Preparation of Alkyl-Substituted Indoles in the Benzene Portion. Part 8.[1] Improved Practical Synthesis of 4,4-Dialkoxy-1-(1-arylsulfonyl-3-pyrrolyl)-1-butanone and 4-(1-Arylsulfonyl-3-pyrrolyl)-4-oxobutanal, and a Novel Synthetic Procedure for 4-Alkoxyindole Derivatives

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Important precursors (1 and 2) for the synthesis of 4-substituted indole derivatives were readily obtained by acid treatment of a tosylamide (13), which was prepared in a single operation by treatment of 10 with *N*-tosyl-*N'*,*N'*-dimethylformamidine (TsN=CHNMe$_2$). Compound (10) was effectively synthesized from nitromethane and acrolein by way of a nitro compound (15). A novel indole formation reaction from the tosyl-amide (13) to gain short access to 4-alkoxyindoles, such as 16, 17, 19, and 21 is presented.

Keywords indole synthesis precursor; 4-substituted indole; acid-induced indole cyclization; 4-(3-pyrrolyl)-4-oxobutanal derivative; 1,1,7,7-tetramethoxy-4-heptanone derivative

In the preceding three papers, we reported novel synthetic methods for alkyl- and alkoxy-substituted indole derivatives, whose substituents are located on the benzene portion of the indole nucleus. The title compounds, 4,4-dialkoxy-1-(1-arylsulfonyl-3-pyrrolyl)-1-butanone (**1**) and 4-(1-arylsulfonyl-3-pyrrolyl)-4-oxobutanal (**2**) are particularly important, because they can serve as common percursors for a variety of 4-substituted indoles, which are of biological significance (Chart 1). In this report we describe a useful practical synthetic method for these important compounds (**1** and **2**) as well as a novel synthetic procedure for 4-alkoxyindole derivatives which can be used for an alternative synthesis of (±)-pindolol.

The well-known Paal–Knorr synthesis of pyrrole derivatives constitutes the condensation of 1,4-dicarbonyl compounds and amine derivatives.[2] A typical example is the formation of 1-(arylsulfonyl) pyrrole (**5**) from a masked 1,4-dicarbonyl compound, 2,5-dimethoxytetrahydrofuran (**3**) and arylsulfonamide (**4**).[3] When we apply these synthetic subunits to the formation of the pyrrole derivative (**1**), a partially acetalized polycarbonyl compound (**6**) is a candidate for condensation with arylsulfonamide (**4**). In this molecule of **6**, a one-carbon unit (formyl equivalent) can be readily introduced into the necessary position, so that our starting compound is simplified to a 4-oxoheptadial derivative (**7**), which fortunately has a structure with C_2 symmetry. Therefore we do not have to worry about a positional isomer in introducing the formyl equivalent, and further we can readily design the preparation of **7** itself in the light of this symmetry advantage. A preliminary study was carried out to test whether this synthetic plan would work.

Preparation of 4,4-Dimethoxy-1-[1-(4-methylphenyl)sulfonyl-3-pyrrolyl]-1-butanone (1) and 4-[1-(4-Methylphenyl)-sulfonyl-3-pyrrolyl]-4-oxobutanal (2) The Grignard reagent (**8**) derived from 3,3-dimethoxypropyl bromide[4] was allowed to react with methyl formate, and the resulting alcohol (**9**), obtained in 97% yield, was oxidized with Collins reagent[5] to give 1,1,7,7-tetramethoxy-4-heptanone (**10**) in 92% yield (Chart 2). This was treated with methyl formate in benzene and dimethylformamide (DMF) (2:1) in the presence of sodium hydride, furnishing **11** in 87% yield as a mixture of a ketoaldehyde form (**6**: R=Me) and a ketoenol form (**11**). The desired condensation of **11** with tosylamide did not occur due to both the unstable nature of **11** and the inadequate reactivity of tosylamide. To introduce the nitrogen function in a reliable manner, **11** was stirred in ammonia-containing methanol to convert it into the enaminone (**12**) in 75.5% yield, and **12** was tosylated with tosyl chloride using sodium hydride in tetrahydrofuran (THF) and DMF (10:1) to produce **13** in 65% yield. This compound (**13**) corresponds to an intermediary substance between the ketoaldehyde (**6**) and the pyrrole derivative (**1**), and was obtained in 43% overall yield from the ketone derivative (**10**). When these three steps were carried out with-

