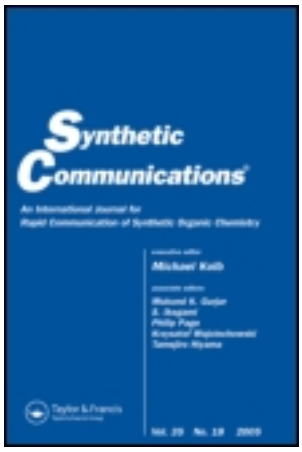

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

EFFICIENT SYNTHESIS OF THE 5-HT_{2C} RECEPTOR AGONIST, ORG 37684

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Published online: 09 Nov 2006.

To cite this article: David R. Adams & Matthew A. J. Duncton (2001) EFFICIENT SYNTHESIS OF THE 5-HT_{2C} RECEPTOR AGONIST, ORG 37684, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 31:13, 2029-2036, DOI: 10.1081/SCC-100104420

To link to this article: http://dx.doi.org/10.1081/SCC-100104420

SYNTHETIC COMMUNICATIONS, 31(13), 2029–2036 (2001)

EFFICIENT SYNTHESIS OF THE 5-HT_{2C} RECEPTOR AGONIST, ORG 37684

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ABSTRACT

An efficient synthesis of the 5-HT_{2C} receptor agonist Org 37684 is presented. The synthesis utilises the regioselective demethylation of an arylether as the key step.

The 5-HT_{2C} receptor is one of the fourteen known subtypes belonging to a family of G-protein coupled receptors whose endogenous agonist is 5-hydroxytryptamine **1**.[1] Activation of the 5-HT_{2C} receptor is thought to play a prominent role in the regulation of feeding *via* involvement in the physiological mechanism of satiety.[2] In addition, 5-HT_{2C} receptor agonists have been proposed as being useful in the treatment of a variety of disorders such as depression, anxiety, impotence and drug abuse.[3,4] Recently, Leysen and Kelder disclosed the structure of a novel, potent and selective 5-HT_{2C} receptor agonist, Org 37684, (3*S*)-[(5-methoxy-2,3-dihydro-1*H*-inden-4-yl)oxy]tetrahydro-1*H*-pyrrole **2**, which was reported to be at the final stages of pre-clinical development.[5] As no synthetic route to **2** was reported

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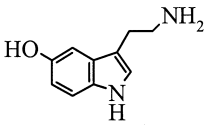
during its initial disclosure, we sought to devise a convenient preparation of this potentially important 5-HT_{2C} receptor agonist. In this communication we disclose an efficient and high-yielding synthesis of Org 37684 that can access large quantities of material without resorting to hazardous materials such as zinc amalgam, aluminium(III) chloride and 1,2-dichloroethane that are a feature of the now reported method to this compound.[6]



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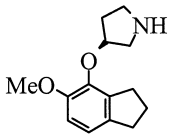

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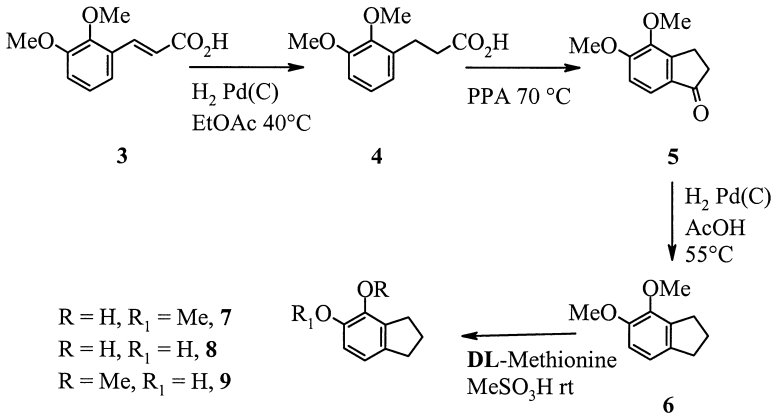
Our synthesis of Org 37684 began with commercially available *trans*-2,3-dimethoxycinnamic acid **3** (Scheme 1). Reduction of **3** with hydrogen over palladium on carbon gave the propanoic acid **4**, which cyclised smoothly to the indanone **5** upon exposure to hot polyphosphoric acid. Removal of the ketone group in **5** (H_2, Pd/C, AcOH, 55°C) afforded the known indane **6**.[7] With sufficient quantity (> 100 mmol) of the indane **6** in-hand, our attention turned to the regio-selective demethylation of the 4-methoxy group. Of the two methods tried (BBr_3 and methionine) the procedure of Yajima *et al.* proved the most successful.[8] Thus, reaction of the indane **6** with 1.1 molar equivalents of **DL**-methionine in methanesulfonic acid gave the desired phenol **7** which was easily separated from the fully deprotected compound **8** and the regio-isomeric phenol **9** by 'flash'



3 **4** **5** **6**

Scheme 1.

