N-Alkylation–Intramolecular Michael Addition: New Reaction Manifold for High Throughput Annulation of Amines

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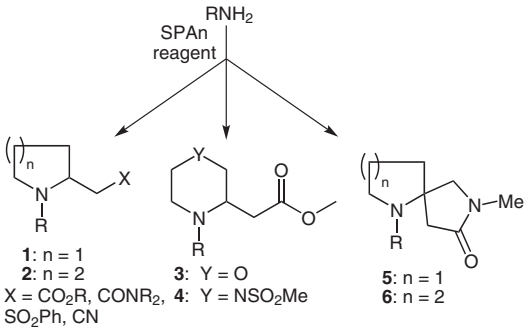
Abstract: Parallel synthesis of α-substituted pyrrolidines, piperidines, morpholines, piperazines and diazaspirocycles was achieved in a single reaction step via the annulation of primary amines with halo-2-alkenyl esters, amides, nitriles and phenylsulfones.

Key words: heterocycle, amine, annulation, intramolecular, parallel synthesis

Chemical libraries of amides, sulfonamides, ureas and higher order amines derived from high throughput amine derivatization chemistries are useful in discovering biologically active compounds.[1] Our laboratory has developed a new family of solid- and solution-phase annulation reagents, termed SPAn reagents, for the single-step conversion of primary amines to heterocycles.[2] SPAn reagents, adaptable to semi-automated library production, complement existing methodology for generating acyclic amine derivatives. Two reaction manifolds for amine annulation were previously described. These include the tandem S_N2 displacement–intramolecular acylation of resin-bound haloalkyl esters affording lactams[2] and the intramolecular N-dialkylation of resin-bound bismesylates affording piperidines, piperazines, and diazaspirocycles.[3] In this Letter, we describe the application of a third reaction manifold to amine annulation, tandem N-alkylation–intramolecular Michael addition (S_N2-Michael reaction), affording α-substituted pyrrolidines **1**, piperidines **2**, morpholines **3**, piperazines **4** and novel diazaspirocycles **5** and **6** (Scheme 1).



Scheme 1 High throughput amine derivatization

Bunce and co-workers reported the one-pot synthesis of *N*-benzyl heterocycles bearing an α-acetate residue by reaction of 6- or 7-halo-2-alkenoates with benzylamine.[4] The reaction proceeds by a tandem N-alkylation–intramolecular Michael addition. Products yielding five- and six-membered rings formed easily while higher order rings were not obtained. We believed that the relatively mild reaction conditions (EtOH, 80 °C, 36 h) and modest yields (ca. 50%) were compatible with primary amines possessing a diverse range of functionality. To investigate this, iodides **7** and **8** were prepared and reacted with the primary amines **a1**–**a4** (Figure 1).

