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A Two-Step Synthesis of Pyridoxatin Analogues

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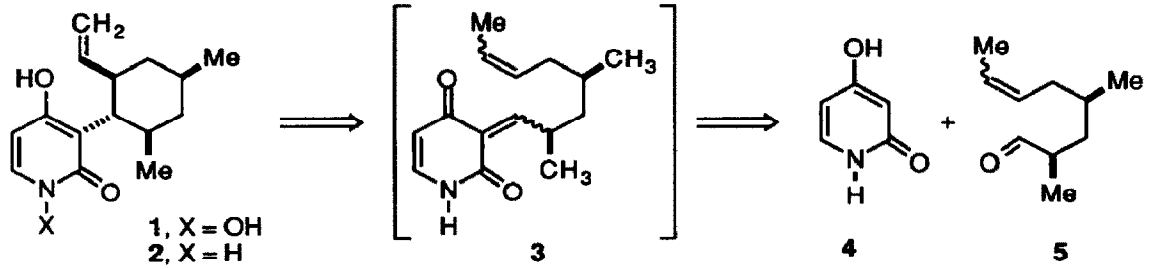
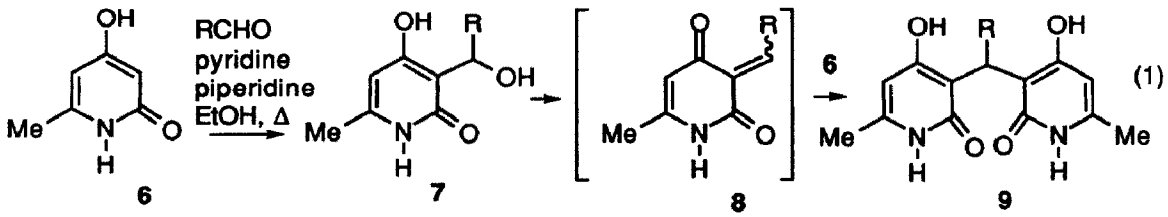
Abstract: Condensation of 4-hydroxy-2-pyridone (**4**) with citronellal (**10**) affords *o*-quinone methide intermediate **11**, which reacts further to give inverse electron Diels-Alder adducts **12** (46%) and **16** (25%) and ene adduct **14** (28%). Oxidation of **12** and **14** by Sammes' procedure affords pyridoxatin analogues **13** (54%) and **15** (48%).

Pyridoxatin (**1**) is a 1-hydroxy-2-pyridone free-radical scavenger isolated from *Acremonium* sp. BX86.[1] Pyridoxatin is approximately 20 times as active as vitamin E in the assay system employed.[1] Pyridoxatin probably functions as an iron chelator since 1-hydroxy-2-pyridone and 1,4-dihydroxy-2-pyridone bind iron tightly under physiological conditions.[2] A variety of other 1-hydroxypyridone antibiotics including BN-227[3a,b] G1549,[3c] and tenellin[4b] are also siderophores.

