Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 6549–6553
Tetrahedron Letters

A novel TFA-mediated *cyclo*-dimerization of 1-substituted 3-alkenylindole derivatives to cyclopent[*b*]indoles

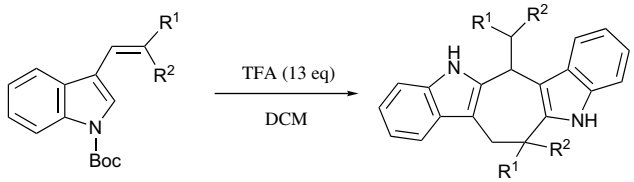
Ikuo Kawasaki, Masami Terano, Ai Kurume, Satoko Hara, Masayuki Yamashita and Shunsaku Ohta*

Department of Functional Molecular Chemistry, 21st Century COE program, Kyoto Pharmaceutical University, Misasagi Yamashinaku, Kyoto 607-8414, Japan

Received 23 May 2005; revised 4 July 2005; accepted 15 July 2005
Available online 9 August 2005

Abstract—Reaction of 1-substituted 3-alkenyl-1*H*-indoles with an equimolar amount of trifluoroacetic acid in dichloromethane gave cyclic dimers, 1,3-*trans*-*N*,*N*′-disubstituted cyclopent[*b*]indoles, in 53–84% yields as sole products through an acid-mediated stereoselective *cyclo*-dimerization process. The structure of the cyclic dimer derived from 3-cyclopentylidenemethyl-1-methyl-1*H*-indole was elucidated by X-ray crystallographic analysis.

A number of bisindole alkaloids have been isolated from various origins and they have become an important focus of scientific attention because of their biological activities and their unique structure.[1,2] Of remarkable importance is the fact that bisindole alkaloids often exhibit more potent biological activity than the monomeric units.[3] For these reasons, over the past several years, efforts have been devoted towards the development of new synthetic methods for this type of natural products.[4] Among them, we reported a new type of trifluoroacetic acid (TFA)-mediated *cyclo*-dimerization of 1-*tert*-butoxycarbonyl-3-alkenyl-1*H*-indoles **1** into cyclohepta[1,2-*b*:4,5-*b*′]diindoles **2** as shown in Scheme 1,[5] which was found in our continuous synthetic research of imidazole–indole alkaloids.[6] In this time, our interest was focused on the investigation of the reactivity of 3-alkenylindoles having an alkyl group instead of Boc group at the 1-position of the indole ring with acids. Thus, we planned preparation of a series of 1-alkylated 3-alkenylindoles **4** and examined their *cyclo*-dimerization reaction. From these experiments, we found that the reactivity of **4** with an equimolecular amount of TFA was drastically different from that of **1** with a large excess of TFA, the reaction of **4** gave five-membered cyclic dimmers, *N*,*N*′-disubstituted cyclopent[*b*]indoles, in good yields. Herein, we would like to present the novel TFA-mediated *cyclo*-dimerization of 3-alkenyl-1-alkyl-1*H*-indole derivatives to give *N*,*N*′-disubstituted cyclopent[*b*]indoles.



1: R^1, R^2 = alkyl, Ph, H

2 (49 - 77 %)

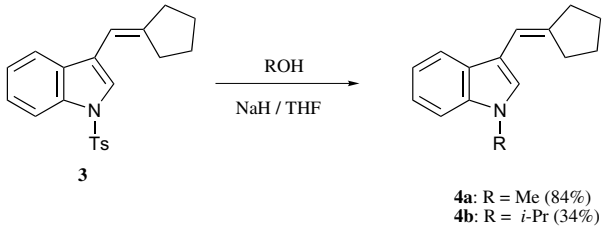
Scheme 1.

