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Asymmetric Synthesis of ß-Lactams via Amine Additions to 5(R)-Menthyloxy-2[5H]-Furanone.

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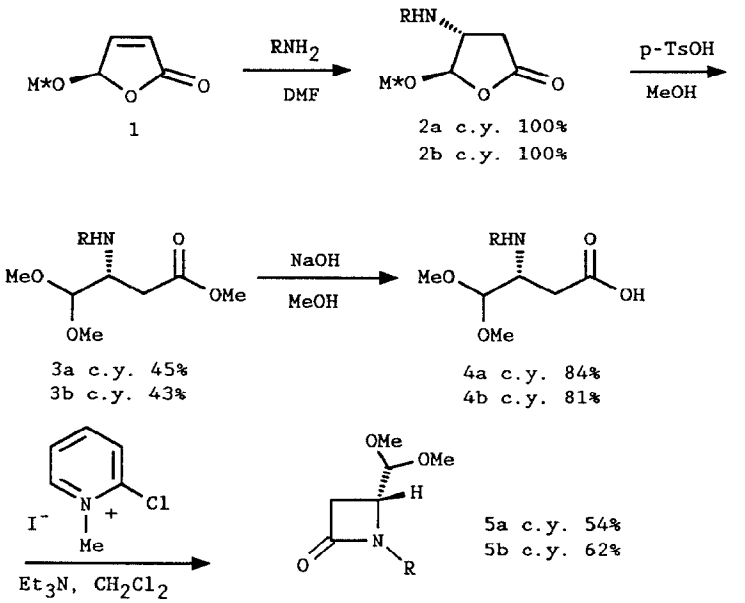
Abstract: The enantioselective synthesis of a N-benzyl substituted ß-lactam **5a**, a precursor for carbapenem antibiotics, starting from the chiral synthon 5(R)-menthyloxy-2[5H]-furanone **1**, is described.

The stereoselective syntheses of enantiomerically pure ß-lactams have been the subject of considerable interest,[1,2] mainly due to the presence of the ß-lactam four-membered ring in many synthetic and naturally occurring antibiotics.[3]

Although the ring-closure of chiral ß-amino acids[4] and ß-amino esters[5] is a common procedure for the synthesis of optically active ß-lactams, few of the syntheses of ß-amino acids or ß-amino esters reported so far, are based on diastereoselective Michael type additions of an amine to an α,β-unsaturated carbonyl compound.[6] We wish to report the facile preparation of optically active ß-lactam synthons in which a π-face selective 1,4-amine addition to 5(R)-menthyloxy-2[5H]-furanone[7] serves as the key step.

Addition of benzylamine to furanone **1** proceeds with high diastereoselectivity (d.e.= 92%)[8] trans with respect to the menthyloxy substituent to yield ß-aminolactone **2a** (scheme).[9] Diastereomerically pure aminolactones are obtained after one crystallization from ether/hexane. We have succeeded in accomplishing the crucial ring opening of **2a** to ß-amino ester **3a** in 45% yield without epimerization at the stereogenic center at the ß-carbon atom.[10] This step involves a simultaneous transesterification and transacetalization with methanol catalyzed by para-toluenesulfonic acid. During the transacetalization the menthol auxiliary is removed. The conversion of **2a** to **3a** is also possible using methanol saturated with HCl in

which case yields are comparable. As the amine moiety in **2a** can readily be modified, this sequence allows facile preparation of γ-substituted β-amino esters. Direct lactamization of **3a** was inconvenient although the use of MeMgBr as base resulted in 30% yield of **5a**. In order to develop a more practical route to **5a** lactamization via the corresponding β-amino acids was investigated.



2a-5a, R=$PhCH_2$; 2b-5b, R=S-(α)-$Ph(CH_3)CH$; M*O=menthyloxy

Scheme: Synthetic route to the optically active β-lactams.

β-Amino ester **3a** could be saponified to the corresponding β-amino acid **4a** in 84% yield.[11] β-Amino acid **4a** was subsequently cyclized to β-lactam **5a** using a procedure described by Mukaiyama and coworkers.[12] β-Lactam **5a** was obtained in 52% yield after purification by chromatography (SiO_2; ether/ methanol).

