Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 4923–4926

TETRAHEDRON LETTERS

Liquid-phase parallel synthesis of tetrahydro-β-carbolines

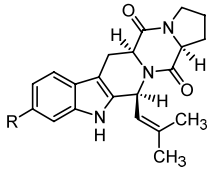
Wen-Ben Yeh, Mei-Jung Lin and Chung-Ming Sun*

Department of Chemistry, National Dong Hwa University, Hualien 974, Taiwan

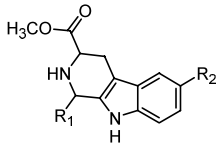
Received 2 January 2003; revised 8 April 2003; accepted 22 April 2003

Abstract—Parallel synthesis of β-carbolines on soluble polyethylene glycol (PEG-OH) support is demonstrated. One-pot condensation of polymer-bound tryptophan residues with various aldehydes and ketones has been carried out in the presence of *p*-TSA as a catalyst to deliver immobilized 1,2,3,4-tetrahydro-β-carbolines. Subsequent disengagement of the appendant from the polymer support afforded the desired products in good yield and acceptable purity.

Combinatorial chemistry employs a novel concept and technique to rapidly synthesize and screen large numbers of compound libraries. The synthetic procedures for generating such libraries are now well documented. Solid-phase organic synthesis has become a selective tool to generate structurally diverse compounds based on known pharmacophores.[1] Being a unique rigid heterocyclic system, β-carboline derivatives are well known for their wide range of pharmacological properties.[2] They have been shown to inhibit monoamine oxidase A and bind with nanomolar affinity to serotonin receptors.[3] Tetrahydro-β-carboline is a common basic nucleus found in a large number of tryptophan-derived natural product alkaloids such as yohimbine, alstophylline and reserpine. The indole alkaloids recently isolated from fungi are found to contain tetrahydro-β-carboline core and they have demonstrated as effective blockers of eukaryotic cell cycle progression. In particular, demethoxyfumitremorgin **1a** has been identified as the most effective among similar natural products isolated.[4] Certain tetrahydro-β-carboline-3-methylcarboxylates such as **2a** and **2b** were shown to exhibit potencies towards benzodiazepine receptor comparable with that of clinically active benzodiazepines[5] (Fig. 1).



1a: R = H; Demethoxyfumitremorgin
1b: R = OCH_3; Fumitremorgin



2a: R_1 = H; R_2 = OH
2b: R_1 = CH_2OH; R_2 = H

Figure 1. Pharmacologically active tetrahydro-β-carbolines.

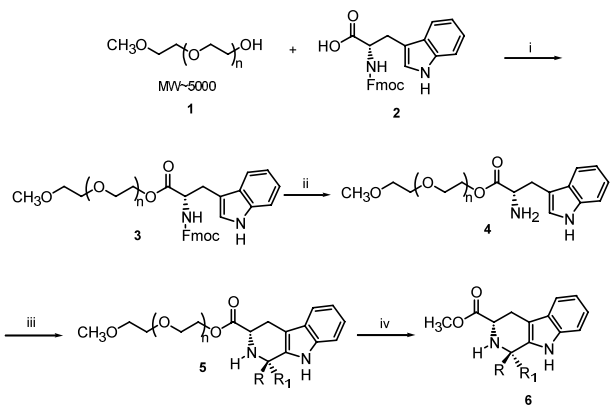
Knowledge of lead structures from screening libraries guides the design of more focused libraries and accelerates the lead optimization process. Tetrahydro-β-carbolines possess multiple sites for functionalization, permitting the generation of a large number of structurally diverse compounds. Our research efforts particularly draw on the development of liquid-phase combinatorial synthesis to construct heterocyclic molecules.[6,7] In our present investigation we wish to report the synthesis of 1,2,3,4-tetrahydro-β-carbolines by liquid-phase methodology using commercially available building blocks. Our synthetic strategy is mainly based on the chemistry of Pictet–Spengler reaction as illustrated in Scheme 1.

