Pergamon

Tetrahedron Letters 43 (2002) 7323–7327

TETRAHEDRON LETTERS

# Syntheses of brostallicin starting from distamycin A

Italo Beria* and Marcella Nesi

*Department of Chemistry, Pharmacia, Discovery Research Oncology, Viale Pasteur, 10-20014 Nerviano (Mi), Italy*

Received 14 June 2002; revised 24 July 2002; accepted 20 August 2002

**Abstract**—Two syntheses of brostallicin, a DNA minor groove binder now undergoing phase II studies, starting from distamycin A are described. One approach is based upon the selective hydrolysis via imide activation of the C-terminus amide. Besides employing traditional solution-phase synthesis, the convenient use of a polymer-supported reagent is also discussed. The other one is based upon the Curtius rearrangement of the C-terminus side chain of a convenient intermediate, easily prepared in two steps by straightforward functional group manipulation of distamycin A. 

In our project aimed at finding novel cytotoxic DNA minor groove binders, we were interested in the synthesis of distamycin-like derivatives. Distamycin A (**1**) is a naturally occurring antibiotic characterized by an oligopeptidic pyrrolic frame ending with an amidino moiety, which reversibly binds DNA minor groove, with high selectivity for thymine-adenine rich sequences[1] (Fig. 1).

Our group synthesized several analogues of distamycin A in which an alkylating moiety is tethered to a distamycin derived DNA binding frame. In particular, tallimustine (**2**) (PNU-152241), a benzoic acid nitrogen mustard derivative of distamycin A, showed excellent cytotoxic and antitumor activity but, due to severe myelotoxicity, its phase II clinical development was abandoned. A series of α-bromoacrylic distamycin-like derivatives was then synthesized and the result of this process was the selection for clinical development of brostallicin (**3**) (PNU-166196)[2a–g] (Fig. 2).

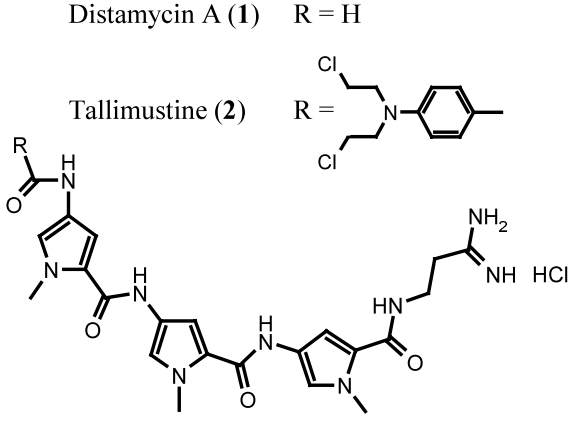



**Figure 1.** Distamycin A and its benzoyl nitrogen mustard tallimustine.

Brostallicin was found to be active against a broad spectrum of tumor cell lines in vitro and tumor xenografts in vivo with an improved cytotoxicity/myelotoxicity ratio in comparison to other minor groove binders.[3,4] Interestingly, the in vitro and in vivo activity of brostallicin is affected by glutathione.[5]

The observations obtained so far indicate that brostallicin is a novel minor groove binder with unique pharmacological properties and a promising toxicological profile.

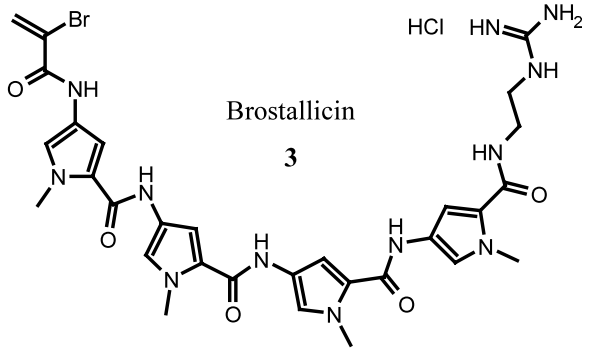



**Figure 2.** Brostallicin (PNU-166196) is undergoing phase II clinical trials.

*Keywords*: minor groove binders; distamycin A; brostallicin; Curtius rearrangement; diphenyl phosphorazidate.

