

Diastereoselective Cationic Tandem Cyclizations to *N*-Heterocyclic Scaffolds: Total Synthesis of (–)-Dysibetaine PP

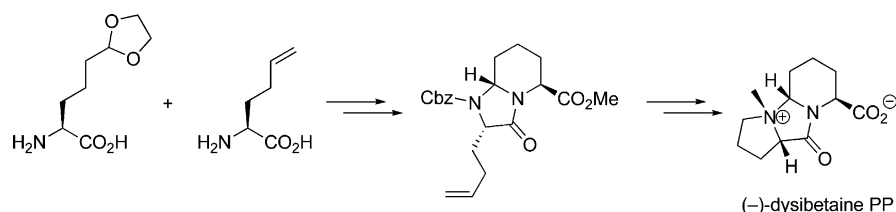
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ABSTRACT



Herein, we report a short and diastereoselective synthesis of the natural product (–)-dysibetaine PP. The key step in the synthetic sequence is a novel highly diastereoselective tandem-cyclization reaction of an enantiomerically pure dipeptide. This cyclization methodology is applied in the synthesis of a broader range of *N*-heterocyclic scaffolds.

(–)-Dysibetaine PP is a natural product that has been recently isolated from the Micronesian sponge *Dysidea herbacea*.¹ Its tricyclic dipeptidyl betaine structure contains an unusual quaternized *N,N*-acetal motif, making it an interesting target for total synthesis.² To approach this particular structural arrangement, we chose L-allysine ethylene acetal (**1**) as a starting material. This unnatural amino acid has already proven to be a versatile chiral building block for the preparation of various pipercolic acid derivatives and natural products.³ We envisaged that a tandem-cyclization strategy as outlined in Scheme 1, could provide an entry to the required *N,N*-acetal moiety.^{4,5} Treatment of L-allysine eth-

ylene acetal-derived dipeptides (**2**) with a catalytic amount of a protic acid, should activate the masked aldehyde and invoke the first cyclization. Then, upon elimination of the ethylene glycol moiety an *N*-acyliminium ion (**3**) is generated,⁶ which can be trapped by the second amine present in the molecule forming the desired bicyclic *N,N*-acetals (**4**).

This paper details the results of our studies on the scope, limitations and diastereoselectivity of the cationic tandem-cyclization strategy, leading to a broad range of enantiomerically pure *N*-heterocyclic scaffolds. Finally, the developed methodology is successfully applied in the first total synthesis of the natural product (–)-dysibetaine PP.

To investigate the scope and selectivity of the tandem-cyclization strategy, we initially focused on dipeptides composed of L-allysine ethylene acetal and different α -amino acids. Cyclization precursors **7a–i** were synthesized by a BOP/DIPEA-mediated coupling of methyl ester **5** with a

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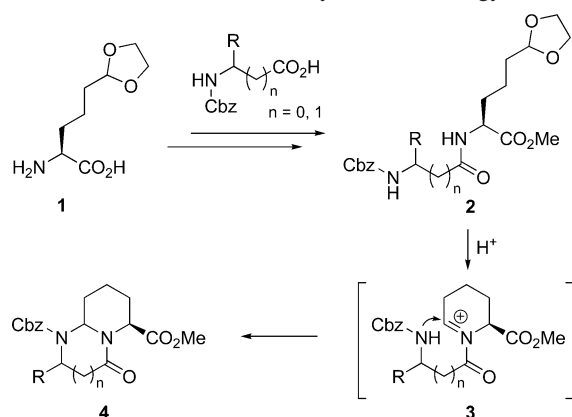
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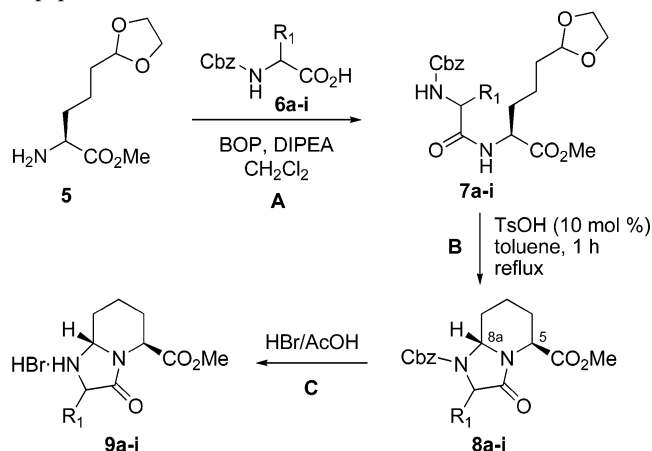
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Scheme 1. Tandem-Cyclization Strategy

variety of *N*-Cbz-protected α -amino acids (**6a–i**) in an average overall yield of 70–80% (Table 1).⁷ Treatment of

