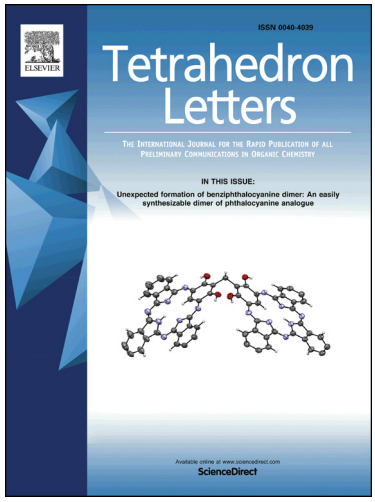

Stereoselective synthesis of orthogonally protected 2,3-disubstituted morpholines using a base-catalysed cascade reaction

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PII: S0040-4039(17)30814-6
DOI: http://dx.doi.org/10.1016/j.tetlet.2017.06.077
Reference: TETL 49069

To appear in: *Tetrahedron Letters*

Received Date: 26 May 2017
Revised Date: 22 June 2017
Accepted Date: 23 June 2017

Please cite this article as: Marlin, F.J., Stereoselective synthesis of orthogonally protected 2,3-disubstituted morpholines using a base-catalysed cascade reaction, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.06.077

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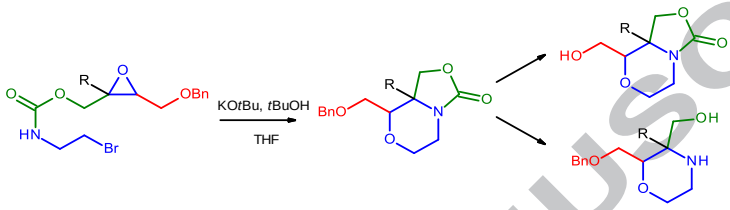

Tetrahedron Letters
journal homepage: www.elsevier.com

Stereoselective synthesis of orthogonally protected 2,3-disubstituted morpholines using a base-catalysed cascade reaction

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
[3-(hydroxymethyl)morpholin-2-yl]methanol
Chiral epoxide
Oxazolidinone
Cascade reaction

ABSTRACT

The stereoselective synthesis of differentially protected [3-(hydroxymethyl)morpholin-2-yl]methanols is described, starting from chiral epoxides. The key step involves a one-pot oxazolidinone formation via intramolecular epoxide opening and concomitant cyclisation to form the morpholine ring. Selective deprotection reveals the free hydroxymethyl group at either the 2- or 3- position of the morpholine.

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The morpholine ring is used extensively in drug discovery research and is present in numerous drugs approved by the FDA.[1] While N-substituted morpholines are often used as a hydrophilic handle to improve the physico-chemical properties of a ligand, carbon-substituted morpholines also display activity[2] and have found applications as antidepressants,[3] appetite suppressants such as Phendimetrazine[4] or anti-emetics such as Aprepitant[5] (Figure 1). Finafloxacin, which possesses a morpholine ring fused onto a pyrrolidine ring, is a fluoroquinolinone antibiotic indicated in the treatment of acute otitis externa (swimmer's ear).[6]

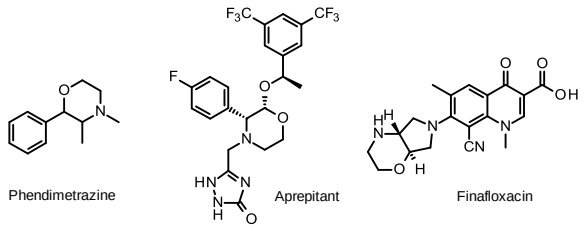
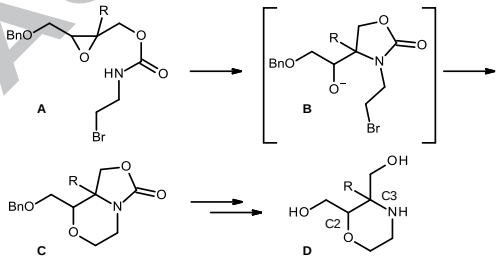


