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Chemoenzymatic Synthesis of Functionalized Cyclohexylglycines and α-Methylcyclohexylglycines via Kazmaier–Claisen Rearrangement

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Abstract—The synthesis of homochiral functionalized cyclohexylglycines and α-methylcyclohexylglycines via chelated Kazmaier–Claisen rearrangement is described. These were shown to be potent scaffolds for the development of MMP inhibitors.

There continues to be a high demand for efficient methods for the preparation of unnatural amino acids as new natural and medicinal targets emerge. Some unnatural amino acids have been demonstrated to be useful scaffolds for the preparation of potent inhibitors of the matrix metalloproteinases (MMPs).[1–4] Many of these inhibitors have been evaluated for efficacy against a wide array of disease processes where tissue remodeling plays a key role,[5] including osteoarthritis,[6] rheumatiod arthritis,[7–9] tumor metastasis,[10,11] multiple sclerosis,[12] congestive heart failure[13] and others (Fig. 1).

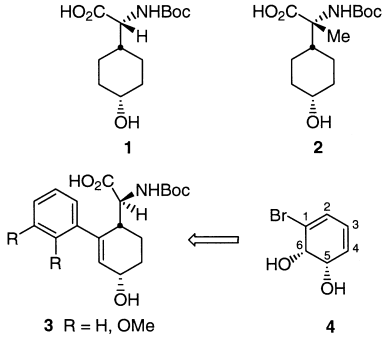

Figure 1. Cyclohexylglycine and α-methylcyclohexylglycine targets.

We sought to prepare a series of chiral, substituted cyclohexylglycine and α-methylcyclohexylglycine derivatives of type **1** and **2** to be used as intermediates in the synthesis of MMP inhibitors. Structural and stereochemical features of these targets are reminiscent of amino acid **3**, which was recently prepared by the Hudlicky group as an intermediate in an anticipated synthesis of morphine.[14] Structures of this type can be synthesized in a stereoselective fashion by means of a chelated Kazmaier–Claisen rearrangement from dienediol **4** after appropriately functionalizing the 5-hydroxyl group. Compound **4** has been exploited in the asymmetric synthesis of many natural products[15] and is readily available by biooxidation of bromobenzene with toluene dioxygenase expressed in one of several suitable hosts.[16,17] In this case, **4** was seen as a convenient potential synthon for the preparation of cyclohexylglycines of type **1** and **2**, which have been previously synthesized asymmetrically from 4-hydroxyphenylglycine, but with no control of *cis* versus *trans* stereochemistry.[18] In this manuscript we report preliminary details for the preparation of both **1** and **2**, and the initial results of their screening.

Our approach to the 4-substituted cyclohexyl glycines was adapted from the synthesis of amino acid **3**.[14] The synthesis of glycine derivative **1** began with potassium azodicarboxylate mediated reduction of **4** followed by the protection of the 5-hydroxyl group with thexyldimethylsilyl chloride and attachment of the *N*-Boc

