2 H, C(3)*H*, SCH_2CH), 3.24–2.62 (2 AB parts of ABX spectrum, 4 H, C(4)H_2, SCH_2CH), 1.62 (t, J = 8.0 Hz, 1 H, S*H*), 1.27 (t, 3 H, OCH_2CH_3).

Registry No. **5a**, 106268-32-0; **5b**, 106268-38-6; **6b**, 534-15-6; **6c**, 1125-88-8; **7b**, 106268-33-1; **7c**, 106268-35-3; **7d**, 106268-50-2; **8b**, 106268-34-2; **8c**, 106268-36-4; **8d**, 106268-37-5; **9a**, 89093-55-0; **9b**, 106268-40-0; (±)-**10a**, 106268-41-1; (±)-**10b**, 106268-44-4; (±)-**10c**, 106268-47-7; (±)-**11a**, 106268-42-2; (±)-**11b**, 106268-45-5; **11c**, 106268-48-8; **12a**, 106268-43-3; **12b**, 106268-46-6; **12c**, 106268-49-9; *S*-(*p*-methoxybenzyl)-*N*-(benzyloxycarbonyl)cysteine methyl ester, 106268-39-7.

Application of an Isoxazolidine in a Stereoselective Approach to the Fumitremorgin Series†

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Reduction of the isoxazolidine **5** provides **7**, which was coupled with the N-protected proline derivative **8**. Subsequent deprotection of the amino group affords **11** which undergoes ring closure and dehydration to yield **6** in good yield. The ^{1}H NMR spectrum of **6** compares unfavorably with that of fumitremorgin C (**1**), indicating that **6** may be the C(14a) epimer of the natural product.

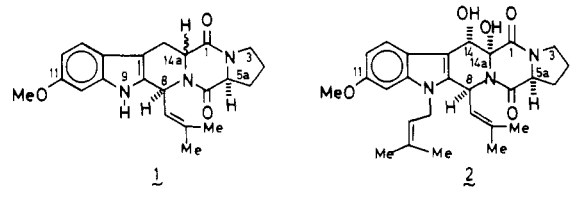
Introduction

Increased research on mycotoxins, in general over the past 15 years, has led to the discovery of fungal metabolites capable of eliciting sustained or intermittent tremors in vertebrate animals.[1-10] All of these tremorgenic mycotoxins, which share an indole moiety as chemical feature, can be conveniently classified into four groups on the basis of structural relationships. The compounds of one of these groups—the fumitremorgin–verruculogen group, two members of which are given in Scheme I—contain three nitrogen atoms per molecule and are biosynthetically derived from tryptophan, proline, and one or more mevalonic acid moieties.[4] In efforts to determine the mode of action of fungal tremorgins, it has become apparent that they provide valuable tools in the study of central nervous system functions.[11-14] Although particular molecular features responsible for tremorgenic activity in the fumitremorgin–verruculogen group have not been completely identified, there are indications that the conformation and configuration of the dioxopiperazine moiety affects tremorgenic activity.[14]

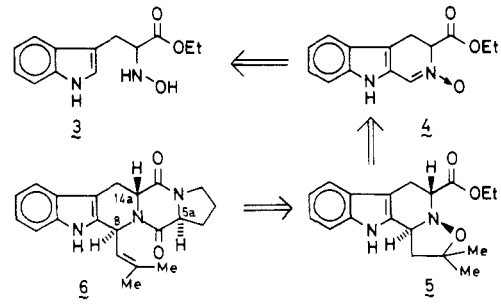
We became interested in the fumitremorgins as attractive synthetic targets because of their biological activity and unique structure. The first target we settled upon was fumitremorgin C (**1**).[1,2,4,6] The structure of this fumitremorgin, as first reported in 1977,[2] contains three chiral carbon atoms. The absolute configuration at C(5a) and C(8) is as depicted in formula **1**.[2-10] The stereochemistry at C(14a) has not been ascertained[15] and at least in one literature report[5] the C(8)-substituent has been presented as being a saturated, tertiary alcohol.

Thus, the total synthesis of fumitremorgin C is desirable for at least two reasons. First, a synthesis would confirm the assigned structure and would allow the chirality to be determined. Second, an efficient synthesis of fumitremorgin C constitutes a challenge, because of its unique structure. Despite some attempts at fumitremorgin synthesis,[16-20] no member of this class of compounds has yet been synthesized. Recently we evaluated the cycloaddition chemistry of nitrone **4**, obtained from the *N*-hydroxy-

Scheme I



Scheme II



† Dedicated to J. H. Ottenheijm, on the occasion of his 65th birthday.

‡ Department of Organic Chemistry.

§ Department of Crystallography.

(1) For the isolation report of fumitremorgin C—also called SM-Q—see: Cole, R. J.; Kirksey, J. W.; Dorner, J. W.; Wilson, D. M.; Johnson, J. C.; Johnson, A. N.; Bedell, D. M.; Springer, J. P.; Chexal, K. K., Clardy, J. C.; Cox, R. H. *J. Agric. Food Chem.* **1977**, *25*, 826.

(2) Cole, R. J. In *Mycotoxins in Human and Animal Health*: Pathotoxicology: Park Forest South, IL 1977; p 583.

(3) Moreau, C. *In Moulds*, Toxins *and Food*; Wiley: Chichester, England 1979; p 301.

(4) Yamazaki, M. In *Biosynthesis of Mycotoxins*; Steyn, P. S., Ed.; Academic: London, 1980; p 204 and references cited therein.

(5) Milczewski van, K. E.; Engel, G.; Teuber, M. In *Mycotoxine in Lebensmitteln*; Reiss, J., Ed.; G. Fischer Verlag: New York, 1981; p 44.

(6) Cole, R. J.; Cox, R. H. *Handbook of Toxic Fungal Metabolites*; Academic: London, 1981; p 355.

(7) Cole, R. J. *J. Food Prot.* **1981** *44*, 715.

