Tetrahedron Letters, Vol. 34, No. 15, pp. 2405-2408, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

TOTAL SYNTHESES OF DAMIRONE A AND DAMIRONE B

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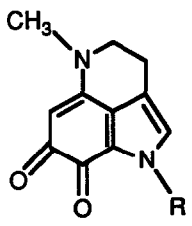
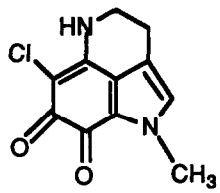
Abstract: The first total syntheses of the tricyclic alkaloids damirone A and damirone B have been achieved starting from 6,7-dimethoxyindole.

Damirone A (**1**) and damirone B (**2**) are marine alkaloids which occur in very small amounts in the shallow water Pacific sponge *Damiria sp. Keller*.[1] They belong to the small class of 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline alkaloids, the only other members of which are the batzellines and the isobatzellines,[2,3] several of which have been found to possess cytotoxic and antifungal activities.[4] A recent publication describes the first syntheses of batzelline C (**3**) and isobatzelline C (**4**).[4] Using a very different strategy, we now report an efficient total synthesis of both damirone A (**1**) and damirone B (**2**) from 6,7-dimethoxyindole (**5**).[5]



1 R = CH_3
2 R = H



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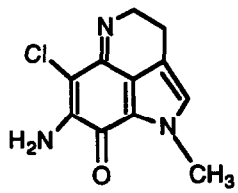

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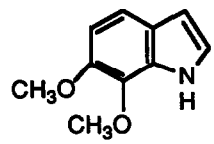
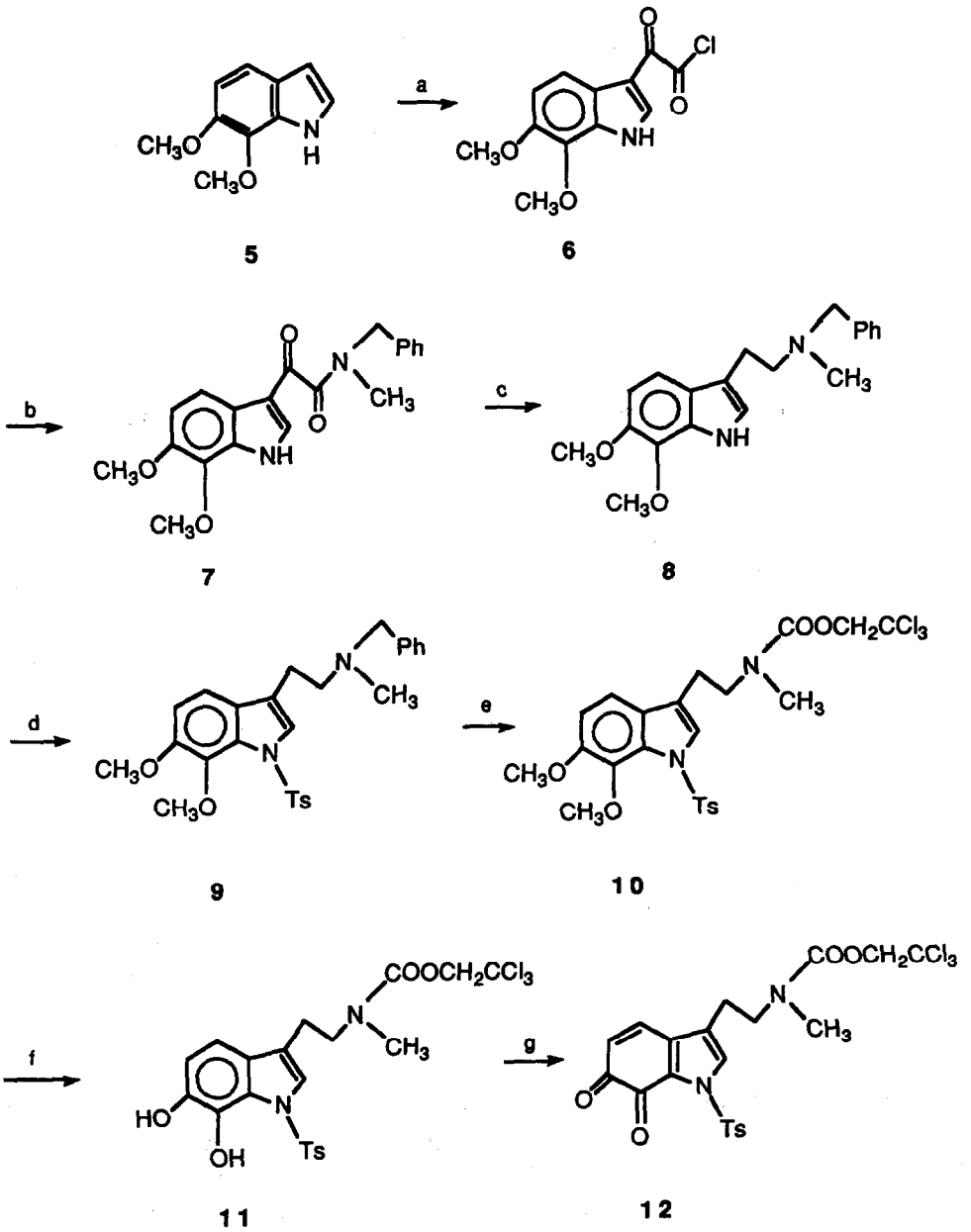
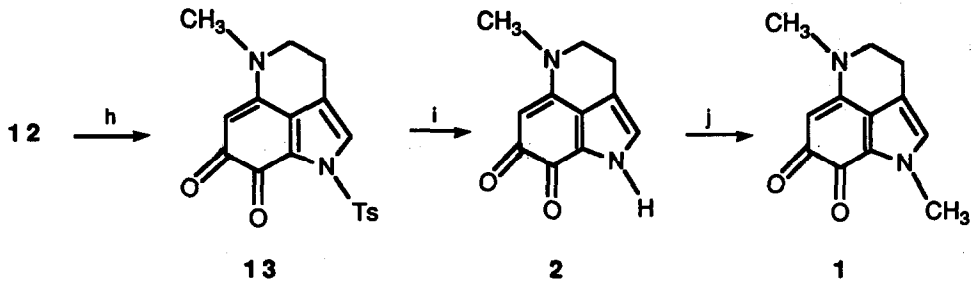


