Pergamon

Tetrahedron Letters 42 (2001) 4963–4968

TETRAHEDRON LETTERS

MCC/S_NAr methodology. Part 1: Novel access to a range of heterocyclic cores

Paul Tempest,* Vu Ma, Michael G. Kelly, Wyeth Jones and Christopher Hulme*

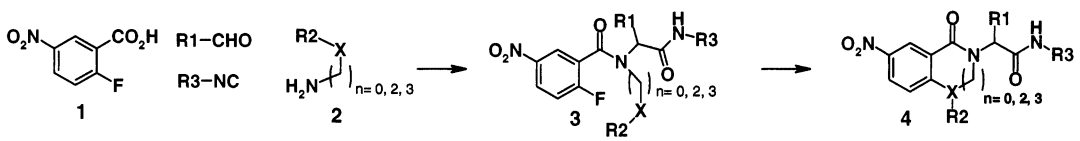
Department of Combinatorial Chemistry, AMGEN Inc., One AMGEN Center Drive, Thousand Oaks, CA 91320, USA

Received 11 December 2000; revised 16 January 2001; accepted 17 January 2001

Abstract—The novel solution-phase syntheses of arrays of biologically relevant indazolinones, benzazepines and benzoxazepines, utilizing multi-component condensation (MCC)/S_NAr methodology is reported. Reaction of commercially available 2-fluoro-5-nitrobenzoic acid with an aldehyde, isonitrile and a primary amine tethered to a Boc-protected internal amino or hydroxyl nucleophile, affords the Ugi product in good yield. Subsequent acid treatment followed by proton scavenging promotes cyclization of internal amino nucleophiles to a variety of ring sizes. Base treatment alone is sufficient to generate benzoxazepines. Interestingly, this communication also introduces a highly efficient two-step route to benzimidazoles.

With the recent emergence of combinatorial chemistry and high-speed parallel synthesis in the lead discovery arena, the multi-component reaction (MCR) has witnessed a resurgence of interest.[1] Easily automated one-pot reactions, such as the Ugi[2] and Passerini[3] reactions, are powerful tools for producing diverse arrays of compounds in high yield. Despite this synthetic potential, the Ugi reaction is limited by producing flexible and peptidic-like products that are often classified as 'non-drug-like'. Recently, several novel intramolecular variations on the reaction have been reported where constrained, more biologically relevant products result from interception of the intermediate nitrilium ion using a bifunctional input.[4] An alternative approach is to constrain the Ugi product via a post-condensation modification by unmasking a protected amino internal nucleophile.[5,6] S_NAr reactions of polymer bound 4-fluoro-3-nitrobenzoic acid, **1**, have been investigated by several groups and have resulted in multi-step syntheses of dihydroquinoxalinones,[7] benzimidazoles,[8] indoles,[9] benzodiazepines,[10] benzothiazepines[11] and macrocycles,[12] respectively. Thus, it was envisioned that combining the efficiency of the Ugi condensation with a post-condensation S_NAr cyclization, via use of an internal amino or hydroxyl nucleophile, would facilitate access to a series of biologically useful cores with generic structure, **4** (Scheme 1). Interestingly, there are no previous reports on the compatibility of fluoronitro aryl derivatives with reaction conditions employed in the Ugi-4-component reaction (U-4CR). A preliminary investigation by reaction of **1**, benzylamine, **6**, 3-phenylpropionaldehyde, **5**, and cyclohexyl isocyanide, **7**, gave excellent conversion (80% as judged by LC/MS at UV215) to the desired condensation product, **8** (Scheme 2).

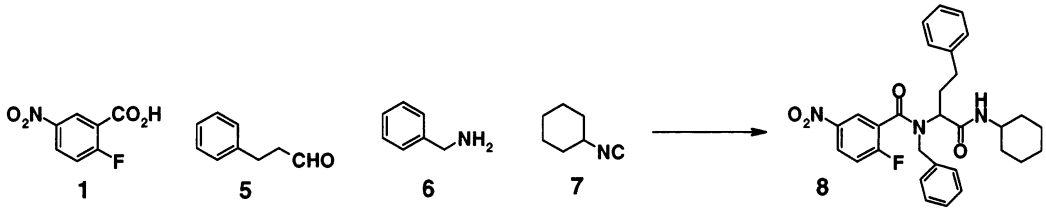
The reaction conditions were then modified to introduce a series of mono-Boc-protected diamines, Boc-hydrazine and amino-alcohols to investigate the feasibility of post condensation base-catalyzed S_NAr cyclization (Scheme 3). Conditions for the initial condensation reaction were standardized so that each reagent was added in the order of its participation in the Ugi reaction.



