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Solid-Phase Synthesis of Cyclic Imides

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A cyclative cleavage strategy for the synthesis of cyclic imides on a polystyrene resin is described. After optimization of the cleavage conditions, a small array of succinimides and phthalimides was synthesized. The methodology was then applied to a drug discovery project, in which it was used to synthesize a new class of δ-opioid receptor ligand by both automated and manual methods.

Cleavage strategies which involve heterocyclization have been used successfully for the solid-phase synthesis of a range of amide-containing ring systems, such as benzodiazepines,[1] hydantoins,[1] pyrimidinediones,[2] diketopiperazines,[3] and pyrazolones.[4] Unusually for solid-phase chemistry, such strategies have the advantage that the coupling and cleavage steps are part of the actual synthesis, rather than additional steps. In addition, since only the heterocyclic product can be released from the resin, the products are, in many cases, very pure.

One class of compound whose synthesis has not, to our knowledge, been reported previously on a resin, and yet which quite often possesses interesting biological activity, is the cyclic imides.[5] In particular, succinimides and phthalimides have been reported to exhibit anticonvulsant, hypnotic, antiviral, anxiogenic, antipsychotic, and antiinflammatory activity.[6] The classical solution-phase method for the formation of cyclic imides involves reacting an amine with a cyclic anhydride, followed by ring closure using acetic anhydride. We found that this solution-phase method was far from ideal for the synthesis of libraries of cyclic imides. In particular, the ring closure step was unreliable, requiring us to purify the products by HPLC before biological testing. Hence our interest in synthesising cyclic imides by solid-phase chemistry, using a cyclative cleavage strategy, was born.

The strategy involves coupling a cyclic anhydride **2** to hydroxymethyl polystyrene resin **1** (Scheme 1) using 4-(dimethylamino)pyridine (DMAP) in *N*,*N*-dimethylformamide (DMF). The resulting carboxylic acid **3** was then converted into an amide **4** using a primary amine in the presence of diisopropylcarbodiimide (DIC) and *N*-hydroxybenzotriazole (HOBT). Finally, heating promoted cyclization and released the cyclic imide **5** from the resin.

A range of conditions for the cleavage reaction was examined for *N*-methylphthalimide **5a** and *N*-methylsuccinimide **5g**: (A) toluene (90 °C; 18 h), (B) 5% acetic acid in toluene (90 °C; 18 h), (C) 5% acetic acid in DMF (130 °C; 18 h). The yields for conditions A−C are given in Table 1.

For *N*-methylphthalimide, high temperature (130 °C) and the presence of acetic acid were required for a good overall yield of product (87%). The lower yield for the succinimide may be due to the increased conformational mobility of the system, which is consequently less preorganized for cyclization.[9]

Scheme 1. Solid-Phase Strategy for Cyclic Imides[7]

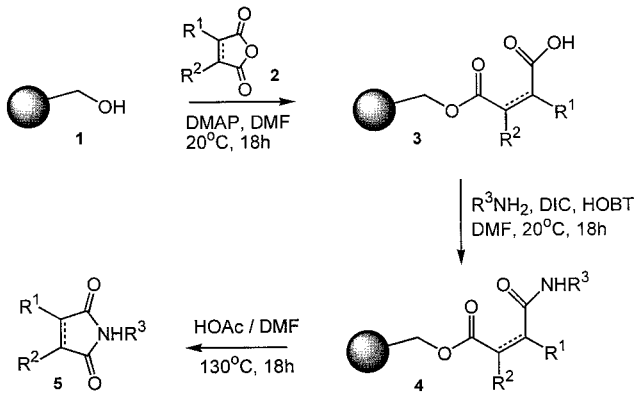

Table 1. Percentage Yields for Three Steps Based on the Resin Substitution Level Determined by the Fmoc Quantitation Method[8,a]

cmpd	A toluene, 90 °C, 18 h (%)	B 5% HOAc/toluene, 90 °C, 18 h (%)	C 5% HOAc/DMF, 130 °C, 18 h (%)
5a	13	51	87
5g	0	6	26

[a] All compounds were >90% purity, as determined by gas chromatography.

