GENERAL METHODOLOGY FOR CIS-HYDROISOQUINOLINE SYNTHESIS. 3. A SIXTEEN STEP SYNTHESIS OF RESERPINE[1,2]

Paul A. Wender,* John M. Schaus,[3] and Alan W. White
Department of Chemistry, Stanford University, Stanford, California 94305, U.S.A.

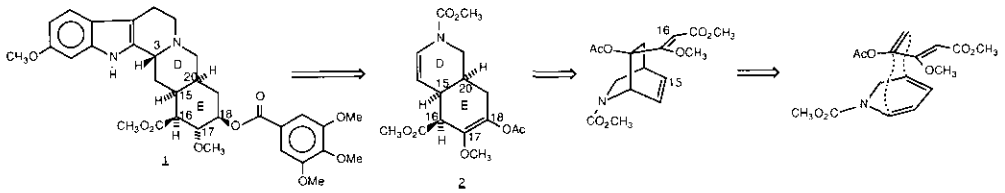
Abstract — A concise synthesis of reserpine is described based on a Diels-Alder cycloaddition, Cope rearrangement sequence for hydroisoquinoline synthesis and on a new procedure for regulating stereochemistry at C-18.

Dedicated to Gilbert Stork, a special friend and scholar, on the occasion of his 65th birthday.

Reserpine (1) has figured prominently during the last three decades as a compound of considerable medicinal importance, due largely to its extensive use in the treatment of hypertension and mental disorders.[4] These and other biological activities have drawn considerable attention to this compound and alkaloid class and have accounted in part for the early report of the first synthesis of reserpine by Woodward and coworkers.[5] The difficulty of this synthetic problem and the impressiveness of this first solution are both underscored by the absence of another synthetic success in this area for more than 20 years. In the past seven years, this situation has changed. In 1979, Pearlman[6] reported the second synthesis of reserpine. The third successful effort was reported from our laboratory in 1980[2b] and, more recently, Martin and coworkers[7] have recorded their novel solution to this problem. Concurrently, syntheses of deserpidine have been described by the groups of Szantay[8a] and Ninomiya.[8b] Works-in-progress hold the potential for further major advances in solving the generic alkaloid synthesis problems embodied in the pentacyclic skeleton of reserpine.[8]

A central problem addressed quite differently in the aforementioned approaches to reserpine is found in the construction of its stereochemically

complex E-ring. The Woodward synthesis[5] solved this problem through the use of a quinone-methyl pentadienoate Diels-Alder reaction, which afforded the reserpine E-ring with three (C-15, C-16 and C-20) of its five stereogenic centers. Pearlman's approach[6] originated from a preformed E-ring and proceeded with its further functionalization, involving at one stage a novel intramolecular, photoinduced [2+2] cycloaddition which was used to set stereochemistry at C-15 and C-20 relative to C-18. In the Martin synthesis[7] the stereochemistry at C-15 and C-16 was established through an intramolecular Diels-Alder reaction which simultaneously and efficiently produced the D- and E-rings of the target. Our own studies[2] in this area evolved from the recognition that reserpine could be elaborated from a cis-hydroisoquinoline such as **2** which in turn could be produced in one operation through a Diels-Alder/Cope rearrangement sequence. In