5

Treatment of **5** with oxalyl chloride in ether resulted in the formation of the acid chloride **6** in 94% yield. Reaction of **6** with N-benzyl-N-methylamine in water afforded the ketoamide **7** in 96% yield. Reduction of **7** with lithium aluminum hydride in tetrahydrofuran-diethyl ether mixture gave the tryptamine **8** in 96% yield. At this point it was necessary to protect the indole nitrogen of **8** with an electron withdrawing group. This was accomplished by a phase transfer reaction of **8** with tosyl chloride in methylene chloride using sodium hydroxide as base and cetyl trimethyl ammonium bromide as catalyst, resulting in the formation of N-tosylated tryptamine **9** in 90% yield. The benzyl group of **9** was displaced by reaction with 2,2,2-trichloroethyl chloroformate in

acetonitrile, to afford the urethane **10** in 76% yield. Demethylation of **10** was carried out with boron tribromide in methylene chloride to give the dihydroxy compound **11** in 71% yield which upon oxidation with ceric ammonium nitrate in acetonitrile furnished the quinone **12** in 86% yield.





13 2 1

(a) $(COCl)_2$, Et_2O, 0 °C, 1h, 94% (b) $PhCH_2NHCH_3$, H_2O, 25 °C, 3h, 96% (c) $LiAlH_4$, THF+ Et_2O, reflux, 4h, 96% (d) TsCl, NaOH, CH_2Cl_2, CTAB, 25 °C, 12h, 90% (e) $ClCOOCH_2CCl_3$, CH_3CN, 0 °C, 30 min, 76% (f) BBr_3, CH_2Cl_2, 0-25 °C, 12h, 71% (g) CAN, CH_3CN, 0 °C, 10 min, 86% (h) dithienyl ditelluride, THF, $NaBH_4$, H_2O, NaOH, 67 °C, 6h, 36 % (i) 10% NaOH, MeOH, 25 °C, 30 min 76% (j) K_2CO_3, MeI, MeOH, 25 °C, 86%.

