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A facile synthesis of bispyrroloquinone and bispyrroloiminoquinone ring system of marine alkaloids

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ABSTRACT

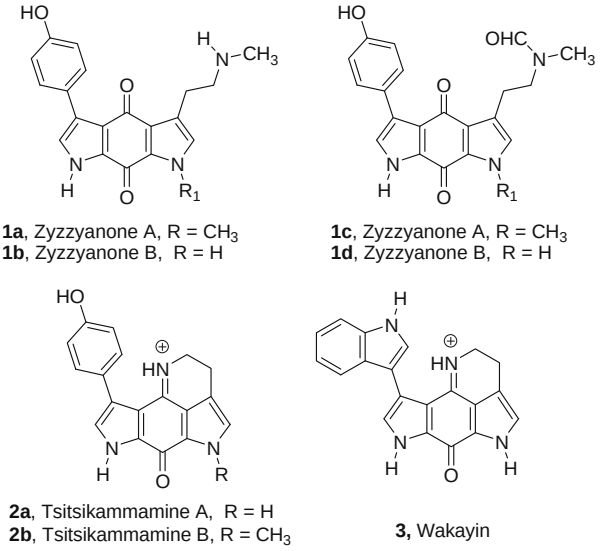
Bispyrroloquinone and bispyrroloiminoquinone are two important polycyclic ring systems present in biologically active marine alkaloids such as Zyzzyanones, tsitsikammamines, and wakayin. A facile synthesis of these two ring systems starting from a 6-benzylamino indole-4,7-quinone or 6-benzylamino pyrroloiminoquinone is described here. This chemistry involves the construction of a pyrrole ring in a single step by treatment of the starting reagents with ethyl acetoacetate or phenylbutane-1,3-dione in the presence of ceric ammonium nitrate in MeOH/CH_2Cl_2 solvent.

1. Introduction

Due to their potential for drug discovery, marine natural products have attracted the attention of scientists from various disciplines. Pharmacological value of the marine alkaloids is illustrated by the fact that about a dozen of marine alkaloids are currently undergoing various phases of human clinical trials for treatment of different cancers.[1–3] A large number of bioactive marine alkaloids with novel structures have been isolated from marine sponges.[4,5] Sponges produce a plethora of chemical compounds with widely varying carbon skeletons. Most bioactive compounds from sponges have exhibited a variety of activities such as anti-inflammatory, antitumor, immunosuppressive, neurosuppressive, antiviral, antimalarial, and antibiotic activities. While a number of these alkaloids have been isolated in quantities sufficient to ascertain their biological profile, many with unique structures are available only in minute quantities, precluding their thorough biological evaluations. Laboratory synthesis of these alkaloids and their analogs is the only practical way to access these materials in larger quantities.

Marine sponges of the genera *Latrunculia*, *Batzella*, *Prianos*, and *Zyzzya* are a rich source of alkaloids bearing a pyrrolo[4,3,2-*de*]quinoline skeleton.[6,7] This series of alkaloids comprise about 60 metabolites including discorhabdins,[8] epinardins,[9] batzellines,[10] isobatzellines,[10] makaluvamines,[11–16] veiutamine,[17] wakayin,[18] and tsitsikammamines.[19,20] Pyrrolo[4,3,2-*de*]quinoline alkaloids have shown a variety of biological activities such as inhibition of topoisomerases I[11] and II,[14] cytotoxicity against different tumor cell lines,[21,14] antifungal[11] and antimicrobial activities.[22] Pyrrolo[4,3,2-*de*]quinoline alkaloids have recently received increasing attention as a source of new anticancer drugs.[23–28] Their unique fused ring skeletons carrying interesting biological properties have made them targets for several synthetic and biological studies. There has been a rapid growth of interest in the synthesis and biological evaluation of this class of compounds and their analogs. Several reviews have been published on the chemistry and bioactivity of this class of compounds.[6,29–31]

Of these alkaloids, wakayin and tsitsikammamines possess a unique tetracyclic bispyrroloiminoquinone ring system (Fig. 1). Wakayin was isolated by Ireland etal in 1991 from an ascidian of *Clavelina* species.[18] It has exhibited cytotoxic properties and inhibition of topoisomerase I. Several aza analogs of these alkaloids re-



1a, Zyzzyanone A, R = CH_3
1b, Zyzzyanone B, R = H
1c, Zyzzyanone A, R = CH_3
1d, Zyzzyanone B, R = H
2a, Tsitsikammamine A, R = H
2b, Tsitsikammamine B, R = CH_3
3, Wakayin

Figure 1. Zyzzyanones, tsitsikammamines, and wakayin.

