JOURNAL OF combinatorial CHEMISTRY

Volume 8, Number 2 March/April 2006

Reports

Traceless and Stereoselective Synthesis of Tetrahydro-β-carbolinethiohydantoins by Microwave Irradiation

Wong-Jin Chang, Manohar V. Kulkarni, and Chung-Ming Sun*

Laboratory of Combinatorial Drug Discovery, Department of Applied Chemistry, National Chiao Tung University, Hsinchu 300-10, Taiwan

Received August 2, 2005

Combinatorial chemistry provides a powerful tool for an incessant demand of novel chemical entities from medicinal chemistry and has greatly influenced the whole gamut of drug discovery process. In recent years it has been experiencing a paradigm shift with special emphasis laid on liquid-phase methodologies.[1,2] Though the idea of a macromolecule acting as a support for organic reactions was born with the synthesis of peptides,[3] it has now grown into an independent methodology for creating a variety of nonpeptidic, drug-like molecular libraries,[4,5] signaling new vistas in classical and combinatorial synthesis.[6] In an *inimitable* way the soluble polymer supported organic synthesis retains the advantage of the homogeneity of the classical organic reaction whose progress can be monitored by conventional analytical techniques.[7] In addition to this, the easy product isolation by precipitation, high yields, and compatibility with microwave (MW) irradiation[8,9] have made this method highly suitable for a multistep organic synthesis involving a variety of functional group interconversions. Polymer supported reactions in which the macromolecular carrier does not *leave* behind any structural imprint on the target molecules are referred to as traceless syntheses, which are a new trend in both solid-phase[10] and liquid-phase[11] methodologies.

* Corresponding author: cmsun@mail.nctu.edu.tw.

Heterocycles are versatile molecular scaffolds, on to which meaningful structural diversity can be introduced to vary the stereochemical and physicochemical properties of the resulting compounds, thus tailoring them for better membrane transport and receptor binding in biological systems. Tetrahydro-β-carbolines are one such class of semirigidized tricyclic heterocycles,[12] which are found to occur as mammalian[13] and plant alkaloids, like jafraine,[14] exhibiting a wide range of biological activities.[15−17] The tetrahydro-β-carbolines such as demethoxyfumitremorgins have been isolated from the fungal species, some of which have been found to exhibit antiviral,[18] topoisomerase II inhibiting,[19] and protein kinase and cell cycle inhibiting[20] activities (Figure 1). Because of their potential biological properties, these tetra- and polycyclic β-carbolines have been synthesized by classical[21,22] as well as solid-phase[23−26] methods.

The design concept of the presently synthesized molecular library has originated from the recognition of the biological role of the thiohydantoin moiety. A large number of thiohydantoins have been associated with calcium mobilization,[27] inhibition of glycogen phosphorylases,[28] aldose reductase inhibition,[29] anti-HIV,[30] and anti-leukemic[31] activities. Thus the generation of a combined tetracyclic skeleton ressembling drug-like molecules has a substantial intellectual appeal. The present paper demonstrates successful application of liquid-phase methodologies toward the parallel stereoselective synthesis of thiohydantoin fused tetrahydro-β-carbolines powered by the microwave irradiation. Application of microwave irradiation for organic reactions has emerged as a practical technique to reduce reaction times and enhance the yields, thus speeding up the drug discovery process.[32,33] It has been applied by our group, leading to the generation of the molecular libraries of thioxotetrahydro pyrimidinones[34] and hydantoins.[35]

The enhanced loading capacity of the dihydric poly(ethylene glycol), PEG-4000(**1**), has been used in the stepwise synthesis toward the target molecular libraries (Scheme 1). The synthesis was initiated by the generation

