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A VERSATILE METHOD FOR CARBON–NITROGEN BOND FORMATION VIA ENE REACTIONS OF ACYLNITROSO COMPOUNDS

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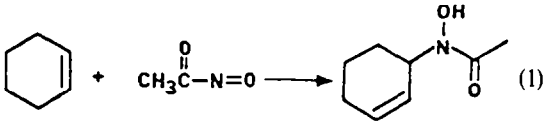
Abstract—The use of acylnitroso compounds of the general formula RCONO as enophiles in the formation of carbon–nitrogen bonds is described. Both inter- and intramolecular ene reactions have been studied. For the intermolecular examples, nitrosocarbonylmethane, thermally liberated from its Diels–Alder adduct with 9,10-dimethylanthracene, is reacted with various olefins giving the corresponding N-alkylhydroxamic acids in moderate to high yields, providing an efficient method for allylic amidation. The regiochemistry of the intermolecular reaction is observed to be the result of kinetic control, and the direction of addition is consistent with attack by the olefin on electron-deficient nitrogen. Several examples of intramolecular ene cyclization are demonstrated, providing efficient entry into both *spiro* and *fused* bicyclic nitrogen containing systems which can be viewed as derived from annulation of 5- and 6-membered nitrogen containing rings onto 5- and 6-membered carbocycles, respectively. Various examples of this hetero-annulation scheme are described. Experimental details are also privided describing typical reaction procedures.

In spite of a history dating to at least 1960, the chemistry of acylnitroso compounds, RCONO, has remained largely unexplored. Such compounds were apparently first recognized by Al-Sayyab, who observed that the reaction of various oxidizing agents, including periodate, bromine, and NBS, with hydroxamic acids in the presence of nucleophilic amines afforded amide products.[1] The proposed mechanism involved oxidation of the hydroxamic acid to the acylnitroso compound, followed by nucleophilic addition of the amine with loss of HNO. Considerably later, Kirby reported trapping of the proposed intermeidate with thebaine in a [4+2]-cycloaddition.[2] The dienophilic reactivity of various acylnitroso compounds has since been amply demonstrated by the elegant investigations of Kirby.[3] To date, however, such compounds have proven too reactive to allow even spectroscopic observation, much less their isolation.[4] The extraordinarily high reactivity of such compounds makes them very attractive intermediates for a number of synthetic operations. We have been led, as a consequence of detailed retrosynthetic analysis of a number of alkaloid natural products, to investigate various electrocyclic reactions involving such compounds, and preliminary accounts of our initial observations of intramolecular [4+2]-cycloadditions and ene reactions utilizing the acylnitroso moiety have appeared.[5] We detail here our studies on both intramolecular and bimolecular variations of ene processes in which the acylnitroso group functions as an enophile.

RESULTS

Bimolecular ene processes

The bimolecular ene reaction of an acylnitroso moiety with simple olefins affords a method for effecting "allylic amidation", as shown in eqn (1) below for the reaction of cyclohexene with nitrosocarbonylmethane, affording an N-alkyl-hydroxamic acid which is easily and efficiently converted to the N-alkylacetamide by a number of methods, as detailed below. The reaction thus complements other methods for achieving the same net result since it proceeds, by necessity, with allylic rearrangement and affords a product at the oxidation level of amide, rather than amine.[7] The cases we have examined are discussed below.



(1)

Generation of acylnitroso compounds. Since the acylnitroso compounds are quite reactive in ways other than as enophiles, their generation for use in ene reactions is problematic. In our experience, attempted bimolecular ene reactions by oxidation of hydroxamic acids in the presence of olefins gave discouraging results. Intractable mixtures containing only poor yields of ene products resulted from our early attempts with such procedures. Such difficulties may be related to further oxidation of initially formed ene products. Secondly, on a qualitative basis, rates for simple bimolecular ene reactions appear slower than those for [4+2]-cycloaddition process, contributing perhaps to the difficulties encountered with direct oxidation of hydroxamic acids as a route to the desired ene products.

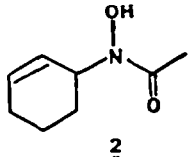
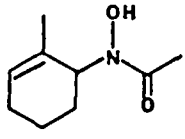
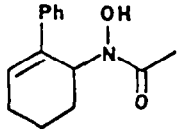
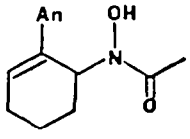
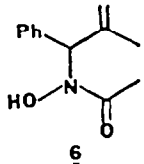
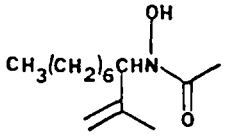
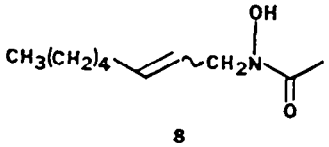
Tetra-n-propylammonium periodate is highly useful for the oxidation of hydroxamic acids to acylnitroso compounds in that it allows the use of periodate in non-nucleophilic solvents such as methylene chloride, chloroform, and dimethylformamide, and is very easily prepared and crystallized. However, it does appear to degrade initially formed ene products by further oxidation. Thus we have performed essentially all successful bimolecular ene reactions via thermal transfer of nitrosocarbonylmethane from its Diels–Alder adduct with 9,10-dimethylanthracene (**1**).[5] This material is readily prepared by oxidation of acetohydroxamic acid with $N(Pr)_4IO_4$ in the presence of 9,10-dimethylanthracene, and is thermally stable at room temperature. Thermal release of nitrosocarbonylmethane is readily accomplished by "pyrolysis" at 80–110° in the presence of olefinic trapping agents. Since this method is neutral and no oxidizing agents are involved, very high yields of ene products are generally obtained. Our intramolecular

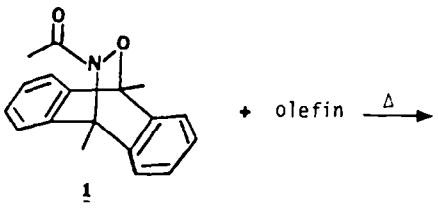
variation of the ene reaction (*vide supra*) relies heavily on the ease with which this masked nitrosocarbonylmethane can be elaborated to complex substrates appropriate for various intramolecular ene insertions. The preparation of this material is detailed in the experimental section.

Scope and regiochemistery of bimolecular ene reactions

Ene reactions of nitrosocarbonylmethane with a number of representative olefins have been carried out by three general methods. Inexpensive olefins with appropriate boiling points (e.g. cyclohexene, 1-octene) may simply be taken as solvent (method A). The procedure then involves simply dissolving the nitrosocarbonylmethane precursor (**1**) in the olefin and heating at reflux under an inert atmosphere until monitoring by tlc indicates that consumption of **1** is complete. Ene reactions using nitrosocarbonylmethane have also been carried out in refluxing benzene, using 1.1–1.2 equiv of olefin with an initial olefin concentration of 0.2 M (method B), or in small sealed tubes (heated at 80°) with an initial olefin concentration of 1.0 M (method C). Method C is preferable for small reactions or where the olefin component is too volatile, expensive, or difficultly accessible. Equation (2) and Table 1 below summarize the results.

