ORGANIC LETTERS

2006
Vol. 8, No. 10
2143−2146

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

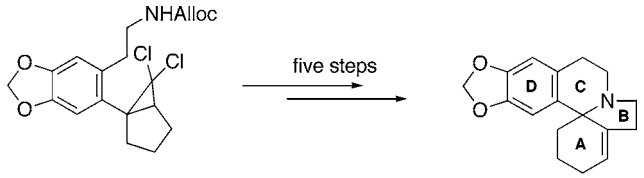
Pauline C. Stanislawski, Anthony C. Willis,[†] and Martin G. Banwell*

Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 0200, Australia

mgb@rsc.anu.edu.au

Received March 15, 2006

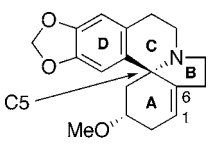
ABSTRACT



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



1

[†] Person to whom correspondence should be addressed regarding the X-ray crystallographic study reported herein (e-mail: willis@rsc.anu.edu.au).

(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.

10.1021/ol060642c CCC: $33.50
Published on Web 04/13/2006

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.

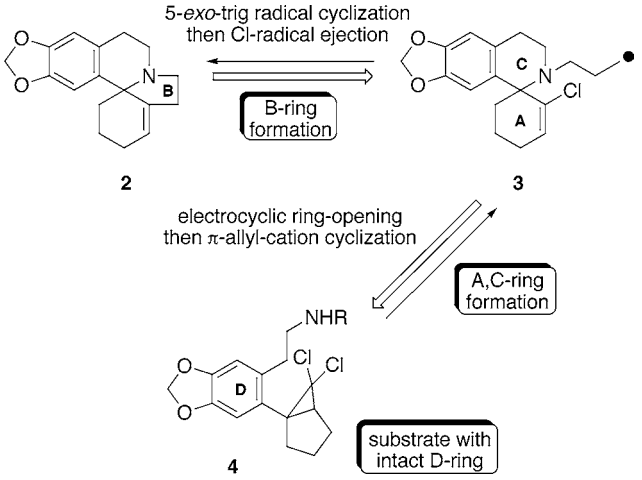


Figure 1. Key ring-forming steps leading to compound **2**.

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.

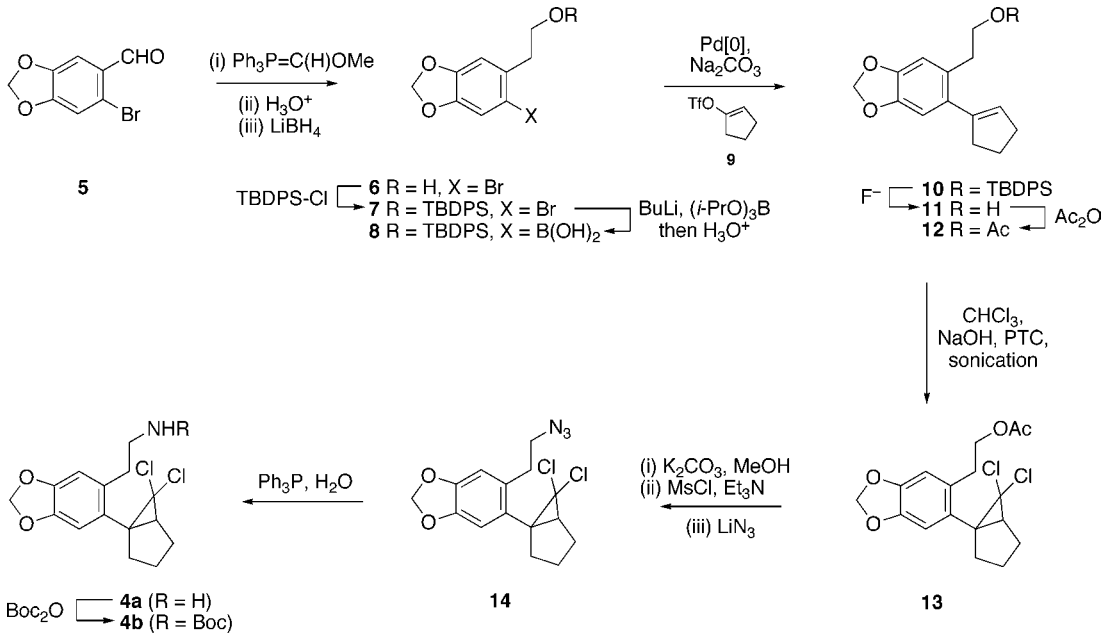
(9) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(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.

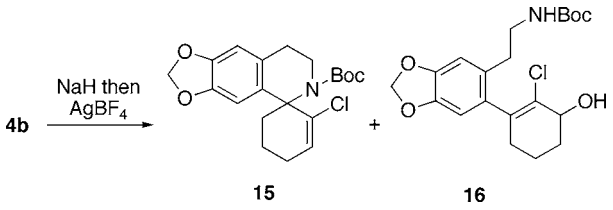
Scheme 1



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

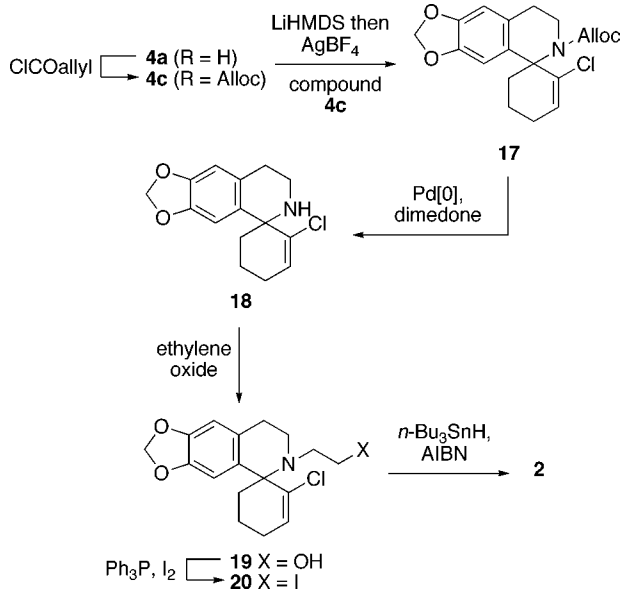


4b was treated with $AgBF_4$ in THF at 0−18 or 45 °C. Under such conditions the hoped-for spirocyclization product **15** was observed but this was accompanied by roughly equal quantities (16%) of a compound tentatively assigned as allylic alcohol **16**. Presumably this by-product arises from cyclopropane 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.

Acknowledgment. We thank the Institute of Advanced Studies and the Australian Research Council for generous financial support. Stimulating discussions with Professor S. Zard are warmly acknowledged.

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.

OL060642C