Pure Appl. Chem., Vol. 72, No. 9, pp. 1763–1768, 2000.

Versatility of β-lactams in synthesis. Studies directed toward the synthesis of complex nucleoside antibiotics and some macrocyclic peptides*

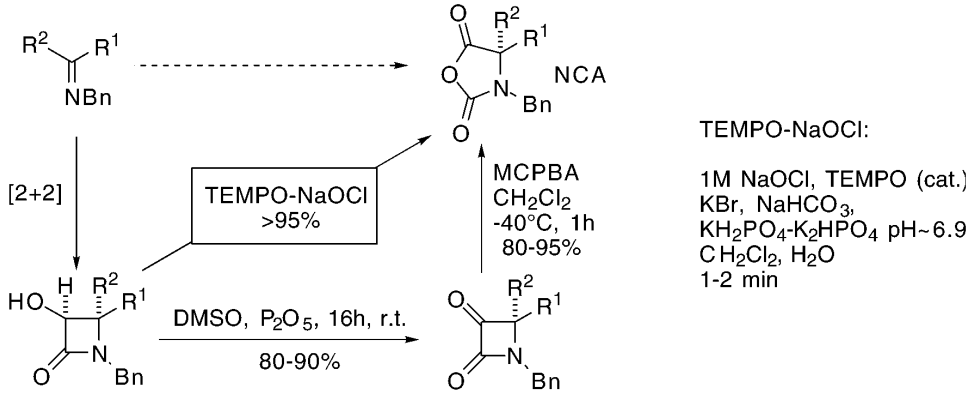
Claudio Palomo†, Jesús M. Aizpurua, Iñaki Ganboa, and Mikel Oiarbide

Departamento de Química Orgánica, Facultad de Química, Universidad del País Vasco, Apdo 1072, 20080 San Sebastián, Spain

Abstract: The diastereoselective [2+2] cycloaddition of α-hydroxyketene equivalents with chiral α,ω–oxyaldehyde-derived imines followed by the 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO)-promoted ring expansion of the resulting α-hydroxy β-lactam adducts provides an unconventional and short route to α-amino acid *N*-carboxy anhydrides (NCAs). The required enantiopure α,ω-oxyaldehydes were obtained either from the chiral pool or through the Sharpless AD methodology. Following the present strategy, several nonproteinogenic NCAs were synthesized, which were further coupled with α-amino acid esters giving rise to key fragments of some nucleoside antibiotics and macrocyclic peptides.

INTRODUCTION

In recent years, the way β-lactams are viewed has changed considerably. Presently, their interest stems not only from being a key structural feature of β-lactam antibiotics, but also from their valuable utility as synthetic intermediates, mainly as masked α- and β-amino acid derivatives. In fact, the cleavage of the otherwise constrained β-lactam ring at either N1–C_4 or N1–C_2 bonds has opened the way to a wide array of α-amino acid and β-amino acid-derived structures [1]. On the other hand, the development of highly stereoselective methods of forming the substituted azetidin-2-one ring [2] has given additional power to such a β-lactam route. In this context, we have been involved in the study of the potential of β-lactams as intermediates in synthesis and have discovered (Scheme 1) that α-hydroxy β-lactams,



Scheme 1 General strategy for the access to NCAs through enantiopure β-lactam intermediates.

*Lecture presented at the 13th International Conference on Organic Synthesis (ICOS-13), Warsaw, Poland, 1–5 July 2000. Other presentations are published in this issue, pp. 1577–1797.

†Corresponding author

upon treatment with nitroxide-free radicals, such as 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO), in combination with a solution of commercial bleach, undergo an unprecedented ring expansion to give α-amino acid *N*-carboxy anhydrides (NCAs) [3]. The well-recognized importance of this particular class of mixed anhydrides for peptide coupling [4] led us to develop this approach into a general method for the synthesis of short peptide segments containing α-amino β-hydroxy and α-amino β,ω-polyhydroxy acids, the key components of complex nucleoside antibiotics and some macrocyclic peptides.

α-AMINO β-HYDROXY ACIDS. SYNTHETIC APPROACH TO THE NONPROTEINOGENIC AMINO ACIDS OF LYSOBACTIN

The practicability of the above strategy relies primarily on the efficiency, in terms of both chemical yield and diastereoselectivity, of the [2+2] hydroxyketene-imine cycloaddition reaction [5]. In particular, the cycloaddition of hydroxyketenes with α-oxyaldehyde-derived imines fulfills these requirements, and we have successfully applied this methodology, in a sequential manner, to the synthesis of the key tripeptide fragment present in the macrocyclic antibiotic lysobactin I [3b,6] (Fig. 1).