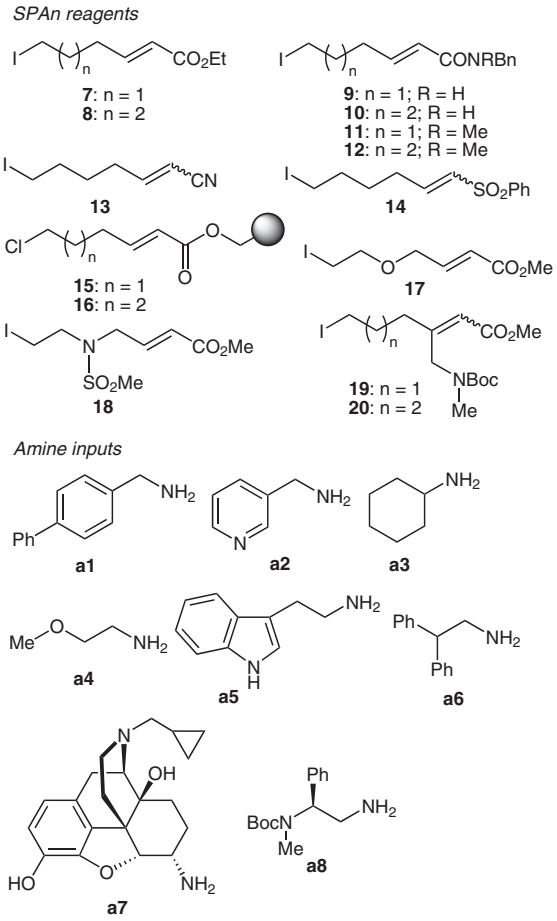


Figure 1 SPAn reagents and amine inputs used in this study

Treatment of one equivalent of amine with one equivalent of iodide in EtOH (0.3 mM) at 80 °C for 72 hours was determined to be the optimized general procedure for annu-

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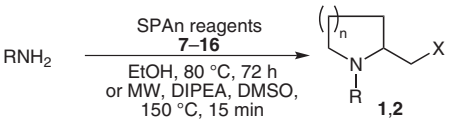
lation under thermal reaction conditions (entries 1–8, Table 1). In many instances the purity of crude products **1a–d/2a–d** was <75%, which did not meet our purity criteria for biological screening. The major by-product present in varying amounts was the corresponding dialkylated amine. It was therefore advantageous to routinely purify the products. This was conveniently carried out using a multichannel CombiFlash system. The yields of the purified products **1a–d/2a–d** ranged from 40–75%.

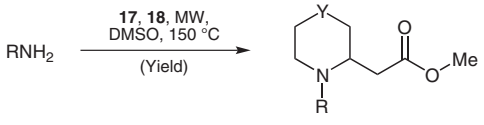
Table 1 Amine Annulation Products



Entry	Amine	SPAn reagent	Product	R	n	X	Yield (%)[a]
1	**a1**	**7**	**1a**	(4-phenyl)phenethyl	1	CO_2Et	(55) 61
2	**a2**	**7**	**1b**	3-pyridinylmethyl	1	CO_2Et	(60) 73
3	**a3**	**7**	**1c**	cyclohexyl	1	CO_2Et	(60) 58
4	**a4**	**7**	**1d**	2-methoxyethyl	1	CO_2Et	(45) 52
5	**a1**	**8**	**2a**	(4-phenyl)phenethyl	2	CO_2Et	(60) 81
6	**a2**	**8**	**2b**	3-pyridinylmethyl	2	CO_2Et	(55) 65
7	**a3**	**8**	**2c**	cyclohexyl	2	CO_2Et	(48) 43
8	**a4**	**8**	**2d**	2-methoxyethyl	2	CO_2Et	(52) 55
9	**a1**	**9**	**1e**	(4-phenyl)phenethyl	1	CONHBn	45
10	**a2**	**9**	**1f**	3-pyridinylmethyl	1	CONHBn	38
11	**a1**	**10**	**2e**	(4-phenyl)phenethyl	2	CONHBn	70
12	**a2**	**10**	**2f**	3-pyridinylmethyl	2	CONHBn	72
13	**a5**	**9**	**1g**	3-indolylethyl	1	CONHBn	35
14	**a3**	**10**	**2g**	cyclohexyl	2	CONHBn	60
15	**a1**	**11**	**1h**	(4-phenyl)phenethyl	1	CON(Me)Bn	62
17	**a2**	**11**	**1i**	3-pyridinylmethyl	1	CON(Me)Bn	60
18	**a2**	**12**	**2h**	3-pyridinylmethyl	2	CON(Me)Bn	53
19	**a3**	**11**	**1j**	cyclohexyl	1	CON(Me)Bn	46
20	**a5**	**12**	**2i**	3-indolylethyl	2	CON(Me)Bn	51
21	**a1**	**13**	**2j**	(4-phenyl)phenethyl	2	CN	78
22	**a2**	**13**	**2k**	3-pyridinylmethyl	2	CN	86
23	**a6**	**13**	**2l**	2,2-diphenylethyl	2	CN	87
24	**a1**	**14**	**2m**	(4-phenyl)phenethyl	2	SO_2Ph	85
25	**a2**	**14**	**2n**	3-pyridinylmethyl	2	SO_2Ph	85
26	**a4**	**14**	**2o**	2-methoxyethyl	2	SO_2Ph	85
27	**a2**	**15**	**1k**	3-pyridinylmethyl	1	CO_2H	92
28	**a2**	**16**	**2p**	3-pyridinylmethyl	2	CO_2H	90
29	**a3**	**15**	**1l**	cyclohexyl	1	CO_2H	92
30	**a5**	**16**	**2q**	3-indolylethyl	2	CO_2H	98

