Iodolactamization of γ,δ-Unsaturated Oxazolines

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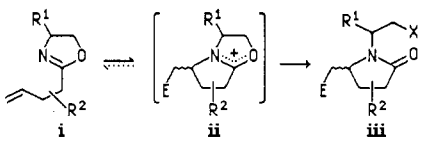
The iodolactamization of a series of γ,δ-unsaturated oxazolines has been studied (i → iii). The data presented establish that the resulting hydroxy iodo lactams are produced in high yield and regioselectively. No asymmetric induction is observed with substituents on the oxazoline ring or at the homoallylic position; however, moderate to high 1,2-asymmetric induction can be obtained with a substituent at the allylic position. Most importantly, these results establish that the iodolactamization of γ,δ-unsaturated oxazolines is a kinetically controlled process proceeding via the intermediacy of ii.

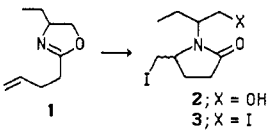
Electrophilic olefin cyclizations that form carbon heteroatom bonds are an efficient method of constructing heterocycles.[2] For example, iodolactonization of γ,δ-unsaturated carboxylic acids has been shown to be both a regio- and stereoselective process. Chamberlin[3] has reported an allylic hydroxyl-directed kinetic iodolactonization, and Yoshida[4] has reported an *N,N*-dimethylamide A(1,3) strain-directed kinetic iodolactonization. We have also reported that a C_3,C_4-dialkyl substitution pattern functions as a third type of diastereoface control element in kinetic iodolactonizations.[5] In contrast to iodolactonization, halolactamization has only recently been investigated and the control elements operative in these cyclizations are relatively less understood.[6] Herein we report the details of our investigation of the iodolactamization of γ,δ-unsaturated oxazolines.

At the outset, there was one report of an analogous cyclization employing phenylselenium bromide as electrophile in the cyclization of 2-(1,1-dimethylbut-3-enyl)-oxazoline.[7] While this work established the feasibility of i → iii, it left unaddressed those issues related to stereocontrol in this transformation, particularly substituent effects on the stereochemical outcome of the cyclization.



i ii iii

Our initial investigation was designed to probe the effects of a C_4-oxazoline substituent on the stereochemical outcome of cyclization i → iii. Treatment of oxazoline **1** with iodine/THF/aq $NaHCO_3$ resulted in cyclization to **2** as a 1:1 mixture of diastereomers. While this complete lack of face selectivity was disappointing, it was not entirely unexpected on the basis of Dreiding model analysis; nonetheless, two points are worth noting in regard to cyclization **1** → **2**. First, the cyclization is both highly efficient and highly regioselective, giving only five-membered ring products in 89% yield. Second, in contrast to phenylselenolactamization[7] in which the intermediate oxazolinium salt undergoes attack by bromide at C_5 (oxazoline numbering) giving lactam iii where E = SePh and X = Br, iodolactamization of **1** results in hydrolysis of the intermediate oxazolinium salt (cf., ii). It is interesting to note that iodolactamization of **1** with iodine in anhydrous THF followed by room-temperature quench with aqueous Na_2SO_3 also gave only **2**. Assuming that solvolysis of a primary iodide would not occur under these mild conditions, this result suggests that the intermediate oxazolinium salt (cf., ii) is stable to iodide and that **3** is not an intermediate in **1** → **2**.



1 **2**; X = OH **3**; X = I

The two diastereomers of **2** were easily separated by radial chromatography and one was crystalline. Recrystallization of this diastereomer from cyclohexane gave crystals suitable for X-ray analysis,[8] thus confirming the structure of **2**.

We next turned our attention to examining the effect of substituents placed on the chain connecting the two reactive sites. Oxazoline **4**, readily obtained by alkylation of the anion derived from 4,5-dihydro-4,4-dimethyl-2-ethyloxazoline[9] with allyl bromide, reacted with iodine at 25 °C in a two-phase THF/aq $NaHCO_3$ reaction mixture to give a 1:1 mixture of the hydroxy iodo lactams **5** and **6** (see Table I). In light of the conformational flexibility of five-membered transition states, this lack of relative asymmetric induction was not surprising for a system with a homoallylic stereocenter and is indeed closely paralleled in iodolactonizations requiring 1,3-asymmetric induction.[10] It is interesting to note that the yield for this cyclization (91%) is excellent in spite of the neopentyl nature of the nitrogen nucleophile.

