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Short stereocontrolled synthesis of *trans* and *cis*-tetrahydro-pyrazinoisoquinolinediones

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Abstract—Addition of aldehyde dimethyl acetals (here acetaldehyde) to unisolated *O*-trimethylsilyl derivatives of 1-acetyl-3-arylmethylpiperazine-2,5-diones (here 2,5-dimethoxyphenyl), in the presence of TMSOTf as the catalyst, gave nearly quantitatively the corresponding *N*-methoxyalkyl derivatives which, under acidic treatment, gave in very good yield through a Pictet–Spengler-type reaction involving *N*-acyliminium cations (6*S**,11a*R**)-2-acetyl-6-alkyl-3,6,11,11a-tetrahydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4-diones. Epimerization of the 11a-stereocentre was accomplished by radical bromination, spontaneous hydrobromide elimination and catalytic hydrogenation, to give the (6*S**,11a*S**)-isomers. We propose these compounds as precursors of tetrahydroisoquinoline antitumour antibiotics.

Many tetrahydroisoquinoline antitumour antibiotics, such as saframycins and ecteinascidins, are widely studied cytotoxic agents.[1] Their development as antitumour drugs, which is headed by ecteinascidin 743 (E-743) currently undergoing advanced clinical trials, has been limited by their natural scarcity and the complexity of their synthesis.[2–6] Although it is known that most of the biological activity of ET-743 is maintained in simpler synthetic analogues such as phtalascidin,[7,8] structure–activity correlations within this group of antibiotics are relatively unexplored[9–12] because most of the synthetic work carried out so far has focused on their total synthesis (Fig. 1).

We propose that the title compounds bearing adequate substituents at ring *A* and C-6 could be precursors of these antibiotics or their analogues since they contain rings *A*-*C*, an *N*-acetyl group to facilitate the formation of C(3) benzylidene derivatives by condensation with aromatic aldehydes, and two carbonyl groups that can be manipulated either to elaborate rings *E*-*D* by aromatic substitution (C(1)=O) or to introduce substituents

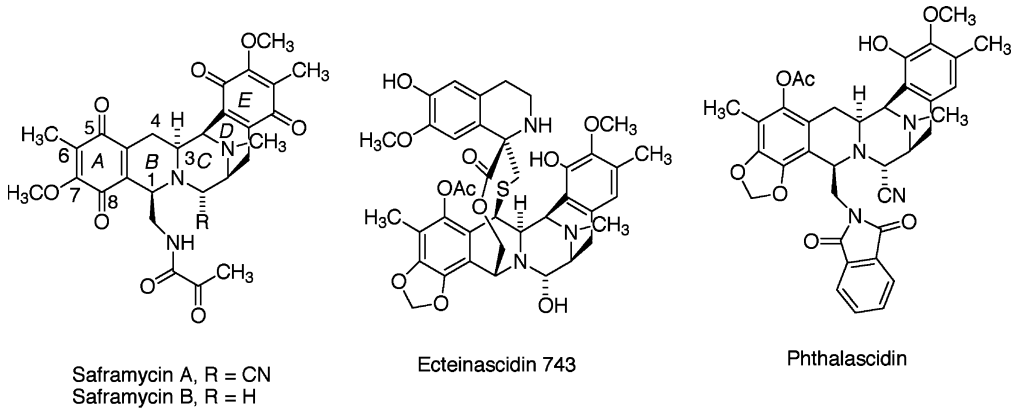

Figure 1.

Keywords: acetals; *N*-acyliminium cations; aromatic substitution; annulations; epimerization.
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such as cyano at C-4 by previous reduction and formation of transient iminium species.

