Total Synthesis of (±)-Leporin A

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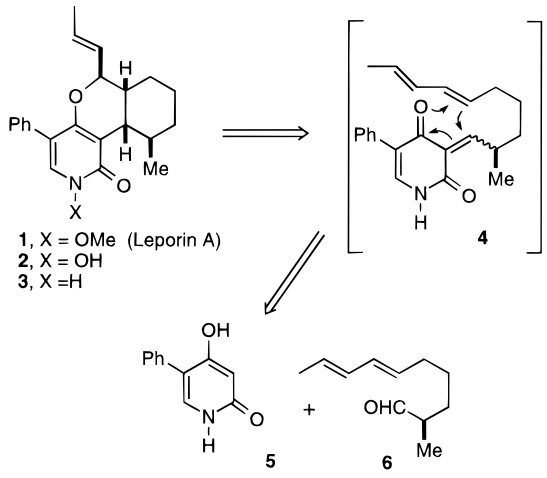
An efficient synthesis of (±)-leporin A (**1**) has been developed using a tandem Knoevenagel condensation−inverse electron demand intramolecular hetero Diels−Alder reaction to construct the key tricyclic intermediate **3** from pyridone **5** and dienal **6** in one pot in 35% yield. Hydroxylation (71%) of **3** and methylation (77%) of the resulting hydroxypyridone **2** completed the first total synthesis of (±)-leporin A (**1**).

Introduction

Gloer and co-workers recently isolated the antiinsectan leporin A (**1**) from the sclerotia of *Aspergillius leporis* (NRRL 3126) and determined its structure by 1D- and 2D-NMR experiments.[1] Leporin A exhibits moderate activity against the corn earworm *Helicoverpa zea*, causing 35.6% reduction in growth rate when incorporated into a standard test diet at a 100 ppm concentration; it also exhibits mild antibacterial activity against *Bacillus subtilis*.[1]

We envisaged that a synthesis of leporin A (**1**) could be carried out by Knoevenagel condensation of 4-hydroxy-5-phenyl-2-pyridone (**5**) with 2-methyl-6*E*,8*E*-decadienal (**6**), to give the unstable *o*-quinone methide **4**, which should undergo an inverse electron demand intramolecular Diels−Alder reaction with the quinone methide functioning as the diene and the acyclic diene functioning as the dienophile to give the tricyclic intermediate **3**. Tandem Knoevenagel condensation−inverse electron demand intramolecular hetero Diels−Alder reactions of this type have been extensively developed by Tietze.[2] N-Hydroxylation[3] of **3** to give **2** followed by *O*-methylation[4] of **2** would complete the synthesis of leporin A.



The proposed one-pot conversion of pyridone **5** and dienal **6** to tricyclic intermediate **3** is well-precedented in our model study for the synthesis of pyridoxatin (**16**),[5] a free-radical scavenger isolated from *Acremonium* sp. BX86.[6] Reaction of 4-hydroxy-2-pyridone (**7**) with citronellal (**8**) in EtOH containing piperidine and pyridine at reflux for 60 h[7] afforded 46% of Diels−Alder adduct **10**, 28% of the desired ene adduct **11**, and 25% of Diels−Alder adduct **12**.[5] The formation of *o*-quinone methide **9** and the inverse electron demand hetero Diels−Alder reaction to give tricycle **10** is analogous to the proposed conversion of **5** and **6** to **4** and then **3**.

The conversion of **9** to **10** and the proposed conversion of **4** to **3** differ in the substitution pattern of the dienophile in **4** and **9** and the ring fusion stereochemistry in the hetero Diels−Alder adducts **3** and **10**. The hetero Diels−Alder and ene reactions fail with the less nucleophilic 1,2-disubstituted alkene of **13**; use of the more nucleophilic allylsilane **14** was necessary for the synthesis of pyridoxatin intermediate **15**. However, the conjugated diene of **4** should make the 1,2-disubstituted double bond of **4** more nucleophilic than the trisubstituted double bond of **9** so that **3** should be formed. More troubling was the formation of **10** with a trans ring fusion and the formation of the trans ring fusion as the exclusive or major product in all of Tietze's studies with aliphatic aldehydes,[2] while the synthesis of leporin A will require the formation of **3** with a cis ring fusion. Although we were comforted by molecular mechanics calculations that suggested that the change from the trisubstituted alkene of **9** to the trans disubstituted alkene of **4** would favor the desired cis ring fusion, the stereochemistry of the hetero Diels−Alder reaction remained a major concern that could only be answered by experimentation.

Results and Discussion

Condensation of phenylacetonitrile with malonyl chloride provided 58% of chloropyridone **17**.[8] Hydrogenolysis[9] (1 atm H_2) over Pd/C in EtOH at 60 °C formed 98% of

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(2) (a) Teitze, L. F. *Chem. Ind.* **1995**, 453. (b) Teitze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. (c) Tietze, L. F. *J. Heterocycl. Chem.* **1990**, *27*, 47. (d) Tietze, L. F.; Geissler, H.; Fennen, J.; Brumby, T.; Brand, S.; Schulz, G. *J. Org. Chem.* **1994**, *59*, 182. (e) Tietze, L. F.; Brand, S.; Brumby, T.; Fennen, J. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 665.

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(4) (a) Cook, M. J.; Katritzky, A. R.; Millet, G. H. *Heterocycles* **1977**, *7*, 227. (b) Gardner, J. N.; Katritzky, A. R. *J. Chem. Soc.* **1957**, 4375.

(5) (a) Snider, B. B.; Lu, Q. *Tetrahedron Lett.* **1994**, *35*, 531. (b) Snider, B. B.; Lu, Q. *J. Org. Chem.* **1994**, *59*, 8065.

(6) Teshima, Y.; Shin-ya, K.; Shimazu, A.; Furihata, K.; Chul, H. S.; Furihata, K.; Hayakawa, Y.; Nagai, K.; Seto, H. *J. Antibiot.* **1991**, *44*, 685.

