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STEREOSELECTIVE KINETIC PROTONATION OF CHIRAL γ-LACTONE ENOLATES

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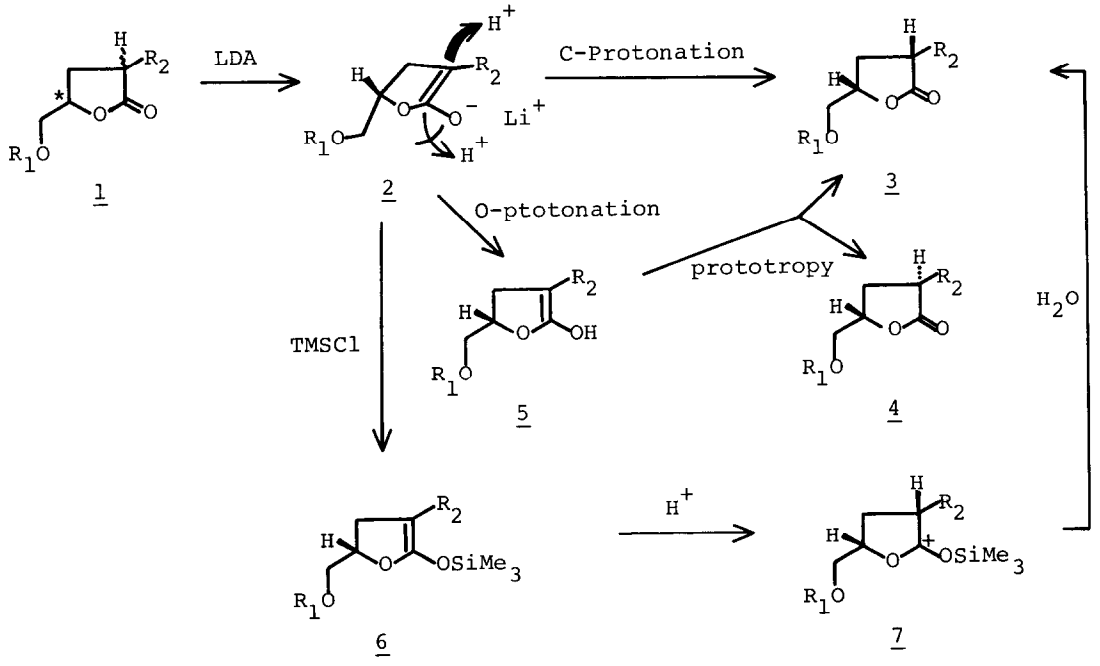
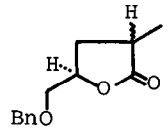
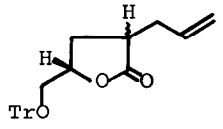
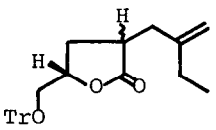
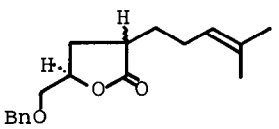
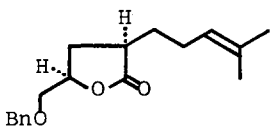
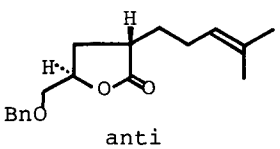
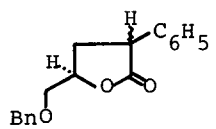
Summary: When lithium enolates generated from five chiral α,γ-disubstituted γ-lactones are treated with proton sources, formation of the α,γ-syn epimers always predominates over the α,γ-anti epimers in ratios of 10.2-2.9:1. Higher syn/anti ratios are obtained via silyl enolates in some cases. Chirality discrimination by chiral proton source is also observed in particular cases.

The protonation under thermodynamic and kinetic conditions for the control of enolizable center of five to seven membered lactone systems has served as the basis of our strategy for the syntheses of some natural products.[1-8] With the γ-lactones, new tertially chiral center can be constructed at α-position of the carbonyl group reflecting the stereochemistry of the pre-existed chirality at γ-position of the substrates (1) by protonation of their lithium enolates (2) under kinetic conditions.[2,5-8] The reaction consistently gives the epimers (3) with α/γ-syn configuration in preference to the epimers (4) with α/γ-anti configuration though ratio varied with substrates and proton sources. The



