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Syntheses of morpholine-2,3-diones and 2-hydroxymorpholin-3-ones: intermediates in the synthesis of aprepitant

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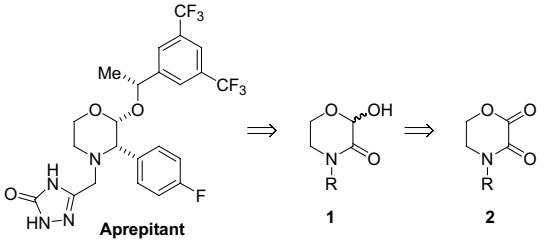
Abstract—The preparation of morpholine-2,3-diones and 2-hydroxymorpholin-3-ones from *N*-substituted β-amino alcohols is reported. These were useful intermediates in the synthesis and development of aprepitant.

Aprepitant has recently been approved, in combination with other agents, as an effective treatment for preventing acute and delayed chemotherapy-induced nausea and vomiting (CINV) that can result from highly emetogenic chemotherapy in adults.[1] This is the first FDA-approved drug for the treatment of CINV that persists for more than 24 h after chemotherapy treatment. A core structural element of this h-NK1 receptor antagonist is an *N*-protected-2-hydroxymorpholin-3-one, which was utilized in a recently disclosed total synthesis of aprepitant.[2] As part of our investigation into the synthesis of this target molecule, we envisioned that potential intermediate lactol **1a** could be derived from the corresponding morpholine-2,3-dione (**2a**) (Scheme 1).



Scheme 1.

The intermediate lactol was to be subjected to a diastereoselective acetalization with (*R*)-3,5-bistrifluoromethylphenyl ethanol.[3] In order to possibly improve this diastereoselective coupling, a variety of chiral *N*-R lactols **1** were desired. In addition, since the success of the overall route to aprepitant depended on crystalline intermediates,[2] numerous *N*-substituted lactols **1** needed to be prepared in order to investigate the crystalline properties of downstream intermediates. Accordingly, we required a versatile procedure to access a variety of *N*-substituted morpholine-2,3-diones **2** and 2-hydroxymorpholin-3-ones **1**.

Surprisingly, the literature describing these structures is rather sparse.[4,5] Conceptually, this ring system can be disconnected to an amino alcohol and a readily available oxalate derivative, such as diethyl oxalate or ethyl chlorooxoacetate. As a proof of concept, the reaction of *N*-benzylethanolamine and diethyl oxalate in EtOH afforded lactone lactam **2** (R = Bn) in 59% isolated yield after crystallization.

N-Substituted ethanolamines can be prepared by reduction of the corresponding imines (Scheme 2). In fact, **5c** and **5d** were prepared from **4c** and **4d** by hydrogenation (Pd/C) and $NaBH(OAc)_3$ reductions, respectively.

Since this method could not readily be extended to chiral *N*-substituted ethanolamines, we decided to use an alternative and simple two-step procedure that would

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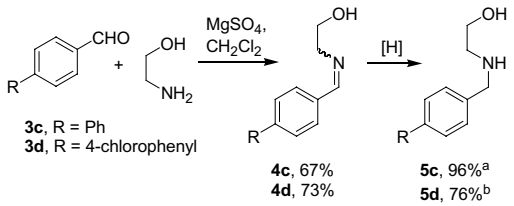
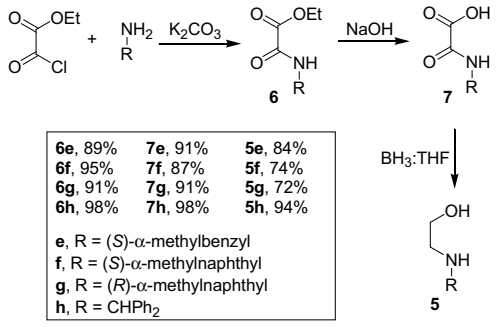


Scheme 2. Reagents: (a) Pd/C, H_2, EtOH; (b) $NaBH(OAc)_3$.

