Pergamon

Tetrahedron Letters 40 (1999) 1713–1716

TETRAHEDRON LETTERS

The First Total Synthesis of Veiutamine, A New Type of Pyrroloiminoquinone Marine Alkaloid

Yoshihiro Moro-oka, Tsutomu Fukuda, and Masatomo Iwao*

Department of Applied Chemistry, Faculty of Engineering, Nagasaki University
1-14 Bunkyo-machi, Nagasaki 852-8521, Japan

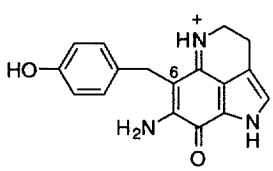
Received 19 November 1998; revised 21 December 1998; accepted 25 December 1998

Abstract

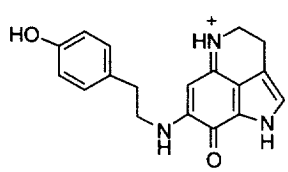
The first total synthesis of veiutamine, a new type of pyrroroiminoquinone marine alkaloid bearing a *p*-hydroxybenzyl substituent at C-6, has been achieved. The key step of the synthesis is 6-selective functionalization of the 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline nucleus *via* *N*-Boc-directed lithiation.

Keywords: antitumour compounds; marine metabolites; indoles; lithiation

Pyrroloiminoquinone marine alkaloids, such as discorhabdins and makaluvamines, have received considerable attention due to their potential antitumor activity [1]. Recently, Ireland *et al.* reported the isolation and characterization of veiutamine (**1**), a new pyrroloiminoquinone derivative from the Fijian sponge *Zyzzya fuliginosa* [2]. Veiutamine was found to exhibit a mean IC_{50} of 0.12 μg/mL in a 25 cell line panel, with some selectivity against solid tumors versus leukemia. It is noteworthy that veiutamine (IC_{50} 0.3 μg/mL) was shown to be 7 times more active than the structurally related makaluvamine D (**2**) (IC_{50} 2.0 μg/mL) against the human colon tumor cell line HCT 116 [2].



1



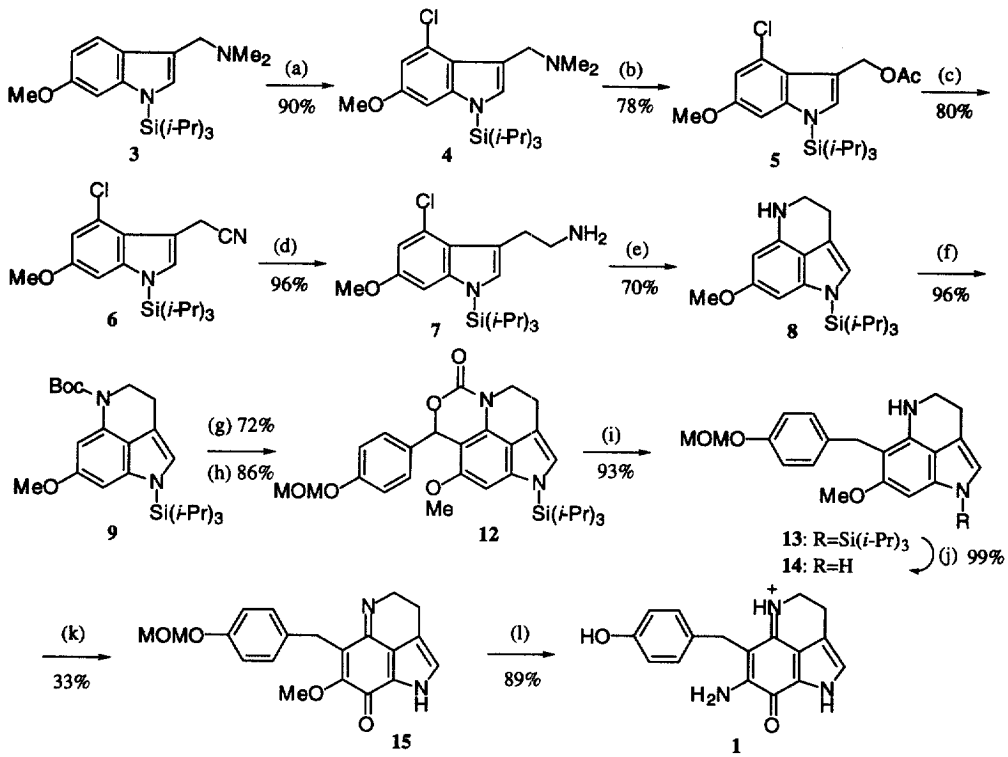
2

Recently, we have developed an efficient route to the pyrroloiminoquinone nucleus and applied it to the total synthesis of makaluvamines A, D, I and K [3]. In this Letter, we present the first total synthesis of veiutamine (**1**) based upon this approach. The synthesis involves a newly developed protocol for 6-selective functionalization of the 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline ring system.