Various 3-alkenyl-1-alkyl-1*H*-indoles **4a**–**g** were prepared by either 'transfer of activation' method for 1-(*p*-toluenesulfonyl)-3-cyclopentylidenemethyl-1*H*-indoles **3** (Scheme 2)[7] or by Wittig reaction of 1-alkyl-3-formyl-1*H*-indoles **5a**–**d** (Scheme 3).[8]

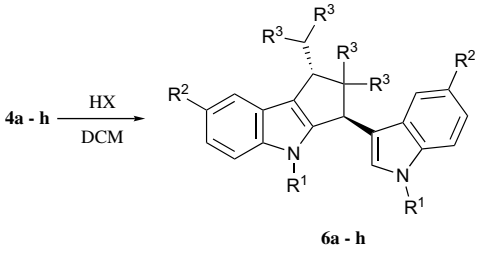
The reaction of the 3-cyclopentylidenemethyl derivative **4a** with acids (HX) under various conditions was examined (Scheme 4), and the results are summarized in Table 1. We found that the treatment of **4a** with several acids afforded 1′,3′-*trans*-1′-cyclopentyl-1′2′3′4′-tetrahydro-4′-methyl-3′-(1-methyl-1*H*-indol-3yl)spiro[cyclopentane-1,2′-cyclopent[*b*]indole] **6a** stereoselectively, and the structure of **6a** was determined by the observation of

* Corresponding author. Tel.: +81 75 595 4703; fax: +81 75 595 4795; e-mail: sohta@mb.kyoto-phu.ac.jp

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.07.089



Scheme 2.



Scheme 4.

the NOE correlation by NOESY experiments and X-ray crystallographic analysis as shown in Figure 1.[9] It is notable that the treatment of 1-*tert*-butoxycarbonyl-3-alkenylindoles **1** with large excess of TFA gave seven-membered *cyclo*-dimers **2**,[5] however, the reaction of **4a** with 13 equiv of TFA provided only a complex mixture (entry 1). We found that the *cyclo*-dimerization reaction of **4a** was smoothly proceeded by use of only 1 equiv of TFA under stirring for 3 h at 0 °C to give the five-membered *cyclo*-dimer, cyclopent[*b*]indole **6a**, in the best yield (79%) (entry 4).[10,11] From the experiments with various acids (entries 4–9), it is considered that the strength of the acid may be important in this stereoselective *cyclo*-dimerization reaction.

The cyclopent[*b*]indole system is found in the basic skeleton of a bisindole alkaloid yeuhchukene **7** (Fig. 2), isolated from the root of *Murraya paniculata*[12] as an anti-implantation agent[13] and is reported to have unique biological properties.[14] Furthermore, the *N*,*N*′-disubstituted cyclopent[*b*]indole structure can be also found in several interesting biologically active agents.[15] Although several examples of dimerization reaction of 3-alkenylindoles[16] into cyclopent[*b*]indoles are known in the literature,[17] most reactions were only applied to synthesis of *N*-unsubstituted indole derivatives and were not examined in a systematic fashion.[18]

Next, the reaction of the prepared 1-alkyl-3-alkenylindoles **4b**–**g** in the presence of 1 equiv of TFA at 0 °C was examined (Scheme 4), and the results are summarized in Table 2. *trans*-1-Alkyl-3-(1-alkylindol-3-yl)cyclopent[*b*]indoles **6b**–**g** were obtained stereoselectively in good to moderate yields (84–57%; entries 1–6) under the same reaction conditions as that of entry 4 in Table 1. When an electron-withdrawing group such as a bromo group attached at the 5-position of the indole ring in 3-cyclopentylidenemethyl-1-methylindole, the cyclic dimer

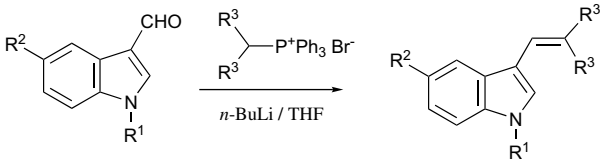
Table 1. *cyclo*-Dimerization of **4a** under various reaction conditions

