Stereocontrolled Synthesis of the Taxol C-13 Side Chain: Methyl (2*R*,3*S*)-3-Benzoylamino-2-hydroxy-3-phenylpropanoate

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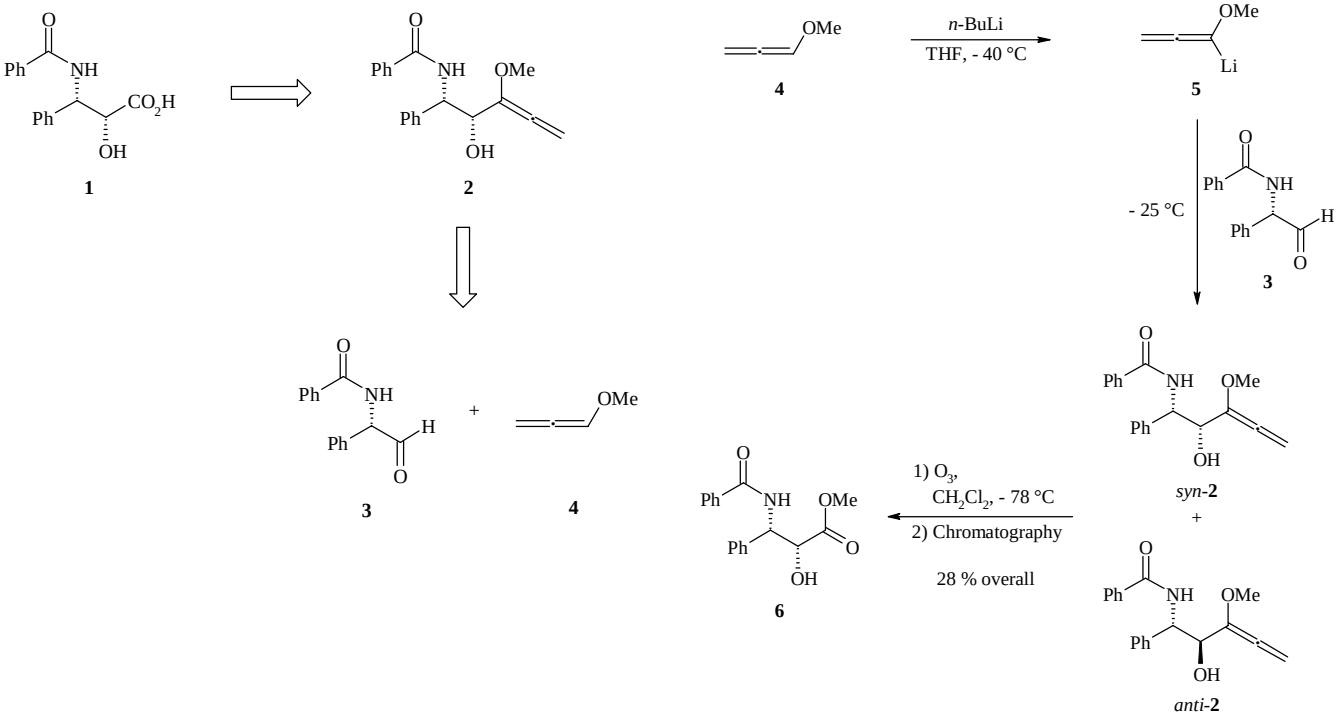
Received June 23rd, 1999

Keywords: Allenes, Amino acids, Amino aldehydes, Lithiation, Ozonolysis

Abstract: Addition of lithiated methoxyallene **5** to literature-known amino aldehyde **3** followed by ozonolysis provided *syn*-configurated α-hydroxy-β-amino ester **6** in moderate overall yield and with an *ee* of 90%. The predominant formation of *syn*-compounds may be due to a chelate controlled addition step.

α-Hydroxy-β-amino acids are present in a number of biologically active compounds and therefore their stereoselective syntheses were object of many recent investigations [1]. We have already described preparation of several *anti*-(2*S*,3*S*)-α-hydroxy-β-amino esters by stereoselective addition of lithiated methoxyallene to optically active *N*-benzyl-BOC-protected amino aldehydes followed by ozonolysis [2]. We anticipated that a modification of the *N*-protecting group could lead to predominant *syn*-configurated products and therefore we envisaged a synthesis of (2*R*,3*S*)-3-benzoylamino-2-hydroxy-3-phenylpropanoic acid (**1**) – the C-13 side chain of the important antitumor drugs Taxol and Taxotere™ [3]. The methyl ester of **1** should be available by ozonolysis of **2** which may arise from literature-known amino aldehyde **3** [4] and methoxyallene **4** [5].