10.1021/cc050098j CCC: $33.50
Published on Web 02/25/2006

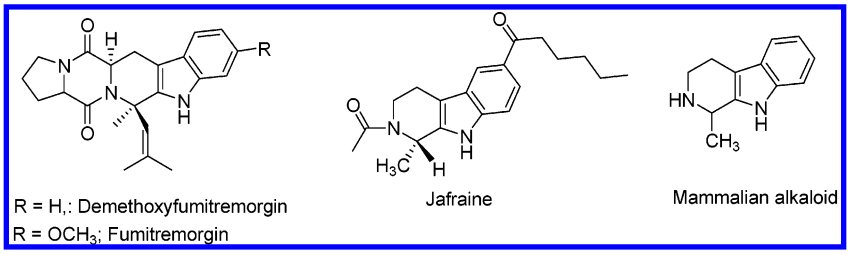
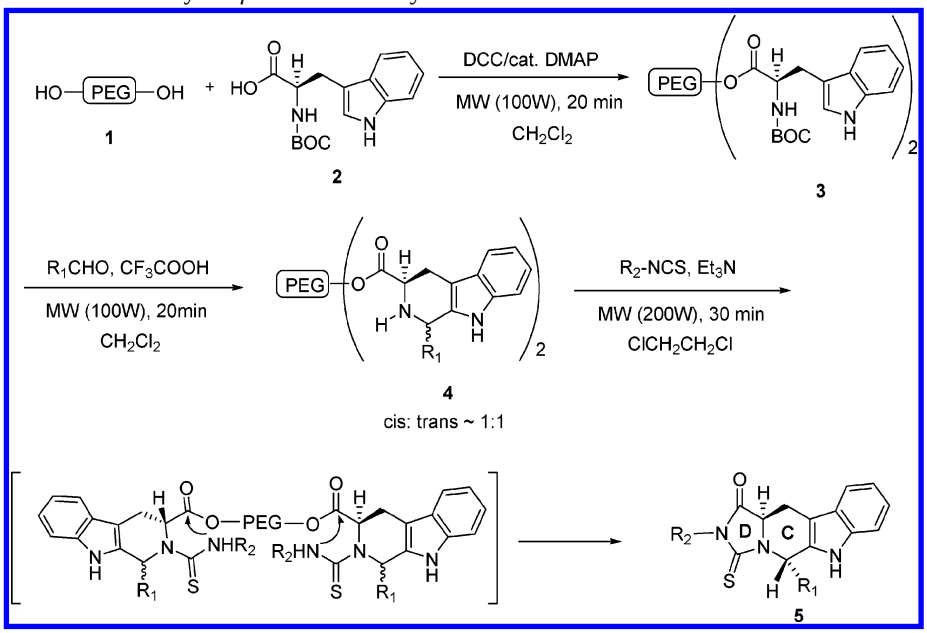


Figure 1. Naturally occurring tetrahydro-β-carbolines.

Scheme 1. Synthetic Route to Tetracyclic-β-carbolinethiohydantoins **5**



of the PEG immobilized bis-ester **3** from the commerciably available Boc protected L-tryptophan **2**. This esterification reaction was brought about via the dicyclohexyl carbodiimide (DCC) activated ester in the presence of catalytic quantities of (dimethylamino)pyridine (DMAP), in a microwave oven under open vessel conditions. The power and time variation studies in this step have lead to an optimized experimental condition of 100 W power and 20 min as the reaction time to obtain maximum yields. The reaction time under refluxing conditions at the same temperature was 48 h to reach completion and has been brought down to 20 min, which shows the remarkable power of microwave irradiation.

Construction of the β-carboline skeleton was perceived in terms of a [5+1] approach for the six-membered heterocycles, which needed the generation of a nucleophilic amino group. The preferential cleavage of the amide bond (N−CO) over the acyl−oxygen bond (O−CO) in the polymer ester conjugate **3** was achieved in microwave cavity with 30% TFA in dichloromethane. The initial study to remove the Boc group was ensured by the disappearance of the crude NMR signal of *tert*-butyl group at 1.4 ppm. The in situ generated amine was treated with an appropriate aldehyde to obtain an imine which underwent an acid-catalyzed intramolecular cyclization.[36,37] Identical results were observed with the simultaneous addition of TFA and the aldehydes, which resulted in the sequential deprotection−nucleophilic addition and cyclization. The introduction of the first point of structural diversity was thus accomplished in one pot.

