A very general new α-olefin synthesis can be illustrated by reactions involving fluoride ion adducts with a fluoro ketone and an acid fluoride. The soluble perfluoroalkoxides so prepared displace fluorosulfate from **1** at 0 °C to form the corresponding perfluoroallyloxy derivatives in good yield.

$$(CF_3)_2C{=}O + KF \rightarrow (CF_3)_2CFOK \xrightarrow{1} (CF_3)_2CFOCF_2CF{=}CF_2$$

$$FSO_2CF_2COF + KF \rightarrow FSO_2CF_2CF_2OK \xrightarrow{1} FSO_2CF_2CF_2OCF_2CF{=}CF_2$$

Details of our studies on the synthesis of **1** and other allylic fluorosulfates as well as the use of these versatile reagents to perfluoroallylate various substrates will be subjects of future publications.

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(11) Miller, W. T.; Fainberg, A. H. *J. Am. Chem. Soc.* **1957**, *79*, 4164.

## Total Synthesis of the Quinonoid Alcohol Dehydrogenase Coenzyme (1) of Methylotrophic Bacteria

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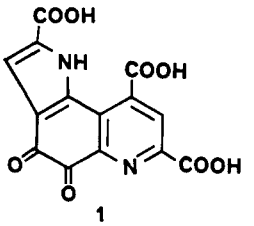
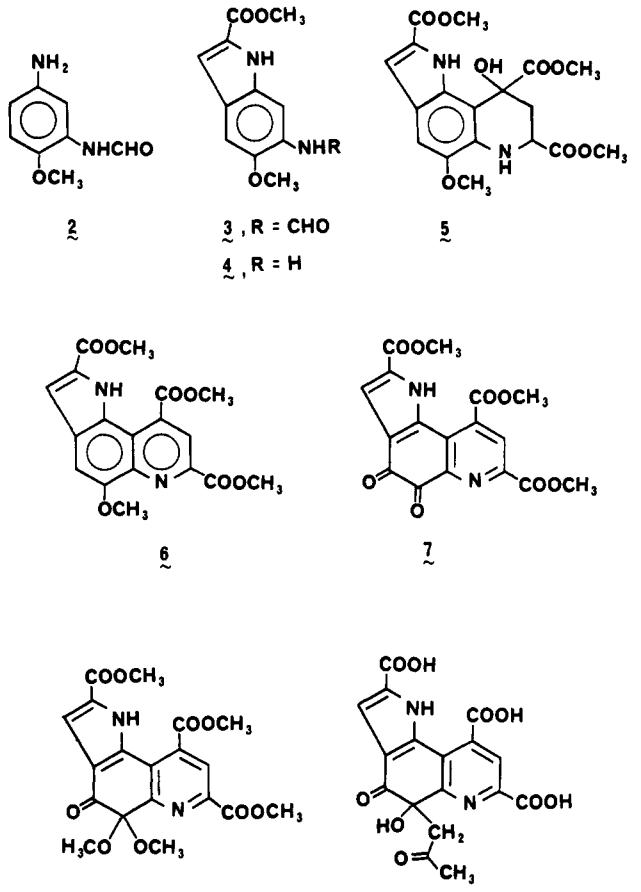
Methylotrophic bacteria which can survive by using one-carbon compounds such as methane or methanol as the sole carbon source contain a novel alcohol dehydrogenase which is neither NAD nor flavin dependent. The coenzyme for this dehydrogenase has recently been assigned structure **1** on the basis of an X-ray diffraction study of a derivative[1] and other evidence.[2-4] Only a few milligrams of this unique cofactor have been obtained thus far, and in consequence, its chemistry and its mode of action in cocatalysis have not been defined.[5] We describe herein a total synthesis of **1**, previously[1] termed methoxatin, which makes this substance readily available by a short and direct method that is well suited to multigram scale. There are several other interesting facets of this synthetic problem and its solution: (1) the general strategy of forming a fused tricyclic system by joining two precursors, each containing a terminal ring (A + C → ABC), which is frequently very powerful, does not appear to be appropriate; (2) two annulation steps involved in the synthesis (B → ABC) are smooth and highly regioselective; (3) the final steps of the synthesis were accomplished expeditiously despite the dearth of knowledge regarding the chemistry and stability of **1**.




