The above account indicates that in imidazole thiol model systems where individual pK_a^{Im} and pK_a^{SH} values approach each other a substantial proportion of zwitterionic material is present at physiological pH and that these species are capable of nucleophilic attack on *p*-NPA.[18] This provides some precedence for the similar situation proposed to occur in papain.[3,4]

Acknowledgment. We gratefully acknowledge the financial support of the University of Alberta and the Natural Sciences and Engineering Research Council of Canada.

(17) Hupe and Jencks (Hupe, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 451-464) have shown that rate constants for acyl transfer from *p*-NPA to thiol anions show a small sensitivity to thiol basicity ($\beta_{nuc} = 0.27$) for rate-limiting attack of basic thiols.

(18) Species **2a** and **3a** are indeed catalysts. We have observed that repeated monitoring of the UV/vis spectra of the reaction of 1×10^{-4} M *p*-NPA and equimolar **2a** or **3a** at pH 7.9 leads to a reduction in [thiolate] at the same rate *p*-nitrophenoxide builds up. The analysis of the kinetic data for this adheres to second-order kinetics. The hydrolysis of the *S*-acyl intermediate, even though subject to intramolecular general base catalysis by the imidazole, is quite slow ($\sim 5 \times 10^{-5}$ s^{-1}). Brown, R. S.; Skorey, K.; Street, J. P. *J. Am. Chem. Soc.*, submitted.

Total Synthesis of (±)-Reserpine

Stephen F. Martin,*[1] Slawomir Grzejszczak, Heinrich Rüeger, and Sidney A. Williamson

Department of Chemistry, The University of Texas Austin, Texas 78712

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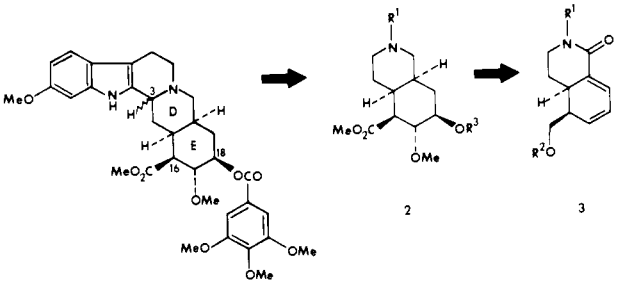
Owing to its importance as a medicinal agent that is widely prescribed for the treatment of hypertension and mental disorders, reserpine (**1**), which was originally isolated from the Indian snake root, *Rauwolfia serpentina* Benth.,[2] has been the subject of extensive chemical and pharmacological investigations.[3,4] These remarkable physiological properties coupled with its structural complexity have made reserpine an attractive target for a number of synthetic efforts,[5,6] three of which have culminated in its total synthesis.[6] The principal synthetic challenge posed by the pentacyclic nucleus of reserpine is the stereoselective elaboration of the D/E ring system, which is a *cis*-hydroisoquinoline richly endowed with stereochemistry and functionality. Consequently, several years ago we initiated an investigation, which was directed toward the design and development of a general strategy for the construction of substituted hydroisoquinolines[7] that featured as a key step the intramolecular Diels-Alder reactions[8] of azatrienes. The application of that methodology to an efficient, total synthesis of reserpine constitutes the substance of the present report.

The overall strategy for the synthesis of reserpine (**1**) required the initial preparation of a hydroisoquinoline derivative such as **3** that would be suitably functionalized for eventual modification



1 : β - H
17 : α - H

to provide the fully intact D/E ring system present in **2**. Subsequent coupling of this key structural subunit with the 6-methoxytryptophyl synthon would then afford a *seco*-dihydroreserpine analogue, which could then be cyclized to reserpine.

The first phase of the total synthesis (Scheme I) thus entailed the construction of an intermediate related to **3** via the intramolecular Diels-Alder reaction of a suitable trienic precursor. To this end, propargyl alcohol was protected (CH_3OCH_2Br, $PhNEt_2$, CH_2Cl_2, -78 °C → room temperature, 5 h; 95%) as its methoxymethyl ether derivative **4**.[9] Subjection of **4** to sequential two-carbon chain extension (*n*-BuLi; $\overline{CH_2OCH_2}$, THF, -78 °C → room temperature, 20 h; 81%) and catalytic hydrogenation (H_2/45 psi, $Pd/CaCO_3/PbO$, EtOAc, room temperature, 15 min; 96%) provided the homoallylic alcohol **5**, which was converted to the olefinic amine **6** by tosylation (*p*-TsCl, Py, CH_2Cl_2, 0 °C, 12 h; 90%) and aminolysis ($PhCH_2NH_2$, catalytic NaI, Me_2SO, room temperature, 20 h; 85%). The amine **6** was then coupled with 2-pyrone-6-carbonyl chloride[10] (Et_3N, CH_2Cl_2, -30 → 5 °C, 1.5 h) to give the trienic amide **7** in 89% yield. Subsequent thermolysis of **7** in refluxing xylene (24 h) proceeded smoothly to afford the cycloadduct **8** in 93% yield.