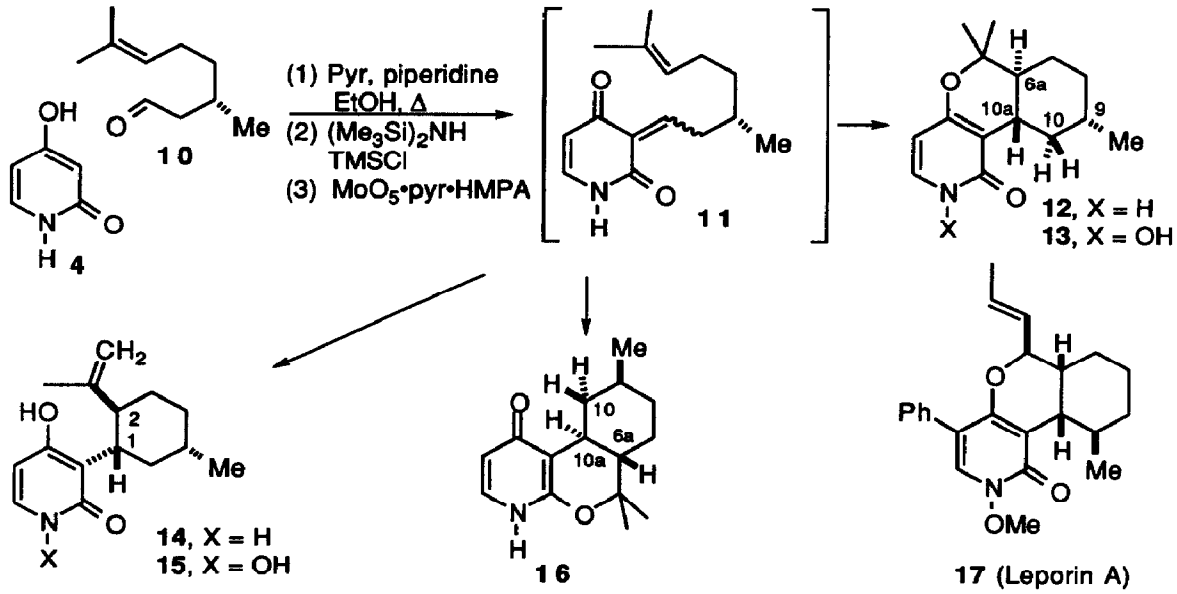


We envisaged that a synthesis of pyridoxatin could be carried out by the intramolecular ene reaction of *o*-quinone methide **3** which should give **2**, with all substituents on the cyclohexane ring equatorial. Oxidation of the pyridone **2** by Sammes' procedure[4] should afford pyridoxatin (**1**).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

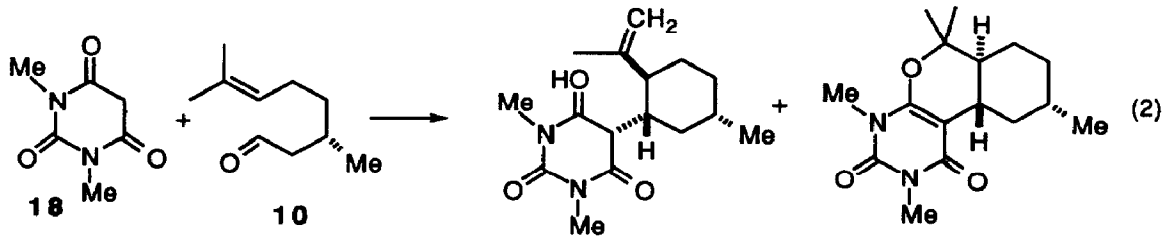


We report here a model study using citronellal (**10**) that establishes the feasibility of this approach to pyridoxatin. Heating a solution of pyridone **4** (23 mmol), citronellal (**10**) (66 mmol), piperidine (0.1 mL), and

pyridine (2.4 mL) in EtOH (300 mL) for 60 h at reflux followed by chromatography of the residue afforded 46% of Diels-Alder adduct **12**[6] followed by 28% of the desired ene adduct **14**[6] and 25% of Diels-Alder adduct **16**.[6]



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.[7] The Diels-Alder reaction is well precedented in the inverse electron Diels Alder reaction of an *o*-quinone methide that leads to hexahydrocannabinol[8] and in the work of Tietze[9] who observed competing intramolecular ene and inverse electron demand Diels-Alder reactions in the condensation of *N,N*-dimethylbarbituric acid (**18**) with citronellal (see eq. 2).



(2)

Mass spectral data established that all three compounds **12**, **14**, and **16** are 1:1 adducts. The ^1H 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** is 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[10] 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.[11] 2-Pyridone **12** absorbs at 281 nm while 4-pyridone **16** absorbs at 258 nm.