Scheme 1.

* Corresponding author.

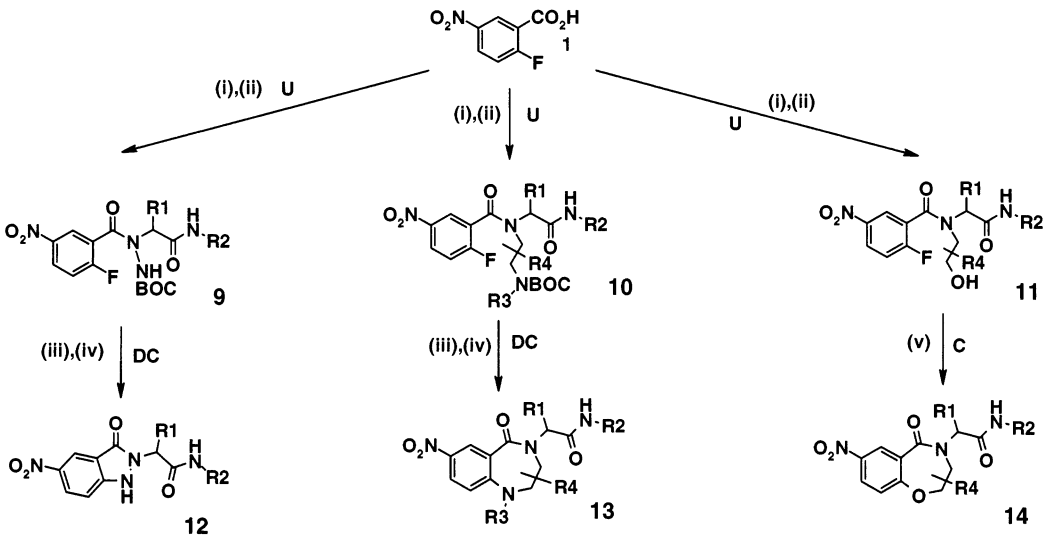
0040-4039/01/$ - see front matter
PII: S0040-4039(01)00920-0



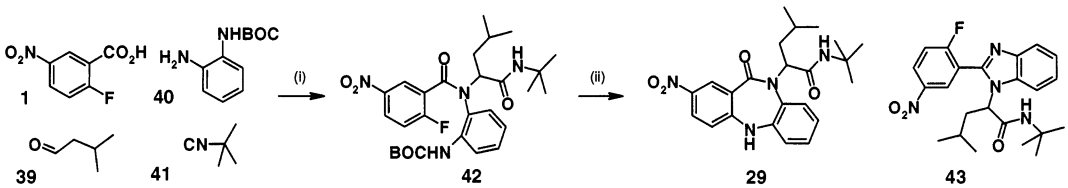
Scheme 2.

Two equivalents of aldehyde (R_1CHO) were employed to promote Schiff base formation, and a one-pot double scavenging protocol with immobilized tosylhydrazine[13] and diisopropylethylamine[13] removed both the excess aldehyde and any unreacted acid, **1**. Noteworthy is the generality of the condensation reaction which performs efficiently for a range of commercially available aldehydes (e.g. with attached aryl, heteroaryl, alkyl, cycloalkyl, thioalkyl, functionality) and isonitriles (e.g. with attached alkyl, aryl, heteroaryl, heterocycloalkyl and basic functionality). The products **9** and **10** were then subjected to treatment with TFA, followed by proton scavenging with resin bound morpholine,[13] to promote cyclization to afford products **12** and **13**, respectively.