**1**

(1) Salisbury, S. A.; Forrest, H. S.; Cruse, W. B. T.; Kennard, O. *Nature (London)* **1979**, *280*, 843. The derivative used was an aldol addition product with acetone formed during extraction with the latter as solvent.
(2) Forrest, H. S.; Salisbury, S. A.; Kilty, C. G. *Biochem. Biophys. Res. Commun.* **1980**, *97*, 248.
(3) Duine, J. A.; Frank, J., Jr.; Verwiel, P. E. J. *Eur. J. Biochem.* **1980**, *108*, 187.
(4) Duine, J. A.; Frank, J., Jr. *Biochem. J.* **1980**, *187*, 213; **1980**, *187*, 221.
(5) This cofactor seems to be involved in the action of a number of nonmethylotrophic bacterial alcohol dehydrogenases including at least two which utilize glucose as substrate. See: (a) Houge, J. G. *J. Biol. Chem.* **1964**, *239*, 3630. (b) Duine, J. A.; Frank, J., Jr.; Van Zeeland, J. K. *FEBS Lett.* **1979**, *108*, 443.

Chart I




Commercially available 2-methoxy-5-nitroaniline was converted (in formic acid using excess formic–acetic anhydride at 25 °C for 10 min and 50 °C for 20 min) to the *N*-formyl derivative (95% yield, mp 197.0–198.5 °C, yellow needles), which was hydrogenated at 3 atm in ethanol at 65 °C over Adams platinum catalyst to give 2-methoxy-5-aminoformanilide (**2**) (93% yield, mp 146.0–147.5 °C) (Chart I).[6] Treatment of **2** in 2 equiv of aqueous 0.3 N hydrochloric acid at 0–5 °C with 1 equiv of sodium nitrite for 10 min produced the diazonium salt which was added to a solution of 1.2 equiv of methyl α-methylacetoacetate and 1.2 equiv of potassium hydroxide in 1:1 methanol–water at 0 °C. After 8 h the resulting arylhydrazone was isolated (80%) and heated at 80 °C in anhydrous formic acid for 9–10 h to produce the indole **3** as a granular solid, mp 215.5–217 °C (72%).[7] Deformylation of **3** with 3 equiv of hydrochloric acid in acetone–water (96:4) at reflux for 1 h produced the aminoindole **4** (79%).

Addition of a third ring was accomplished by a remarkably facile Doebner–vonMiller type of annulation in a single step.[8] A solution of **4** and 1.5 equiv of the dimethyl 2-oxaglutaconate[9] in

(6) Satisfactory proton magnetic resonance ($^1$H NMR), infrared (IR), ultraviolet (UV), and mass spectral data were obtained for each purified intermediate.
(7) This combination of the Japp–Klingemann reaction (Philpott, P. G. *J. Chem. Soc.* **1965**, 7185) and Fischer indolization afforded <3% of position isomeric indole.
(8) In contrast, the related Combes annulation (Jones, G. *Heterocycl. Comp.* **1977**, *32*, 119) could not be effected from **4** and dimethyl 2,4-dioxoglutarate, despite extensive experimentation.
(9) Although diethyl 2-oxoglutaconate has been described previously (Cornforth, J. W.; Cornforth, R. H. *J. Chem. Soc.* **1946**, 755), the yield reported was only 2%. However, crystalline dimethyl 2-oxoglutaconate (pure by NMR analysis) could be synthesized in 97% yield from dimethyl 2-ketoglutarate by the following sequence: (1) dropwise addition of 1.01 equiv of bromine in dry methylene chloride at reflux to the keto ester, (2) removal of solvent and hydrogen bromide in vacuo, and (3) treatment of the resulting α-bromo ketone with 1 equiv of triethylamine in ether at 25 °C for 20 min, filtration, passage of the filtrate through a pad of silica gel, and concentration in vacuo.

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methylene chloride was kept at 25 °C for 7 h and then for an additional 10 h after addition of a catalytic amount of dry hydrogen chloride. During the first stage of this reaction the amino group of **4** adds in a conjugate manner and specifically to the carbon $\beta$ to the ketonic function of dimethyl 2-oxoglutaconate, and cyclization occurs to give the cyclized piperidinol **5**.[10] Addition of acid catalyst in the second stage of the annulation effects dehydration and aromatization to form the desired tricyclic product **6** which is isolated from the reaction mixture by washing with aqueous sodium bicarbonate followed by saturated brine solution, drying, and concentration in vacuo. The yield of **6**, obtained as yellow crystals, mp 224-225 °C, homogeneous by TLC ($R_f$ 0.37 on silica gel with 4:1 methylene chloride-ethyl acetate), was >90%.[11]

