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Solution- and solid-phase asymmetric synthesis of substituted *N*-hydroxypyrrolidine dicarboxylic acids

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Abstract—Nitrone ylids prepared from α-amino aldehyde derivatives undergo 1,3-dipolar cyclocondensation reactions to give enantiopure C-4 branched *N*-hydroxy proline esters. The different functional groups can be manipulated to provide diversely substituted *N*-hydroxypyrrolidine dicarboxylic acids. The reaction can be adapted to solid-phase synthesis. © 2002 Elsevier Science Ltd. All rights reserved.

The 1,3-dipolar cycloaddition reaction is one of the most efficient methods for the synthesis of substituted pyrrolidines and prolines.[1] For example, the reaction of azomethine ylids[2] with alkenes generates substituted pyrrolidines and related structures. Saturated nitrogen heterocycles are common subunits of many natural alkaloids.[3] Many synthetic pyrrolidine and proline analogues exhibit enzyme inhibitory activities,[4] and agonist or antagonist properties toward certain receptors.[5]

Recently, we reported the synthesis of polysubstituted *N*-hydroxypyrrolidines from the cycloaddition of nitrone ylids derived from glycinate esters with electron deficient alkenes.[6] In this paper, we report the stereoselective synthesis of substituted *N*-hydroxypyrrolidine dicarboxylic acids from the reaction of nitrone ylids (prepared from α-amino aldehydes) with acrylates. The products corresponding to the general expression **A** (Fig. 1) represent prototypes of versatile *N*-containing scaffolds for diversity-oriented synthesis projects. They can also be considered as intermediates for the synthesis of a novel class of neuraminidase inhibitors such as A-192558 and A-315675 (Fig. 1).[7,8]

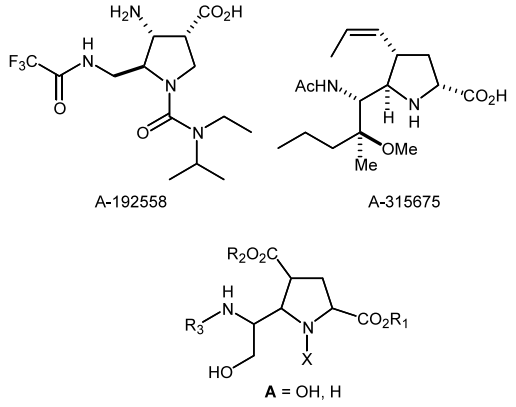

Figure 1.

Treatment of *N*,*O*-bis(*tert*-butoxycarbonyl)hydroxylamine ethyl or benzyl glycinate **1** with TFA, followed by condensation[9] with aldehydes **3**–**5**, easily prepared from the corresponding amino acids,[10] afforded the intended nitrones **6**–**9** as single isomers based on NOE studies (Scheme 1).

Cycloadditions of benzyl acrylate with nitrones **6**–**9** were carried out in THF at 0°C in the presence of lithium bromide and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as catalyst,[2] which afforded a single diastereomer of the substituted *N*-hydroxypyrrolidines **11**–**14** (Scheme 2).[11,12] The resulting cycloadducts can be formed via an *endo*-like transition state as shown in Fig. 2.[13] The observed diastereoselectivity can be explained by minimizing 1,3-allylic strain,[14] in the transition state model where H*a* is in the same plane as the nitrone oxygen. Attack occurs from the less encumbered *Re* face of the nitrone. Under the reactions conditions utilized, no formation of isoxazolidine was observed.

We chose to study a number of chemoselective transformations that would differentiate the functional

Keywords: cycloaddition; nitrone; amino acid; *N*-hydroxylactone.

