Notes

Synthesis of Optically Active Piperidine and Pyrrolidine Alkaloids from L-Lysine, L-Ornithine, or L-Proline Using Anodic Oxidation as Key Steps[1]

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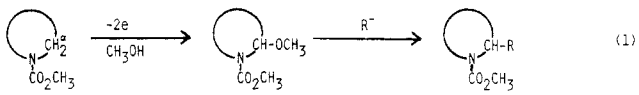
We have already exploited several convenient methods[2] for introducing nucleophiles (R^-) to the position α to the nitrogen atom of carbamates **1** using anodically prepared α-methoxylated carbamates **2** as the key intermediates (eq 1).[3]



(1)

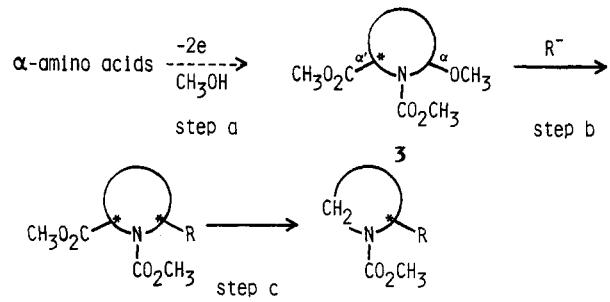
Although this method is applicable to syntheses of a variety of alkaloids,[2,4] enantioselective introduction of R^- at the α position remains to be investigated. Our methodology for this purpose is shown in Scheme I in which (1) chiral compounds **3** are anodically prepared from α-amino acids (step a), (2) R^- is diastereoselectively introduced to the α-position through the influence of a substituent on the chiral α'-position (step b), (3) the α'-substituent is eliminated after R^- is introduced (step c), and (4) formally enantioselective introduction of R^- to the α-position is thus attained through these steps.

Although we have already described this methodology in a preliminary note,[5] recent publication of a report[6] on the synthesis of optically active alkaloids using our methodology prompted us to report our new findings.

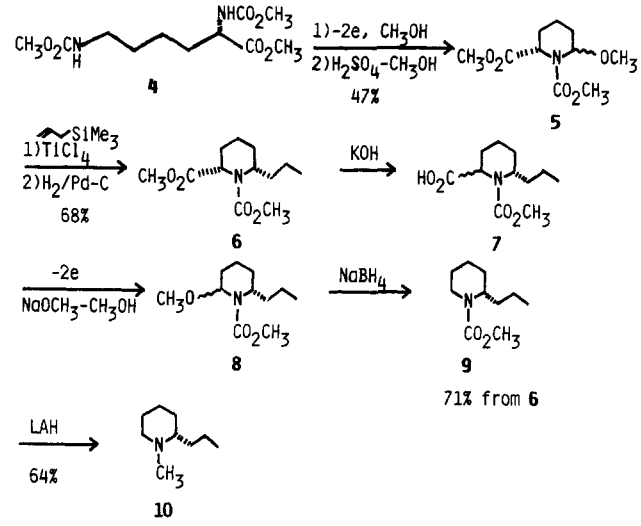
Optically active (+)-*N*-methylconiine **10** was synthesized according to the route outlined in Scheme II.

The key intermediate **5** was prepared by anodic oxidation of **4** derived from L-lysine followed by treatment with acid.[5] Treatment of **5** with allyltrimethylsilane followed by hydrogenation gave the cis isomer **6** exclusively. Hydrolysis of **6** followed by anodic decarboxylation[7] gave **8**, which was then successively reduced with $NaBH_4$ and LAH to afford **10** in 96% optical purity.[8]

