of ketone **5** and hydroxylamine. Anal. Calcd for $C_{13}H_8Cl_2INO$: C, 39.83; H, 2.06; Cl, 18.09; I, 32.37; N, 3.57. Found: C, 39.78; H, 2.08; Cl, 18.39; I, 32.58; N, 3.35.

2,3'-Dichlorobenzophenone (*Z*)-Oxime (26). This compound was obtained in the attempt to couple iodo oxime **25** with propargyl alcohol. The coupling experiment was carried out in the manner and on the scale described for the preparation of compound **24**. The crude product was a light brown solid: mp 100–112 °C; 1.1 g (81%). A sample recrystallized from toluene/petroleum ether with charcoal treatment gave colorless crystals: mp 111–113 °C; IR ($CHCl_3$) 3600, 3300, 1595, 1565 cm^{-1}; mass spectrum, *m/e* 265 (M^+); ^1H NMR ($CDCl_3$) 7.2–7.6 (m, aromatic H), 9.1 (br s, OH). Anal. Calcd for $C_{13}H_9Cl_2NO$: C, 58.67; H, 3.41; Cl, 26.64; N, 5.16. Found: C, 58.86; H, 3.40; Cl, 26.82; N, 5.28.

Acknowledgment. We are grateful to Dr. Eugene Trybulski for many helpful discussions and for reference samples.

Registry No. **4**, 76988-39-1; **5**, 76049-50-8; **6**, 51957-32-5; **7**, 16357-68-9; **14**, 36056-90-3; **15**, 636-26-0; **16**, 17758-52-0; **17**, 87999-60-8; **18**, 87999-62-0; **19**, 3096-47-7; **20**, 87999-61-9; **21**, 87999-63-1; **22**, 87999-64-2; (*Z*)-**23**, 87999-65-3; **24**, 87999-66-4; (*E*)-**25**, 87999-68-6; (*Z*)-**26**, 87999-69-7; (*Z*)-**27**, 24048-12-2; (*E*)-**27**, 34609-76-2; **28**, 87999-67-5; $Ni(COD)_2$, 1295-35-8; 2-amino-2',5-dichlorobenzophenone, 2958-36-3; ethyl 2-bromopropionate, 535-11-5; triethyl orthoformate, 122-51-0; thiourea, 62-56-6; propargyl alcohol, 107-19-7; cuprous iodide, 7681-65-4; bis(triphenylphosphine)palladium(II) chloride, 13965-03-2.

Efficient Synthesis of Pyrrolizidine and Indolizidine Alkaloids Utilizing Anodically Prepared α-Methoxy Carbamates as Key Intermediates[1]

Tatsuya Shono,* Yoshihiro Matsumura, Kenshi Uchida, Kenji Tsubata, and Atsushi Makino

Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Yoshida, Sakyo, Kyoto 606, Japan

Received July 21, 1983

Pyrrolizidine and indolizidine skeletons were constructed effectively by 1,2-annulation on a pyrrolidine ring by utilizing anodically prepared 1-(alkoxycarbonyl)-2-methoxypyrrolidines as key intermediates. *Elaeocarpus* alkaloids (±)-elaeokanine A and (±)-elaeokanine C were synthesized in five steps from 1-(methoxycarbonyl)-2-methoxypyrrolidine, and also the synthesis of necins of *Senecio* alkaloids (±)-trachelanthamidine and (±)-isoretronecanol was achieved in six steps from 1-(benzyloxycarbonyl)-2-methoxypyrrolidine.

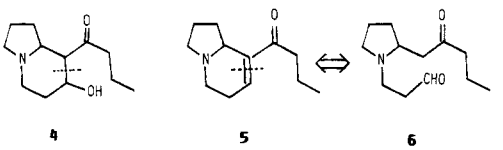
The alkaloids containing a pyrrolizidine **1** or an indolizidine **2** skeleton have been widely found in plants and hence attracted much attention as the targets of organic synthesis.[2]

1 **2**

Although a variety of synthetic methods[3] for constructing such skeletons have been exploited so far, it is worthwhile to exploit new methods starting from easily accessible compounds.

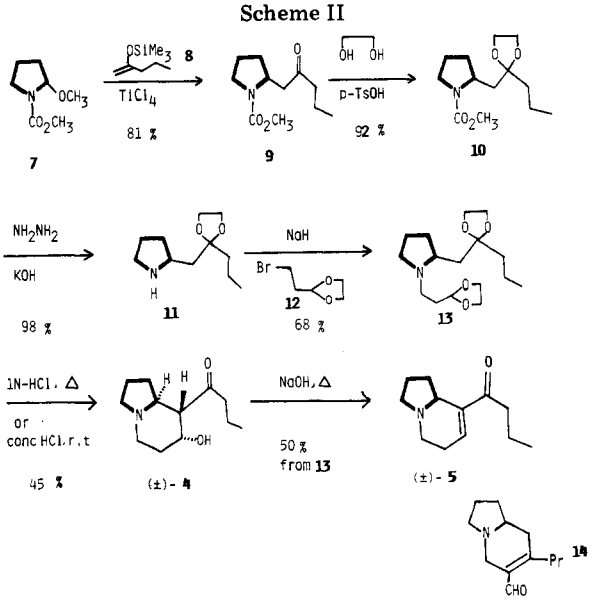
Since we have already found versatile methods of carbon–carbon bond formation[4,5] at the α-position of pyrrolidine utilizing anodically α-methoxylated *N*-(methoxycarbonyl)pyrrolidine[7] as the key starting compound, we have successfully applied these methods to the synthesis of skeletons **1** and **2** as exemplified in the present study by the synthesis of *Elaeocarpus* alkaloids (±)-elaeokanine A and (±)-elaeokanine C and the necins of *Senecio* alka-

Scheme I



4 **5** **6**

Scheme II



(1) Electroorganic Chemistry. 79.