Table 1. Tandem Cyclizations of α -Amino Acid-Based Dipeptides

entry	amino acid	R ¹	yield A (%)	yield B (%)	dr (trans/cis) ^b	yield C (%)
1	Gly (6a)	H	70	82	5:1	99
2	L-Ala (6b)	Me	72	79	15:1 ^c	<i>e</i>
3	D-Ala (6c)	Me	75	76	2:1 ^c	<i>e</i>
4	L-Val (6d)	<i>i</i> Pr	69	76	9:1	97
5	D-Val (6e)	<i>i</i> Pr	72	80	4:1 ^d	84
6	L-Phe (6f)	Bn	79	87	13:1	95 ^f
7	D-Phe (6g)	Bn	78	88	1:1	95
8	L-Alg ^a (6h)	allyl	72	78	15:1	83
9	D-Alg ^a (6i)	allyl	76	70	1:1 ^d	81

^a Alg = allylglycine. ^b Determined by HPLC analysis of the crude reaction mixtures. ^c Diastereomers were separated by preparative HPLC. ^d Determined by ¹H NMR of the crude reaction mixture. ^e Deprotection not performed. ^f Deprotected by treatment with H₂ over Pd/C.

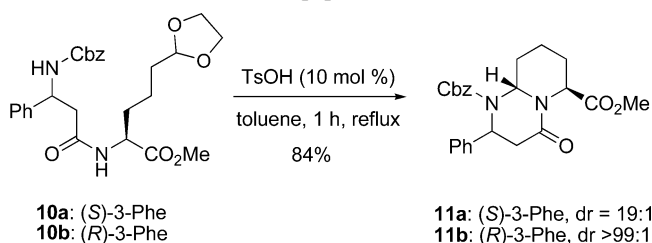
dipeptide **7a**, bearing glycine as the second amino acid, with a catalytic amount of TsOH in refluxing toluene resulted in

the smooth formation of *N,N*-acetal **8a** in a yield of 82% (entry 1). The cyclization product was obtained as a 5:1 mixture of diastereomers, of which the major isomer proved to be the depicted C5–C8a *trans*-isomer.

In the cyclizations of dipeptides **7b** and **7c**, bearing L-alanine and D-alanine, respectively, a pronounced influence of the stereochemistry of the amino acid side chain was observed (entries 2 and 3). The dipeptide containing the natural antipode (**7b**) yielded bicyclic product **8b** with an excellent selectivity of 15:1, again in favor of the C5–C8a *trans*-isomer. However, the D-alanine-containing dipeptide **7c** cyclized to a 2:1 mixture of diastereomers, albeit still with the *trans*-isomer in excess. In these two particular examples, the diastereomers were separated by preparative HPLC in order to unequivocally determine the relative stereochemistry of the *N,N*-acetal products by 2D NMR analysis.⁸

The same side-chain influence was observed when the tandem cyclizations were performed with dipeptides **7d–i** containing the two enantiomers of valine (entries 4 and 5), phenylalanine (entries 6 and 7), and allylglycine (entries 8 and 9), respectively. The products of the L,L-dipeptides were formed with consistently high diastereoselectivities, whereas the reactions with the D,L-dipeptides were much less selective. Although the diastereomers of products **8d–i** were not separated, the ¹H NMR spectra closely resembled those of products **8b** and **8c**, allowing the determination of the stereochemistry by comparison. Especially the chemical shift of the C5-proton, adjacent to the methyl ester, proved to be characteristic for the two diastereomers. For the C5–C8a *trans*-isomers this proton resonated at approximately 5.0 ppm, whereas in the C5–C8a *cis*-isomers the proton signal was found at about 4.0 ppm. This difference in chemical shift was observed for all products **8**. Finally, the Cbz protective groups of the cyclized products **8** could easily be removed under acidic conditions yielding the corresponding amines **9** as the corresponding HBr salts.

We now turned our attention to the tandem-cyclizations of β -amino acid-containing dipeptides. To this end, methyl ester **5** was coupled to both the enantiomers of *N*-Cbz- β -phenylalanine, using the same protocol as for the synthesis of peptides **7a–i**. In this way, cyclization precursors **10a** and **10b** were obtained (Scheme 2). Activation of the acetal

Scheme 2. Cyclizations of β -Amino Acid-Containing Dipeptides

with TsOH initiated the formation of *N,N*-acetals **11a** and **11b** respectively, both in 84% yield.

(8) For more details, see the Supporting Information.

The selectivity of these reactions proved to be excellent. The (*S*)- β 3-phenylalanine-containing product **11a** was isolated with a diastereomeric ratio of 19:1, while the (*R*)- β 3-phenylalanine-containing counterpart **11b** was formed as a single diastereomer (>99:1).⁹ In both cases, the depicted C5–C8a *trans*-isomer was formed, as determined by NMR studies. Furthermore, the stereochemical assignment was unequivocally proven by the crystal structure determination of Cbz-deprotected product **12b** (Figure 1).