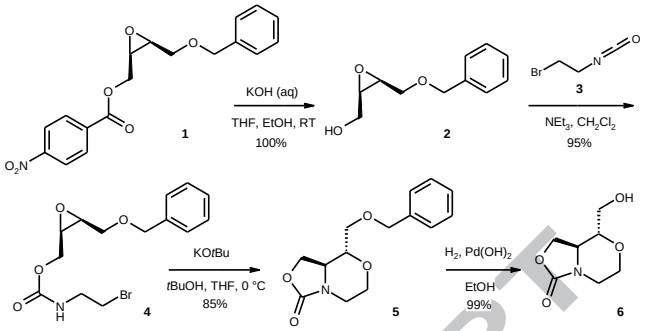
Figure 1. Representative bioactive morpholines.

We became interested in the [3-(hydroxymethyl)morpholin-2-yl]methanol scaffold (**D**, Scheme 1)[7,8] in an attempt to modulate the pharmacokinetic properties of a morpholine-based ligand. An orthogonally protected morpholine was required to allow subsequent sequential functionalization of the 2 hydroxyl groups, while a stereoselective approach had to be designed that would allow access to all diasteroisomers. Herein, we disclose the results of our strategy for the development of a base-catalysed cascade reaction for the synthesis of chiral morpholines. The bespoke synthesis relies on the pool of readily available chiral epoxide starting materials, or where necessary, the stereochemistry is readily installed and assigned unambiguously from the well-known Sharpless asymmetric epoxidation of allylic alcohols.[9]

Single-pot cascade reactions are an efficient way to generate molecular complexity in a concise fashion.[10] The key stage of our synthesis is the unprecedented one-pot 2-step synthesis of morpholine **C** by formation of the O-C bond via S_N2 displacement of the bromide with the alkoxide [intermediate **B**] resulting from regio- and stereoselective epoxide opening using the nitrogen atom of the carbamate **A**, and an appropriate base (Scheme 1).



Scheme 1. One-pot synthesis of morpholines from epoxyurethanes.



Scheme 2. Synthesis of *trans*-disubstituted morpholine **6**.

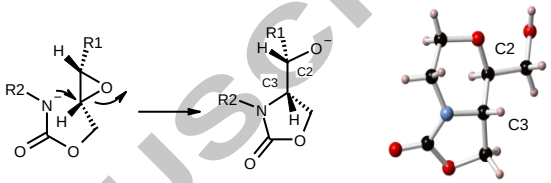
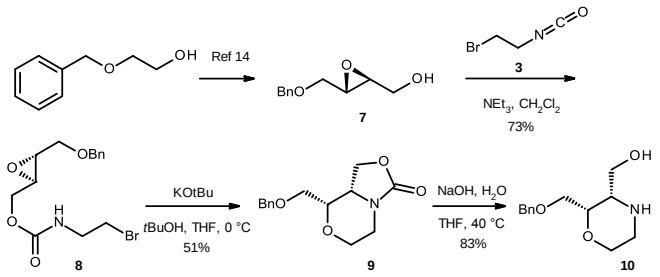


Figure 2. Inversion of configuration at C3 and X-Ray crystal structure of compound **6**.

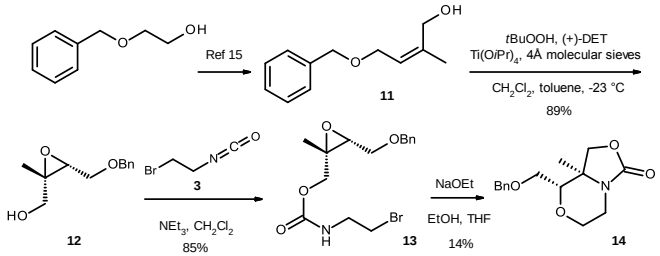
In such an approach the nitrogen atom and one of the hydroxyl groups are tied up together as an oxazolidinone,[11,12,13] and the free aminoalcohol could be revealed in a subsequent step, while the other methanol functionality, protected as benzyl ether, can be independently deprotected at any subsequent stage.

