Total Synthesis of (±)-Pyridoxatin

Barry B. Snider* and Qing Lu

Department of Chemistry, Brandeis University, P.O. Box 9110, Waltham, Massachusetts 02254

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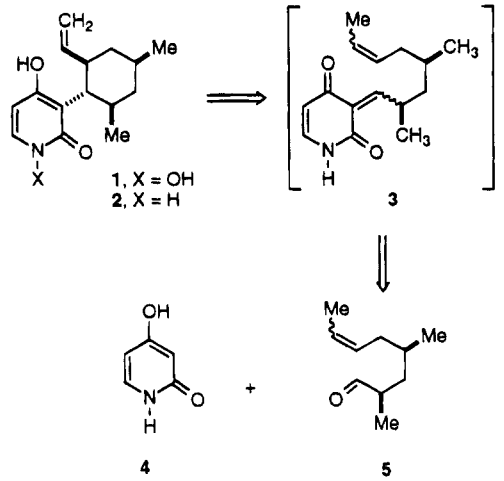
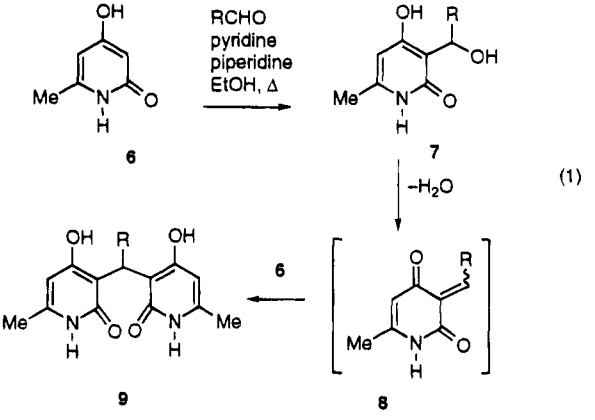
An efficient two-step route to pyridoxatin analogues **13** and **15** has been developed. Condensation of 4-hydroxypyridone (**4**) with citronellal (**10**) affords *o*-quinone methide intermediate **11**, which reacts further to give inverse electron demand Diels–Alder adducts **12** and **16** and ene adduct **14**. Oxidation of **12** and **14** with MoO_5 by Sammes' procedure completes the synthesis of **13** and **15**. Using this approach, the first total synthesis of (±)-pyridoxatin (**1**) has been carried out in seven steps from *cis*-2,4-dimethylcyclohexanone (**21**). The key step is the condensation of 4-hydroxypyridone (**4**) with the allylic silane aldehyde **26** to give 35% of cyclohexylpyridones **2** and **30**.

Introduction

Free radical scavengers could be generally useful therapeutic agents since free radicals are known to play a role in a variety of diseases including cardiovascular disease, connective tissue damage, inflammatory disorders, and CNS injury.[1] Pyridoxatin (**1**), a 1-hydroxy-2-pyridone free radical scavenger isolated from *Acremonium* sp. BX86, is approximately 20 times as active as vitamin E in the assay system employed.[2] It probably functions as an iron chelator since 1-hydroxy-2-pyridone and 1,4-dihydroxy-2-pyridone bind iron tightly under physiological conditions.[3] A variety of other 1-hydroxypyridone antibiotics including BN-227[4ab] G1549,[4c] and tenellin[5b] are also siderophores.



We envisaged that a synthesis of pyridoxatin could be carried out by the intramolecular ene reaction of *o*-quinone methide **3** which should give **2**, with all substituents on the cyclohexane ring equatorial. Oxidation of the pyridone **2** by Sammes' procedure[5] should afford pyridoxatin (**1**). This approach was especially attractive since *o*-quinone methide **8** has been proposed as an intermediate by Findlay and co-workers in the base-catalyzed formation of 2:1 adduct **9** from 4-hydroxy-6-methyl-2-pyridone (**6**) and an aldehyde (eq 1).[6] If the double bond of **3** reacts with the *o*-quinone methide faster than the *o*-quinone methide reacts with a second molecule of pyridone **4**, it should be possible to form **2** in a single step by condensation of 4-hydroxy-2-pyridone (**4**) with aldehyde **5**.



Results and Discussion

Preparation of the Model Compounds 13 and 15. The feasibility of this approach to pyridoxatin was examined in a model study using the readily available aldehyde citronellal (**10**), which has a more nucleophilic trisubstituted double bond and a different methyl substitution pattern. We were delighted to find that the one-pot reaction of pyridone **4** and citronellal (**10**) in EtOH containing piperidine and pyridine at reflux for 60 h by Findlay's procedure afforded 46% of Diels–Alder adduct **12**, 28% of the desired ene adduct **14**, and 25% of Diels–Alder adduct **16**.[7]

[⊗] Abstract published in *Advance ACS Abstracts,* November 15, 1994.

