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Total Syntheses of Tambjamines C, E, F, G, H, I and J, BE-18591, and a Related Alkaloid from the Marine Bacterium *Pseudoalteromonas tunicata*

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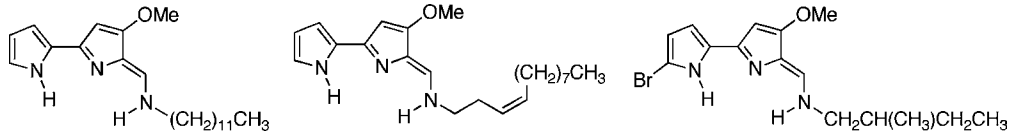
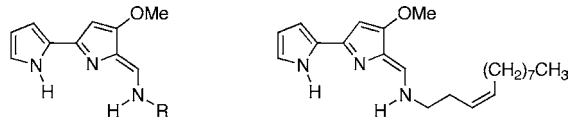
ABSTRACT



BE-18591 (**5**) "new" Tambjamine (**6**) Tambjamine J (**11**)

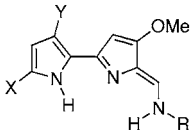
The acetate salts of tambjamines C, E, and F (2–4, respectively), as well as those of the related alkaloids BE-18591 (5) and 6, have been prepared by treatment of bipyrrole aldehyde 16 with the relevant amine in the presence of acetic acid. The 5′-bromo-analogue, 30, of compound 16 has also been prepared and used to obtain the acetate salts of tambjamines G, H, I, and J (8–11 respectively).

The tambjamines (**1**−**12**)[1] are a group of bipyrrolic alkaloids that have been isolated from various marine and terrestrial sources.[2] In some instances they have been implicated in the chemical defense mechanisms of the organisms from which they were first obtained.[3] A number of these compounds have also been shown to possess intriguing biological properties, a feature that is probably unsurprising given their structural relationship to the tripyrrolic prodigiosin family of alkaloids, members of which display very promising cytotoxic and immunosuppressive properties.[4] For example, tambjamine **5** (aka BE-18591) has been shown to inhibit immunoproliferation and gastritis in rabbits,[5] while screening of tambjamine I (**10**) against a 60-cell-line panel shows that



1 R = H (T.A)
2 R = $CH_2CH(CH_3)_2$ (T.C)
3 R = CH_2CH_3 (T.E)
4 R = $(CH_2)_2Ph$ (T.F)
5 R = $(CH_2)_{11}CH_3$ (BE-18591)

6



7 R = H, X = Br, Y = H (T.B)
8 R = CH_2CH_3, X = Br, Y = H (T.G)
9 R = $CH_2CH_2CH_3$,X = Br, Y = H (T.H)
10 R = $CH_2CH(CH_3)_2$,X = Br, Y = H (T.I)
11 R = $CH_2CH(CH_3)CH_2CH_3$, X = Br, Y = H (T.J)
12 R = $CH_2CH(CH_3)_2$, X = H, Y = Br (T.D)

(1) For convenience, and because they each possess the same bipyrrolic core, we have designated all of the natural products **1**−**12** as tambjamines even though one of these, **5**, has been assigned the code-name BE-18591 while another, **12**, has only been identified as a "...new member of the tambjamine class..." and remains to be given a letter designation.

(2) (a) Carté, B.; Faulkner, D. J. *J. Org. Chem.* **1983**, *48*, 2314 (tambjamines A−D). (b) Lindquist, N.; Fenical, W. *Experientia* **1991**, *47*, 504 (tambjamines E and F). (c) Kojiri, K.; Nakajima, S.; Suzuki, H.; Okura, A.; Suda, H. *J. Antibiot.* **1993**, *46*, 1799 (BE-18591). (d) Blackman, A. J.; Li, C. *Aust. J. Chem.* **1994**, *47*, 1625 (tambjamines G−J). (e) Franks, A.; Haywood, P.; Holmström, C.; Egan, S.; Kjelleberg, S.; Kumar, N. *Molecules* **2005**, *10*, 1286 (cmpd **6**).

(3) Carté, B.; Faulkner, D. J. *J. Chem. Ecol.* **1986**, *12*, 795.

(4) For reviews of such topics see: (a) Manderville, R. A. *Curr. Med. Chem. − Anti-Cancer Agents* **2001**, *1*, 195. (b) Fürstner, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 3582. See also: (c) Baldino, C. M.; Parr, J.; Wilson, C. J.; Ng, S.-C.; Yohannes, D.; Wasserman, H. H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 701.

