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PREPARATION AND OPTICAL RESOLUTION OF A NEW HELICAL LACTONE CARRYING THE 2,8-DIOXABICYCLO[3.3.0]OCTANE RING SYSTEM

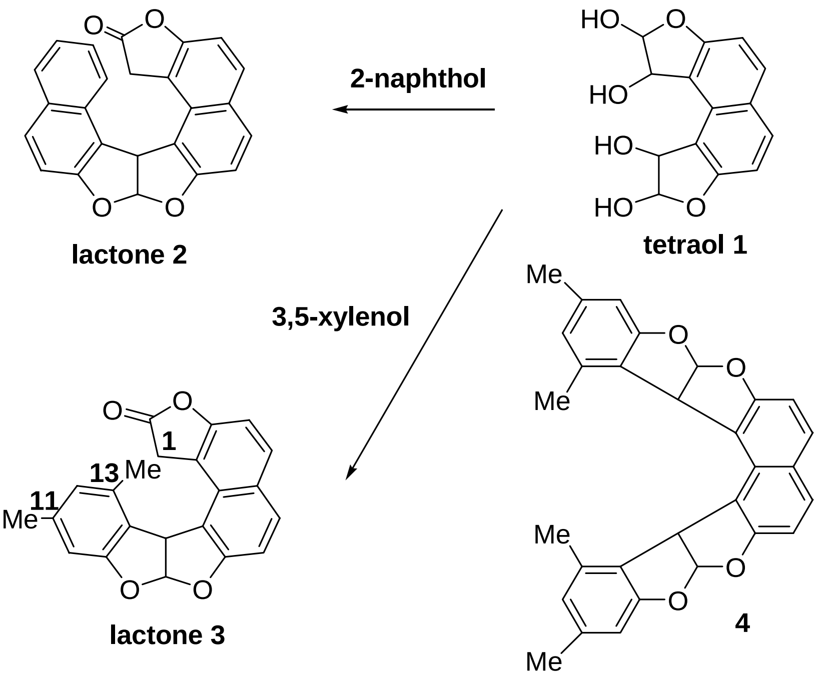
Makoto Yamaye,[a*] **Yusuke Ikeda**,[a] **Namiko Cho (Toh)**,[a] **Yoshinori Miura**,[b] **Tetsutaro Yoshinaga**,[c] **Katsuya Mukae,**[d] **and Toshiaki Tsuru**[d]

[a]Faculty of Engineering, Kyushu Kyoritsu University, 1-8 Jiyugaoka, Yahatanishi, Kitakyushu 807-8585, Japan
[b]The Center for Advanced Instrumental Analysis, Kyushu University, 6-1 Kasugakoen, Kasuga, Fukuoka, 816-8580, Japan
[c]Department of Chemistry, Kyushu Institute of Technology, 1-1 Sensuicho, Tobata, Kitakyushu 804-8550, Japan
[d]Department of Industrial Chemistry, Faculty of Engineering, Kyushu Sangyo University, 3-1 Matsukadai, 2-Chome, Higashiku, Fukuoka 813-8503, Japan

*Corresponding author. Tel: 093-603-3056; fax: 093-603-8186; e-mail: yamaye@kyukyo-u.ac.jp

Abstract ─ A new overcrowded lactone (**3**) carrying the 2,8-dioxabicyclo[3.3.0]octane ring system was prepared by a simple treatment of tetraol (**1**) (prepared from 2,7-dihydroxynaphthalene and glyoxal) with 3,5-xylenol, and readily resolved into its enantiomers having a specific rotation of >800° (absolute value). A preliminary experiment demonstrated that **3** would be a promising resolving agent.

We previously reported a convenient method for preparing a series of heterocyclic compounds containing the unique 2,8-dioxabicyclo[3.3.0]octane ring system.[1] During the course of the study, treatment of tetraol (**1**) with 2-naphthol gave a rigidly held butterfly-shaped lactone (**2**),[1c] which contains the same heterocyclic ring system (Scheme 1).



Scheme 1. Formation of lactone (**2**) and (**3**) (and an expected product (**4**)).

