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Concise Pathway to New Multifunctionalized Constrained Pentacin Derivatives by Means of Two Stereospecific Tandem Reactions

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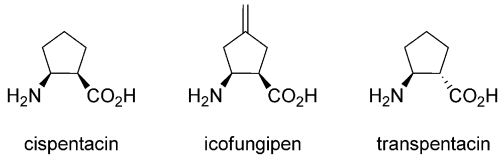
Starting from Boc-activated diketopiperazines, original bicyclic derivatives of *trans*- and *cis*-2-aminocyclopentanecarboxylic acid were prepared by using two stereospecific tandem reactions. One of them is a tandem transannular rearrangement of activated lactams/alkylation process leading to the stereoselective synthesis of suitably chiral pyrrolidine-2,4-diones, allowing subsequent Michael-initiated ring closure, a simple and concise route to original multifunctionalized alicyclic β-amino esters.

Introduction

Alicyclic β-amino acids[1,2] are of increasing interest in the context of drug development, initially due to their intriguing potent biological activities and protease-resistant properties.[3–6] For example, Tilidine is a synthetic opioid analgesic used for the treatment of moderate to severe pain; *cis*-pentacin [(1*R*,2*S*)-ACPC, (1*R*,2*S*)-2-aminocyclopentanecarboxylic acid, Scheme 1],[6] an element of the antibiotic amipurimycin, possesses antifungal and antibiotic properties, whereas its synthetic derivative, iconfungipen (PLD-118), is a representative of a novel class of strong oral antifungals.[7] In addition to the research of more-potent pentacin derivatives, we noticed the emergence of such backbones in the design of chiral catalysts used in enantioselective synthesis,[8] but also a growing interest in the production of pentacin oligomer derivatives leading to the development of attractive edifices, which could adopt stable folded conformations. *trans*-Pentacin [(1*S*,2*S*)-ACPC] could be a building block for the preparation of helical foldamers, whereas homo-oligomers of *cis*-pentacin form sheet-like secondary structures in solution.[9]



Scheme 1. Examples of bioactive five-membered alicyclic β-amino acids.

Although numerous substituted derivatives of alicyclic α- and γ-amino acids have been synthesized and extensively studied for their biological properties,[10,11] β-derivatives have been investigated only in a limited number of cases[12] and mainly for their ability to form original structures.[13–19] In the cyclopentanic series, a more specific concern has been dedicated to alkyl derivatives,[20,21] aminated[22] and/or hydroxylated analogues,[22–27] which is certainly correlated with the structure of the antibiotic oryzoxymicin.[22] Recently, substituted chiral cyclopentamine derivatives were synthesized by an original pathway. Their incorporation into peptide nucleic acids improves binding to RNA and DNA.[28]

In order to enlarge the molecular diversity of ACPC analogues, for both pharmacological and structural investigations, we report here an original and concise pathway to access orthogonally protected multifunctionalized cyclopentane β,γ-diamino esters by using two tandem reaction sequences. Modern design in organic chemistry requires minimization of the number of steps to construct complex molecules. Tandem reactions are efficient synthetic approaches for the construction of relatively complex compounds in a limited number of steps. In the perspective of stereoselective synthesis of cyclic β-amino acids synthesis, the MIRC (Michael-initiated ring closure) reaction, a tandem conjugate addition/aldol reaction on ε-oxo-α,β-unsaturated esters, is probably the most extensively applicable. Initiated by Yamamoto et al.[29–31] and developed by Davies et al.,[25] nucleophilic addition to α,β-unsaturated esters is followed by subsequent intramolecular cyclization of the resulting enolate onto an internal electrophilic entity. Aiming at the synthesis of rigid pentacin derivatives, we have applied this relevant reaction to a suitable chiral synthon fashioned

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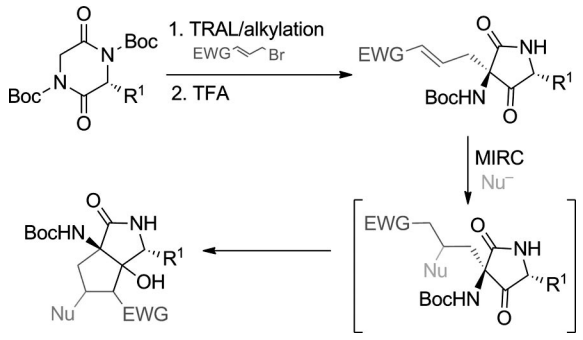
from a regioselective and stereospecific tandem reaction: the transannular rearrangement of activated lactams (TRAL)/alkylation (Scheme 2).[32–35]