The total synthesis is shown in **Scheme 1**. The readily prepared gramine derivative **3** was lithiated with *t*-BuLi at C-4 [3,4] and subsequently reacted with hexachloroethane to give 4-chlorinated compound **4** in 90% yield. In the previous study [3], we observed complete elimination

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00034-9

of the triisopropylsilyl (TIPS) group during cyanation of **4** under the conventional gramine substitution conditions (1. MeI; 2. KCN), probably because the reaction proceeded through an elimination-addition mechanism [5]. Since the protection of the indole nitrogen with the TIPS group was essential for ring metalations at the later stages, we devised a new procedure for cyanation which allowed the TIPS group to be kept intact under the reaction conditions. Thus, **4** was converted to the reactive acetate **5** by treatment with acetic anhydride in 78% yield. The reaction of **5** with diethylaluminium cyanide [6] in toluene went very smoothly (0 °C, 20 min) to give the desired nitrile **6** in 80% yield. Without chromatographic purification of the rather unstable intermediate **5**, the nitrile **6** was obtained in 71% overall yield from **4**. Magnesium perchlorate-promoted substitution [7] of the acetoxy group of **5** with trimethylsilyl cyanide afforded only a complex mixture. The nitrile **6** thus prepared was then reduced to the tryptamine derivative **7** with $LiAlH_4$ in a benzene-diethyl ether mixed solvent in 96% yield. Aryne-mediated cyclization [3, 8] of **7** using 5 equiv of lithium isopropylcyclohexylamide (LICA) as a base afforded the key tricyclic 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline derivative **8** in 70% yield.

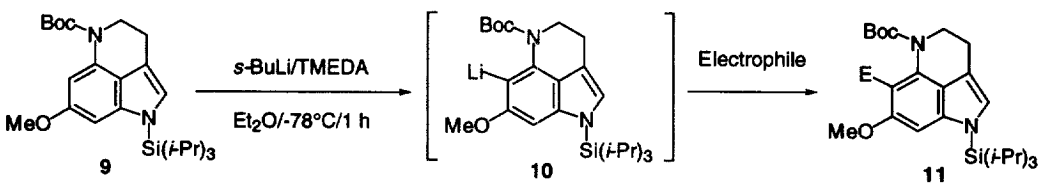


Reagents and conditions: (a) 1) *t*-BuLi (1.2 equiv), Et_2O, 0°C, 1h; 2) Cl_3CCl_3. (b) Ac_2O (3 equiv), toluene, 0°C, 15 h. (c) Et_2AlCN (2 equiv), toluene, 0°C, 20 min. (d) $LiAlH_4$ (5 equiv), benzene-Et_2O, reflux, 0.5 h. (e) LICA (5 equiv), THF, 0°C, 15 min. (f) Boc_2O (3 equiv), reflux, 8 h. (g) 1) *s*-BuLi (1.5 equiv), TMEDA, ether, -78°C, 1 h; 2) *p*-MOM-C_6H_4-CHO. (h) NaH (1.5 equiv), THF, 0°C, 20 min. (i) H_2, $Pd(OH)_2$-C, MeOH-AcOEt, rt, 6 h. (j) TBAF (1.2 equiv), THF, rt, 15 min. (k) $(KSO_3)_2NO$ (2 equiv), MeOH-phosphate buffer (pH=7.0), 0°C, 10 min. (l) 1) NH_4Cl (10 equiv), MeOH, rt, 36 h; 2) cat. HCl, reflux, 1 h; 3) $NaHCO_3$; 4) CF_3COOH.

