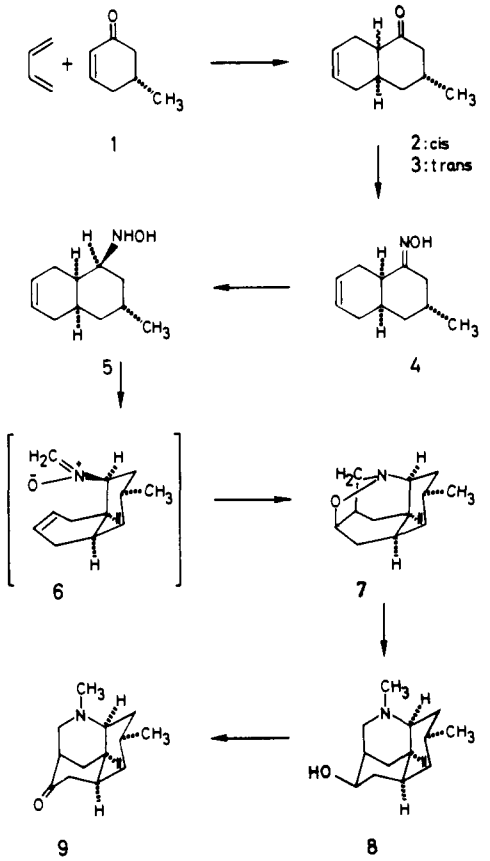
Scheme II



The first step of our synthesis (Scheme II) consisted in the reaction of butadiene in the presence of 1.0 equiv of $SnCl_4$ in dry CH_3CN[6a] with 5-methylcyclohexenone, **1**.[7] Addition took place exclusively from the side opposite to the methyl substituent to give a 3:2 mixture of the *cis*-octalone, **2**, together with its trans-isomer **3**.[8-10] Oximation of this mixture (26 mmol) with hydroxylamine hydrochloride (31 mmol) in aqueous ethanol, followed by chromatography on silica gel furnished the cis-oxime **4**[9] (mp 143–145 °C; 40%). It was noticed that the *cis*-octalone **2** reacted faster with hydroxylamine than its trans isomer **3**. Consequently the reaction of the mixture of **2** and **3** with a stoichiometric amount (relative to **2**) of hydroxylamine hydrochloride and NaOAc in methanol enabled the pure cis-oxime **4** to be separated from unchanged trans-ketone **3**[11] by simple crystallization from isopropyl alcohol. Reduction[12] of the oxime **4** with 2 equiv of $NaBH_3CN$ in methanol[6b] afforded exclusively the hydroxylamine **5**[9] (mp 133–135 °C; 100%). Heating of **5** with 5 equiv of paraformaldehyde in the presence of molecular sieve in toluene[6c] gave the bridged isoxazolidine **7**[9] as an oil (70%). This transformation presumably involves a transient nitrone, **6**, which undergoes a highly regioselective intramolecular addition to a nonpolarized olefinic bond. Not even a trace of the corresponding positional isomer (isomer D in Scheme I) was found in the reaction mixture. Methylation of the adduct **7** with 1.5 equiv of methyl fluorosulfonate in ether,[6d] followed by reduction of the resulting salt with $LiAlH_4$[6e] gave the alcohol **8**[10,13] (mp 75–77 °C; 97%). Oxidation of **8** with Jones' reagent furnished the hydrochloride of the racemic alkaloid **9** (mp 238–240 °C, sealed capillary, reported mp 171–172 °C;[5] 98%). The free base **9** was identified by comparison of its ir, ^1H NMR, and mass spectra as well as its TLC and GC behavior with those of natural *d*- and synthetic *d,l*-luciduline.

A key feature of our approach is that during the conversion of **1** to **9** the original chiral center largely controls the developing configurations of the four other chiral centers. It may be further pointed out that this synthesis nicely illustrates the utility of intramolecular additions of *N*-alkenylnitrones as an equivalent of the Mannich reaction. The scope of the thermal reaction of *N*-alkenylhydroxylamines with aldehydes is presently being explored by using a variety of model compounds.

Acknowledgment. We are grateful to Professor D. A. Evans, California Institute of Technology, for kindly providing a sample of *d,l*-luciduline. We thank the Fonds National Suisse de la Recherche Scientifique, Sandoz Ltd, Basel, and Givaudan SA, Vernier for financial support of this work.