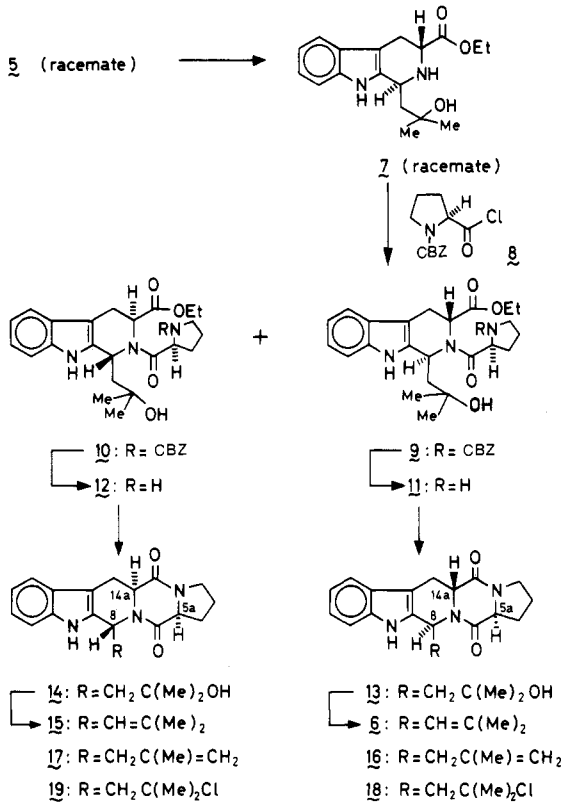
(8) Cole, R. J. In *Antinutrients and Natural Toxicants in Foods*; Ory, R. L., *Ed.*; Food and Nutrition: Westport, CT, 1981; p 17.

(9) Steyn, P. S.; Vleggaar, R.; Rabie, C. J. *Phytochemistry* **1981**, *20*, 538.

(10) Steyn, P. S.; Vleggaar, R. In *Fortschritte der Chemia organischer Naturstoffe*; Herz, W., Grisebach, H., Kirby, G. W., Tamm, Ch., Eds.; Springer Verlag: Wien, 1985; Vol. 48, p 1.

0022-3263/87/1952-0560$01.50/0

Scheme III



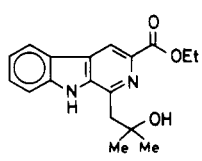
tryptophan ester **3** and methyl orthoformate[21] (Scheme II). 1,3-Dipolar cycloaddition of isobutene proceeded regio- and stereoselectively to give quantitatively the isoxazolidine **5**.

This report highlights the fact that the cycloadduct **5** can serve as an intermediate for the stereoselective synthesis of the fumitremorgin C analogue **6**. We have evidence, though inconclusive, that analogue **6** is the C(14a) epimer of fumitremorgin C.

Results

1-Alkyl-1-1,2,3,4-tetrahydro-β-carboline-3-carboxlic acid derivatives have been prepared previously by the Pictet–spengler reaction of tryptophan derivatives and appropriate aldehydes.[22] This reaction fails, however, when β-hydroxy or α,β-dehydro aldehydes are employed.[19] Accordingly, we felt that use of **5**—a masked β-hydroxy aldehyde—might circumvent the use of such aldehydes. Of critical importance to the successful employment of **5** was the ability to reduce the N–O bond of the isoxazolidine ring.

The isoxazolidine moiety of **5** is remarkably stable and withstood prolonged treatment with conventional reagents used for related reactions. Compound **5** was recovered quantitatively after treatment with aluminum amalgam,[23] Raney nickel,[23] and a variety of hydrogenation catalysts at 70 psi. These failures are probably due to steric hindrance caused by the geminal methyl groups. The reagent of choice for the anticipated reduction appeared to be zinc dust in acetic acid at elevated temperature (50 °C). Formation of compound **7** (Scheme III)—isolated in 85% yield—is often accompanied by up to 10% of the β-carboline derivative **20**.



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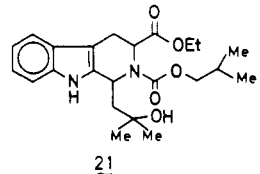

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Subsequently, the projected scheme called for coupling the racemate of **7** with *N*-(benzyloxycarbonyl)-L-proline. Activation of the latter with dicyclohexylcarbodiimide-(DCC) and 1-hydroxybenzotriazole (HOBT) failed to give a coupling product. When the mixed anhydride method was employed, using isobutyl chloroformate,[24] the only product isolated was the urethane **21**. Coupling was achieved efficiently by employing acid chloride **8**, which can be prepared without racemization.[25] In order to retain the homochirality of **8** during the coupling procedure, amine **7** and triethylamine were added dropwise together to a cooled (−20 °C) solution of an excess of **8**. That no racemization took place, is shown below. This procedure provided (82% yield) amines **9** and **10** (ratio 2:3); to our satisfaction the alcohol function of **7** was not affected by **8**. Formation of **10** in slight excess over **9** might be rationalized by kinetic resolution of **7** and concomittant partial decomposition of **8**. The occurrence of kinetic resolution in this reaction was made acceptable by the following experiment.

Racemic **7** was coupled with a mixture of D- and L-CBZ-Pro-Cl (ratio 3:2). The resulting diasteromers were separated and converted (vide infra) separately into the corresponding dioxopiperazines **13** and **14** (both partially racemic). The product ratio was found to be 5:95, indicating that kinetic resolution had occurred indeed. The ratio of enantiomers present in **13** and **14** was found to be 3:2 in both cases as established by ^{1}H NMR spectroscopy using a chiral shift reagent. This ratio is equal to the enantiomeric ratio of the CBZ-Pro-Cl used. This observation is an indication that the coupling of the acid chloride occurs without racemization.[26]

The diastereomeric amides **9** and **10** were separated by careful column chromatography and subsequently converted in one step into the pentacyclic structures **13** and **14** as follows. Removal of the *N*-benzyloxycarbonyl group

