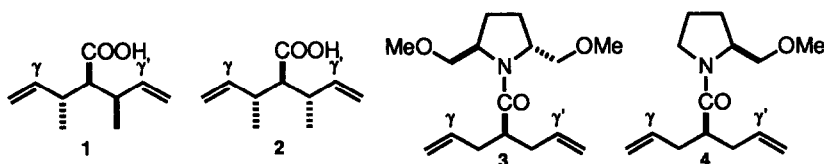


ENANTIOSELECTIVE IODOLACTONIZATION THROUGH DIASTEREOTOPIC GROUP DIFFERENTIATION

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Abstract: Diastereotopic olefins were differentiated in iodolactonization with concomitant face differentiation using (2*R*,5*R*)-bis(methoxymethyl)pyrrolidine as a chiral auxiliary to afford chiral lactones in enantioselective manner.

Halolactonization has become an important tool in synthetic organic chemistry because a high degree of diastereoselectivity can be attained depending upon the reaction conditions.¹ Discrimination of diastereotopic groups or faces is one of the prevailing methods for asymmetric induction. Recently, Kurth *et al.*² reported remarkable differentiation between diastereotopic olefinic groups with concomitant face differentiation in halolactonization; 3,5-dimethylheptadienoic acid **1** selects the γ -carbon preferentially (γ - versus γ' -attack was 147:1) with concomitant *re*-face selectivity (30:1). With *meso*-olefin **2**, 14:1 *re*-face selectivity was observed. Attempted chiral iodolactonization by discrimination of two identical groups has been reported but the enantiomeric excess (ee) is too low to make it useful (10-25%).³ Here, we describe an interesting extension of their work involving enantioselective iodolactonization with high ee through the diastereotopic olefin differentiation as well as face differentiation using (2*R*,5*R*)-bis(methoxymethyl)pyrrolidine as a chiral auxiliary.



We selected amide **3** as our substrate because prediction of the stereochemical outcome was easier and more convincing. Since **3** has chiral carbons, both olefins and the faces of each olefin are diastereotopic. The absolute stereochemistry at C(3) in the expected products **6a** -**6d** is governed by the differentiation of diastereotopic olefins, while the selection of diastereotopic faces

determines the absolute configuration at C(5). Four diastereomeric transition states **5a** - **5d** are possible, of which **5a** and **5d** afford the trans isomers **6a** and **6d**, respectively. The cis isomers **6b** and **6c** can be obtained from **5b** and **5c**, respectively. Transition states **5c** and **5d** result from attack at the γ' -carbon and are less stable than transition states resulting from γ -carbon attack because of the severe steric interaction between an allyl substituent and a methoxymethyl group. The lack of 1,3-diaxial-like interactions makes **5a** more stable than **5b**. These analyses lead to the conclusion that **6a** is the anticipated major product. Indeed, treatment of **3** with iodine in tetrahydrofuran under kinetic conditions⁴ afforded **6a**⁵ in 54% yield and 91% ee. Use of an unsymmetrical chiral auxiliary remarkably decreases the enantioselectivity. Kinetic iodolactonization of amide **4** provided 3*R*,5*S*-iodolactone **6d**⁶ with an ee of only 37%.

Chart I. Possible Transition States **5a** - **5d** for **3** Leading to Products **6a** - **6d**, respectively.

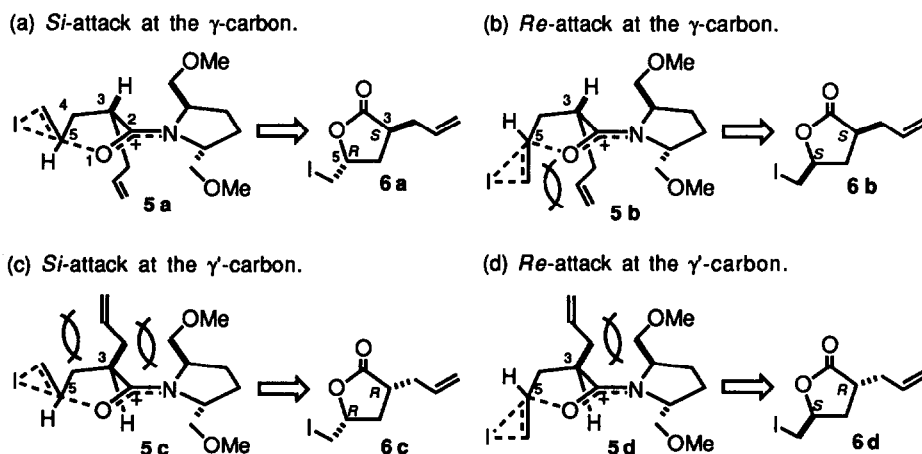
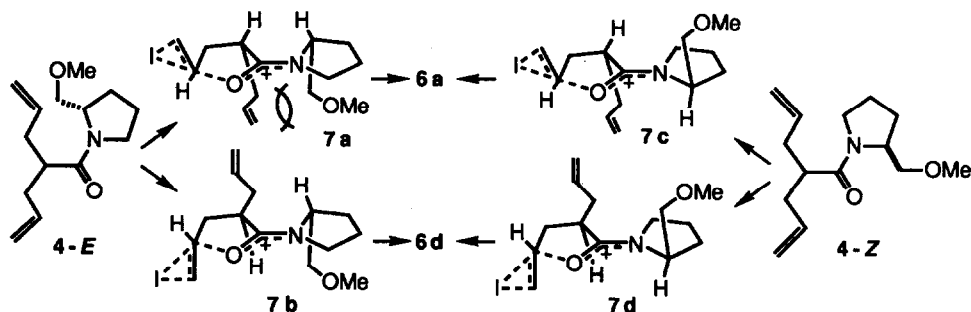
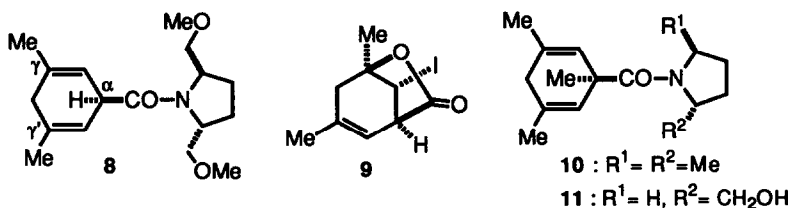