Very moderate 1,2-asymmetric induction was observed when the methyl substituent was moved to the allylic position. Treatment of **7** with iodine/THF/aq $NaHCO_3$ gave a 2:1 mixture of hydroxy iodo lactams **8** and **9** (see

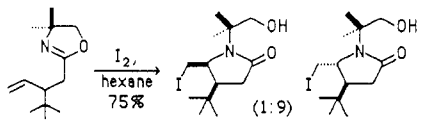
(1) Recipient of an Alfred P. Sloan Research Fellowship, 1987-1989.
(2) Bartlett, P. A. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; Vol. 3, Part B, p 411.
(3) Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819-5825.
(4) Tamaru, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.; Yoshida, Z.; Yanagi, K.; Minobe, M. *J. Am. Chem. Soc.* **1984**, *106*, 1079-1085.
(5) Kurth, M. J.; Brown, E. G. *J. Am. Chem. Soc.* **1987**, *109*, 6844-6845.
(6) (a) Biloski, A. J.; Wood, R. D.; Ganem, B. *J. Am. Chem. Soc.* **1982**, *104*, 3233-3235. (b) Rajendra, G.; Miller, M. J. *Tetrahedron Lett.* **1985**, *26*, 5385-5388. (c) Knapp, S.; Rodriques, K. E.; Levorse, A. T.; Ornaf, R. M. *Tetrahedron Lett.* **1985**, *26*, 1803-1806. (d) Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Heterocycles* **1987**, *26*, 359-360. (e) Takahata, H.; Takamatsu, T.; Mozumi, M.; Chen, Y-S.; Yamazaki, T.; Aoe, K. *J. Chem. Soc., Chem. Commun.* **1987**, 1627-1629.
(7) Toshimitsu, A.; Terao, K.; Uemura, S. *J. Chem. Soc., Chem. Commun.* **1986**, 530-531. During the course of our investigation, a full account of phenylselenolactamization was published: Toshimitsu, A.; Terao, K.; Uemura, S. *J. Org. Chem.* **1987**, *52*, 2018-2026.
(8) Olmstead, M. M.; Kurth, M. J.; Bloom, S. H. *Acta Crystallogr.*, in press.
(9) Meyers, A. I.; Temple, D. L.; Nolen, R. L.; Mihelich, E. D. *J. Org. Chem.* **1974**, *39*, 2778-2783.
(10) Gunther, H. J.; Guntrum, E.; Jager, V. *Liebigs Ann. Chem.* **1984**, 15-30. For exceptions, see ref 4 and 6e.

0022-3263/89/1954-0411$01.50/0

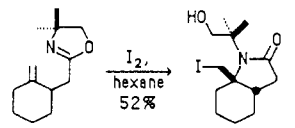
Table I). The diastereomeric ratio was determined by examining the ^1H NMR of the crude reaction mixture and the two diastereomers were easily separated by radial chromatography. The relative stereochemistry in **8** and **9** was established on the basis of NOESY NMR spectroscopy[11] and ^{13}C NMR data that showed an upfield shift of the iodomethyl resonance in *cis*-**8** relative to *trans*-**9**, a manifestation of steric compression.[12] The formation of a 2:1 ratio of *cis*-**8** to *trans*-**9** suggests, in parallel with iodolactonization, that iodolactamization of **7** represents a kinetic process.

In contrast to a kinetic process, we would anticipate an approximately 1:10 ratio of diastereomers for a thermodynamic process.[13] Therefore, to increase the diastereomer ratio of **8** and **9**, a number of cyclization conditions were explored in an attempt to effect the cyclization under "thermodynamic" conditions, that is, reaction conditions which would result in reversible formation of the proposed oxazolinium intermediate (i.e., ii) and thus selective formation of *trans*-**9**. These studies, which are summarized in Table I, indicate that under all conditions cyclization to the intermediate oxazolinium salt is apparently not reversible and the hydroxy lactam products are thus formed under kinetic control. Interestingly, treatment of an analogous γ,δ-unsaturated *N,O*-bis(trimethylsilyl)-imidate with iodine in THF has been observed to give a 1:11 ratio of cis and trans iodo lactam products, respectively.[6c]

In certain instances, the fact that i → ii is a kinetically controlled cyclization can be exploited to our advantage. For example, a bulky allylic substituent should significantly increase the olefin facial selectivity in the cyclization. Indeed, *tert*-butyl analogue **10** underwent very selective lactamization, giving a 1:9 mixture of **11** and **12**, respectively. That **12** was the major product was established by both ^{13}C and NOESY NMR spectroscopy.[14] It is interesting to note that the reaction **7** → **8**/**9** favors the cis product while **10** → **11**/**12** favors the trans product; however, the exact reason for this reversal is unclear. In another case, the cyclization of oxazoline **13** is highly stereoselective and gave only cis-fused hydroxy lactam **14** as evidenced both by HPLC and ^{13}C NMR.



