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A versatile stereospecific synthesis of the 1,3-disubstituted benzo[*a*]quinolizidine framework via 2-aryl substituted pyridines

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Abstract

The stereospecific synthesis of the 1,3-disubstituted benzo[*a*]quinolizidine **6** is described starting from the easily accessible 3-arylated-6-substituted oxazinone **2**. The skeleton is elaborated via an intramolecular aromatic substitution on the α-amino aldehyde obtained by treatment of the intermediate piperidine **4** with glycidol and consecutive oxidative cleavage of the diol.

Keywords: dehalogenation; Diels–Alder reactions; nitrogen heterocycles; pyridines.

With numerous examples we have already illustrated the usefulness of 3,5-dichloro-2*H*-1,4-oxazin-2-ones (e.g. **1**) for the synthesis of complex heterocyclic frameworks leading to natural products and analogues.[1] These compounds have turned out to be outstanding starting materials in the synthesis of, inter alia, various functionalised pyridines.[2]

In this communication, we wish to describe the use of compound **1** in the stereospecific synthesis of the 1,3-disubstituted benzoquinolizidine **6**, which displays pharmacological equivalence with the interesting class of biologically active indoloquinolizidine compounds (Scheme 1).

Our synthetic approach starts with the addition–elimination process on the previously described 6-methyl 3,5-dichloro-2*H*-1,4-oxazin-2-one **1**[1a,b] with veratrole and $AlCl_3$ in dichloromethane at room temperature yielding the 3-arylated oxazinone **2** in 91%.[1i,3] This was converted into the 2-arylated pyridine **3** via Diels–Alder reaction and concomitant loss of carbon dioxide. The cycloaddition with methyl propiolate at 80°C turned out to be highly regioselective providing 90% of the 3-substituted pyridine (and only 9% of the regioisomer). Reductive dehalogenation and concomitant conversion into the piperidine **4** by treatment with hydrogen and Pd on carbon and PtO_2 as the catalyst system in acetic acid containing K_2CO_3 (to capture the liberated HCl) at 1 atm yielded compound **4** in 92%. As expected ^1H NMR analysis revealed an all-*cis* relationship for this 2,3,5-substituted piperidine **4**.[4] A three-step sequence was further used to construct the benzoquinolizidine framework.[5] The piperidine

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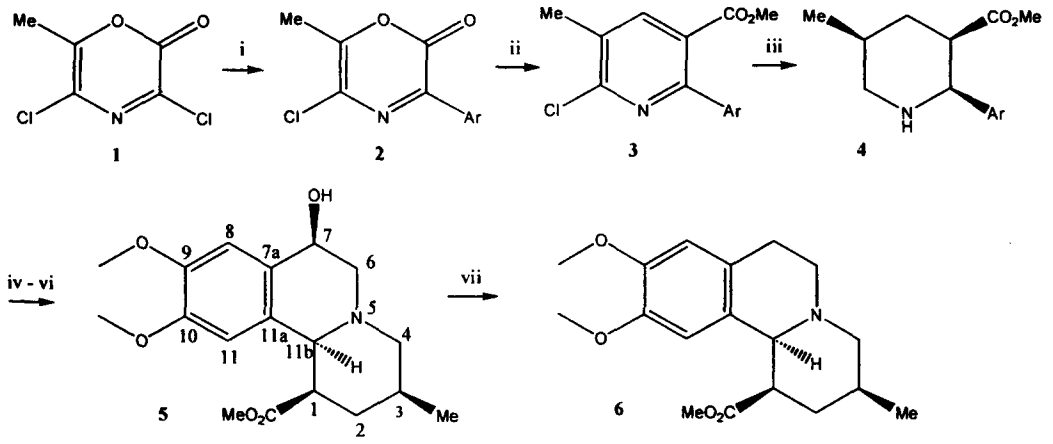
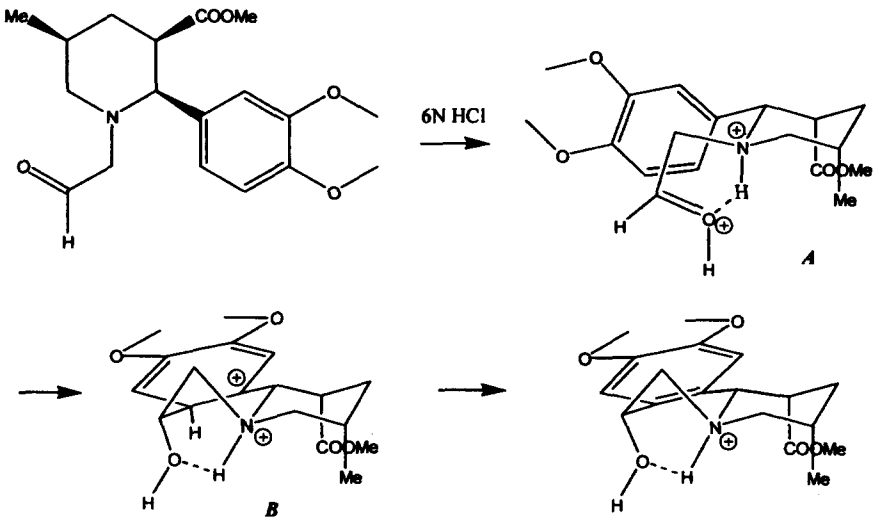