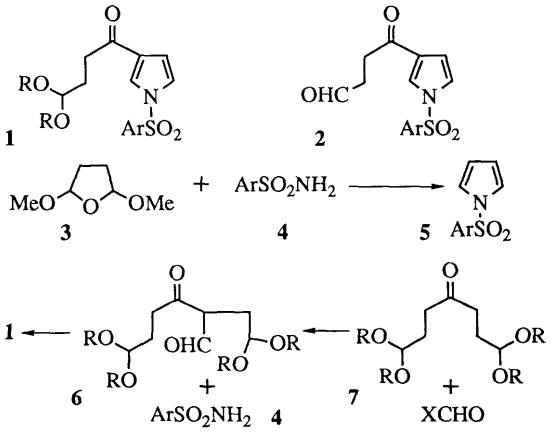

Chart 1

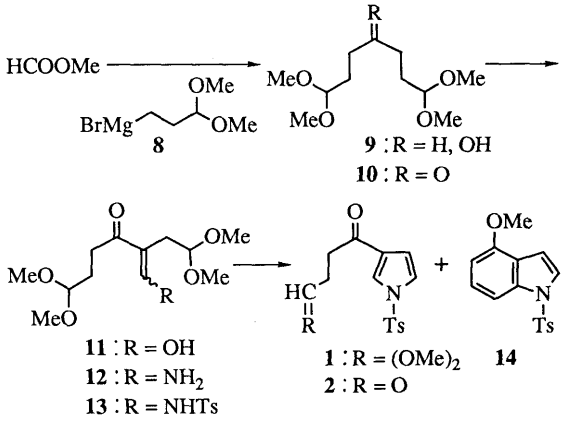

Chart 2

out purification of the unstable intermediates (**11** and **12**), the tosylamide (**13**) was obtained in 54% yield from **10**.

Next we tested an acid-catalyzed pyrrole cyclization from the tosylamide (**13**). For the formation of the pyrrole derivative (**1**) having the ketone and acetal groups, catalysis with a mineral acid proved to be a little too strong, because an over-cyclization reaction took place in part to produce 4-methoxy-1-[(4-methylphenyl)sulfonyl]indole (**14**) in a considerable amount. For instance, when the tosylamide (**13**) was warmed in 1% sulfuric acid–containing methanol and water (99 : 1) at 55—60 °C for 45 min, the pyrrole derivative (**1**) was obtained in 74.5% yield, accompanied by the indole (**14**) in 10% yield. The bast result was achieved by using a catalytic amount of *p*-toluenesulfonic acid, and **1** was prepared in 83.5% yield by heating in methanol at reflux for 20 min. Still, however, the formation of **14** was unavoidable (2% yield).

Preparation of the pyrrole derivative (**2**) having the ketone and aldehyde groups required the mineral acidic conditions. Warming of tosylamide (**13**) in acetic acid at 55—60 °C for 5 h afforded **2** in only 64% yield. In sharp contrast, the yield was raised to 94% when **13** was heated in a mixture of THF and water (1 : 1) containing 2.5% hydrochloric acid at 70 °C for 30 min. Neither **14** nor any other by-product was formed in this case. So **1** and **2** were prepared as expected from the ketone derivative (**10**) in good overall yields.

Practical Synthesis of 3-[(4-Methylphenyl)sulfonylaminomethylene]-1,1,7,7-tetramethoxy-4-heptanone (13) and Its Direct Conversion into 4-Alkoxy-1-[(4-methylphenyl)sulfonyl]indole Derivatives Our task in this study was to establish a practical large-scale preparative method for 4-substituted indole derivatives. In the above pathway, we must improve the following three points for this purpose. i) It is necessary to devise an efficient and economical procedure for preparation of the symmetrical ketone derivative (**10**) to avoid the Grignard reaction using **8**. ii) The three-step conversion of **10** to the tosylamide (**13**) must be shortened by finding a suitable new reagent. iii) The pyrrole derivatives (**1** and **2**) are not the target molecules but the intermediates for the objective indole derivatives. As we experienced the formation of an unavoidable by-product, the 4-methoxyindole derivative (**14**), in the case of the transformation of **13** into **1**, and as we reported exactly the same type of acid-catalyzed indole cyclization reaction from **1** to **14** in the previous work,[6] direct preparation of 4-alkoxyindoles might be possible by skipping the stage of **1** or **2** in acid treatment of **13**, if we select appropriate reaction conditions. Now we describe the successful achievement of a new synthetic route to 4-alkoxyindole derivatives based on these considerations.

