Stereoselective Indium-Promoted Allylation of γ-Hydroxy-γ-Lactones under Aqueous Conditions. The Neighboring Carboxyl Effect

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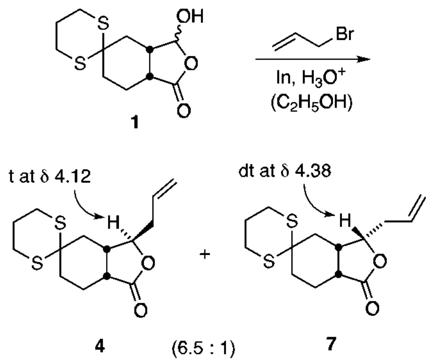
Indium-mediated carbon−carbon bond-forming reactions have commanded considerable attention recently because of the high efficiency with which In promotes these processes in water[1] and the ability of proximal hydroxy,[2] dimethylamino,[3] and keto substituents[4] to control diastereoselectivity through chelation to organoindium reagents under aqueous conditions.[5] No examples involving comparable intramolecular complexation to a carboxylic acid residue have yet been reported. In connection with the development of a general enantioselective approach toward 3,10-epoxy-2,11-cyclized cembranoids, the occasion to examine the stereoselectivity associated with addition of the allylindium reagent to γ-hydroxy γ-lactones presented itself. We now report that introduction of an allyl side chain into such systems proceeds with a synthetically useful stereochemical bias, a result presumably due to internal chelation to the neighboring carboxyl group once unmasked.

The required enantiopure γ-hydroxy γ-lactones **1**−**3** were derived by hydrolysis of the corresponding γ-menthyloxy γ-lactones under acidic conditions.[6] In this way, undesired epimerization next to the hemiacetal center was effectively skirted. Each substrate was stirred vigorously overnight at rt with allyl bromide and indium powder in dilute HCl (pH 3) containing 10% of ethanol or tetrahydrofuran. The acidic environment accelerated the rate of lactol ring opening, and the limited amount of organic solvent guaranteed complete miscibility of the nonmetallic reagents.[7] The results are provided in Table 1.

The major diastereomer in each instance was easily recognized from examination of the multiplicity and chemical shift of its α-oxy proton, in tandem with NOE experiments. Since an endo-oriented proton is displaced 90° out of plane from the adjacent tertiary hydrogen, it appears uniquely as an upfield triplet (see **4**). A doublet of triplets as depicted for **7** is seen for the minor isomers. A typical set of NOE experiments is shown for **5** and **8**.



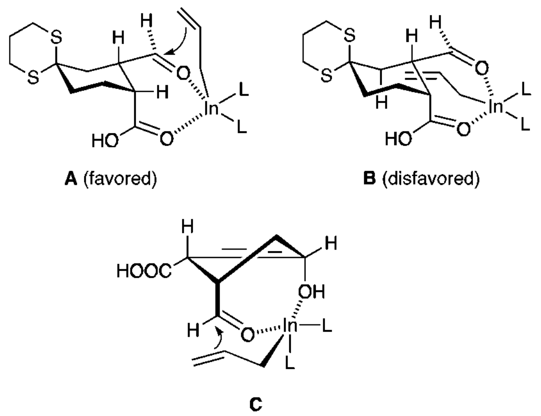
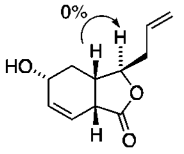
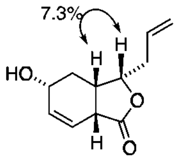


Figure 1.



5



8

The high diastereoselectivity observed for **1** and **3** can be rationalized in terms of preferred coupling via a chelated transition state in which the carboxylic acid group coordinates to the allylindium species prior to nucleophilic attack.[8] As seen in Figure 1, this process locks the conformation of the bicyclic ring system, thereby causing allylation to occur via a six-membered transition state preferentially on the *Re* face of the aldehyde as in **A**. Under these circumstances, intramolecular delivery from the *Si* face as in **B** is disfavored due to nonbonded steric interactions involving the allyl group and bicyclic framework. The higher selectivity observed for **3** can be attributed to increased shielding of the *Si* face of the aldehyde by the *tert*-butyldiphenylsilyl substituent.

In Table 1, entry 4, the presence of a salt such as tetra-*n*-butylammonium bromide is seen to induce a significant increase in diastereoselectivity. The phenomenon, which

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[1] (a) Li, C.-J. *Chem. Rev. (Washington, D.C.)* **1993**, *93*, 2023. (b) Chan, T.-H.; Li, C.-J.; Lee, M. C.; Wei, Z. Y. *Can. J. Chem.* **1994**, *72*, 1181. (c) Lubineau, A.; Auge, J.; Queneau, Y. *Synthesis* **1994**, 741.

