Tetrahedron Letters 50 (2009) 1128–1130

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Total synthesis of the marine pyrroloiminoquinone alkaloid tsitsikammamine A

Arnaud Rives, Tamara Delaine, Laurent Legentil, Evelyne Delfourne *

Université Paul Sabatier, UMR CNRS 5068, Laboratoire de Synthèse et Physicochimie de Molécules d'Intérêt Biologique, 118 route de Narbonne, 31062 Toulouse Cédex 9, France

ARTICLE INFO

Article history:
Received 24 October 2008
Revised 15 December 2008
Accepted 16 December 2008
Available online 24 December 2008

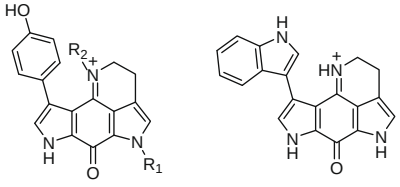
Keywords:
Synthesis
Marine alkaloid
Pyrroloiminoquinone
Tsitsikammamine

ABSTRACT

A concise route to the marine pyrroloiminoquinone alkaloid tsitsikammamine A and a regioisomer was developed. The synthesis was based on a Michael reaction between the indole dione **6** and 2′-amino-1-(4-methoxyphenyl)ethanol.

Marine organisms provide a valuable source for natural products. In the past several years, many new pyrroloiminoquinone alkaloids have been isolated mainly from sponges.[1] This class of compounds consisting of prianosins, discorhabdins, batzellins, wakayin, damirone, and makaluvamines possesses a pyrrolo[4,3,2-*de*]quinoline skeleton. Due to their remarkable biological activities, a number of synthetic methodologies have been developed to prepare the natural products[2] and analogues.[3]

Tsitsikammamines A (**1**) and B (**2**)[4], two alkaloids closely structurally related to wakayin **3**[5] and isolated from a *Latrunculid* sponge, have been reported to exhibit cytotoxicity and topoisomerase I inhibition.

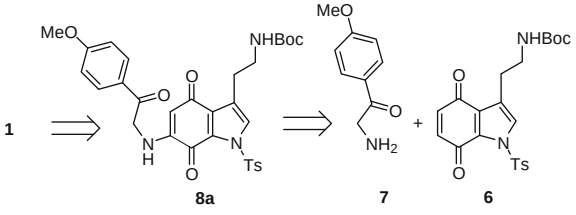


1, R_1= R_2 = H
2, R_1= Me, R_2 = H
4, R_1= H, R_2 = OH
5, R_1= Me, R_2 = OH

3

Recently, reinvestigation of extracts of the same sponge searching for minor pyrroloiminoquinone metabolites yielded N-18 oxime analogues of tsitsikammamine A and B, **4** and **5,** respectively. These compounds exhibited significantly reduced cytotoxicity against human colon tumor (HCT-116) when compared with their parent alkaloids.[6] Despite different works by our group[7] and by others[8] to propose analogues of wakayin and tsitsikammamines with potential antitumor activity, and thought that these alkaloids have been isolated for quite a while now, no synthesis of these marine metabolites has been reported to date. We describe herein the first total synthesis of tsitsikammamine A and one of its regioisomers.

The initial retrosynthetic pathway investigated was based on a Michael addition between the previously described indole dione **6**[7b] and 4′-methoxy-2-aminoacetophenone **7**.



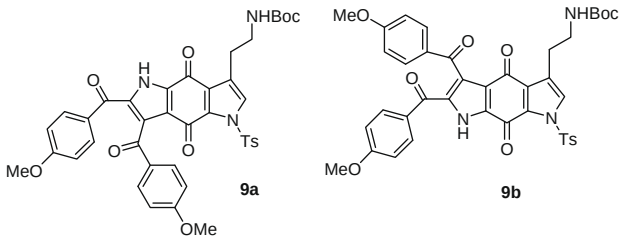
8a **7** **6**

This last β-ketoamine was synthesized in one step according to Grayson and Heyes' method[9] involving anisole which was reacted with gaseous HCl in the presence of $AlCl_3$. Compound **7** was obtained as a hydrochloride salt in 50% yield. The coupling reaction of this salt with compound **6** did not give the expected adduct **8a** whatever the experimental conditions used, but afforded mainly (41% yield) one of regioisomers **9a** or **9b**. It is noteworthy that the same reaction was observed when the methoxyphenyl group was

* Corresponding author. Tel.: +33 561 55 62 93; fax: +33 561 55 60 11.
E-mail address: delfourn@chimie.ups-tlse.fr (E. Delfourne).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.12.078

replaced by a phenyl group (77% yield) or by an indole group (58% yield).

