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Synthesis of (±)-Phloeodictine A1

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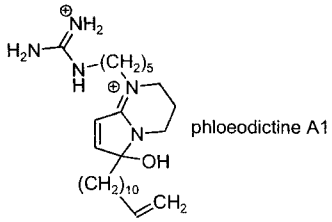
ABSTRACT

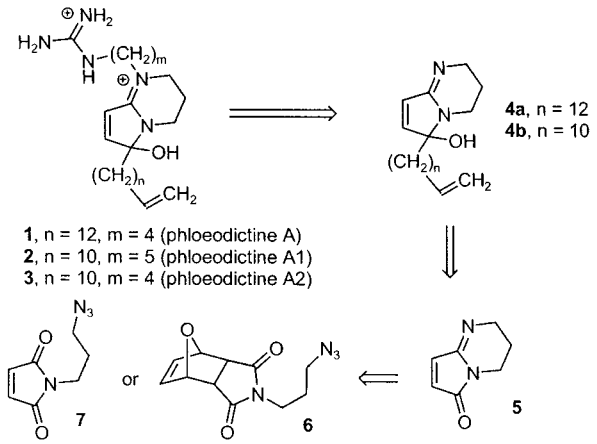


The antitumor antibiotic phloeodictine A1 (2) has been synthesized by a convergent seven-step route in 8% overall yield. The key step was the Eguchi aza-Wittig reaction of 6 to give 13 followed by a retro Diels−Alder reaction to liberate 5. Addition of 11-dodecenylmagnesium bromide to 5 to give 4b, alkylation with 18b, and deprotection completed the first synthesis of 2.

Phloeodictines A (**1**), A1 (**2**), and A2 (**3**) were isolated from the New Caledonian sponge *Phloeodictyon* sp. by Païs and co-workers.[1] They exhibit in vitro antibacterial activity against Gram-positive and Gram-negative bacteria and are moderately cytotoxic against KB cells. They possess a 6-hydroxy-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrimidinium skeleton that presents a considerable synthetic challenge. We envisaged that they could be prepared from **4** by alkylation with the appropriate length guanidino alkyl side chain (Scheme 1). Addition of the appropriate length side chain to amide **5** should provide **4**. We envisioned that **5** might be available from azido maleimide **7** by an Eguchi aza-Wittig reaction.[2] However, we were concerned that the electron-poor double bond of **7** would not be compatible with introduction of the azide or the phosphine used for the aza-Wittig reaction,[3] so we developed an alternate route using azide **6** in which the double bond of **7** was protected as the Diels−Alder adduct with furan.

Reaction of the furan-maleic anhydride Diels−Alder adduct **8** with 3-aminopropanol in MeOH at 56 °C for 3 days provided 70% of imide **9**,[4] which was converted quantitatively to mesylate **10** with Et_3N and MsCl (Scheme 2). Reaction of **10** with NaN_3 in DMF for 14 h at 25 °C afforded azide **6**. To our surprise, azide **6** rapidly polymerized on concentration, presumably by cycloaddition of the azide

Scheme 1



(1) (a) Kourany-Lefoll, E.; Païs, M.; Sévenet, T.; Guittet, E.; Montagnac, A.; Fontaine, C.; Guénard, D.; Adeline, M. T. *J. Org. Chem.* **1992**, *57*, 3832−3835. (b) Kourany-Lefoll, E.; Laprévote, O.; Sévenet, T.; Montagnac, A.; Païs, M. *Tetrahedron* **1994**, *50*, 3415−3426.

(2) Eguchi, S.; Takeuchi, H. *J. Chem. Soc., Chem. Commun.* **1989**, 602−603.

(3) In fact, reaction of the mesylate precursor to **7** with azide destroyed the double bond. For addition of azide to maleimides, see: Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959−8960.

(4) Zhou, Z.-h.; Chen, R.-y. *Synth. Commun.* **2000**, *30*, 3527−3533.