The use of conditions C enabled the parallel synthesis of a small array of nine succinimide and phthalimide derivatives[10] (see Chart 1).

The yields of *N*-methylphthalimide **5a** and *N*-methylsuccinimide **5g** were similar to the previous experiment (Table 1), showing the reproducibility of the method. Substituents on the carbon atoms of the succinimide ring improve the yield of product: **5h** (57%) and **5i** (53%). Compound **5h** ("phensuximide") has been used as an anticonvulsant.[6] Chlorine substituents on the aromatic ring of the phthalimide are tolerated, but the yields are somewhat lower (**5e** and **5f**). Compounds **5b** and **5d** were made from the commercially available diacids using DIC in the coupling step to form the cyclic anhydrides. Interestingly, cyclic imides such as **5d**, containing a pyridine ring, were obtained in good yield (53%) using this solid-phase strategy. In contrast, the traditional

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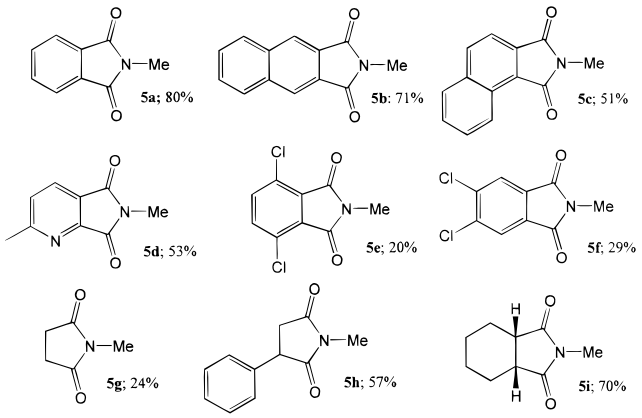
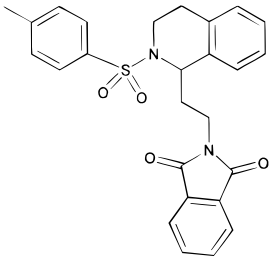
Chart 1



solution-phase method, opening of the anhydride followed by ring closure using acetic anhydride, results in decarboxylation at the intermediate carboxylic acid stage, giving predominantly the amide rather than an imide.[11] It was not possible to obtain any *N*-methylglutarimide or *N*-methylhomophthalimide using conditions C, presumably due to the high conformational freedom of these systems disfavoring six-membered ring formation.[9]

Having developed the basic methodology, we were obviously keen to apply it to a drug discovery project at Organon. One of the hits that we obtained through screening of the corporate compound collection at the δ-opioid receptor was **6**. δ-Opioid ligands are of potential interest as analgesics