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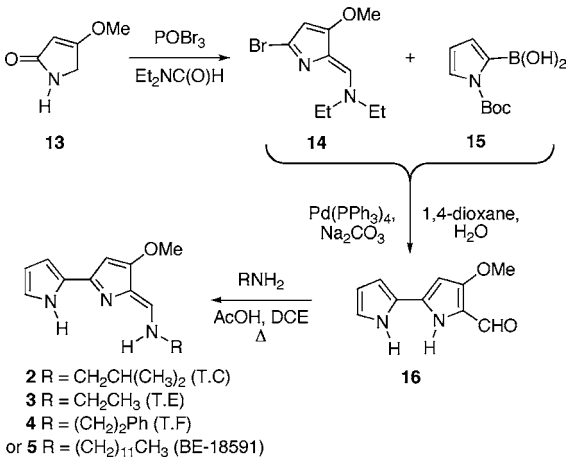
it has average GI_{50} and LC_{50} values of 1.6 and 18 μM, respectively.[4a] Certain tambjamines have also been observed to bind duplex DNA and can cleave this biomolecule in the presence of Cu(II).[4a] While the tambjamines have been manipulated chemically for the purposes of securing a library of analogues,[6] they do not appear to have been the subject of any total synthesis studies. Accordingly, we now report the de novo preparation of all but three members of the class using straightforward and unambiguous methods that have permitted the confirmation of the structures of these compounds. The present work should also allow for a more comprehensive evaluation of the biological properties of these intriguing alkaloids.

The route used in establishing total syntheses of tambjamines **2**−**5** is shown in Scheme 1. This relies upon the

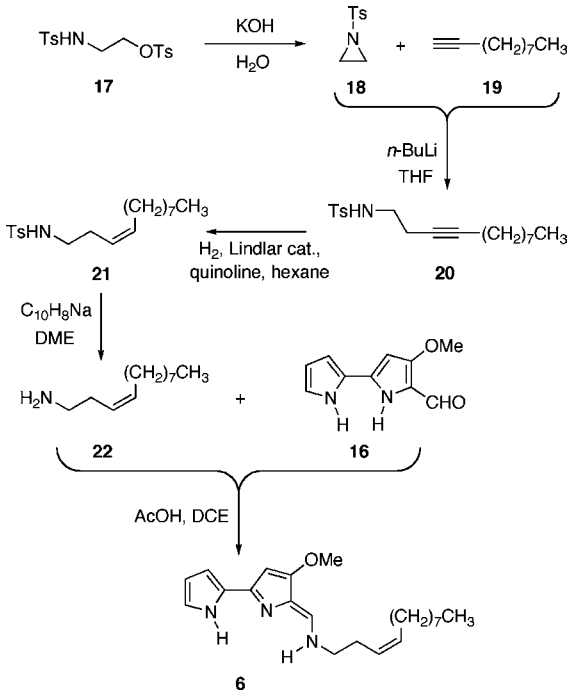
Scheme 1



recently reported and very concise protocol of Lavallée and co-workers[7] for the synthesis of aldehyde **16**, a pivotal but previously difficult to access intermediate associated with various syntheses of prodigiosin[4] and a compound that is also generated by base hydrolysis of the non-brominated tambjamines.[6] Thus, as reported by Lavallée and co-workers,[7] commercially available 4-methoxy-3-pyrolin-2-one (**13**) was subjected to a Vilsmeier−Haack reaction using $POBr_3$ and diethylformamide, and the ensuing azafulvene **14** (49%) engaged in a Suzuki−Miyaura cross-coupling reaction[8] with the readily available boronic acid **15**[9] to give the required aldehyde **16** in 95% yield. Reaction of a solution of this last compound in 1,2-dichloroethane (DCE) with the relevant range of commercially available alkyl amines in the presence of acetic acid at 18−50 °C then afforded the acetate salts of tambjamines **2**−**5** in yields ranging from 69 to 100%. For example, treatment of aldehyde **16** with 1-aminododecane under the specified conditions produced the acetate salt of BE-18591 (**5**) in 100% yield. The spectral data derived from this material matched those reported for the natural product.[2c,10] Thus far, we have been unable to identify conditions under which aldehyde **16** reacts with ammonia or a surrogate thereof so as to provide useful quantities of tambjamine A (**1**).

