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SHORT COMMUNICATION

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Enantioselective Synthesis of Functionalized Quaternary Stereocenters

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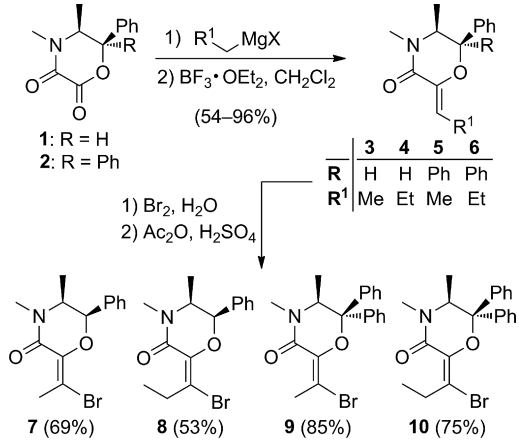
An enantioselective synthesis of functionalized quaternary stereocenters was developed from amino alcohol derived (bromoalkylidene)morpholinones. Stereoselective cross-coupling of the morpholinones with arylboronic acids or alkyl trifluoroborates provided a variety of disubstituted alkylidenemorpholinones. A highly stereoselective Prins reaction of the cross-coupling products generated the target quaternary stereocenter. The Prins products are readily converted into a variety of acyclic, enantiomerically enriched, functionalized building blocks with a quaternary stereocenter.

Introduction

Quaternary stereocenters are interesting structural motifs, which present a unique synthetic challenge. They are encountered as structural units in several natural products and hence enantioselective approaches to quaternary stereocenters have been intensely investigated in recent years.[1] Several non-catalytic[2] as well as catalytic[3] enantioselective methods have been developed for assembling quaternary stereocenters. While some of these efforts are in the realm of natural product synthesis,[1a,1c] other studies showcase methodology for the construction of quaternary stereocenters by employing suitably functionalized starting materials.[1d,2,3] In this context, opportunities exist for the construction of quaternary centers in acyclic fragments that have functionality for further elaboration.[4] To explore this prospect, we chose to examine the synthesis of hydroxy aldehydes and carboxylic acids with a quaternary α-stereocenter. Herein, we describe preliminary results toward this objective.

Results and Discussion

The focus of our strategy is the stereoselective functionalization of amino alcohol derived alkylidenemorpholinones. The synthesis of these morpholinones begins with morpholinediones **1**[5] and **2** (Scheme 1), which are readily prepared by the reaction of ethyloxalyl chloride with 1*R*,2*S*-ephedrine hydrochloride and of oxalyl chloride with *S*-2-(methylamino)-1,1-diphenylpropanol[6] respectively. The amino alcohol used for making **2** was chosen as a potential alternative to ephedrine, which is a controlled drug precursor. In recent years, this has limited its availability for research. Treatment of **1** and **2** with ethylmagnesium bromide or propylmagnesium chloride provided the corresponding hemiacetals, which were dehydrated to furnish the alkylidenemorpholinones **3**[5b] (96%), **4**[5c] (98%), **5** (74%) and **6** (54%, Scheme 1). These were converted into the key (*Z*-bromoalkylidene)morpholinones **7**, **8**, **9** and **10**, respectively by conversion to the bromohemiacetals (Br_2/H_2O) and subsequent dehydration. Notably, under optimized conditions (Scheme 1), the corresponding *E*-isomers were generally not obtained. The *Z*-alkene geometry in **7**, **8** and **10** was assigned on the basis of anisotropic deshielding (^{1}H NMR) of the γ-hydrogen atoms[7] in the embedded butenamide motif (methyl group in **7** and methylene group in **8**, **10**) as compared to the corresponding *E*-isomers [(*E*)-**7**, (*E*)-**8** and (*E*)-**10** respectively], which were occasionally obtained in trace amounts [<5%, (*E*)-**7** and (*E*)-**8**] or obtained by dehydration of the corresponding bromohemiacetal at elevated temperature [ca. 5% at 50 °C for (*E*)-**10**].[8] The morpholinone (*E*)-**9** could not be obtained for comparison with **9**. However, since dehydration of the bromohemiacetal ob-



Scheme 1. Synthesis of (bromoalkylidene)morpholinones.