Polyethylene glycol (PEG-OH, MW ~5000) has been used as a soluble support to maintain homogeneous conditions at different steps of the reaction but purification of the product is as similar as solid-phase method, i.e. simple filtration and washings. To demonstrate the feasibility of the Pictet–Spengler reaction in liquid-phase methodology, we used a wide variety of aldehydes and ketones to fuse with the tryptophan nucleus and build up diverse 1,2,3,4-tetrahydro-β-carboline moieties.

The polymer support PEG-OH was esterified with Fmoc-L-tryptophan in the presence of DCC, and a catalytic amount of DMAP in dichloromethane at room temperature. Polymer-bound Fmoc-L-tryptophan **3** was then deprotected using 5% piperidine to knock off Fmoc in dichloromethane to furnish tryptophan **4** connected to the support.

* Corresponding author. Tel.: +(886)-3-8662500 ext. 21215; fax: +(886)-3-8663910; e-mail: cmsun@mail.ndhu.edu.tw

0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)01100-6

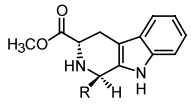


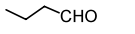
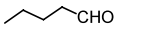
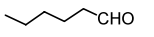
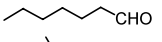
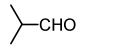
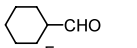
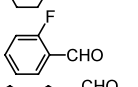
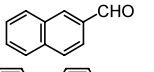
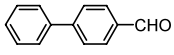
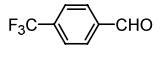
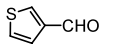
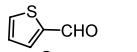
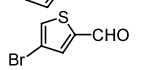
Scheme 1. Synthesis of 1,2,3,4-tetrahydro-β-carbolines. *Reagents and conditions*: (i) DCC (3.0 equiv.), DMAP (0.1 equiv.), CH_2Cl_2, rt, 48 h; (ii) 5% piperidine in CH_2Cl_2, rt, 8 h; (iii) aldehyde (3.0 equiv.), *p*-TSA (0.1 equiv.), CH_2Cl_2, rt, 8 h or ketone (3.0 equiv.), *p*-TSA (0.1 equiv.), $CHCl_3$, reflux, 8 h; (iv) 1% KCN/CH_3OH (10 mL), rt, 24 h.

Most of the literature reports on the synthesis of 1,2,3,4-tetrahydro-β-carbolines used strong acidic conditions, usually excess trifluoroacetic acid (TFA).[8] To avoid such harsh reaction conditions, we used a catalytic amount of *p*-toluenesulphonic acid (*p*-TSA) to enhance cyclization. To the best of our knowledge, there has not been any report on the liquid-phase synthesis of tetrahydro-β-carboline using *p*-TSA as a catalyst. Immobilized tryptophan **4** was treated with various aldehydes and catalytic amount of *p*-TSA in dichloromethane at room temperature to afford PEG-bound tetrahydro-β-carbolines **5** (Table 1).

In our reaction condition, the use of *p*-TSA catalyst during the cyclization was found to be advantageous in the improvement of yields and help to obtain cleaner products. Besides aldehydes, various ketones also underwent cyclocondensation smoothly with compound **4** in refluxing chloroform to afford PEG-supported tetrahydro-β-carbolines in excellent crude yield and acceptable purity (Table 2).

