branching ideality and stoichiometry should be diminished at this generation due to unique packing-induced steric interactions. Preliminary evidence has shown that this may indeed occur.[8]

In conclusion, the synthesis of topological shell molecules has been demonstrated and substantiated by physical measurements. Their development is dramatically affected by the branch juncture symmetry and presumably results from inefficient surface packing. These novel entities should be of immense interest in that their hollowness is reminiscent of a covalently fixed liposome yet their dimensions, shape, and topology are very much like that of a micelle. This latter analogy has been examined in our laboratory and will be reported shortly.[9]

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Synthesis of (-)-Vindoline

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Received November 10, 1986

We report a chirospecific synthesis of (-)-vindoline ((-)-**1**),[1] the most abundant alkaloid isolated from *Catharanthus roseus*, a highly oxygenated indoline which is part of the potent oncolytic agent vinblastine.[2,3] Several syntheses of (±)-**1** have been reported,[4] all of which use linear sequences beginning with 6-methoxytryptamine, or a similar compound, and construct upon it the remaining carbon framework of **1**. Recently, we reported a convergent route to vindoline in which tetrahydroquinolinate **2**, the E-ring precursor of **1**, was synthesized in enantiomerically pure form from L-aspartic acid.[5] Coupling **2** with 6-methoxytryptophyl bromide (**3**), itself prepared from *p*-cresol,[6] gave **4**, which was converted to quinolizine **5**α/**5**β (1/3.9) by using an α-amino acid decarbonylation iminium ion cyclization. Subsequent transformation of this mixture to (-)-**1** was to proceed via the precedented thionium ion promoted skeletal rearrangement to generate **8** from **7**.[4c] However, an intervening reversible Mannich reaction in the execution of this step led to racemic **8**[5] (see route A, Scheme I).

To avoid this racemization, a modified hexahydroindoloquinolizine was needed for the skeletal rearrangement. An attractive alternative substrate would be one in which the carbon α to the C-15 carbonyl is nucleophilic and would inhibit delocalization of the N_b lone pair of electrons into the carbonyl. This strategy, as opposed to that of route A, reverses the role of C-14 (electrophile to nucleophile) and C-2 (nucleophile to electrophile) during the skeletal rearrangement and makes the C-15 oxo function much less likely to participate in the racemizing reverse Mannich reaction. Methodology for applying this concept followed from a recent report describing the synthesis of hexahydropyrrolidino[2,3-*d*]carbazoles from tetrahydro-β-carbolines.[7] Since these transformations are initiated by intramolecular attack of a stabilized anion onto the electron-deficient C-2 of a chloroindolenine, β-keto ester **11**α was the ideal substrate. As applied to vindoline synthesis, it provides a stabilized anion as well as the functionality for extension to **1**.

Attempts to synthesize **11**α via a Claisen condensation of **5**α with methyl lithioacetate failed due to facile lactam formation that generated **6** in high yield. Successful synthesis of **11**α was effected via an intramolecular condensation followed by lactam methanolysis. This strategy avoided the problems of bringing an external nucleophile into the congested environment of the ester and protected the indole nitrogen during Dieckmann cyclization. The two-step protocol commenced with acetylation of **5**α (400 mol % KH, DMF, 0 °C, 20 min, 400 mol % Ac_2O; 55%, 85% based on recovered **5**α followed by Dieckmann condensation (225 mol % LDA/THF, -78 °C, 30 min; 0 °C, 15 min). Lactam **10**α was not isolated but was opened in situ (1000 mol % 1 M NaOMe/MeOH, 23 °C, 1 h) to **11**α (73% yield after chromatography on silica gel deactivated with TEA[8]). Exposing **11**α to silica gel without TEA yielded a small amount of **11**β believed to be formed by an acid-catalyzed reversible Mannich reaction. Epimer **5**β was not transformed to **11**β; rather, it was converted to **5**α by equilibration to an easily separable 3.6/1 mixture of **5**α/**5**β (TFA[8], Δx, 2 h, 91%).[5] β-Keto ester **11**α is the desired epimer for subsequent rearrangement, since its C-3 stereochemistry provides the correct C-19 stereochemistry in **12**.[9] Thus conversion of **11**α to **12** was accomplished in 75% yield with one recycle (90 mol % *t*-BuOCl,[10] CH_2Cl_2, 0 °C, 5 min/300 mol % DBU,[8] 0 °C, 20 min). The order of addition of *t*-BuOCl and DBU was crucial to the success of the reaction, since simultaneous addition of the reagents gave a small amount of **13** and mostly material bis chlorinated at C-14 of the chloroindolenine.

