CHEMISTRY LETTERS, pp. 843-846, 1988.

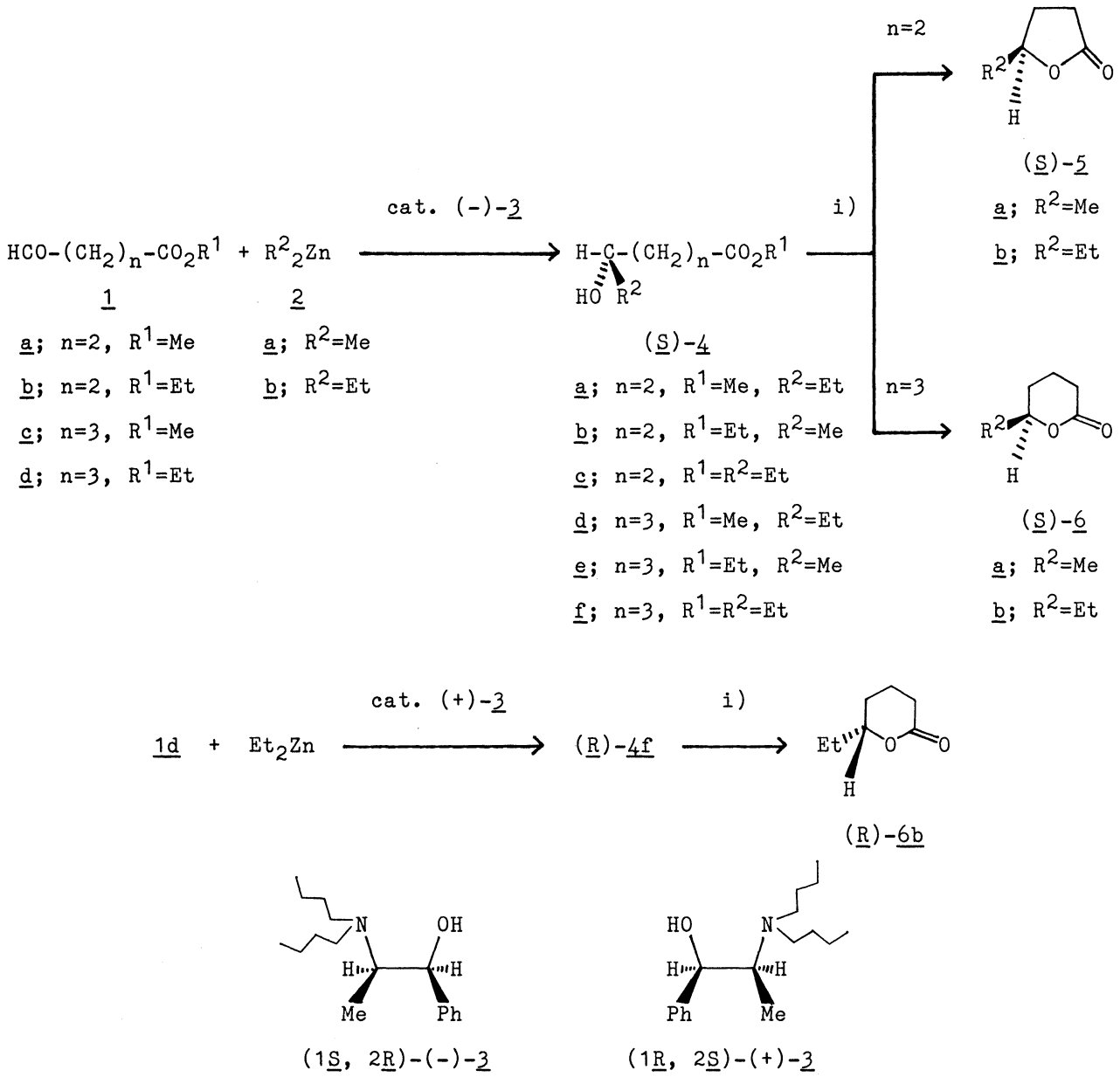
Catalytic Asymmetric Synthesis of Alkyl Substituted Lactones by Enantioselective and Chemoselective Alkylation of Formylesters with Dialkylzincs Using N,N-Dibutylnorephedrine