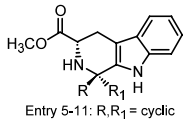
Table 1. *p*-TSA-catalysed synthesis of tetrahydro-β-carbolines

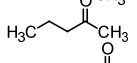
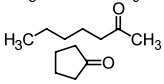
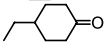
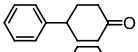
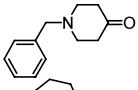
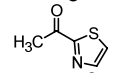
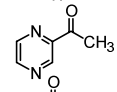
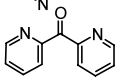


Entry	RCHO	Obs.mass	Crude yield[a](%)	Purity[b](%)
1	CH_3CHO	244	98	79(50:29)[c]
2		272	96	86(57:29)
3		286	85	86(49:37)
4		300	95	70(31:39)
5		314	98	63(29:34)
6		272	99	83(25:57)
7		312	80	64(31:33)
8		324	97	86(47:39)
9		356	91	62(32:30)
10		382	86	85(34:51)
11		374	98	83(35:48)
12		312	91	78(22:56)
13		312	99	73(21:52)
14		390/392	86	85(32:53)

a. Yields were determined based on the weight of crude sample.
b. Purity was determined by HPLC analysis of crude distereomeric products. All products showed satisfactory ^1H NMR and MS (EI) data.
c. diastereomeric ratio

Table 2. *p*-TSA-catalysed synthesis of tetrahydro-β-carbolines



Entry	$RCOR_1$	Obs.Mass	Crude yield[a](%)	Purity[b](%)
1		258	91	92
2		272	89	71(46:25)[c]
3		286	88	74(10:64)
4		314	99	88(32:56)
5		284	90	86
6		298	91	72
7		326	81	75
8		374	99	77
9		389	99	90
10		312	99	94
11		300	98	82(25:24:16:17)
12		311	97	76(29:47)
13		322	86	64(35:29)
14		384	51	50

a. Yields were determined based on weight crude sample.
b. Purity was determined by HPLC analysis of crude distereomeric products. All products showed satisfactory ^1H NMR and MS (EI) data.
c. diastereomeric ratio

At the last stage the target molecules **6** were isolated by the detachment of the polymer support using KCN/CH_3OH and the reaction was monitored by the conventional ^1H NMR.[7f] Cyclocondensation of aldehydes and ketones with PEG-bound tryptophan **4** results in the formation of *cis* and *trans* diastereomeric tetrahydro-β-carbolines **5** which were differentiated by their ^{13}C NMR data.[9] The ratio of *cis* and *trans* diastereomers was determined by HPLC and subsequently were separated by flash chromatograph on silica gel. The NMR spectra of the individual diastereomers clearly explained which proton signals differed significantly between two isomers. The carbon signals (entry 14, Table 1) for C-1 and C-3 assigned to *cis* isomer [C-1 (53.67 ppm), C-3 (56.78 ppm)] resonated at further down field from that of its *trans* counterpart in which C-1 and C-3 resonated at 52.29 and 52.51, respectively.[10] Comparsion of the NMR spectra before and after cleavage assured that the diastereochemical ratio has not been changed. Epimerization of the stereocenter at C-1 has not detected during the cleavage.

Liquid-phase combinatorial synthesis described herein has proved to be a powerful tool in generating β-carboline libraries. Furthermore, the 1,2,3,4-tetrahydro-β-carboline motif is more amenable to molecular modifications. Skolnick et al.[5] demonstrated that substitution at the 3-position resulted in increased potency of carboline moiety. Particularly compounds having methyl ester functionality at the 3-position such as **2a** and **2b** turned out to be more potent [^3H] diazepam binding agents than those analogs without the methyl ester functional group. In summary, we have demonstrated in this report a rapid parallel synthesis of biologically important β-carboline libraries **6** bearing a variety of functional groups. This methodology exemplifies the importance of liquid-phase combinatorial synthesis for lead optimization and offers easy access to compound collections containing this crucial heterocycle.

Acknowledgements

We thank the National Science Council (NSC) of Taiwan for its general financial support and Ms. Shu-Yun Sun, Instrumentation Center, National Taiwan University for assistance in mass spectral measurements.