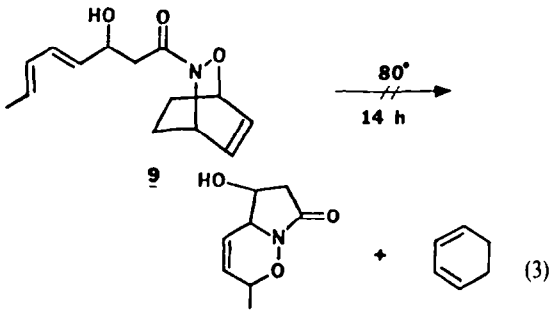
Table 1. Results of bimolecular ene reactions

olefin	method	product	(yield)
cyclohexene	A	 **2**	(85)
1-methylcyclohexene	C	 **3**	(92)
1-phenylcyclohexene	C	 **4**	(95)
1-*p*-methoxyphenylcyclohexene	B	 **5**	(89)
2-methyl-1-phenylpropene	C	 **6**	(88)
2-methyl-2-decene	C	 **7**	(83)
1-octene	A	 **8**	(89)



1

9,10-DMA + hydroxamic acid (2)



9 (3)

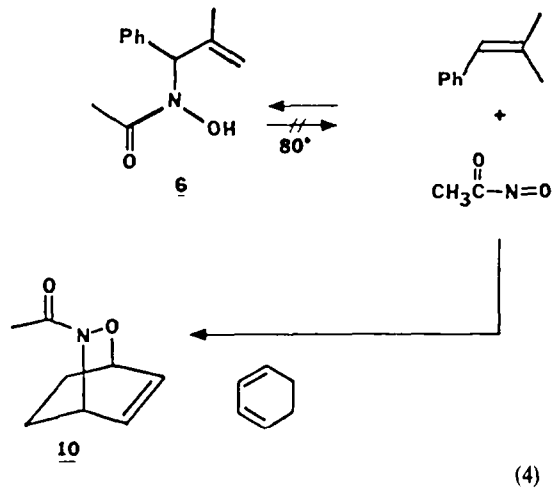
With such simple olefins, uniformly high isolated yields of ene products are obtained, with the notable exception of 1,1-diphenylpropene. Here no conversion to the expected ene product could be detected, although consumption of **1** was observed. Apparently, loss of olefin conjugation with two phenyl groups is sufficient to preclude ene reaction in this case. Ene reaction involving the deconjugation of one phenyl group, however, can be accomplished as shown by the results with 2-methyl-1-phenylpropene. With both dihydropyran and cyclohexenone, however, complex mixtures of products were obtained.

The regiochemistry of the reaction is of interest, since several of the examples shown could give rise to multiple ene products. In each case, there are two possible rationales for the observed regiochemistry. The first would involve thermodynamic control of a highly reversible ene process, affording the most stable possible products. The second involves a kinetically controlled process with a product determining stage of the reaction in which nitrogen adds to the olefin π system to generate a species with significant free valence (odd electron density or positive charge) on carbon. This would then result (for the case above) in bonding of nitrogen to the less substituted unsaturated carbon. Mechanisms involving an initial stage of reaction in which abstraction of allylic hydrogen by nitroso oxygen runs ahead of N–C bonding do not appear consistent with the data unless the ene products generated would be very thermally unstable. It was thus of interest to examine the reversibility of the observed ene reactions.

Several considerations, most importantly the results of attempted ene reactions with 1,1-dipenylpropene, suggest that ene product **6**, from 2-methyl-1-phenylpropene, should be the most prone of the entries in Table 1 to reversal. Thus phenyl conjugation is restored upon reversal of the ene reaction, and the C–N bond in **6**, being both allylic and benzylic, should be the weakest of those available in substrates **2–8**. Hence, we selected this substrate to investigate the reversibility of the ene process.

If retro-ene fragmentation of **6** were occurring under the conditions employed, it should be revealed by trapping nitrosocarbonylmethene with some external agent to afford a product which is thermally stable under the conditions of the experiment. Cyclohexadiene satisfies these requirements nicely, since it reacts readily with CH_3CONO via Diels–Alder cycloaddition, and the resulting [4 + 2]-adduct is recovered unchanged after prolonged pyrolysis at 80°. The kinetic stability of the adduct is demonstrated by the observation that compound **9** below is recovered unchanged on 80° pyrolysis.[5a] Here retro [4 + 2]-fragmentation would be revealed by release of cyclohexadiene and formation of an intramolecular [4 + 2]-cycloadduct (**10**). Note eqn (3):

Pyrolysis of **6** was conducted at 80° in benzene in presence of 1.0 M cyclohexadiene. Even after 12 hr at 80°, no retro-ene fragmentation was discernible, and **6** was recovered unchanged. Since samples of both 1,1-diphenylpropene and adduct **10** were in hand, it is unlikely that even 5% conversion could escape detection. Thus, the ene processes described by Table 1 can be reliably described as the results of kinetically controlled reactions. Note eqn (4) below:



(4)

Thus, the observed regiospecificity appears best rationalized by a mechanism involving initial bonding of electron deficient nitrogen to the olefinic π system. Similar behavior for other ene reactions has been proposed based on MO calculations.[8]

Several experimental points should be noted briefly. First of all, the hydroxamic acid products obtained via ene reaction, after chromatographic purification as described in the experimental section, frequently give poorly resolved ^1H NMR spectra. We do not know at present if this is due to generation of traces of paramagnetic acylnitroxyls or to H-bonding association of these very polar materials. However, the PMR spectra of the corresponding acetates are very sharp, hence many of our materials are characterized after acetylation. Secondly, experimental work is greatly simplified by tlc monitoring with 2%$FeCl_3$ in ethanol for visualization. Simply dipping an eluted plate into this solution affords immediate purple spots on a yellow background for the N-alkyl hydroxamic acids, the N-alkyl-O-acyl derivatives are stained after brief heating on a hotplate. These procedures greatly simplify the monitoring of reactions or chromatography.

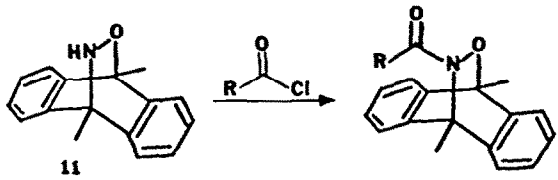
Intramolecular ene reactions

Construction of substrates. As previously mentioned, direct generation of acylnitroso compounds by periodic oxidation of the corresponding hydroxamic acids is frustrated by overoxidation of the hydroxamic acid product, with the formation of dark intractable mixtures. This complication plagues the intramolecular process as well. Moreover, since we envisioned eventual use of such intramolecular reactions in natural product total synthesis, we were concerned with effecting the ene process under the mildest possible conditions. We therefore chose to investigate methods for elaboration of adduct **1** such that it could serve as a protected acylnitroso function in a complex substrate.

