Synthesis of 6-Substituted 7*H*-Pyrido[4,3-*c*]carbazoles

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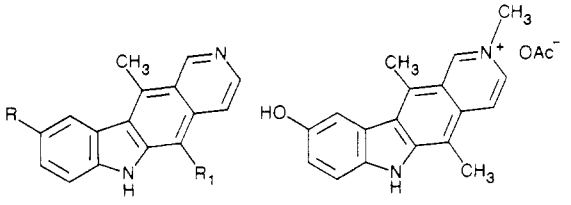
Condensation of *N*-(phenylsulfonyl)-2-methoxalylindole and its 5-methoxy analogue with a modified Wittig reagent prepared from diphenyl(4-pyridylmethyl)phosphine oxide furnished the olefins **16** and **17**, respectively. Oxidative photocyclization furnished the 6-carbomethoxy-7*H*-pyrido[4,3-*c*]carbazoles **18** and **24**. Reduction with lithium aluminum hydride gave the carbinols **19** and **23**, which when treated with methyl isocyanate gave the corresponding *N*-methylcarbamates **20** and **26**, which are potential antitumor agents. Manganese dioxide oxidation of **19** and **25** furnished the aldehydes **21** and **27**. Treatment with methylenetriphenylphosphorane gave olefins **22** and **28**, which upon catalytic reduction afforded the 6-ethyl-7*H*-pyrido[4,3-*c*]carbazoles **23** and the known **29**.

Ellipticine (1; 5,11-dimethyl-6H-pyrido[4,3-*b*]carbazole) and its methoxy analogue **2** are alkaloids that exhibit antitumor activity in rodent models.[1] To the best of our knowledge, of the many ellipticine analogues that have been synthesized, only **2** and elliptinium acetate (**3**; 9-hydroxy-2,5,11-trimethyl-6*H*-pyrido[4,3-*b*]carbazolium acetate) demonstrated significant antitumor activity in humans.[2]



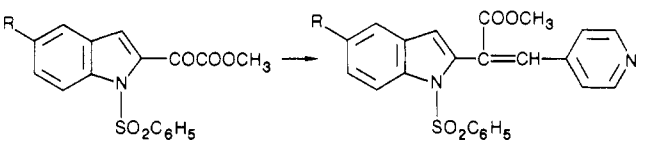
3

1: R = H, R_1 = CH_3
2: R = CH_3O, R_1 = CH_3
4: R = OH, R_1 = CH_3
5: R = OH, R_1 = CH_2OH
6: R = OH, R_1 = $CH_2OSO_3^-$ or $CH_2OPO_3H^-$
7: R = OH, R_1 = CH_2^+
8: R = OH, R_1 = CH_2DNA
9: R = H, R_1 = CH_2OH
10: R = H, R_1 = $CH_2OOCNHCH_3$

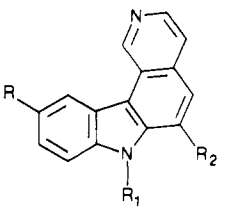
In a previous paper,[3] we proposed a new mechanism of action at the molecular level to account for the antitumor activity of ellipticine. It was suggested that in the host, **1** was metabolized to **4**, which in turn was subjected to biooxidation followed by enzymatic esterification to give first **5** and then **6**. The latter dissociates nonenzymatically to give the ion **7** or its equivalent, which then alkylates DNA. In support of this hypothesis, **9** was synthesized and converted to **10**, which served as a surrogate for **6**. The carbamate **10** showed antitumor activity in P388 murine leukemia and inhibited thymidine uptake by HeLa cells after drug exposure followed by washing to remove any noncovalently bound drug. We proposed that the lethal event was the stabilization of the DNA–topoisomerase II complex as suggested for the clinically useful antitumor agents adriamycin and *m*-AMSA.[4]

Pelaprat et al.[5] synthesized and tested a series of 7*H*-pyrido[4,3-*c*]carbazoles for antitumor activity in the L1210 murine leukemia model. Several compounds behaved as intercalating agents, but none was as active as ellipticine itself. These authors did not prepare any derivatives at C_6 which could furnish a carbonium ion such as **31** which could alkylate DNA. Accordingly, we undertook the preparation of **20** and **26** for evaluation as antitumor agents. The synthesis of these carbamates is the subject of this paper. In contrast to the large number of synthetic