(2) (a) Leonard, N. J. "The Alkaloids"; Manske, R. H. F., Ed; Academic Press: New York, 1960; Vol. VI, p 35. (b) Warren, F. L. *Ibid.*, 1970, Vol. XII, p 245. (c) Johns, S. R.; Lamberton, J. A. *Ibid.*, 1973, Vol. XIV, p 325. (d) Hart, N. K.; Johns, S. R.; Lamberton, J. A. *Aust. J. Chem.* **1972**, *25*, 817.

(3) For example, see: (a) Stevens, R. V. "The Total Synthesis of Natural Products"; ApSimon, J., Ed; Wiley: New York, 1977; Vol. 3, p 439. (b) Robins, D. J. "Advances in Heterocyclic Chemistry"; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1979; Vol. 24, p 247. (c) Khatri, N. A.; Schmitthenner, H. F.; Shringarpure, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 6387. (d) Howard, A. S.; Gerrans, G. C.; Meerholz, C. A. *Tetrahedron Lett.* **1980**, *21*, 1373. (e) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396. (f) Stevens, R. V. *Ibid.* **1977**, *10*, 193. (g) Wijnberg, B. P.; Speckamp, W. N. *Tetrahedron Lett.* **1981**, *22*, 5079. (h) Ban, Y. *J. Synth. Org. Chem. Jpn.* **1982**, *40*, 866. (i) Macdonald, T. L.; Narayanan, B. *J. Org. Chem.* **1983**, *48*, 1129.

(4) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172.

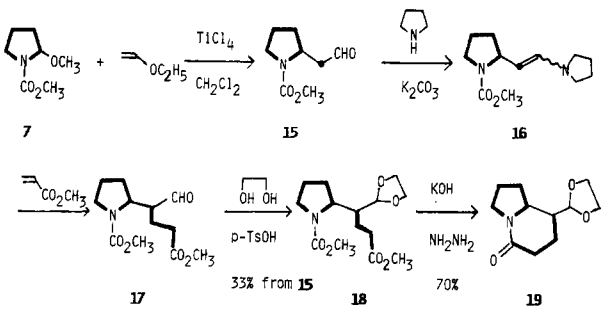
(5) The carbon–carbon bond-forming reaction at the α-position of **3** has also been carried out by utilizing a pyrrole ring,[3b] pyrrolidine-2-thione,[3d] nitrone,[3e] acyliminium ions[6] derived from imide,[3g] and lactam,[3h] cyclopropyl imine,[3f] or α-carbanions of 3-pyrrolines.[3i]

(6) For amidoalkylation, see: Zaugg, H. E. *Synthesis* **1970**, 49.

(7) Shono, T.; Hamaguchi, H.; Matsumura, Y. *J. Am. Chem. Soc.* **1975**, *97*, 4264.

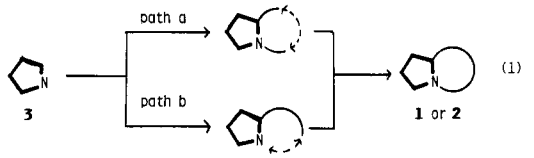
0022-3263/84/1949-0300$01.50/0

Scheme III



loids (±)-trachelanthamidine and (±)-isoretronecanol.

The construction of **1** and **2** by starting from pyrrolidine was achieved by 1,2-annulation on a pyrrolidine ring **3** via path a or b (eq 1).[8]



The methods described in this report are highly efficient from the standpoint of nucleus construction and also show some similarity with the biogenetic formation of alkaloids containing a pyrrolidine ring in plants, since the latter is postulated to involve Δ^1-pyrroline formed from L-ornithine as the common intermediate.[3a,9]

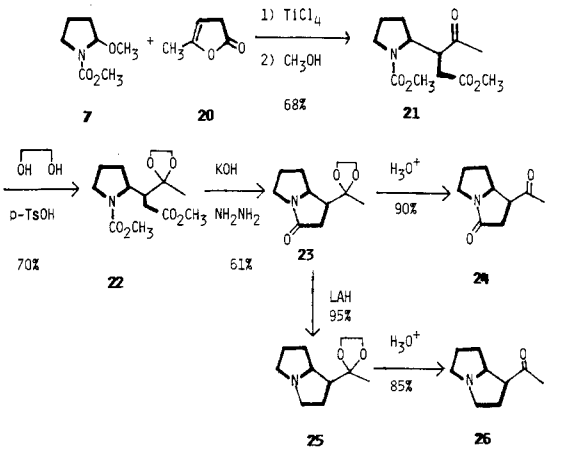
Preparation of Indolizidine Skeletons via Path a. The structures of (±)-elaeokanine C (**4**) and (±)-elaeokanine A (**5**) clearly suggest that the intramolecular condensation of the key intermediate **6** is a reasonable route belonging to path a for the synthesis of **4** and **5** (Scheme I).

Thus, treatment of **7**, anodically prepared from 1-(methoxycarbonyl)pyrrolidine in 80% yield, with $TiCl_4$[10] followed by the addition of silyl enol ether **8** gave **9** in 81% yield (Scheme II). Then, the carbonyl group of **9** was protected with ethylene glycol (92% yield), the carbomethoxyl group of **10** was hydrolyzed with alkali to give **11** (98% yield), and finally the bisketal **13** of the key intermediate **6** was obtained by the N-alkylation of **11** with bromo acetal **12** (68% yield). The aldol condensation of **13** with acid catalysts (1 N HCl, Δ, or concentrated HCl, room temperature) afforded (±)-**4**, whereas (±)-**5** was directly obtainable without the isolation of (±)-**4** by successive heating of **13** in 1 N HCl and in 1 N NaOH.

