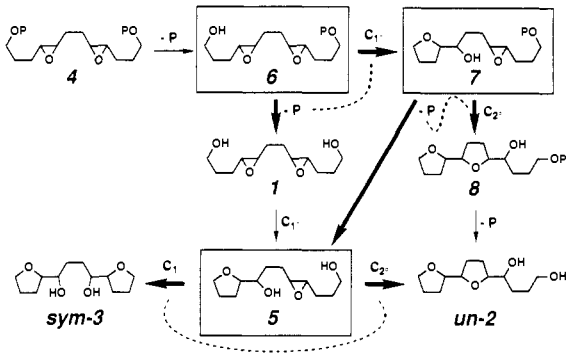
Scheme I[a]



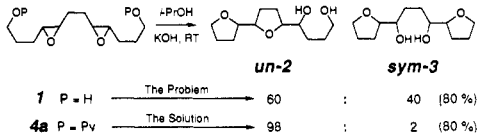
[a] Intermediates which lie at crucial branch points are boxed. Heavy arrows are the competitive partitioning events. C and -P denote cyclization and protecting group loss, respectively.

Table I. Results of Cyclization (at ~25 °C) of Diol **1** and the Bis-Acetate and Bis-Pivalate Derivatives **4b** and **4a** to the Desired and Undesired Bis-THFs *un*-**2** and *sym*-**3**

entry	substrate	P (in **4**)	catalyst	solvent	product ratio[a] *un*-**2**:*sym*-**3**
1	**1**	H	KOH	*i*-PrOH	60:40
2	**1**	H	CSA	CH_2Cl_2	55:45
3	**4b**	Ac	KOH	MeOH	61:39
4	**4b**	Ac	KOH	EtOH	60:40
5	**4b**	Ac	KOH	*i*-PrOH	56:44
6	**4a**	Pv	KOH	MeOH	83:17
7	**4a**	Pv	KOH	EtOH	96:4
8	**4a**	Pv	KOH	*i*-PrOH	98:2

[a] Determined by acetylation of crude reaction product mixtures and subsequent capillary GC analysis; in several instances this was further substantiated by preparative-scale SiO_2 separation of the diols. Controls to ensure nonselective partitioning during aqueous workup were also performed.

the desired, *un*symmetrical, bis-THF diol *un*-**2** while minimizing concurrent production of the *sym*metrical counterpart, *sym*-**3**. It was not surprising[5] to learn that base-catalyzed cyclization of a ~1:1 diastereomeric mixture[6] of the *d,l* and meso forms of diol **1** was relatively nonselective, giving a 60:40 ratio of *un*-**2**:*sym*-**3**. This problem of end-differentiation was solved simply by using as substrate the bis-pivalate ester derivative **4a**. Under the same reaction conditions, a 98:2 ratio favoring the desired product *un*-**2** was realized. Why?



The important neutral intermediates for these reactions are gathered in Scheme I. Starting from the diol **1** a single branch point is encountered. The obligatory monoepoxide **5** partitions by competitive intramolecular attack on the remaining epoxide ring by secondary vs primary hydroxyl groups to give **un-2** vs **sym-3**, respectively. The 60:40 product ratio confirms that the rates of these two events are comparable under base (or acid) catalysis (see entries 1 and 2 in Table I).[7]

Use of **4**, a doubly protected derivative of diol **1**, demands that at least one of the protecting groups P be removed before even the first epoxide can cyclize. Two additional branch points are then encountered. The relative rates of deprotection vs cyclization clearly dictate the **6** → **1** vs **7** and the **7** → **5** vs **8** partitionings.

Under circumstances where protecting group loss is considerably faster than cyclization, the intermediate monoprotected diepoxide **6** will be drained essentially entirely to **1** (vs **7**), as will the minor amount of **7** to **5** (vs **8**). The resulting ratio of bis-THFs *un*-**2**:*sym*-**3** should be nearly identical to that observed starting with **1** itself. However, if the loss of protecting group is tailored to be significantly slower than the cyclization, then intermediate **6** should be effectively shunted to **8** via **7**. A second, leisurely deprotection would then afford *un*-**2**.