Scheme I



14: R = H
15: R = OMe
16: R = H
17: R = OMe



18: R = R_1 = H, R_2 = $COOCH_3$
19: R = R_1 = H, R_2 = CH_2OH
20: R = R_1 = H, R_2 = $CH_2OOCNHCH_3$
21: R = R_1 = H, R_2 = CHO
22: R = R_1 = H, R_2 = $CH{=}CH_2$
23: R = R_1 = H, R_2 = C_2H_5
24: R = OCH_3, R_1 = H, R_2 = $COOCH_3$
25: R = OCH_3, R_1 = H, R_2 = CH_2OH
26: R = OCH_3, R_1 = H, R_2 = $CH_2OOCNHCH_3$
27: R = OCH_3, R_1 = H, R_2 = CHO
28: R = OCH_3, R_1 = H, R_2 = $CH{=}CH_2$
29: R = OCH_3, R_1 = H, R_2 = C_2H_5
30: R = OCH_3, R_1 = $C_6H_5SO_2$, R_2 = $COOCH_3$
31: R = OCH_3, R_1 = H, R_2 = CH_2^+
32: R = OCH_3, R_1 = H, R_2 = CH_3

schemes developed for the preparation of 6*H*-pyrido[4,3-*b*]carbazoles,[6,7] very few methods are available for the synthesis of 6-substituted 7*H*-pyrido[4,3-*c*]carbazoles.[8-10] Léon et al.[11] and Roques et al.[12] have synthesized **29** and

† Deceased July 5, 1988.

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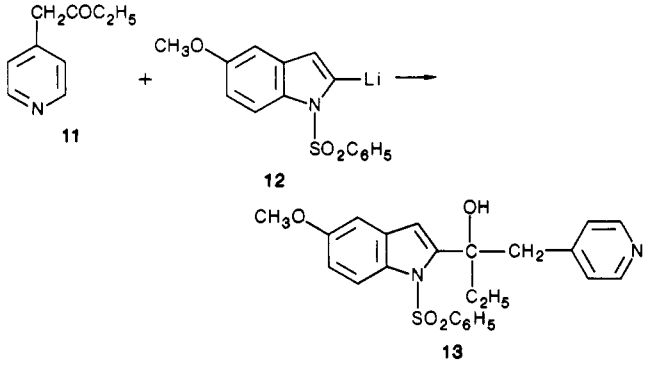
32. The limiting factor in the synthesis of **29** was the preparation of the intermediate **13** while the synthesis of **32** required a large number of steps. The pyridyl ketone **11** was prepared in 41% yield, and the condensation with **12** gave **13** in only 14% yield. In their procedure there is no common intermediate in the later stages of the synthesis that can be converted to homologous compounds.



In the course of the synthesis of the target compounds **20** and **26**, we developed what appears to be a general method for the preparation of 6-alkyl-7*H*-pyrido[4,3-*c*]-carbazoles (Scheme I).

N-(Phenylsulfonyl)-2-methoxyalylindole (**14**)[13] was treated with a modified Wittig reagent derived from diphenyl(4-pyridylmethyl)phosphine oxide[14] to furnish **16** in 79% yield. Oxidative photocyclization[15] of **16** gave the 7*H*-pyrido[4,3-*c*]carbazole **18** in 52% yield. The absence of the *N*-phenylsulfonyl group was confirmed by elemental analysis, NMR, and mass spectroscopy.

The methoxy analogue **17** was prepared from **15**. Cyclization afforded the desired 7*H*-pyrido[4,3-*c*]carbazole **24** in 23% yield accompanied by the phenylsulfonyl derivative **30**, which separated from the reaction mixture in 11% yield during the photocyclization reaction. The structures of both compounds were secured by elemental analyses and spectroscopic analyses.

Reduction of the esters **18** and **24** gave the carbinols **19** and **25**, respectively. These were treated with methyl isocyanate to give the *N*-methylcarbamates **20** and **26**. The carbinols **19** and **25** were oxidized to the corresponding aldehydes **21** and **27** with the aid of MnO_2. Treatment with the Wittig reagent methylenetriphenylphosphorane gave the required olefins **22** and **28**, which after catalytic hydrogenation gave **23** and **29**, respectively. Although the olefin **28** furnished the expected NMR spectrum, it was extremely difficult to obtain in an analytically pure state. Nevertheless, on reduction it gave a compound identical with the material prepared previously by Léon et al.[11]

Experimental Section

All reactions with the exception of the catalytic hydrogenations were carried out in an argon atmosphere, using flame-dried glassware. Tetrahydrofuran was dried by distillation from sodium–benzophenone and used immediately. Melting points were taken on a Mel-Temp apparatus and are uncorrected. Infrared spectra were run on a Perkin-Elmer Model 298 spectrometer, NMR spectra were run on a Varian XL-200 (200 MHz) spectrometer using $(CH_3)_4Si$ as the internal standard, and mass spectra were obtained on a Hewlett-Packard Model 5987A GC/MS spectrometer using isobutane as the CI gas.

Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA. The 6-substituted 7*H*-pyrido[4,3-*c*]carbazoles retained water tenaciously despite careful drying. Proton signals attributed to H_2O were observed in the NMR spectra.

1-Carbomethoxy-1-[*N*-(phenylsulfonyl)-2-indolyl]-2-(4-pyridyl)ethylene (16). A mixture of 3.40 g (11.6 mM) of diphenyl(4-pyridylmethyl)phosphine oxide[14] and 1.11 g (46.4 mM) of powdered NaH in 160 mL of THF was refluxed for 2 h. The deep yellow solution was cooled to 0 °C, and a solution of 3.80 g (11.0 mM) of *N*-(phenylsulfonyl)-2-methoxalylindole (**14**) in 50 mL of THF was added slowly to the stirred mixture. The whole was stirred at room temperature for 19 h and filtered. The insoluble material was washed with benzene until the filtrate was colorless. The combined filtrates were concentrated to dryness, and the residue was redissolved in benzene. The solution was washed with H_2O followed by a brine solution. The dried benzene solution was evaporated to leave 4.1 g of a crude product, which after crystallization from CH_3OH afforded 3.67 g (79%) of **16**: mp 174–176 °C; IR (KBr) 3050, 1695, 1580, 1410, 1355–1340, 1210, 1150, 1050, 825, 745 cm^{-1}; MS, *m/e* 419 (M + 1), NMR ($CDCl_3$) δ 8.28–8.24 (3 H, m), 7.84–7.76 (3 H, m), 7.53–7.19 (6 H, m), 6.77–6.74 (2 H, m), 6.53 (1 H, s), 3.79 (3 H, s, $COOCH_3$).

Anal. Calcd for $C_{23}H_{18}N_2O_4S$: C, 66.03; H, 4.31; N, 6.70. Found: C, 65.93; H, 4.41; N, 6.66.

6-Carbomethoxy-7*H*-pyrido[4,3-*c*]carbazole (18). A solution of 1.8 g (40 mM) of **16** and 0.79 g (5.5 mM) of I_2 in 1.8 L of CH_3OH was irradiated by an Ace-Hanovia UV lamp for 24 h. The solvent was removed in vacuo, and the residue was dissolved in 300 mL of $CHCl_3$. The solution was washed successively with 160 mL of saturated $NaHCO_3$, 110 mL of aqueous $Na_2S_2O_3$, water, and finally brine. The dried organic layer was evaporated to leave a residue, which was triturated with hot CH_3OH and cooled to give 620 mg of almost pure **18** (52%). After one crystallization from CH_3OH, the crystals melted at 344–346 °C dec: IR (KBr) 3320–2100, 1685, 1428, 1310, 1265, 1210–1190, 910, 890, 735 cm^{-1}; NMR (DMSO-d_6) δ 12.04 (1 H, br s, NH), 10.29 (1 H, s, H_1), 8.77–8.63 (3 H, m), 8.17 (1 H, d, J = 5.6, H_8), 7.94 (1 H, d, J = 8.0, H_4), 7.55–7.39 (2 H, m), 4.09 (3 H, s, $COOCH_3$), 3.39 (H_2O); MS, *m/e* 277 (M + 1).

Anal. Calcd for $C_{17}H_{12}N_2O_2 \cdot 0.5H_2O$: C, 71.57; H, 4.56; N, 9.82. Found: C, 71.87; H, 4.57; N, 9.74.

6-(Hydroxymethyl)-7*H*-pyrido[4,3-*c*]carbazole (19). A solution of 82 mg (22 mM) of LAH in 10 mL of THF was stirred at 0 °C while 100 mg (0.36 mM) of the ester **18** was added portionwise over a period of 5 min. The green suspension was stirred for an additional 15 min before 0.1 mL of H_2O, 0.1 mL of 15% aqueous NaOH, and 0.3 mL of H_2O were added in that order. After 5 min, the suspension was filtered and the solid was washed with 50 mL of a 20:1 THF–CH_3OH solution followed by 50 mL of a 20:1 ether–CH_3OH solution. The combined organic layers were evaporated to dryness to leave 85 mg (95%) of **19**, which after one crystallization from acetonitrile gave analytically pure crystals: mp 246–248 °C; IR (KBr) 3570, 3400–2700, 1575, 1430, 1235, 1020, 870, 735 cm^{-1}; NMR (DMSO-d_6) δ 10.13 (1 H, s, H_1), 8.67 (1 H, d, J = 7.8, H_3), 8.51 (1 H, d, J = 5.4, H_{11}), 8.31–8.21 (1 H, m), 7.97–7.92 (2 H, m), 7.74 (1 H, d, J = 7.8, H_4), 7.82–7.34 (3 H, m), 5.05 (2 H, s, CH_2OH), 3.36 (H_2O); MS, *m/e* 249 (M + 1).