* Corresponding author. Tel.: +39-2-48385339; fax: +39-2-48383833; e-mail: italo.beria@pharmacia.com

0040-4039/02/$ - see front matter 
PII: S0040-4039(02)01733-1

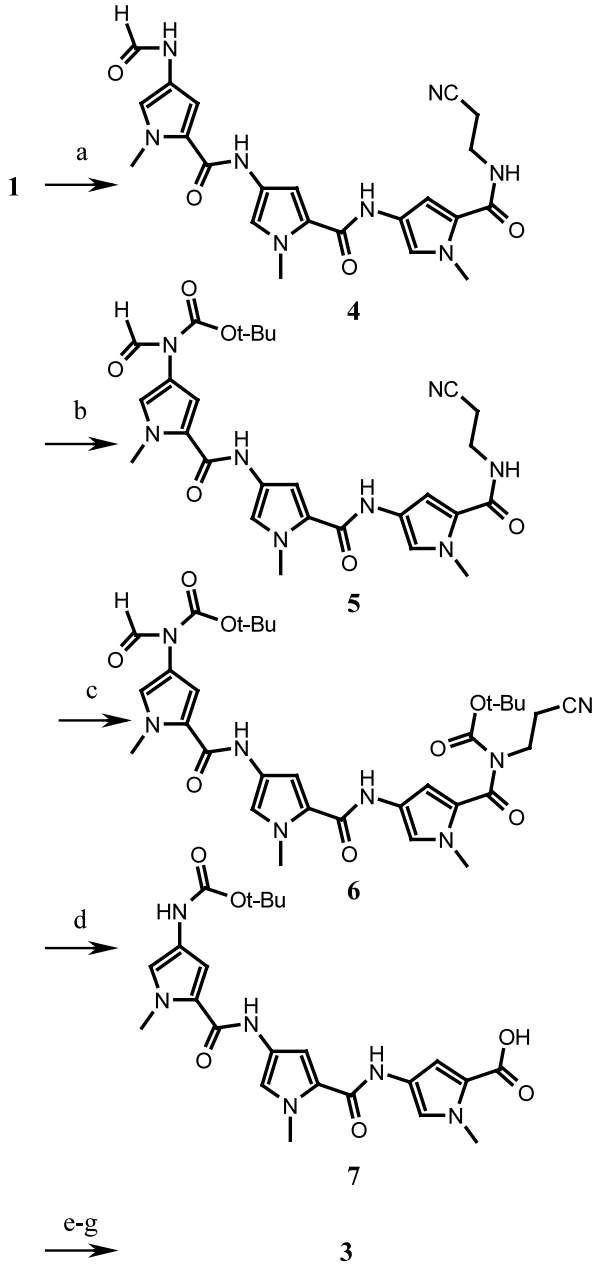
A tetrapyrrolecarbamoyl skeleton ending with a guanidine function characterizes this compound, at present undergoing phase II studies.

While most distamycin analogues have been prepared by us modifying the amidino terminus typical of distamycin, the polypyrrolic frame of brostallicin has been obtained so far in our laboratories by total synthesis from guanidinoethylamine, by iterative acylation with 4-nitro-pyrrolecarboxylic acid chloride and catalytic reduction of the nitro group.[2c] Although the overall yield of the process was good (20% for nine steps) we also investigated alternative syntheses of brostallicin starting from distamycin A, which we produce in house by a proprietary fermentation process.[1b] Two different approaches have been studied one based upon the selective cleavage via imide activation of the C-terminus amide (Method A) and a second one based upon the Curtius rearrangement of the C-terminus side chain (Method B).