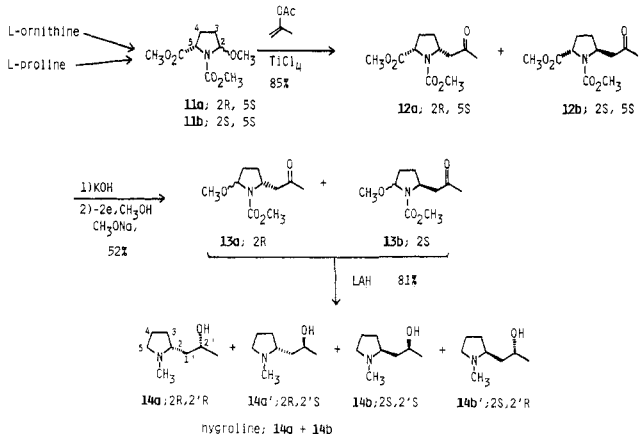
Scheme I



Scheme II



Scheme III



The synthetic route of optically active (+)-hygroline is shown in Scheme III.[9] Starting compounds **11a** and **11b** were prepared from L-ornithine or L-proline by using our

(1) Electroorganic Chemistry, 96.

(2) (a) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1982**, *103*, 1172; (b) *Tetrahedron Lett.* **1981**, *22*, 2411; (c) *Ibid.* **1981**, *22*, 3249.

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

(4) Shono, T.; Matsumura, Y.; Uchida, K.; Tsubata, K.; Makino, A. *J. Org. Chem.* **1984**, *49*, 300.

(5) (a) Whole process of this methodology has been presented at the 3rd Synoposium on Electroorganic Chemistry, Osaka, Japan (1982), Abstr. p 59. (b) Shono, T.; Matsumura, Y.; Inoue, K. *J. Chem. Soc., Chem. Commun.* **1983**, 1169. (c) Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y.; Yamane, S.; Kanazawa, T.; Aoki, T. *J. Am. Chem. Soc.* **1982**, *104*, 6697.

(6) Irie, K.; Aoe, K.; Tanaka, T.; Saito, S. *J. Chem. Soc., Chem. Commun.* **1985**, 633.

(7) Iwasaki, T.; Horikawa, H.; Matsumoto, K.; Miyoshi, M. *J. Org. Chem.* **1979**, *44*, 1552.

(8) Pure **10** $[\alpha]_D$ +74.9° (95% ethanol, c 0.2–2.0). Craig, J. C.; Lee, S.-Y. C.; Pereira, W. E., Jr.; Beyerman, H. C.; Moat, L. *Tetrahedron* **1978**, *34*, 501.

(9) Synthesis of optically active 2,5-dialkylpyrrolidines starting from pyroglutamic acid has been presented in a recent report: Shiosaki, K.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1229.

0022-3263/86/1951-2590$01.50/0

previously reported methods.[5,10] Treatment of **11a** with isopropenyl acetate in the presence of $TiCl_4$ gave a mixture of stereoisomers **12a** and **12b** in a ratio of 7:3 (85% yield). A similar mixture of **12a** and **12b** was also obtained by the reaction of **11b** with isopropenyl acetate under similar conditions. These results suggested that both **11a** and **11b** formed the same active intermediate in this C–C bond-forming reaction and hence the mechanism was similar to S_N1.

The absolute configuration of C-2 position in **12a** and **12b** was determined on the basis of the configuration of the final products **14a** and **14b**. A mixture of **13a** and **13b** was obtained by alkaline hydrolysis of a mixture of **12a** and **12b** followed by anodic oxidation. Subsequent reduction of **13a** and **13b** with LAH yielded a mixture of hygroline (**14a** and **14b**) and its diastereoisomers pseudohygroline (**14a'** and **14b'**) in a ration of 2:3, which were separated by GLC. The optical rotations $[\alpha]^{21}_D$ of the resulting hygroline (a mixture of **14a** and **14b**) and pseudohygroline (a mixture of **14a'** and **14b'**) were +21.32° (42.6% optical purity)[11] and +45.62°, respectively. The optical purity of the obtained hygroline indicated that the ratio of **14a** to **14b** is 71 to 29. Thus, the main isomer in the C–C bond-forming reaction is assigned as **12a**, in which the configuration at the C-2 position was *R*, since the absolute configuration of (+)-hygroline (**14a**) at C-2 is known to be *R*.