We were interested in the structure and properties of **2**, which provides an intriguing chiral environment. However, chemistry of **2** has not so far been elaborated, because its scarce solubility in common organic solvents prevented us from further study. Instead, we have designed and prepared a new lactone (**3**) containing the same skeleton, which was found to have an improved solubility. As in the preparation of **2**, lactone (**3**) was the sole product, though we had expected the formation of product (**4**). We report herein a convenient preparation of a new helical lactone (**3**) carrying the 2,8-dioxabicyclo[3.3.0]octane ring system and a facile resolution into its enantiomers, which possess a large specific rotation (absolute value >800°). To our knowledge, this type of helicity is unprecedented and commercially available resolving agents showing such high specific rotations are few except ferrocene derivatives.

Racemic lactone (**3**) was prepared from condensation of **1**[1c] (14.5 mmol) with 3,5-xylenol (58.0 mmol) in the presence of $MeSO_3H$ at room temperature for 4 h. Precipitates formed were simply collected by suction to yield **3** (17.4% based on **1**). Based on a molecular model study, we speculate the formation of **3** was in due course because of an excessive steric repulsion between the two 2,8-dioxabicyclo[3.3.0]octane skeletons in **4**.

Lactone (**3**) was characterized by elemental analysis and spectroscopic methods.[2] The molecular ion (*m*/*z* 344) was the base peak in the MS spectrum. A strong lactone absorption appeared at 1800 cm^{-1} in the IR spectrum. Noteworthy was the ^1H NMR spectrum of **3**, showing that the geminal methylene protons at the C1 atom were unequivalent to each other, possessing a large coupling constant ($^2J_{HH}$ = 23.2 Hz). The two methyl proton signals of **3** appeared at δ 2.01 and 2.26 ppm and were assigned to the methyl protons at the C13 and C11 atom, respectively. Because NOE measurements confirmed a close proximity between the C1 methylene group and the methyl group at the C13 atom. Based on an X-Ray crystallographic study, the nonbonding C-C distance between these two groups was estimated to be 3.45 Å and the two planes containing the lactone ring and the xylene moiety cannot flip-flop with each other, thus forming helical (**3**) with the O9-C8a-C13b-C13c (or O8-C8a-C13b-C13a) dihedral angle of 112-113° (Figure 1).[3]

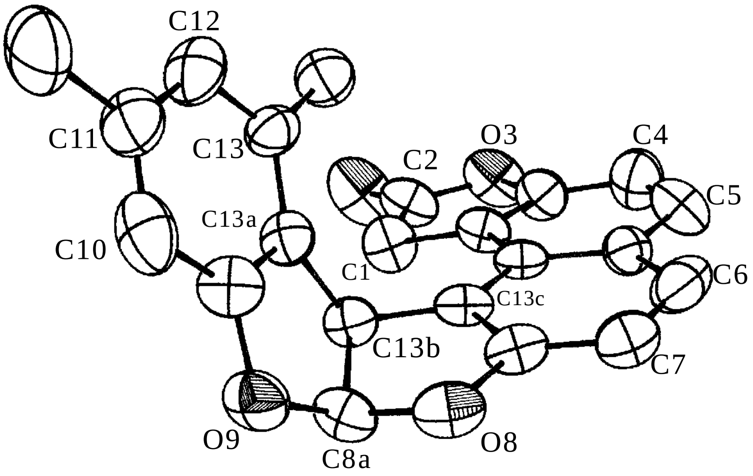


Figure 1. ORTEP view of (+)-**3**. Hydrogen atoms are omitted for clarity.

In view of a possible utilization of **3** as a resolving agent, *etc*., we examined its susceptibility to a couple of ring-opening transformations on the lactone ring, with retaining sufficient resistance to change on the framework, especially chemical stability of the bicyclic skeleton. In fact, its transformations into some corresponding ester and amide derivatives smoothly proceeded in satisfactory yields as shown in Table 1.

Table 1. Several ester and amide derivatives of lactone (**3**).

	Ester	Amide		
	Me	*i*-Pr	*n*-Bu	*sec*-Bu
Yield (%)[a]	79	95	89	100

[a] Conditions: The Me ester prepared in excess MeOH at rt for 30 min. The amides prepared with 10 equiv of the corresponding amines in MeOH at rt for 40 min to 5 h.

