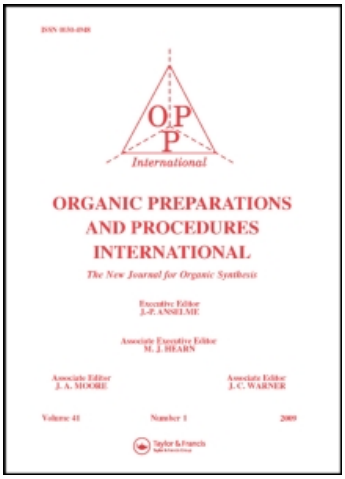

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SYNTHESIS OF MODELS RELATED TO TASPINE

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SYNTHESIS OF MODELS RELATED TO TASPINE

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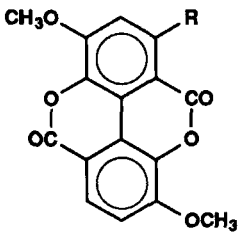
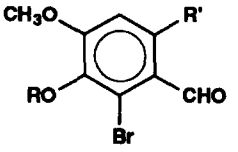
Taspine (**1a**)[1] is an alkaloid with an unusual diphenylic skeleton, whose synthesis has not been yet reported. A previous note[2] described the synthesis of a model compound **1b**, which was not suitable for further transformation into taspine, owing to its insolubility in most common solvents. Our efforts torward the total synthesis of **1a**, led us to develop a similar strategy for the synthesis of another model compound **1c**, which has a direct structural relationship to taspine. Furthermore, we expected that **1c** would be more soluble than **1b**, owing to the presence of the propionic acid chain, which could be converted into the 2-(N-dimethylamino)ethyl group of taspine **1a**, by a previously discovered modification of the Curtius reaction that gave good yields when applied to dihydroferulic acid.[3]



1

a R = $(CH_2)_2NMe_2$
b R = Me
c R = $(CH_2)_2CO_2H$
d R = H

By analogy to the synthesis of the dilactone **1b** , we initially synthesized the diphenylic dialdehyde **3** (41% yield), by Ullmann coupling[4] of an excess of the less reactive bromoaldehyde **2c**[2] with the bromoaldehyde **2b**;[5] however, **3** could not be transformed into the dilactone **1c** due to the resistance of the formyl groups to oxidation, presumably for steric reasons. We thus oxidized the bromoaldehyde **2b** with Jones reagent[6] under controlled conditions to give acid **4a**, which was treated with diazomethane to afford ester **4b**. The Ullmann reaction was performed in boiling DMF with an excess of bromoester **5**,[2] to avoid losses of component **4b** by self-condensation. This lower temperature of about 70°, as compared to previous conditions,[2] gives better yields. The asymmetric diphenylic diester **6a** was isolated in 52% yield, along with the previously described[2] dimer of **5**. Hydrogenolysis of **6a** gave, in quantitative yield, debenzylated **6b** which was hydrolyzed in alkaline medium; acid **6c**, which was not isolated, was converted in high yield into the dilactone **1c** by the

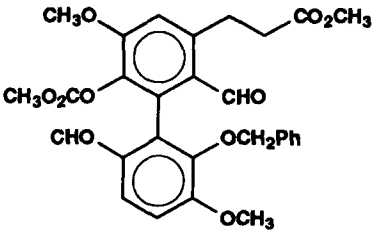


2

a R = H R' = $(CH_2)_2CO_2Me$

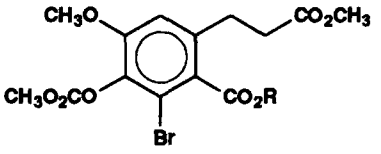
b R = CO_2Me R' = $(CH_2)_2CO_2Me$

c R = CH_2Ph R' = H



3

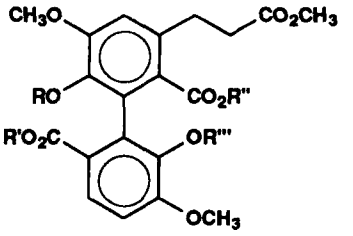
action of 10 N sulfuric acid. Compound **1c** shows the same insolubility observed for **1b** and for the symmetric dilactone **1d**;[2] it is in fact only slightly soluble in boiling DMF (from which it crystallizes)