The result obtained in this study indicates that our methodology is applicable to the optically active piperidine alkaloids, while the synthesis of the optically active pyrrolidine alkaloids is achieved with moderate optical purity.[12]

Experimental Section

General Methods. Proton nuclear magnetic resonance spectra (^{1}H NMR) were measured on a Varian Associates EM-360 or EM-390 spectrometer with chemical shifts given in parts per million (δ) downfield from tetramethylsilane as an internal standard. Infrared spectra (IR) were recorded on Hitachi 215 or 260-10 spectrometers. Elemental analyses were determined by the Center for Instrumental Analysis of Kyoto University. Optical rorations were measured with Perkin-Elmer 241 polarimeter. Mass spectra were recorded on a JEOL IMS-DS300 mass spectrometer. Electrochemical oxidation was carried out by using a DC power supply (GP 050-2) of Takasago Seisakusho, Ltd.

Preparation of 1,2-Bis(methoxycarbonyl)-6-propylpiperidine (6). To a stirred solution of $TiCl_4$ (0.3 mL, 2.73 mmol) in methylene chloride (5 mL) was added dropwise a solution of **5**[5b] (600 mg, 2.6 mmol) and allyltrimethylsilane (575 mg, 5 mmol) in methylene chloride (5 mL) at −70 °C under an atmosphere of nitrogen. The mixture was gradually warmed to room temperature in 2.7 h. Water was added to the solution and the organic portion was extracted with methylene chloride. The combined organic layer was dried with $MgSO_4$ and the solvent was removed. A mixture of the residue and a catalytic amount of 10% Pd–C in methanol (20 mL) was stirred overnight at room temperature under an atmosphere of hydrogen (1 atm). After the catalyst and solvent were removed, the residue was subjected to column chromatography on silica gel (AcOEt–hexane) to give **6** (428 mg, 1.76 mmol, 68% yield): IR (neat) 2960, 2890, 1760, 1742, 1710, 1455, 1410, 1370, 1330, 1305, 1270, 1220, 1105, 790, 700 cm^{-1}; NMR (CCl_4) δ 0.77–1.03 (m, 3 H), 1.07–1.78 (m, 9 H), 2.13–2.39 (m, 1 H), 3.70 (s, 6 H), 4.03–4.27 (m, 1 H), 4.73–4.90 (m, 1 H). Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.02; H, 8.88; N, 5.58.

Preparation of 1-(Methoxycarbonyl)-2-propylpiperidine (9). A solution of **6** (395 mg, 1.63 mmol) and KOH (694 mg, 12.4 mmol) in a mixed solvent of methanol (16 mL) and water (16 mL) was stirred at 0 °C and gradually warmed to room temperature. After stirring for 4 h, the solvent was evaporated to remove methanol, and the residual aqueous layer was washed with methylene chloride and acidified with concentrated HCl. The organic portion was extracted with methylene chloride. The combined organic layer was dried and the solvent was removed to give **7** (361 mg): NMR ($CDCl_3$) δ 0.70–1.05 (m, 3 H), 1.05–1.93 (m, 9 H), 2.10–2.53 (m, 1 H), 3.75 (s, 3 H), 4.03–4.37 (m, 1 H), 4.74–5.02 (m, 1 H), 9.70–10.04 (m, 1 H).

Into a cell equipped with a carbon rod anode and cathode (8 mm i.d.) was added a solution of **7** (361 mg) and sodium methoxide (47 mg) in methanol (30 mL). After 3.95 f/mol of electricity was passed at a constant current (0.2 A), the solvent was removed in vacuo to give a residue, which was chromatographed on silica gel (AcOEt–hexane) to yield **8** (282 mg): IR (neat) 2960, 1705, 1448, 1410, 1370, 1325, 1275, 1120, 1105, 1070, 945, 930, 775 cm^{-1}; NMR (CCl_4) δ 0.83–1.05 (m, 3 H), 1.10–2.10 (m, 10 H), 3.25 (s, 3 H), 3.68 (s, 3 H), 3.90–4.23 (s, 1 H), 5.17–5.45 (m, 1 H).