Entry	HX (equiv)	Temperature (°C)	Time (h)	Yield of **6a**[a] (%)
1	TFA (13)	RT	24	CM[b]
2	TFA (4.3)	−78	3	54
3	TFA (1.0)	RT	3	57
4	TFA (1.0)	0	3	79
5	HCO_2H (1.0)	RT	3	NR[c]
6	TsOH (1.0)[d]	0	3	24
7	HCl (1.0)[e]	0	3	52
8	TfOH (1.0)	0	3	49
9	Amberlyst 15 (1.0)[f]	0	3	41

[a] Isolated yield.
[b] A complex mixture was obtained.
[c] No reaction, recovery of **4a**.
[d] Monohydrate was used.
[e] 38% aqueous HCl was used.
[f] Ion-exchange resin with $ArSO_3H$ moiety.

6d was obtained in higher yield than the case of an electron-donating methoxy group at the 5-position (entries 3 and 4). The present reaction system could be also applied to the *N*-unsubstituted 3-alkenylindole **4h**[5] to afford the corresponding five-membered cyclic dimer, cyclopent[*b*]indole **6h**, in 66% yield (entry 7).

Then, the reaction of **4c** with 1 equiv of CF_3CO_2D instead of TFA was performed, and it was found that deuterium was incorporated into the 1′-position (20%) in the product ***d*-6c** (Scheme 5). From the fact, we propose a possible reaction mechanism as shown in Scheme 5. Protonation at the 2′-position of 3-alkenylindole **4** might be the first step of this reaction to give the active iminium intermediate **8**; the dimerized intermediate **9** is then given by the nucleophilic attack onto the 1′-position in the intermediate **8** at the 2′-position



5a: R^1 = Me, R^2 = H
5b: R^1 = Me, R^2 = Br
5c: R^1 = Me, R^2 = OMe
5d: R^1 = *i*-Pr, R^2 = H

4c: R^1 = Me, R^2 = H, R^3 = Me (80%)
4d: R^1 = Me, R^2 = Br, R^3 = -$(CH_2)_4$- (89%)
4e: R^1 = Me, R^2 = OMe, R^3 = -$(CH_2)_4$- (82%)
4f: R^1 = Me, R^2 = H, R^3 = -$(CH_2)_5$- (15%)
4g: R^1 = *i*-Pr, R^2 = H, R^3 = Me (100%)

Scheme 3.

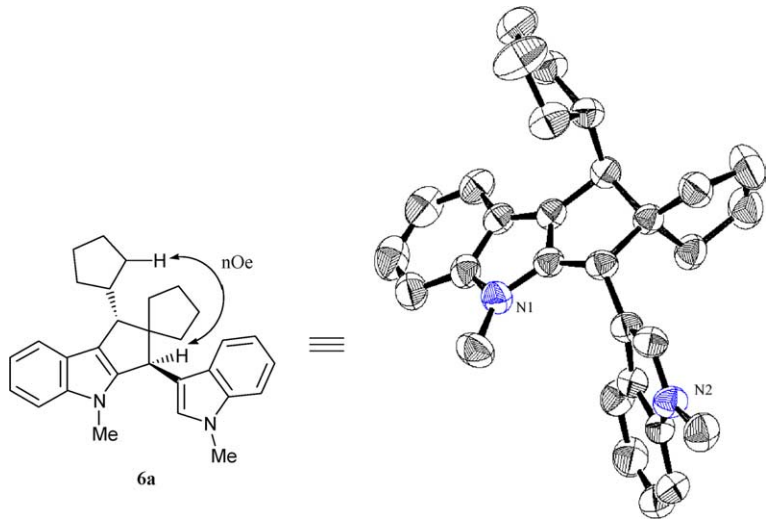


Figure 1. Selected NOE and ORTEP drawing for **6a**.