**Method A.** Protection of the amide NH by the *tert*-butoxycarbonyl (Boc) group using di-*tert*-butyl dicarbonate ($Boc_2O$) and 4-dimethylaminopyridine (DMAP) was pioneered by Grieco[6] and Ragnarsson[7]. In addition to serving as a protecting group, the Boc group also promotes selective cleavage of the resulting imide at the less hindered carbonyl.[6,8] Moreover, it has been shown that derivatization of a secondary amide to *N*-nitrosoamide also facilitates its hydrolysis. Evans group has described some applications of both methodologies to natural product synthesis demonstrating that *N*-nitrosoamide derivatives are much more reactive than the corresponding imides.[9]

Activation by means of the Boc group was chosen since preliminary investigation showed that selective nitrosation of the amide could not be carried out on the pyrrolic system.[10] Distamycin A **1** was first transformed into the corresponding nitrile **4** using a methodology developed by our group useful to circumvent the basicity and reactivity of the amidino group (Scheme 1).[11]

Treatment of **4** with $Boc_2O$ (2 equiv.) and DMAP (0.2 equiv.) afforded exclusively the mono-Boc derivative **5**. More conveniently this could be obtained using an excess of $Boc_2O$ and polymer-supported dimethylaminopyridine (PS-DMAP) in DMF.[12] The mono-Boc derivative **5** was not be isolated and upon treatment with additional $Boc_2O$ gave, after removal with trifluoroethanol (TFE) of excess $Boc_2O$,[13] the di-Boc derivative **6** as main product together with various by-products arising from the non selective *tert*-butoxycarbonylation of the intra-pyrrolic amides which occurred when excess of reagent was added in order to drive the reaction to completion.[14] The reaction was purified by flash chromatography affording the desired di-Boc derivative **6** in 40% yield. As far as selectivity is concerned, the same results were also observed employing standard solution-phase chemistry. However, the use of PS-DMAP followed by TFE quenching was found to be attractive for work-up simplification: filtration of the resin followed by evaporation of volatile components (solvent and O-Boc TFE) afforded the crude product with no need for conventional work-up.[15]




**Scheme 1.** Reagents and conditions: (a) succinic anhydride (2.5 equiv.), $Na_2CO_3$ (3.2 equiv.), DMF, 70°C, 3 h, 87%; (b) $Boc_2O$ (2 equiv.), DMAP (0.2 equiv.), $CH_2Cl_2$, 25°C, 45 min, 90% or $Boc_2O$ (4 equiv.), PS-DMAP (2 equiv.), DMF, 25°C, 3 h; (c) $Boc_2O$ (4 equiv.), PS-DMAP (2 equiv.), DMF, 25°C, 3 h then $Boc_2O$ (4 equiv.), 2 h, then TFE, 15 min or $Boc_2O$ (4 equiv.), DMAP (2 equiv.), $Et_3N$ (2 equiv.), DMF, 4°C, 20 h, 40%; (d) LiOH (6 equiv.), $THF/H_2O$ (8:2), 25°C, 20 h, 50%; (e) *N*-(2-aminoethyl)guanidine dihydrochloride, (1.1 equiv.), TBTU (1 equiv.), $Et_3N$ (2.1 equiv.), DMF, 25°C, 12 h, quant.; (f) $CH_2Cl_2$/TFA (1:1), 25°C, 12 h, quant.; (g) 4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carbonyl chloride (1.7 equiv.), 1,4-dioxane/$H_2O$ (7:3), $NaHCO_3$ (6.4 equiv.), 25°C, 1 h, 60%.