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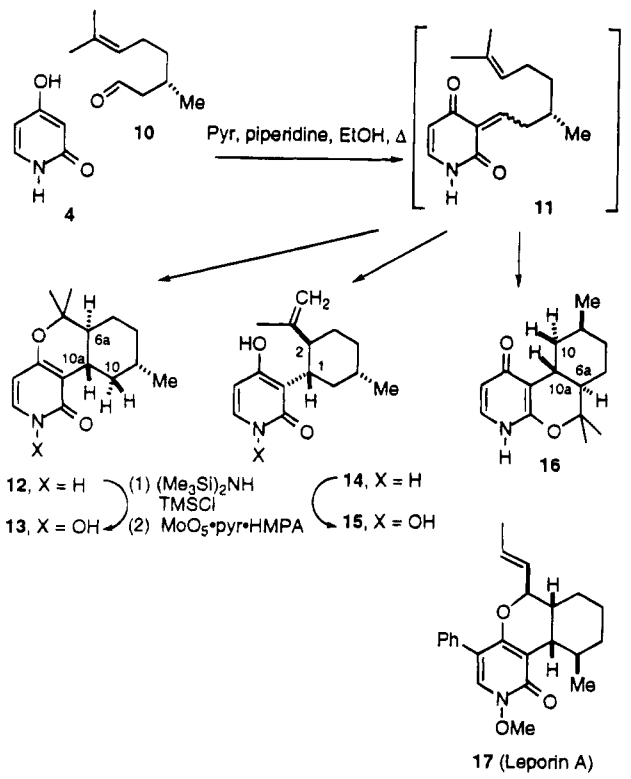
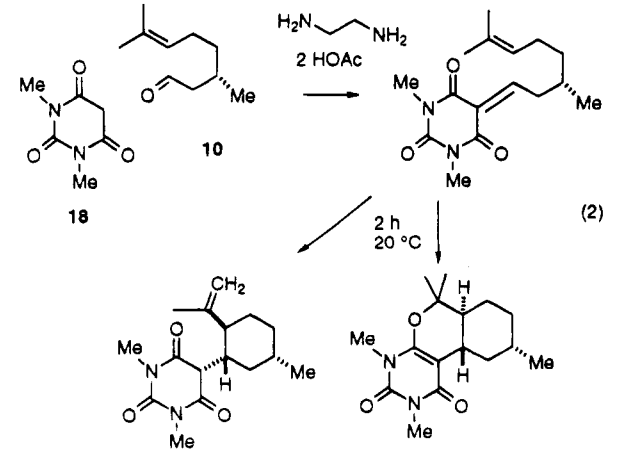


All three products appear to arise from the proposed *o*-quinone methide intermediate **11**. The desired ene reaction affords isopropenylcyclohexane **14**. Inverse electron demand Diels–Alder reaction with the enone provides Diels–Alder adduct **12**, while a similar Diels–Alder reaction with the enamide furnishes Diels–Alder adduct **16**. The formation of **12** as the major product suggests that this approach will be useful for the synthesis of the antiinsectan *N*-alkoxypyridone leporin A (**17**), which has the identical ring system.[8] The inverse electron demand Diels–Alder reaction is well precedented in the intramolecular cycloaddition of an *o*-quinone methide that leads to hexahydrocannabinol[9] and in the work of Tietze,[10] who observed competing intramolecular ene and inverse electron demand Diels–Alder reactions in the condensation of *N,N*-dimethylbarbituric acid (**18**) with citronellal (eq 2).



Mass spectral data established that all three compounds **12**, **14**, and **16** are 1:1 adducts. The ^{1}H NMR spectral data suggested that **12** and **16** are inverse electron demand Diels–Alder adducts since there are two methyl singlets and no alkene hydrogens. The stereochemistry of the ring fusion of **12** was assigned from the coupling constant between H-6a and H-10a of 11.5 Hz which requires that the hydrogens be trans and diaxial. The π system profoundly influences the chemical shift of the two hydrogens on C-10. The equatorial hydrogen is deshielded[11] and absorbs downfield at δ 3.34 while the axial hydrogen is in the shielding cone of the π system and absorbs upfield at δ 0.58. The coupling constant between H-9 and H-10ax of 11.5 Hz established that H-9 is axial and the methyl group is therefore equatorial.

The ^{1}H NMR spectra of **12** and **16** are virtually identical in the aliphatic region since the only difference between these two compounds is the position of the nitrogen in the ring. The slight differences in the position of the olefinic protons are not sufficient to distinguish between these compounds. UV spectra, on the other hand, are quite useful for distinguishing 2-pyridones from 4-pyridones.[12] 2-Pyridone **12** absorbs at 281 nm while 4-pyridone **16** absorbs at 258 nm.

The ^{1}H NMR spectrum of **14** clearly shows the presence of the isopropenyl group at δ 4.61 (br s, 1) and δ 4.42 (br s, 1) and shows the presence of two atropisomers due to hindered rotation about the bond between the two rings as is observed in pyridoxatin itself.[2] The coupling constant between H-1 and H-2 of 11.5 Hz establishes that these hydrogens are trans diaxial, suggesting that the stereochemistry is as shown.

Silylation of 2-pyridone **12** with HMDS and TMSCl afforded the crude ((trimethylsilyl)oxy)pyridine, which was treated with MoO_5•pyr•HMPA[13] in CH_2Cl_2 for 15 h at rt as described by Sammes[5a] to provide the molybdenum complex of **13**. Washing with tetrasodium EDTA solution removed the molybdenum to give 54% of **13**. Hydroxypyridone **14** was converted analogously to the bis((trimethylsilyl)oxy)pyridine and oxidized to afford 48% of **15**. The mass spectral data confirm that hydroxy groups have been added to the molecules. The ^{1}H and ^{13}C NMR spectra are similar to those of the starting materials except for the expected small shifts in the pyridone portion of the molecule.[14]

N-Hydroxypyridones **13** and **15** are both effective free radical inhibitors, preventing Fe^{2+}-initiated lipid peroxidation in rat brain homogenate with an IC_{50} of 20–25 μM (6 μg/mL).[15] The two-step sequence to these compounds from commercially available 4-hydroxypyridone (**4**) and citronellal (**10**) makes these compounds very readily available for further study.