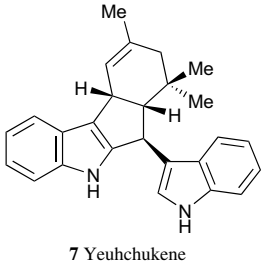


Figure 2.

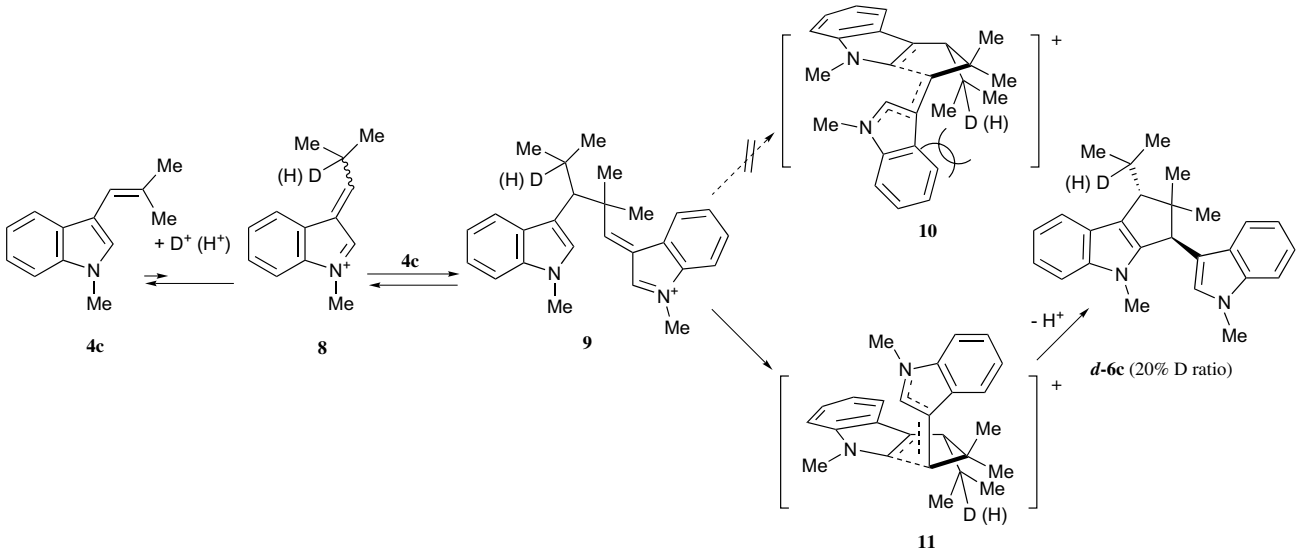
of the substrate **4c**.[19] The 1,3-*trans*-oriented cyclopent[*b*]indole **6c** is furnished by the '5-*endo*'-type ring closure of **9** through the transition state **11** rather than **10** because of steric hindrance, followed by aromatization. In the presence of a more strong acid or 13 equiv of TFA, the concentration of **8** may be increased; however, that of **4c** may be decreased to retard the dimerization step of **8** to **9**. Therefore, the acidity and the amount of the acid may be important factors in this reaction.

Table 2. *cyclo*-Dimerization of **4b–h** to **6b–h**[a]

Entry	Substrate	R^1	R^2	R^3	Product	Yield[b] (%)
1	**4b**	Me	H	$-(CH_2)_5-$	**6b**	80
2	**4c**	Me	H	Me	**6c**	70
3	**4d**	Me	Br	$-(CH_2)_4-$	**6d**	84
4	**4e**	Me	OMe	$-(CH_2)_4-$	**6e**	57
5	**4f**	2-Pr	H	$-(CH_2)_4-$	**6f**	72
6	**4g**	2-Pr	H	Me	**6g**	83
7	**4h**	H	H	$-(CH_2)_4-$	**6h**	66

[a] All reactions run with 0.3 mmol of **4** and 0.3 mmol of TFA in DCM (3.0 mL) at 0 °C for 3 h.
[b] Isolated yield.