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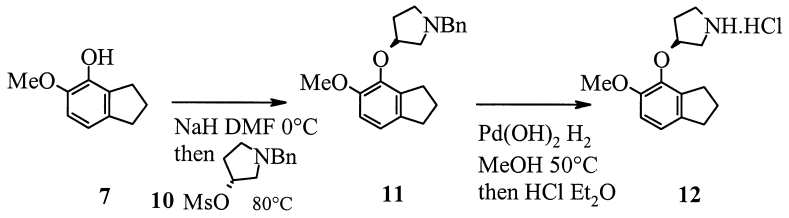
chromatography on silica gel. The overall yield of the phenol **7** in the four step process from the cinnamic acid **3** was 52% and the ratio of **7**:**8**:**9** in the deprotection step was 57:21:2. Upon scale-up of this demethylation reaction no drop in yield, or no change in the ratio of products was observed.

Completion of the synthesis was accomplished in two steps from the phenol **7**. Formation of the aryl-ether bond by reaction of the mesylate **10** with the phenol **7** progressed with clean inversion of stereochemistry to give the desired 3-substituted pyrrolidine **11**. Removal of the *N*-benzyl protecting group in compound **11** gave Org 37684 **2** (e.e. > 99% by chiral HPLC) which was isolated as the hydrochloride **12** by reaction with HCl in anhydrous ether (Scheme 2).



7 **10** **11** **12**

Scheme 2.

In conclusion this paper describes a rapid (6 step) and high yielding (32% overall yield from cinnamic acid **3**) synthesis of the 5-HT$_{2C}$ receptor agonist Org 37684. Our synthesis is especially noteworthy as it allows the production of gram quantities of material without the need to resort to toxic heavy metals or chlorinated solvents.

EXPERIMENTAL

Melting points were determined on a Stuart scientific melting point apparatus model SMP2 and are uncorrected. Infra red spectra were obtained on a Perkin Elmer Paragon 1000 FT-IR spectrometer. ^{1}H NMR were obtained on a Bruker DPX 400 NMR spectrometer using tetramethylsilane as an internal standard. Microanalytical data were obtained on a CEC 240 XA or Caloebra 1106 microanalysis machine. All reagents and solvents were purchased from the Aldrich Chemical Company, Dorset, United Kingdom.

3-(2,3-Dimethoxyphenyl)propanoic Acid 4: *Trans*-2,3-dimethoxycinnamic acid **3** (70 g, 340 mmol) was hydrogenated at 50 psi over 10% palladium on charcoal (4 g) in ethyl acetate (300 ml) at 45°C. After completion of the reaction (*ca.* 2 h) the mixture was filtered through celite®. The

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filter cake was washed with ethyl acetate (200 ml) and the filtrate was concentrated *in vacuo* to leave the product (70.7 g, 100%) as a white solid. Mp 62–63°C (lit.[9] 64–66°C); ν_{max} (nujol) 2923, 2854, 1705, 1560, 1486, 1464, 1436, 1290, 1217, 1169, 1087, 1046, 1004, 937, 794, 751 and 669 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 11.6 (1H, br. s, $CO_2\boldsymbol{H}$), 6.95 (1H, app. t, $J = 8$ Hz, Ar-$\boldsymbol{H}$), 6.77–6.80 (2H, m, $2 \times$ Ar-$\boldsymbol{H}$), 3.84 (3H, s, $OC\boldsymbol{H}_3$), 3.83 (3H, s, $OC\boldsymbol{H}_3$), 2.93 (2H, t, $J = 8$ Hz, $ArCH_2C\boldsymbol{H}_2CO_2H$), 2.64 (2H, t, $J = 8$ Hz, $ArC\boldsymbol{H}_2CH_2CO_2H$).