10 **11** **12**



13 **14**

In summary, this study demonstrates that treatment of γ,δ-unsaturated oxazolines with iodine results in the regioselective formation of hydroxy iodo lactams in good yields and by a kinetically controlled process. Although no asymmetric induction is observed for substituents on the oxazoline ring or in the homoallylic position, moderate to high 1,2-asymmetric induction can be obtained with a substituent at the allylic position.

Experimental Section

General. Infrared spectra were determined on a IBM FTIR-32 spectrometer with an IBM 9000 data system. ^1H and ^{13}C NMR spectra were determined on a GE QE-300 spectrometer and are reported in ppm (δ) relative to internal Me_4Si (^1H at 300 MHz and ^{13}C at 75 MHz). Mass spectra were determined on a Dupont 21-492 B instrument (electron impact, EI) through the Facility for Advanced Instrumentation, University of California, Davis. Flash chromatography was performed on silica gel (Merck 60, 230–400 mesh). Radial chromatography was performed on silica gel (Merck 60, 230–400 mesh). Radial chromatography was performed on a Chromatotron (Harrison Research) with silica gel (EM Reagents 60 PF_{254}). Melting points were determined on a Thomas-Hoover Uni-Melt melting point apparatus and are uncorrected. Elemental analyses were performed by the University of California, Berkeley, analytical laboratories.

General Procedure A: (±)-2-(3-Butenyl)-4,5-dihydro-4-ethyloxazole (1). A solution of 4-pentenoic acid (7.70 g, 76.9 mmol), 2-amino-1-butanol (6.60 g, 76.9 mmol), and xylene (200 mL) was heated to reflux for 3 h, whereupon a Dean–Stark trap was fitted and the product water was collected over 36 h. After being cooled to room temperature, the solution was extracted with CH_2Cl_2 (2×) and the combined organics were dried (K_2CO_3) and concentrated. Distillation (55–57 °C/40 Torr) gave **1** (8.82 g, 57.6 mmol, 77%) as a colorless oil [R_f 0.5 (hexane/ethyl acetate = 1:1); IR (film) 3095, 2990, 2910, 1665, 1450, 1375, 1235, 1185, 1075, 1015, 985, 915 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 0.83 (t, J = 7.4 Hz, 3 H), 1.42 (dq, J = 7.0, 6.8 Hz, 1 H), 1.58 (dq, J = 7.4, 6.1 Hz, 1 H), 2.28 (s, 4 H), 3.50 (apt t, J = 4.2, 3.3 Hz, 1 H), 3.75 (apt quintet, J = 7.8, 7.7 Hz, 1 H), 3.88 (apt t, J = 8.9, 6.7 Hz, 1 H), 4.90 (d, J = 10.1 Hz, 1 H), 4.97 (d, J = 17.6 Hz, 1 H), 5.70 (ddd, J = 17.6, 10.1, 7.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 9.6, 27.3, 28.3, 29.9, 67.1, 71.7, 115.2, 136.6, 166.8; exact mass calcd for $C_9H_{15}NO$ (M^+) 153.1154, found, 153.1151].

(±)-4,5-Dihydro-4,4-dimethyl-2-(1-methyl-3-butenyl)oxazole (4). The anion of 4,5-dihydro-4,4-dimethyl-2-ethyloxazole[10] (5.08 g, 40 mmol) was treated with allyl bromide (8.91 g, 100 mmol) according to the procedure reported by Meyers.[15] Distillation (85–88 °C/35 Torr) gave **4** (4.76 g, 28.5 mmol, 71%) as a colorless oil [IR (film) 3079, 2966, 2931, 1685, 1653, 1636, 1457, 1437, 1420, 1370, 1340, 1305, 1257, 1213, 1134, 1044, 1015, 906 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 1.11 (d, J = 6.9 Hz, 3 H), 1.20 (s, 6 H), 2.17 (apt quintet, J = 6.9 Hz, 1 H), 2.35 (apt quintet, J = 6.9 Hz, 1 H), 2.45 (apt quintet, J = 7.0 Hz, 1 H), 3.81 (s, 2 H), 4.98 (d, J = 10.3 Hz, 1 H), 5.0 (d, J = 17.2 Hz, 1 H), 5.7 (ddd, J = 17.2, 10.3, 7.2 Hz, 1 H); exact mass calcd for $C_{10}H_{17}NO$ (M^+) 167.1310, found 167.1310].