Interestingly, the resin bound guanidine, PS-TBD[14] was found to be most effective for conversion of the alcohol **11** into the benzoxazepine, **14**.[15] Area % (*A*%) purities [LC/MS (UV220)][16] are shown in Table 1, along with the observed molecular ion. The indazolinones, **15**, **16**, **17** and **18** were observed with *A*% purities in the range 35–63% and exhibited lower conversions than both the benzazepines and benzoxazepines series, respectively. The benzazepines **19**, **20**, **21**, **22** and **23**, were formed in good to excellent yield (46–100%), with cyclization often being complete in ca. 2 h. Cyclization also progressed satisfactorily with secondary internal amino nucleophiles, as exemplified with **24** (*A*% 68%) and **25** (*A*% 78%), respectively. Similarly, tricyclic systems were also accessible via the use of aminomethyl piperidines and pyrrolidines to give **26** (*A*% 89%) and **28** (*A*% 57%), respectively. Eight-membered ring formation was, as expected, slower than seven, often needing up to 24 h for complete conversion. Thus, use of *N*-Boc-protected 1,3-diamino-propane and aminopropanol

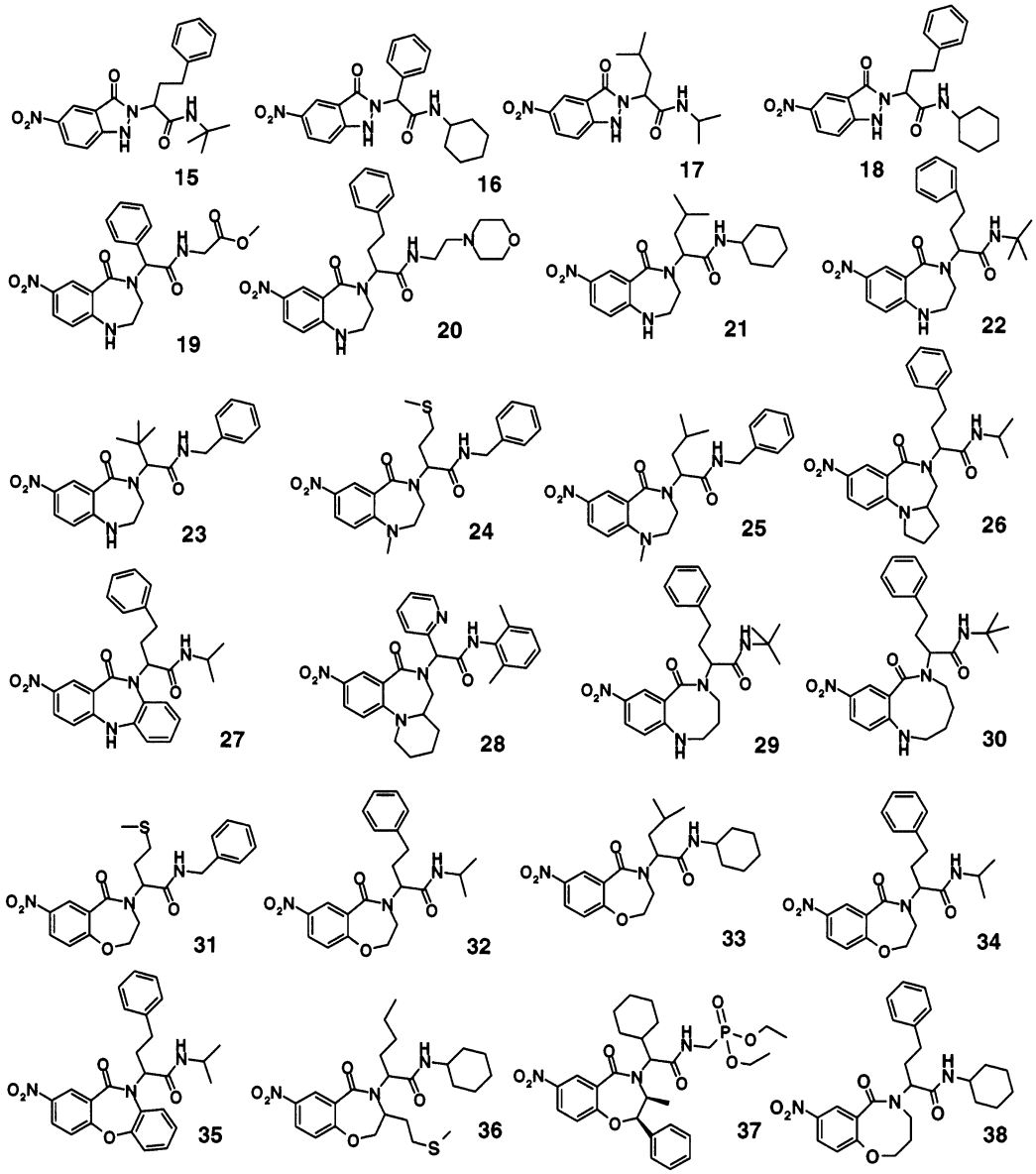


Scheme 3. *Reagents and conditions*: (i) R_1CHO (0.2 M, 200 μl, MeOH), R_2NC (0.1 M, 200 μl, MeOH), **1** (0.1 M, 200 μl, MeOH), Boc-protected diamine or amino-alcohol (0.1 M, 200 μl, MeOH), rt, 48 h; (ii) PS-tosylhydrazine (3 equiv.), PS-diisopropylethylamine (3 equiv.), THF:CH_2Cl_2 (600 μl, 1:1), 24 h; (iii) 20% TFA/CH_2Cl_2 (600 μl), 4 h; (iv) PS-morpholine (3 equiv.), DMF (600 μl), 36 h; (v) PS-TBD (7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene), DMF (600 μl), rt, 36 h.