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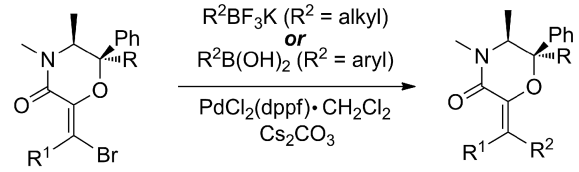
tained from **6** at ambient temperature had provided **10** as the only isolable product, **9** was assigned the *Z*-geometry by analogy.

At this stage, the morpholinones **7**–**10** possess one (methyl or ethyl) of three substituents that would eventually adorn the quaternary α-carbon in the target carboxylic acids or aldehydes. The next objective was the introduction of an additional substituent by cross-coupling of the vinyl bromide moiety in **7**–**10**. Clearly, the stereoselectivity of this C–C bond forming step was critical for the formation of a stereodefined (at the alkene) alkylidenemorpholinone.[9] Initial attempts to introduce an alkyl substituent in **7** by the Negishi or Kumada cross-coupling of alkylmetal reagents with the vinyl bromide were uniformly unsuccessful under a variety of conditions. These reactions either proceeded in very low yield or resulted in reduction of the vinyl bromide to the corresponding alkene. Attempted Suzuki–Miyaura cross-couplings of **7** with alkylboronic acids[10a] or B-alkyl MIDA boronates[10b] were similarly unsuccessful. Fortunately, the use of potassium alkyltrifluorobrates[11] as the cross-coupling partners provided the required products in good yields and a variety of primary alkyltrifluoroborates were successfully coupled with morpholinones **7**–**10** (Table 1). With the exception of cyclopropyltrifluoroborate, secondary alkylboronic acids or secondary alkyltrifluoroborates did not furnish the expected cross-coupling products. However, cross-coupling reactions of **7**, **8** and **9** with arylboronic acids proceeded smoothly and provided the corresponding alkyl/aryl-substituted morpholinones **11**–**13**. These results are summarized in Table 1.

The stereoselectivity of the cross-coupling reaction was ascertained by the conversion of diastereomerically pure bromoalkenes to diastereomeric cross-coupling products. Thus, cross-coupling of bromoalkene **8** with potassium benzyltrifluoroborate provided the alkylidenemorpholinone (*Z*)-**12**, whereas (*E*)-**8** gave the diastereomeric (*E*)-**12** (Scheme 2). Similarly, the cross-coupling of **10** with potassium methyltrifluoroborate provided (*E*)-**13a**, but (*Z*)-**13a** was obtained from a similar reaction of (*E*)-**10** (Scheme 2). Notably, the cross-coupling of **9** with potassium ethyltrifluoroborate also provided (*Z*)-**13a**. Since none of the diastereomeric cross-coupling product was detected (^{1}H NMR) in the reactions of **8**/(*E*)-**8** and **10**/(*E*)-**10**, all of the cross-coupling reactions of **7**–**10** were assumed to proceed with retention of configuration to provide the morpholinones **11**–**13**. As in the bromoalkenes, the stereochemical assignments for the cross-coupling products are based on the anisotropic deshielding of the γ-hydrogen atoms in the alkene substituent that is *syn* to the morpholinone carbonyl group.[7]

Table 1. Suzuki–Miyaura cross-coupling of **7**–**10**.