To test the configurational integrity of the transformation **11**α to **12**, **12** was converted to the known vindoline degradation product **17**.[1,4b] With $NaCNBH_3$ (800 mol %)/(TFA/MeOH, 1/10), 23 °C,[4c] imine **12** was rapidly isomerized to the more polar enamine, which was slowly reduced to **14**. N-Methylation of **14** with aqueous H_2CO (1000 mol %)/$NaCNBH_3$ (300 mol %)/(HOAc/CH_3CN, 1/10), 23 °C,[11] generated **15** in 85% yield from **12**. Hydrogenation of the E-ring double bond using H_2 (50 psi)/MeOH/HOAc gave **16**, which was subsequently decarbomethoxylated[12] (LiCl (1000 mol %)/Me_2SO/H_2O/ 150 °C, 25 min) to **17**. The optical rotation of **15** was the same as the reported value, within experimental error; however, unambiguous proof of

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(8) TEA is triethylamine; TFA is trifluoroacetic acid; DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene; Yb(hfc)$_3$ is tris[3-[(heptafluoropropyl)hydroxymethylene]-*d*-camphorato]ytterbium(III).
(9) The mechanism postulated for the transformation of **11**α to **12** follows from the discussion given in ref 7. After chloroindolenine formation, the anion of the β-keto ester attacks the imine carbon, C-2. Subsequent Wagner-Meerwein rearrangement of the C-2-C-3 bond to C-12 (vindoline numbering) with concomitant chloride expulsion gives **12**. Since Wagner-Meerwein rearrangements proceed with retention of stereochemistry at the migrating carbon, the C-3 stereochemistry in **11**α determines the configuration at C-19 of **12**.
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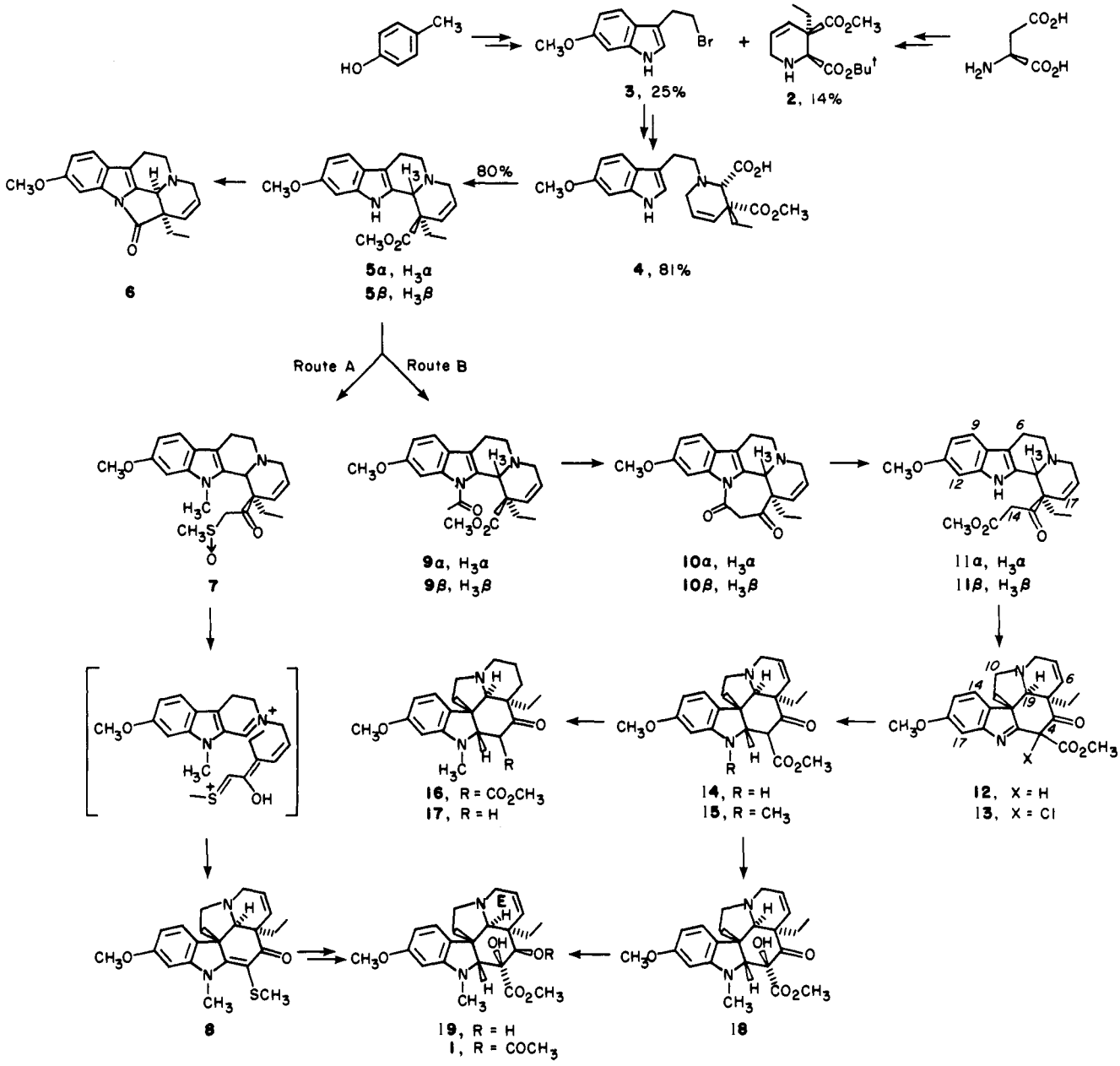
0002-7863/87/1509-1603$01.50/0

Scheme I



the enantiomeric purity was sought. It was shown that the H-17 enantiotopic protons of racemic **17**[5] could be resolved in the 250-MHz ^{1}H NMR spectrum by using Yb(hfc)$_3$[8] as the chiral shift reagent. Subsequent ^{1}H NMR experiments demonstrated that route B generated **17** in >98% enantiomeric purity.