To a stirred solution of **8** (282 mg) in acetic acid (10 mL) was portionwise added $NaBH_4$ (1 g). The mixture was stirred for 8.5 h at room temperature and poured into aqueous $NaHCO_3$. The organic portion was extracted with methylene chloride and the combined organic layer was dried with $MgSO_4$. The solvent was removed to give a residue, and it was chromatographed on silica gel to yield **9** (215 mg, 1.16 mmol). The overall yield was 71% from **6**.

9: IR (neat) 2935, 2865, 1685, 1445, 1370, 1260, 1180, 1148, 1090, 767 cm^{-1}; NMR (CCl_4) δ 0.93 (t, 3 H, J = 6.0 Hz), 1.10–1.92 (m, 10 H), 2.78 (d t, J = 12.0 Hz and 3.0 Hz, 1 H), 3.60 (s, 3 H), 3.81–4.40 (m, 2 H). Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.96; H, 10.64; N, 7.58.

(+)-*N*-Methylconiine (10). To a stirred suspension of LAH (200 mg, 5.26 mmol) in dry ether (10 mL) was added dropwise a solution of **9** (251 mg, 1.36 mmol) in ether (10 mL). The mixture was refluxed for 2 h and cooled to room temperature. Usual workup gave **10** (123 mg, 0.87 mmol, 64% yield). The optical rotation was measured after bulb-to-bulb distillation (bp 110–120 °C (20 mmHg)): $[\alpha]^{21}_D$ +71.73° (ethanol, *c* 0.38);[8] IR (neat) 2950, 2790, 1470, 1380, 1280, 1140, 1105, 1040 cm^{-1}; NMR (CCl_4) δ 0.70–2.10 (m, 15 H), 2.15 (s, 3 H), 2.60–2.90 (m, 1 H); MS, *m/e* 141 (M^+), 98 (base); high resolution mass spectrum calcd for $C_9H_{19}N$ 141.1517, found 141.1385.

Synthesis of a mixture of 11a and 11b has already been reported[5c] by us. The mixture of **11a** and **11b** with the ratios of 1 to 1 was obtained from ornithine or proline. The isomers are separable by column chromatography.

The first isomer: IR (neat) 2960, 1750, 1710, 1445, 1370, 1200, 1085 cm^{-1}; NMR (CCl_4) 1.70–2.67 (m, 4 H), 3.29 and 3.36 (2 s, 3 H), 3.65, 3.70, and 3.73 (3 s, 6 H), 4.25 (d, J = 10 Hz, 1 H), 5.09–5.35 (m, 1 H); MZ, *m/e* 217 (M^+), 186, 158 (base), 126, 82.

The second isomer: IR (neat) 2990, 2955, 2840, 1755, 1710, 1448, 1380, 1200, 1125, 1090 cm^{-1}; NMR (CCl_4) δ 1.60–2.43 (m, 4 H), 3.36 (s, 3 H), 3.70 and 3.71 (2 s, 6 H), 4.26 (t, J = 10 Hz, 1 H), 5.06–5.40 (br, 1 H); *m/e* 217 (M^+), 186, 158 (base), 126, 82.

Preparation of 12a and 12b. A solution of **11a** or **11b** (10.08 g, 46.4 mmol) in methylene chloride (10 mL) was added to a stirred solution of $TiCl_4$ (5 mL, 45.5 mmol) in methylene chloride (10 mL) at −70 °C, and to this mixture was added isopropenyl acetate (5.64 g, 56.4 mmol) at the same temperature. The mixture was gradually warmed to room temperature and stirred for 2.5 h. Brine was added to the solution and the organic portion was extracted with methylene chloride. The combined organic layer was distilled to give a mixture of **12a** and **12b** (9.57 g, 39.4 mmol, 85% yield) in a ratio of 7 to 3. The isomers are separable by GLC (PEG).

A mixture of **12a** and **12b**: bp 125–145 °C (0.9 mmHg); IR (neat) 2960, 1740, 1700, 1450, 1380, 1300, 1200, 1125, 1010, 775 cm^{-1}; NMR (CCl_4) δ 1.50–3.33 (m, 6 H), 2.10 (s, 3 H), 3.58, 3.62, 3.67, and 3.69 (4 s, 6 H), 3.92–4.45 (m, 2 H). Anal. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.40; H, 7.18; N, 5.87.