(±)-4,5-Dihydro-4,4-dimethyl-2-(2-methyl-3-butenyl)oxazole (7). Following procedure A, a mixture of 3-methyl-4-pentenoic acid[11] (12.0 g, 105 mmol) and 2-amino-2-methylpropan-1-ol (8.91 g, 100 mmol) gave **7** (12.7 g, 7.60 mmol, 76%) as a colorless oil [bp 30–32 °C (2 mmHg); R_f 0.5 (hexane/ethyl acetate = 1:1); IR (film) 3079, 2966, 2931, 1685, 1653, 1636, 1457, 1437, 1420, 1370, 1340, 1305, 1257, 1213, 1134, 1044, 1015, 906 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 1.02 (d, J = 6.7 Hz, 3 H), 1.21 (s, 3 H), 1.22 (s, 3 H), 2.16 (dd, J = 14.2, 7.7 Hz, 1 H), 2.25 (dd, J = 14.2, 7.2 Hz, 1 H), 2.56 (apt quintet, J = 7.1 Hz, 1 H), 3.85 (s, 2 H), 4.91 (d, J = 10.4 Hz, 1 H), 4.97 (d, J = 17.2 Hz, 1 H), 5.70 (ddd, J = 17.2, 10.4, 7.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 19.5, 20.6, 20.9, 34.3, 41.7, 45.5, 48.3, 112.4, 143.3, 170.5; exact mass calcd for $C_{10}H_{17}NO$ (M^+) 167.1310, found, 167.1307].

(±)-3-(1,1-Dimethylethyl)pentenoic Acid. A solution of 4,4-dimethylpentenol[16] (0.240 g, 2.10 mmol), triethyl orthoacetate (5.49 mL, 30.0 mmol), and propanoic acid (3 drops) was treated according to the procedure reported by Johnson.[17] Flash chro-

(11) The NOESY spectrum was recorded on a GE QE-300 spectrometer using a program supplied by the manufacturer. For *cis*-**8**, an NOE was observed between H_4 and H_5 and between CH_2I and the methyl group at C_4.

(12) Levy, G. C.; Lichter, R. L.; Nelson, G. N. *Carbon-13 NMR Spectroscopy*, 2nd. ed.; Wiley: New York, 1980.

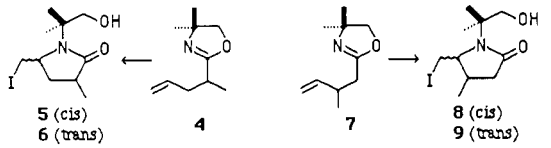
(13) Iodolactonization of 3-methylpentenoic acid under thermodynamic conditions gave a 1:10 (cis:trans) ratio of products, Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc.* **1978**, *100*, 3950–3951.

(14) A strong NOE was observed between H_5 and the *t*-Bu group and between H_4 and CH_2I, but no NOE was observed between the iodomethyl and the *t*-Bu group or between H_4 and H_5. These observations indicate that the major product is *trans*-**12**.

(15) Meyers, A. I. *Pure Appl. Chem.* **1979**, *51*, 1255.

(16) Stahle, M.; Hartmann, J.; Schlosser, M. *Helv. Chim. Acta* **1977**, *60*, 1730–1738.

Table I. Iodolactamization of Oxazolines 4 and 7



ratio 5:6	reactn conds	ratio 8:9
1:1	I_2/THF/aq $NaHCO_3$, 12 h	2:1
1:1	I_2/THF, 25 °C, 12 h	2:1
	I_2/THF, reflux, 12 h	2:1
1.1:1	I_2/CH_3CN, 25 °C, 12 h	1.5:1
	I_2/CH_3CN, reflux, 2 h	1.5:1
1:1	I_2/hexane, 25 °C, 12 h	1:1
	I_2/Et_2O, 25 °C, 12 h	2:1
	I_2/$CHCl_3$, 25 °C, 12 h	2:1

matography (hexane/ethyl acetate = 1:1) gave the desired product (0.272 g, 1.75 mmol, 83%) as a yellow oil [IR (film) 3100, 2990, 2940, 1700, 1440, 1405, 1375, 1295, 990, 915 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 0.9 (s, 9 H), 2.17–2.60 (m, 2 H), 2.57 (dd, J = 13.8, 2.7 Hz, 1 H), 5.01–5.1 (m, 2 H), 5.6–5.8 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 27.4, 32.5, 35.3, 50.8, 117.0, 137.4, 179.5; exact mass calcd for $C_9H_{16}O_2$ (M^+) 156.1150, found 156.1148].

