Tetrahedron Letters,Vol.27,No.44,pp 5381-5382,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

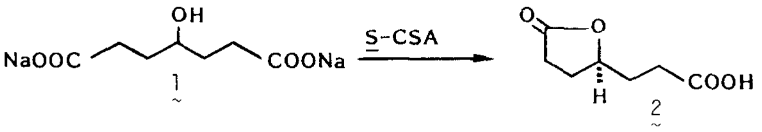
KINETIC RESOLUTION OF LACTONES BY ENANTIOSELECTIVE PROTONATION OF THE CORRESPONDING CARBOXYLATE WITH A CHIRAL ACID

Kaoru Fuji,* Manabu Node, and Makoto Murata
Institute for Chemical Research, Kyoto University, Uji Kyoto 611, Japan

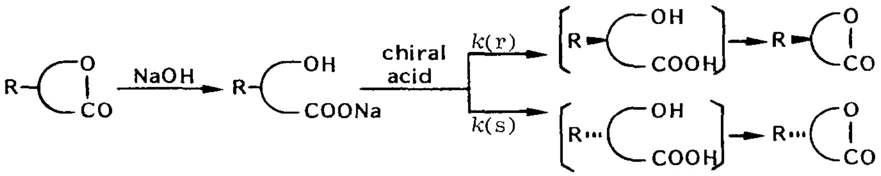
Shunji Terada and Keiji Hashimoto
Kyoto College of Pharmacy, Yamashina, Kyoto 607, Japan

Summary: *Racemic lactones were optically activated through the hydrolysis with sodium* hydroxide followed by the partial neutralization with (1S)-(+)-10-camphorsulfonic acid in ethanol to afford R- or S-isomer with 99 - 38% ee.

Recently we reported enantiotopic group differentiation between two carboxylate groups in sodium 4-hydroxypimelate (1) by protonation with (1S)-(+)-10-camphorsulfonic acid (S-CSA) monohydrate giving (S)-2 with a high ee (eq.1).[1] Similar type of kinetic protonation with chiral acids can be applied to the kinetic resolution of dl-lactones because the rate constants k(r) and k(s) for the protonation to R- and S-hydroxycarboxylate derived from dl-lactones by the alkaline hydrolysis must be different each other (eq.2).



(eq.1)



(eq.2)

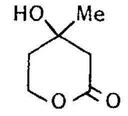
As an initial probe of this concept, dl-pantolactone (0.083 mol) was stirred in ethanol (50 ml) with NaOH (0.085 mol) for 2 hrs. and the solvent was distilled off. Benzene was added to the residue and refluxed with a water-separator to remove any trace of water. Evaporation of benzene afforded the corresponding dl-hydroxycarboxylate as a white powder in quantitative yield. A 5.9 mmol solution of the dl-hydroxycarboxylate in 99.5% EtOH was partially neutralized with S-CSA monohydrate (0.2 mol eq.) at -78°C followed by evaporation of ethanol. The residue was taken with methylene chloride and washed with water, dried over MgSO , and evaporated in vacuo to afford (R)-(-)-pantolactone (62% based on S-CSA) with 88% optical purity (o.p.). Not surprisingly, o.p. decreased as the amount of neutralization increased (Table I). Initial concentration of dl-carboxylate has a significant effect on o.p. Thus, the o.p. of the product decreased to 18% when a 8.8 mmol solution was employed. This may suggest that the degree of aggregation in the solution would be crucial factor for the successful optical activation.

The application of this method to the other lactones was examined and proved to be successful (Table II). Mention should be made of several pitfalls that can result in an unexpected low o.p. of the product. A solution of 4-7 mmol of hydroxycarboxylate should be employed. The o.p. of the lactone decreased as the molar concentration increased. The addition of S-CSA requires 2 hours or more in a 200 ml-scale experiment, since rapid addition again decreases o.p. Azeotropic removal of any trace of water from the racemic hydroxycarboxylate is indispensable to obtain the reproducible results.

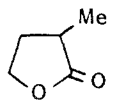
Table I. Optical Resolution of dl-Pantolactone[a]

run	S-CSA mol eq.	$[\alpha]^{25}_D$	% ee[b]	yield, %[c]
1	0.10	-50.6	99.4	79.5
2	0.20	-45.0	88.4	61.5
3	0.30	-44.9	88.2	86.0
4	0.50	-11.9	23.4	62.0
5	0.70	-0.1	0.2	62.0
6	0.90	0	0	81.0

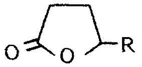
[a] All reactions were carried out with 5.9 mmol solution of sodium dl-pantoate in ethanol.
[b] Calculated from the maximum rotation (MeOH, -50.9) of pure (R)-pantolactone. [c] Based on S-CSA monohydrate.



3



4



5 : R = Et
6 : R = $^{n}C_7H_{15}$
7 : R = $^{n}C_8H_{17}$

Table II. Optical Resolution of Lactones

dl-lactone	concentration hydroxycarboxylate	S-CSA mol eq.	yield,%[a]	$[\alpha]^{25}_D$	abs. config.	%ee[b]	ref
3	6.0 mmol	0.1	62	-19.8[c]	R	86	2
4	7.1 mmol	0.1	67	-20.0[c]	S	93	3
		0.3	69	-12.5[c]	S	58	3
5	6.5 mmol	0.1	71	-42.1[d]	S	79	4
		0.3	66	-20.1[d]	S	38	4
6	4.5 mmol	0.1	70	-27.8[d]	S	63	5
7	4.2 mmol	0.1	66	-27.2[d]	S	66	5

[a] Based on S-CSA monohydrate. [b] Calculated from the maximum rotation reported. [c] In EtOH. [d] In MeOH.

References

1. Fuji, K.; Node, M.; Terada, S.; Murata, M.; Nagasawa, H. J. Am. Chem. Soc. 1985, 107, 6404.
2. Cornforth, R.H.; Cornforth, J.W.; Popjak, G. Tetrahedron 1962, 18, 1351.
3. Kaneko, T.; Wakabayashi, K.; Katsura, H. Bull. Chem. Soc. Jpn. 1962, 35, 1149.
4. Ravid, U.; Silverstein, R.M.; Smith, L.R. Tetrahedron 1978, 34, 1449.
5. Muys, G.T.; van der Ven, B.; de Jonge, A.T. Appl. Microbiol. 1963, 11, 389.

(Received in Japan 10 June 1986)