It is known from the literature that both steric hindrance about the nitrogen and the acidity of the amide NH (lower amide NH p$K_a$-higher reactivity) can influence the conversion times for DMAP catalyzed reaction of amides with $Boc_2O$.[16] Thus, while the sterically unhindered N-terminus formamide in **4** reacts very selectively with $Boc_2O$, unfortunately there is only a slight preference for the *tert*-butoxycarbonylation of the C-terminus amide over the two intra-pyrrolic amides of the molecule. We tried several reaction conditions but the regio-selectivity could not be improved any further than 40% in favor of the di-Boc derivative **6**.[17,18]

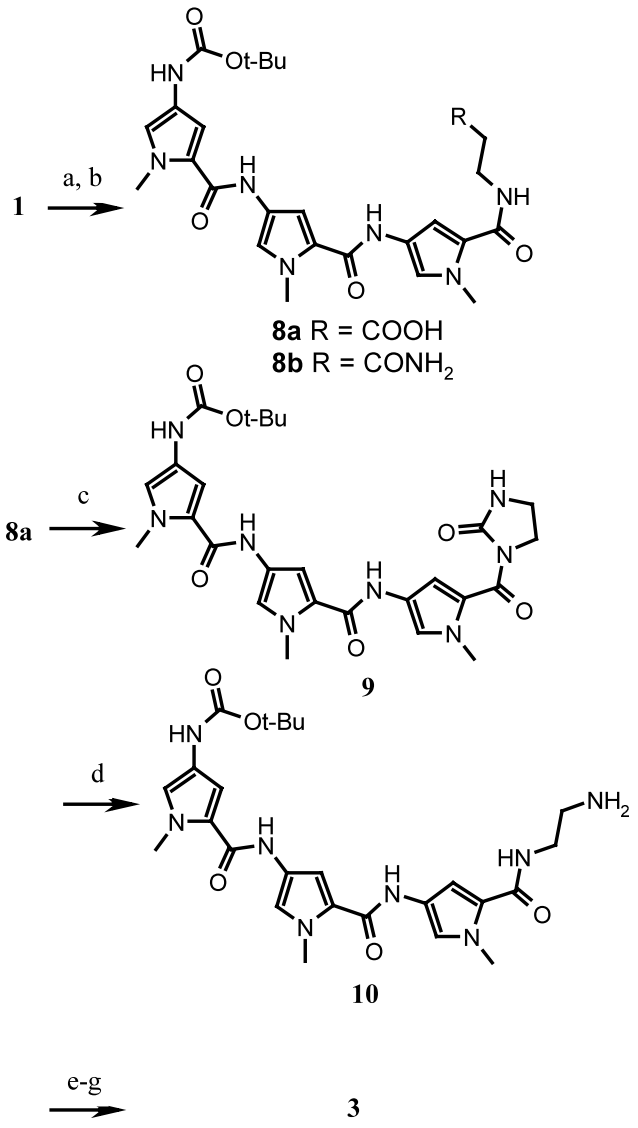
Saponification of **6** with lithium hydroxide according to the Grieco procedure afforded, after precipitation from water-10% AcOH, the N-Boc protected carboxylic acid **7**.[6,19] This conveniently protected amino acid that other groups have previously obtained by total synthesis, represents a very useful intermediate for the straightforward preparation of several distamyin A analogues.[20]

The synthesis was then completed by standard methodology. Coupling of **7** with *N*-(2-aminoethyl)guanidine dihydrochloride using TBTU, removal of the Boc group and final coupling with 4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carbonyl chloride afforded the desired final compound. Direct aminolysis of **6** using *N*-(2-aminoethyl)guanidine dihydrochloride was also attempted but unfortunately it did not work.[8a,21]

**Method B.** Diphenyl phosphorazidate (DPPA) is a useful and versatile reagent in organic synthesis, and can be conveniently used for the Curtius rearrangement under mild reaction conditions, using carboxylic acids as starting material.[22] However, it is reported in the literature that amide and urethane functions, when properly situated, can undergo intramolecular addition to the intermediate isocyanate formed in the rearrangement process.[23] For example, the rearrangement of β-alanine amide or urethane derivatives is known to afford 1-acyl-2-imidazolidin-ones when DPPA is employed.[24] This type of reactivity has been exploited in the synthesis of the 2-aza analog of pyrrolizidine-3,5-dione (Lukes–Sorm dilactam) by treatment of [(2*S*)-5-oxopyrrolidin-2-yl]-acetic acid with DPPA.[25]

Treatment of the natural product **1** under forcing basic conditions in order to remove both the formyl and the amidino groups followed by N-Boc protection of the terminal amine led directly to the carboxylic acid **8a**. On this intermediate the next degradation step was performed (Scheme 2).