The unsaturated primary amine required for the preparation of tambjamine **6** by the method just described has not been reported in the literature but was readily generated by the route outlined in Scheme 2. Thus, following a protocol

Scheme 2



reported by Bulkowski,[11] the bis-tosyl derivative, **17**, of ethanolamine was treated with aqueous KOH to give aziridine **18**[11] (96%) that was then subjected to nucleophilic ring-opening with the anion derived from 1-decyne (**19**) using a procedure reported by Gronquist and Meinwald.[12] The ensuing internal alkyne **20** (42%) was subject to hydrogenation using Lindlar's catalyst in the presence of quinoline[13] so as to afford the *Z*-alkene **21** in 99% yield. Reductive cleavage of the sulfonamide residue within this last compound using sodium naphthalenide in 1,2-dimethoxyethane

(5) Tanigaki, K.; Sato, T.; Tanaka, Y.; Ochi, T.; Nishikawa, A.; Nagai, K.; Kawashima, H.; Ohkuma, S. *FEBS Lett.* **2002**, *524*, 37.

(6) Davis, R. A.; Carroll, A. R.; Quinn, R. J. *Aust. J. Chem.* **2001**, *54*, 355.

(7) Dairi, K.; Tripathy, S.; Attardo, G.; Lavallée, J.-F. *Tetrahedron Lett.* **2006**, *47*, 2605.

(8) For a review of the palladium-catalyzed cross-coupling and related reactions involving pyrroles see: Banwell, M. G.; Goodwin, T. E.; Ng, S.; Smith, J. A.; Wong, D. J. *Eur. J. Org. Chem.* **2006**, 3043.

(9) Martina, S.; Enkelmann, V.; Wegner, G.; Schlüter, A.-D. *Synthesis* **1991**, 613.

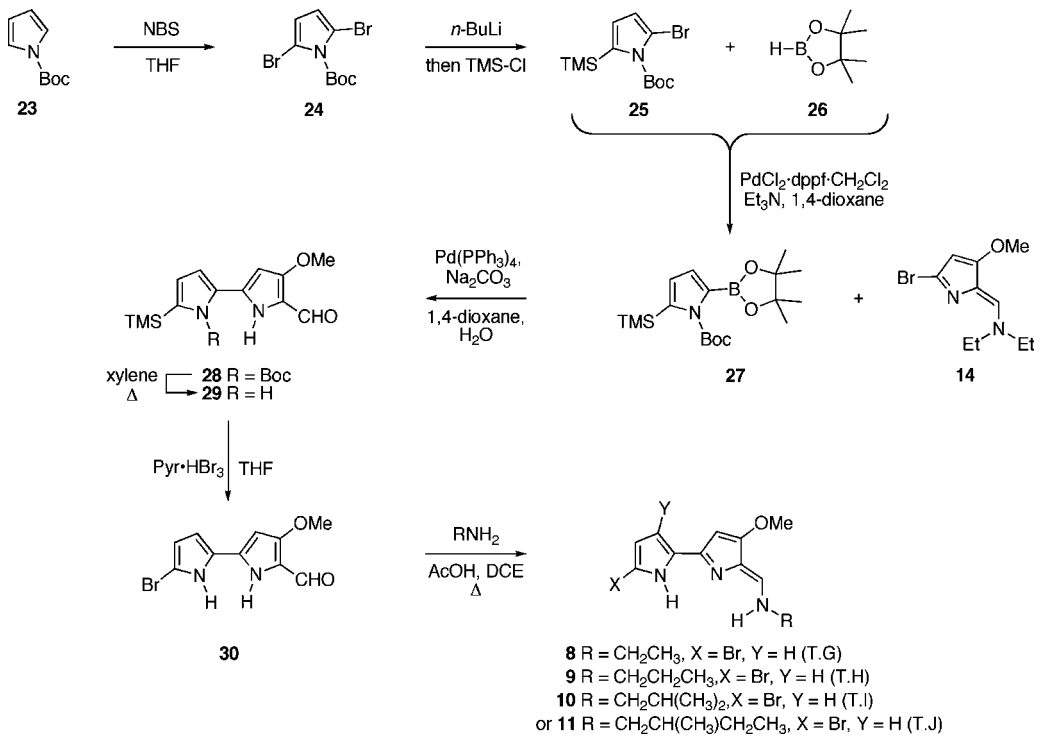
(10) We believe such comparisons are legitimate since it has been reported (see ref 2d) that there is little difference between the NMR spectra of various tambjamines and those of the corresponding acetate salts.

(11) Martin, A. E.; Ford, T. M.; Bulkowski, J. E. *J. Org. Chem.* **1982**, *47*, 412.

(12) Gronquist, M. R.; Meinwald, J. *J. Org. Chem.* **2001**, *66*, 1075.