Thus our chirospecific synthesis proceeds from L-aspartic acid and *p*-cresol to keto ester **15** in 19 transformations in 3.6% overall yield. Completion of the syntheis of (−)-vindoline followed literature precedent. Hydroxylation of **15** at C-3 produced **18**,[4c] which was reduced to desacetylvindoline[4a,13] (**19**) and then acetylated[14] to afford (−)-vindoline.[15,16] A noteworthy feature in the latter part of the synthesis is the enantiospecific skeletal rearrangement of **11**α to **12**. This method provides a general route to optically pure Aspidosperma alkaloids from readily accessible optically pure indoloquinolizines.

Acknowledgment. We thank Dr. Gary Kaiser and the Eli Lilly Co. for a generous supply of natural vindoline. P.L.F. is the recipient of an Eastman Kodak Fellowship, 1986–1987.

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(15) The reported yields for the last three are 89%,[4c] 56%,[4a] and 100%,[4c] respectively. No experimental details were provided for the conversion of **18** to **19**, and we experienced some difficulties in this conversion. This point will be addressed in detail in our full paper.

(16) All compounds gave satisfactory spectral and/or analytical data. **11**α: mp 121–122 °C; $[\alpha]^{23}_D$ −420° (*c* 1, $CHCl_3$); ^{1}H NMR δ 7.68 (s, 1 H), 7.31 (d, 1 H, *J* = 8.53 Hz), 6.81 (d, 1 H, *J* = 2.04), 6.73 (dd, 1 H, *J* = 8.55, 2.21), 6.16 (ddd, 1 H, *J* = 10.0, 4.99, 1.58), 5.44 (br d, 1 H, *J* = 10.0), 3.98 (d, 1 H, *J* = 16.5), 3.82 (s, 3 H), 3.76 (s, 1 H), 3.73 (s, 1 H, *J* = 16.5), 3.35 (s, 3 H), 1.04 (t, 3 H, *J* = 7.51). **12**: mp 148–149 °C; $[\alpha]^{23}_D$ 165° (*c* 1, $CHCl_3$); ^{1}H NMR δ 7.22 (d, 1 H, *J* = 8.17 Hz), 7.05 (d, 1 H, *J* = 2.27), 6.69 (dd, 1 H, *J* = 8.20, 2.33), 5.98 (ddd, 1 H, *J* = 10.2, 3.70, 2.0), 5.75 (br d, 1 H, *J* = 10.2), 5.32 (s, 1 H), 3.83, 3.75 (2s, 6 H), 2.91 (s, 1 H), 0.79 (t, 3 H, *J* = 7.35). **14**: mp 172–174 °C; $[\alpha]^{23}_D$ −170° (*c* 1.8, $CHCl_3$); ^{1}H NMR δ 7.01 (d, 1 H, *J* = 8.16 Hz), 6.29 (dd, 1 H, *J* = 8.16, 2.25), 6.15 (d, 1 H, *J* = 3.13), 5.87 (ddd, 1 H, *J* = 9.7, 4.85, 1.46), 5.39 (dd, 1 H, *J* = 9.7, 0.9), 5.1 (d, 1 H, *J* = 1.95), 4.89 (d, 1 H, *J* = 3.12), 4.17 (br s, 1 H), 3.82, 3.75 (2s, 6 H), 2.32 (s, 1 H), 0.44 (t, 3 H, *J* = 7.49). **15**: $[\alpha]^{23}_D$ −125° (*c* 1.68, $CHCl_3$). **16**: $[\alpha]^{23}_D$ − 66.7° (*c* 0.8, $CHCl_3$), lit.[4b] $[\alpha]^{20}_D$ −13.7° (*c* 0.73, $CHCl_3$). **17**: mp 137–138 °C, lit.[1,4b] mp 130–132 °C; $[\alpha]^{23}_D$ 11.5° (*c* 0.95, $CHCl_3$), lit.[1,4b,e] $[\alpha]^{20}_D$ 12° (*c* 1.0, $CHCl_3$). **18**: $[\alpha]^{23}_D$ −85.5° (*c* 1.0, $CHCl_3$); from natural vindoline $[\alpha]^{23}_D$ −89.5° (*c* 1.0, $CHCl_3$). Natural vindoline (**1**) was converted to **18** by acid hydrolysis to **19**[13] followed by oxidation according to the procedure of: Huang, S. L.; Omura, K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 3329.