importance in bleomycin coordination chemistry has been previously documented.[1]

The manner in which Co(III)-**2** was synthesized and isolated establishes the compound as an important structural model for the biologically significant iron-bleomycins.

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Total Synthesis of (±)-Dihydroperiphylline

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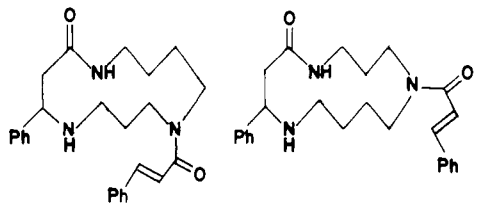
Among the polyamine alkaloids recently isolated from plant sources are dihydroperiphylline (**1**)[1] and the isomeric lactam celacinnine (**2**),[2] both of which incorporate spermidine and cinnamic acid residues in 13-membered rings. These and related



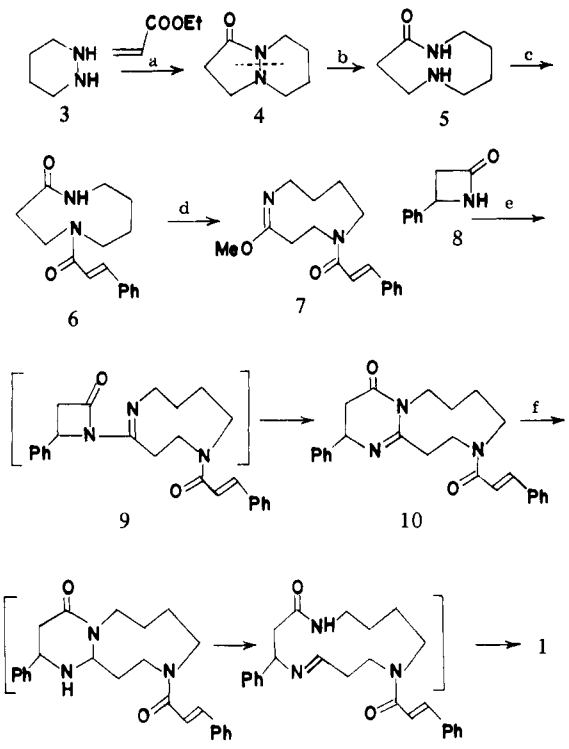
1 2

macrocyclic lactams are of special interest because of the notable biological activity shown by members of the polyamine family.[3] In two recent syntheses of celacinnine, the parent ring system was formed by direct amino acid cyclization[4] or by a transamidation process involving an amino lactam.[5] Preferred acylation of the less hindered secondary amino group then yielded the natural product. Other synthetic work leading to the formation of 13-membered lactams in this series has been reported by Husson.[6]

We now describe a total synthesis of dihydroperiphylline by an efficient six-step sequence in which the macrocyclic ring is formed by successive ring expansions of smaller heterocyclic units. Our procedure (Scheme I) permits clear-cut differentiation of the two secondary amino groups in the 13-membered lactam system by selective acylation in an early step.

Piperidazine (**3**) was condensed with ethyl acrylate to form 7-oxo-1,6-diazabicyclo[4.3.0]nonane (70%) (**4**)[7] which could be

Scheme I[a]



[a] (a) 25 °C, 1 h; 180 °C, 12 h (70%); (b) Na/NH_3 (3 equiv), 1.75 h (87%); (c) *trans*-PhCH=CHCOCl, 4-dimethylaminopyridine, CH_2Cl_2, 25 °C, 10 h (95%); (d) $Me_3O^+BF_4^-$, CH_2Cl_2, 25 °C, 23 h; 50% aqueous K_2CO_3 (83%); (e) PhCl, reflux, 21 h (67%); (f) $NaBH_3CN$ (3 equiv), 25 °C, 3 h; 50 °C, 2 h; then 25 °C, 12 h (93%).

readily cleaved with sodium in liquid ammonia under the conditions reported by Kemp[8] to form the amino lactam (**5**)[7] (87%, mp 82-84 °C). Treatment of **5** with *trans*-cinnamoyl chloride in methylene chloride in the presence of 4-(dimethylamino)pyridine yielded **6**[7] (95%, mp 147-148 °C). Conversion of **6** to the imino ether (**7**)[7] (83%) was achieved by using Meerwein's reagent (Me_3O^+, BF_4^-) followed by workup in 50% aqueous potassium carbonate.[9]

(1) Dihydroperiphylline is one of six alkaloids isolated from the leaves of *Peripterygia marginata*. All of these alkaloids contain a 13-membered ring system derived from dicinnamoylspermidine. R. Hocquemiller, A. Cavé, and H.-P. Husson, *Tetrahedron*, **33**, 645 (1977).

