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DIRECTED REGIOCHEMICAL CONTROL IN THE RING EXPANSION REACTIONS OF A SUBSTITUTED TRANS-DECALONE

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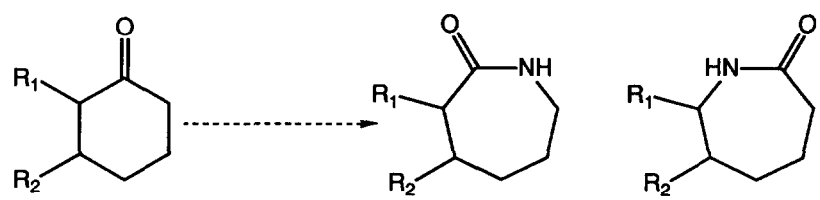
Summary: A derivative of the Wieland-Miescher ketone can selectively be converted into either regioisomeric ring-expanded lactam. The synthesis of the diastereomeric *N*-α-methylbenzyl oxaziridine derivatives determines the regiochemistry of the product lactam and additionally allows the separation of a racemic substrate into regio- and enantioisomeric lactams.

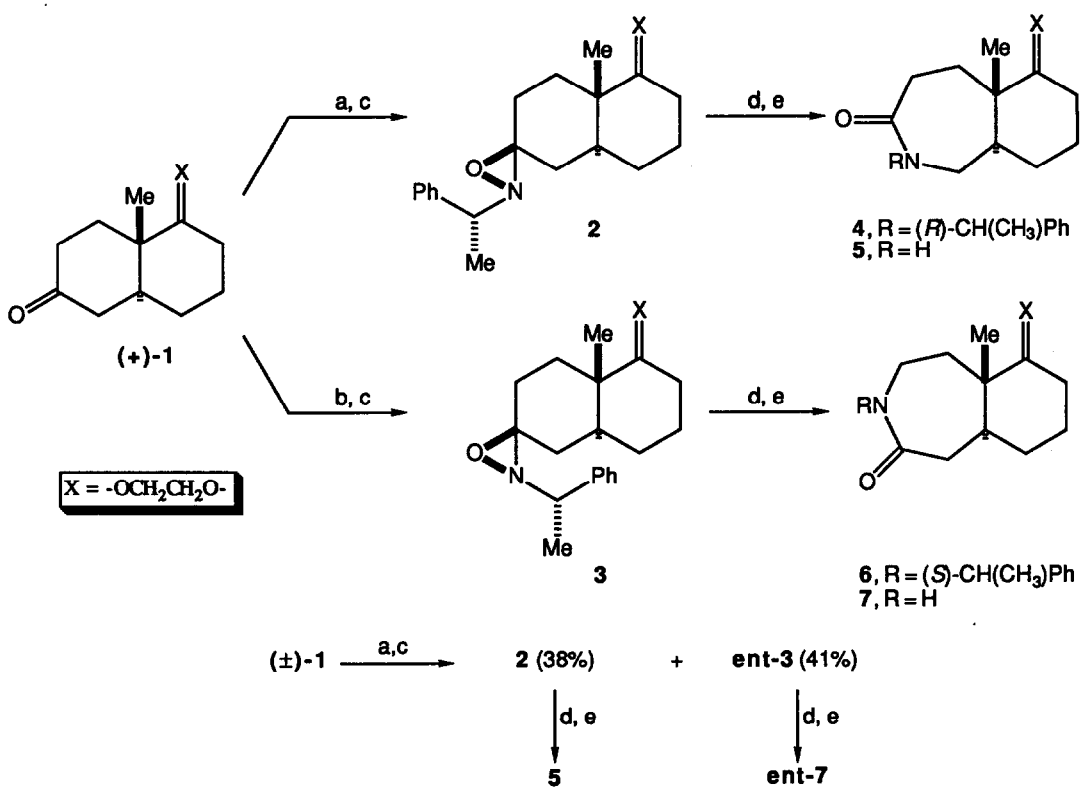
A key issue in carbonyl chemistry is the need to control the regiochemistry of reactions of unsymmetrically substituted ketones, such as ring expansion processes (Equation). For example, the regiochemistry of the Beckmann rearrangement arises from the formation of a particular oxime stereoisomer, usually due to steric factors, followed by a stereoelectronically controlled migration reaction.[1,2] Difficulties can result from the inability to determine oxime stereochemistry prior to participation in the rearrangement reaction, and usually only a single regioisomer is preparable through the application of a given insertion sequence. In cases where substituents are further removed from the reacting ketone, regiochemical control is rarely achieved at all, although exceptions exist.[3] *Herein we report the first examples whereby regioselectivity in an insertion reaction is directed using a switchable stereocontrol element.* The reaction involves the selective ring expansion of a derivative of the Wieland-Miescher ketone to *either* possible regioisomeric lactam. The virtues of this protocol are that: (1) it effects remote regiochemical control, (2) it is possible to obtain either regioisomer by a simple change in reagent stereochemistry,[4] and (3) it simultaneously allows optically active lactam to be obtained from racemic ketone.



