SYNTHESIS OF 6-FLUOROQUINOLONES SUBSTITUTED AT C-7 BY 1'-DEMETHYLLINCOMYCIN AND BY DIHYDROCONESSIMINE

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Abstract -- The boron-chelated carboxylic acid of 6,7-difluoroquinolone (**8**) was substituted at C-7 by the 2,3,4,7-tetra-*Q*-acetate of 1'-demethyllincomycin (**4**) and by dihydroconessimine (**14**). The resulting dechelated products did not reveal any antibacterial activity. A new efficient procedure for the preparation of the 2,3,4,7-tetra-*Q*-acetate of 1'-demethyllincomycin (**4**) is proposed.

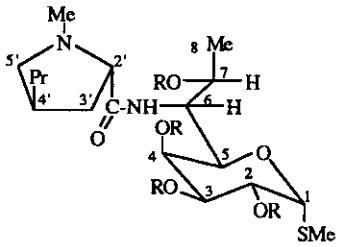
Considerable efforts have been devoted during recent years towards the synthesis of new 6-fluoroquinolones as highly efficient antibacterial agents.[1] Structure-activity relationship studies have shown that substitution of their aromatic ring at C-7 by specifically substituted pyrrolidine unit markedly enhance their *in vitro* antibacterial activity.[1] These biological results prompted us to attempt the covalent association of a 6-fluoroquinolone (**7**) with two pyrrolidine containing substances: 2,3,4,7-tetra-*Q*-acetyl-1'-demethyllincomycin (**4**) and dihydroconessimine (**14**),[2-4] readily available from naturally occurring lincomycin (**1**) and conessine derived 5,6-dihydroconessine (**12**),[2] respectively.

RESULTS AND DISCUSSION

Lincomycin (**1**), a clinically important antibiotic exerts its antibacterial activity by the inhibition of protein synthesis at the ribosomal level.[5] Improvement of lincomycin type activity of the target molecule (**11**) could not reasonably be expected on the basis of previous structure-activity relationship investigations within this family of compounds.[5] However, it was of interest to test whether the appropriate association between lincomycin - with its unique pyrrolidine structure - and a 6-fluoroquinolone, *via* its C-7 site, would enhance the quinolone type antibacterial activity of the combined product. Quinolones are almost insoluble in water[1] and the influence upon activity of the four hydroxyl groups of the lincomycin moiety was also thought worth to be investigated.

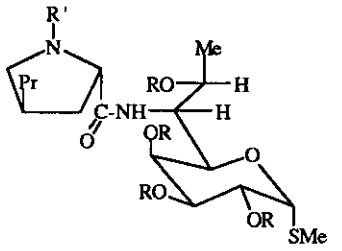
The microbial and chemical synthesis of 1'-demethyllincomycin (**5**) has been reported previously.[6-9] However, all the procedures used furnished **5** only in moderate yields. We succeeded in preparing 2,3,4,7-tetra-*Q*-acetyl-1'-demethyllincomycin (**4**), from lincomycin base (**1**), in three steps with an overall yield of 47%.

Tetra-*Q*-acetylation of lincomycin base (**1**) was followed by 2,2,2-trichloroethyl chloroformate treatment[10,11] furnishing **3** and then reductive removal of the carbamate group,[12] using zinc/tetrahydrofuran/pH 4.2 phosphate



1 R = H

2 R = Ac



3 R = Ac ; R' = $CO_2CH_2CCl_3$

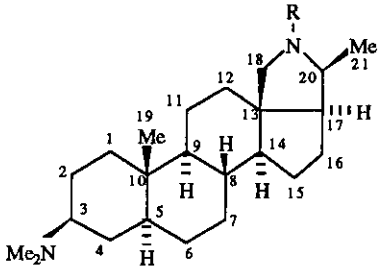
4 R = Ac ; R' = H

5 R = R' = H

buffer, gave **4**.

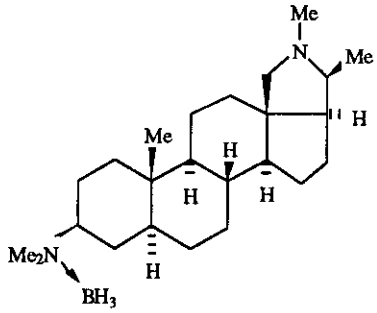
Although, conessine and its derivatives are not known for their antibacterial properties,[2] we were interested to associate the tetrasubstituted pyrrolidine ring of dihydroconessimine (**14**) with the C-7 site of a 6-fluoroquinolone and evaluate the activity of the product thus generated.