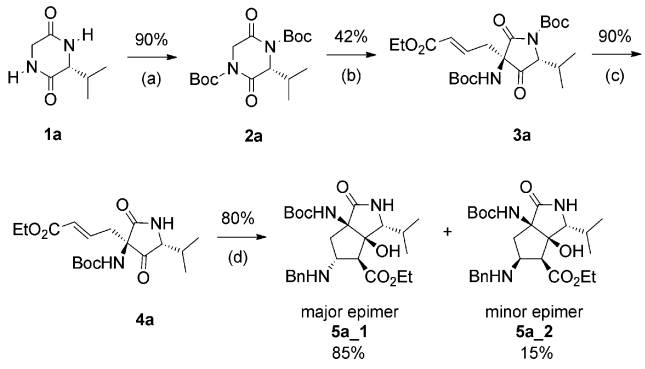
Scheme 2. Chemical strategy involving two tandem reactions to access rigid pentacin derivatives, where Nu = –NHR and EWG = –COOR.

The alkylating version of TRAL[32] is a useful ring-contraction reaction for the stereoselective construction of pyrrolidine-2,4-dione motifs from Boc-activated 2,5-diketopiperazines (DKPs) as precursors.[35] The challenge of this work was to combine and potentiate two methodologies, TRAL/alkylation and MIRC, for the stereoselective synthesis of multifunctionalized alicyclic β-amino esters, ideally to synthesize derivatives of *cis*-pentacin or *trans*-pentacin. Especially, we focused on the access to novel conformationally restricted structures.

Results and Discussion

The synthetic route we developed is based on pioneered results on the TRAL/alkylation, allowing the preparation of substituted pyrrolidine-2,4-diones from suitably activated DKPs with total stereoselectivity. Particularly, the *N*-Boc-activated DKP *cyclo*-[Gly-(D)-Val] has revealed to be an appropriate model to investigate new pathways to original heterocycles.[35] It was then envisaged that insertion of a relevant chain possessing the required properties to be involved in a MIRC reaction could allow access to original pentacins.

We have previously shown that *cyclo*-[Gly-(D)-Val] (**1a**) after appropriate protection and activation could be successfully engaged in a TRAL/alkylation reaction. In the presence of LiHMDS and ethyl 4-bromocrotonate, **3a** can be prepared in 42% yield in a totally diastereoselective manner (Scheme 3). Introduction of an α,β-unsaturated ester at this position leading to the creation of a suitable ε-oxo-α,β-unsaturated ester sequence was crucial at this stage when the goal was to achieve subsequent conjugate addition/cyclization (MIRC). This methodology is well documented on acyclic α,β-diunsaturated diesters and also on ε- and ζ-formyl-α,β-unsaturated esters,[25] and we thought that the reaction could be extended to cyclic ketones to provide access to bicyclic pentacin structures. Instead of homochiral lithium *N*-benzyl-*N*-α-methylbenzylamide, our synthetic route involved achiral amines reacting on a chiral unit. Thus, we could imagine that the spatial position of the α,β-unsaturated ester chain, related to the configuration of the new stereogenic center fashioned during the TRAL/alkylation, will influence the subsequent intramolecular cyclization.

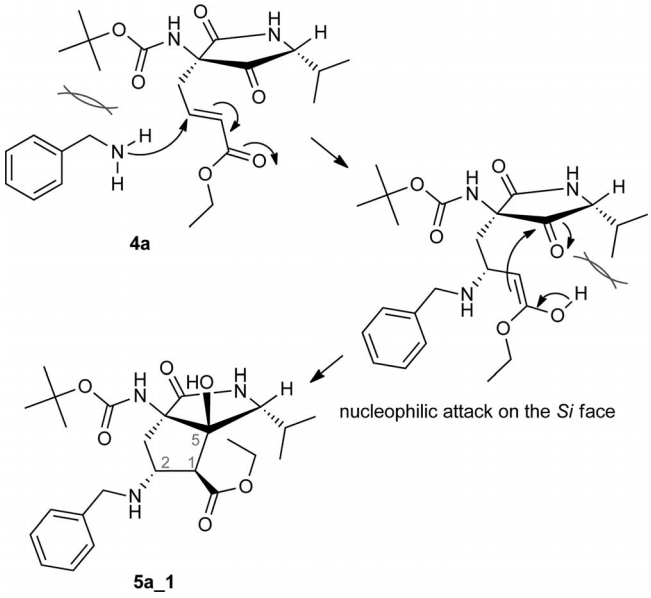


Scheme 3. Reagents and conditions: (a) Boc_2O, DMAP, DMF, r.t., 1.5 h; (b) ethyl 4-bromocrotonate, LiHMDS, THF, –78 °C to r.t., overnight; (c) 3% TFA in DCM, 0 °C, 2.5 h; (d) $BnNH_2$, EtOH, reflux, 4 d.

