Fused Lactones as a Route to Functionalized 1-Substituted Indoles

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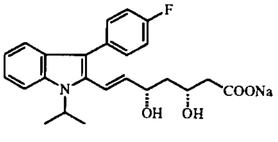
Received February 24, 1994

Indole lactones **8** and **14** were synthesized as a means of functionalizing the 1-isopropyl substituent of the indole nucleus. Lactone **8**, upon reduction with diisobutylaluminum hydride, produces lactol **9** which behaves like a masked hydroxy aldehyde and undergoes a Horner-Emmons reaction with triethyl phosphonoacteate to give α,β-unsaturated ester **3** which possesses a hydroxyl group on the 1-isopropyl moiety.

J. Heterocyclic Chem., **31**, 1381 (1994).

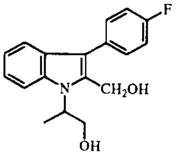
Fluvastatin (**1**) is an extremely potent inhibitor of 3-hydroxy-3-methylglutaryl Coenzyme A (HMG-CoA) reductase, the rate limiting enzyme in the biosynthesis of cholesterol [1].



1

As part of our program to modify the hydrophobic (indole) portion of **1**, we were interested in methods for functionalizing the *N*-isopropyl group while maintaining a suitable "synthetic handle" for elaboration to the pharmacophoric *erythro*-dihydroxyheptenoic acid chain at the 2-position.

One potential method for accomplishing this task is to employ an appropriately *N*-substituted phenylhydrazine in a classical Fischer indole synthesis. Although mechanistically feasible, the reaction's success would depend on the nature and complexity of the desired functional group on the nitrogen atom of the target indole. If the *N*-substituent were to contain an oxygen or an olefin, construction of the appropriate phenylhydrazine would be problematic. Moreover, some of these groups might be sensitive to the reaction conditions required for indole formation.



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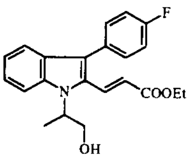

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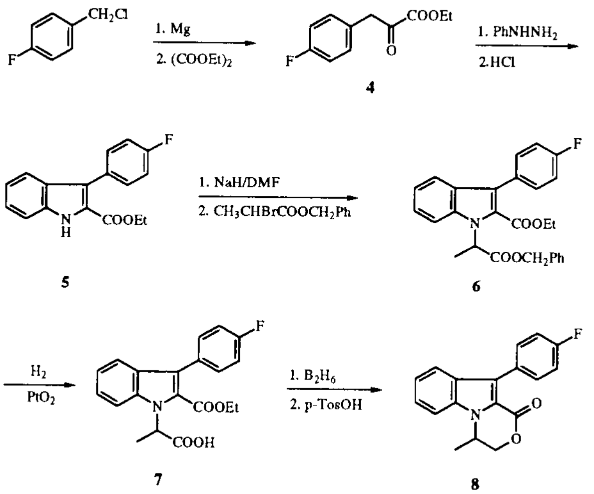
One of our desired molecules was designed to contain a hydroxyl group attached directly to a carbon atom of the *N*-isopropyl group on the indole ring. Additionally, the hydrophobic fragment was to have a readily manipulatable functional group attached to position 2 of the indole which has the capability of being converted to the required side chain of **1**. Molecules such as **2** or **3** would fit these criteria and therefore were chosen as our targets.

We rationalized that the most efficient approach to these molecules would be one in which both functionalities at the 1 and 2 position of the indole were incorporated into a common ring. A lactone intermediate such as **8** would allow appropriate chemical manipulation at the 2 position while releasing the camouflaged hydroxy group at the last moment.

The synthesis of **8** was accomplished in five steps according to the route outlined in Scheme 1. Indole **5** was prepared in 66% yield from the condensation of α-ketoester **4** and phenylhydrazine under Fischer conditions. Alkylation of **5** with benzyl 2-bromopropionate furnished **6** in 72% yield. Catalytic hydrogenolysis of the benzyl ester over platinum provided the acid **7** in 67% yield. Reduction of the acid functionality to the alcohol was accomplished with diborane in 92% yield and subsequent lactonization with *p*-toluenesulfonic acid in toluene furnished the desired product **8** in 76% yield.