Conversion of **1** to its Li enolate is readily accomplished using lithium diisopropylamide in THF-HMPA at −78°; without inclusion of HMPA the enolate precipitates and cannot be used satisfactorily in condensation or alkylation reactions. The enolate of **1** has been used successfully in a number of alkylations and condensations. In general, highest yields of elaborated products are obtained from the reaction of **1** with aldehydes. α,β-Unsaturated aldehydes such as methacrolein, crotonaldehyde, and cyclopentencarboxaldehyde undergo exclusive 1,2 addition as do dienals such as sorbaldehyde. One β-γ unsaturated aldehyde (cyclohexenacetaldehyde) has been successfully utilized. Similar results have been obtained for the condensation with α,β-unsaturated ketones such as cyclohexenone, cycloheptenone, and 3-aryl-cyclohexenones. The results of attempted alkylations of the Li enolate of **1**, although less thoroughly investigated, are less satisfactory. Highly reactive bromides such as 1-bromo-3-methyl-2-butene afford satisfactory yields of alkylated product, but no useful results were obtained upon attempted reaction with less reactive halides such as 3-bromocyclohexene or (2-bromoethyl)cyclohexene. However, (2-iodoethyl) cyclohexene smoothly alkylates **1** to afford the alkylated product **25** in 72% yield.

The condensation products are, in general, easily converted to protected derivatives. Tertiary alcohols resulting from 1,2 addition to alkenones may be masked as TMS ethers by reaction with N,O-*bis*-trimethylsilyltrifluoroacetamide in chloroform at 23°, with no detectable elimination. Secondary alcohols from condensation with aldehydes are easily converted to either acetates or t-butyldimethylsilylethers using standard procedures,[9] again with no complication from elimination or other decomposition. One attempted conversion of a secondary allylic alcohol to a MEM protected derivative failed; however, we do not know if this is general since no further examinations of this protecting group have been made.

An alternative strategy for the elaboration of complex substrates for intramolecular ene reactions involves the acylation of carboxylic acid derivatives with the known hydroxylamine **11**, easily prepared by treatment of **1** with sodium methoxide in methanol at room temperature,[10] but this approach suffers from the rather low thermal stability of hydroxylamine **11**. (Note eqn 5.)



11

(5)

An equivalent procedure would involve conversion of the carboxylic acid to the corresponding hydroxamic acid, followed by oxidation in the presence of 9,10-dimethylanthracene. This procedure generally works well for the preparation of protected acylnitroso derivatives for intramolecular ene reactions. For instance, substrate **35** (Note Table 2) was assembled in 85% isolated yield (from the carboxylic acid) using this approach. It is necessary to point out, however, that such an approach to the construction of precursors for intramolecular Diels–Alder reactions can generally be expected to give

Table 2. Results of intramolecular ene reactions

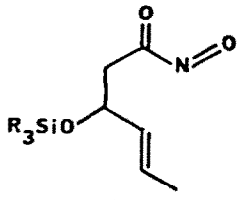
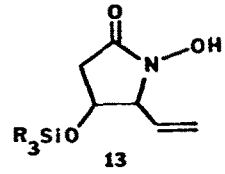
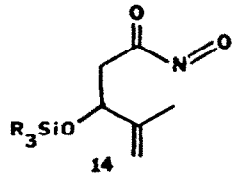
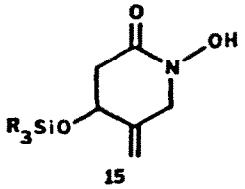
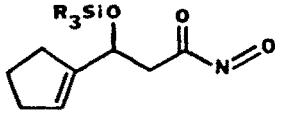
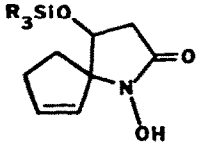
ene substrate	(yield)	product	(yield)
 **12**	(67)	 **13**	(100)
 **14**	(79)	 **15**	(100)
 **16**	(80)	 **17**	(95)

Table 2(*Contd*)

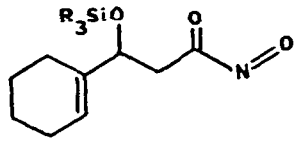
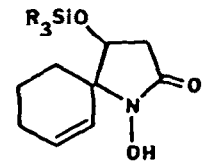
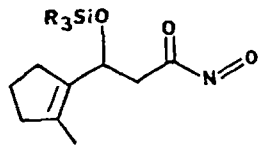
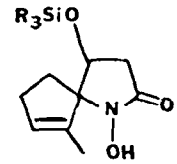
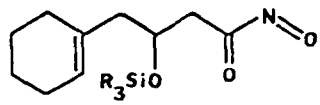
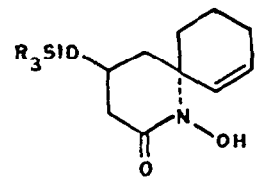
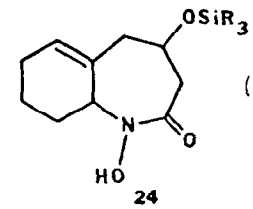
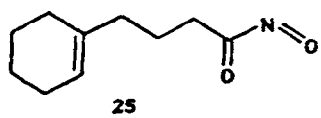
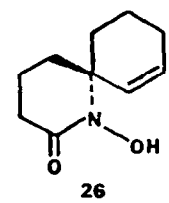
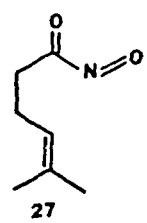
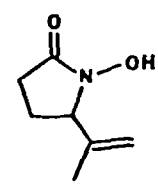
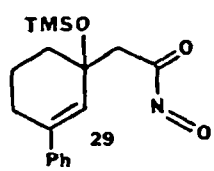
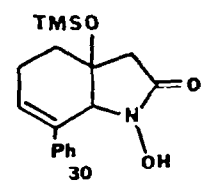
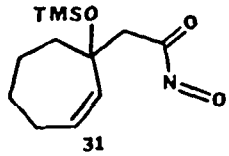
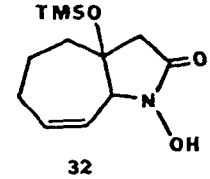
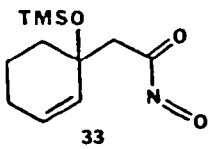
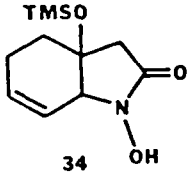
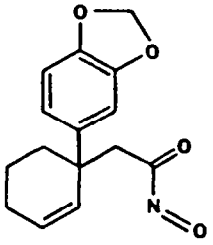
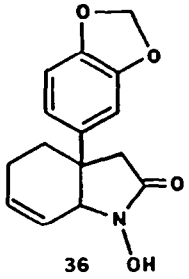
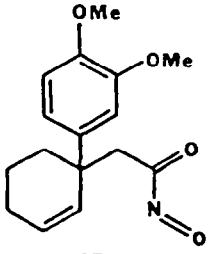
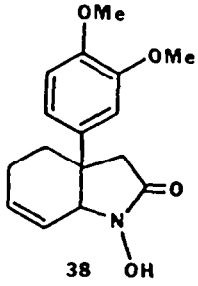
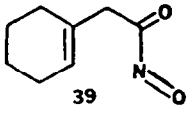
ene substrate	(yield)	product	(yield)
 18	(77)	 19	(92)
 20	(81)	 21	(100)
 22	(85)	 23	(85)
		 24	(15)
 25	(72)	 26	(100)
 27	(74)	 28	(100)
 29	(76)	 30	(96)
 31	(75)	 32	(100)