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(7) Spectroscopic and analytical data for new compounds are provided as follows: **4**: IR (neat) 1680 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 4.35-2.25 (8 H, m including d at 2.55), 1.95-1.35 (4 H, m, N-C-CH_2). **5**: IR (neat) 3340, 1650, 1550 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 6.80 (1 H, br s, CONH), 3.70 (1 H, m, CONH-C*H*), 3.50-2.35 (5 H, m), 2.15 (2 H, t, J = 6 Hz, NH-CH_2), 1.90-1.25 (5 H, m, N-C-CH_2, NH). Anal. Calcd for $C_7H_{14}N_2O$: C, 59.13; H, 9.92; N, 19.70. Found: C, 59.38; H, 10.11; N, 19.94. **6**: IR ($CDCl_3$) 3320, 1650, 1600 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 7.90-6.70 (7 H, m, phenyl, vinyl), 5.80-5.40 (1 H, br s, CONH), 3.90-3.00 (5 H, m, CON-CH_2, CONH-C*H*), 2.90-2.30 (3 H, m, $COCH_2$, CONH-C*H*), 2.00-1.40 (4 H, m, N-C-CH_2). Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.40; H, 7.40; N, 10.17. **7**: IR ($CDCl_3$) 1670, 1650, 1600 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 7.69 (1 H, d, J = 16 Hz, =C*H*Ph), 7.50-7.30 (5 H, m, phenyl), 6.99 (1 H, d, J = 16 Hz, =C*H*CO), 3.70-3.30 (9 H, OCH_3, $CONCH_2$, C=NCH_2), 2.80-2.60 (2 H, m, =CCH_2), 2.00-1.40 (4 H, m, $NCCH_2$). **10**: IR ($CDCl_3$) 1690, 1640, 1600 cm^{-1}; NMR (270 MHz, $CDCl_3$, 50 °C) δ 7.72 (1 H, d, J = 15.4 Hz, =C*H*Ph), 7.54-7.25 (10 H, m, phenyl), 6.97 (1 H, d, J = 15.4 Hz, =CHCO), 4.65 (1 H, dd, J = 4.8, 13.4 Hz, PhC*H*N), 4.34-2.57 (10 H, m), 2.11-1.39 (4 H, $NCCH_2$). Anal. Calcd for $C_{25}H_{27}N_3O_2$: C, 74.79; H, 6.78; N, 10.47. Found: C, 74.56; H, 6.62; N, 10.43. **1**: IR ($CDCl_3$) 3300, 1660 (sh), 1648, 1600, 1546, 1523 cm^{-1}; NMR (270 MHz, $CDCl_3$, 50 °C) δ 7.67 (1 H, d, J = 15.4 Hz, =C*H*Ph), 7.47-7.16 (11 H, m, phenyl, NHCO), 6.79 (1 H, d, J = 15.4 Hz, =C*H*CO), 3.91 (1 H, m, C*H*Ph), 3.89-3.06 (6 H, m, CH_2NCO), 2.68-2.55 (1 H, m, C*H*NH), 2.50-2.32 (3 H, m, C*H*NH, CH_2CO), 2.01-1.49 (7 H, m, $NCCH_2$, N*H*). **14**: IR ($CDCl_3$) 3430, 3300, 1660 (sh), 1640 (sh), 1625, 1550 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 7.70 (1 H, br s, NHCO), 7.40-7.10 (10 H, m, phenyl), 4.00-2.00 (15 H, m), 1.90-1.30 (7 H, $NCCH_2$, NH).

(8) Cleavage of 1,2-diacylhydrazides with Na/NH_3 has been reported by D. S. Kemp, M. D. Sidell, and T. J. Shortridge, *J. Org. Chem.*, **44**, 4473 (1979).

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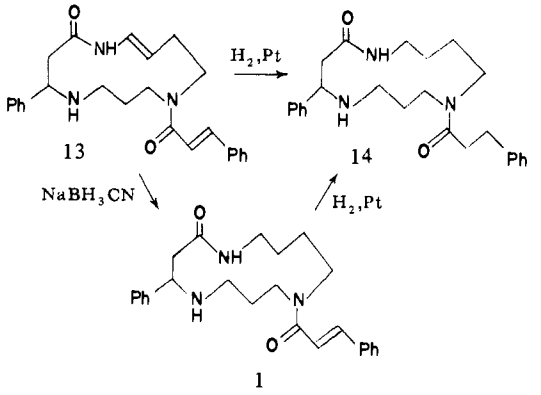
In the formation of the bicyclic 4-oxotetrahydropyrimidine derivative (**10**) from **7**, we adapted a reaction reported earlier by Bormann in which β-lactams react with cyclic imino ethers in an addition-ring expansion process.[10] Thus, heating **7** with 4-phenyl-2-azetidinone (**8**) in chlorobenzene for 21 h yielded the ring-enlarged product **10**[7] (67%, mp 195-197 °C), most probably through the intermediate **9**. The final conversion of **10** to dihydroperiphylline (**1**)[7] (most probably, through **11** and **12**) was accomplished in one step (93%) by treatment with sodium cyanoborohydride (3 equiv) in acetic acid[6,11] under conditions noted in Scheme I. This reduction sequence was mild enough to leave the double bond in the cinnamic acid residue unaffected.

