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New Protocols for the Assembly of the Tetracyclic Framework Associated with the Aromatic Erythrina Alkaloids

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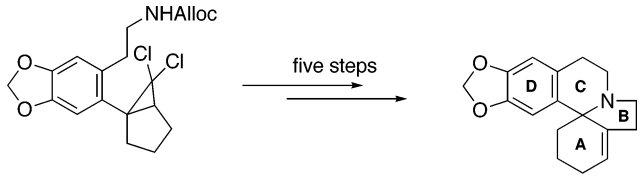
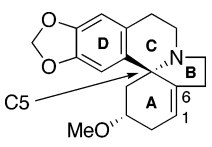
ABSTRACT



4c **2**

Treatment of the anion derived from the ring-fused *gem*-dichlorocyclopropane 4c with silver tetrafluoroborate afforded the spirocyclic compound 17 in 74% yield. Product 17 was readily converted, over three steps, into the *β*-iodoethyl derivative 20 and treatment of this latter compound with *n*-Bu_3SnH then afforded, in 93% yield and via a radical addition/elimination sequence, compound 2 incorporating the ABCD framework of the aromatic erythrina alkaloids.

The erythrina alkaloids represent a relatively large group of compounds that have been isolated from a variety of plant sources, most particularly those of the genus *Erythrina*, which is common in tropical and subtropical regions.[1] From a structural point of view, these natural products can be divided into two subgroups which vary in the nature of the D-ring, with erythramine (**1**) being representative of those where this is an aromatic one.[1,2] Extracts of the source plants have been used in folkloric medicine in various parts of the world and it has been shown that certain of the title alkaloids display curare-like and hypnotic activity. Some also display interesting insecticidal properties. As a result, significant effort has been devoted to the assembly of the erythrinan framework associated with such alkaloids as well as to the synthesis of the natural products themselves.[2b,3,4] Padwa's analysis[3a] of



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(1) (a) Chawla, A. S.; Kapoor, V. K. In *The Alkaloids*: *Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Elsevier Science Ltd.: Oxford, UK, 1995; Vol. 9, pp 86−153. (b) Tsuda, Y.; Sano, T. In *The Alkaloids*; Cordo, G. A., Ed.; Academic Press: New York, 1996; Vol. 48, pp 249−337. (c) Tanaka, H.; Tanaka, T.; Etoh, H.; Goto, S.; Terada, Y. *Heterocycles* **1999**, *51*, 2759 and references therein.

(2) Homoerythrina alkaloids, in which the C-ring is seven- rather than six-membered (see structure **2**), are a group of closely related (and relatively common) natural products. For useful points-of-entry into the literature on such compounds see: (a) Toda, J.; Niimura, Y.; Sano, T.; Tsuda, Y. *Heterocycles* **1998**, *48*, 1599. (b) Tietze, L. F.; Rackelmann, N. *Pure Appl. Chem*. **2004**, *76*, 1967. (c) Cassidy, M. P.; Özdemir, A. D.; Padwa, A. *Org. Lett*. **2005**, *7*, 1339.

(3) For a comprehensive listing of synthetic studies reported up until early 2003 see: (a) Lee, H. I.; Cassidy, M. P.; Rashatasakhon, P.; Padwa, A. *Org. Lett*. **2003**, *5*, 5067. More recent work includes: (b) Fukumoto, H.; Esumi, T.; Ishihara, J.; Hatakeyama, S. *Tetrahedron Lett*. **2003**, *44*, 8047. (c) Reimann, E.; Ettmayr, C. *Monatsh. Chem*. **2004**, *135*, 1143. (d) Allin, S. M.; Streetly, G. B.; Slater, M.; James, S. L.; Martin, W. P. *Tetrahedron Lett*. **2004**, *45*, 5493. (e) Kim, G.; Kim, J. H.; Lee, K. Y. *J. Org. Chem*., **2006**, *71*, 2185. (f) Blake, A. J.; Gill, C.; Greenhalgh, D. A.; Simpkins, N. S.; Zhang, F. *Synthesis* **2005**, 3287. See, also, ref 2b.