Synthesis of (±)-Pyridoxatin. Use of *cis*-6-nonenal instead of citronellal in the condensation with **4** did not provide ene or Diels–Alder adducts, indicating that the 1,2-disubstituted double bond is not nucleophilic enough

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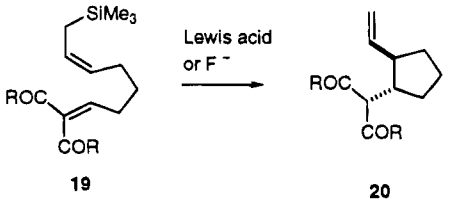
(15) We thank Drs. Tian-Li Yue and Giora Feuerstein, SmithKline Beecham Pharmaceuticals, for measuring the free radical inhibitory properties of **13** and **15**.

to react with the *o*-quinone methide. We therefore turned our attention to the condensation of **4** with the more nucleophilic 8-(trimethylsilyl)-6-octenal **26** to introduce the vinyl group present in pyridoxatin. Tietze and Ruther have shown that alkylidenemalonate derivatives **19** containing an allylic silane undergo fluoride or Lewis acid induced cyclization to give the *trans*-1,2-disubstituted cyclopentanes **20** in good to excellent yield.[16]

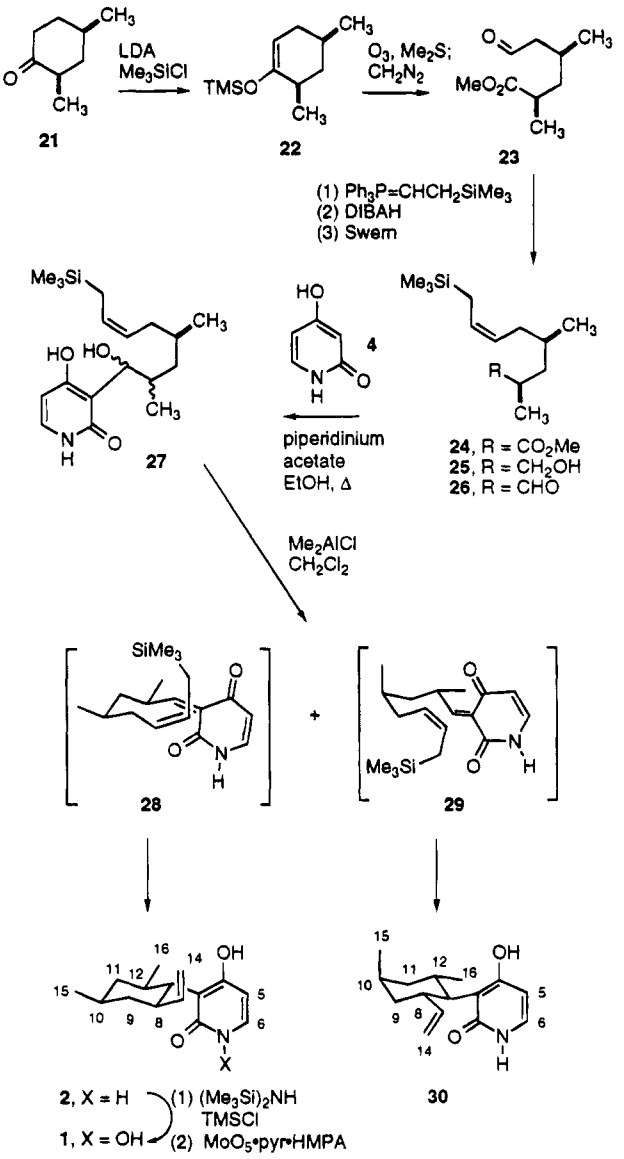


19 **20**

cis-2,4-Dimethylcyclohexanone (**21**) was prepared by a modification of the literature procedure.[17] Hydrogenation of 2,4-dimethylphenol over Rh/Al[18] at 50 psi followed by Jones oxidation of the mixture of cyclohexanols gave 60% of **21** containing 10–15% of the trans isomer.[17] Enolization with LDA and trapping with chlorotrimethylsilane afforded 75% of the less substituted enol silyl ether **22**[19] that was ozonolyzed[20] at −78 °C and treated with dimethyl sulfide and diazomethane[21] to provide 72% of the aldehydo ester **23** containing 10–15% of the diastereomer (Scheme 1). Wittig reaction of **23** with ((trimethylsilyl)ethylidene)triphenylphosphorane,[22] prepared from (iodomethyl)trimethylsilane and methyltriphenylphosphonium bromide by Fleming's one-pot procedure, provided 73% of **24**, predominantly as the *Z*-isomer.[16,23,24] DIBAH reduction afforded 80% of alcohol **25**, which was subjected to Swern oxidation to afford 80% of the required aldehyde **26**.

Unfortunately, condensation of **4** and **26** under the conditions used with citronellal gave none of the desired cyclohexylpyridone **2**. A variety of other conditions, including the use of phenylboronic acid as a catalyst,[25] were also unsuccessful. Success was eventually achieved by a two-step sequence. Condensation of **4** with **26** in the presence of piperidinium acetate in EtOH at reflux for 12 h provided alcohol **27** as a complex mixture of stereoisomers, which was treated with excess Me_2AlCl in CH_2Cl_2 for 12 h at 25 °C to afford 35% of a 1:1 mixture of **2** and **30**, both as 1:1 mixtures of atropisomers. Fractional recrystallization from MeOH five times gave **2** that contained <10% of **30**.

Scheme 1



Unfortunately, the relative stereochemistry of the methyl groups of **26** was lost in the preparation of **2** and **30**. This occurred by epimerization of the aldehyde prior to condensation with **4**, since attempted condensation of **4** with **26** with piperidinium acetate in EtOH at 25 °C for 12 h led to recovered **4** and a 1:1 mixture of **26** and its diastereomer.

The ^1H and ^{13}C NMR spectra indicate that the C-15 methyl group is axial in the undesired diastereomer **30**. The axial methyl group is shifted downfield by 0.17 ppm in the ^1H NMR spectrum and C-8, 9, 10, 11, 12, and 15 are shifted upfield by 4–6 ppm in the ^{13}C NMR spectrum from their absorptions in **2**.[26] As expected, the coupling constant to the axial methyl group (7.1 Hz) in **30** is larger than the coupling constant to the equatorial methyl group (6.1 Hz) of **2**.[27] The absorption of H-7 as a dd (J = 11, 11 Hz) in both **2** and **30** indicates that H-7, 8, and 12 are axial and that the pyridone ring and vinyl and C-16 methyl groups are equatorial in both diastereomers.

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The cyclization of quinone methides **28** and **29** is stereospecific, affording **2** and **30**, respectively. The stereospecific formation of **2** from **28** was anticipated since substituents strongly prefer to be equatorial.[10] Cyclization of **29** must give a product with one equatorial and one axial methyl group. The observed product **30** is formed exclusively since there would be severe steric interactions between the carbonyl group and an axial C-16 methyl group in the transition state.