As a conclusion, we have found a TFA-mediated *cyclo*-dimerization of 1-substituted 3-alkenyl-1*H*-indole



Scheme 5.

derivatives to give the cyclopent[*b*]indoles stereoselectively. Further investigation and applications of this reaction are under way, and the results of these studies will be reported elsewhere in due course.

Acknowledgements

We are grateful for financial support in part by the Frontier Research Program and the 21st Century COE Program 'Development of Drug Discovery Frontier Integrated from Traditional to Proteome' from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan, and a Grant-In-Aid for the promotion of the advancement of education and research in graduate schools in subsidies for ordinary expenses of private schools from the Promotion and Mutual Aid Corporation for Private Schools.

References and notes

1. For reviews, see: (a) Hibino, S.; Choshi, T. *Nat. Prod. Rep.* **2002**, *19*, 148–180; (b) Falkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1–49; (c) Lounasmaa, M.; Nemes, A. *Tetrahedron* **1982**, *38*, 223–243.
2. Recent contributions: (a) Zhao, S.; Liao, X.; Wang, T.; Flippen-Anderson, J.; Cook, J. M. *J. Org. Chem.* **2003**, *68*, 6279–6295; (b) Kawasaki, T.; Kouko, T.; Totsuka, H.; Hiramatsu, K. *Tetrahedron Lett.* **2003**, *44*, 8849–8852; (c) Miyake, F. Y.; Yakushijin, K.; Horn, D. A. *Org. Lett.* **2002**, *4*, 941–943; (d) Jiang, B.; Yang, C. G.; Wang, J. *J. Org. Chem.* **2002**, *67*, 1396–1398; (e) Schneider, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4217–4219; (f) Faul, M. M.; Sullivan, K. A. *Tetrahedron Lett.* **2001**, *42*, 3271–3273; (g) Kam, T. S.; Lim, T. M.; Tan, G. H. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1594–1604; (h) Ishikura, M.; Imaizumi, K.; Katagiri, N. *Heterocycles* **2000**, *53*, 553–556; (i) Lewin, G.; Schaeffer, C.; Hocquemiller, R.; Jacoby, E.; Léonce, S.; Pierré, A.; Atassi, G. *Heterocycles* **2000**, *53*, 2353–2356.
3. Zhao, S.; Liao, X.; Cook, J. M. *Org. Lett.* **2002**, *4*, 687–690, and references cited therein.
4. Bandini, M.; Fagioli, M.; Melloni, A.; Umani-Ronchi, A. *Synthesis* **2003**, 397–402.
5. Kawasaki, I.; Terano, M.; Yada, E.; Kawai, M.; Yamashita, M.; Ohta, S. *Tetrahedron Lett.* **2005**, *46*, 1190–1203.
6. (a) Kawasaki, I.; Katsuma, H.; Nakayama, Y.; Yamashita, M.; Ohta, S. *Heterocycles* **1998**, *48*, 1887–1901; (b) Kawasaki, I.; Yamashita, M.; Ohta, S. *Chem. Pharm. Bull.* **1996**, *44*, 1831–1839; (c) Kawasaki, I.; Katsuma, H.; Nakayama, Y.; Yamashita, M.; Ohta, S. *Heterocycl. Commun.* **1996**, *2*, 189–191; (d) Kawasaki, I.; Yamashita, M.; Ohta, S. *Chem. Commun.* **1994**, 2085–2086.
7. (a) Sobolov, S. B.; Sun, J.; Cooper, B. A. *Tetrahedron Lett.* **1998**, *39*, 5685–5688; (b) Rubiralta, M.; Diez, A.; Bosch, J. *J. Org. Chem.* **1989**, *54*, 5591–5597.
8. Kaufman, M. D.; Grieco, P. A. *J. Org. Chem.* **1994**, *59*, 7197–7198.
9. Crystal data of the compound **6a**: $C_{30}H_{34}N_2$, $M = 422.61$, triclinic, $a = 12.548(2)$, $b = 12.799(1)$, $c = 14.725(2)$ Å, $\alpha = 90.004(9)°$, $\beta = 93.050(12)°$, $\gamma = 90.001(9)°$; $V = 2361.5(5)$ Å^3; $Z = 4$, μ(Cu Kα) = 5.19 cm^{-1}; $T = 296$ K; $R1 = 0.059$ for 4577 observations, space group *P*-1(#2). Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as a supplementary number CCDC 277890. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