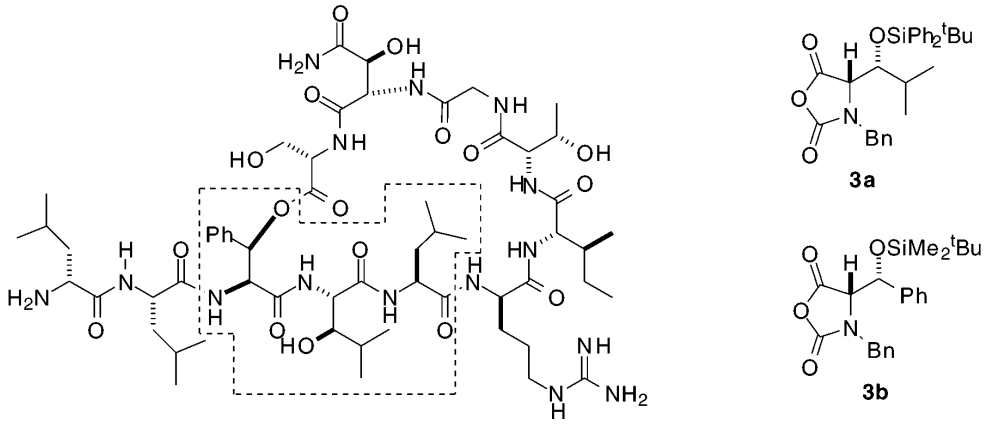
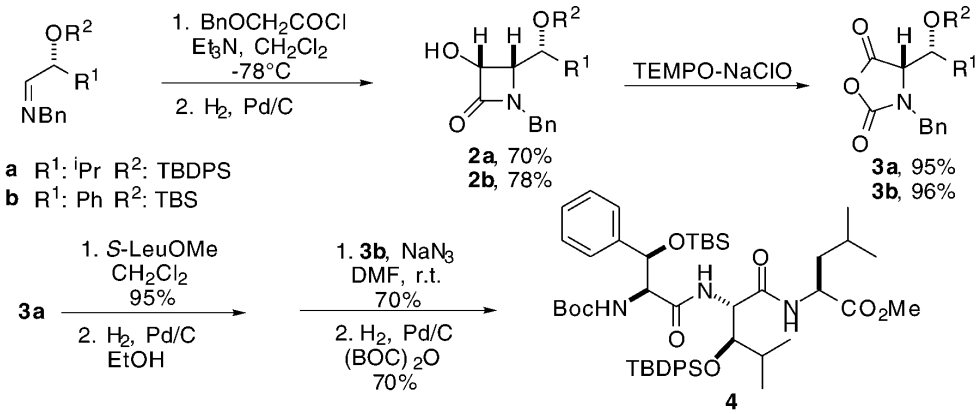


Fig. 1 Chemical structure of lysobactin. The tripeptide segment approached is framed.

Thus, the stereoselectively formed β-lactams **2** (Scheme 2) were transformed into the NCA **3a** and **3b**. Compound **3a** was first opened by *S*-leucine methyl ester, and the resulting dipeptide adduct was coupled with **3b** to afford, after amine deprotection-reprotection steps, tripeptide **4**.



Scheme 2 Synthesis of tripeptide **4** by sequential opening of NCAs **3a** and **3b**.

SYNTHETIC APPROACH TO PEPTIDYL NUCLEOSIDE ANTIBIOTICS FROM CHIRAL POOL SOURCES

Several nucleoside antibiotics are structurally comprised of a polyhydroxylated α-amino acid fragment coupled to another α-amino acid bearing a nucleoside unit. In the case of polyoxins **5** (Fig. 2), the polyhydroxylated α-amino acid is identified as polyoxamic acid **6** (R=H), and much effort has been devoted to its synthesis [7].