Hydroxylation of **2** as described above for **14** afforded 44% of pure (±)-pyridoxatin (**1**) whose spectral data are identical to those previously reported.[2] The first synthesis of pyridoxatin has been accomplished in seven steps from 2,4-dimethylcyclohexanone. The condensation of unsaturated aldehydes such as citronellal (**10**) and **26** with 4-hydroxypyridone (**4**) has been developed as a general route to 3-cyclohexylpyridones such as **2**, **12**, **14**, and **16**.

Experimental Section

(6aα,9α,10aβ)-2,6,6a,7,8,9,10,10a-Octahydro-6,6,9-trimethyl-1*H*-[2]benzopyrano[4,3-*c*]pyridin-1-one (12), 4-Hydroxy-(1α,2β,5α)-3-(5-methyl-2-(methylethenyl)cyclohexyl)-2(1*H*)-pyridinone (14), and (6aα,9α,10aβ)-4,6,6a,7,8,9,10,-10a-Octahydro-6,6,9-trimethyl-1*H*-[2]benzopyrano[3,4-*b*]pyridin-1-one (16). A solution of 2,4-dihydroxypyridine (**4**) (2.55 g, 22.9 mmol), piperidine (0.1 mL), pyridine (2.4 mL), and citronellal (**10**) (85–90% pure, 10.20 g, 66.1 mmol) in absolute EtOH (300 mL) was heated at reflux for 60 h by the procedure of Findlay.[6] Removal of the solvent under reduced pressure followed by flash chromatography on silica gel (3:7 hexane–EtOAc) gave 2.29 g (46%) of **12** as a pale yellow, waxy solid, followed by 1.39 g (28%) of **14** as a white powder, followed by 1.27 g (25%) of **16** as a brown, waxy solid.

Data for **12**: mp 78–80 °C; ^{1}H NMR 7.14 (d, 1, J = 7.1), 5.85 (d, 1, J = 7.1), 3.34 (ddd, 1, J = 11.5, 2.5, 2.5, H-10eq), 2.34 (ddd, 1, J = 11.5, 11.5, 2.5, H-10a), 1.82 (ddd, 1, J = 11.5, 11.5, 2.5, H-6a), 1.58–1.68 (m, 1), 1.41–1.22 (m, 2), 1.38 (s, 3), 1.17–1.0 (m, 2), 1.13 (s, 3), 0.94 (d, 3, J = 6.4), 0.58 (ddd, 1, J = 11.5, 11.5, 11.5, H-10ax); ^{13}C NMR 165.7, 162.7, 132.4, 109.9, 101.6, 79.2, 48.4, 37.0, 35.4, 34.5, 32.3, 27.7, 27.3, 22.4, 19.2; IR (neat) 1630; UV (MeOH) λ_{max} nm (ϵ) 281 (5500); MS m/e (rel intensity) 248 (21), 247 (100, M$^+$), 232 (60), 230 (48), 218 (64), 204 (73). Decoupling experiments established that the absorption at δ 2.34 is coupled to the absorptions at δ 3.34, 1.82, and 0.58. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 71.78; H, 8.69; N, 5.15.

Data for **14** (1:1 mixture of atropisomers): mp 226 °C dec; ^{1}H NMR (CD_3OD) 7.06 (d, 0.5 × 1, J = 7.2), 7.05 (d, 0.5 × 1, J = 7.2), 5.98 (d, 0.5 × 1, J = 7.2), 5.97 (d, 0.5 × 1, J = 7.2), 4.61 (m, 1), 4.42 (m, 1), 3.17 (ddd, 0.5 × 1, J = 11.5, 11.5, 3.5), 2.94 (ddd, 0.5 × 1, J = 11.5, 11.5, 3.5), 3.12–3.06 (m, 1), 1.88–1.34 (m, 5), 1.58 (s, 3), 1.16–1.0 (m, 2), 0.91 (d, 0.5 × 3, J = 6.2), 0.90 (d, 0.5 × 3, J = 6.2); ^{13}C NMR (167.4, 167.2), (151.3, 151.2), (133.2, 133.0), 116.9, (110.3, 110.1), 103.5, 102.6, 47.5, (39.7, 39.3), (39.2, 38.5), (36.8, 36.6), (34.9, 34.8), (34.4, 34.2), (23.4, 23.3), (19.7, 19.4); IR (KBr) 1645, 1610; UV (MeOH) λ_{max} nm (ϵ) 285 (1800), 212 (5900); MS m/e (rel intensity) 247 (13, M$^+$), 204 (41), 125 (100). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 71.12; H, 8.49; N, 5.46.

Data for **16**: mp 102–105 °C; ^{1}H NMR 7.34 (d, 1, J = 6.4), 6.27 (d, 1, J = 6.4), 3.35 (ddd, 1, J = 11.9, 2.4, 2.4, H-10eq), 2.44 (ddd, 1, J = 11.9, 11.9, 2.4, H-10a), 1.84 (ddd, 1, J = 11.9, 11.9, 2.4, H-6a), 1.7–1.5 (m, 1), 1.5–1.3 (m, 2), 1.38 (s, 3), 1.2–1.0 (m, 2), 1.14 (s, 3), 0.91 (d, 3, J = 6.6), 0.59 (ddd, 1, J = 11.9, 11.9, 11.9, H-10ax); ^{13}C NMR 176.7, 156.4, 135.6, 111.7, 107.7, 81.1, 48.8, 37.2, 35.4, 34.6, 32.4, 27.7, 27.3, 22.4, 19.5; IR (neat) 1633; UV (MeOH) λ_{max} nm (ϵ) 258 (8400), 202 (18 700); MS m/e (rel intensity) 248 (18), 247 (100, M$^+$), 232 (33), 230 (14), 205 (13), 204 (84). Decoupling experiments established that the peak at δ 2.44 is coupled to the peaks at δ 3.35, 1.84, and 0.59. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 71.63; H, 8.50; N, 5.49.