Kenso SOAI,* Shuji YOKOYAMA, Tomoiki HAYASAKA, and Katsumi EBIHARA
Department of Applied Chemistry, Faculty of Science,
Science University of Tokyo, Shinjuku-ku, Tokyo 162

Optically active 4-alkyl-γ-butyrolactones and 5-alkyl-δ-valerolactones were obtained in high enantiomeric excesses (85 - 95% e.e.) from the catalytic asymmetric alkylation of 3- and 4-formylesters with dialkylzincs using N,N-dibutylnorephedrine as catalyst.

Optically active 4-alkyl-γ-butyrolactone (5) and 5-alkyl-δ-valerolactone (6) form an important class of compounds because some of them are pheromones and key intermediates of a pheromone and a retro steroid. As to the asymmetric synthesis of these compounds, both biochemical[1] and chemical[2] methods have been reported. However, the yields of 5 and 6 are zero or very low in the reduction of γ- and δ-keto acid with baker's yeast because of its severe substrate specificity.[1a] In the reduction of β-ketoester with baker's yeast, tedious chemical modification of the substrate and many steps are required to synthesize 5b.[1b] In chemical methods such as reduction of ketone,[2a] alkynylation of aldehyde,[2b] and chiral transformation from α-amino acid,[2c] stoichiometric amounts of chiral auxiliaries are required.

We report a new method of the asymmetric synthesis of 5 and 6 which includes a catalytic asymmetric alkylation of prochiral 3- and 4-formylesters (1). When ethyl 4-formylbutanoate (1d)[3] was reacted with Et_2Zn (2b) using (1S, 2R)-(-)-N, N-dibutylnorephedrine [2-(N,N-dibutylamino)-1-phenylpropan-1-ol] [(3), 0.06 equivalent to (1d)][4] as catalyst in hexane at 0 °C, the corresponding (S)-5-hydroxyheptanoic acid ethyl ester (4f) was obtained in 87% yield (Table 1, entry 6).



Scheme 1. i) 1 M aq.NaOH then 2 M H_2SO_4.

This shows that Et_2Zn reacted with the aldehyde of 1d in enantioselective and chemoselective manner in the presence of an ester group. The subsequent hydrolysis of the ester of 4f and the following spontaneous cyclization afforded (S)-(-)-5-heptanolide (6b), a key intermediate of a retro steroid,[5] in 98% yield and in 95% e.e. (Table 2, entry 6). On the other hand, using ethyl 3-formylpropanoate (1b), reaction under the same conditions afforded (S)-(-)-4-hexanolide (5b) in 92% e.e. (Table 2, entry 3), a key intermediate in the synthesis of chalcograne (a

Table 1. Enantioselective Alkylation of Formylesters (1) with Dialkylzincs (2) Using 3 as Catalyst

Entry	1	R^2 in 2	Sign of 3	4		
					$[\alpha]_D$/°(temp/°C, c, $CHCl_3$)	Yield/%[a]
1	a	Et	(-)	a	-11.00 (25, 1.00)	88
2	b	Me	(-)	b	-10.00 (22, 3.00)	78
3	b	Et	(-)	c	-12.00 (24, 3.00)	90
4	c	Et	(-)	d	-12.20 (26, 1.50)	83
5	d	Me	(-)	e	-12.67 (22, 3.00)	88
6	d	Et	(-)	f	-15.13 (23, 3.00)	87
7	d	Et	(+)	f	+15.23 (24, 3.00)	85

a) Isolated yields of pure products.

Table 2. Conversion of Hydroxyesters (4) into Optically Active Lactones (5 or 6)[a].