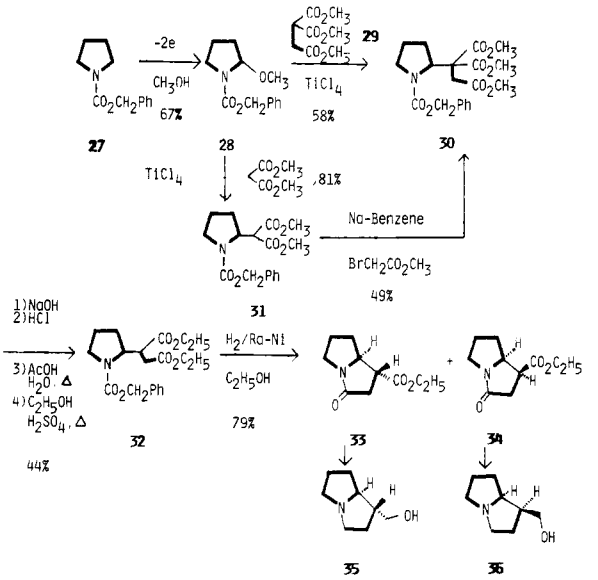
In these aldol condensations, the formation of a byproduct **14** was negligible (~10:1 **4**/**14** and >30:1 **5**/**14**). The stereochemistry of **4** was confirmed by comparison of its spectra with the reported ones.[11]

Preparation of Indolizidine Skeleton via Path b. Our method also permits one to synthesize an indolizidine skeleton via path b. This approach requires introduction of a four-carbon chain at the α-position of **7**, which was achieved by two successive alkylations (Scheme III). The first alkylation was carried out by treatment of **7** with ethyl

Scheme IV



Scheme V



vinyl ether in the presence of $TiCl_4$ to yield **15** (75%). Subsequently, **15** was alkylated with methyl acrylate through the formation of enamine **16** to give **17**, which was protected with ethylene glycol (33% overall yield from **15**). The final step was the alkaline hydrolysis of **18** which afforded **19** (70%) as expected.

Preparation of Pyrrolizidine Skeletons via Path b. Our method was also applied to the synthesis of pyrrolizidine skeleton via path b, which requires the introduction of a three-carbon chain at the α-position of **7**. Thus, the first key intermediate **21** was obtained (68% yield) by the reaction of α-angelica lactone **20** with **7** in the presence of $TiCl_4$ as a catalyst. Protection of the keto group of **21** followed by alkaline hydrolysis of **22** gave the pyrrolizidine compound **23**. Deprotection of **23** gave **24**, and the reduction of **23** followed by the deprotection yielded **26** (Scheme IV). With the successful preparation of pyrrolizidine skeletons from **7** via path b, our attention was directed to the synthesis of (±)-trachelanthamidine (**35**) and (±)-isoretronecanol (**36**).

Scheme V shows our route of the synthesis of **35** and **36**, in which benzyl carbamate **27** was used as the starting carbamate, since removal of the benzyloxycarbonyl group under mild conditions was necessary in the final step.

The α-methoxylated carbamate **28** was prepared by the anodic oxidation of **27** in 67% yield. The acid-catalyzed generation of a carbomethoxy iminium ion from **28** and a subsequent carbon–carbon bond-forming reaction with

(8) Although Speckamp et al. have synthesized pyrrolidine alkaloids starting from N-alkylated imides,[3g] the starting materials and the reaction patterns of nucleus construction in their methods are different from those in our methods.

(9) Herbert, R. B. "Rodd's Chemistry of Carbon Compounds"; Coffey, S., Ed; Elsevier: Amsterdam, 1980; Vol. IV, Part L, p 291.

(10) Coupling reactions of enol derivatives with a variety of electrophiles in the presence of $TiCl_4$, see: Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 817.

(11) Tufariello, J. J.; Ali, S. A. *Tetrahedron Lett.* **1979**, 4445.

29 gave the product 30 in 58% yield. The preparation of 30 was also achieved by the successive reaction of 28 with dimethyl malonate (81% yield) and methyl bromoacetate (49% yield). After 30 was hydrolyzed in aqueous alcohol, decarboxylated, and esterified, successively, the resultant diester 32 (overall yield 44% from 30) was hydrogenated by using Raney Ni as a catalyst. Distillation of the hydrogenated residue under reduced pressure directly gave a mixture of 33 and 34 in a ratio of 62:38 (79% yield), which were separable by chromatography. After the isolation of each isomer, 35 was synthesized quantitatively by the reduction of 33 with $LiAlH_4$. The synthesis of 36 from 34 has been reported (62% yield).[12]

Experimental Section

General Methods. Infrared (IR) spectra were recorded on a Hitachi 215 or 260-10 spectrometer. Proton nuclear magnetic resonance spectra (^1H NMR) were measured on a Varian Associates EM-390 or EM-360 spectrometer with chemical shifts given in parts per million (δ) downfield from tetramethylsilane as an internal standard. Mass spectra were obtained on a JEOL IMS-DX300 instrument. Elemental analyses were determined by the Center for Instrumental Analysis of Kyoto University. Silica gel column chromatography was carried out by using Kieselgel 60 (from Merk, 70–230 mesh ASTM). Alumina (Woelm, B, Akt I, from Woelm Pharma) containing 3% water was used for alumina column chromatography. Gas chromatography was performed by using a Shimadzu GC-6AM instrument equipped with a stainless steel column packed with 20% polyethylene glycol on Celite 545.

