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THE MAGNITUDE OF THE STEREODIRECTING EFFECT OF AN ALLYLIC ALKOXY-SUBSTITUENT IN AN AMIDOMERCURATION CYCLIZATION

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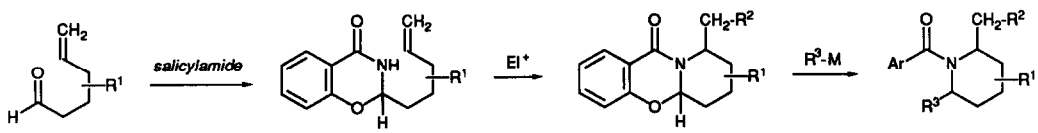
Summary: A surprisingly large stereodirecting effect for the allylic alkoxy-substituent (> 4 kcal/mol) is revealed in the amidomercuration cyclization of an unsaturated amidal in which the stereodirecting effect of the allylic alkoxy-substituent competes against the stereodirecting effect of a stereogenic amidal center.

Electrophile-induced heterocyclizations are commonly employed for the stereoselective preparation of oxygen- and nitrogen-heterocycles.[2,3] While chiral auxiliaries have found a great deal of utility for directing the stereochemical course of reactions involving carbonyl derivatives, there has been much less progress toward the design of efficient stereodirecting auxiliaries for heterocyclization reactions.[4-10] We are interested in exploiting the stereodirecting effect and chemistry of a stereogenic amidal center in amidomercuration cyclizations as outlined below. A previous study gave some insight into the magnitude of the stereodirecting effect of the amidal center relative to the bias exerted by alkyl substituents (R^1) on the tether chain connecting the amide and alkene.[11] Hydroxy-substituted pyrrolidine[12], piperidine[13] and related ring systems[14] are of current synthetic and pharmacological interest. We therefore decided to investigate how strongly the stereodirecting effect of an allylic alkoxy-substituent might augment or oppose the influence of the resident amidal stereocenter in the amidomercuration cyclization of salicylamide-derived substrates.

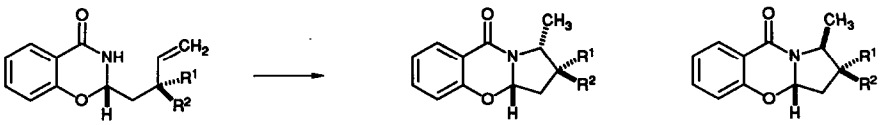
Figure 1.



The diastereoselectivities of electrophile-induced lactonization[15,16] and etherification[17-20] cyclizations can be strongly influenced by the presence of an allylic hydroxy- or alkoxy-substituent. The preferred product is usually the diastereomer in which the alkoxy-substituent and the electrophile-substituted carbon are cis on the newly formed ring. In the case of electrophile-induced heterocyclization involving carbon-nitrogen bond formation, an allylic hydroxyl directs diastereoselective pyrrolidine formation in the iodoamidation of unsaturated N-sulfonyl[21,22] or thioimidate substrates[23], and in the amidomercuration of unsaturated N-carbamoyl substrates[24]. Sugar-derived substrates possessing an allylic benzyloxy-substituent undergo six-membered ring-forming amino-mercuration with modest-to-good stereoinduction.[25] In each case, the *cis*-diastereomer predominates.

The results obtained from a series of five-membered ring-forming amidomercuration cyclizations are summarized in Table 1. The parent substrate **1a** ($R^1 = R^2 = H$) cyclizes upon exposure to 1.5 equivalents of Hg(II) salts (1. 1:1 mixture of $Hg(OAc)_2$:$Hg(OTFA)_2$ / CH_3CN / 25° / 0.5-2 h; 2. aq NaCl workup). Reduction of the carbon-mercury bond (2 eq $LiBH_4$ / THF / -78°) affords a 12.4:1 mixture of diastereomers **2a** and **3a**. The predominant diastereomer **2a** has the newly formed methyl-substituent oriented cis with respect to the oxygen-substituent of the amidal stereocenter. (±)**2a** and (±)**3a** interconvert under acid catalysis. At equilibrium,

Table 1.