(±)-4,5-Dihydro-4,4-dimethyl-2-[2-(1,1-dimethylethyl)-3-butenyl]oxazole (10). Following procedure A, a mixture of 3-(1,1-dimethylethyl)-4-pentenoic acid (0.624 g, 4.00 mmol) and 2-amino-2-methylpropan-1-ol (0.356 g, 4.00 mmol) gave **10** (0.628 g, 3.00 mmol, 75%) as a colorless oil [R_f 0.54 (hexane/ethyl acetate = 3:1); IR (film) 3076, 2966, 2895, 2871, 1670, 1638, 1478, 1465, 1420, 1366, 1301, 1257, 1213, 1162, 1061, 997 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 0.86 (s, 9 H), 1.19 (s, 3 H), 1.20 (s, 3 H), 2.1–2.5 (m, 3 H), 3.82 (s, 2 H), 4.91–5.1 (m, 2 H), 5.5–5.7 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 27.4, 28.3, 28.5, 28.6, 32.5, 52.2, 66.7, 78.8, 116.5, 13891, 165.4; exact mass calcd for $C_{13}H_{23}NO$ (M^+) 209.178, found, 209.1797].

(±)-4,5-Dihydro-4,4-dimethyl-2-[(2-methylenecyclohexyl)methyl]oxazole (13). Following procedure A, a mixture of 2-methylenecyclohexaneacetic acid[18] (3.01 g, 19.5 mmol) and 2-amino-2-methyl-1-propanol (2.08 g, 23.3 mmol) gave **13** (1.72 g, 8.30 mmol, 43%) as a colorless oil [R_f 0.5 (hexane/ethyl acetate = 1:1); IR (film) 3080, 2965, 2930, 2860, 1660, 1455, 1430, 1360, 1350, 1290, 1250, 1210, 1170, 1090, 995, 975 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 1.15 (s, 6 H), 1.2–2.5 (m, 11 H), 3.78 (s, 2 H), 4.48 (br s, 1 H), 4.55 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 24.4, 28.2, 28.3, 31.3, 33.4, 35.0, 40.1, 66.7, 78.6, 105.4, 151.2, 164.9; exact mass calcd for $C_{13}H_{21}NO$ (M^+) 207.1623, found, 207.1622].

General Procedure B: (±)-*N*-[1-(Hydroxymethyl)propyl]-5-(iodomethyl)-2-pyrrolidone (2). A solution of 2-(3-butenyl)-4,5-dihydro-4-ethyloxazole (0.521 g, 3.40 mmol), THF (3 mL), and saturated aqueous $NaHCO_3$ (15 mL) was cooled to 0 °C, and a solution of iodine (2.59 g, 10.2 mmol) and THF (15 mL) was added dropwise. The solution was allowed to warm to 25 °C. Reaction progress was monitored by TLC. After 12 h, the reaction was quenched by the addition of saturated aqueous sodium sulfite, the organic phase separated, and the aqueous portion extracted with ethyl acetate (3 × 25 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated. Analysis of the crude reaction mixture by ^1H NMR indicated a 1:1 mixture of diastereomers. Radial chromatography (ethyl acetate) gave, in order of elution, (*R**,*S**)-**2** (0.452 g, 1.52 mmol, 45%) as a clear oil [IR (film) 3388, 2965, 2935, 2876, 1666, 1459, 1418, 1368, 1324, 1283, 1253, 1198, 1174, 1107, 1060, 1015, 987, 915, 836, 782, 731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 0.94 (t, J = 7.3 Hz, 3 H), 1.59–2.05 (m, 3 H), 2.2–2.4 (m, 2 H), 2.55–2.68 (m, 1 H), 3.1–3.17 (m, 1 H), 3.2 (dd, J = 10.2, 8.3 Hz, 1 H), 3.43 (dd, J = 10.2, 2.7 Hz, 1 H), 3.55–3.63 (m, 1 H), 3.72–3.83 (m, 2 H). Anal. Calcd for $C_9H_{16}NO$: C, 36.38; H, 5.43; N, 4.71. Found: C, 36.55; H, 5.51; N, 4.69.] and (*R**,*R**)-**2** (0.446 g, 1.50 mmol, 44%) as a white solid [IR (CCl_4) 3388, 2965, 2935, 2876, 1666, 1459, 1418, 1368, 1324, 1283, 1253, 1198, 1174, 1107, 1060, 1015, 987, 915, 836, 782, 731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 0.96 (t, J = 7.3 Hz, 3 H), 1.59–2.68 (m, 6 H), 3.1–3.2 (m, 1 H), 3.24 (dd, J = 10.7, 7.2 Hz, 1 H), 3.40 (dd, J = 10.7, 2.6 Hz, 1 H), 3.64–3.72 (m, 1 H), 3.72–3.83 (m, 2 H), 4.39–4.45 (m, 1 H). Anal. Calcd for $C_9H_{16}NO_2I$: C, 36.38; H, 5.43; N, 4.71. Found: C, 36.44; H, 5.46; N, 4.71.].