References and Notes

(1) N. A. LeBel, M. E. Post, and J. J. Whang, *J. Am. Chem. Soc.*, **86**, 3759 (1964); W. Oppolzer and K. Keller, *Tetrahedron Lett.*, 1117, 4313 (1970); for a recent review on intramolecular 1,3-dipolar additions see A. Padwa, *Angew. Chem., Int. Ed. Engl.*, **15**, 123 (1976).
(2) The regio- and stereoselective thermolysis of *N*-but-3-enyl-*C*-phenylnitrone (prepared from butenyl iodide and benzaldoxime) has been reported by W. C. Lumma, Jr., *J. Am. Chem. Soc.*, **91**, 2820 (1969), for an internal addition of 5-allyl-3,3,5-trimethyl-1-pyrroline 1-oxide see J. B. Bapat, D. S. C. Black, R. F. C. Brown, and C. Ichlov, *Aust. J. Chem.*, **25**, 2445 (1972).
(3) For the related reaction of *N*-acyl-*N'*-alkenylhydrazines with aldehydes see W. Oppolzer, *Tetrahedron Lett.*, 1707 (1972).
(4) W. A. Ayer, N. Masaki, and D. S. Nkunika, *Can. J. Chem.*, **46**, 3631 (1968).
(5) W. L. Scott and D. A. Evans, *J. Am. Chem. Soc.*, **94**, 4779 (1972).
(6) (a) The addition was carried out in a silylated Pyrex flask at 25 °C for 6–24 h; (b) at pH 3 at 25 °C for 1 h; (c) in a closed flask at 115 °C for 14 h; (d) at 0 °C for 1 h; (e) in THF at 25 °C for 5 h.
(7) H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, **33**, 949 (1968).
(8) The addition of butadiene to 5-methylcyclohexenone in presence of BF_3–etherate in benzene has been reported to furnish a 1:5 mixture of **2** and **3**, which are interconvertible by base: T. Harayama, H. Cho, M. Ohtani, and Y. Inubushi, *Chem. Pharm. Bull.*, **22**, 2784 (1974).
(9) Ir, ^1H NMR, and mass spectra are in full agreement with the assigned structure.
(10) Analyzed by GC using a steel column 12 ft × ⅛ in., 5% FFAP on 60–100 mesh chromosorb W; 170 °C; 24 kg of N_2/cm^2; **2**, retention time 14.2 min; **3**, retention time 16.5 min.
(11) For recycling of the trans-ketone **3** to the desired cis-ketone **2** see ref 8.
(12) R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, **93**, 2897 (1971).
(13) **8** displayed identical ^1H NMR and mass spectra as the alcohol obtained by reduction of natural luciduline with $NaBH_4$; see ref 4.

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A Total Synthesis of Gliotoxin

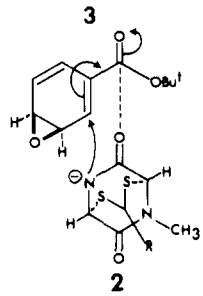
Sir:

Gliotoxin **1**,[1] an antibiotic produced by various species of *Gladiocladium, Trichoderma, Aspergillus,* and *Penicillium,* presents a formidable challenge to synthetic chemists. Difficulties in controlling stereochemistry as well as functionality are accumulated in this small molecule. Four asymmetric centers in addition to two delicate ring systems—hydrated benzene and epidithiapiperazinedione—are present. We would like to report the first total synthesis of gliotoxin, using a novel solvent-dependent Michael reaction as a key step.