In order to synthesize dihydroconessimine (**14**)[2-4] from the selectively *N*-dimethylamino protected dihydroconessine (**13**),[3] preparation of the corresponding 2,2,2-trichloroethyl carbamate was first attempted, as described above in the 1'-demethylation of lincomycin. However, the reaction afforded under various conditions pyrrolidine ring-opened unsaturated products. Therefore, for the preparation of dihydroconessimine (**14**) the method advocated by Picot and Lusinchi was adopted.[4]



12 R = Me

14 R = H



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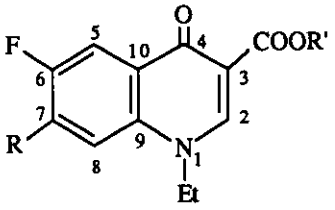
Nucleophilic aromatic substitution at C-7 of a 6,7-difluoroquinolone :

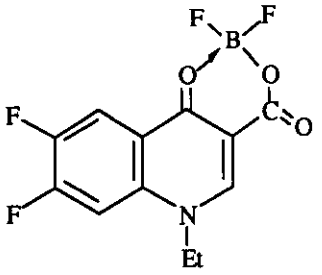
Aromatic substitution at C-7 of 7-chloro-6-fluoroquinolone (**6**) with C-2 cyclic pyrrolidine or piperidine nucleophiles gave disappointing results in our hands. However, such substitution reactions could be readily performed with virtually quantitative yields, when the boron-chelated derivative of carboxylic acids[13,14] of 6,7-difluoroquinolones were used in dimethyl sulfoxide at room temperature, and in the presence of 1.5 equiv. of pyrrolidine (**4**) or (**14**) and also 1.5 equiv. of triethylamine. The boron-chelated compound (**8**) was prepared from carboxylic ester (**7**) with boron trifluoride etherate in diphenyl ether at 200 °C. This procedure allowed the preparation of **9** and **15** which after liberation of the free carboxylic acids, by reflux in the appropriate solvent system, gave **10** and **16**, respectively. The water soluble deacetylated **11** could be directly obtained by base

treatment from **9**. The structure of **10**, **11** and **16** was unambiguously established by ^{13}C nmr spectroscopy.[16] Compounds (**10**, **11** and **16**) were unfortunately devoided of any antibacterial activity.



6 R = Cl ; R' = H

7 R = F ; R' = Et



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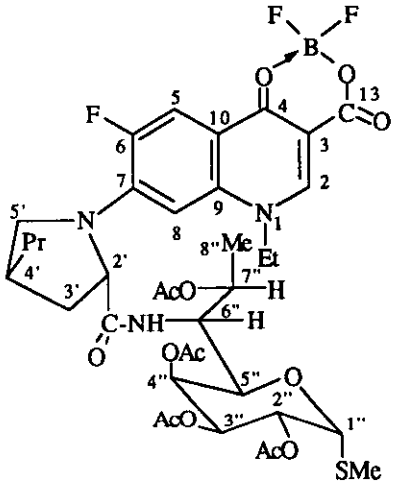

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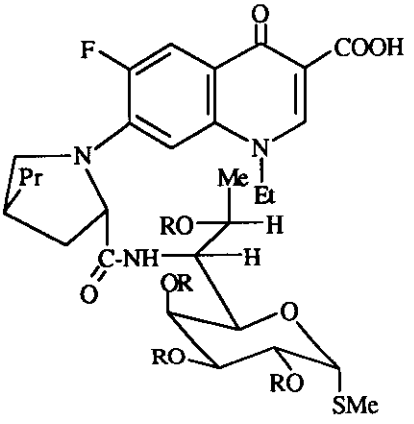
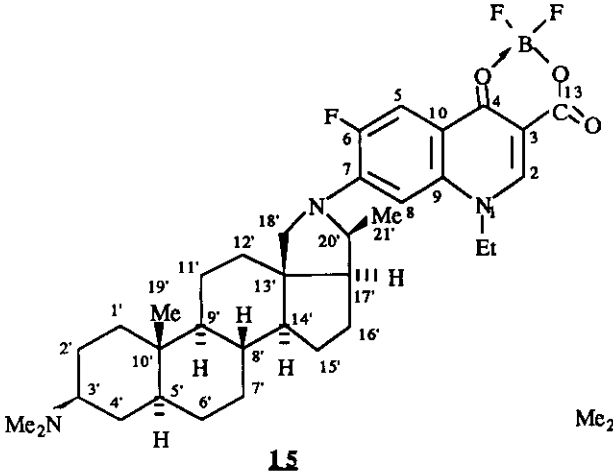


10 R = Ac

11 R = H



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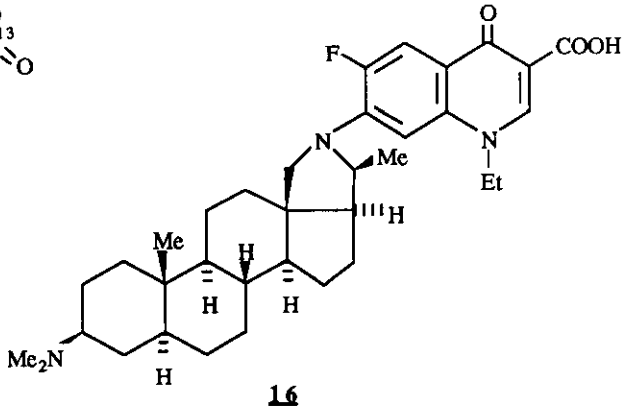