Scheme 1. Ar=3,4-dimethoxyphenyl. Reagents and conditions: (i) veratrole, $AlCl_3$, CH_2Cl_2, rt; (ii) methyl propiolate, 80°C; (iii) H_2, Pd/C, PtO_2, 1 atm, K_2CO_3, CH_3COOH, rt; (iv) glycidol, 100°C; (v) $NaIO_4$, $CHCl_3$:H_2O 1:1, pH=8, 0°C–rt; (vi) 6N HCl, rt; (vii) H_2, Pd/C, MeOH, HCl, 1 atm, rt

4 was reacted with glycidol at 100°C followed by cleavage of the vicinal diol with $NaIO_4$ in a two-phase chloroform/water system affording the α-amino aldehyde. The latter was cyclised upon treatment with 6N HCl yielding the 1,3-substituted-7-hydroxybenzo[*a*]quinolizidine **5** (72% overall yield). This cyclisation turned out to be completely stereoselective providing only one diastereoisomer pair depicted in Scheme 1. According to ^1H and ^{13}C NMR analysis ($CDCl_3$) **5** has a *trans*-fused quinolizidine system with the three substituents (1-$COOCH_3$, 3-CH_3 and 7-OH) taking an axial position. The low absorption value of the H_{11b} proton of **5** (3.41 ppm in comparison with 4.38 ppm for the analogous *cis*-fused quinolizidine system **6**; vide infra) and the presence of strong Bohlmann bands in the IR-spectrum corroborate a *trans*-fused benzoquinolizidine.[6] Also the high absorption value for C_{11b} in the ^{13}C NMR spectrum of **5** (63.0 ppm in comparison with 59.0 ppm for the analogous *cis*-fused quinolizidine system **6**; vide infra) together with a small $^1J_{CH}$ value (126 Hz), as well as the $^1J_{CH}$ values detected for C_6 (129 and 139 Hz) confirm a *trans*-fused system. The two smaller $^1J_{CH}$ values of C_{11b} and C_6 are due to the coupling with the protons H_{11b} and H_6 having a *trans*-diaxial relationship with the nitrogen lone pair thus establishing a *trans*-fused quinolizidine.[7] As no large *trans*-diaxial $^3J_{H-H}$ values are found for H_1, H_2, H_3, H_4, H_6 and H_7 the three substituents (1-$COOCH_3$, 3-CH_3 and 7-OH) adopt an axial position. Moreover, it is known from the literature[6] that an axial 3-CH_3 absorbs at lower fields (**5**: 1.08 ppm) and has a larger *J* value (**5**: $J_{CH3,H3eq}$=7 Hz) compared with an equatorial one (for the analogous benzoquinolizidine **6** bearing an equatorial 3-CH_3 we found: 0.89 ppm and $J_{CH3,H3eq}$=6.5 Hz; vide infra). Only this configuration allows an intramolecular hydrogen bond between the 7-OH and the nitrogen lone pair. Indeed, no shift of the hydroxyl absorption (4.42 ppm) is detected in the ^1H NMR spectrum of **5** upon extreme dilution.