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(9) (a) Hung, N. C.; Bisagni, E. *Synthesis* **1984**, 765. (b) Davis, S. J.; Elvidge, J. A.; Foster, A. B. *J. Chem. Soc.* **1962**, 3638.

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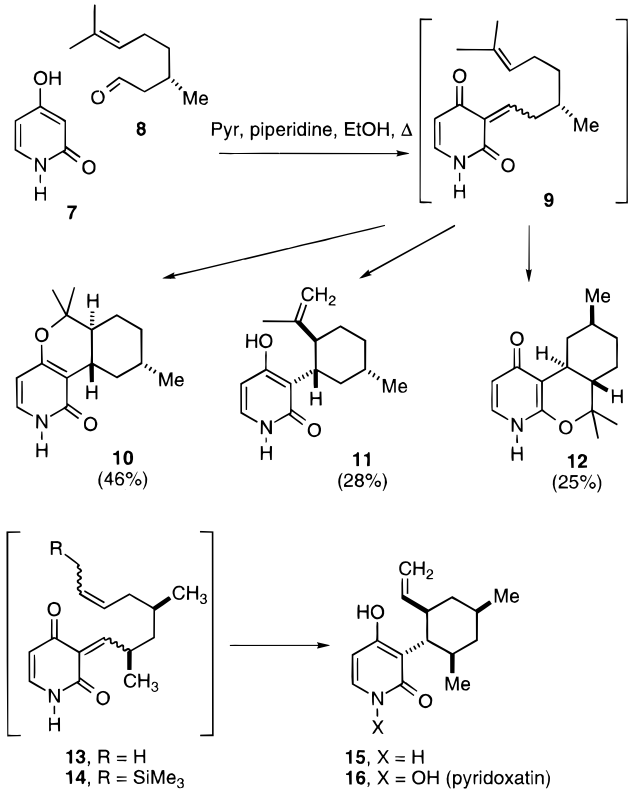
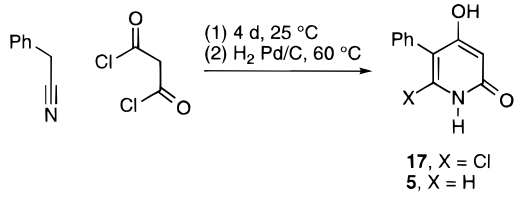
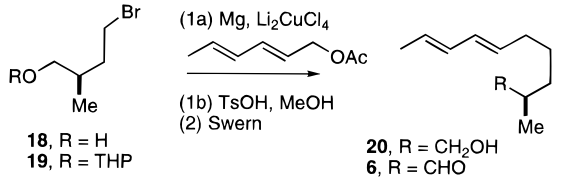


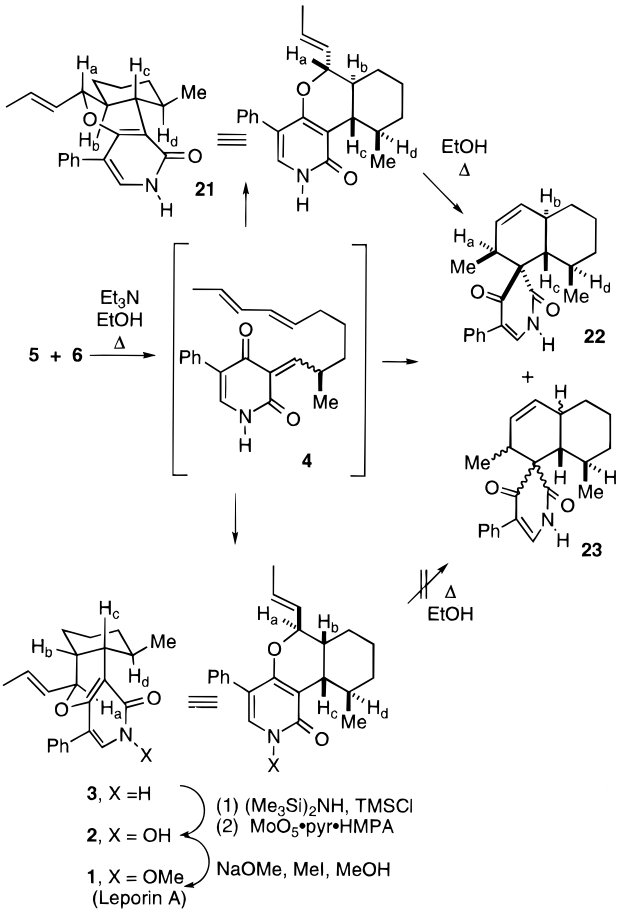
the requisite pyridone **5**.[10] Hydrogenolysis at 25 °C was unsuccessful because of the limited solubility of **17** in EtOH.



Ring opening of 2-methylbutyrolactone with HBr in ethanol (96%) and reduction of the bromo ester with LAH in ether at 0 °C (75%) gave 4-bromo-2-methyl-1-butanol (**18**).[11] Protection of the alcohol (dihydropyran, CH_2Cl_2, TsOH) afforded 68% of THP ether **19**. Reaction of **19** with Mg in THF provided the Grignard reagent, which was added to a mixture of Li_2CuCl_4 and 2*E*,4*E*-hexadien-1-yl acetate in THF to give 44% of dienol **20** after acid hydrolysis of the THP ether.[12] Swern oxidation gave 79% of dienal **6** completing the synthesis of the second coupling component.



The condensation of **5** and **6** in EtOH containing piperidine and pyridine[5,7] afforded variable amounts of the desired cis fused tricyclic inverse electron demand hetero Diels–Alder adduct **3**, the trans fused diastereomer **21**, and two spiro fused Diels–Alder adducts **22** and **23**, which could be formed from the quinone methide acting as the dienophile in a normal Diels–Alder reaction. Similar, poorly reproducible results were obtained in dioxane, MeOH, and with pyridine, piperidine, or mixtures of both bases. The yield of **3** was highest when most of the EtOH evaporated during the reaction.



