Pergamon

Tetrahedron 55 (1999) 1755–1762

TETRAHEDRON

(4*S*)-2,4-Dimethyl-2,4-dihydro-3,6-dioxo-(1*H*)-pyrazino[2,1-*b*]quinazolyl Tosylate as an Electrophilic Glycine Template

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Received 4 September 1998; revised 16 November 1998; accepted 10 December 1998

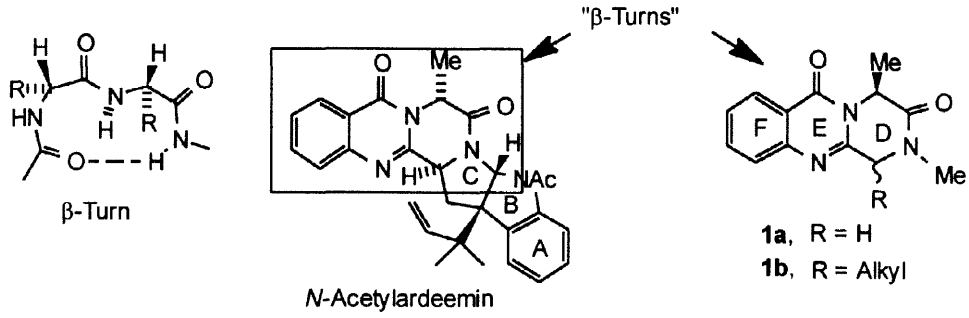
Abstract

(4*S*)-2,4-Dimethyl-2,4-dihydro-(1*H*)-pyrazino[2,1-*b*]quinazoline-3,6-dione was converted into to the *cis*-tosylate **2**, whose reactivity as an electrophilic glycine template is discussed. It was found that this compound does not give direct S_N2-type displacement of the tosyloxy group. However, the 1-hydoxy derivative **3**, obtained by hydrolysis of **2** with net retention of the stereochemistry, and its 1-methoxy derivative **4a** are electrophilic glycine templates.

Keywords: Electrophilic glycine templates, nucleophilic substitution, pyrazinoquinazolines, tosylates.

1. Introduction

N-Acetylardeemin, a fungal metabolite that reverses multiple drug resistance (MDR) in tumour cell lines [1-3] can be considered a peptidomimetic, resembling in its D-F fragment a conformationally restrained β-turn. Under this assumption, we have found that some simple *N*-acetylardeemin analogues of type **1b**, easily obtained by regio- and diastereo-selective alkylation of (4*S*)-2,4-dialkyl-2,4-dihydro-(1*H*)-pyrazino[2,1-*b*]quinazoline-3,6-diones [4-6] can retain most of the biological activity of the prototype as MDR-reversal agents. In these and other reactions [7,8] the N(2)-CH_2C=N(11) fragment of the starting compound **1a** behaves as a nucleophilic glycine template. Here we study the reactivity of electrophilic derivatives, primarily for the Friedel-Crafts type of C-C bond-forming reactions.



