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Chemoenzymatic Synthesis of Unnatural Amino Acids *via* Modified Claisen Rearrangement of Glycine Enolates. Approach to Morphine Synthesis

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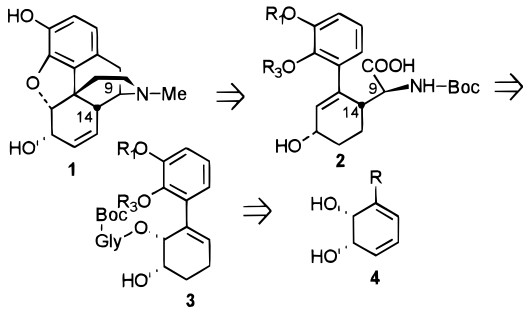
Enzymatic transformations of achiral molecules combined with modern techniques for the control of diastereoselectivity constitute a powerful tool for asymmetric synthesis[1] and contribute greatly to the brevity of synthetic ventures.[2] We have made use of biotransformations as a synthetic tool for the preparation of many natural products,[3] including the pursuit of a synthesis of morphine (**1**) and structurally related molecules by chemoenzymatic means.[4]

Of the five stereogenic centers in morphine, the most difficult to control in a relative sense are C-9 and C-14.[5] A possible disconnection of the morphine skeleton, not attempted to date, indicates that the target alkaloid can be derived from a suitably functionalized α-cyclohexenyl amino acid such as **2**, obtained *via* a [3,3]-sigmatropic rearrangement of a substituted glycine ester enolate derived from **3**, in which the chirality is set by arene dioxygenase oxidation of an aromatic precursor (Scheme 1).

Arene *cis*-diols of the type **4** have been reasonably exploited in asymmetric synthesis as indicated by vigorous synthetic activity.[2,6] As of this writing, no report exists on the application of Claisen rearrangement to either of the allylic systems in **4**, even though this was suggested in our first publication in this area.[7] The first synthesis of amino acids by Claisen rearrangement was described in 1975 by Steglich.[8] Since 1982, when the

Scheme 1



Ireland−Claisen rearrangement of glycine allylic esters was reported by Bartlett and co-workers,[9] this method has found ample application in amino acid synthesis.[10] In 1994, a variation of the Claisen rearrangement was reported by Kazmaier,[11] in which the silylketene acetals were replaced by chelate-bridged metal enolates, claimed to be superior to ketene acetals both in terms of their selectivity (fixed configuration of the enolate) and reactivity (anion accelerated rearrangement).

In order to test Kazmaier's methodology to obtain synthon **2**, we performed model studies on aminoesters **5a**−**d**, prepared from the microbially derived diols **4a**−**d** (Scheme 2).

Exploratory studies to find the conditions for the Claisen rearrangement involved the use of lithium enolates of glycine ester **5a** and zinc enolates of its *N*-methyl derivative, none of which led to rearranged products. The lithium enolate of **5a** decomposed before any rearrangement could take place, whereas the zinc enolate of the *N*-methyl derivative gave no reaction, indicating perhaps that chelation is required for the rearrangement to occur.[11a]

When the four amino esters were subjected to Kazmaier's Claisen conditions the corresponding rearranged amino acids were obtained in fair to excellent yields (Scheme 2). The substrates were mixed with anhydrous $ZnCl_2$ in THF, LDA was added at −78 °C, and the reaction mixture was allowed to warm to room temperature over 12 h.

The ratio of the rearranged amino acids, epimeric at C-9 (morphine numbering), was determined by ^{1}H-NMR analysis of the crude mixtures. The relative and absolute stereochemistry of amino acids **6a,b** and **7a,b** was determined by transforming them to the corresponding lactone derivatives **8a,b** and **9a,b** (Scheme 3). The structure of lactone **8a** was unambiguously established by X-ray structural analysis.[16] In this way, the absolute stereochemistry of the amino acid **6a** was assigned as shown. Comparison of spectral data for amino acids **6a**−**d** and **7a**−**d**, and their corresponding methyl esters, established their stereochemistry. In summary, the assigned stereochemistry of acids **6** and **7** is *2R,3R* (*2R,3S* in the case of the chloro compound **6c**) and *2S,3R*, respectively.