Underlying the development of this strategy was the presumption that we could dictate the rate of deprotection. For example, for the subset of protecting groups P comprising esters removable under base-induced transesterification/saponification conditions, two obvious parameters likely to *differentially* affect the deprotection vs cyclization events are the nature of the protecting group itself and the steric hindrance of the nucleophilic solvent molecules. These could be readily and independently adjusted to influence the rate of loss of P.

The bis-acetate derivative **4b** (P = Ac) gave essentially the same ratio of *un*-**2**:*sym*-**3** as did diol **1** itself, regardless of the degree of steric hindrance of the solvent used for the deprotection/cyclization reaction (entries 3-5, Table I). Apparently the rate of transesterification of the acetate **6** to give **1** was faster than the rate of cyclization of **6** to generate **7**.

In contrast, alcoholysis of the more hindered bis-pivalate derivative **4a** (P = Me_3CCO) proceeded as hypothesized (entries 6-8, Table I). In methanol a modest enhancement of product ratio was realized. Changing to the more hindered solvents ethanol and isopropyl alcohol provided substantial improvement in the *un*-**2**:*sym*-**3** ratio. Loss of the pivalate group in isopropyl alcohol was sufficiently slow to allow intermediate **6** to be efficiently siphoned to *un*-**2** (98:2) via **8**, thereby exemplifying this protecting group strategy for desymmetrization.

Acknowledgment. This investigation was supported by Grant GM-34492 awarded by the DHHS.

Registry No. DL-**1**, 142395-88-8; *meso*-**1**, 142436-23-5; **2**, 142395-91-3; **3**, 142421-10-1; DL-**4a**, 142395-89-9; *meso*-**4a**, 142436-24-6; DL-**4b**, 142395-90-2; *meso*-**4b**, 142436-25-7; **5**, 142421-10-1; DL-**6** (P = $COC(CH_3)_3$), 142395-93-5; *meso*-**6** (P = $COC(CH_3)_3$), 142436-26-8; DL-**6** (P = Ac), 142395-95-7; *meso*-**6** (P = Ac), 142436-27-9; **7** (P = $COC(CH_3)_3$), 142395-94-6; **7** (P = Ac), 142395-96-8.

(5) Cf. Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330.

(6) These and related diastereomeric 1,4-bisepoxides have always proven inseparable by standard liquid or gas chromatographic techniques in our hands, but ratios are discernible from ^1H and ^{13}C NMR data.[4a-c]

(7) Perhaps the slight preference (≤1.5) for regioselective attack by the secondary hydroxyl group is a manifestation of the Thorpe-Ingold or reactive rotamer effect; for example: Jung, M. E. *Synlett* **1990**, 186.

Palladium-Catalyzed Cycloisomerizations of Alkynyl *N*-Acyl Enamines

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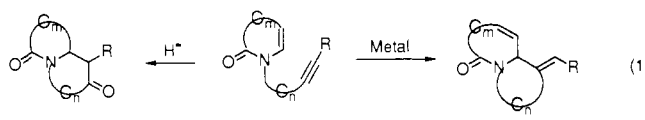
The vast importance of nitrogen heterocycles has stimulated the development of new methodology for their construction. Among the most useful recently developed methods are iminium ion initiated cyclizations[1-3] as illustrated in eq 1 (**1** → **2**).[1]



(1)

(1) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. For a leading reference on the question of regioselectivity in the acid-catalyzed cyclization, see: Hiemstra, H.; Ino, M. H. A. M.; Vijin, R. J.; Speckamp, W. N. *J. Org. Chem.* **1985**, *50*, 4014.

(2) Also see: Blumenkopf, T. A.; Overman, L. E. *Chem. Rev.* **1986**, *86*, 857.