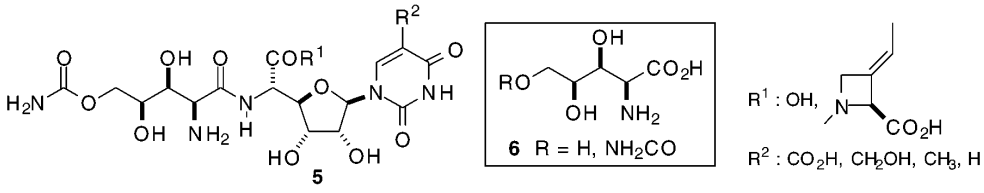
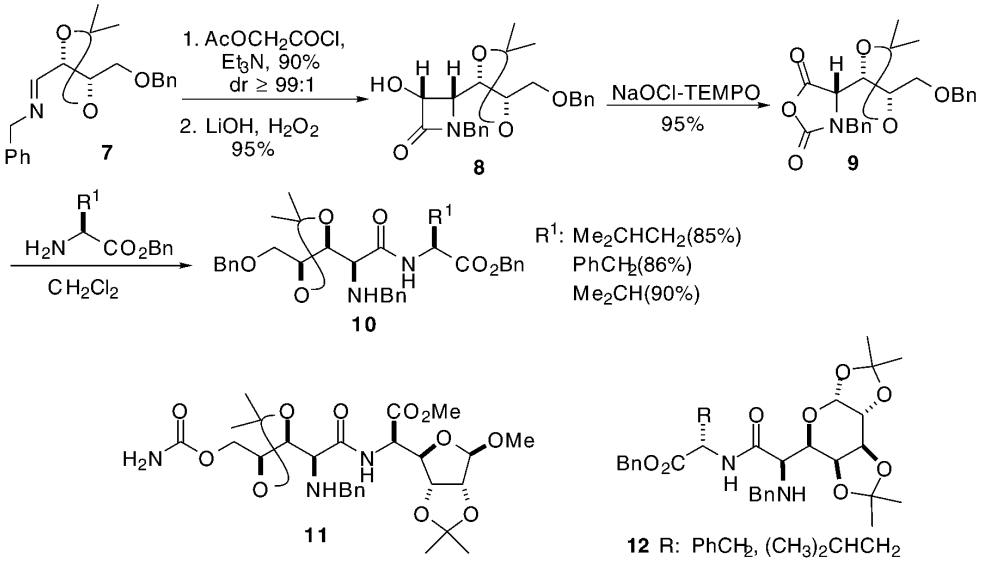


Fig. 2 Structure of some polyoxins.

Our approach began from commercially available tartaric acid esters, which can be easily transformed into the Mukaiyama's aldehyde through procedures well established in the literature [8]. Imine **7** (Scheme 3), directly formed from such an aldehyde, was then subjected to [2+2] cycloaddition to afford β-lactam **8** as single stereoisomer. Further oxidative ring expansion promoted by TEMPO gave rise to NCA **9**, which was smoothly coupled with the desired α–amino acid ester to yield polyoxamic acid-derived peptides **10** [9]. Following the same strategy, compounds **11** and **12** were also synthesized [10]. It is worth mentioning that the degree of epimerization during the coupling of **9** with amino acid esters proved solvent-sensitive. While in either CH_2Cl_2 or Et_2O the isomerization degree was below the limit of detection (less than 0.5%), it was significant in more polar solvents (MeCN, 15%, $MeNO_2$, 8%; DMF, 50%; HMPA, 72%).



Scheme 3 Synthesis of polyhydroxylated α-amino acid-containing peptides.

SYNTHESIS OF THE SOUTHWEST TRIPEPTIDE SEGMENT OF ECHINOCANDIN B. AN ALTERNATIVE STRATEGY TO THE CHIRAL POOL APPROACH

Finally, the above strategy has been slightly modified, *vide infra*, to accomplish the synthesis of peptides incorporating β,γ-dihydroxy α-amino acids. These subunits are present, for example, in echinocandin B (Fig. 3), a cyclic hexapeptide with potent antifungal activity [11].

