Notes

New Synthesis of α,β-Unsaturated γ-Butyrolactones Involving β-Lactam-Induced Ring Closure

Shinzo Kano,* Tsutomu Ebata, Kentaro Funaki, and Shiroshi Shibuya

Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

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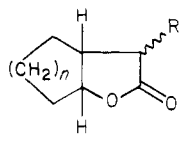
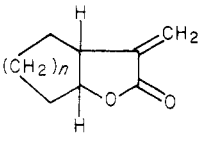
It is well-known that a β-lactam shows high chemical reactivity, and its amide bond is easily cleaved by nucleophiles such as amine and alcohol.[1,2] Therefore, simple monocyclic β-lactams have not only been proposed[1] but also clearly demonstrated by our previous work[2] as a potential synthon of the CO–C–C–N functional group, which can be easily converted to α,β-unsaturated carbonyl compounds.[3] Consideration of this high chemical reactivity led us to investigate a conversion of epoxides of 3-vinylazetidin-2-ones to α-methylene-γ-butyrolactones[4] through α-anilinomethyl-1,2-butenolides as an outgrowth of the previous work.[5] The epoxides **4** were prepared as follows. Condensation of 1-phenyl-β-lactam (**1**)[6] with ketones afforded 3-alkylideneazetidin-2-ones **2**,[5] which were isomerized by treatment with lithium diisopropylamide (LDA) in THF at 0 °C by the method of Snieckus[7] to give the corresponding 3-vinylazetidin-2-ones **3** without recovery of any starting material. In the case of **2g**, two isomers, *E* and *Z* forms, were obtained in a ratio of ca. 1:1. Oxidation of **3** with *m*-chloroperbenzoic acid in CH_2Cl_2 at room temperature for 14 h gave the corresponding epoxides **4** in good yield (Scheme I). The epoxides **4** were effectively converted to the α-anilinomethyl-1,2-butenolides **5** by treatment with CH_3SO_3H–benzene (1:4) under reflux for 1.5 h. These results were summarized in the Table I.

Catalytic hydrogenation of **5d** and **5f** over Adams catalyst in ethanol at 70 °C for 6 h gave 2-(*cis*-2-hydroxycyclohexyl)propanoic acid lactone (**6a**)[8] and 2-(*cis*-2-hydroxycycloheptyl)propanoic acid lactone (**6b**), respectively, in nearly quantitative yield. On the other hand, catalytic hydrogenation of **5d** and **5f** over Raney Ni catalyst[9] in ethanol at 70 °C for 7 h yielded α-anilinomethyl *cis*-fused γ-butyrolactones **7a** and **7b**, respectively. Hofmann degradation of the quaternary methiodide (**9a**) derived from **7a** (**7a** → **8a** → **9a**) with sodium ethoxide in ethanol under reflux gave 2-(*cis*-2-hydroxycyclohexyl)-propenoic acid lactone (**10a**)[10] in 40% yield. In a similar fashion, **7b** was also converted to 2-(*cis*-2-hydroxycycloheptyl)propenoic acid lactone (**10b**)[10] through **8b** and **9b** in 45% yield. These reaction sequences should be widely applicable to a synthesis of a variety of α-methylene-γ-butyrolactones.





6a, $n = 2$, R = CH_3
b, $n = 3$, R = CH_3
7a, $n = 2$, R = $CH_2NHC_6H_5$
b, $n = 3$, R = $CH_2NHC_6H_5$
8a, $n = 2$, R = $CH_2N(CH_3)C_6H_5$
b, $n = 3$, R = $CH_2N(CH_3)C_6H_5$
9a, $n = 2$, R = $CH_2N^+(CH_3)_2C_6H_5\ I^-$
b, $n = 3$, R = $CH_2N^+(CH_3)_2C_6H_5\ I^-$

10a, $n = 2$
10b, $n = 3$

Experimental Section

All reactions were carried out under a nitrogen atmosphere unless otherwise stated. Tetrahydrofuran (THF) was dried and distilled from $LiAlH_4$ before use. Nuclear magnetic resonance spectra were recorded on Varian T-60 and JEOL PS-100 instruments and mass spectra were determined on a Hitachi RMU-7L spectrometer.