Facile reduction of lactone **8** to lactol **9** with diisobuty-

Scheme 1

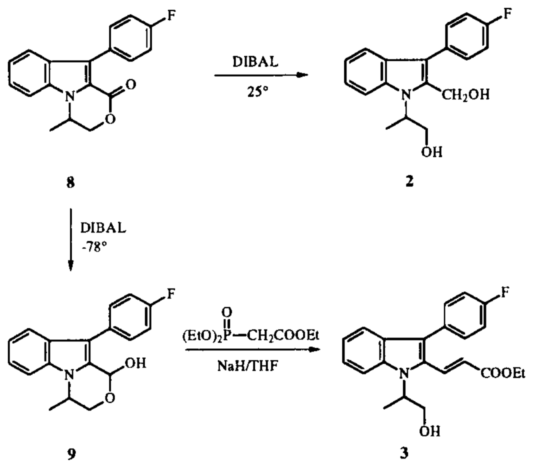


laluminum hydride at -78° is accomplished within 30 minutes and the product is isolated in 85% yield. If the reduction of **8** is performed at room temperature, complete reduction of the lactone to diol occurs within 15 minutes and the product **2** is isolated as a foam in nearly quantitative yield.

As expected, lactol **9** behaves like a masked hydroxy aldehyde. Consequently, when **9** is treated with the anion of triethyl phosphonoacetate under Horner-Emmons conditions, the desired α,β-unsaturated ester **3** is obtained in 78% yield (Scheme 2).

The reverse lactone **14** is prepared by employing similar chemistry described for the preparation of **8**. The only requirement for its synthesis is that the nature of the ester groups in intermediate **6** be switched. Alkylation of the carboxylic acid of indole **10** with benzyl bromide in the presence of triethylamine gives the corresponding benzyl ester **11** in 86% yield. Alkylation of the indole nitrogen with ethyl 2-bromopropionate produces the differentiated diester **12** in nearly quantitative yield. Hydrogenolysis of the benzyl ester affords the indole-2-carboxylic acid **13**. Diborane reduction of the acid to the alcohol and subsequent treatment of the crude alcohol with *p*-toluenesulfonic acid gives lactone **14** in a 69% combined yield (Scheme 3).

Scheme 2



Chemistry associated with lactone **14** will be reported on at a later date.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were recorded on an Analect FX-6200 spectrometer. Absorption frequencies are quoted in reciprocal centimeters. Nuclear magnetic resonance spectra were recorded on Jeol FX-90Q and Jeol FX-200 spectrometers using tetramethylsilane as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). The mass spectra were determined on a Finnegan 4600 spectrometer either in EI or CI modes.

All carbanion generating reactions were conducted under argon atmosphere using tetrahydrofuran which was freshly distilled over lithium aluminum hydride. Unless otherwise stated, all solutions of organic compounds were washed with saturated sodium chloride solution then were dried over magnesium sulfate. No attempt has been made to optimize the yields of the described reactions.

4-Fluoro-α-oxobenzenepropanoic Acid Ethyl Ester (4).