(6aα,9α,10aβ)-2,6,6a,7,8,9,10,10a-Octahydro-2-hydroxy-6,6,9-trimethyl-1*H*-[2]benzopyrano[4,3-*c*]pyridin-1-one (13). HMDS (3.88 mL, 18.4 mmol) containing a catalytic amount of chlorotrimethylsilane was added to **12** (454 mg, 1.84 mmol). The solution was heated at reflux for 7 h under N_2, and the excess HMDS was then removed under reduced pressure. The residue was treated with oxodiperoxymolybdenum(pyridine)(HMPA) complex[13] in CH_2Cl_2 at rt for 15 h by the procedure of Sammes.[5a] Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (1:4 hexane–CH_2Cl_2) gave the molybdenum complex of **13** (616 mg). This material was dissolved in CH_2Cl_2 (30 mL) and stirred with saturated aqueous tetrasodium EDTA (30 mL) for 2 h. The EDTA solution was removed, and the organic layer was washed with water. This process was repeated twice to remove all the molybdenum. The solvent was removed under reduced pressure. The residue was dissolved in chloroform and concentrated under reduced pressure to give white crystalline platelets that were washed with chloroform–hexane (1:1), affording 260 mg (54%) of **13**: mp 106–108 °C; ^{1}H NMR 7.51 (d, 1, J = 7.6), 5.87 (d, 1, J = 7.6), 3.28 (ddd, 1, J = 11.3, 3.0, 3.0, H-10eq), 2.41 (ddd, 1, J = 11.3, 11.3, 3.0, H-10a), 1.83 (ddd, 1, J = 11.3, 11.3, 3.0, H-6a), 1.61 (m, 1), 1.38 (s, 3), 1.34–1.26 (m, 2), 1.14–1.0 (m, 2), 1.09 (s, 3), 0.94 (d, 3, J = 6.5), 0.63 (ddd, 1, J = 11.3, 11.3, 11.3, H-10ax); ^{13}C NMR 159.8, 157.4, 128.0, 109.1, 99.2, 79.6, 47.8, 36.9, 35.3, 34.9, 32.4, 27.6, 27.3, 22.4, 19.3; IR (neat) 1633; UV (MeOH) λ_{max} nm (ϵ) 288 (4500), 215 (31 000); (MeOH + HCl) 244 (6300), 211 (35 000); (MeOH + NaOH) 306 (4500), 221 (28 000); MS m/e (rel intensity) 264 (15), 263 (87, M$^+$), 248 (10), 247 (20), 246 (100), 220 (14), 204 (35). Decoupling experiments established that the peak at δ 2.41 is coupled to the peaks at δ 3.28, 1.83, and 0.63. Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.24; H, 8.16; N, 5.19.

(1α,2β,5α)-3-(5-Methyl-2-(methylethenyl)cyclohexyl)-1,4-dihydroxy-2(1*H*)-pyridinone (15). HMDS (2.10 mL, 13.0 mmol) containing a catalytic amount of chlorotrimethylsilane (0.15 mL) was added to **14** (127.4 mg, 0.87 mmol). The solution was heated at reflux for 16 h under N_2, and the excess HMDS was removed under reduced pressure. The residue was treated with oxodiperoxymolybdenum(pyridine)(HMPA) complex[13] in dry CH_2Cl_2 at rt overnight by the procedure of Sammes.[5a] The solvent was removed under reduced pressure, and the residue was taken up in EtOAc (15 mL). The solution was stirred for 2 h with saturated aqueous tetrasodium EDTA solution (15 mL). The layers were separated, and the organic layer was washed with water. This process was repeated twice. The organic layer was concentrated to give 109.5 mg (48%) of **15** as a light yellow solid. Recrystallization from EtOAc afforded 80.1 mg (37%) of pure **15** as white needles: mp 208–209 °C; ^{1}H NMR 7.49 (d, 0.5 × 1, J = 7.7), 7.48 (d, 0.5 × 1, J = 7.7), 5.91 (d, 0.5 × 1, J = 7.7), 5.90 (d, 0.5 × 1, J = 7.7), 4.59 (m, 1), 4.42–4.39 (m, 1), 3.14–3.07 (m, 1), 3.20 (ddd, 0.5 × 1, J = 11.6, 11.6, 2.5), 2.95 (ddd, 0.5 × 1, J = 11.6, 11.6, 2.5), 1.80–1.62 (m, 1), 1.59–1.36 (m, 4), 1.57 (s, 3), 1.13–0.99 (m, 2), 0.91 (d, 0.5 × 3, J = 6.3), 0.90 (d, 0.5 × 3, J = 6.3); ^{13}C NMR (164.1, 162.6), (162.2, 161.0), 151.1, 133.0, 117.0, 112.7, (110.5, 110.2), (100.5, 99.3), (40.2, 39.5), (39.2, 39.0), (36.7, 36.5), 34.7, (34.4, 34.0), 23.3, (19.7, 19.4); IR (KBr) 1631; UV (MeOH) λ_{max} (ϵ) 289 (5700), 214 (31 000); (MeOH + HCl) 247 (6300), 207 (34 000); (MeOH + NaOH) 224 (29 000) 201 (71 000); MS m/e (rel intensity) 263 (16, M$^+$), 247 (13), 246 (52), 204 (33), 141 (60), 124 (100). Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04; N, 5.32. Found: C, 67.89; H, 7.82; N, 5.29.

