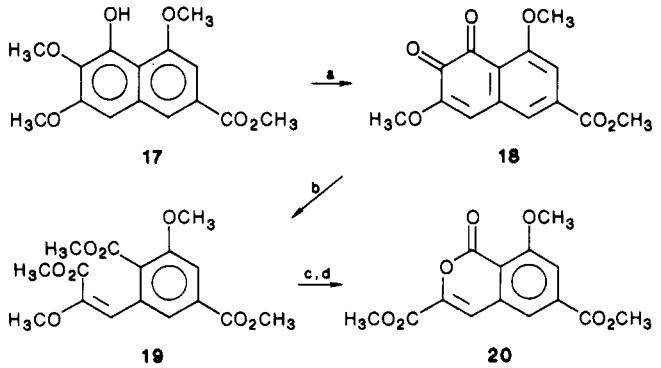

Reagents (a) $NaIO_4$, HOAc-H_2O (2/1 v/v); 0 °C, 6 min; 0-20 °C, 5 min; 22 °C, 18 min; (b) $Pb(OAc)_4$ (1.15 equiv), CH_3OH-benzene (1/1 v/v); 0 °C, 1.2 h; room temperature, 0.5 h; (c) HOAc/concentrated HCl (1/3 v/v), 4 h reflux; (d) CH_2N_2, CH_3OH.

however, was able to cleave simple benzoquinones to *cis*-muconic acid dimethyl esters using lead tetraacetate, and an earlier Italian paper[16] describes the use of the same reagent for the cleavage of phenanthraquinones and simple 1,2-diones. Thus we felt that this reaction might be applied to *o*-naphthoquinones despite the fact that $Pb(OAc)_4$ will oxidize[17] guaiacols (2-methoxyphenols) to the *p*-quinones. In any event our expectations were rewarded in that treatment of **18** in benzene–methanol with this reagent caused cleavage and afforded the triester **19** in 98% yield (mp 121–123 °C). Finally when the latter was heated under reflux with HCl/HOAc/H_2O the diacid corresponding to **20** was obtained (96%) (mp 307–310 °C), and this on brief treatment with diazomethane afforded the desired benzo-α-pyrone diester **20** in 75% yield (mp 248–249 °C). Further investigations of **12**, **16**, and **20** as synthons for the elaboration of the complete tetracyclic portion of the thermorubin molecule will be reported in subsequent papers.

Acknowledgment. We thank Dr. C. R. Iden for mass spectral data and R. Krant for secretarial assistance. We are grateful to the National Institutes of Health for a grant (AI 19709) which made this work possible.

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(15) Wiessler, M. *Tetrahedron Lett.* **1977**, *18*, 233.

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(17) (a) Teuber, H. J.; Rau, W. *Chem. Ber.* **1953**, *86*, 1036. (b) Wessely, F.; Kotlan, J. *Monatsh. Chem.* **1953**, *84*, 291.

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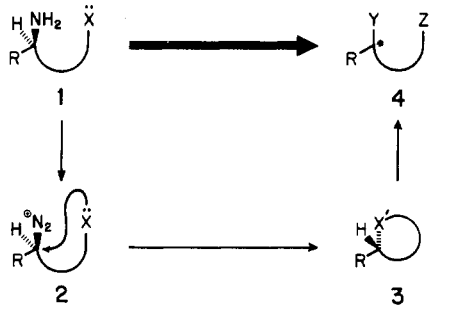
Sodium Nitroprusside Mediated Substitution of Oxygen for Nitrogen at Saturated Carbon Centers

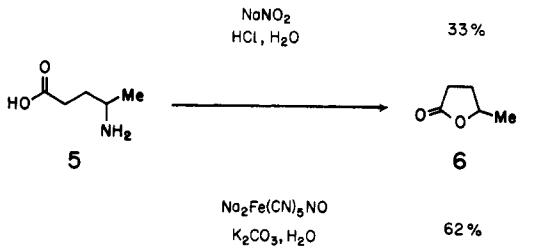
Summary: Sodium nitroprusside under mildly basic conditions has been found to effect the conversion of nitrogen to oxygen at saturated carbon centers.