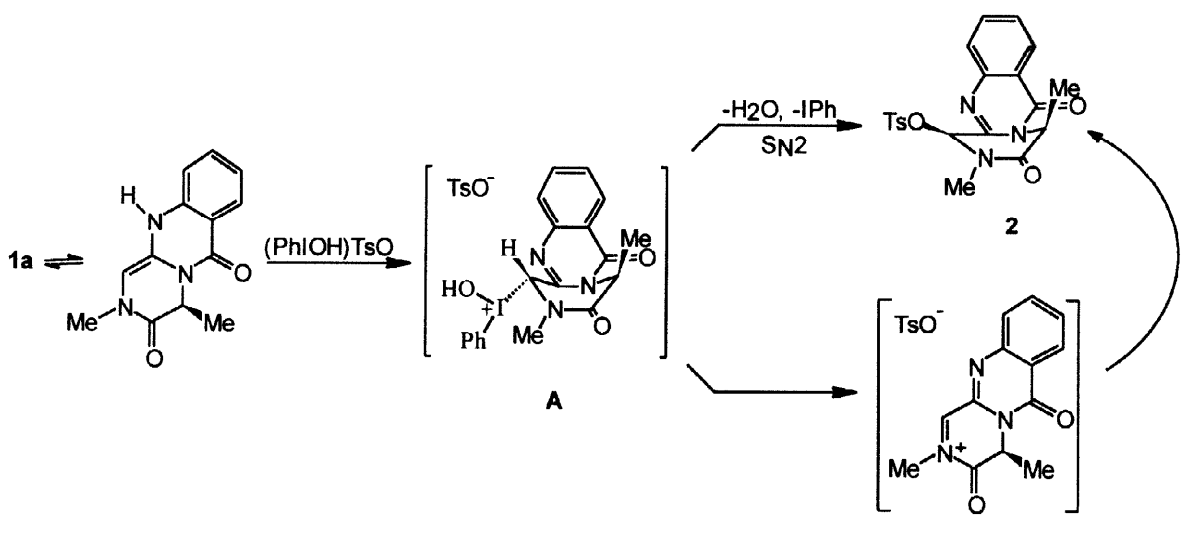
PII: S0040-4020(98)01188-0

Halogenation or diazotation derivatives of **1a** could provide the starting compounds for this study [9-12]. However, our previous experience on the easy oxidation of this system to give alcohols or ketones at C-1 [6-8] prompted us to select for this purpose the treatment of **1a** with [hydroxy(tosyloxy)iodo]benzene, a very efficient reagent for the oxidation of ketones to their α-tosyloxyderivatives [13].

2. Results and discussion

Treatment of **1a** with the above mentioned reagent gave the expected tosylate in 71% yield. The NMR data of this compound supported a *cis* relationship with pseudoaxial and pseudoequatorial positions for C(4)-Me and C(1)-OTs substituents, respectively. The chemical shift of the H-4 signal shows its coplanarity with the carbonyl group at C-6. As the C(4)-Me is anchored in a pseudoaxial position, the steric interaction with this carbonyl is avoided. The reciprocal NOE enhancements found after irradiation of H-1 and N(2)-Me protons are characteristic of *cis*-1,4-dialkyl derivatives of this system [4]. Furthermore, the absence of NOE effects between C(4)-Me and H-1 protons excludes their *cis* relationship [2], thus confirming the stereochemistry of **2**.

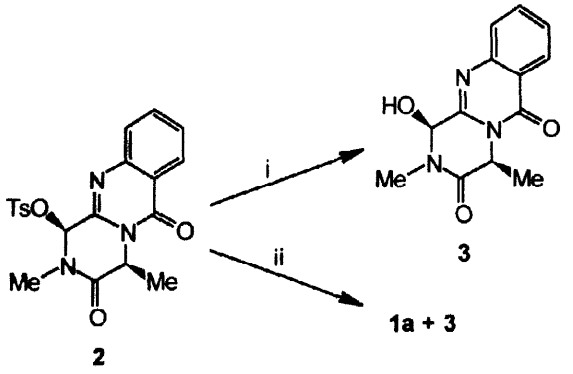
This geometry may be the result of a first electrophilic addition of $(PhIOH)^+TsO^-$ to the enamine tautomer of **1a** directed by the C(4)-substituent, to give the intermediate *trans*-hydroxy(phenyl)iodonium tosylate **A**, that yields **2** through subsequent S_N2 displacement by the tosylate anion with inversion at C-1 (Scheme 1). Alternatively, taking into account that the intermediate **A** may generate the *N*-acyliminium ion **B** [14], compound **2** may be formed through a S_N1 mechanism and equilibration of the *trans*-isomer (if any) to the most stable *cis*-isomer.



Scheme 1

Although secondary tosylates **2** might be a substrate for S_N2-type reactions with lithium dialkylcuprates [15], when it was treated with these reagents and the reaction mixture was poured onto aqueous ammonium chloride, the only product was the hydroxy derivative **3**, which was quantitatively obtained with retention of configuration (reciprocal NOE enhancements between H-1 and H-4). Attempted nucleophilic substitution of tosylate **2** with LiCN gave the same result, while the reaction with NaI gave a mixture of compounds **3** and **1a**. Given the capto-dative effects of the C=N(11) and N(2)-Me groups, compound **2** may be a

