(t, 1 H, =CH, $J \simeq 1$ Hz), 7.39 (s, 5 H, Ar H); IR (KBr) 3110, 2950, 1780, 1740, 1620 cm^{-1}. Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.61; H, 5.53.

Preparation of 3-Alkyl-4-hydroxy-2(5*H*)-furanone (4). General Method. To a well-stirred equimolar amount of 1 and alcohol 3 was added 1 mL of concentrated H_2SO_4. The mixture was allowed to stir at 35–40 °C for 3 h and then diluted with water and extracted with ether. The organic layer was dried over anhydrous $MgSO_4$. The solvent was removed by distillation and the product was isolated by column chromatography using ether as an eluent.

3-(1,1-Dimethyleth-1-yl)-4-hydroxy-2(5*H*)-furanone (4a): from 1 and 2-methyl-2-propanol, yield 80%; mp 186 °C; ^1H NMR (Me_2SO-d_6) δ 1.16 (s, 9 H, 3 CH_3), 4.43 (s, 2 H, OCH_2), 11.3 (br s, 1 H, OH); IR (KBr) 1700 cm^{-1}; MS, *m/e* (relative intensity) 156 (M^+, 4), 101 ($M^+ - R + 1$, 100). Anal. Calcd for $C_8H_{12}O_3$: C, 61.53; H, 7.75. Found: C, 61.59; H, 7.81.

3-(1-Methylcyclohex-1-yl)-4-hydroxy-2(5*H*)-furanone (4b): from 1 and 1-methylcyclohexanol, yield 25.5%; mp 190–191 °C; ^1H NMR (Me_2SO-d_6) δ 0.9–1.8 (m, 13 H, aliphatic H), 4.5 (s, 2 H, OCH_2), 11.4 (br s, 1 H, OH); IR (KBr) 2920, 1692 cm^{-1}; MS, *m/e* (relative intensity) 196 (M^+, 1), 101 ($M^+ - R + 1$, 100), 96 (31), 95 (12). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.80; H, 8.16.

3-[1-Methyl-2-(1-methylcyclopent-1-yl)cyclopent-1-yl]-4-hydroxy-2(5*H*)-furanone (4c): from 1 and 1-methylcyclopentanol, yield 17% based on the alcohol charged to the reaction); mp 199 °C, ^1H NMR (Me_2SO-d_6) δ 0.6–2.3 (m, 22 H, aliphatic H), 4.47 (s, 2 H, OCH_2), 11.34 (br s, 1 H, OH); IR (KBr) 2920, 1705 cm^{-1}; MS, *m/e* (relative intensity) 264 (M^+, 8.5), 164 (100). Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.53; H, 9.08.

Improved Synthesis of *N*-Benzyl-5-ethyl-1,2,3,4-tetrahydropyridine

Mark H. Norman and Clayton H. Heathcock*

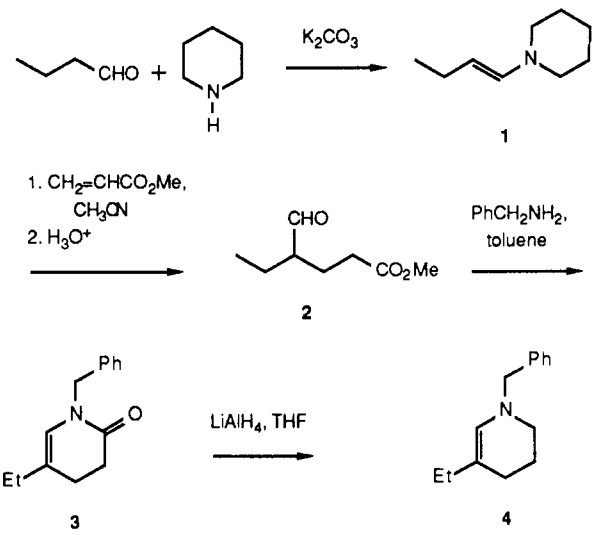
Department of Chemistry, University of California, Berkeley, California 94720

Received January 28, 1988

The title compound (4) is a useful synthon for the elaboration of indole alkaloids.[1] To date, the most convenient synthesis of 4 appears to be that of Ziegler and coworkers.[1b,c] In this synthesis, 4 is prepared from butanal in a seven-step route that proceeds in 31% overall yield. In this paper, we report an improved synthesis which delivers enamine 4 in only four steps in an overall yield of 80%.

