A stereocontrolled enantiospecific route to tirandamycin B

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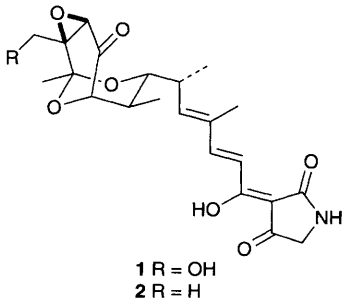
The enal 15 was synthesized in enantiomerically pure form starting from (*S*)-3-benzyloxy-2-methylpropanol 3 *via* highly regio- and stereo-selective methylation of the γ,δ-epoxy acrylate 5 with trimethylaluminium in the presence of water, developing an enantiospecific route to tirandamycin B.

Tirandamycin B **1** was isolated together with tirandamycin A **2** from a culture broth of *Streptomyces flaveolus*.[1] 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.[2] In 1991, DeShong and coworkers succeeded in the first synthesis of tirandamycin B in racemic form.[3] 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 γ,δ-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-2-methylpropanol **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[10] to give the γ,δ- epoxy acrylate **5**,† $[\alpha]_D^{22}$ +7.3 (*c* 0.97, $CHCl_3$), in 96% yield. Upon treatment of **5** with trimethylaluminium in the presence of water,[7] the methylation reaction took place with complete regio- and stereo-selectivity to give the alcohol **6**, $[\alpha]_D^{22}$ −6.4 (*c* 0.50, $CHCl_3$), 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**, $[\alpha]_D^{22}$ −18.9 (*c* 1.69, $CHCl_3$), 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,[3] giving a 3:2 epimeric mixture of the furfuryl alcohols **9a**, $[\alpha]_D^{22}$ +19.2 (*c* 0.86, $CHCl_3$), and **9b**, $[\alpha]_D^{22}$ −7.1 (*c* 1.81, $CHCl_3$), 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 α-alcohol **9b** to the tetrahydropyran **10**, making isolation of the unchanged β-alcohol **9a** easy.§ Treatment of **9a** with MCPBA brought about smooth oxidative cyclisation[5,6] to give the pyranone **11** as an inseparable epimeric mixture in 85% yield.



1 R = OH
2 R = H

The crucial assembly of the 2,9-dioxabicyclo[3.3.1]nonane framework followed DeShong's protocol.[3] 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, $CHCl_3$), in 74% yield. Reduction of **12** with sodium borohydride in the presence of cerium(III) chloride[11] gave the allylic alcohol **13**, $[\alpha]_D^{22}$ −2.5 (*c* 0.4, $CHCl_3$), and oxidation of the latter with MCPBA afforded the epoxide **14**, $[\alpha]_D^{22}$ −14.7 (*c* 1.65, $CHCl_3$), in 62% yield. Reduction of **14** with DIBAL-H followed by oxidation with pyridinium dichromate furnished the enal **15**, $[\alpha]_D^{22}$ −4.0 (*c* 0.53, $CHCl_3$), in 82% yield. The enal **15** thus obtained exhibited identical spectral properties (^1H and ^{13}C NMR, IR) to those of the racemic enal.[3]

Since the racemic enal has already been converted to (±)-tirandamycin B in good overall yield,[3] 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.

We thank Professor Philip DeShong (University of Maryland, USA) for providing us with spectral data of the racemic enal.