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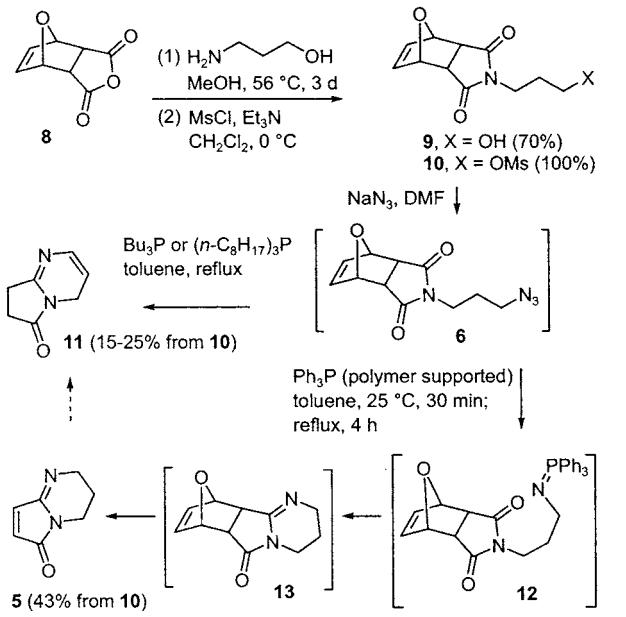
Scheme 2



and strained double bond.[5] The DMF solution of azide **6**, was therefore diluted with toluene, washed with water to remove DMF, dried, and immediately subjected to the aza-Wittig reaction.

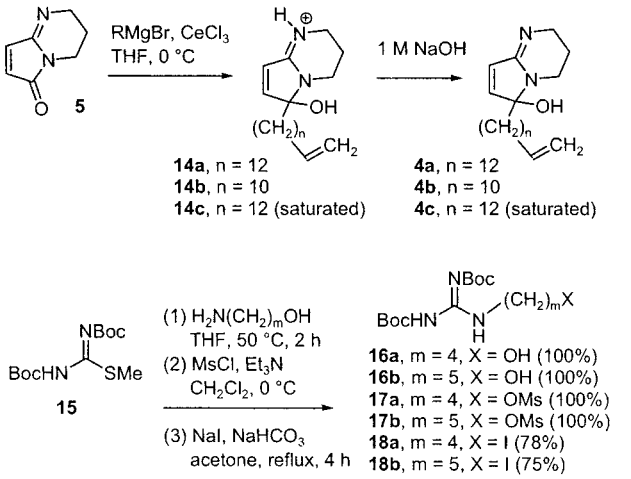
Reaction of **6** with Bu_3P or $(n\text{-}C_8H_{17})_3P$[6] in toluene at reflux for 4 h gave bicyclic amidine **11**[7] in 15−25% yield from mesylate **10**, rather than the desired amidine **5**. A plausible mechanism involves loss of nitrogen from azide **6** at 25 °C to give ylide **12**, which should undergo an aza-Wittig reaction on heating to provide **13**. A thermal retro Diels−Alder reaction will give **5**, which might undergo a base-catalyzed isomerization to give **11**. We thought that this isomerization might be prevented by the use of less basic Ph_3P.[8]

Reaction of **6** with Ph_3P in toluene at reflux for 4 h gave the desired amidine **5**, which cannot be easily separated from Ph_3PO. Fortunately, polystyrene-supported Ph_3P[9] worked equally well. Unreacted phosphine and phosphine oxide byproducts were removed by filtration, giving pure **5** in 43% yield from **10** after Florisil chromatography. Heating the reaction for only 2−3 h provided 8−13% of **13** and 20−25% of **5**, indicating that the retro Diels−Alder reaction occurs, at least primarily, after the aza-Wittig reaction. Reaction of **5** with either Bu_3P or Bu_3PO in toluene at reflux for 4 h gave only traces of **11**, while heating **5** with DBU gave 5−10% of **11**, indicating that the mechanism for the formation of **11** from **10** and trialkylphosphines is complex.

Although we were able to use **5** successfully for the synthesis of phloeodictine A1, it would have been desirable to keep the double bond protected as the Diels−Alder adduct until later in the synthesis. The aza-Wittig reaction requires toluene at reflux, so it was not possible to prepare **13** without also converting most of it to **5**. We therefore investigated more stable Diels−Alder adducts. The anthracene−maleic anhydride adduct was elaborated to the aza-Wittig product analogous to **13**. However, it now was impossible to effect the retro Diels−Alder reaction. The aza-Wittig product distilled at 300 °C under reduced pressure without loss of anthracene.

Addition of Grignard reagents to **5** proceeded poorly. The best results were obtained by adding the appropriate Grignard reagent[10] to a 1:1 mixture of **5** and $CeCl_3$ in THF at 0 °C (Scheme 3). The reaction was quenched with aqueous

Scheme 3



NH_4Cl solution, and the mixture was extracted into CH_2Cl_2 and concentrated. The residue was triturated with pentane to give 40−45% of 80−90% pure **14** as a brownish unstable solid. Washing a CH_2Cl_2 solution of **14** with 1 M NaOH solution afforded **4** as a brown oil that was used immediately for the next step.