The ^{1}H NMR spectrum of **14** clearly show 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 atrope isomers due to hindered rotation about the bond between the two rings as is observed in pyridoxatin itself.[1] 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 affords the crude trimethylsilyloxypyridine, which was treated with MoO_5•pyr•HMPA[12] in CH_2Cl_2 for 15 h at rt as described by Sammes[4a] to provide the molybdenum complex of **13**. The chromatographed molybdenum complex was taken up in CH_2Cl_2 and washed for 2 h with saturated aqueous tetrasodium EDTA solution. This process was repeated twice to remove all the molybdenum affording 54% of **13**, mp 106-108 °C. Hydroxypyridone **14** was converted analogously to the bistrimethylsilyloxypyridine and oxidized to afford 48% of **15**, mp 208-209 °C (EtOAc). 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.[13]

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).[14] 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.

Initial experiments using *cis*-6-nonenal instead of citronellal did not provide ene or Diels-Alder adducts suggesting that the 1,2-disubstituted double bond is not nucleophilic enough to react with the *o*-quinone methide. We are currently investigating the condensation of **4** with more nucleophilic 8-trimethylsilyl-6-octenals to introduce the vinyl group present in pyridoxatin.

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(6) The spectral 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) 3124, 2921, 2865, 1630, 1455, 1239, 1135, 790, 629; UV (MeOH) λ_{max} nm (ε) 281 (5,500); MS *m/e* (%) 248 (21), 247 (100, M^+), 232 (60), 230 (48), 218 (64), 204 (73), 179 (29), 178 (61), 176 (19), 165 (21), 164 (22), 162 (14), 150 (24), 138 (27), 136 (70), 125 (74), 124 (71), 123 (15), 98 (10).

The spectral data for **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) 2912, 2857, 1633, 1561, 1441, 1222, 1134, 926, 897, 750; UV (MeOH) λ_{max} nm (ε) 288 (4,500), 215 (31,000); (MeOH + HCl) 244 (6,300), 211 (35,000); (MeOH + NaOH) 306 (4,500), 221 (28,000); MS *m/e* (%) 264 (15), 263 (87, M$^+$), 248 (10), 247 (20), 246 (100), 220 (14), 204 (35), 190 (19), 178 (10), 164 (11), 141 (16), 124 (29), 123 (12).

The spectral data for **14**: 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, 4), 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) 3854, 3821, 3752, 3100, 2921, 2854, 2680, 2360, 1645, 1610, 1559, 1374, 1126, 796, 564; UV (MeOH) λ_{max} nm (ε) 285 (1,800), 212 (5,900); MS *m/e* (%) 247 (13, M$^+$), 204 (41), 178 (9), 164 (8), 150 (7), 136 (17), 125 (100), 124 (42).

The spectral data for **15**: 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) 3089, 2953, 2853, 2697, 1631, 1542, 1535, 1438, 1269, 1236, 1122, 1041, 896, 298; UV (MeOH) λ_{max} (ε) 289 (5,700), 214 (31,000); (MeOH + HCl) 247 (6,300), 207 (34,000); (MeOH + NaOH) 224 (29,000) 201 (71,000); MS *m/e* (%) 263 (16, M$^+$), 247 (13), 246 (52), 204 (33), 190 (13), 164 (15),141 (60), 140 (27), 138 (13), 136 (13), 125 (34), 124 (100),123 (37).

The spectral 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) 3421, 2921, 2355, 2360, 1633, 1506, 1280, 1212, 1170, 1409, 1059; UV (MeOH) λ_{max} nm (ε) 258 (8,400), 202 (18,700); MS *m/e* (%) 248 (18), 247 (100, M$^+$), 232 (33), 230 (14), 205 (13), 204 (84), 178 (24), 177 (17), 164 (13), 162 (13), 150 (15), 138 (27), 136 (31), 125 (63), 124 (56), 123 (22), 98 (16).

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