From this observation we developed reproducible conditions that led to acceptable yields of **3**. A mixture of **5** (1.6 equiv), Et_3N (2 equiv), and **6** (0.2 M in EtOH) was stirred under N_2 for 2 h and placed in an oil bath that was heated to 160 °C. The oil bath was kept at 160 °C for 20 h during which time most of the EtOH evaporated from the solution. This protocol afforded 35% of **3**, 7% of **21**, and 32% of an inseparable ≈1:1 mixture of **22** and a diastereomer **23**, whose stereochemistry was not assigned.

Spiro adducts **22** and **23** could be formed by a normal Diels–Alder reaction of **4** or by Claisen rearrangement[13] of the inverse electron demand hetero Diels–Alder adducts **3** and **21**. Heating trans fused adduct **21** in EtOH at reflux for 12 h gave 65% conversion to spiro adduct **22** with 20% recovered **21** indicating that the Claisen rearrangement occurs under the conditions used for the condensation of **5** and **6**. On the other hand, the desired cis fused adduct **3** was completely stable under these

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(11) Collins, D. J.; James, A. M. *Aust. J. Chem.* **1989**, *42*, 223.
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conditions. Therefore the 5:1 ratio of **3** and **21** isolated from the condensation of **5** and **6** does not reflect the kinetic preference of the inverse electron demand hetero Diels–Alder reaction, but simply the instability of **21** under the reaction conditions.

The stereochemistry of **3** and **21** was easily established by analysis of the coupling constants. In **3**, H_c absorbs at δ 2.79 (dd, J_{bc} = 3.7 Hz, J_{cd} = 10.9 Hz). The large coupling between H_c and H_d indicated that these hydrogens are trans and axial on the cyclohexane, while the small coupling between H_b and H_c established that H_b is equatorial on the cyclohexane. H_a absorbs at δ 4.58 (dd, J_{ab} = 11.3, $J_{a,CH=}$ = 8.1 Hz). The large coupling between H_a and H_b showed that these hydrogens are trans and axial on the dihydropyran. These coupling constants are very similar to those reported for leporin A.[1] In **21**, H_c absorbs at δ 2.39 (dd, J_{bc} = 10.0 Hz, J_{cd} = 10.0 Hz). The large coupling between H_b and H_c, and H_c and H_d established that all three hydrogens are trans and axial on the cyclohexane. H_a absorbs at δ 3.95 (dd, J_{ab} = 10.0, $J_{a,CH=}$ = 7.7 Hz). The large coupling between H_a and H_b indicated that these hydrogens are trans and diaxial on the dihydropyran.

A total of four inverse electron demand hetero Diels–Alder adducts could have been formed from addition of the acyclic diene to the enone of **4**. As has been observed in related reactions,[2d,e] the two diastereomers of **3** and **21** with H_c trans to the methyl group were not formed. There are severe steric interactions between the methyl group and the carbonyl groups of the quinone methide **4** in the transition state for the hetero Diels–Alder reactions leading to these diastereomers. H_a and H_b must be trans in all four possible inverse electron demand hetero Diels–Alder adducts since a concerted cycloaddition results in cis addition to the trans double bond of the dienophile.

Four additional hetero Diels–Alder adducts could have been formed by inverse electron demand hetero Diels–Alder addition to the enamide, rather than the enone, of **4** as in the formation of **12** from **9**. Analysis of UV spectra is the most reliable technique for distinguishing 2-pyridones from 4-pyridones. 2-Pyridone **10** absorbs at 281 nm while 4-pyridone **12** absorbs at 258 nm.[5] Use of UV spectral data to establish the structures of **3** and **21** was complicated by the phenyl substituent which dominates the UV spectra. 5-Phenyl-4-methoxy-2-pyridones absorb at 235–250 nm with a much weaker absorption at 290–300 nm, while 5-phenyl-2-methoxy-4-pyridones absorb at 225–235 nm with a much weaker absorption at 255–260 nm.[8] Hetero Diels–Alder adducts **3** and **21** absorb at 240 nm with a strong shoulder at 290–300 nm, indicating that they are 2-pyridones. It is possible that a hetero Diels–Alder adduct analogous to **12** was formed and reacted further by a Claisen rearrangement to give **23**.

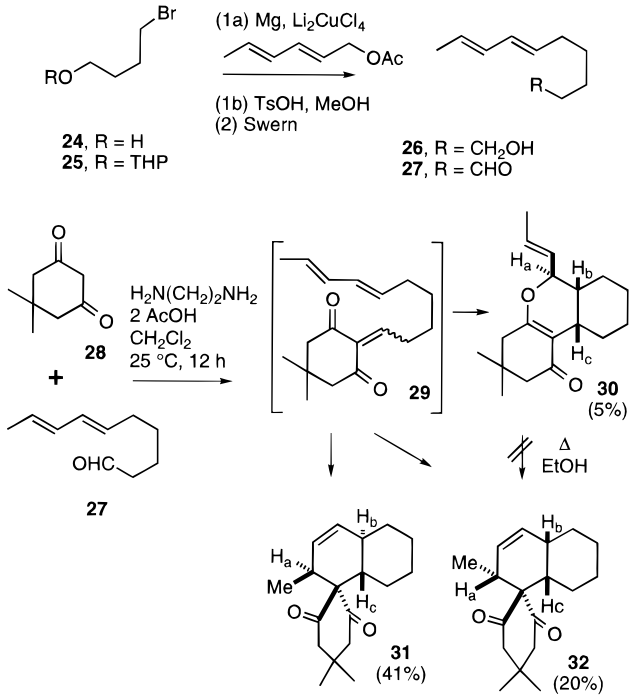
The structure of **22** was established by its formation from **21** by a Claisen rearrangement, which must proceed through a boat transition state since the allyl vinyl ether is a vinyldihydropyran.[13] The stereochemistry of the cyclohexane ring was confirmed by the absorption for H_c at δ 2.02 (dd, 1, J_{bc} = 10.5 Hz, J_{cd} = 10.5 Hz), which indicates that H_b, H_c, and H_d are trans and axial on the cyclohexane ring. Rearrangement of **21** through a boat transition state will give **22** with the methyl group and the ketone carbonyl group cis to H_c on the cyclohexene ring. Reaction through a chair transition state, which is precluded by geometric considerations,[13] would have given a diastereomer of **22** with the methyl group trans to the ketone carbonyl group and H_c. The stereochemistry of the other diastereomer **23**, which could not be obtained pure, was not assigned. The first total synthesis of (±)-leporin A (**1**) was completed by silylation of **3** with TMSCl and HMDS and oxidation with MoO_5·pyr·HMPA[14] in CH_2Cl_2 at rt as described by Sammes[3] to provide the molybdenum salt of **2**. Washing with tetrasodium EDTA solution removed the molybdenum to give 57% (71% based on recovered **3**) of hydroxypyridone **2**. Methylation of **2** with NaOMe and MeI in methanol[4] afforded 77% of (±)-leporin A (**1**), whose spectral data and chromatographic properties are identical with those of a natural sample provided by Prof. Gloer.