1 2 3

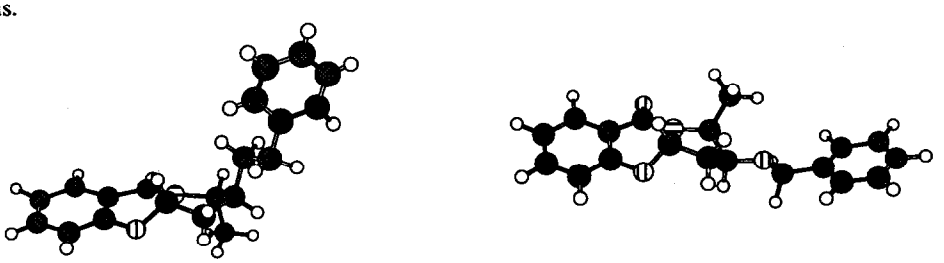
entry	cmpd	R^1	R^2	% yield	2 : 3
1	**1a**	H	H	90	12.4 : 1
2	**1b**	CH_2CH_2Ph	H	89	1.2 : 1
3	**1c**	H	CH_2CH_2Ph	87	10.4 : 1
4	**1d**	OCH_2Ph	H	89	>50 : 1
5	**1e**	H	OCH_2Ph	78	1 : >50
6	**1f**	$OSiMe_2tBu$	H	77	40 : 1
7	**1g**	H	$OSiMe_2tBu$	74	1 : >50

2a is found to be the thermodynamically less stable diastereomer. The 12.4:1 kinetic ratio establishes the sense and magnitude of the stereodirecting effect by the amidal stereocenter in the absence of other substituents.

Condensation of salicylamide with 3-(phenylethyl)-4-pentenal affords a mixture of amidals **1b** (R^1 = CH_2CH_2Ph; R^2 = H) and **1c** (R^1 = H; R^2 = CH_2CH_2Ph). The amidals are separated by chromatography on silica and each diastereomer individually cyclized. One of the diastereomers (**1b**) cyclizes with greatly diminished stereoselectivity (**2b**:**3b** 1.2:1) relative to the parent substrate, indicating that the two resident stereogenic centers oppose each other (i.e. are mismatched[26,27]) in their stereochemical influence on the forming C-N bond. Diastereomer **1c** cyclizes with diastereoselectivity comparable to that of the parent substrate (10.4:1). The stereochemistry of the major diastereomer produced from **1c** is unambiguously assigned as **2c** by single crystal x-ray analysis (figure 2).[11] The stereodirecting effects of both chiral elements present in substrate **1c** complement each other so as to favor orienting the resulting methyl-substituent trans with respect to adjacent alkyl substituent and cis with respect to the amidal oxygen.[28]

The cyclizations of the amidals derived from 3-(benzyloxy)-4-pentenal reveal a surprisingly large stereodirecting effect for the allylic benzyloxy-substituent. Diastereomer **1d** cyclizes as expected to afford **2d** as the only detected diastereomer (**2d**:**3d** > 50:1). The methyl-substituent in **2d** resides cis with respect to the amidal oxygen and cis to the allylic benzyloxy-substituent. The very high diastereoselectivity favoring the formation of **2d** is consistent with the expectation of matched stereodirecting effects. Surprisingly, the

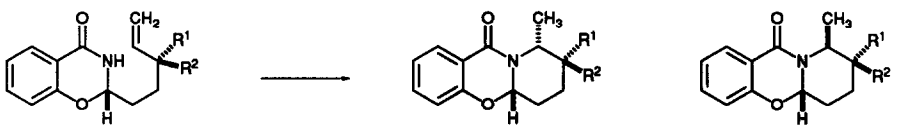
Figure 2. The three-dimensional structures of **2c** (left) and **3e** (right) as determined by single crystal x-ray analysis.



mismatched diastereomer, **1e**, also cyclizes to a single diastereomer. Single crystal x-ray analysis reveals the structure of the product as **3e** (figure 2).[1] The stereodirecting effects of the two chiral elements present in **1e** should oppose each other, yet, the allylic benzyloxy-substituent completely controls the stereochemical course of the cyclization. *Given the inherent 12.4:1 bias imposed by the amidal center, we can estimate that the magnitude of the stereodirecting effect imposed by the allylic alkoxy-substituent in this room temperature cyclization is greater than 4 kcal/mol!* Similar results are obtained when substrates containing an allylic silyloxy-substituent (**1f-g**) are cyclized.[29]