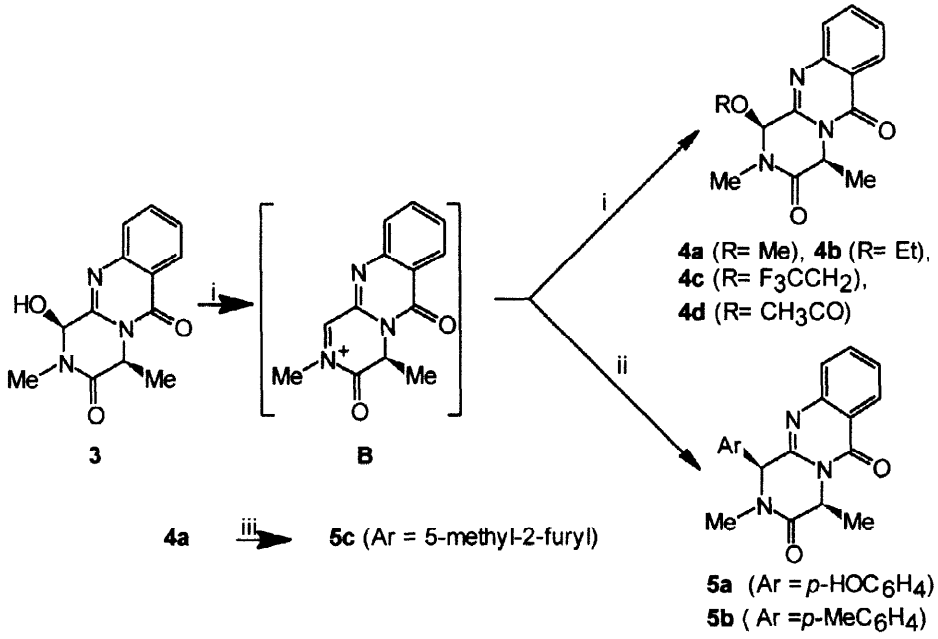
radical precursor [16], and it is probable that the reductive elimination observed in the treatment of **2** with NaI-acetone to give **1a** (Scheme 2) occurs through an electron-transfer radical mechanism, in which the iodide acts as reducing agent with formation of iodine, and acetone as a proton source. Partial reduction of other bromoglycine templates with electron-rich organometallics has been reported [17].



Scheme 2

Conversion of **3** to the *trans* benzoate under Mitsunobu conditions [18] also failed, the starting material being quantitatively recovered, thus corroborating that derivatives of **3** are inert to S_N2 reactions.

From these results we concluded that hydrolysis of tosylate **2** to the alcohol **3** either takes place in the aqueous work up of the attempted substitution reactions through cleavage of the SO_2-O bond, instead of the O-C(1) bond, with retention of configuration [19] or through an S_N1 mechanism, followed by equilibration to the most stable *cis*-isomer.



Reagents and conditions: i. TsOH (0.1 equiv.), ROH (solv.), r.t. 20 h. ii. conc. H_2SO_4 (0.1 equiv.), ArH (2 equiv.), r.t., 48 h. iii. $BF_3.Et_2O$ (1equiv.), ArH (4 equiv.), r.t., 24 h.

Scheme 3

At this point we decided to use the hydroxy derivative **3** as an equivalent of a glycine cation. Solutions of **3** in alcohols or carboxylic acids in the presence of 0.1 equivalent of *p*-toluenesulfonic acid, afforded the corresponding substituted compounds **4** (Scheme 3) with good yields and total diastereoselectivity (d.e.>99%) in favour of the *cis*-isomers. The enantiomeric purity of the products was established by the absence of splitting of any signals in the ^{1}H-NMR spectra after addition of 1 equivalent of Eu(hfc)$_3$. Friedel-Crafts reactions required electron-rich arenes, giving compounds **5a-b** with similar yields and the same diastereoselectivity.

The use of alkoxy derivatives **4** in the presence of Lewis acids instead of the alcohol **3**, in order to enhance the scope of the procedure with nuclophiles which are labile in acid conditions, was investigated by performing the reaction of **4a** with 2-methylfuran in the presence of boron trifluoride etherate [20]. Under these reaction conditions, compound **5c** was obtained. The same reaction with furan gave the derivative susbstituted by a polymer of furan at C-1.

The stereochemistry of compounds **4-5** can be explained by nucleophilic attack on the intermediate cation **B** from the α-face, *trans* with respect to the C(4)-Me group, followed by equilibration of the *trans*-isomers thus formed to the *cis*-isomers. A theoretical study of the attack on the anion [4,5] and cation (this work) derived from **1a** at C-1 by electrophiles and nucleophiles, respectively, is currently in progress.