The transient imine was found to undergo an intramolecular electrophilic ring closure at the C-2 position of the indole nucleus, forming a tricyclic polymer intermediate **4**. This cyclization step which required 24 h under refluxing conditions in chloroform also proceeded remarkably well in 20 min under microwave conditions. Cyclocondensation of aldehydes with PEG bound tryptophan **3** resulted in the formation of *cis* and *trans* diastereomers around 1:1 ratio. Building up of the terminal thiohydantoin ring across the N-2/C-3 bond of the tetrahydro-β-carboline skeleton was achieved by the reaction of β-carboline derivatives **4** with various isothiocyanates. This nucleophilic addition was achieved without the use of any metal salt or activating agent. The application of MW (200 W) conditions in this step also resulted in fast completion of intramolecular cyclative cleavage in 30 min in ethylene dichloride. The reactive thioureas would induce an acyl−oxygen bond cleavage of the ester by a S_Ni reaction via N−CO bond concomitant formation leading to a traceless and stereoselective synthesis of substituted indole alkaloids **5**.

The stereochemical outcome in the Pictet−Spengler reaction has been of immense interest, since the diastereomeric proportion depends on the acidity of the medium, steric bulk of the ester function, and the substituent on the nitrogen of the tryptophan moiety.[38] We have observed that the ester polymer conjugates also lead to the formation of a mixture of *cis* and *trans* diastereomer which varies with the nature of the carbonyl group in *p*-toluenesulfonic acid (*p*-TSA)

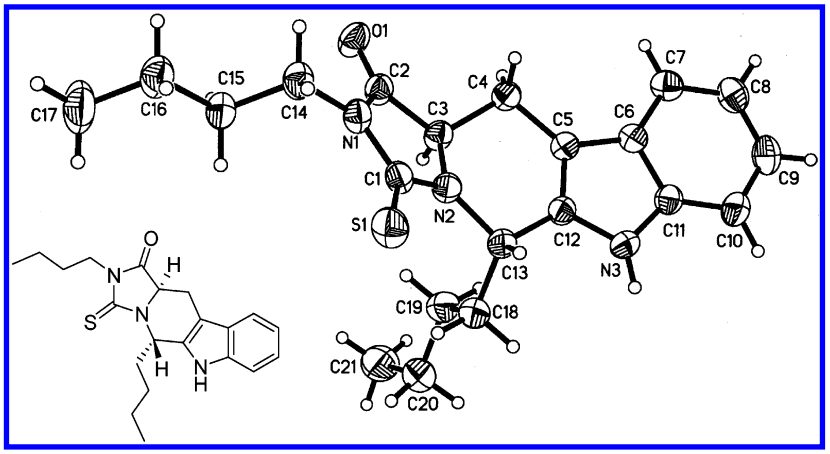
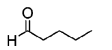
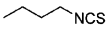
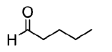
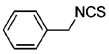
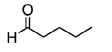
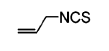
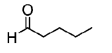
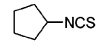
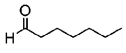
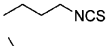
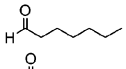
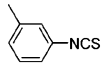
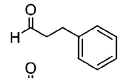
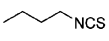
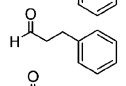
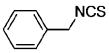
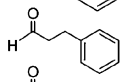
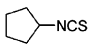
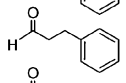
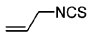
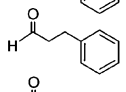
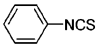
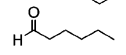
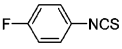
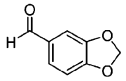
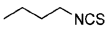
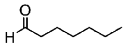
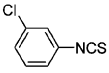
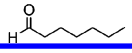
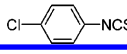


Figure 2. ORTEP diagram of **5a** (R = R_1 = CH_3−$(CH_2)_3$−) with crystallographic numbering system.