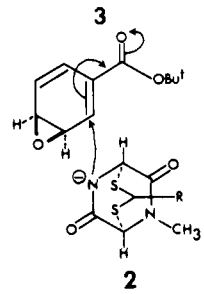
The thioacetal **2**[2,3] (mp 250–252 °C) was synthesized from glycine sarcosine anhydride in six steps[4] in 30% overall yield by the method previously reported.[5] Michael reaction of 4-carbo-*tert*-butoxybenzene oxide **3**[6] (excess) with **2** in methylene chloride containing Triton B at room temperature for a short period afforded the alcohol **4**[3] (mp 217–218 °C dec) as the major product (45% yield) and the epimeric alcohol **5**[3] (mp 255–257 °C dec) as the minor product (15% yield). The ratio of alcohols **4** and **5** produced in this Michael reaction was found to be dependent on the solvent and the time of reaction. A 3:1 ratio (88% yield) favoring the alcohol **5**, the minor

product in CH_2Cl_2–Triton B, was finally realized in dimethyl sulfoxide containing Triton B at room temperature for a short period. Retro-Michael reaction was observed with alcohols **4** and **5** in CH_2Cl_2 or Me_2SO in the presence of Triton B. Thus, an approximate 1:1 mixture of the alcohols **4** and **5** resulted from either **4**, or **5**, or **2** on Triton B treatment in CH_2Cl_2 or Me_2SO in the presence of **3** (excess) overnight.

Since overall trans-opening of the epoxide ring is expected for **3**,[7] alcohols **4** and **5** must be the epimers regarding the relative configuration of the thioacetal bridge and the alcoholic group. Two probable orientations A and B—note *d,l*-thioacetal **2** and *d,l*-benzene oxide **3**[8] are used—are considered for the transition state of the Michael reaction, when **2** and **3** approach in such a way as to cause the least steric hindrance. Interestingly, the favorable dipole interaction involved in A should make it preferred to B in nonpolar solvents such as methylene chloride. Thus, the desired stereochemistry was tentatively assigned to the alcohol **5** and the undesired stereochemistry to the alcohol **4**.[9] The importance of such a dipole interaction in the transition state determining the stereochemistry of the Robinson annelation is known in several cases.[10]



A

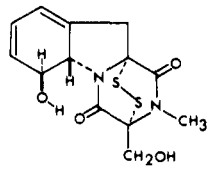


B

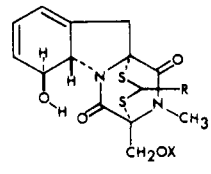
The alcohol **5** was converted to the acetate **6**[3] (mp 195–196 °C, Ac_2O/Py/room temperature; 90% yield) and then to the hydroxymethyl derivative **7**[3] (mp 181–182 °C) in three steps (1, TFA/room temperature; 2, $ClCO_2Et/Et_3N$-CH_2Cl_2/room temperature; 3, $NaBH_4/CH_3OH$-CH_2Cl_2/0 °C) in 70% overall yield. Mesylation of **7** ($MsCl/Et_3N$-CH_2Cl_2/room temperature), followed by lithium chloride treatment in DMF[11] and then hydrolysis ($NaOCH_3/CH_3OH$-CH_2Cl_2/room temperature), gave the chloride **8**[3] (mp 200–201 °C) in 95% overall yield.

Phenyllithium, slowly added to a mixture of **8** and chloromethyl benzyl ether (excess) in THF at −78 °C with monitoring by TLC, gave the benzylgliotoxin anisaldehyde adduct **9**[3] (mp 210–212 °C), which was isolated in 45% yield.[12] Boron trichloride treatment of **9** in CH_2Cl_2 at 0 °C furnished the gliotoxin anisaldehyde adduct **10**[3] (mp 241–242 °C) in 50% yield.[13] *m*-Chloroperbenzoic acid oxidation of **10**, followed by perchloric acid treatment in methylene chloride at room temperature,[5] yielded *d,l*-gliotoxin **1**[3] (mp 165–166 °C) in 65% yield. Synthetic substance was identical with natural gliotoxin[14] by spectroscopic (NMR, ir, uv, MS) and TLC comparison.

Further efforts to the synthesis of an optically active form of gliotoxin and a biogenetic-type approach toward the toxin are in progress in our laboratories.[15]

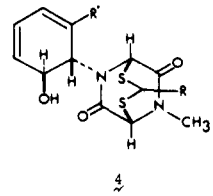


1 : gliotoxin

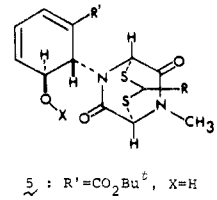


9 : X=$CH_2C_6H_5$

10 : X=H



4



5 : R'=CO_2Bu^t, X=H

6 : R'=CO_2Bu^t, X=Ac

7 : R'=CH_2OH, X=Ac

8 : R'=CH_2Cl, X=H

R=$C_6H_4OCH_3$-*p*

References and Notes

(1) See, for example, The Merck Index 8th ed, Merck & Co., Ltd., Rahway, N.J., 1968, p 491, and references therein.