In accordance with the literature, we found that the Curtius reaction of carboxylic acid **8a** using DPPA proceeded smoothly to give the imidazolidinone derivative **5** via intramolecular trapping of the intermediate isocyanate by the neighboring carboxamide function.[26] It is worth noting that when the reaction was carried out in the presence of an alcohol, mixtures of products were obtained and only small amounts of the corresponding urethane could be isolated.[27]




**Scheme 2.** Reagents and conditions: (a) **8a**: 20% NaOH, MeOH, reflux, 24 h, quant.; **8b**: 1N NaOH (3 equiv.), MeOH, 60°C, 4 h, 75%; (b) $Boc_2O$ (2 equiv.), $Et_3N$ (2 equiv.), DMF, 25°C, 2 h, 92%; (c) DPPA (1.1 equiv.), $Et_3N$ (1.1 equiv.), DMF, 80°C, 4 h, 62%; (d) 1N NaOH (1.1 equiv.), DMF, 25°C, 4 h, 54%; (e) *N*,*N*′-di-Boc-*N*″-trifyl-guanidine, $Et_3N$ (2 equiv.), DMF, 40°C, 2 h, quant.; (f) 6N HCl in MeOH, 25°C, 12 h, quant.; (g) 4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carbonyl chloride (1.7 equiv.), 1,4-dioxane/$H_2O$ (7:3), $NaHCO_3$ (6.4 equiv.), 25°C, 1 h, 60%.

Moreover, the use of bis[(trifluoroacetoxy)phenyl]iodine (PIFA), a mild reagent reported to effect a Hoffmann-like rearrangement without trapping by neighboring urethane or carboxamide functions, was also tried.[28] However, treatment of amide **8b**, obtained from partial hydrolysis of distamycin A followed by N-Boc protection of the terminal amine, with PIFA, in the presence of pyridine, resulted in extensive degradation of the distamycin system.

Treatment of 1-acyl-2-imidazolidinones under basic conditions usually affords a carboxylic acid derivative

and 2-imidazolidinones. In addition to this type of reactivity, it is also reported that secondary amines, when reacted with N-(2-nitrobenzenesulfonyl)-2-imidazolidinone, open the imidazolidinone ring and give ureas.[29]

Therefore, we were positively surprised to find out that imidazolidinone derivative **9**, upon treatment of with 1N NaOH in DMF, afforded amine **10**.[30] As far as our knowledge is concerned this type of ring opening of 1-acyl-2-imidazolidinones has not been reported so far.

The synthesis was then completed by standard methodology. Guanidinylation of amine **10** with *N*,*N*′-di-Boc-*N*″-trifyl-guanidine,[31] removal of the Boc groups and final coupling with 4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carbonyl chloride afforded brostallicin **3**.

In summary, we have described two syntheses of brostallicin, starting from distamycin A. Method A is based on the selective hydrolysis of **6** that leads to the formation of the N-Boc protected carboxylic acid **7**. This is a key intermediate for the preparation of several distamycin-like derivatives and up to now has only been prepared by total synthesis. Furthermore, the rather non-selective di-*tert*-butoxycarbonylation of **4** can also be achieved using PS-DMAP that allows a more simple reaction work-up by filtration of the resin and evaporation of the volatile components.

