Highly *syn*-Diastereoselective Synthesis of *NH*-3-Benzyloxy-4-aryl-azetidin-2-ones via a Two-Step Staudinger Reaction

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Abstract: New conditions for the Staudinger reaction provide *NH*-3-benzyloxy-4-aryl-β-lactams in good yields with complete *cis*-diastereoselectivity.

Diastereochemically pure *cis*-3-hydroxy-4-aryl-azetidin-2-ones are useful intermediates for the preparation of α-hydroxy-β-aminoacids, including the biologically important phenylisoserine, side chain of paclitaxel (Fig. 1), one of the most promising new drugs in cancer chemotherapy, recently approved for treatment of metastatic ovarian and breast cancer. Other researchers have revealed its effects against non-small cell lung cancer, head and neck cancer, glioblastoma and oesophageal cancer.[1]

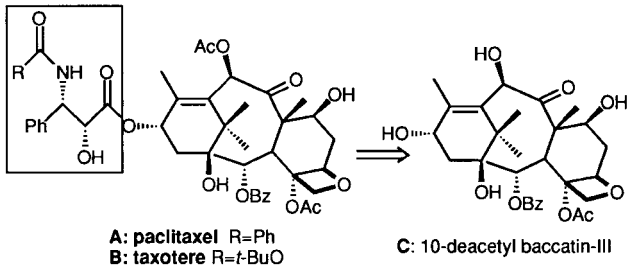


Figure 1

Recently, it has been found that paclixatel **A** and related derivatives may be obtained from the renewable material, 10-deacetyl baccatin-III **C**, by its coupling with suitable protected β-lactams **5**.[2] Therefore, the development of short and practical synthetic routes towards this class of intermediates, characterised by the presence of different aryl groups at C-4, has become very important.[3] Among the many synthetic methods available for the preparation of the key β-lactam intermediates, the most popular are the [2+2] cycloaddition reaction of imines and ketenes, known as the Staudinger reaction,[4a,b] or the ester enolates-imine condensation route.[4c-e] Recently, we have reported a new variant of Staudinger reaction, starting from *N*-trimethylsilyl imines,[5] which allows the preparation of *NH* azetidinone derivatives avoiding the usual deprotection-step of the p-methoxy-phenyl group (or its equivalent) directly linked to the β-lactam nitrogen. In this paper we report our preliminary results on the preparation of *cis*-3-benzyloxy-4-aryl-azetidin-2-ones with a complete *cis*-diastereoselectivity. The results, shown in Table 1,[6] warrant some comments:

a) The relative stereochemistry of the substituents at the β-lactam ring is invariably *cis* regardless of the nature of the R group on the imine. This is in contrast to the results obtained using ketenes derived from *N*-amido-glycine, in which a *complete trans diastereoselectivity* has been observed.[5a,b]

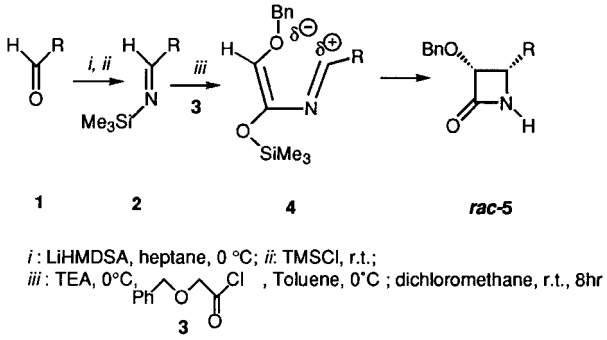
b) Cyclization to the β-lactam ring is faster and proceeds under much milder conditions (see experimental part) than in the case of the amido-glycine derivatives. In that case a stable azadiene intermediate was isolated in the *Z-anti* form. A conrotatory ring closure gave rise to the *trans* product. Since the real difference between the amido-glycine derivative and the benzyloxy-derivative is the presence of an amidic nitrogen versus an ethereal oxygen, we can postulate the possible formation of a weak electrostatic bond between ethereal oxygen and the iminic carbon which stabilises the *E-anti* azadiene. A similar effect has already been invoked to explain the *cis*-diastereoselectivity observed in the classical Staudinger cycloaddition reactions.[7] Preliminary semiempirical (PM3) or *ab initio* (HF/3-21G*) calculations on a model compound have confirmed the preference (2.5 kcal/mol) for the reported (*E-anti*)-**4** azadiene structure over the corresponding (*Z-anti*) structure.

c) Despite considerable efforts, we could not isolate and characterise the postulated intermediate azadiene **4** so far. Work is continuing towards the elucidation of the structure of this intermediate since knowledge of the stereochemistry of **4** may clarify the reaction mechanism and lead to a rationale for the surprising stereochemical outcome of the reaction.

Table 1. Synthesis of *cis*-Azetidin-2-ones **5**

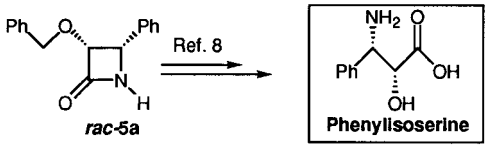
Entry	R	Products	Yields[a,b](%)
1	Ph	**5a**	81
2	p-Cl-Ph	**5b**	96
3	2,4-di-Cl-Ph	**5c**	55
4	o-NO_2-Ph	**5d**	58
5	p-NO_2-Ph	**5e**	90
6	p-MeO-Ph	**5f**	45
7	2-Naphthyl	**5g**	93
8	7-MeO-2-Naphtyl	**5h**	50
9	2-Thienyl	**5i**	58
10	2-Pyridyl	**5j**	40

a) Yields are in pure isolated products (racemic mixture). b) All the products gave satisfactory IR, ^{1}H, ^{13}C NMR and MS analysis. The *cis* stereochemistry has been assigned by the H3-H4 coupling constant (J=4-6 Hz).[5e] No *trans* -derivatives were detected on the crude mixture by ^{1}H and ^{13}C NMR analyses (300 and 75 MHz)



Scheme 1

The conversion of compound *rac*-**5a** into the enantiopure phenylisoserine, according reported protocols,[8] may represent a useful application of our methodology.



Scheme 3

Work is in progress to apply this methodology to enantiopure β-lactam derivatives as well as to fully clarify the reaction mechanism.

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References and Notes

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(6) *General procedure* : To a solution of aldehyde **1** (1 mmol) in hexane (5 ml) was added LiHMDSA (1 mL of 1M solution in THF) at 0°C. The reaction mixture was allowed to reach r.t. spontaneously while the stirring was continued for 1 h. TMSCl (1.1 mmol) was added in one portion and the reaction mixture further stirred for 1 h. A white precipitate formed. The solution was cooled at 0°C and triethylamine (1 mmol) was added in one portion. The benzyloxyacetyl chloride **3** (1mmol), dissolved in toluene (3 mL), was added dropwise. Stirring was maintained for 1 h while a new copious precipitate appeared. The precipitate was filtered under argon, the solvent removed *in vacuo*, dichloromethane (10 mL) was added and the resulting pale yellow solution was stirred overnight at r.t. The crude mixture was poured into a 1 N HCl solution and extracted with ethyl acetate. Flash chromatography of the residue (cyclohexane/ethyl acetate 1/1) yielded the pure isolated *cis*-*N*-unsubstituted-3-benzyloxy-4-aryl-β-lactams **5** in the yields reported in Table 1.

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