The optical resolution of racemic **3** was performed *via* diastereomeric amide formation. (±)-Lactones (**3**) were transformed into the corresponding diastereomeric amides (–)-**5** and (+)-**6** by stirring with (*S*)-(–)-1-phenylethylamine (PEA) in methanol at room temperature.[4] To this mixture were added ether and toluene to precipitate less soluble (–)-**5**, which was separated and recrystallized once from toluene. The (–)-**5** thus purified, which yielded a de of 100% by HPLC, was hydrolyzed under acidic conditions to produce enantiopure (–)-**3**, exhibiting $[\alpha]^{20}_{\mathrm{D}}$ –815° (c 0.1, 1,4-dioxane).[5] In a similar manner, (+)-**3** showing $[\alpha]^{20}_{\mathrm{D}}$ +816° (c 0.1, 1,4-dioxane) was obtained with using (*R*)-(+)-PEA (Table 2).

Table 2. Resolution of racemic lactones (**3**) *via* the corresponding diastereomeric amides.

	Separated diastereomeric amides (**5**) and (**6**)			Lactone (**3**)			
	Yield (%)[a]	mp (°C)	$[\alpha]^{20}_{\mathrm{D}}$ (°)[b]	Yield (%)	mp (°C)	$[\alpha]^{20}_{\mathrm{D}}$ (°)[b]	ee (%)[c]
(–)-**5**	73	214	–721	quant.	210	–815	100
(+)-**6**	74	215	+719	quant.	207	+816	100

[a] Based on half the amount of (±)-lactone (**3**).

[b] c 0.1, 1,4-dioxane.

[c] Determined by HPLC with Daicel Chiralcel OD-H column.

The circular dichroism spectra of both enantiomers were mirror images of one another as would be expected (Figure 2).

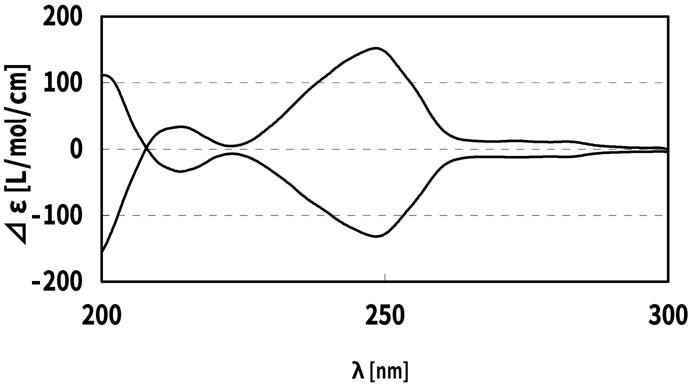


Figure 2. CD spectra of (+)- and (–)-**3** in CH_3CN at 30 °C.

To demonstrate an application of **3** as a resolving agent, a preliminary experiment was done by treating (±)-PEA (8.7 mmol) with (+)-**3** (0.87 mmol) in methanol (15 mL) at room temperature for 3 h. Removal of the solvent left an oily product. This was dissolved in ethyl acetate and washed with 1 N HCl, H_2O, and evaporated the solvent to leave the corresponding diastereomeric amides (84%), which were taken up in toluene and ether to give precipitates (100 mg). HPLC analysis proved this diastereomeric precipitates had a de of 56%.

REFERENCES AND NOTES

1. (a) T. Kito, K. Yoshinaga, M. Yamaye, and H. Mizobe, *J. Org. Chem.*, 1991, **56**, 3336. (b) X. Fan, M. Yamaye, Y. Kosugi, H. Okazaki, H. Mizobe, T. Yanai, and T. Kito, *J. Chem. Soc., Perkin Trans. 2*, 1994, 2001. (c) X. Fan, T. Yanai, H. Okazaki, M. Yamaye, H. Mizobe, Y. Kosugi, and T. Kito, *J. Org. Chem.*, 1995, **60**, 5407.
2. Characterization of **3**: mp 235 °C (toluene). UV (CH_3CN): λ_{max} (ε) 246 nm (4.29×10^4). IR (KBr): ν 1810 cm^{-1} (lactone CO). ^1H NMR (400 MHz, $CDCl_3$): δ 2.01 (s, 3H), 2.26 (s, 3H), 4.07 (d, 1H, J = 23.2 Hz), 4.37 (d, 1H, J = 23.2 Hz), 5.02 (d, 1H, J = 5.2 Hz), 6.53 (s, 1H), 6.75 (s, 1H), 6.93 (d, 1H, J = 5.2 Hz), 7.02 (d, 1H, J = 8.9 Hz), 7.21 (d, 1H, J = 8.9 Hz), 7.71 (d, 1H, J = 8.9 Hz), 7.81 (d, 1H, J = 8.9 Hz) ppm. ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 18.3, 20.7, 34.5, 48.3, 108.8, 109.0, 110.4, 114.4,