The stereospecific ring closure can be rationalised as follows: after protonation of the aldehyde group (Scheme 2) a stabilising five-membered ring intermediate ***A*** is formed. Nucleophilic attack of the aromatic ring is only possible if the piperidine ring adopts a chair conformation with the aryl group in an equatorial position, and the methyl and ester groups in an axial position. A half chair is formed during ring closure (***B***) resulting in a *trans*-fused quinolizidine **5** with axial orientation of the substituents allowing the intramolecular hydrogen bond.

After hydrogenolysis[8] of the 7-OH the *trans*-fused system is inverted into a *cis*-fused quinolizidine **6**. Due to the absence of the intramolecular hydrogen bond, the ester and methyl groups now take the



Scheme 2.

energetically favoured equatorial position. The absence of strong Bohlmann bands in the IR-spectrum of **6** and the high absorption value of H_{11b} (4.38 ppm) in the ^1H NMR spectrum[6] as well as the low δ-value (59.0 ppm) and the large J value ($^1J_{CH}$=139 Hz) of C_{11b} in the ^{13}C NMR spectrum[7] are indicative for a *cis* benzoquinolizidine. Three large diaxial $^3J_{H-H}$ values are found for H_1, H_2, H_3 and H_4 indicating the two substituents (1-$COOCH_3$ and 3-CH_3) adopt an equatorial position. The low δ-value and small J value of the 3-CH_3 (0.89 ppm and 6.5 Hz) confirm an equatorial position.[6]

We can conclude that the described methodology opens a new way for the stereospecific synthesis of various 1,3-substituted benzo[*a*]quinolizidines as different C_3 substituents can be introduced starting from the suitable six-substituted oxazinone.[1a,b] The nature of the C_1 substituent depends upon the choice of the dienophile during the Diels–Alder reaction.

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3. All compounds described in the whole sequence display satisfactory analytical and spectroscopic results.
4. ^1H NMR of **4** (250 MHz, δ, $CDCl_3$): 0.95 (d, $J_{CH3,H5ax}$=6.5 Hz, 3H, 5-CH_3), 1.74 (m, 1H, H_{5ax}), 1.81 (d×d×d, $J_{ax4,eq4}$=11, $J_{ax4,ax3}$=11, $J_{ax4,ax5}$=11, 1H, H_{4ax}), 2.11 (d×d×d, $J_{eq4,ax4}$=11, $J_{eq4,ax3}$=5, $J_{eq4,ax5}$=5, 1H, H_{4eq}), 2.39 (d×d, $J_{ax6,eq6}$=12,

$J_{ax6,ax5}$=9, 1H, H_{6ax}), 2.77 (d×d, $J_{cq6,ax6}$=12, $J_{cq6,ax5}$=3.5, 1H, H_{6cq}), 3.08 (d×d×d, $J_{ax3,ax4}$=11, $J_{ax3,cq2}$=5, $J_{ax3,cq4}$=5, 1H, H_{3ax}), 3.57 (s, 3H, 3-$COOCH_3$), 3.87 and 3.89 (2×s, 6H, 2-Ar-(OCH_3)), 4.51 (d, $J_{cq2,ax3}$=5, 1H, H_{2cq}), 6.78 (d, J_{ortho}=8, 1H, 2-Ar-$H_{5'}$), 6.89 (d×d, J_{ortho}=8, J_{meta}=2, 1H, 2-Ar-$H_{6'}$), 6.98 (d, J_{meta}=2, 1H, 2-Ar-$H_{2'}$). It can easily be deduced that the C2 substituent takes an axial position whilst the C3 and C5 substituents have an equatorial position.