Preparation of 2-(Trimethylsiloxy)-1-pentene (8). To a solution of diisopropylamine (13 g, 0.129 mol) in THF (100 mL) was added a solution of *n*-BuLi (8.26 g, 0.129 mol) in hexane (86 mL) at −70 °C under an atmosphere of nitrogen, and then 2-pentanone (10 g, 0.116 mol) was added dropwise. After the solution was stirred for 1 h at the temperature, chlorotrimethylsilane (15 g, 0.138 mol) was added dropwise. The resulting reaction mixture was stirred for 1 h at −70 °C, poured into cold aqueous $NaHCO_3$, and extracted with hexane. The organic layer was washed with diluted HCl and aqueous $NaHCO_3$, successively, and dried with $MgSO_4$. The solvent was removed to give a residue, which was distilled for the isolation of 8: 12.1 g (0.077 mol, 66% yield); bp 130–135 °C; IR (neat) 2970, 1650 cm^{-1}; NMR (CCl_4) δ 0.21 (s, 9 H), 0.91 (t, 3 H, J = 6.5 Hz), 1.23–1.79 (m, 2 H), 2.02 (m, 2 H), 4.04 (s, 2 H); mass spectrum, m/e 158 (M^+), 143, 73 (base).

Preparation of 9. To a stirred solution of titanium tetrachloride (6.7 g, 35 mmol) in CH_2Cl_2 (50 mL) was added dropwise a solution of 7[4,7] (5.04 g, 32 mmol) in CH_2Cl_2 (5 mL) under an atmosphere of nitrogen at −70 °C, and then a solution of 8 (5.5 g, 34.8 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The mixture was warmed to −20 °C, stirred at the temperature for 2 h, and poured into brine, successively. The organic layer was extracted with CH_2Cl_2 and dried with $MgSO_4$. After the solvent was removed, the residue was distilled to yield 9: 5.46 g (25.7 mmol, 81% yield); bp 116–118 °C (1.3 mmHg); IR (neat) 2968, 2880, 1602, 1450, 1388, 1340, 1305, 1288, 1250, 1198, 1128, 1110, 1038, 985, 960, 772 cm^{-1}; NMR (CCl_4) δ 0.94 (t, 3 H, J = 7.0 Hz), 1.28–2.65 (m, 9 H), 2.75–3.12 (m, 1 H), 3.25–3.58 (m, 2 H), 3.70 (s, 3 H), 3.85–4.40 (m, 1 H). Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 62.14; H, 9.10; N, 6.40.

Preparation of 10. A solution of 9 (2.157 g, 10 mmol) in ethyl orthoformate (6 mL) and ethylene glycol (4 mL) containing a catalytic amount of *p*-TsOH·H_2O was refluxed for 5 h. The reaction mixture was poured into water and extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$. The solvent was removed, and the residue was distilled to yield 10: 2.37 g (9.22 mmol, 92% yield); bp 130–133 °C (2.5 mmHg); IR (neat) 2960, 2875, 1692, 1445, 1382, 1310, 1195, 1110, 947, 772 cm^{-1}; NMR (CCl_4) δ 0.80–1.08 (m, 3 H), 1.24–2.30 (m, 10 H), 3.28 (t, 2 H, J = 6.0 Hz), 3.62 (s, 3 H), 3.69–4.01 (m, 1 H), 3.86 (s, 4 H); mass spectrum, m/e 257 (M^+), 214, 142, 128 (base), 115. Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.59; H, 9.14; N, 5.22.

Preparation of 11. Deprotection of carbomethoxyl group was carried out by the method using $NH_2NH_2 \cdot H_2O$.[13] A solution of 10 (5.3 g, 20.6 mmol), KOH (30 g, 535 mmol), and $NH_2NH_2 \cdot H_2O$ (5 mL, 100 mmol) in ethylene glycol (150 mL) was refluxed for 1.5 h, poured into water, and extracted with ether. The organic layer was dried with $MgSO_4$, and the solvent was removed to give a residue, which was distilled to yield 11: 4.025 g (98% yield); bp 68 °C (2.5 mmHg); IR (neat) 3300 (br), 2945, 2880, 1650, 1460, 1420, 1380, 1200, 1145 (sh), 1048, 950, 880 cm^{-1}; NMR (CCl_4) δ 0.82–1.08 (m, 3 H), 1.10–2.06 (m, 8 H), 1.67 (d, 2 H, J = 5.8 Hz), 2.20–2.42 (br, 1 H), 2.57–3.18 (m, 3 H), 3.88 (s, 4 H); mass spectrum, m/e 199 (M^+), 156, 115, 87, 70 (base). Anal. Calcd for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62, N, 7.03. Found: C, 66.46; H, 10.86; N, 6.79.

Preparation of 13. With vigorously string, 11 (1.5 g, 7.5 mmol) was added dropwise to a suspension of 50% sodium hydride (0.36 g, 7.5 mmol) in dry DMF (20 mL) under an atmosphere of nitrogen at about 0 °C and stirred for 1 h, and then 12[14] (2 g, 11 mmol) was added. After the mixture was stirred for 2 h at about 0 °C, the stirring was continued overnight at room temperature. The reaction mixture was poured into brine and extracted with ether. The organic extract was dried with $MgSO_4$. After the solvent was removed, the residue was distilled to afford 13: 1.53 g (5.12 mmol, 68% yield); bp 106 °C (0.6 mmHg); IR (neat) 2962, 2880, 2805, 1460, 1440, 1410, 1380, 1300, 1135, 1070, 945, 910, 815 cm^{-1}; NMR (CCl_4) δ 0.72–1.08 (m, 3 H), 1.10–2.35 (m, 14 H), 2.65–3.16 (m, 2 H), 3.28–4.00 (m, 1 H), 3.69–3.95 (m, 4 H), 3.86 (s, 4 H), 4.85 (t, 1 H, J = 5 Hz); mass spectrum, m/e 299 (M^+), 256, 212, 170 (base), 115, 84, 70. Anal. Calcd for $C_{16}H_{29}NO_4$: C, 64.18; H, 9.76; N, 4.68. Found: C, 63.89; H, 10.03; N, 4.39.