The key intermediate **4** underwent competing inverse electron demand intramolecular hetero Diels–Alder reactions to give **3** and **21** and normal intramolecular Diels–Alder reactions to give **22** and **23**. This is not the ideal system to study these competing reactions since the asymmetry of the carbonyl groups of **4** and the methyl group on the tether complicated the stereochemical analysis of the products. Furthermore, the intramolecular hetero Diels–Alder adduct **21** undergoes a Claisen rearrangement to give **22** at the high temperature required for the Knoevenagel condensation that produces *o*-quinone methide **4**, so that **22** can be formed by both a normal Diels–Alder reaction and Claisen rearrangement of hetero Diels–Alder adduct **21**.

To study these competing Diels–Alder reactions in simpler systems at lower temperatures, we prepared aldehyde **27** analogously to **6** and condensed it at 25 °C with the symmetrical dicarbonyl compounds extensively studied by Tietze.[2] Protection of 4-bromobutanol (**24**) (dihydropyran, CH_2Cl_2, TsOH) provided 70% of the THP ether **25**. Reaction of **25** with Mg in THF provided the Grignard reagent, which was added to a mixture of Li_2CuCl_4 and 2*E*,4*E*-hexadien-1-yl acetate in THF to give 25% of dienol **26** after acid hydrolysis. Swern oxidation afforded 92% of dienal **27**.

Condensation of dienal **27** with 5,5-dimethylcyclohexane-1,3-dione (**28**) and ethylenediammonium diacetate in CH_2Cl_2 for 12 h at 25 °C as described by Tietze[2] afforded only 5% of the inverse electron demand hetero Diels–Alder adduct **30** and 61% of a partially separable 2:1 mixture of normal Diels–Alder adducts **31** and **32**. The allylic ring fusion hydrogen H_c of **30** absorbs at δ 2.87 with only one large axial–axial coupling establishing that the ring fusion is cis. The allylic ring fusion hydrogen (H_b) of **31** absorbs at δ 2.70 ppm with two large axial–axial couplings establishing that the ring fusion is trans. No Claisen rearrangement occurred on heating **30** for 12 h in ethanol at reflux so that **32** is formed by a normal Diels–Alder reaction rather than a hetero Diels–Alder reaction followed by a Claisen rearrangement. Since the condensation is carried out at 25 °C, **31** is also probably formed directly by a normal Diels–Alder reaction. Similar condensation of dienal **27** with 1,3-dimethylbarbituric acid or Meldrum's acid gave only the normal Diels–Alder adducts. The absence of significant amounts of hetero Diels–Alder adducts in these condensations precludes further study of the Claisen rearrangement or of the effect of double bond substitution pattern on ring fusion stereochemistry of the hetero Diels–Alder reaction. Presumably, the hetero Diels–Alder adducts **3** and **21** are signficant products from *O*-quinone methide **4** since

(14) Vedejs, E.; Larsen, S. *Org. Synth.* **1989**, *64*, 127.



the aromatic stabilization of the products is reflected in lower transition state energies, while the normal Diels–Alder products **22** and **23** are not aromatic. The hetero Diels–Alder adducts, e.g. **30**, formed from 5,5-dimethylcyclohexane-1,3-dione, 1,3-dimethylbarbituric acid, and Meldrum's acid are not aromatic so the normal Diels–Alder adducts, e.g. **31** and **32** are the major or exclusive product.

A short and efficient synthesis of leporin A has been developed using a tandem Knoevenagel condensation–inverse electron demand intramolecular hetero Diels–Alder reaction to construct the key tricyclic intermediate **3** in one pot in 35% yield from the readily available pyridone **5** and dienal **6**. A similar process may occur in the biosynthesis of leporin A. The formation of the cis fused product **3** as the major product with the *E*,*E*-diene as the dienophile is particularly noteworthy since the trans fused products **10** and **12** are formed exclusively with trisubstituted alkenes as the dienophile.[2,5] This first synthesis provides (±)-leporin A in only ten steps from inexpensive commercially available starting materials, with a longest linear sequence of eight steps, in 4% overall yield.

Experimental Section

General. NMR spectra were recorded at 300 MHz in $CDCl_3$ unless otherwise indicated; chemical shifts are reported in δ and coupling constants in Hz.

6-Chloro-4-hydroxy-5-phenyl-2(1*H*)-pyridone (17) was prepared by the literature procedure.[8] Malonyl dichloride (8 mL, 82 mmol) and phenylacetonitrile (4.5 mL, 39 mmol) were stirred together under anhydrous conditions for 4 d. Diethyl ether (25 mL) was added, and the precipitated **17** was filtered and washed with diethyl ether. Recrystallization from EtOAc gave 5 g (58%) of pyridone **17** as a buff solid: mp 300–302 °C (lit.[8] mp 297–299 °C); ^{1}H NMR (CD_3SOCD_3) 10.98 (br s, 2), 7.47–7.22 (m, 5), 6.17 (s, 1); ^{13}C NMR 166.3, 162.9, 145.6, 134.0, 130.7 (2 C), 128.0 (2 C), 127.4, 117.2, 94.3.