The main conclusion of this work is that, unlike other similar tosylates, compound **2** does not react as an electrophile in bimolecular nucleophilic substitutions, while compounds **3** and **4a** are accessible glycine cation precursors, with potential in the synthesis of C(1)-substituted 2,4-dialkyl-2,4-dihydro-(1*H*)-pyrazino[2,1-*b*]quinazoline-3,6-diones, a system that is present in other fungal metabolites besides *N*-acetylardeemin, like fumiquinazolines and fiscalins [21].

3. Experimental

All reagents were of commercial quality (Aldrich, Fluka, SDS, Probus) and were used as received. Solvents (SDS, Scharlau) were dried and purified using standard techniques. Petroleum ether refers to the fraction boiling at 40-60 °C. Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel with fluorescent indicator (Macherey-Nagel Alugram Sil G/UV$_{254}$). Separations by flash chromatography were performed on silica gel (SDS 60 ACC, 230-400 mesh). Melting points were measured on a Reichert 723 hot stage microsope, and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrophotometer, with solid compounds compressed into KBr pellets and liquid compounds placed between NaCl disks. NMR spectra were obtained on a Bruker AC-250 spectrometer (250 MHz for ^{1}H, 63 MHz for ^{13}C), with Cl_3CD or DMSO-d_6 as solvents (Servicio de Espectroscopía, Universidad Complutense). When necessary, assignments were aided by DEPT, COSY and ^{13}C-^{1}H correlation experiments. Optical rotations were determined at 25 °C using a Perkin Elmer 240 polarimeter operating at the emission wavelength of a sodium lamp; concentrations are given in g/100 ml. Elemental analyses were determined by the Servicio de Microanálisis, Universidad Complutense, on a Perkin-Elmer 2400 CHN microanalyzer.

3.1.(1S,4S)-2,4-Dimethyl-1-tosyloxy-2,4-dihydro-1H-pyrazino[2,1-b]quinazoline-3,6-dione(2).

A suspension of **1a** [22] (0.5 g, 2 mmol) and (PhIOH)OTs (0.888 g, 2.2 mmol) in ethyl acetate

(35 ml) was refluxed for 8 h. Compound **2** was obtained after cooling as a white precipitate by filtration. Yield, 0.603 g (71%). Mp 183-185 °C. IR (KBr) ν 1685, 1660 cm^{-1}. ^{1}H-NMR (Cl_3CD) 8.38 (d, 1H, J = 7.8 Hz, H-7); 8.92 to 7.92 (m, 2H, H-9,10); 7.84 (d, 2H, J = 8.0 Hz, H-2', 6'); 7.81 to 7.74 (m, 1H, H-8); 7.24 (d, 2H, J = 8.0 Hz, H-3', 5'); 6.47 (s, 1H, H-1); 5.37 (q, 1H, J = 7.0 Hz, H-4); 3.21 (s, 3H, CH_3-N); 2.40 (s, 3H, CH_3'); 1.87 (d, 3H, J = 7.0 Hz, CH_3-4). ^{13}C-NMR (Cl_3CD) δ 167.0 (C-3); 153.9 (C-6); 141.3 (C-11a); 137.4 (C-9); 136.6 (C-10a); 130.5 (C-7); 129.1 (C-2', 6'); 128.2 (C-8); 125.9 (C-3', 5'); 121.0 (C-10); 118.4 (C-6a); 77.5 (C-1); 53.5 (C_4); 32.4 (N-Me); 21.4 (Me-4'); 19.5 (Me-4). Anal. Calcd. for $C_{19}H_{19}N_3O_5S$: C, 56.86; H, 4.74; N, 10.47. Found: C, 56.68; H, 4.99; N, 10.43.

3.2(1S,4S)-2,4-Dimethyl-1-hydroxy-2,4-dihydro-1H-pyrazino[2,1-b]quinazoline-3,6-dione (3).

