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Intramolecular Asymmetric Lactonization Using Optically Active 1,2-Diphenylethylenediamine as a Chiral Auxiliary

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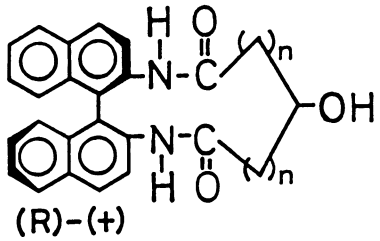
Intramolecular asymmetric lactonizations of two cyclic hydroxydiamides bearing (R,R)-1,2-diphenylethylenediamine as a chiral auxiliary were performed by the use of trifluoroacetic acid as an acid catalyst. The reactions proceeded smoothly at r.t. affording the corresponding (S)-γ- and (S)-δ-lactonamides with 96 and 98 %e.e. respectively.

Enantiotopic group differentiation reaction[1] by use of C_2-symmetric chiral auxiliary[2] has become a progressing area of asymmetric synthesis. We recently reported a novel asymmetric lactonization based on this concept.[3] Of the system

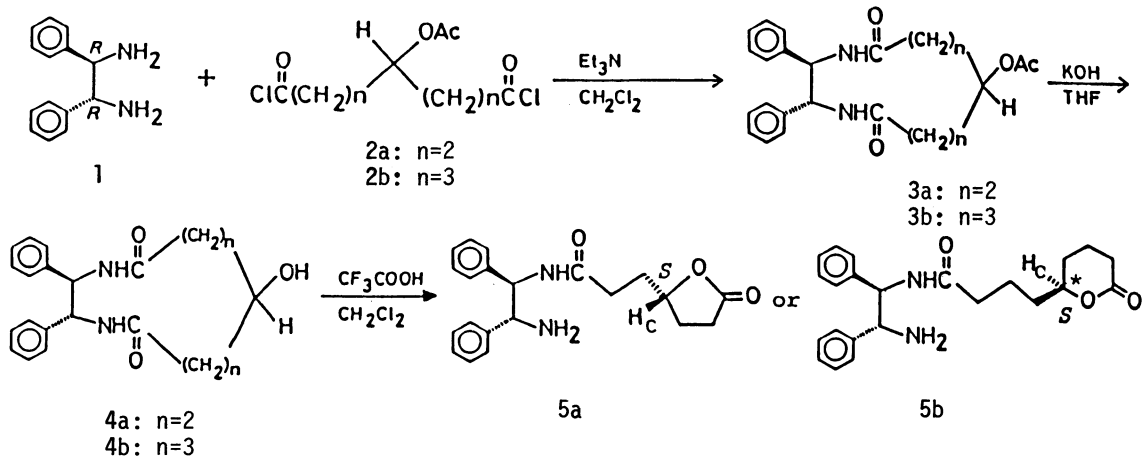


(R)-(+) n= 2 or 3

examined, when a hydroxydiamide (n=3) bearing optically active binaphthyldiamine as a chiral auxiliary was treated with trifluoroacetic acid in dichloromethane at -20 °C, only δ-lactone was obtained with almost complete enantioselectivity.[3] However, for γ-lactone formation from the corresponding alcohol (n=2), the e.e. was not so high as the δ-lactone. Therefore, to make superior system for this reaction, we replaced the binaphthyldiamine moiety to chiral (R,R)-1,2-diphenylethylenediamine (1) which was also C_2-symmetric but not aromatic amine and ro-

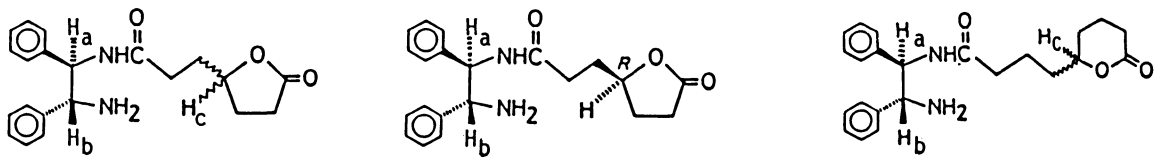
tationally more flexible than binaphthyldiamine. Here, cyclic hydroxydiamides **4a**, **4b** were prepared from the diamine **1**[4] and the dichloride **2a** and **2b**(Scheme 1).[5]

Typical lactonization procedure was as follows: To a mixture of the alcohol **4a**,(0.31 mmol) in dry dichloromethane (57 ml) was added trifluoroacetic acid



Scheme 1 Asymmetric lactonization with chiral 1,2-diphenylethylenediamine

(7.5 mmol) in dichloromethane(26 ml) and the mixture was stirred at r.t. for 12 h. The reaction mixture was washed with saturated sodium bicarbonate solution twice and solvent evaporation afforded the lactones **5a**(82%) and **5b**(79%) which were pure enough for diastereomer ratio determination by 200 or 400 MHz ^{1}H NMR. For unambiguous chemical shifts assignments of diastereomeric methyne protons of the lactone moiety in **5a**, the lactone-amide **6** was prepared from **1** and the racemic γ-lactonic acidchloride in addition to **7** from **1** and the (R)-γ-lactonic acid activated with carbonylimidazole. Chemical shift correlation for H_a, H_b and H_c in **5a**, **6**