[a] Isolated yields in brackets are from the thermal reaction conditions while all other yields are from the microwave-assisted reaction conditions.

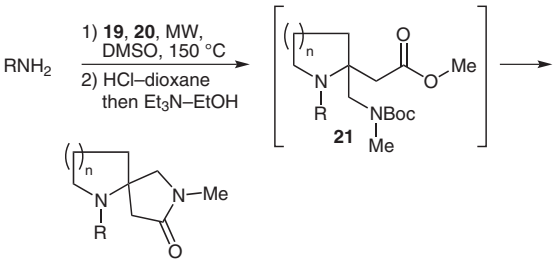
Given the success of this initial study, a set of annulation reagents was conceived to diversify the α,β-unsaturated ester.[5] The new SPAn reagents included the α,β-unsaturated amides **9**–**12**, α,β-unsaturated nitrile **13** and α,β-unsaturated phenyl sulfone **14**. The optimized reaction conditions used to prepare **1a–d/2a–d** from **7** and **8** were only modestly successful in the annulation of amine **a1** with **9**–**12**. The yields were generally poor (<30%). In fact, the desired products derived from the tandem S_N2-Michael reaction with reagents **13** and **14** were not observed under these reaction conditions. Conducting the reactions in a variety of solvents, temperatures and reaction times did not lead to a significant improvement in yield. The application of microwaves was then investigated to potentially circumvent this problem. After some experimentation, optimized reaction conditions were identified: one equivalent each amine and SPAn reagent with five equivalents of either diisopropylethylamine (DIEA) or macroporous carbonate resin (MP-carbonate) in DMSO at 150 °C for 15 minutes. Under microwave-assisted conditions, SPAn reagents **9**–**14** reacted smoothly with a range of amines to give α-substituted pyrrolidines and piperidines (entries 9–30, Table 1). The resin-bound SPAn reagents **15/16** (1.5 equiv) were found sufficiently reactive as their alkyl chlorides and performed well with a range of amines furnishing carboxylic acids (entries 27–30, Table 1) after standard TFA-mediated resin cleavage in high yield without resorting to chromatography. The microwave reaction conditions were also successfully applied to **7/8** → **1a–d/2a–d**, significantly reducing reaction time from three days to less than one hour. DMSO was the critical solvent choice for the microwave-assisted annulation as poor results were achieved with EtOH and other solvents. Further structure diversity in the annulation products was possible by introducing a heteroatom into the iodoalkenyl chain as per α,β-unsaturated iodoalkyl ether **17** and sulfonamide **18** (Scheme 2). The corresponding morpholines **3a**,**b** and *N*-methylsulfonyl piperazines **4a**,**b** were obtained in ca. 60–90% yield from representative amines **a2** and **a6** under the optimized microwave-assisted reaction conditions.



3a: R = 3-pyridinylmethyl; Y = O (61%)
3b: R = 2,2-diphenylethyl; Y = O (91%)
4a: R = 3-pyridinylmethyl; Y = NSO_2Me (73%)
4b: R = 2,2-diphenylethyl; Y = NSO_2Me (65%)

Scheme 2 Morpholine and piperazine annulation products

The iodoacrylates **19** and **20** were also examined as SPAn reagents (Scheme 3). It was thought that the Boc-*N*-methylaminomethyl group at the C-3 position in combination with the ester function might act as a latent *N*-methylcaprolactam. Amines **a2**, **a5** and **a6** were reacted with **19/20** under the optimized thermal reaction conditions. The intermediate S_N2-Michael adducts (**21**) were purified by silica gel chromatography to remove unwanted dimer, and then treated with 4 N HCl–dioxane in EtOH (80 °C 1 h) followed by triethylamine in EtOH (80 °C, 2 h). Lactams **5a**,**b** and **6a**,**b** were isolated in up to 55% yield establishing the feasibility of spirocyclic ring formation. Further refinement of this two-pot three-step process is ongoing using the microwave protocol and exploring alternatives to nitrogen protection.