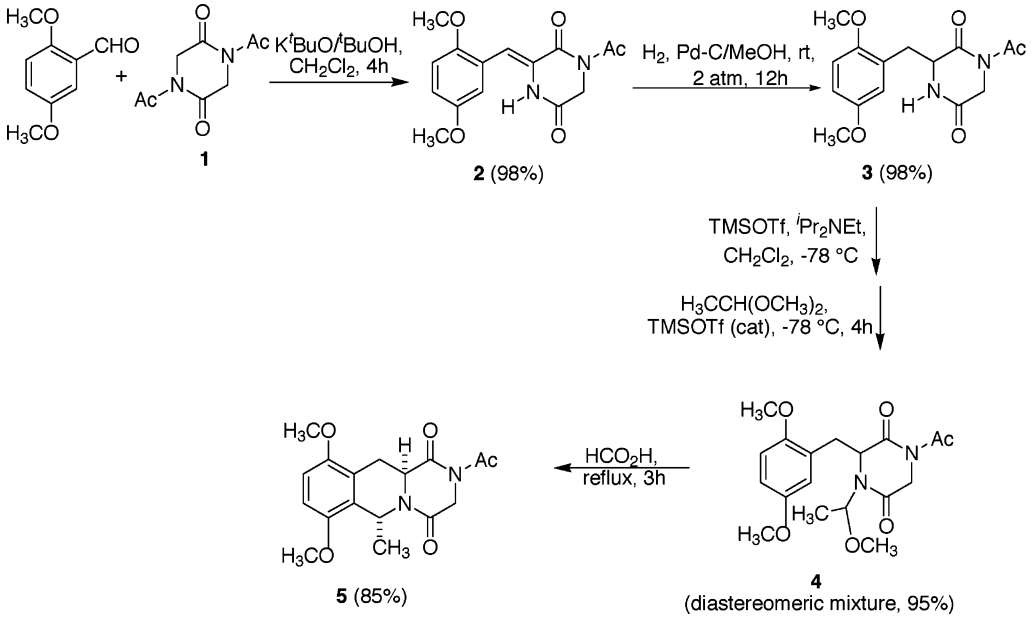
We here report an efficient route to obtain (6*S**,11a*R**) and (6*S**,11a*S**)-2-acetyl-7,10-dimethoxy-6-methyl-3,6,11,11a-tetrahydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4-diones (**5** and **7**) as model compounds through a Pictet–Spengler-type reaction involving *N*-acyliminium cations.

Compound **2** was obtained (98%) by condensation in K^{t}BuO/^{t}BuOH of 2,5-dimethoxybenzaldehyde with **1** when CH_2Cl_2 was used as solvent instead of DMF,[13] since the insolubility of the product drove the equilibrium to completion. After reduction under standard conditions, compound **3** was *N*-alkylated with acetaldehyde dimethylacetal by using trimethylsilyl triflate to activate the unsubstituted lactam as nucleophile and the acetal as electrophile.[14,15] The success of this *N*-amidoalkylation may be explained considering that the catalyst forms a triflate-acetal ion pair that fragments to methyl ethylydeneoxonium triflate, which is subsequently trapped by the *O*-trimethylsilyl derivative of **3**. Compound **4**, obtained as a mixture of diastereomers, underwent an *N*-acyliminium ion-mediated *6-exo-trig* cyclization in refluxing formic acid to give the *trans*-isomer (±)-**5** as the only product in 85% yield (Scheme 1).

It is significant that, besides the good yield, these reaction conditions are compatible with the *N*-acetyl group necessary to facilitate the planned subsequent condensation, while a previously described procedure gave ca. 50% yield of a mixture of (±)-**5** with its *N*-deacetyl derivative,[16] where **5** was the minor component. We have also corroborated that our method allows variations of ring *A* by using different aromatic aldehydes, as well as variations of the C(6)-substituent with other dimethyl acetals.

Although the *trans*-relationship between H-6 and H-11a protons in compound **5**[17] is opposite to that of ring *B* in the antibiotics above mentioned, this stereochemistry was the expected one for a cyclization mediated by acyliminium cations, since these ions would adopt an *E*-configuration in order to minimize the steric interactions between the R substituent (CH_3 in the case of compound **4**) and the C(5)=O group of the piperazinedione ring (Fig. 2).

In a very advanced pentacyclic precursor of saframycin B, Kubo achieved the epimerization of a benzylic position, corresponding to C-6 in **5**, through *N*-oxidation of an α-amine group to give an iminium cation that was subsequently reduced.[18] Since this protocol cannot be applied to the lactam nitrogen of compound **5**, we



Scheme 1.