(11) Peterson, D. W.; Bradford, H. F.; Mantle, P. G. *Biochem. Pharmacol.* **1982**, *31*, 2807.
(12) Yamazaki, M.; Suzuki, S.; Kukita, K. *J. Pharmacobio-Dyn.* **1979**, *2*, 119.
(13) Shreeve, B. J.; Patterson, D. S. P.; Roberts, B. A.; MacDonald, S. M. *Vet. Res. Commun.* **1983**, *7*, 155.
(14) Yamazaki, M.; Fujimoto, H.; Kawasaki, T. *Chem. Pharm. Bull.* **1980**, *28*, 245.
(15) The stereochemistry at C(14a) of **1** is not given in the only report available on the structure elucidation by single-crystal x-ray crystallography.[2] Unfortunately, the crystallographic data cannot be traced anymore (Clardy, J., personal communication), and authentic material is hard to come by.
(16) Nakagawa, M.; Matsuki, K.; Hasumi, K.; Taniguchi, M.; Hino, T. *Heterocycles* **1982**, *19*, 156.
(17) Nakagawa, M.; Matsuki, K.; Hino, T. *Tetrahedron Lett.* **1983**, *24*, 2171.
(18) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Chem. Abstr.* **1979**, *90*, 152436t; *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **1978**, *21st*, 22.
(19) Harrison, D. M. *Tetrahedron Lett.* **1981**, *22*, 2501.
(20) Harrison, D. M., Sharma, R. B. *Tetrahedron* **1986**, *27*, 521.
(21) Plate, R.; Harmkens, P. H. H.; Smits, J. M. M.; Ottenheijm, H. J. C. *J. Org. Chem.* **1986**, *51*, 309.
(22) For recent work in this field, see: Ungemach, F.; Soerens, D.; Weber, R.; DiPierro, M.; Campos, O.; Mokry, P.; Cook, J. M.; Silverton, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 6976.
(23) Takeuchi, Y.; Furusaki, F. *Advances in Heterocyclic Chemistry*; Academic: New York, 1977; Vol. 21, p 207.
(24) Chen, E. M. F. *J. Org. Chem.* **1983**, *48*, 2939.
(25) Cassal, J. M.; Fuerst, A.; Meyer, W. *Helv. Chim. Acta* **1976**, *59*, 1917.
(26) Analogous proline acid chlorides have been used to establish optical purities of amino acids, see: Knudson, C. G.; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 2260. Maurer, P. J.; Takahata, H.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 1095.

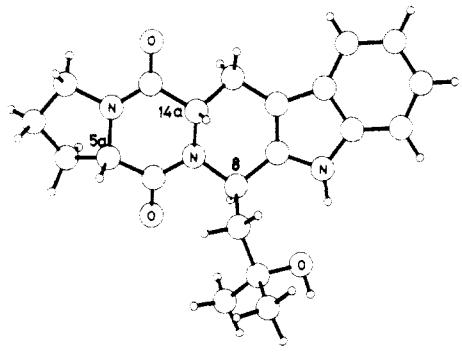

Figure 1. PLUTO drawing 14.

by catalytic hydrogenation (H_2, Pd/C) caused ring closure of the intermediate amines **11** and **12** to provide quantitatively the dioxopiperazines **13** and **14**, respectively.

That no racemization or epimerization had taken place in the proline moiety was secured as follows. When tris-[3-((heptafluoropropyl)hydroxymethylene)-*d*-camphorato]europium(III) was used as a chiral shift reagent the partially racemic mixture of **13** (ratio 3:2)—the synthesis of which is described above—showed two sets of two signals each with an integration ratio of 3:2 for the two diastereomeric methyl groups. Thus enantiomeric purity could be established easily by integration. The same observation was made when partially racemic **14** (ratio 3:2) was used. It was gratifying to observe that the ^{1}H NMR spectrum of **13** as well as **14**—prepared from L-CBZ-Pro-Cl—showed only one set of two signals for the two diastereotopic methyl groups when the above mentioned chiral shift reagent was used.

Unequivocal evidence for the relative configuration of **14** was forthcoming from x-ray crystallographic studies[27] (Figure 1). Suffice it to say that the C(8) and the C(14a) protons are in a *E* relationship, whereas the latter proton and the C(5a) proton are on the same side of the dioxopiperazine ring. From this, the absolute configuration of the other diastereomer **13** can be assigned, as depicted on Scheme III.

Finally, an appropriate method was explored for the conversion of the tertiary alcohol group into an alkene function.[28] Treatment of a pyridine solution of **13** or **14** with $SOCl_2$ at −40 °C afforded the desired alkenes **6** (54%) and **15** (49%), respectively, together with the chlorides **18** (18%) and **19** (6%) as well as the products of a Hofmann elimination, i.e., **16** (27%) and **17** (11%), respectively. As of yet no attempts were made to convert **16–19** into the corresponding alkenes **6** and **15**.

Having achieved the construction of the demethoxyfumitremorgin analogues **6** and **15**, attention was focused on their ^{1}H NMR spectra. It was disappointing to observe that the chemical shift value reported for, e.g., the C(8) proton of fumitremorgin C[6] (δ 6.06) compares unfavorably with the chemical shift value for the corresponding proton of **6** (δ 6.49). For the time being, we are reluctant to conclude, however, that these discrepancies point at a C(14a) epimeric relationship between fumitremorgin C and structure **6** for the following reason. The differences observed in the ^{1}H NMR spectra might be attributed to the presence of the C(11) methoxy group in fumitremorgin C.[29] To settle this ambiguity we are currently pursuing the synthesis of the C(14a) epimer of **6** as well as **6** possessing a methoxy group at C(11).

Experimental Section

Melting points were taken on a Koefler hot stage (Leitz-Wetzlar) and are uncorrected. Ultraviolet spectra were measured with a Perkin-Elmer spectrometer, Model 555. Proton magnetic resonance spectra were measured on a Varian Associates Model T-60 or a Bruker WH-90 spectrometer. Chemical shifts are reported as δ values (parts per million) relative to tetramethylsilane as an internal standard. As a chiral reagent we used tris[3-((heptafluoropropyl)hydroxymethylene)-*d*-camphorato]europium(III) (Janssen Chimica, Belgium). Mass spectra were obtained with a double-focusing VG 7070E spectrometer. Thin-layer chromatography (TLC) was carried out by using Merck precoated silica gel F-254 plates (thickness, 0.25 mm). Spots were visualized with a UV hand lamp, iodine vapor, Cl_2-TDM.[30] For column chromatography Merck silica gel H (type 60) was used on preparative HPLC (Jobin Yvon). Solvent systems used were as follows: system A, CH_2Cl_2/MeOH/HOAc, 87/10/3, v/v/v; system B, $CHCl_3$/MeOH, 93/7, v/v; system C, EtOAc.

