SYNTHESIS OF NOVEL HIGHLY FUNCTIONALIZED CYCLIC β–AMINO ACIDS

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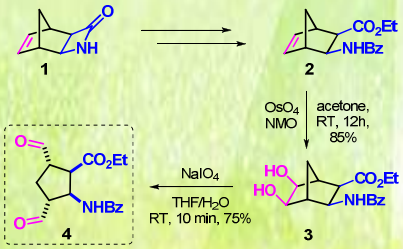
Introduction

Cyclic β-amino acids possessing valuable pharmacological potential have attracted a great interest during last two decades. A number of cyclic amino acids exhibit remarkable antifungal and antiinflammatory activities, such as cispentacin, icofungipen, and oryzoxymicin.[1-3] The synthetic generation of alkylated cyclic β-amino acids has been slightly examined. The aim of the current project was the design and synthesis of novel *trans* and *cis* dialkylated cispentacin derivatives.

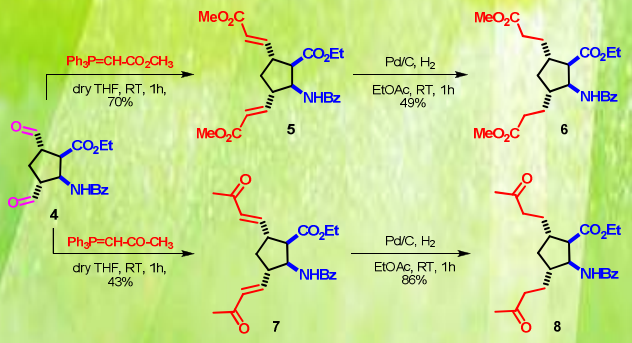
Results and Discussion

The concept of the synthetic route was the functionalization of the C-C double bond of diexo-norbornene β-lactam **1** through stereoselective dihydroxylation and oxidative ring cleavage. The resulted key intermediate dialdehyde **4** was then subjected to Wittig reaction, followed by the reduction of the C-C double bond.



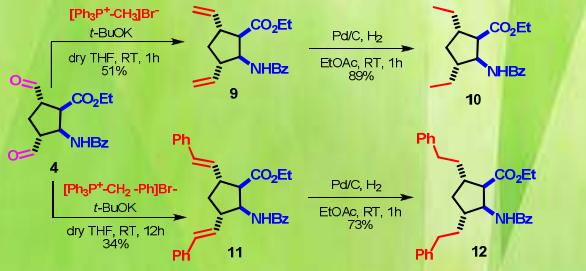
Scheme 1. Generation of di-*trans*-dialdehyde **4** starting from β-lactam **1**

Ring-opening reaction of diexo-β-lactam **1**, followed by an *N*-benzoylation led to diexo-bicyclic *N*-protected β-amino ester **2.** Then, **2** was treated with catalytic amount of OsO_4 in the presence of *N*-methylmorpholine-*N*-oxide, affording dihydroxylated derivative **3**. Subsequent rapid oxidative C-C bond cleavage by means of $NaIO_4$ resulted in the di-*trans*-dialdehyde **4**, which could be isolated in a stable form. (Scheme 1).



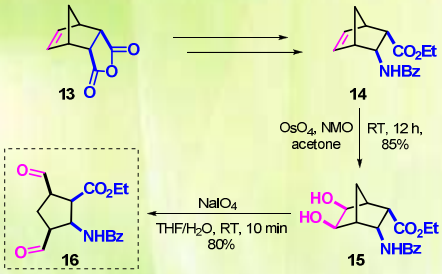
Scheme 2. Synthesis of dialkenylated products **5** and **7** and saturated final products **6** and **8**

Next, key intermediate **4** was transformed into the corresponding dialkenylated products **5** and **7** *via* a Wittig reaction. Subsequent catalytic hydrogenation gave access to saturated final products **6** and **8** in moderate yields. (Scheme 2).



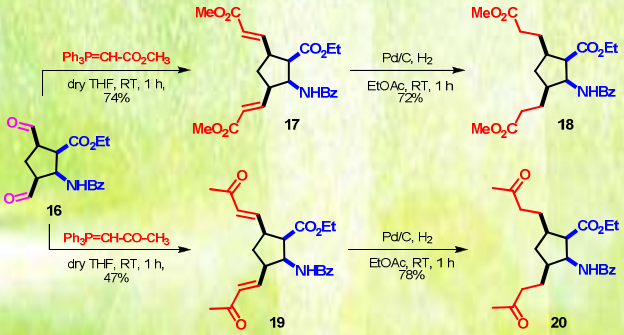
Scheme 3. Synthesis of dialkenylated products **9** and **11** and saturated final products **10** and **12**

Ylides for the next two reactions were prepared *in situ* by stirring the methyl- and benzyltriphenylphosphonium bromide salts with *t*-BuOK in dry THF. Then, the solution of dialdehyde **4** was added dropwise to the ylides, furnishing the corresponding dialkenylated products **9** and **11** in moderate yields. Similarly to the previous case, Pd-catalyzed hydrogenation gave access to saturated final product **10** and **12**. (Scheme 3).



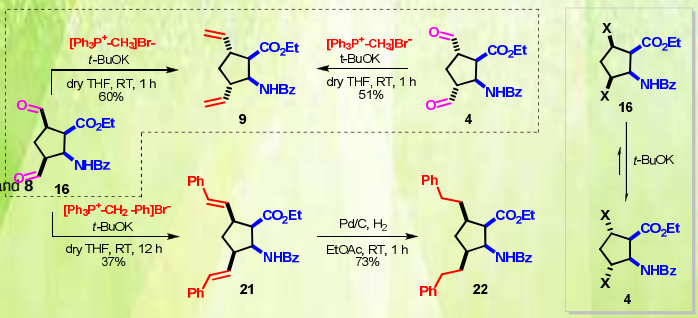
Scheme 4. Generation of all-*cis*-dialdehyde **16** starting from anhydride **13**

Diendo bicyclic amino ester **14** was synthesized from diendo anhydride **13** by a ring-opening reaction/Hoffmann degradation/*N*-protection strategy. All-*cis* dialdehyde **16** was prepared using the same methodology as earlier presented.



Scheme 5. Synthesis of dialkenylated products **17** and **19** and saturated final products **18** and

Using the same methodology and ylides, 'all-*cis*' dialkenylated Wittig products were successfully prepared and following catalytic hydrogenation led to the desired saturated final products in good yields. Surprisingly, in case of methyltriphenylphosphonium bromide we obtained the di-*trans* dialkylated derivative **9,** which was also prepared from di-*trans* dialdehyde **4,** instead of the 'all-*cis*' derivative. Probably a base induced inversion of the dialdehyde or the Wittig product could take place and the equilibrium was shifted to the more stable *trans* form.



Scheme 6. Synthesis of dialkenylated products **9** and **21** and saturated final product **22**

Conclusion

In summary, a number of novel di-*trans* and all-*cis* 3,5-dialkenylated and dialkylated cispentacin derivatives were successfully synthesized. The monocyclic dialdehydes were prepared *via* an oxidative C-C bond cleavage of the bicyclic system. Wittig transformation of these key intermediates, followed by a reduction led to 14 novel highly functionalized cispentacin analogues.

References

1. Kiss, L.; Forró, E.; Fülöp, F. Synthesis of carbocyclic β-amino acids. *Amino Acids, Peptides and Proteins in Organic Chemistry.* Vol. 1, Hughes, A. B., Ed. Wiley: Weinheim, **2009**, 367.
2. Fülöp, F. *Chem. Rev.* **2001**, *101*, 2181.
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