General Procedure for Preparation of 3-Alkylidene-1-phenylazetidin-2-one (2). To a stirred solution of 2.2 equiv of LDA (prepared from 1.11 g of diisopropylamine and 7.4 mL of a 1.5 M hexane solution of *n*-BuLi in 20 mL of THF at −78 °C as usual) was added a solution of **1** (735 mg, 5 mmol) in THF (20 mL) at −78 °C. After 5 min, to this solution was added trimethylchlorosilane (555 mg, 5.5 mmol) at the same temperature. After the stirring had been continued for 10 min, a solution of ketones (5 mmol) in THF (10 mL) was added. After 15 min, the solution was poured into a NH_4Cl solution, warmed at 40 °C for 20–30 min, and extracted with $CHCl_3$. The extract was washed with water and dried over Na_2SO_4. Evaporation of the solvent afforded **2a–e**[5] in 90–95% yields.

3-Cycloheptylidene-1-phenylazetidin-2-one (2f): mp 107–108.5 °C (MeOH–ether); ^1H NMR ($CDCl_3$) δ 1.45–1.84 (m, 8 H), 2.18–2.45 (m, 2 H), 2.70–2.95 (m, 2 H), 3.99 (s, 2 H), 6.92–7.46 (m, 5 H); MS *m/e* 241 (M^+). Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.89; H, 7.89; N, 5.77.

α-Ethyl-3-benzylidene-1-phenylazetidin-2-one (2g): mp 105–107 °C (ether–hexane); ^1H NMR ($CDCl_3$) δ 1.1 (t, J = 7.5 Hz, 3 H), 3.07 (q, J = 7 Hz, 2 H), 4.16 (s, 2 H), 6.88–7.48 (m, 10 H); MS *m/e* 263 (M^+). Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.94; H, 6.44; N, 5.11.

General Procedure for Preparation of 1-Phenyl-3-vinylazetidin-2-ones (3). To a stirred solution of 1.1 equiv of LDA (prepared from 1.11 g of diisopropylamine and 7.4 mL of a 1.5 M hexane solution of *n*-BuLi in THF at 0 °C) was added 10.0 mmol of **2**. After the stirring had been continued for 15 min at 0 °C, the solution was quenched with *t*-BuOH at −78 °C and extracted with $CHCl_3$. The extract was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave **3** as an oil in 80–85% yield.

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(2) S. Kano, T. Ebata, Y. Denta, S. Hibino, and S. Shibuya, *Heterocycles*, 8, 411 (1977).
(3) (a) F. F. Blicke, *Org. React.*, 1, 303 (1942); (b) A. D. Hammon and C. R. Hutchinson, *Tetrahedron Lett.*, 1293 (1973); (c) C. R. Hutchinson, *J. Org. Chem.*, **39**, 1854 (1974); (d) J. C. Jain, C. M. Banks, and J. E. McCloskey, *Tetrahedron*, **32**, 765 (1976).
(4) (a) P. A. Grieco, *Synthesis*, 67 (1975), and references cited therein; (b) T. F. Murray, V. Verma, and J. R. Norton, *J. Chem. Soc., Chem. Commun.*, 907 (1976); (c) S. F. Martin and D. R. Moore, *Tetrahedron Lett.*, 4459 (1976); (d) R. C. Larock and B. Riefling, *ibid.*, 4661 (1976); (e) R. M. Carlson and A. R. Oyler, *J. Org. Chem.*, **41**, 4065 (1976).
(5) S. Kano, T. Ebata, K. Funaki, and S. Shibuya, *Synthesis*, 756 (1978).
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(7) J. A. Oakeaf, M. T. Homas, A. Wu, and V. Snieckus, *Tetrahedron Lett.*, 1645 (1978).
(8) A. E. Greene, J.-C. Muller, and G. Ourisson, *J. Org. Chem.*, **39**, 186 (1974).
(9) The use of freshly activated catalyst is recommended.
(10) J. A. Marshall and N. Cohen, *J. Org. Chem.*, **30**, 3475 (1965). The stereochemistry of the products (**10a** and **10b**) was determined by comparison of their spectral data with those in the literature, and trans-fused isomers were excluded by this method: J. A. Marshall and N. Cohen, *Tetrahedron Lett.*, 1997 (1964).