To a solution of compound **2** (0.5 g, 1.25 mmol) in dichloromethane (15 ml) a saturated ammonium chloride solution (15 ml) was added, and the mixture was stirred at r.t. for 6 h. After separation of the organic phase, the aqueous liquids were washed with dichloromethane (3 x 15 ml). The combined organic layers were dried and concentrated to give a residue that, after purification by flash chromatography with ethyl acetate as eluent, gave **3**. Yield 0.3 g (95%). Mp 200-202 °C. $[\alpha]_D$ (0.35, Cl_3CH) +54.57. IR (KBr) ν 3520, 1685, 1660 cm^{-1}. ^{1}H-NMR (Cl_3CD) δ 8.31 (d, 1H, J = 7.8 Hz, H-7); 7.81 (t, 1H, J = 8.4 Hz, H-9); 7.68 (d, 1H, J = 7.5 Hz, H-10); 7.55 (t, 1H, J = 8.3 Hz, H-8); 5.80 (s, 1H, H-1); 5.37 (q, 1H, J = 7.1 Hz, H-4); 4.97 (br s, 1H, OH); 3.22 (s, 3H, N-Me); 1.80 (d, 3H, J = 7.1 Hz, Me-4). ^{13}C-NMR (Cl_3CD) δ 169.5 (C-3); 159.9 (C-6); 149.3 (C-11a); 146.8 (C-10a); 135.0 (C-9); 128.0 (C-7); 127.1 (C-8); 127.0 (C-10); 121,.0 (C-6a); 82.8 (C-1); 52.7 (C-4); 32.9 (N-Me); 19.5 (Me-4). Anal. Calcd. for $C_{13}H_{13}N_3O_3$: C, 60.23; H, 5.02; N, 16.22. Found: C, 60.59; H, 5.34; N, 16.33.

3.3. Nucleophilic substitutions of compound 3 with alcohols and carboxylic acids.

To a solution of compound **3** (0.1 g, 0.39 mmol) in 2 ml of the corresponding alcohol or carboxylic acid, *p*-toluenesulfonic acid (7 mg, 0.039 mmol) was added. The mixture was stirred overnight at r.t. After elimination of the unreacted solvent under reduced presure, the residue was washed with a saturated solution of sodium bicarbonate and extracted with ether (3 x 10 ml). The organic layers were dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography.

Data for **4a**. Eluent: ethyl acetate/hexane 5:5. Yield 0.104 g (99%). Mp 189-191 °C. $[\alpha]_D$ (2.4, EtOH) +152.0. IR (KBr) ν 1686, 1590 cm^{-1}. ^{1}H-NMR (Cl_3CD) δ 8.29 (d, 1H, J = 8.0 Hz, H-7); 7.78 (t, 1H, J = 7.5 Hz, H-9); 7.70 (d, 1H, J = 7.9 Hz, H-10); 7.52 (t, 1H, J = 7.4 Hz, H-8); 5.30 (q, 1H, J = 7.1 Hz, H-4); 5.20 (s, 1H, H-1); 3.57 (s, 3H, OCH_3); 3.19 (s, 3H, N-Me); 1.73 (d, 3H, J = 7.1 Hz, Me-4). ^{13}C-NMR (Cl_3CD) δ 169.3 (C-3); 160.0 (C-6); 146.9(C-11a); 146.5 (C-10a); 134.7 (C-9); 127.7 (C-7); 127.6 (C-8); 126.8 (C-10); 120.9 (C-6a); 90.3 (C-1); 57.2 (OCH_3); 52.7 (C-4); 33.7 (N-Me); 19.2 (Me-4) . Anal. Calcd. for $C_{14}H_{15}N_3O_3$: C, 61.54; H, 5.49; N, 15.38. Found: C, 61.80; H, 5.58; N, 15.50.

Data for **4b**. Eluent: ethyl acetate/hexane 5:5. Yield 0.109 g (99%). Mp 187-188 °C. $[\alpha]_D$ (1.0, EtOH) +102.1. IR (KBr) ν 1679, 1591 cm^{-1}. ^{1}H-NMR (Cl_3CD) δ 8.22 (d, 1H, J = 7.9 Hz, H-7); 7.55 to 7.75 (m, 2H, H-9,10); 7.41 (t, 1H, J = 7.4 Hz, H-8); 5.25 (q, 1H, J = 7.0 Hz, H-4); 5.23 (overlapped s, 1H, H-1); 3.71 (q, 2H, J = 6.8 Hz, CH_2'); 3.05 (s, 3H, N-Me); 1.65 (d, 3H, J = 7.0 Hz, Me-4); 1.10 (t, 3H, J = 6.8 Hz, CH_3'). ^{13}C-NMR (Cl_3CD) δ 169.1 (C-3); 160.2 (C-6);