Synthesis of Elaeokanine C ((±)-4). A solution of 13 (216 mg, 0.72 mmol) in concentrated HCl (1 mL) was stirred for 2 h at room temperature, and then the reaction mixture was poured into cold aqueous $NaHCO_3$. The organic portion was extracted with CH_2Cl_2 and dried with $MgSO_4$. Evaporation of the solvent gave a residue which was subjected to column chromatography (Al_2O_3; AcOEt–hexane, 1:1) to give (±)-4 (69 mg, 0.33 mmol, 45% yield) and 14 (~5 mg, ~0.026 mmol, ~3.6% yield). The NMR spectrum of the crude residue before the isolation showed the existence of (±)-4 and 14, the ratio of which was about 10:1. The identification of (±)-4 was carried out by comparison of its spectra with reported ones of authentic samples.[2d] The NMR and IR spectra of 14 also showed the characteristic peaks described in the literature.[11]

Synthesis of Elaeokanine A ((±)-5). Elaeokanine A ((±)-5) was obtainable without the isolation of (±)-4 from 13 by procedures as described below.

A solution of 13 (278 mg, 0.93 mmol) in 1 N HCl (5 mL) was refluxed for 1 h. At this stage, the formation of (±)-4 together with a small amount of (±)-5 was observed. To this solution was added sodium hydroxide (436 mg, 10.9 mmol), and the mixture was refluxed for 1 h, cooled, poured into water, and extracted with CH_2Cl_2. The extract was dried with $MgSO_4$, and the solvent was removed. The NMR spectrum of this residue showed the presence of (±)-5 with a small amount of aldehyde 14 (>30:1). The residue was subjected to column chromatography (Al_2O_3, AcOEt–hexane, 1:1) to afford (±)-5 (90 mg, 0.466 mmol, 50% yield).[2d]

Preparation of 18. Enamine 16 was synthesized by the modified method of Mannich and Davidsen.[15] To a suspension of pyrrolidine (1.86 mL, 20 mmol) and anhydrous pottasium carbonate (0.8 g, 5.8 mmol) in ether (5 mL) was added 15[4] (1.71 g, 10 mmol) at −10 °C, and the mixture was stirred at −10 °C for 1 h. After the reaction mixture was diluted with ether (50 mL) and dried ($MgSO_4$), filtration and evaporation of the solvent gave the crude product of 16. A mixture of the crude material 16 and methyl acrylate (1.72 g, 20 mmol) in dioxane (20 mL) was refluxed for 5 h, water (10 mL) was added, and the mixture was refluxed for 3 h. Brine (70 mL) was added to the mixture, and organic products were extracted with CH_2Cl_2 (4 × 30 mL). Drying ($MgSO_4$), filtration, and evaporation of the solvent followed by

(12) Pinnick, H. W.; Chang, Y. H. *J. Org. Chem.* **1978**, *43*, 4662.

(13) Muraca, R. F.; Whittick, J. S.; Daves, G. D., Jr.; Friis, P.; Folkers, K. *J. Am. Chem. Soc.* **1967**, *89*, 1505.

(14) Büchi, G.; Wüest, H. *J. Org. Chem.* **1969**, *34*, 1122.

(15) Mannich, C.; Davidsen, H. *Chem. Ber.* **1936**, *69*, 2106.

column chromatography on silica gel (*n*-hexane–AcOEt, 2:1) afforded **17** (1.503 g, 5.8 mmol).

A solution of **17** (0.920 g, 3.6 mmol) and ethylene glycol (3 mL, 54 mmol) in benzene (20 mL) containing *p*-toluenesulfonic acid monohydrate (0.2 g, 1.05 mmol) was refluxed for 3 h. After brine (50 mL) was added to the mixture, the products were extracted with ether (4 × 20 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography on silica gel (*n*-hexane–AcOEt, 2:1) to give **18**: 0.61 g (2.03 mmol, 33% yield from **15**); IR (neat) 1730, 1685, 1447, 1380, 1195, 1108, 775 cm^{-1}; NMR (CCl_4) δ 1.21–2.60 (m, 8 H), 3.20–4.11 (m, 8 H), 3.63 (s, 6 H), 4.64–4.90 (m, 1 H). Anal. Calcd for $C_{14}H_{23}NO_6$: C, 55.80; H, 7.69; N, 4.65. Found: C, 55.50; H, 7.81; N, 5.01.

Preparation of 19. A mixture of **18** (0.755 g, 2.5 mmol) and potassium hydroxide (1.7 g, 30 mmol) in ethylene glycol (15 mL) containing $NH_2NH_2 \cdot H_2O$ (0.5 mL, 10 mmol) was refluxed for 1.5 h.[13] The mixture was poured into cold brine (30 mL), and the products were extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a residue, which was purified by column chromatography on silica gel (AcOEt) to afford **19**: 0.369 g (1.75 mmol, 70% yield); IR (neat) 1618, 1453, 1415, 1325, 1290, 1270, 1230, 1210, 1195, 1130, 1090, 1070, 1035, 998, 980, 950, 845 cm^{-1}; NMR (CCl_4) δ 1.21–2.53 (m, 9 H), 3.14–3.66 (m, 3 H), 3.77–4.02 (m, 4 H), 4.71–4.83 (m, 1 H); mass spectrum, *m/e* 211 (M^+). Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.31; H, 8.22; N, 6.66.

Preparation of 21. To a stirred solution of titanium tetrachloride (9.49 g, 50 mmol) in CH_2Cl_2 (50 mL) was added a solution of **7** (7.95 g, 50 mmol) in CH_2Cl_2 (5 mL) at −70 °C under an atmosphere of nitrogen. After the mixture was stirred for 5 min, a solution of **20**[16] (7.358 g, 75 mmol) in CH_2Cl_2 (5 mL) was added, and the resulting reaction mixture was stirred at −10 °C for 5 h. The mixture was treated with methanol (30 mL) and stirred for 1 h. Then brine (50 mL) was added to the solution, which was stirred for 30 min. After the organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (4 × 30 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography on silica gel (*n*-hexane–AcOEt, 2:1) to give **21**: 8.809 g (34 mmol, 68% yield); IR (neat) 2970, 2895, 1742, 1710, 1460, 1388, 1260, 1240, 1208, 1175, 1125, 780 cm^{-1}; NMR (CCl_4) δ 1.50–2.10 (m, 4 H), 2.17 and 2.20 (2 s, 3 H), 2.29–2.87 (m, 2 H), 2.90–3.80 (m, 3 H), 3.63 (s, 3 H), 3.70 (s, 3 H), 3.80–4.28 (m, 1 H); mass spectrum, *m/e* 257 (M^+). Anal. Calcd for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.44. Found: C, 55.98; H, 7.35; N, 5.55.