As a first example, a straight-forward hydrolysis of commercially available 4-nitrobenzoic ester **1** gave the primary alcohol **2** with the chiral epoxide already in place and of known stereochemistry (Scheme 2). 2-Bromoethyl isocyanate **3** is a very useful synthon in organic synthesis in that it has two reactive electrophilic centres that can be sequentially engaged. Carbamate formation afforded the required cyclisation precursor **4** in excellent yield. Subsequently, treatment of **4** with 2 equivalents of KO*t*Bu at RT in *t*BuOH/THF very rapidly effected the cascade sequence to deliver **5** in 85% yield with no intermediate detected. The benzyl protecting group could be removed using hydrogenation conditions to give the free alcohol **6**. X-Ray crystallography of alcohol **6** (Figure 2) confirmed not only the validity of the synthetic design of our approach but also the relative stereochemistry of the 2 contiguous stereocentres: with the stereochemistry at C2 being dictated by that of the commercial epoxide, stereochemistry at C3 arises from a regiospecific 5-*exo*-*tet* cyclisation and opening of the epoxide with inversion of configuration.

We then turned our attention to the *cis*-disubstituted morpholine isomers. The corresponding chiral epoxide **7** was made in 3 steps according to literature precedent via 1-pot oxidation-Wittig olefination, followed by ester reduction and Sharpless asymmetric epoxidation, starting from 2-benzyloxyethanol.[14] Carbamate formation proceeded well to give **8** in 73% yield and set the stage for our key morpholine formation cyclisation step (Scheme 3). Using our standard conditions (KO*t*Bu, *t*BuOH, THF, RT), cyclisation occurred to give the desired product **9** in 51% yield. A non-quantified by-product of this reaction is the alcohol **7** resulting from cleavage of the carbamate. It is noteworthy that reaction time took much longer for this set of diastereoisomers (typically overnight) and following the reaction by LCMS suggested the oxazolidinone intermediate could be isolated.



Scheme 3. Synthesis of *cis*-disubstituted morpholine **10**.



Scheme 4. Synthesis of trisubstituted morpholine **14** bearing a quaternary carbon

The decreased yield and the longer reaction time can potentially be explained by the two *cis*-substituents now having a pseudo axial – equatorial relationship in the cyclised product as opposed to a much more energy efficient state in the two *trans*-substituents in a pseudo equatorial relationship. Hydrolysis of the oxazolidinone functionality revealed the amino alcohol **10** in good yield.

Lastly, we investigated the possibility of incorporating a quaternary C3 carbon. Retrosynthetically this meant adjusting our synthetic design to start with an adequately tri-substituted allylic alcohol. Based on our experience with the difference of reactivity for the *cis*- and *trans*-isomers, we envisaged that we would stand a better chance of exploring the feasibility of the key cyclisation targeting the intermediate by having the two hydroxymethyl groups in a trans-relationship. Therefore, the *E*-allylic alcohol **11** was prepared using a literature procedure starting from 2-benzyloxyethanol (Scheme 4).[15] This was advanced following Sharpless asymetric epoxidation and carbamate formation to cyclisation precursor **13** in good overall yield. In a first attempt, potassium *tert*-butoxide (2 eq, RT, extended reaction time) gave complete hydrolysis of the carbamate. Varying the temperature, the number of equivalents or the reaction time, as well as other bases (NaH, DBU), failed to yield any desired product. Lewis acids (Et_2AlCl, $BF_3.OEt_2$) seemed to open the epoxide but no oxazolidinone nor morpholine product were isolated. Eventually, sodium ethoxide proved to be the most successful base tested, giving 14% desired product **14** when reacted with 2 eq in EtOH, THF at RT.

In summary, we have developed a concise route to a new morpholine scaffold. The useful synthon is accessible as any of the 4 possible diastereoisomers and should serve for the preparation of novel C2-C3 disubstituted chiral morpholines.

Supplementary data

Supplementary data associated with this article can be found in the online version.

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Research highlights:

- Stereoselective synthesis of C2-C3 disubstituted morpholines
- One-pot intramolecular epoxide opening and concomitant S_N2 with the resulting alkoxide
- Chiral synthon available as any of the 4 possible diastereoisomers

16.