References

1. (a) Thompson, L. A.; Ellman, J. A. *Chem. Rev*. **1996**, *96*, 555; (b) Dolle, R. E. *J. Comb. Chem*. **2000**, *2*, 383.
2. (a) Hermkens, P. H. H.; Plate, R.; Kruse, C. G.; Scheeren, H. W.; Ottenheijm, H. C. J. *J. Org. Chem*. **1992**, *57*, 3881; (b) Chi, D. Y.; O'Neil, J. P.; Anderson, C. J.; Welch, M. J.; Katzenellenbogen, J. A. *J. Med. Chem*. **1994**, *37*, 928; (c) Leteurtre, F.; Sackett, D. L.; Madalengoitia, J.; Kohlhagan, G.; Macdonald, T. L.; Hamel, E.; Paul, K. D.; Pommier, Y. *Biochem. Pharmacol*. **1995**, *19*, 128.
3. Ho, B. T. *J. Pharm. Sci*. **1972**, *61*, 821.
4. (a) Wang, H.; Ganesan, A. *Org. Lett*. **1999**, *1*, 1647; (b) Cui, C. B.; Kakeya, H.; Osada, A. *Tetrahedron* **1997**, *53*, 59; (c) Usui, T.; Kondoh, M.; Cui, C. B.; Mayumi, T.; Osada, H. *Biochem. J*. **1998**, *333*, 543–548; (d) Kondoh, M.; Usui, T.; Mayumi, T.; Osada, H. *J. Antibiot*. **1998**, *51*, 801; (e) Liu, X.; Deschamp, J. R.; Cook, J. M. *Org. Lett*. **2002**, *4*, 3339.
5. Cain, M.; Weber, R. W.; Guzman, F.; Cook, J. M.; Barker, S. A.; Rice, K. C.; Crawley, J. N.; Paul, S. M.; Skolnick, P. *J. Med. Chem*. **1982**, *25*, 1081.
6. (a) For a review, see: Sun, C. M. *Comb. Chem. High Throughput Screening* **1999**, *2*, 299; (b) For a book chapter, see: Sun, C. M. In *Combinatorial Chemistry Methods and Protocols*, *Methods in Molecular Biology Series*; Bellavance, L., Ed.; Soluble Polymer-Supported Synthesis of Heterocyclic Libraries. Humana Press: New Jersey, 2002; Chapter 10, pp. 345–371; (c) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F. *Chem. Eur. J*. **2000**, *6*, 133; (d) Reggelin, M.; Brenig, V.; Zur, C. *Org. Lett*. **2000**, *2*, 531.
7. (a) Pan, P. C.; Sun, C. M. *Tetrahedron Lett*. **1998**, *39*, 9505; (b) Shey, J. Y.; Sun, C. M. *Synlett* **1998**, *12*, 1423; (c) Shey, J. Y.; Sun, C. M. *J. Comb. Chem*. **1999**, *1*, 361; (d) Yeh, C. M.; Tung, C. L.; Sun, C. M. *J. Comb. Chem*. **2000**, *2*, 341; (e) Bendale, P. M.; Sun, C. M. *J. Comb. Chem*. **2002**, *4*, 359; (f) Shey, J. Y.; Sun, C. M. *Tetrahedron Lett*. **2002**, *43*, 1725; (g) Wu, C. Y.; Sun, C. M. *Synlett* **2002**, *10*, 1709; (h) Sun, C. M.; Swamy, K. M. K.; Lin, M. J.; Yeh, W. B.; Chen, F. Y.; Tseng, W. H. *Comb. Chem. High Throughput Screening* **2003**, *6*, 123.
8. For solid-phase Pictet–Spengler reaction, see: (a) Mayer, J. P.; Bankaitis-Davis, D.; Zhang, J.; Beaton, G.; Bjergarde, K.; Andersen, C. M.; Goodman, B. A.; Herrera, C. J. *Tetrahedron Lett*. **1996**, *37*, 5633; (b) Yang, L.; Guo, L. *Tetrahedron Lett*. **1996**, *37*, 5041; (c) Fantauzzi, P. P.; Yanger, K. M. *Tetrahedron Lett*. **1998**, *39*, 1291; (d) van Loevezijn, A.; van Maarseveen, J. H.; Stegman, K.; Visser, G. M.; Koomen, G.-J. *Tetrahedron Lett*. **1998**, *39*, 4737; (e) Li, X.; Zhang, L.; Zhang, W.; Hall, S. E.; Tam, J. P. *Org. Lett*. **2000**, *2*, 3075.
9. Ungemach, F.; Sorens, D.; Weber, R.; Dipierro, M.; Campos, O.; Mokry, P.; Cook, J. M.; Silverton, J. V. *J. Am. Chem. Soc*. **1980**, *102*, 6976.
10. *Typical procedure for the synthesis of tetrahydro-β-carboline*: The loading of PEG-OH **1** with Fmoc-L-tryptophan **2** to give **3** was carried out by the conventional DCC/DMAP coupling method. Piperidine (5%) in CH_2Cl_2 was used for the deprotection of Fmoc group from **3** to obtain PEG-L-tryptophan **4**. The PEG-bound L-tryptophan **4** (500 mg) was stirred magnetically with 4-bromothiophene-2-carboxaldehyde (1.5 equiv.) in CH_2Cl_2 (10 mL) at room temperature for 8 h. After completion of the reaction, a sufficient amount of diethyl ether (90 mL) was added to the reaction mixtures under vigorous stirring to precipitate out the immobilized 1,2,3,4-tetrahydro-β-carboline **5**. The precipitate was filtered and washed thoroughly with ether (3×20 mL). The cleavage of polymer-bound product was done in KCN/CH_3OH at room temperature with stirring overnight. The polymer support was separated by precipitation by the addition of diethyl ether. The filtrate on evaporation yielded the desired crude compound. The *cis*/*trans* isomers were then

