These results are to be compared with those obtained from the fragmentation reaction of 3-halo-2-cycloalken-1-ols[11] where a high reaction temperature was required; i.e., the present reaction proceeds smoothly at around room temperature. Furthermore, although a fragmentation reaction using arenesulfonyl moiety as a nucleofuge has been successfully applied to the synthesis of *dl*-muscone,[13] simple cyclohexanol derivatives, for example, 3-(phenylsulfonyl)cyclohexanol, did not undergo the expected C–C bond cleavage even under rather drastic conditions, e.g., treament with potassium *tert*-butoxide in refluxing toluene. The high efficiency of the phenylselenonyl moiety as a leaving group is again pointed out.

However, the present fragmentation reaction has important limitations. Employment of other nucleophiles such as active methylene compounds did not meet with alkylative fragmentation.

Registry No. 1, 79681-30-4; (*E*)-2, 79681-31-5; (*Z*)-2, 79681-32-6; 3, 79681-33-7; 5,5-dimethyl-3-(phenylselenonyl)-2-cyclohexen-1-ol, 79681-34-8; 1-butyl-3-(phenylselenonyl)-2-cyclopenten-1-ol, 79681-35-9; (*E*)-10-ethoxy-9-decen-5-one, 79681-36-0; (*Z*)-10-ethoxy-9-decen-5-one, 79681-37-1; 10-(phenylthio)-9-decen-5-one, 79681-38-2; (*E*)-7,7-dimethyl-10-methoxy-9-decen-5-one, 79681-39-3; (*Z*)-7,7-dimethyl-10-methoxy-9-decen-5-one, 79681-40-6; 7,7-dimethyl-10-(phenylthio)-9-decen-5-one, 79681-41-7; (*E*)-3,3-dimethyl-6-methoxy-5-hexanal, 79681-42-8; (*Z*)-3,3-dimethyl-6-methoxy-5-hexenal, 79681-43-9; (*E*)-9-methoxy-8-nonan-5-one, 79681-44-0; (*Z*)-9-methoxy-8-nonen-5-one, 79681-45-1; 1-butyl-2-methyl-3-(phenylselenonyl)-2-cyclohexen-1-ol, 79681-46-2; 1-butyl-3-(phenylselenonyl)-2-cycloocten-1-ol, 79681-47-3; 9-undecyn-5-one, 79681-48-4; 7,7-dimethyl-9-decyn-5-one, 61882-83-5; 11-dodecyn-5-one, 79681-49-5; sodium methoxide, 124-41-4; sodium ethoxide, 141-52-6; sodium benzenethiolate, 930-69-8; sodium hydride, 7646-69-7.

(13) Fischli, A.; Branca, Q.; Daly, J. *Helv. Chim. Acta* **1976**, *59*, 2443.

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Intramolecular Nitrile Oxide Cycloaddition (INOC) Reactions in the Indole Series. 2. Total Synthesis of Racemic and Optically Active Paliclavine and 5-*epi*-Paliclavine

Summary: The first total synthesis of the ergot alkaloid paliclavine and the formal total synthesis of paspaclavine in optically active form are described.

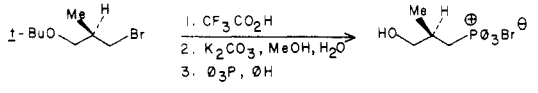
Sir: We have reported previously a synthesis of the ergot alkaloid chanoclavine I via the intramolecular [3 + 2] dipolar cycloaddition reaction of a nitrile oxide.[1] We now describe the first *total* synthesis of the related ergot alkaloid paliclavine[2] and one of its isomers, 5-*epi*-paliclavine, through a variant of this strategy. This work further underscores the versatility and generality of the nitrile oxide approach to the ergot alkaloids. We had chosen paliclavine as our second target primarily from the standpoint that its synthesis would require the preparation of an intermediate that could be used *ideally* to construct no fewer than six other naturally occurring ergot products (agroclavine, costaclavine, fumigaclavine, lysergine, pyroclavine, festuclavine, etc.).[3]

Our work began with the Wittig reaction of *N*-tosylindole-4-carboxaldehyde (1)[4] and the γ-oxidophosphorane **2**. The phosphonium salt precursor to **2** was prepared in both racemic form from methyl β-bromomethacrylate and in optically active form [$[\alpha]^{25}_D$ +0.1° (*c* 0.102, Me_2SO)] from the known (*R*)-(−)-3-*tert*-butoxy-2-methyl-1-bromopropane.[5] In Scheme I, only the optically active series is depicted. The Wittig condensation produced predominantly the trans olefin **3** (ratio *E*/*Z* = 12:1) as ascertained from ^{1}H NMR [*J* = 16 Hz; $[\alpha]^{25}_D$ −22.1° (*c* 0.080, $CHCl_3$)].