147.3 (C-11a); 147.0 (C-10a); 134.8 (C-9); 127.8 (C-7); 127.6 (C-8); 126.9 (C-10); 121.0 (C-6a); 88.9 (C-1); 65.3 (CH_2'); 52.9 (C-4); 33.7 (N-Me); 19.3 (Me-4); 15.1 (CH_3'). Anal. Calcd. for $C_{15}H_{17}N_3O_3$: C, 62.72; H, 5.92; N, 14.63. Found: C, 62.99; H, 6.09; N, 14.78.

Data for **4c**. Eluent: ethyl acetate/hexane 8:2. Yield 0.066 g (50%). Mp 178-181 °C. $[\alpha]_D$ (0.3, EtOH) +46.5. IR (KBr) ν 1679, 1598 cm^{-1}. ^{1}H-NMR (Cl_3CD) δ 8.32 (d, 1H, J = 8.1 Hz, H-7); 7.83 (t, 1H, J = 8.2 Hz, H-9); 7.73 (d, 1H, J = 7.9 Hz, H-10); 7.58 (t, 1H, J = 8.0 Hz, H-8); 5.46 (s, 1H, H-1); 5.35 (q, 1H, J = 7.1 Hz, H-4); 4.30 (m, 1H, CH_2); 4.11 (m, 1H, CH_2); 3.22 (s, 3H, N-Me); 1.35 (d, 3H, J = 7.1 Hz, Me-4). ^{13}C-NMR (Cl_3CD) δ 169.5 (C-3); 160.1 (C-6); 147.0 (C-11a); 145.6 (C-10a); 134.9 (C-9); 128.2 (C-7); 127.7 (C-8); 126.9 (C-10); 121.4 (C-6a); 89.7 (C-1); 52.5 (C-4); 33.1 (N-Me); 29.7 (CH_2); 19.5 (Me-4). Anal. Calcd. for $C_{15}H_{14}F_3N_3O_3$: C, 52.79; H, 4.11; N, 12.32. Found: C, 53.01; H, 4.44; N, 12.52.

Data for **4d**. Eluent: ethyl acetate/hexane 7:3. Yield 0.058 g (50%). Mp 183-185 °C. $[\alpha]_D$ (0.5, EtOH) + 76.6. IR (KBr) ν 1698, 1680, 1597 cm^{-1}. ^{1}H-NMR (Cl_3CD) δ 8.31 (d, 1H, J = 8.0 Hz, H-7); 7.84 to 7.71 (m, 2H, H-9, 10); 7.56 (m 1H, H-8); 6.92 (s, 1H, H-1); 5.42 (q, 1H, J = 7.1 Hz, H-4); 3.18 (s, 3H, N-Me); 2.16 (s, 3H, $COCH_3$); 1.80 (d, 3H, J = 7.1 Hz, Me-4) . ^{13}C-NMR (Cl_3CD) δ 169.7 (CO); 169.3 (C-3); 159.8 (C-6); 147.0 (C-11a); 145.6 (C-10a); 134.9 (C-9); 128.1 (C-7); 127.8 (C-8); 126.8 (C-10); 120.9 (C-6a); 81.5 (C-1); 52.7 (C-4); 33.6 (N-Me); 20.9 ($COCH_3$); 19.5 (Me-4). Anal. Calcd. for $C_{15}H_{15}N_3O_4$: C, 59.80; H, 4.98; N, 13.95. Found: C, 59.87; H, 4.87; N, 13.72.

3.4. Nucleophilic substitutions in compound 3 with arenes (5).

To a suspension of compound **3** (0.1 g, 0.39 mmol) in the corresponding arene (0.78 mmol), 5 ml of concentrated sulfuric acid was added, and the mixture was stirred for 48 h. After addition of ice and extraction with ethyl acetate, the organic layers were washing with water, dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography.