1-(2′-Hydroxy-2′-methylpropyl)-3-(ethoxycarbonyl)-1,2,3,4-tetrahydro-β-carboline (7) and 1-(2′-Hydroxy-2′-methylpropyl)-3-(ethoxycarbonyl)-β-carboline (20). Activated zinc dust (10 g) was added portionwise to a stirred solution of **5**[21] (3.2 g, 10 mmol) in 400 mL of glacial acetic acid at room temperature. Subsequently, the reaction mixture was kept at 50 °C in an argon atmosphere and monitored by TLC (solvent system A). The reaction was complete after 16 h. The reaction mixture was filtered, and the residue was washed with CH_2Cl_2. The acetic acid layer was then concentrated to dryness, the residue was dissolved in CH_2Cl_2, and this solution was washed successively with water and brine and dried with Na_2SO_4. The solvent was evaporated in vacuo and the residue subjected to flash column chromatography (silica gel 60H, CH_2Cl_2/MeOH/HOAc, 95/4/1) to yield crude **7** and 0.32 g of **20** (10%), which was recrystallized (Et_2O).

Compound 7. To remove the acetic acid, crude **7** was dissolved in 1/1 EtOH/H_2O (50 mL) and poured onto an ionic exchange column (Amberlite, IRA 410). The column was washed (EtOH/H_2O, 1/1) unit no more UV-positive material was detectable. Evaporation of the eluent gave 2.75 g of **7** (85%), which was recrystallized from CH_2Cl_2/*n*-hexane: m.p. 167–169 °C; R_f 0.23 (solvent system A); UV (methanol) λ_{max} 218, 272, 277, 280, 288 nm, λ_{min} 244, 274, 279, 286 nm; EIMS (70 eV), *m/e* (relative intensity) 316 (M^+, 47), 243 ($[M-COOC_2H_5]^+$, 100), 169 ($[C_{11}H_9N_2]^+$, 58); exact mass calcd for $C_{18}H_{24}N_2O_3$ 316.1787, found 316.1786; ^{1}H NMR (90 MHz, $CDCl_3$) δ 8.03 (br s, 1 H, N(9)H), 7.51–7.04 (m, 4 H, C(5)C(8)H), 4.53 (X part of ABX spectrum, 1 H, C(1)*H*C(1′)H_2), 4.21 (q, 2 H, O*C*H_2CH$_3$), 3.92 (X part of ABX spectrum, 1 H, C(3)*H*C(4)H2), 3.50 (br s, 2 H, OH and N(2)H), 3.13 and 2.76 (AB part of ABX spectrum, 2 H, ^2J = 15.3 Hz, ^{3}J = 5.1 Hz, ^{3}J = 9.9 Hz, C(4)H_2C(3)H, 1.97 and 1.77 (AB part of ABX spectrum, 2 H, ^2J = 14.7 Hz, ^{3}J = 11.5 Hz, ^3J = 3.8 Hz, C(1′)H_2C(1)H), 1.40 (s, 3 H, CH$_3$), 1.29 (t, 3 H, OCH$_2$C*H*$_3$), 1.26 (s, 3 H, CH$_3$). Anal. Calcd for $C_{18}H_{24}N_2O_3$ (M_r 316.40): C, 68.33; H, 7.65; N, 8.85. Found: C, 68.09; H, 7.55; N, 8.94.

Compound 20: R_f 0.39 (solvent system A); m.p. 108–111 °C (Et_2O); UV (methanol) λ_{max} 216, 236, 270, 302, 332, 346 nm, λ_{min} 221, 247, 296, 324, 340 nm; EIMS (70 eV), m/e (relative intensity) 312 (M^+, 11), 254 ($[M - C_3H_6O)]^+$, 86), 180 ($[C_{12}H_8N_2]^+$, 100); exact mass calcd for $C_{18}H_{20}N_2O_3$ 312.1474, found 312.1470; ^{1}H NMR (90 MHz, $CDCl_3$) δ 9.80 (br s, 1 H, NH), 8.76 (s, 1 H, C(4)H), 8.16 (d, 1 H, (C(5)H), 7.58–7.22 (m, 3H, C(6)C(8)H), 4.47 (q, 2 H, O*C*H_2CH$_3$), 3.34 (s, 2 H, C(1′)H_2), 1.73 (br s, 1 H, OH), 1.43 (t, 3 H, OCH$_2$C*H*$_3$), 1.31 (s, 6 H, 2 × CH$_3$). Anal. Calcd. for $C_{18}H_{20}N_2O_3 \cdot H_2O$ (M_r 330.38): C, 65.44; H, 6.71; N, 8.48. Found: C, 65.51; H, 6.71; H, 8.44.

8-(2′-Hydroxy-2′-methylpropyl)-4,5,5a,8,14,14a-hexahydro-3*H*-pyrrolo[1′,2′:4,5]pyrazino[1,2-*b*]-β-carboline-(5a*H*α,8*H*α,14a*H*β)-1,6-dione[31] **(13) and 8-(2′-Hydroxy-2′-**

(27) Behm, H.; Beurskens, P. T.; Plate, R.; Ottenheijm, H. C. J. *Recl. Trav. Chim. Pays-Bas.* **1986**, *105*, 235.

(28) It is worthwhile to mention here that several members of the fumitremorgin class possess a C(8) side chain as present in **13** and **14**, see ref 1–10.

(29) We observed recently that the presence of a 6-methoxy group in the indole nucleus affects considerably the chemical shift values of protons in the tryptophan side chain.