Scheme 4. *Reagents and conditions*: (i) **39** (0.2 M, 200 μl, MeOH), **40** (0.1 M, 200 μl, MeOH), **1** (0.1 M, 200 μl, MeOH), **41** (0.1 M, 200 μl, MeOH), rt, 48 h; (ii) PS-tosylhydrazine (3 equiv.), PS-diisopropylethylamine (3 equiv.), THF:CH_2Cl_2 (600 μl, 1:1), 24 h; (iii) 20% TFA/CH_2Cl_2 (600 μl), 4 h; (iv) PS-morpholine (3 equiv.), DMF (600 μl), 36 h.

Table 1.



Cpd #	*A*%[a]	MH^{+}[b]	Cpd #	*A*%[a]	MH^{+}	Cpd #	*A*%[a]	MH^{+}
15	63	397	**23**	100	411	**31**	67	430
16	35	394	**24**	68	442	**32**	73	412
17	56	336	**25**	78	425	**33**	87	404
18	53	423	**26**	89	451	**34**	66	412
19	46	412	**27**	58	459	**35**	55	460
20	80	482	**28**	57	500	**36**	85	477
21	67	403	**29**	60	439	**37**	80	587
22	84	425	**30**	0	453	**38**	60	465

[a] Area % purities as judged by LC/MS UV220, LC/MS-HP1100 LC with LCQ, YMC-AM 4.6×150 mm column, ESI source.[15]
[b] Isolated yields: **17** = 50%, **22** = 76% **25** = 40%, **27** = 30%, **32** = 60%, **35** = 25%.

afforded **29** (*A*% 60%) and **38** (*A*% 60%), respectively. Cyclization to the analogous nine- or ten-membered ring benzazepine (e.g. **32**) was not observed even after prolonged treatment with base (up to 48 h). S_NAr substitution with anilines proved possible via the use of *N*-Boc phenylene diamine, **42**, with deprotection and base treatment of **42** giving **27** (*A*% 58%) in good overall purity (Scheme 4). Interestingly, acid treatment of the product, **42**, also gave rise to the benzimidazole, **43** (*A*% 34%), presumably an acid-catalyzed process with loss of water. The analogous side reaction to afford imidazolines[17] was not observed with mono-Boc-protected ethylene diamine, possibly due to the higher pK_a of primary alkyl amines compared to anilines.

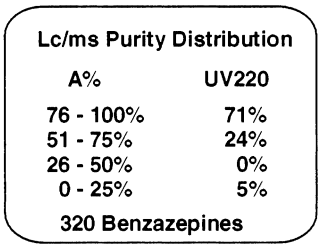


Figure 1.