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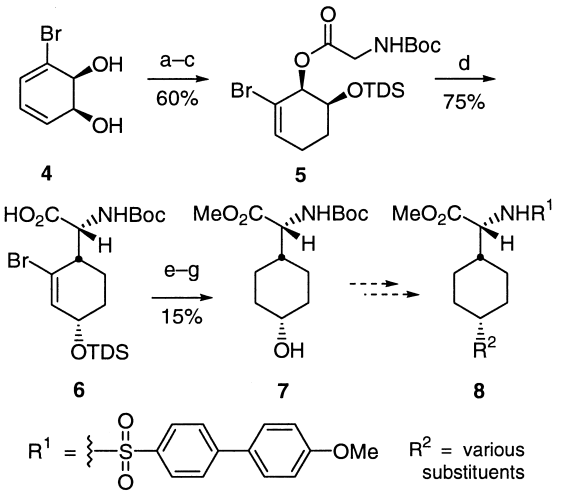
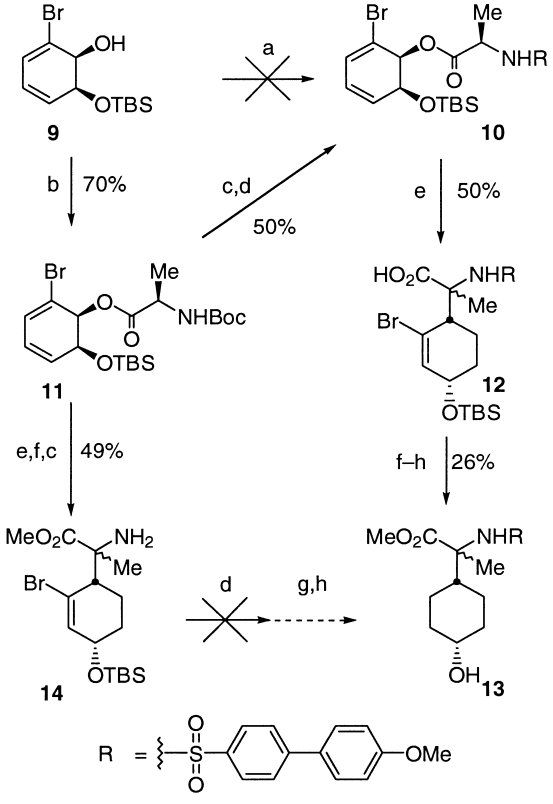
glycine side chain via DCC coupling to provide **5** in 60% yield over three steps (Scheme 1). Exposure of **5** to 2 equiv of LDA in the presence of $ZnCl_2$ with slow warming from −78 °C to room temperature over a 36 h period provided, via the chelated Kazmaier–Claisen rearrangement, amino acid **6** in reasonable diastereomeric excess (4:1, in favor of the *syn* isomer) and excellent chemical yield (75%). The crude acids were converted immediately to their methyl esters, which were easily separated by flash chromatography. It is interesting to note here that the faster-eluting major (*R*)-isomer can be equilibrated to the (*S*)-isomer, which is the intermediate required for the targeted synthesis of morphine and is a precursor to amino acid **3**.

The reasons for the non-stereospecific rearrangement stem from competition between the mixed transition states (chair and boat) operating in the Claisen rearrangement of moderately to heavily substituted systems such as **5**, as rationalized in an earlier report[15] and as explained by Kazmaier.[19] It is highly probable that only the chelated (*Z*)-enolate is generated prior to the rearrangement and that both transition states operate with preference for the chair transition state.[15] Ester **7** was eventually converted to a series of MMP inhibitors of the general structure **8**, as outlined in Scheme 1.



Scheme 1. Reagents and conditions: (a) potassium azodicarboxylate, HOAc, MeOH; (b) thexyldimethylsilyl chloride, imidazole, DMF; (c) DCC, DMAP, *N*-Boc-glycine, CH_2Cl_2; (d) $ZnCl_2$, LDA, THF, −78 °C; (e) CH_2N_2, Et_2O; (f) H_2 (40 psi), PtO_2, Et_3N, MeOH; (g) tBu$_4$NF, THF.

This protocol was also applied to the synthesis of the α-methyl derivative **2**. Approaches to compounds of this type are difficult via enolate alkylation or aldol-type condensation. As the Claisen route seems especially suited for preparation of this type of hindered amino acid, we adapted the glycinate route to this target as well. Starting with mono-TBS protected diol **9**, we were unable to introduce the α-methyl moiety already equipped with the biphenylsulfonyl group via DCC coupling (Scheme 2). We therefore prepared ester **11** and, following the removal of the Boc group, were able to install the sulfonamide[20] to furnish **10**. The Claisen rearrangement of **10** to **12** worked smoothly under the conditions employed for the preparation of the glycine derivative, albeit in a lower yield, presumably because of the lowered chelating potential of the sulfonamide as compared to carbamate **5**. The synthesis of **12** also did not proceed with the same preference for the *R* isomer, probably because of the increased size of the sulfonamide functionality and reduced preference for the chair transition state. Nevertheless, acids **12** (3:1 mixture of isomers at the α-center) were converted to methyl esters **13**, the precursors for MMP inhibitors (Scheme 2). Because the Claisen rearrangement also worked well with the alanine ester (**11**), we prepared **14** (49% yield over three steps, 3:1 ratio) and attempted to introduce the sulfonamide group at this stage. However, as all attempts to transform the methyl ester of **14** to **13** produced only trace amounts of product, we settled for the longer but higher yielding route. The sulfonation was attempted wth the esters of **14** as well as with its fully hydrogenated derivative, but the hindered nitrogen proved very unreactive.