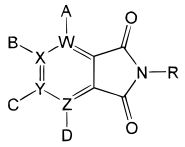
6

which may lack the numerous side effects (e.g., respiratory depression) associated with clinically used μ-opioids such as fentanyl and its analogues. Compound **6** (racemate) was found to have good affinity (98 nM) at the cloned human δ-opioid receptor and exhibits excellent selectivity over the μ- and κ-opioid receptors (200- and 180-fold, respectively).[12] Our first objective was to synthesize **6** using the above methodology. Hydroxymethylpolystyrene resin **1** was reacted with phthalic anhydride **7** to generate the resin-bound acid **8**. This was then coupled with 1-(2-aminoethyl)-2-(4-toluenesulfonyl)-1,2,3,4-tetrahydroisoquinoline **9**[13] to generate amide **10**. Heating of **10** in the presence of 25% acetic acid in toluene (110 °C; 18 h) released **6** from the resin in 63% yield and greater than 90% purity.[10] The same reaction sequence was repeated on Wang resin, giving **6** in 58% yield. In view of the slightly superior yield of **6**, it was decided to use hydroxymethylpolystyrene for all further experiments. Our next objective was the automated synthesis of a compound library in which the phthalimide group of **6** was varied. Using a Syro II automated synthesizer, all reactions were performed using conditions identical to those of the manual synthesis, except that the cleavage was done at a lower temperature (90 °C; 18 h). This was necessary since the Syro II synthesizer has no facility for the condensation of solvents at reflux temperature. It was decided to use toluene as the solvent for the cleavage, in place of DMF, in view of the much easier evaporation of the former from the cleaved products. The yield of **6** (**11**{*1*} in Table 2) from this automated synthesis was lower (31%), probably due to the lower cleavage temperature, but the LC purity was still very good (typically >90%). The yields of the other products ranged from 4% for **11**{*18*} to 79% for **11**{*22*}, with an overall average yield of 27%. Compound **11**{*3*}, containing a 2-nitrophthalimide group, gave an unusually poor yield, whereas the other ortho-substituted phthalimides gave moderate to good yields. All the meta-substituted phthalimides were obtained in reasonable yield, ranging from 29% for **11**{*4*} to 53% for **11**{*16*}. Since the yields from this automated synthesis are nonoptimized, the low yields of certain phthalimides are not easily explained in terms of electronic and steric factors and may in part be due to technical difficulties with the robotic synthesizer. The yield of the unsubstituted succinimide system **11**{*17*} (27%) was similar to that obtained for **5g** (24%). Again introduction of a substituent in the 2-position of the succinimide ring improved the yield, e.g., compounds **11**{*27*} and **11**{*28*}. Branching diminishes the mobility, and hence the entropy of chains, but has much less effect on mobility within small rings. Thus, the entropy change in ring closure is made more favorable (less negative) by alkyl substitution. In contrast, the 2,3-dimethyl derivative **11**{*26*} gave a poorer yield than the unsubstituted system. This may be due to the unfavorable steric effect of an additional methyl group adjacent to the ester carbonyl outweighing the favorable entropic effect of substitution upon the rate of cyclization. Two bicyclic ring systems fused at the 2- and 3-positions, **11**{*22*} and **11**{*25*}, gave particularly good yields. The purity of the products determined by LC−MS was generally good, in the range 72−99%. All 30 products were tested in the δ-opioid binding assay. The difluoro-substituted analogue **11**{*6*} was found to possess higher affinity (16 nM) at the δ-opioid receptor compared to **6** (98 nM), indicating the importance of this region for receptor binding.

Thus we knew we could introduce diversity at the position of the phthalimide ring using a range of commercially available diacids and cyclic anhydrides. Ideally we also wanted to simultaneously introduce diversity at the position occupied by the *p*-toluenesulfonyl group. Thus we went on to investigate the synthesis of **6** via the Boc-protected intermediate **13** (Scheme 2). After coupling of **12** to the resin, the Boc group was removed from **13** using 50% trifluoroacetic acid (TFA) in DCM. The liberated secondary amine was reacted with *p*-toluenesulfonyl chloride to give the sulfonamide **10**. As before, cleavage was promoted by heating with 25% acetic acid in toluene (110 °C; 18 h) to give **6** in 41% yield and >90% purity.[10] Using this route, a small scope determination library of eight compounds **14**{*1*−*8*} was prepared using the Syro II synthesizer in similar yield and purity,[10] containing eight variants at the sulfonamide

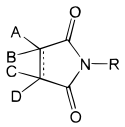
Table 2. A Library of Analogues of the δ-Opioid Ligand **6**[a]

Phthalimides **11**



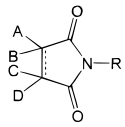
phthalimides	yield[b] (%)	purity[c] (%)	phthalimides	yield[b] (%)	purity[c] (%)
11{*1*}	31	98	**11**{*9*}; A, D = Cl	24	72
11{*2*}; W = N	24	93	**11**{*10*}; B, C = Cl	24	99
11{*3*}; A = NO_2	6	83	**11**{*11*}; B = Cl	37	96
11{*4*}; B = NO_2	29	89	**11**{*12*}; W, Z = N	18	93
11{*5*}; A = F	42	98	**11**{*13*}; B = F	44	98
11{*6*}; A, D = F	8	98	**11**{*14*}; A−B = CHCHCHCH	72	94
11{*7*}; A, B, C, D = F	27	97	**11**{*15*}; B−C = CHCHCHCH	28	99
11{*8*}; B = Me	30	99	**11**{*16*}; W = N, B = Me	53	95

