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Unprecedented Stereochemical Control in the Organoaluminum-Promoted Intramolecular Ene Reactions of δ,ε-Unsaturated Aldehydes

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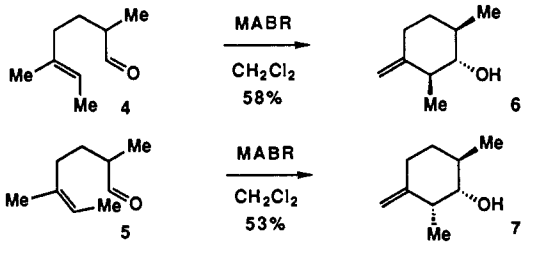
The Lewis acid promoted ene reactions of unsaturated carbonyl compounds are a valuable route to the stereoselective synthesis of highly functionalized cyclic compounds.[1] Among these, type II intramolecular ene reactions of δ,ε-unsaturated aldehydes **1** with α-substituents were reported to furnish *cis*-methylenecyclohexanols **2** with high selectivity (Scheme I).[2] The opposite, trans selectivity, however, has not yet been achieved. Here we disclose new, stereocontrolled ene reactions of δ,ε-unsaturated aldehydes **1** with α-substituents leading to *trans*-cyclohexanols **3** with exceptionally bulky methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide) (MABR).[3] Our results are summarized in Table I.

The Lewis acid promoted cyclizations of 2,5-dimethyl-5-hexenal (**1**, R = Me) are known to generally afford *cis*-6-methyl-3-methylenecyclohexanol (**2**, R = Me) predominantly (entries 1–3).[2] In marked contrast, however, treatment of **1** (R = Me) in CH_2Cl_2 with exceptionally bulky MABR (1.2–2 equiv) at −78 to −40 °C gave rise to *trans*-6-methyl-3-methylenecyclohexanol (**3**, R = Me) with excellent stereoselectivity (entries 4 and 5). The trans selectivity is markedly decreased with less bulky dimethylaluminum 4-bromo-2,6-di-*tert*-butylphenoxide or methylaluminum bis(2,6-diphenylphenoxide) (ratios of **2**:**3** (R = Me) = 3:2 and 2:1, respectively).

In a similar manner, the type II intramolecular ene reactions of α-substituted aldehydes, **4** and **5**, possessing trisubstituted double bonds under the influence of MABR gave rise exclusively to the desired alcohols, **6** and **7**, respectively, with excellent stereoselectivity.[4]



The stereochemical outcome in the present intramolecular ene reactions can be explained by the work of Snider,[2] in which the α-alkyl substituent of **1** selectively adopts the equatorial and axial

Scheme I

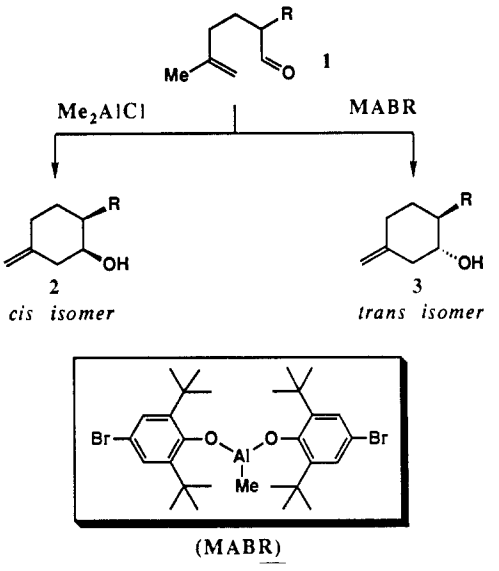
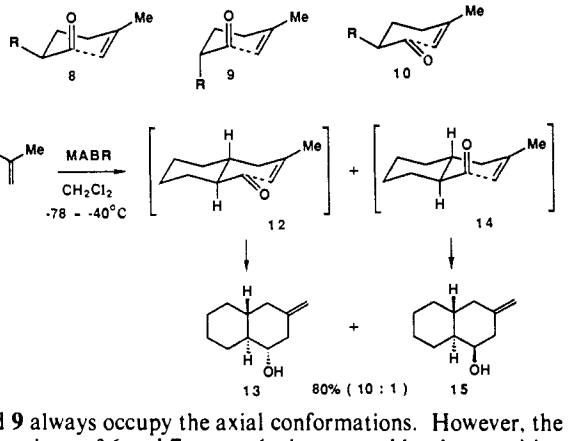


