Table I. Observed Second-Order Rate Constants and Product Distribution of the Conversion of 1 to 3 and 4 at 37.5 °C and Selected Reaction pH Values

pH	k_{obsd},[a] M^{-1} s^{-1}	3[b]	4[b]
2.0	0.00304	7	93
4.0	0.224	10	90
6.0	9.08	22	78
7.4	30.1	35	65
8.0	36.8	40	60
10.0	40.7	48	52

[a] Each value is the mean of five determinations. [b] Expressed as percent of product mixture.

tabolized in brain of the intact animal. Details of one possible pathway of THP metabolism, i.e., methylation by catechol-O-methyltransferase, have been described.[9] Another metabolic possibility involves condensation of THP with formaldehyde to form 2,3,9,10- and 2,3,10,11-tetrahydroxyberbine (THB) alkaloids (**3** and **4**, Scheme I). Although conversion of **1** to a mixture of **3** and **4** has long been known,[10,11] the kinetics involved have not been described.[12] Such data would be helpful in assessing the potential for nonenzymatic conversion of THP to THB alkaloids in vivo. Accordingly, kinetics and product distribution of the reaction under physiological conditions were determined.

Authentic **1**, **3**, and **4** were prepared by demethylating tetrahydropapaverine,[13] tetrahydropalmatine,[14] and xylopinine,[15] respectively, in refluxing constant-boiling HBr or in concentration HCl at 160 °C in a sealed tube. Demethylations proceeded for 2 h and provided the materials in analytical purity (within 0.3% of calculated values) in 90–95% yields.[16]

Reactions were monitored by high-performance liquid chromatography.[17] Reactions for kinetic measurements were initiated by injecting thermally equilibrated formaldehyde into amine–buffer solutions contained in 3-mL vials equipped with Teflon-faced septa. Reactions with half-times greater than approximately 10 min were analyzed by injecting aliquots directly onto the chromatography column. More rapid reactions were quenched by 1:1 dilution with cold 0.1 M phosphoric acid prior to analysis. Kinetics were determined under pseudo-first-order conditions with formaldehyde in at least 10-fold molar excess by plots of ln THP concentration vs. time, or under second-order conditions with equal concentrations of alkaloid and aldehyde (1 mM) by plotting 1/THP concentration with time.[18]

The rate of condensation of **1** with formaldehyde is strongly base catalyzed. At pH 8 the second-order rate constant is 10^4 times greater than the rate constant at pH 2 (Table I). However, above pH 8 further increases in hydroxyl ion concentration have little effect on the rate constant.

The product distribution of the reaction is also strongly dependent on pH. At pH 2 the reaction produces mainly **4**, while under basic conditions cyclization proceeds to give nearly equivalent amounts of **3** and **4** (Table I).

The generally accepted mechanism of the Pictet–Spengler reaction (Scheme I) involves preliminary formation of a cationic imine, following by nucleophilic attack by the electron-rich 2′ or 6′ carbon.[10] The data presented appear to be consistent with this mechanism. High pH should facilitate cyclization of the intermediate by increasing electron density at the positions ortho and para to the 3′-hydroxyl group. The reaction should be relatively pH insensitive above the p*Ka* of the 3′-hydroxyl group. Product distribution should be approximately 1:1 if electron density at the condensing carbons of the benzylic group is sufficient to insure reaction each time close proximity is achieved. It should be emphasized that the mechanism depicted in Scheme I represents extreme simplification. Many factors that might potentially contribute to the reaction (e.g., equilibria, general acid–base catalysis) are not represented.

The data presented, however, indicate that nonenzymatic Pictet–Spengler condensation of THP (**1**) with formaldehyde under physiological conditions is a rapid process that appears to be sufficiently facile to maintain the reaction as a possible candidate for production of tetrahydroprotoberberine alkaloids in vivo.

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Synthesis of a Chiral Steroid CD-Ring Synthon from D-Leucine by means of Diastereotopic Face-Selection

Summary: Synthesis of (−)-(1*R*,7a*R*)-7a-methyl-7,7a-dihydro-1-[3(*R*)-hydroxy-5-methyl-1(*Z*)-hexenyl]-5(6*H*)-indanone (**11**) by highly stereoselective double Michael addition and determination of its optical purity and absolute configuration by ^{19}F NMR of the PIPA ester and CD spectra, respectively, are presented.