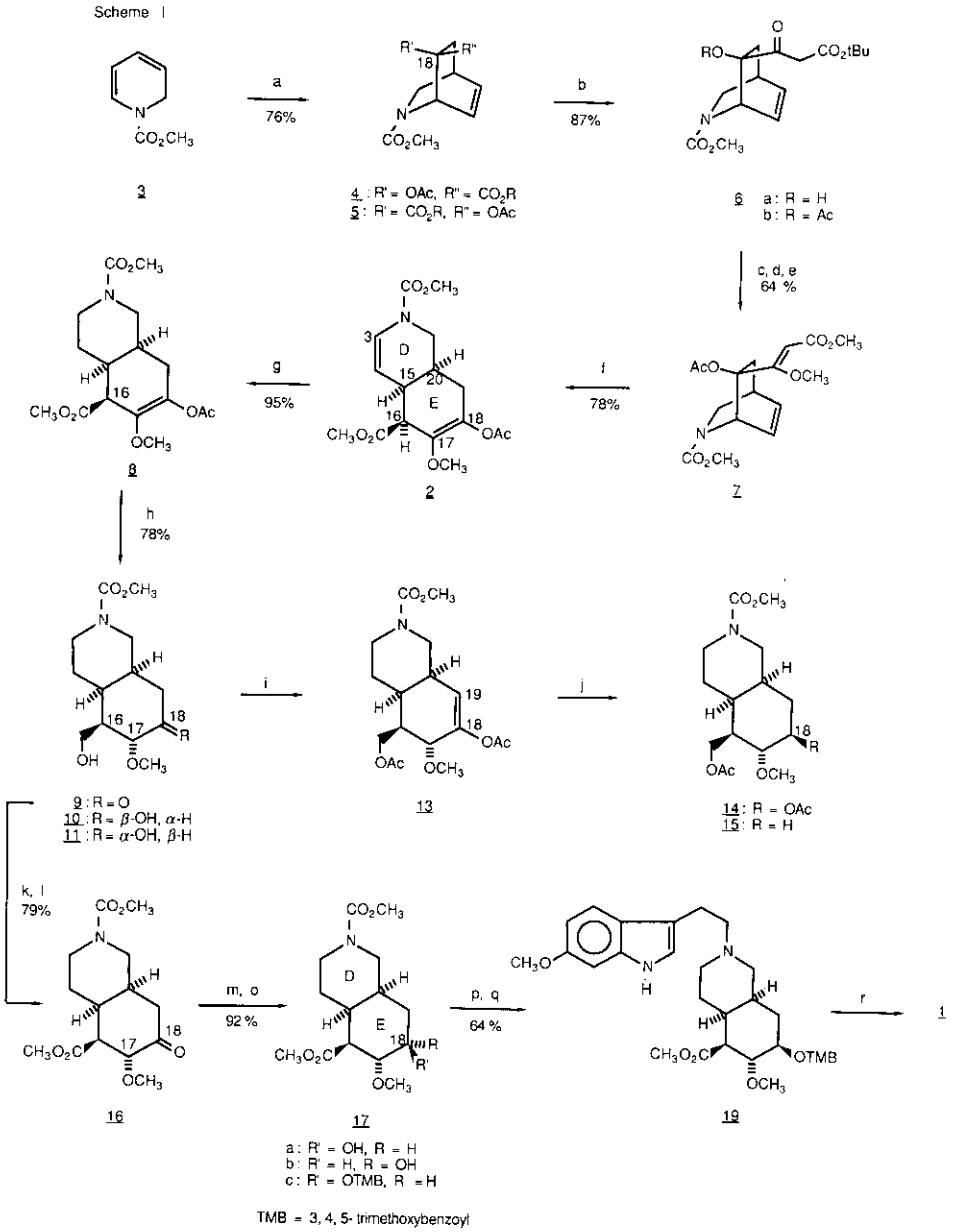


practice, this sequence was more readily achieved in separate operations which *additionally allowed for greater control over substituent introduction.* As previously reported,[2] this approach resulted in a seven step synthesis of hydroisoquinoline **2** from which reserpine was subsequently prepared. We describe herein a significantly simplified version of this strategy which more fully capitalizes on the above method for hydroisoquinoline synthesis and introduces a new method for controlling stereochemistry at the C-18 center of reserpine. This strategy provides reserpine in a uniquely short sequence of sixteen steps based on pyridine as starting material.

The synthesis of the key intermediate **2**, the first subgoal in our reserpine synthesis, was readily achieved through the general strategy for hydroisoquinoline synthesis outlined in Scheme I. The sequence starts with the Fowler[9] reduction of pyridine, employs the resultant 1,2-dihydropyridine (**3**) as a versatile diene[10] for the selective construction of ester **4**, and stereospecifically provides hydroisoquinoline **2** from **7** through a Cope rearrangement which is geometrically constrained to proceed through a boat-like transition state. Overall, this sequence produces multigram quantities of the highly functionalized hydroisoquinoline in seven steps and 20% yield based on pyridine.