Table 2 (*Contd*)

ene substrate	(yield)	product	(yield)
 **33**	(75)	 **34**	(85)
 **35**	(85)	 **36**	(100)
 **37**	(83)	 **38**	(100)
 **39**	(80)		

(a) All acylnitroso compounds (shown "free" for convenience) were generated by thermolysis of their Diels–Alder adducts with 9,10-dimethylanthracene.

(b) R_3Si = tert-butyldimethylsilyl.

(c) Yields for the acylnitroso compounds shown are overall yields for the processes as detailed in the experimental section.

low yields, since the product upon reaction with 9,10-DMA will of course contain a 1,3 diene unit which can intercept a second acylnitroso compound, yielding "dimeric" products.

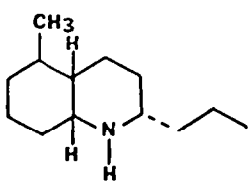
Using the substrates in Table 2, intramolecular ene reactions were effected simply by pyrolysis of dilute solutions in refluxing benzene or toluene. In contrast to the relatively long reaction times typical of the bimolecular process, rates appear to be governed solely by the first order release of 9,10-DMA, and typical reaction times for complete consumption of strating material are *ca.* 4 hr at 80°, or 30–40 min at 110°. Isolation of products is easily accomplished as detailed in the experimental section, and yields are uniformly high (Note Table 2).

DISCUSSION

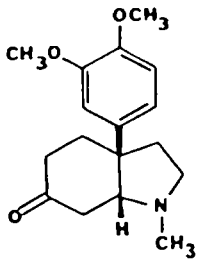
Ene reactions of acrylnitroso compounds as a synthetic method for the formation of C–N *bonds and the annulation of nitrogen containing rings*

Before considering in detail the results outlined in Table 2, it is appropriate to consider the intramolecular ene process in the context which led us to investigate the viability and scope of the process, that of natural products total synthesis. It is apparent upon perusal of the structures of a large number of alkaloids of considerable recent interest that a significant structural simplification can be made by regarding the structure as some parent carbocycle onto which a nitrogen containing ring has been annulated. Several alkaloids are shown below to illustrate this dissection.[11]

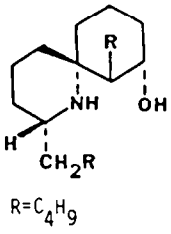
The intramolecular ene methodology outlined above affords a two step method for the construction of such ring systems, the first step being the introduction of a protected acylnitroso moiety into a carbocyclic substrate, followed by a second step of thermal liberation of the enophile with concomitant ene reaction. However, application of the method to natural products such as those shown above clearly requires some understanding of the regiochemistry of the ene reaction, since in general more than one viable ene reaction exists for a given substrate. We now turn to an examination and discussion of the results outlined in Table 2.



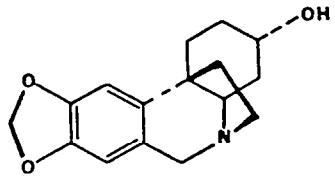
Pumiliotoxin C



Mesembrine

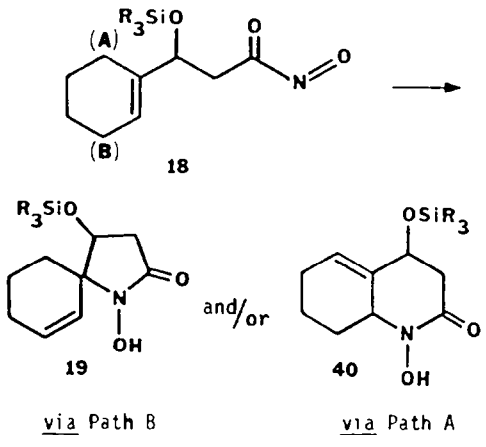


Perhydrohistrionicotoxin



Elwesine

The above considerations are nicely illustrated by a consideration of the possible outcomes of pyrolysis of substrate **18** in Table 2.



(6)

Two sets of allylic methylene groups ("A" and "B" above) exist in **18**, giving rise to two possible ene results, as shown in eqn (6) above, which correspond to Type I and Type II ene reactions according to the classification scheme of Oppolzer and Snieckus.[12] The Type I alternative leads to a spiro fusion with five ring hydroxamic acid **19**, while the Type II process affords a fused bicyclic structure with a six ring hydroxamic acid **40**. Both appear to be reasonable alternatives, however, only the Type I process is observed. Similar results are obtained wherever (note entries **16**, **20**, **22** and **25**) potentially competing Type I and Type II ene processes are available. Thus it appears that highly selective conversion to spiroannulated products can be anticipated for such cases. Although the reasons for such preferences are somewhat obscure, the results above with acylnitroso enophiles do in fact parallel previous results with a variety of other enophiles.[12] It is of interest to note, however, that the dramatic preference for Type I ene reaction over an available Type II alternative is exactly opposite from the regiochemistry observed in the bimolecular reaction; in the intramolecular Type I with the substrates in Table 2, C–N bond formation occurs at the more substituted olefinic carbon, while in bimolecular examples a marked preference for C–N bonding at the less substituted carbon was noted. The intramolecular reaction must therefore be governed by some other control element which overrides the "inherent" regiochemistry of the reaction observed in bimolecular cases. At some point, as the separation between olefin and enophile increases, the regiospecificity of the intramolecular process can be expected to diminish. An examination of the results using substrates **22** and **25** shows that this limit is, fortunately, not reached when the nitrogen and proximal olefinic carbon are six atoms apart, allowing for a facile entry to the [5.5]-spiro system. It is of interest to note in this context that the reaction is somewhat sensitive to effects of remote substituents. Thus, ene substrate **25** affords exclusively the spirocyclic hydroxamic acid **26**, while **22**, with an added *tert*-butyldimethylsilyl ether β to CO, yields both spiro and fused products in an 85 : 15 ratio, respectively.

The effect of increasing alkyl substitution on the olefin component has been examined in only one case, that of **20**. Here both endocyclic and exocyclic olefins could potentially be produced upon Type I intramolecular ene reaction, but only the endocyclic product is observed.