Preparation of 24. A solution of **21** (8.75 g, 34 mmol) in ethylene glycol (25 mL) and ethyl orthoformate (30 mL) containing *p*-toluenesulfonic acid (0.2 g, ~1 mmol) was refluxed for 2 h. The mixture was poured into brine (100 mL) and extracted with ether (3 × 60 mL). Concentration and filtration of the combined ethereal solution through a silica gel column (*n*-hexane–AcOEt, 1:1) gave nearly pure **22**: 7.15 g (24 mmol, 70% yield); IR (neat) 1733, 1695, 1450, 1380, 1200, 1150, 1120, 1045 cm^{-1}; NMR (CCl_4) δ 1.28 and 1.33 (2 s, 3 H), 1.50–2.60 (m, 7 H), 2.77–3.50 (m, 2 H), 3.55, 3.57, 3.63, and 3.65 (4 s, 6 H), 3.73–4.15 (m, 1 H), 3.91 (s, 4 H). A mixture of **22** (2.272 g, 7.54 mmol) and potassium hydroxide (5.6 g, 0.1 mol) in ethylene glycol (30 mL) containing hydrazine (3 mL, 60 mmol) was refluxed for 1.8 h.[13] After the mixture was poured into brine (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL), the combined organic layer was concentrated and filtered through a silica gel column (AcOEt) to afford nearly pure **23**: 0.975 g (4.62 mmol, 61% yield); IR (neat) 1675, 1425, 1380, 1260, 1180, 1095, 1045, 955, 880 cm^{-1}; NMR (CCl_4) δ 1.26 and 1.30 (2 s, 3 H), 1.35–3.85 (m, 10 H), 3.96 (s, 4 H). Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.48; H, 8.05; N, 6.38. A solution of **23** (0.915 g, 4.3 mmol) in 5% H_2SO_4 (4 mL) was stirred at room temperature for 4 h. The mixture was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography on silica gel (AcOEt) to give **24**: 0.648 g (3.9 mmol, 90% yield); IR (neat) 1708, 1685, 1420, 1365, 1185 cm^{-1}; NMR (CCl_4) δ 0.82–2.35 (m, 4 H), 2.17 (s, 3 H), 2.40–3.73 (m, 5 H), 3.81–4.18 (m, 1 H); mass spectrum, *m/e* 167 (M^+), 152 ($M^+ - CH_3$), 124 ($M^+ - COCH_3$). Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.35; H, 7.80; N, 8.18.

Preparation of 25. To a stirred suspension of $LiAlH_4$ (0.5 g, 13 mmol) in ether (20 mL) was added a solution of **23** (1.210 g, 5.7 mmol) in ether (5 mL) and THF (5 mL). The mixture was refluxed for 3.5 h and worked up with H_2O (2 mL). The solution was filtered and concentrated to give the residue, which was distilled (bulb-to-bulb) to afford **25**: 1.067 g (5.4 mmol, 95% yield); bp 85–95 °C (0.45 mmHg); IR (neat) 1450, 1377, 1255, 1170, 1092, 1045, 952, 870 cm^{-1}; NMR (CCl_4) δ 1.23 and 1.27 (2 s, 3 H), 1.33–2.10 (m, 7 H), 2.25–2.60 (m, 2 H), 2.63–3.40 (m, 3 H), 3.89 (s, 4 H); mass spectrum, *m/e* 197 (M^+).

Preparation of 26. A solution of **25** (1.00 g, 5.08 mmol) in 10% sulfuric acid (7 mL) was stirred at room temperature for 1 h. The solution was made basic with aqueous sodium hydroxide and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and distilled (bulb-to-bulb) to give **26**: 0.660 g (4.3 mmol, 85% yield); bp 100–105 °C (2 mmHg); IR (neat) 1708, 1452, 1425, 1360, 1288, 1250, 1180, 1100 cm^{-1}; NMR (CCl_4) δ 1.33–2.25 (m, 6 H), 2.10 (s, 3 H), 2.25–2.75 (m, 3 H), 2.75–3.24 (m, 2 H), 3.24–3.64 (m, 1 H); mass spectrum, *m/e* 153 (M^+), 138 ($M^+ - CH_3$), 110 ($M^+ - COCH_3$).

1-(Benzyloxycarbonyl)pyrrolidine (27). To a stirred solution of pyrrolidine (22 g, 0.305 mol) and sodium hydroxide (12 g, 0.3 mol) in water (100 mL) was added dropwise benzyloxycarbonyl chloride (50 g, 0.293 mol) with external cooling in an ice–water bath. The reaction mixture was warmed to room temperature and stirred for 1.5 h. The organic layer was extracted with CH_2Cl_2 and dried with $MgSO_4$. The solvent was removed, and the residue was distilled to yield **27**: 52.3 g (0.255 mol, 87% yield); bp 125–128 °C (1.5 mmHg); IR (film) 2960, 2880, 1695, 1420, 1360, 1135, 1100, 1030 cm^{-1}; NMR (CCl_4) δ 1.60–2.10 (m, 4 H), 3.15–3.65 (m, 4 H), 5.01 (s, 2 H), 7.27 (s, 5 H). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.60; H, 7.51; N, 6.86.