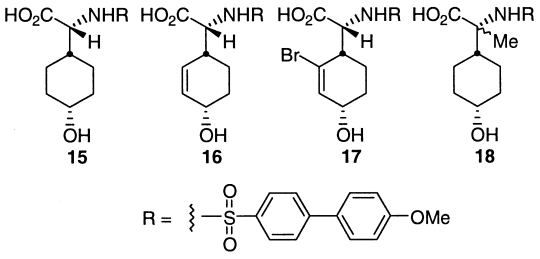


Scheme 2. Reagents and conditions: (a) alanine *N*-sulfonamide, DCC; (b) *N*-Boc alanine, DCC; (c) TFA, CH_2Cl_2; (d) 4-methoxy-1,1′-biphenylsulfonyl chloride, Et_3N, THF; (e) $ZnCl_2$, LDA, THF, −78 °C; (f) CH_2N_2, Et_2O; (g) H_2 (40 psi), PtO_2, Et_3N, MeOH; (h) tBu$_4$NF, THF.

The Kazmaier–Claisen route appears to be the most effective means of preparation for these compounds. Improvement of stereocontrol remains a priority both in the MMP inhibition area and in the morphine total synthesis effort. Although it is possible to isomerize the (*R*)-isomer of glycinate **7** to the corresponding (*S*)-isomer,

it will be instructive to study the potentials for stereocontrol in the rearrangement of the glycinates in more detail. The substrates used by us differ in complexity from the ones previously reported by Kazmaier,[21] Bartlett,[22] and Steglich.[23] The stereospecificity of the transfer of sp^3 stereochemistry from C-6 of the diol to C-2 depends on the steric bulk of groups at the adjacent positions. As long as both these positions are substituted, the only possibility for optimizing the operation of either the chair or boat transition state is to adjust the kind and the size of the chelating agent. Such a strategy has been successfully employed in the area of aldol condensation and the control of *syn* and *anti* ratios from stereospecifically generated enolate species. We expect that the bulk of the chelating Lewis acid (with attendant solvent participation) can override the size of either the halogen or phenyl groups at C-1, the ether at C-5, or the amide or carbamate moieties on the nitrogen atom. Further studies will investigate the use of lanthanide or transition-metal-based Lewis acids in this rearrangement. We will report the results in this area as well as progress toward morphine from acid **3** in due course.

Table 1. MMP enzyme inhibition data, IC_{50} (nM)[a]



	15	16	17	18
MMP-2	12	20	38	251
MMP-3	1220	2490	3795	6150
MMP-13	30	176	131	338

[a]Experimental details for enzyme assays.[1] Standard deviations for enzyme assays were typically ±60% of the mean or less. All assays were conducted at pH 7.4.

Four of the esters prepared in this study have been saponified and tested for inhibition activity against gelatinase A (MMP-2), stromelysin (MMP-3), and collagenase 3 (MMP-13). The data presented in Table 1 reveals promising activity against MMP-2 and MMP-13 in this series of carboxylic acids. The parent structure **15** proved to be the most potent especially when compared against its alanine analogue **18**, which suffered an order of magnitude loss in binding affinity. Compound **15** thus served as a scaffold for analogue derivatization and detailed SAR data from this study will be disclosed in a forthcoming paper, along with the experimental details for the preparation of derivatives of type **8**.[2]

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