Only one failure has been encountered in our study of such ene reactions, which occurred upon attempts to extend the method to the production of spiro fused β-lactams. Acylnitroso compound **39**, formed in the normal way by thermolysis of its Diels–Alder adduct with 9,10-DMA, yielded a mixture of products from which we were unable to isolate the desired β-lactam, nor were any other readily identifiable products produced.

The utility of the ene reactions discussed depends critically upon the availability of simple and efficient processes to convert the hydroxamic acids so produced to compounds containing more useful oxidation states of nitrogen. Three methods have proven useful for reductive cleavage of the N–O bond in such substrates, to yield the corresponding amides. Reduction of the derived (Ac_2O–pyr, 23°) acetates with 6% sodium amalgam has been employed for this conversion in our laboratories.[5b] However, since our initial report, we have found that results here are highly dependent on the batch of soduim amalgam employed for the reduction. On some cases, base induced acetate hydrolysis can occur to the exclusion of reductive cleavage. More satisfactory is reductive cleavage of allyl ethers, which are easily formed in high yield by treatment of the hydroxamic acid with allyl bromide and potassium carbonate in acetone. Using this procedure, for example, hydroxamic acids **26** and **36** were converted to the corresponding amides in 95% yields. A third very useful procedure is that of Mattingly and Miller,[13] who reported the reduction of hydroxamic acids with $TiCl_3$ in mildly basic aqueous solution. Using this procedure, hydroxamic acids **17**, **36**, and **38** were converted to the corresponding amides in >90% yield in each case.

Conventional procedures with appropriate ene products have been employed in a number of cases to afford naturally occurring materials. For instance, hydroxamic acid **36** has been converted to (±)-crinane via the four step sequence of hydrogenation, reduction with $TiCl_3$, LAH reduction, and Pictet-Spengler cyclization.[14] Additionally, formal total systheses of (±)-

mesembrine, (±)-dihydromaritidine, and (±)-perhydrohistrionicotoxin, all recently completed in our laboratories, serve to further illustrate the power of acylnitroso ene reactions in alkaloid synthesis and will be reported in due course.

EXPERIMENTAL

General. M.ps were obtained on an electrothermal m.p. apparatus and are uncorrected. IR spectra were recorded using a Perkin–Elmer 298 spectrophotometer with polystyrene reference; values reported are in cm^{-1}. NMR spectra were recorded using Varian EM-390 or Varian SC-300 spectrometers, chemical shifts are reported in ppm downfield from internal Me_4Si. Mass spectra were recorded using a Varian MAT-112 mass spectrometer in the indicated mode. Yields reported are for materials judged homogeneous by NMR and tlc (or vpc), and, for crystalline solids, material with the indicated m.p. Tlc was performed on Merck 0.25 mm glass silica gel plates, visualization of developed plates was by fluorescence quenching, and by staining with phosphomolybdic acid or with $FeCl_3$ for hydroxamic acids. Column chromatography was performed using Merck Silica Gel 60, 60-240 mesh. "Mplc" refers to medium pressure liquid chromatography over Merck Silica Gel 60, 230-400 mesh, using an FMI lab pump operated at 60–100 psi. Altex columns and UV detector, and ISCO fraction collector. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee; values obtained were within 0.3% of those calculated for the formula given.

Solvents used were purified as follows: THF by distillation from Na-benzophenone under argon; toluene, benzene, diisopropylamine, hexamethylphosphoramide (HMPA), hexane, and N,N-dimethylformamide (DMF) by distillation from CaH_2 under argon; $CHCl_3$ by passage through Woelm basic alumina, CH_2Cl_2 by distillation from P_2O_5; EtOH and MeOH by distillation from Mg; and pyridine by stirring with KOH followed by distillation from BaO.

9,10-*Dimethylanthracene.* To a cold (0°C) mechanically stirred soln of LAH (1.80 g; 73 mmol) in 250 ml THF was added 9,10-*bis*-chloromethylanthracene 20.0 g; 73 mmol,[15] in small portions as the solid. The resulting mixture was slowly warmed to 23° then heated at reflux for 2 hr, then cooled to 0° and quenched by cautions portionwise addition of ground $Na_2SO_4 \cdot IOH_2O$-Celite mixture (ca. 1 : 1 volume/volume). The resulting slurry was filtered, concentrated *in vacuo*, and the residue was dissolved in a minimal volume of hot CH_2Cl_2, then diluted with hexane until the soln became cloudy. After standing 12 hr, the mixture was filtered and concentrated *in vacuo*. Crystallization of the crude product so obtained from minimal hot toluene give 11.0 g (75%) of 9,10-dimethylanthracene, identical in all respects with an authentic sample.

10 - (1 - Oxoethyl) - 9,10 - dihydro - 9,10 - dimethyl - 10,9 - (epoxyimino)anthracene (**1**)[16] A stirring soln of 9,10-dimethylanthracene (4.0 g; 20 mmol) and tetra-n-propylammonium periodate (11.0 g; 30 mmol) in 50 ml $CHCl_3$ awas cooled to 5° and a soln of acetohydroxamic acid (2.20 g; 30 mmol)in 15 ml DMF was added dropwise at such a rate that the temp did not exceed 15°. After the addition was complete, the soln was poured into EtOAc and washed with sat $Na_2S_2O_3$aq, water, and brine. The EtOAc, and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield 5.20 g (95%) of **1** as a crystalline solid, m.p. 133–136 (d), *Rf* 0.39 (35% THF-hexanes), NMR ($CDCl_3$) 7.52 (m, 8H), 2.80 (s, 3H), 2.28 (s, 3H), 1.90 (s, 3H), IR ($CHCl_3$) 2920, 1640, 1440, 1380, 1360. Anal. $C_{18}H_{17}NO_2$ (C, H).

Reaction of nitrosocarbonylmethane with olefins—General procedure for bimolecular ene reactions

(*A*) *Reaction of cyclohexene with nitrosocarbonyl methane—Preparation of* **2**. A soln of **1** (99 mg; 0.35 mmol) in 5 ml cyclohexene was heated at reflux for 6 hr under argon, at which time tlc monitoring indicated complete consumption of **1**. Concentration *in vacuo* and chromatography over a short silica gel column (5% THF-hexanes with gradient to 35% THF-hexanes) yielded 47 mg (85%) of **2**, R_f 0.31 (35% THF-hexanes); NMR ($CDCl_3$) δ 8.9 (br. S, 1H, OH), 6.1 (br. d, J = 10, 1H), 5.36 (d, J = 10, 1H), 5.2 (br. m, 1H), 2.13 (s, 3H), 1.5–2.3 (6H); IR ($CHCl_3$) 3150, 3020, 2930, 1600, 1420, 1300, 1160, and 910 cm^{-1}.