(30) Arx, E. v.; Faupel, M.; Bruggen, M. *J. Chromatogr.* **1976**, *120*, 224.

methylpropyl)-4,5,5a,8,14,14a-hexahydro-3*H*-pyrrolo-[1′,2′:4,5]pyrazino[1,2-*b*]-β-carboline-(5aHα,8Hβ,14aHα)-1,6-dione (14). To a stirred solution L-CBZ-Pro-Cl (**8**)[25] (3.53 g, 13.2 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise a cooled solution (−20 °C) of **7** (1.58 g, 5 mmol) and Et_3N (0.5 g, 4.95 mmol) in dry CH_2Cl_2 (65 mL) in an argon atmosphere. The reaction mixture was allowed to warm to room temperature and was monitored by TLC (solvent system B; **9**, R_f 0.50; **10**, R_f 0.57). After completion of the reaction, the reaction mixture was washed successively with 0.1 N HCl, 0.1 N $NaHCO_3$, and brine and dried with Na_2SO_4. Evaporation of the solvent in vacuo gave a crystalline material, which was subjectd to flash column chromatography (silica gel 60H; CH_2Cl_2/MeOH, 98.8/1.2) to yield 0.92 g of **9** (34%) and 1.32 g of **10** (48%). Of these N-protected dipeptides **9** and **10** the N-protecting group was removed directly by catalytic hydrogenation using 10% Pd–C in ethanolic solution at room temperature and atmospheric pressure. Filtration and evaporation of the solvent gave 615 mg of **13** (34%) and 885 mg of **14** (48%).

Compound 13: R_f 0.48 (solvent system B); oil; $[\alpha]^{22}_D$ +98° (*c* 0.1, methanol); IR (KBr) 3455 and 3310 (ν_{NH} and ν_{OH}), 1655 and 1641 ($2 \times \nu_{C=O}$) cm^{-1} UV (methanol) λ_{max} 220, 270, 276, 279, 287 nm, λ_{min} 242, 273, 278, 284 nm; CIMS (100 eV), *m/e* (relative intensity) 368 ($[M + 1]^+$, 55), 350 ($[M- OH]_+$, 16), 294 ($[C_{17}H_{16}N_3O_2]^+$, 100), 169 ($[C_{11}H_9N_2]^+$, 14); exact mass calcd. for $C_{21}H_{26}N_3O_3$ (M + 1) 368.1974, found 368.1967; ^1H NMR (90 MHz, $CDCl_3$) δ 8.82 (br s, 1 H, NH), 7.51–7.08 (m, 4 H, C(10)C(13)H), 5.97 (t, 1 H, ^3J = 5.5 Hz, C(8)*H*C(1′)H_2), 4.38 (X part of ABX spectrum, 1 H, C(14a)*H*C(14)H_2), 4.22–4.03 (m, 1 H, C(5a)H), 3.82–3.59 (m, 2 H, C(3)H_2), 3.33 and 2.92 (AB part of ABX spectrum, 2 H, ^2J = 15.0 Hz, ^3J = 12.0 Hz, C(14)H_2C(14a)H), 2.52 (br s, 1 H, OH), 2.44–1.76 (m, 6 H, C(4)H_2C(5)H_2, and d, C-(1′)H_2C(8)H, 1.45 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3). Addition of the chiral shift reagent tris[3-((heptafluoropropyl)hydroxymethylene)-*d*-camphorato]europium(III) to the $CDCl_3$ solution of **13** did not cause splitting of signals.

Compound 14: R_f 0.45 (solvent system B); m.p. 228–230 °C (CH_2Cl_2/*n*-pentane); $[\alpha]^{22}_D$ −183° (*c* 0.1, methanol); IR (KBr) 3408 and 3295 (ν_{NH} and ν_{OH}), 1662 and 1631 ($2 \times \nu_{C=O}$) cm^{-1}; UV (methanol) λ_{max} 220, 270, 276, 279, 287 nm, λ_{min} 244, 274, 278, 284 nm; CIMS (100 eV), *m/e* 368 ($[M + 1]^+$,96), 350 ($[M - OH]^+$, 64), 294 ($[C_{17}H_{16}N_3O_2]^+$, 100), 169 ($[C_{11}H_9H_2]^+$, 16); exact mass calcd for $C_{21}H_{26}H_3O_3$ (M + 1) 368.1974, found 368.1978; ^1H NMR (90 MHz, $CDCl_3$) δ 9.20 (br s, 1 H, NH), 7.50–7.07 (m, 4 H, C(10)C-(13)H), 5.96 (X part of ABX spectrum, 1 H, C(8)*H*C(1′)H_2), 4.39 (X part of ABX spectrum, 1 H, C(14a)*H*C(14)H_2), 4.19–3.32 (m, 3 H, C(5a)H and C(3)H_2), 3.63 and 2.83 (AB part of ABX spectrum, 2 H, ^2J = 15.9 Hz, ^3J = 4.1 Hz, ^3J = 11.5 Hz, C(14)H_2C-(14a)H), 2.56–1.74 (m, 6 H, C(4)H_2C(5)H_2 and AB part of ABX spectrum, C(1′)H_2C(8)H), 2.33 (s, 1 H, OH), 1.51 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3). Addition of the chiral shift reagent tris[3-((heptafluoropropyl)hydroxymethylene)-*d*-camphorato]europium(III) to the $CDCl_3$ solution of **14** did not cause splitting of signals. Anal. Calcd for $C_{21}H_{25}N_3O_3 \cdot {}^1/_{15}CH_2Cl_2$ (*M* 373.111): C, 67.82; H, 6.79; N, 11.26. Found: C, 67.85; H, 6.83; N, 11.35.