Table I. Stereocontrolled Ene Reactions of δ,ε-Unsaturated Aldehydes[a]

entry	aldehyde **1**	Lewis acid (equiv)	conditns: temp (°C), time (h)	yield, % (ratio of **2**:**3**)[b]
1	R = Me	Me_2AlCl (1.2)	−78, 0.3	65 (9:1)[c]
2		$BF_3{\cdot}OEt_2$ (2)	−78, 0.3	58 (19:1)
3		$SnCl_4$ (2)	−78, 0.3	47 (9:1)
4		MABR (1.2)	−78, 2; −40.1	85 (1:32)
5		MABR (2)	−78, 5; −40, 0.3	82 (1:32)
6	R = Et	Me_2AlCl (1.2)	−78, 0.3	60 (19:1)
7		MABR (2)	−78, 2.5; −40, 0.5	89 (1:30)
8	R = *i*-Pr	Me_2AlCl (1.2)	−78, 0.3	70 (33:1)[d]
9		MABR (2)	−78, 0.5; −40, 2	85 (1:17)[d]
10	R = allyl	Me_2AlCl (1.2)	−78, 0.7	59 (17:1)
11		MABR (2)	−78, 0.5; −40, 1	82 (1:62)
12	R = Ph	Me_2AlCl (1.2)	−78, 0.5	95 (26:1)[e]
13		MABR (2)	−78, 0.5; −40, 2	98 (1:62)[e]
14	R = SPh	Me_2AlCl (1.2)	−78, 0.3	95 (1:3)[e,f]
15		$BF_3{\cdot}OEt_2$ (2)	−78, 0.2	86 (1:2)[e,f]
16		$SnCl_4$ (2)	−78, 0.5	66 (1:3)[e,f]
17		MABR (2)	−78, 1.5	75 (1:200)[e]

[a] The reaction was carried out in CH_2Cl_2 with 1.2-2 equiv of Lewis acids under the indicated conditions. [b] Determined by GLC analysis. [c] See ref 2. [d] The stereochemistry of **3** (R = *i*-Pr) was confirmed by correlation to menthol after hydrogenation of **3** with 10% Pd/C. [e] The authentic hydrogenated samples of **3** (R = Ph or SPh) were independently synthesized. [f] The trans selectivity with normal Lewis acids is ascribed to the effect of the electron-withdrawing phenylthio substituent. See also: Snider, B. B.; Deutsch, E. A. *J. Org. Chem.* **1983**, *48*, 1822.

conformations, **8** and **9**, in the transition states leading to the cis and trans alcohols, **2** and **3**, respectively. Here the carbonyl groups



of **8** and **9** always occupy the axial conformations. However, the stereochemistry of **6** and **7** cannot be interpreted by the transition

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(4) The stereochemistry of **6** and **7** was tentatively assigned by 500-MHz ^1H NMR analysis. Furthermore, the authentic samples of the hydrogenated **6** and **7** were independently synthesized.

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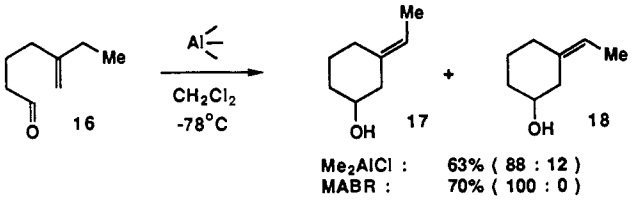
state of type **9** for trans selectivity, suggesting the intervention of an alternative transition state **10** with both R and the carbonyl group equatorial. This finding prompted us to further examine the intramolecular ene reaction of rigidly maintained cyclic substrate **11**, in which only the equatorial conformation (as in **12**) of both the α-alkyl substituent and the carbonyl group should afford the desired trans alcohol **13**. Indeed, treatment of **11** with MABR in CH_2Cl_2 at −78 °C for 2 h and at −40 °C for 1 h gave trans alcohol **13** predominantly.[5] Consequently, in the type II intramolecular ene reactions of δ,ϵ-unsaturated aldehydes **1**, the trans selectivity is best accounted for by the transition state **10** with both R and the carbonyl group equatorial rather than the alternative **9**.

Another interesting feature of MABR in the intramolecular ene reactions is the remote stereochemical control observed in the transformation of substrate **16** to *E*-olefinic alcohol **17** exclusively.[2]



Supplementary Material Available: Experimental details of the Lewis acid preparation, ene reactions with MABR, and preparation of compounds **11** and **13** (2 pages). Ordering information is given on any current masthead page.