Sir: The discovery of interesting steroids with novel side chains has stimulated the research on the two major problems in steroid synthesis: (1) the stereoselective in-

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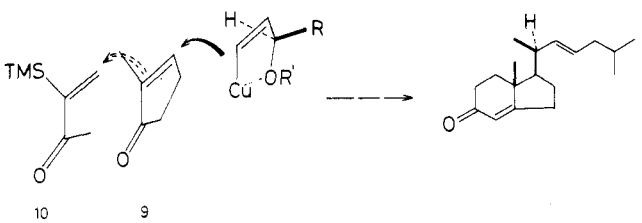
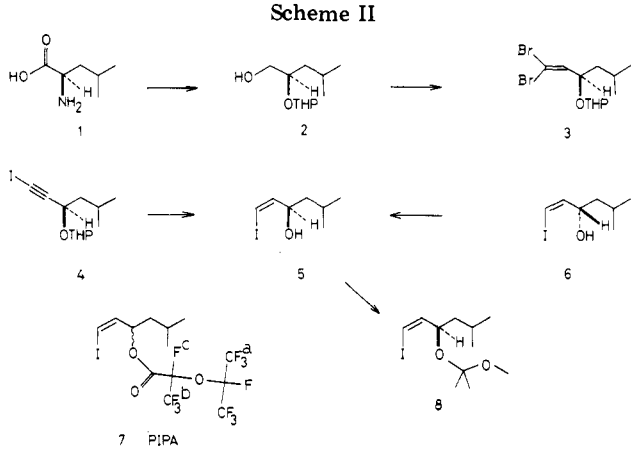
Scheme I



Scheme II



troduction of side chain onto the basic steroid nucleus[1] and (2) the development of efficient synthetic strategy for the construction of steroid CD ring and side chain.[2] So far, the acceptable synthetic strategies for the preparation of chiral CD-ring synthons including side chain are few.[3] We recently reported the simple synthesis of (±)-de-AB-isocholesta-8(14),22-dien-9-one by highly stereoselective double Michael addition[4] (Scheme I) and predicted that the *cis*-vinylcopper phosphine complex with *R* configuration should provide the chiral steroid CD ring. We report here the synthesis of (−)-(1*R*,7a*R*)-7a-methyl-7,7a-dihydro-1-[3(*R*)-hydroxy-5-methyl-1(*Z*)-hexenyl]-5(6*H*)-indanone (**11**), in which the correct absolute configuration is produced from D-leucine (**1**) via the *cis*-vinyl iodide **5**, which serves to control the chirality of the rest of the hydrindenone **11** by means of a remarkably effective diastereotopic face selection (Scheme I).

We first describe the construction of **5** from D-leucine (Scheme II). The alcohol **2** was prepared from **1** in 47% overall yield by applying Mori's procedure.[5] Oxidation of **2** [Me_2SO, $(COCl)_2$ in CH_2Cl_2, and then Et_3N] followed by one-carbon elongation of the resultant aldehyde [$PPh_3/CBr_4/Zn$ in CH_2Cl_2 at 0 °C][6] gave the dibromide **3** in 86% overall yield. Dehydrobromination of **3** [2 equiv of *n*-BuLi at −78 °C in THF] and quenching of the resultant lithium derivative with iodine at −78 °C gave the acetylenic iodide **4** in 90% yield. The partial hydrogenation of the triple bond to the *cis*-vinyl iodide [KO_2CN=NCO_2K/AcOH at 0 °C] and the removal of the protecting

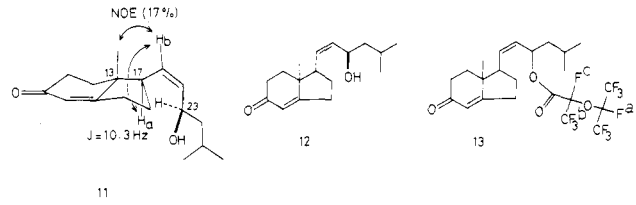


Figure 1.

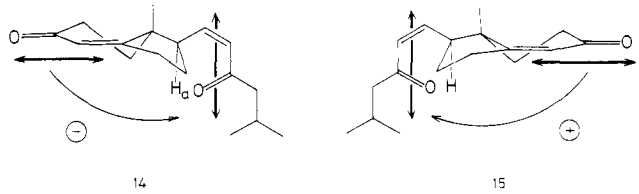


Figure 2.