(±)-*N*-(1,1-Dimethyl-2-hydroxyethyl)-5-(iodomethyl)-3-methyl-2-pyrrolidone (*cis*-5 and *trans*-6). Following procedure B, 4,5-dihydro-4,4-dimethyl-2-(1-methyl-3-butenyl)oxazole (0.501 g, 3.0 mmol) gave **5** and **6**. Analysis of the crude reaction mixture by ^1H NMR indicated a 1:1 mixture of diastereomers. Flash chromatography gave **5** and **6** (0.851 g, 2.73 mmol, 91%) as a yellow oil, which was an inseparable mixture of diastereomers [IR (film) 3312–3279, 2965, 2876, 1666, 1464, 1371, 1182, 991, 916 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, two component mixture) 1.15 (d, J = 6.7 Hz, 1.5 H), 1.26 (d, J = 6.7 Hz, 1.5 H), 1.3 (s, 6 H), 1.6–2.7 (m, 3 H), 3.09–3.9 (m, 5 H), 4.59 (t, J = 6.5 Hz, 0.5 H), 4.59 (t, J = 6.5 Hz, 0.5 H). Anal. Calcd for $C_{10}H_{18}NO_2I$: C, 36.38; H, 5.43; N, 4.71. Found: C, 36.44; H, 5.46; N, 4.71.].

(±)-*N*-(1,1-Dimethyl-2-hydroxyethyl)-5-(iodomethyl)-4-methyl-2-pyrrolidone (8 and 9). Following procedure B, 4,5-dihydro-4,4-dimethyl-2-(2-methyl-3-butenyl)oxazole (0.167 g, 1.0 mmol) gave **8** and **9**. Analysis of the ^1H NMR of the crude reaction mixture indicated a 2:1 mixture of diastereomers. Radial chromatography (ethyl acetate) gave, in order of elution, **9** (0.0783 g, 0.252 mmol, 25%) as a white solid [mp 85–88 °C; IR ($CHCl_3$) 3400–3200, 3010, 2940, 1664, 1465, 1402, 1350, 1265, 1220, 1170, 1015, 910 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 1.1 (d, J = 7.0 Hz, 3 H), 1.31 (s, 3 H), 1.33 (s, 3 H), 1.84 (apt d, J = 17.3 Hz, 1 H), 2.40 (apt quintet, J = 7.3 Hz, 1 H), 2.75 (dd, J = 17.3, 9.5 Hz, 1 H), 3.04 (apt t, J = 10.3 Hz, 1 H), 3.36 (dd, J = 10.3, 2.2 Hz, 1 H), 3.51 (dd, J = 10.3, 2.2 Hz, 1 H), 3.67 (dd, J = 11.8, 6.5 Hz, 1 H), 3.75 (dd, J = 11.8, 5.9 Hz, 1 H), 4.47 (t, J = 6.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 8.5, 20.9, 23.6, 24.5, 32.1, 38.7, 59.1, 67.4, 70.5, 176.0. Anal. Calcd for $C_{10}H_{18}NO_2I$: C, 36.38; H, 5.43; N, 4.71. Found: C, 36.51; H, 5.57; N, 4.92.] and **8** (0.183 g, 0.588 mmol, 59%) [mp 107–110 °C; IR ($CHCl_3$) 3400–3200, 3010, 2940, 1664, 1465, 1402, 1350, 1265, 1220, 1170, 1015, 910 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 1.26 (d, J = 6.7 Hz, 3 H), 1.33 (s, 3 H), 1.39 (s, 3 H), 2.31 (dd, J = 16.1, 8.1 Hz, 1 H), 2.40 (apt t, J = 16.1, 12.4 Hz, 1 H), 2.6–2.7 (m, 1 H), 3.25 (dd, J = 11.4, 1.6 Hz, 1 H), 3.32 (dd, J = 11.4, 6.3 Hz, 1 H), 3.73 (d, J = 6.5 Hz, 2 H), 3.92 (apt t, J = 6.3 Hz, 1 H), 4.45 (t, J = 6.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 4.3 14.26, 23.9, 24.3, 32.0, 38.6, 59.5, 61.7, 70.4, 176.4. Anal. Calcd for $C_{10}H_{18}NO_2I$: C, 36.38; H, 5.43; N, 4.71. Found: C, 36.38; H, 5.55; N, 4.82.].