To a 2l round bottom flask charged with 9.6 g (0.4 mole) of magnesium turnings, two crystals of iodine and 150 ml of anhydrous ether was added 15 ml of a solution of 60 g (0.415 mole) of 4-fluorobenzyl chloride in 50 ml of ether. After initiation of the reaction, the remainder of the solution was added dropwise at such a rate that maintained reflux. Upon complete addition, the mixture was stirred at room temperature for 2 hours, then transferred to an addition funnel and rapidly added to a solution of 120 g (0.82 mole) of diethyl oxalate in 1l of ether at 0°. After addition, the mixture was stirred at room temperature for 30 minutes and the resulting orange resinous precipitate dissolved by addition of tetrahydrofuran. The solution was poured into 500 ml of water/saturated ammonium chloride (1:1), extracted twice into 300 ml of ether and the combined extracts dried over magnesium sulfate. The solvent was removed under reduced pressure, the residual oil was distilled at 0.5 mm and the fraction boiling at 90-110° was collected. The product, 42 g (50%) of **4**, was used immediately in the following step; ir (chloroform): 3459, 3021, 2986, 2940, 2907, 1733, 1728, 1696, 1474, 1466, 1371, 1331, 1110, 867 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.70-7.58 (m, 1H), 7.28-6.80 (m, 3H), 6.50-6.38 (m, 1H), 4.33 (q, 2H), 2.85 (s, 1H, OH), 1.33 (t, 3H).

3-(4-Fluorophenyl)-1*H*-indole-2-carboxylic Acid Ethyl Ester (5).

To a mixture of 36.6 g (0.174 mole) of **4** and 18.8 g (0.174 mole) of phenylhydrazine was added 4 drops of concentrated sulfuric acid and the mixture was heated at 120 ° for 15 minutes to produce a clear orange oil which was then cooled and dissolved in 200 ml of ethanol. Gaseous hydrogen chloride was bubbled through the solution until a vigorous reaction was initiated and ammonium chloride precipitated. The mixture was refluxed for 1 hour, cooled, poured into 400 ml of water and extracted twice with 250 ml of ether. The combined extracts were washed with saturated sodium chloride and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue flash chromatographed using hexane/ethyl acetate (4:1) to elute the product, 35.3 g (72%) of **5** as a solid, mp 131.5-133 °C; ir (potassium bromide): 3327, 1681, 1676, 1671, 1541, 1500, 1439, 1383, 1176, 1141, 1018, 838 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 9.01 (s, broad, 1H, NH), 7.58-6.97 (m, 8H), 4.28 (q, J = 7.5 Hz, 2H), 1.25 (t, J = 7.5 Hz, 3H); ms (DCI-isobutane): 326 (5), 301 (4), 285 (18), 284 (100, MH^{+}), 283 (14).

Anal. Calcd. for $C_{17}H_{14}NO_2F$: C, 72.08; H, 4.95; N, 4.95. Found: C, 71.56; H, 5.01; N, 4.96.

2-(Ethoxycarbonyl)-3-(4-fluorophenyl)-α-methyl-1*H*-indole-1-acetic Acid Phenylmethyl Ester (6).

To a suspension of 0.8 g (18.5 mmoles) of sodium hydride (60% in mineral oil) in 100 ml of *N,N*-dimethylformamide (under argon) was added dropwise a solution of 5.1 g (18.0 mmoles) of **5** in 50 ml of *N,N*-dimethylformamide. The mixture was stirred at room temperature for 15 minutes then a solution of 4.9 g (20.0 mmoles) of benzyl 2-bromopropionate [2] in 25 ml of *N,N*-dimethylformamide was added dropwise and the solution was stirred at room temperature for 18 hours. The mixture was poured into saturated ammonium chloride solution, extracted twice with 250 ml of ether, and the combined organic extracts were dried over magnesium sulfate. The solvent was removed under reduced pressure and the resulting oil was flash chromatographed using hexane/ethyl acetate (4:1) to elute the product, 5.2 g (67%) of **6** as a yellow oil; ir (neat): 3020, 2981, 1742, 1699, 1544, 1500, 1455, 1419, 1381, 1368, 1356, 1334, 1298, 1187, 1104, 1016 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.50-7.03 (m, 13H), 6.01 (q, J = 7.6 Hz, 1H), 5.24-5.08 (m, 2H), 4.09 (q, J = 7.5 Hz, 2H), 1.89 (d, J = 7.6 Hz, 3H), 1.02 (t, J = 7.5 Hz, 3H).