(5) The structure of **13** was confirmed by conversion to the known *trans*-decalin-1,3-diol (Grutzmacher, H.-F.; Tolkien, G. *Tetrahedron* **1977**, *33*, 221).

Probing Conformational Changes in Proteins by Mass Spectrometry

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Mass spectrometry has found wide application for the elucidation of the primary structures of proteins.[1] However, with the exception of topographical studies of membrane-bound proteins,[2] mass spectrometry has not previously been utilized to obtain information concerning the three-dimensional conformation of proteins. In the present communication, we describe the first use of mass spectrometry for probing conformational changes in proteins in a manner analogous to that employed in techniques like optical rotary dispersion, circular dichroism, and spectrophotometry.[3,4]

The new technique for probing the protein conformational changes makes use of electrospray ionization, which is a gentle method of ionization that produces intact multiply charged gas-phase ions from protein molecules in solution.[5,6] The multiply charged ions observed in the positive ion spectra are produced primarily as a result of proton attachment to available basic sites in the protein molecule. The availability of ionizable basic sites is determined by the conformation of the protein under the conditions of study, which include pH, temperature, and the presence of denaturing agents. In general, a protein in a tightly folded conformation will have fewer basic sites available for protonation compared to the same protein in an unfolded conformation. If the charge states of the gas-phase ions observed in the electrospray

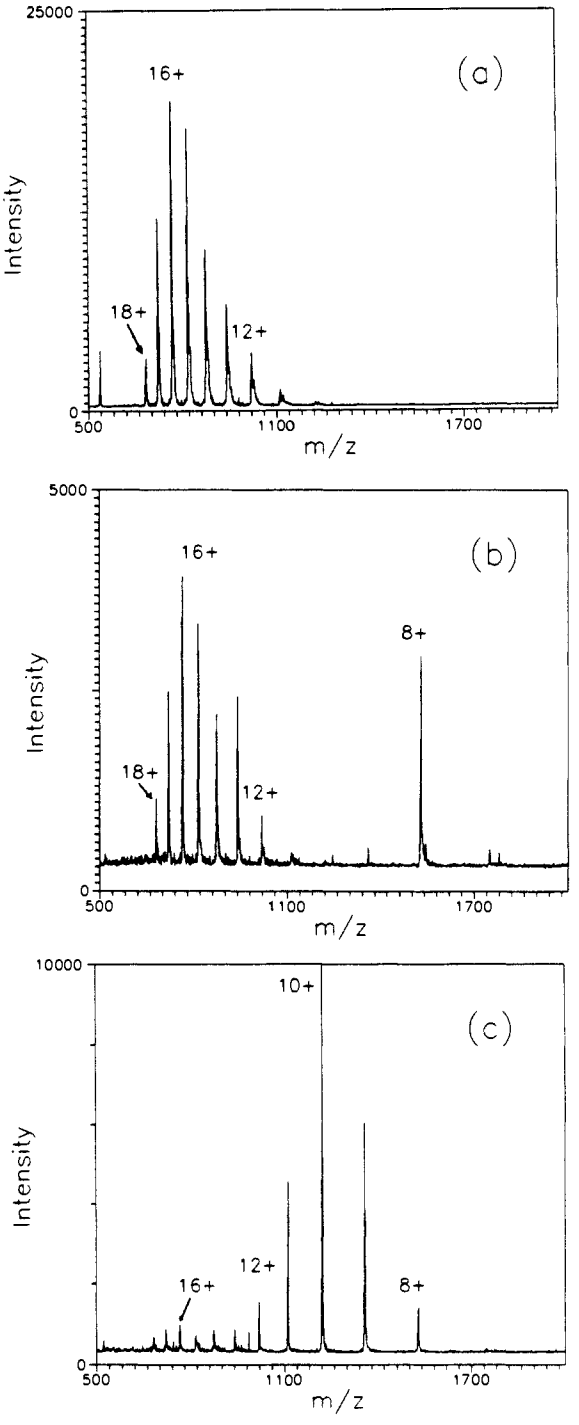

Figure 1. Electrospray ionization mass spectra of bovine cytochrome *c* obtained with different acetic acid concentrations in aqueous protein solutions. Protein concentration is 1×10^{-5} M: (a) 4% acetic acid, pH = 2.6, (b) 0.2% acetic acid, pH = 3.0, and (c) no acid, pH = 5.2. The labels on the peaks, *n*+, indicate the number of protons, *n*, attached to the protein molecule.

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