4-Hydroxy-5-phenyl-2(1*H*)-pyridone (5). Chloropyridone **17** (3.5 g, 15.8 mmol) and 10% palladium on charcoal (580 mg) in absolute EtOH (150 mL) were heated at 60 °C under a hydrogen atmosphere for 40 h. The catalyst was filtered off and washed with hot ethanol. The solvent was evaporated under reduced pressure to give 2.9 g (98%) of pyridone **5** as a buff solid which was recrystallized from EtOAc: mp 179–180 °C (lit.[10] mp 171–177 °C); ^{1}H NMR (CD_3OD) 7.86 (s, 1), 7.52–7.41 (m, 5), 6.51 (s, 1); ^{13}C NMR 171.7, 163.2, 137.8, 133.6, 130.4 (2 C), 129.7 (2 C), 129.6, 122.6, 97.9; IR (KBr) 3423, 2956, 1642, 1420; UV (MeOH) λ_{max} nm (ϵ) 295 (6,000, sh), 238 (41,300).

4-Bromo-2-methylbutan-1-ol (18).[11] 2-Methylbutyrolactone (5.3 g, 53 mmol) was added to a freshly prepared saturated solution of dry hydrogen bromide in absolute ethanol (50 mL). The solution was stirred at rt for 3 d, poured into ice–water, and extracted with ether (3 × 100 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (100 mL) and water (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give 10.7 g (96%) of ethyl 4-bromo-2-methylbutyrate.

A solution of the above ester (10 g, 47.8 mmol) in dry ether (50 mL) was added dropwise over 30 min to a suspension of LAH (1.9 g, 47.8 mmol) in dry ether (100 mL) at 0 °C under N_2. The reaction mixture was stirred for 2 h at 0 °C. Methanol (1 mL) was added dropwise to the suspension, and the mixture was poured into ice-cold 2 N HCl solution (200 mL). The mixture was extracted with ether, which was dried ($MgSO_4$) and concentrated to give 6 g (75%) of **18**, whose spectral data are identical to those previously described.[11]

4-Bromo-2-methylbutyl Tetrahydropyranyl Ether (19). A solution of dihydropyran (3.4 mL, 36.9 mmol), alcohol **18** (5.6 g, 33.5 mmol), and a catalytic quantity of *p*-TsOH (14 mg) in CH_2Cl_2 (50 mL) was stirred at rt for 2 h. A few drops of Et_3N were added, and the mixture was evaporated under reduced pressure. Filtration through a short silica gel plug eluting with hexane, followed by flash chromatography on silica gel (10:1 hexane–EtOAc) gave 5.5 g (68%) of **19**: ^{1}H NMR 4.58–4.55 (m, 1), 3.87–3.80 (m, 1), 3.60 (ddd, 1, J = 9.5, 8.2, 6.2), 3.53–3.42 (m, 3), 3.24 (ddd, 1, J = 9.5, 8.5, 5.7), 2.10–1.91 (m, 2), 1.86–1.44 (m, 7), 0.96 (d, 0.5 × 3, J = 6.7), 0.95 (d, 0.5 × 3, J = 6.7); ^{13}C NMR (99.0, 98.8), (72.2, 72.1), (62.2, 62.1), (37.2, 37.1), (32.4, 32.3), (32.0, 31.9), 30.6, 25.6, (19.5, 19.4), (16.6, 16.5); IR (neat) 2942, 2872, 1448, 1260, 1201.

2-Methyl-6*E*,8*E*-decadienol (20). To a suspension of Mg (1.2 g, 47.8 mmol) in 19 mL of THF was added dibromoethane (0.5 mL). When all the dibromoethane had reacted, the gray solution was removed by syringe. After rinsing the Mg with THF (20 mL) twice, 20 mL of THF was added. Bromide **19** (4.8 g, 19.1 mmol) was added dropwise to the Mg suspension. The mixture was stirred at rt for 2 h. This gray solution was then added dropwise under N_2 to a cooled (−10 °C) solution of 2*E*,4*E*-hexadien-1-yl acetate (2.3 g, 16.2 mmol) and Li_2CuCl_4 (6.48 mL, 0.1 M in THF) in THF (20 mL). The color changed from orange to dark brown to green and finally to purple. The resulting mixture was held at 0 °C for 2 h and then at rt overnight. Saturated NH_4Cl was added, and the mixture was extracted with ether. The ether layers were evaporated under reduced pressure. The crude oily residue was dissolved in methanol (30 mL) containing *p*-TsOH (518 mg, 2.7 mmol) and stirred for 2 h at rt. Et_3N (330 μL, 2.4 mmol) was added, and the solvent was removed under reduced pressure. The residue was dissolved in ether, which was washed with 0.1 N HCl and water and then dried ($MgSO_4$). Removal of the solvent and flash chromatography of the residue on silica gel (5:1 hexane–EtOAc) gave 1.5 g (44%) of **20**: ^{1}H NMR 6.03 (dt, 1, J = 14.5, 1.1), 6.06–5.96 (m, 1), 5.64–5.50 (m, 2), 3.50 (dd, 1, J = 10.5, 5.8), 3.41 (dd, 1, J = 10.5, 6.5), 2.05 (ddd, 2, J = 6.6, 6.6, 6.6), 1.73 (d, 3, J = 6.5), 1.68–1.58 (m, 2), 1.46–1.32 (m, 2), 1.16–1.08 (m, 1), 0.91 (d, 3, J = 6.8); ^{13}C NMR 132.0, 131.8, 130.6, 127.1, 68.5, 35.9, 33.0, 32.9, 27.0, 18.2, 16.7; IR (neat) 3346, 3015, 2928, 1461. Anal. Calcd for $C_{11}H_{20}O$: C, 78.58; H, 11.90. Found: C, 77.73; H, 12.06.