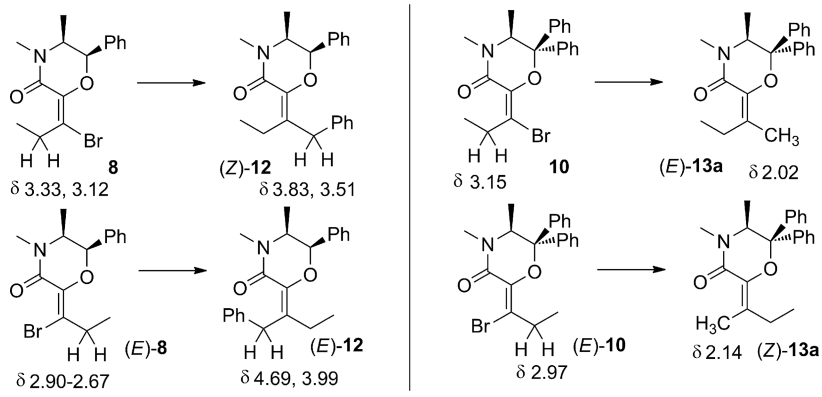


7–10 **11–13**

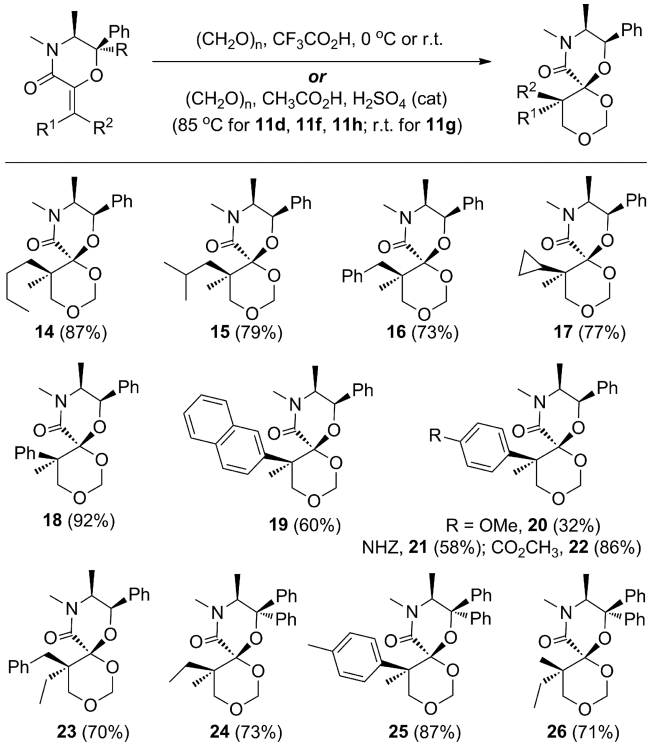
Morpholinone	R	Product	R^1	R^2	Yield [%]
7	H	**11a**	Me	Bu	92
	H	**11b**		*i*Bu	80
	H	**11c**		Bn[a]	72
	H	**11d**		cyclopropyl	75
	H	**11e**		Ph	92
	H	**11f**		2-naphthyl	96
	H	**11g**		4-OMe-C_6H_4	94
	H	**11h**		4-NHZ-C_6H_4	88
	H	**11i**		4-CO_2MeC_6H_4	89
8	H	(*Z*)-**12**	Et	Bn	85
9	Ph	(*Z*)-**13a**	Me	Et	87
	Ph	**13b**	Me	4-Me-C_6H_4	93
10	Ph	(*E*)-**13a**	Et	Me	64

[a] Pinacolate of benzylboronic acid was used.

With the disubstituted alkylidenemorpholinones in hand, the stage was set for the final step in the construction of the quaternary stereocenter. To this effect, the alkylidenemorpholinones were subjected to a Prins-type reaction[12] with paraformaldehyde. Depending on the substrate, two methods were developed for this reaction, one employing TFA as the solvent (at ambient temperature or at 0 °C), and the other employing the more classical acetic acid/cat. H_2SO_4 protocol with heating if necessary. Pleasingly, these reactions generated the spiromorpholinones **14**–**26** in good yield (Scheme 3).