The synthesis of enamine 4 is summarized in Scheme I. The piperidine enamine of butanal (1) is prepared in 81% yield by the reaction of the aldehyde with 2.4 equiv of piperidine in the presence of anhydrous potassium carbonate.[2] Aldehyde ester 2 is obtained in 65% yield by the Michael addition of enamine 1 to methyl acrylate in acetonitrile.[2b] Nitrogen is introduced by condensation of 2 with benzylamine to provide unsaturated lactam 3. This reaction proceeds cleanly by distilling and draining off the toluene–water and toluene–methanol azeotropes; unsaturated lactam 3 is obtained in a 96% yield. Reduction of 3 with 5 equiv of lithium aluminum hydride in tetrahydrofuran at room temperature for 24 h affords enamine 4 in 89% yield after distillation. Each of the reactions in this sequence proceeds sufficiently cleanly that the four-step sequence can be carried out without purification of intermediates. When the crude intermediates are carried on in this manner, endocyclic enamine 4 is obtained in 80% overall yield.

Scheme I



Experimental Section

1-(*N*-Piperidinyl)-1-butene (1). Piperidine (25.0 g, 29.0 mL, 0.294 mol) and anhydrous K_2CO_3 (6.00 g, 0.0434 mol) were added to a 100-mL round-bottomed flask equipped with a magnetic stirring bar. The mixture was placed under nitrogen and cooled to 0 °C with an ice bath. Butanal (9.00 g, 11.0 mL, 0.125 mol) was added over a 1-h period with a syringe pump. The reaction mixture was stirred for an additional 2 h at 0 °C. The solids were filtered and washed with ether. The solvent was removed with a rotary evaporator, and the resulting crude product was purified by distillation under reduced pressure to give 14.0 g (81%) of 1 as a colorless liquid: bp 35–36 °C (1.0 Torr) [lit.[2a] bp 70–71 °C (10 Torr)]; IR (film) 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (t, 3, J = 7.4), 1.55 (m, 6), 1.98 (ddq, 2, J = 7.4, 6.8, 1.0), 2.73 (t, 4, J = 5.3), 4.42 (dt, 1, J = 13.9, 6.8), 5.83 (d, 1, J = 13.9); ^{13}C NMR ($CDCl_3$) δ 15.81, 23.69, 24.34, 25.43, 50.08, 103.24, 139.51. Anal. Calcd for $C_9H_{17}N$: C, 77.63; H, 12.31; N, 10.06. Found: C, 77.38; H, 12.52; N, 10.01.

Methyl 4-Formylhexanoate (2). A 250-mL round-bottomed flask equipped with a magnetic stirring bar was charged with a solution of 7.00 g (50.0 mmol) of enamine 1 in 35 mL of dry acetonitrile. The solution was cooled below 5 °C with an ice–salt bath. A solution of methyl acrylate (5.66 mL, 5.41 g, 63.0 mmol, 1.25 equiv) in acetonitrile (15.0 mL) was added with stirring to the reaction mixture over a 0.5-h period with a syringe pump. The reaction mixture was allowed to warm to room temperature and stirred for 8 h. A reflux condenser was attached, and the solution was heated at reflux for 36 h. Acetic acid (3.0 mL) and distilled water (20.0 mL) were added, and the resulting solution was heated at reflux for 8 h. The mixture was allowed to cool to room temperature, the aqueous phase was saturated with NaCl, and the solution was extracted with ether. The organic extract was washed with 5% HCl, 5% $NaHCO_3$, and saturated aqueous NaCl. The ether layer was dried over $MgSO_4$, filtered, and reduced in volume with a rotary evaporator to give 5.80 g of crude product. The material was purified by distillation under reduced pressure to give 5.14 g (65%) of 2 as a colorless liquid, bp 42–48 °C (0.22–0.12 Torr) [lit.[2b] bp 95–98 °C (10 Torr)]; IR (film) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (t, 3, J = 7.5), 1.49–1.86 (m, 3), 1.96 (m, 1), 2.32 (m, 3), 3.67 (s, 3), 9.60 (d, 1, J = 2.4); ^{13}C NMR ($CDCl_3$)