The electron-deficient ring double bond of **4** is too reactive to permit the elaboration of the guanidine after addition of the side chain.[11] We therefore chose a convergent route using iodide **18** containing a protected guanidine on the other end of the chain. Reaction of **15** with the appropriate ω-amino-1-alkanol in THF at 50 °C for 2 h gave **16** quantitatively.[12] Mesylation and displacement with iodide afforded **18** as shown in Scheme 3.

(5) For related polymerizations, see: (a) Johnson, K. E.; Lovinger, J. A.; Parker, C. O.; Baldwin, M. G. *J. Polym. Sci., Polym. Lett. Ed.* **1966**, *4*, 977−979. (b) Gilliams, Y.; Smets, G. *Makromol. Chem.* **1968**, *117*, 1−11.

(6) Separation of **11** from $(n\text{-}C_8H_{17})_3PO$ was easier than from the more polar Bu_3PO.

(7) For related compounds, see: (a) Jokić, M.; Škarić, V. *J. Chem. Soc., Perkin Trans. 1* **1989**, 757−763. (b) Spiessens, L. I.; Anteunis, M. J. O. *Bull. Soc. Chim. Belg.* **1984**, *93*, 191−203.

(8) Issleib, V. K.; Bruchlos, H. *Z. Anorg. Allg. Chem.* **1962**, *316*, 1−11.

(9) Bernard, M.; Ford, W. T. *J. Org. Chem.* **1983**, *48*, 326−332.

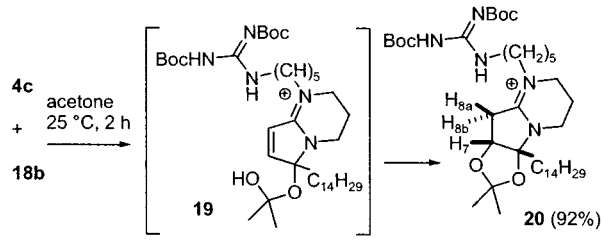
(10) Unsaturated Grignard reagents were prepared in THF from Mg and the known ω-bromo-1-alkenes: Watson, M. D.; Wagener, K. B. *Macromolecules* **2000**, *33*, 5411−5417.

(11) Alkylation of **4c** with 4-chlorobutyl triflate proceeded cleanly. Azide added to the ring double bond during attempted S_N2 reaction with the chlorobutyl side chain.

(12) (a) Botta, M.; Corelli, F.; Maga, G.; Manetti, F.; Renzulli, M.; Spadari, S. *Tetrahedron* **2001**, *57*, 8357−8367. (b) Ishiwata, T.; Hino, T.; Koshino, H.; Hashimoto, Y.; Nakata, T.; Nagasawa, K. *Org. Lett.* **2002**, *4*, 2921−2924. (c) Slassi, A.; Sumanas, R. PCT Int. Appl. Patent WO 9,514,-027, 1995; *Chem. Abstr.* **1996**, *124*, 9337b.

Nucleophilic substitution of a neutral substrate (**18**) with a neutral nucleophile (**4**) should proceed best in a polar solvent, since the transition state is much more polar than the starting materials. Reaction of **4c** with **18b** in acetone for 2 h at 25 °C provided 92% of acetonide **20** (Scheme 4).

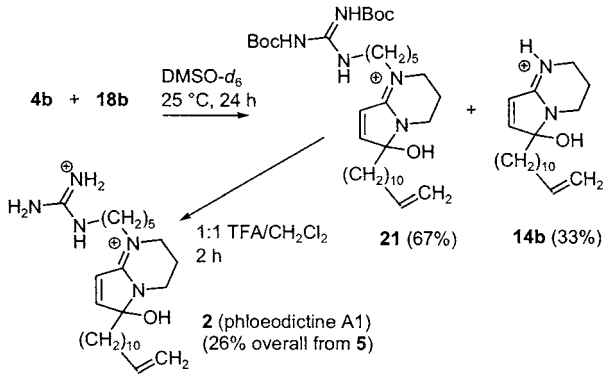
Scheme 4



The structure was confirmed by HSQC and HMBC experiments. H_7, H_{8a}, and H_{8b} absorb at δ 4.67 (dd, 1, $J = 5.2$, <1 Hz), 3.85 (dd, 1, $J = 17.5$, 5.2 Hz), 2.96 (dd, 1, $J = 17.5$, <1 Hz), respectively. The initial alkylation reaction occurred as expected. The hydroxy group reacted with acetone to form hemiacetal **19**, which underwent an intramolecular conjugate addition to give **20**. Amidine **4** is insoluble in CH_3CN, so we then investigated the use of DMSO as a solvent. This was particularly appealing since the progress of the reaction could be monitored by the shifts of the absorptions of the alkene hydrogens in DMSO-d_6.