group with 65% dichloroacetic acid gave the (+)-vinyl iodide **5** in 73% overall yield [mp 73.7–74.1 °C; $[\alpha]^{25}_D$ +54.13° (*c* 3.0, benzene)]. Furthermore, we prepared the (−)-vinyl iodide **6** [mp 74 °C; $[\alpha]^{25}_D$ −53.28° (*c* 3.0, benzene)] from L-leucine by the same manner as above, and (−)-**6** was converted to (+)-**5** [EtO_2CN=NCO_2Et/PPh_3/AcOH, K_2CO_3/MeOH; 28% overall yield] with the complete inversion of the stereochemistry of the alcohol. The optical purity of (+)-**5** was checked as follows. The (±)-vinyl iodide **5**,[4] prepared from isovaleraldehyde and acetylene, was allowed to react with (+)-*F*-2-isopropoxypropionyl chloride[7] in dichloromethane containing triethylamine to give a (1:1) mixture of the two diastereomers **7** in 97% yield, which were distinguishable by the following sets of ^{19}F NMR ($CDCl_3$, $CFCl_3$ as external standard) peaks. Diastereomer I; F_a δ 143.96 (d, $J_{a,c}$ = 14.4 Hz), F_b 82.25 (d, $J_{b,c}$ = 2.54 Hz). Diastereomer II: F_a 143.83 (d, $J_{a,c}$ = 14.4 Hz), F_b 82.20 (d, $J_{b,c}$ = 2.54 Hz). The (+)-vinyl iodide **5** was similarly converted to the PIPA (*F*-2-isopropoxypropionic acid) ester corresponding to **7**. The ester showed only one set of ^{19}F NMR peaks corresponding to that of diastereomer II. Thus the optical purity of (+)-**5** was higher than 95% ee (Scheme II).

The construction of the CD ring by the double Michael addition[8] using 2-methyl-2-cyclopenten-1-one (**9**) (1.0 mmol) and 2-(trimethylsilyl)-1-buten-3-one (**10**) (1.0 mmol) and subsequent aldol condensation were carried out as previously described. After six steps [*n*-BuLi (1.3 mmol), $CuIP(n\text{-}Bu)_3$ (1.2 mmol), **9**, **10**, MeONa, 1 N HCl], an easily separable mixture of diastereomers **11** and **12** was obtained in a 13:1 ratio of diastereomers [**11**, 58% overall yield based on **9**, R_f 0.33 (1:2, *n*-hexane: AcOEt), $[\alpha]^{25}_D$ −34.0 (*c* 0.73, benzene); high-resolution mass spectrum, calcd for $C_{17}H_{26}O_2$ *m/e* 262.1932, found 262.1938; **12**, 4.5% overall yield, R_f 0.36]. The optical purity of the major product **11** was checked as follows. The (−)-enone **11** and (±)-enone **11**, prepared from (±)-vinyl iodide **5** as previously described,[4] were allowed to react with PIPA chloride to give the PIPA esters corresponding to **13** in 72% and 91% yields, respectively. It is advisable to choose a PIPA chloride that has higher reactivity than (−)-MTPA [(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid] chloride for sterically hindered alcohols like **11**. No MTPA ester corresponding to **13** could be obtained. The ^{19}F NMR spectrum of the PIPA ester **13**, derived from (±)-enone **11**, showed a (1:1) mixture of the diastereomers [diastereomer I, F_a 143.3 (d, $J_{a,c}$ = 14.4 Hz), F_b 81.75 (d, $J_{b,c}$ = 2.54 Hz); diastereomer

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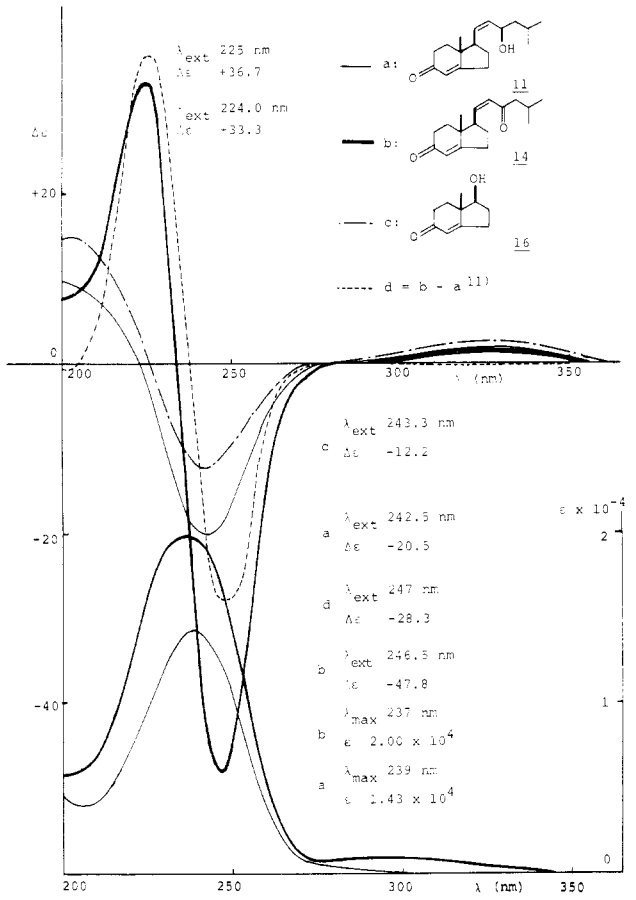

Figure 3.