5. Procedure for the synthesis of **5**: A mixture of the piperidine **4** (10 mmol) and glycidol (12 mmol) were heated at 100°C for 2 h. The crude mixture was dissolved in $CHCl_3$ (15 cm^3) and water (15 cm^3) was added. A solution of $NaIO_4$ (10 mmol) in water (15 cm^3) was added dropwise at 0°C. A 1N NaOH solution was added until the mixture reached pH=8 and the two-phase system was stirred for 3 h. Then the organic layer was separated and the water phase was twice extracted with $CHCl_3$. The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude amino aldehyde was dissolved in HCl (6N, 50 cm^3). In case of solubility problems methanol was added and the mixture was stirred for 18 h at rt. The solvents were evaporated under reduced pressure and the residue was brought to pH=10 with water and NH_4OH. This water layer was extracted with $CHCl_3$ (3×100 cm^3). The collected organic layers were dried over $MgSO_4$ and concentrated. The crude 7-hydroxybenzo[*a*]quinolizidine **5** was purified on an Al_2O_3 column (eluent: $CHCl_3$) and recrystallised from ethanol. Yield: 72%; mp: 160–176°C decomposition; IR (NaCl) cm^{-1}: 3478 (OH), 2755, 2800 and 2836 (strong Bohlmann bands), 1733 (C=O); *m/z* (%): 355 ($M^{+\cdot}$, 13), 318 ($M^{+\cdot}$–OH, 61), 274 ($M^{+\cdot}$–OH–CO_2, 20), 248 (19), 207 (18), 190 (10), 178 (100); exact mass for $C_{18}H_{25}NO_5$: 335.1733; found: 335.1723; ^{1}H NMR (250 MHz, δ, $CDCl_3$): 1.08 (d, $J_{CH3,H3cq}$=7, 3H, 3-CH_3), 1.96 (m, 1H, H_{3cq}), 2.10 (d×d×d, $J_{ax2,cq2}$=14, $J_{ax2,cq1}$=6, $J_{ax2,cq3}$=6, 1H, H_{2ax}), 2.28 (br d, $J_{cq2,ax2}$=14, 1H, H_{2cq}), 2.69 (d×d, $J_{ax4,cq4}$=11, $J_{ax4,cq3}$=3.5, 1H, H_{4ax}), 2.73 (d×d, $J_{cq4,ax4}$=11, $J_{cq4,cq3}$=3.5, 1H, H_{4cq}), 2.73 (d×d, $J_{ax6,cq6}$=11, $J_{ax6,cq7}$=2, 1H, H_{6ax}), 2.97 (d×d, $J_{cq6,ax6}$=11, $J_{cq6,cq7}$=2, 1H, H_{6cq}), 3.10 (d×d×d, $J_{cq1,ax2}$=6, $J_{cq1,cq2}$=3, $J_{cq1,ax11b}$=3, 1H, H_{1cq}), 3.41 (br signal, 1H, H_{11b}), 3.52 (s, 3H, $COOCH_3$), 3.82 and 3.88 (2×s, 6H, Ar–OCH_3), 4.42 (d, $J_{OH,cq7}$=11, 1H, 7-OH), 4.47 (br d, $J_{cq7,OH}$=11, 1H, H_{7cq}), 6.48 and 6.84 (2×s, 2H, H_8 and H_{11}); ^{13}C NMR (100.9 MHz, δ, $CDCl_3$): 18.9 (C3-*C*H_3), 28.2 (C-3), 34.4 (C-2), 42.5 (C-1), 51.3 (COO*C*H_3), 55.7 (Ar-O*C*H_3), 55.9 (Ar-O*C*H_3), 58.5 (C-6), 61.9 (C-4), 63.0 (C-11b), 67.3 (C-7), 106.8 (C-8), 111.6 (C-11), 128.9 (C-7a), 129.5 (C11a), 147.4 (C-10), 148.8 (C-9), 174.2 (*C*$OOCH_3$).