114.9, 117.0, 122.1, 125.5, 126.6, 127.6, 131.0, 131.6, 135.1, 138.7, 153.2, 157.4, 158.1, 174.4 ppm. MS (EI): *m*/*z* (%) 344 (100, M^+), 315 (48), 301 (39). Anal. Calcd for $C_{22}H_{16}O_4$: C, 76.73; H, 4.68; Found: C, 76.46; H, 4.75. The rest of new compounds prepared were also characterized by spectroscopic methods, and gave the correct elemental analyses.

3. X-Ray crystal data for (+)-**3**: $C_{22}H_{16}O_4$: colorless block crystals（0.25×0.29×0.14 mm）. $M = 344.37$, orthorhombic, $a = 11.8647(8)$, $b = 17.973(2)$, $c = 36.990(6)$ Å, $V = 7888(2)$ Å^3, $Z = 16$, space group: $C222_1$ $\rho_{calc} = 1.161$ g cm^{-3}. Data were collected at 294 K, ENRAF-NONIUS CAD4 FR586 diffractometer, Cu *Ka* radiation $\lambda = 1.54184$ Å, ω-2θ motion, $\theta_{max} = 75°$, 8604 reflections were measured, of which 2742 reflections were unique with $|F_0| > 3\sigma(|F_0|)$ decay: 5.024%. The structure was solved using the SIR-88 software, *R*(F) = 0.08532 and *Rw* (F) = 0.11726 for 2736 reflections, 490 parameters. Residual electron density: 0.508/-0.760 eÅ^{-3}.
4. Preparation of (–)-**5**: To (±)-**3** (4.00 g, 11.6 mmol) suspended in methanol (100 mL) was added (*S*)-(–)-PEA (7.50 mL, 57.7 mmol). The mixture was stirred at rt for 6 h, and concentrated under reduced pressure to remove the solvent. The resulting viscous liquid was taken up in ethyl acetate (100 mL), and washed with 1 N HCl and with H_2O. Removal of the solvent gave crude amides, which were mixed with ether (30 mL) and toluene (15 mL) to leave the less soluble (–)-**5** as a white solid. (–)-Amide (**5**) was washed with ether and weighed 1.97 g (73%, de 100%). Recrystallization from toluene gave (–)-**5** as crystallites, mp 214 ℃, $[\alpha]_D^{20}$ –721° (*c* 0.1, 1,4-dioxane). In a similar manner, (±)-**3** and (*R*)-(+)-1-PEA produced (+)-**6**, mp 215 ℃, $[\alpha]_D^{20}$ +719° (*c* 0.1, 1,4-dioxane).
5. Preparation of (–)-**3**: A mixture of recrystallized (–)-**5** (1.00 g, 2.15 mmol), toluene (30 mL), and 1 N HCl (30 mL) was stirred for 5 h under reflux until (–)-**5** was completely dissolved. The toluene phase was separated from the mixture and the aqueous phase was extracted with ethyl acetate (30 mL×2). The combined organic phase was washed with 1 N HCl, H_2O, and dried over $MgSO_4$. Evaporation of the solvent gave crude (–)-**3** as white powders (0.74 g, 100%, ee 100%). Recrystallization from toluene afforded (–)-**3** as colorless plates, mp 210 ℃, $[\alpha]_D^{20}$ –815° (*c* 0.1, 1,4-dioxane), CD ($c = 7.44\times10^{-6}$ M, CH_3CN), λ_{ext} ($\Delta\varepsilon$) 214 (-8), 223 (-2), 248 nm (-32). Similarly

obtained was (+)-**3**, mp 207 °C, $[\alpha]_{D}^{20}$ +816° (*c* 0.1, 1,4-dioxane), CD (*c* = 7.20×10^{-6} M, CH_3CN), λ_{ext} ($\Delta\varepsilon$) 214 (8), 223 (1), 248 nm (36).