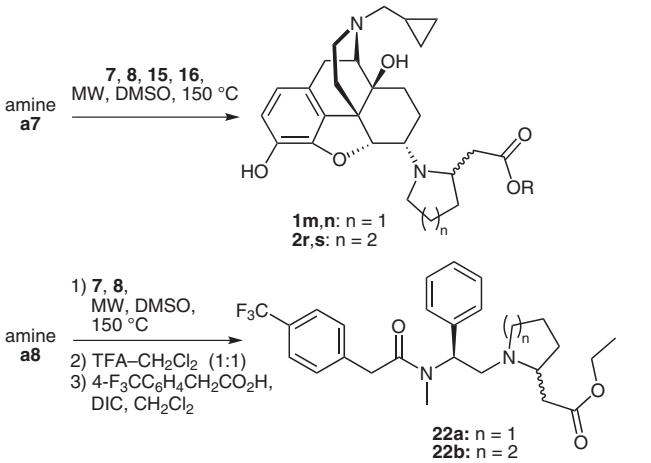
5a: R = 3-pyridinylmethyl; n = 1 (31%)
5b: R = 2,2-diphenylethyl; n = 1 (42%)
6a: R = 3-pyridinylmethyl; n = 2 (55%)
6b: R = 3-indolylethyl; n = 2 (40%)

Scheme 3 Spirocyclic annulation products

As a demonstration of the utility of the new SPAn reagents to generate structure–activity relationship (SAR) information, 6β-naltrexamine **a7** was derivatized with reagents **7/8** and **15/16** (Table 2). The novel heterocyclic derivatives **1m**,**n** and **2r**,**s** (obtained as mixture of their respective diastereomers) were screened for binding (K_i) against the human opioid receptors μ, κ, and δ.[6] The resulting nascent SAR indicates that agents **1m** and **2r** are potent dual κ/δ ligands with ca. 6- to 13-fold selectivity over μ. Interestingly, the μ receptor appears relatively insensitive to the change in the pendent ester versus carboxylic acid group (esters **1m/2r** versus acids **1n/2s**). This is in contrast to the κ and δ receptor affinity which is clearly sensitive to the negatively charged carboxylate group (up to a 15-fold loss in affinity). In a final study, mono-*N*-Boc-protected diamine **a8** was annulated with reagents **7** and **8** followed by Boc-deprotection and acylation with 4-trifluoromethylphenylacetic acid furnishing **22a** and **22b** (obtained as a mixture of their respective diastereomers). This is the first demonstration of bidirectional functionalization of a diamine using first a SPAn reagent and then traditional N-acylation. Compounds **22a** and **22b** displayed opioid receptor binding with **22a** being a four-fold more potent κ ligand (K_i = 200 nM).

In summary, α-substituted pyrrolidines, piperidines, morpholines, piperazines and diazaspirocycles were obtained in a single reaction step from primary amines and SPAn reagents **7**–**20**.[7] Microwave irradiation resulted in a substantial reduction in overall reaction time versus conventional heating, improvement in product yields and was essential for the formation of derivatives with α-methylcyano (**13** → **2j**–**l**) and α-methyl(phenylsulfonyl) (**14** → **2m**–**o**) ring substituents. The new annulation chemistry represents a valuable complement to existing acyclic amine derivatization methodologies. Further examples of

Table 2 Biologically Active Annulation Products



Entry	Prod	R	$K_i(\mu)$ nM	$K_i(\kappa)$ nM	$K_i(\delta)$ nM
1	**1m**	Et	32	5.4	6.0
2	**2r**	Et	91	6.8	6.7
3	**1n**	H	55	40	91
4	**2s**	H	44	54	81
5	**22a**	–	1840	200	1100
6	**22b**	–	1500	840	>5000

SPAn reagents affording medicinally relevant heterocycles will be reported subsequently.