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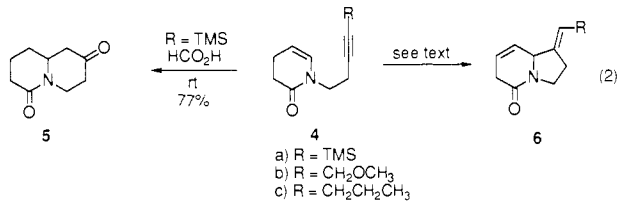
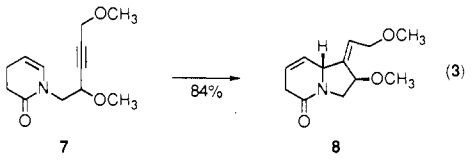
Changing the reaction profile whereby the same readily available intermediate can be channeled into a different product greatly expands synthetic flexibility. Our interest in the synthesis of alkaloids ranging from mitomycins to castanospermine led us to consider whether a transition metal complex may play the role of such a reactivity switch for the easily accessible *N*-acyl enamines to lead to 1,4-dienes (eq 1, **1** → **3**).[4]

We initiated our probe with the *N*-acyl enamine **4a**, which, as expected, undergoes the cationic cyclization to generate the quinolizidine ring system (i.e., **5**[5]) in the presence of formic acid.

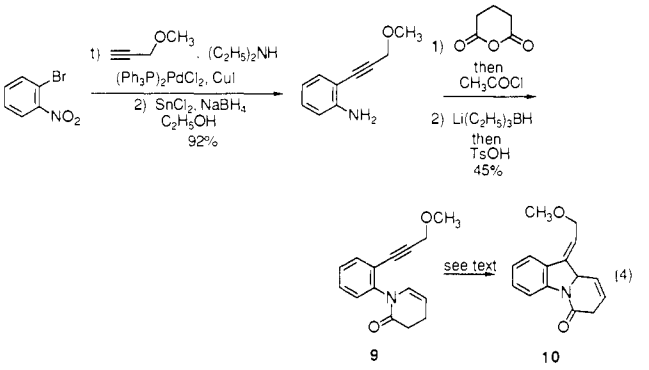


Remarkably, exposure of **4a** to 5 equiv of acetic acid in the presence of 2.5 mol % $(dba)_3Pd_2{\cdot}CHCl_3$ and 10 mol % triphenylphosphine (TPP) in benzene-d_6 at 60–65 °C redirects the reaction to give a 77% yield of the indolizidine **6a**.[6] Use of the sterically more bulky ligand tri-*o*-tolylphosphine or poorer σ donator ligand triphenylstibine causes the yield to drop to 11–22%. On the other hand, use of the stronger σ donator ligand *N*,*N*′-bis(benzylidene)ethylenediamine[7] (BBEDA, 5%, method A) significantly increases the yield to 90%. That the cause of the yield enhancement does not stem from the feasibility of BBEDA serving as a bidentate ligand derives from the complete inhibition of reaction by bidentate phosphine ligands like dppe or dppb. Solvent choice proved critical, with the yield decreasing in the order benzene > chloroform > 1,2-dichloroethane. This order mirrors the order of increasing dielectric constant; thus the solvent of lowest dielectric constant is preferred.

Acetylene substitution is readily accommodated, as shown by **4b** and **4c** giving the corresponding indolizidines **6b**[6] and **6c**[6] in 55% and 80% yields, respectively. Surprisingly, high diastereoselectivity was observed in the cyclization of **7** to form a single stereoisomer, tentatively assigned as depicted in **8**[6] on the basis of mechanistic considerations (eq 3). The effect of geometric