Intermediate **2** is imbued by design with attributes needed for its destined

Scheme I



[a] CH_2=C(OAc)CO_2R, $PhCH_3$, hydroquinone, 120°C, 56 h. [b] $LiCH_2CO_2$-*t*-Bu, THF, -78°C ---> room temperature. [c] Ac_2O, NEt_3, DMAP. [d] CF_3CO_2H, room temperature. [e] CH_2N_2, CH_3OH, Et_2O. [f] Xylene solution, 243°C, 3 h. [g] H_2, Pd / C, EtOAc. [h] LAH, Et_2O, 0°C, 2 min. [i] $LiN(SiMe_3)_2$, -10°C, THF; then AcCl, -78°C. [j] H_2, 10% Pd / C, EtOAc. [k] Jones reagent. [l] CH_2N_2. [m] $NaBH_4$, $CeCl_3$. [o] $(TMB)_2O$, DMAP. [p] TMSI. [q] 6-methoxytryptophyl tosylate. [r] ref. 16, 7.

role in the synthesis of reserpine. In addition to possessing the required stereochemistry at C-15, C-16 and C-20 (reserpine numbering), it has differentiated oxygen functionalities at C-17 and C-18 and an oxidation level at C-3 appropriate for eventual regioselective indolization. In our first synthesis of reserpine, efforts to exploit these features were partially frustrated by the difficulty of performing sensitive reactions on such a densely functionalized framework. This problem was ameliorated by catalytic hydrogenation of the D-ring double bond (**2** → **8**) which ultimately proved more efficacious than heroic attempts to retain it through an operationally protracted exercise in protecting group chemistry. Efforts to preserve the oxidation level of the C-16 ester were also curtailed when it was found that reduction of this group under conditions (LAH) which converted the enol acetate to the corresponding enolate resulted in an enhanced selectivity for the expected axial protonation at C-17. Thus, reduction of **8** gave a single ketone isomer **9** and minor amounts of a 1:1 mixture of over-reduction products **10** and **11**. While the precise mechanistic basis for the exclusive formation of one stereoisomer corresponding to **9** was not pursued, it is reasonable to assume that the inherent axial protonation selectivity expected from conventional stereoelectronic control was augmented in this case either by a coordinative delivery of a proton from the reduced C-16 residue during workup or by complexation of this residue to the C-17 methoxy group via an aluminum bridge. The latter would then lead to a transient tricyclic intermediate with enhanced proclivity toward axial protonation. The possibility that formation of **9** was thermodynamically controlled was excluded by the finding that exposure of **9** to sodium methoxide gives a 6:1 mixture of **9** and its C-17 epimer. In view of the complete selectivity offered by the kinetic axial protonation and the operational simplification provided by reduction of the D-ring olefin, we elected to incorporate these modifications into our approach to reserpine.

The next subgoal in our design centered on the introduction of stereochemistry at C-18. The absence of stereocontrol in the formation of over-reduction products **10** and **11** when ester **8** was treated with LAH provided forewarning of the difficulty in setting the proper C-18 configuration. This concern was further afforced by the finding that reduction of the acetate of **9** with sodium borohydride gave predominantly the undesired alpha-C-18 alcohol isomer (alpha:beta = 6:1). This undesired selectivity may result in part from the stereoelectronic influence of the C-17 methoxy group which for some alpha-alkoxy ketones has been