Entry	4	5 or 6	$[\alpha]_D$/°(temp/°C, c, solvent)	Yield/%[b]	e.e./%[c]	Config.
1	a	5b	-45.20 (27, 1.00, MeOH)	96	85	S
2	b	5a	-26.59 (22, 1.29, CH_2Cl_2)	95	90	S
3	c	5b	-48.80 (24, 1.00, MeOH)	97	92	S
4	d	6b	-44.29 (27, 1.63, THF)	97	88	S
5	e	6a	-46.45 (22, 2.00, EtOH)	97	91	S
6	f	6b	-47.61 (23, 1.63, THF)	98	95	S
7	f	6b	+47.91 (25, 1.63, THF)	97	95	R

a) Entry numbers correspond to those of Table 1. b) Isolated yields of pure products. c) Based on the maximum values of optical rotations, $[\alpha]^{27}_D$ -53.2° (c 1.00, MeOH) for (S)-5b (Ref. 2c), $[\alpha]^{23}_D$ -29.6° (c 1.29, CH_2Cl_2) for (S)-5a (Ref. 7), $[\alpha]_D$ +50.3° (c 1.63, THF) for (R)-6b (Ref. 1a), $[\alpha]^{19}_D$ -51° (EtOH) for (S)-6a (Ref. 8).

pheromone of a species of beetle).[6]

One of the advantages of the present alkylation method over the reduction methods[1,2a,2c] is its easy access to various 5 and 6 by merely using various dialkylzincs (2). Thus using Me_2Zn (2a), (S)-5a and (S)-6a were obtained in 90 and

91% e.e. respectively (Table 2, entries 2, 5).

Because the both enantiomers of norephedrine are readily available, either enantiomer of the lactones was synthesized by using the appropriate enantiomer of the catalyst 3. Thus, by using (1R, 2S)-(+)-3 [$[\alpha]^{25}_{D}$ +15.75° (c 2.00, $CHCl_3$)], (R)-6b was synthesized in 95% e.e. (Table 2, entry 7).

Typical experimental procedure is as follows (Table 2, entry 6). A mixture of (1S, 2R)-(-)-3 (0.032 g, 0.12 mmol) and 1d (0.288 g, 2.00 mmol) in hexane (4 ml) was stirred for 20 min at room temperature. The mixture was cooled to 0 °C, then Et_2Zn (2b)(4.40 ml of 1 M hexane solution) was added. After stirring for 14 h, the reaction was quenched with 1 M hydrochloric acid (10 ml). The extraction (dichloromethane, 4 x 12 ml), drying (Na_2SO_4), evaporation, and the purification with silica gel TLC (EtOAc as developing solvent) afforded (S)-4f (0.303 g, 1.74 mmol) in 87%. Hydrolysis of 4f with 1 M aq.NaOH (30 min), acidification (2 M H_2SO_4) and the usual work up afforded (S)-6b (bulb-to-bulb distillation, bath temperature 130 °C/ 15 mmHg) in 98%.

We thank Tri Chemical Laboratory Inc. for a generous gift of Me_2Zn.

References

1) a) M. Utaka, H. Watabu, and A. Takeda, J. Org. Chem., 52, 4363 (1987) and references cited therein; b) K. Mori, H. Mori, and T. Sugai, Tetrahedron, 41, 919 (1985).

2) a) J. P. Vigneron and V. Bloy, Tetrahedron Lett., 1980, 1735; b) T. Mukaiyama and K. Suzuki, Chem. Lett., 1980, 255; c) U. Ravid, R. M. Silverstein, and L. R. Smith, Tetrahedron, 34, 1449 (1978).

3) M. Huckstep and R. J. K. Taylor, Synthesis, 1982, 881.

4) K. Soai, S. Yokoyama, K. Ebihara, and T. Hayasaka, J. Chem. Soc., Chem. Commun., 1987, 1690.

5) G. Saucy and R. Borer, Helv. Chim. Acta, 54, 2121, 2217 (1971); M. Rosenberger, R. Borer, and G. Saucy, J. Org. Chem., 43, 1550 (1978).

6) L. R. Smith, H. J. Williams, and R. M. Silverstein, Tetrahedron Lett., 1978, 3231.

7) K. Mori, Tetrahedron, 31, 3011 (1975).

8) "Dictionary of Organic Compounds," ed by J. Buckingham, Chapman and Hall, New York (1982).

(Received March 4, 1988)