(1) (a) Stevens, R. V. *Acc. Chem. Res.* **1977**, *10*, 193. (b) Ziegler, F. E.; Kloek, J. A.; Zoretic, P. A. *J. Am. Chem. Soc.* **1969**, *91*, 2342. (c) Ziegler, F. E.; Zoretic, P. A. *Tetrahedron Lett.* **1968**, 2639–2641. (d) Stevens, R. V.; Mehra, R. K.; Zimmerman, R. L. *Chem. Commun.* **1968**, 1104. (e) Stevens, R. V.; Mehra, R. K.; Zimmerman, R. L. *Chem. Commun.* **1968**, 1104. (f) Ziegler, F. E.; Spitzner, E. B. *J. Am. Chem. Soc.* **1973**, *95*, 7146. (g) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289. (h) Stevens, R. V.; Mehra, R. K.; Zimmerman, R. L. *J. Chem. Soc. D* **1969**, 877.

(2) (a) Mannich, C.; Davidsen, H. *Chem. Ber.* **1936**, *69*, 2106. (b) Stork, G.; Brizzolara, N.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.

0022-3263/88/1953-3370$01.50/0

δ 10.94, 21.49, 22.84, 31.06, 51.32, 52.12, 173.11, 204.07. Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 61.01; H, 9.01.

***N*-Benzyl-5-ethyl-3,4-dihydro-2-pyridone (3).** Methyl 4-formylhexanoate (**2**, 3.00 g, 19.0 mmol), benzylamine (2.07 mL, 2.03 g, 19.0 mmol, 1.0 equiv), and dry toluene (20.0 mL) were placed in a 50-mL round-bottomed flask equipped with a magnetic stirring bar and a Dean–Stark trap. The reaction mixture was heated at reflux for 6 h, and 10 mL of the toluene–water azeotrope was drained off. An additional 30 mL of fresh toluene was added, and the solution was heated at 95 °C for 12 h. The reaction mixture was heated to reflux, and 20 mL of the toluene–methanol azeotrope was drained off. The remaining solvent was removed with a rotary evaporator to give a crude product, which was purified by bulb-to-bulb distillation under reduced pressure to afford 3.93 g (96%) of **3** as a colorless liquid: bp 120–130 °C (0.15–0.50 Torr); IR (film) 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (t, 3, J = 7.4), 2.02 (q, 2, J = 7.4), 2.27 (t, 2, J = 8.0), 2.58 (t, 2, J = 8.0), 4.67 (s, 2), 5.75 (quintet, 1, J = 1.3), 7.28 (m, 5); ^{13}C NMR ($CDCl_3$) δ 12.09, 23.93, 26.50, 31.03, 48.55, 121.64, 122.70, 127.04, 127.26, 128.30, 137.16, 168.56. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 77.96; H, 7.98; N, 6.45.