4,5-Dimethoxy-1-indanone 5: 3-(2,3-dimethoxyphenyl)propanoic acid **4** (70.7 g, 336 mmol) was added in one portion to stirred polyphosphoric acid (600 g) at 70°C. The mixture was stirred at 70°C for 45 min then a further aliquot of polyphosphoric acid (100 g) was added and the mixture was stirred at 70°C for a further 30 min. After allowing the mixture to cool to room temperature it was poured into ice/water (1.5 l) and extracted with diethyl ether (400 ml). The organic extract was washed with saturated sodium hydrogen carbonate (300 ml) and brine (300 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave the product (58.7 g, 92%) as an orange solid. Mp 74–75°C (lit.[10] 74–75°C); ν_{max} (nujol) 2927, 2854, 1704, 1599, 1586, 1499, 1457, 1430, 1378, 1337, 1282, 1239, 1222, 1194, 1077, 1053, 1017, 981, 934, 878, 831, 808, 743, 642, 612 and 526 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.50 (1H, d, $J = 8.4$ Hz, Ar-$\boldsymbol{H}$), 6.96 (1H, d, $J = 8.4$ Hz, Ar-$\boldsymbol{H}$), 3.95 (3H, s, $OC\boldsymbol{H}_3$), 3.91 (3H, s, $OC\boldsymbol{H}_3$), 3.08 (2H, app. t, $J = 6$ Hz, $ArC\boldsymbol{H}_2$), 2.65–2.68 (2H, app. t, $J = 6$ Hz, $ArCH_2C\boldsymbol{H}_2$); Found: C, 68.42; H, 6.22; $C_{11}H_{12}O_3$ requires C, 68.74; H, 6.29%

4,5-Dimethoxyindan 6: 4,5-Dimethoxy-1-indanone **5** (50 g, 260 mmol) was hydrogenated at 55 psi over 10% palladium on charcoal (3 g) in acetic acid (150 ml) at 55°C. After completion of the reaction (*ca.* 3 h) the mixture was filtered through celite® and the filter cake was washed with acetic acid (100 ml). Water (500 ml) was added to the filtrate and the mixture was adjusted to pH 9 with 5N sodium hydroxide. The mixture was extracted with diethyl ether (3×200 ml) and the combined organic extracts were washed with saturated sodium hydrogen carbonate (200 ml) and brine (100 ml), then dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave the product (46.3 g, 100%) as an orange oil. ν_{max} (film) 2949, 2844, 1612, 1586, 1488, 1461, 1439, 1427, 1337, 1309, 1279, 1260, 1220, 1169, 1150, 1078, 1047, 857, 894, 797, 734, 684 and 634 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 6.87 (1H, d, $J = 8$ Hz, Ar-$\boldsymbol{H}$), 6.70 (1H, d, $J = 8$ Hz, Ar-$\boldsymbol{H}$), 3.84 (3H, s, $OC\boldsymbol{H}_3$), 3.84 (3H, s, $OC\boldsymbol{H}_3$), 2.91 (2H, app. t, $J = 7.5$ Hz, $ArC\boldsymbol{H}_2$), 2.82 (2H, app. t, $J = 7.5$ Hz, $ArC\boldsymbol{H}_2$), 2.04–2.08 (2H, m, $ArCH_2C\boldsymbol{H}_2$).

5-Methoxy-4-indanol 7: **DL**-Methionine (47.2 g, 286 mmol) was added portion-wise over 10–15 min to a stirred solution of 4,5-dimethoxyindan **6** (46.3 g, 260 mmol) in methanesulfonic acid (350 ml) at 15°C. The mixture