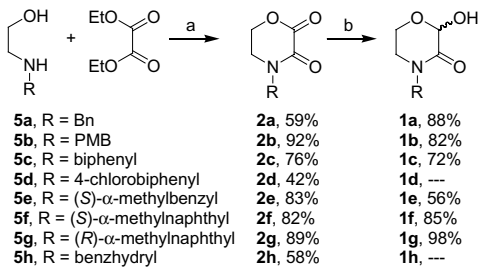
provide intermediate amido acids **7**, since these were also potentially useful intermediates for our program. The synthesis of enantiomerically pure (*R*)-α-methylbenzylethanolamine has been achieved in this fashion.[6,7] Thus, addition of the chiral amines to ethyl chlorooxoacetate cleanly afforded the amido esters (**6e**–**g**), which were readily saponified to the corresponding chiral amido acids (**7e**–**g**) (Scheme 3). These compounds were then reduced to the desired amino alcohols (**5e**–**g**) with diborane. Each of the individual steps in this chiral amino alcohol synthesis was high yielding (72–98%). This method was also applied to benzhydrylamine in order to form the corresponding *N*-diphenylmethylethanolamine (**5h**) in 89% overall yield.

Each of these amino alcohols [**5c**–**d** (from Scheme 2) and **5e**–**h** (from Scheme 3)] was condensed with diethyl oxalate in order to provide the corresponding morpholine-2,3-diones **2** (Scheme 4).

Next, the reduction of lactones **2** to the corresponding lactam lactols **1** was investigated. Reducing agents were screened to maximize the lactol yield and to minimize



Scheme 3.

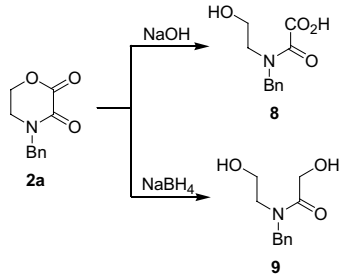


Scheme 4. Reagents: (a) EtOAc or EtOH/hexane; (b) $LiB[CH(CH_3)C_2H_5]_3H$.

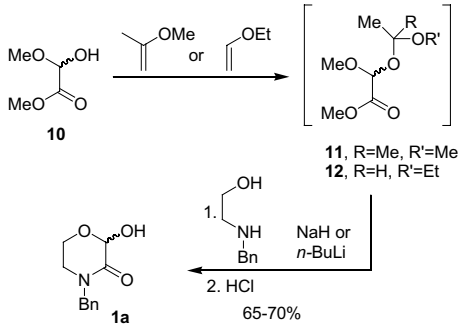
hydrolysis to the hydroxy acid **8** and/or over reduction to the diol **9** (Scheme 5). DIBAL-H had been used in a similar reduction of 2,3-dioxo-1,4-benzoxazines;[8] however, when lactam lactone **1a** was reduced, a low assay yield of lactol **1a** was obtained. This yield could be improved by utilizing 2 equiv of DIBAL-H, but the workup and isolation of pure lactam lactol **1a** became problematic. While a good HPLC assay yield (82%) was obtained with 0.25 equiv of $LiBH_4$, we viewed the balance between unreacted starting material (9% HPLC assay) and over-reduced diol formation (5% HPLC assay) to be problematic. Both lithium tri-*tert*-butoxyaluminum hydride and lithium tri-*sec*-butylborohydride offered a solution to these problems. Other reducing agents that were screened that were inferior to these include Red-Al, $NaBH_4$, KBH_4, $NaBH_4$/TMSCl, and $Na(OAc)_3BH$. Authentic samples of the acid **8** and diol **9** were prepared by treating lactone **2a** with NaOH and $NaBH_4$, respectively (Scheme 5).

Upon comparison of the reductions performed with lithium tri-*tert*-butoxyaluminum hydride and lithium tri-*sec*-butylborohydride, the former system required much larger volumes during workup and also resulted in higher levels of hydroxy acid **8** (6% LC assay). Therefore, the method of choice that was utilized for the conversion of lactam lactones **2** to lactam lactols **1** was lithium tri-*sec*-butylborohydride. This method afforded an 88% isolated yield of lactol **1a** on a 200 g scale. This protocol provided numerous 2-hydroxymorpholin-3-ones from the corresponding morpholine-2-3-diones (Scheme 4).

Utilization of these 2-hydroxymorpholine-3-ones in the subsequent steps of the synthesis en route to aprepitant indicated that the preferred lactol was *N*-Bn derivative **1a**. Consequently an improved synthesis of this intermediate was pursued. A primary objective was to employ substrates that were at the correct oxidation state, so as to obviate superfluous oxidation/reduction chemistry in the second generation synthetic route. In an initial alternative approach, hemiacetal **10** was protected with 2-methoxypropene or ethyl vinyl ether to give the corresponding mixed acetals **11** and **12**, respectively (Scheme 6). These were then added to a solution of *N*-benzylethanolamine (**3a**) that had been treated with 1.1 mol equiv of either NaH or *n*-BuLi. Addition of dilute HCl to the resulting amidation products afforded the desired lactol **1a** in 65–70% isolated yield. These reactions were performed in either THF or MTBE.