8-(2′-Methyl-1′-propenyl)-4,5,5a,8,14,14a-hexahydro-3*H*-pyrrolo[1′,2′:4,5]pyrazino[1,2-*b*]-β-carboline-(5aHα,8Hα,14aHβ)-1,6-dione (6) and 8-(2′-Methyl-2′-propenyl)-4,5,5a,8,14,14a-hexahydro-3*H*-pyrrolo[1′,2′:4,5]-pyrazino[1,2-*b*]-β-carboline-(5aHα,8Hα,14aHβ)-1,6-dione (16) and 8-(2′-Chloro-2′-methylpropyl)-4,5,5a,8,14,14a-hexahydro-3*H*-pyrrolo[1′,2′:4,5]pyrazino[1,2-*b*]-β-carboline-(5aHα,8Hα,14aHβ)-1,6-dione (18). To a stirred and cooled (−50 °C) solution of **13** (150 mg, 0.41 mmol) in dry pyridine (1.5 mL) was added freshly distilled thionyl chloride (50 μL, 0.68 mmol) in an argon atmosphere. The reaction was monitored by TLC (solvent system C). The solution was allowed to warm to room temperature. Then CH_2Cl_2 (20 mL) was added, and the reaction mixture was washed successively with 2 N HCl and brine and dried with Na_2SO_4. Evaporation of the solvent in vacuo gave a solid material, which was subjected to flash column chromatography (silica gel 60H; EtOAc/*n*-exane, 60/40) to yield 70 mg of **6** (49%), 15 mg of **16** (11%), and 10 mg of **18** (6%).

Compound 6: R_f 0.53 (solvent system C); m.p. 208–212 °C (EtOAc); $[\alpha]^{22}_D$ +281° (*c* 0.1, methanol); UV (methanol) λ_{max} 223, 272, 279, 282, 289, 317 nm, λ_{min} 245, 276, 280, 286, 306; EIMS (70 eV), *m/e* (relative intensity) 349 (M^+, 13), 294 ($[C_{17}H_{16}N_3O_2]^+$, 14), 251 ($[C_{16}H_{15}N_2O]^+$, 72), 182 (68), 169 ($[C_{11}H_9N_2]^+$, 40), 70 (77), 43 (100); exact mass calcd for $C_{21}H_{23}N_3O_2$ 349.1790, found 379.1785; ^1H NMR (90 MHz, $CDCl_3$) δ 8.10 (br s, 1 H, NH), 7.47–7.04 (m, 4 H, C(10)C(13)H), 6.49 (d, 1 H, ^3J 9.3 Hz, C(8)-*H*C(1′)H), 5.36 (d, 1 H, ^3J = 9.3 Hz, C(1′)*H*C(8)H, 4.41 (X part of ABX spectrum, 1 H, C(14a)*H*C(14)H_2), 4.22–3.98 (m, 1 H, C(5a)H), 3.83–3.56 (m, 2 H, C(3)H[2), 3.34 and 2.93 (AB part of ABX spectrum), 2 H, ^2J = 15.0 Hz, ^3J = 3.9 Hz, ^3J = 12.0 Hz, C(14)H_2C(14a)H), 2.62–1.71 (m, 4 H, C(4)H_2C(5)H_2), 1.98 (s, 3 H, CH_3), 1.76 (s, 3 H, CH_3). Anal. Calcd for $C_{21}H_{23}N_3O_2 \cdot {}^1/_3$ EtOAc (*M* 478.803): C, 70.81; H, 6.83; N, 11.09. Found: C, 70.82; H, 6.50; N, 10.97.

Compound 16: R_f 0.58 (solvent system C); oil; EIMS (70 eV) *m/e* 349 (M^+, 12), 294 ($[C_{17}H_{16}N_3O_2]^+$, 100), 169 ($[C_{11}H_9N_2]^+$, 54); ^1H NMR (90 MHz, $CDCl_3$) δ 8.07 (br s, 1 H, NH), 7.50–7.05 (m, 4 H, C(10)C(13)H), 5.91 (t, 1 H, ^3J = 7.2 Hz, C(8)*H*C(1′)H), 4.93 and 4.84 (AB spectrum, 2 H, C(3′)H_2), 4.40 (X part of ABX spectrum, 1 H, C(14a)*H*C(14)H_2), 4.18–4.00 (m, 1 H, C(5a)H), 3.82–3.57 (m, 2 H, C(3)H_2), 3.35 and 2.91 (AB part of ABX spectrum, 2 H, ^2J = 15.0 Hz, ^3J = 3.9 Hz, ^3J = 12.0 Hz, C-(14)H_2C(14a)H), 2.53 (d, 2 H, ^3J = 7.2 Hz, C(1′)H_2C(8)H), 2.44–1.67 (m, 4 H, C(4)H_2C(5)H_2), 1.88 (s, 3 H, CH_3).

Compound 18. R_f 0.63 (solvent system C); oil; FABMS (7.1 kV at 1.4 mA) *m/e* (relative intensity) 388 ($[M + 3]^+$, 16), 386 ($[M + 1)^+$, 46), 350 ($[M - Cl]^+$, 45), 294 ($[C_{17}H_{16}N_3O_2]^+$, 100), 169 ($[C_{11}H_9H_2]^+$, 82); ^1H NMR (90 MHz, $CDCl_3$) δ 8.24 (br s, 1 H, NH), 7.44–7.03 (m, 4 H, C(10)C(13)H), 6.11 (t, 1 H, ^3J = 5.1 Hz, C-(8)*H*C(1)H_2), 4.39 (X part of ABX spectrum, 1 H, C(14a)*H*C-(14)H_2), 4.19–4.01 (m, 1 H, C(5a)H), 3.84–3.58 (m, 2 H, C(3)H_2), 3.31 and 2.94 (AB part of ABX spectrum, 2 H, ^2J = 15.1 Hz, ^3J = 4.5 Hz, ^3J = 12.0 Hz, C(14)H_2C(14a)H), 2.58–1.89 (m, 4 H, C(4)H_2C(5)H_2), 2.33 (d, 2 H, ^3J = 6.0 Hz, C(1′)J_2C(8)H), 1.72(s, 3 H, CH_3), 1.68 (s, 3 H, CH_3).