***cis*-2,4-Dimethylcyclohexanone (21).** Rhodium-on-alumina (5%, 2.5 g) was placed in a nitrogen-flushed 250 mL Parr hydrogenation bottle. Absolute ethanol (4 mL) was added cautiously to wet the catalyst, and a solution of 10.0 g (81.8 mmol) of 2,4-dimethylphenol and 0.9 mL of HOAc in 36 mL of absolute ethanol was added. The mixture was shaken in a Parr apparatus at an initial pressure of 55 psi of hydrogen at rt for 9 h at which time 3 equiv of hydrogen had been absorbed. The solution was filtered by suction, and the catalyst was washed with ethanol. The filtrate was concentrated under

reduced pressure to yield 10.5 g (85%) of 2,4-dimethylcyclohexanol as a viscous oil consisting of the four stereoisomers, which was used without further purification.

Oxidation of a solution of crude 2,4-dimethylcyclohexanol (10.0 g) in 200 mL of acetone with Jones reagent (12.0 g of CrO_3 and 10 mL of concd H_2SO_4 in 20 mL of water) as previously described[17] gave crude **21**. Distillation (33–35 Torr, 77–86 °C) gave 7.28 g (71%) of **21** containing 10–15% of the trans isomer:[17] ^{1}H NMR 2.58–1.35 (m, 8), 1.11 (d, 3, J = 6.9), 1.10 (d, 3, J = 6.9); ^{13}C NMR 213.5, 44.5, 44.3, 41.2, 35.9, 32.0, 21.2, 14.4; IR (neat) 1712.

***cis*-3,5-Dimethyl-2-(trimethylsiloxy)cyclohexene (22).** *n*-Butyllithium (22.7 mL of 2.5 M in hexane, 56.8 mmol) was added to 8.0 mL (56.8 mmol) of freshly distilled *i*-Pr_2NH in 100 mL of dry THF at −78 °C. The solution was stirred for 30 min at 0 °C and recooled to −78 °C. 2,4-Dimethylcyclohexanone (**21**) (7.2 g, 56.8 mmol) was added over a 10 min period, and the solution was stirred for an additional 20 min at −78 °C. Chlorotrimethylsilane (10.8 mL, 85.2 mmol) was added rapidly, and the solution was stirred for 2 h at rt. The solvent was removed under reduced pressure, and the residue was taken up in petroleum ether. The mixture was filtered to remove triethylammonium chloride, and the filtrate was concentrated under reduced pressure to provide crude **22**. Flash chromatography on silica gel (hexane) gave 8.4 g (75%) of pure **22** containing 10–15% of the trans isomer: ^{1}H NMR 4.71 (m, 1), 2.20–1.38 (m, 6), 0.93 (d, 3, J = 6.5), 0.87 (d, 3, J = 6.5); ^{13}C NMR 153.9, 103.3, 41.8, 34.6, 33.2, 29.2, 21.8, 13.7, 0.3; IR (neat) 1660.

Methyl (2*R,4*S**)-2,4-Dimethyl-6-oxohexanoate (23).** A solution of 8.35 g (42.1 mmol) of enol silyl ether **22** in a mixture of 8 mL of CH_2Cl_2 and 34 mL of CH_3OH was treated with ozone at −78 °C until the solution turned light blue. Dimethyl sulfide (4 mL, 42.1 mmol) was added and the solution stirred for 1 h at −78 °C, 1 h at 0 °C, and 1 h at rt. The solution was concentrated under reduced pressure, and the residue was taken up in ether and treated with diazomethane until the yellow color persisted. Water was added, and the layers were separated. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (6:1 hexane–EtOAc) gave 5.2 g (72%) of **23** as a colorless oil containing 10–15% of the 2*R**,4*R** diastereomer: ^{1}H NMR 9.74 (dd, 1, J = 1.8, 2.5), 3.69 (s, 3), 2.58–2.52 (m, 1), 2.38 (ddd, 1, J = 16.2, 5.6, 1.8), 2.24 (ddd, 1, J = 16.2, 7.8, 2.5), 2.09–2.05 (m, 1), 1.74 (ddd, 1, J = 13.7, 9.4, 5.3), 1.26 (ddd, 1, J = 13.7, 9.4, 5.3), 1.17 (d, 3, J = 6.8), 0.98 (d, 3, J = 6.8); ^{13}C NMR 202.3, 176.9, 51.6, 51.0, 41.0, 37.2, 26.2, 19.7, 18.0; IR (neat) 1730.

Methyl (2*R,4*S**)-2,4-Dimethyl-8-(trimethylsilyl)-6(*Z*)-octenoate (24).** *n*-Butyllithium (8.0 mL, 2.5 M in hexane, 20.0 mmol) was added dropwise with stirring over 0.5 h to a suspension of methyltriphenylphosphonium bromide (6.4 g, 18.0 mmol) in 38 mL of dry THF at 0 °C under N_2. The solution was warmed to rt, stirred for 1 h, and recooled to 0 °C. (Iodomethyl)trimethylsilane (2.7 mL, 18.0 mmol) was added over 10 min, and the solution was allowed to warm slowly to rt while the ((trimethylsilyl)ethyl)phosphonium salt precipitated. After 1 h, the reaction mixture was treated with a second equivalent of *n*-butyllithium (8.0 mL, 2.5 M in hexane, 20.0 mmol) at −78 °C. The mixture was allowed to warm slowly to rt and stirred for a further 1.5 h to give a dark red solution of (β-(trimethylsilyl)ethylidene)triphenylphosphorane.[21] Aldehyde **23** (2.7 g, 16.0 mmol) in dry THF (10 mL) was added dropwise over 15 min to the ylide solution at −78 °C. The reaction mixture was stirred for 0.5 h at −78 °C, allowed to warm slowly to rt, stirred for a further 16 h, and quenched by being poured into saturated NH_4Cl solution (80 mL). The mixture was extracted with ether (3 × 200 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure, giving crude **24**. Flash chromatography (30:1 hexane–EtOAc) gave 2.9 g (73%) of **24** containing 15–25% of the 2*R**,4*R** diastereomer and the 6*E* stereoisomer: ^{1}H NMR 5.55–5.16 (m, 2), 3.63 (s, 3), 2.62–2.52 (ddq, 1, J = 5.6, 9.5, 6.9), 2.02–1.71 (m, 4), 1.45 (d, 2, J = 8.6), 1.20–1.10 (m, 1), 1.14 (d, 3, J = 6.9), 0.98 (d, 3, J = 6.6), 0.02 (s, 9); ^{13}C NMR 177.4, 126.5, 125.5, 51.4, 41.3, 37.4, 34.3, 31.5, 19.4, 18.5, 18.0, −1.7; IR (neat) 1733. Anal. Calcd for $C_{14}H_{28}O_2Si$: C, 65.57; H, 11.00. Found: C, 65.49; H, 10.79.