2-Methyl-6*E*,8*E*-decadienal (6). Dimethyl sulfoxide (0.23 mL, 3.2 mmol) was added slowly to a solution of oxalyl chloride (0.14 mL, 1.6 mmol) in 5 mL of dry CH_2Cl_2 at −78 °C. The mixture was stirred for 20 min, and a solution of alcohol **20** (177 mg, 1.0 mmol) in 1 mL of CH_2Cl_2 was added slowly to the mixture, which was then stirred at −78 °C for 20 min. Et_3N (0.90 mL, 6.4 mmol) was added slowly to the mixture, which was then warmed to rt. Ether was added, and the

solution was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (10:1 hexane−EtOAc) gave 139 mg (79%) of **6** as a colorless oil: ^{1}H NMR 9.60 (d, 1, J = 1.9), 6.06−5.95 (m, 2), 5.6−5.47 (m, 2), 2.33 (dtq, 1, J = 1.9, 6.9, 6.9), 2.07 (dt, 2, J = 6.9, 6.9), 1.73 (d, 3, J = 6.3), 1.73−1.66 (m, 1), 1.47−1.35 (m, 3), 1.08 (d, 3, J = 6.9); ^{13}C NMR 205.3, 131.7, 131.2, 131.0, 127.4, 46.4, 32.6, 30.1, 26.9, 18.2, 13.5; IR (neat) 3016, 1726.

(6α(*E*),6aα,10α,10aα)-2,6,6a,7,8,9,10,10a-Octahydro-10-methyl-4-phenyl-6-(1-propenyl)-1*H*-[2]benzopyrano[4,3-*c*]pyridin-1-one (3), (6α(*E*),6aα,10*β*,10a*β*)-2,6,6a,7,8,9,10,-10a-Octahydro-10-methyl-4-phenyl-6-(1-propenyl)-1*H*-[2]benzopyrano[4,3-*c*]pyridin-1-one (21), and 4a,5,6,7,-8,8a,1′,4′-Octahydro-2,5-dimethyl-5′-phenylspiro[naphthalene-1(2*H*),3′(2′*H*)-pyridine]-2′,4′-dione (22 and 23). A solution of pyridone **5** (39 mg, 0.21 mmol), Et_3N (35 μL, 0.25 mmol), and aldehyde **6** (22.8 mg, 0.13 mmol) in absolute EtOH (0.6 mL) was stirred at rt for 2 h and placed in an oil bath which was heated to 160 °C over 30 min. The oil bath was kept at 160 °C for 20 h under N_2. Most of the solvent evaporated during this time. If the ethanol did not evaporate, the yield of **22** and **23** increased at the expense of **3** and **21**. The solvent was removed under reduced pressure. The combined residue from three reactions (a total of 78.8 mg of aldehyde **6**) was purified by flash chromatography on silica gel (EtOAc) giving 48 mg (32%) of a 1:1 mixture of **22** and **23** as a brown, waxy solid, followed by 10 mg (7%) of **21** as a white solid, followed by 53 mg (35%) of **3** as a white powder. **3** and **21** were recrystallized from CH_2Cl_2/EtOAc.

Analysis of the NMR spectra indicated that an inseparable 1:1 mixture of **22** and **23** was present. Partial data for **23**: ^{1}H NMR 5.82 (ddd, 1, J = 9.3, 2.7, 2.7), 1.11 (d, 3, J = 7.3), 0.75 (d, 3, J = 6.4).

Data for **21**: mp 203−205 °C; ^{1}H NMR 7.44−7.26 (m, 5), 7.16 (s, 1), 5.67 (dq, 1, J = 15.0, 6.6), 5.44 (ddq, 1, J = 15.0, 7.7, 1.5), 3.95 (dd, 1, J = 10.0, 7.7), 2.39 (dd, 1, J = 10.0, 10.0), 1.86−1.06 (m, 8), 1.70 (dd, 3, J = 6.6, 1.5), 1.19 (d, 3, J = 6.5); ^{13}C NMR 165.5, 163.7, 134.3, 131.0, 130.3, 129.0 (2 C), 128.6, 128.1 (2 C), 126.9, 115.6, 112.0, 83.2, 47.7, 44.3, 40.5, 36.5, 29.1, 25.9, 22.9, 17.8; IR (neat) 2928, 1641, 1600, 1447, 1229; UV (MeOH) λ_{max} nm (ϵ) 300 (7 500, sh), 240 (31 000), 201 (43 700); (MeOH + HCl) 236 (34 600), 202 (51 100); (MeOH + NaOH) 300 (6 400, sh), 240 (29 900).

Data for **3**: mp 228−229 °C; ^{1}H NMR 7.43−7.28 (m, 5), 7.21 (s, 1), 5.76 (dq, 1, J = 15.2, 6.5), 5.39 (ddq, 1, J = 15.2, 8.1, 1.5), 4.58 (dd, 1, J = 11.3, 8.1), 2.79 (dd, 1, J = 10.9, 3.7), 1.72 (dd, 3, J = 6.5, 1.5), 1.83−1.26 (m, 8), 1.01 (d, 3, J = 6.5); ^{13}C NMR 165.2, 160.5, 134.7, 131.8, 131.0, 129.7, 129.3 (2 C), 128.3 (2 C), 127.2, 115.3, 111.7, 78.3, 37.3, 36.2, 36.1, 35.4, 26.7, 21.1, 20.7, 18.0; IR (neat) 2925, 1643, 1454, 1218; UV (MeOH) λ_{max} nm (ϵ) 295 (4 400, sh), 240 (23 600); (MeOH + HCl) 235 (26 200); (MeOH + NaOH) 295 (6 400, sh), 240 (22 000). Anal. Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51, N, 4.18. Found: C, 78.56; H, 7.69; N, 4.17.