Chart II. Possible Transition States **7a** - **7d** for **4** Leading to Enantiomers **6a** and **6d**.

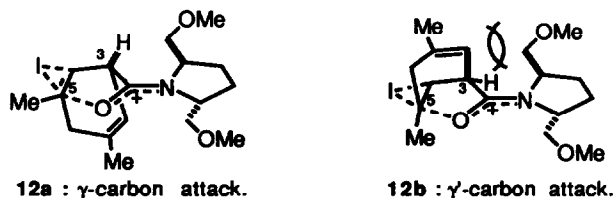


The existence of *E*- and *Z*-isomers (4-*E* and 4-*Z*) about the amide bond makes its analysis more complicated than that of 3. ¹H NMR showed that 4 existed as a mixture of 4-*E* and 4-*Z* in a ratio of 1:2. The transition state 7a is least stable among the four transition states 7a - 7d for 4-*E* and 4-*Z* leading to trans isomers 6a and 6d. No notable difference in stability is expected for 7b - 7d. Thus, 4-*E* is expected to give 6d through 7b, while 4-*Z* might furnish an approximately 1:1 mixture of 6a and 6d via 7c and 7d, provided that the original geometries are retained in the transition state. This accounts for the roughly 2:1 preference of 6d over 6a from 4.



Amide 8⁸ provides another interesting example. Restricted rotation about the C(α)-C(β) and C(α')-C(β') bonds simplifies the situation when face differentiation is eliminated and diastereotopic olefin differentiation is the sole factor determining the product enantioselectivity. In the event, kinetic iodolactonization of 8 provided 9 or its enantiomer with 86% ee¹⁰ in 89% yield. Selection of the γ'-carbon would cause a severe steric repulsion between a methoxymethyl group and the substituent at C(3) in transition state 12b. Attack on the γ-carbon would afford the more stable transition state 12a. The above analysis predicts the absolute structure of the product to be as shown in 9 though it remains to be proven experimentally. Recently, Hart *et al.*⁹ reported an asymmetric iodolactonization of 10 and 11 with low enantioselectivity (~40% ee) and predicted that larger substituents at the α-carbon might increase the selectivity. It should be interesting to examine the effect of α-substituents on the enantioselectivity, because our analysis indicates that extremely bulky substituents will produce the opposite chirality to that occurring from 8 which carries the smallest substituent (H) at C(α).

Chart III. Possible Transition States 12a and 12b from 8.



In conclusion, our studies have shown that proper choice of chiral auxiliary can increase differentiation of diastereotopic olefins in halolactonization in a predictable manner.

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References and Notes

- (1) For leading references, see: (a) Bartlett, P. A.; Myerson, J. *Tetrahedron* **1984**, *40*, 2317 and the literatures cited therein. (b) Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819. (c) Tamaru, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.; Yoshida, Z.; Yanagi, K.; Minobe, M. *J. Am. Chem. Soc.* **1984**, *106*, 1079.
- (2) Kurth, M. J.; Brown, E. G. *J. Am. Chem. Soc.* **1987**, *109*, 6844.
- (3) Takano, S.; Murakata, C.; Imamura, Y.; Tamura, N.; Ogasawara, K. *Heterocycles* **1981**, *16*, 1291.
- (4) To a solution of the amide **3** (79 mg) in 3 mL of THF-water (1:1) was added iodine (214 mg, 3 mol. eq.) and the mixture was stirred for 78 h at room temperature in the dark. After addition of ether (50 mL), the mixture was washed with aqueous NaHSO₃ and brine, successively, dried over MgSO₄, and evaporated to dryness. The residue was purified by preparative TLC to afford **6a** [40 mg, 54%, [α]_D²⁵ +20.5°, 91% ee determined by ¹H NMR with Eu(hfc)₃].
- (5) No cis isomer was detected in the reaction mixture.
- (6) The absolute configuration was determined by its conversion into the known 3*R*,5*S*-3-allyl-5-trityloxymethyltetrahydro-2-furanone⁷ through successive treatment with silver nitrate in acetonitrile and zinc in methanol followed by tritylation.
- (7) Takano, S.; Tamura, N.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1981**, 1155.
- (8) This compound was easily prepared from 3,5-dimethylbenzoic acid through the similar route to that of Hart *et al.*⁹
- (9) Hart, D. J.; Huang, H.-C.; Krishnamurthy, R.; Schwartz, T. *J. Am. Chem. Soc.* **1989**, *111*, 7507.
- (10) Determined by ¹H NMR with Eu(hfc)₃.

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