Sir: Methodology for the stereocontrolled displacement of amines at saturated carbon centers is surprisingly limited, given the potential utility of such synthetic transformations.[1] The examples where these substitutions have been successful generally share several common features, including an amine activation step (i.e., **1** → **2**) followed by intramolecular displacement to give a cyclic species (**2** → **3**), which may be cleaved (**3** → **4**) to afford the product with either overall retention or inversion of configuration (Scheme I).[2] In connection with studies targeting the total synthesis of polyketide-derived natural products, we were interested in developing a method by which asymmetric amines, derived from readily available amino acids, could be utilized as synthetic precursors to asymmetric alcohols. We report herein that using sodium nitroprusside for the amine activation step of the scheme in Scheme I (**1** → **2**) offers a promising method for realizing the desired nitrogen → oxygen conversion.

Scheme I



When standard conditions for diazotization ($NaNO_2$, HCl, H_2O) were applied to model substrate **5**, the desired lactone **6** was afforded in 33% yield together with 24% of the pentenecarboxylic acids resulting from elimination of the diazonium ion intermediate.[3,4] We anticipated that



undesirable side reactions could be suppressed if participation by the carboxyl functionality was enhanced through deprotonation. With this in mind, our attention was drawn to sodium nitroprusside [$Na_2Fe(CN)_5NO$] as a result of its apparently unique ability to effect diazotization under basic conditions.[5,6] Our expectations were fulfilled when basic $Na_2Fe(CN)_5NO$ treatment led to a 62% yield of the

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(3) The acids were obtained as a 2:1 mixture of 3-pentenoic acid/4-pentenoic acid.

(4) All yields are reported subsequent to distillation or chromatographic purification.

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(6) $Na_2Fe(CN)_5NO$ mediates diazotization reactions up to pH 12.5. See ref 5a and references cited therein.

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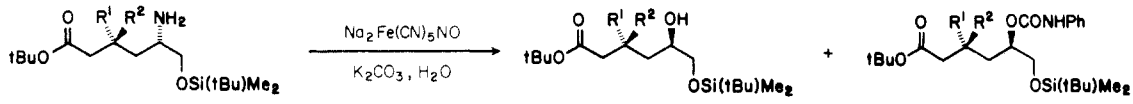
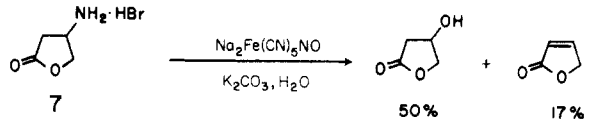
Scheme II



	YIELD		
21a: R¹=H, R²=OCONHPh	67 %	**22a**: R¹=H, R²=OCONHPh	**23a**: R¹=H, R²=OH
21b: R¹=OCONHPh, R²=H	83 %	**22b**: R¹=OCONHPh, R²=H	**23b**: R¹=OH, R²=H

desired product **6**, accompanied by less than 10% of the olefinic acid side products.[7]

The conspicuous decrease in products resulting from deprotonation, despite the basic conditions employed, prompted us to explore the scope of this reaction through an examination of substrates expected to favor elimination of the intermediate diazonium species. Thus, simple β-amino carbonyl compounds **7** and **8** were subjected to



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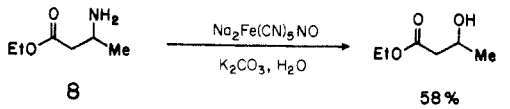

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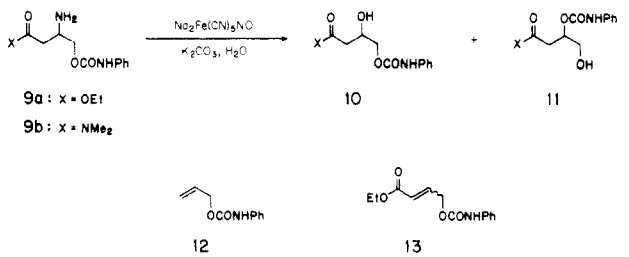
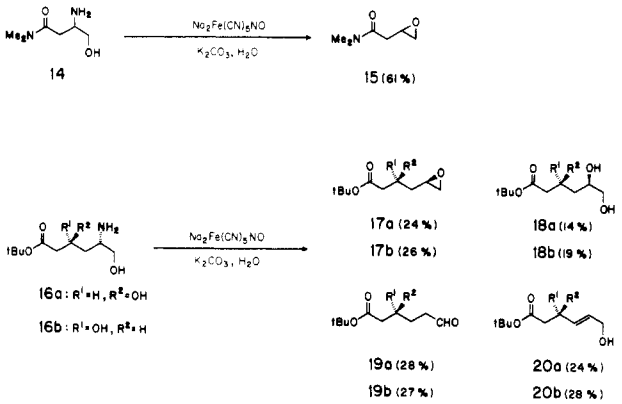
sodium nitroprusside diazotization with the surprising result that displacement of the amine remains the major reaction pathway.[8] As a consequence of these results a potentially valuable synthetic equivalency between aldol materials and β-amino carbonyl compounds becomes available.