Selection of the functional unit corresponding to the ketone group is a key point for the first problem in preparing **10** (Chart 3). Expensive reagents such as acetonedicarboxylate might be used, but we chose nitromethane for the one-carbon unit of the carbonyl equivalent, since this is not only commercially available in the pure state but also is safe and inexpensive as a 50% methanol solution, and the nitro group can be converted readily into the ketone function at a later stage of the synthesis. Selection of nitromethane made the other partner for constructing **10** self-evidently acrolein and the next our concern was how to condense two molecules of acrolein with nitromethane

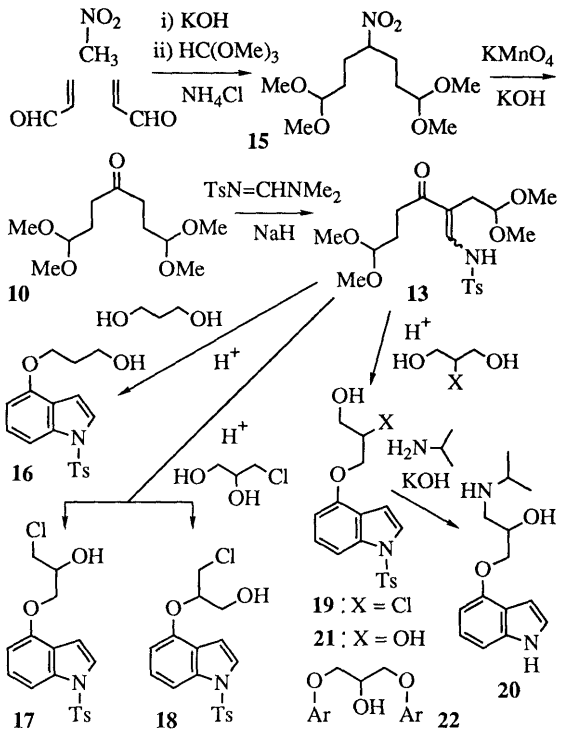

Chart 3

predominantly to minimize the formation of a variety of by-products. The reaction conditions to meet this requirement were studied at first using pure nitromethane. The best result was obtained by dropping a methanol solution of a little more than two equivalents of acrolein into a methanol solution of nitromethane containing a catalytic amount of potassium hydroxide during 1 h at −20 °C, and stirring the reaction mixture at the same temperature for 30 min. The crude product was transformed at once into the bisdimethyl acetal by treatment with trimethyl orthoformate in the presence of ammonium chloride to afford **15**, in 55% yield, calculated from nitromethane. The nitro group in **15** was changed to a ketone group by oxidation with potassium permanganate[7] to furnish the required compound (**10**) in 90% yield. When a 50% methanol solution of nitromethane was used as a starting material and the crude **15** was submitted without purification to the next oxidation, the desired compound (**10**) was obtained in 55% overall yield.

The second improvement was the insertion step of the tosylamidomethine function into **10**. For that purpose, *N*-tosyl-*N'*,*N'*-dimethylformamidine[8] (TsN=CHNMe$_2$), easily prepared from *N*-sulfinyltosylamide and DHF, was introduced as a reagent to execute the necessary transformation in a single operation. The formation of **13** from **10** was realized in 75% yield by treating **10** with this reagent in the presence of sodium hydride in a mixture of benzene and DHF (1 : 2) at room temperature. The tosylamide derivative (**13**) obtained here is a relatively stable, crystalline compound and can be stored without decomposition when kept in the absence of moisture. As **13** can be transformed into the precursors (**1** and **2**) for the indole cyclization, this study opens a way to synthesize various kinds of important indole derivatives starting from commercially available, inexpensive raw materials, nitro-

methane and acrolein, in a straightforward manner.