The stage was now set to deprotect the nitrogen of the side chain of **12**, and then cyclize it to the quinone ring to form the expected tricyclic ring system. This was achieved by the treatment of **12** with dithienyl ditelluride[6] in tetrahydrofuran under refluxing conditions followed by air oxidation. The tricyclic quinone **13** was obtained thus in 36% yield. Hydrolytic removal of the tosyl group of **13** with cold 10% sodium hydroxide in methanol occured rapidly to afford damirone B (**2**) in 76% yield. Damirone B was easily methylated by methyl iodide using potassium carbonate as base in methanol to afford damirone A (**1**) in 86% yield. The spectral data of synthetic samples were found to be in accordance with those of the natural products.[7]

Acknowledgment. This work was supported by a grant from the National Institutes of Health (5-R01 GM44713).

References and Notes

1. Stierle, D. B.; Faulkner, D. J. *J. Nat. Prod.* **1991**, *54*, 1131.
2. Sakemi, S.; Sun, H. H. *Tetrahedron Lett.* **1989**, *30*, 2517.
3. Sun, H. H.; Sakemi, S.; Burres, N.; McCarthy, P. *J. Org. Chem.* **1990**, *55*, 4964.
4. Tao, X. L.; Nishiyama, S.; Yamamura, S. *Chem. Lett.* **1991**, 1785.
5. Rajeswari, S.; Drost, K. J.; Cava, M. P. *Heterocycles* **1989**, *29*, 415.
6. Lakshmikantham, M.V.; Jackson, Y.A.; Jones, R. J.; O'Malley, G. J.; Ravichandran, K.; Cava, M. P. *Tetrahedron Lett.* **1986**, *27*, 4687.
7. Compound **1**:
   UV-Vis (MeOH): λ_{max} (log ε); 241.5 (4.10), 346.8 (4.01) and 518.1 (2.96) nm.
   IR (KBr): 1670 and 1600 cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ 2.83 (t, 2H, J=7 Hz), 3.04 (s, 3H), 3.56 (t, 2H, J=7 Hz), 3.90 (s, 3H), 5.26 (s, 1H) and 6.62 (s, 1H).
^{13}C NMR (360 MHz, $CDCl_3$): δ 20.4, 35.9, 38.2, 51.7, 93.5, 115.6, 124.7, 124.9, 127.2, 153.7, 171.5 and 179.3.
MS (EI): m/e (%); 216 (M^+, 80), 202 (11), 188 (100), 173 (19), 159 (66), 145 (31), 132 (53) and 118 (80).
Compound 2:
UV-Vis (MeOH): λ_{max} (log ε); 240.3 (3.85), 351.0 (3.65) and 504.1 (2.41) nm.
IR (KBr): 1670 and 1600 cm^{-1}.
^{1}H NMR (360 MHz, d_6-DMSO): δ 2.83 (t, 2H, J=7 Hz); 3.05 (s, 3H), 3.61 (t, 2H, J=7 Hz), 5.12 (s, 1H), 7.01 (s, 1H) and 8.77 (bs, 1H).
^{13}C NMR (360 MHz, d_6-DMSO): δ 19.8, 37.7, 51.2, 92.4, 116.2, 123.8, 124.5, 124.8, 153.5, 170.4 and 178.6.
MS (EI): m/e (%); 202 (M^+, 91), 188 (74), 174 (100), 159 (31), 145 (70), 131 (27), 118 (75) and 104 (70).
All intermediate compounds had satisfactory spectral data.

(Received in USA 12 January 1993; accepted 1 February 1993)