(4) For synthetic approaches involving annulation of a B-ring to ACD-ring substructures see: (a) Danishefsky, S. J.; Panek, J. S. *J. Am. Chem. Soc*. **1987**, *109*, 917. (b) Ahmed-Schofield, R.; Mariano, P. S. *J. Org. Chem*. **1987**, *52*, 1478. (c) Chou, C.-T.; Swenton, J. S. *J. Am. Chem. Soc*. **1987**, *109*, 6898. (d) Irie, H.; Shibata, K.; Matsuno, K.; Zhang, Y. *Heterocycles* **1989**, *29*, 1033. (e) Yasui, Y.; Suzuki, K.; Matsumoto, T. *Synlett* **2004**, 619.

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such work reveals that a dozen or so different approaches have been explored including ones that are relevant to the studies described below and involving B-ring annulation to a C5-spiro-tetrahydroisoquinoline or ACD-tricyclic substructure.[4] The method by which the latter substructure is obtained and then annulated with the B-ring varies considerably. For example, in the Danishefsky synthesis of (±)-3-demethoxyerythratidinone[4a] this tricyclic motif was assembled by using a two-step cyclization/fragmentation sequence involving a readily accessible AD-ring precursor. The B-ring was then incorporated through a radical cyclization process that led to site-specific enol acetate formation and, thence, completely regioselective introduction of the $\Delta^{1(6)}$-double bond within the target natural product. In the Mariano synthesis[4b] of the erythrina alkaloid framework, the ACD system was generated via an electron-transfer-induced photocyclization process and this was followed by the application of Claisen or ketone−enolate alkylation/cyclization sequences to install the B-ring. On the other hand, in their synthesis of (±)-3-demethoxyerythratidinone, Irie and co-workers[4d] employed, as key steps, an iminium ion-mediated spirocyclization reaction to assemble the ACD substructure from an AD-ring precursor and then an intramolecular Wittig olefination protocol to annulate the B-ring.

The continuing need for the development of more efficient routes to the D-ring aromatic erythrina alkaloid framework,[2−4] as well as our interest in exploiting *gem*-dihalocyclopropanes as building blocks for the synthesis of natural products,[5] prompted us to pursue the synthetic strategy defined in Figure 1. In particular, we considered the possibility that the framework, **2**, associated with the title alkaloids (e.g., **1**) could be assembled from the ACD-ring precursor **3** by using a C-radical-initiated 5-*exo*-trig cyclization/Cl-radical elimination process to annulate the B-ring.[6] It was expected that an appropriate precursor to compound **3** would be accessible via a spirocyclization process initiated by the Ag(I)-promoted electrocyclic ring-opening of the *gem*-dichlorocyclopropane **4** then trapping of the resulting π-allyl cation by a tethered nitrogen nucleophile. Such a sequence of events would not only serve to simultaneously establish the A- and C-rings of the target framework but also introduce the chlorocyclohexene residue required for the anticipated B-ring forming step. To the best of our knowledge, no such spirocyclization processes (i.e., ones initiated by electrocyclic ring-opening of *gem*-dihalocyclopropanes) have been reported previously. We now detail the successful implementation of this strategy.

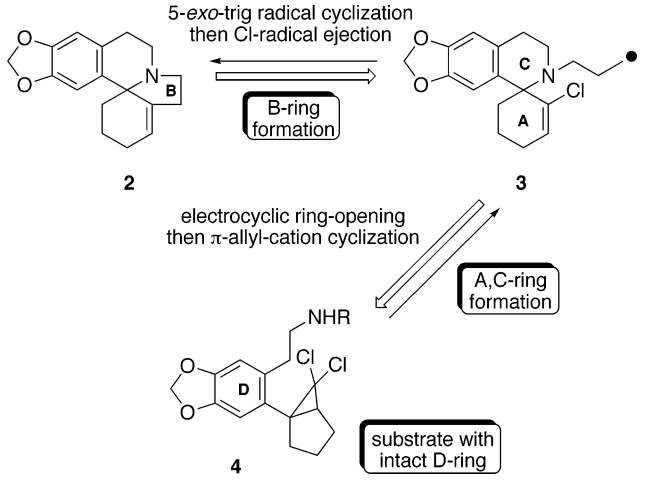


Figure 1. Key ring-forming steps leading to compound **2**.

