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Synthesis of Diverse Tetrahydro-β-Carboline-3-Carboxamides and -2,3-Bis-lactams On a Versatile 4-Hydroxythiophenol-Linked Solid Support.

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Abstract: A practical method for solid phase organic synthesis has been developed using the known, but heretofore underutilized, 4-hydroxythiophenol linker of Marshall and Liener. The utility of this linker is demonstrated by the synthesis of 1,2,3,4-tetrahydro-β-carboline-3-carboxamides and -2,3-bis-lactams. Acylation of the resin with L-Boc-tryptophan followed by deprotection and Pictet-Spengler cyclization with a variety of aldehydes provided tetrahydro-β-carbolines with excellent conversion. Cleavage from the resin with primary amines provided the amides and an additional diversity element. Alternatively, acylation at the carboline 2-position with Boc- protected α- or β-amino acid derivatives followed by deprotection and neutralization resulted in intramolecular cyclization and cleavage to afford 6- and 7-membered bis-lactams.

Renewable sources of molecular diversity remain a critical component of many modern drug discovery programs. Attempts to satisfy this requirement have led to a vast body chemical research focused on rendering non-oligomeric, small molecule synthesis to solid supports; the cornerstone of combinatorial chemistry. The development of new strategies and techniques continues unabated.[1] In our laboratories, the emphasis has shifted from the preparation of traditional combinatorial libraries (*i.e.* compressed formats) to one of high throughput organic synthesis and rapid parallel processing which leads to discrete chemical entities. While the requirement for general and efficient methods remains paramount, the increased number of samples processed, either manually or by automation, requires that maximum diversity be gained in a minimum of synthetic operations. React and release strategies, which involve cleavage of bound substrates from the solid support with diverse reagents, provide an attractive solution.[2] Herein, the classic Pictet-Spengler[3,4] synthesis of biologically relevant[5] tetrahydro-β-carbolines provides the first example of non-peptide, organic synthesis on 4-hydroxythiophenol-linked Merrifield resin. Significantly, and in contrast to the original peptide applications reported by Marshall and Liener,[6] we have determined that oxidation of the linker is not necessary for efficient cleavage of substrates by amines. This advance, along with other improvements[7] by our group, greatly expands the types of structures that can be assembled on this solid support.

Carbodiimide mediated esterification (diisopropylcarbodiimide, DMF, 27 °C, 24 h) of the 4-hydroxythiophenol-linked resin[7] with L-Boc-tryptophan provided ester **1**, which upon deprotection (3% HCl in MeOH) provided resin-bound indole **2** (Scheme I). The progress of both the acylation and deprotection steps was conveniently monitored by single-bead FT-IR spectroscopy using the diagnostic ester (1760 cm^{-1}) and carbamate (1740 cm^{-1}) absorption bands. We were pleased to find that both imine formation and cyclization proceeded smoothly upon heating **2** (toluene, 85 °C, 18 h) in the presence of an aldehyde (6 equiv) without the need for additional acid.[8] In general, both imine formation and subsequent cyclization were tolerant of a wide variety of aliphatic, aromatic and heteroaromatic aldehydes. Two structural types did, however, prove problematic. The first were α,β-unsaturated aldehydes (*i.e.* citral and cinnamaldehyde) which failed to undergo the desired cyclization presumably due to the poor reactivity of the intermediate α,β-unsaturated imines. The second class included

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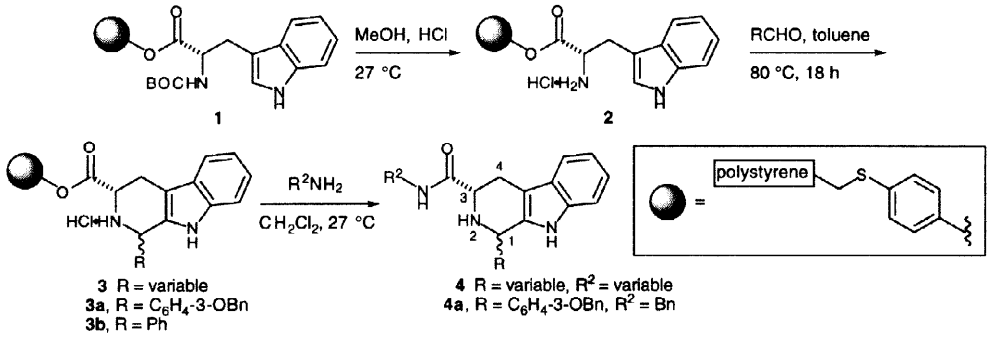
aromatic aldehydes having substituents capable of reducing the electrophilicity of the imine double bond by electron donation (*i.e.* 2 and/or 4-alkoxy or hydroxy benzaldehydes and 4-pyridine carboxaldehyde).[8] The desired β-carboline-2-carboxamides **4** were then obtained after evaporation by allowing **3** to react with substoichiometric primary amine (0.5 equiv, CH_2Cl_2, 27 °C, 18 h).