In the hopes of ultimately conferring stereochemical control over the nitrogen replacement step, ester **8** was modified to include a suitable neighboring group participant (**9a**). This resulted in a significantly altered reaction course as ester **9a** produced a 1:1:2 mixture of products **10**, **11**, and **12**, respectively, in 68% yield with *no observable*



α,β-unsaturated ester **13**.[9] Reasoning that fragmentation product **12** results from hydroxide ion attack upon the ester carbonyl, the less electrophilic amide **9b** was similarly treated to afford *only* compounds **10** and **11** in 68% yield. These results underscore a remarkable preference for nucleophilic processes even under highly basic reaction conditions.

Toward pursuing our interest in applying this methodology to the synthesis of polyoxygenated natural products, amino alcohol **14** was subjected to the conditions of diazotization with the unexpected result of smooth epoxide formation (**15**).[10] Unfortunately, this cyclization exhibits



marked substrate dependency, as attempts to form the stereoisomeric epoxides **17a** and **17b** from amino alcohol precursors **16a** and **16b** demonstrates. Acting on the assumption that product mixtures **17a–20a** and **17b–20b** are attributable to inefficient participation by neighboring alcohol and ester functionality, a more potent internal nucleophile, in the form of a carbamate, was installed on an adjacent alcohol center (**21a/b**). This resulted in the restoration of clean substitution for nitrogen as 1:1 mixtures of carbamates **22a/23a** and **22b/23b** were obtained from amines **21a** and **21b**, respectively (Scheme II). These examples illustrate the manner by which a neighboring group participant can influence not only the course of the reaction in favor of substitution but also the stereochemical outcome of the transformation.[11,12]

While it is clear that further study is necessary to clarify the substrate structural requirements for smooth nitroprusside-mediated displacement of alkyl amines, this investigation serves to lay the groundwork for a broader examination of amine activation using metal–nitrosyl reagents.[13] As the scope and mechanistic details of sodium nitroprusside diazotizations are further probed, it is expected that many new intramolecular processes will become available that are triggered by this method of amine activation. Progress in this direction, as well as further exploitation of the synthetic equivalency of β-amino carbonyl substrates and aldol materials, will be reported in due course.

(7) Where possible, the products of these diazotization reactions were compared with authentic samples. Otherwise, the reaction products displayed satisfactory spectral and analytical characteristics.

(8) Under the conditions of isolation employed it was not possible to ascertain the amount of olefin, if any, formed from amino ester **8** due to its volatility.

(9) Presumably, products **10** and **11** arise from competitive collapse of a bridged intermediate resulting from carbamate participation in the displacement of the diazonium salt.

(10) To our knowledge, this is the first time a secondary amine has been cyclized to an epoxide through diazotization. See ref 1a.

(11) The stereochemistry of these products was revealed through comparison with independently synthesized samples of the biscarbamates derived from products **22a/23a** and **22b/23b**.

(12) Attempts to carry out this diazotization reaction on substrates with the CONHPh and Si(*t*-Bu)Me_2 substituents transposed in **21a** and **21b** were frustrated by competitive lactam formation prior to amine activation.

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A Concise Total Synthesis of (±)-Ipalbidine by Application of the Aldimine–Diene Cyclocondensation Reaction

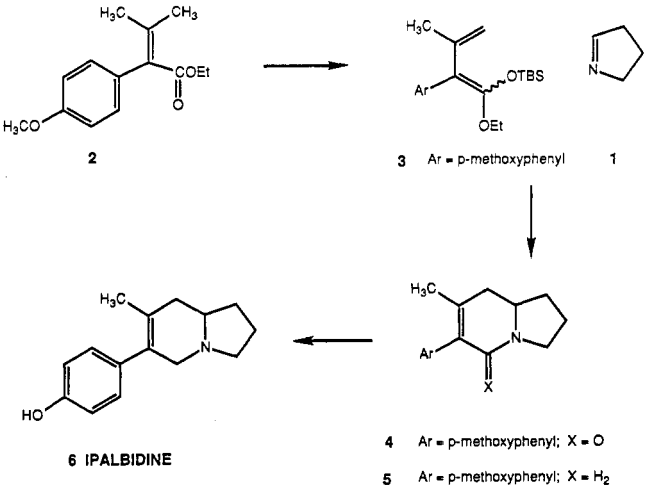
Summary: The scope of the diene–imine cyclocondensation reaction has been extended to the unstable Δ^1-pyrroline. Cyclocondensation of this compound with the silylketene acetal derived from ethyl 2-*p*-anisyl-3-methylcrotonate provides the basis for a rapid synthesis of (±)-ipalbidine.