Scheme 1

It is very important to establish a general procedure to introduce substituents at the 6 position of **8**, because this is not only essential for the synthesis of veiutamine but also allows easy generation of the 6-substituted analogues of pyrroloiminoquinone alkaloids. For this reason, we investigated the 6-selective functionalization of **8** using a directed lithiation reaction [9]. Since the directed *ortho* lithiation of *N*-Boc-1,2,3,4-tetrahydroquinoline [10] or *N*-Boc-indoline [11] has been well-established, we applied the standard lithiation conditions to the *N*-Boc derivative **9**. Thus, the compound **9** was treated with *s*-BuLi-TMEDA in diethyl ether at -78°C for 1 h, and the resulting lithio species **10** was reacted with a range of common electrophiles to give the corresponding 6-substituted compounds **11a-f** in good yields (**Table 1**). None of the products derived from other lithio species was isolated, apparently due to the powerful *ortho* directing effect of the *N*-Boc group [11a] and to the steric shielding of the C-2 and C-8 protons with the bulky 1-TIPS group[1] [4].

Table 1. Synthesis of 6-Substituted 1,3,4,5-Tetrahydropyrrolo[4,3,2-*de*]quinoline Derivatives **11**



Entry	Electrophile	Product	E	Yield (%)
1	MeI	**11a**	Me	74
2	DMF	**11b**	CHO	79
3	MeSSMe	**11c**	MeS	71
4	Cl_3CCCl_3	**11d**	Cl	79
5	$BrCF_2CF_2Br$	**11e**	Br	78
6	*p*-MOMO-C_6H_4-CHO	**11f**	*p*-MOMO-C_6H_4-CH(OH)	72

Having established a protocol for C-6 functionalization, the remaining part of the total synthesis was then achieved. Thus, the alcoholic product **11f** was briefly treated with NaH in THF to generate cyclic carbamate **12** (86%). Hydrogenolysis of the benzylic C-O bond of **12** over the Pearlman catalyst [12] caused concomitant decarboxylation to give **13** in 93% yield. After deprotection of the TIPS group with TBAF, compound **14** was oxidized to the corresponding iminoquinone **15** with Fremy's salt in 33% yield. Compound **15** was then treated with 10 equiv of NH_4Cl in MeOH at room temperature for 36 h to introduce an amino group at C-7. The reaction mixture was heated under reflux in the presence of a catalytic amount of HCl to remove the methoxymethyl (MOM) protecting group. Veiutamine (**1**) thus synthesized was isolated and

characterized as its trifluoroacetate salt (89%). The spectroscopic data[2] of the synthetic veiutamine were shown to be identical with those reported for the natural product [2].

In summary, we have accomplished the first total synthesis of veiutamine in 12 steps from readily available gramine derivative **3** in 6.1% overall yield. During this synthetic effort, we have developed an efficient procedure for functionalization at the 6 position of the 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline ring system using directed lithiation reaction. This allows an easy access to a variety of 6-substituted pyrroloiminoquinone derivatives which are essential for structure-activity relationship studies of this type of potential antitumor compounds.

Acknowledgment: We thank the Ministry of Education, Science, Sports and Culture of Japan for financial support; Grant-in-Aid for Scientific Research (C) (No. 09680571).

References

[1] (a) Perry, N. B.; Blunt, J. W.; McCombs, J. D.; Munro, M. H. G. *J. Org. Chem.* **1986**, *51*, 5476. (b) Perry, N. B.; Blunt, J. W.; Munro, M. H. G. *Tetrahedron* **1988**, *44*, 1727. (c) Kobayashi, J.; Cheng, J.; Ishibashi, M.; Nakamura, H.; Ohizumi, Y.; Hirata, Y.; Sasaki, T.; Lu, H.; Clardy, J. *Tetrahedron Lett.* **1987**, *28*, 4939. (d) Cheng, J.; Ohizumi, Y.; Wälchi, M. R.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1988**, *53*, 4621. (e) Radisky, D. C.; Radisky, E. S.; Barrows, L. R.; Copp, B. R.; Kramer, R. A.; Ireland, C. M. *J. Am. Chem. Soc.* **1993**, *115*, 1632. (f) Barrows, L. R.; Radisky, D. C.; Copp, B. R.; Swaffar, D. S.; Kramer, R. A.; Warters, R. L.; Ireland, C. M. *Anti-Cancer Drug Design* **1993**, *8*, 333. (g) Schmidt, E. W.; Harper, M. K.; Faulkner, D. J. *J. Nat. Prod.* **1995**, *58*, 1861.