An indirect method was used for the e.e. determination of β-lactam **5a**. The above described reaction sequence was repeated starting from β-aminolactone **2b**, derived from the optically pure S-(α)-methylbenzylamine to provide the optically active N-(S)-α-methylbenzyl substituted β-lactam **5b**. Furthermore **5b** as a mixture (1:1 ratio) of two epimers at the C4 stereogenic centre was prepared from racemic

5-methoxy-2[5H]-furanone and (S)-α-methylbenzylamine. The diastereoisomers of **5b** are readily distinguished by 300 MHz ^{1}H NMR which indicated that the d.e. of ß-lactam **5b** is 92%. This value corresponds to the d.e. of the starting aminolactone **2b**. By analogy it can be assumed that the enantiomeric excess of **5a** corresponds to the d.e. of **2a** These results clearly show that the stereochemical integrity at the ß-carbon is completely retained during the conversion of aminolactones **2a** and **2b** into ß-lactams **5a** and **5b**.

In conclusion, we have developed a new route to optically active ß-lactams starting from the readily available chiral synthon 5(R)-menthyloxy-2[5H]-furanone **1** via ß-aminolactone **2a**. ß-Lactam **5a** possesses an easily removable protecting group on the amide nitrogen and moreover the masked aldehyde functionality offers the possibility of carbon-carbon bond forming reactions. For these reasons, ß-lactam **5a**[13] seems an attractive precursor for carbapenem antibiotics.

References and notes:

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8. In contrast to the complete diastereoselective addition of various primary and secondary amines to 1 (see ref. 9), the Michael type addition of benzylamine and S-(α)-methylbenzylamine to 1 proceeds with a d.e. of 92%.
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10. In a typical experiment 1.4 mmol aminolactone together with 3.0 mmol para-toluenesulfonic acid monohydrate were dissolved in 25 ml of dry methanol. The solution was refluxed for 72 hours. After cooling to room temperature, 2 equivalents of sodium methoxide, dissolved in 5 ml of methanol, were added to the reaction mixture. The methanol was removed in vacuo and the residue was taken up in a mixture of 25 ml ether and 25 ml water. After separation of the layers the water layer was brought to pH=9 by addition of a saturated sodium carbonate solution and extracted with ether (3 x 25 ml). After drying of the combined ether layers and filtration the solvent was evaporated. Menthol was removed by bulb-to-bulb distillation (60°C, 0.02 mm Hg). The resulting yellow oil was further purified by bulb-to-bulb distillation (140°C, 0.02 mm Hg) yielding the amino ester as a colourless oil.
11. In a typical experiment 2.0 mmol of the ß-amino ester was dissolved in 20 ml of a 1N solution of sodium hydroxide in methanol. After refluxing for three hours and cooling to room temperature the reaction mixture was brought to pH=7 by addition of 0.5 N aqueous sulfuric acid. The resulting solution was evaporated to dryness and 25 ml of chloroform was added to the residue. After drying over sodium sulfate and filtration the solvent was removed in vacuo yielding a colourless oil which was used for the subsequent ring closure without further purification.
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13. All new compounds showed spectroscopic and HRMS data in accordance with their proposed structure. The spectroscopic data for **5a** are as follows: IR; neat, cm^{-1}: 3090-3030 (arom. C-H), 2980-2820 (aliph. C-H), 1750 (C=O), 720, 700 (monosubst. arom.). ^1H NMR ($CDCl_3$, 300 MHz); δ 2.77 (dd, 1H, J=14.7Hz, 2.2Hz); 2.92 (dd, 1H, J=14.7Hz, 5.1Hz); 3.23 (s, 3H); 3.28 (s, 3H); 3.56 (m, 1H); 4.20 (d, 1H, J=14.3Hz); 4.23 (d, 1H, J=5.9Hz); 4.54 (d, 1H, J=14.3Hz); 7.27 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 38.64 (t); 45.26 (t); 51.03 (d); 54.17 (q); 54.26 (q); 105.11 (d); 127.24 (d); 128.00 (d); 128.37 (d); 136.27 (s); 166.83 (s). HRMS; calcd: 235.121, found: 235.121. $[\alpha]_D^{25}$ = -18.7 (c 3, $CHCl_3$).