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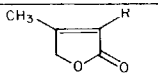
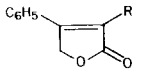
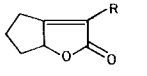
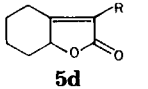
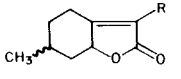
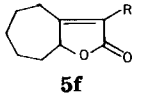
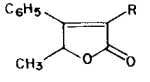
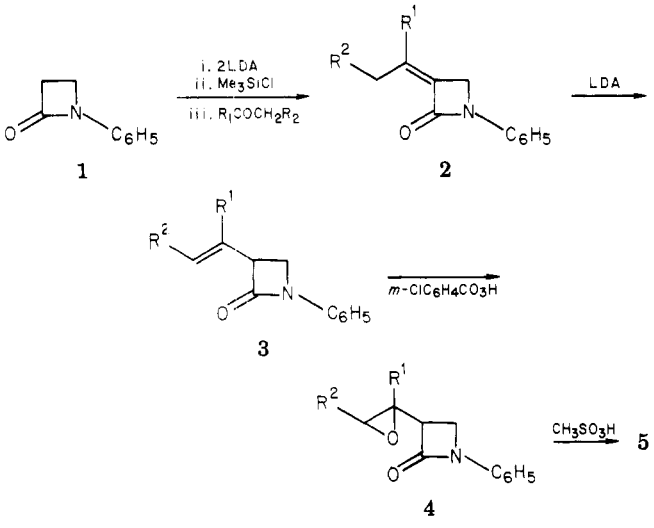
Table I. Preparation of α-Anilinomethyl-1,2-butenolides through Ring Closure of Epoxy-β-lactams (4) of 3-Vinyl-β-lactams (3)

3-alkylidene compd	3-vinyl-β-lactam[a] compd	yield, %	^{1}H NMR,[e,f] δ	epoxy-β-lactam[b] compd	yield, %	mp, °C	*m/e* M$^+$	α-aninilimethyl-1,2-butenolide (R=-$CH_2NHC_6H_5$)[b,c] compd	mp, °C	yield, %	IR,[g] cm^{-1}	*m/e* M$^+$	^{1}H NMR,[e] δ
2a	3a	80	4.97 (m, 1 H)	4a	90	70–72[c]	203	 5a	113–115	65	1730	203	2.11 (s, 3 H), 4.00 (s, 2 H), 4.62 (s, 2 H), 6.52–7.31 (m, 5 H)
2b	3b	85	5.55 (m, 2 H)	4b	80	93–95[d]	265	 5b	130–132	70	1730	265	4.18 (s, 2 H), 5.03 (s, 2 H), 6.40–7.48 (m, 10 H)
2c	3c	80	5.68 (m, 1 H)	4c	95	71–73[d]	229	 5c	oil	25	1735	229	1.70–2.60 (m, 6 H), 4.04 (s, 2 H), 6.68 (m, 1 H), 6.55–7.42 (m, 5 H)
2d	3d	80	5.75 (m, 1 H)	4d	95	115–117[d]	243	 5d	61–63	75	1735	243	0.95–3.75 (m, 8 H), 3.99 (s, 2 H), 4.40 (m, 1 H), 6.50–7.33 (m, 5 H)
2e	3e	80	5.70	4e	95	116–118[d]	257	 5e	77–79	78	1720	257	0.96 (d, *J* = 6.5 Hz, 3 H), 0.83–3.73 (m, 7 H), 3.97 (s, 2 H), 4.53 (m, 1 H), 6.48–7.30 (m, 5 H)
2f	3f	82	5.89 (m, 1 H)	4f	93	109–111[d]	257	 5f	98–100	75	1720	257	1.20–2.85 (m, 10 H), 3.98 (s, 2 H), 4.83 (m, 1 H), 6.63–7.32 (m, 5 H)
2g	3g	80	4.12 (q, 0.5 H), 4.57 (q, 0.5 H)	4g	75	oil	279	 5g	91–92	45	1730	279	1.44 (d, *J* = 6.5 Hz, 3 H), 4.11 (s, 2 H), 5.34 (q, *J* = 6.5 Hz, 1 H), 6.32–7.57 (m, 10 H)

[a] Satisfactory mass spectral data were obtained. [b] Satisfactory analytical data were obtained for all compounds. [c] Recrystallized from ether–hexane. [d] Recrystallized from methanol–ether. [e] The solvent was $CDCl_3$. [f] Olefinic H. [g] ν(C=O) vibration; solvent was $CHCl_3$.