Succinimides **11**



succinimides	yield[b] (%)	purity[c] (%)	succinimides	yield[b] (%)	purity[c] (%)
11{*17*}	27	95	**11**{*24*}; A = HCONH (*R*)	23	96
11{*18*}; A−C = $CH_2CHCHCH_2$ (*cis*)	4	72	**11**{*25*}; A−C = CH_2	50	97
11{*19*}; A−C = $CH_2CH_2CH_2CH_2$ (*cis*)	5	97	**11**{*26*}; A, B = Me	7	91
11{*20*}; A−C = $CH_2CH_2CH_2CH_2$ (*trans*)	4	81	**11**{*27*}; A = Ph	43	96
11{*21*}; A = $PhCH_2OCONH$ (*S*)	14	90	**11**{*28*}; A = Me	39	98
11{*22*}; A−C = bicyclo[2.2.1]hept-5-ene (*endo*)	79	97	**11**{*29*}; A, C = Me	12	96
11{*23*}; A−C = bicyclo[2.2.2]oct-5-ene (*endo*)	28	97			

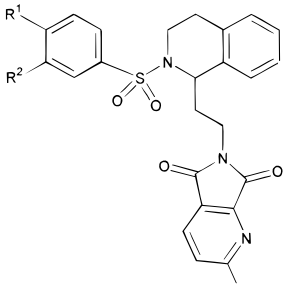
Maleimides **11**



maleimide	yield[b] (%)	purity[c] (%)
11{*30*}; A−B = $CH_2CH_2CH_2CH_2$	19	95

[a] Unless stated otherwise, A, B, C, and D represent hydrogen, and W, X, Y, and Z represent carbon. "A, B" indicates both positions are substituted as shown. "A−B" indicates a bridging group between the two positions. R = 1-(2-ethyl)-2-(4-toluenesulfonyl)-1,2,3,4-tetrahydroisoquinoline. [b] Percent yields for three steps based on the resin substitution level determined by the Fmoc quantitation method.[8] [c] Percent purity determined by liquid chromatography−mass spectrometry.

position, in combination with the pyridine-containing cyclic imide found in **11**{*16*}.



14 {*1*}; R^1 = Me, R^2 = H
14 {*2*}; R^1 = nBu, R^2 = H
14 {*3*}; R^1 = Cl, R^2 = H
14 {*4*}; R^1 = Et, R^2 = H
14 {*5*}; R^1 = nBuO, R^2 = H
14 {*6*}; R^1 = Et_2NCH_2, R^2 = H
14 {*7*}; R^1 = H, R^2 = Me
14 {*8*}; R^1 = CF_3O, R^2 = H

The stage is now set for the synthesis of larger optimization libraries based upon this novel class of nonbasic δ-opioid ligands. A more detailed discussion of the biological data for these libraries will be reported in due course. In summary, we have found this new cyclative cleavage methodology provides a facile synthesis of libraries of cyclic imides in higher purity than could easily be realized by traditional solution-phase methods, thereby accelerating the process of hit optimization.