With the lactam **8** in hand, the next subgoal of the synthetic effort involved the stereoselective refunctionalization of the E ring. In the event, regioselective epoxidation of the more nucleophilic carbon-carbon double bond (*m*-CPBA, CH_2Cl_2, 0 °C, 6 h) proceeded with a high degree of stereoselectivity from the less encumbered α face to provide the epoxide **9** in 88% yield. Acid-catalyzed opening of the epoxide moiety [BuCH(Et)-COOH/BuCH(Et)COOLi, DME, reflux, 12 h; 90%] occurred exclusively at the allylic terminus at C(18) to afford the alcohol **10**, which was smoothly converted to the corresponding methyl ether **11** in 98% yield upon treatment with methyl iodide in the presence of silver(I) oxide. Transformation of **11** into **12**, which incorporates all of the requisite stereocenters present in the D/E ring of reserpine, was smoothly effected by catalytic hydrogenation [H_2/1800 psi, 20% $Pd(OH)_2/C$,[11] MeOH, 24 h, room tempera-

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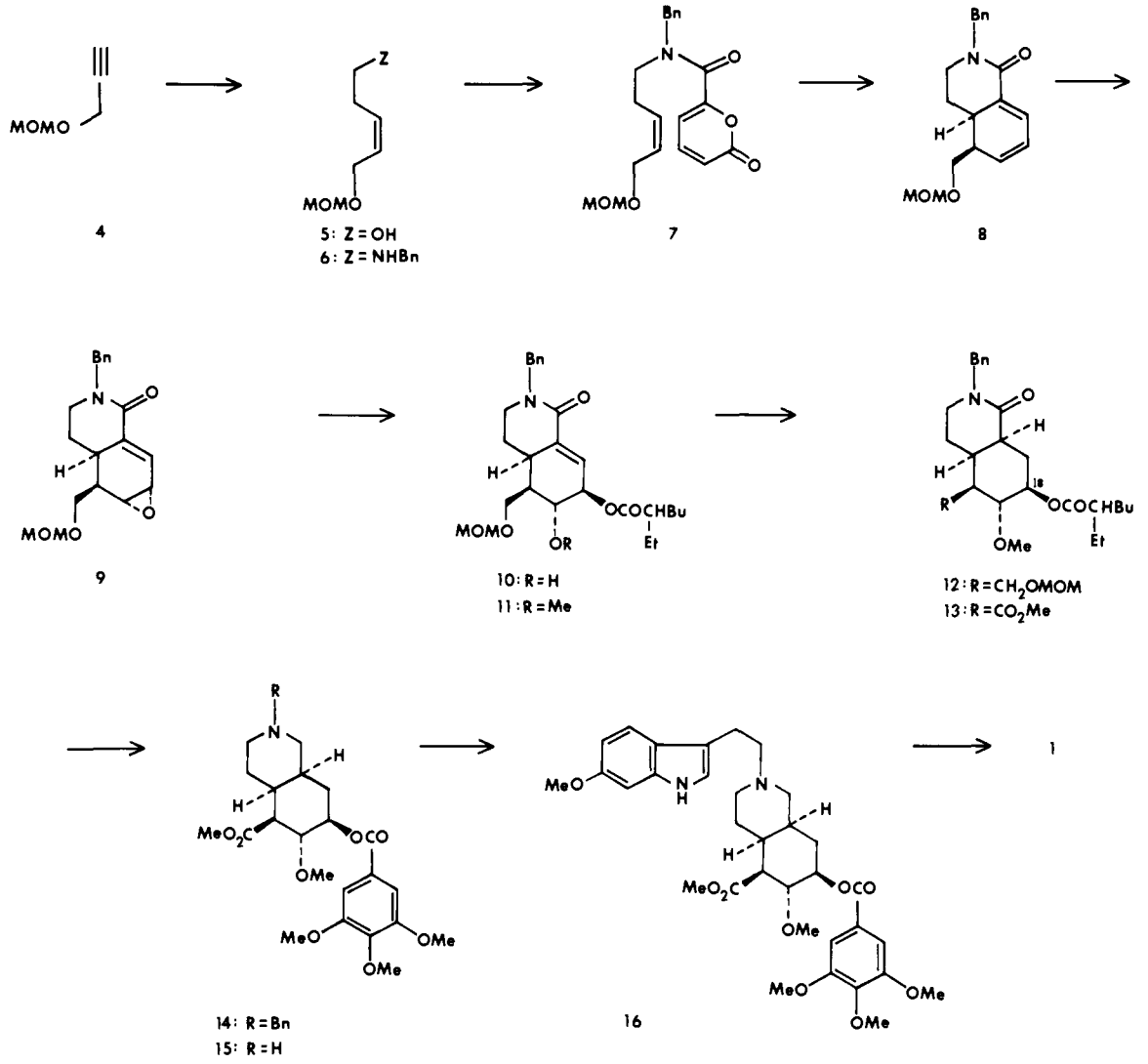
Scheme I