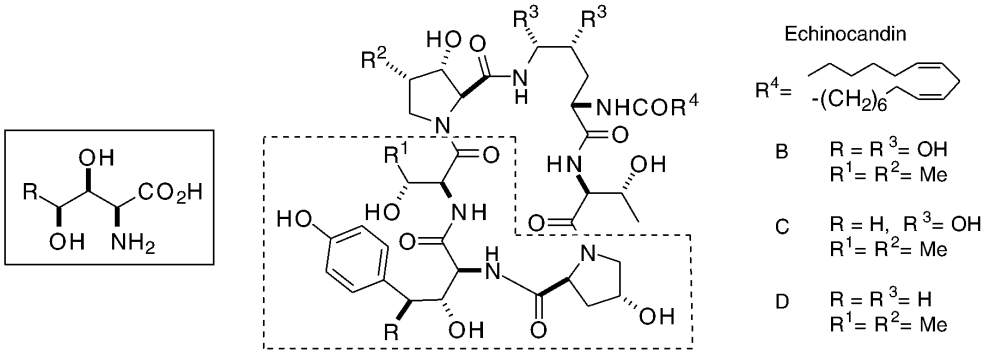
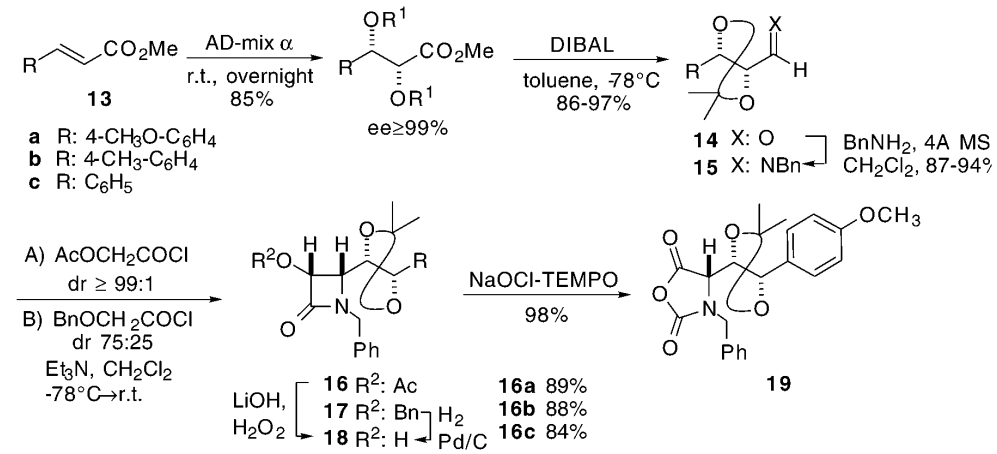


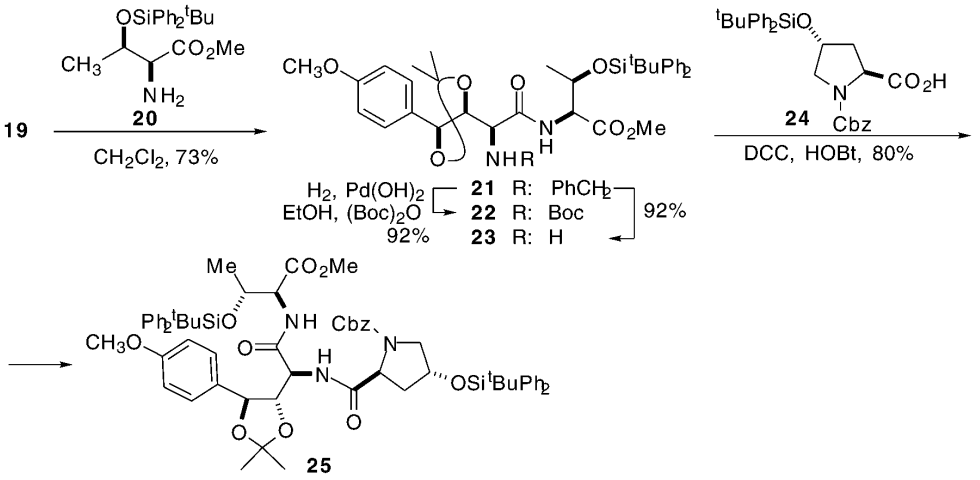
Fig 3 Chemical structures of several echinocandins isolated from fungi.

In this instance, the α,β-dihydroxy aldehydes required as starting materials did not come from the chiral pool [8]. Instead, they were prepared in a stereodivergent way by the Sharpless AD technique [12] (Scheme 4). The [2+2] cycloaddition of either acetoxy- or benzyloxyketene to the corresponding α,β-dihydroxy aldehyde-derived imines **15** resulted critical. In general, cycloadducts **16** were obtained as single stereoisomers, while poorer diastereomeric ratios (typically 75:25) were attained for adducts **17**.



Scheme 4 Sharpless AD, [2+2] oxyketene-imine cycloaddition and final ring expansion sequence giving rise to enantiopure NCA **19**.

With NCA **19** in hand, the synthesis was concluded (Scheme 5) with the coupling of **19** with the serine derivative **20** to afford dipeptide **21**, which, after protecting group manipulation and further peptide coupling with the 4-hydroxyproline derivative **24**, gave rise to the protected tripeptide **25** in good yield [13].



Scheme 5 Final coupling steps toward the southwest tripeptide segment of echinocandin B.

ACKNOWLEDGMENT

We are grateful to the University of the Basque Country, the Spanish Ministery of Education and Culture, and, in part, to the Basque Government for generous financial support.

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