Table 1. Synthesis of Tetracyclic Tetrahydro-β-carbolines

Entry	R_1CHO	R_2NCS	crude yield[a] (%)	crude purity[b] (%)	LR-mass
5a			91	84	370(M+1)
5b			98	97	404(M+1)
5c			93	92	353
5d			85	90	381
5e			85	84	397(M+1)
5f			94	73	431
5g			91	92	418(M+1)
5h			98	95	452(M+1)
5i			96	98	429
5j			90	97	402
5k			92	83	437
5l			96	80	407
5m			84	87	433
5n			91	93	451
5o			85	90	451

[a] Yields were based on the weight of the isolated crude samples. [b] Purity was estimated by HPLC without considering the peak of excess R−NCS.

catalyzed Pictet−Spengler reaction at room temperature.[39] The MW conditions employed during the present work favor the thermodynamically stable *trans* congeners than the *cis* isomers.[40−42] Further, in the formation of the thiohydantoin ring D, the orientation of the nitrogen lone pair also requires the bulkier group to be in *trans* orientation to keep the electronic repulsions to the minimum. The unprecedented 100% *trans* diastereomeric selectivity under the MW conditions has been confirmed by ^{13}C NMR and homo- and hetero-COSY experiments. HPLC analysis of crude products also indicated only one diastereomer was obtained (Table 1).

Additional support for the configuration of the structure as *trans* diastereomer was obtained from the X-ray diffraction studies which indicated *R,S* configuration at the two chiral centers depicted in the ORTEP diagram (Figure 2). From the ORTEP diagram for **5a**, it is also clear that the rings C and D are *trans* fused and are nonplanar. The hydrogens on C-3 and C-13 are anti-periplanar, and the substituent at C-13 is α-oriented.

In summary, we have demonstrated a microwave-assisted traceless, liquid-phase methodology[43] to assemble substituted indole alkaloids with exceedingly high stereoselectivity. All the steps in this synthetic sequence have been accomplished under focused microwave irradiation, resulting in significantly reduced reaction times—from hours to minutes—and enhanced yields. It should be noted that polymer supported intermediates and polymer itself are stable during the harsh MW irradiation. The presently reported rapid synthesis of tetracyclic tetrahydro-β-carboline pharmacophores with two points of diversity has the potential for the creation of a diverse array of polycyclic fused heterocyclic systems, which closely resemble biologically active natural products.

Acknowledgment. The authors thank the National Science Council of Taiwan for the financial assistance and the authorities of the National Chiao Tung University for providing the laboratory facilities.

Supporting Information Available. Representative experimental procedures, spectral data of compounds **5a**−**5o**, and the bond angle and bond length data for **5a**. Comparison of microwave and thermal conditions for the above reactions are also included. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489−509.

(2) (a) Sun, C. M. *Comb. Chem. High Throughput Screening* **1999**, *2*, 299−309. (b) Sun, C. M. Soluble Polymer-Supported Synthesis of Heterocyclic Libraries. In *Combinatorial Chemistry Methods and Protocols*; Bellavance, L., Ed.; Methods in Molecular Biology Series; The Humana Press Inc.: New Jersey, 2002; Chapter 10, 345−371.