ture; 90%]. Removal of the protecting group from the hydroxyl group at C(22) (*p*-TsOH, MeOH, 45 °C, 20 h) followed by oxidation (PDC,[12] DMF, room temperature, 18 h) and esterification [CH_2N_2, MeOH/Et_2O (1:3), 0 °C] produced **13** in 75% overall yield from **12**. Sequential, chemoselective reduction of the lactam carbonyl group (AlH_3, THF, −70 → −20 °C, 2 h; 79%) and removal of the hydroxyl protecting group at C(18) by acid-catalyzed transesterification (*p*-TsOH, MeOH, 85 °C, 72 h; 81%) followed by acylation of the resulting alcohol with 3,4,5-trimethoxybenzoyl chloride (Py, catalytic DMAP, CH_2Cl_2, room temperature, 24 h; 91%) provided the tertiary amine **14**. Catalytic hydrogenolysis (H_2/15 psi, 20% $Pd(OH)_2/C$,[11] AcOH, room temperature, 15 h; 94%) of the *N*-benzyl protecting group then gave the secondary amine **15**.

At this juncture, the completion of the total synthesis of reserpine merely requires coupling of the intact D/E ring subunit **15** with the 6-methoxytryptophyl fragment followed by oxidative cyclization to form the C ring. Thus, N-alkylation of the secondary amine **15** with 6-methoxytryptophyl bromide[6c,13] [Me_2SO, $(i\text{-}Pr)_2NEt$, room temperature, 60 h] afforded 2,3-*seco*-2,3-dihydroreserpine (**16**)[14,15] in 69% yield. Subsequent oxidative cyclization [$Hg(OAc)_2$ (10 equiv), 5% aqueous HOAc, 85 °C, 1.5 h; H_2S][16,17] of **16** followed by treatment of the resulting crude product mixture with zinc in 7% aqueous $HClO_4$/acetone/THF (1:1:1) (reflux, 20 min)[18] produced reserpine (**1**)[19] (35%) and isoreserpine (**17**) (8%) together with the two corresponding inside derivatives (18%, 4%). Experiments to improve the stereo- and regiochemical course of this final sequence of oxidation, cyclization, and reduction are the subject of current investigations.

Thus, a concise and efficient total synthesis of the pentacyclic indole alkaloid reserpine (**1**) has been completed by a sequence that features an intramolecular Diels–Alder cycloaddition as the key step for the facile construction of the highly functionalized hydroisoquinoline **15**, which constitutes the fully elaborated D/E

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ring subunit of reserpine. Application of this general strategy to the syntheses of other alkaloid natural products is the subject of active investigations, the results of which will be described in due course.

Acknowledgment. We thank the National Institutes of Health (GM 25439) and the Robert A. Welch Foundation for generous support of this research.

