A Stereospecific Approach to Diterpene Alkaloids with a Bridge Across Ring B

We wish to report a simple and stereospecific synthesis[1] of the pentacyclic keto lactam **2** which we hope to use as an intermediate in the construction of the alkaloid songorine **1**. Analogs of **2** ($-CH_2-O-CH_3$ and $-OCH_3$ instead of $-CH_3$ and $-OH$) could be prepared in exactly the same manner and serve as intermediates for alkaloids of the delphinine type.

The starting material for the synthesis was the tricyclic ester **3**[2]. This compound was prepared by a diene addition between methoxy-*p*-benzoquinone and methyl cyclopentadiene carboxylate in acetone at 5°C, followed by the isomerization of the major adduct (ratio 3:2) by acetylation, hydrolysis and chromatography on silica gel[3].

Compound **3** was converted to the ether **4** in quantitative yield by treatment with 1-phenyl-5-chlorotetrazole[4]. Compound **4** was treated with a large excess of benzenesulphonyl azide in benzene-chloroform. The aziridine **5** was produced in a yield of 92%. A careful NMR study of this product was in agreement with the expected exo configuration of the aziridine ring.

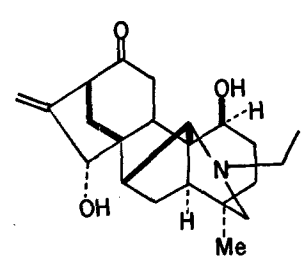
The rearrangement of **5** to **6** was accomplished in glacial acetic acid at 100°C in a yield of 72%. Hydrogenolysis of **6** with palladium on charcoal in tetrahydrofuran-ethanol[4] gave compound **7** in a yield of 80% after crystallization.

The operations which had to be performed at this stage were: removal of the benzene-sulphonyl group, blocking of the secondary alcoholic function and finally transformation of the bridgehead ester group to an aldehyde. These changes were executed via the intermediates **7** through **12** in an overall yield of 48%. Compound **7** was converted to **8** by lithium aluminum hydride reduction followed by acetylation. The secondary acetate of **8** was selectively hydrolyzed with potassium carbonate in aqueous methanol. The conversion of **9** to **11** was performed in the standard manner by tetrahydropyranylation and alkaline hydrolysis. Finally the oxidation **11** → **12** was accomplished quantitatively by the dimethyl sulfoxide carbodiimide method[5]. Compound **12** was an oil homogeneous in TLC [IR: 2740, 1715 cm^{-1}; NMR: singlet (1H) $\tau = -0.10$ ppm (–CH=O)].

The aldehyde **12** was treated with the Grignard reagent prepared from 1-bromo-3-benzyloxybutane[6]. The product (88%) was a mixture of the epimers **13** and **14** which were converted to the acetates **15** and **16** and separated by chromatography on silica gel. The assignment of configuration to the two epimers was based on NMR spectra of derivatives from both series after the closure of ring A.

The undesirable acetate **15** was converted to the desirable one **16** by alkaline hydrolysis to **13**, oxidation with chromium trioxide in pyridine to the ketone **17**, reduction with lithium tri-t-butoxyaluminum hydride to the alcohol **14** and acetylation. The whole process was accomplished in a yield of 89%. Hydrogenolysis of the acetate **16** with palladium on charcoal gave the diol **18** which was oxidized with chromium trioxide in pyridine to the diketone **19**. The yield of this material after crystallization was 90%. [IR: 3400 cm^{-1} (NH), 1750, 1716, 1690 cm^{-1} (ketones amide)]. An aldol condensation of **19** with potassium carbonate in boiling methanol gave the highly crystalline compound **20** in quantitative yield. [UV: $\lambda_{max}^{EtOH} = 232$ nm, log $\varepsilon = 4.01$; IR: 1725, 1695 cm^{-1} (conj. ketone, amide), NMR: singlet (3H) $\tau = 7.87$ ppm (C=C(CH$_3$)–)]. Irradiation of **20** in tetrahydrofuran with an excess of vinylacetate at −10°C (Hanovia Hg lamp, pyrex filter) gave the two acetoxy epimers **21** in a yield of 95%. [Spectral data of mixture, IR; 1748 cm^{-1} (ketone); NMR: singlet (3H) $\tau = 9.70$ ppm (–C(CH$_3$)–, shifted to high field since it is situated in the shielding region of the benzene ring. This signal is strong evidence for the stereochemistry of the photoadduct].