Data for **5a**. Eluent: ethyl acetate/hexane 9:1. Yield 0.077 g (60%). Mp 173-175 °C. $[\alpha]_D$ (0.3, EtOH) +34.5. IR (KBr) ν 3567, 1678, 1596 cm^{-1}. ^{1}H-NMR (Cl_3CD) δ 8.24 (d, 1H, J = 7.8 Hz, H-7); 7.81 (m, 2H, H-9, 10); 7.48 (m, 1H, H-8); 7.31 (d, 2H, J = 9.0 Hz, H-2', 6'); 6.82 (d, 2H, J = 9.0 Hz, H-3', 5'); 6.30 (br s, 1H, OH); 5.64 (s, 1H, H-1); 5.37 (q, 1H, J = 6.9 Hz, H-4); 3.24 (s, 3H, N-Me); 1.47 (d, 3H, J = 6.9 Hz, Me-4). ^{13}C-NMR (Cl_3CD) δ 168.9 (C-3); 160.5 (C-6); 156.9 (C-4'); 150.2 (C-11a); 147.3 (C-10a); 135.0 (C-9); 127.6 (C-2', 6'); 127.4 (C-7); 127.2 (C-8); 126.9 (C-1'); 126.8 (C-10); 120.3 (C-6a); 116 (C-3', 5'); 65.2 (C-1); 52.7 (C-4); 33.4 (N-Me); 18.3 (Me-4). Anal. Calcd. for $C_{19}H_{17}N_3O_3$: C, 68.06; H, 5.07; N, 12.53. Found: C, 68.07; H, 5.00; N, 12.52.

Data for **5b**. Eluent: ethyl acetate/hexane 9:1. Yield 0.086 g (67%). Mp 199-200 °C. $[\alpha]_D$ (0.2, EtOH) +23.6. IR (KBr) ν 1683, 1588 cm^{-1}. ^{1}H-NMR (Cl_3CD) δ 8.25 (d, 1H, J = 7.4 Hz, H-7); 7.82 to 7.73 (m, 2H,H-9, 10); 7.49 (t, 1H, J = 7.2 Hz, H-8); 7.40 (d, 2H, J = 8.2 Hz,H-2', 6'); 7.20 (d, 2H, J = 8.2 Hz, H-3', 5'); 5.71 (s, 1H, H-1); 5.38 (q, 1H, J = 7.2 Hz, H-4); 3.23 (s, 3H, N-Me); 2.33 (s, 3H, Me-4'); 1.44 (d, 3H, J = 7.2 Hz, Me-4). ^{13}C-NMR (Cl_3CD) δ 168.6 (C-3); 160.4 (C-6); 150.2 (C-11a); 147.4 (C-10a); 138.8 (C-1'); 134.8 (C-9); 132.7 (C-4'); 129.9 (C-3', 5'); 127.4 (C-7); 127.3 (C-8); 126.8 (C-10); 120.4 (C-6a); 65.4 (C-1); 52.7 (C-4); 34.2 (N-Me); 21.1 (Me-4'); 18.3 (Me-4). Anal. Calcd. for $C_{20}H_{19}N_3O_2$: C, 72.07; H, 5.70; N, 12.61. Found: C, 71.77; H, 5.68; N, 12.52.

3.5. Nucleophilic substitution in compound 4a with arenes (5c).

To a solution of compound **4a** (0.2 g, 0.73 mmol) in dry ether was added consequently BF_3-etherate (0.1 ml, 0.73 mmol) and 2-methylfuran (0.23 ml, 4 mmol). The mixture was stirred at r.t. for 24 h, and then poured into a mixture of EtOAc (20 ml) and ice-saturated $NaHCO_3$ (20 ml). The aqueous phase was further extracted with EtOAc (2 x 20 ml), the organic layers were washing with water, dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography with ethyl acetate as eluent giving **5c**. Yield 0.89 g (78%). Mp 185-187 °C. $[\alpha]_D$ (0.55, EtOH) +26.7. IR (KBr) ν 1690, 1589 cm^{-1}. ^{1}H-NMR (Cl_3CD) δ 8.29 (d, 1H, J = 8.0 Hz, H-7); 7.81 to 7.67 (m, 2H, H-9, 10); 7.51 (t, 1H, J = 8.1 Hz, H-8); 6.30 (d, 1H, J = 3.1 Hz, H-3'); 5.96 (dd, 1H, J = 3.1 and 1.0 Hz, H-4'); 5.60 (s, 1H, H-1); 5.38 (q, 1H, J = 7.1 Hz, H-4); 3.16 (s, 3H, N-Me); 2.25 (s, 3H, Me-5'); 1.71 (d, 3H, J = 7.1 Hz, Me-4). ^{13}C-NMR (Cl_3CD) δ 167.7 (C-3); 167.6 (C-5'); 160.3 (C-6); 153.7 (C-11a); 147.7 (C-10a); 146.2 (C-2'); 134.7 (C-9); 127.3 (C-7); 127.1 (C-8); 126.8 (C-10); 120.4 (C-6a); 110.7 (C-3'); 106.8 (C-4'); 61.0 (C-1); 52.6 (C-4); 33.3 (N-Me); 18.0 (Me-4); 13.6 (Me-5'). Anal. Calcd. for $C_{18}H_{17}N_3O_3$: C, 66.87; H, 5.26; N, 13.00. Found: C, 66.92; H, 5.39; N, 12.95.

