Pergamon

Tetrahedron Vol. 51, No. 35, pp. 9519-9522, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4020/95 $9.50+0.00

0040-4020(95)00541-2

Employment of a Steroidal Aldehyde in a New Synthesis of β-Lactam Derivatives

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Abstract: In this article a ß-lactam-steroid product 4 containing a steroid and a ß-lactam unit is described. Product 4 is easily produced in one step by the means of Ugi reactions. A medium scale high yield procedure for the synthesis of dehydrocholic aldehyde is described.

Multi component reactions are superior in several aspects compared to normal reactions involving two or less starting materials.[1] Not only are these kinds of reactions less time consuming, affording higher yields and often showing higher stereocontrol compared to their sequential analogues, but also especially suitable for the combination of building blocks to construct materials with new properties. In the typical four component reaction (Ugi reaction)[2] an oxo compound, which might be an aldehyde or a ketone reacts together with an amine, an acid component,[3] which mostly is a carboxylic acid and an isocyanide to form a peptide derivative. Apart from the isocyanide functionality, the others are the archaetypes of functionalities in organic chemistry. By taking only commercially available compounds containing these four functionalities, a high diversity[4] of new products can be synthesized.

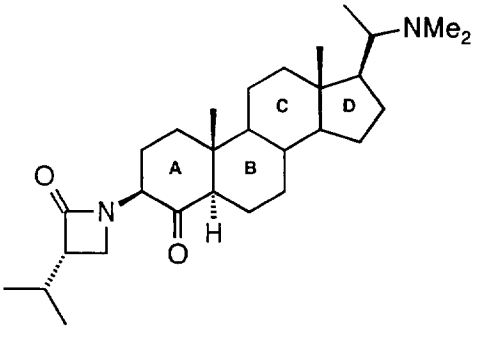


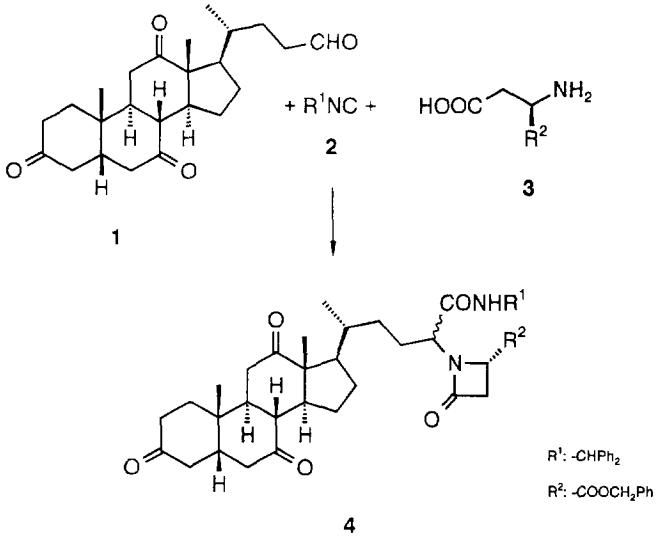
Figure 1: Pachystermin A is a naturally occurring ß-lactam-steroid found in the buxaceous plant *Pachysandra terminalis* Sieb. et Zucc.[5]

In this communication we show for the first time a simple one-pot synthesis of a ß-lactam-steroid product via the building block approach by four component reaction.[6]

Until now, only one natural product is known which contains both a ß-lactam moiety and a steroid moiety (Figure 1).[5]

One building block constitutes the steroid moiety, the ß-lactam moiety is introduced by a ß-amino acid. The steroid is introduced as the oxo component. Therefore, commercially available dehydrocholic acid is reduced to the aldehyde **1** by lithium tri-*tert*-butoxyaluminium hydride.

One ß-amino acid **3**, L-aspartic acid α-benzyl ester[7] and one isocyanide **2** were tested according to Scheme 1, to give the product **4**. In pachystermin A the ß-lactam moiety is attached to ring A in contrast to our product, where it is attached to ring D. Generally, the diasteromeric excesses during ß-lactam syntheses via Ugi-reaction are low due to the great distance of the chiral substituents in the step forming the new stereocenter, a seven-membered ring. Interestingly ß-lactam **4** is formed in an unusual high ratio of 5:1. We were not able to separate the diastereomers by column chromatography.