Treatment of the mixture **21** with 1% methanolic potassium hydroxide at room temperature gave quantitatively the homogeneous aldehyde **22**. [NMR: singlet (3H) $\tau = 9.54$ ppm (–C(CH$_3$)–), triplet (1H) $\tau = 0.17$ ppm (–CH$_2$–CH=O)]. The high field methyl signal requires an A/B *cis* ringjunction. Enolacetylation of **22** with acetic anhydride and sodium acetate gave compound **23** in a yield of 82%. The enolacetate was smoothly converted to



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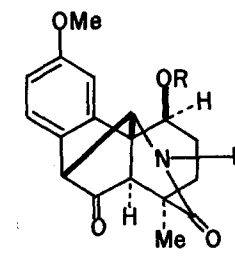
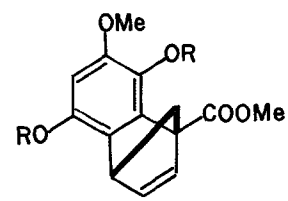
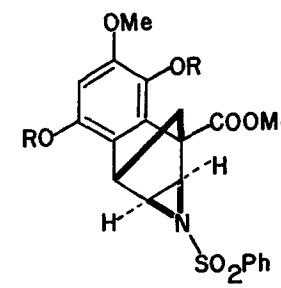
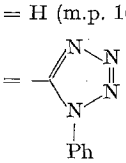
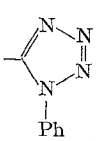


2 R = H (m.p. 301°)
2b R = Ac (m.p. 231°)





3 R = H (m.p. 161°)

4 R =  (m.p. 108°) **5** R =  (m.p. 190°)

[1] For a model study see K. WIESNER and A. PHILIPP, Tetrahedron Lett. *14*, 1467 (1966); K. WIESNER, A. PHILIPP and PAK-TSUN HO, Tetrahedron Lett. *10*, 1209 (1968); and KARIN BJAMER BIRNBAUM, K. WIESNER and PAK-TSUN HO, Tetrahedron Lett. *14*, 1071 (1969).

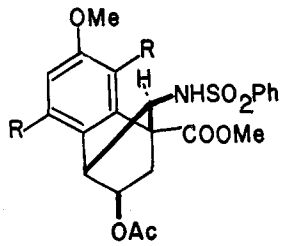
[2] Satisfactory spectral data (IR, NMR and mass) were obtained for all compounds reported. All crystalline compounds gave a correct elemental analysis. For brevity, only some spectral data of special significance are reported.

[3] The position of the methoxyl in **3** was rigorously proved by conversion to 7-methoxy-1-naphtoic acid. A simpler and regiospecific synthesis of compounds of the type **3** has been being worked out in our laboratory.

[4] W. J. MUSLINER and J. W. GATES JR., J. Am. chem. Soc. *88*, 4272 (1966).

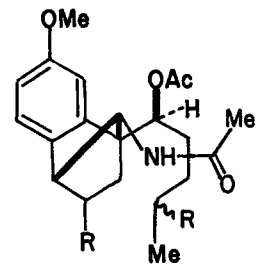
[5] K. E. PFITZNER and J. G. MOFFATT, J. Am. chem. Soc. *87*, 5661 (1965).

[6] G. STORK, Pure appl. Chem. *9*, 131 (1964) and private communication.



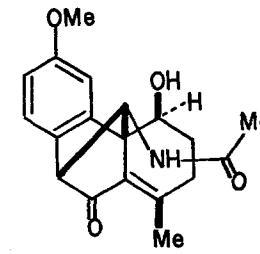
6 R = O–(triazole)–Ph (m.p. 200°)