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was stirred at 15°C for 1 h then allowed to warm to room temperature and stirred for a further 2 h. The mixture was poured into ice/water (1.2 l) and extracted with diethyl ether (3×200 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a brown oil. The oil was purified by chromatography on silica gel using ethyl acetate/hexane (1:24) as eluent to give the product (26.4 g, 57%) as a white solid. Mp 68–70°C; ν_{max} (nujol) 3406, 2927, 2855, 1494, 1459, 1444, 1377, 1354, 1423, 1304, 1285, 1234, 1148, 1076, 1000, 914, 894, 790, 725, and 546 cm^{-1}. δ_H (400 MHz: $CDCl_3$) 6.69 (1H, d, $J=8$ Hz, Ar-***H***), 6.66 (1H, d, $J=8$ Hz, Ar-***H***), 5.59 (1H, br. s, O***H***), 3.85 (3H, s, OC***H***$_3$), 2.89 (2H, app. t, $J=7.2$ Hz, ArC***H***$_2$), 2.84 (2H, app. t, $J=7.5$ Hz, ArC***H***$_2$), 2.08 (2H, m, $ArCH_2C$***H***$_2$); Found C, 73.11; H, 7.40; $C_{10}H_{12}O_2$ requires C, 73.15; H, 7.40%. Further elution with ethyl acetate/hexane (1:24) gave 4-methoxy-5-indanol **9** (1.1 g, 2%) as a yellow oil. ν_{max} (film) 3425, 2945, 2845, 1850, 1729, 1611, 1483, 1460, 1437, 1351, 1288, 1268, 1229, 1194, 1161, 1042, 1006, 969, 936, 906, 811, 742 and 673 cm^{-1}. δ_H (400 MHz; $CDCl_3$) 6.81 (1H, d, $J=8$ Hz, Ar-***H***), 6.73 (1H, d, $J=8$ Hz, Ar-***H***), 5.56 (1H, br, s, O***H***), 3.86 (3H, s, OC***H***$_3$), 2.95 (2H, app. t, $J=7.5$ Hz, $ArCH_2$), 2.79 (2H, app. t, $J=7.5$ Hz, ArC***H***$_2$), 2.04–2.11 (2H, m, $ArCH_2C$***H***$_2$). Further elution with ethyl acetate/hexane (3:7) gave 4,5-dihydroxyindan **8** (9 g, 21%) as a yellow oil. ν_{max} (nujol) 3318, 2925, 2853, 1632, 1595, 1508, 1479, 1466, 1438, 1377, 1338, 1311, 1279, 1234, 1197, 1141, 1009, 940, 904, 780, 760, 723 and 686 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 6.63–6.67 (2H, m, 2 × Ar-***H***), 5.20 (2H, br, s, 2 × O***H***), 2.81 (4H, app. t, $J=7.5$ Hz, 2 × ArC***H***$_2$), 2.04–2.11 (2H, m, $ArCH_2C$***H***$_2$).

(3*R*)-1-Benzyl-3-methanesulfonyloxy pyrrolidine 10: Methanesulfonyl chloride (11.6 ml, 149 mmol) was added dropwise over 30 min to a stirred solution of (3*R*)-1-benzyl-3-pyrrolidinol (22 g, 120 mmol) and triethylamine (26.1 ml, 186 mmol) in dichloromethane (200 ml) at 0°C under argon. The mixture was stirred at 0°C for a further 3 h. The solvent was removed *in vacuo* to leave a crude residue. The residue was partitioned between water (200 ml) and diethyl ether (200 ml) and the aqueous layer was re-extracted with diethyl ether (2 × 100 ml). The combined organic extracts were washed with brine (1×100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave the product (27.7 g, 100%) as a yellow oil. ν_{max} (film) 3028, 2940, 2799, 1959, 1734, 1604, 1586, 1496, 1479, 1454, 1416, 1354, 1249, 1171, 1146, 1075, 1028, 958, 895, 851, 796, 743, 702, 630, 534, 524 and 466 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.26–7.32 (5H, m, 5 × Ar-***H***), 5.17–5.21 (1H, m, C***H***OSO_2CH_3), 3.67 (1H, d, $J=12.5$ Hz, NC***H***HPh), 3.61 (1H, d, $J=12.5$ Hz, NC***H***HPh), 2.99 (3H, s, OSO_2C***H***$_3$), 2.73–2.92 (3H, m, NC***H***$_2$ + NC***H***H), 2.48–2.54 (1H, m, NC***H***H), 2.27–2.36 (1H, m, NCH_2C***H***H), 2.05–2.12 (1H, m, NCH_2C***H***H).