For the third problem, to effect direct preparation of 4-alkoxyindole derivatives from the above tosylamide (**13**), it was found that the reaction conditions reported in Part 6[6] for the indole cyclization of the pyrrole derivative (**1**) were also applicable to this transformation. Thus, the important precursor[6] (**16**) for 4-hydroxyindole was obtained in 77.5% yield by refluxing a 1,2-dichloroethane solution of **13** in the presence of 1,3-propanediol and a catalytic amount of sulfuric acid. Similarly 1-chloro-2,3-propanediol was reacted with **13** in refluxing dichloromethane with sulfuric acid catalysis to afford the precursor[6] (**17**) for the pindolol synthesis in 66% yield, accompanied by the by-product (**18**) in 6.5% yield. To avoid the formation of this by-product, a symmetrical diol, 2-chloro-1,3-propanediol,[9] was used for the condensation with the tosylamide (**13**). Again, refluxing in 1,2-dichloroethane with sulfuric acid as a catalyst was sufficient and **19** was produced in 70% yield. This compound (**19**) was a good substrate for substitution with isopropylamine *via* an intermediary epoxide by refluxing in 0.5 N sodium hydroxide–containing ethanol, and (±)-pindolol (**20**) was prepared in 64% yield. Glycerol could also be condensed with the tosylamide (**13**) by employing similar reaction conditions, resulting in the formation of **21** in 61.5% yield, together with a by-product (**22**) in 9% yield. (±)-Pindolol (**20**) can be prepared from **21** by way of the monotosylate of the primary alcohol.[10]

In summary we have achieved efficient preparative synthesis of an important precursor (**10**) in two ways. One is a laboratory-scale method, carried out by using the Grignard reaction as shown in Chart 2. The other method is suitable for a large-scale preparation and employs nitromethane and acrolein as the starting materials (Chart 3). Secondly, by utilizing a reagent, *N*-tosyl-*N'*,*N'*-dimethylformamidine, compound (**10**) is effectively converted into the tosylamide (**13**), which serves as a key compound for the synthesis of 4-substituted indole derivatives. Variously modified 4-alkylindoles can be prepared from **13** by way of the pyrrole derivative (**1**). 4-Alkoxyindole compounds are directly accessible from **13** by treatment with an acid. The last reaction was successfully applied to an alternative synthesis of (±)-pindolol (**20**).

Experimental

For general descriptions, see the preceding paper.[1] NaH in mineral oil was washed with benzene before use.

1,1,7,7-Tetramethoxy-4-heptanol (9) A solution of 3,3-dimethoxypropyl bromide[4] (11.028 g, 6.06 mmol) in THF (15 ml) was added dropwise to a suspension of Mg (1.449 g, 59.6 mg atom) in THF (30 ml) during 30 min with stirring at room temperature. After 1 h 20 min, a solution of methyl formate (1.081 g, 18.0 mmol) in THF (5 ml) was added at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. Saturated NH_4Cl–H_2O was added, the whole was extracted with CH_2Cl_2, and the organic solution was worked up as usual. The residue was purified by chromatography over silica gel (35 g) using hexane–EtOAc (1 : 1) to give 4.116 g (97%) of **9** as a colorless oil. MS *m/z*: 173 ($M^+ - MeOH - OMe$). ^{1}H-NMR δ: 2.93 (1H, br s, OH), 3.30 (6H, s), 3.34 (6H, s), 3.45—3.75 (1H, m), 4.34 (2H, t, J=5 Hz).

1,1,7,7-Tetramethoxy-4-heptanone (10) from 9 Collins' reagent[5] (1.343 g, 5.21 mmol) was added to a stirred solution of **9** (154 mg, 0.653 mmol) in CH_2Cl_2 (15 ml) at 0 °C. After stirring at 0 °C for 30 min, 5% NaOH–H_2O was added and the mixture was extracted with CH_2Cl_2. The organic layer was successively washed with saturated $CuSO_4$–H_2O, H_2O, saturated $NaHCO_3$–H_2O and H_2O, and worked up as usual. Purification by cchromatography over silica gel (15 g) using hexane–EtOAc (1 : 1) afforded 140 mg (92%) of **10** as a colorless oil. bp 120—124 °C (1 mmHg). MS *m/z*: 234 (M^+). IR (neat) cm^{-1}: 1720. ^{1}H-NMR δ: 1.86 (4H, dt, J=5.5, 7 Hz), 2.47 (4H, t, J=7 Hz), 3.33 (12H, s), 4.32 (2H, t, J=5.5 Hz).