Scheme 1: Synthesis of one ß-lactam-steroid product **4**

EXPERIMENTAL

Dehydrocholic aldehyde (1)

The reductions were run in a modified procedure according to literature: [8]

N,N-Dimethylchloromethylammonium chloride was synthesized as reported[8] and dissolved in 40 ml of dry THF and 23 ml of dry acetonitrile. This solution was slowly dropped into a suspension of 8 g (20 mmol) dehydrocholic acid and 1.66 g of pyridine in 100 ml of dry THF at -40 °C. After one hour of stirring at -30

°C, the mixture was cooled to -90 °C. Then 5.85 g of lithium tri-*tert*-butoxyaluminium hydride in 10 ml of dry THF was slowly dropped into the mixture. This suspension was further stirred for 30 min at -30 °C. The working up procedure was as follows: 25 ml of 2 m HCl was added, then the resulting mixture was extracted five times with 25 ml of chloroform. The combined extracts were washed twice with 25 ml aqueous conc. sodium hydrogen carbonate, then dried over magnesium sulfate. The solvent was removed with a rotatory evaporator giving 4.5 g (60%)of **1** as a colourless powder.

$C_{24}H_{39}O_3$= 376.6 g/mol; Yield: 4.5 g, (60 %); R_f = 0.30 (EE/H, 1:1, v/v); $[\alpha]_D^{20}$ (c = 1, $CHCl_3$) = +141; Mp.: 205 °C; ^{1}H NMR ($CDCl_3$, 360 MHz): 0.85 (d, 3H, ^3J = 6.5 Hz), 1.07 (s, 3H), 1.29 - 1.46 (m, 7H), 1.40 (s, 3H), 1.62 (m, 2H), 1.82 - 2.58 (m, 18H), 2.82 - 2.93 (m, 3H), 9.78 (tr, 1H, ^3J = 1.7 Hz). ^{13}C NMR (90 MHz): 11.8, 18.7, 21.9, 25.1, 27.4, 27.7, 35.3, 35.5, 36.0, 36.5, 38.6, 41.1, 42.8, 45.0, 45.6, 45.7, 46.8, 49.0, 51.8, 56.9, 202.9, 208.7, 209.0, 211.9. IR (KBr): 1700, 1710, 1735 (shoulder) [cm^{-1}]. GC-MS (CI) m/z: 378 (MH^+).

Typical procedure for the synthesis of ß-lactam-steroids:

4-Benzyloxycarbonylmethyl-1-[(N-diphenylmethylcarbamoyl) (dehydrocholyic) methyl]azetidin-2-one (4)

A solution of L-aspartic acid α-benzyl ester **3** (2.23 g, 10.0 mmol) in methanol (80 ml) is cooled to -10°C. To this solution 3.77g (10.0 mmol) dehydrocholic aldehyde and 1.93g (10.0 mmol) diphenylmethyl isocyanide are added under vigorous stirring. After 1h, the mixture is allowed to warm to room temperature and stirring is continued until the starting material has completely disappeared (tlc control). The colourless solution is evaporated and the residue taken up in methylene chloride (50 ml). This solution is extracted with 5% phosphoric acid (30 ml) and water (50 ml), respectively. The solvent is removed in vacuo giving 4.8 g (61%) of the product **4** in an amorphous foam.

The data are given for the major diastereomer only.
$C_{49}H_{56}N_2O_7$= 784.98 g/mol; Yield: 4.8g (61%) colourless foam; R_f: 0.28 (EE/H, 1:1, v/v). ^{1}H NMR ($CDCl_3$, 360 MHz): 0.76-2.91 (m, 34H); 3.1 (dd, 1H, ^2J = 14.82 Hz, ^3J = 5.84 Hz, -CH_2-CO-N-); 4.04 (t, 1H, ^3J = 7.4 Hz, -N-CH-CO); 4.31 (dd, 1H, ^2J = 2.69 Hz, ^3J = 5.84 Hz, -CH-COO); 5.1 (s, 2H, -CH_2Ph); 6.21 (d, 1H, ^3J = 8.08 Hz, -CH-Ph_2); 7.2-7.4 (m, 15H, Ar), 7.83 (d, 1H, ^3J = 8.08 Hz, -NH-). ^{13}C NMR ($CDCl_3$, 360 MHz): 11.65; 18.74; 21.69; 24.94; 27.5; 27.61; 31.9; 35.02; 35.98; 36.3; 38.43; 41.3; 42.78; 44.8; 45.26; 45.73; 46.59; 48.79; 51.57; 51.98; 56.69; 56.9; 58.9; 67.35; 127.2; 127.34; 128.47; 134.71; 141.19; 166.25; 168.6; 170.82; 208.74; 209.18; 211.94.

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This article is dedicated to Professor Wang Yu.

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(*Received in Germany* 4 *November* 1994; *revised* 6 *July* 1995; *accepted* 7 *July* 1995)