Before applying the MIRC conditions to **3a**, a chemoselective deprotection of the Boc-protected lactam ring was essential. Indeed, the carbonyl group of the protected lactam, highly activated by the Boc group, is susceptible to nucleophilic attack. However, complete *N*-deprotection of **3a** will liberate a nucleophilic amine, in competition with the nucleophilic entity present during the MIRC reaction. Without any cleavage of the Boc protecting group of the primary amine, taking advantage of the difference in reactivity between the two functions, monoprotected heterocycle **4a** was obtained in 90% yield.

The most challenging step was the construction of the pentacin cycle, motivated by the work developed by the group of S. G. Davies.[25] To promote the tandem Michael addition and cyclization reaction, ε-oxo-α,β-unsaturated ester **4a** previously prepared was heated at reflux in ethanol in the presence of benzylamine. A mixture of isomers **5a_1** and **5a_2** was obtained in an overall yield of 80%, after back recovery of the starting material. Indeed, incomplete conversion of about 50% of the starting material was observed, as described by S. G. Davies et al.[25] The starting product was isolable during the purification by silica gel chromatography of the crude material, and the reaction was performed one more time to increase the overall efficiency of the process. Intramolecular cyclization onto the cyclic ketone of the β-amino enol created by benzylamine addition allowed the formation of two unprecedented structures. To the best of our knowledge, constrained derivatives of pentacin possessing such quaternary stereocenters have not yet been investigated. The bicyclic structures fashioned possess an innovative succession of polyfunctionalities, with an interesting orthogonality in protecting groups, making either future incorporation in peptidic sequence or oligomerization feasible. Without any involvement of a chiral amine as nucleophilic chiral inducer, using instead a chiral platform as a Michael acceptor, a diastereomeric excess of

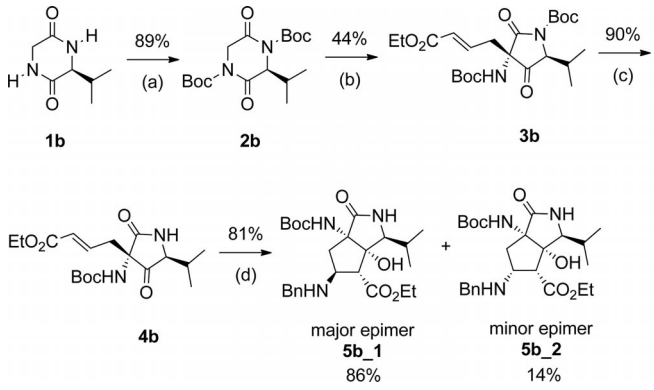
70% was highlighted. The one-step creation of three novel stereogenic centers led only to two different epimers that could be easily separated by simple silica gel chromatography. The stereochemical identity of each pentacin derivative was determined and confirmed by ^{1}H NMR spectroscopy. Particularly, the $^3J_{H,H}$ coupling constants of the BnNH-C*H*-C*H*-CO_2Et moiety in the ring system of the major isomer (14.0 Hz) was much higher than that of the minor isomer (8.0 Hz). We could establish that the hydroxy group and the ester moiety of the major isomer were positioned in a *trans* configuration, similarly to *trans*-pentacin. A possible mechanism for the asymmetric MIRC is shown in Scheme 4.



Scheme 4. Proposed model to elucidate the stereospecific tandem conjugate addition/cyclization reaction.

Inspired by the mechanistic studies described by S. G. Davies et al.,[25] we could easily assume that the initial step involved Michael addition of benzylamine to the α,β-unsaturated ester, the conjugate addition being concomitant with the intramolecular addition of the enol onto the cyclic ε-ketone. However, the mechanism to explain the stereoselectivity observed here is innovative, being specific and totally dependent of the conformational nature of the scaffold generated by the TRAL/alkylation. Among the three chiral centers fashioned in one step, only the one bearing the benzylamine group is not created in a total stereoselective manner. The partial stereoselectivity of its addition can be explained by preferential addition of the benzylamine on the less bulky face of **4a**, rather than on the space occupied by the hindered *N*-Boc group present on the pyrrolidine moiety. Thereafter, the resulting enol has no alternative but to attack stereoselectively the *Si* face of the cyclic ketone, forcing the positioning of the carboxy moiety, clustered by the presence of the isopropyl moiety. To summarize, the configuration of the chiral center created by the addition of the benzylamine is guided by the configuration of the chiral center fashioned during the TRAL/alkylation, whereas the two other chiral centers created on the pentacin isomers seems to be guided by the configuration of the chiral center of the initial (D)-valine present on the starting reagent.