shown to direct reduction preferentially to cis products.[11] Since catalytic hydrogenations of such systems are expected to be less influenced by this factor, reduction of **9** was studied using platinum over ferrous sulfate as catalyst.[12] This approach proved moderately successful in providing the desired beta-alcohol product as the major isomer (alpha:beta = 1:2). It was further reasoned that this selectivity could be enhanced if the functionality being reduced were more directly influenced by the structural element which was thought to control the desired selectivity, i.e., the cis-ring fusion. Thus, while the stereochemical destiny of the C-18 ketone carbon in **9** is only remotely (1,3) influenced by this ring fusion, the fate of the C-18 center could be coupled to that of the more proximate C-19 center through formation of the enol acetate **13**. Reduction of **13** should then be under vicinal stereoinductive control which, for a syn addition mechanism and convex face approach control, would result in effective 1,3-stereoinduction. In accord with this analysis, hydrogenation of **13**[13a] over 10% palladium on activated carbon produced a single C-18 acetate (**14**) in 79% yield which was subsequently shown to have the desired configuration. Hydrogenolysis product **15** was also obtained in 14% yield.

While the above sequence proved effective in completely regulating the stereochemistry at C-18 and providing an initial route to reserpine, it also increased the length of our synthesis. Differentiation of the two hydroxy groups and selective oxidation in the presence of the sensitive indole nucleus required a number of sequence-lengthening, protecting group manipulations. Subsequent studies have rectified this problem through the development of a direct method for stereocontrolled alpha-face reduction of the C-18 ketone. Toward this end, hydroxyketone **9**, the product of the ninth step in our synthesis, was oxidized with Jones reagent and the resultant acid converted with diazomethane to ester **16** in 79% overall yield. This racemic ester (**16**) was spectroscopically identical to enantiomerically pure material derived from (-)-reserpine in four steps.[13b] Because of the ready and early availability of the latter, it was used for the remaining studies. As was found with ketone **9**, reduction of **16** with sodium borohydride gave predominantly the undesired alpha-C-18 alcohol **17b**[13b] (alpha:beta = 73:27). However, when this reduction was conducted in the presence of $CeCl_3$,[14] the desired beta-C-18 alcohol **17a**[13b] was obtained in 90% yield along with less than 3% of its alpha isomer. Thus, this simple change in reaction conditions resulted in a reversal of selectivity from ca. 3:1 to 1:30,

(alpha:beta, respectively).

This new method for regulating the C-18 stereochemistry greatly simplified the remaining requirements for the synthesis of reserpine. Thus, treatment of hydroxy-ester **17a** with trimethoxybenzoyl anhydride in the presence of DMAP[15] allowed for completion of the E-ring and provided ester **17c**, spectroscopically and chromatographically identical with an authentic sample obtained by degradation of reserpine.[13b,16] Completion of the reserpine synthesis from **17c** required only deprotection of the D-ring nitrogen, attachment of the methoxytryptophyl moiety and indolization. The first task was accomplished by reaction of **17c** with trimethylsilyl iodide[17] which gave the free amine **18** in 90% yield. It is noteworthy that only one of the six methoxy groups in **17c** was cleaved under these conditions. The next step of our sequence, alkylation of the amine **18**, proceeded best with 6-methoxytryptophyl tosylate and gave 2,3-secoreserpine (**19**), which has been previously converted to reserpine in one operation by Sakai and Ogawa[16,18] and more recently by Martin and coworkers.[7] It is noteworthy that these indolizations preferentially give reserpine with 4:1 to 8:1 selectivity over isoreserpine.

In summary, the above plan allows for the synthesis of reserpine in sixteen steps from pyridine. The key intermediate **2** is prepared in multigram quantities in seven steps which proceed in 20% overall yield. This sequence can also be readily extended to other hydroisoquinoline syntheses.[2] Transformation of **2** to the completed D- and E-rings of reserpine in **17c** involves a six step sequence which proceeds in 53% overall yield. The stereochemistry at C-17 is completely controlled through axial protonation of an enolate while that at C-18 is set with 97% selectivity by sodium borohydride-cerium chloride reduction. The last three steps of our synthesis proceed in 22% yield with the final, precedented[7,16,18] indolization step giving reserpine in approximately 80-90% selectivity over its C-3 epimer.

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