The synthesis of an appropriate form of the *gem*-dihalocyclopropane **4** required for investigating the pivotal electrocyclic ring-opening/spirocyclization sequence was achieved in the manner shown in Scheme 1. Thus, bromopiperonal **5**[7] was subject to reaction with (methoxymethylene)triphenylphosphorane and the resulting *E*/*Z* mixture of vinyl ethers then hydrolyzed in aqueous acid to give the expected but rather unstable α-arylacetaldehyde. Reduction of this latter material with lithium borohydride in diethyl ether then afforded the previously reported alcohol **6**[8] in 81% yield (from **5**). The readily derived TBDPS-ether **7** (99%) was then treated with *n*-butyllithium in the presence of triisopropylborate and after acidic workup the boronic acid **8** (89%) was obtained. Suzuki−Miyaura cross-coupling[9] of compound **8** with the enol triflate **9**[10] derived from cyclopentanone gave the arylated cyclopentene **10**, which was then treated with tetra-*n*-butylammonium fluoride. The ensuing alcohol **11** (49% from **8**) was converted, under standard conditions, into the corresponding acetate **12** (84%). Compound **12** was then subjected to reaction with dichlorocarbene generated under Makosza's phase-transfer catalysis (PTC)[11] conditions and with accompanying ultrasonication as defined by Xu and Brinker.[12] The resulting cyclopropane-acetate **13** was treated with potassium carbonate in methanol and the ensuing alcohol (97% from **12**) converted into the corresponding mesylate (94%), which was, in turn, reacted with

(5) (a) Banwell, M. G.; Gable, R. W.; Peters, S. C.; Phyland, J. R. *J. Chem. Soc., Chem. Commun.* **1995**, 1395. (b) Banwell, M.; Edwards, A.; Harvey, J.; Hockless, D.; Willis, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2175. (c) Banwell, M. G.; Harvey, J. E.; Hockless, D. C. R.; Wu, A. W. *J. Org. Chem.* **2000**, *65*, 4241. (d) Banwell, M. G.; Ebenbeck, W.; Edwards, A. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 114. (e) Banwell, M. G.; Harvey, J. E.; Jolliffe, K. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2002. (f) Banwell, M. G.; Edwards, A. J.; Jolliffe, K. A.; Smith, J. A.; Hamel, E.; Verdier-Pinard, P. *Org. Biomol. Chem.* **2003**, *1*, 296. (g) Taylor, R. M. *Aust. J. Chem.* **2003**, *56*, 631. (h) Banwell, M. G.; Sydnes, M. O. *Aust. J. Chem.* **2004**, *57*, 537. For a review of certain aspects of our work in this area see: (i) Banwell, M. G.; Beck, D. A. S.; Stanislawski, P. C.; Sydnes, M. O.; Taylor, R. M. *Curr. Org. Chem.* **2005**, *9*, 1589.

(6) For a related cyclization process involving C-radical addition to a haloalkene see: Knapp, S.; Gibson, F. S.; Choe, Y. H. *Tetrahedron Lett.* **1990**, *31*, 5397.

(7) Conrad, P. C.; Kwiatkowski, P. I.; Fuchs, P. L. *J. Org. Chem.* **1987**, *52*, 586.

(8) Ogata, Y.; Ikeda, M.; Nomoto, S.; Okita, M.; Shimomura, N.; Kaneko, T.; Yamanaka, T.; Hishinuma, I.; Nagakawa, J.; Hirota, K.; Miyamoto, K.; Horie, T.; Wakabayashi, T. European patent EP0281098, 1988; *Chem. Abstr.* **1989**, *110*, 95206.