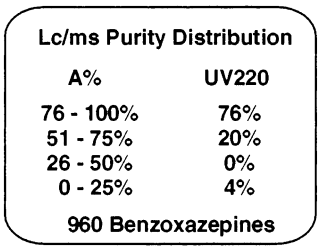


Figure 2.

Further study of this novel two-step benzimidazole forming reaction will be the subject of future reports. Several of the products were produced on a larger scale and their isolated yields corresponded closely with observed *A*% yields reported in Table 1. For example, **29** was prepared with an isolated yield of 76%.[18]

Representative scaled-up and characterized examples for each series are included at the end of this communication.[18] Encouraged with the results shown in Table 1, the protocol was advanced to 96-well production status. Production runs of a 320-member array of benzazepines and a 960-member array of benzoxazepines were successfully completed in Whatman 96-well plates, with reagents being dispensed using either a Quadra 96® (Tom-tech) or Rapid Plate 96® (Zymark). Scavenging with PS-TsNHNH$_2$ (3 equiv.) and PS-diisopropylethylamine (3 equiv.) for the condensation reaction, and either PS-morpholine or PS-TBD for S_NAr cyclization was performed at the plate level, with resins added using a Millipore® column loader. TFA solutions in dichloromethane were dispensed using a Robbins Jet Pipette and solutions evaporated in a SAVANT® evaporator. The purity distribution (*A*% as judged by UV220) of the 320-member library [8 (RCHO)×4 (RNH$_2$)×10 (RNC)] (Fig. 1) and the 960-member benzoxazepine library (Fig. 2) are shown.

In summary, this communication has described the first reported post-condensation modifications of the Ugi product, utilizing S_NAr methodology, allowing access to arrays of indazolinones, benzazepines and benzoxazepines with a variety of accessible ring sizes. With final products containing 3 or more points of potential diversity and a facile and rapid production protocol, access to thousands of diverse analogues with the aforementioned core structures is now feasible. Additionally, cyclization with aniline derived internal nucleophiles revealed a novel two-step protocol for the synthesis of benzimidazoles. Further study of this interesting side reaction will be reported in due course. Current efforts are now focusing on the development of potentially higher yielding solid-phase approaches to this methodology, in particular, via exploitation of nitro group reduction and functionalization.

Acknowledgements

The authors would like to thank Balan Chenara and Vijay Gore for proof-reading this document.

References

1. For two recent excellent reviews, see: (a) Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, *3*, 366; (b) Dax, S. L.; McNally, J. J.; Youngman, M. A. *Curr. Med. Chem.* **1999**, *6*, 255.
2. (a) Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 8; (b) Ugi, I.; Steinbruckner, C. *Chem. Ber.* **1961**, *94*, 734; (c) Ugi, I.; Domling, A.; Horl, W. *Endeavor* **1994**, *18*, 115; (d) Domling, A. *Comb. Chem. High Throughput Screen.* **1998**, *1*, 1; (e) Armstrong, R. W.; Combs, A. P.; Tempest, P.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123.
3. (a) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 126; (b) Gokel, G.; Ludke, G.; Ugi, I. In *Isonitrile Chemistry*; Ugi, I., Ed.; Academic Press: New York, 1971; p. 145.
4. (a) Blackburn, C.; Guan, B.; Fleming, P.; Shiosaki, K.; Tsai, S. *Tetrahedron Lett.* **1998**, *39*, 3635; (b) Bienayme, H.; Bouzid, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 2234; (c) Bossio, R.; Marcaccini, S.; Paoli, P.; Pepino, R. *Synthesis* **1994**, 672; (d) Park, S.-J.; Keum, G.; Kang, S.-B.; Koh, H.-Y.; Kim, Y. *Tetrahedron Lett.* **1998**, *39*, 7109.
5. (a) Hulme, C.; Tang, S.-Y.; Burns, C. J.; Morize, I.; Labaudiniere, R. *J. Org. Chem.* **1998**, *63*, 8021; (b) Hulme, C.; Peng, J.; Louridas, B.; Menard, P.; Krolikowski, P.; Kumar, N. V. *Tetrahedron Lett.* **1998**, *39*, 8047; (c) Hulme, C.; Peng, J.; Morton, G.; Salvino, J. M.; Herpin, T.; Labaudiniere, R. *Tetrahedron Lett.* **1998**, *39*, 7227; (d) Hulme, C.; Morrissette, M.; Volz, F.; Burns, C. *Tetrahedron Lett.* **1998**, *39*, 1113.
6. (a) Keating, T. A.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 8935; (b) Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1995**, *117*, 7842–7843; (c) Rosendahl, F. K.; Ugi, I. *Ann. Chem.* **1963**, *666*, 65; (d) Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 2574; (e) Stroker, A.; Keating, T. A.; Tempest, P. A.; Armstrong, R. W. *Tetrahedron Lett.* **1996**, *37*, 1149.
7. Morales, G. A.; Corbett, J. W.; Degrado, W. F. *J. Org. Chem.* **1998**, *63*, 1172.
8. (a) Phillips, G. B.; Wei, G.-P. *Tetrahedron Lett.* **1996**, *37*, 4887; (b) Tumelty, D.; Schwarz, M. K.; Cao, K.; Needels, M. C. *Tetrahedron Lett.* **1999**, *40*, 6185.
9. Stephensen, H.; Zaragoza, F. *Tetrahedron Lett.* **1999**, *40*, 5799.
10. Lee, J.; Gauthier, D.; Rivero, R. A. *J. Org. Chem.* **1999**, *64*, 3060.