II, F_a 143.3 (d, $J_{a,c}$ = 14.4 Hz), F_b 81.65 (d, $J_{b,c}$ = 2.54 Hz)], whereas the PIPA ester **13**, derived from (−)-enone **11**, showed only one set of ^{19}F NMR peaks corresponding to that of diastereomer II (Figure 1).

The relative stereochemistry among C(13), C(17), and C(23) (steroidal numbering) in both (±)-**11** and (±)-**12** was confirmed[4] previously by the stereoselective conversions of (±)-**11** and (±)-**12** to (±)-de-AB-isocholesta-8(14),22-dien-9-one and its (±)-C(20) isomer, respectively. We determined here the relative and absolute configuration of (−)-**11** and (−)-**14**, derived from (−)-**11** by Swern oxidation (81% yield), by CD and NMR spectra as follows. The CD spectra of (−)-**11**, (−)-**14**, and the (+)-enone **16** are shown in Figure 3. The simple comparison of CD spectrum of (−)-**11** (curve a) with that of (+)-**16** (curve c, the absolute configuration of **16** is known[9]) led to an *R* configuration at C(13) of (−)-**11**. The NMR spectal studies of (−)-**11** [^1H NOE (17%) between C(13)-methyl and H_b, the coupling constant (J = 10.3 Hz) between H_a and H_b] indicated the cis stereochemistry between the C(13)-methyl and vinyl chain at C(17) and the trans stereochemistry between H_a and H_b. Moreover, the inspection of molecular model of **14** and the observation of lower chemical shift (3.4–4.0 ppm) of H_a in **14** indicated that the side chain of (−)-**14** (Figure 2) was revealed to be *s*-cis configuration. Based on the above consideration, we have applied the exiton chirality method[10] to the conjugated enones for determining the relative and absolute configuration of side chain of (−)-**14**. The exiton theory predicted that (−)-**14** derived from the major product (−)-**11** should have a negative exiton chirality, i.e., left-hand screwness between the two enone chromophores located in C ring and side chain, while the dienone **15**, the enantiomer of (−)-**14** derived from the minor product **12**, should have a positive exiton chirality (Figure 2). The exiton-split CD curve of the enone–enone interaction (Figure 3, curve d[11]) exhibited the strong negative first Cotton effect in the region of the $\pi-\pi^*$ transition around 247 nm, the sign of which was in accordance with the negative exiton chirality between the enone and enone chromophores. These results indicated that the initial 1,4-addition of the (*R*)-vinyl iodide **8** to the cyclopentenone **9** led predominantly to the C(17*R*) configuration as shown in **11** and **14**. Moreover the present (+)-PIPA chloride and the exiton chirality methods should be applicable to determination of the optical purity and the absolute configuration, respectively, in complex molecules.

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Supplementary Material Available: Experimental procedures and data for compounds used in this study (25 pages). Ordering information is given on any current masthead page.

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(11) The CD curve of (−)-**14** contains two Cotton effects, one is due to the enone–enone interaction and the other is due to the helicity of the twisted enone in the C ring, therefore the difference between curve b and curve a shows the real exciton-split CD curve of the enone–enone interaction.

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2-Cyclopentenones from 1-Ethynyl-2-propenyl Acetates

Summary: $PdCl_2(MeCN)_2$ catalyzes the cyclization of 1-ethynyl-2-propenyl acetates **1** to 1,4-cyclopentadienyl acetates **2**, which are cleaved in situ to 2-cyclopentenones **3**.

Sir: The vast literature dealing with the synthesis of 2-cyclopentenones contains a relatively small number of basic strategies.[1] This paper describes a new approach that is, formally, a Pd-catalyzed variant of the Nazarov cyclization[3] and that provides a shortcut to the Ber-

(1) For a recent review, see: Demole, E. P. In "Fragrance Chemistry"; Theimer, E. T., Ed.; Academic Press: New York, 1982; pp 349–396. In addition, see: Ho, T.-L.; Liu, S.-H. *Chem. Ind. (London)* **1982**, 371–372. McCurry, P. M.; Singh, R. K. *J. Org. Chem.* **1974**, *39*, 2317–2319. Reference 2. Also references in each.

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