2-(Ethoxycarbonyl)-3-(4-fluorophenyl)-α-methyl-1*H*-indole-1-acetic Acid (**7**).

A mixture of 5.0 g (1.15 mmoles) of **6** and 0.5 g of platinum oxide in 50 ml of ethanol was hydrogenated at 1 atmosphere for 18 hours. The catalyst was filtered from the reaction mixture through Celite and the solvent was removed under reduced pressure. The residue was dissolved in 175 ml of 10% sodium bicarbonate solution and was washed with ether. The aqueous phase was acidified with 2 *N* hydrochloric acid, extracted twice with 75 ml of ether and the combined organic extracts were dried over magnesium sulfate. The solvent was removed under reduced pressure and the resulting oil was flash chromatographed using methyl *t*-butyl ether/ethyl acetate (4:1) to elute the product, 2.84 g (69%) of **7** as a white solid; ir (chloroform): 3020, 2986, 2941, 2906, 1608, 1545, 1476, 1421, 1380, 1355, 1030, 1015, 838 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 9.13 (s, broad, 1H, COOH) 7.54-6.98 (m, 9H), 5.98 (q, J = 7.6 Hz, 1H), 4.19 (q, J = 7.5 Hz, 2H), 1.88 (d, J = 7.6 Hz, 3H), 1.05 (t, J = 7.5 Hz, 3H); ms (DCI-ammonia): 373 (22, MNH_4^+), 372 (100), 359 (6), 356 (5, MH^+), 355 (22), 300 (8), 134 (8).

Anal. Calcd. for $C_{20}H_{18}NO_4F$: C, 67.60; H, 5.11; N, 3.94. Found: C, 67.53; H, 5.13; N, 3.88.

10-(4-Fluorophenyl)-3,4-dihydro-4-methyl-1*H*-[1,4]oxazino[4,3-*a*]indol-1-one (**8**).

To 25 ml of a 1.0 *M* solution of diborane in tetrahydrofuran (under argon) was added dropwise a solution of 2.6 g (7.3 mmoles) of 7 in 50 ml of tetrahydrofuran. After stirring at room temperature for 6 hours, the mixture was cooled to 0-5° and carefully quenched with 25 ml of saturated ammonium chloride solution. The mixture was extracted twice with 125 ml of ether and the combined extracts were dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was flash chromatographed with hexane/ethyl acetate (7:3) to elute 2.37 g (92%) of 3-(4-fluorophenyl)-1-(2-hydroxy-1-methylethyl)-1*H*-indole-2-carboxylic acid ethyl ester as an oil.

The above oil was dissolved in 40 ml of toluene and 15 mg of *p*-toluenesulfonic acid were added. The mixture was refluxed for 5 minutes then, after cooling to room temperature, was poured into water, extracted with 100 ml of ether and the organic phase was dried over magnesium sulfate. The solvent was removed under reduced pressure to give an oil which solidified. The solid was triturated with hexane to give 1.55 g (76%) of **8**, mp 134.5-135.5°; ir (chloroform): 3019, 1727, 1606, 1553, 1520, 1451, 1418, 1405, 1376, 1331, 1307, 1262, 1124, 1114, 1044, 845 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.78-7.06 (m, 8H), 4.88-4.52 (m, 3H, CH_3CH and CH_2O), 1.63 (d, J = 6.5 Hz, 3H, CH_3CH); ms (DCI-isopropane): 297 (22), 296 (100, MH^+), 295 (10), 107 (7).

Anal. Calcd. for $C_{18}H_{14}NO_2F$: C, 73.21; H, 4.78; N, 4.74. Found: C, 73.12; H, 4.72; N, 4.76.

10-(4-Fluorophenyl)-3,4-dihydro-4-methyl-1*H*-[1,4]oxazino[4,3-*a*]indol-1-ol (**9**).

