## Novel Asymmetric Synthesis of Optically Active $\delta$ - and $\gamma$ -Lactones Using a $C_2$ -Chiral Auxiliary<sup>1</sup>

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Asymmetric induction based on the differentiation between enantiotopic groups in prochiral molecules has been recognized as a new strategy for the synthesis of chiral compounds.<sup>2</sup> Asymmetric syntheses in this category have been successful in enzymatic discrimination between prochiral diesters.<sup>3</sup> The disadvantage of this process is that asymmetric yields are substantially lower when methylene groups intervene between the prochiral center and the ester groups.<sup>4</sup> Should the functional group at the prochiral center be designed so as to participate in the reaction, the intramolecular asymmetric synthesis would be well expected to exhibit a higher selectivity. On the basis of this rationale, we undertook the development of new methodology for asymmetric lactonization. Thus designed and prepared are the cyclic compounds 5a,b containing a  $C_2$ -chiral auxiliary in the ring structure constrained so as to allow the hydroxyl group to attack preferentially either of the pro-S or pro-R carbonyl groups of the substrate. In accord with the expectation, high selectivity in the lactonization was observed as follows.

Diacids 2a,b were prepared from the known keto diacids  $1a^5,b^6$ according to Scheme I. The condensation of the diacid dichlorides derived from 2a,b and  $(R)-(+)-[1,1'-binaphthyl]-2,2'-diamine (3)^7$ under a high-dilution condition gave the key intermediates 4a,b (4a: yield 56%; 4b: yield 39%). Alkaline hydrolysis of 4a,b afforded the hydroxyl derivatives 5a,b (5a: MS, m/e (M<sup>+</sup>) calcd for  $C_{29}H_{28}N_2O_3$  452.2100, obsd 452.2119; **5b**: MS, m/e (M<sup>+</sup>) calcd for  $C_{27}H_{24}N_2O_3$  424.1787, obsd 424.1779), which were the starting materials for the present asymmetric synthesis.

When the cyclic diamide alcohol 5a was treated with hydrochloric acid, the desired valerolactone derivative 6a was obtained in 36% yield along with the further hydrolyzed racemic product 7. This fact can be rationalized by postulating an equilibrium between 6a and the hydroxy acid derivative 8 through which the amide linkage is hydrolyzed to yield 7. After examining several inorganic and organic acids as the lactonization catalysts, we found trifluoroacetic acid (TFAA) to be most effective. Thus sixmembered lactone 6a was derived quantitatively from 5a with 1%



<sup>a</sup>(a) Isobutene, catalytic H<sub>2</sub>SO<sub>4</sub>, THF; (b) NaBH<sub>4</sub>, EtOH; (c) Ac<sub>2</sub>-O, pyridine; (d) 90%  $HCO_2H$ ; (e)  $SOCl_2$ ; (f) 3,  $Et_3N$ ,  $CH_2Cl_2$ ; (g) TFAA, CH<sub>2</sub>Cl<sub>2</sub> or toluene.

Scheme II<sup>a</sup>



<sup>a</sup>(a) Ac<sub>2</sub>O, pyridine; (b) LiBH<sub>4</sub>, EtOH; (c) p-TsOH, CH<sub>2</sub>Cl<sub>2</sub>; (d)  $(COCl)_2$ , DMSO,  $CH_2Cl_2$ ; (e)  $C_7H_{15}PPh_3Br$ , t-BuOK, THF; (f)  $H_2/$ 5% Pd-C; (g) Ac<sub>2</sub>O, Et<sub>3</sub>N; (h) 3 N HCl, H<sub>2</sub>O-dioxane.

TFAA in dichloromethane at -20 °C for 12 h. The diastereomeric excess (de) of 6a was determined to be 97% with <sup>1</sup>H NMR (400 MHz) monitoring of the methine protons ( $\delta$  3.92–4.00 for the R isomer and  $\delta$  4.07-4.16 for the S isomer). In toluene, 6a with 89% de was afforded quantitatively. The S configuration of the product was established by converting it to the naturally occurring pheromone<sup>8</sup> (R)-(+)-5-hexadecanolide  $(11a)^{9,10}$  according to Scheme II. It should be noted that the inversion of the configuration is ascribed to carboxyl interchange during the synthetic sequence. The enantiomeric excess (ee) of 11a thus obtained  $([\alpha]^{20}_{D} + 39.17^{\circ} (c \ 1.08, \text{THF}))$  was proved to be 98% based on the reported maximum rotation,  $[\alpha]^{20}_{D,max} + 39.97^{\circ}$  (c 1, THF).<sup>9</sup> This value agreed well with the de of the lactone amide 6a assessed with <sup>1</sup>H NMR. An optically pure sample was obtained by recrystallization from hexane,  $[\alpha]^{20}_{D}$  +39.81° (c 1.05, THF). Consequently, the present asymmetric lactonization was found to proceed with exclusive attack on the pro-S group.