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8. Procedure for the synthesis of **6**: A saturated solution of HCl in MeOH (5 cm^3) and Pd/C (0.25 g, 10% Pd) was added to a solution of the 7-hydroxybenzo[*a*]quinolizidine **5** (5 mmol) in MeOH (30 cm^3). Hydrogen (1 equivalent) was added via a burette. The mixture was degassed, the catalyst filtered off and washed with MeOH (200 cm^3) and CH_2Cl_2 (200 cm^3). The solvents were evaporated and the residue was brought to pH 9–10 by adding water (100 cm^3) and NH_4OH. The water layer was extracted with CH_2Cl_2 (3×100 cm^3) and the extract was dried over $MgSO_4$. After filtration and evaporation of the solvents the crude product **6** was purified by column chromatography (Al_2O_3, eluent $CHCl_3$, EtOAc); yield: 89% (oil); IR (NaCl) cm^{-1}: 2950 (C–H), 2834 (weak Bohlmann bands), 1732 (C=O); *m/z* (%): 319 ($M^{+\cdot}$, 50), 304 ($M^{+\cdot}$–CH_3, 12), 233 ($M^{+\cdot}$–H_2C=CHCOOCH_3, 12), 205 (16), 191 (100), 190 (21); exact mass for $C_{18}H_{25}NO_4$: 319.1784; found: 319.1784; ^{1}H NMR (250 MHz, δ, $CDCl_3$): 0.89 (d, $J_{CH3,H3ax}$=6.5, 3H, 3-CH_3), 1.46 (d×d×d, $J_{ax2,cq2}$=13, $J_{ax2,ax1}$=11, $J_{ax2,ax3}$=11, 1H, H_{2ax}), 1.85 (m, 1H, H_{3ax}), 2.00 (d×d×d, $J_{cq2,ax2}$=13, $J_{cq2,ax1}$=4, $J_{cq2,ax3}$=4, 1H, H_{2cq}), 2.33 (d×d, $J_{ax4,cq4}$=10.5, $J_{ax4,ax3}$=10.5, 1H, H_{4ax}), 2.50 and 2.92–3.22 (m, 4H, $H_{6cq,ax}$, $H_{7cq,ax}$), 2.53 (d×d, $J_{cq4,ax4}$=10.5, $J_{cq4,ax3}$=4, 1H, H_{4cq}), 3.08 (d×d×d, $J_{ax1,ax2}$=11, $J_{ax1,cq2}$=4, $J_{ax1,cq11b}$=4, 1H, H_{1ax}), 3.70 (s, 3H, $COOCH_3$), 3.75 and 3.84 (2×s, 6H, Ar-OCH_3), 4.38 (br signal, 1H, H_{11b}), 6.42 and 6.59 (2×s, 2H, H_8, H_{11}); ^{13}C NMR (62.5 MHz, δ, $CDCl_3$): 19.1 (C3-*C*H_3), 24.3 (C-7), 29.8 (C-2), 30.7 (C-3), 44.7 (C-1), 51.4 (C-4), 51.4 (C-6), 51.5 (COO*C*H_3), 55.7 (2× Ar-O*C*H_3), 59.0 (C-11b), 108.6 (C-8), 112.0 (C-11), 126.4 (C-7a), 127.3 (C-11a), 147.2 (C-10), 147.3 (C-9), 174.4 (*C*$OOCH_3$).