(3) Bayer, E.; Mutter, M. *Nature* **1972**, *237*, 512−513.
(4) Wentworth, P. *Trends Biotechnol.* **1999**, *17*, 448−452.
(5) Lee, M. J.; Sun, C. M. *Chin. Pharm. J.* **2003**, *55*, 405−452.
(6) Harwig, C. W.; Gravert, D. J.; Janda, K. D. *Chemtracts* **1999**, *12*, 1−27.
(7) Yeh, C. M.; Tung, C. L.; Sun C. M. *J. Comb. Chem.* **2000**, *2*, 341−348.
(8) Su, Y. S.; Lin, M. J.; Sun, C. M. *Tetrahedron Lett.* **2005**, *46*, 177−180.
(9) Lin, M. J.; Sun, C. M. *Synlett* **2004**, 663−666.
(10) Blaney, P.; Grigg, R.; Sridharan, V. *Chem. Rev.* **2002**, *102*, 2607−2624.
(11) Zong, Y. X.; Wang, J. K.; Yue, G. R.; Feng, L.; Song, Z. E.; Song, H.; Han, Y. Q. *Tetrahedron Lett.* **2005**, *46*, 5139−5141.
(12) Gremmen, C.; Brigitte, A.; Burn, M. J.; Koomen, G. J. *Tetrahedron Lett.* **1998**, *39*, 1441−1445.
(13) Schouten, M. J.; Bruinvels, J. *Anal. Biochem.* **1985**, *147*, 401−409.
(14) Fazai, S.; Naz, A. *Tetrahedron Lett.* **2002**, *58*, 6185−6197.
(15) Maw, G. N.; Allerton, C. M. N.; Gbekor, E.; Million, W. A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1425−1428.
(16) Abdel-Moty, S. G.; Sakai, S.; Aini, N.; Takayama, H.; Kitajima, M.; El-Shorbagi, A.; Ahmed, A. N.; Omar, M. N. *Eur. J. Med. Chem.* **1998**, *32*, 1009−1017.
(17) Allen, M. S.; Tan, Y. C.; Trudel, M. L.; Narayan, K.; Schindler, L. R.; Martin, M. J.; Schultz, C.; Hagen, T. R.; Koehler, K. F. *J. Med. Chem.* **1990**, *33*, 2343−2357.
(18) van Maarseveen, J. H.; Scheeren, H. W.; De Clercq, E.; Balzarini, J.; Kruse, C. G. *Biorg. Med. Chem.* **1997**, *5*, 955−970.
(19) Deveau, A. M.; Labroli, M. C.; Dieckhans, C. M.; Barthen, M. T.; Smith, K. S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1251−1255.
(20) Osada, H.; Cui, C. B.; Onose, R.; Hanaka, F. *Bioorg. Med. Chem.* **1997**, *5*, 193−203.
(21) O'Malley, G. J.; Cava, M. P. *Tetrahedron Lett.* **1987**, *28*, 1131−1134.
(22) (a) Wang, H.; Ganesan, A. *Tetrahedron Lett.* **1997**, *38*, 4327−4328. (b) Wang, H.; Usui, T.; Osada, H. Ganesan, A. *J. Med. Chem.* **2000**, *43*, 1577−1585. (c) Revell, J. D.; Srinivasan, N.; Ganesan, A. *Synlett* **2004**, *8*, 1428−1430.
(23) van Loevezijn, A.; van Maarseveen, J. H.; Stegman, K.; Visser, G. M.; Koomen, G. J. *Tetrahedron Lett.* **1998**, *39*, 4737−4740.
(24) Fanatauzzi, P. P.; Yager, K. M. *Tetrahedron Lett.* **1998**, *39*, 1291−1294.
(25) Wang, H.; Ganesan, A. *Org. Lett.* **1999**, *1*, 1647−1649.
(26) (a) Klein, G. J.; Ostresh, J. M.; Nefzi, A. *Tetrahedron Lett.* **2003**, *44*, 2211−2215. (b) Yen, Y. H.; Chu, Y. H. *Tetrahedron Lett.* **2004**, *45*, 8137−8140.
(27) Incesu, Z.; Benkli, K.; Akaalin, G. Kaplancikli, Z. A. *Cell Biol. Int.* **2004**, *28*, 267−272.
(28) Oikonomakos, N. G.; Skamnaki, V. T.; Osz, E.; Szilagyi, L.; Somsak. L.; Docsa, T.; Toth, B.; Gergly, P. *Bioorg. Med. Chem.* **2002**, *10*, 261−268.
(29) Buyukbingol, E.; Suzen, S.; Klopman, G. *Farmaco* **1994**, *49*, 443−447.
(30) Suzen, S.; Buyukbingol, E. *Farmaco* **1998**, *53*, 525−527.
(31) Suzen, S.; Buyukbingol, E. *Farmaco* **2000**, *55*, 246−248.