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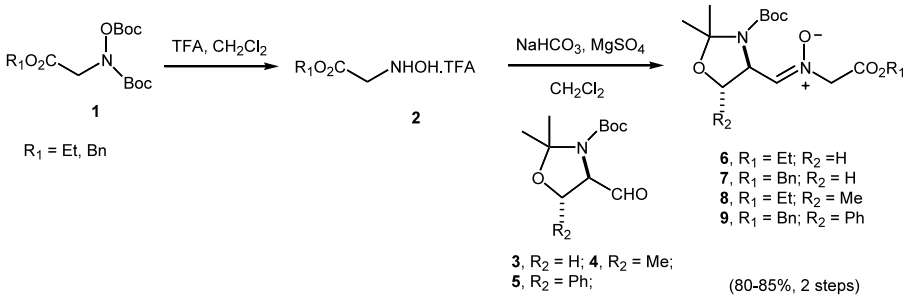
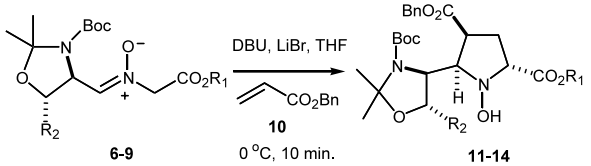
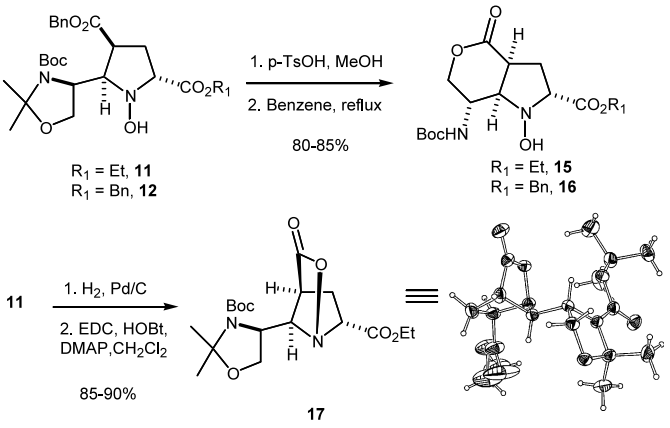


Scheme 1.



Entry	R_1	R_2	yield (%)
1	Et	H	70 (**11**)
2	Bn	H	75 (**12**)
3	Et	Me	75 (**13**)
4	Bn	Ph	65 (**14**)

Scheme 2.



Scheme 3.

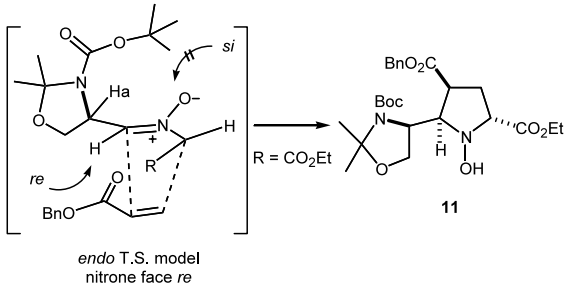


Figure 2.

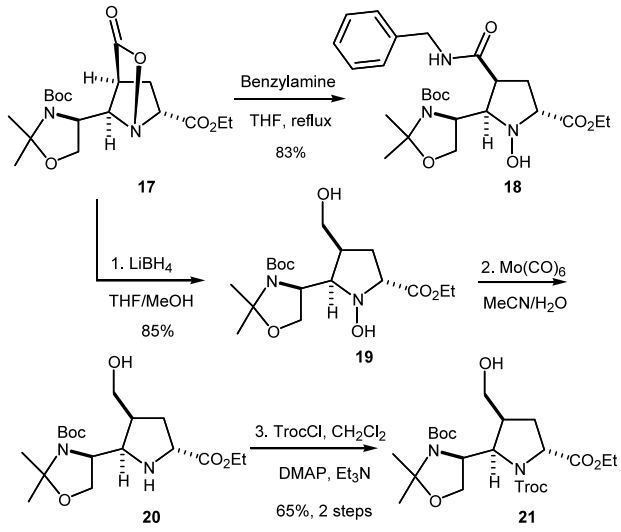
appendages and offer opportunities for further modification in the context of a program aimed at generating diversity in a proline-type scaffold.[6,15] Acid-catalyzed acetal cleavage of **11** and **12** afforded bicyclic lactones **15** and **16**, respectively. Hydrogenolysis of the benzyl ester **11** and intramolecular transesterification afforded the novel bicyclic lactone **17**, whose configuration was confirmed by an X-ray crystal structure (Scheme 3).

The unique internal *N*-hydroxy lactone[6] offers several possibilities for functional group diversification while maintaining the original oxidation state at nitrogen. Thus, selective opening of bicyclic lactone **17** with a prototypical amine gave benzylamide **18**, while a reduction afforded diol **19**. Cleavage of the N–O bond using molybdenum hexacarbonyl[16] afforded amine **20**, which was transformed into the *N*-Troc derivative **21** (Scheme 4).