8-(2′-Methyl-1′-propenyl)-4,5,5a,8,14,14a-hexahydro-3*H*-pyrrolo[1′,2′:4,5]pyrazino[1,2-*b*]-β-carboline-(5aHα,8Hβ,14aHα)-1,6-dione (15) and 8-(2′-Methyl-2′-propenyl)-4,5,5a,8,14,14a-hexahydro-3*H*-pyrrolo[1′2′:4,5]-pyrazino[1,2-*b*]-β-carboline-(5aHα,8Hβ,14aHα)-1,6-dione (17) and 8-(2′-Chloro-2′-methylpropyl)-4,5,5a,8,14,14a-hexahydro-3*H*-pyrrolo[1′,2′:4,5]pyrazino[1,2-*b*]-β-carboline-(5aHα,8Hβ,14aHα)-1,6-dione (19). Compound **14** (50 mg, 0.14 mmol) was treated with thionyl chloride (17 μL, 0.23 mmol) in dry pyridine as described for compound **13** (vide supra). This procedure gave 25 mg of **15** (53%), 13 mg of **17** (27%), and 10 mg of **19** (20%).

Compound 15. R_f 0.27 (solvent system C); m.p. 159–163 °C (CH_2Cl_2/*n*-pentane); $[\alpha]^{22}_D$ −436° (*c* 0.1, methanol); UV (methanol) λ_{max} 224, 273, 279, 282, 290, 317 nm, λ_{min} 246, 276, 280, 287, 308 nm; EIMS (70 eV), *m/e* (relative intensity) 349 (M^+, 100), 294 ($[C_{17}H_{16}N_3O_2]^+$, 45), 251 ($[C_{16}H_{15}N_2O]^+$, 80), 182 (52), 169 ($[C_{11}H_9N_2]^+$, 35); exact mass calcd for $C_{21}H_{23}N_3O_2$ 349.1790, found 319.1787; ^1H NMR (90 MHz, $CDCl_3$) δ 7.78 (br s, 1 H, NH), 7.53–7.06 (m, 4 H, C(10)C(13)H), 6.42 (d, 1 H, ^3J = 9.6 Hz, C(8)*H*C(1′)H), 5.25 (d, 1 H, ^3J = 9.6 Hz, C(1′)*H*C(8)H), 4.45 (X part of ABX spectrum, 1 H, C(14a)*H*C(14)H_2), 4.22–3.34 (m, 3 H, C(5a)H and C(3)H_2), 3.64 and 2.84 (AB part of ABX spectrum, 2 H, ^2J = 15.9 Hz, ^3J = 4.5 Hz, ^3J = 10.8 Hz, C(14)H_2C(14a)H), 2.60–1.60 (m, 4 H, C(4)H_2C(5)H_2), 2.05 (s, 3 H, CH_3), 1.78 (s, 3 H, CH_3). Anal. calcd for $C_{21}H_{23}N_3O_2 \cdot {}^1/_4CH_2Cl_2$ (M_r 370.667): C, 68.86; H, 6.39; N, 11.34. Found: C, 68.82; H, 6.35; N, 11.29.

Compound 17. R_f 0.32 (solvent system C); oil; EIMS (70 eV), *m/e* (relative intensity) 349 (M^+, 6), 294 ($[C_{17}H_{16}N_3O_2]^+$, 100), 169 ($[C_{11}H_9N_2]^+$, 60); exact mass calcd for $C_{21}H_{23}N_3O_2$ 349.1790, found 349.1784; ^1H NMR (90 MHz, $CDCl_3$) δ 8.16 (br s, 1 H, NH), 7.52–7.08 (m, 4 H, C(10)C(13)H), 5.94 (t, 1 H, ^3J = 6.6 Hz, C-(8)*H*C(1′)H_2), 4.96 and 4.83 (AB spectrum, 2 H, C(3′)H_2), 4.44 (X part of ABX spectrum, 1 H, C(14a)*H*C(14)H_2), 4.24–3.33 (m, 3 H, C(5a)H and C(3)H_2), 3.64 and 2.83 (AB part of ABX spectrum, 2 H, ^2J = 15.9 Hz, ^3J = 4.5 Hz, ^3J = 11.1 Hz, C(14)H_2C-(14a)H), 2.58 (d, 2 H, ^3J= 6.6 Hz, C(1′)H_2C(8)H), 2.44–1.71 (m, 4 H, C(4)H_2C(5)H_2), 1.89 (s, 3 H, CH_3).

(31) The numbering for substituents in this and ensuing compounds is not systematic but is indicated (e.g., see Scheme III).

Compound 19: R_f 0.39 (solvent system C); oil; FABMS (7 kV at 1.4 mA), *m/e* (relative intensity) 388 ([M+3]$^+$, 18), 386 ([M + 1]$^+$, 43), 350 ([M - Cl]$^+$, 54), 294 ([$C_{17}H_{16}N_3O_2$]$^+$, 100), 169 ([$C_{11}H_9N_2$]$^+$, 89); ^{1}H NMR (90 MHz, $CDCl_3$) δ 8.51 (br s, 1 H, NH), 7.44-7.02 (m, 4 H, C(10)C(13)H), 6.24 (t, 1 H, ^3J = 5.7 Hz, C(8)*H*C(1')H_2), 4.50 (X part of ABX spectrum, 1 H, C(14a)*H*C(14)H_2), 4.20-3.28 (m, 3 H, C(5a)H and C(3)H_2), 3.53 and 2.81 (AB part of ABX spectrum, 2 H, ^2J = 15.6 Hz, ^3J = 4.8 Hz, ^3J = 11.1 Hz, C(14)H_2C(14a)H), 2.50-1.85 (m, 4 H, C(4)H_2C(5)H_2), 2.32 (d, 2 H, ^3J = 5.7 Hz, C(1')H_2C(8)H), 1.71 (s, 3 H, CH_3), 1.67 (s, 3 H, CH_3).

Registry No. (±)-**5**, 99708-07-3; **6**, 106211-91-0; (±)-**7**, 106211-87-4; **8**, 61350-60-5; **9**, 106211-89-6; **10**, 106211-90-9; **13**, 106211-88-5; **14**, 106292-67-5; **15**, 106292-68-6; **16**, 106211-93-2; **17**, 106292-69-7; **18**, 106211-92-1; **19**, 106292-70-0; **20**, 106211-94-3.