1-(Benzyloxycarbonyl)-2-methoxypyrrolidine (28). Anodic oxidation of **27** (15 g, 73 mmol) according to the reported procedure[4] yielded **28** (11.45 g, 48.7 mmol). It was isolated by column chromatography (silica gel, AcOEt–hexane, 1:2): oil; 67% yield (at 3.43 F/mol); IR (neat) 2945, 1700, 1440, 1400, 1355, 1325, 1180, 1080 cm^{-1}; NMR (CCl_4) δ 1.47–2.16 (m, 4 H), 2.96–3.57 (m, 2 H), 3.20 (br s, 3 H), 4.76–5.22 (m, 1 H), 4.95 (s, 2 H), 7.14 (s, 5 H). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.07; H, 7.50; N, 5.92.

Preparation of 30 from 28. To a stirred solution of titanium tetrachloride (3.83 g, 20 mmol) in CH_2Cl_2 (40 mL) was added dropwise a solution of **28** (4.72 g, 20.1 mmol) in CH_2Cl_2 (5 mL) under an atmosphere of nitrogen at −70 °C. A solution of **29**[17] (6.12 g, 30 mmol) and triethylamine (3 g, 30 mmol) in CH_2Cl_2 (5 mL) was added dropwise to this cold solution, and the mixture was gradually warmed to 0 °C over 7 h. The reaction mixture was poured into brine, and the organic layer was extracted with CH_2Cl_2 and dried with $MgSO_4$. The solvent was evaporated in vacuo, and excess **29** was removed by vacuum distillation [97–100 °C (2 mmHg)]. The residue was purified by column chromatography on silica gel (AcOEt–hexane, 1:2) to yield **30**: 4.74 g (11.64 mmol, 58% yield); IR (neat) 2960, 2900, 1737, 1705, 1438, 1405, 1353, 1275, 1220, 1108, 1030, 1005, 755, 700 cm^{-1}; NMR (CCl_4) δ 1.26–2.42 (m, 4 H), 2.74–3.00 (m, 2 H), 3.00–3.41 (m, 1 H), 3.41–3.90 (m, 1 H), 3.60, 3.66, and 3.67 (3s, 9 H), 4.52–4.82 (m, 1 H), 5.05 (s, 2 H), 7.34 (s, 5 H). Anal. Calcd for $C_{20}H_{25}NO_8$: C, 58.96; H, 6.18; N, 3.44. Found: C, 59.06; H, 6.31; H, 3.34.

Preparation of 31. To a stirred solution of titanium tetrachloride (0.816 g, 4.3 mmol) in CH_2Cl_2 was added dropwise a solution of **28** (1 g, 4.3 mmol) in CH_2Cl_2 under an atmosphere of nitrogen at −70 °C. A solutin of dimethyl malonate (0.85 g, 6.43 mmol) and triethylamine (0.65 g, 6.42 mmol) in CH_2Cl_2 was added to the solution and stirred for 6 h at this temperature. This solution was poured into brine and extracted with CH_2Cl_2. The

(16) Leonard, R. H. *Ind. Eng. Chem.* **1956**, *48*, 1331.

(17) Hall, H. K., Jr.; Ykman, P. *J. Am. Chem. Soc.* **1975**, *97*, 800.

organic layer was dried with $MgSO_4$, and the solvent was removed. The residue was purified by column chromatography on silica gel (AcOEt-hexane, 1:2) to afford **31**: 1.166 g (3.48 mmol, 81% yield): IR (neat) 2950, 2875, 1735, 1700, 1500, 1410, 1360, 1305, 1260, 1194, 1160, 1027, 976, 770, 695 cm^{-1}; NMR (CCl_4) δ 1.55–2.30 (m, 4 H), 3.10–3.75 (m, 2 H), 3.63 (s, 6 H), 3.90–4.50 (m, 2 H), 5.06 (s, 2 H), 7.29 (s, 5 H). Anal. Calcd for $C_{17}H_{21}NO_6$: C, 60.88; H, 6.31; N, 4.18. Found: C, 61.03; H, 6.27; N, 4.19.

Preparation of 30 from 31. A solution of **31** (1.524 g, 4.55 mmol), methyl bromoacetate (1.03 g, 6.75 mmol), and sodium (175 mg, 7.6 mmol) in benzene (15 mL) was refluxed for 33.5 h. The solution was poured into water and extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, the solvent was removed, and the residue was purified by column chromatography (silica gel, AcOEt-hexane, 1:2) to yield **30** (908 mg, 2.23 mmol, 49% yield).

Preparation of 32. Hydrolysis and subsequent decarboxylation were carried out by a method similar to the reported procedure.[18] A solution of **30** (3.14 g, 7.72 mmol) and sodium hydroxide (1.26 g, 31.5 mmol) in a mixture of EtOH (20 mL) and H_2O (10 mL) was heated at 60–70 °C for 6 h. The reaction mixture was acidified with dilute HCl and extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, and then the solvent was removed in vacuo. The residue was dissolved in a mixed solvent of acetic acid (30 mL) and H_2O (20 mL) and refluxed for 13 h, and the solvent was removed in vacuo. A solution of the residue in EtOH (50 mL) containing concentrated H_2SO_4 (1 mL) was refluxed for 13 h and poured into cold aqueous Na_2CO_3. The organic layer was extracted with CH_2Cl_2 and dried with $MgSO_4$. The solvent was removed, and the residue was purified by column chromatography on silica gel (AcOEt-hexane, 1:2) to yield **32**: 1.29 g (3.4 mmol, 44% yield); IR (neat) 2980, 2890, 1730, 1705, 1503, 1452, 1410, 1360, 1260, 1180, 1117, 1030, 918, 860, 772, 748, 700 cm^{-1}; NMR (CCl_4) δ 1.22 and 1.23 (2 t, 6 H, J = 7.0 Hz), 1.58–2.18 (m, 4 H), 2.18–2.85 (m, 2 H), 3.00–3.78 (m, 3 H), 3.78–4.45 (m, 1 H), 4.04–4.07 (2 q, 4 H, J = 7.0 Hz), 5.70 (s, 2 H), 7.30 (s, 5 H). Anal. Calcd for $C_{20}H_{27}NO_6$: C, 63.64; H, 7.21; N, 3.71. Found: C, 63.76; H, 7.04; N, 3.62.