Sir: Recently we described the Lewis acid catalyzed cycloaddition of siloxydienes with aldimines.[1] Prior to our work, examples of such reactions had been restricted to specially activated imines.[2,3] The use of highly nucleophilic dienes and Lewis acid catalysts allowed for extension of the process to a broad range of imines,[1] including dihydro-β-carboline.[4]

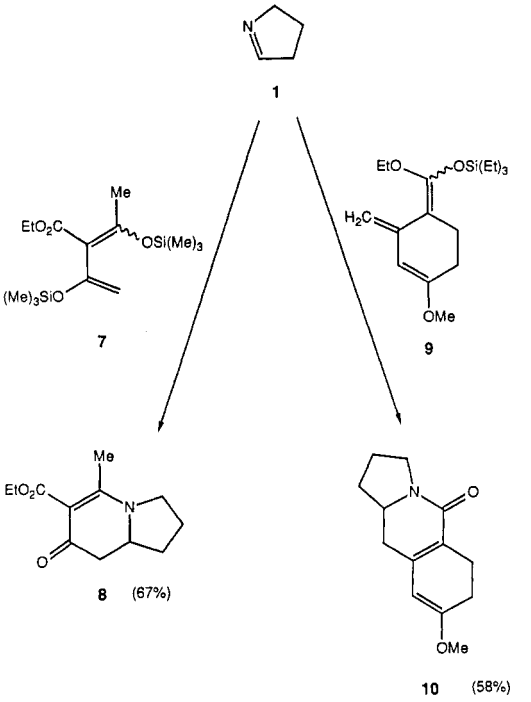
It was of interest to learn whether the parent Δ^1-pyrroline (**1**)[5] could participate in such cyclocondensations. If the reaction could be applied to imines of this type, it could have a major impact in the synthesis of various alkaloidal systems, many of which are of considerable current biological interest.[6] We report an affirmative finding regarding this question, in the context of a particularly straightforward synthesis of ipalbidine (**6**).[7]

Reaction of the known α-aryl-β-methylcrotonate derivative **2**[8] with lithium diisopropylamide in THF in the presence of HMPA, followed by quenching of the resultant ester enolate with *tert*-butyldimethylsilyl chloride afforded the silylketene acetal **3** in near quantitative recovery. Reaction of **3** with **1** in methylene chloride under the influence of BF_3 etherate (−78 °C → room temperature) affords a 40–45% yield of unsaturated lactam **4**, mp 141–142 °C. Reduction of this lactam to the hexahydroindolizine **5** was accomplished (73%) through reaction with $LiAlH_4$–$AlCl_3$. Demethylation of **5** via boron tribromide in methylene chloride afforded a 78% yield of (±)-ipalbidine (**6**), mp 149–150 °C (lit.[7] mp 149–150 °C). The assignment of the ipalbidine structure to the synthetic compound follows from comparison of its spectral properties with those previously reported.[7]

Compound **1** participates as the aldimine component with a variety of other activated dienes under Lewis acid catalysis. Two particularly interesting cases are shown.



Reaction of **1** with **7**[4,9] under the influence of zinc chloride in acetonitrile at room temperature produces vinylogous lactam **8**, mp 93–95 °C in 67% yield. Similarly, reaction of **1** with silylketene acetal **9**[4,10] in chloroform at room temperature (no catalysis) gives rise to lactam **10**, mp 126–128 °C in 58% yield.



These results are suggestive of a broad potential of the cyclic aldimine–diene cyclocondensation process. We are currently exploring its stereochemical ramifications in situations with substituents at the 4-position of the diene. We are also investigating the applicability of the reaction to more complex variations of compound **1**. It now seems likely that this reaction will play an important role in heterocyclic synthesis.

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