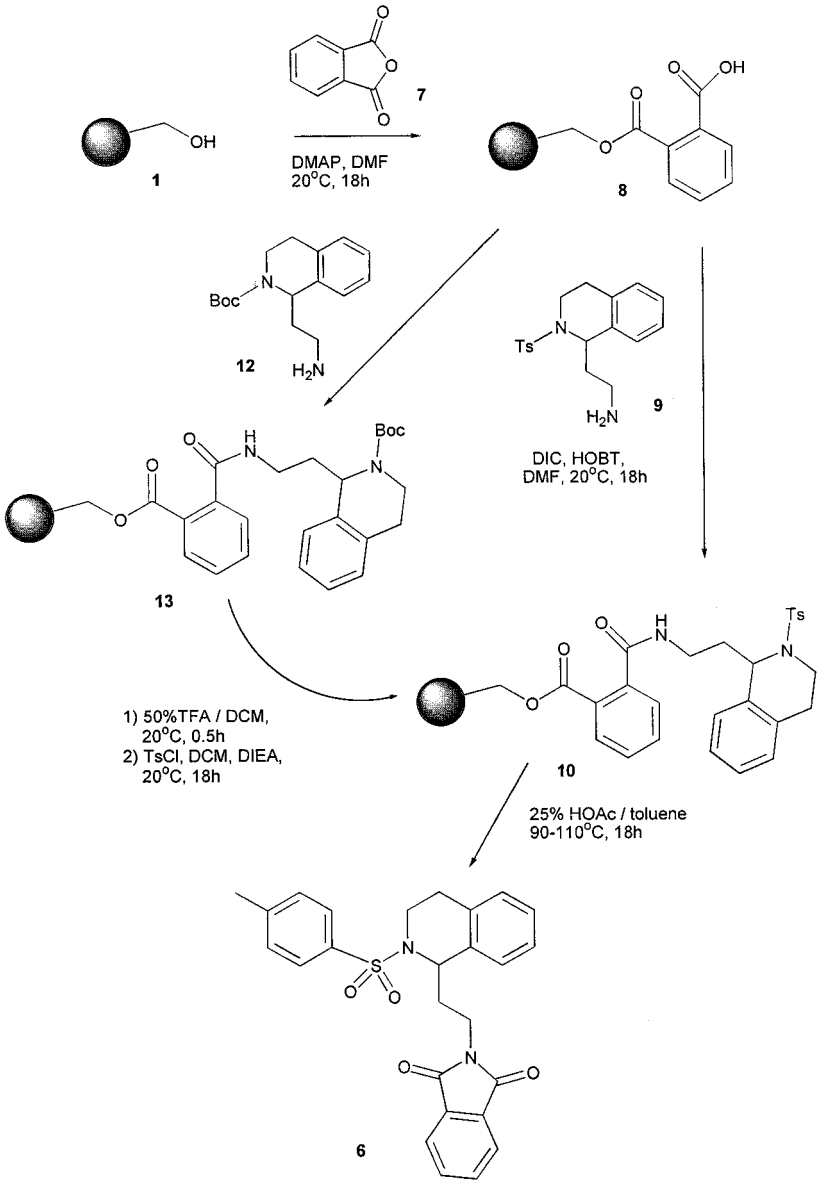
Experimental Section

General Procedure for the Esterification. To a suspension of hydroxymethyl polystyrene resin (400 mg; 0.3 mmol; Bachem; 0.74 mmol/g) in DMF (4.5 mL) in a 10 mL fritted polypropylene tube [Crawford Scientific] were added triethylamine (278 μL; 2 mmol), DMAP (50 mg; 0.4 mmol), and phthalic anhydride (296 mg; 2 mmol). The vessel was agitated on a blood tube rotator [Stuart Scientific] for 18 h at 20 °C. The tube was then transferred to a Vac Master sample processing station for washing (3 × 4 mL of DMF; 3 × 4 mL of DCM; 2 × 4 mL of CH_3OH), then dried in a vacuum oven at 45 °C.

The cyclic anhydrides used in the synthesis of compounds **5b** and **5d** were preformed from the diacids (2 mmol) by adding DIC (2 mmol) in DMF (2 mL). After the mixture stood for 10 min at 20 °C, it was added to a suspension of the resin (0.3 mmol), triethylamine (2 mmol), and DMAP (0.4 mmol) in DMF (2.5 mL).

General Procedure for the Amidation. The resin was suspended in a solution of HOBT (276 mg; 2 mmol) and DIC (313 μL; 2 mmol) in DMF (2 mL) and then treated

Scheme 2. Solid-Phase Synthesis of a δ-Opioid Ligand



with 1 mL of a 2 M solution of methylamine (2 mmol) in THF. The vessel was agitated on a tube rotator [Stuart Scientific] for 18 h at 20 °C. The tube was then transferred to a Vac Master sample processing station for washing (3 × 4 mL of DMF; 3 × 4 mL of DCM; 2 × 4 mL of CH_3OH) and then dried in a vacuum oven at 45 °C.