Reaction of **4b** [δ 6.51 (d, 1, $J = 6.1$) and 6.00 (d, 1, $J = 6.1$)] and **18b** in DMSO-d_6 for 1 day afforded a 2:1 mixture of the desired alkylation product **21** [δ 7.39 (d, 1, $J = 6.1$) and 7.13 (d, 1, $J = 6.1$)] and protonated amidinium salt **14b** [δ 7.30 (d, 1, $J = 6.1$) and 6.52 (d, 1, $J = 6.1$)] (Scheme 5).

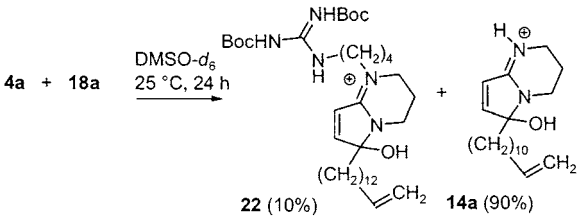
Scheme 5



The mixture was diluted with water and extracted with CH_2Cl_2, which was concentrated. Even though **21** is a salt, it is more soluble in CH_2Cl_2 than in water, while **14b** remains in the water layer. Purification at this point was difficult, so the mixture was deprotected by stirring in 1:1 TFA/CH_2Cl_2 for 2 h. Concentration and reverse-phase flash chromatography using MeOH, 0.2 M aqueous NaCl, and THF adjusted to pH 2 as described in the isolation paper afforded phloeodictine A1 (**2**) in 26% overall yield from **5**. The ^{1}H and ^{13}C NMR, HSQC, and FAB mass spectral data are identical to those reported.[1b]

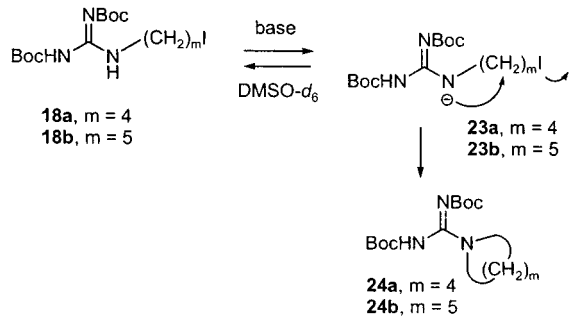
We then turned our attention to the preparation of phloeodictine A (**1**) from **4a** and **18a**. Unfortunately, reaction in DMSO-d_6 as described above for the preparation of **21** yielded only 10% of the desired product **22** and 90% of protonated amidinium salt **14a** (Scheme 6).

Scheme 6



Amidine **4** is not only a nucleophile but also a strong base that can reversibly deprotonate the protected guanidine of **18** to give anion **23**. We thought that **23a** should undergo an intramolecular S_N2 reaction to give five-membered ring pyrrolidine **24a**[13] much more rapidly than **23b** does to give six-membered ring piperidine **24b**[14] (Scheme 7). This was

Scheme 7



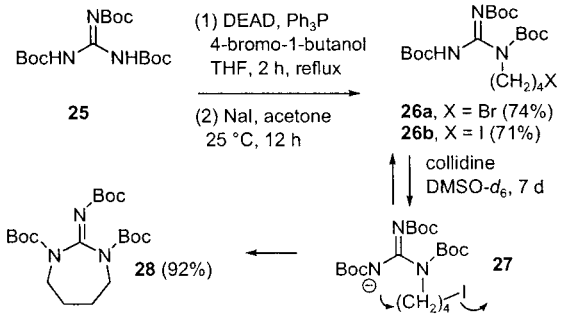
confirmed by examination of the cyclization of **18a** and **18b** with 2 equiv of collidine or $(i\text{-Pr})_2$EtN in DMSO-d_6. After 1 day, **18a** cyclized to give 80−90% of **24a**, while **18b** afforded only 10−15% of **24b**.