To a solution of 0.5 g (1.69 mmoles) of **8** in 25 ml of tetrahydrofuran at -78° (under argon) was added dropwise 7.0 ml of a 1.0 *M* solution (7.0 mmoles) of diisobutylaluminum hydride in tetrahydrofuran. The mixture was stirred at -78° for 30 minutes then quenched with 20 ml of saturated ammonium chloride, warmed to room temperature, 25 ml of water were added and the mixture was extracted twice with 100 ml of ether. The combined organic extracts were dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The resulting yellow oil was flash chromatographed using hexane/methyl *t*-butyl ether (1:1) to give 0.43 g (85%) of **9** as a waxy solid; ir (chloroform): 3018, 2978, 2936, 1559, 1508, 1458, 1433, 1386, 1365, 1303, 1266, 1131, 1075, 972, 914 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.75-7.08 (m, 8H), 6.22 (d, J = 2.0, 1H, CHOH), 4.82-4.77 (dd, J_1 = 2.0, J_2 = 5.2 Hz, OCH_2), 4.55-4.42 (m, 1H), 3.83 (d, J = 5.2 Hz, 1H), 3.13 (d, J = 2.0 Hz, 1H, OH), 1.52 (d, J = 2.7 Hz, 3H); ms (DCI-isobutane): 354 (4), 340 (4), 299 (19), 298 (100, MH^+), 297 (20), 282 (4), 281 (19), 280 (99).

Anal. Calcd. for $C_{18}H_{16}NO_2F{\bullet}0.1H_2O$: C, 72.28; H, 5.46; N, 4.68. Found: C, 72.23; H, 6.26; N, 4.21.

(E)-3-[3-(4-Fluorophenyl)-1-(2-hydroxy-1-methylethyl)-1*H*-indol-2-yl]-2-propenoic Acid Ethyl Ester (**3**).

To a solution of 0.6 g (2.7 mmoles) of triethyl phosphonoacetate in 25 ml of tetrahydrofuran was added 0.1 g (2.7 mmoles) of sodium hydride (60% in mineral oil). After stirring at room temperature for 1 hour, a solution of 0.4 g (1.35 mmoles) of **9** in 5 ml of tetrahydrofuran was added and stirring was continued for an additional 4 hours. The mixture was poured into 25 ml of saturated ammonium chloride and was extracted twice with 100 ml of ether. The combined organic extracts were dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure to give a yellow oil. The oil was flash chromatographed using hexane/methyl *t*-butyl ether (1:1) to elute the product, 0.38 g (78%) of **3** as a solid, mp 120-123°; ir (chloroform): 2934, 1731, 1554, 1503, 1458, 1428, 1397, 1120, 1104, 1094, 1023, 838 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.62-7.04 (m, 9H), 6.01-5.67 (m, 1H), 4.53-4.04 (m, 1H), 2.52 (d, J = 10 Hz, 1H), 1.64 (d, J = 6.0 Hz, 3H), 1.21 (t, 3H); ms (DCI-isobutane): 424 (6), 410 (7), 406 (5), 370 (4), 369 (25), 368 (100, MH^+), 367 (21), 97 (2), 93 (4).

Anal. Calcd. for $C_{22}H_{22}NO_3F$: C, 71.92; H, 6.04; N, 3.81. Found: C, 71.73; H, 6.17; N, 3.77.

3-(4-Fluorophenyl)-1*H*-indole-2-carboxylic Acid (**10**).

To a 500 ml round bottom flask charged with 10 g (35.4 mmoles) of **4** and 250 ml of ethanol was added 38 ml of 1.0 *N* sodium hydroxide and the mixture was vigorously stirred at room temperature for 18 hours followed by refluxing for an additional 2 hours. The ethanol was removed under reduced pressure, 250 ml of water were added to the residue and the mixture was washed with ether. The separated aqueous phase was acidified with 2 *N* hydrochloric acid, extracted twice with 200 ml of ethyl acetate and the combined extracts were dried over magnesium sulfate. The solvent was removed under reduced pressure to give 8.78 g (97%) of **10**, mp 255-256° dec.