Protection of the hydroxyl group as its tetrahydropyranyl ether [DHP, pyridinium *p*-toluenesulfonate, CH_2Cl_2, 99%; $[\alpha]^{25}_D$ −13.1° (*c* 0.128, $CHCl_3$)], N-detosylation [KOH, MeOH, 99%; $[\alpha]^{25}_D$ −15.0° (*c* 0.139, $CHCl_3$)], and reaction of the indole with excess nitroethylene in the dark at room temperature[6] gave the 3,4-disubstituted product **4** [$[\alpha]^{25}_D$ −12.1° (*c* 0.201, $CHCl_3$)] in 53% yield. A three-step sequence consisting of phenyl isocyanate/triethylamine treatment (91%), N-acetylation (85%),[7] and Dowex 50 W-X8 assisted cleavage of the tetrahydropyranyl group (84%)[8] served to convert **4** to the isoxazoline alcohols **5a** and **6a**. We had hoped that as a consequence of the suggested operation of the anti-periplanar effect in the addition of electrophiles to π systems[9] the nitrile oxide would exhibit some selectivity in its addition to the olefinic appendage (see structure **4** in Scheme I). Unfortunately, the ratio of diastereoisomers was approximately 1.1:1 in the dipolar cycloaddition reaction. These could, however, be conveniently separated at a latter stage (vide infra).

From our various attempts to dehydrate the alcohols **5** and **6**, we discovered that it was best to carry out the dehydration prior to reduction of the isoxazoline, since the more basic nitrogen atom of the isoxazolidine interfered with the preparation of the various derivatives required to activate the hydroxyl group toward elimination. Rather curiously, our first attempt to dehydrate the isoxazoline alcohols **5b** and **6b** (in the racemic series) through their corresponding mesylates led not to the desired product but rather to the fully aromatic isoxazole **7** instead. To avoid this presumably base-assisted aromatization reaction, we sought a milder method for accomplishing the dehydration

(1) Kozikowski, A. P.; Ishida, H. *J. Am. Chem. Soc.* **1980**, *102*, 4265.
(2) (a) Tscherter, H.; Hauth, H. *Helv. Chim. Acta* **1974**, *57*, 113. (b) Fehr, T.; Stadler, P. A. *Ibid.* **1975**, *58*, 2484. (c) Acklin, W.; Fehr, T.; Stadler, P. A. *Ibid.* **1975**, *58*, 2492.
(3) For recent reviews on the ergot alkaloids, see: Kozikowski, A. P. *Heterocycles* **1981**, *16*, 267. Horwell, D. C. *Tetrahedron* **1980**, *36*, 3123. Floss, H. G. *Tetrahedron* **1976**, *32*, 873.
(4) Kozikowski, A. P.; Ishida, H.; Chen, Y. Y. *J. Org. Chem.* **1980**, *45*, 2236. The *N*-tosyl-protected indole was used in this reaction because it gave a higher yield of product than did the unprotected indole-4-carboxaldehyde.
(5) Cohen, N.; Eichel, W. F.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3505. The *tert*-butyl ether was cleaved by trifluoroacetic acid to yield the corresponding trifluoroacetate [$[\alpha]^{25}_D$ −0.22° (*c* 0.188, $CHCl_3$)]. Cleavage of the trifluoroacetate (K_2CO_3, MeOH, H_2O) gave the bromo alcohol [$[\alpha]^{25}_D$ −8.13 (*c* 0.21, $CHCl_3$)] which was reacted with triphenylphosphine in benzene to furnish the phosphonium salt precursor to **2**.



(6) Ranganathan, D.; Rao, C. B.; Ranganathan, S.; Mehrotra, A. K.; Iyengur, R. *J. Org. Chem.* **1980**, *45*, 1185. Exposure of the reaction to the laboratory lighting or sunlight resulted in lower yields as a consequence of free radical induced side reactions.
(7) Nickisch, K.; Klose, W.; Bohlmann, F. *Chem. Ber.* **1980**, *113*, 2036.
(8) Beir, R.; Mundy, B. P. *Synth. Commun.* **1978**, 272.
(9) Caramella, P.; Rondan, N. G.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2438.