Method B is based on the Curtius rearrangement of carboxylic acid **8a** to give the acyl imidazolidinone **9**. Although intramolecular isocyanate trapping by carboxamide functions has already been reported in the literature, we have shown its useful application in the degradation of an oligopeptidic natural product. Furthermore, the unusual ring opening by aqueous bases of the imidazolidinone led to the identical product obtainable in a typical Curtius reaction and therefore the inconvenience of the isocyanate trapping by a carboxamide function was eventually overcome.

Both approaches have been carried out on small scale and most of the single steps have not been optimized. However, the overall yields with method A and method B, 10% and 18%, respectively, are comparable with that reported for the step-by-step total synthesis approach[2c].

## Acknowledgements

We thank Paolo Cozzi and Nicola Mongelli (Pharmacia, Department of Chemistry) for helpful discussions.

## References

1. (a) Arcamone, F.; Orezzi, P. G.; Barbieri, W.; Nicolella, V.; Penco, S. *Gazz. Chim. Ital.* **1967**, *97*, 1097–1115; (b) Arcamone, F.; Penco, S.; Orezzi, P. G.; Nicolella, V.; Pirelli, A. *Nature* **1964**, *203*, 1064–1065.
2. (a) Baraldi, P. G.; Beria, I.; Cacciari, B.; Cozzi, P.; Franzetti, C.; Mongelli, N.; Romagnoli, R.; Spalluto, G. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1241–1246; (b) Baraldi, P. G.; Beria, I.; Cacciari, B.; Coplongo, L.; Cozzi, P.; Mongelli, N.; Romagnoli, R.; Spalluto, G. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1247–1252; (c) Cozzi, P.; Beria, I.; Biasoli, G.; Caldarelli, M.; Capolongo, L.; Geroni, C.; Mongelli, N. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2979–2984; (d) Cozzi, P.; Beria, I.; Biasoli, G.; Caldarelli, M.; Capolongo, L.; D'Alessio, R.; Geroni, C.; Mazzini, S.; Ragg, E.; Rossi, C.; Mongelli, N. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2985–2990; (e) Cozzi, P.; Beria, I.; Caldarelli, M.; Capolongo, L.; Geroni, C.; Mongelli, N. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1269–1272; (f) Cozzi, P.; Beria, I.; Caldarelli, M.; Geroni, C.; Mongelli, N.; Pennella, G. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1273–1276; (g) Baraldi, P. G.; Romagnoli, R.; Beria, I.; Cozzi, P.; Geroni, C.; Mongelli, N.; Bianchi, N.; Mischiati, C.; Gambari, R. *J. Med. Chem.* **2000**, *43*, 2675–2684.
3. Geroni, C.; Pennella, G.; Capolongo, C.; Moneta, D.; Rossi, R.; Farao, M.; Marchini, S; Cozzi, P. *Proc. AACR Annual Meeting*, *San Francisco* **2000**, 41 Abstr. 2708, 425.
4. Ciomei, M.; Pastori, W.; Cozzi, P.; Geroni, C. *Proc. AACR Annual Meeting*, *Philadelphia* **1999**, 40, Abstr. 1490, 224.
5. Geroni, C.; Marchini, S.; Cozzi, P.; Galliera, E.; Ragg, E.; Colombo, T.; Battaglia, R.; Howard, M.; D'Incalci, M.; Broggini, M. *Cancer Res.* **2002**, *62*, 2332–2336.
6. Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424–2426.
7. (a) Grehn, L.; Ragnarsson, U. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 510–511; (b) Grehn, L.; Gunnarsson, K.; Ragnarsson, U. *Acta Chem. Scand., Ser. B* **1986**, *40*, 745–750.
8. (a) Grehn, L.; Gunnarsson, K.; Ragnarsson, U. *Acta Chem. Scand., Ser. B* **1987**, *41*, 18–23; (b) Kano, S.; Yokomatsu, T.; Shibuya, S. *J. Org. Chem.* **1989**, *54*, 513–515.
9. Evans, D. A.; Carter, P. H.; Dinsmore, C. J.; Barrow, J. C.; Katz, J. L.; Kung, D. W. *Tetrahedron Lett.* **1997**, 38, 4535–4538. For some recent applications see also: (a) Magnus, P.; Westwood, N.; Spyvee, M.; Frost, C.; Linnane, P.; Tavares, F.; Lynch, V. *Tetrahedron* **1999**, 55, 6435–6452; (b) Oscarsson, K.; Classon, B.; Kvarnström, I.; Hallberg, A.; Samuelsson, B. *Can. J. Chem.* **2000**, 78, 829–837; (c) Evans, D. A.; Katz, J. L.; Peterson, G. S.; Hintermann, T. *J. Am. Chem. Soc.* **2001**, 123, 12411–12413.
10. Treatment of intermediate **5** in dichloromethane at 0–25°C with $i$-$C_5H_{12}ONO$ afforded a complex mixture of products. Both $^1H$ NMR and MS spectra determinations were consistent with extensive nitrosation of the pyrrolic rings.
11. Caldarelli, M.; Biasoli, G.; Cozzi, P.; Mongelli, N. *Tetrahedron Lett.* **1998**, *39*, 3551–3554.
12. Dimethylaminopyridine, polymer-bound, dry ~2.5 mmol $g^{-1}$, available from Sigma-Aldrich Cat. No. 35,988–2.
13. Basel, Y.; Hassner, A. *Synthesis* **2001**, *4*, 550–552.
14. The reaction seems to start selectively in favor of intermediate **6** but when forced to completion non-selective paths take over.
15. For recent advances in the field of polymer-supported reagents see (a) Ley, S. V.; Baxendale, I. R.; Bream, R.