Anal. Calcd. for $C_{15}H_{10}NO_2F$: C, 70.58; H, 3.95; N, 5.49. Found: C, 70.22; H, 3.93; N, 5.33.

3-(4-Fluorophenyl)-1*H*-indole-2-carboxylic Acid Phenylmethyl Ester (**11**).

A mixture of 8.4 g (32.9 mmoles) of **10**, 5.7 g (33.3 mmoles) of benzyl bromide and 6.7 g (66 mmoles) of triethylamine in 250 ml of *N,N*-dimethylformamide was stirred at room temperature for 18 hours. The mixture was poured into 500 ml of saturated sodium chloride solution, extracted twice with 250 ml of ether and the combined extracts were dried over magnesium sulfate. The solvent was removed under reduced pressure and the resulting solid was triturated with ether/hexane to give 9.7 g (86%) of **11**, mp 136-138°; ir (potassium bromide): 3336, 3060, 1618, 1606, 1461, 1118, 1092, 994, 969 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.00 (m, 1H, NH), 7.55-6.95 (m, 13H), 5.27 (s, 2H, OCH_2); ms (DCI-ammonia): 365 (3), 364 (24), 363 (100, MNH_4^+), 347 (6), 346 (27), 345 (6, MH^+), 302 (6), 273 (6).

Anal. Calcd. for $C_{22}H_{16}NO_2F$: C, 76.51; H, 4.67; N, 4.06. Found: C, 76.54; H, 4.62; N, 4.04.

3-(4-Fluorophenyl)-α-methyl-2-[(phenylmethoxy)carbonyl]-1*H*-indole-1-acetic Acid Ethyl Ester (**12**).

To a suspension of 1.1 g (28 mmoles) of sodium hydride (60% in mineral oil) in 50 ml of *N,N*-dimethylformamide (under argon) was added dropwise a solution of 9.5 g (27.5 mmoles) of **11** in 150 ml of *N,N*-dimethylformamide. After stirring at room temperature for 15 minutes a clear solution formed. To this solution was added dropwise a solution of 6.5 g (35 mmoles) of ethyl 2-bromopropionate and the mixture was stirred at room temperature for 24 hours. The mixture was poured into saturated ammonium chloride solution, extracted twice with 100 ml of ether, and the combined extracts were dried over magnesium sulfate. The solvent was removed under reduced pressure to furnish 12.1 g (98%) of **12** as a yellow oil. The material was used in the next step without further purification; ^1H nmr (deuteriochloroform): δ 7.45-6.85 (m, 13H), 5.96 (q, J = 7.6 Hz, 1H), 5.10 (s, 2H), 4.21 (q, J = 7.5 Hz, 2H), 1.85 (d, J = 7.6 Hz, 3H), 1.16 (t, J = 7.5 Hz, 3H)

2-Carboxy-3-(4-fluorophenyl)-α-methyl-1*H*-indole-1-acetic Acid Ethyl Ester (**13**).

A mixture of 12.1 g (27.2 mmoles) of **12** and 0.4 g of platinum oxide in 100 ml of ethanol was hydrogenated at 1 atmosphere for 48 hours. The catalyst was filtered from the mixture and the solvent removed under reduced pressure to furnish an orange oil. The oil was purified by flash chromatography using hexane/ethyl acetate (6:4) to elute the product, 5.42 g (56%) of **13** as a foam; ir (chloroform): 3021, 2984, 2944, 2904, 2613, 2401, 1734, 1672, 1610, 1595, 1334, 1094, 1061, 1028, 979 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.50-6.95 (m, 8H), 5.92 (q, J = 7.6 Hz, 1H), 4.15 (q, J = 7.5 Hz, 2H), 1.83 (d, J = 7.6 Hz, 3H), 1.15 (t, J = 7.5 Hz, 3H); ms (DCI-ammonia): 374 (10), 373 (47, MNH_4^+), 356 (38, MH^+), 329 (19), 327 (18), 313 (100), 281 (12), 275 (10), 273 (12), 232 (11), 230 (29), 196 (14), 191 (24), 153 (25), 151 (11), 142 (36), 140 (69).