The overwhelming stereodirecting effect of the allylic benzyloxy-substituent is also found in the homologous six-membered ring-forming cyclizations of **4a-e** (Table 2). In this series, the inherent bias of the amidal stereocenter favors orientation of the newly-formed methyl-substituent trans with respect to the amidal oxygen (**5a**:**6a** 1:12.1), while the allylic benzyloxy-substituent again directs formation of the cis oxygen-methyl relationship. High diastereoselection for formation of **6d** is obtained in the amidomercuration of the matched diastereomer **4d**. A 5:1 mixture of **5e**:**6e** is obtained from the mismatched diastereomer **4e**. The influence of the allylic benzyloxy-substituent is still dominant, but not to as large an extent as in the five-membered ring-forming case. The chemical yield of cyclized material from **4e** is poor, perhaps indicating that the intermolecular amidomercuration reaction competes with the cyclization.

Table 2.



4 **5** **6**

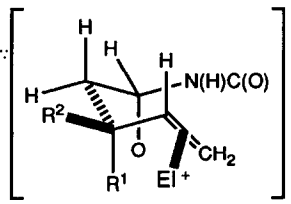
entry	cmpd	R^1	R^2	% yield	**5** : **6**
1	**4a**	H	H	86	1 : 12.1
2	**4b**	CH_2Ph	H	86	1 : 5.1
3	**4c**	H	CH_2Ph	42	1 : 10
4	**4d**	OCH_2Ph	H	56	1 : >50
5	**4e**	H	OCH_2Ph	24	5 : 1

In summary, the present study establishes that for the amidomercuration cyclization of salicylamide-derived substrates containing an allylic alkoxy-substituent: 1) the magnitude of the kinetic stereodirecting effect can be extremely large (> 4 Kcal/mol in the case of **1e** and **1g**); 2) the cis relationship between the oxygen-substituent and the electrophile-substituted carbon is preferred in both five- and six-membered ring-forming cyclizations; and 3) the magnitude of the stereodirecting effect is dependent on the ring size being formed (i.e. **1g** vs **4e**). Several mechanisms have been proposed to account for the stereodirecting effect of allylic oxygen-substituent in heterocyclization reactions.[17-20,30] Given the magnitude of the effect in the cyclizations of **1** and **4**, it is unlikely that any mechanistic argument involving the relative population of ground state conformers or solely non-bonded interactions within diastereomeric transition state structures can fully account for the level of stereoinduction. Although the precise nature of the attacking nitrogen nucleophile in the transition state is not known[31], the

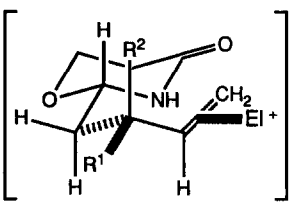
products obtained from the cyclization of **1** or **4** can be rationalized using the model proposed by Chamberlin, *et. al.*[30] or the functional equivalent proposed by Labelle and Guindon.[17] That is, cyclization apparently proceeds via an intermediate in which the O-C-C(H)=CH2 subunit is roughly co-planar, and the electrophile adds to the less hindered face of the π-system (figure 3). Further studies and synthetic application of the amidal amidomercuration cyclizations are in progress.

Figure 3. Partial structures illustrating the Chamberlin, *et. al.*[30] model applied to the amidomercuration cyclizations of **1**.

Favored Cyclization Model for:
1a (R^1, R^2 = H)
1c (R^1 = H, R^2 = CH_2CH_2Ph)
1d (R^1 = OCH_2Ph, R^2 = H)
1f (R^1 = OTBDMS, R^2 = H)



Favored Cyclization Model for:
1e (R^1 = H, R^2 = OCH_2Ph)
1g (R^1 = H, R^2 = OTBDMS)



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(28) At first, it seems surprising that the ratio of **2c**:**3c** (10.4:1) obtained from the cyclization of the "matched" diastereomer **1c** is not greater than the selectivity exhibited by the parent system (**2a**:**3a** = 12.4:1). However, in cases wherein the two chiral elements interact with each other as well as with the centers undergoing reaction, the combined stereodirecting effects are not be strictly additive. For example, see reference 11.
(29) It should also be noted that each pair of products (**2d**/**3e** or **2f**/**3g**) possesses the cis relationship between the allylic alkoxy-substituent and the newly formed methyl-substituent. Consequently, for the purposes outlined in figure 1, the diastereomers **1d**/**e** or **1f**/**g** need not to be separated prior to cyclization.
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