(2*R,4*S**)-2,4-Dimethyl-8-(trimethylsilyl)-6(*Z*)-octen-1-ol (25).** A solution of DIBAH (35 mL, 1.0 M in hexane, 35 mmol) was added slowly to a solution of ester **24** (4.5 g, 17.6 mmol) in 40 mL of hexane at 0 °C. The reaction was stirred at rt for 4 h and then quenched with MeOH (3 mL). The mixture was treated with hexane (60 mL) and saturated NH_4Cl solution (40 mL). The precipitated alumina was removed by filtration and washed with hexane (40 mL). The organic layer was separated from aqueous layer, washed with water, dried (Na_2SO_4), and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (15:1 hexane–EtOAc) gave 3.2 g (80%) of **25** as a colorless oil containing 15–25% of the 2*R**,4*R** diastereomer and the 6*E* stereoisomer: ^{1}H NMR 5.45 (m, 1), 5.30 (m, 1), 3.58–3.40 (m, 2), 2.08–1.92 (m, 1), 1.82–1.12 (m, 4), 1.46 (d, 2, J = 8.6), 1.20–1.10 (m, 1), 0.95 (d, 3, J = 6.9), 0.90 (d, 3, J = 6.6), 0.00 (s, 9); ^{13}C NMR 126.3, 125.9, 68.3, 40.7, 33.9, 33.2, 30.8, 20.4, 18.5, 17.4, −1.7; IR (neat) 3335, 1035.

(2*R,4*S**)-2,4-Dimethyl-8(*Z*)-(trimethylsilyl)-6-octenal (26).** Dimethyl sulfoxide (1.4 mL, 19.2 mmol) was added slowly to a solution of oxalyl chloride (0.84 mL, 9.6 mmol) in 30 mL of dry CH_2Cl_2 at −78 °C. The solution was stirred for 20 min, and a solution of alcohol **25** (1.46 g, 6.0 mmol) in 5 mL of CH_2Cl_2 was added slowly to the mixture, which was then stirred at −78 °C for 20 min. Et_3N (5.4 mL, 38.4 mmol) was added slowly to the mixture, which was then warmed to rt. Ether was added, and the solution was washed with water and dried ($MgSO_4$) to give 1.16 g (80%) of **26** containing 15–25% of the 2*R**,4*R** diastereomer and the 6*E* stereoisomer, which was used without purification: ^{1}H NMR 9.58 (d, 1, J = 2.5), 5.45 (m, 1), 5.27 (m, 1), 2.44 (m, 1), 1.97 (m, 2), 1.89–1.72 (m, 2), 1.45 (d, 2, J = 8.6), 1.20–1.13 (m, 1), 1.09 (d, 3, J = 7.0), 0.92 (d, 3, J = 6.6), 0.00 (s, 9); ^{13}C NMR 205.4, 126.8, 125.2, 44.2, 37.9, 34.0, 31.0, 19.9, 18.6, 14.2, −1.7; IR (neat) 2705, 1728.

(1β,2α,4α,6α)-3-(2-Ethenyl-4,6-dimethylcyclohexyl)-4-hydroxy-2(1*H*)-pyridinone (2) and (1β,2α,4β,6α)-3-(2-Ethenyl-4,6-dimethylcyclohexyl)-4-hydroxy-2(1*H*)-pyridinone (30). A solution of piperidinium acetate (15 mL of a 10^{-1} M solution in absolute EtOH, 1.5 mmol) and 2,4-dihydroxypyridine (**4**) (266.8 mg, 2.4 mmol) was warmed to dissolve the pyridone. Aldehyde **26** (524 mg, 2.2 mmol) in 1 mL of EtOH was added, and the solution was then heated at reflux for 12 h. The solvent was removed under reduced pressure to give a complex mixture containing **27**. The residue was taken up in 15 mL of CH_2Cl_2, and Me_2AlCl (2 mL, 1.98 M in hexane, 3.96 mmol) was added dropwise. The reaction mixture was stirred at rt for 12 h and quenched with a few drops of MeOH. EtOAc and water were added, and the layers were separated. The aqueous layer was extracted with several portions of EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (9:1 $CHCl_3$–MeOH) gave 200 mg (35%) of a 1:1 mixture of **2** and **30** as a white solid. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 71.92; H, 8.54, N, 5.41.

Fraction recrystallization of 100 mg of this mixture from MeOH five times gave 10 mg of **2** containing <10% of **30** as a 1:1 mixture of atropisomers: mp 270–271 °C dec; ^{1}H NMR (CD_3OD) 7.10 (d, 1, J = 7.2), 6.00 (d, 1, J = 7.2), 5.56 (ddd, 0.5 × 1, J = 17.2, 10.2, 8.6), 5.52 (ddd, 0.5 × 1, J = 17.2, 10.2, 8.6), 4.79 (ddd, 0.5 × 1, J = 17.2, 2.4, 0.9), 4.75 (ddd, 0.5 × 1, J = 17.2, 2.4, 0.9), 4.62 (dd, 0.5 × 1, J = 10.2, 2.4), 4.61 (dd, 0.5 × 1, J = 10.2, 2.4), 2.98 (dddd, 0.5 × 1, J = 11.5, 11.0, 8.6, 3.0), 2.84 (dddd, 0.5 × 1, J = 11.5, 11.0, 8.6, 3.0), 2.58 (dd, 0.5 × 1, J = 11.0, 11.0), 2.45 (dd, 0.5 × 1, J = 11.0, 11.0), 2.36 (m, 0.5 × 1), 2.23 (m, 0.5 × 1), 1.78–1.52 (m, 3), 0.95–0.68 (m, 2), 0.92 (d, 3, J = 6.1), 0.72 (d, 0.5 × 3, J = 6.7), 0.70 (d, 0.5 × 3, J = 6.6); ^{13}C NMR (168.2, 167.4), (166.6, 166.2), 145.2, (133.6, 133.3), (115.5, 115.2), (113.2, 113.1), (103.0, 102.0), (47.5, 47.0), (46.3, 46.2) (C-11), (45.6, 44.4) (C-8), (44.1, 44.0) (C-9), (34.5, 33.5) (C-10*), (33.4, 33.3) (C-12*), 23.5 (C-15), (21.4, 21.2); IR (KBr) 1620; UV (MeOH) λ_{max} nm (ϵ) 284 (12 000), 206 (54 000);