Scheme 2. Diastereoselective cross-coupling reactions of (bromoalkylidene)morpholinones.

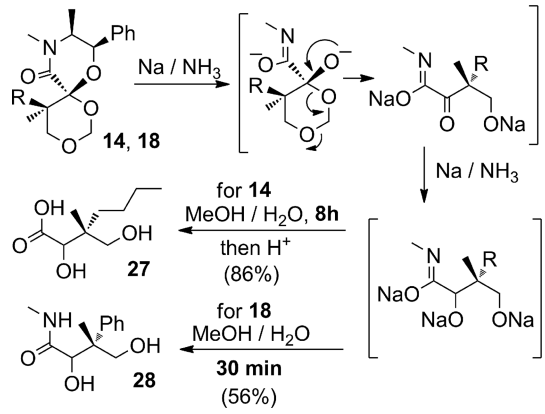


Scheme 3. Prins reactions of alkylidenemorpholinones.

The yield of **20**, from morpholinone **11g**, is relatively low (32%) due to competing substitution on the aromatic ring. Notably, the Prins products were obtained as single diastereomers, the only exception being **26**, which was obtained as a 5:1 mixture of diasteromers. In this case, purification provided diastereomerically pure **26** (71%). The stereochemistry at the newly formed quaternary carbon atom and at the spiroacetal stereocenter in **14**–**26** is assigned by analogy to other reactions of the morpholinone template,[5b,5c] which proceed from the less-substituted face of the morpholinone ring. The reason for the moderate diastereoselectivity for **26** is not clear at present.

Having constructed the quaternary stereocenter, we next examined the removal of the amino alcohol portion in the spiromorpholinones in order to liberate the functionalized quaternary carbon atom bearing building blocks that were the objective of this study. Previous studies[5b,5c] on ephedrine-derived morpholinones had shown that dissolving metal reduction accomplishes cleavage of the benzylic C–O bond as well as the C–N bond β to the phenyl group in the morpholinone. Hence, we anticipated that dissolving metal reduction of the spiromorpholinones prepared in this study would generate hydroxy amides based on the 1,3-dioxanyl scaffold.

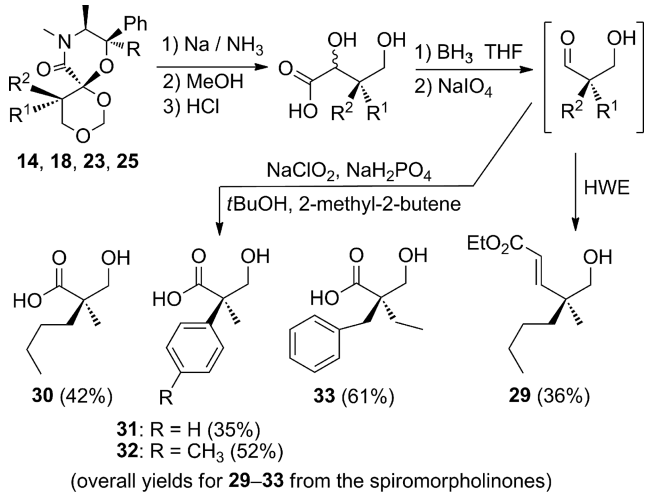
In initial studies two representative spiromorpholinones, one with two alkyl groups at the quaternary carbon atom (**14**) and the other with an alkyl and an aryl substituent (**18**), were subjected to dissolving metal reduction (Na/NH_3). Unexpectedly, but pleasingly, the reduction of **18** provided the α,γ-dihydroxy amide **28** (56%) after quenching the reaction with MeOH/water followed by stirring at room temperature for 30 min (Scheme 4). Presumably, initial C–O and C–N bond cleavage in the morpholinone generates an intermediate, which undergoes fragmentation of the dioxane ring to provide a α-keto amide, which is reduced further to the dihydroxy amide. Thus, four transformations are accomplished in one step. Notably, products arising from reduction of the phenyl ring on the dioxane portion in **18** were not observed. Furthermore, stirring the quenched reaction mixture, obtained from **14**, at ambient temperature for 8 h directly provided the hydroxy acid **27** in good yield (86%).



