# An Asymmetric Synthesis of 2,4-Dimethylvalerolactone and Mevalonolactone using Chiral Binaphthyldiamine Derivatives

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Axially dissymmetric binaphthyldiamine derivatives formed by asymmetric ring opening of the cyclic anhydrides (**3**) and (**4**) ring close on hydrolysis to give (−)-*cis*-2,4-dimethylvalerolactone (**6**) and (−)-mevalonolactone (**7**) in 92% and 58% enantiomeric excess (e.e.), respectively; similarly the derivative of the racemic cyclic anhydride (±)-(**3**) ring closes to give (−)-*trans*-2,4-dimethylvalerolactone with 74% e.e.

Syntheses of optically active lactones through discrimination between enantiotopic groups have been successfully achieved using dehydrogenases and hydrolases.[1] Non-enzymic asymmetric syntheses involving selective use of a chiral 1,3-thiazolidine-2-thione derivative[2] and the partial reduction of chiral imides[3] have also been reported. The selective ring opening of prochiral cyclic acid anhydrides has been attempted[4] but the selectivity was too low for efficient syntheses of optically active lactones. We report the highly selective differentiation between two enantiotopic groups of anhy-

**Table 1.** Asymmetric ring opening reactions of acid anhydrides (**3**) and (**4**) and the diastereoisomeric ratio of the amide-esters (**5**).

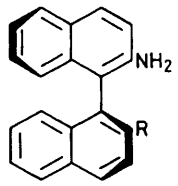
| Run | Amine | Anhydride | Solvent[a] | Amide-ester | Diastereoisomeric ratio |
|---|---|---|---|---|---|
| 1 | (−)-(**2a**) | *cis*-(**3**) | Toluene | (**5a**) | 4 : 96 |
| 2 | (−)-(**2b**) | *cis*-(**3**) | Toluene | (**5b**) | 10 : 90 |
| 3 | (−)-(**2a**) | (**4**) | Dichloromethane | (**5c**) | 20 : 80 |
| 4 | (−)-(**2b**) | (**4**) | Dichloromethane | (**5d**) | 17 : 83 |
| 5 | (−)-(**2a**) | *trans*-(**3**) | Toluene | (**5a**) | 87 : 13 |

[a] The reaction vessel was left at −20 °C for 2—7 days.

drides using axially dissymmetric binaphthyldiamine derivatives and the synthesis of optically active *cis*- and *trans*-2,4-dimethylvalerolactones and mevalonolactone.

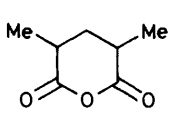
The reductive alkylation of 1,1′-binaphthyl-2,2′-diamine [(−)-(*S*)-(**1**)][5] with glutaraldehyde or 3-oxapentanedial† using sodium cyanoborohydride gave the piperidino derivative (−)-(*S*)-(**2a**)‡ or the morpholino derivative (−)-(*S*)-(**2b**), respectively. An equimolar amount of *meso*-2,4-dimethylglutaric anhydride [*cis*-(**3**)][6] or 3-hydroxy-3-methylglutaric anhydride (**4**)[7] reacted with (**2a**) or (**2b**) to give the amide acids. After treatment with diazomethane, the diastereoisomeric ratio in the resulting amide-esters (**5**) was determined by h.p.l.c. (Table 1). The amide-ester (**5a**) derived from (**2a**) and *cis*-(**3**) was subjected to selective reduction of the ester group by lithium borohydride. Hydrolysis then gave (−)-(2*R*,4*S*)-*cis*-2,4-dimethylvalerolactone (**6**) with $[\alpha]_D^{25}$ −37.8° in an overall yield of 77% from (**3**). The optical purity was 92% based on the maximum rotation of $[\alpha]_D^{25}$ −41.1° [1b] which coincided with the diastereoisomeric ratio in (**5a**). The same treatment of the amide-ester (**5d**) derived from (**2b**) and (**4**) afforded (−)-(*R*)-mevalonolactone (**7**) with $[\alpha]_D^{25}$ −12.2° in an overall yield of 44%. The enantiomeric excess (e.e.) of (−)-(**7**) was determined to be 58% using a chiral shift reagent§ and was somewhat lower than the calculated value from the diastereoisomeric ratio in (**5d**). This may be due to partial racemization during the reaction sequence. The stereochemical outcome shows that the pro-*R* carbonyl group was attacked preferentially in the reactions.

The piperidino derivative (**2a**) reacted with a five-fold excess of racemic 2,4-dimethylglutaric anhydride [*trans*-(**3**)]. The (−)-*trans* lactone (**8**) with $[\alpha]_D^{25}$ −60.1° was obtained in the same manner as above in an overall yield of 47% from (**2a**). The e.e. of (−)-(**8**) was calculated to be 74% from the diastereoisomeric ratio in (**5a**). The absolute configuration of (−)-(**8**) was determined according to the lactone chirality rule.[9] The conformation (A) predicted by $^1$H n.m.r. spectroscopy and the negative maximum at 221 nm in its c.d. spectrum suggest the 2*R*,4*R* configuration for the (−)-*trans* lactone (**8**). Accordingly, it was the 2*R*,4*R*-enantiomer of *trans*-(**3**) that reacted preferentially with (**2a**).¶

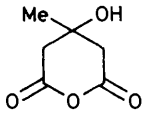



(**1**) R = $NH_2$

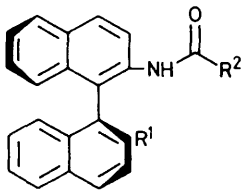
(**2**)**a**; R = piperidino
**b**; R = morpholino



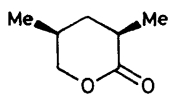

(**3**)



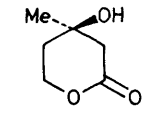

(**4**)



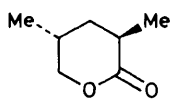

(**5**) **a**; $R^1$ = piperidino, $R^2$ = $CHMeCH_2CHMeC(O)OMe$
**b**; $R^1$ = morpholino, $R^2$ = $CHMeCH_2CHMeC(O)OMe$
**c**; $R^1$ = piperidino, $R^2$ = $CH_2C(OH)MeCH_2C(O)OMe$
**d**; $R^1$ = morpholino, $R^2$ = $CH_2C(OH)MeCH_2C(O)OMe$



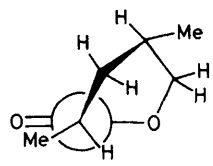

(**6**)




(**7**)




(**8**)




(**A**)

† This compound was prepared by ozonolysis of 2,5-dihydrofuran and was employed *in situ* for the synthesis of (−)-(**2b**).

‡ I.r. and n.m.r. spectra substantiated the proposed structures of all the compounds described herein.

§ Because the rotatory method for the determination of the e.e. of (**7**) was reported to be unreliable, an n.m.r. determination was carried out, ref. 8a. The maximum rotation has been reported as $[\alpha]_D^{20}$ −23.0°, ref. 8b.

¶ The selectivity of the reaction, $k_1/k_2$, was calculated to be 9.2 with a new kinetic treatment which will be reported elsewhere.

We thank the Ministry of Education of Japan for a Grant-in-Aid for Special Project Research.

*Received, 19th March 1984; Com. 368*

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