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On the other hand, when **5b** was treated with hydrochloric acid, the butyrolactone derivative **6b** was obtained with 84% yield and 53% de. When a solution of **5b** was treated with 1% TFAA as described for **5b** except using toluene, **6b** having a maximum de of 71% was obtained quantitatively. In dichloromethane, **6b** with 54% de was formed quantitatively. However, this reaction did not proceed in EtOH or THF. The de of **6b** was determined with HPLC and <sup>1</sup>H NMR (200 MHz) monitoring of the methine protons ( $\delta$  3.90-4.09 for the *R* isomer and  $\delta$  4.27-4.43 for the *S* isomer). Alcohol **10b** ([ $\alpha$ ]<sup>25</sup><sub>D</sub> -24.0° (*c* 0.58, EtOH)) was derived from **6b** with 47% de according to Scheme II. The ee of **10b** was determined to be 47% according to Jones,<sup>11</sup> which agreed well with the de of **6b**. Consequently, the *R* configuration of the lactone moiety of **6b** was established based on the *S* configuration of (-)-**10b**.<sup>2e</sup>

Contrary to our hypothetical transition state predicting attack upon the pro-S carbonyl group of **5b** as **5a**, the pro-R carbonyl group of **5b** was preferentially attacked. The unexpected direction of the asymmetric bias in **5b** could be rationalized by distortion of the ring resulting in a highly strained bicyclic transition state. Consideration using a CPK model shows that the pro-R amide group is oriented out of the plane of the distorted naphthyl ring in **5b**. In such a conformation, stereochemical requirements are fulfilled by an intramolecular approach of the hydroxyl group to the pro-R carbonyl group.

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Supplementary Material Available: Experimental details about preparation of 5a,b lactonization and stereochemical correlation of 6a,b and spectral data of all the compounds herein (9 pages). Ordering information is given on any current masthead page.

## Extension of Chromatographically Derived Molecular Recognition Concepts to First-Order Asymmetric Transformations

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The equilibration of diastereomeric species in solution has been defined as a first-order asymmetric transformation.<sup>1,2</sup> Processes under kinetic rather than thermodynamic control are excluded from this definition and are termed stereodifferentiating reactions.<sup>2</sup> Interconversion and equilibration of *covalent* diastereomers, *intramolecular* asymmetric induction, is relatively common, mutarotation of glucose being a prime example of such a process. Interconversion and equilibration of noncovalent diastereomeric species, a somewhat less common process, is exemplified by the "Pfiffer effect", an alteration of the 1:1 equilibrium ratio of interconverting enantiomers of certain metal ion complexes by the presence of chiral solvents or other chiral species.<sup>3</sup> Typically, first-order asymmetric transformations of enantiomers do not proceed with extreme stereochemical bias nor are they amenable

to mechanistic rationalization. In this communication, we describe a first-order asymmetric transformation which is both effective and readily explained by a chiral recognition model recently advanced to account for the chromatographic separation of enantiomers on a chiral stationary phase.<sup>4</sup> This mechanistic picture should enable one to predictably extend such asymmetric transformations to other systems.

By altering the usual 1:1 equilibrium ratio of interconverting enantiomers, one is, in essence, performing a deracemization.<sup>5</sup> For a thermodynamically controlled deracemization to occur, several conditions must be fulfilled: (1) to eliminate the energetic degeneracy of the enantiomers, it is necessary, but not necessarily sufficient, that the transformation solvent be either chiral nonracemic or contain a species which is chiral nonracemic; (2) the chiral nonracemic species must be stereochemically stable under the transformation conditions; (3) the species to be deracemized must be stereochemically labile.

Immobilization of 1 onto silica affords chiral stationary phase 1a. This phase exhibits highly enantioselective behavior toward the enantiomers of esters and amides of N-(3,5-dinitrobenzoyl) amino acids.<sup>4a</sup> Similar behavior occurs with the corresponding



thioesters, and since "the acidifying effect of a thioalkyl substituent is substantial",<sup>7</sup> it was anticipated that the differential complexation of 1 with the enantiomers of a thioester such as 2 coupled with base-promoted interconversion of the thioester enantiomers would afford first-order asymmetric transformation of the racemic thioester. Indeed, deracemization of racemic 2 occurs in the presence of triethylamine and (R)-1.

A 3:1 cyclohexane/methylene chloride solution 0.045 M in 2, 0.18 M in triethylamine, and 0.20 M in (R)-1 was periodically examined by HPLC using a column packed with chiral stationary phase 1a. This column effectively separates all components of the mixture. After a period of 28 days, equilibrium was achieved with a 78% ee of (R)-2. The equilibrium position of deracemization is dependent upon the conditions employed. In general, more polar solvents reduce enantiomeric enrichment while lower temperatures increase the extent of enrichment. An increase in the concentration of the complexing agent, 1, increases the enantiomeric enrichment, albeit, with diminishing return, evidence of a saturation effect. The concentration of triethylamine, necessary as a basic catalyst to promote interconversion of the enantiomers, affects the rate of deracemization but has little effect upon the ultimate extent of enrichment over the range 0.05-0.30 Μ.

Differential complexation of 1 with the enantiomers of the thioester supplies the energetic driving force for the deracemization in solution. The sense and degree of differential complexation are rationalized simply by application of the previously reported chromatographically derived chiral recognition mechanism.<sup>4</sup> In this mechanism, three simultaneous attractive interactions are proposed to occur during the complexation of (R)-1 with the (R) thioester. These are (1) a hydrogen bond between the amino

<sup>(11)</sup> The alcohol **10b** was treated with *tert*-butyldimethylsilyl chloride and triethylamine to give the protected lactone (95%), which was analyzed according to the following report. See: Jakovac, I. J.; Jones, J. B. J. Org. Chem. **1979**, *44*, 2165.

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<sup>(5)</sup> This term has been applied by Duhamel and Duhamel<sup>6</sup> to the asymmetric protonation of achiral enolates, a kinetically controlled process and hence not a first-order asymmetric transformation. We view the term "deracemization" as being sufficiently broad to cover any process in which a racemate is made nonracemic by increasing the quantity of one enantiomer at the expense of the other. The process may be under either thermodynamic or kinetic control and does not preclude a phase change.

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