***N*-Benzyl-5-ethyl-1,2,3,4-tetrahydropyridine (4). (a) From *N*-Benzyl-5-ethyl-3,4-dihydro-2-pyridone (3).** To a flame-dried 50-mL round-bottomed flask equipped with a magnetic stirring bar was added $LiAlH_4$ (1.30 g, 34.2 mmol, 7.0 equiv) and dry THF (10.0 mL). The gray suspension was cooled to 0 °C in an ice bath and placed under a nitrogen atmosphere. A solution of lactam **3** (1.05 g, 4.89 mmol) in 5.0 mL of dry THF was added over a 10-min period. After 30 min at 0 °C and 24 h at room temperature, the solution was cooled in an ice bath and the reaction was quenched by the slow addition of water (1.30 mL), 15% NaOH (1.30 mL), and water (3.90 mL). The resulting salts were filtered and washed with ether. The ether filtrate was dried over $MgSO_4$, filtered, and reduced in volume to afford 0.98 g of crude material. The product was purified by bulb-to-bulb distillation under reduced pressure to give 0.873 g (89%) of **4** as a colorless liquid: bp 95–100 °C (0.30 Torr) [lit.[1b] bp 91–94 °C (0.25 Torr)]; IR (film) 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (t, 3, J = 7.4), 1.89 (m, 6), 2.73 (t, 2, J = 5.4), 3.87 (s, 2), 5.76 (s, 1), 7.28 (m, 5); ^{13}C NMR ($CDCl_3$) δ 13.07, 22.54, 24.55, 28.21, 47.34, 59.89, 112.34, 126.82, 128.10, 128.20, 130.43, 138.70. Anal. Calcd for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.56; H, 9.56; N, 6.82.

(b) From Butanal. The foregoing procedure was employed without purification of intermediates. Piperidine (25.00 g, 29.00 mL, 0.294 mol) and anhydrous K_2CO_3 (6.00 g, 0.0434 mol) gave rise to 19.81 g of crude 1-(*N*-piperidinyl)-1-butene (**1**) as a colorless oil. A solution of this material and methyl acrylate (13.66 g, 14.28 mL, 0.159 mol, 1.25 equiv) in 100 mL of acetonitrile was heated at reflux for 21.5 h to obtain 17.72 g of aldehyde ester **2** as a light, yellow oil. This material was refluxed with benzylamine (12.24 g, 0.114 mol, 1.02 equiv) in 120 mL of dry toluene with removal of water to obtain 25.56 g of *N*-benzyl-5-ethyl-3,4-dihydro-2-pyridone (**3**) as a light yellow oil. Lactam **3** was reduced as indicated in the foregoing procedure with $LiAlH_4$ (8.88 g, 0.254 mol, 2.0 equiv) to obtain 22.22 g of crude **4**. Purification by bulb-to-bulb distillation under reduced pressure gave 20.43 g (80% from butanal) of **4** as a light yellow oil, identical spectrally with that obtained by method a.

Acknowledgment. This work was supported by a research grant from the National Science Foundation (CHE 8418437).

Communications

Retention of Configuration in the Coupling of Aluminated Heterocycles with Glycopyranosyl Fluorides

Summary: Coupling reactions between glycopyranosyl fluorides and 2-(diethylaluminio)furan and 2-(diethylaluminio)-1-methylpyrrole giving the corresponding sugar heterocycles are observed to proceed with retention of configuration at the anomeric center. Couplings of the same aluminated heterocycles with ribofuranosyl fluorides gave predominantly the β-ribofuranosyl heterocycle.

Sir: In connection with our ongoing studies toward the total synthesis of *C*-glycosyl antibiotics,[1] we became interested in the preparation of glycopyranosylfurans. Although there is ample precedent in the literature for the construction of glucosyl heterocyclic ring systems from various precursors,[2] recent reports concerning the coupling of sugar fluorides with organoaluminum reagents[3] suggested an alternative, more convergent route to glycopyranosylfurans. This communication reports that coupling for glycopyranosyl fluorides with certain aluminated heterocycles occurs readily, and moreover, *the coupling proceeds with retention of configuration at the anomeric center.* Ribofuranosyl fluorides in similar coupling reactions give predominantly the β-ribofuranosyl heterocycle.