R_1 or R_2 = alkyl, aryl, etc.

Spirocyclic oxaziridines[5] can be synthesized with a high degree of stereoselectivity[6] and their rearrangement chemistry is subject to stereoelectronic control (the substituent *trans* to the lone pair on nitrogen undergoes preferential migration to nitrogen upon photochemical activation).[7,8] Therefore, these oxaziridines are well-suited to function as surrogates in Beckmann-type rearrangement processes.[9] Thus, condensation of (+)-1[11] with (*R*)-α-methylbenzylamine followed

by oxidation with monoperoxycamphoric acid[12] ((+)-MPCA) affords oxaziridine **2**[13] as a single stereoisomer as determined by ^{1}H- and ^{13}C-NMR in 79% overall yield. Similar treatment of the same substrate with (*S*)-α-methylbenzylamine leads instead to oxaziridine **3**, again as a single isomer (88% yield for two steps). The stereochemical outcomes of these reactions result from a combination of two diastereofacially selective processes. Firstly, attack of oxidant from the β face is ascribed to the known tendency of imines to suffer equatorial attack by peracids.[15] In addition, the stereochemistry at nitrogen in **2** and **3** arises from approach of peracid to predominantly give the *unlike* (*u*)[16] stereochemical relationship between the benzylic carbon and the emerging nitrogen stereocenter.[17] Taken together, these control features permit the establishment of either possible configuration at the nitrogen stereogenic center by choosing either (*R*)- or (*S*)-α-methylbenzylamine. (Incidentally, we utilized (+)-MPCA as an oxidant in these reactions because it is a conveniently prepared, bulky reagent; control experiments show that there is little, if any, chiral interactivity between the chiral substituent on nitrogen and (+)-MPCA in these systems. Whereas meta-chloroperoxybenzoic acid is a useful agent for the conversion of imines to oxaziridines, the use of (+)-MPCA affords superior product ratios.)



Scheme. Reagents: (a) (*R*)-α-methylbenzylamine; (b) (*S*)-α-methylbenzylamine; (c) (+)-MPCA; (d) hν (254 nm, quartz tubes, Rayonet Merry-Go-Round, 2 h), CH_3CN; (e) Na/NH_3.

Since the rearrangement of each oxaziridine is also stereospecific, the ability to dictate the formation of either oxaziridine stereoisomer can be directly translated into a regiochemically controlled ring expansion process. Thus, photolysis of oxaziridine **2** leads smoothly to lactam **4** (80% yield), in which the methylene group *anti* to the lone pair on the nitrogen atom has undergone exclusive migration to nitrogen. Removal of the α-methylbenzyl substituent is accomplished using sodium in liquid ammonia, affording **5** in 67% yield. The rearrangement of **3** when carried out under the same conditions affords a 5.3 : 1 mixture of lactams in 75% combined yield; homogeneous **6** can be isolated using silica gel chromatography. The conversion of **6** to **7** takes place in 67% yield. We have not as yet determined the reasons for the diminished selectivity in this photolysis reaction, but note that recovered oxaziridine recovered from an incomplete reaction showed no signs of isomerization.

In the above examples, optically active ketone was used. However, since the chirality inherent in each antipode of *racemic* **1** and the chiral amine remain invariant throughout the sequence, it is not possible to achieve the synthesis of a single diastereomer resulting from their union and subsequent oxidation. However, treatment of **(±)-1** with (*R*)-α-methylbenzylamine followed by (+)-MPCA yields the readily separable oxaziridines **2** and **ent-3** in 38% and 41% yields, respectively. Rearrangement and removal of the α-methylbenzyl group as before can be carried out to effect the conversions **2**→**5** and **ent-3**→**ent-7**, respectively. In this way, a racemic ketone has been simultaneously "resolved" and converted to regio- and stereochemically homogeneous lactams; choice of either amine antipode affords access on demand to any of the four possible optically active ring expansion products.

The lactams synthesized in this study should be useful intermediates for the preparation of A-ring azasteroid derivatives. In addition, the synthetic method should be widely applicable to a variety of substrates which demonstrate diastereofacial control in the reactions of the starting ketones. We are currently examining the scope of the process.

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9. In fact, the "natural" rearrangement tendencies of 2-alkylcyclohexanones via the Beckmann reactions versus those of spirocyclic oxaziridines[10] are complementary, insofar as the latter reaction generally results in migration of the less substituted adjacent carbon atom. This is because both oximes and oxaziridines tend to be more stable when the nitrogen substituent is *trans* to the more substituted carbon atom, coupled with the divergent stereoelectronic preferences of the two reactions.

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