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ported recently have shown inhibition of both topoisomerases I and II. Tsitsikammamines A and B were isolated from four new species of South African latrunculid sponges namely, *Tsitsikamma pedunculata*, *Tsitsikamma favus*, *Latrunculia bellae*, and *Strongylodesma algoaensis*.[19,20] They do exhibit cytotoxic properties, but do not inhibit either topoisomerase I or II. A related class of tricyclic bispyrroloquinone alkaloids called Zyzzyanones A–D (Fig. 1) has been isolated recently from the Australian marine sponge *Zyzzya fuliginosa*.[32,33]

Because of their potent biological activities and unique structural features several attempts were made toward the synthesis of these alkaloids and the unique ring system present in these alkaloids.[34,35] While there is a very recent report of total synthesis of tsitsikammamine A,[36] there are several other reports available on the synthesis and biological evaluation of the analogs of these alkaloids.[37,26,27,38]

As a part of our work on the synthesis and biological evaluation of analogs of marine natural products,[39,40] we were interested in studying the anticancer activity of analogs of zyzzyanones, tsitsikammamines, and wakayin. We report herein a facile synthesis of bispyrroloquinone ring system present in zyzzyanones and bispyrroloiminoquinone ring system present in wakayin and tsitsikammamines (Fig. 2).

Synthesis of bispyrroloquinone ring system (**4**) is outlined in Scheme 1. The synthesis was started with the previously reported *N*-tosyl-6-(benzylamino)-1*H*-indole-4,7-dione (**6**).[41] Treatment of compound **6** with ethyl acetoacetate (**7a**) in the presence of ceric ammonium nitrate (CAN) in $MeOH/CH_2Cl_2$ resulted in the formation of bispyrroloquinone derivative **8a** in 58% yield. The reaction was also carried out with 1-phenylbutane-1,3-dione (**7b**) under the same reaction conditions to afford bispyrroloquinone derivative **8b** in 67% yield. This cyclization reaction proceeds via an oxidative free radical mechanism as reported previously in the cases of aminoquinones such as 2-amino-1,4-benzoquinones[42] and 2-amino-1,4-naphoquinones.[43,44] Tosyl groups present in compounds **8a** and **8b** were removed by treatment with NaOEt in anhydrous EtOH to form the detosylated compounds **9a** and **9b** in 71% and 86%, respectively. Debenzylation of compounds **9a** and **9b** using Pd black in the presence of $HCOONH_4$ in anhydrous EtOH afforded the debenzylated compounds **10a** and **10b** in 75% and 74% yields, respectively.

We employed the same synthetic methodology for the synthesis of bispyrroloiminoquinone ring system (**5**) present in wakayin and tsitsikammamines as outlined in Scheme 2.

Treatment of previously reported *N*-tosylpyrroloiminoquinone derivative, **11a**[40] with ethyl acetoacetate (**7a**) in the presence of CAN in MeOH resulted in the formation of bispyrroloiminoquinone derivative **12a** in 38% yield. Similarly, cyclization reaction of previously reported detosylated compound **11b**[40] with ethyl acetoacetate (**7a**) in the presence of CAN in MeOH proceeded smoothly and resulted in the formation of bispyrroloiminoquinone derivative **12b** in 41% yield.