4

a R = H

b R = Me

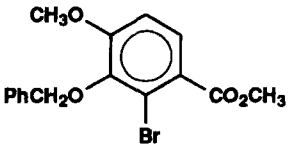


6

a R = CO_2Me, R' = R'' = Me, R''' = CH_2Ph

b R = CO_2Me, R' = R'' = Me, R''' = H

c R = R' = R'' = R''' = H



5

and consequently is not useful for the synthesis of taspine.

We are now attempting to use the Ullmann condensation product **6a** directly, with suitable protective groups, for the conversion of its side-chain into the 2-(N-dimethylamino)ethyl group of taspine. In this way, by changing the order of the reactions, we plan to form the planar dilactone system, which is responsible for the insolubility of the molecule, in the last step of the synthesis.

EXPERIMENTAL SECTION

^1H NMR spectra were determined with a Varian XL 300 instrument with chemical shifts recorded in ppm downfield from internal TMS and coupling constants in Hz. All mps. are uncorrected.

Methyl 2-Formyl-3-bromo-dihydroferulate (2a) and its 4-Methoxycarbonyl Ester (2b).- To a stirred solution of methyl 2-formyldihydroferulate[5] (16.0 g, 67.0 mmol) in 50 mL of methanol, 12.4 g

of bromine (77.0 mmol) in MeOH (10 mL) were added dropwise in 30 min at 25° with stirring. After 90 min, excess Br_2 was reduced with $Na_2S_2O_3$ (aqueous 4% sol.), then crushed ice was added until complete precipitation; the mixture was allowed to stand at 5° overnight. After filtration, 20 g of **2a** were obtained as a pale yellow solid, pure by TLC. Compound **2a** crystallizes from MeOH/H_2O (1:1), mp. 102-104°, yield 94%. ^1H NMR (acetone-d_6): δ 10.10 (CHO, s), 8.30 (OH, bs), 6.80 (H-2, s), 3.85 (CH_3OCO, s), 3.50 (CH_3O, s), 3.02 (CH_2-CH_2Ph, t, J = 7.0), 2.50 (CH_2-CH_2Ph, t, J = 7.0).
Anal. Calcd. for $C_{12}H_{13}BrO_5$: C, 45.45; H, 4.13. Found: C, 45.31; H, 4.25

The methoxycarbonyl derivative (**2b**) was obtained in 90% yield by reaction of **2a** with methyl chloroformate in anhydrous dioxane/pyridine. Compound **2b** crystallizes from MeOH/H_2O (8:2), mp. 96-98°. ^1H NMR (acetone-d_6): δ 10.10 (CHO, s), 7.02 (H-2, s), 3.88, 3.82 (CH_3OCO_2, CH_3OCO, s), 3.55 (CH_3O, s) 3.28 (CH_2-CH_2Ph, t, J = 7.0), 2.55 (CH_2-CH_2Ph, t, J = 7.0).
Anal. Calcd. for $C_{14}H_{15}BrO_7$: C, 44.82; H, 4.03. Found: C, 44.69; H, 4.15