Anal. Calcd for $C_{16}H_{12}N_2O \cdot 0.75H_2O$: C, 73.56; H, 5.17. Found: C, 73.57; H, 5.14.

6-(Hydroxymethyl)-7*H*-pyrido[4,3-*c*]carbazole *N*-Methylcarbamate (20). A solution of 160 mg (0.65 mM) of the carbinol **19** in 4.0 mL of dry pyridine was stirred at room temperature for 1 h before being treated with 380 mg of freshly distilled CH_3NCO. Stirring was continued at room temperature until all the carbinol had been consumed (TLC, 72 h). The reaction mixture was evaporated to dryness, and the residue was chromatographed on a silica gel column using ethyl acetate–hexane as the eluant. There was obtained 120 mg (62%) of the desired carbamate, which melted at 237–239 °C after one crystallization from ethyl acetate: IR (KBr) 3390, 3280, 2945, 1670, 1510, 1405, 1315, 1210, 1080, 945, 770 cm^{-1}; NMR (DMSO-d_6) δ 12.09 (1 H, s, NH), 10.17 (1 H, s, H_1), 8.70 (1 H, d, J = 8.0, H_3), 8.55 (1 H,

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d, J = 5.6, H_{11}), 7.97–7.92 (2 H, m), 7.74 (1 H, d, J = 8.0, H_4), 7.72 (1 H, t, H_9), 7.41–7.28 (2 H, m), 5.55 (2 H, s, CH_2O), 3.36 (s, H_2O), 2.65 (3 H, d, J = 4.6, NHCH_3); MS, m/e 306 (M + 1).

Anal. Calcd for $C_{18}H_{15}N_3O\cdot0.67H_2O$: C, 68.14; H, 5.15; N, 13.25. Found: C, 67.82; H, 5.12; N, 13.26.

6-Formyl-7*H*-pyrido[4,3-*c*]carbazole (21). A mixture of 112 mg (0.45 mM) of **19** and 483 mg (5.6 mM) of activated MnO_2 in 100 mL of $CHCl_3$ was stirred under reflux for 6 h and then at room temperature for 12 h. The mixture was filtered through a bed of Celite and the collected solid washed with warm $CHCl_3$. The combined filtrates were concentrated to dryness to leave a crystalline residue, which, after crystallization from CH_3CN–CH_3OH (2:1), gave 77 mg (69%) of pure aldehyde **21**: mp 277–280 °C; IR (KBr) 3390, 3280, 2945, 1670, 1510, 1405, 1315, 1210, 1080, 945, 770 cm^{-1}; NMR (DMSO-d_6) δ 12.36 (1 H, s, NH), 10.44 (1 H, s, CHO), 10.29 (1 H, s, H_1), 8.77–8.64 (3 H, m), 8.17 (1 H, d, J = 5.4, H_8), 7.95 (1 H, d, J = 8.0, H_4), 7.75–7.40 (2 H, m, H_9, H_{10}), 3.36 (s, H_2O); MS, m/e 247 (M + 1).

Anal. Calcd for $C_{16}H_{10}N_2O\cdot0.67H_2O$: C, 74.13; H, 4.37; N, 10.81. Found: C, 74.15; H, 4.05; N, 10.73.