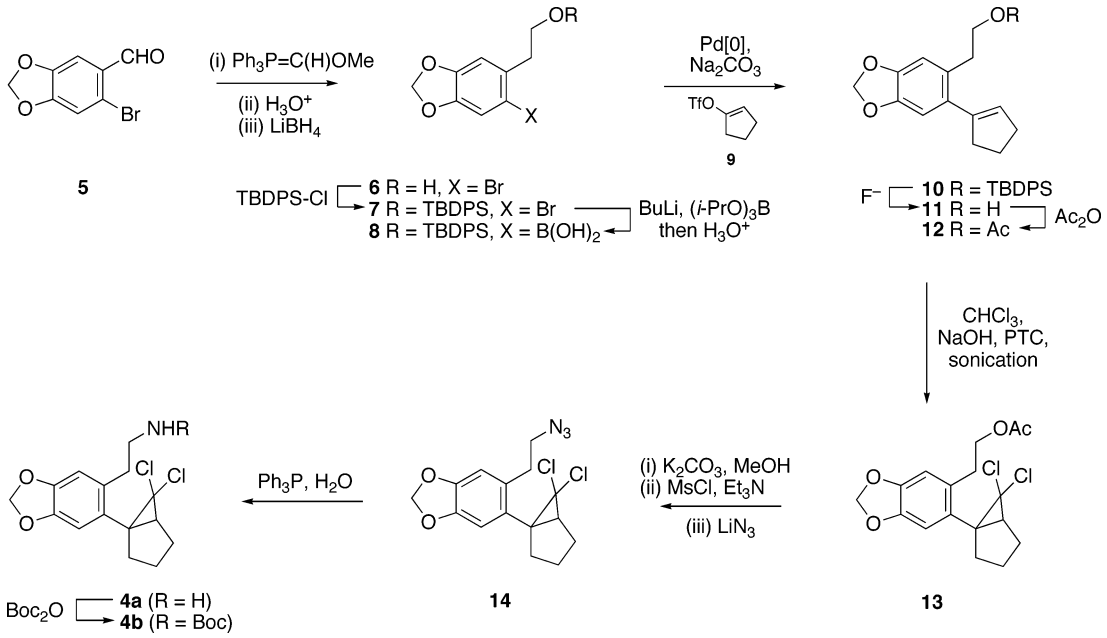
(9) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(10) Takagi, J.; Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 8001 and references therein.

(11) (a) Makosza, M.; Wawrzyniewicz, M. *Tetrahedron Lett.* **1969**, 4659. For a discussion of the methods available for the generation of dihalocarbenes see: (b) Banwell, M. G.; Reum, M. E. In *Advances in Strain in Organic Chemistry*; Halton, B., Ed.; JAI Press: London, UK, 1991; Vol. 1, pp 19−64.

(12) Xu, L.; Brinker, U. H. In *Synthetic Organic Sonochemistry*; Luche, J.-L., Ed.; Plenum Press: New York, 1998; pp 344−345.

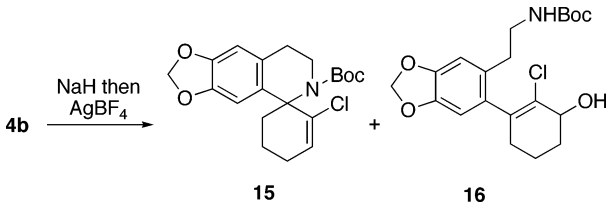
Scheme 1



lithium azide in DMF (at 18 °C for 16 h then 35 °C for 2−3 h), thereby producing azide **14** (87%). In the penultimate step of the reaction sequence, compound **14** was subjected to a Staudinger reaction by using triphenylphosphine in aqueous THF and the primary amine **4a** was thus obtained. Since we have shown, in earlier work,[5] that carbamate derivatives of primary amines act as effective nitrogen-centered nucleophiles in the intramolecular trapping of π-allyl cations derived from electrocyclic ring-opening of *gem*-dihalocyclopropanes, compound **4a** was converted, through reaction with Boc_2O, into the corresponding Boc-derivative **4b** (45% from **14**). The spectral data derived from compound **4b** and all of its precursors were in full accord with the assigned structures.

With the requisite substrate, **4b**, in hand, examination of the proposed spirocyclization reaction [viz. **4** → precursor of **3**] began. In initial experiments (Scheme 2), the carbamate