This hypothesis could be supported by further studies, where Boc-activated DKP *cyclo*-[Gly-Val] was used as the starting material. Following a similar synthetic pathway, we were able to access novel isomers **5b_1** and **5b_2** of aminohydroxypentacins with comparable yields and diastereomeric excess values (Scheme 5). The stereoselectivity observed was consistent with the above mechanistic predictions, allowing us to conclude to a high stereospecificity of the two tandem reactions involved. Whatever the configuration of the isopropyl moiety present on the starting DKP, the major product possessed a relative 1,2-*trans*-1,5-*cis* configuration, whereas the minor product acquired a relative 1,2-*cis*-1,5-*cis* configuration.



Scheme 5. Reagents and conditions: (a) Boc_2O, DMAP, DMF, r.t., 1.5 h; (b) ethyl 4-bromocrotonate, LiHMDS, THF, –78 °C to r.t., overnight; (c) 3% TFA in DCM, 0 °C, 2.5 h; (d) $BnNH_2$, EtOH, reflux, 96 h.

Conclusions

The tandem TRAL/alkylation combined to the intramolecular tandem conjugate addition/aldol reaction provided an efficient method for the diastereoselective synthesis of ethyl 2,4-amino-5-hydroxycyclopentanecarboxylate derivatives. To the best of our knowledge, the polyfunctionalization accessible by this synthetic route has no precedent, leading to the synthesis of highly valuable scaffolds. Further work will be devoted to their incorporation into novel β-peptide architectures, and more especially to oligomerization processes to access original foldamers.

Experimental Section

General Procedure for the Synthesis of Pyrrolidine-2,4-diones 3a,b: To a stirred solution of **2a,b** (7.00 mmol) in dry THF (30 mL), cooled to –78 °C under an atmosphere of argon, was added dropwise a solution of LiHMDS (1.0 M in THF, 7.00 mmol). After 45 min, the alkylating agent (7.00 mmol) was added. The reaction was left at room temperature overnight. The mixture was then diluted with AcOEt (20 mL) and washed with 0.1 N HCl (10 mL). The organic layer was then dried with $MgSO_4$ and concentrated in vacuo. The

crude mixture obtained was purified by column chromatography (petroleum ether/AcOEt) to provide the desired pyrrolidine-2,4-dione.

General Procedure for the Chemoselective Monodeprotection of Pyrrolidine-2,4-diones 3a,b: To a solution of **3a,b** (100 mg, 0.21 mmol) in dichloromethane (5 mL) was added dropwise trifluoroacetic acid (0.15 mL) at 0 °C. The reaction mixture was stirred for 2.5 h at 0 °C. The reaction media was then evaporated to dryness, and the remaining TFA was co-evaporated with toluene to afford the corresponding monodeprotected compound **4a,b**.

General Procedure for the Tandem Conjugate Addition/Aldol Reaction: A solution of ε-oxo-α,β-unsaturated ester **4a,b** (0.90 mmol) and freshly distilled benzylamine (8.99 mmol) in absolute ethanol (20 mL) was heated at reflux for 96 h. After evaporation of the solvent under reduced pressure, the excess amount of benzylamine was removed by using the 4-benzyloxybenzaldehyde polystyrene as polymer-supported scavenger reagent following the procedure described below: 4-benzyloxybenzaldehyde polystyrene (24.27 g, 11.56 mmol, 2.10 mmol/g) and dichloromethane (30 mL) were added to the crude mixture, and the reaction mixture was left to slowly shake at reflux for 3 h. The reaction mixture was then filtered and the resin washed with dichloromethane (3 × 30 mL) and methanol (3 × 30 mL). The filtrate was evaporated in vacuo. The crude mixture obtained was purified by column chromatography (dichloromethane/MeOH), providing the desired 2 diastereoisomers **5a_1/5b_1** and **5a_2/5b_2** (respectively ≈6:1).

Supporting Information (see footnote on the first page of this article): Characterization data for all compounds (including NMR assignments and HRMS).

Acknowledgments

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