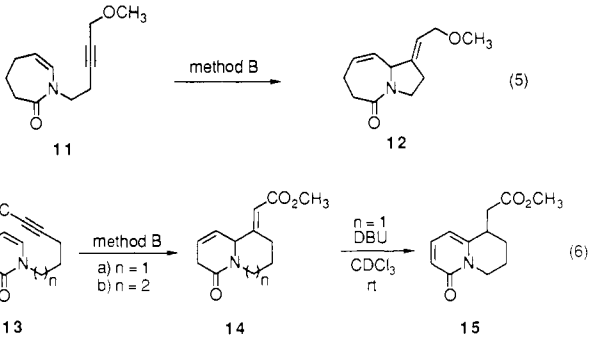


restrictions in the tether induced by benzannulation was probed by the cyclization of **9**, whose synthesis illustrates the general availability of the requisite substrates (eq 4). The catalyst system described above (method A) effected cyclization in good yield (80%) but as a mixture of regioisomeric double-bond isomers. Replacing the Pd(0) complex by 5% palladium acetate (5% BBEDA, 5 equiv of HOAc, method B) remarkably avoided this problem and gave only the indolizidine **10**.[6] These catalyst



conditions proved more generally efficacious. For example, the yield of cyclized product **6c** (eq 2) increased to 95% using method B.

Variation of ring size was briefly explored. Cyclization onto a seven-membered ring was equally effective (**11** → **12**,[6] eq 5, 68%). Forming a six-membered (**13a** → **14a**, eq 6, 72%) and even a seven-membered (**13b** → **14b**, eq 6, 46%) ring succeeded. In the former case, the initial cyclization product, which was a 3:1 regioisomeric olefin mixture, was isomerized to the pyridone **15** for characterization. The latter, which was isolated as a 5:1 regioisomeric mixture with the major regioisomer depicted,[8] represents the first example of seven-membered-ring formation by palladium-catalyzed enyne cyclizations.[4] In all cases, the exocyclic double bond was a single geometry.



The speculative nature of any mechanistic discussion of this palladium-catalyzed enyne cyclization prevents detailed commentary. While the beneficial effect of BBEDA as ligand parallels results in enyne carbocyclizations,[4] two key observations do not: the requirement for a significant excess of acetic acid and the beneficial effect of palladium acetate as the precatalyst rather than Pd(0). These observations suggest that a Pd(+4) cycle should at least be considered especially with the growing evidence for the ease of formation of Pd(+4) complexes in the presence of nitrogen ligands.[9] The above reactions are the first examples of enamine derivatives being able to participate in such Pd-catalyzed processes: a particularly intriguing success considering the potential sensitivity of these substrates to an oxidant like palladium acetate. Not only is this substituent tolerated but it also seems to expand the scope of the process. Synthetically, the ability to totally change the reaction profile of the *N*-acyl enamines even in the presence of acid by simple addition of a catalytic amount of palladium and the juxtaposition of functionality created should allow the evolution of useful synthetic strategies to alkaloids. As a cycloisomerization, this approach is highly atom economical.

Acknowledgment. We thank the National Institutes of Health, General Medical Sciences, and the National Science Foundation for their generous support of our programs. C.P. thanks the Spanish Ministerio de Educacion Y Cienca for a fellowship. Mass

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spectra were kindly provided by the University of California—San Francisco Mass Spectrometry Facility supported by the NIH, Division of Research Resources.

Supplementary Material Available: Characterization data for **6a–c**, **8–10**, **12**, **14b**, and **15** (3 pages). Ordering information is given on any current masthead page.

Synthesis and Characterization of the Model Compound of Active Site Cofactor TTQ of Bacterial Methylamine Dehydrogenases