Preparation of 13a and 13b. Alkaline hydrolysis of a mixture of **12a** and **12b** (11.75 g, 48.35 mmol) according to the similar method to the synthesis of **7** gave corresponding carboxylic acids

(10) The ratios of **11a** to **11b** were identical in the two routes (1:1).
(11) Pure **14a** $[\alpha]^{21}_D$ +50° (ethanol, *c* 0.77). Fitzgerald, J. S. *Aust. J. Chem.* **1965**, *18*, 589.
(12) The reaction of **11** with allyltrimethylsilane also gave a mixture of diastereoisomers of 1,2-bis(methoxycarbonyl)-5-allylpyrrolidine in a ratio of 72:28 with 74% yield.

(9.281 g). The carboxylic acids (9.281 g) were electrochemically oxidized in methanol (100 mL) containing sodium medthoxide (1.69 g, 30 mmol) as described in the synthesis of **8**. After 2.27 f/mol of electricity was passed, methanol was evaporated in vacuo. Extraction of the residue with ethyl acetate followed by distillation gave a mixture of **13a** and **13b** (5.422 g, 25.2 mmol). The overall yield was 52% from **12a** and **12b**.

A mixture of **13a** and **13b**: bp 103–105 °C (1 mmHg); IR (neat) 2950, 1695, 1445, 1370, 1320, 1195, 1160, 1115, 1080, 1000 cm^{-1}; NMR ($CDCl_3$) δ 1.50–2.10 (m, 4 H), 2.17 (s, 3 H), 2.20–2.73 (m, 2 H), 3.33 (s, 3 H), 3.72 (s, 3 H), 4.00–4.33 (m, 1 H), 5.14–5.33 (m, 1 H). Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.53; H, 8.07; N, 6.59.

Hygroline (14a + 14b) and Pseudohygroline (14a′ + 14b′). To a stirred suspension of LAH (1 g, 26.3 mmol) in dry ether (25 mL) was added dropwise a solution of a mixture of **13a** and **13b** (1.136 g, 5.28 mmol) in ether. The mixture was refluxed for 10 h under an atmosphere of nitrogen. Usual workup gave a residue, and it was distilled (bulb-to-bulb) to afford a mixture of hygroline (**14a + 14b**) and pseudohygroline (**14a′ + 14b′**)[2a] in a ratio of 2 to 3 (611 mg, 4.27 mmol, 81% yield). Hygroline and pseudohygroline were isolated by preparative GLC and separable by column chromatography (alumina, AcOEt–hexane).

Hygroline: $[\alpha]^{21}_D$ +21.32° (ethanol, *c* 3).[11]

Pseudohygroline: $[\alpha]^{21}_D$ +45.62° (ethanol, *c* 3).

1,2-Bis(methoxycarbonyl)-5-allylpyrrolidines were prepared in 74% yield with the ratio of 72 to 28 by utilizing a similar method to the synthesis of **12a** and **12b**: IR (neat) 3090, 2960, 1760, 1705, 1645, 1450, 1385, 1280, 1200, 1180, 1130, 1118, 1005, 925, 780 cm^{-1}; NMR (CCl_4) δ 1.50–2.93 (m, 6 H), 3.65, 3.68, and 3.70 (3 s, 6 H), 3.77–4.10 (m, 1 H), 4.16–4.37 (m, 1 H), 4.88–5.22 (m, 2 H), 5.50–6.07 (m, 1 H). Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 57.98; H, 7.78; N, 6.16.

Acknowledgment. This work was partly supported by a grant from the Asahi Glass Foundation for Industrial Technology.