Scheme 4. Dissolving metal reduction of spiromorpholinones **14** and **18**.

Although the in-situ reduction of the α-keto amides is not diastereoselective (1:1 *dr*), we expect that the α-stereocenter can be manipulated by oxidation of a suitably protected derivative to the ketone followed by diastereoselective reduction.[13] If required, the diastereomers of **27** and **28** can be easily separated by chromatography. α,γ-Dihydroxy acids and amides such as **27** and **28** are precursors of β,β-disubstituted γ-butyrolactones that are analogs of pantolactone.[14] Such lactones provide synthetic pantothenamides (*N*-modified α,γ-dihydroxy amides) by aminolysis.[15] Recent studies[16] have shown that the biological activity of pantothenamides depends on the substitution at, and the configuration of, the quaternary carbon atom. Notably, these key structural features can be controlled with the modular assembly of quaternary stereocenters described for **27** and **28**.

Determination of the absolute configuration of the quaternary carbon atom in the hydroxy acids required their conversion to known aldehydes or carboxylic acids for correlation. This conversion would also achieve our objective of preparing quaternary stereocenter containing acyclic motifs that are amenable to functionalization. Hence, in order to demonstrate the generality of the amino alcohol removal and conversion of the α-hydroxy acid products into the targets, selected spiromorpholinones derived either from 1*R*,2*S*-ephedrine or from *S*-2-(methylamino)-1,1-diphenylpropanol, both bearing alkyl, aryl or arylalkyl substituents were converted into functionalized, quaternary stereocenter containing building blocks (Scheme 5).



Scheme 5. Conversion of spiromorpholinones to functionalized quaternary stereocenters.

The crude carboxylic acid obtained from the dissolving metal reduction of the spiromorpholinones was subjected to a two-step protocol involving reduction with borane followed by oxidative cleavage of the resulting vicinal diol to an aldehyde.[17] The aldehyde was directly employed in a Horner–Wadsworth–Emmons (HWE) reaction to provide **29** or oxidized to the corresponding carboxylic acid **30** (from **14**). Similarly, **31**, **32** and **33** were obtained from morpholinones **18**, **25** and **23** respectively (Scheme 5). Comparison of the optical rotations of the acids **31**[18] and **32**[19] with reported values confirmed the "*R*" configuration. The formation of the "*R*" enantiomer also confirms the stereochemical outcome of the Prins reaction. The configurations of **29**, **30** and **33** are assigned by analogy.

Notably, the methyl ester of the hydroxy acid **32** prepared in this study serves as a key starting material in the synthesis of (+)-α-cuparenone, a quaternary stereocenter containing sesquiterpene. We anticipate that the other spiromorpholinones prepared in this study will also provide quaternary stereocenter containing hydroxy aldehydes or carboxylic acids by employing a protocol similar to the one described in Scheme 5.[20]

Conclusions

In conclusion, we have developed a modular synthesis of functionalized quaternary carbon containing building blocks by sequential, stereoselective C–C bond forming reactions on chiral amino alcohol derived morpholinones. The methodology has the potential to rapidly assemble a variety of quaternary carbon atoms that are adorned with a selection of alkyl and aryl substituents. This study has also identified *S*-2-(methylamino)-1,1-diphenylpropanol as a potential replacement for 1*R*,2*S*-ephedrine in the morpholinone template based methodology. Current efforts focus on other applications of the alkylidenemorpholinones.

Supporting Information (see footnote on the first page of this article): Experimental procedures and spectroscopic data for all compounds.

Acknowledgments

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