

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. © 1999 Elsevier Science Ltd. All rights reserved.

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 IC₅₀ of 0.12 μ g/mL in a 25 cell line panel, with some selectivity against solid tumors versus leukemia. It is noteworthy that veiutamine (IC₅₀ 0.3 μ g/mL) was shown to be 7 times more active than the structurally related makaluvamine D (2) (IC₅₀ 2.0 μ g/mL) against the human colon tumor cell line HCT 116 [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

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 LiAlH4 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), Et₂O, 0°C, 1h; 2) Cl₃CCl₃. (b) Ac₂O (3 equiv), toluene, 0°C, 15 h. (c) Et₂AlCN (2 equiv), toluene, 0°C, 20 min. (d) LiAlH₄ (5 equiv), benzene-Et₂O, reflux, 0.5 h. (e) LICA (5 equiv), THF, 0°C, 15 min. (f) Boc₂O (3 equiv), reflux, 8 h. (g) 1) s-BuLi (1.5 equiv), TMEDA, ether, -78°C, 1 h; 2) p-MOM-C₆H₄-CHO. (h) NaH (1.5 equiv), THF, 0°C, 20 min. (i) H₂, Pd(OH)₂-C, MeOH-AcOEt, rt, 6 h. (j) TBAF (1.2 equiv), THF, rt, 15 min. (k) (KSO₃)₂NO (2 equiv), MeOH-phosphate buffer (pH=7.0), 0°C, 10 min. (l) 1) NH₄Cl (10 equiv), MeOH, rt, 36 h; 2) cat. HCl, reflux, 1 h; 3) NaHCO₃; 4) CF₃COOH.

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 group¹ [4].

MeO N 9	S-BuLi/TMEDA Et₂O/-78°C/1 h (⊬Pr) ₃	MeO 10 Boc N Si(<i>i</i> -Pr	Be Electrophile Ba Electrophile Ba Electrophile Ba Electrophile Ba Electrophile Ba	N Si(<i>i</i> -Pr) ₃
Entry	Electrophile	Product	E	Yield (%)
1	Mel	11a	Me	74
2	DMF	11b	СНО	79
3	MeSSMe	11c	MeS	71
4	Cl ₃ CCCl ₃	11d	CI	79
5	BrCF ₂ CF ₂ Br	11e	Br	78
6	<i>p</i> -MOMO-C ₆ H ₄ -CHO	11f	<i>р-</i> МОМО-С ₆ Н ₄ -СН(ОН)	72

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

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 NH₄Cl 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 data² 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-<u>1-methyl</u>-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 $C_{17}H_{16}N_{3}O_{2}$ 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; ¹H NMR (300 MHz, DMSOd₆) 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, NH₂), 8.57 (br s, 1H, NH₂), 9.23 (br s, 1H, OH), 10.07 (br s, 1H, NH-5), 13.04 (br s, 1H, NH-1); ¹H NMR (300 MHz, methanol-d₄) 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); ¹³C NMR (75 MHz, DMSO-d₆) 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; ¹³C NMR (75 MHz, methanol-d₄) 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.