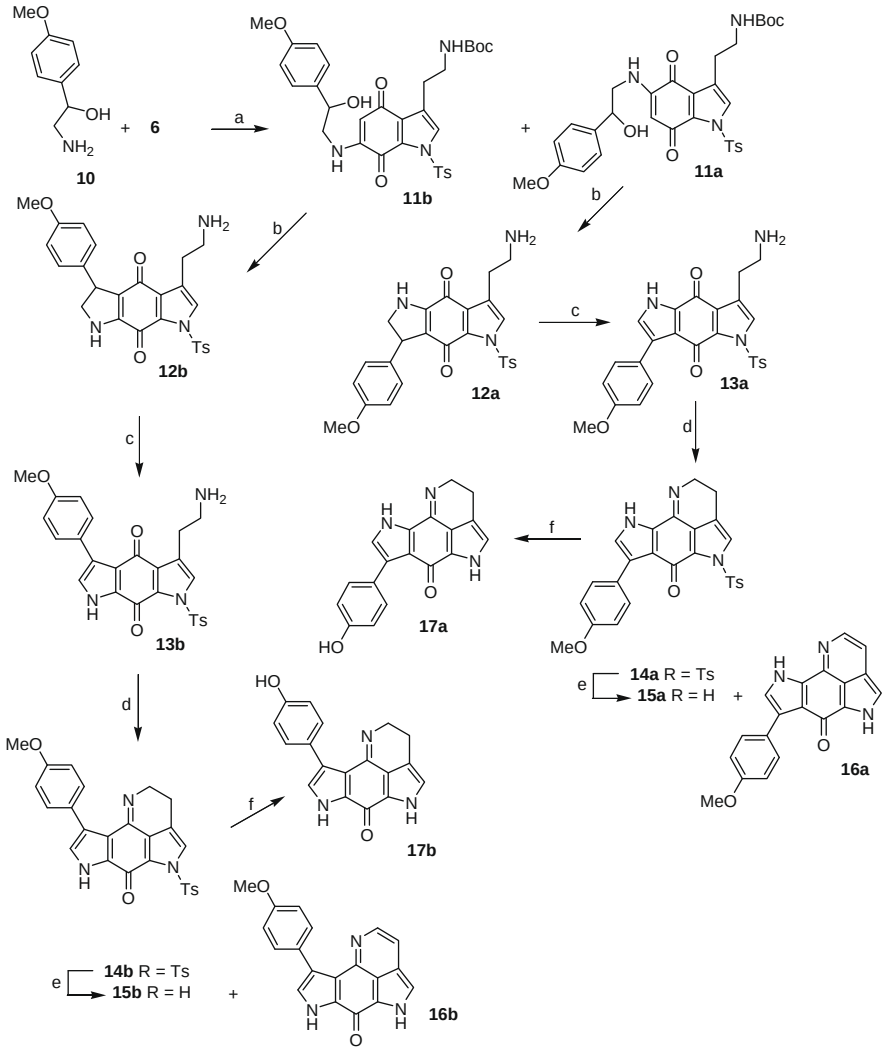


An alternative route to prepare intermediate **8** relied on the reduction of the carbonyl function of **7** prior to the Michael addition. This reduction effected by $NaBH_4$ provided β-hydroxyamine **10** in 72% yield. Reaction of **10** with quinone **6** in absolute ethanol gave two regioisomers **11a** and **11b** (57% and 19%, respectively, **a** and **b** refer to the order of elution during the purification by silica gel flash chromatography). Dess–Martin periodinane oxidation of these alcohols provided the two corresponding β-keto-adducts **8a** and **8b**.[10] Attempts to cyclize these products failed.

Surprisingly, the formation of the second five-membered nitrogen ring was achieved by direct cyclization of the hydroxy-derivatives **11a** and **11b** in trifluoroacetic acid and CH_2Cl_2, and was concomitant with the cleavage of the Boc protective group leading to compounds **12a** and **12b**.

MnO_2 oxidation of these compounds gave the bispyrroloquinone derivatives **13a** and **13b** which were subsequently cyclized into the corresponding iminoquinones **14a** and **14b**. The overall yields of these three steps were 16% and 22%, respectively. It has to be noted that few amounts (<4%) of compounds **14a** and **14b** were also formed during the cyclization step involving trifluoroacetic acid when the reaction was conducted in the absence of solvent. The tosyl group of **14a** and **14b** was removed by action of 1 N NaOH in dioxane leading to compounds **15a** and **15b** (46% and 40% yield, respectively), together with secondary compounds **16a** and **16b**. The free base of tsitsikammamine A **17b** was readily obtained by demethylation of compound **15b** using BBr_3, whereas the same reaction conditions applied on compound **15a** afforded the non-natural regioisomer **17a**.[11]

The spectroscopic data of the trifluoroacetic salt of **17b** were shown to be identical with those reported for tsitsikammamine A (**1**).[4] Investigations are currently in progress to apply this synthetic route to the other marine metabolite wakayin **3**.



a- abs EtOH, rt, 2h. b- TFA, CH_2Cl_2, rt, 4h. c- MnO_2, CH_2Cl_2, rt, overnight. d- abs EtOH, 4A molecular sieve, reflux, 3h. e- 1N NaOH, dioxane, rt, overnight. f- BBr_3, CH_2Cl_2, N_2, 4h.