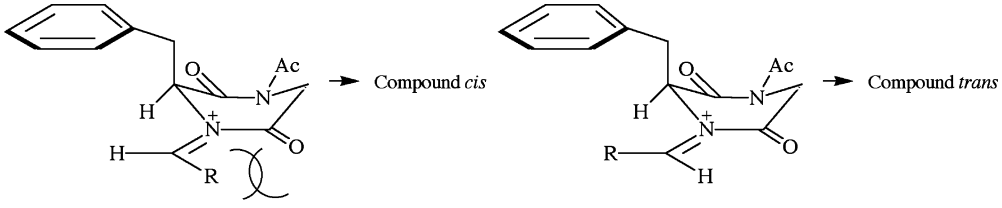
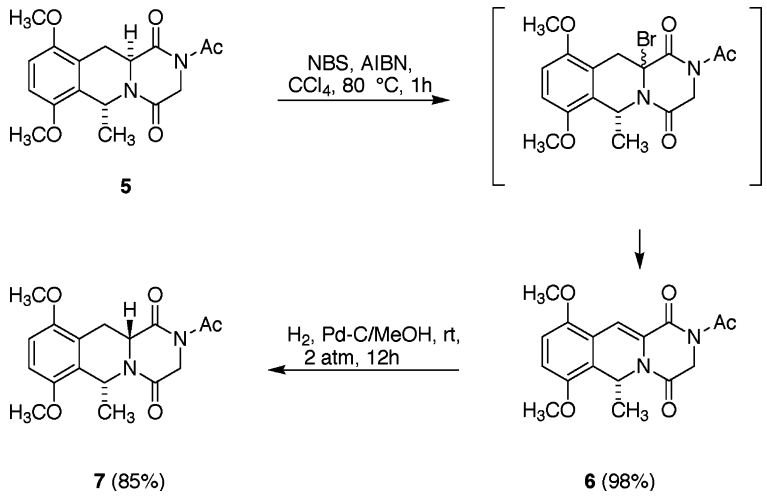


Figure 2.



Scheme 2.

planned to obtain its *cis*-isomer by catalytic hydrogenation of the unsaturated compound **6**. With this aim, compound **2** was transformed into the corresponding *N*-methoxyalkyl derivative, but all cyclization attempts to give **6** were unsuccessful. Next, we studied the epimerization of the stereocentre C-11a through a regioselective bromination in radical conditions because, in spite of the presence of two benzylic positions, we expected a radical intermediate at that stereocenter, taking into account its captodative character.[19] In fact, the reaction of **5** with NBS and AIBN in CCl_4 gave quantitatively the unsaturated compound **6** which, after catalytic hydrogenation gave a very good yield of the *cis*-isomer (±)-**7** (Scheme 2).

In conclusion, the detailed study of the tandem *N*-alkylation–Pictet–Spengler-type reactions on 3-arylmethylpiperazine-2,5-diones has progressed from the discovery of a very much improved *N*-alkylation procedure to the optimization of the subsequent cyclization[20] and, although this cyclization is not possible in arylmethylydene derivatives, the imposed *trans*-relationship between H-6 and H-11a protons may be reverted by radical bromination followed by catalytic hydrogenation.[21]

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17. The *trans*-relationship between protons H-6 and H-11a in **5** was confirmed by conclusive NOE experiments (H-11a and C(6)-methyl).
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19. Caballero, E.; Avendaño, E.; Menéndez, J. C. *Tetrahedron* **1999**, *55*, 14185–14198.
20. *N-Amidoalkylation of* **3** *and cyclization of* ***4***. Synthesis of (±)-**5**: To a solution of **2** (500 mg, 1.63 mmol) in dry CH_2Cl_2 (25 mL), under an Ar atmosphere and at −78°C was added with stirring $^{i}Pr_2NEt$ (0.31 mL, 1.79 mmol) and TMSOTf (0.35 mL, 1.96 mmol). After 4 h at the same temperature, acetaldehyde dimethyl acetal (0.21 mL, 1.96 mmol) and TMSOTf (0.01 mL) were added, and the reaction was kept for additional 4 h. This mix-

ture was poured onto a saturated $NaHCO_3$ aqueous solution and extracted with CH_2Cl_2 (30 mL×3). The combined extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered and concentrated. Flash chromatography of the crude product (hexane/ethyl acetate, 3:2) gave pure **4** (560 mg, 95%) as a 1:1 mixture of diastereomers. IR (KBr) 1699 and 1651 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 6.74 (s, 2H), 6.73 (s, 2H), 6.72 (d, 1H, $J=2.0$ Hz), 6.59 (d, 1H, $J=2.0$ Hz), 5.74 (q, 1H, $J=6.1$ Hz), 5.65 (q, 1H, $J=6.2$ Hz), 4.79 (d, 1H, $J=17.8$ Hz), 4.76 (d, 1H, $J=17.9$ Hz), 4.40 (dd, 1H, $J=8.8$ and 5.5 Hz), 4.34 (dd, 1H, $J=9.5$ and 5.8 Hz), 3.91 (d, 1H, $J=17.8$ Hz), 3.71 (s, 3H), 3.70 (s, 3H), 3.69 (s, 3H), 3.66 (s, 3H), 3.64 (d, 1H, $J=17.9$ Hz), 3.41 (s, 3H), 3.34–3.18 (m, 3H), 3.12 (s, 3H), 3.04 (dd, 1H, $J=13.4$ and 9.0 Hz), 2.45 (s, 3H), 2.40 (s, 3H), 1.39 (d, 1H, $J=6.2$ Hz), 1.37 (d, 1H, $J=6.1$ Hz); δ_C (62.5 MHz, $CDCl_3$) 171.2, 167.6, 167.1, 165.6, 165.5, 153.3, 153.2, 151.6, 151.4, 123.8, 123.7, 117.1, 113.0, 112.9, 110.9, 110.7, 81.2, 81.1, 57.8, 56.7, 55.8, 55.5, 55.4, 55.4, 55.3, 55.2, 53.3, 46.0, 45.7, 34.0, 33.9, 26.7, 26.6, 19.7, 18.5. Anal. calcd for $C_{18}H_{24}N_2O_6$: C, 59.33; H, 6.64; N, 7.69. Found: C, 58.98; H, 6.50; N, 7.60.