Lithiation of methoxyallene **4** was performed under standard conditions [6] in THF, and to the resulting solution of **5** freshly prepared aldehyde **3** was added to give a mixture of *syn*-**2** (major) and *anti*-**2** (minor). The best yield, highest ratio of diastereomers (85:15), and purity were obtained by reaction of 8 equivalents of **5** with **3** at – 25 °C. Lower or higher temperatures and addition of cerium trichloride or diethylaluminum chloride as Lewis acids did not improve the result. Also, an attempt to generate a cuprate from **5** [7] was unsuccessful giving only an intractable product mixture after reaction with aldehyde **3**. The crude product *syn*-**2**/*anti*-**2** could not be purified, but after ozonolysis under standard conditions a mixture of methyl esters was obtained from which the desired *syn*-**6** could be isolated in pure crystalline form in 28% overall yield. The optical rotation of **6** could be com-



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pared with a literature value and it indicates an *ee* of 90%. Since aldehyde **3** has a relatively high tendency to racemize it is possible that this process had occurred during reaction of **5** with **3** [8]. The predominant formation of *syn*-**2** can be interpreted with the model of chelate control [9].

Support of this work by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is most gratefully acknowlegded.

Experimental

Starting materials: **3**[4], **4**[5]. For general informations see [10].

(1S,2R)- and *(1S,2S)-N-(2-hydroxy-3-methoxy-1-phenylpenta-3,4-dienyl)benzamide (syn-**2**)* and *(anti-**2**)*

Lithiated methoxyallene **5** was generated under an atmosphere of dry argon by treating a solution of 0.492 g (7.00 mmol) of **4** in 20 ml of THF at −40 °C with 2.7 ml (6.25 mmol) of *n*-BuLi (2.5M in hexane). After warming the solution to −25 °C, a solution of 0.168 g (0.70 mmol) of **3** in 10 ml of THF was added over a period of 10 min. The mixture was quenched after 20 min with 5 ml of ice water. Warming to 10 °C was followed by extraction with diethyl ether (3 × 10 ml) and drying of the combined extracts with $MgSO_4$. Removal of solvents and volatile components *in vacuo* yielded 0.181 g (75%) of crude **2** (*syn* : *anti* = 85 : 15) as a brownish oil which was not purified. – ^{1}H NMR ($CDCl_3$, 300 MHz): δ/ppm = 7.80−7.70, 7.50−7.10 (2 m, 2H, 8H, Ph), 5.53 (d, J = 2.3 Hz, 2H, 5-H), 4.52 (s_{broad}, 1H, NH), 3.40 (s, 3H, OMe) unambiguous assignment of the missing signals of *syn*-**2** and those of *anti*-**2** was not possible with this crude product sample. – ^{13}C NMR ($CDCl_3$, 75.5 MHz), *syn*-**2**: δ/ppm = 197.0 (s, C-4), 167.2 (s, C=O), 139.7 (s, C-3), 134.5, 134.2 (2s, Ph), 131.3 (d, Ph), 128.4−126.7 (several d, Ph), 93.6 (t, C-5), 73.3 (d, C-2), 56.7 (q, OMe), 55.9 (d, C-1); *anti*-**2**: δ/ppm = 197.2 (s, C-4), 166.8 (s, C=O), 139.4 (s, C-3), 93.4 (t, C-5), 72.7 (d, C-2); other signals could not be assigned due to overlap with signals of the major isomer.

Methyl (2R,3S)-3-benzoylamino-2-hydroxy-3-phenylpropanoate (**6**)

A solution of crude *syn*/*anti*-**2** (0.181 g; 0.58 mmol) in CH_2Cl_2 was cooled to −78 °C and ozone was bubbled through the mixture until a blue colour persisted. Excess of ozone was purged out with oxygen, and the mixture was allowed to warm up to −20 °C. Ice-water (20 ml) was added, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 ml). Drying of the combined organic phases with $MgSO_4$ and evaporation of the solvent *in vacuo* afforded crude **6** (*syn*: *anti* ≈ 85 : 15) as a brownish oil. After filtration through alumina (III, hexane/EtOAc = 7 : 3) the crude product was further purified by MPLC on alumina (III, hexane/EtOAc = 8.5 : 1.5) providing 0.060 g (28% overall) of pure **6** as colourless crystals. – $[\alpha] = -43°$ (c = 1.0, CH_3OH), [11] : $[\alpha] = -48°$ (c = 0.92, CH_3OH). – ^{1}H NMR ($CDCl_3$, 300 MHz): δ/ppm = 7.78−7.76, 7.53−7.30 (2 m, 2H, 8H, Ph), 6.97 (d_{broad}, $J \approx 9$ Hz, 1H, NH), 5.75 (dd, J = 2.0, 9.0 Hz, 1H, 3-H), 4.64 (t_{broad}, $J \approx 3.0$ Hz, 1H, 2-H), 3.85 (s, 3H, OMe), 3.30 (d, J = 3.9 Hz, 1H, OH).

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