4. Acknowledgements

We thank CICYT for financial support (Projects SAF94-0517 and SAF97-0143).

5. References

[1] Karwowsky JP, Jackson M, Rasmussen RR, Humphrey PE, Poddig JB, Kohl WL, Scherr MH, Kadam S, McAlpine JB. J. Antibiot. 1993;46:374-379.

[2] Holchlowki JE, Mullally MM, Spanton SG, Whittern DN, Holl P, McAlpine JB. J. Antibiot. 1993;46:380-386.

[3] Marsden SP, Depew KM, Danishefsky SJ. J. Am. Chem. Soc. 1994;11:11143-11144.

[4] Martín-Santamaría S, Buenadicha F, Espada M, Söllhuber M, Avendaño C. J. Org. Chem. 1997;62:6424-6428.

[5] Martín-Santamaría S, Espada M, Avendaño C. Tetrahedron, 1997; 53:16795-16802.

[6] Buenadicha F, Bartolomé MT, Aguirre MJ, Avendaño C, Söllhuber M. Tetrahedron: Asymmetry 1998;9:483-501.

[7] Fernández M, Heredia ML, de la Cuesta E, Avendaño C. Tetrahedron, 1998;54:2777-2784.

[8] Bartolomé MT, Buenadicha F, Avendaño C, Söllhuber M. Tetrahedron: Asymmetry 1998;9:249-258.

[9] Schöllkopf U, Neubauer HJ, Hauptreif M. Angew. Chem. Int. Ed. Engl. 1985;24:1066-1067.

[10] Sinclair PJ, Zhai D, Reibenspies J, Williams RM. J. Am. Chem. Soc. 1986;108:1103-1104.

[11] Schöllkopf U, Hupfeld B, Kuper S, Egert E, Dyrbusch M. Angew. Chem. Int. Ed. Engl. 1988;27:433-434.

[12] Badran TW, Easton CJ, Koimba K, May BL, Schliebs DM, Tiekink ERT. Tetrahedron:Asymmetry 1993;4:197-200.

[13] Koser GF, Relenyi AG, Kalos AN, Rebrovic L, Wettach RH. J. Org. Chem. 1982;47:2487-2489.

[14] Hiemstra H, Speckamp WN. Additions to *N*-acyliminium ions. In: Trost B, Fleming I, Heathcock CH, editors. Comprehensive Organic Synthesis. Pergamon Press, 1991:1047-1056

[15] Johnson CR, Dutra GA. J. Am. Chem. Soc. 1973;95:7777-7781.

[16] Viehe HG, Merényi R, Stella L, Janousek Z. Angew. Chem. Int. Ed. Engl. 1979;18:917-932.

[17] Williams RM, Sinclair PJ, Zhai D, Chen D. J. Am. Chem. Soc. 1988;110:1547-1557.

[18] Mitsunobu O. Synthesis 1981;1-43.

[19] Chang FC. Tetrahedron Lett. 1964;305-309.

[20] Ben-Ishai D, Satati I, Bernstein Z. Tetrahedron 1976;32:1571-1573.

[21] Wang H, Ganesan A. J. Org. Chem. 1998;63:2432-2433.

[22] Rajappa S, Advani BG. Tetrahedron 1973;29:1299-1302.