The structure of **1** was established by using natural periphylline (**13**) as a reference material.[12] Hydrogenation of dihydroperiphylline (**1**)[7] with platinum oxide yielded tetrahydroperiphylline (**14**), identical (IR, NMR, TLC) with the product obtained from periphylline by the uptake of 2 mol of hydrogen. Selective reduction of periphylline (**13**)[12] by using $NaBH_3CN$ in formic acid yielded a dihydro product identical (IR, NMR, TLC) with synthetic dihydroperiphylline (**1**).



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Epoxy Alcohol Rearrangements: Hydroxyl-Mediated Delivery of Lewis Acid Promoters

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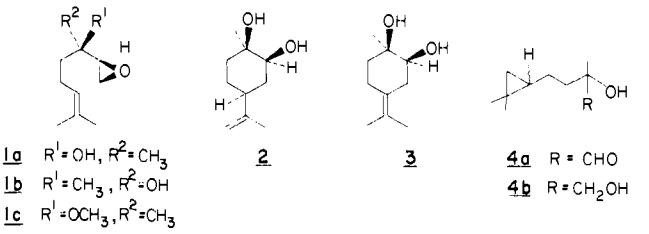
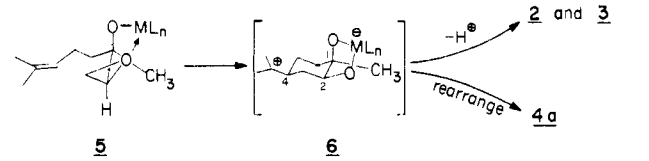
In connection with our interest in the chemistry of epoxy alcohols, we have investigated the Lewis acid mediated rearrangement of these substrates which are available stereo-[1a] and enantioselectively[1b] from allylic alcohols. Although Lewis acid promoted rearrangements of epoxides are well-known, we have observed a few novel and selective transformations which suggest that the standard behavior of epoxide substrates may be substantially altered by the presence of an α-hydroxyl substituent.

Initially, our studies were focused on 1,2-epoxylinalool, **1**.[1a]



This substrate (erythro-threo mixture) was transformed to *cis*-diol **2**[2,3] and up to 15% of another cyclic diol, presumably **3**, upon treatment with $OV(OEt)_3$ (CH_2Cl_2, room temperature, 10 h). We were unable to detect *trans*-diols or either starting epoxy alcohol diastereomer. Furthermore, examination[4] of the reaction mixture before disappearance of the epoxy alcohols revealed that the epoxylinalool remaining was substantially enriched in the threo isomer. We felt that the isomeric selectivity was best explained by hydroxyl-assisted delivery of the metal via a strictly defined arrangement as shown in **5**. For the erythro isomer (**1a**), cyclization involving the 6,7 double bond leads to **2** or **3** whereas the threo isomer (**1b**), which cannot cyclize, presumably decomposes. Indeed, exposure of pure **1a**[2,5] to these conditions led to cyclized products, while **1b**[2,5] slowly decomposed without formation of characterizable products. Since the total mass recovery in these experiments was quite low (<40%), we next sought a metal promoter which would exhibit the same behavior toward the erythro isomer and not decompose the threo isomer. Our first choice, $Ti(Oi\text{-}Pr)_4$, proved expeditious. Isomer **1a**[2,5] was completely consumed upon treatment with 1.4 equiv of $Ti(O\text{-}i\text{-}Pr)_4$ at room temperature (0.2 M in substrate, CH_2Cl_2, 12 h), while **1b**[2,5] could be recovered (80%) unchanged under identical conditions. The product mixture from **1a** was more complex in this case, consisting of **2** and **3** (20-30%) and cyclopropanes **4a**[2,6] and



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(2) Satisfactory spectral data (IR, NMR, MS) were obtained for this substance.
(3) An authentic sample of **2** (mp 70-73 °C) was prepared in optically active form from *cis*-carveol by epoxidation (*m*-chloroperbenzoic acid, CH_2Cl_2) followed by hydride reduction ($LiAlH_4$, Et_2O, room temperature).
(4) Gas chromatographic analysis of **1** is best accomplished on a 10 ft × $^1/_8$ in. glass column packed with 10% 20 M Carbowax on Gas-Chrom Q (80/100 mesh) and programmed from 70-230 °C at 6 °C/min. Retention times: *threo*-**1b**, 20.5 min; *erythro*-**1a**, 20.9 min.
(5) The erythro isomer (**1a**) was prepared from 2,3-epoxygeraniol in 87% overall yield as follows: (a) TsCl, pyridine, -10 °C, 36 h; (b) 3:1 THF:H_2O, catalytic $HClO_4$, reflux, 1 h; (c) excess anhydrous Na_2CO_3, MeOH, room temperature, 8 h. The threo isomer was prepared in an analogous manner from 2,3-epoxy nerol.
(6) An authentic sample was prepared from 1,1-dimethyl-2-(3-oxobutyl)-cyclopropane[7] via lithio-1,3-dithiane addition followed by hydrolysis (NBS method[8]).
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