General Procedure for the Cleavage [Conditions C]. The resin was transferred to a Quickfit glass test tube and swollen in DMF (5 mL). Acetic acid (250 μL) was then added, and the suspension was heated at 130 °C for 18 h. The vessel was transferred to the VacMaster station and filtered into a test tube. The solvent was then removed using a Savant vacuum centrifuge. *N*-methylphthalimide **5a** was obtained in 87% yield (42 mg) and 98% purity, as determined by gas chromatography.

Compounds **5a**, **5b**, **5c**, **5e**, **5f**, **5g**, **5h**, and **5i** are known compounds. For these, CAS registry numbers are given below in brackets. (All registry numbers are supplied by the author.) A literature search failed to uncover prior reports of compounds **5d**, **6**, **9**, and **12**.

5a [149273-25-6].

5b [42896-23-1].

5c [885-07-4].

5d, 2-Methyl-6-methyl-pyrrolo<3,4-*b*>pyridine-5,7-dione: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05 (d, J = 8.7 Hz, 2H), 7.45 (d, J = 8.8 Hz, 2H), 3.24 (s, 3H), 2.77 (s, 3H).

5e [169479-72-5].

5f [86611-81-6].

5g [1121-07-9].

5h [34367-67-4].

5i [64090-28-4].

1-(*N*-Phthaloyl-2-aminoethyl)-2-(*tert*-butyloxycarbonyl)-1,2,3,4-tetrahydroisoquinoline. To a suspension of 1-(*N*-Phthaloyl-2-aminoethyl)-1,2,3,4-tetrahydroisoquinoline (2.70 g; 8.8 mmol) and sodium hydrogen carbonate (2.18 g) in methanol (50 mL) was added di-*tert*-butyl dicarbonate (1.91 g; 8.8 mmol). The mixture was sonicated for 10 min and then filtered to remove inorganic material. The filtrate was evaporated, and the residue was purified by flash silica chromatography, eluting with 5% methanol in DCM, giving

the product (1.97 g) in 55% yield: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.82 (m, 2H), 7.70 (m, 2H), 7.15 (m, 4H), 5.41−5.09 (m, 1H), 4.36−3.64 (m,3H), 3.45−3.21 (m, 1H), 3.12−2.64 (m, 2H), 2.30−2.05, (m, 2H), 1.47 (s, 9H).

1-(*N*-phthaloyl-2-aminoethyl)-2-(4-toluenesulfonyl)-1,2,3,4-tetrahydroisoquinoline, 6. To a solution of 1-(*N*-phthaloyl-2-aminoethyl)-1,2,3,4-tetrahydroisoquinoline (3.0 g; 9.8 mmol) and *N*-diisopropylethylamine (1.74 mL; 10 mmol) in DCM at 20 °C was added *p*-toluenesulfonyl chloride (1.91 g; 10 mmol). After being stirred at 20 °C for 2 h, the solution was washed with water, dried ($MgSO_4$), filtered, and evaporated to dryness. Purification by flash silica chromatography, eluting with 5% methanol in DCM, gave the product (4.22 g) in 93% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84 (m, 2H), 7.70 (m, 2H), 7.59 (d, J = 7.8 Hz, 2H), 7.00−7.15 (m, 5H), 6.85 (d, J = 6.3 Hz, 1H), 5.10 (m, 1H), 3.98−3.80 (m, 3H), 3.6 (m, 1H), 2.53 (m, 2H), 2.30 (s, 3H), 2.25−2.00 (m, 2H).

General Procedure for the Dephthaloylation. To a solution of 1-(*N*-phthaloyl-2-aminoethyl)-2-(4-toluenesulfonyl)-1,2,3,4-tetrahydroisoquinoline (5.2 g; 11.3 mmol) in ethanol (50 mL) was added hydrazine monohydrate (10.4 mL; 215 mmol) (*CARE: CARCINOGEN*). After being stirred at reflux for 18 h, the mixture was partitioned between ethyl acetate (60 mL) and brine (100 mL). The organic layer was washed with water, dried ($MgSO_4$), filtered, and evaporated to give the product (3.6 g) in 96% yield.