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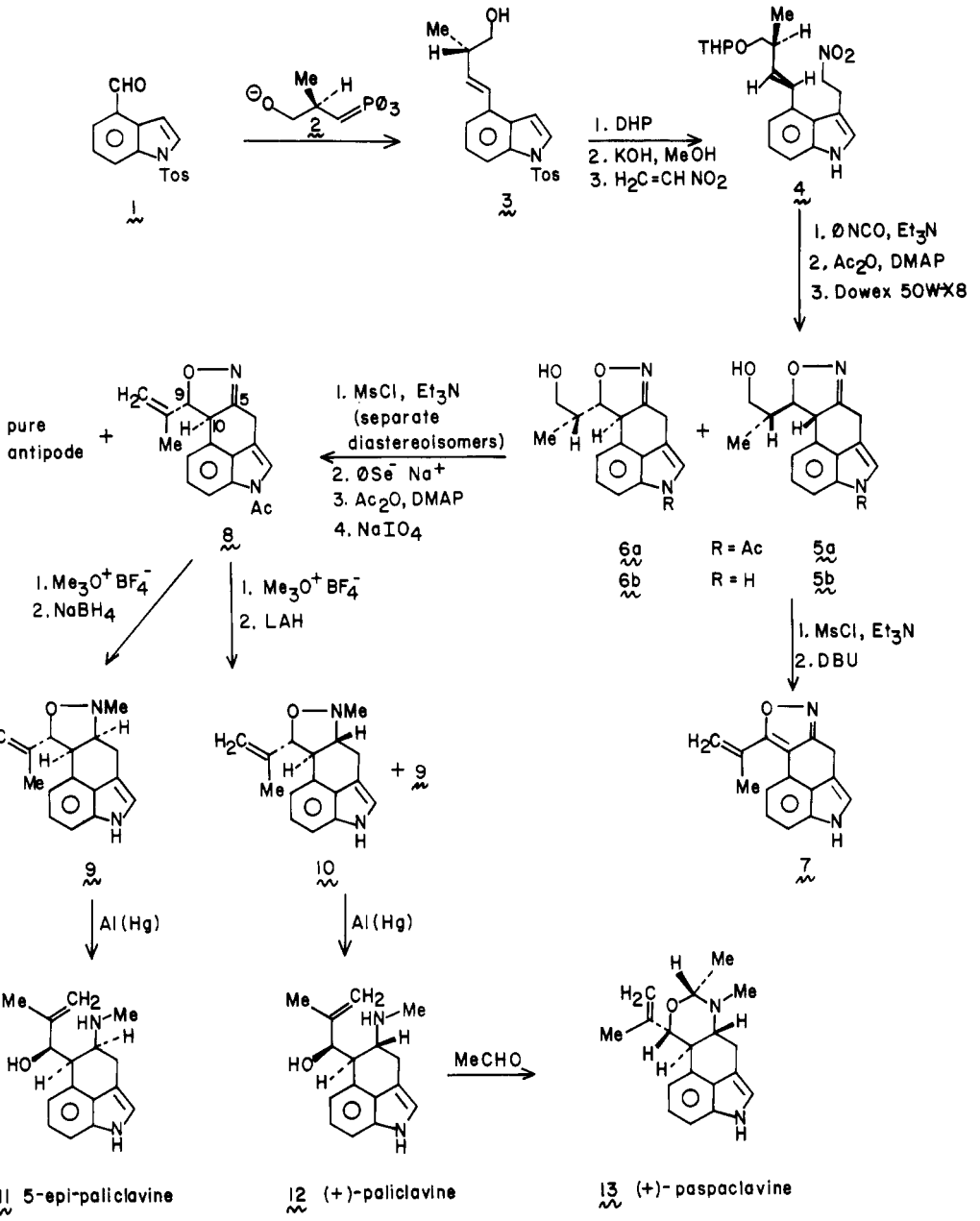
Scheme I. Synthesis of (+)-Paliclavine and 5-*epi*-Paliclavine



reaction. While the direct conversion of the alcohol to its selenide by the tri-*n*-butylphosphine/diphenyl diselenide method failed,[10] again perhaps because of the presence of the basic nitrogen atom, a somewhat more circuitous route involving mesylate formation (99%), displacement of the mesylate by the phenyl selenide anion (99%),[11] reacetylation (99%), and periodate oxidation–syn elimination (79%) afforded the desired olefin (none of the corresponding isoxazole could be detected).