10. Preparation of **6a** as a typical experiment: TFA (0.023 mL, 0.3 mmol) was added to a stirred solution of 3-cyclopentylidenemethyl-1-methyl-1*H*-indole **4a** (63 mg, 0.3 mmol) in DCM (3.0 mL) under N_2 at 0 °C. After stirring for 3 h at 0 °C, the reaction mixture was neutralized by addition of satd $NaHCO_3$ aq and the products were extracted with $CHCl_3$ (30 mL × 3). The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was purified by silica gel column chromatography (*n*-hexane to AcOEt/*n*-hexane = 1/20) to give pure **6a** (50 mg, 79%) as a colorless solid. Analytical sample was obtained by recrystallization from AcOEt (mp 224 °C).
11. Spectral data of **6a**: δ_H (400 MHz, $CDCl_3$, 60 °C): 0.90–1.89 (14H, m and br, CH_2 in cyclopentane), 1.91–2.07 (2H, m, CH_2 in cyclopentane), 2.14–2.24 (1H, m, CH in cyclopentane), 3.24 (3H, br s, Me), 3.31 (1H, br s, 1′-CH), 3.73 (3H, br s, Me), 4.52 (1H, br s, 3′-CH), 6.10–7.22 (7H, m and br, Ar–H), 7.26 (1H, d, $J = 8.1$ Hz, Ar–H), 7.57 (1H, dd, $J = 2.6$, 6.4 Hz, Ar–H). ν_{max} ($CHCl_3$, cm^{-1}): 2940, 2860, 1459, 1325. EIMS (*m*/*z*, %): 144 (100), 222 (20), 353 (72), 354 (21), 422 (M^+, 20). HRMS (EI) *m*/*z*: found M^+ 422.2724, $C_{30}H_{34}N_2$ requires M^+ 422.2722. Anal. Calcd for $C_{30}H_{34}N_2$: C, 85.26; H, 8.11; N, 6.33. Found: C, 85.44; H, 8.15; N, 6.52. We could not observe ^{13}C NMR signals because of their broadening.
12. (a) Kong, Y. C.; Cheng, K. F.; Cambie, R. C.; Waterman, P. G. *Chem. Commun.* **1985**, 47–48; (b) Kong, Y. C.; Ng, K. H.; Wat, K. H.; Wong, A.; Saxena, I. F.; Cheng, K. F.; But, P. P.; Chang, H. T. *Planta Med.* **1985**, 304–307; (c) Waterman, P. G. *Fitoterapia* **1987**, *58*, 333–335.
13. Ho, D. D.; Lau, C. P.; Ng, K. H.; Kong, Y. C.; Cheng, K. F.; Chan, K. P. *Eur. J. Pharmacol.* **1991**, *205*, 209–212.
14. (a) Estrogenic and anti-estrogenic activities: Wong, D. C. C.; Fong, W. P.; Lee, S. S. T.; Kong, Y. C.; Cheng, K. F.; Stone, G. *Eur. J. Pharmacol.* **1998**, *362*, 87–93; (b) Ng, P. C.; Ho, D. D.; Ng, K. H.; Kong, Y. C.; Cheng, K. F.; Stone, G. *Eur. J. Pharmacol.* **1994**, *264*, 1–12; Potential in chemohormonal therapy for breast cancer: Leung, T. W. T.; Cheng, G.; Chui, C. H.; Ho, S. K. W.; Lau, F. Y.; Tjong, J. K. J.; Poon, T. C. C.; Tang, J. C. O.; Tse, W. C. P.; Cheng, K. F.; Kong, Y. C. *Chemotherapy* **2000**, *46*, 62–68.
15. Anti-tumor: Skibo, E. B.; Xing, C. *J. Med. Chem.* **2001**, *44*, 3545–3562; Inhibitors of acetylcholinesterase and monoamine oxidase: Fink, D. M.; Palermo, M. G.; Bores, G. M.; Huger, F. P.; Kurys, B. E.; Merriman, M. C.; Olsen, G. E.; Petko, W.; O'Malley, G. J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 625–630; Melatonin agonists and antagonists: Davies, D. J.; Garratt, P. J.; Tocher, D. A.; Vonhoff, S. *J. Med. Chem.* **1998**, *41*, 451–467; Agonists at the human 5-hydroxytryptamine 2C receptor: Sabb, A. L.; Vogel, R. L.; Welmaker, G. S.; Sabalski, J. E.; Coupet, J.; Dunlop, J.; Rosenzweig-Lipson, S.; Harrison, B. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2603–2607; Insecticides: (a) Meinke, P. T.; Smith, M. M.; Shoop, W. L. *Curr. Top. Med. Chem.* **2002**, *2*, 655–674; (b) Ondeyka, J. G.; Helms, G. L.; Hensens, O. D.; Goetz, M. A.; Zink, D. L.; Tsipouras, A.; Shoop, W. L.; Slayton, L.; Dombrowski, A. W.; Polishook, J. D.; Ostlind, D. A.; Tsou, N. N.; Ball, R. G.; Simgh, S. B. *J. Am. Chem. Soc.* **1997**, *119*, 8809–8816; . Antidepressant: Asselin, A. A.; Humber, L. G.; Komlossy, J. *J. Med. Chem.* **1976**, *19*, 792–797.
16. (a) Cheng, K. F.; Kong, Y. C.; Chan, T. Y. *Chem. Commun.* **1985**, 48–49; (b) Wenkert, E.; Moeller, P. D. R.; Piettre, S. R.; McPhail, A. T. *J. Org. Chem.* **1988**, *53*,