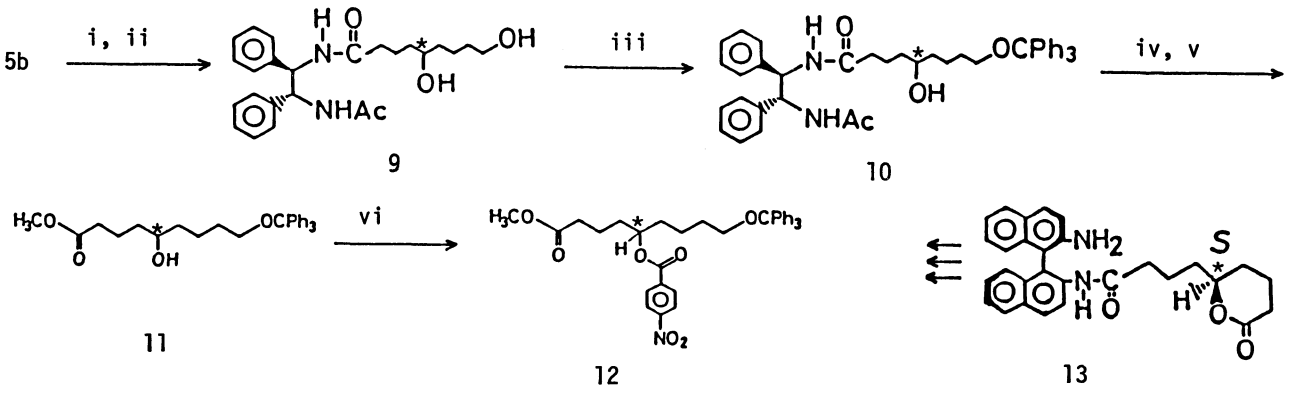


and **7** clearly demonstrated that the asymmetric carbon on the lactone ring of **5a** had (S)-configuration with more than 96 %e.e. in a range of 200 MHz NMR noise level. This outcome also indicated that pro-(S) carbonyl of **4a** was attacked preferentially by the hydroxyl group.

The hydroxydiamide **4b** was also submitted to intramolecular lactonization

under the same condition giving **5b**. For product proof, an authentic but racemic lactone-amide **8** was prepared which showed too small chemical shift differences of H_a, H_b, and H_c(400 MHz ^{1}H NMR) between the diastereomers to estimate the %d.e. for **5b**. However, when H_b in **8** was irradiated in a homo-decoupling experiment, H_a showed two doublets clearly at 5.19 and 5.20 ppm owing to the diastereomeric non-equivalence. Since H_a in **5b** gave only one doublet at 5.20 ppm by irradiation to H_b, the lactone-amide **5b** was composed of either of the diastereomers alone leading to a conclusion that this lactonization from **4b** to **5b** also proceeded with more than 98 %d.e. in a range of the NMR noise level.

The absolute configuration of the asymmetric center of the lactone **5b** was determined as follows (Scheme 2) since the optically active δ-lactonic acid could not be prepared because of an internal lactone exchange. The lactone-amide **5b** was converted to **12** and this ester showed positive sign with $[\theta]_{303}$=+430 ± 30 (CH_3CN) in CD spectrum. Similarly, the lactone-amide **13** with the known absolute configu-



Scheme 3. i. Ac_2O, pyridine ii. $LiBH_4$ iii. $ClCPh_3$ iv. 4M-NaOH, H^+
v. CH_2N_2 vi. p-NO_2-BzCl, pyridine

ration[3] was transformed to **12** which also afforded positive sign with $[\theta]_{303}$= +430±30 (CH_3CN). By this coincidence, it was established that the absolute configuration of the asymmetric center with asterisk in **12** and **5b** was (S). Therefore, pro-(S) carbonyl group of **4b** was proved to be attacked preferentially by the hydroxyl function.

The present study manifested that when 11- and 13-membered cyclic hydroxy-diamides carrying the chiral diamine **1** were treated with trifluoroacetic acid in dichloromethane, stereospecific lactonizations occurred even at room temperature concurrently with preferential scission of pro-(S) amide group in both cases. Their absolute configuration of the carbon atom in the lactone rings were found to be (S) when (R, R)-diamine **1** was employed. This makes a contrast with the bi-

naphthyldiamine system[3] where γ- and δ-lactone had (R)- and (S)-configurations respectively when (R)-binaphthyldiamine was applied. More important was a fact that the replacement of binaphthyldiamine to the diamine **1** realized a significant increase of stereoselectivity (71 → 96 %e.e.) in formation of the γ-lactone and this result might be ascribed to the rotationally more allowed flexibility of the C-C bond in the 1,2-diphenylethylenediamine moiety. It implies that, compared with binaphthyldiamine, the diamine **1** provides topologically more homogeneous transition state in both γ- and δ-lactonizations.

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5) The structure and integrity of all of the compounds described here were confirmed by ^{1}H NMR, TLC analysis, and/or high resolution MASS.

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