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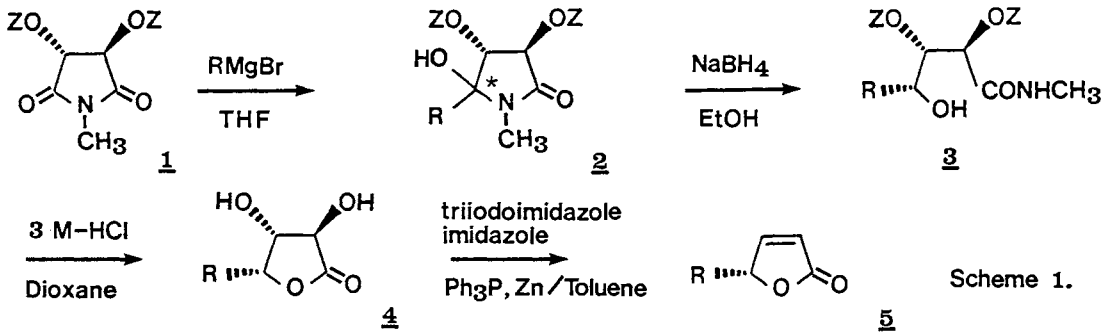
Novel Asymmetric Synthesis of γ-Alkylated Lactones via Successive Alkylation and Reduction of Chiral Cyclic Imides with C_2-Symmetry

Hidemi YODA,* Koji SHIRAKAWA, and Kunihiko TAKABE*
Department of Applied Chemistry, Faculty of Engineering,
Shizuoka University, Hamamatsu 432

Consecutive treatment of chiral cyclic imides containing a C_2-axis of symmetry with Grignard reagents and sodium borohydride followed by cyclization furnished γ-alkylated lactones with high diastereoselectivity. Products were converted to synthetically useful R-butenolides after removal of the chirality inducing groups.

Asymmetric reaction employing reagents of C_2-symmetry has been receiving increasing interest as a powerful strategy for the synthesis of biologically active compounds.[1] Most C_2-symmetrical reagents are utilized as chiral auxiliaries, and thus, the preparation of these substances in optically pure form is subject to continual refinement. On the other hand the synthetic utility of N-acyliminium ions obtained from the partial reduction of cyclic imides has been reviewed by Speckamp and Hiemstra[2] and nucleophilic addition to these species was demonstrated to be a valuable method for the preparation of nitrogen-containing natural products.[3] In spite of the impressive behavior of acyliminium ions, little, if any, progresses have been made toward new employment of carbinolamides prepared from direct alkylations of cyclic imides.[4] Taking these facts into consideration, we were interested in developing new application of our preceding method and wish to report herein novel asymmetric reactions employing C_2-symmetrical imides.

Starting chiral imides 1 were prepared by sequential treatment of L-tartaric acid with acetyl chloride, methylamine, acetyl chloride again[3a,b]



Scheme 1.

Table 1. Asymmetric Induction Using Chiral Imides 1

Entry	R	Z	Yield[a]/% 3	4	5	$[\alpha]_D$/deg[b] (Temp/°C,c)	Optical[c] yield/%	(confign)
1	n-C_4H_9	t-Bu(Me)$_2$Si	51	82	59	-86.2(23,2.43)[d]	85	(R)
2	n-C_8H_{17}	t-Bu(Me)$_2$Si	64	76	72	-61.5(24,1.50)	89	(R)
3	n-C_8H_{17}	(i-Pr)$_3$Si	89	44[e]	69	-44.8(24,1.29)	65	(R)
4	n-$C_{13}H_{27}$	t-Bu(Me)$_2$Si	44	82	74	-46.2(24,1.04)	89	(R)
5	n-$C_{13}H_{27}$	(i-Pr)$_3$Si	85	47	78	-47.4(23,1.62)	92	(R)

a) Isolated yield. b) Measured in dioxane. c) Optical purity based on $[\alpha]_D^{25}$ -101.0°($CHCl_3$) for (R)-4-butyl-, $[\alpha]_D^{25}$-69.2°(c 2,dioxane) for (R)-4-octyl-, and $[\alpha]_D^{25}$-51.7°(c 2,dioxane) for (R)-4-tridecylbutenolide. See Ref. 8b,c. d) Measured in $CHCl_3$. e) Treated with Bu_4NF after cyclization. $(i\text{-Pr})_3SiOH$ was obtained as a by-product.

and hydrolysis[5] followed by protection in 47-50% yields. Nucleophilic addition of Grignard reagents to 1 in THF at -78 to 0 °C would occur at the less hindered side owing to steric repulsion and afforded labile intermediates 2[6] which were immediately subjected to reduction with $NaBH_4$ in ethanol at r. t. to produce optically active amides 3 (Scheme 1). Cyclization and concomitant deprotection of silyl groups could be performed simultaneously under acidic conditions to furnish γ-lactones 4 including three contiguous stereogenic centers. The results are summarized in Table 1. The absolute configuration and e.e. of 4 were established by converting them to optically active butenolides 5 with triiodoimidazole, Ph_3P, and Zn in toluene[7] which are significant intermediates for the asymmetric synthesis of natural products.[8]

Thus, asymmetric synthesis of γ-alkylated lactones using C_2-symmetrical imides was accomplished by simple operations in enantiomeric excesses as high as 90%. We are currently investigating the stereochemical outcome and the results will be reported in due course.

References

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