We then decided to prepare iodobutyl guanidines with the internal nitrogen protected so that a pyrrolidine could not be formed by deprotonation and intramolecular S_N2 reaction. Alkylation of *N*,*N*′,*N*″-tri-Boc-guanidine (**25**) with 4-bromo-1-butanol, DEAD, and Ph_3P by the procedure of Goodman[15]

(13) Feichtinger, K.; Zapf, C.; Sings, H. L.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 3804−3805.
(14) (a) Yong, Y. F.; Kowalski, J. A.; Lipton, M. A. *J. Org. Chem.* **1997**, *62*, 1540−1542. (b) Guo, Z.-X.; Cammidge, A. N.; Horwell, D. C. *Synth. Commun.* **2000**, *30*, 2933−2943.
(15) Feichtinger, K.; Sings, H. L.; Baker, T. J.; Matthews, K.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 8432−8439.

afforded 74% of bromide **26a**, which was converted to 71% of iodide **26b** with NaI in acetone (Scheme 8). Unfortunately,

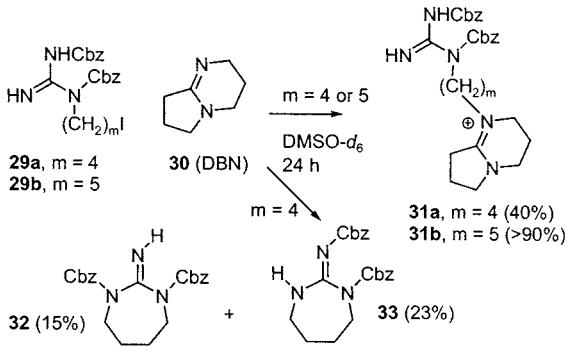
Scheme 8



attempted alkylation of **4a** with **26b** in DMSO-d_6 gave only protonated amidinium salt **14a**. Deprotonation followed by cyclization was still the major reaction. Treatment of **26b** with 2 equiv of collidine in DMSO-d_6 provided 50% of **28**[16] after 1 day and 92% after 7 days. Even though the cyclization of **26b** was slower than the cyclization of **18a**, the alkylation was no more successful. The third Boc group will make the remaining NH proton more acidic, so that the equilibrium may be shifted to protonated amidinium salt **14a** and anion **27**.

We then prepared bis Cbz-protected guanidines **29a** and **29b** from the known alcohols.[17] Alkylation of DBN (**30**) with **29b** in DMSO-d_6 provided **31b** quantitatively, while alkylation with **29a** affords only 40% of **31a** and 15 and 23% of cyclization products **32** and **33**, respectively (Scheme 9). We did not investigate this approach to **1** further because the alkylation proceeds much more cleanly with DBN than with

Scheme 9



4, the Cbz groups cannot be removed in the presence of the side chain double bond, and the bis Boc protected guanidine analogous to **29a** cannot be prepared by the same procedure.

In conclusion, we have developed a convergent seven-step route to the antitumor antibiotic phloeodictine A1 (**2**) that proceeds in 8% overall yield. We have developed a four-step synthesis of the novel and synthetically versatile bicyclic amidine **5** using the furan Diels−Alder adduct as a protecting group for the double bond. The key step is the Eguchi aza-Wittig reaction of **6** to give **13** followed by a retro Diels−Alder reaction to liberate **5**. Use of polystyrene-supported Ph_3P prevents isomerization of **5** and facilitates purification of the polar product. Addition of 11-dodecenylmagnesium bromide, alkylation with **18b**, and deprotection completes an efficient synthesis of **2**.

Acknowledgment. We thank the National Institutes of Health (GM-50151) for financial support. We thank Mr. Zheng Chen for carrying out preliminary experiments.

Supporting Information Available: Experimental procedures and copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For similar cyclizations, see: (a) Ueda, T.; Oh, R.; Nagai, S.-i.; Sakakibara, J. *J. Heterocycl. Chem.* **1998**, *35*, 135−139. (b) Meszárosová, K.; Holý, A.; Masojídková, M. *Collect. Czech. Chem. Commun.* **2000**, *65*, 1109−1125. (c) Le Merrer, Y.; Gauzy, L.; Gravier-Pelletier, C.; Depezay, J.-C. *Bioorg. Med. Chem.* **2000**, *8*, 307−320.

(17) Snider, B. B.; Shi, Z. *J. Org. Chem.* **1993**, *58*, 3828−3839.