(±)-*N*-(1,1-Dimethyl-2-hydroxyethyl)-4-(1,1-dimethylethyl)-5-(iodomethyl)-2-pyrrolidone (*cis*-11 and *trans*-12). Following procedure B, 4,5-dihydro-4,4-dimethyl-2-[2-(1,1-dimethylethyl)-3-butenyl]oxazole (0.440 g, 2.10 mmol) gave **11** and **12**. Analysis of the ^1H NMR of the crude reaction mixture indicated a 1:9 mixture of diastereomers **11** and **12**, respectively. Flash chromatography (hexane/ethyl acetate = 1:1) gave **11** and **12** (0.577 g, 1.58 mmol, 75%) as an inseparable mixture (1:9) of diastereomers. **12**: IR ($CHCl_3$) 3200, 2960, 2870, 1655, 1465, 1370, 1280, 1215, 1175, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 0.88 (s, 9 H, t-Bu), 1.34 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 1.83 (d, J = 9.7 Hz, 1 H, H_3), 2.2 (d, J = 18.3 Hz, 1 H, H_4), 2.69 (apt dd, J = 18.3, 9.7 Hz, 1 H, H_3), 3.17 (dd, J = 10.3, 8.2 Hz, 1 H, CH_2I), 3.38 (dd, J = 10.3, 1.5 Hz, 1 H, CH_2I), 3.60 (dd, J = 11.8, 6.5 Hz, 1 H, CH_2OH), 3.69 (apt d, J = 6.0 Hz, 2 H, CH_2OH), 3.71 (apt d, J = 5.5, 1 H, H_5), 4.63 (t, J = 6.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 12.6, 23.8, 24.1, 26.6, 32.7, 33.6, 47.5, 59.3, 60.8, 70.9, 176.6. Anal. Calcd for $C_{13}H_{24}NO_2I$: C, 44.20; H, 6.85; N, 3.97. Found: C, 44.30; H, 6.57; N, 4.12.

***rel*-(3a*R*,7a*R*)-1-(1,1-Dimethyl-2-hydroxyethyl)-7a-(iodomethyl)octahydro-2-oxo-1*H*-indole (14).** Following procedure B, 4,5-dihydro-4,4-dimethyl-2-[(2-methylenecyclohexyl)methyl]oxazole (0.207 g, 1.00 mmol) gave **14**. Analysis of the ^{13}C NMR and HPLC (5-μm silica column using hexane/ethyl acetate = 1:1) of the crude reaction mixture indicated one diastereomer. Flash chromatography (hexane/ethyl acetate = 1:1) gave **14** (0.183 g, 0.520 mmol, 52%) as a yellow oil: IR ($CHCl_3$) 3200, 2960, 2870, 1655, 1465, 1370, 1280, 1215, 1175, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 1.38 (s, 6 H), 1.4–1.6 (m, 7 H), 1.90 (dt, J = 14.2, 4.0 Hz,

(17) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, J. D.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741–743.

(18) Greehow, E. J. *Chem. Ind. (London)* **1972**, 422.

1 H), 2.23 (dt, J = 15.1, 3.4 Hz, 1 H), 2.33 (d, J = 10.5 Hz, 1 H), 2.4–2.5 (m, 1 H), 3.51 and 3.76 (AB q, J = 11.6 Hz, 2 H), 3.57 and 4.02 (AB q, J = 11.9 Hz, 2 H), 4.75 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 18.0, 20.0, 21.7, 23.4, 24.2, 24.6, 32.7, 34.8, 36.7, 62.3, 68.5, 72.1, 177.9. Anal. Calcd for $C_{13}H_{22}NO_2I$: C, 44.46; H, 6.31; N, 3.99 Found: C, 44.46; H, 6.49; N, 3.87.

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Stereoselective Formation of (Porphinato)aluminum Enolates

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(Porphinato)aluminum enolates ((P)AlOCR^1=CHR^2) were formed by the hydrogen abstraction from a ketone by (porphinato)aluminum diethylamide ((P)AlNEt$_2$), quantitatively. (Porphinato)aluminum enolates were also formed by the conjugate addition of (porphinato)aluminum ethyl ((P)AlEt) or thiolate ((P)AlSR) to an α,β-unsaturated ketone. The NMR spectra of (porphinato)aluminum enolates showed that only one of the geometrical isomers was formed invariably, and the structure was found to be Z form by ^{1}H NMR spectroscopy and by the derivation to the corresponding silyl enol ether. It is of particular interest that the enolate groups exchange between the aluminum porphyrin molecules reversibly, where the Z forms are retained.