Claisen Rearrangement of 21 to 22. A solution of **21** (10 mg, 0.03 mmol), piperidine (0.05 mL), and pyridine (0.05 mL) in absolute EtOH (0.5 mL) was heated at 100 °C for 12 h. Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (3:4 hexane−EtOAc) gave 6.5 mg (65%) of **22** as a white, waxy solid followed by 2 mg (20%) of recovered **21**: mp 75−76 °C; ^{1}H NMR 8.47 (br s, 1, NH), 7.37−7.27 (m, 5), 7.36 (s, 1), 5.77 (ddd, 1, J = 9.4, 2.5, 2.5), 5.46 (ddd, J = 9.4, 3.1, 3.1), 2.77 (m, 1), 2.44 (m, 1), 2.02 (dd, 1, J = 10.5, 10.5), 1.98 (m, 1), 1.92−0.90 (m, 6), 1.04 (d, 3, J = 7.3), 0.69 (d, 3, J = 6.6); ^{13}C NMR 196.5, 177.3, 138.3, 135.9, 133.5, 128.4 (2 C), 128.3 (2 C), 128.2, 127.7, 119.8, 64.6, 52.8, 41.8, 38.7, 36.5, 34.4, 33.6, 25.7, 21.7, 18.1; IR (neat) 3260, 2923, 1699; UV (MeOH) λ_{max} nm (ϵ) 324 (7 400), 240 (14 000); (MeOH + HCl) 324 (7 400), 240 (14 000); (MeOH + NaOH) 385 (7 000), 270 (10 500).

A solution of **21** in absolute EtOH (1 mL) was heated at 100 °C for 12 h. About 30% conversion to **22** was obtained based on analysis of the NMR spectrum.

A solution of **3** (10 mg, 0.03 mmol), piperidine (0.05 mL), and pyridine (0.05 mL) in absolute EtOH (0.5 mL) was heated at 100 °C for 12 h. No reaction occurred as determined by analysis of the NMR spectrum.

(6α(*E*),6aα,10α,10aα)-2,6,6a,7,8,9,10,10a-Octahydro-2-hydroxy-10-methyl-4-phenyl-6-(1-propenyl)-1*H*-[2]benzopyrano[4,3-*c*]pyridin-1-one (2). HMDS (1.0 mL, 6.2 mmol) containing chlorotrimethylsilane (0.5 mL) was added to pyridone **3** (25 mg, 0.03 mmol). The solution was heated at reflux for 6 h under N_2, and the excess HMDS was removed under reduced pressure. The residue was treated with oxodiperoxymolybdenum−pyridine−HMPA complex (65 mg, 0.15 mmol) in dry CH_2Cl_2 at rt overnight by the procedure of Sammes.[3] Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (EtOAc) gave the molybdenum complex of **2**, followed by 5 mg (19%) of recovered **3**. The molybdenum complex of **2** was dissolved in EtOAc (3 mL) and stirred with saturated aqueous tetrasodium EDTA solution (3 mL) for 2 h. The mixture was neutralized with 0.1 M HCl solution. The layers were separated, and the organic layer was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure to give a white solid that was washed with EtOAc to give 15.0 mg (57%, 71% based on recovered **3**) of pure **2** as a white solid: mp 117−118 °C; ^{1}H NMR 7.61 (s, 1), 7.44−7.28 (m, 5), 5.74 (dq, 1, J = 15.1, 6.6), 5.38 (ddq, 1, J = 15.1, 8.3, 1.5), 4.82 (dd, 1, J = 11.1, 8.3), 2.80 (dd, 1, J = 10.7, 3.6), 1.73 (dd, 3, J = 6.6, 1.5), 1.80−1.23 (m, 8), 0.91 (d, 3, J = 6.5); ^{13}C NMR 158.2, 157.5, 133.6, 131.0, 129.3, 129.2, 129.1 (2 C), 128.2 (2 C), 127.3, 113.4, 111.0, 78.1, 38.0, 35.8, 35.7, 35.1, 26.4, 20.8, 20.3, 17.8; IR (neat) 2945, 1637, 1497, 1219, 942; UV (MeOH) λ_{max} nm (ϵ) 300 (5 500, sh), 241 (25 100); (MeOH + HCl) 235 (28 000); (MeOH + NaOH) 330 (6 400, sh), 282 (12 300), 241 (22 900).

(6α(*E*),6aα,10α,10aα)-2,6,6a,7,8,9,10,10a-Octahydro-2-methoxy-10-methyl-4-phenyl-6-(1-propenyl)-1*H*-[2]benzopyrano[4,3-*c*]pyridin-1-one (Leporin A, 1). NaOMe (1 mL, 0.5 M in MeOH) and MeI (0.3 mL, 4.8 mmol) were added to *N*-hydroxypyridone **2** (10 mg, 0.028 mmol). The mixture was heated at 55 °C for 2 h. The solvent was removed under reduced pressure, and the residue was dissolved in EtOAc and washed with water three times. The layers were separated, and the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (4:1 hexane−EtOAc) gave 8 mg (77%) of leporin A (**1**): mp 168−169 °C; ^{1}H NMR 7.43−7.31 (m, 5), 7.38 (s, 1), 5.75 (dq, 1, J = 15.2, 6.5); 5.37 (ddq, 1, J = 15.2, 8.1, 1.5), 4.82 (dd, 1, J = 11.1, 8.1), 4.06 (s, 3), 2.84 (dd, 1, J =10.7, 3.8), 1.73 (dd, 3, J = 6.5, 1.5), 1.82−1.24 (m, 8), 1.00 (d, 3, J = 6.6); ^{13}C NMR 158.5, 157.9, 133.7, 131.4, 130.9, 129.3, 129.0 (2 C), 128.2 (2 C), 127.3, 113.7, 113.1, 78.0, 64.6, 37.7, 36.0, 35.8, 35.2, 26.4, 20.8, 20.6, 17.8; IR (neat) 2926, 1651, 1537, 1232; UV (MeOH) λ_{max} nm (ϵ) 287 (6 200, sh), 242 (23 900), 201 (26 900); (MeOH + HCl) 295 (3 000, sh), 242 (23 000), 200 (27 000); (MeOH + NaOH) 295 (3 000, sh), 242 (23 000), 213 (62 700). The ^{1}H NMR and ^{13}C NMR spectral data in $CDCl_3$ are identical to those of natural (−)-leporin A.[1] Natural and synthetic leporin A are also identical by TLC (4:1 hexane:EtOAc) comparison.