(MeOH + HCl) 264 (11 200), 241 (8100), 203 (54 200); (MeOH+NaOH) 277 (14 400), 209 (151 700).

Partial data for **30** were determined from the 1:1 mixture: ^{1}H NMR (CD_3OD) 7.09 (d, 1, J = 7.2), 6.03 (d, 1, J = 7.2), 3.20 (dddd, 0.5 × 1, J = 11.5, 11.0, 8.6, 3.0), 3.02 (dddd, 0.5 × 1, J = 11.5, 11.0, 8.6, 3.0), 2.59 (dd, 0.5 × 1, J = 11.0, 11.0), 2.46 (dd, 0.5 × 1, J = 11.0, 11.0), 2.36 (m, 0.5 × 1), 2.23 (m, 0.5 × 1), 2.1−1.9 (m, 1), 1.22−1.50 (m, 1), 1.15 (d, 0.5 × 3, J = 7.1), 1.11 (d, 0.5 × 3, J = 7.2), 0.69 (d, 0.5 × 3, J = 6.9), 0.67 (d, 0.5 × 3, J = 6.8); ^{13}C NMR (168.2, 167.4), (166.6, 166.2), 145.2, (133.6, 133.3), (115.5, 115.2), (113.2, 113.1), (103.0, 102.0), (48.2, 47.8), 42.8 (C-11), (40.8, 40.7) (C-9), (39.6, 38.6) (C-8), (29.9, 29.8) (C-10), (28.3, 27.4) (C-12), (21.6, 21.5), (19.7, 19.6) (C-15).

A similar reaction of piperidinium acetate and 2,4-dihydroxypyridine and aldehyde **26** in ethanol at rt for 12 h gave recovered 2,4-dihydroxypyridine and a 1:1 mixture of **26** and its diastereomer. Partial spectral data for the diastereomer of **26**: ^{1}H NMR 9.61 (d, 1, J 2.0), 1.07 (d, 1, J = 7.0), 0.90 (d, 1, J = 6.2).

(1β,2α,4α,6α)-3-(2-Ethenyl-4,6-dimethylcyclohexyl)-1,4-Dihydroxy-2(1*H*)-pyridinone (1, Pyridoxatin). HMDS (2.0 mL, 12.4 mmol) containing chlorotrimethylsilane (1.0 mL) was added to pyridone **2** (10 mg, 0.04 mmol). The solution was heated at reflux for 16 h under N_2, and the excess HMDS was removed under reduced pressure. The residue was treated with oxodiperoxymolybdenum(pyridine)(HMPA) complex in dry CH_2Cl_2 at rt overnight by the procedure of Sammes.[5a] The solvent was removed under reduced pressure, and the residue containing the molybdenum complex of **1** was taken up in EtOAc (2 mL). The solution was stirred for 4 h with saturated aqueous tetrasodium EDTA solution (2 mL) and 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 $CHCl_3$ to give 4.7 mg (44%) of pure **1** as a white solid as a 1:1 mixture of atropisomers: mp 194−196 °C dec; ^{1}H NMR 7.53 (d, 0.5 × 1, J = 7.6), 7.52 (d, 0.5 × 1, J = 7.6), 5.55 (ddd, 0.5 × 1, J = 16.9, 10.2, 8.9), 5.51 (ddd, 0.5 × 1, J = 16.9, 10.2, 8.9), 4.77 (dd, 0.5 × 1, J = 16.9, 2.0), 4.75 (dd, 0.5 × 1, J = 16.9, 2.0), 4.61 (dd, 0.5 × 1, J = 16.9, 2.0), 4.60 (dd, 0.5 × 1, J = 16.9, 2.0), 3.01 (dddd, 0.5 × 1, J = 12.0, 11.0, 8.9, 3.0), 2.84 (dddd, 0.5 × 1, J = 12.0, 11.0, 8.9, 3.0), 2.63 (dd, 0.5 × 1, J = 11.0, 11.0), 2.46 (dd, 0.5 × 1, J = 11.0, 11.0), 2.38 (m, 0.5 × 1), 2.23 (m, 0.5 × 1), 1.72−1.59 (m, 3), 0.95−0.73 (m, 2), 0.92 (d, 3, J = 6.4), 0.71 (d, 0.5 × 3, J = 6.6), 0.69 (d, 0.5 × 3, J = 6.4); ^{13}C NMR (163.9, 163.2), (162.7, 160.4), 144.7, 132.7, (115.3, 115.0), (113.0, 112.9), (99.9, 98.9), (47.5, 48.1), (46.0, 45.9), (45.2, 44.1), (43.8, 43.6), (34.1, 33.2), (33.1, 33.0), (23.2, 23.1), (21.0, 20.9); IR (KBr) 1636; UV (MeOH) λ_{max} nm (ϵ) 289 (6800), 214 (34 900); (MeOH + HCl) 267 (5800), 247 (6900); (MeOH + NaOH) 297 (5100), 264 (7400), 229 (31 900). The spectral data are identical to those previously reported for (−)-pyridoxatin.[2]

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