N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 23, 3815–4195; (b) Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem., Int. Ed.* **2001**, 40, 650–679.

16. Hansen, M. M.; Harkness, A. R.; Coffey, D. S.; Bordwell, F. G.; Zhao, Y. *Tetrahedron Lett*. **1995**, *36*, 8949–8952.
17. $CH_3CN$, THF, $CH_2Cl_2$ were tried as reaction solvents but no significant difference was observed. The catalytic use of DMAP gave slower conversions but no improvement in selectivity. The addition of $Et_3N$ gave faster conversions but also did not improve the selectivity. Since $Boc_2O$ decomposes in the presence of DMAP, the use of an excess of $Boc_2O$ was necessary in order to drive the reaction to completion.
18. To a solution of **5** (0.464 g) in dry DMF (2 ml) cooled at 4°C, di-*tert*-butyldicarbonate (0.873 g), $Et_3N$ (0.278 ml) and DMAP (0.244 g) were added. The solution was stirred for 5 h and the organic solvent was then evaporated under vacuum. The residue was purified by flash chromatography (dichloromethane/ethyl acetate = 6:4) yielding **6** (0.261 g; $y = 40\%$) as a beige powder. FAB MS: $m/z$ 665 (100, $[M+H]^+$); 565 (20); 465 (55); PMR (DMSO-$d_6$) $\delta$: 9.97 (s, 1H), 9.89 (s, 1H), 9.25 (s, 1H), 7.49 (d, $J = 1.8$ Hz, 1H), 7.20 (d, $J = 1.8$ Hz, 1H), 7.06 (d, $J = 1.8$ Hz, 1H), 6.99 (d, $J = 1.8$ Hz, 1H), 6.85 (d, $J = 1.8$ Hz, 1H), 6.65 (d, $J = 1.8$ Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.72 (s, 3H), 3.83 (m, 2H), 2.45 (t, $J = 6.2$ Hz, 2H), 1.48 (s, 9H), 1.27 (s, 9H).
19. The yield of the hydrolysis was not optimized.
20. Boger, D. L.; Fink, B. E.; Hedrick, M. P. *J. Am. Chem. Soc*. **2000**, *122*, 6382–6394.
21. **6**, *N*-(2-aminoethyl)guanidine dihydrochloride (2 equiv.) and $Et_3N$ (4 equiv.) were reacted in DMF at 25–60°C. After several hours only starting material **6** was present.
22. (a) Shioiri, T.; Yamada, S. *Org. Synth*. **1984**, *62*, 187; (b) Hamada, Y.; Shioiri, T. *Org. Synth*. **1984**, *62*, 191; (c) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc*. **1972**, *94*, 6203; (d) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151.
23. (a) Kanewskaja, S. J. *Chem. Ber*. **1936**, *69*, 266; (b) Schneider, F. *Justus Liebigs Ann. Chem*. **1937**, *529*, 1; (c) Karrer, P.; Schlosser, A. *Helv. Chim. Acta* **1923**, *6*, 411.