(*B*) *Reaction of 2-methyl-2-decene with nitrosocarbonylmethane—Preparation of* **7**. A solution of **1** (73 mg; 0.28 mmol) and of 2-methyl-2-decene (52 mg; 0.34 mmol) in 0.3 ml benzene were placed in a sealed Pyrex tube (under argon) and heated at 80° for 12 hr. The crude product so obtained was chromatographed over silica gel (elution with 5 to 35% THF-hexanes) to yield 35 mg (83%) of **7**, R_f 0.24 (35% THF-hexanes), NMR ($CDCl_3$) δ 4.9 (br. s, 2H), 3.9 (m, 1H), 2.0 (s, 3H), 1.8 (s, 3H), 1.4-1.1 (m, 12H), 0.9 (dist. t, 3H), IR 3500-3000, 2910, 2860, 1600, 1510, and 1160 cm^{-1}.

(*C*) *Reaction of p-methoxyphenylcyclohexene with nitrosocarbonylmethane—Preparation of* **5**. A soln of **1** (125 mg; 0.45 mmol) and of 1-*p*-methoxyphenylcyclohexene (101 mg; 0.54 mmol) in 2 ml toluene was heated at reflux under argon for 3 hr, then concentrated *in vacuo* and chromatographed over silica gel (elution with 5–30% THF-hexanes) to give 103 mg (89%) of acid **5**, R_f 0.29 (35% THF-hexanes), NMR ($CDCl_3$) δ 7.2 (d, J = 9, 2H), 6.8 (d, J = 9, 2H), 6.1 (m, 1H), 5.7 (m, 1H), 3.7 (s, 3H), 1.75 (s, 3H), 2.2-1.6 (m, 6H), IR ($CHCl_3$) 3500-3000, 2920, 1600, 1510, 1450, 1290, 1250, 1180, 1040.

Condensation of 10 - (1 - *oxoethyl*) - 9,10 - *dihydro* - 9,10 - *dimethyl* - 10,9 - (*epoxy*)*iminoanthracene* (**1**) *with crotonaldyhyde—Preparation of* **12**. The following procedure for the preparation of **12** was utilized for the condensation of **1** with aldehydes and silation of the resulting alcohol.

To a soln of diisopropylamine (0.70 ml; 5.0 mmol) in 12 ml THF, at 0° under argon, was added n–BuLi (1.65 ml) [Alfa, 2.5 M in hexanes, 4.8 mmol], followed by 0.8 ml of HMPA (to give a 5% soln). The resulting soln was cooled to −78°, and **1** (1.00; 3.58 mmol) in 2.5 ml THF was added dropwise via syringe. After stirring 15 min at −78°, crotonaldehyde (0.41 ml, 5.0 mmol) was added in one portion via syringe, and the resulting mixture was allowed to warm slowly to −30° (*ca.* 1 hr) at which time 3 ml MeOH was added, followed by 3 ml water. The mixture was then poured into water overlaid with ether-EtOAc (1 : 1) and the phases were separated. The aqueous phase was extracted with 3 portions of EtOAc, and the combined organic phases were washed once with water and brine, then dried over Na_2SO_4 and concentrated *in vacuo*. The crude product so obtained was chromatographed by MPLC on a 2 × 200 cm column eluted with 35% THF-hexanes, 15 ml fractions were collected. Fractions 9–17 gave 0.92 g (75%) of colorless crystalline solid, m.p. 108–110° (d); IR ($CHCl_3$) 3350-3250, 3010, 2950, 2870, 1660, 1470, and 1390 cm^{-1}.

Reaction of this alcohol (0.50 g;1.43 mmol) with t-butyldimethylchlorosilane (0.64 g; 4.3 mmol) and imidazole (0.58 g; 8.58 mmol) in 12 ml of chloroform-DMF (5 : 1) at 23° for 12 hr, followed by normal extractive workup (CH_2Cl_2) furnished 0.643 g (95%) of **12** as a colorless crystalline solid, m.p.109–112° (d), NMR ($CDCl_3$) 7.1–7.3 (m, 8H), 5.1 (m, 2H), 4.2 (m, 1H), 2.6 (s, 3H), 2.3 (t, J = 6, 2H), 2.1 (s, 3H), 1.36 (d, J = 5, 3H), 0.81 (s, 9H), 0.0 (s, 6H); IR ($CHCl_3$)3010, 2940, 2860, 1665, 1475, 1370.

Using the general procedure above, the substrates **14**, **16**, **18**, **20**, and **22** were prepared by condensation of **1** with methacrolein, cyclopentencarboxaldehyde, cyclohexencarboxaldehyde, 2-methylcyclopentencarboxaldehyde, and cyclohexenacetaldehyde, respectively, followed by reaction with t-butyldimethylchlorosilane. The overall yields for the two steps are given in Table 2. Pyrolysis and chromatography as described afforded hydroxamic acids **13**, **15**, **17**, **19**, **21**, **23**, and **25** (Note Table 2) in the indicated yields.

The same procedure was utilized for the condensation of **1** with ketones, except that silyation was accomplished with N,O-bis-trimethylsilyltrifluoroacetamide in chloroform at 23°. Substrates **29**, **31**, and **33** were prepared in this manner from 3-phenylcyclohexenone, cycloheptenone, and cyclohexenone, respectively.

Preparation of **34** *from β-(3',4'-methylendioxyphenyl)cyclohex-2-enyl acetic acid*

The following procedure utilized for the preparation of **35** illustrates the preparation of protected acylnitroso compounds from the corresponding carboxylic acid.

(A) β - (3',4' - Methylendioxyphenyl)cyclohex - 2 - enylaceto-hydroxamic acid. To a soln of β-(3',4'-methylenedioxyphenyl)cyclohex-2-enyl acetic acid[14] (1.30 g; 5.0 mmol) in 30 ml benzene was added $SOCl_2$ (0.50 ml; 6.00 mmol). The resulting mixture was heated at reflux for 2 hr, then cooled to 0°, and diluted with ether (20 ml); solid $NH_2OH \cdot HCl$ (0.5 g; 6 mmol) and Na_2CO_3 (1.5 g; 12 mmol) were then added. After 5 min stirring, 5 ml water were added followed by 5 ml 5 min later. The mixture was allowed to warm to room temp over 12 hr, then acidified to pH 2 with conc HCl, and the layers separated. The aqueous phase was extracted with 5 × 20 ml EtOAc, and the combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to yield 1.29 gm (93%) of a light yellow oil which was used in the next step without purification. NMR ($CDCl_3$, TMS) 8.28 (s, broad, 2H) 7.05 (s, 1H) 6.98 (s, 2H) 6.10 (s, 4H, methylene overlapping vinyl) 2.58 (s, 2H) 2.00 (m, complex, 4H) 1.55 (m, 2H); IR ($CHCl_3$) 3400 (w), 2810–3200 (br, s), 1760 (s, br), 1480 (s), 1430, 1195–1245 (br) 1050 (vs), 940, 917; ^{13}CNMR ($CDCl_3$, TMS) 169.3, 147.8, 145.9, 140.6, 131.6, 129.4, 120.2, 107.9, 100.9, 46.0, 41.7, 36.5, 24.8, 18.3.