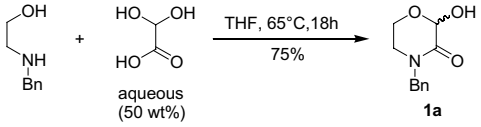
Scheme 5.



Scheme 6.

While this route met our objective of using starting materials that had the correct oxidation state, we envisioned that a more straightforward entry to this substrate could be achieved. Disconnection of lactol **1a** at both the amide bond and acetal linkage provided *N*-benzylethanolamine (NBEA) and glyoxylic acid as the potential starting materials (Scheme 7). A direct condensation between NBEA (1 equiv) and crystalline glyoxylic acid hydrate (1 equiv) in THF resulted in 30% yield of **1a**. Performing the reaction in aqueous glyoxylic acid (50 wt%) resulted in a 38% HPLC assay yield of product. The reaction profiles were clean but the progress of the reaction stalled. An additional equivalent of glyoxylic acid (50 wt%) was added at four intervals, which allowed the reaction to ultimately achieve 87% yield (Table 1).

NMR studies have shown that aqueous glyoxylic acid is primarily in the form of monomeric hydrate (69–88%) with dimeric hemiacetals (3–12%) and higher oligomers (<5%).[9] Regardless, of the acetal content, we viewed the reaction as being thermodynamically driven by the formation of the amide.[10] Hence, the exact composition of glyoxylic acid was irrelevant, as long as under the acidic aqueous conditions an equilibrium pathway with the NBEA could occur. Exogenous acid sources and alcohol additives showed no rate or yield enhancement. Thus, the optimized conditions for the formation of lactol **1a** were to slowly add neat NBEA to a preheated solution of THF and 50 wt% glyoxylic acid (2.2:1; v/v). Prewarming the glyoxylic acid to a point below reflux drove off dissolved CO_2 that could potential react with

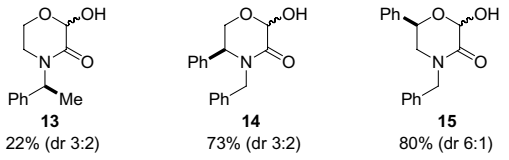


Scheme 7.

Table 1. Effect of glyoxylic acid charge

Glyoxylic acid (equiv)	Concentration (g/L)	Yield[a] (%)
1	76	38
2	110	61
3	138	84
4	131	87

[a] Based on no solvent loss during reaction.



Scheme 8.

NBEA. In addition, an initial *N*,*O*-acetal adduct crystallizes from solution if the reaction is performed at room temperature.[2] After heating for 18 h, the THF was distilled,[11] and lactol **1a** was crystallized from water (72% isolated). A mechanistic discussion of this transformation has been reported.[2]

A brief investigation into the scope of this condensation was performed. Attempts to condense unprotected amino alcohols (ethanolamine and phenyl glycinol) failed to produce the desired lactam lactols.

Increasing the size of the *N*-substituent (α-methylbenzyl ethanolamine) resulted in a low yield of lactol **13** (22%) (Scheme 8). However, there did not appear to be an effect from the substitution on the ethanol backbone. Both *N*-benzyl phenyl glycinol and *N*-benzyl-1-phenylethanolamine provided good yields of the desired lactols **14** and **15** (73% and 80%, respectively).

In summary, we have described simple, practical and high yielding protocols for the synthesis of 2-hydroxymorpholin-3-ones and morpholine-2,3-diones. The general method for the synthesis of numerous 2-hydroxymorpholin-3-ones was by the mono-reduction of the corresponding morpholine-2,3-diones. However, the preferred method for the synthesis of desired *N*-benzyl morpholinone **1a**, which was used in the synthesis of aprepitant, was by the condensation of *N*-benzylethanolamine and glyoxylic acid.

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11. It was important to stop the distillation when the solvent composition is ca. 3–8% (v/v) of THF/H_2O. If there is too much THF present, increased mother liquor losses occur. If there is <3% (v/v) of THF/H_2O, then impurities are not completely rejected.