4-Bromobutyl tetrahydropyranyl ether (25) was prepared from dihydropyran (3.9 mL, 42.3 mmol), alcohol **24** (6.0 g, 39.2 mmol), and *p*-TsOH (11 mg), as described above for the preparation of **19**, giving 6.5 g (70%) of **25**: ^{1}H NMR 4.59−4.56 (m, 1), 3.89−3.73 (m, 2), 3.54−3.39 (m, 2), 3.46 (t, 2, J = 6.8), 2.03−2.0 (m, 2), 1.99−1.70 (m, 4), 1.68−1.48 (m, 4); ^{13}C NMR 98.8, 66.4, 62.3, 33.6, 30.6, 29.8, 28.3, 25.4, 19.6; IR (neat) 2942, 2870, 1440, 1201.

6*E*,8*E*-Decadien-1-ol (26) was prepared from magnesium (262 mg, 10.7 mmol), bromide **25** (1.9 g, 8.0 mmol), 2*E*,4*E*-hexadien-1-yl acetate (448 mg, 3.2 mmol) and Li_2CuCl_4 (1.28 mL, 0.1 M in THF) in THF (15 mL), as described for the preparation of **20**, giving 307 mg (25%) of **26** after hydrolysis of the THP ether: ^{1}H NMR 6.00−5.95 (m, 2), 5.63−5.49 (m, 2), 3.63 (t, 2, J = 6.6), 2.07 (td, 2, J = 6.8, 6.8), 1.72 (d, 3, J = 6.3), 1.57 (tt, 2, J = 7.0, 7.0), 1.43−1.32 (m, 4); ^{13}C NMR 131.7, 131.6, 130.4, 126.8, 62.9, 32.6, 32.4, 29.2, 25.2, 18.0; IR (neat) 3350, 2933, 2860, 1457.

6*E*,8*E*-Decadienal (27) was prepared from alcohol **26** (276 mg, 1.8 mmol), as described above for the preparation of **6**,

providing 251 mg (92%) of dienal **27** as a colorless oil: ^{1}H NMR 9.76 (t, 1, J = 1.7), 6.00−5.95 (m, 2), 5.64−5.47 (m, 2), 2.42 (td, 2, J = 7.3, 1.7), 2.08 (td, 2, J = 7.2, 7.2), 1.72 (d, 3, J = 6.4), 1.64 (tt, 2, J = 7.6, 7.3), 1.42 (tt, 2, J = 7.6, 7.2); ^{13}C NMR 202.6, 131.5, 131.0, 130.8, 127.2, 43.7, 32.2, 28.8, 21.6, 18.0; IR (neat) 2935, 2851, 1722, 1457.

Condensation of Dienal 27 and 5,5-Dimethylcyclohexane-1,3-dione (28). A solution of dienal **27** (41.2 mg, 0.26 mmol), dione **28** (41.7 mg, 0.23 mmol), and ethylenediammonium diacetate (0.4 mg) in CH_2Cl_2 (4 mL) was stirred at rt for 12 h. The solvent was removed under reduced pressure. The combined residue (134 mg) from two reactions (a total of 65 mg of dienal **27**) was purified by flash chromatography on silica gel (6:1 hexane−EtOAc), giving 47 mg (40%) of a 1:1 mixture of **31** and **32** as a colorless oil, followed by 36 mg (21%) of **31** as a white solid, followed by 9 mg (5%) of **30** as a colorless oil.

Data for **30**: ^{1}H NMR 5.79 (dq, 1, J = 15.2, 6.4), 5.45 (ddq, 1, J = 15.2, 8.7, 1.6), 3.94 (dd, 1, J = 10.0, 8.7), 2.87 (br d, 1, J = 12.8), 2.24 (br s, 2), 2.22 (d, 1, J = 16.4), 2.16 (d, 1, J = 16.4), 2.14−2.04 (m, 1), 1.84−1.66 (m, 2), 1.72 (dd, 3, J = 6.4, 1.6), 1.44−1.22 (m, 4), 1.06 (s, 3), 1.04 (s, 3), 1.02−0.67 (m, 2); ^{13}C NMR 187.9, 169.4, 132.0, 128.4, 113.9, 82.7, 51.5, 44.4, 42.8, 37.8, 31.4, 30.0, 29.4, 28.3, 27.2, 26.4, 26.0, 17.9; IR (neat) 2930, 2860, 1651, 1611.

Data for **31**: mp 70−74 °C; ^{1}H NMR 5.48 (br d, 1, J = 10.1), 5.41 (ddd, 1, J = 10.1, 4.6, 2.3), 2.89 (d, 1, J = 14.4), 2.70 (dddddd, 1, J = 10.1, 10, 4, 2.3, 1, 1), 2.62 (dddq, 1, J = 4.6, 1, 1, 6.7), 2.55 (d, 1, J = 14.4), 2.39 (dd, 1, J = 14.4, 3.0), 2.37 (dd, 1, J = 14.4, 3.0), 1.82−1.72 (m, 4), 1.61−1.57 (m, 1), 1.4 (br dd, 1, J = 10, 10), 1.28−0.98 (m, 3), 1.12 (s, 3), 0.88 (d, 3, J = 6.7), 0.85 (s, 3); ^{13}C NMR 208.7, 208.3, 132.4, 126.3, 69.0, 53.2, 52.6, 39.0, 37.9, 37.1, 34.3, 30.7, 30.1, 27.6, 27.4, 27.1, 26.2, 18.8; IR (neat) 2930, 2852, 1723, 1693.

Partial data for **32**: ^{1}H NMR 5.68 (ddd, 1, J = 9.8, 3.7, 2.2), 5.31 (br d, 1, J = 9.8).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **1**−**3**, **6**, **20**−**22** (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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