Ullmann Coupling of 2b and 2c to Diphenylic Dialdehyde (3).- A mixture of 1 g of **2b** (2.6 mmol) and 2.56 g of **2c** (7.9 mmol)[2] was treated under nitrogen atmosphere at 180/200° in a test tube with 4 g of freshly activated copper-bronze.[4b] The copper powder was added in small portions in 20 min while stirring with a glass rod. After further heating (30 min) at the same temperature, aldehyde **2b** had completely reacted. After cooling to 25°, the reaction mixture was treated with acetone (50 mL); the insoluble components were centrifugated and exhaustively washed with acetone. The combined solution was evaporated *in vacuo* and the residue was chromatographed on silica gel [(benzene/diethyl ether (8:2)], giving **3** (450 mg, 41% yield calculated on the component **2b**) as a crystalline powder, pure by TLC; **3** crystallizes from acetone, mp. 136-139°. ^1H NMR (acetone-d_6): δ 10.02, 10.20 (2H, 2xCHO), 7.18 (H-4, s), 7.72 (H-4′, d, J_{ortho} = 7.0), 7.35 (H-5′, d, J_{ortho} = 7.0), 7.30-7.60 (5H, CH_2-Ph), 5.30 and 5.00 (CH_2-Ph, AB system, J_{AB}=13.0), 3.98, 3.90 (6H, CH_3OCO, CH_3OCO_2, s), 3.62, 3.52 (6H, 2xCH_3O, s), 3.20 (CH_2-CH_2Ph, t, J = 7.0), 2.53 (CH_2-CH_2Ph, t, J = 7.0).
Anal. Calcd. for $C_{29}H_{28}O_{10}$: C ,64.92; H, 5.26. Found: C, 64.80; H, 5.30

From the same chromatographic column, the symmetric dimer of **2c**, described in the previous note,[2] was also obtained (820 mg).

Methyl 2-Carbomethoxy-3-bromo-4-methoxycarbonyldihydroferulate (4b). - A solution of **2b** (750 mg, 2 mmol) in 20 mL of acetone, distilled over $KMnO_4$, was treated at 0-5° with 1.2 mL of Jones reagent[6] (2.2 mmol) added during 30 min. After 5 hrs at 25°, the reaction mixture was treated with crushed ice and excess CrO_3 reduced with a 4% aqueous solution of $Na_2S_2O_3$. The resultant solution was extracted with ether and the acid **4a** was removed with an ice cooled sat. solution of $NaHCO_3$, according the usual work-up; crude **4a** was treated with the required amount of diazomethane, affording 570 mg of ester **4b** (overall yield 70%). Compound **4b** crystallizes from MeOH/H2O (9:1), mp. 75-77°. ^1H NMR ($CDCl_3$): δ 6.84 (H-6, s), 3.92, 3.85 (9H, CH_3OCO_2 ,CH_3OCO, CH_3O, s),3.67 (CH_3OCOCH_2, 6), 2.85 (CH_2-CH_2Ph, t, J = 7.0), 2.63 (CH_2-CH_2Ph, t, J = 7.0).
Anal. Calcd for $C_{15}H_{17}BrO_8$: C, 44.46; H, 4.23. Found: C, 44.28; H, 4.46

Ullmann Coupling of 4b and 5 to Diphenylic Diester (6a).- A mixture of 300 mg of **4b** (0.74 mmol) and 1.0 g of 52 (2.96 mmol) was dissolved in 1.5 mL of anhydrous recently distilled dimethylformamide (DMF). The solution was warmed at 140° under nitrogen atmosphere and a suspension of 600 mg of freshly activated copper bronze[4b] in 1.0 mL of DMF was added over 30 min. The reaction mixture was refluxed for 30 min until the ester **4b** had completely reacted. After cooling at 25°, benzene was added and the insoluble components were centrifugated and exhaustively washed with benzene. The combined organic solution was washed with water, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. After chromatography on silica gel [benzene/diethyl ether (8:2)], 230 mg were obtained, as crystalline powder. The yield was 52% as based on component **4b**; **6a** crystallizes from ethanol, mp. 79-81°. MS: m/e 596 (M^+). ^1H NMR ($CDCl_3$): 7.70 (H-5′, d, J_{ortho} = 7.0), 7.20-7.60 (7H, H-4, H-4′, Ph), 4.72 (CH_2-Ph), 3.80, 3.60, 3.62, 3.58 (15H, 2xCH_3OCO, 2xCH_3O, CH_3OCO_2), 3.40 (CH_3OCOCH_2, s), 2.95 (CH_2-CH_2Ph, t, J = 7.0), 2.50 (CH_2-CH_2Ph, t, J = 7.0).