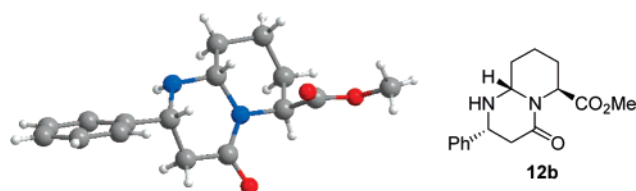
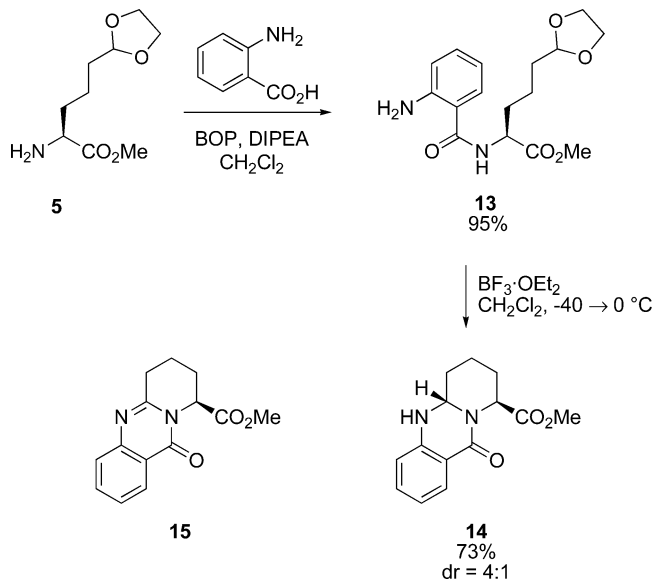


Figure 1. Chem3D representation of the crystal structure of **12b**.

To further investigate the scope of the tandem-cyclization strategy, precursor **13** was prepared by coupling of **5** with anthranilic acid (Scheme 3). Cyclization of **13** under the

Scheme 3. Cyclization of an Anthranilic Acid-Based Dipeptide



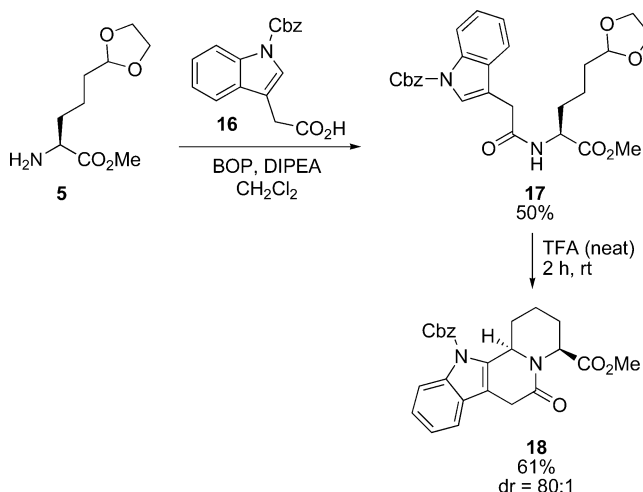
standard conditions (cat. TsOH, toluene, reflux) suffered severely from oxidation of the anticipated product, leading to a nearly 1:1 mixture of desired product **14** and side product **15**. Even when the reaction was carried out under an atmosphere of argon, the formation of **15** could not be suppressed. However, this problem could be circumvented

(9) Only one diastereomer of **11b** could be detected by HPLC.

by changing the cyclization conditions to $\text{BF}_3 \cdot \text{OEt}_2$ (1.6 equiv) in CH_2Cl_2 at lower temperature, which resulted in the efficient formation of tricyclic product **14**. The *N,N*-acetal was isolated as a 4:1 mixture of diastereomers, which could be separated by preparative HPLC. Again, the major isomer was determined to be the C5–C8a *trans*-isomer by NMR studies.

To probe whether the cyclization methodology could be extended to C–C bond formation, precursor **17** was prepared by coupling of **5** with indolyl derivative **16**¹⁰ (Scheme 4).

Scheme 4. Intramolecular C–C Bond Formation



As with the anthranilic acid-based precursor, cyclization with TsOH (10 mol %) in toluene at reflux did not lead to a satisfactory result. However, when the reaction was performed in neat TFA the desired tetracyclic product **18** was obtained in 61% yield as an 80:1 mixture of diastereomers (HPLC). In sharp contrast to all previous examples, in this case, the major diastereomer was determined to be the depicted C5–C8a *cis*-isomer.