Scheme

Table

substrate (1)	conditions[a]	ratio[b] syn : anti	yield[c] (%)
 (A) syn(1.81):anti(1)	(i)	2.9 : 1	95.2
	(ii)[d] (d)	2.45 : 1	73.2
	(ii)[d] (l)	2.73 : 1	74.8
	(iii) ⓐ	3.6 : 1	93.7
 (B) syn(1):anti(6.43)	(i)	4.03 : 1	79.4
	(ii)[d] (d)	3.41 : 1	92.7
	(ii)[d] (l)	8.36 : 1	92.8
	(iii) ⓑ	4.39 : 1	87.5
	(iii) ⓒ	5.56 : 1	80.5
 (C) syn(1):anti(8.37)	(i)	10.2 : 1	89.4
	(ii)[d] (d)	9.22 : 1	90.6
	(ii)[d] (l)	2.47 : 1	98.9
	(iii) ⓑ	3.8 : 1	91.7
	(iii) ⓒ	4.9 : 1	93.6
 (D) syn(1):anti(1)	(i)	2.9 : 1	81.6
	(ii)[d] (d)	2.72 : 1	86.4
	(ii)[d] (l)	2.58 : 1	86.7
	(iii) ⓐ	5.4 : 1	85.4
 (E) syn	(i)	———	———
	(ii)[d] (d)	———	———
	(ii)[d] (l)	———	———
	(iii) ⓐ	4.55 : 1	88.6
 (F) anti	(i)	———	———
	(ii)[d] (d)	———	———
	(ii)[d] (l)	———	———
	(iii) ⓐ	4.34 : 1	86.7
 (G) syn(3.42):anti(1)	(i)	4.5 : 1	89.7
	(ii)[d] (d)	2.46 : 1	98.7
	(ii)[d] (l)	5.87 : 1	98.1
	(iii) ⓐ	1.1 : 1	91.6

a) (i) Treating the substrate (1) with LDA (1.2 eq) in THF at -70 - 0 °C, then the mixture is exposed to 5% HCl (A, D, F, G) or saturated aq. Na_2SO_4 (B, C)

all at once at -70 °C. (ii) Treating the substrate (1) with LDA (1.2 eq) in THF at -70 - 0 °C, then the mixture is exposed to 5% solution of the acid in THF all at once at -70 °C. (iii) Treating the substrate (1) with LDA (1.2 eq) in THF at -70 - 0 °C, then the mixture is treated with trimethylsilyl chloride (3.0 eq), then the mixture is exposed to ⓐ trifluoroacetic acid, or ⓑ saturated aq. Na_2SO_4, or ⓒ 10% aq. Na_2SO_4 all at once at -70 °C. b) determined by HPLC (EYELA PLC-10 instrument using a column of Microsorb (80-115, 4.6 x 150 mm) with 2% isopropanol in n-hexane. C) isolated total yield. D) (d) stands for d-camphorsulfonic acid monohydrate (l) stands for l-camphorsulfonic acid monohydrate.

stereochemical outcome has been believed to involve preferential electrophylic attack from the less hindered face of the enolate (2). Our continuing interest in kinetic protonation of α,γ-disubstituted γ-lactones led us to examine the scope of the reaction using five optically active α,γ-disubstituted γ-lactones, α-alkyl (1A),[9] α-allyl, (1B)[10] and (1C),[11] α-homoallyl (1D),[9] and α-aryl (1G),[9] as substrates.[12] The each substrate was deprotonated with lithium diisopropylamide to generate the lithium enolate (2) which was then exposed to proton sources in water or tetrahydrofuran all at once, respectively, and results are summerized in Table (conditions (i) and (ii)).

Our experimental data indicate that higher syn/anti ratio was obtained in the allyl, (1B) and (1C), and the aryl (1G) substrates with aqueous proton sources and camphorsulfonic acid of particular chirality, while lower syn/-anti ratio was obtained in the alkyl (1A) and the homoallyl (1D) substrates with proton sources both in water and tetrahydrofuran. Lower syn/anti ratio observed in (1A) and (1D) may be attributed to preferential O-protonation to give the transient enol (5) which in turn isomerized to the syn/anti-mixture by non-selective prototropy under the conditions.

In order to force C protonation, the substrates were first converted into the corresponding trimethylsilyl enolates (6) with expectation that it would form the β-silyl cations (7) regioselectively on protonation by directing effect of the silyl group.[13] As expected the alkyl (1A) and the homoallyl (1D) substrates gave much increased syn/anti ratio when the corresponding silyl enolates generated in situ were exposed to trifluoroacetic acid in the same reaction flask. However, the allyl, (1B) and (1C), and the aryl (1G) substrates gave virtually no improvement upon a similar treatment. Although the trimethylsilyl enolates (6) were not isolated in all cases, their formation may be secured since both the syn-(1E) and anti-(1F) epimers of the homoallyl substrate yielded the syn-anti mixture (1D) in essentially the same ratios (conditions (iii)).

The results of this study clearly suggest that (i) the protonation occurs competitively at α-carbon and at the enolate oxygen though the ratios depend on the nature of the α-substituents, (ii) a proton source with appropriate chirality must be used for the protonation of a chiral substrate, and (iii) asymmetric induction may be expected with α-substituted γ-lactone substrates using appropriate chiral proton sources. Further studies on the asymmetric induction by employing the present methodology are in progress.

Acknowledgments

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14. Cf. S. Takano, M. Akiyama, and K. Ogasawara, Synthesis, 503 (1985).

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