(B) 12 - (3',4' - Methylenedioxyphenyl) - cyclohex - 2 - enyaceto-9,10 - dihydro - 9,10 - dimethyl - 10,9 - (epoxyimino)anthracene. (**35**). A soln of hydroxamic acid (1.29 g, 4.7 mmol) in $CHCl_3$ (5 ml) and DMF (1 ml) was added slowly dropwise (syringe drive) to a suspension of 9,10-dimethylanthracene (0.967 g; 4.7 mmol) and tetra-n-propyl ammonium periodate (1.94 g, 5.19 mmol) in $CHCl_3$ (10 ml) and DMF (2 ml). The syringe drive was adjusted to deliver 1 drop every 8–10 sec, and the addition was completed after 5 hr. The dark yellow soln was then poured into CH_2Cl_2 overlaid with satd $Na_2S_2O_3$aq and the phases were separated. The aqueous phase was back-extracted with 3 × 10 ml CH_2Cl_2, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a brown solid. The crude product was dissolved in CH_2Cl_2-THF and chromatographed on a 1 × 100 cm silica gel column slurry packed in 35%THF-hexanes, elution with same. *Results*: Fractions 1–10, nil; 11–12, 9,10-dimethylanthracene, 13–15 unidentified impurity; 16–18, nil; 19–33, product; 34–40, nil (40 fractions total, 30 ml each). Fractions 19–33 were combined and concentrated *in vacuo* to give 1.90 g (85%) of white solid, homogeneous by 1NMR and TLC analysis, m.p. 67–70° (d); 300 MHz ^{1}H NMR ($CDCl_3$, TMS) 7.43 (nm, complex, 4H), 7.29 (nm, complex, 4H) 6.77 (d, J = 2, 1H), 6.57 (d, J = 8, 1H), 6.48 (d of d, J = 2, J = 8, 1H), 2.70 (ABq, J = 18, 2H), 2.63 (s, 3H), 2.26 (s, 3H), 1.88 (m, 2H), 1.6 (m, 2H), 1.34 (m, 2H); IR ($CHCl_3$) 3060, 3020, 2980, 2921, 1680 (s, br), 1498, 1480, (vs), 1466, 1440, 1369, 1238 (s, br), 1170, 1040 (s), 920 (s), 732 (vs); ^{13}CNMR ($CDCl_3$, TMS) 176.6, 147.1, 145.0, 142.2, 141.5, 141.2, 141.1, 141.0, 133.0, 127.5, 127.4, 127.3, 127.1, 121.4, 121.3, 120.5, 120.4, 119.3, 107.4, 107.3, 100.5, 79.5, 63.6, 46.6, 41.6, 37.5, 24.6, 18.2, 16.2, 14.8. *Anal.*: ($C_{31}H_{29}NO_4$) C,H.

N - Hydroxy - 2 - keto - 3a - (3',4' - methylenedioxyphenyl) - 2,3,3a,4,5,7a-hexahydroindole. (**36**). Diels–Alder adduct **35** (0.9 g; 1.87 mmol) was decomposed in refluxing toluene (250 ml). After 15 min, tlc detailed the consumption of starting material with formation of 9,10-dimethylanthracene and a polar UV spot which stained purple on exposure to $FeCl_3$ (2% in EtOH, 1% HCl). The crude yellow solid that remained after removal of the toluene was chromatographed on a 1 × 50 cm silica gel column slurry packed in $CHCl_3$, and eluted with 2% MeOH in $CHCl_3$. *Results*: Fractions 1–5, nil; 6–10, 9,10-dimethylanthracene, 11–20, nil; 21–25, product; 26–30, nil (30 fractions total, 20 ml each). Fractions 21–25 were combined and concentrated *in vacuo* to yield 508 mg (100%) of light pink solid. One crystallization from CH_2Cl_2-pentane yielded analytically pure material as colorless rosettes, m.p. 160–163°; NMR ($CDCl_3$) 9.70 (s, broad, 1H), 6.90 (m, 3H), 6.32 (s, 2H), 6.05 (s, 2H), 4.45 (s, broad, 1H), 2.70 (s, 2H), 1.80 (m, 4H); IR ($CHCl_3$, solution) 2600–3400 (broad, s), 1690 (s), 1470 (s), 1420, 1370, 1200–1240 (broad, m), 1050, 920, 860; ^{13}C NMR ($CDCl_3$, TMS) 168.7, 148.3, 146.8, 138.6, 134.5, 122.6, 119.0, 108.4, 106.7, 101.4, 60.4, 43.5, 33.9, 22.0; *MS* (EI) m/e 274.3 (M+), 273.3 (P), 256.3 (P – H_2O), 228.3 (P – CH_2CO), 151.1 (P – $C_7H_5O_2$, aromatic). *Anal.*: ($C_{15}H_{15}NO_4$) C,H.

General procedure for alkylation of **1**

Preparation of **25**. To a soln of diisopropylamine (1.32 g; 1.83 ml; 13.1 mmol) in 32 ml THF, at −20° under argon, was added 2.3 M n-BuLi in hexanes (5.24 ml; 12.0 mmol), followed by 8.0 ml hexamethylphosphoramide. After cooling to −78°, a soln of **1** (2.80 g; 10.0 mmol) in 23 ml THF was added dropwise. After stirring at −78° for 30 min, (2-iodoethyl)-1-cyclohexene (3.32 g; 14.1 mmol) in 16.0 ml THF was added dropwise. An internal thermometer was used to insure that the temp did not rise above −70° during these additions. The resulting soln was allowed to warm to −20° over 2 hr, then quenched with 3 ml MeOH, concentrated *in vacuo*, taken up in EtOAc, and washed with water and with brine. After drying over Na_2SO_4, concentration *in vacuo* followed by chromatography of the crude product over silica gel (elution with 10% THF-hexanes) yielded 2.80 g (72%) of **25** as a crystalline solid, m.p. 104–106 (d), R_f 0.44 (35% THF-hexanes); NMR ($CDCl_3$) δ 7.50 (m, 8H), 5.45 (br. m, 1H), 2.80 (s, 3H), 2.30 (s, 3H), 2.2–1.3 (m, 14H); IR ($CHCl_3$), 2940, 1660, 1462, 1385. *Anal.* ($C_{26}H_{29}NO_2$) C, H.

This procedure was also used to obtain **26** by reaction of **1** with 1-bromo-3-methyl-2-butene.