3-Formyl-1,1,7,7-tetramethoxy-4-heptanone (11) NaH in mineral oil (60%, 98 mg, 2.45 mmol) and methyl formate (0.50 ml, 8.1 mmol) were added successively to a stirred solution of **10** (471 mg, 2.01 mmol) in benzene (6 ml) and DMF (3 ml) at room temperature. The mixture was stirred for 14 h at room temperature, then the solvent was evaporated off under reduced pressure. The residue was diluted with brine and acidified to pH 4 by addition of 10% citric acid–H_2O. The mixture was extracted with CH_2Cl_2 and worked up as usual. Chromatography over silica gel (15 g) using hexane–EtOAc (1 : 1) gave 460 mg (87%) of **11** as a slightly yellow oil. MS *m/z*: 230 ($M^+ - MeOH$). IR (neat) cm^{-1}: 1712, 1642 (sh), 1626. ^{1}H-NMR δ: 3.26, 3.30, 3.34, 3.39, 3.44 (total 12 H, s each), 4.17—4.48 (2H, m), 7.95 (br d, J=5.5 Hz, s by addition of D_2O, vinyl proton of the enol form), 9.54 (d, J=2 Hz, CHO).

3-Aminomethylene-1,1,7,7-tetramethoxy-4-heptanone (12) NH_3 gas was bubbled into a solution of **11** (423 mg, 1.61 mmol) and NH_4Cl (117 mg, 2.19 mmol) in MeOH (3 ml) at 0 °C until saturation, and the solution was stirred at room temperature for 48 h, while the container was stoppered. The solution was diluted with brine, extracted with CH_2Cl_2, and worked up as usual. Purification by preparative thin layer chromatography (PTLC) [benzene–EtOAc (1 : 1)] afforded 318 mg (75.5%) of **12** as a colorless syrup. MS *m/z*: 261 (M^+). IR ($CHCl_3$) cm^{-1}: 1650, 1620, 1595. ^{1}H-NMR δ: 1.77—2.07 (2H, m), 2.37—2.77 (4H, m), 3.33 (6H, s), 3.39 (6H, s), 4.20 (1H, t, J=5 Hz), 4.34 (1H, t, J=5.5 Hz), 5.12 (2H, br d, J=10.5 Hz, NH_2), 6.74, 7.51 (1H, t each, J=10.5 Hz).

3-[4-(Methylphenyl)sulfonylaminomethylene]-1,1,7,7-tetramethoxy-4-heptanone (13) NaH in mineral oil (60%, 50 mg, 1.25 mmol) was added to a stirred solution of **12** (180 mg, 0.69 mmol) in THF (3 ml) and DMF (0.3 ml), and after 10 min, *p*-TsCl (161 mg, 0.845 mmol) was further added. The mixture was stirred at room temperature for 1 h. Saturated $NaHCO_3$–H_2O was added, then the mixture was extracted with CH_2Cl_2, and the organic layer was worked up as usual. The residue was purified by PTLC [hexane–EtOAc (1 : 1)], and recrystallization from Et_2O–hexane gave 186 mg (65%) of **13** as colorless prisms, mp 80—82 °C. *Anal.* Calcd for $C_{19}H_{29}NO_7S$: C, 54.92; H, 7.04; N, 3.37. Found: C, 54.69; H, 6.97; N, 3.47. MS *m/z*: 384 ($M^+ - OMe$). IR (KBr) cm^{-1}: 1658 (sh), 1640. ^{1}H-NMR δ: 1.91 (2H, dt, J=5.5, 7 Hz), 2.42 (3H, s), 2.50—2.80 (4H, m), 3.28 (6H, s), 3.34 (6H, s), 4.14 (1H, t, J=4.5 Hz), 4.38 (1H, t, J=5.5 Hz), 6.91, 7.56 (1H, d each, J=10.5 Hz), 7.33 and 7.77 (A_2B_2, J=8.5 Hz), 8.60 (1H, br d, J=10.5 Hz, NH).