Resolution, Circular Dichroism Spectrum, Molecular Structure, and Absolute Configuration of *cis,trans*-1,3-Cyclooctadiene

Roland Isaksson, Jan Roschester, Jan Sandström,* and Lars-Göran Wistrand

Division of Organic Chemistry 3, Chemical Center University of Lund, P.O. Box 124, S-221 00 Lund, Sweden

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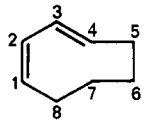
cis,trans-1,3-Cyclooctadiene (**1**) has been known for a considerable time,[1,2] and its thermal and photochemical transformations have been carefully studied.[2-6] Models indicate that **1** is chiral and not readily racemized, but, while *cis,trans*-1,5-cyclooctadiene as well as *trans*-cyclooctene have been resolved by formation of diastereomeric metal complexes,[7,8] no resolution of **1** has been reported in spite of the inherent interest in the chiroptical properties of this nonplanar conjugated diene.

Chromatography on swollen, microcrystalline triacetylcellulose (TAC) has proven valuable for resolution of racemic compounds lacking functional groups,[9-12] and we have used this technique to resolve racemic **1**.



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The $AgNO_3$ adduct of **1** was prepared according to Liu,[2] and the hydrocarbon was liberated with aqueous NH_3 and taken up in *n*-pentane.[2,13] Careful evaporation gave pure racemic **1**.[14] One passage of a solution of 30 mg of **1** in 12 mL of *n*-pentane through the TAC column[15] gave partial enantiomer separation, considerably improved after recycling[16] 3 times. The first eluted enantiomer has negative rotation and the eluate gave $[\alpha]^{20}_D$ −649°, $[\alpha]^{20}_{365}$ −2450° (*c* 0.017, ethanol),[17] and a CD spectrum with a smooth, nearly Gaussian negative band with λ_{max} 230.5 nm, $\Delta\epsilon$ −8.83, and width 61 nm at ϵ_{max}/e, followed by another negative band with λ_{max} < 190 nm (Figure 1). Since the chromatographic procedure did not give base-line separation, attempts were made to determine the enantiomeric purity by ^{1}H NMR spectroscopy, using Eu(hfbc)$_3$[18-20] and Eu(hfbc)$_3$ + Ag(fod)[21] as chiral shift reagents. However, none of these achieved splitting of the signals from racemic **1**, but computer simulation of the optical rotation chromatogram[11,15] obtained on reinjection of the resolved material on the TAC column indicates an enantiomeric excess >90%.

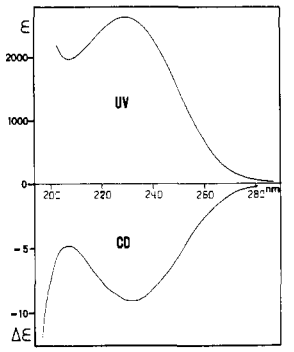

Figure 1. Ultraviolet and CD spectra of (−)-**1** in ethanol.

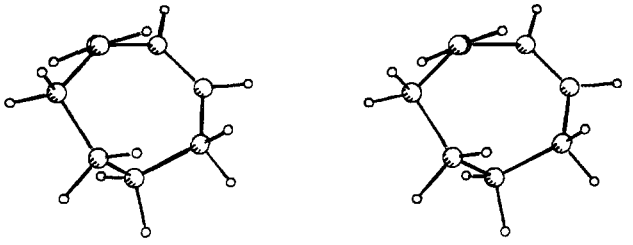

Figure 2. Stereoview of **1** along the C4-C3 bond.

Molecular mechanics calculations[22] covering all feasible combinations of the 1-2-3-4 and 5-6-7-8 dihedral angles revealed only two energy minima, with an energy difference of 2.75 kcal/mol. This corresponds to less than 1% of the minor form at room temperature, and is in agreement with the observed complete temperature independence of the CD spectrum in ethanol from +20 to −112 °C.

According to the calculations, the stable form has a nearly planar cis double bond with the 3-2-1-8 angle 3.5° and a strongly twisted trans double bond with the 2-3-4-5 angle −133.4° (*P* helicity assumed), rather similar to the −136° found for (−)-*trans*-cyclooctene.[23-25] The dihedral angle between the double bonds (1-2-3-4) is 50.2° and the 5-6-7-8 angle is 82.4° (Figure 2). The corresponding angles for the less stable form are 9.0°, −131.9°, 67.9°, and −96.8°. Early calculations with the Hendrickson force field[26] gave four energy minima, the dihedral angles for the stable form being, in the order given above, 0°, −147.5°, 42.5°, and 84.3°, respectively.

Attempts to study the thermal racemization of **1** are likely to be thwarted by the cyclization to *cis*-bicyclo[4.2.0]oct-7-ene (**2**).[3,4]

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