At this juncture, the stereochemical outcome of one condensation/cyclization reaction was pursued in-depth using **4a** (R = C_6H_4-3-OBn, R^2 = Bn) derived from the solid phase. Separation of the resultant diastereomers by silica gel chromatography followed by ^{1}H-NMR, ^{13}C-NMR and RP-HPLC analyses, indicated an original 1.7:1 ratio of 1,3-*trans* and 1,3-*cis* isomers, respectively.[9] Although the stereochemistry (typically a *ca.* 2:1 mixture of stereoisomers) was not pursued for all samples derived from the solid phase, literature[10] and the results from **4a** suggests that the mixtures are enriched with the trans isomer.

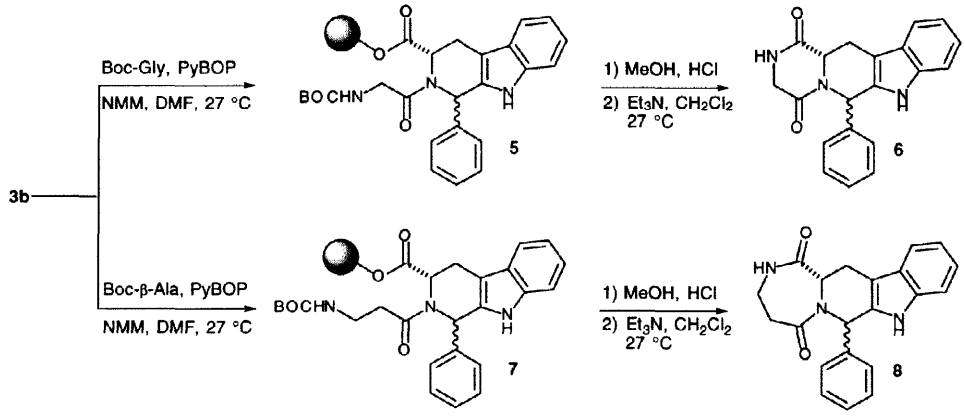
Scheme I. Solid phase synthesis of tetrahydro-β-carboline-3-carboxamides.



A 345-membered library of discrete tetrahydro-β-carboline-3-carboxamides **4** (mixture of diastereomers) was prepared as follows. Resin-bound β-carbolines **3** were prepared in bulk from fifteen structurally diverse aldehydes. The derivatized resins were then divided into groups of twenty three, and the cleavage of the substrates effected by aminolysis with twenty three different primary amines as described.[9] Analysis of the library by RP-HPLC indicated purity levels typically in excess of 95% with the major contaminant in each case being unreacted primary amine.[11]

An attractive feature of the thiophenol linker is the ability to effect intramolecular cleavage from the solid support by incorporating a suitably disposed amine functionality. This strategy should result in exceptionally pure products since intermediates that failed to undergo cyclization remain bound to the solid support and, due to the well known "pseudo-dilution" effect,[12] intermolecular cleavage is of little concern. To test the viability of this approach, the 2 position nitrogen of **3b** (R = Ph) was acylated (PyBOP, DMF, NMM, 27 °C, 17 h) with the simple Boc-protected amino acids Boc-glycine and Boc-β-alanine providing **5** and **7**, respectively (Scheme II). With the requirement that the cyclized products be obtained free of chemical contaminants, we initially attempted the required deprotection-cyclization step using glacial acetic acid. Unfortunately this method, as well as attempts to achieve thermolytic cleavage of the Boc group, failed to yield detectable product with decomposition of the solid support being the result under the latter conditions. At this point a conventional strategy for removal of the protecting group was adopted. Acylated derivatives **5** and **6** were exposed to acid (3% HCl in MeOH, 4 h, 27 °C) followed by exhaustive washing of the resin. Treatment of the resulting hydrochloride salts with excess triethylamine (CH_2Cl_2, 27 °C, 4 h) resulted in cyclization and liberation of the desired six- and seven-membered bis-lactams **6** and **8**, respectively, accompanied only by a stoichiometric amount of Et_3N•HCl upon evaporation.[11]

Scheme II. Solid phase synthesis of tetrahydro-β-carboline-2,3-bis-lactams.