6-Ethenyl-7*H*-pyrido[4,3-*c*]carbazole (22). An 80% suspension of 310 mg (0.01 M) of NaH in mineral oil was washed thoroughly with hexane. Six milliliters of dry DMSO was added, and the mixture was kept at 70 °C for 1.5 h. The resulting dark solution was cooled to 0 °C before being treated with a solution of 3.57 g (0.01 M) of methyltriphenylphosphonium bromide in 10 mL of warm DMSO. The resulting deep yellow-orange solution was stirred at room temperature for 20 min before use. To 9 mL of the above solution there was added with stirring a solution of 122 mg (0.496 mM) of the aldehyde **21** in 8 mL of warm DMSO. After being stirred for 16 h, the suspension was poured into 50 mL of H_2O. The mixture was extracted with $CHCl_3$, and the organic layer was washed with brine, dried, and concentrated to leave an oily residue, which was chromatographed on a column of silica gel by using ethyl acetate–hexane (1:2) as the eluant. There was obtained 78 mg (65%) of the desired olefin **22**, which melted at 258–260 °C after crystallization from CH_3CN–CH_3OH: IR (KBr) 3280–2700, 1605, 1500, 1435, 1355, 1225, 1110, 1055, 905 cm^{-1}; NMR (DMSO-d_6) δ 12.18 (1 H, s, NH), 10.15 (1 H, s, H_1), 8.71 (1 H, d, J = 7.8, H_3), 8.52 (1 H, d, J = 5.4, H_{11}), 8.18 (1 H, s, CH=CH_2), 7.96 (1 H, d, J = 3.4, H_8), 7.74 (1 H, d, J = 7.8, H_4), 7.56–7.37 (3 H, m), 6.34 (1 H, d, CH=CH_2), 6.26 (1 H, d, CH=CH_2), 3.34 (s, H_2O); MS, m/e 245 (M + 1).

Anal. Calcd for $C_{17}H_{12}N_2\cdot0.25H_2O$: C, 82.09; H, 5.03; N, 11.26. Found: C, 82.25; H, 5.11; N, 11.21.

6-Ethyl-7*H*-pyrido[4,3-*c*]carbazole (23). The olefin **22** (45 mg, 0.18 mM) was dissolved in 40 mL of CH_3OH and hydrogenated in the presence of 12 mg of 10% Pd/C at 3 atm. After 2 h, the mixture was filtered and the catalyst was washed with fresh CH_3OH. Evaporation of the combined filtrates gave 30 mg (80%) of **23**, mp 293–295 °C after crystallization from CH_3OH: IR (KBr) 3425, 3250, 1605, 1355, 1225, 1110, 1050, 915, 860, 730 cm^{-1}; NMR (DMSO-d_6) δ 12.13 (1 H, s, NH), 10.12 (1 H, s, H_1), 8.67 (1 H, d, J = 7.4, H_{11}), 8.50 (1 H, d, J = 5.6, H_3), 7.91 (1 H, d, J = 5.6, H_4), 7.81–7.71 (1 H, m, H_5), 7.54–7.36 (3 H, m), 3.37 (s, H_2O), 3.15 (2 H, q, CH_2CH$_3$), 1.44 (3 H, t, CH$_2$CH_3); MS, m/e 247 (M + 1).

Anal. Calcd for $C_{17}H_{14}N_2\cdot0.33H_2O$: C, 80.95; H, 5.82; N, 11.11. Found: C, 80.93; H, 5.82; N, 10.91.

***N*-(Phenylsulfonyl)-2-methoxalyl-5-methoxyindole (15).** A 1.7 M solution of *tert*-butyllithium (16 mL, 27.1 mM) in pentane was added dropwise to a solution of 6.0 g (20.1 mM) of *N*-(phenylsulfonyl)-5-methoxyindole[11] in 50 mL of THF kept at −10 °C. The clear red solution was stirred for 20 min at −5 °C and for an additional 20 min at room temperature. The solution was transferred to a dropping funnel and added dropwise to a stirred solution of 10.0 g (85.5 mM) of dimethyl oxalate in 35 mL of THF at 0 °C. After 1 h at room temperature, the reaction was quenched by the addition of 50 mL of 5% NH_4Cl. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with H_2O and brine and then dried. Evaporation of the solution left an oil, which was dissolved in CH_3OH and cooled. There was obtained 4.18 g (54%) of the desired ester: mp 147–149 °C; IR (KBr) 2960, 2740, 1770, 1695, 1540, 1472, 1455, 1371 cm^{-1}; NMR ($CDCl_3$) δ 7.96 (1 H, d, J = 8.8, H_7), 7.75–7.71 (2 H, m), 7.52–7.35 (4 H, m), 7.09 (1 H, dd, H_6), 6.97 (1 H, s, H_3), 3.99 (3 H, s, OCH_3), 3.80 (3 H, s, $COOCH_3$); MS, m/e 374 (M + 1).

Anal. Calcd for $C_{18}H_{15}NO_6S$: C, 57.90; H, 4.05; N, 3.75. Found: C, 57.99; H, 4.09; N, 3.71.