11. Schwarz, M. K.; Tumelty, D.; Gallop, M. A. *J. Org. Chem.* **1999**, *64*, 2219.
12. Kiselyov, A. S.; Smith, L.; Tempest, P. *Tetrahedron* **1999**, *55*, 14813.
13. Purchased from Argonaut® technologies.
14. Purchased from Novabiochem® technologies.
15. Performed in a SAVANT® evaporator for 2 h.
16. LC/MS analysis was performed using a C18 Hypersil BDS 3μ 2.1×50 mm column with a mobile phase of 0.1% TFA in CH_3CN/H_2O, gradient from 10% CH_3CN to 100% over 15 min. HPLC was interfaced with APCI techniques.
17. Hulme, C.; Ma, L.; Romano, J.; Morrissette, M. *Tetrahedron Lett.* **1999**, *40*, 7925.
18. The following procedure was followed for the large-scale preparation of **22**: A mixture of 3-phenylpropionaldehyde (0.4 M, 250 μl in MeOH), *N*-Boc ethylene diamine (0.4 M, 250 μl in MeOH), *tert*-butyl isonitrile (0.4 M, 250 μl in MeOH) and 2-fluoro, 5-nitro benzoic acid (0.4 M, 250 μl in MeOH) was shaken at room temperature for 48 h. The reaction mixture was dried, redissolved in 1:1 DCM:THF and 5 equiv. of PS-$TsNHNH_2$ and PS-morpholine were added and shaken for 4 h. The reaction was filtered and the solvent stripped. A 20% TFA/DCM solution (5 ml) was added and let stand for 2 h and stripped at room temperature. The resulting yellow oil was dissolved in DMF and 5 equiv. of PS-morpholine was added and the reaction mixture shaken for 4 h. The reaction was filtered and the solvent was evaporated in vacuo and purified by column chromatography to yield **22** (32 mg, 76%) as an oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (1H, s, C_6H_3), 8.02 (1H, m, C_6H_3), 7.28 (2H, m, C_6H_5), 7.20 (3H, m, C_6H_5), 6.55 (1H, m, C_6H_3), 6.13 (1H, s, NH)(10H, 3×m, 2×C_6H_5), 5.17 (1H, s, NH), 5.09 (1H, m, CH), 3.52 (4H, 2×m, 2×CH_2), 2.62 (2H, m, CH_2), 1.97–2.27 (2H, 2×m, CH_2), 1.34 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.77, 268.42, 162.55, 149.45, 140.74, 138.67, 131.461, 128.55, 128.40, 127.30, 126.28, 118.08, 117.31, 63.65, 57.82, 51.51, 48.71, 42.10, 36.49, 32.24, 31.46, 30.01, 28.63. HRMS: theoretical value 425.2189; actual value 425.2203. dM/M = 3.3 ppm.
The following procedure was followed for the preparation of **17**: A mixture of isovaleraldehye (0.4 M, 250 μl in MeOH), *tert*-butyl carbazate (0.4 M, 250 μl in MeOH), isopropyl isonitrile (0.4 M, 250 μl in MeOH) and 2-fluoro, 5-nitro benzoic acid (0.4 M, 250 μl in MeOH) was shaken at room temperature for 48 h. The reaction mixture was dried, redissolved in 1:1 DCM:THF and 5 equiv. of PS-$TsNHNH_2$ and PS-DIEA were added and shaken for 14 h. The reaction was filtered and the solvent evaporated. A 20% TFA/DCM solution (5 ml) was added and let stand for 2 h and evaporated at room temperature. The resulting yellow oil was dissolved in DMF and 5 equiv. of PS-DIEA was added and the reaction mixture shaken for 14 h. The reaction was filtered and the solvent evaporated in vacuo. The crude oil purified by flash chromatography (3:1 hexane:ethyl acetate) to yield **17** (17 mg, 50%) as an oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.77 (1H, s), 8.39 (1H, m), 7.35 (1H, m), 5.14 (1H, m), 3.96 (1H, m), 2.06 (1H, m), 1.69 (1H, m), 1.28 (1H, m), 1.19 (6H, m), 0.95 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 160.1, 147.3, 142.4, 127.0, 121.5, 115.7, 112.3, 54.9, 41.7, 40.5, 24.7, 22.8. 22.0. HRMS: theoretical value 335.1714; actual value 335.1721. dM/M = 2.1 ppm.