References and Notes

(1) Dolle, R. E.; Le Bourdonnec, B.; Goodman, A. J.; Morales, G. A.; Thomas, C. J.; Zhang, W. *J. Comb. Chem.* **2008**, *10*, 753.

(2) (a) Dolle, R. E.; Macleod, C.; Martinez-Teipel, B. I.; Barker, W. M.; Seida, P.; Herbetz, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 5830. (b) The acronym SPAn is derived from solid/solution-phase annulation.

(3) Macleod, C.; Martinez-Teipel, B. I.; Barker, W. M.; Dolle, R. E. *J. Comb. Chem.* **2006**, *8*, 132.

(4) Bunce, R. A.; Peeples, C. J.; Jones, P. B. *J. Org. Chem.* **1992**, *57*, 1727.

(5) SPAn reagents **7**–**12** and **15**–**18** were prepared from the requisite chloroalkyl aldehydes and the Horner–Emmons–Wadsworth reaction: (a) Kametani, T.; Higashiyama, K.; Otomasu, H.; Honda, T. *Israel. J. Chem.* **1986**, *27*, 57. (b) Lipshutz, B. H.; Chrisman, W.; Noson, K.; Papa, P.; Sclafani, J. A.; Vivian, R. W.; Keith, J. M. *Tetrahedron* **2000**, *56*, 2779. (c) SPAn reagents **13** and **14** were obtained and used as a mixture of *E*- and *Z*-isomers by the cross-metathesis reaction of 6-chlorohex-1-ene with acrylonitrile and phenyl vinyl sulfone. SPAn reagents **19** and **20** were derived from the modification of experimental procedures described by: Dieter, R. K.; Lu, K. *J. Org. Chem.* **2002**, *67*, 847. (d) Because the iodo-based solution-phase reagents gave annulation products in consistently higher yield and purity than the corresponding chloro congeners, the Finkelstein Cl → I exchange reaction was used (5 equiv NaI, acetone, reflux, 3 h) to prepare the final reagent set. SPAn reagents **15** and **16** were obtained via DIC coupling of the corresponding chloroalkenoic acids to Wang resin under standard reaction conditions.

(6) DeHaven, R. N.; Cassel, J. A.; Windh, R. T.; DeHaven-Hudkins, D. L. In *Current Protocols in Pharmacology*; Enna, S. J.; Williams, M.; Barrett, J. F.; Ferkany, J. W.; Kenakin, T.; Porsolt, R. D., Eds.; John Wiley and Sons: New York, **2005**, 1.4.1–1.4.44.

(7) **General Procedure for High-Throughput Annulation**: DMSO (750 μL) and diisopropylethylamine (DIPEA, 150 μL) were added to Milestone CombiCHEM Microwave reaction vials containing the individual SPAn reagents (0.30 mmol). The amines (0.30 mmol) were then added and the reaction vials transferred to a 48-well Milestone CombiCHEM plate. The unit was securely fitted to the Milestone CombiCHEM rotor and inserted into the Milestone Microwave (equipped with thermocouple). A microwave program (with rotation of the CombiCHEM block) was applied: full power (500 W) ramping from 25 °C → 150 °C over a period of 25 min and holding at 150 °C for 15 min. Upon cooling, the CombiCHEM block was removed and transferred to a Genevac. The vials were concentrated in vacuo and the resulting residues were purified by silica gel chromatography to give the annulation products.