Preparation of 33 and 34. A solution of **32** (1.04 g, 3.08 mmol) in EtOH (30 mL) was placed in an autoclave with a catalytic amount of W-2 Raney Ni. The apparatus was tightly closed, filled with 15 kg/cm^2 of hydrogen, and shaken at room temperature for 15 h. After removal of the catalyst by filtration, the filtrate was condensed and distilled to yield a mixture of **33** and **34**: 79% yield (478 mg, 2.43 mmol); bp 92–134 °C (0.4 mmHg, bulb-to-bulb). Esters **33** and **34** are separable by GLC (PEG) or TLC (silica gel, AcOEt-hexane, 1:1). Ester **33** was less polar than **34** on silica gel plate and GLC (PEG). The ratio of **33** and **34** was 62:38 (by GLC).

33: IR (neat) 2975, 1730, 1700, 1420, 1375, 1337, 1262, 1190, 1098, 1038 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (t, 3 H, J = 7.0 Hz), 1.73–2.33 (m, 4 H), 2.35–3.23 (m, 4 H), 3.23–3.80 (m, 1 H), 3.80–4.33 (m, 3 H); mass spectrum, m/e 197 (M^+), 169, 96 (base).

34: the spectroscopic data was identical with that described in the report.[12] Also, mass spectrum coincided with assigned structure.

Synthesis of 35 and 36. A solution of **33** (84 mg, 0.4264 mmol) in THF (2 mL) was added to a suspension of $LiAlH_4$ (53 mg, 1.4 mmol) in THF (3 mL) at room temperature. The suspension was refluxed for 6 h under an atmosphere of nitrogen. The usual workup gave **35** quantitatively [picrate mp 174–177.5 °C (lit.[19] mp 170–172, 173–174 °C)]. Transformation of **34** and **36** has been described (62% yield)[12].

Acknowledgment. T.S. is grateful for the partial financial support donated by the Asahi Glass Foundation for Industrial Technology.

Registry No. (±)-**4**, 36451-37-3; (±)-**5**, 73971-21-8; (±)-**7**, 88001-28-9; **8**, 40911-68-0; (±)-**9**, 88001-27-8; (±)-**10**, 88001-29-0; (±)-**11**, 88001-30-3; **12**, 18742-02-4; (±)-**13**, 88001-31-4; (±)-**14**, 74045-76-4; **15**, 76470-03-6; **16**, 88001-32-5; **17**, 88001-33-6; **18**, 88001-34-7; **19**, 88001-35-8; **20**, 591-12-8; **21**, 88001-36-9; **22**, 88001-37-0; **23**, 88001-38-1; **24**, 88001-39-2; **25**, 88001-40-5; **26**, 88001-41-6; **27**, 25070-74-0; (±)-**28**, 88001-42-7; **29**, 40967-67-7; (±)-**30**, 88001-43-8; (±)-**31**, 88001-44-9; **32**, 88001-45-0; (±)-**33**, 88001-46-1; (±)-**34**, 67800-68-4; (±)-**35**, 18929-91-4; (±)-**35** (picrate), 81255-00-7; (±)-**36**, 18929-90-3; $BrCH_2CO_2CH_3$, 96-32-2; 1-(methoxycarbonyl)pyrrolidine, 56475-80-0; 2-pentanone, 107-87-9; chlorotrimethylsilane, 75-77-4.

(18) Battersby, A. R.; Turner, J. C. *J. Chem. Soc.* **1960**, 717.

(19) Borch, R. F.; Ho, B. C. *J. Org. Chem.* **1977**, *42*, 1225.

1-Lithio- and 1,3-Dilithioisobenzofuran: Formation and Reactions with Electrophiles

Stephen L. Crump and Bruce Rickborn*

Department of Chemistry, University of California, Santa Barbara, California 93106

Received August 1, 1983

The acetal **1** reacts with 1 equiv of alkyllithium in the presence of catalytic diisopropylamine to form isobenzofuran (**2**), which with an additional equivalent of alkyllithium gives 1-lithioisobenzofuran (**3**). Solutions of **3** have been treated with various electrophiles and the resulting products characterized by NMR and as cycloadducts formed on addition of dienophiles. Lithiation of **2** occurs cleanly at C-1, as shown by quenching with D_2O. Both the metalation and subsequent alkylation reactions are more rapid in THF than in ether. Reaction of **3** with CH_3I gives 1-methylisobenzofuran (**6**) as the major product, accompanied by some 1,3-dialkylated material. Further treatment of **6** with alkyllithium results in specific lithiation at C-3 to give **14**, as demonstrated by deuteration and analysis of cycloadducts by ^2H NMR. Ethylation of **14** gives 1-ethyl-3-methylisobenzofuran, illustrating the feasibility of a one-pot procedure for preparing unsymmetrically disubstituted isobenzofurans. Dilithiation of **2** occurs when excess base is employed in THF, and this allows the direct formation of some symmetrical 1,3-disubstituted isobenzofurans. The 1-alkyl- and 1,3-dialkylisobenzofurans are moderately stable in neutral or mildly basic solution, resembling the parent **2** in this respect. Exchange reactions demonstrate that isobenzofuran is more acidic than both furan and diisopropylamine.

Since the earliest report of generating isobenzofuran (**2**) as a reactive intermediate by a thermolytic process, several variants have been developed which allow either the isolation or in situ formation and use of this interesting

0022-3263/84/1949-0304$01.50/0