An Acid-Catalyzed Hydroxyalkylation of Uracil: A Facile Synthesis of 5-(Arylhydroxymethyl)uracils

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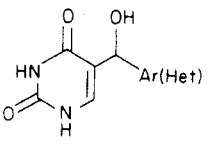
Previously reported syntheses of 5-substituted pyrimidinones **1** have usually found it expedient to incorporate formation of the pyrimidinone ring as a central part of the synthesis. Such approaches involve the use of multifunctionalized precursors such as α-formylhydrocinnamates,[2] α-(arylmethyl)cyanoacetates,[3] α-(arylmethyl)malonitriles,[3] α-(alkoxymethyl)cinnamonitriles,[4] or α-arylmethyl enamino nitriles.[5] In connection with ongoing work in this laboratory, we had the need to develop a more efficient synthesis of 2,4-pyrimidinones such as **1**. We chose to begin our synthesis with inexpensive



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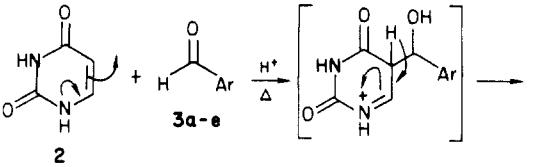
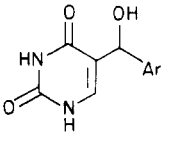
uracil **2** and explore functionalization of the relatively electronegative C-5 carbon with an appropriately substituted electrophilic carbon. Even though 5-hydroxymethylation[6] and 5-chloromethylation[7] of uracil have been extensively studied, we found only one other example of a successful carbon monoalkylation on *unsubstituted* uracil. Roth[2,8] reported that uracil reacts with phenolic Mannich bases to yield 5-benzyluracils in ethylene glycol at 140–160 °C.

We now report that under aqueous acidic conditins unsubstituted uracil **2** reacts with aromatic aldehydes containing an electron-deficient ring **3a-e** (especially heterocyclic aldehydes) to yield 5-(arylhydroxymethyl)-2,4(1*H*,3*H*)-pyrimidinones **4a–e** in good to excellent yields (Table I). Equimolar quantities of **2** and **3** were heated under reflux in aqueous mineral acids (e.g., concentrated HCl, HBr, HI, or H_2SO_4; preferably HCl) for 1–8 h to yield upon neutralization the product **4** (eq 1). These represent,



2 **3a-e**



(1)

4a-e

to the best of our knowledge, the first successful examples utilizing the enamino ketone character of unsubstituted uracil to alkylate C-5 with an aldehyde other than formaldehyde.[6b,9–11] We have been unable to effect this reaction

(1) Present address: Smith Kline Chemicals, Conshohocken, PA 19428.

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(6) (a) Cline, R. E.; Fink, R.; Fink, K. *J. Am. Chem. Soc.* **1959**, *81*, 2521. (b) Brown, D. J. *The Pyrimidines*; Weisburger A., Ed.; Wiley: New York, 1962; Chapter 1.

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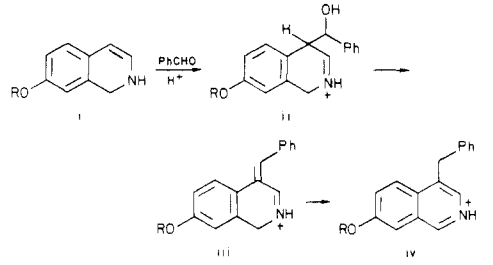
(9) Chevrier, M.; Bensaude, O.; Guillerez, J.; Dubois, J. E. *Tetrahedron Lett.* **1980**, 3359 and references therein.

(10) (a) Iida, H.; Aoyagi, S.; Kawano, K.; Kibayashi, C. *Chem. Pharm. Bull.* **1978**, *26*, 3229. (b) For a review on enamino ketones, see: Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277.

(11) Dyke,[12a] has reviewed the reaction of 1,2-dihydroisoquinolines, a heterocyclic enamine, with aromatic aldehydes to form β-substituted derivatives. Included is an appropriate example initially reported by Bobbitt[13] but refined by Dyke[12b] where 1,2-dihydroisoquinoline i reacted with benzaldehyde in refluxing concentrated HCl to yield the 4-benzylisoquinoline iv via the proposed intermediates ii and iii.



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