(2) The anti-series[4] with respect to the anisaldehyde residue and the NH group is used to describe the properties of the intermediates in this paper. Results parallel to the anti-series were obtained on the syn-series as well.

(3) Satisfactory spectroscopic (MS, NMR, ir, uv) data were obtained on this substance.

(4) Six steps were 1, $ClCH_2OCH_3$/*t*-BuOK/*t*-BuOH; 2, NBS/$(C_6H_5CO_2)_2$/CCl_4; 3, KSAc/CH_2Cl_2; 4, HCl/CH_3OH; 5, *p*-$CH_3OC_6H_4CHO/BF_3$-Et_2O/CH_2Cl_2; and 6, concentrated HCl/EtOH. The product was a mixture of anti- and syn-thioacetal **2** with respect to the anisaldehyde residue and the NH group. Chromatographic separation of the mixture was performed on the *N*-benzoyl derivative of **2**. Pure anti-thioacetal **2**[3] (mp 250–252 °C) and syn-derivative[3] (mp 249–251 °C) were obtained by ammonolysis of the separated *N*-benzoate. The stereochemical assignment was concluded by converting **2** into *N*-methyl-*C*-monomethyl derivative of **2** and comparing with the authentic sample.[5]

(5) Y. Kishi, T. Fukuyama, and S. Nakatsuka, *J. Am. Chem. Soc.*, **95**, 6490, 6492 (1973); Y. Kishi, S. Nakatsuka, T. Fukuyama, and M. Havel, *ibid.*, **95**, 6433 (1973); S. Nakatsuka, T. Fukuyama, and Y. Kishi, *Tetrahedron Lett.*, 1549 (1974); K. Sasaki, T. Fukuyama, S. Nakatsuka, and Y. Kishi, *J. Chem. Soc., Chem. Commun.*, 542 (1975).

(6) R. M. DeMarinis, C. N. Filer, S. M. Waraszkiewicz, and G. A. Berchtold, *J. Am. Chem. Soc.*, **96**, 1193 (1974).

(7) 1,6-Nucleophilic addition of CH_3O^- and HO^- to **3** is known to result the overall trans-opening of the epoxide ring.[6]

(8) The presence of the benzene oxide valence isomer was demonstrated by various reactions on **3**, although **3** exists predominantly as the oxepin form in solution.[6]

(9) This assignment was confirmed from the fact that the alcohol **5** yielded *d,l*-gliotoxin, while the alcohol **4** gave epigliotoxin regarding the configuration of the sulfur bridge. Detail results in the epi-series will be reported in the full paper.

(10) C. J. V. Scanio and R. M. Starrett, *J. Am. Chem. Soc.*, **93**, 1539 (1971), and references therein.

(11) The intermediate (R' = CH_2Cl, X = Ac in structure **8**; mp 179–180 °C) was isolated at this stage.

(12) A stepwise procedure,[5] i.e., 1, $C_6H_5CH_2OCH_2Cl/BuLi/THF$; 2, PhLi/THF, gave less satisfactory results.

(13) At this stage, the synthetic gliotoxin anisaldehyde adduct **10** was found to be identical with the authentic substance, prepared from natural gliotoxin[14] in two steps (1, $NaBH_4/CH_3OH$-CH_2Cl_2; 2, *p*-$CH_3OC_6H_4CHO/BF_3$-Et_2O/CH_2Cl_2).

(14) We are indebted to Dr. R. Nagarajan, Eli Lilly Company, for providing a sample of natural gliotoxin.

(15) Financial assistance from National Institutes of Health, Harvard University, and Hoffmann-La Roche Company is gratefully acknowledged.

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Organocobalt Cluster Complexes. 20. Novel Chemistry of Acyl- and Aroylmethylidynetricobalt Nonacarbonyl Complexes. Unusual Thermal Ketone Decarbonylation Reactions[1]

Sir:

Acyl- and aroylmethylidynetricobalt nonacarbonyl complexes, I, are readily available by reaction of the appropriate