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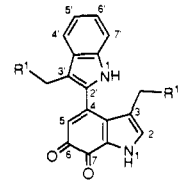
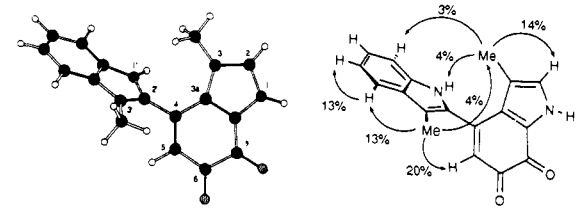
Methylamine dehydrogenase (EC 1.4.99.3, MADH) is a quinoprotein (quinone-containing enzyme) which is isolated from a variety of methylotrophic and autotrophic bacteria and catalyzes the oxidation of methylamine to formaldehyde and ammonia in a two-electron step.[1] One of the most interesting aspects of MADH is the chemical structure of the active site cofactor. PQQ (pyrroloquinolinequinone, a novel coenzyme of bacterial alcohol, aldehyde, and glucose dehydrogenases) or a closely related compound used to be regarded as a plausible candidate for the cofactor,[2-4] and the redox behavior of MADH has been investigated by taking account of the *o*-quinone structure of the cofactor.[5] Recently, however, McIntire and his co-workers revealed the structure of the cofactor to be that of tryptophan tryptophylquinone (TTQ), not PQQ, by ^{1}H NMR and mass spectroscopic investigations on isolated cofactor-bearing peptides.[6] Studies on amino acid sequences and X-ray crystallographic analysis of the native enzymes also supported the proposed structure.[7,8]



R^1 = peptide: TTQ
R^1 = H: 1

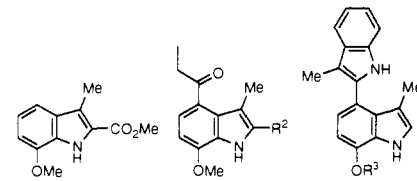
The enzymatic mechanism of amine oxidation by MADH has not been clearly demonstrated yet. A transamination mechanism has been recently proposed for the enzymatic reaction,[6,9] but little was known about the details. Thus in this study, we synthesized and characterized a model compound of TTQ in order to obtain further information on the structure and the reactivity of the active site cofactor.



A B

Figure 1. (A) Fully optimized structure of **1** by AM1. The dihedral angle of the two indole rings defined by C(3a)–C(4)–C(2′)–N(1′) is 54.7°. (B) Selected NOE correlations for **1**.

The synthesis of model compound **1** was accomplished as follows. Friedel–Crafts acylation on indole derivative **2**[10] with propionyl chloride by the standard method gave the 4-acylated compound **3** (93%), which was converted into **5** by ester hydrolysis (79%) followed by thermal decarboxylation using $CuCrO_4$ in quinoline (59%). The second indole ring was constructed by Fischer indolization on **5** with phenylhydrazine hydrochloride in 71% yield. Deprotection of the methoxy group of **6** by trimethylsilyl iodide gave the 7-hydroxy derivative **7** (93%), which was finally converted into the expected quinone **1** by oxidation with Fremy's salt in 57% yield.[11]



2 3, R^2 = CO_2Me 4, R^2 = CO_2H 5, R^2 = H 6, R^3 = Me 7, R^3 = H

X-ray crystallographic investigation of MADHs from *Paracoccus denitrificans* and *Thiobacillus versutus* indicated that the dihedral angle of the two indole rings of TTQ is about 42°.[8] AM1 calculations indicated that the dihedral angle of the two indole rings of compound **1** defined by C(3a)–C(4)–C(2′)–N(1′) is 54.7° and the distances between the protons of 3′-Me and those of 3-Me and 5-H are about 4 and 2.5 Å, respectively (Figure 1A).[12] Such a molecular geometry was also suggested by the observed NOE correlations for **1** (Figure 1B). An approximately 4% NOE was detected between the two methyl groups, but this value seems to be relatively small compared to that between 3′-Me and 5-H (20%). In the case of MM2 calculations on a structurally related compound, 4-(3′-methylindol-2′-yl)skatole, minimum steric energy was obtained when the dihedral angle of the two indole rings was 45.8°.[13]

The two-electron redox potential of **1** was determined to be −188 mV vs SCE by cyclic voltammetry at pH 7.4.[14] This value is comparable to that of native MADH from bacterium W3A1 ($E_{1/2}$ = −148 mV vs SCE at pH 7.5).[15] Compound **1** shows a strong absorption at 407 nm ($\epsilon = 1.07 \times 10^4$ M^{-1} cm^{-1}) with a broad

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