[2] (a) Paquette, L. A.; Mitzel, T. M. *J. Am. Chem. Soc.* **1996**, *118*, 1931. (b) Paquette, L. A.; Lobben, P. C. *J. Am. Chem. Soc.* **1996**, *118*, 1917. (c) Isaac, M. B.; Paquette, L. A. *J. Org. Chem.* **1997**, *62*, 5333 and related references cited in these papers.

[3] Paquette, L. A.; Mitzel, T. M.; Isaac, M. B.; Crasto, C. F.; Schomer, W. W. *J. Org. Chem.* **1997**, *62*, 4293.

[4] Paquette, L. A.; Isaac, M. B. *Heterocycles*, in press.

[5] Paquette, L. A. In *Green Chemistry: Frontiers in Benign Chemical Synthesis and Processing*; Anastas, P., Williamson, T., Eds.; Oxford University Press: Oxford, 1997, in press.

[6] Bernardelli, P. Ph.D. Dissertation, The Ohio State University, 1997.

[7] Direct exposure of the γ-menthyloxy γ-lactones to allyltrimethylsilane in the presence of trimethylsilyl triflate as recommended for dimethyl acetals (Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899) did not result in consumption of the starting material. This lack of reactivity is attributable to the steric bulk of the menthyloxy substituent, which impedes formation of the oxonium ion.

[8] Since the hydroxy acids are the presumed intermediates in this reaction, the possibility exists that cyclization to the lactone with an exo substituent may be faster than cyclization to give the lactone with an *endo*-allyl group. While no guarantee can be made that both hydroxy acids have completely cyclized, none were observed spectroscopically in any experiments. More importantly, the exo allyl products were invariably isolated in yields well in excess of 50% (Table 1, entries 1, 3, and 4), even when a counterbalancing chelating substituent was present (Table 1, entry 2). Consequently, the results are entirely consistent with the intervention of chelated transition states as proposed.

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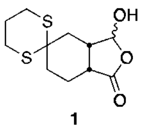
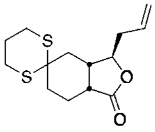
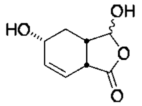
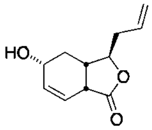
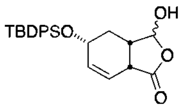
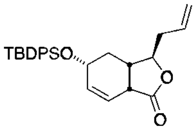
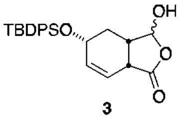
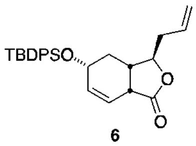
Table 1. Indium-Mediated Allylation of 1–3 (CH_2=$CHCH_2Br$, 25 °C)[a]

entry	lactol	solvent system	additive	major product	β/α ratio	composite yield, %
1	 **1**	HCl (pH 3), EtOH (9:1)	none	 **4**	6.5 : 1	73
2	 **2**	HCl (pH 3), EtOH (9:1)	none	 **5**	2 : 1	79
3	 **3**	HCl (pH 3), THF (9:1)	none	 **6**	9.6 : 1	93
4	 **3**	HCl (pH 3), THF (10:1)	*n*-$Bu_4N^+Br^-$ [b]	 **6**	13.2 : 1	81

[a] All reactions were stirred vigorously overnight. The product distributions in all cases were determined by ^1H NMR integration at 300 MHz of the unpurified reaction mixtures. The error limits are ≤ 3%. [b] The proportion of salt to **3** was 1.3:1.

has previously been observed with α-hydroxy aldehydes,[2a] is also accompanied by considerable rate acceleration.

Interestingly, the free hydroxy derivative **2** exhibits quite low diastereoselectivity. This increase in the proportion of the α-allyl isomer is consistent with competition between the OH and COOH groups for complexation to the incoming indium reagent. Transition state **C** in Figure 1 reflects the expectation that chelation to the hydroxyl substituent can bring about favored attack on the *Si* face of the aldehyde. It is particularly relevant that the product ratio determined for **2** is not inverted. This observation may suggest that the carboxylic acid functionality is a more effective chelator of allylindium than the hydroxyl group in aqueous acidic environments.

For comparison purposes, **1** was treated with allylmagnesium bromide in THF[9] and relactonized with 10% HCl. A 1:1.5 mixture of **4** and **7** resulted, with **4** being the minor product. Thus, indium is a significantly better chelating metal than magnesium for this reaction.

The methodology outlined herein constitutes a convenient and reliable means for the stereoselective synthesis of bicyclic γ-allyl lactones from γ-hydroxy precursors. For this new application of indium-promoted Barbier allylations in aqueous media, reliance is placed on the ability of a neighboring carboxylic acid group to guide C–C bond formation by means of chelation to the organometallic species.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds (11 pages).

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[9] Canonne, P.; Plamondon J.; Akssira, M. *Tetrahedron* **1988**, *44*, 2903.