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(3S)-1-Benzyl-3-[(5-methoxy-2,3-dihydro-1*H*-inden-4-yl)oxy]tetrahydro-1*H*-pyrrole 11: 5-Methoxy-4-indanol **7** (10 g, 61 mmol) was added portionwise over 30 min to a stirred suspension of sodium hydride (60% in oil; 2.56 g, 64 mmol) in *N*,*N*-dimethylformamide (200 ml) at 0°C under argon. The reaction was stirred at 0°C for a further 1 h then (3*R*)-1-benzyl-3-methanesulfonyloxy pyrrolidine **10** (27.7 g, 124 mmol) was added in *N*,*N*-dimethylformamide (50 ml) in one portion. The mixture was heated to 80°C and stirred at this temperature for 12 h. After allowing to cool to room temperature the mixture was poured into water (600 ml) and the aqueous solution was extracted with diethyl ether (3 × 200 ml). The combined organic extracts were washed with brine (100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a crude oil. The oil was purified by column chromatography on silica gel using ethyl acetate/hexane (3:7) as eluent to give the product (16.7 g, 85%) as a yellow oil. ν_{max} (film) 2951, 2843, 2790, 1736, 1606, 1585, 1484, 1464, 1453, 1440, 1379, 1329, 1308, 1278, 1258, 1212, 1148, 1129, 1078, 1028, 957, 901, 797, 740 and 670 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.20–7.33 (5H, m, NCH_2Ar-***H***), 6.82 (1H, d, $J = 8$ Hz, Ar-***H***), 6.65 (1H, d, $J = 8$ Hz, Ar-***H***), 4.82–4.85 (1H, m, C***H***OAr), 3.75 (3H, s, $OC\boldsymbol{H}_3$), 3.69 (1H, d, $J = 12.6$ Hz, NC***H***HAr), 3.56 (1H, d, $J = 12.6$ Hz, NC***H***HAr), 2.72–2.86 (7H, m, $2 \times ArC\boldsymbol{H}_2 + NC\boldsymbol{H}_2 + NC\boldsymbol{H}H$), 2.51–2.57 (1H, m, NC***H***H), 1.95–2.14 (4H, m, $ArCH_2C\boldsymbol{H}_2 + OCHC\boldsymbol{H}_2CH_2N$).

(3*S*)-3-[(5-Methoxy-2,3-dihydro-1*H*-inden-4-yl)oxy]tetrahydro-1*H*-pyrrole hydrochloride 12: (3*S*)-1-Benzyl-3-[(5-methoxy-2,3-dihydro-1*H*-inden-4-yl)oxy]tetrahydro-1*H*-pyrrole **11** (16.5 g, 51 mmol) was hydrogenated at 50 psi over palladium(II) hydroxide on charcoal (1 g) in methanol at 50°C. After 12 h a further aliquot of palladium(II) hydroxide on charcoal (1 g) was added and the mixture was hydrogenated at 50 psi and 50°C for a further 24 h. After allowing to cool to room temperature the mixture was filtered through celite® and the filtrate was concentrated *in vacuo* to leave a crude oil. The oil was purified by column chromatography on silica gel using ethyl acetate as eluent to give recovered starting material (2 g) as a yellow oil. Further elution with ethyl acetate/methanol/concentrated ammonium hydroxide (90:8:2) as eluent gave a pale yellow oil (8.5 g). The oil was dissolved in diethyl ether (50 ml) and an anhydrous solution of hydrogen chloride in diethyl ether (1 N, 40 ml) was added. The emerging precipitate was filtered and dried to give the product (8.8 g, 64%) as a white solid, Mp 172–174°C; ν_{max} (nujol) 2922, 2853, 2732, 2675, 2576, 2539, 2560, 2479, 1609, 1596, 1582, 1491, 1456, 1400, 1377, 1342, 1328, 1305, 1281, 1258, 1242, 1210, 1193, 1150, 1078, 1034, 1009, 953, 933, 900, 887, 796, 738, 722 and 684 cm^{-1}; δ_H (400 MHz; DMSO) 9.56 (1H, br. s, N***H***H), 9.38 (1H, br. s, N***H***H), 6.90 (1H, d, $J = 8$ Hz, Ar-***H***), 6.81 (1H, d, $J = 8$ Hz, Ar-***H***), 4.90–4.91 (1H, m, C***H***OAr), 3.74 (3H,s, $OC\boldsymbol{H}_3$), 3.30–3.40 (4H, m,

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2 × NCH_2), 2.76–2.80 (4H, m, 2 × ArCH_2), 1.87–2.09 (4H, ArCH$_2$CH_2 + NCH$_2$-CH_2); Found C, 62.52; H, 7.62; N, 5.17; $C_{14}H_{19}NO_2$.HCl requires C, 62.33; H, 7.47; N, 5.19%

The recovered starting material was re-subjected to the deprotection conditions to give the title compound (1.2 g; total yield 10 g, 72%) as a white solid.

ACKNOWLEDGMENTS

We thank Dr. Ken Heatherington, Dr. Peter Clayton and Dr. Graeme Harden for performing the analysis on compounds **4** to **12**. We also thank Dr. Ian Cliffe for helpful suggestions whilst preparing this manuscript and acknowledge the work of Mrs. Lyn Heaney in typing this paper.

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7. Our procedure to indane **6** is a modification to that reported by Jardon, P.W.; Vickery, E.H.; Pahler, L.F.; Pourahmady, N.; Mains, G.J.; Eisenbraun, E.J. J. Org. Chem. **1984**, *49*, 2130.
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Received in the UK May 10, 2000

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