(32) (a) Santagada, V.; Perissuti, E.; Caliendo, G. *Curr. Med. Chem.* **2002**, *9*, 1251−1283. (b) Al-Obeidi, F.; Austin. R. E.; Okonya, J. F.; Bond, D. R. S. *Mini-Rev. Med. Chem.* **2003**, *3*, 459−470. (c) Blackwell, H. E. *Org. Biomol. Chem.* **2003**, *1*, 1251−1255. (d) Swamy, K. M. K.; Yeh, W. B.; Lin, M. J.; Sun, C. M. *Curr. Med. Chem.* **2003**, *10*, 2403−2424. (e) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250−6284.
(33) Yoon, D. S.; Han, Y.; Stark. T. M.; Haber, J. C.; Gregg, B. T.; Stankovich, S. B. *Org. Lett.* **2004**, *6*, 4775−4778.
(34) Yeh, W. B.; Lin, M. J.; Lee, M. J.; Sun, C. M. *Mol. Diversity* **2003**, *7*, 185−198.
(35) (a) Lin, M. J.; Sun, C. M. *Tetrahedron Lett.* **2003**, *44*, 8739−8742. (b) Lee, M. J.; Sun, C. M. *Tetrahedron Lett.* **2004**, *45*, 437−440.
(36) Mayer, J. P.; Davis, D. B.; Zhang, J.; Beaton, G.; Bjergarde. K.; Anderson, C. M.; Goodman, B. A.; Herrera, C. J. *Tetrahedron Lett.* **1996**, *37*, 5633−5636.
(37) Connors, R. V.; Zhang, A. J.; Shuttleworth, S. J. *Tetrahedron Lett.* **2002**, *43*, 6661−6663.
(38) Cox, E. D.; Hamaker, L. K.; Li, J.; Peng, Yu.; Czerwinski, K. M.; Deng, Li.; Bennet, D. W.; Cook, J. M. *J. Org. Chem.* **1997**, *62*, 44−61.
(39) (a) Yeh, W. B.; Lin, M. J.; Sun, C. M. *Tetrahedron Lett.* **2003**, *44*, 4923−4926. (b) Campiglia, P.; Gomez-Monterrey, I.; Lama, T.; Novellino, E.; Grieco, P. *Mol. Diversity* **2004**, *8*, 427−430.
(40) Kowalski, P.; Bojarski, A. J.; Mokrosz, J. L. *Tetrahedron* **1995**, *51*, 2737−2742.
(41) Gremmen, C.; Willemse, B.; Wanner, M. J.; Koomen, G. J. *Org. Lett.* **2000**, *2*, 1955−1958.
(42) Lopez-Rodriguez, M. L.; Morcillo, M. J.; Garrido, M.; Benhamu, B.; Perez, V.; de la Campa, J. G. *J. Org. Chem.* **1994**, *59*, 1583−1585.
(43) All the microwave assisted polymer supported reactions described here were performed in a 50 mL round-bottom flask (attached to the reflux condenser) with the CEM Discover Microwave System at a frequency of 2450 Hz (0−300 W). The spectral data for **5a** is as follows: $[\alpha]_D^{20} = -46.41°$ ($c = 1.03$; CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (s, 1H, N_3−H), 7.46 (d, 1H, $J = 7.8$ Hz, C_8−H), 7.35 (d, 1H, $J = 7.8$ Hz, C_9−H), 7.24∼7.12 (m, 2H), 5.87 (t, 1H, $J = 6.9$ Hz, C_{13}−H), 4.38 (dd, 1H, $J = 5.7$, 10.8 Hz, C_3−H), 3.90 (t, 2H, $J = 7.8$ Hz), 3.38 (dd, 1H, $J = 6.0$, 15.0 Hz, C_4−H), 2.70 (dd, 1H, $J = 11.1$, 15.3 Hz, C_4−H), 2.19 (m, 1H, C_{18}−H), 1.90 (m, 1H, C_{18}−H), 1.76∼1.67 (m, 4H), 1.47∼1.31 (m, 4H), 0.99 (t, 3H, $J = 7.2$ Hz, CH_3), 0.87 (t, 3H, $J = 4.8$ Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.3(C_1), 173.6(C_2), 136.4(C_{12}), 132.4(C_{11}), 126.1(C_6), 122.7(C_8), 120.2(C_9), 118.2(C_7), 111.1(C_8), 105.9(C_5), 56.8(C_3), 52.6(C_{13}), 41.4(C_{14}), 34.7(C_{18}), 29.9(C_{19}), 27.6(C_{15}), 23.7(C_4), 22.9(C_{20}), 20.1(C_{16}), 14.0(C_{21}), 13.8(C_{17}); LRMS (FAB) found 370; HRMS(EI) calcd 369.1875, found 369.5316; IR (KBr, cm^{-1}) 3390, 2950, 1730, 1645, 1462.

CC050098J