2-{1-[2-(1*H*-Indol-3-yl)methyl]pyrrolidin-2-yl}-*N*-benzylacetamide (1g): ^{1}H NMR (400 MHz, $CDC1_3$): δ = 8.55 (s, 1 H), 8.20 (s, 1 H), 6.95–7.55 (m, 9 H), 5.65 (m, 1 H), 4.00, 4.34 (m, 2 × 1 H), 2.45–3.45 (m, 6 H), 0.90–2.05 (m, 7 H). ^{13}C NMR (75 MHz, $CDC1_3$): δ = 172.7, 137.7, 136.8, 128.5, 127.4, 127.1, 123.0, 121.5, 119.8, 118.5, 113.0, 110.8, 65.5, 56.1, 55.1, 44.0, 32.5, 30.8, 23.4, 21.5. MS (ESI): *m/z* = 362 $[M + H]^+$. HRMS (TOF): *m/z* $[M + H]^+$ calcd for $C_{23}H_{28}N_3O$: 362.2232; found: 362.2245.

2-{1-[2-(1*H*-Indol-3-yl)ethyl]piperidin-2-yl}-*N*-benzyl-*N*-methylacetamide (2i): ^{1}H NMR (400 MHz, $CDC1_3$) δ = 8.68, 8.78 (m, 1 H), 6.95–7.55 (m, 9 H), 4.52 (m, 2 H), 4.00 (m, 1 H), 2.95–3.70 (m, 6 H), 2.80, 2.95 (2 × s, 3 H, NMe rotomers), 0.90–2.20 (m, 9 H). MS (ESI): *m/z* = 390 $[M + H]^+$. HRMS (TOF): *m/z* $[M + H]^+$ calcd for $C_{25}H_{32}N_3O$: 390.2545; found: 390.2561.

2-[1-(2,2-Diphenylethyl)piperidin-2-yl]acetonitrile (2l): ^{1}H NMR (400 MHz, $CDC1_3$): δ = 7.10–7.35 (m, 10 H), 4.15 (m, 1 H), 3.12 (m, 1 H), 2.95 (m, 1 H), 2.75 (m, 1 H), 2.65 (m, 1 H), 2.30 (m, 3 H), 1.30–1.75 (m, 6 H). ^{13}C NMR (75 MHz, $CDC1_3$): δ = 144.0, 129.3, 128.5, 126.0, 117.9, 59.8, 59.5, 57.9, 49.3, 31.1, 26.2, 22.8, 22.3. MS (ESI): *m/z* = 305 $[M + H]^+$. HRMS (TOF): *m/z* $[M + H]^+$ calcd for $C_{21}H_{25}N_2$: 305.2018; found: 305.2050.

3-{[2-(Phenylsulfonylmethyl)piperidin-1-yl]methyl}pyridine (2n): ^{1}H NMR (400 MHz, $CDC1_3$): δ = 8.45 (m, 1 H), 7.98 (m, 1 H), 7.50–7.75 (m, 6 H), 7.20 (m, 1 H), 3.25–3.60 (m, 5 H), 2.30 (m, 2 H), 1.40–1.90 (m, 6 H). ^{13}C NMR (75 MHz, $CDC1_3$): δ = 150.8, 146.9, 145.5, 139.5, 137.0, 133.1, 129.5, 128.0, 122.5, 64.8, 65.9, 59.4, 55.6, 55.5, 29.9, 26.8, 22.5. MS (ESI): *m/z* = 331 $[M + H]^+$. HRMS (TOF): *m/z* $[M + H]^+$ calcd for $C_{18}H_{23}N_2O_2S$: 331.1480; found: 331.1492.

2-{1-[2-(1*H*-Indol-3-yl)ethyl]piperidin-2-yl}acetic Acid (2q): ^{1}H NMR (400 MHz, $CDC1_3$): δ = 10.95 (s, 1 H), 7.38, 7.60 (2 × d, *J* = 7.4 Hz, 2 × 1 H), 6.85–7.20 (m, 3 H), 1.50–3.50 (m, 15 H). ^{13}C NMR (75 MHz, $CDC1_3$): δ = 180.0, 136.2, 127.0, 123.1, 121.1, 120.2, 119.5, 113.9, 110.5, 67.0, 58.1, 57.9, 55.0, 32.3, 26.1, 23.8, 23.5. MS (ESI): *m/z* = 287 $[M + H]^+$. HRMS (TOF): *m/z* $[M + H]^+$ calcd for $C_{17}H_{23}N_2O_2$: 287.1793; found: 287.1810.