Scheme I



a, $R^1 = CH_3$, $R^2 = H$; b, $R^1 = C_6H_5$, $R^2 = H$; c, R^1, $R^2 = (CH_2)_3$; d, R^1, $R^2 = (CH_2)_4$; e, R^1, $R^2 = (CH_2)_2CH(CH_3)CH_2$; f, R^1, $R^2 = (CH_2)_5$; g, $R^1 = C_6H_5$, $R^2 = CH_3$

Oxidation of 3 with *m*-Chloroperbenzoic Acid. To a solution of **3** (10 mmol) in CH_2Cl_2 (30 mL) was added *m*-chloroperbenzoic acid (1.90 g, 11 mmol), and the mixture was allowed to stir at room temperature for 14 h. The mixture was washed with 5% $NaHCO_3$ solution and water and was dried over Na_2SO_4. Evaporation of the solvent left the corresponding epoxides **4** which gave the specific melting points shown in Table I except for **4g** (oil).

General Procedure for Preparation of α-Anilinomethyl-1,2-butenolides (5). A mixture of CH_3SO_3H (1 mL), benzene (4 mL), and **4** (1 mmol) was heated for 1.5 h under reflux. The mixture was made basic with 28% NH_4OH and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated to leave **5**. The results are summarized in Table I.

2-(*cis*-2-Hydroxycyclohexyl)propanoic Acid Lactone (6a). A mixture of **5d** (486 mg, 2 mmol), EtOH (25 mL), and prereduced Pt catalyst (300 mg) was shaken under atmospheric pressure of H_2 at 70 °C for 6 h. After removal of the catalyst, the solvent was evaporated. A solution of the resulting residue in benzene (60 mL) was washed with 5% HCl and water and was dried over Na_2SO_4. Evaporation of the solvent gave **6a** (290 mg, 94%), which was identified by comparison of spectral data with those of an authentic specimen.[8]

2-(*cis*-2-Hydroxycycloheptyl)propanoic Acid Lactone (6b). A sample of **5f** (514 mg, 2 mmol) was reduced in the presence of prereduced Pt catalyst (300 mg) as above. The mixture was worked up as above to yield **6b** (309 mg, 92%) as an oil: ^1H NMR ($CDCl_3$) δ 1.16 (d, J = 7.5 Hz, 3 H), 1.15–2.98 (m, 12 H), 4.41–4.80 (m, 1 H); MS m/e 168 (M^+), 166 ($M^+ - 2$), 166.100 65 (calcd for $C_{10}H_{14}O_2$, 166.099 394); IR ($CHCl_3$) ν(C=O) 1715 cm^{-1}.

Reduction of 5d with Raney Ni. A mixture of **5d** (486 mg, 2 mmol), EtOH (35 mL), and Raney Ni catalyst (6 mL) was shaken under atmospheric pressure of H_2 at 70 °C for 6 h. After removal of the catalyst, the solvent was evaporated, and the resulting solid was recrystallized from ether–hexane to give **7a** (460 mg, 95%): mp 94–96.5 °C; ^1H NMR ($CDCl_3$) δ 1.04–1.89 (m, 4 H), 2.15–2.58 (m, 5 H), 3.00 (m, 1 H), 3.38 (d, J = 6 Hz, 1 H), 3.45 (d, J = 6 Hz, 1 H), 4.44 (m, 1 H), 6.59–7.29 (m, 5 H); MS m/e 245 (M^+). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.50; H, 7.72; N, 5.53.

Reduction of 5f with Raney Ni. A mixture of **5f** (514 mg, 2 mmol), EtOH (40 mL), and Raney Ni catalyst (7 mL) was shaken under atmospheric pressure of H_2 and worked up as above to give **7b** (502 mg, 80%): MS m/e 259 (M^+); ^1H NMR ($CDCl_3$) 1.14–2.85 (m, 11 H), 3.00 (m, 1 H), 3.37 (d, J = 8 Hz, 2 H), 4.62 (m, 1 H), 6.70–7.26 (m, 5 H). Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.28; H, 8.33; N, 5.21.