Preparation of hydroxamic acid **26**. A soln of **25** (2.80 g) in 500 ml toluene was heated at reflux under argon for 45 min, then cooled, concentrated *in vacuo*, and chromatographed over silica gel. After 9,10-dimethylanthracene was eluted with 10% THF-hexanes, elution with 4% MeOH in $CHCl_3$ gave 1.30 g (100%) of **26** as a crystalline solid, m.p. 123–125°; R_f 0.12 (35% THF-hexanes), 0.27 (8% MeOH–$CHCl_3$); NMR ($CDCl_3$) δ 9.80 (br. s, 1H), 6.08 (dt, J = 12, 3, 1H), 5.70 (d, J = 12, 1H), 2.65–1.60 (m, 12H); IR ($CHCl_3$) 3400–3100, 2950, 1605, 1390, 1130. *Anal.* ($C_{10}H_{15}NO_2$) C, H.

General procedure for the reductive cleavage of allyl ethers with sodium amalgam

(A) Conversion of **26** *to the corresponding amide.* A soln of **25** (0.260 g; 1.44 mmol) and 3-bromopropene (1.74 g; 14.4 mmol) in 2 ml acetone containing K_2CO_3 (1.00 g; 7.25 mmol) was heated at reflux under argon for 12 hr, then filtered and concentrated *in vacuo* to yield 0.353 g (greater than theory) of a crude allyl ether which was used without purification, R_f 0.58 (8% MeOH–$CHCl_3$); IR ($CHCl_3$) 2940, 2860, 1650, 1450, 1370, 1350, 1110, 980.

To a soln of the crude allyl ether in 5 ml anhyd. EtOH containing anhyd disodium hydrogen phosphate (800 mg; 5.63 mmol) was added 1.50 g of freshly ground 6% sodium amalgam. After stirring 1.5 hr at 23°, the soln was filtered through glass wool, concentrated, and chromatographed in a short silica gel column (elution with 2% MeOH in $CHCl_3$) to yield 0.215 g (95%) of the amide as a crystalline solid, m.p. 108–110°, R_f 0.38 (8% MeOH–$CHCl_3$); NMR ($CDCl_3$)δ 6.25 (br. s, 1H), 5.9 (dt, J = 12, 3, 1H), 5.7 (dt, J = 12, 1H), 2.35 (d, J = 6, 2H), 2.0 (br. m, 2H), 1.80 (br. s, 8H); IR ($CHCl_3$) 2940, 2860, 1650, 1450, 1370, 1350, 1110, 980. *Anal.* ($C_{10}H_{15}NO$) C, H.

(B) Conversion of **36** *to the corresponding amide.* A soln of **36** (0.179 g, 0.65 mmol) in reagent grade acetone (10 ml) was treated with excess (2.0 eq) allyl bromide and excess anhyd, K_2CO_3 (4.0 eq), and the resulting suspension stirred for 2 hr at reflux, at which time tlc revealed the absence of starting material and the presence of the allyl ether (R_f 0.35, 50% THF-hexanes) which stained purple on exposure to $FeCl_3$ only after the plate had been heated considerably. The mixture was then diluted with $CHCl_3$, filtered, concentrated *in vacuo*, and chromatographed on a 1 × 100 cm silica gel column slurry packed with 8%MeOH–$CHCl_3$, elution with same. *Results*: Fractions 1–5, nil; 6–10, unidentified material; 11–13, nil; 14–20, product; 21–30, nil (30 fractions total, 5 ml each). Fractions 14–20 were combined and concentrated *in vacuo* to yield 180 mg (95%) of the allyl ether as a colorless oil; NMR ($CDCl_3$) 6.68 (nm, 3H, ArH), 6.16 (nm, 3H, vinylic), 5.98 (s, 2H, methylene), 5.46 (m, complex, 2H, vinylic), 4.50 (d, J = 8, 2H, allylic), 4.31 (m, 1H, methine), 2.62 (s, 2H, CH_2 C = 0), 1.85 (m,

4H); IR ($CHCl_3$) 3050 (w), 3010, 2950 (s), 2840, 1715 (vs), 1600 (w), 1505, 1460, 1410, 1255 (s), 1148, 1032, 910, 850, 708.

A soln of the allyl ether above (.180 g; .622 mmol) in 20 ml anhyd. EtOH was treated with Na_2HPO_4 (.265 g; 1.86 mmol), and the suspension was cooled to −20° (cold room) under argon. Then freshly ground 6% sodium amalgam was added in portions, and the soln stirred overnight. The next day, tlc revealed the total absence of starting material, and the presence of a much lower R_f spot (0.09, 8% MeOH–$CHCl_3$). Filtration and concentration *in vacuo* yielded 155 mg (100%) of a colorless oil which crystallized on standing, m.p. 214–216°; NMR ($CDCl_3$) 7.43 (s, 1H, NH), 6.70 (nm, 3H, ArH), 5.90 (m, 2H, vinyl), 5.88 (s, 2H, methylene), 4.20 (nm, 1H, methine) 2.66 (ABq, J = 18, 2H, methylene next to CO), 1.78 (m, 4H); IR ($CHCl_3$) 3400, 2960, 1690 (s), 1474 (m), 1440 (broad, w) 1180–1240 (broad) 1041, 936; *MS* (CI, isobutane) m/e 260.1 (M + 1), m/e 259.1, m/e 258.1 (base) m/e 257.1. *Anal.*: ($C_{15}H_{15}NO_3$) C, H.

General procedure for $TiCl_3$ *reductions of hydroxamic acids*

The procedure of Mattingly and Miller was employed,[13] as illustrated by the reduction of **38**. Thus, a soln of **38** (0.400 g; 1.38 mmol) in 5 ml H_2O and 5 ml MeOH was treated with Na_2CO_3 (0.337 g; 2.76 mmol) and $TiCl_3$ (Alfa, 0.839 g; 5.52 mmol) and the resulting purple mixture stirred for 18 hr under argon at room temp. The white suspension was then extracted exhaustively with EtOAc, the combined EtOAc layers were then dried and concentrated *in vacuo* to yield 0.370 g (98%) of the desired amide as colorless plates (CH_2Cl_2-pentane), m.p. 168–170°, ^1H NMR ($CDCl_3$) 7.7 (s, 1H), 6.84 (d, J = 10, 1H), 6.75 (m, complex, 2H), 4.27 (d, J = 4, 1H), 3.86 (s, 6H), 2.72 (ABq, J = 16, 2H), 1.96 (m, complex, 2H), 1.67 (m, complex, 2H); IR ($CHCl_3$) 3090 (w), 2918 (s), 2831, 1680 (vs), 1578 (w), 1500, 1460, 1350, 1190–1250 (m, broad), 1150, 1041; ^{13}C NMR ($CDCl_3$) 176.4, 149.2, 148.0, 137.8, 133.2, 124.6, 118.6, 118.4, 111.4, 111.3, 110.0, 56.09, 56.02, 55.8, 46.3, 44.5, 32.6, 22.0; *MS* (EI) 274.1 (M+), 273.1 (M − 1), 135.1 (P, M-vertryl). *Anal.*: ($C_{16}H_{19}NO_3$) C, H.

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