This sequence also derived merit from the fact that the diastereoisomeric mesylates could be separated cleanly by column chromatography. Accordingly, after the selenoxide elimination, we had in hand optically pure **8** [mp 179 °C, $[\alpha]^{25}_D$ −184.8° (*c* 0.071, $CHCl_3$)] and its antipode [mp 179 °C, $[\alpha]^{25}_D$ +185.8° (*c* 0.068, $CHCl_3$)]. The Wittig reagent **2** had thus served as a very convenient resolving tool.

To complete the sequence, the isoxazoline **8** was N-methylated with Meerwein's salt, and the iminium ion was reduced with sodium borohydride (82% overall) to provide nearly a single stereoisomer. The reduction product was assumed to be, *however*, the C,D-cis-fused product **9**, for addition of hydride was anticipated to occur preferentially on the convex face of the molecule.

The isoxazolidine ring of **9** was cleaved by the action of aluminum amalgam in a 10:1 mixture of tetrahydrofuran and water (90%).[12] N,O-Diacetylation of **11** produced a more readily soluble derivative [$[\alpha]^{25}_D$ +81° (*c* 0.007, $CHCl_3$)] whose 300-MHz ^1H NMR spectrum failed to match that obtained for the *N,O*-diacetyl derivative of authentic paliclavine. We had indeed generated an isomer of paliclavine, 5-*epi*-paliclavine, in a highly stereoselective manner and thus confirmed our assumption about the convex face approach of borohydride in the reduction step.

Several possible schemes could be envisioned for ad-

(10) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.

(11) Liotta, D.; Markiewicz, W.; Santiesteban, H. *Tetrahedron Lett.* **1977**, 4365.

(12) Keck, G. E.; Fleming, S.; Nickell, D.; Weider, P. *Synth. Commun.* **1979**, *9*, 281.

justing the stereochemistry at C-5. This might involve, for example, epimerizing the amino group through a process related to that employed by Stork and Guthikonda in their yohimbine synthesis.[13] Alternatively, one could consider oxidizing the alcohol of the antipode corresponding to 11 to ketone, epimerizing the C-10 center, and then reducing ketone to the stereoinverted alcohol.

Since neither of these possibilities appeared especially attractive, we opted instead to simply vary the hydride agent used to reduce the isoxazolinium salt to isoxazolidine.[14] We hoped that by employing a reducing agent such as lithium aluminum hydride that would complex with the heterocyclic system, the C-9 substituent might better be able to exert its steric effect as a consequence of the tighter transition state. Reduction might then occur on the concave face of the molecule.[15] This did, in fact, prove to be the case. Although the cis-fused product **9** was still the major isomer of the lithium aluminum hydride reduction, a sufficient amount of the correct isomer was generated to complete the synthesis (ratio 2-3:1). Aluminum amalgam treatment of the mixture of **9** and **10**, chromatographic separation, and N,O-diacetylation of pure **10** gave an oil which was identical by TLC, IR, NMR, MS, and optical rotation [$[\alpha]^{25}_D$ -48.4° (*c* 0.0064, pyridine)] with the N,O-diacetylation product of natural (+)-paliclavine [$[\alpha]^{25}_D$ -49.6° (*c* 0.005, pyridine)].[16]

The work thus completes the first total synthesis of paliclavine, and does furthermore constitute the first total synthesis of a naturally occurring ergot alkaloid in optically active form. Since the reaction of (+)-paliclavine with acetaldehyde has been reported to yield (+)-paspaclavine (**13**),[2a] the synthesis of paliclavine does also constitute a total synthesis of the latter ergot alkaloid as well. The use of intermediate **5a** in the preparation of other ergot alkaloids as well as improvements in stereocontrol at C-5 are being examined.[17]

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(13) Stork, G.; Guthikonda, R. N. *J. Am. Chem. Soc.* **1972**, *94*, 5109.
(14) Yet another possibility would be to use a reducing agent that would cleave the N–O bond of the isoxazoline first and then effect reduction of the C–N bond. Sodium in ethanol is known to operate in this fashion. At present, however, we have not been able to obtain desirable products from this reduction procedure. See, for example, Jäger, V.; Buss, V. *Justus Liebigs Ann. Chem.* **1980**, 101.
(15) Reduction of isoxazolines by lithium aluminum hydride is believed to involve Li···O complexation during hydride transfer, see: Jäger, V.; Buss, V.; Schwab, W. *Justus Liebigs Ann. Chem.* **1980**, 122.
(16) We thank Dr. W. Acklin of the Eidgenössischen Technischen Hochschule and Dr. P. A. Stadler and Dr. T. Fehr of Sandoz Ltd. for generous samples of authentic paliclavine.
(17) All new compounds reported gave satisfactory spectral and analytical data or correct high-resolution mass spectral values for the molecular ion. The optical rotations were measured on a Perkin-Elmer 241 polarimeter.