(13) Overman, L. E.; Brown, M. J.; McCann, S. F. *Org. Synth.* **1989**, *68*, 182.

Scheme 3



(DME)[14] then afforded the required amine **22** (72%) that engaged in the by now standard condensation with aldehyde **16** to give tambjamine **6** (32%). The ^{1}H and ^{13}C NMR spectra derived from compound **6** match those recorded on the natural product.[2e] Furthermore, the infrared and mass spectral data obtained on the synthetic material were in full accord with the assigned structure.

Our initial attempts to generate the requisite bromo-analogues of compound **16** that could be used to prepare tambjamines **7**−**12** involved treating the aldehyde **16** with various electrophilic brominating agents. Unfortunately, under all the conditions investigated only complex mixtures of products were obtained. Accordingly, directed syntheses of such compounds were pursued. Eventually, the route shown in Scheme 3 was established as a method for obtaining the 5′-bromo-analogue, **30**, of compound **16**. Thus, following protocols established by Weinreb et al.,[15] the readily available *N*-Boc protected pyrrole **23** was subjected to 2-fold bromination with *N*-bromosuccinimide (NBS) and the ensuing 2,5-dibrominated derivative **24** (98%) treated with *n*-BuLi then trimethylsilyl chloride (TMS-Cl). In this manner the *C*-silylated compound **25**[15] was obtained in 61% yield. Miyaura borylation of this material[8] using borane **26** then afforded the pyrrole **27** (80%) that could be engaged in a Suzuki−Miyaura cross-coupling reaction with azafulvene **14** so as to afford a chromatographically separable mixture of compounds **28** (23%) and **29** (60%). Heating the former product in refluxing xylene effected thermolytic cleavage of the associated Boc-group and thus delivered further quantities of the TMS-derivative **29** (100%) of the aldehyde **30**. The spectral data derived from compound **29** were in full accord with the assigned structure, but final confirmation of this followed from a single-crystal X-ray analysis. The derived ORTEP diagram is shown in Figure 1. Disappointingly, the silylated pyrrole **29** failed to engage in a clean *ipso*-

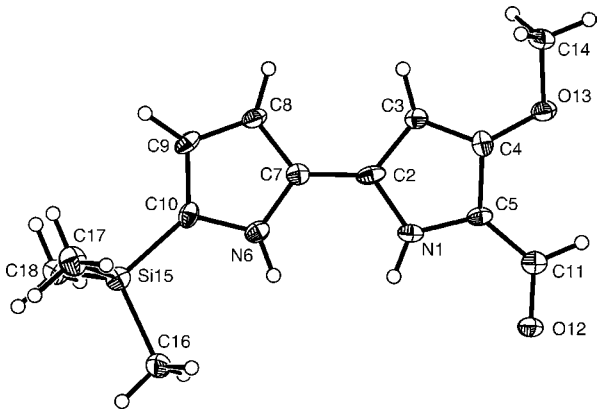


Figure 1. Structure of molecule one of $C_{13}H_{18}N_2O_2Si$ (**29**) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

(14) Ji, S.; Gortler, L. B.; Waring, A.; Battisti, A.; Bank, S.; Closson, W. D.; Wriede, P. *J. Am. Chem. Soc.* **1967**, *89*, 5311.
(15) Stein, D.; Anderson, G. T.; Chase, C. E.; Koh, Y.-h.; Weinreb, S. M. *J. Am. Chem. Soc.* **1999**, *121*, 9574.

substitution reaction upon exposure to NBS. In contrast, reaction of substrate **29** with freshly prepared pyridinium hydrobromide perbromide[16] led to the desired product **30** in 76% yield. Reaction of this last compound with the relevant range of alkyl amines in the presence of acetic acid under the same sorts of conditions defined above then afforded, after conventional flash chromatographic purification over silica gel, the acetate salts of tambjamines **8**−**11** in yields ranging from 81 to 99%. The spectral data derived from each of these materials matched those reported for the corresponding natural products, some of which have also been isolated as their acetate salts.[2d]

(16) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; John Wiley and Sons: New York, 1967; p 967.

Acknowledgment. We thank the Institute of Advanced Studies and the Australian Research Council for generous financial support.

Supporting Information Available: Full experimental procedures; ^{1}H and/or ^{13}C NMR spectra of compounds **2**−**6**, **8**−**11**, **14**, **16**, **20**−**22**, and **27**−**30**; the single-crystal X-ray data for compound **29** (CCDC number 659930). This material is available free of charge via the Internet at http://pubs.acs.org.

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