7 R = H (m.p. 137°)

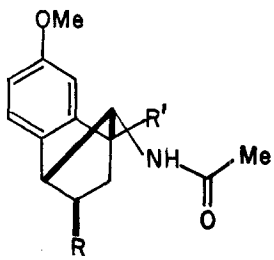


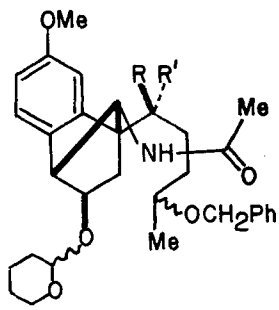
18 R = OH

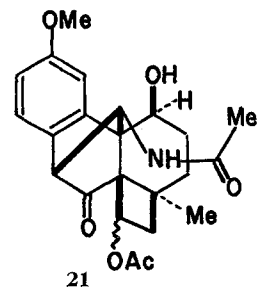
19 R = =O (m.p. 154°)



20 (m.p. 205°)







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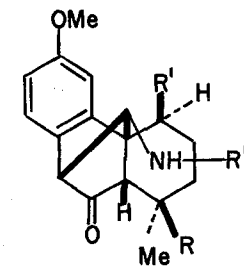

8 R = OAc, R′ = CH_2OAc (m.p. 119°)

9 R = OH, R′ = CH_2OAc (m.p. 165°)

10 R = O–(dioxolane), R′ = CH_2OAc

11 R = O–(dioxolane), R′ = CH_2OH

12 R = O–(dioxolane), R′ = CHO

13 R = H, R′ = OH

14 R = OH, R′ = H

15 R = H, R′ = OAc

16 R = OAc, R′ = H

17 R′R = O

22 R = CH_2CHO, R′ = OH, R″ = $-\overset{O}{\overset{\|}{C}}-CH_3$

23 R = CH=CHOAc, R′ = OAc, R″ = $-\overset{O}{\overset{\|}{C}}-CH_3$

24 R = CHO, R′ = OAc, R″ = $-\overset{O}{\overset{\|}{C}}-CH_3$

25 R = COOMe, R′ = OAc, R″ = $-\overset{O}{\overset{\|}{C}}-CH_3$

26 R = COOMe, R′ = OAc, R″ = $-\overset{O}{\overset{\|}{C}}-$(Br-phenyl) (m.p. 248°)

the noraldehyde **24** by osmic acid periodate oxidation [NMR: singlet (3H) τ = 9.70 ppm ($-\underset{|}{C}-CH_3$), singlet (1H) τ = 0.40 ppm (–CH=O)]. The aldehyde **24** was oxidized with chromic acid in 10% aqueous sulfuric acid in acetone to the corresponding carboxylic acid, which was directly esterified with diazomethane. The ester **25** was obtained in a yield of 96%. [IR: 1750, 1725, 1720, 1669 cm^{-1} (ketone, esters, amide); NMR: singlet (3H) τ = 9.44 ppm ($-\underset{|}{C}-CH_3$)]. In order to corroborate the structure and stereochemistry of **25**, this material was converted to the crystalline derivative **26** by mild alkaline hydrolysis followed by treatment with m-bromo-benzoyl bromide in refluxing benzene. The structure of **26** was determined in Nutley by X-ray analysis. The compound crystallized in monoclinic crystals, space group P $2_1/c$, a = 10.54, b = 12.07, c = 20.73 A, β = 93.55°, Z = 4; R = 6.6% (all atoms anisotropic, no hydrogens). The formation of **26** clearly involved an N→O acetylmigration followed by m-bromobenzoylation of the nitrogen. The ester **25** was dissolved in 6% potassium hydroxide in methanol-t-butanol (8:2) and allowed to stand at room temperature for 24 h. The highly crystalline lactam **2** was obtained in a yield of 94% [IR: 3380, 3280, 1750, 1670 cm^{-1} (NH, OH, ketone, lactam); NMR singlet (3H) τ = 8.70 ppm ($-\underset{|}{C}-CH_3$ A/B *trans*!)]. The product was also characterized as the crystalline acetate **2**b (*m/e* 355.1425). The overall yield of **2** from **3** was 6%. Developments now in progress are expected to raise this substantially.

Zusammenfassung. Die Herstellung eines Schlüsselprodukts für die Synthese von Alkaloiden des Songorin- und Delphinin-Typs wird beschrieben.

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University of New Brunswick,
Fredericton (N.B., Canada), and
Hoffmann La Roche Company Inc.,
Nutley (New Jersey, USA), 8 December 1971.

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