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EXPERIMENTAL PART

General procedures. A Perkin-Elmer Model 141 MC polarimeter and 1-dm tubes were used for measurement of specific rotations. ^{1}H Nmr spectra were recorded in chloroform-*d*, DMSO-d_6, MeOH-d_4 solutions at 200, 250 and 400 MHz. The ^{13}C nmr spectra were measured in chloroform-*d*, DMSO-d_6, MeOH-d_4 solutions at 50.33 MHz with a Bruker WP-200 spectrometer or at 62.91 MHz with a Bruker WP-250 spectrometer. Chemical shifts are given in parts per million, and tetramethylsilane was the internal standard (δ 0.000). Microanalyses were performed by the Service Central de Microanalyse du CNRS. Silica gel 60 PF_{254} (Merck) activated at 120°C was the support for tlc and for column chromatography.

2,3,4,7-Tetra-*O*-acetyl-1'-[2,2,2-trichloroethoxycarbonyl]-1'-demethyllincomycin (3). To a solution of **2** (2.0 g, 3.48 mmol) in dry toluene (40 ml) was added potassium carbonate (0.24 g, 1.74 mmol) and the mixture was stirred at reflux for 15 min. Then, 2,2,2-trichloroethyl chloroformate (1.25 ml, 9.26 mmol) was added dropwise and the reflux maintained for 48 h. The mixture was poored into ice-water saturated with $NaHCO_3$, extracted with CH_2Cl_2 and the organic layer dried over Na_2SO_4 and concentrated. The residue was chromatographed affording pure syrupy **3** (1.65 g, 64%); $[\alpha]_D$ +93° (c 1.0, $CHCl_3$), mass spectrum : *m/z* 736 (M^+ + H), ^{1}H nmr (250 MHz, $CDCl_3$) δ 7.26 (d, 1H, $J_{NH,6}$ = 10.5 Hz, NH), 5.63 (d, 1H, $J_{1,2}$ = 6 Hz, H-1), 5.24 (m, 2H, H-2,4), 5.05 (m, 2H, H-3,7), 5.00 and 4.74 (2d, 2H, J_{gem} = 13.5 Hz, $NCO_2CH_2CCl_3$), 4.57 (dt, 1H, $J_{NH,6} = J_{5,6}$ = 10.5 Hz, $J_{6,7}$ = 3 Hz, H-6), 4.35 (d, 1H, $J_{2',3'}$ = 9 Hz, H-2'), 4.23 (d, 1H, $J_{5,6}$ = 10.5 Hz, H-5), 3.77 (m, 1H, H-5'a), 3.02 (m, 1H, H-5'b), 2.49-2.25 (m, 2H, H-3'a and H-4'), 2.20-1.92 (m, 15H, 4 x OAc + SMe), 1.54 (m, 1H, H-3'b), 1.45-1.21 [m, 7H, αCH_2(Pr) + βCH_2(Pr) + Me-8], 0.95 [m, 3H, γMe(Pr)]; ^{13}C nmr (62.91 MHz, $CDCl_3$) δ 170.5-169.9 (CONH + 4 x OAc), 154.9 ($N\underline{C}O_2CH_2CCl_3$), 95.6 ($NCO_2CH_2\underline{C}Cl_3$), 84.8 (C-1), 75.4 ($NCO_2\underline{C}H_2CCl_3$), 70.7 (C-3), 68.5-67.0 (C-2,4,5,7), 60.2 (C-2'), 52.5 (C-5'), 49.5 (C-6), 37.5 (C-4'), 35.2 [αCH_2(Pr)], 33.8 (C-3'), 21.2 [βCH_2(Pr)], 21.1-20.7 (4 x OAc), 14.8 (C-8), 14.1 [γMe(Pr)], 13.7 (SMe). Anal. Calcd for $C_{28}H_{41}N_2O_{12}Cl_3S$: C, 45.69; H, 5.61; N, 3.80. Found : C, 45.77; H, 5.61; N, 3.52.