References and notes

1. (a) Ding, Q.; Chichak, K.; Lown, J. W. *Curr. Med. Chem.* **1999**, *6*, 1–27; (b) Urban, S.; Hickford, S. J. H.; Blunt, J. W.; Munro, M. H. G. *Curr. Org. Chem.* **2000**, *4*, 765–778; (c) Antunes, E. M.; Copp, B. R.; Davies-Colemen, M. T.; Samaai, T. *Nat. Prod. Rep.* **2005**, *22*, 62–72.
2. Harayama, Y.; Kita, Y. *Curr. Org. Chem.* **2005**, *9*, 1567–1588.
3. (a) Delfourne E. *Anti-Cancer Agents Med. Chem.*, in press.; (b) Shinkre, B. A.; Raisch, K. P.; Fan, L.; Velu, S. E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2890–2893; (c) Shinkre, B. A.; Raisch, K. P.; Fan, L.; Velu, S. E. *Bioorg. Med. Chem.* **2008**, *16*, 2541–2549; (d) Passarella, D.; Belinghieri, F.; Scarpellini, M.; Pratesi, G.; Zunino, F.; Gia, O. M.; Via, L. D.; Santoro, G.; Danieli, B. *Bioorg. Med. Chem.* **2008**, *16*, 2431–2438.
4. Hooper, G. J.; Davies-Coleman, M. T.; Kelly-Borges, M.; Coetzee, P. S. *Tetrahedron Lett.* **1996**, *37*, 7135–7138.
5. Copp, B. R.; Ireland, C. M.; Barrows, L. R. *J. Org. Chem.* **1991**, *56*, 4596–4597.
6. Antunes, E. M.; Beukes, D. R.; Kelly, M.; Samaai, T.; Barrows, L. R.; Marshall, K. M.; Sincich, C.; Davies-Coleman, M. T. *J. Nat. Prod.* **2004**, *67*, 1268–1276.
7. (a) Legentil, L.; Lesur, B.; Delfourne, E. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 427–429; (b) Legentil, L.; Benel, L.; Bertrand, V.; Lesur, B.; Delfourne, E. *J. Med. Chem.* **2006**, *49*, 2979–2988.
8. (a) Zhang, L.; Cava, M. P.; Rogers, R. D.; Rogers, L. M. *Tetrahedron Lett.* **1998**, *39*, 7677–7678; (b) Barret, R.; Roue, N. *Tetrahedron Lett.* **1999**, *40*, 3889–3890; (c) LaBarbera, D. V.; Skibo, E. B. *Bioorg. Med. Chem.* **2005**, *13*, 387–395; (d) Hoang, H.; LaBarbera, D. V.; Mohammed, K. A.; Ireland, C. M.; Skibo, E. B. *J. Med. Chem.* **2007**, *50*, 4561–4571; (e) Hoang, H.; Huang, X.; Skibo, E. B. *Org. Biomol. Chem.* **2008**, *6*, 3059–3064.
9. Grayson, J. I.; Heyes, G. EP 0 431 871 A2, 1990.
10. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.
11. *Tsitsikammamine A* (*free base*, **17b**) HRMS (ESI) calcd for $C_{18}H_{14}N_3O_2$ 304.1086 (MH^+), found 304.1130. ^{1}H NMR (DMSO-d_6) 2.71 (t, 2H, J = 7.8 Hz), 3.97 (t, 2H, J = 7.8 Hz), 6.74 (d, 2H, J = 8.4 Hz), 6.96 (d, 1H, J = 2.1 Hz), 7.16 (d, 1H, J = 3.0 Hz), 7.68 (d, 2H, J = 8.4 Hz), 9.37 (br s, 1H), 12.15 (br s, 1H), 12.44 (br s, 1H). ^{13}C (DMSO-d_6) 18.35, 49.07, 115.07 (3C), 118.13, 121.84, 122.18, 122.52, 123.51, 125.27, 125.49, 130.16 (2C), 133.83, 154.96, 156.71, 167.99. **(17a)** HRMS (ESI) calcd for $C_{18}H_{14}N_3O_2$ 304.1086 (MH^+), found 304.1064. ^{1}H NMR (DMSO-d_6) 2.73 (t, 2H, J = 8.1 Hz), 4.05 (t, 2H, J = 8.1 Hz), 6.72 (d, 2H, J = 8.7 Hz), 6.82 (s, 1H), 6.95 (s, 1H), 7.47 (d, 2H, J = 8.7 Hz), 7.60 (br s, 1H), 7.70 (br s, 1H), 11.81 (br s, 1H). ^{13}C (DMSO-d_6) 18.92, 49.05, 11.83 (2C), 115.04, 116.13, 119.85, 120.66, 120.93, 125.57, 126.41, 129.46, 130.36 (2C), 134.26, 150.57, 156.58, 174.49.