1-[*N*-(Phenylsulfonyl)-5-methoxy-2-indolyl]-1-carbomethoxy-2-(4-pyridyl)ethylene (17). A mixture of 1.5 g (5.12 mM) of diphenyl(4-pyridylmethyl)phosphine oxide and 490 mg (20.5 mM) of NaH in 120 mL of THF was refluxed for 2 h and then cooled to 0 °C. To the stirred reaction mixture there was added a solution of 1.82 g (4.88 mM) of the glyoxylate ester, **15**, in 50 mL of warm THF, and the whole was stirred at room temperature for 20 h, after which time the reaction mixture was worked up as in the case of **16** (vide supra). The crude product was crystallized from CH_3OH to give 1.42 g (65%) of the pure olefin **17**: mp 156–158 °C; IR (KBr) 2950, 1725, 1590, 1445, 1365, 1210, 1090–1030, 820, 760, 725, 690, 625 cm^{-1}; NMR ($CDCl_3$) δ 8.68–8.65 (2 H, m), 8.07 (1 H, d, J = 9.2), 7.71–7.67 (2 H, m), 7.53–7.26 (5 H, m), 7.02–6.91 (3 H, m), 6.66 (1 H, s), 3.83 (3 H, s, OCH_3), 3.74 (3 H, s, $COOCH_3$); MS, m/e 449 (M + 1).

Anal. Calcd for $C_{24}H_{20}N_2O_5S$: C, 66.03; H, 4.31; N, 6.70. Found: C, 65.93; H, 4.41; N, 6.60.

***N*-(Phenylsulfonyl)-6-carbomethoxy-10-methoxy-7*H*-pyrido[4,3-*c*]carbazole (30) and 6-Carbomethoxy-10-methoxy-7*H*-pyrido[4,3-*c*]carbazole (24).** A solution of 1.3 g (29 mM) of **17** and 400 mg of I_2 in 1.3 L of CH_3OH was irradiated in an Ace-Hanovia UV lamp for 43 h. The yellow crystals that had separated were collected and washed with CH_3OH to give 140 mg (11%) of **30**: mp 249–251 °C; IR (KBr) 3415, 1705, 1480, 1210, 1135, 1085, 890, 840, 760, 725 cm^{-1}; NMR (DMSO-d_6) δ 11.31 (1 H, s, H), 10.08 (1 H, s, H_{11}), 8.60–8.58 (2 H, m), 8.32 (1 H, s, H_5), 8.15–8.02 (3 H, m), 7.67 (4 H, m), 4.12 (3 H, s, OCH_3), 4.03 (3 H, s, $COOCH_3$), 3.35 (s, H_2O); MS, m/e 447 (M + 1).

Anal. Calcd for $C_{24}H_{18}N_2O_5S\cdot0.25H_2O$: C, 64.00; H, 4.11; N, 6.27. Found: C, 64.02; H, 4.17; N, 6.25.

The filtrate was taken to dryness, and the residue was worked up as in the case of **18**. There was obtained 200 mg (23%) of **24**: mp 206–208 °C. IR (KBr) 3305–3100, 1700, 1570, 1430, 1305, 1200, 1145, 1080, 810, 790 cm^{-1}; NMR (DMSO-d_6) δ 11.85 (1 H, s, NH), 10.26 (1 H, s, H), 8.66 (1 H, s, H_{11}), 8.61 (1 H, d, J = 5.6, H_8), 8.17–8.11 (2 H, m), 7.34 (1 H, d, J = 9.0, H_4), 7.23–7.18 (1 H, dd, J = 8.9, 2.2, H_9), 4.13 (3 H, s, OCH_3), 4.09 (3 H, s, $COOCH_3$), 3.35 (s, H_2O); MS, m/e 307 (M + 1).

Anal. Calcd for $C_{18}H_{14}N_2O_3\cdot0.5H_2O$: C, 68.57; H, 4.76; N, 8.88. Found: C, 68.53; H, 4.75; N, 8.86.

6-(Hydroxymethyl)-10-methoxy-7*H*-pyrido[4,3-*c*]carbazole (25). According to the procedure described for the preparation of compound **19**, 285 mg of the ester **24** was reduced with 400 mg of LAH to afford 195 mg (75%) of the desired carbinol pure enough to use in the subsequent step. Recrystallization from CH_3CN gave the analytical sample: mp 254–256 °C; IR (KBr) 3460–3020, 1560, 1435, 1300, 1210, 1145, 1023, 877 cm^{-1}; NMR (DMSO-d_6) δ 11.70 (1 H, s, NH), 10.11 (1 H, s, H_1), 8.51 (1 H, d, J = 5.9, H_3), 8.06 (1 H, d, J = 2.9, H_{11}), 7.94 (1 H, d, J = 5.9, H_4), 7.85 (1 H, s, H_5), 7.65 (1 H, d, J = 5.8, H_8), 7.14 (1 H, dd, J = 8.9, 2.2, H_9), 5.65 (1 H, br, s, OH), 5.03 (2 H, s, CH_2OH), 3.98 (3 H, s, OCH_3), 3.35 (s, H_2O); MS, m/e 279 (M + 1).