Footnotes

† All new compounds exhibited satisfactory spectra (^1H and ^{13}C NMR, IR) and HRMS analytical data.
‡ After filtration of the reaction mixture through Celite, the filtrate was washed with saturated $NaHCO_3$. 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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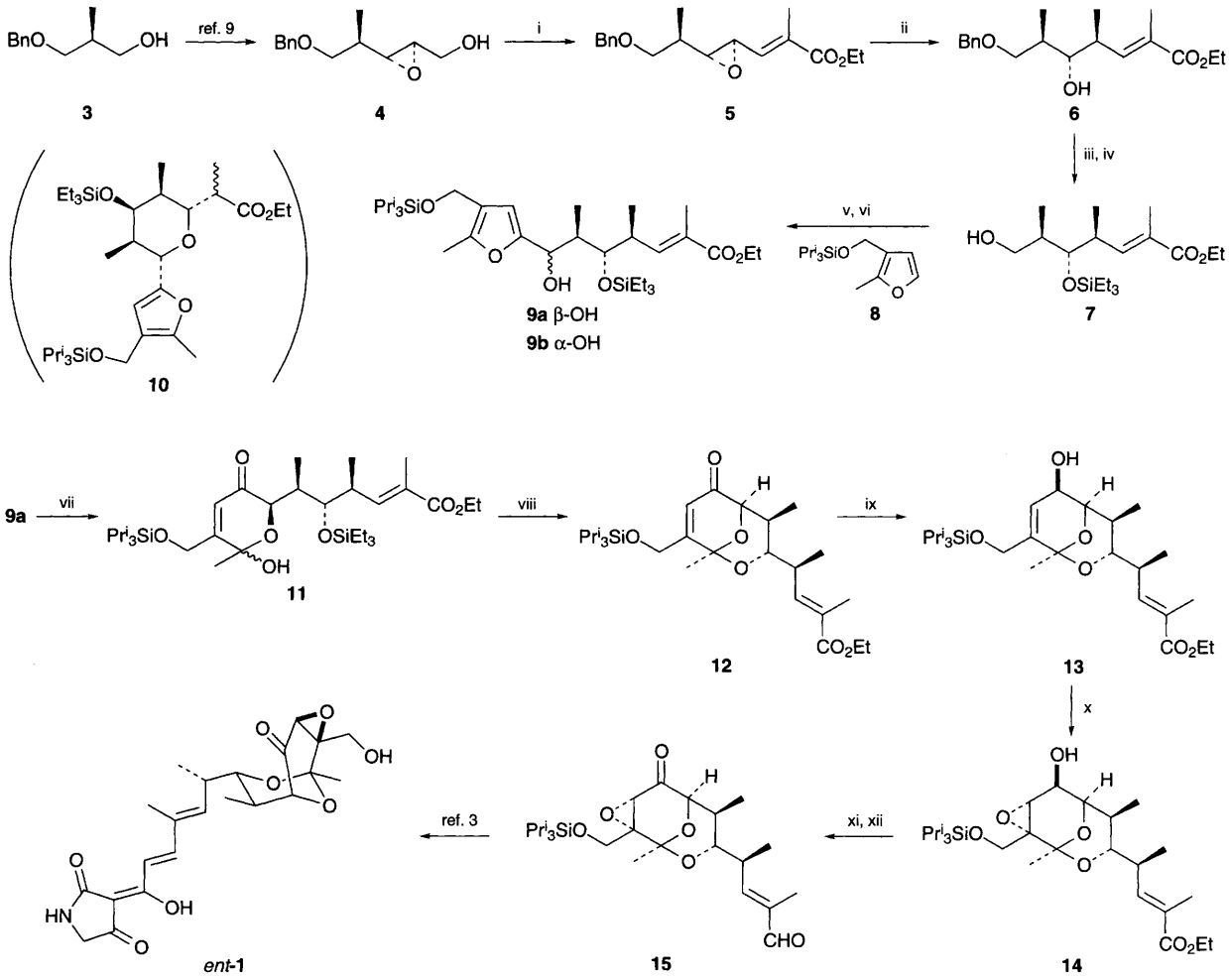

Scheme 1 *Reagents and conditions*: i, $(COCl)_2$, Me_2SO, Et_3N, CH_2Cl_2, −60 to 25 °C, then $Ph_3P{=}C(Me)CO_2Et$; ii, Me_3Al in hexane (2 mol dm^3, 10 equiv.), H_2O (6 equiv.), $ClCH_2CH_2Cl$, −30 °C; iii, Et_3SiCl, imidazole, DMAP (cat.), CH_2Cl_2; iv, H_2, 10% Pd–$BaSO_4$, Et_2O; v, $(COCl)_2$, Me_2SO, Et_3N, CH_2Cl_2, −60 to 25 °C; vi, **8** (3 equiv.), Bu^tLi in hexane (1.8 mol dm^{-3}, 3 equiv.), TMEDA (3 equiv.), Et_2O, 0 °C, then the aldehyde, −78 °C; vii, MCPBA, CH_2Cl_2, 0 °C; viii, 48% HF (1.5 equiv.), 25% H_2SiF_6 (1.5 equiv.), MeCN (5×10^{-3} mol dm^{-3}); ix, $NaBH_4$, $CeCl_3$, MeOH; x, MCPBA, $NaH_2PO_4{\cdot}2H_2O$, 1% H_2O–CH_2Cl_2; xi, DIBAL-H, CH_2Cl_2, −78 °C; xii, PDC, CH_2Cl_2

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