Product 9: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.58 (d, J = 8.0 Hz, 2H), 7.00−7.20 (m, 5H), 6.85 (d, J = 6.3 Hz, 1H), 5.15 (m, 1H), 3.85−4.00 (m, 1H), 3.45 (m, 1H), 2.80−3.10 (m, 2H), 2.45 (m, 2H), 2.30 (s, 3H), 2.1−1.55 (m, 4H).

Product 12: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.17 (m, 4H), 5.35−5.07 (m, 1H), 4.32−3.96 (m, 1H), 3.30−2.40 (m, 7H), 2.19−1.76 (m, 2H), 1.48 (s, 9H).

Procedure for the Solid-Phase Boc Deprotection. The resin (650 mg; 0.48 mmol) was swollen in TFA/DCM (3 mL/3 mL) and allowed to stand for 30 min. The resin was drained, washed with DCM (10 mL) and methanol (3 × 5 mL), and dried in vacuo (669 mg).

Procedure for the Solid-Phase Tosylation. To a suspension of the resin (140 mg) in DCM (1 mL) was added a solution of *p*-toluenesulfonyl chloride (57 mg; 0.3 mmol) and N-diisopropylethylamine (39 mg; 0.3 mmol) in DCM (2 mL). After the mixture was agitated at 20 °C for 18 h, the resin was drained, washed with DCM (3 × 2 mL) and methanol (3 × 2 mL), and dried in vacuo (140 mg).

General Procedure for the Cleavage of 6. The resin was swollen with 25% acetic acid in toluene (5 mL) and heated at reflux for 24 h. The resin was drained and washed with DCM (3 × 2 mL) and methanol (3 × 2 mL), and the filtrate was evaporated to dryness. The yield of **6** from the manual synthesis via intermediate **12** was 19 mg (41%). The NMR for **6** was consistent with that described above.

General Procedure for the Automated Synthesis. Hydroxymethylpolystyrene resin (200 mg, 0.148 mmol) was added to two 5 mL glass reaction vessels of a MultiSynTech SyRo II synthesis robot. The robot then added 200 μL of a molar solution of DMAP in DMF and 1 mL of a molar solution of triethylamine in DMF to each of the two vessels. To the first vessel was added 1 mL of a molar solution of phthalic anhydride in DMF and to the second vessel 1 mL of a molar solution of 2,3-naphthalenedicarboxylic anhydride in DMF. The suspensions were then agitated by intermittant magnetic stirring to minimize resin disintegration (64 cycles of 1 min stirring, 14 min standing). The resins were drained and then washed with DMF (2 mL), DCM (2 mL), methanol (2 mL), DMF (2 mL), DCM (2 mL), and methanol (2 mL). The robot then added to each of the two vessels 400 μL of a molar solution of HOBT in DMF, 1.5 mL of a 0.25 M solution of 1-(2-aminoethyl)-2-(4-toluenesulfonyl)-1,2,3,4-tetrahydroisoquinoline in DMF, and 400 μL of a molar solution of DIC in DMF. The suspensions were then agitated by intermittant magnetic stirring (64 cycles of 1 min stirring, 14 min standing). The resins were drained and then washed with DMF (2 mL), DCM (2 mL), methanol (2 mL), DMF (2 mL), DCM (2 mL) and methanol (2 mL). After the vessels were sealed with luer caps, the robot added 4 mL of a 25% solution of glacial acetic acid in toluene to each. The suspensions were then heated at 90 °C and agitated by intermittant magnetic stirring (72 cycles of 1 min stirring, 14 min heating at 90 °C). The reaction vessels were transferred to a VacMaster station and filtered into test tubes. The solvent was then removed using a Savant vacuum centrifuge. For example, 1-(*N*-phthaloyl-2-aminoethyl)-2-(4-toluenesulfonyl)-1,2,3,4-tetrahydroisoquinoline **11**{*1*} was obtained in 31% yield (21 mg) and 98% purity, as determined by LC−MS. All products (**11**{*1*−*30*} and **14**{*1*−*8*}) gave satisfactory 400 MHz ^{1}H NMR spectra (see the Supporting Information).