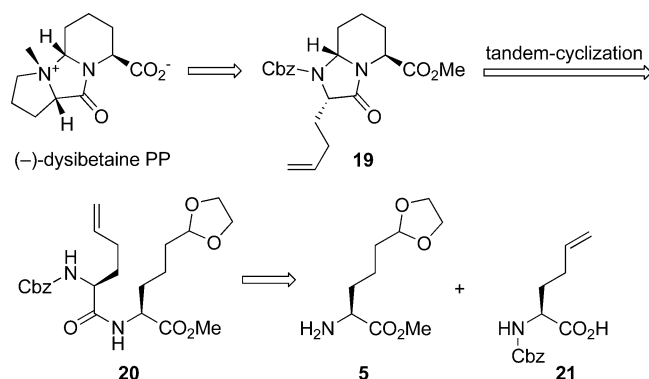
With the tandem-cyclization methodology in hand, we now turned our attention to the total synthesis of the natural product (–)-dysibetaine PP (Scheme 5). It was envisaged that tandem cyclization of dipeptide **20**, constructed from L-allysine ethylene acetal methyl ester **5** and (*S*)-*N*-Cbz-2-amino-5-hexenoic acid **21**,¹¹ would provide *N,N*-acetal **19** efficiently and with good diastereoselectivity. This intermediate could then be converted to the required tricyclic skeleton by ozonolysis and a subsequent reductive cyclization, after which the natural product should be readily obtainable.

Consequently, dipeptide **20** was prepared using the same protocol as for all previous cyclization precursors. Gratifyingly, treatment of **20** with a catalytic amount of TsOH in

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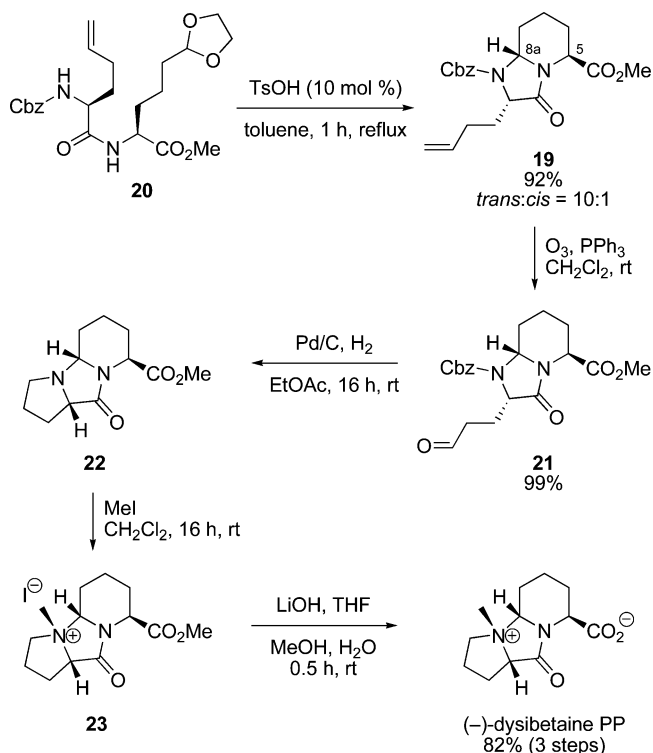
Scheme 5. Retrosynthetic Approach toward (–)-Dysibetaine PP



refluxing toluene, resulted in a very smooth cyclization to afford bicyclic *N,N*-acetal **19** (Scheme 6). The product was obtained as a 10:1 mixture of diastereomers in favor of the desired C5–C8a *trans*-isomer, which was in good agreement with the results obtained with other L,L-dipeptides (Table 1). Next, the olefinic side chain of **19** was subjected to an ozonolysis reaction, yielding aldehyde **21** in a virtually quantitative yield. Subsequent treatment of **21** with Pd/C under an atmosphere of hydrogen not only effected the removal of the Cbz protecting group but also the concomitant intramolecular reductive amination, yielding very efficiently the tricyclic product **22**. The final steps of the synthesis involved the stereoselective quaternization of the amine by treatment with methyl iodide followed by the formation of the inner salt via saponification of the methyl ester, affording the natural product (–)-dysibetaine PP in a yield of 82% over the last three steps.

In conclusion, we have developed a diastereoselective cationic tandem-cyclization strategy for the preparation of a diverse range of *N*-heterocyclic scaffolds. This versatile method allows the conversion of L-allylsine ethylene acetal-containing dipeptides to densely functionalized *N,N*-acetals. The tandem-cyclization reaction was successfully applied as the key step in the first total synthesis of the natural product (–)-dysibetaine PP. Investigations into the origin of the

Scheme 6. Total Synthesis of (–)-Dysibetaine PP



diastereoselectivity of the tandem cyclizations are currently in progress.

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Supporting Information Available: Experimental details and spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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