Scheme 2

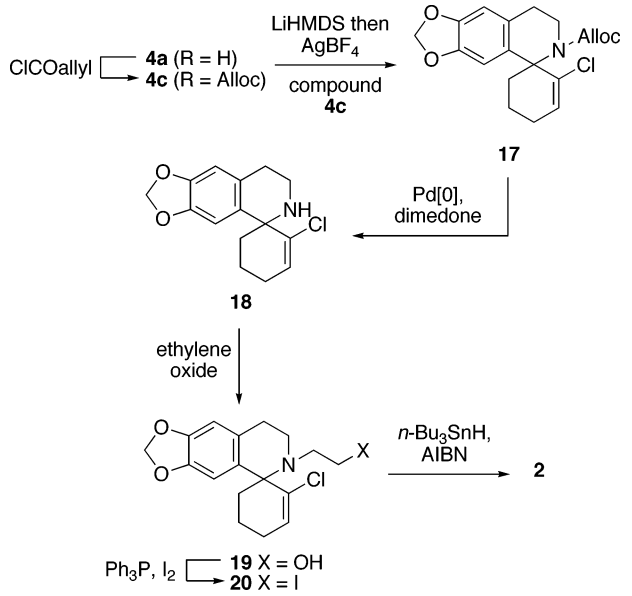


4b was treated with $AgBF_4$ in THF at 0−18 or 45 °C. Under such conditions the hoped-for spirocyclization product **15** was observed but this was accompanied by roughly equal quantities (16%) of a compound tentatively assigned as allylic alcohol **16**. Presumably this by-product arises from cyclopropane ring-cleavage within substrate **4b** then trapping of the resulting cation by water. This outcome suggested that the carbamate nitrogen was not sufficiently nucleophilic (perhaps because of the intervention of steric and/or electronic factors) to capture the allylic cation resulting from cyclopropane ring-opening. In an effort to enhance the nucleophilicity of the carbamate nitrogen within compound **4b** this was first treated with NaH and the *N*-centered anion presumed to have been generated under such conditions was then treated with $AgBF_4$. Once again, however, a ca. 1:1 mixture of products **15** and **16** was obtained.

In view of the difficulties just described, the less sterically demanding Alloc-protected species **4c** (97% ex. amine **4a**) was prepared (Scheme 3) and then deprotonated with LiHMDS. The conjugate base so formed was then treated with $AgBF_4$ and under such conditions the desired spirocyclic compound **17** was now obtained in 74% yield and as the only characterizable product of reaction. Removal of the Alloc group within the latter compound was achieved under conditions first defined by Kunz and Unverzagt[13] and afforded the corresponding secondary-amine **18** (95%). As a necessary prelude to installing the B-ring associated with final target **2**, compound **18** was reacted with an excess of ethylene oxide in methanol contained in a sealed tube and heated at 45 °C for 23 h. The structure of the resulting crystalline alcohol **19** (68%, mp 113−115 °C), which contains the two carbons required for annulating the final (B-) ring, was established by single-crystal X-ray analysis. Conversion of compound **19** into the corresponding iodide, **20**, was achieved under standard conditions and in 82% yield. Gratifyingly, treatment of this last species with *n*-Bu_3SnH and a trace of AIBN in toluene at 80 °C effected the

(13) Kunz, H.; Unverzagt, C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 436.

Scheme 3



anticipated C-radical cyclization/Cl-radical elimination reaction sequence and thus afforded compound **2** in 93% yield. The structure of the non-crystalline product **2** follows from comprehensive spectroscopic analysis.

The conversion of compound **4c** into the C5-spiro-tetrahydroisoquinoline **17** serves to highlight the capacity of appropriately constructed ring-fused *gem*-dihalocyclopropanes to undergo tandem electrocyclic ring-cleavage/spirocyclization reaction sequences and thus expanding the repertoire[5] of useful processes in which such readily accessible compounds can engage. Furthermore, this work also demonstrates that the halogenated alkene so-formed can be exploited in C-radical addition/halide radical elimination processes that allow for a novel and potentially highly versatile mode of carbon−carbon single-bond formation that proceeds with retention of the positional integrity of the associated carbon−carbon double bond. Work aimed at exploiting these features in a variety of contexts, including in the synthesis of various alkaloidal natural products, is now underway in these laboratories. Results will be reported in due course.

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Supporting Information Available: Preparation and characterization of compounds **5**−**14**, **4a**−**c**, **17**−**20**, and **2**; ^{1}H or ^{13}C NMR spectra of compounds **4c**, **18**, and **2** together with the ORTEP and certain other material derived from the single-crystal X-ray analysis of amino-alcohol **19** (CCDC 291532). This material is available free of charge via the Internet at http://pubs.acs.org.

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