Conversion of 10 into 13 without Isolation of 11 and 12 Compound **10** (1.083 g, 4.63 mmol) was formylated with methyl formate (1.00 ml, 16.3 mmol) and 60% NaH in mineral oil (373 mg, 9.33 mmol) in benzene (3 ml) and DMF (7 ml) for 16 h. The solvent was evaporated off under reduced pressure below 50 °C, the residue was dissolved in MeOH (9 ml), and NH_4Cl (612 mg, 11.4 mmol) was added to decompose excess NaH. NH_3 gas was bubbled into this mixture for 5 min, and the whole was stirred at room temperature for 30 h. After treatment as described for the preparation of **12**, the crude product (1.218 g) was tosylated with TsCl (890 mg, 4.67 mmol) and 60% NaH in mineral oil (279 mg, 6.98 mmol) in benzene (5 ml) and DMF (2 ml) at room temperature for 1 h to afford 1.047 g (54%) of **13**, with recovery of **10** (43 mg, 4%).

4,4-Dimethoxy-1-[1-(4-methylphenyl)sulfonyl-3-pyrrolyl]-1-butanone (1) A solution of **13** (212 mg, 0.511 mmol) and *p*-TsOH·H_2O (57 mg, 0.29 mmol) in MeOH (5 ml) was refluxed for 20 min, then cooled. Saturated $NaHCO_3$–H_2O was added, and the mixture was extracted with EtOAc, and worked up as usual. Purification by PTLC [hexane–EtOAc (3 : 2)] afforded 146 mg (83.5%) of **1**[6] as a colorless syrup and 2 mg (2%) of **14**.[6]

4-[1-(4-Methylphenyl)sulfonyl-3-pyrrolyl]-4-oxobutanal (2) A solution of **13** (890 mg, 2.00 mmol) and 5% HCl–H_2O (6 ml) in THF (6 ml) was heated at 70 °C with stirring for 30 min, then cooled. Saturated $NaHCO_3$–H_2O was added, and the mixture was extracted with EtOAc, and worked up as usual. Purification by chromatography over silica gel (20 g) using hexane–EtOAc (1 : 1) afforded 571 mg (94%) of **2**[6] as a colorless syrup.

4-Nitro-1,1,7,7-tetramethoxyheptane (15) A solution of 80% acrolein (1.635 g, 2.34 mmol) in MeOH (8 ml) was added dropwise during 1 h to a stirred mixture of nitromethane (616 mg, 10.1 mmol) and powdered KOH (144 mg, 2.19 mmol) in MeOH (8 ml) at −20 °C. Stirring was continued at the same termperature for 30 min, then the reaction mixture was diluted with brine and made acidic (pH 4) by addition of citric acid. The mixture

was extracted with CH_2Cl_2 and the organic layer was worked up as usual to give *ca.* 1.75 g of the crude condensation product. This was dissolved in MeOH (3 ml) and after addition of $CH(OMe)_3$ (3 ml, 27 mmol) and NH_4Cl (191 mg, 3.57 mmol), the mixture was stirred at room temperature for 14 h. H_2O was added, the mixture was extracted with CH_2Cl_2, and the organic layer was worked up as usual. Chromatography over silica gel (40 g) using hexane–EtOAc (2 : 1) gave 1.479 g (55%) of **15** as a colorless oil. MS *m/z*: 265 (M^+). IR (neat) cm^{-1}: 1557. ^{1}H-NMR δ: 3.30 (12H, s), 4.32 (2H, t, J=5.5 Hz), 4.32—4.67 (1H, m).

1,1,7,7-Tetramethoxy-4-heptanone (10) from 15 Powdered KOH (352 mg, 5.34 mmol) was added to a stirred solution of **15** (1.340 g, 5.06 mmol) in MeOH (10 ml) at 0 °C, and the mixture was stirred at the same temperature for 25 min. To this stirred mixture, a solution of $KMnO_4$ (541 mg, 3.42 mmol) and $MgSO_4$ (503 mg, 4.19 mmol) in MeOH (15 ml) was added dropwise during 30 min at 0 °C, and the whole was further stirred at the same temperature for 30 min. The precipitate was decomposed by addition of saturated $NaHSO_3$–H_2O, and the mixture was acidified to pH 4 with 10% citric acid–H_2O, and extracted with CH_2Cl_2. Usual work-up and purification by chromatography over silica gel (40 g) using hexane–EtOAc (2 : 1) afforded 1.065 g (90%) of **10**.