With the recently developed reagents for the preparation of particular anomeric glycosyl fluorides[4,5] and the constant need for new *C*-glycosyl forming reactions for total synthesis of natural products and biologically active compounds, this methodology may prove to be particularly useful.

The sugar fluorides were prepared according to literature procedures. Thus 2,3,4,6-tetra-*O*-benzyl-β-D-glyco-

(1) Ravidomycin: Findlay, J. A.; Liu, J.-S.; Radics, L.; Rakhit, S. *Can. J. Chem.* **1981**, *59*, 3018. Findlay, J. A.; Liu, J.-S.; Radics L. *Can. J. Chem.* **1983**, *61*, 323. Synthetic studies include: Findlay, J. A.; Daljeet, A.; Murray, P. J.; Rej, R. N. *Can. J. Chem.* **1987**, *65*, 427. McKenzie, T. C.; Hassen, W. *Tetrahedron Lett.* **1987**, *28*, 2563. McKenzie, T. C.; Hassen, W.; Macdonald, S. J. F. *Tetrahedron Lett.* **1987**, *28*, 5435. Macdonald, S. J. F.; McKenzie, T. C.; Hassen, W. D. *J. Chem. Soc., Chem. Commun.* **1987**, *1528*. Outten, R. A.; Daves, G. D. *J. Org. Chem.* **1987**, *52*, 5064. Toromycin: Hori, S.; Fukase, H.; Mizuta, E.; Hatano, K.; Mizano, K. *Chem. Pharm. Bull.* **1980**, *28*, 3601. Albacarcin: Matson, J. A.; Myllymaki, R. W.; Doyle, T. W.; Bush, J. A. U.S. Pat 4 461 831, 1984; *Chem. Abstr.* **1985**, *102*, P4456a. Gilvocarcin: Takahashi, K.; Yoshida, M.; Tomita, F.; Shirahata, K. *J. Antibiot.* **1981**, *34*, 271. Virenomycin: Brazhnikova, M.; Kudinova, M. K.; Kulyaeva, V. V.; Potapova, N. P.; Rubasheva, L. M.; Rozynova, B. V.; Horvath, G. *Antibiotika (Moscow)* **1984**, *29*, 884; *Chem. Abstr.* **1985**, *102*, 185366q. Chrysomycin: Weiss, V.; Yoshihira, K.; Highet, R. J.; White, R. J.; Wei, T. T. *J. Antibiot.* **1982**, *35*, 1194.

(2) For examples, see: Buchanan, J. G. In *Progress in the Chemistry of Organic Natural Products*; Herz, W.; Grisebach, H., Kirby, G. W.; Ed.; Springer-Verlag: New York, 1983; Vol. 44, pp 243–299. Schmidt, R. R.; Effenberger, G. *Liebigs Ann. Chem.* **1987**, 825.

(3) (a) Nicolaou, K. C.; Dolle, R. E.; Chucholowski, A.; Randall, J. L. *J. Chem. Soc., Chem. Commun.* **1984**, 1153, 1155. (b) Nicolaou, K. C.; Dolle, R. E.; Papahatjis, D. P.; Randall, J. L. *J. Am. Chem. Soc.* **1984**, *106*, 4189. (c) Posner, G. H.; Haines, S. R. *Tetrahedron Lett.* **1985**, *26*, 1823.

(4) Rosenbrook, W.; Riley, D. A.; Lartey, P. A. *Tetrahedron Lett.* **1985**, *26*, 3. Posner, G. H.; Haines, S. R. *Tetrahedron Lett.* **1985**, *26*, 5.

(5) Hayashi, M.; Hashimoto, S.; Noyori, R. *Chem. Lett.* **1984**, 1747. Szarek, W. A.; Grynkiewicz, G.; Doboszewski, B.; Hay, G. W. *Chem. Lett.* **1984**, 1751.

0022-3263/88/1953-3371$01.50/0