In summary, we have developed a general synthesis of tetrahydro-β-carbolines on Merrifield resin utilizing an acid-stable, amine-cleavable 4-hydroxythiophenol linker. In addition to distinct economic advantages, this solid support system readily liberates bound substrates upon exposure to primary amines thus providing an additional diversity element during this essential step. The mode of cleavage from the solid support also allows for the preparation of cyclic bis-lactams via intramolecular cyclization. The method is extremely efficient and thus readily amenable to high throughput synthesis techniques.

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REFERENCES AND NOTES

1. (a) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555-600. (b) Gallop, M. A.; Barret, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233-1251. (c) Gordon, E. M.; Barret, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385-1401.

2. For other amine-cleavable linkers and applications thereof, see: (a) Kaiser, E. T.; Mihara, H.; Kelly, J. W.; Walters, L.; Findeis, M. A.; Sasaki, T. *Science*, **1989**, *243*, 187. (b) Voyer, N.; Lavoie, A.; Pinette, M.; Bernier, J. *Tetrahedron Lett.* **1994**, *35*, 355-358 and references cited therein. (c) Kenner, G. W.; McDermott, J. R.; Sheppard, R. C. *J. Chem. Soc., Chem. Commun.* **1971**, 636-637. (d) Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 11171-11172.

3. Pictet, A.; Spengler, T. *Chem. Ber.* **1911**, *44*, 2030-2036.

4. While this work was in progress, other examples of Pictet-Spengler reactions on solid supports were reported, see: (a) Mayer, J. P.; Bankaitis-Davis, D.; Zhang, J.; Beaton, G.; Bjergarde, K.; Andersen, C. M.; Goodman, B. A.; Herra, C. J. *Tetrahedron Lett.* **1996**, *37*, 5633-5636. (b) Yang, L.; Guo, L. *Tetrahedron Lett.* **1996**, *37*, 5041-5044. (c) Mohan, R.; Chou, Y.-L.; Morrissey, M. M. *Tetrahedron Lett.* **1996**, *37*, 3963-3966. (d) Kaljuste, K.; Unden, A. *Tetrahedron Lett.* **1995**, *36*, 9211-9214.

5. For examples of biologically active tetrahydro-β-carbolines, see: (a) Audia, J. E.; Evrard, D. A.; Murdoch, G. R.; Droste, J. J.; Nissen, J. S.; Schneck, K. W.; Fludzinski, P.; Lucaites, V. L.; Nelson, D. L.; Cohen, M. L. *J. Med. Chem.* **1996**, *39*, 2773-2780. (b) Kuhn-Velten, W. K. *European Journal of Pharmacology* **1993**, *250*, R1-R3. (c) Duka, T.; Schutt, B.; Krause, W.; Dorow, R.; McDonald, S.; Fichte, K. *Br. J. Clin. Pharmac.* **1993**, *35*, 386-394. (d) Cooper, S. J.; Greenwood, S.

E. *Brain Research* **1992**, *144*, 144-147. (e) Jackson, H. C.; Nutt, D. J. *European Journal of Pharmacology* **1991**, *193*, 179-184. (f) Tse, S. Y. H.; Mak, I-T.; Dickens, B. F. *Biochemical Pharmacology* **1991**, *42*, 459-464.

6. Marshall, D. L.; Liener, I. E. *J. Org. Chem.* **1970**, *35*, 867-868.

7. Breitenbucher, J. G.; Johnson, C. R.; Haight, M.; Phelan, J. C. *Tetrahedron Lett.* **1998**, *39*, 1295-1298.

8. Soerens, D.; Sandrin, J.; Ungemach, F.; Mokry, P.; Wu, G. S.; Yamanaka, E.; Hutchins, L.; DiPierro, M.; Cook, J. M. *J. Org. Chem.* **1979**, *44*, 535-545.