21. A solution of **4** (150 mg, 0.41 mmol) in formic acid (8 mL) was refluxed for 3 h. The solution was cooled to rt and poured onto a saturated $NaHCO_3$ aqueous solution and extracted with CH_2Cl_2 (10 mL×3). The combined extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered and evaporated. The residue was chromatographed using ethyl acetate/hexane (8:2) as eluent to give pure (±)-**5** (116 mg, 85%): mp 208°C (lit.[16] 206–207°C). δ_C (62.5 MHz, $CDCl_3$) 171.9, 168.2, 161.5, 150.7, 149.7, 126.8, 121.0, 108.4, 108.2, 55.6, 55.5, 52.8, 45.8, 44.6, 27.6, 27.3, 18.4.

*Isomerizarion of **5**. Synthesis of (±)-**6***: A solution of **5** (13 mg, 0.039 mmol), AIBN (0.6 mg, 0.004 mmol) and NBS (7 mg, 0.04 mmol) in CCl_4 (2 mL) was refluxed under an Ar atmosphere for 1 h. The unreacted NBS was filtered from the cooled reaction, the solvent was evaporated under reduced pressure and the residue was chromatographed (ethyl acetate/hexane, 8:2) to give (±)-**6** (13 mg, ~100%): mp 170–171°C, IR (KBr) 1697 and 1621 cm^{-1}, δ_H (250 MHz, $CDCl_3$) 7.60 (s, 1H, H-11), 6.86 (d, 1H, $J=9.0$ Hz, H-9), 6.74 (d, 1H, $J=9.0$ Hz, H-8), 6.17 (q, 1H, $J=6.6$ Hz, H-6), 4.96 (d, 1H, $J=17.6$ Hz, H-3), 3.94 (d, 1H, $J=17.6$ Hz, H-3), 3.84 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 2,66 (s, 3H, Ac), 1.26 (d, 1H, $J=6.6$ Hz, 6-Me); δ_C (62.5 MHz, $CDCl_3$) 172.1 (Ac), 161.8 (C-1), 160.7 (C-4), 150.2 (C-10), 148.7 (C-7), 125.0 and 125.1 (C-6a and C10a), 118.2 (C-11a), 109.8 (C-11), 56.0 and 55.8 (OMe), 44.9 (C-6), 45.5 (C-3), 27.1 (6-Me), 19.1 (Ac). Anal. calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8,48. Found: C, 61.57; H, 5.32; N, 8.16.

*Compound (±)-**7***: mp 153–154°C, IR (KBr) 1713 and 1674 cm^{-1}, δ_H (250 MHz, $CDCl_3$) 6.75 (s, 2H, H-8 and H-9), 5.83 (q, 1H, $J=6.7$ Hz, H-6), 5.13 (d, 1H, $J=16.9$ Hz, H-3), 4.06 (dd, 1H, $J=12.2$ and 4.4 Hz, H-11a), 3.82 (m, 2H, H-11 and H-3), 3.81 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 2.76 (dd, 1H, $J=16.0$ and 12.2 Hz, H-11), 2.64 (s, 3H, Ac), 1.33 (d, 1H, $J=6.7$ Hz, 6-Me); δ_C (62.5 MHz, $CDCl_3$) 171.1 (Ac), 168.3 (C-1), 165.1 (C-4), 150.0 and 149.1 (C-10 and C-7), 127.5 and 121.8 (C-6a and C10a), 109.8 and 109.4 (C-8 and C-9), 56.5 (C-6), 55.9 and 55.6 (OMe), 45.8 and 45.7 (C-11a and C-3), 27.2 (6-Me), 21.9 (C-11), 19.1 (Ac). Anal. calcd for $C_{17}H_{20}N_2O_5$: C, 61.44; H, 6.07; N, 8.43. Found: C, 61.50; H, 6.02; N, 8.17.