Preparation of 10 from Nitromethane and Acrolein without Isolation of 15 Powdered KOH (707 mg, 11 mmol) was added to a stirred solution of 57% nitromethane–MeOH[11] (10.720 g, 100 mmol) in MeOH (100 ml) at −20 °C. Stirring was continued at −20 °C for 15 min, then a solution of freshly distilled acrolein (16.520 g, 295 mmol) in MeOH (100 ml) was added dropwise during 1 h at −20 °C, and the reaction mixture was further stirred at the same temperature for 1 h. Citric acid (2.677 g, 13.9 mmol) was added, the mixture was concentrated to about 30 ml under reduced pressure, brine was added, and the whole was worked up as above. The residue was dissolved in MeOH (25 ml) together with $HC(OMe)_3$ (25 ml) and NH_4Cl (611 mg, 11.4 mmol), and the mixture was stirred at room temperature for 14 h. It was acidified to pH 4 with 10% citric acid–H_2O, diluted with brine and treated as above. The residue (25.834 g) obtained here in MeOH (100 ml) was treated with powdered KOH (7.054 g, 107 mmol) as before, and then a solution of $KMnO_4$ (7.832 g, 49.6 mmol) and $MgSO_4$ (7.472 g, 62.3 mmol) in H_2O (130 ml) was added dropwise at 0 °C during 1 h. The mixture was stirred at 0 °C for 30 min, then EtOAc (300 ml) and Celite (40 g) were added with stirring, and the whole was filtered through a Celite bed, while the solid was washed with EtOAc (200 ml). The combined solution of the filtrate and the washings was saturated with NaCl, the organic layer was separated, the water solution was extracted thoroughly with EtOAc, and the combined organic layer was worked up as usual. Distillation *in vacuo* and chromatography over silica gel using hexane–EtOAc (2 : 1) furnished 12.876 g (55%) of **10**.

Direct Preparation of 3-[(4-Methylphenyl)sulfonylaminomethylene]-1,1,7,7-tetramethoxy-4-heptanone (13) from 10 NaH in mineral oil (60%, 403 mg, 10.1 mmol) was added to a solution of **10** (1.177 g, 5.03 mmol) in benzene (5 ml) and DMF (10 ml). The mixture was stirred at room temperature for 5 min, then $TsN{=}CHNMe_2$[8] (2.273 g, 10.1 mmol) was added at room temperature, and the mixture was stirred at the same temperature for 14 h. The solvents were removed *in vacuo* below 50 °C, saturated NH_4Cl–H_2O was added to the residue, and the whole was extracted with EtOAc, and worked up as usual. Hexane–EtOAc (2 : 1) (30 ml) was added to the residue, and the precipitate (446 mg of the reagent) was separated by filtration. The residue (*ca.* 2.7 g) from the filtrate was purified by chromatography over silica gel using hexane–EtOAc (1 : 1), followed by recrystallization from Et_2O–hexane to afford 1.556 g (75%) of **13** and a further 201 mg of the reagent.

3-[1-(4-Methylphenyl)sulfonyl-4-indolyloxy]-1-propanol (16) A mixture of **13** (208 mg, 0.501 mmol), $HO(CH_2)_3OH$ (0.5 ml, 7 mmol) and 95% H_2SO_4 (23 mg, 0.22 mmol) in $Cl(CH_2)_2Cl$ (13 ml) was refluxed using a Dean-Stark apparatus for 4 h, then cooled. Saturated $NaHCO_3$–H_2O was added, and the mixture was extracted with CH_2Cl_2, and worked up as usual. Purification by PTLC [hexane–EtOAc (7 : 4)] gave 134 mg (77.5%) of **16**[6] as a colorless syrup.