Addition of ceric ammonium nitrate (5.5 equiv) to a solution of **6** in 4:1 acetonitrile-water at 0 °C, further reaction for 10 min at 0 °C, dilution with water, extraction with ethyl acetate-methylene chloride (4:1), and recrystallization of the solid product so obtained from hot acetonitrile afforded 60% of the quinone **7** as orange crystals, mp 260-263 °C dec, homogeneous by TLC ($R_f$ 0.14 on silica gel with 4:1 methylene chloride-ethyl acetate); $UV_{max}$ ($H_2O$) 252, 344 nm;[12] $UV_{max}$ ($CH_3OH$) 251, 321, 373 nm.[13] Thus it was possible to introduce the *o*-quinone unit directly from the methyl ether **6** without deprotection and establish the complete functionality of methoxatin.

Successful conversion of the trimethyl ester **7** to methoxatin required considerable experimentation. Trifluoroacetic acid-water (2:1) treatment of **7** at 25 °C rapidly hydrolyzed one of the carbomethoxy groups (presumably that on the $\alpha$ carbon of the pyridine ring), and at 90 °C in this medium a second ester function could be hydrolyzed. The remaining carbomethoxy group (on the pyrrole ring) was resistant to hydrolysis under conditions which did not cause major decomposition. The sensitivity of the methoxatin system to base precluded the use of alkaline conditions. The triacid corresponding to **6** could be obtained readily by saponification of **6** with 0.5 M potassium carbonate in water at 85 °C for 4 h. Direct Ce(IV) oxidation of this triacid failed to give methoxatin. A variety of other approaches also proved fruitless.[14] A simple and effective solution was found as follows.

Reaction of **7** with 10 equiv of methyl orthoformate and a trace of *p*-toluenesulfonic acid in methanol at reflux for 4 h produced the monoketal **8** in 92% yield. Exposure of **8** to excess 0.5 M aqueous potassium carbonate at 85 °C for 4 h followed by acidification to pH 2.5 with hydrochloric acid produced a precipitate of methoxatin (**1**) which was obtained as a deep red solid after collection and drying in vacuo (98% yield). The UV absorption spectra,[3] fluorescence spectra,[4] and reversed-phase high-performance chromatographic (RP-HPLC) behavior[3] of synthetic and naturally derived methoxatin were identical.[15]

Treatment of synthetic **1** with dimethyl sulfate-potassium carbonate in dry dimethylformamide results in formation of a trimethyl ester, as previously described for native **1**,[3] which is identical with the synthetic intermediate trimethyl ester **7**.[16]

Exposure of synthetic **1** to 10% aqueous acetone brought to pH 9 with ammonium hydroxide at 23 °C for 30 min resulted in formation of the previously described "aldol" adduct of **1** with acetone (**9**),[1] the structure of which was ascertained by X-ray diffraction studies. The acetone adduct **9** derived from synthetic **1** was identical with that formed from native methoxatin as determined by measurement of UV spectra ($UV_{max}$ 250, 317, 360 nm in water at pH 5.5), fluorescence (excitation at 365, fluorescence maximum at 465 nm), and proton and $^{13}C$ NMR spectra.[17] Synthetic and naturally derived **9** showed identical behavior by RP-HPLC analysis (retention volume for each 2.52 under the conditions described above for **1**; lit.[5b]), and a mixture of the two showed a single sharp elution peak.

With the successful completion of the synthesis of methoxatin and its ready accessibility, it is now feasible to study critically the chemistry of this interesting substance and such an investigation is under way.[18]

(10) The intermediate **5** was isolated and characterized spectroscopically. The NMR spectrum ($CDCl_3$) revealed the presence of indole NH (br s, $\delta$ 8.68) and CH ($\delta$ 7.06, d, $J$ = 1.6 Hz, 1 H), and a single benzenoid proton ($\delta$ 6.93, s, 1 H), in addition to the other peaks expected for **5**; $UV_{max}$ in $C_2H_5OH$ 209 and 247 nm; $M^+$ (molecular ion) at 392. In a separate experiment **5** was transformed into the simple dehydration product which could also be isolated and characterized.