Methyl 2-[4-(2,2-Diphenylethyl)morpholin-3-yl]acetate (3b): ^{1}H NMR (400 MHz, $CDC1_3$): δ = 7.10–7.35 (m, 10 H), 4.10 (m, 1 H), 3.65 (s, 3 H), 3.40–3.60 (m, 4 H), 2.90–3.10

(m, 3 H), 2.65 (m, 1 H), 2.50 (m, 2 H), 2.30 (m, 1 H). ^{13}C NMR (75 MHz, $CDC1_3$): d = 174.1, 144.8, 129.9, 129.1, 126.6, 72.3, 69.0, 64.1, 660.9, 52.3, 51.8, 38.1. MS (ESI): *m/z* = 340 $[M + H]^+$. HRMS (TOF): *m/z* $[M + H]^+$ calcd for $C_{21}H_{26}NO_3$: 340.1913; found: 340.1944.

Methyl 2-[4-(Methylsulfonyl)-1-(pyridin-3-ylmethyl)piperazin-2-yl]acetate (4a): ^{1}H NMR (400 MHz, $CDC1_3$): δ = 8.50 (m, 2 H), 7.35, 7.75 (m, 2 × 1 H), 3.70 (s, 3 H), 3.62 (m, 2 H), 3.50 (m, 1 H), 2.92 (s, 3 H), 2.20–2.75 (m, 8 H). ^{13}C NMR (75 MHz, $CDC1_3$): δ = 173.8, 152.0, 147.8, 156.1, 137.0, 123.2, 60.8, 60.1, 54.7, 51.8, 51.1, 48.5, 40.2, 38.3. MS (ESI): *m/z* = 328 $[M + H]^+$. HRMS (TOF): *m/z* $[M + H]^+$ calcd for $C_{14}H_{22}N_3O_4S$: 328.1331; found: 328.1362.

1-(2,2-Diphenylethyl)-7-methyl-1,7-diazaspiro[4.4]nonan-8-one (5b): ^{1}H NMR (400 MHz, $CDC1_3$): δ = 7.10–7.35 (m, 10 H), 4.05 (t, *J* = 7.5, 1 H), 3.40 (s, 3 H), 3.17 (d, *J* = 10.2 Hz, 1 H), 2.65–3.00 (m, 5 H), 2.50, 2.12 (2 × d, *J* = 17.2 Hz, 2 × 1 H), 1.75 (m, 4 H). MS (ESI): *m/z* = 335 $[M + H]^+$. HRMS (TOF): *m/z* $[M + H]^+$ calcd for $C_{22}H_{27}N_2O$: 335.2123; found: 335.2148.

Ethyl {6β-[17-(Cyclopropylmethyl)-3,14-dihydroxy-4,5-epoxymorphinan-6β-yl]pyrrolidin-2-yl}acetate (1m): mixture of diastereomers. ^{1}H NMR (400 MHz, $CDC1_3$): δ = 6.71, 6.74 (2 × d, *J* = 8.1 Hz, 2 × 0.5 H), 6.52, 6.54 (2 × d, *J* = 8.1 Hz, 2 × 0.5 H), 4.75 (d, *J* = 7.4, 0.5 H), 4.53 (d, *J* = 8.2 Hz, 0.5 H), 4.21 (m, 1 H), 4.07 (dd, *J* = 7.0, 14.0 Hz, 1 H), 3.60 (br s, 1 H), 1.38–3.20 (m, 24 H), 1.30, 1.21 (2 × t, *J* = 7.1 Hz, 2 × 1.5 H), 0.85 (m, 1 H), 0.54 (s, 2 H), 0.15 (s, 2 H). MS (ESI): *m/z* = 483 $[M + H]^+$. HRMS (TOF): *m/z* $[M + H]^+$ calcd for $C_{28}H_{39}N_2O_5$: 483.2859; found: 483.2885.