The intermediates and final products shown in Scheme 1 were found to exist as a single regioisomer in each case, as evident from one set of signals found in the NMR spectra. The structures of tricyclic quinones **9a** and **9b** were further confirmed by two-dimensional NOESY experiments. The 2D NOESY experimental data for

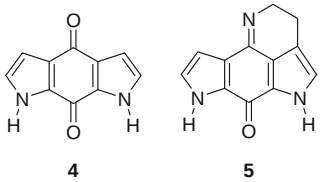
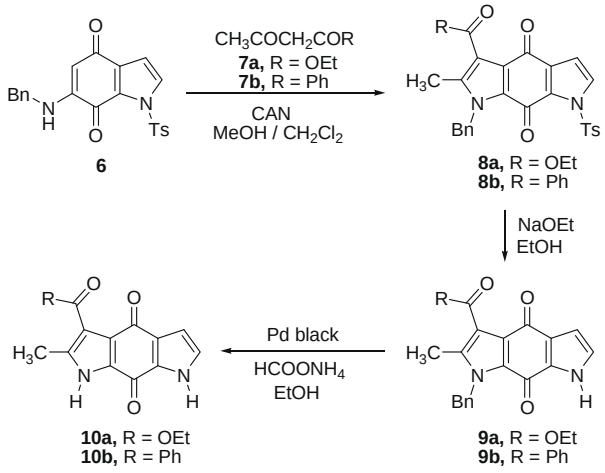
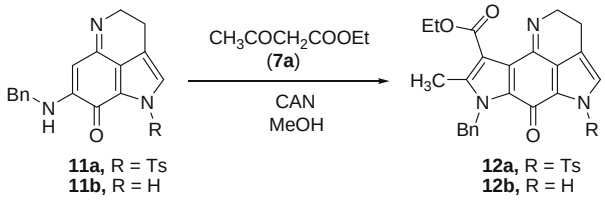


Figure 2. Bispyrroloquinone and bispyrroloiminoquinone ring systems.



Scheme 1. Synthesis of bispyrroloquinone ring system.



Scheme 2. Synthesis of bispyrroloiminoquinone ring system.

9b are shown in Figure 3. The three-proton singlet at 2.18 ppm is assigned to the methyl group at C-6 position. The two-proton singlet at 5.77 ppm is assigned to CH_2 group at N-7 position, which has a NOESY correlation with the singlet at 2.18 ppm. This assignment clearly shows that the more stable regioisomer **A** is formed as opposed to less stable regioisomer **B**. This is presumably due to the steric interaction between the benzyl group at N-7 and the phenyl ring at C-6 position in **B** regioisomer.

Similarly, the products **12a** and **12b** shown in Scheme 2 were found to exist as a single regioisomer in each case, as evident from one set of signals found in the NMR spectra. The structure of tetracyclic quinone **12b** was also confirmed by 2D NOESY spectroscopic studies (Fig. 4). The three-proton singlet at 2.55 ppm is assigned to the methyl group on the newly formed pyrrole ring. The two-pro-

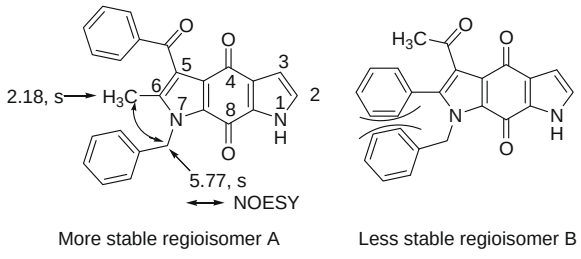


Figure 3. Two-dimensional NOESY correlation in **9b**.

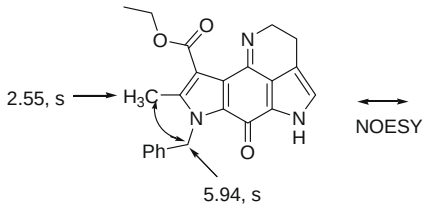


Figure 4. Two-dimensional NOESY correlation in **12b**.

ton singlet at 5.94 ppm is assigned to the benzyl CH_2 group, which has a NOESY correlation with the singlet at 2.55 ppm. This clearly shows that the structure of **12b** is the regioisomer shown in Figure 4.