1-Chloro-3-[1-(4-methylphenyl)sulfonyl-4-indolyloxy]-2-propanol (17) A mixture of **13** (101 mg, 0.243 mmol), 1-chloro-2,3-propanediol (269 mg, 2.43 mmol) and 95% H_2SO_4 (25 mg, 0.24 mmol) in CH_2Cl_2 (5 ml) was vigorously refluxed using a Dean-Stark apparatus for 2 h. The same work-up as above and purification by PTLC [hexane–EtOAc (9 : 2)] afforded 61 mg (66%) of **17**,[1] colorless syrup, as the more polar substance and 6 mg (6.5%) of **18**,[1] colorless syrup, as the less polar substance.

2-Chloro-1-[1-(4-methylphenyl)sulfonyl-4-indolyloxy]-3-propanol (19) A mixture of **13** (91 mg, 0.22 mmol), 2-chloro-1,3-propanediol[9] (233 mg, 2.11 mmol) and 95% H_2SO_4 (36 mg, 0.35 mmol) in $Cl(CH_2)_2Cl$ (5 ml) was refluxed for 4.5 h and worked up as described for the preparation of **16**. Purification by PTLC [hexane–EtOAc (2 : 1)] afforded 58 mg (70%) of **19** as a colorless syrup. HRMS Calcd for $C_{18}H_{18}ClNO_4S$: 379.0644, 381.0614. Found: 379.0639, 381.0606. ^{1}H-NMR δ: 2.17 (1H, br s, OH), 2.30 (3H, s), 3.70—4.14 (2H, m), 4.13—4.44 (3H, m), 6.62 (1H, d, J=7.5 Hz), 6.73 (1H, d, J=3 Hz), 7.05—7.33 (3H, m), 7.45 (1H, d, J=3 Hz), 7.61 (1H, d, J=7.5 Hz), 7.72 ($\underline{A}_2B_2$, J=8.5 Hz).

(±)-Pindolol (20) A mixture of **19** (36 mg, 0.095 mmol) and isopropylamine (1 ml, 12 mmol) in EtOH (1 ml) containing 1 N NaOH–H_2O (1 ml) was refluxed for 20 h, then cooled. Brine was added, and the whole was extracted with 10% MeOH in $CHCl_3$, and worked up as usual. Purification by Al_2O_3 PTLC [CH_2Cl_2–MeOH (99 : 1)], followed by recrystallization from EtOH gave 15 mg (64%) of **20** as colorless prisms.[1]

1-[1-(4-Methylphenyl)sulfonyl-4-indolyloxy]-2,3-propanediol (21) A mixture of **13** (101 mg, 0.243 mmol), glycerol (203 mg, 2.21 mmol) and 95% H_2SO_4 (61 mg, 0.58 mmol) in $Cl(CH_2)_2Cl$ (6 ml) was vigorously refluxed for 5.5 h as above. Brine was added, the whole was extracted with 10% MeOH in CH_2Cl_2, and worked up as usual. Separation by PTLC [benzene–EtOAc (1 : 1)] afforded 7 mg (9%) of a by-product (**22**), 39 mg of **21**, and 52 mg of a mixture of intermediates in increasing order of polarity. This mixture was heated again with glycerol (191 mg), 95% H_2SO_4 (32 mg) in $Cl(CH_2)_2Cl$ (8 ml) as above for 3 h. Purification of the crude residue gave a further 15 mg of **21**, totaling 54 mg (61.5%). Compound **21**: Colorless syrup. HRMS Calcd for $C_{18}H_{19}NO_5S$: 361.0983. Found: 361.1006. ^{1}H-NMR δ: 2.28 (3H, s), 2.67 (2H, br s, OH), 3.53—4.23 (4H, m), 6.56 (1H, d, J=8 Hz), 6.69 (1H, d, J=3 Hz), 7.00—7.28 (3H, m), 7.41 (1H, d, J=3 Hz), 7.58 (1H, d, J=8 Hz), 7.69 ($\underline{A}_2B_2$, J=8.5 Hz). Compound **22**: MS *m/z*: 630 (M^+). ^{1}H-NMR δ: 2.30 (6H, s), 4.03—4.62 (5H, m), 6.62 (2H, d, J=8 Hz), 6.69 (2H, d, J=4 Hz), 7.01—7.32 (6H, m), 7.42 (2H, d, J=4 Hz), 7.59 (2H, d, J=8 Hz), 7.71 ($\underline{A}_2B_2\times2$, J=8.5 Hz).

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References and Notes

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