3170–3178; (c) Sheu, J. H.; Chen, Y. K.; Hong, Y. L. V. *Tetrahedron Lett.* **1991**, *32*, 1045–1046; (d) Sheu, J. H.; Chen, Y. K.; Hong, Y. L. V. *J. Org. Chem.* **1993**, *58*, 5784–5787; (e) Sheu, J. H.; Chen, Y. K.; Chung, H. F.; Lin, S. F.; Sung, P. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1959–1965; (f) Sheu, J. H.; Chen, C. A.; Chen, B. H. *Chem. Commun.* **1999**, 203–204.

17. (a) Bergman, J.; Janosik, T.; Koch, E.; Pelcman, B. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2615–2621; (b) Sheu, J. H.; Chen, Y. K.; Chung, H. F.; Sung, P. J.; Lin, S. F. *Heterocycles* **1996**, *43*, 1751–1758; (c) Black, D. S. C.; Craig, D. C.; Kumar, N. *Tetrahedron Lett.* **1991**, *32*, 1587–1590; (d) Bergman, J.; Norrby, P.-O.; Tilstam, U.; Venemalm, L. *Tetrahedron* **1989**, *45*, 5549–5564.
18. (a) Pfeuffer, L.; Pindur, U. *Helv. Chim. Acta* **1988**, *71*, 467–471; (b) Inhoffen, H. H.; Nordsiek, K. H.; Schafer, H. *Liebigs Ann. Chem.* **1963**, *668*, 104–121.
19. Pindur, U.; Kim, M. H. *Tetrahedron* **1989**, *45*, 6427–6438.