These results are somewhat surprising since the configuration at the α-amino position for the major product

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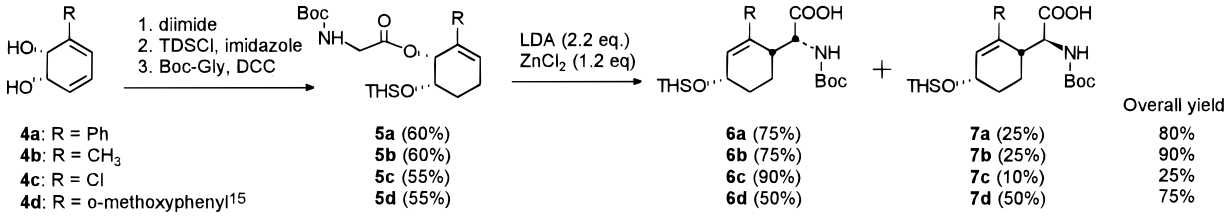
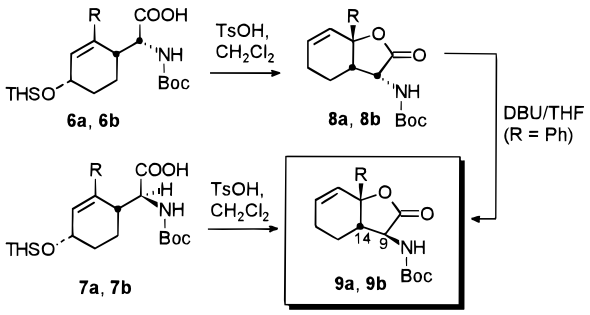
Scheme 2



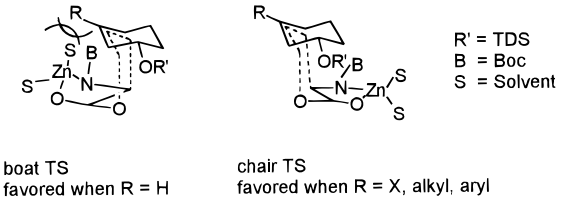
4a: R = Ph	**5a** (60%)	**6a** (75%)	**7a** (25%)	80%
4b: R = CH_3	**5b** (60%)	**6b** (75%)	**7b** (25%)	90%
4c: R = Cl	**5c** (55%)	**6c** (90%)	**7c** (10%)	25%
4d: R = o-methoxyphenyl[15]	**5d** (55%)	**6d** (50%)	**7d** (50%)	75%

Scheme 3



is reversed from that reported for closely related compounds.[11b] Because of the fixed enolate geometry arising from chelate formation, the stereochemical outcome of the rearrangement depends exclusively on the preference for either a chair- or a boatlike transition state. The observed selectivity is explained in terms of the rearrangement proceeding *via* a chairlike transition state. For six-membered ring substrates the preference for a boatlike transition state is generally accepted.[12] This is based on the presence of steric interactions in a chairlike transition state between the cyclohexenyl ring and the solvated metal, which are absent in a boatlike transition state (Chart 1). As Ireland and co-workers have pointed out for the rearrangement of the related silylketene acetals,[13] with cyclohexene derivatives both chair- and boatlike transition states should be expected, depending on the size and position of the substituents on the ring. The effect of the bulky silyl ether may be considered negligible, as evidenced by many results of these rearrangements reported in the carbohydrate field in which no changes in selectivity were reported with bulky oxygenated substituents on the ring.[14] Conversely,

Chart 1



the cyclohexenyl derivatives used in this study bear substituents at the α-position of the allylic carbon. These substituents may interact unfavorably with the solvated metal in a boatlike transition state as shown in Scheme 4.

As a result of the two opposing steric interactions, the cyclohexenyl ring destabilizes a chairlike transition state, and the substituents on the α-position of the allylic carbon destabilize a boatlike transition state. Consequently, the energy difference between both transition states is small. This is in accord with observed product selectivities ranging from 3:1 to 9:1 for **6a**−**c**:**7a**−**c**, with a chairlike transition state always predominating, to afford acids of type **6**. In the case of **6d** the selectivity drops to 1:1, perhaps because the coordination between the oxygen atom in the methoxy group present in **6d** and the Zn^{2+} ion decreases the energy of the boatlike transition state sufficiently to compete favorably with the chairlike transition state that predominates for the rest of the series.

The lack of stereoselectivity drew our attention to the possibility of epimerization of lactones **8** to their isomers **9**, since the bulky protected amino group is situated on the concave face of the bicyclic system in **8**. Accordingly, **8b** epimerized to the more stable **9b** (80% after 37 h) when treated with DBU in THF at room temperature (Scheme 3). Lactones **9** contain the same relative stereochemistry as morphine at the crucial centers C-9 and C-14 and are ideally suited for further elaboration. The introduction of the ethylamino bridge by means of Pd-catalyzed allylic displacement and the closure of C-10 C-11 bond by Friedel−Crafts acylation of an activated dimethoxyphenyl derivative[15] form the basis of our strategy. Studies on the generality and stereoselectivity of the rearrangement and application to morphine synthesis are ongoing and will be reported in due course.

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Supporting Information Available: Experimental procedures and compounds characterization data (56 pages).

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(16) The author has deposited atomic coordinates for **8a** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.