9. Representative experimental procedures. **Preparation of 1:** To a slurry of 4-hydroxythiophenol-linked Merrifield resin[7] (15g, 11.3 mmol) in DMF (60 mL) was added L-Boc-tryptophan (6.85 g, 22.5 mmol) followed by 1-hydroxybenzotriazole (3.04 g, 22.5 mmol), DMAP (0.14 g, 1.13 mmol) and diisopropylcarbodiimide (3.52 mL, 22.5 mmol). The slurry was shaken for 24 hours at 27 °C, filtered, and the resin washed thoroughly with DMF and CH_2Cl_2. **Preparation of 2:** A suspension of the derivatized resin in 3% methanolic HCl (50 mL) was shaken for 4 hours at 27 °C, filtered, and thoroughly rinsed with MeOH and CH_2Cl_2. **Preparation of 3a (R = C_6H_4-3-OBn):** A solution of 3-benzyloxybenzaldehyde (1.62 g, 7.7 mmol) in toluene (10 mL) was allowed to react with **2** (1.7 g, 1.3 mmol) at 85°C for 18 hours. The mixture was cooled to room temperature, filtered, and washed with CH_2Cl_2. **Preparation of 4a (R = C_6H_4-3-OBn, R^2 = Bn)**: Solid supported **3a** was washed with 50% Et_3N-CH_2Cl_2 then with CH_2Cl_2. It was then suspended in CH_2Cl_2 (5 mL) and allowed to react with benzylamine (56 µL, 0.5 mmol, 0.5 equiv) for 18 hours at room temperature. The slurry was filtered, rinsed with CH_2Cl_2, and the combined solutions concentrated to afford **4a** (120 mg, 50% yield). Chromatography on silica gel (gradient elution, 0.5% - 1 % MeOH-CH_2Cl_2) provided **4a** as a colorless solid: Analytical data for major (trans) isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 1 H), 7.57 (d, *J* = 7.0 Hz, 1 H), 7.50-7.20 (m, 12 H), 6.91 (dd, *J* = 2.0, 7.0 Hz, 1 H), 6.79 (s, 1 H), 5.18 (s, 1 H), 4.96 (s, 2 H), 4.53 (dd, *J* = 14.8, 6.2 Hz, 1 H), 4.38 (dd, *J* = 14.7, 5.4 Hz, 1 H), 3.69 (dd, *J* = 9.6, 5.0 Hz, 1 H), 3.33 (dd, *J* = 15.9, 5.0 Hz, 1 H), 2.96 (dd, *J* = 15.9, 9.7 Hz, 1 H); mass spectrum (EI) *m/z* 487.6 (M^+). **Preparation of 8:** A suspension of **3b** (R = Ph) (0.15 g, 0.11 mmol) in dry DMF (0.15 mL) was treated with NMM (49 µL, 0.45 mmol), Boc-β-alanine (64 mg, 0.34 mmol) and PyBOP (0.23 g, 0.45 mmol). The mixture was shaken at 27 °C for 18 hours, filtered, washed thoroughly with DMF and CH_2Cl_2, then allowed to react with 3% methanolic HCl (1.2 mL) at 27 °C for 4 hours. The deprotected material was then rinsed with CH_2Cl_2, and then shaken with 50% Et_3N/CH_2Cl_2 at 27 °C for 4 hours. The resin was then filtered, washed well with CH_2Cl_2 and the combined washings concentrated in vacuo to provide **8** (25 mg, 66% yield) as a white solid: Mass spectrum (EI) *m/z* 345.4 (M^+).

10. Ungemach, F.; Soerens, D.; Weber, R.; DiPierro, M.; Campos, P.; Mokry, P.; Cook, J. M.; Silverton, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 6976.

11. Subsequent to the completion of this study, our group devised an efficient method of processing multiple solution- and solid phase-derived samples which effectively removes all traces of polar impurities such as Et_3N•HCl. See: Johnson, C. R.; Zhang, B.; Fantauzzi, P. P.; Hocker, M.; Yager, K. M. "Solution Synthesis of Heterocyclic Libraries: Nucleophilic Aromatic Substitution and Automated Solid Supported Liquid-Liquid Extraction." Fifth International Symposium, Solid Phase Synthesis and Combinatorial Chemical Libraries, September 1997, London, U. K.

12. For a review, see: Andreu, D.; Albericio, F.; Sole, N. A.; Munson, M. C.; Ferrer, M.; Barany, G. *Methods Mol. Biol.* (*Totowa, N. J.*) **1994**, *35* (Peptide Synthesis Protocols), 91.