Serial Radical Cyclization of Pyranose-Derived Dienes in the Stereocontrolled Synthesis of Densely Functionalized Cyclohexanes. A Route to Woodward's Reserpine Precursor[1]

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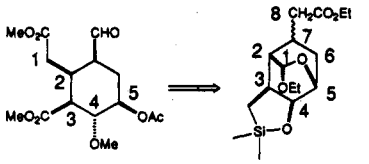
Summary: Serial radical 5-exo/6-exo cyclizations of a readily prepared hexopyranose derivative having unsaturations on-template at C-2 and off-template at C-7 lead to a tricyclic cage in which all but one of the stereocenters in an optically pure form of Woodward's densely functionalized carbocyclic precursor have been established, the "one" requiring an hydroxyl epimerization.

In their recent review of syntheses of yohimbine alkaloids, Baxter and Mariano[3] identify two major approaches: (1) elaboration of the DE ring system, followed by condensation with a tryptophyl unit containing the AB rings, and finally elaboration of ring C,[4] and (2) use of a β-carboline derivative to supply rings ABC followed by sequential development of rings D and C.[5] The first category is distinguished by Woodward's landmark synthesis of reserpine[6] and the second by the pioneering work of Szantay.[7] By-and-large, strategies in the first category have relied upon cycloaddition reactions of the 4 + 2 and 2 + 2 varieties that provide frameworks for installing the rich DE functionality. Our laboratory is interested in developing methodology for converting carbohydrates into densely functionalized carbocyles,[8] hence our attraction to the Woodward intermediate **1**. In this paper we add a novel strategy for the first approach, which features a serial 5-*exo*/6-*exo* radical cyclization of a dienic carbohydrate substrate as the key transformation, whereby the penultimate precursor of **1** has been obtained as a stable, optically pure material (*vide infra*).



1 **2**

We envisaged that both double bonds of a nona-2,7-dienyl pyranoside could be induced to undergo sequential 5-*exo* and 6-*exo* ring closures to furnish a tricyclic cage, **2**, bearing all synthons necessary for the Woodward intermediate **1**. Accordingly compound **4** was set as our first objective, and its synthesis from the Ferrier alkene **3a**[9] was readily achieved by free radical coupling of the corresponding iodide **3b** with a tin acrylate developed in the laboratories of Russell[10] and Baldwin,[11] and modified recently by us.[12] The silicon tether popularized by Nishiyama[13] and Stork[14] was attached in **5**, and treatment with tri-*n*-butyltin hydride led to the desired cage molecule **2** in high yield. Juxtaposition of **2** and **1** shows that complete functional and chiral overlap has already been achieved, except at C4, where an inversion is needed, and at C7 which exists as an epimeric mixture. With respect to the latter stereocenter, the epimeric composition depended upon the geometry of the pendant olefin in precursor **5**, which in turn depended upon the *cis*/*trans* ratio of the tin acrylate precursors.[12] However, this circumstance was of no consequence, since it proved possible to utilize both C7 epimers. In practice, tricycle **2** was not isolated but was directly subjected to Tamao's oxidation[15] leading to diol **6**.

The C7 carbethoxymethyl group of **6** is a formyl synthon, and with this in mind a vinyl group was elaborated by means of hydride reduction and selenoxide elimination as the key steps. The resulting diols **7** and **8** (1.6:1 ratio) were readily separated chromatographically. The "wrong" C7 configuration of **7** could be corrected, if necessary, by ozonolysis–epimerization–methylenation to obtain more of **8**.