Anal. Calcd. for $C_{20}H_{18}NO_4F \cdot 0.4H_2O$: C, 66.25; H, 5.23; N, 3.86. Found: C, 66.24; H, 5.25; N, 3.59.

10-(4-Fluorophenyl)-4-methyl-1*H*-[1,4]oxazino[4,3-*a*]indol-3(4*H*)-one (**14**).

To 50 ml of a 1.0 *M* solution of diborane in tetrahydrofuran (under argon) was added dropwise a solution of 4.97 g (14 mmoles) of **13** in 100 ml of tetrahydrofuran. After stirring at room temperature for 3 hours, the mixture was poured into 250 ml of cold saturated ammonium chloride solution, extracted with 150 ml of ether, and the organic phase was dried over magnesium sulfate. The solvent was removed under reduced pressure and the residual oil was flash chromatographed using hexane/ethyl acetate (7:3) to elute 1.75 g (36%) of 3-(4-fluorophenyl)-2-hydroxymethyl-α-methyl-1*H*-indole-1-acetic acid ethyl ester; ir (chloroform): 3478, 3458, 2996, 1606, 1564, 1423, 1392, 1307, 1145, 977 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.60-6.98 (m, 9H), 5.43 (q, J = 7.6 Hz, 1H), 4.78 (d, J = 5.6 Hz, 2H), 4.20 (q, J = 7.5 Hz, 2H), 1.88 (d, J = 7.6 Hz, 3H), 1.21 (t, J = 7.5 Hz, 3H).

A mixture of 1.6 g (4.69 mmoles) of the above alcohol and 25 mg of *p*-toluenesulfonic acid in 25 ml of toluene was heated to reflux for 2 minutes. The solvent was removed under reduced pressure and the residue was flash chromatographed using hexane/ethyl acetate (7:3) to elute the product, 0.96 g (69%) of **14** as a white solid, mp 158.5-159.5°; ir (potassium bromide): 1751, 1573, 1505, 1463, 1445, 1385, 1368, 1239, 1212, 1155, 1034, 845, 807 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.78-7.62 (m, 1H), 7.41-7.03 (m, 7H), 5.61 (d, J = 5.6 Hz, 2H), 5.29 (q, J = 7.6 Hz, 1H), 1.83 (d, J = 7.6 Hz, 3H); ms (DCI-ammonia): 365 (3), 364 (24), 363 (100, MNH_4^+), 347 (6), 346 (27), 345 (6, MH^+), 302 (6), 273 (6).

Anal. Calcd. for $C_{18}H_{14}NO_2F$: C, 73.21; H, 4.78; N, 4.74. Found: C, 73.27; H, 5.08; N, 4.74.

REFERENCES AND NOTES

[1] F. G. Kathawala, *Med. Res. Rev.*, **11**, 121 (1991).

[2] J. I. DeGraw, P. H. Christie, R. L. Kisliuk, Y. Gaumont and F. M. Sirotnak, *J. Med. Chem.*, **33**, 212 (1990).

[3] Y. Arata, M. Sakai, and S. Yasuda, *Chem. Pharm. Bull.*, ***20***, 1745 (1972).

[4] A. Liguori, R. Ottana, G. Romeo, G. Sindona, and N. Uccella, *Heterocycles*, **27**, 1365 (1988).

[5] P. Coutrot and C. Legris, *Synthesis*, 118 (1975).

[6] J. I. Degraw, P. H. Christie, R. L. Kisliuk, Y. Gaumont, and F. M. Sirotnak, *J. Med. Chem.*, **33**, 212 (1990).