separated by column chromatograph (gradient elution:50% ethyl acetate/hexane).

cis-3-Methoxycarbonyl-1-(4-bromothiophen-2-yl)-1,2,3,4-tetrahydro-β-carboline (Table 1, entry 14): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (s, NH), 7.53 (d, $J=7.8$ Hz, 1H), 7.28 (d, $J=7.8$ Hz, 1H), 7.26 (s, 1H), 7.22–7.13 (m, 2H), 7.11 (s, 1H), 5.57 (s, 1H), 3.95 (dd, 1H, $J=11.1$, 4.2 Hz), 3.83 (s, 3H), 3.22 (dd, 1H, $J=15.3$, 4.2 Hz), 3.01 (dd, 1H, $J=15.3$, 11.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 145.8, 136.2, 132.9, 128.6, 127.0, 123.6, 122.4, 119.9, 118.5, 111.1, 109.2, 108.7, 56.7, 53.6, 52.4, 25.2; mass specrum (EI) m/z 390 (M+). HRMS calcd for $C_{17}H_{15}BrN_2O_2S$: m/z 390.0037. Found 390.0022.

trans-3-Methoxycarbonyl-1-(4-bromothiophen-2-yl)-1,2,3,4-tetrahydro-β-carboline (Table 1, entry 14): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, NH), 7.54 (d, $J=7.5$ Hz, 1H), 7.29 (d, $J=7.5$ Hz, 1H), 7.26 (s, 1H), 7.22–7.11(m, 2H), 6.88 (s, 1H), 5.61 (s, 1H), 4.02 (dd, $J=7.5$, 5.1 Hz, 1H), 3.75 (s, 3H), 3.23 (dd, $J=15.6$, 5.1 Hz, 1H), 3.05 (dd, $J=15.6$, 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 147.7, 136.1, 131.9, 128.3, 126.8, 123.2, 122.4, 119.7, 118.5, 111.1, 109.2, 108.3, 52.5, 52.2, 50.3, 24.6; mass specrum (EI) m/z 390 (M+). HRMS calcd for $C_{17}H_{15}BrN_2O_2S$: m/z 390.0037. Found 390.0022.