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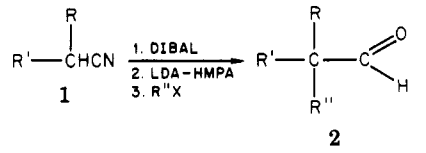
Direct Conversion of Nitriles to α-Alkylated Aldehydes

Summary: An efficient one-pot process for direct conversion of primary and secondary nitriles to α-alkylated aldehydes has been developed.

Sir: We report a simple general method for direct conversion of primary and secondary nitriles (**1**) to α-alkylated aldehydes (**2**). This three-step one-pot synthesis is outlined by eq 1. Results of some applications of this method are presented in Table I. These reactions were carried out on 10–20-mmol scales and yields are for isolated pure products.



(1)

In most cases this synthesis offers important advantages over alternate routes to α-alkylated aldehydes with regard to availability of starting material, scope, convenience, and yield. Other methods include direct[1] and indirect[2-4] alkylation of aldehydes. Direct alkylation has been successful in certain cases; however, this method is very limited because of side reactions (viz.) self-condensation and O-alkylation).[1] Moreover, overalkylation can not be avoided if the aldehyde has two α-hydrogen atoms.[1b] Indirect methods that avoid these complications involve alkylation of imine[2,3] or hydrazone[4] derivatives of aldehydes. Alkylation of aldehydes via imines is a general method and has been used to prepare a number of alkylated aldehydes.[2] However, overall yields for the two steps are usually modest and the parent aldehyde is required. Modifications of this two-step process,[3] including a one-pot version,[3b] appear to offer little advantage over the original procedure.[2]

Aldehydes with two α-alkyl (or aryl) groups can be prepared from glycidic esters.[5] However, overall yields for preparation of glycidic esters and subsequent conversion to aldehydes are poor, and the method is limited to aldehydes with no more than two α-substituents.[5] Other routes to α-alkylated aldehydes include syntheses based on the dihydro-1,3-oxazine[6] and 2-thiazoline systems.[6] In general, these elegant aldehyde syntheses are not convenient for preparation of α-alkylated aldehydes.

The present method starts with generally readily available nitriles and gives good results with both primary and secondary nitriles (including cyclic nitriles, experiments 9 and 10) without complications from side reactions such as overalkylation or N-alkylation.[7] The first step involves treatment of the nitrile with diisobutylaluminum hydride (DIBAL) to form an aluminum imide (**3**). This reaction is very rapid in hexane at 0 °C. In experiment

(1) (a) Dietl, H. K.; Brannock, K. C. *Tetrahedron Lett.* **1973**, 1273. (b) Groenewegen, P.; Kallenberg, H.; Van der Gen, A. *Ibid.* **1978**, 491.
(2) (a) Stork, G.; Dowd, S. R. "Organic Syntheses"; Wiley: New York, 1974; Vol. 54, p 46. (b) Stork, G. U.S. Patent 3 230 216, 1966.
(3) (a) Cuvigny, Th.; Normant, H. *Bull. Soc. Chim. Fr.* **1970**, 3976. Curphey, T. J.; Hung, J. C.-Y. *Chem. Commun.* **1967**, 510. (b) Ho, T.-L.; Wong, C. M. *Synth. Commun.* **1974**, *4*, 147.
(4) Enders, D.; Eichenauer, H. *Tetrahedron Lett.* **1977**, 191.
(5) (a) Newman, M. S. "Organic Reactions"; Wiley: New York, 1949; Vol. 5, p 413. (b) Allen, C. F. H.; Van Allen, J. "Organic Syntheses", Collect. Vol. 3; Wiley: New York, 1955; p 733.
(6) Meyers, A. I. "Heterocycles in Organic Synthesis"; Wiley: New York, 1974; pp 201-212.
(7) Nitriles can also be converted to aldehydes directly by alkylation of the nitrile followed by reduction with DIBAL. However, with this sequence, overalkylation of primary nitriles is a serious side reaction.

0022-3263/81/1946-5250$01.25/0