Furfural, a Convenient Precursor for Intramolecular Diels-Alder Reactions via Umpolung with Trimethylsilyl Cyanide[1]

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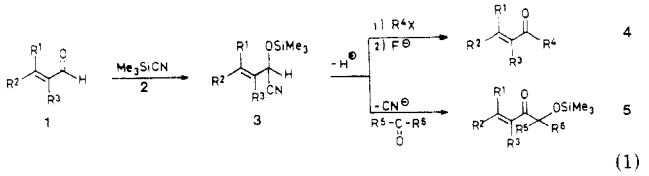
The deactivating effect of a 2-acyl group on the reactivity of furan as a diene in Diels-Alder reactions can be eliminated by protecting the carbonyl group. Therefore, the addition product **10** of trimethylsilyl cyanide and furfural offers a convenient starting material for intramolecular Diels-Alder reactions after deprotonation and reaction with suitable olefinic electrophiles (umpolung). In this way, 5-bromo-1-pentene and 1-hexen-5-one, respectively, were reacted with **10** and products **14** and **22** thermally transformed into cycloadducts **15** and **23**. Due to the mild conditions of the deprotection, cycloreversion can be suppressed so that the tricyclic ketones **19** and **25** can be obtained in high yields. Ketones **19** and **25** constitute the first examples of intramolecular Diels-Alder adducts with furan carrying a carbonyl group in the bridgehead position. On heating, these ketones cyclorevert in over 90% yields to **18** and **24**, demonstrating the usefulness of our approach.

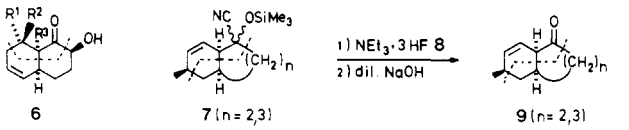
During the last decade, the intracular version of the Diels-Alder reaction has gained primary importance for the construction of bi- and polycyclic ring systems, especially for natural product synthesis.[3] Within certain limits the intramolecular [4 + 2] cycloaddition can be smoothly performed. Thus, the synthetic problem is essentially reduced to an efficient connection of the diene and dienophile precursors through a tether that carries the appropriately situated desired substituents.

By means of two different model systems, we have recently demonstrated that diene-dienophile precursors of a unique substituent pattern can be constructed by employing the well-developed method of umpolung of unsaturated aldehydes **1** with trimethylsilyl cyanide (**2**). Allowing the corresponding carbanions to react with alkylating agents produces ketones of type **4**[4] whereas with carbonyl compounds as electrophiles O-silylated acyloins **5** are obtained in high yield:[5]



(1)

Employing these principles resulted in the smooth synthesis of the new bicyclic ketones **6**[6] and **9**,[7] in which the diene and dienophile are delineated by the dotted lines. It should be stressed that so far intramolecular Diels-Alder reactions failed for tetrahydroindanones of type **9**[8] (n = 2) where instead of the expected octalones **9** (n = 3) only



the isomers with a conjugated double bond could be isolated.[9] The key to smooth formation of **9** (n = 2, 3) lies in the mild conditions for both the cyclization of the precursor of **7** (n = 2, 3) and the desilylation by triethylamine dihydro-[10] or preferentially trihydrofluoride **8**.[11]

The advantage of this protocol becomes crucial if a 2-acylfuran is intended to serve as a diene moiety. In view of the well-known diminished reactivity of furan as a 4π component and the retro reaction of the Diels-Alder ad-

(1) Paper XIV of the series: Trimethylsilyl Cyanide—A Reagent for Umpolung. Paper XIII: See ref 6.
(2) Dissertation, University of Würzburg, 1985.
(3) (a) Oppolzer, W. *Angew. Chem.* **1977**, *89*, 10; *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10. (b) Oppolzer, W. In *New Synthetic Methods*; Verlag Chemie: Weinheim, 1979; Vol. 6, p 1f. (c) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63. (d) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183. (e) Ciganek, E. *Org. React. (N.Y.)* **1984**, 32f. Taber, F. *Intramolecular Diels-Alder Reactions and Alder-Ene Reactions*; Springer Verlag: New York, 1984.
(4) Hertenstein, U.; Hünig, S.; Reichelt, H.; Schaller, R. *Chem. Ber.* **1986**, *119*, 722. Reichelt, H.; Hünig, S. *Chem. Ber.* **1986**, *119*, 1772.
(5) Hünig, S.; Öller, M. *Chem. Ber.* **1981**, *114*, 959.
(6) Fischer, K.; Hünig, S. *Chem. Ber.*, **1986**, *119*, 3344.
(7) Fischer, K.; Hünig, S. *Chem. Ber.* **1986**, *119*, 2590.
(8) (a) Oppolzer, W.; Fehr, L.; Warneke, J. *Helv. Chim. Acta* **1977**, *60*, 48. (b) Roush, W. R.; Gillis, H. R. *J. Org. Chem.* **1980**, *45*, 4283. Roush, W. R.; Pesckis, S. W. *J. Am. Chem. Soc.* **1981**, *103*, 6696. Roush, W. R.; Ko, A. I.; Gillis, H. R. *J. Org. Chem.* **1980**, *45*, 4264. Compare also ref 1.
(9) (a) Näf, F.; Decorzant, R.; Thommen, W. *Helv. Chim. Acta* **1979**, *62*, 114. Näf, F.; Decorzant, R.; Thommen, W. *Helv. Chim. Acta* **1982**, *65*, 2212. (b) Roush, W. R.; Hall, S. E. *J. Am. Chem. Soc.* **1981**, *103*, 5200. Compare also ref 1.
(10) Hünig, S.; Wehner, G. *Synthesis* **1975**, 391.
(11) Purchased from Riedel de Haen, Seelze, BRD; with this reagent the reaction stops exclusively at the cyanohydrin stage.

0022-3263/87/1952-0564$01.50/0