(11) Spectral data for **6** are as follows: NMR ($CDCl_3$, $\delta$): 11.0 (br, 1 H, NH), 8.97 (s, 1 H), 7.35 (s, 1 H), 7.26 (d, 1 H), 4.17 (s, 3 H), 4.12 (s, 3 H), 4.09 (s, 3 H), 4.0 (s, 3 H); $IR_{max}$ ($CHCl_3$, $cm^{-1}$) 3340, 3150, 2955, 1720, 1265, 1255; $UV_{max}$ in $C_2H_5OH$ 205.5, 275, 320.5 nm; $M^+$ at 372.

(12) The same $UV_{max}$ have been reported[3] for methoxatin trimethyl ester (of natural origin) in aqueous solution.

(13) Other spectral data for **7** are as follows: NMR ($CDCl_3$, $\delta$) 12.98 (br s, 1 H, indole NH), 8.87 (s, 1 H, quinoline $\beta$-H), 7.47 (d, $J$ = 2 Hz, 1 H, indole $\beta$-H), 4.18, 4.07, 3.98 (each s, 3 H, $OCH_3$), essentially identical with that reported; $IR_{max}$ ($CHCl_3$) 1722, 1687 $cm^{-1}$; fluorescence in $H_2O$ 462 nm (excitation at 365 nm); fluorescence in $CH_3OH$ 455 nm (excitation at 394 nm).

(14) For example, studies using the triisopropylsilyl, methoxymethyl and benzhydryl esters corresponding to **6**, prepared from the corresponding triacid, did not lead to success in the oxidation step.

(15) In aqueous solution at pH 5.5 synthetic methoxatin (**1**) showed $UV_{max}$ at 247, 330 nm with a shoulder at 270 nm; at pH 2.5 $UV_{max}$ at 250 and 340 nm were observed. Excitation of synthetic **1** in water at 365 nm results in $fluorescence_{max}$ at 483 nm. Synthetic methoxatin was homogeneous by RP-HPLC on a Waters Associates $C_{18}$-$\mu$-Bondapak column using 95:5 water-methanol containing 0.1% acetic acid (pH ca. 4.5) and was eluted at 3.55 retention volumes. The $^{13}C$ NMR spectrum of synthetic **1** (in $CD_3SOCD_3$) showed peaks at (tetramethylsilane) $\delta$ 113.86, 122.76, 125.97, 127.71, 130.68, 137.60, 144.63, 146.41, 147.62, 161.25, 165.48, 166.45, 173.30, and 180.00.

(16) Attempted conversion of **1** to the trimethyl ester **7** using diazomethane in methanol-water was unsuccessful due to the high reactivity of the *o*-quinone unit with this reagent. Even the monomethylketal of **7** underwent rapid reaction with diazomethane to form an epoxide by methylene transfer to the dienone carbonyl.

(17) We are indebted to Professor Hugh S. Forrest for an authentic sample of **9** (200 $\mu$g) and spectral data. The $^{13}C$ NMR spectrum of synthetic **9** in $CD_3SOCD_3$ solution showed peaks at (tetramethylsilane) $\delta$ 29.77, 51.06, 74.82, 111.96, 120.75, 121.13, 125.59, 126.88, 135.21, 139.19, 144.92, 161.01, 161.47, 165.17, 168.61, 190.16, and 207.03.

(18) This research was supported by the National Institutes of Health. It is a pleasure to acknowledge helpful discussions with Professors H. S. Forrest and R. Abeles.

## Oxidative Addition of Allyl Acetate to Pd(0) Complexes

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It is generally accepted that the interaction of Pd compounds such as $Pd(PPh_3)_4$ with allyl acetates, $R^1CH{=}CHCHR^2OAc$, causes activation of the allyl-O bond of allyl acetate to afford $\eta^3$-allyl(acetato)palladium-type species. Actually a variety of organic synthetic reactions proceeding through the supposed $\eta^3$-allyl(acetato)palladium intermediate have been developed.[1-4] There is, however, no example in which the $\eta^3$-allyl(acetato)-palladium intermediate was isolated from the reaction mixture

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(3) (a) Tsuji, J. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1896. (b) Tsuji, J.; Yamakawa, T. *Tetrahedron Lett.* **1979**, 613. (c) Tsuji, J.; Yamakawa, T.; Kaito, M.; Mandai, T. *Ibid.* **1978**, 2075.

(4) Tsuda, T.; Chujo, Y.; Nishi, S.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 6381.

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