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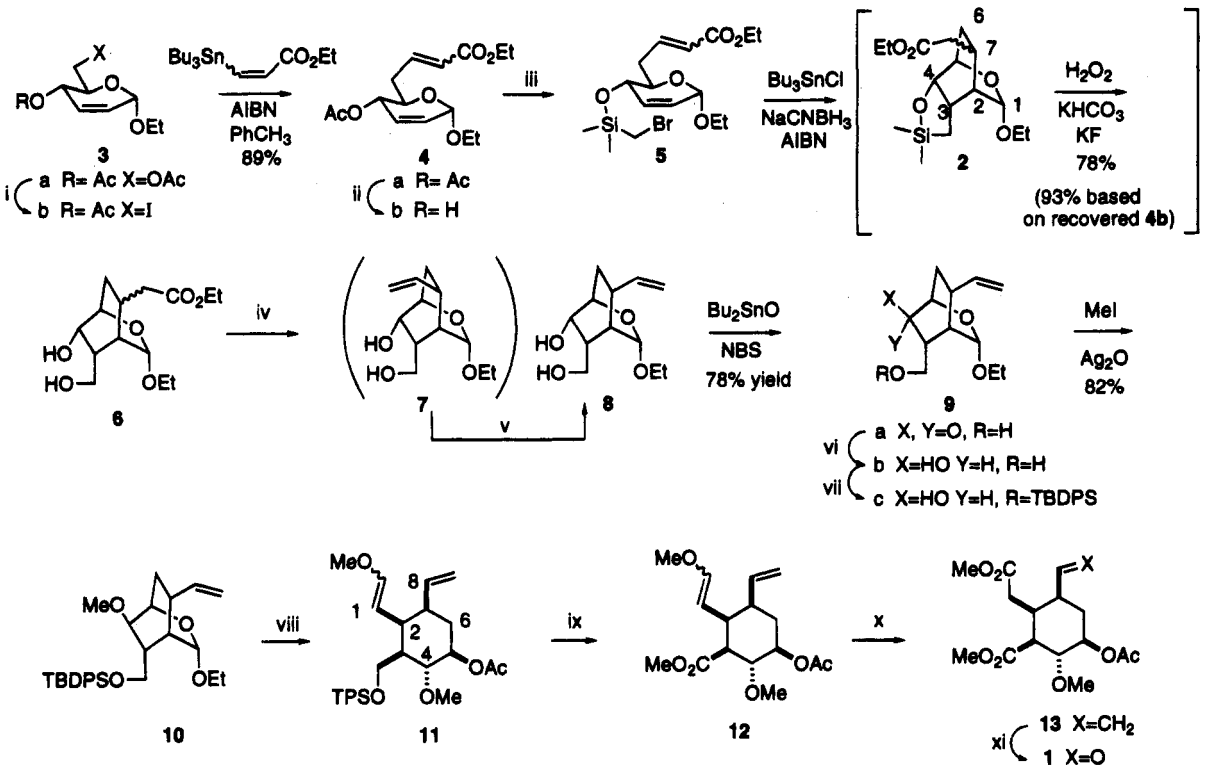
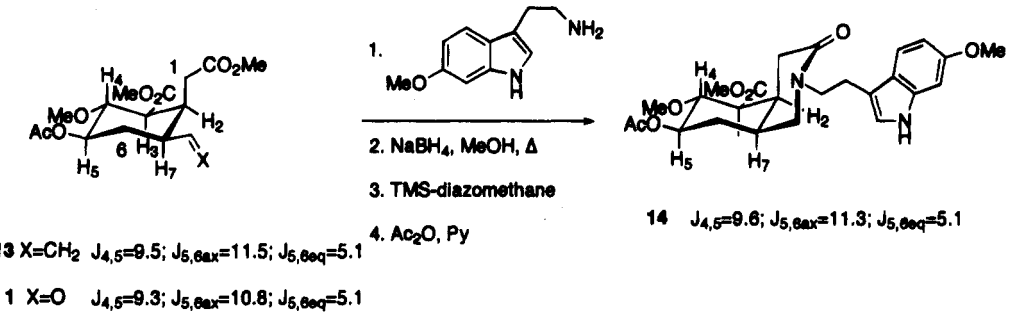
Scheme 1[a]