2. Typical experimental procedure for the pyrrole ring formation

A solution of bicyclic quinone **6** (81 mg, 0.2 mmol) and 1-phenylbutane-1, 3-dione **7b** (130 mg, 0.8 mmol) in a mixture of MeOH (10 mL) and CH_2Cl_2 (2 mL) was stirred at room temperature for 5 min. Ceric ammonium nitrate (384 mg, 0.7 mmol) was added to this reaction mixture in four portions at 10-min intervals. The reaction mixture was stirred for another 10 min at room temperature. TLC examination (hexanes/EtOAc, 1:1) revealed that the reaction was complete. Solvent was completely removed under high vacuum, and the crude product was dissolved in CH_2Cl_2 (40 mL) and was washed with water (3×20 mL) and brine (20 mL) and dried over Na_2SO_4. The drying agent was filtered off and the solvent was concentrated in vacuo to obtain the crude product which was purified by column chromatography over silica gel (eluted with 9:1 hexanes/EtOAc) to obtain the pure tricyclic quinones **8b** in 67% yield.

In conclusion, an efficient protocol for the synthesis of the bispyrroloquinone and bispyrroloiminoquinone ring systems present in biologically active marine alkaloids such as zyzzyanones, tsitsikammamines, and wakayin is reported. While this methodology does not accomplish the synthesis of these alkaloids as such, the method reported here is the first report of the synthesis of these complex ring systems present in these alkaloids. This methodology will particularly be useful in the synthesis of various analogs of these alkaloids with specific substitution patterns. This will eventually assist in the structure activity relationship studies and optimization of the lead molecules derived from these natural products. Further studies along these lines are currently in progress.

Acknowledgments

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Supplementary data

Supplementary data associated with this paper can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.021.