The reactions of metalloporphyrins are of interest in relation to a variety of biochemical reactions and biomimetic syntheses. The reactions of the axial ligand bound to the metal covalently, ionically, or by coordination (e.g., oxygen, olefin) are the subjects of particular interest, together with the possible effect of the photoexcitation of the metal–axial ligand bond. In these reactions, specificity in stereochemical aspects is expected because of the reactions taking place on a rigid macrocycle of porphyrin.

Recently, we have made extensive studies on the reactions of aluminum porphyrins and found some interesting catalytic behaviors. Catalytic fixations of carbon dioxide[1,2] and a catalytic reaction taking place on both sides of the porphyrin ring[3] are the examples. More recently, we found a novel catalytic formation of carbon–carbon bond induced by visible light.[4] The reaction is the polymerization of methacrylic esters initiated by (tetraphenylporphinato)aluminum methyl, and the reactive species involved is a (porphinato)aluminum enolate.

In the present paper, we report that the (porphinato)aluminum enolates formed by various routes are invariably in Z form with very high selectivity. Of particular interest is the fact that the intermolecular exchange of the enolate group on aluminum porphyrin takes place, in which the selectivity in geometrical isomerism is also retained. This is the first example with evidence as to the exchange of enolates groups on metal.

Results and Discussion

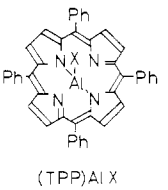
1. Formation of (Porphinato)aluminum Enolate. (Porphinato)aluminum enolates can be formed either by the hydrogen abstraction from a ketone by (porphinato)aluminum diethylamide or by the conjugate addition of (porphinato)aluminum ethyl or thiolate to an α,β-unsaturated ketone.

$$(P)AlNEt_2 + R^1COCH_2R^2 \xrightarrow{-HNEt_2} (P)AlOCR^1{=}CHR^2 \quad (1)$$

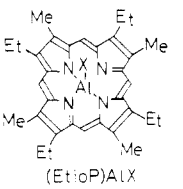
$$(P)AlX + R^1COCH{=}CH_2 \rightarrow (P)AlOCR^1{=}CHCH_2X \quad (2)$$

$$X = Et,SR$$

Formation of (Porphinato)aluminum Enolates by the Reaction of (Porphinato)aluminum Diethylamide with Ketone. First, (tetraphenylporphinato)aluminum diethylamide ((TPP)AlNEt$_2$, **2**) was formed by the equimolar reaction of (tetraphenylporphinato)aluminum chloride ((TPP)AlCl, **1**) and lithium diethylamide (eq 3).



(TPP)AlX



(Et$_8$oP)AlX

$$\underset{\mathbf{1}}{(TPP)AlCl} + LiNEt_2 \xrightarrow{-LiCl} \underset{\mathbf{2}}{(TPP)AlNEt_2} \quad (3)$$

The formation of (TPP)AlNEt$_2$ (**2**) was confirmed by the ^{1}H NMR spectrum of the reaction mixture in C_6D_6. In the high magnetic field, a signal of CH_2 (δ −1.32, q) and a signal of CH_3 (δ −1.38, t) of the NEt$_2$ group appeared. These characteristic signals at unusually high magnetic field region are due to the strong shielding effect of the porphyrin ring.[5] The upfield shifts of the signals of NEt$_2$ group from those of Et$_2$AlNEt$_2$ are 4.3 ppm for CH_2 and

(1) Aida, T.; Inoue, S. *J. Am. Chem. Soc.* **1983**, *105*, 1304.
(2) Kojima, F.; Aida, T.; Inoue, S. *J. Am. Chem. Soc.* **1986**, *108*, 391.
(3) Aida, T.; Inoue, S. *J. Am. Chem. Soc.* **1985**, *107*, 1358.
(4) Kuroki, M.; Aida, T.; Inoue, S. *J. Am. Chem. Soc.* **1987**, *109*, 4737.
(5) Scheer, H.; Kats, J. J. In *Porphyrins and Metalloporphyrins*; Smith, K. M., Ed.; Elsevier: New York, 1975; pp 399–524.

0022-3263/89/1954-0414$01.50/0