected to Swern oxidation followed by Wittig reaction in the same flask<sup>10</sup> to give the  $\gamma$ , $\delta$ - epoxy acrylate 5,† [ $\alpha$ ]<sub>D</sub><sup>22</sup> +7.3 (*c* 0.97, CHCl<sub>3</sub>), in 96% yield. Upon treatment of 5 with trimethylaluminium in the presence of water,<sup>7</sup> the methylation reaction took place with complete regio- and stereo-selectivity to give the alcohol 6, [ $\alpha$ ]<sub>D</sub><sup>22</sup> -6.4 (*c* 0.50, CHCl<sub>3</sub>), as the sole product in 88% yield. No isomeric products were produced. After protection of the hydroxy group of 6 as its triethylsilyl ether, selective debenzylation was effected cleanly by hydrogenolysis using Lindlar catalyst in diethyl ether‡ to give the alcohol 7, [ $\alpha$ ]<sub>D</sub><sup>22</sup> -18.9 (*c* 1.69, CHCl<sub>3</sub>), in 93% yield. Swern oxidation of 7 afforded the corresponding aldehyde which was directly submitted to condensation with the furyllithium generated from 8 by the action of *tert*-butyllithium,<sup>3</sup> giving a 3:2 epimeric mixture of the furfuryl alcohols 9a, [ $\alpha$ ]<sub>D</sub><sup>22</sup> +19.2 (*c* 0.86, CHCl<sub>3</sub>), and 9b, [ $\alpha$ ]<sub>D</sub><sup>22</sup> -7.1 (*c* 1.81, CHCl<sub>3</sub>), in 70% yield. In this particular



case, elongation of the reaction period and elevation of the reaction temperature from -78 °C to room temperature resulted in cyclisation of the  $\alpha$ -alcohol **9b** to the tetrahydropyran **10**, making isolation of the unchanged  $\beta$ -alcohol **9a** easy.§ Treatment of **9a** with MCPBA brought about smooth oxidative cyclisation<sup>5,6</sup> to give the pyranone **11** as an inseparable epimeric mixture in 85% yield.

The crucial assembly of the 2,9-dioxabicyclo[3.3.1]nonane framework followed DeShong's protocol.<sup>3</sup> Thus, exposure of **11** to a mixture of hydrofluoric acid and fluorosilicic acid in acetonitrile allowed simultaneous selective desilylation of the triethylsilyl group and intramolecular ketalisation to provide the bicyclic enone **12**,  $[\alpha]_D^{22} + 105.5$  (*c* 1.45, CHCl<sub>3</sub>), in 74% yield. Reduction of **12** with sodium borohydride in the presence of cerium(III) chloride<sup>11</sup> gave the allylic alcohol **13**,  $[\alpha]_D^{22} - 2.5$  (*c* 0.4, CHCl<sub>3</sub>), and oxidation of the latter with MCPBA afforded the epoxide **14**,  $[\alpha]_D^{22} - 14.7$  (*c* 1.65, CHCl<sub>3</sub>), in 62% yield. Reduction of **14** with DIBAL-H followed by oxidation with pyridinium dichromate furnished the enal **15** thus obtained exhibited identical spectral properties (<sup>1</sup>H and <sup>13</sup>C NMR, IR) to those of the racemic enal.<sup>3</sup>

Since the racemic enal has already been converted to  $(\pm)$ -tirandamycin B in good overall yield,<sup>3</sup> the present work enables us to synthesize natural tirandamycin B as well as its antipode starting from either (*R*)- or (*S*)-3-benzyloxy-2-methylpropanol.

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## Footnotes

<sup>†</sup> All new compounds exhibited satisfactory spectra (<sup>1</sup>H and <sup>13</sup>C NMR, IR) and HRMS analytical data.

<sup>‡</sup> After filtration of the reaction mixture through Celite, the filtrate was washed with saturated NaHCO<sub>3</sub>. Without this operation, the triethylsilyl ether was partly cleaved during evaporation.

§ When the reaction mixture was allowed to stand at room temperature for 12 h, 9a and 10 were produced in 42 and 35% yield, respectively.

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Scheme 1 Reagents and conditions: i, (COCl)<sub>2</sub>, Me<sub>2</sub>SO, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, -60 to 25 °C, then Ph<sub>3</sub>P=C(Me)CO<sub>2</sub>Et; ii, Me<sub>3</sub>Al in hexane (2 mol dm<sup>3</sup>, 10 equiv.), H<sub>2</sub>O (6 equiv.), ClCH<sub>2</sub>CH<sub>2</sub>Cl, -30 °C; iii, Et<sub>3</sub>SiCl, imidazole, DMAP (cat.), CH<sub>2</sub>Cl<sub>2</sub>; iv, H<sub>2</sub>, 10% Pd–BaSO<sub>4</sub>, Et<sub>2</sub>O; v, (COCl)<sub>2</sub>, Me<sub>2</sub>SO, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, -60 to 25 °C; vi, **8** (3 equiv.), Bu<sup>1</sup>Li in hexane (1.8 mol dm<sup>-3</sup>, 3 equiv.), TMEDA (3 equiv.), Et<sub>2</sub>O, 0 °C, then the aldehyde, -78 °C; vii, MCPBA, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; viii, 48% HF (1.5 equiv.), 25% H<sub>2</sub>SiF<sub>6</sub> (1.5 equiv.), MeCN (5 × 10<sup>-3</sup> mol dm<sup>-3</sup>); ix, NaBH<sub>4</sub>, CeCl<sub>3</sub>, MeOH; x, MCPBA, NaH<sub>2</sub>PO<sub>4</sub>·2H<sub>2</sub>O, 1% H<sub>2</sub>O-CH<sub>2</sub>Cl<sub>2</sub>; xi, DIBAL-H, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C; xii, PDC, CH<sub>2</sub>Cl<sub>2</sub>

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