Anal. Calcd. for $C_{31}H_{32}O_{12}$: C, 62.41; H, 5.40. Found: C ,64.28; H, 5.55

Debenzylation of 6a to Diphenylic diester (6b).- A solution of 230 mg of **6a** (0.38 mmol) in 8 mL of methanol/dioxane (4:1) was treated with H_2/C-Pd (10%, 20 mg) at 25° at atmospheric pressure; after evaporation *in vacuo* of organic solvents, 195 mg of debenzylated product **6b**, pure by TLC, were obtained, yield 98%. **6b** crystallizes from MeOH, mp. 93- 95°. MS: m/e 506 (M^+). ^1H NMR ($CDCl_3$): δ 7.20 (H-5′, d, J_{ortho} = 7.5), 6.85 (H-4′, d, J_{ortho} = 7.5), 6.95 (H-4, s), 5.70 (OH, s), 3.82, 3.80, 3.68, 3.60 (15H, 2xCH_3OCO, 2xCH_3O, CH_3OCO_2), 3.50 (CH_3OCOCH_2, s), 3.10 (CH_2-CH_2Ph, t, J = 7.0), 2.82 (CH_2-CH_2Ph, t, J = 7.0).

Anal. Calcd. for $C_{24}H_{26}O_{12}$: C, 56.91; H, 5.17. Found: C, 56.78; H, 5.22

Dilactone (1c).- A solution of 194 mg of **6b** (0.38 mmol) in 3 mL of 1 N NaOH was left at 25° for 18 hrs under a nitrogen atmosphere. The solution was neutralized with 1 N H_2SO_4 and concentrated *in vacuo* to a small volume; 4 mL of 10 N H_2SO_4 were added and the solution was kept 24 hrs at 25° and 1 hr at 80°. The white solid **1c** was filtered, washed with water and finally with methanol to yield 120 mg (80%).The dilactone **1c** is insoluble in common solvents, it is soluble in trifluoroacetic acid and in boiling DMF, from which it crystallizes, mp. 270° (dec.). MS: m/e 370 (M^+).^1H NMR (CF_3COOD): δ 8.45 (H-5′, d, J_{ortho} = 7.5), 7.60 (H-4′, d, J_{ortho} = 7.5), 7.55 (H-4, s), 4.30 (6H, 2xCH_3O, s), 3.85 (CH_2-CH_2Ph, t, J = 7.0), 3.10 (CH_2-CH_2Ph, t, J = 7.0).

Anal. Calcd. for $C_{19}H_{14}O_8$: C, 61.62; H, 3.81. Found: C, 61.47; H, 3.85.

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A CONVENIENT METHOD FOR THE PREPARATION OF *cis*-3,4,8,8a-TETRAHYDRO-6H-[1,3]-DIOXEPINO[5,6-d]OXAZOLES[§]

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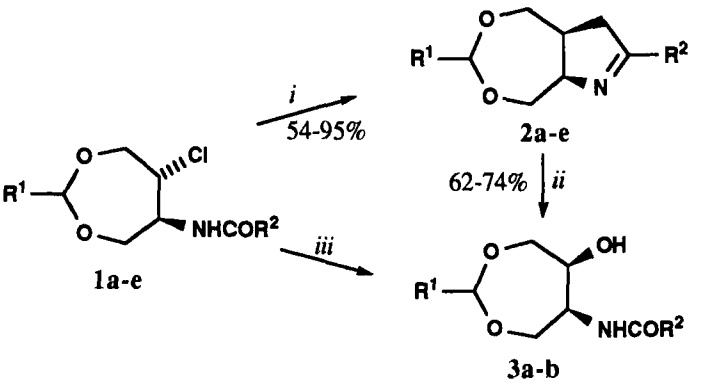
1,3-Dioxepine[1] and 2-oxazoline[2] derivatives find application in several fields, e.g. polymers, biomaterials and corrosion inhibitors. 3,4,8,8a-Tetrahydro-6H-[1,3]-dioxepino[5,6-d]oxazoles **2**, due to the combination of both above structures, may be regarded as the useful intermediates for the same



i) KOH/EtOH, reflux, 60 minutes; *ii*) KOH/H_2O, reflux, 90 minutes; *iii*) Na_2CO_3/H_2O, reflux, 90 minutes[4]