24. Olsen, R. K.; Hennen, W. J.; Wardle, R. B. *J. Org. Chem*. **1982**, *47*, 4605.
25. Nagasaka, T.; Hakamada, R.; Kunii, S.; Hamaguchi, F. *Heterocycles* **1992**, *33*, 619–630.
26. To a solution of **4a** (6.5 g), in dry DMF (100 ml) warmed to 80°C, TEA (1.8 ml) and DPPA (2.77 ml) were added dropwise. The solution was stirred at 80°C for 5 h. The solution was concentrated under vacuum and 2% aqueous $CH_3COOH$ solution (200 ml) was added. The suspension was stirred for 1 h, the aqueous phase removed by filtration and the precipitate washed with water (100 ml). Desiccation under vacuum at 50°C yielded compound **5** (4.2 g; $y = 65\%$) as a hazel powder. FAB MS: $m/z$ 553 (60, $[M+H]^+$); PMR (DMSO-$d_6$) $\delta$: 9.87 (s, 1H), 9.83 (s, 1H), 9.05 (s, 1H), 7.50 (bs, 1H), 7.35 (d, $J = 1.7$ Hz, 1H), 7.19 (d, $J = 1.7$ Hz, 1H), 7.03 (d, $J = 1.7$ Hz, 1H), 6.87 (bs, 1H), 6.81 (bs, 1H), 6.72 (d, $J = 1.7$ Hz, 1H), 3.85–3.80 (m, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.70 (s, 3H), 3.32–3.37 (m, 2H), 1.44 (s, 9H).
27. *tert*-BuOH and MeOH have been tried.
28. Waki, M.; Kitajima, Y.; Izumya, N. *Synthesis* **1981**, *4*, 266–268.
29. Feichtinger, K.; Zapf, C.; Sings, H. L.; Goodman, M. *J. Org. Chem*. **1998**, *63*, 3804–3805.
30. To a solution of compound **9** (3 g), in dry DMF (50 ml), 1N NaOH (7.5ml) and water (3 ml) were added and the solution was stirred at room temperature for 2 h. The organic solvent was removed under vacuum and water (60 ml) was added. The mixture was then extracted with ethyl acetate (3×150 ml), the combined organic phases were dried ($Na_2SO_4$), acidified with trifluoroacetic acid and concentrated in vacuum yielding compound **6** (1.7 g, $y = 54\%$) as a yellow powder. FAB MS: $m/z$ 527 (100, $[M+H]^+$), 471 (35), 427 (55); PMR (DMSO-$d_6$) $\delta$: 9.85 (s, 1H), 9.82 (s, 1H), 9.05 (s, 1H), 8.01 (t, $J = 5.6$ Hz, 1H), 7.19 (d, $J = 1.7$ Hz, 1H), 7.16 (d, $J = 1.7$ Hz, 1H), 7.02 (d, $J = 1.7$ Hz, 1H), 6.89 (d, $J = 1.7$ Hz, 1H), 6.87 (bs, 1H), 6.82 (bs, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.26–3.20 (m, 2H), 2.74 (t, $J = 5.6$ Hz, 1H).
31. Wilson, M. E.; Nowick, J. S. *Tetrahedron Lett*. **1998**, *39*, 6613–6616.