Anal. Calcd for $C_{17}H_{14}N_2O_2\cdot0.5H_2O$: C, 71.08; H, 5.23. Found: C, 70.77; H, 5.38.

6-(Hydroxymethyl)-10-methoxy-7*H*-pyrido[4,3-*c*]carbazole *N*-Methylcarbamate (26). According to the procedure described for the preparation of **20**, 51 mg (0.18 mM) of the carbinol **25** and 0.35 mL of freshly distilled CH_3NCO in 1.3 mL of dry pyridine gave 45 mg (73%) of the carbamate **26**: mp 251–252 °C; IR (KBr) 3250, 1690, 1280, 1215, 1145, 795 cm^{-1}; NMR (DMSO-d_6) δ 11.88 (1 H, s, NH), 10.15 (1 H, s, H_1), 8.54 (1 H, d, J = 5.6, H_3), 8.08 (1 H, d, J = 2.2, H_{11}), 7.93 (1 H, d, J = 5.6, H_4), 7.88 (1 H, s, H_5), 7.64 (1 H, d, J = 8.8, H_8), 7.30–7.28 (1 H, m, NH), 7.16 (1 H, dd, J = 8.8, 2.4, H_9), 5.52 (2 H, s, CH_2), 3.98 (3 H, s, OCH_3), 3.35 (s, H_2O), 2.64 (3 H, d, J = 4.6, NHCH_3); MS, m/e 336 (M + 1).

Anal. Calcd for $C_{19}H_{17}N_3O_3\cdot0.5H_2O$: C, 66.28; H, 5.23; N, 12.21. Found: C, 66.32; H, 5.32; N, 12.20.

6-Formyl-10-methoxy-7*H*-pyrido[4,3-*c*]carbazole (27). A suspension of 108 mg (0.39 mM) of **25** in 100 mL of CH_2Cl_2 was heated to reflux, and 460 mg (5.29 mM) of activated MnO_2 was added. After being refluxed for an additional 4 h, the suspension was allowed to stand overnight and then worked up as in the case

of the aldehyde **21**. After crystallization from methanol–ethyl acetate, there was obtained 70 mg (65%) of the pure aldehyde: mp 241–242 °C; IR (KBr) 3430, 1675, 1475, 1435, 1300, 1215, 1142, 1085, 1055, 965, 880, 725 cm^{-1}; NMR (DMSO-d_6) δ 12.17 (1 H, s, NH), 10.42 (1 H, s, CHO), 10.28 (1 H, s, H_1), 8.66–8.64 (2 H, m), 8.17–8.11 (2 H, m), 7.84 (1 H, d, J = 9.0, H_4), 7.21 (1 H, dd, J = 8.8, 2.2, H_9), 3.99 (3 H, s, OCH_3), 3.34 (H_2O); MS, m/e 277 (M + 1).

Anal. Calcd for $C_{17}H_{12}N_2O_2 \cdot H_2O$: C, 69.39; H, 4.76. Found: C, 69.66; H, 4.49.

6-Ethyl-10-methoxy-7*H*-pyrido[4,3-*c*]carbazole (29). A solution of 44 mg of the aldehyde **27** in 6 mL of dry DMSO was added to a solution of 0.01 M methylenetriphenylphosphorane in 6 mL of DMSO. The mixture was stirred overnight and poured into H_2O. The mixture was worked up as in the case of the olefin **22**. There was obtained 30 mg (72%) of the desired olefin, mp 220–224 °C, suitable for use in the next step: NMR (DMSO-d_6) δ 12.03 (1 H, s, NH), 10.13 (1 H, s, H_1), 8.52 (1 H, d, J = 5.6, H_3), 8.14 (1 H, s, H_{11}), 8.08 (1 H, d, C*H*=CH_2), 7.95 (1 H, d, J = 5.6, H_4), 7.76–7.52 (2 H, m), 7.18 (1 H, dd, J = 8.8, 2.2, H_9), 6.28 (1 H, d, CH=CH_2), 5.72 (1 H, d, CH=CH_2), 3.98 (3 H, s, OCH_3), 3.37 (s, H_2O); MS, m/e 275 (M + 1).