[a] Reagents and yields: (i) (a) MeONa, MeOH, rt, 100%, (b) TsCl, CH_2Cl_2, Py, rt, 2.5 h, 70%, (c) NaI, Ac_2O, 60 °C, overnight, 89%; (ii) MeOH, NEt_3, H_2O (8:2:1), overnight, 100%; (iii) $ClSi(CH_3)_2CH_2Br$, NEt_3, CH_2Cl_2; (iv) (a) ClTBS, imidazole, DMF, (b) $LiAlH_4$, Et_2O, 0 °C, (c) MsCl, NEt_3, CH_2Cl_2, (d) PhSeSePh, $NaBH_4$, overnight, then H_2O_2, reflux, 2 h, 75% yield from **6**, (e) $(^nBu_4)NF$, THF, 95%; (v) (a) O_3, MeOH then Me_2S, (b) K_2CO_3, MeOH, 24 h, (c) $Ph_3P^+CH_3Cl^-$, KHMDS, 72% yield of a 1:1 mixture of **7** and **8**; (vi) $NaBH(OAc)_3$, EtOAc, 0 °C to rt, 88%; (vii) TBDPSCl, NEt_3, DMAP, CH_2Cl_2, 85%; (viii) (a) AcOH, THF, H_2O (4:2:1), 90 °C, 12 h, (b) $Ph_3P^+CH_3OMeCl^-$, BuLi, THF, 74%, two steps, (c) Ac_2O, Py, 95%; (ix) (a) $(nBu_4)NF$, THF, (b) pyridiniumdichromate (PDC), DMF, (c) TMS-diazomethane, 66% three steps; (x) (a) AcOH, THF, H_2O, (4:2:1), 90 °C, (b) PDC, DMF, (c) TMS-diazomethane, 64% three steps; (xi) O_3, MeOH, then Me_2S.

Scheme 2



13 X=CH_2 $J_{4,5}$=9.5; $J_{5,6ax}$=11.5; $J_{5,6eq}$=5.1

1 X=O $J_{4,5}$=9.3; $J_{5,6ax}$=10.8; $J_{5,6eq}$=5.1

14 $J_{4,5}$=9.6; $J_{5,6ax}$=11.3; $J_{5,6eq}$=5.1

With respect to the C4 configuration, attempts to effect epimerization by Mitsunobu procedures proved unavailing,[16] even when *p*-nitrobenzoic[16b] or chloracetic[16c] acids were used. So an oxidation/reduction sequence was examined. David's bromine induced oxidation of stannylene acetals[17] proceeded with the expected regioselectivity to give ketone **9a**, and reduction with sodium triacetoxyborohydride[18] ensured hydrogen delivery from "below" to give the desired C4 orientation in **9b**. After silylation to give **9c** and methylation, the anomeric center of **10** was liberated, and use of the Levine reagent[19] paved the way to the enol ether **11**.

Simultaneous development of both methoxycarbonyl groups of **1** would have been ideal, but preliminary experiments were not encouraging. Therefore, the C3 siloxymethyl group was first processed by routine methods to give the methoxycarbonyl in **12**, and then the enol ether was converted into the second methoxycarbonyl group of **13**. Compound **13** existed as colorless, stable oil, which gave correct elemental analysis and had a specific rotation, $[\alpha]^{21}_D = -35.5°$ in chloroform. Ozonolysis then led to **1**.

In spite of its central place in reserpine synthetic methodology, it is noteworthy that aldehyde **1** has not

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been previously characterized. The "instability" recognized by Woodward,[6] and the ready epimerization subsequently suggested by Pearlman,[4a] have always been obviated by immediate reductive amination with a tryptophane derivative. Indeed, we have followed that precedent to obtain the advanced intermediate **14**. However, we have also been able to record ^{1}H NMR data which are entirely consistent with the presumed structure **1** revealing, among other things, that **1**, **13**, and **14** exist in similar conformations as revealed by the parameters shown in Scheme 2.

Supplementary Material Available: Listings of experimental procedures for the preparation of all key compounds and their NMR data (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.