2-(*cis*-2-Hydroxycyclohexyl)propenoic Acid Lactone (10d). A mixture of **7a** (500 mg, 2.06 mmol), methyl iodide (2 mL), and MeOH (10 mL) was heated for 5 h under reflux. The solvent was evaporated, and the resulting residue was made basic with 28% NH_4OH and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated to leave **8a** (470 mg, 88%); this was further methylated, without purification, with methyl iodide (2 mL) in MeOH under reflux for 5 h. The solvent was evaporated, and the remaining residue was heated in EtOH (10 mL) in the presence of EtONa (150 mg) under reflux for 2 h. The solvent was evaporated, and the resulting residue was extracted with benzene. The extract was washed with 5% HCl (20 mL) and water and dried over Na_2SO_4. Removal of the solvent afforded **10a** (125 mg, 40%), the spectral data of which were identical with those of the authentic specimen.[10]

2-(*cis*-2-Hydroxycycloheptyl)propenoic Acid Lactone (10b). A mixture of **7b** (500 mg, 1.9 mmol), methyl iodide (2 mL), and MeOH (10 mL) was heated and worked up as above to yield **8b** (415 mg, 85%); this was further methylated with methyl iodide (2 mL) in MeOH (10 mL) as above. The remaining residue, obtained on evaporation of the solvent, was heated with EtONa (150 mg) in EtOH (10 mL) for 2 h. The solvent was evaporated, and the resulting residue was extracted with benzene. The extract was washed with 5% HCl and water and dried over Na_2SO_4. Removal of the solvent yielded **10b** (141 mg, 45%), the spectroscopic data of which were identical with those of the authentic specimen:[10] MS m/e 166.098 371 (M^+) (calcd for $C_{10}H_{14}O_2$) m/e 166.099 364).

Registry No. 1, 5099-95-6; **2a**, 68695-52-3; **2b**, 68695-57-8; **2c**, 68695-53-4; **2d**, 68695-54-5; **2e**, 68695-55-6; **2f**, 71250-55-0; **2g**, 71250-56-1; **3a**, 71250-57-2; **3b**, 71250-58-3; **3c**, 71250-59-4; **3d**, 71250-60-7; **3e**, 71250-61-8; **3f**, 71250-62-9; (*E*)-**3g**, 71250-63-0; (*Z*)-**3g**, 71250-64-1; **4a**, 71250-65-2; **4b**, 71250-66-3; **4c**, 71250-67-4; **4d**, 71250-68-5; **4e**, 71250-69-6; **4f**, 71250-70-9; **4g**, 71250-71-0; **5a**, 71250-72-1; **5b**, 71250-73-2; **5c**, 71250-74-3; **5d**, 71250-75-4; **5e**, 71250-76-5; **5f**, 71250-77-6; **5g**, 71250-78-7; **6a**, 2205-25-6; **6b**, 33366-33-5; **7a**, 71250-79-8; **7b**, 71250-80-1; **8a**, 71250-81-2; **8b**, 71250-82-3; **10a**, 16822-06-3; **10b**, 3725-04-0; methyl iodide, 74-88-4; propanone, 67-64-1; acetylbenzene, 98-86-2; cyclopentanone, 120-92-3; cyclohexanone, 108-94-1; 4-methylcyclohexanone, 589-92-4; cycloheptanone, 502-42-1; 1-phenylpropanone, 93-55-0.

Synthesis of Isotubaic Acid (Rotenic Acid)

Günes Batu and Robert Stevenson*

Department of Chemistry, Brandeis University, Waltham, Massachusetts 02254

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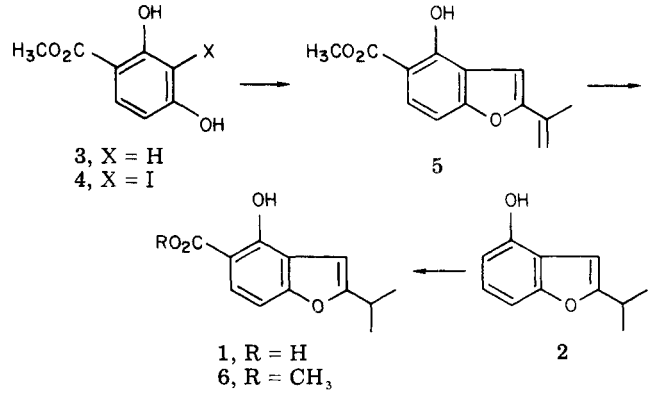
Isotubaic acid (rotenic acid) was first obtained from the natural insecticide rotenone as a significant degradation product. Extensive investigations, which have been reviewed,[1] led to proposed structure 1. By an unusual



(1) F. B. LaForge, H. L. Haller, and L. E. Smith, *Chem. Rev.*, 12, 181 (1933).

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