Determination of Resin Loading. The loading of hydroxymethyl polystyrene resin was determined by the Fmoc quantitation method, i.e., coupling of Fmoc-glycine, followed by deprotection using piperidine. The absorbance due to the liberated fulvene adduct was measured at 300 nm.

Gas Chromatography Procedure. The compounds were dissolved in methanol and loaded onto a Shimadzu 14A GC, fitted with a RTX-1 column (100% dimethyl polysiloxane; 30 m × 0.25 mm): film thickness, 0.25 mm; carrier gas, helium; pressure: 2 kg/cm^2; flame ionization detector; external standard, *n*-hexadecane.

FT-IR Procedure. The resin sample was prepared as a 13 mm diameter 2% w/w KBr disk, and the spectrum was recorded on a Perkin-Elmer 16 PC fourier transform infrared spectrometer: resolution, 2 cm^{-1}; apodization, weak; number of scans, 5; range, 4000−400 cm^{-1}; smooth: 6.

Acknowledgment. We thank the analgesia pharmacology team at Organon Newhouse, led by Ms. J. Cottney, for testing the compounds in the δ-opioid binding assay and the analytical department for providing NMR, IR, MS, and HPLC data in support of this work.

Supporting Information Available. Characterization data for all novel compounds (**5d**, **6**, **9**, **11**{*1*−*30*}, **12**, and **14**{*1*−*8*}), including 400 MHz ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) The formation of succinimides on a polystyrene resin has been observed as a side reaction during acidic cleavage of peptides containing an Asp-Gly sequence in which the aspartic acid residue is protected with a β-benzyl ester. See Yang, C. C.; Merrifield, R. B. *J. Org. Chem.* **1976**, *41*, 1032.
(6) This information was obtained by searching the World Drugs Index (Derwent Information Ltd.) for compounds containing substituted succinimide rings, including phthalimides.
(7) The progress of the reactions was monitored qualitatively using single-bead FT-IR. After the coupling reaction, two carbonyl bands were apparent at 1740 and 1713 cm^{-1}. After the amidation reaction, the 1713 cm^{-1} band was replaced by an amide band at 1677 cm^{-1}. As the cleavage reaction proceeded, both ester and amide bands diminished in intensity.
(8) Ramage, R.; Stewart, A. S. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1947.
(9) Judging by the intensity of the carbonyl bands in the FT-IR spectra, the coupling and amidation reactions appear to occur equally successfully for the phthalic, succinic, and glutaric systems. However, after the cleavage step (conditions C), whereas the phthalimide carbonyl bands are much reduced in intensity, the intensity of the succinyl bands are only slightly reduced and the glutaryl bands are not reduced at all.
(10) The product purity was determined by 400 MHz ^{1}H NMR spectroscopy.
(11) Barnes, R. A.; Godfrey, J. C. *J. Org. Chem*. **1957**, *22*, 1043.
(12) The binding affinities of the compounds described for the δ-opioid receptor were determined by inhibition of binding of [^{3}H]-naltrindole (0.15 nM) to membranes from CHO cells expressing the human DOR. μ-Opioid binding affinity was determined by the ability of test compounds to displace binding of [^{3}H]-DAMGO (0.15 nM) to rat brain membranes. κ-opioid binding affinity was determined by the ability of test compounds to displace binding of [^{3}H]-U69593 (0.15 nM) to guinea pig brain membranes.
(13) Compounds **9** and **12** were synthesised in two steps (tosylation/Boc protection, followed by dephthaloylation) from 1-(*N*-phthaloyl-2-aminoethyl)-1,2,3,4-tetrahydroisoquinoline, itself prepared according to the procedure in *Biomed. Biochem. Acta* **1990**, *49* (1), 103−113.

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