[2] Venables, D. A.; Barrows, L. R.; Lassota, P.; Ireland, C. M. *Tetrahedron Lett.* **1997**, *38*, 721.

[3] Iwao, M.; Motoi, O.; Fukuda, T.; Ishibashi, F. *Tetrahedron* **1998**, *54*, 8999.

[4] Iwao, M. *Heterocycles* **1993**, *36*, 29.

[5] Iwao, M.; Motoi, O. *Tetrahedron Lett.* **1995**, *36*, 5929, and references cited therein.

[6] (a) Nagata, W.; Yoshioka, M.; Hirai, S. *J. Am. Chem. Soc.* **1972**, *94*, 4635. (b) Nagata, W.; Yoshioka, M. *Organic Reactions* **1977**, *25*, 255.

[7] Grieco, P. A.; Handy, S. T. *Tetrahedron Lett.* **1997**, *38*, 2645.

[8] Bailey, W. F.; Longstaff, S. C. *J. Org. Chem.* **1998**, *63*, 432, and references cited therein.

[9] For reviews of aromatic and heteroaromatic directed lithiations, see: (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (b) Rewcastle, G. W.; Katritzky, A. R. *Adv. Heterocycl. Chem.* **1993**, *56*, 155. (c) Gray, M.; Tinkl, M. Snieckus, V.;"Comprehensive Organometallic Chemistry II", McKillop, A. Ed; Pergamon: Oxford, 1995; Vol. 11, Chapter 1.

[10] (a) Beak, P.; Lee, W.-K. *Tetrahedron Lett.* **1989**, *30*, 1197. (b) Meyers, A. I.; Milot, G. *J. Org. Chem.* **1993**, *58*, 6538.

[11] (a) Iwao, M.; Kuraishi, T. *Heterocycles* **1992**, *34*, 1031. (b) Iwao, M.; Kuraishi, T. *Organic Syntheses* **1996**, *73*, 85.

[12] Pearlman, W. M. *Tetrahedron Lett.* **1967**, *17*, 1663.

---

(1) The lithiation of 5-(*t*-butoxycarbonyl)-7-methoxy-1-methyl-1,3,4,5-tetrahydro[4,3,2-*de*]quinoline under similar conditions afforded 2-, 6- and 8-lithio species in *ca.* 1:1:1 ratio. Moro-oka, Y.; Fukuda, T.; Iwao, M. unpublished result.

(2) **Veiutamine (1)**: HRMS(FAB) calcd for $C_{17}H_{16}N_3O_2$ 294.1243, found 294.1243; FTIR (KBr) 3160, 1678, 1607, 1552, 1514, 1439, 1414, 1335, 1202, 1132, 1074, 1025, 989, 958, 908, 832, 799, 720, 592, 513, 465 ; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.86 (t, 2H, H-3, *J*=7.5 Hz), 3.68 (s, 2H, benzylic H), 3.79 (dt, 2H, H-4, *J*=2.5 and 7.5 Hz), 6.68 (d, 2H, ArH, *J*=8.5 Hz), 7.02 (d, 2H, ArH, *J*=8.5 Hz), 7.31 (d, 1H, H-2, *J*=2.5 Hz), 8.49 (br s, 1H, NH_2), 8.57 (br s, 1H, NH_2), 9.23 (br s, 1H, OH), 10.07 (br s, 1H, NH-5), 13.04 (br s, 1H, NH-1); ^{1}H NMR (300 MHz, methanol-d_4) δ 2.94 (t, 2H, H-3, *J*=7.5 Hz), 3.72 (s, 2H, benzylic H), 3.84 (t, 2H, H-4, *J*=7.5 Hz), 6.72 (d, 2H, ArH, *J*=8.5 Hz), 7.06 (d, 2H, ArH, *J*=8.5 Hz), 7.14 (s, 1H, H-2); ^{13}C NMR (75 MHz, DMSO-d_6) δ 18.33, 26.36, 43.30, 98.63, 115.23, 119.25, 122.85, 123.71, 126.75, 127.92, 128.98, 153.63, 155.93, 156.72, 168.09; ^{13}C NMR (75 MHz, methanol-d_4) δ 19.47, 27.94, 44.69, 99.76, 116.47, 120.57, 123.92, 125.23, 126.97, 128.63, 129.69, 155.06, 157.19, 159.25, 168.84.