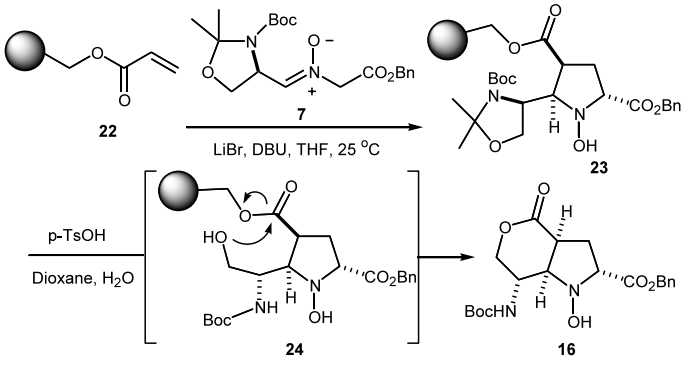
Solid-phase synthesis has been established as a versatile method for preparing potentially bioactive molecules in high throughput screening assays.[17] Highly substituted pyrrolidine libraries have been achieved by several research groups through solid-phase synthesis.[18]

The nitrone cycloaddition methodology described here for generating polyfunctional *N*-hydroxypyrrolidine dicarboxylic acid motifs was readily adapted to solid-phase synthesis to produce core scaffolds with functionally diverse appendages (Scheme 5). The Wang acrylate resin[19] **22** was treated with **7**, LiBr, DBU in THF to afford a resin-bound cycloadduct **23**.[20,21] Acidic cleavage of the *N*,*O*-acetal in **23** released the bicyclic lactone **16** from the resin in a clean and efficient manner (overall yield of 40%from **7**).

Diverse sets of functionalized *N*-hydroxypyrrolidine dicarboxylic acids with orthogonal protective groups can now be readily prepared in solution or on solid-support based on this nitrone ylid cycloaddition methodology. These motifs represent useful scaffolds onto which a variety of functional groups can be deployed as potential pharmacophores. In addition, the methodology can find immediate application in the synthesis of neuraminidase inhibitors related to those shown in Fig. 1.



Scheme 4.



Scheme 5.

Acknowledgements

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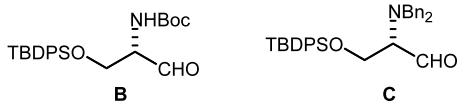
11. With the less reactive benzyl crotonate and benzyl cinnamate, the cycloaddition reaction failed and decomposition of the nitrone was observed. Furthermore, replacement of LiBr with other additives (AgOAc, $MgBr_2$, KBr, etc.) resulted in the recovery of the nitrone.
12. The cycloaddition reaction of nitrones, derived from aldehydes **B** and **C**, did not generate the desired *N*-hydroxypyrrolidines presumably due to β-elimination.



13. The reaction may proceed in a concerted asynchronous manner. Although we did not observe single addition products, we cannot exclude a stepwise mechanism of cycloaddition formation. The stereochemistry of the adducts can be rationalized based on an *anti*-oriented nitrone ylide/enolate, and *s-cis* conformation of the *endo*-placed acrylate ester. The stereochemical outcome of the cycloadducts **13** and **14** was assigned by analogy to **11**.
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21. To a solution of nitrone **7** (235 mg, 0.60 mmol) in THF (5 mL), was added Wang acrylate resin **22** (100 mg, 0.06 mmol) followed by LiBr (16 mg, 0.18 mmol) and DBU (18 μL, 18 mg, 0.12 mmol) at rt. The suspension was shaken for 24 h at rt, filtered, washed with THF (2×3 mL) and MeOH (2×3 mL), and dried to give resin bound cycloadduct **23**. To a solution of **23** in a mixture dioxane/H_2O (4 mL, 10:1), was added *p*TsOH (11 mg, 0.06 mmol) at rt. The suspension was shaken for 24 h at rt, filtered and washed with EtOAc (3×5 mL). The filtrate was washed with a saturated solution of $NaHCO_3$ (4 mL), dried (Na_2SO_4), filtered and evaporated to dryness. The resulting residue was purified by flash chromatography (EtOAc/hexanes, 1:1) to give the desired bicyclic *N*-hydroxypyrrolidine lactone as a colorless oil.