References and notes

1. Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2004**, *67*, 1216–1238.
2. Haefner, B. *Drug Discovery Today* **2003**, *8*, 536–544.
3. Simmons, T. L.; Andrianasolo, E.; McPhail, K.; Flatt, P.; Gerwick, W. H. *Mol. Cancer Ther.* **2005**, *4*, 333–342.
4. Higa, T.; Tanaka, J.; Kitamura, A.; Koyama, T.; Takahashi, M.; Uchida, T. *Pure Appl. Chem.* **1994**, *66*, 2227–2230.
5. Sipkema, D.; Franssen, M. C.; Osinga, R.; Tramper, J.; Wijffels, R. H. *Mar. Biotechnol.* **2005**, *7*, 142–162.
6. Antunes, E. M.; Copp, B. R.; Davies-Coleman, M. T.; Samaai, T. *Nat. Prod. Rep.* **2005**, *22*, 62–72.
7. Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1–48.
8. Dijoux, M. G.; Gamble, W. R.; Hallock, Y. F.; Cardellina, J. H.; van Soest, R.; Boyd, M. R. *J. Nat. Prod.* **1999**, *62*, 636–637.
9. D'Ambrosio, M.; Guerriero, A.; Chiasera, G.; Pietra, F.; Tatò, M. *Tetrahedron* **1996**, *52*, 8899–8906.
10. Chang, L. C.; Otero-Quintero, S.; Hooper, J. N.; Bewley, C. A. *J. Nat. Prod.* **2002**, *65*, 776–778.
11. Carney, J. R.; Scheuer, P. J.; Kelly-Borges, M. *Tetrahedron* **1993**, *49*, 8483–8486.
12. Casapullo, A.; Cutignano, A.; Bruno, I.; Bifulco, G.; Debitus, C.; Gomez-Paloma, L.; Riccio, R. *J. Nat. Prod.* **2001**, *64*, 1354–1356.
13. Hu, J. F.; Schetz, J. A.; Kelly, M.; Peng, J. N.; Ang, K. K.; Flotow, H.; Leong, C. Y.; Ng, S. B.; Buss, A. D.; Wilkins, S. P.; Hamann, M. T. *J. Nat. Prod.* **2002**, *65*, 476–480.
14. Radisky, D. C.; Radisky, E. S.; Barrows, L. R.; Copp, B. R.; Kramer, R. A.; Ireland, C. M. *J. Am. Chem. Soc.* **1993**, *115*, 1632–1638.
15. Schmidt, E. W.; Harper, M. K.; Faulkner, D. J. *J. Nat. Prod.* **1995**, *58*, 1861–1867.
16. Venables, D. A.; Concepcion, G. P.; Matsumoto, S. S.; Barrows, L. R.; Ireland, C. M. *J. Nat. Prod.* **1997**, *60*, 408–410.
17. Venables, D. A.; Barrows, L. R.; Lassota, P.; Ireland, C. M. *Tetrahedron Lett.* **1997**, *38*, 721–722.
18. Copp, B. R.; Ireland, C. M.; Barrows, L. R. *J. Org. Chem.* **1991**, *56*, 4596–4597.
19. 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.
20. Hooper, G. J.; Davies-Coleman, M. T.; Kelly-Borges, M.; Coetzee, P. S. *Tetrahedron Lett.* **1996**, *37*, 7135–7138.
21. Gunasekera, S. P.; Zuleta, I. A.; Longley, R. E.; Wright, A. E.; Pomponi, S. A. *J. Nat. Prod.* **2003**, *66*, 1615–1617.
22. Perry, N. B.; Blunt, J. W.; Munro, M. H. G. *Tetrahedron* **1988**, *44*, 1727–1734.
23. Bénéteau, V.; Besson, T. *Tetrahedron Lett.* **2001**, *42*, 2673–2676.
24. Beneteau, V.; Pierre, A.; Pfeiffer, B.; Renard, P.; Besson, T. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2231–2234.
25. Kokoshka, J. M.; Capson, T. L.; Holden, J. A.; Ireland, C. M.; Barrows, L. R. *Anticancer Drugs* **1996**, *7*, 758–765.
26. Legentil, L.; Benel, L.; Bertrand, V.; Lesur, B.; Delfourne, E. *J. Med. Chem.* **2006**, *49*, 2979–2988.
27. Legentil, L.; Lesur, B.; Delfourne, E. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 427–429.
28. Zhao, R.; Oreski, B.; William Lown, J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2169–2172.
29. Ding, Q.; Chichak, K.; Lown, J. W. *Curr. Med. Chem.* **1999**, *6*, 1–28.
30. Urban, S.; Hickford, S. J. H.; Blunt, J. W.; Munro, M. H. G. *Curr. Org. Chem.* **2000**, *4*, 778–821.
31. Harayama, Y.; Kita, Y. *Curr. Org. Chem.* **2005**, *9*, 1567–1588.
32. Utkina, N. K.; Makarchenko, A. E.; Denisenko, V. A. *J. Nat. Prod.* **2005**, *68*, 1424–1427.
33. Utkina, N. K.; Makarchenko, A. E.; Denisenko, V. A.; Dmitrenok, P. S. *Tetrahedron Lett.* **2004**, *45*, 7491–7494.
34. Barret, R.; Roue, N. *Tetrahedron Lett.* **1999**, *40*, 3889–3890.
35. Zhang, L.; Cava, M. P.; Rogers, R. D.; Rogers, L. M. *Tetrahedron Lett.* **1998**, *39*, 7677–7678.
36. Rives, A.; Delaine, T.; Legentil, L.; Delfourne, E. *Tetrahedron Lett.* **2009**, *50*, 1128–1130.
37. Hoang, H.; Huang, X.; Skibo, E. B. *Org. Biomol. Chem.* **2008**, *6*, 3059–3064.
38. Pringel, E.; Gentili, J.; Terreux, R.; Fenet, B.; Barret, R. *Lett. Org. Chem.* **2005**, *2*, 378–381.
39. Shinkre, B. A.; Raisch, K. P.; Fan, L.; Velu, S. E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2890–2893.
40. Shinkre, B. A.; Raisch, K. P.; Fan, L.; Velu, S. E. *Bioorg. Med. Chem.* **2008**, *16*, 2541–2549.
41. Sadanandan, E. V.; Pillai, S. K.; Lakshmikantham, M. V.; Billimoria, A. D.; Culpepper, J. S.; Cava, M. P. *J. Org. Chem.* **1995**, *60*, 1800–1805.
42. Chuang, C.-P.; Tsai, A. I. *Tetrahedron* **2007**, *63*, 11911–11919.
43. Chen, H.-L.; Lin, C.-Y.; Cheng, Y.-C.; Tsai, A.-I.; Chuang, C.-P. *Synthesis* **2005**, 977–985.
44. Tseng, C.-M.; Wu, Y.-L.; Chuang, C.-P. *Tetrahedron* **2004**, *60*, 12249–12260.