The following procedure was followed for the preparation of **27**: A mixture of 3-phenylpropionaldehyde (0.4 M, 250 μl in MeOH), *ortho*-phenylene diamine *tert*-butyl carbamate (0.4 M, 250 μl in MeOH), isopropyl isonitrile (0.4 M, 250 μl in MeOH) and 2-fluoro, 5-nitro benzoic acid (0.4 M, 250 μl in MeOH) was shaken at room temperature for 48 h. The reaction mixture was dried, redissolved in 1:1 DCM:THF and 5 equiv. of PS-$TsNHNH_2$ and PS-DIEA were added and shaken for 14 h. The reaction was filtered and the solvent evaporated. A 20% TFA/DCM solution (5 ml) was added and let stand for 2 h and evaporated at room temperature. The resulting yellow oil was dissolved in DMF and 5 equiv. of PS-DIEA and PS-TrisAmine were added and the reaction mixture shaken for 14 h. The reaction was filtered and the solvent evaporated in vacuo. The crude oil purified by flash chromatography (3:1 hexane:ethyl acetate) to yield **27** (15 mg, 30%) as an oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.82 (1H, s), 8.20 (1H, m), 7.4–6.9 (10H, m), 4.9 (1H, m), 2.52 (2H, m), 2.12 (2H, m), 1.24 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 169.3, 156.7, 142.8, 142.4, 140.9, 130.2, 128.5, 128.4, 127.8, 127.7, 126.1, 125.5, 123.2, 121.1, 119.3, 41.8, 31.7, 29.5, 22.5. HRMS+Na: theoretical value 481.1846; actual value 481.1843. dM/M = 0.6 ppm.
The following procedure was followed for preparation of **32**: A mixture of 3-phenylpropionaldehyde (0.4 M, 250 μl in MeOH), ethanolamine (0.4 M, 250 μl in MeOH), isopropyl isonitrile (0.4 M, 250 μl in MeOH) and 2-fluoro, 5-nitro benzoic acid (0.4 M, 250 μl in MeOH) was shaken at room temperature for 48 h. The reaction mixture was dried, redissolved in 1:1 DCM:THF and 5 equiv. of PS-$TsNHNH_2$ and PS-DIEA were added and shaken for 14 h. The reaction was filtered and the solvent evaporated. The resulting yellow oil was dissolved in DMF and 5 equiv. of PS-TBD (Nova Biochem) was added and the reaction mixture shaken for 14 h. The reaction was filtered and the solvent evaporated in vacuo. The crude oil purified by flash chromatography (3:1 hexane:ethyl acetate) to yield **32** (27 mg, 60%) as an oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.82 (1H, s), 8.23 (1H, m), 7.29–7.05 (5H, m), 6.29 (1H, m), 5.13 (1H, m), 4.51 (1H, m), 4.39 (1H, m), 4.06 (1H, m), 3.81 (1H, m), 3.60 (1H, m), 2.67 (2H, m), 2.29 (1H, m), 2.03 (1H, m), 1.13 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 168.6, 159.0, 142.5, 140.4, 129.1, 128.3, 127.8, 126.2, 123.9, 122.3, 73.8, 57.0, 42.0, 41.6, 32.4, 31.3, 22.5. HRMS+Na: theoretical value 434.1686; actual value 481.1674. dM/M = 2.8 ppm.
The following procedure was followed for preparation of **35**: A mixture of 3-phenylpropionaldehyde (0.4 M, 250 μl in MeOH), 2-aminophenol (0.4 M, 250 μl in MeOH), isopropyl isonitrile (0.4 M, 250 μl in MeOH) and 2-fluoro, 5-nitro benzoic acid (0.4 M, 250 μl in MeOH) was shaken at room temperature for 48 h. The reaction mixture was dried, redissolved in 1:1 DCM:THF and 5 equiv. of PS-$TsNHNH_2$ were added and shaken for 14 h. The reaction was filtered and the solvent evaporated. The resulting yellow oil was dissolved in DMF and 5 equiv. of PS-DIEA was added and the reaction mixture shaken for 14 h. The reaction was filtered and the solvent evaporated in vacuo. The crude oil purified by flash chromatography (3:1, hexane:ethyl acetate) to yield **35** (14 mg, 25%) as an

oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (1H, s), 8.33 (1H, m), 7.40–6.90 (10H, m), 4.90 (1H, m), 4.14 (1H, m), 2.52 (2H, m), 2.25 (1H, m), 1.91 (1H, m), 1.24 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 165.1, 154.2, 145.0, 140.4, 129.0, 128.5, 128.3, 126.9, 126.1, 125., 124.5, 121.5, 120.8, 119.1, 41.8, 31.9, 29.5, 22.6. HRMS+Na: theoretical value 482.1686; actual value 482.1675. dM/M = 2.3 ppm. The following procedure was followed for the preparation of **25**: A mixture of isovaleraldehye (0.4 M, 250 μl in MeOH), *N*-Boc-*N*-methylene diamine (0.4 M, 250 μl in MeOH), benzyl isonitrile (0.4 M, 250 μl in MeOH) and 2-fluoro, 5-nitro benzoic acid (0.4 M, 250 μl in MeOH) was shaken at room temperature for 48 h. The reaction mixture was dried, redissolved in 1:1 DCM:THF and 5 equiv. of PS-$TsNHNH_2$ and PS-DIEA were added and shaken for 14 h. The reaction was filtered and the solvent evaporated. A 20% TFA/DCM solution (5 ml) was added and let stand for 2 h and evaporated at room temperature. The resulting yellow oil was dissolved in DMF and 5 equiv. of PS-DIEA was added and the reaction mixture shaken for 14 h. The reaction was filtered and the solvent evaporated in vacuo. The crude oil purified by flash chromatography (3:1 hexane:ethyl acetate) to yield **25** (17 mg, 40%) as an oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (1H, s), 8.12 (1H, m), 7.22 (5H, m), 6.73 (1H, m), 5.32 (1H, m), 4.27–4.50 (2H, m), 3.60 (1H, m), 3.37 (2H, m), 2.88 (3H, s), 1.84 (1H, m), 1.62 (2H, m), 0.97 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 169.6, 151.7, 139.9, 138.4, 129.0, 127.9, 127.8, 124.8, 116.8, 64.0, 59.4, 55.3, 43.8, 41.5, 40.9, 37.5, 25.3, 23.1, 23.0. HRMS+Na: theoretical value 447.2003; actual value 447.2009. dM/M = 1.3 ppm.