A solution of 15 mg of the above olefin was hydrogenated in the presence of 10% Pd/C at 3 atm. The product was isolated as in the case of the olefin **22** to give 10 mg of the known **29**: mp 236–238 °C (lit.[11] mp 238 °C); IR (KBr) 3520–3300, 1435, 1185, 1115, 755, 725, 700 cm^{-1}; NMR (DMSO-d_6) δ 11.85 (1 H, s, NH), 10.09 (1 H, s, H_1), 8.49 (1 H, d, J = 5.8, H_3), 8.05 (1 H, d, J = 2.0, H_{11}), 7.89 (1 H, d, J = 5.8, H_4), 7.72–7.33 (2 H, m), 7.17 (1 H, dd, J = 8.8, 2.2, H_9), 3.97 (3 H, s, OCH_3), 3.34 (s, H_2O), 3.17 (2 H, q, CH_2CH_3), 1.44 (3 H, t, CH_2CH_3); MS, m/e 277 (M + 1).

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Synthesis of Homoallylic Alcohols in Aqueous Media

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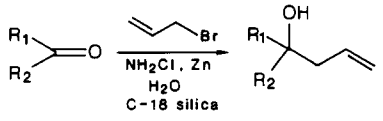
The reaction of aldehydes or ketones with allyl halides/Zn takes place readily in aqueous NH_4Cl solution in the presence of C-18 silica as a solid organic cosolvent. This efficient and high-yield reaction parallels the Grignard reaction in terms of stereo- and regioselectivity. There are two applications, however, where this process has special advantages. The formation of the Grignard reagent with dimethylallyl halides is plagued by coupling side products while our aqueous cases react smoothly. Another advantage is that the reaction can be carried out without the protection of additional hydroxy functional groups. A diverse selection of examples are presented, and a potential mechanism is discussed.

While the Grignard reaction is perhaps the most widely used and general C–C bond forming reaction in organic chemistry, large-scale industrial application is limited[1] by the expense of the metal, the anhydrous ether solvents required, and complications of waste solvent disposal. For these reasons we were intrigued by a unique C–C bond forming reaction, the allylation of aldehydes *in aqueous media* reported by Luche (eq 1).[2] This reaction is one of



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the few carbon–carbon bond forming processes that occurs in water. We have carried out an extensive study[3] of the scope and stereochemistry of the Luche reaction and most importantly have devised a modification that involves the use of a solid organic support instead of the cosolvent THF (eq 1). Thus, the organic phase can be reused and disposal of the reaction solvent after the reaction is uniquely enviromentally safe!

A Solid Organic Cosolvent. The most efficient modification of the Luche reaction we have examined uses a solid organic phase instead of THF as the cosolvent. Our results are summarized in Table I. All the reactions were carried out on a 1-mmol scale, with 1 mL of the aqueous phase and 100–200 mg of the organic phase. The reaction times vary from 0.5 to 16 h.

The reactions proceed at about the same rate as reactions with THF as a cosolvent. Reverse-phase C-18 silica gel was used as our standard although another excellent support for the reaction was biobeads S-X8, a spherical, porous styrene divinylbenzene copolymer with 8% cross-links. The reaction also proceeded satisfactorily on GC column packing OV-101 on Chromosorb.

The simplicity of the allylation reaction and its workup makes this procedure highly recommended. A slurry of zinc, C-18 silica (reverse-phase chromatography support), allyl bromide, and the aldehyde in saturated aqueous ammonium chloride solution was stirred at room temperature in an open beaker. After the reaction was complete (as monitored by GC), filtration and washing the residue with water left the product adsorbed on the support. Elution with ether, drying, and evaporation led to high yields of pure alcohols. The organic solid remaining can be reused, although it appears gray in color.

Scope and Limitations

After this work was completed,[3] a report by the Luche group[2c] appeared which largely confirmed our stereochemical conclusions. While no special selectivity was observed for this reaction, some unique features are apparent. In addition, since formation of the allyl Grignard reagents is often plagued by low yields due to competing coupling reactions,[4] this modification is a valuable alter-

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(2) (a) Petrier, C.; Luche, J. L. *J. Org. Chem.* **1985**, *50*, 910. (b) Petrier, C.; Einhhorn, J.; Luche, J. L. *Tetrahedron Lett.* **1985**, *26*, 1449. (c) Einhorn, C.; Luche, J.-L. *J. Organomet. Chem.* **1987**, *322*, 177.
(3) Taken, in part, from the Ph.D. Thesis of Maria Guazzaroni, New York University, October 1987.

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