2,3,4,7-Tetra-*O*-acetyl-1'-demethyllincomycin (4). To a solution of **3** (1.44 g, 1.95 mmol) in tetrahydrofuran (70 ml) was added activated zinc (1.9 g, 2.9 mmol) and a buffer solution (14 ml) of Na_2HPO_4 (95 : 5) whose pH was adjusted to 4.2. The reaction mixture was vigorously stirred at room temperature for 4 h. After filtration and washing of the metal with tetrahydrofuran, addition of a saturated solution of $NaHCO_3$ and extraction with ethyl acetate, the organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed affording pure syrupy **4** (0.88 g, 80%); $[\alpha]_D$ +130° (c 1.0, $CHCl_3$), mass spectrum : *m/z* 561 (M^+ + H), ^{1}H nmr (200 MHz, $CDCl_3$) δ 8.01 (d, 1H, $J_{NH,6}$ = 11.5 Hz, NH), 5.65 (d, 1H, $J_{1,2}$ = 5.7 Hz, H-

1), 5.27 (m, 2H, H-2,4), 5.12 (m, 2H, H-3, 7), 4.54 (dt, 1H, $J_{NH,6} = J_{5,6} = 11.5$ Hz, $J_{6,7} = 3.3$ Hz, H-6), 4.28 (d, 1H, $J_{5,6} = 11.5$ Hz, H-5), 3.73 (dd, 1H, $J_{2',3'a} = 10$ Hz, $J_{2',3'b} = 3.3$ Hz, H-2'), 3.08 (m, 1H, H-5'), 2.78 (s, 1H, NH), 2.60 (m, 1H, H-5'), 2.18-1.93 (m, 17H, 4 x OAc, SMe, H-4', 3'a), 1.65 (m, 1H, H-3'b), 1.28 [m, 7H, Me-8, αCH_2(Pr), βCH_2(Pr)], 0.92 [m, 3H, γMe(Pr)]; ^{13}C nmr (62.91 MHz, $CDCl_3$) δ 174.9 (CONH), 170.3-170.0 (4 x OAc), 84.7 (C-1), 69.9 (C-3), 68.5 (C-7), 68.0 (C-5), 67.7-67.0 (C-2,4), 59.9 (C-2'), 52.8 (C-5'), 48.8 (C-6), 38.2 (C-4'), 36.2 (C-3'), 35.3 [αCH_2(Pr)], 21.3 [βCH_2(Pr)], 21.0-20.5 (4 x OAc), 14.3 and 14.1 [γMe(Pr) + C-8], 13.6 (SMe). Anal. Calcd for $C_{25}H_{40}N_2O_{10}S$: C, 53.55; H, 7.19; N, 4.99; S, 5.72. Found : C, 53.50; H, 6.89; N, 4.87; S, 5.92.

Compound (8). To a solution of **7** (1.5 g, 5.3 mmol) in diphenyl ether (30 ml) was added at 200 °C anhydrous BF_3 etherate (787 µl, 6.4 mmol) and the mixture was stirred for 30 min at 200 °C. After cooling the precipitate was collected, washed with ethyl acetate and dried furnishing **8** (1.5 g, 93%) of good quality for further operations. A sample was recrystallized from diphenyl ether; mp 292 °C, mass spectrum: *m/z* 324 (M^+ + Na), ^{1}H nmr (200 MHz, DMSO-*d*6) δ 9.63 (s, 1H, H-2), 8.72 (dd, 1H, $J_{5,F6} = 12.5$ Hz, $J_{5,F7} = 7$ Hz, H-5), 8.57 (t, 1H, $J_{8,F6} = J_{8,F7} = 9$ Hz, H-8), 4.88 [q, 2H, $J_{11,12} = 7.1$ Hz, (CH_2)Et], 1.50 [t, 3H, $J_{11,12} = 7.1$ Hz, Me(Et)]; ^{13}C nmr (50.33 MHz, DMSO-*d*6) δ 167.5 (C-4), 159.9 (C-13), 154.7 (dd, $J_{6,F6} = 259.8$ Hz, $J_{6,F7} = 15.0$ Hz, C-6), 150.9 (C-2), 149.6 (dd, $J_{7,F7} = 256.6$ Hz, $J_{7,F6} = 15.0$ Hz, C-7), 137.6 (d, $J_{9,F7} = 11.0$ Hz, C-9), 119.4 (C-10), 112.6 (d, $J_{5,F6} = 19.6$ Hz, C-5), 108.5 (d, $J_{8,F7} = 23.4$ Hz, C-8), 107.1 (C-3), 51.6 [CH_2(Et)], 14.5 [Me(Et)]. Anal. Calcd for $C_{12}H_8NO_3BF_4$: C, 47.88; H, 2.67; N, 4.65; B, 3.59; F, 25.24. Found : C, 47.78; H, 2.81; N, 4.46; B, 3.73; F, 25.01.

Compound (9). To a solution of **8** (210 mg, 0.69 mmol) and **4** (588 mg, 1.05 mmol) in dimethyl sulfoxide (3 ml) was added triethylamine (147 µl, 1.05 mmol) and the mixture was stirred overnight at room temperature. After concentration, the residue was chromatographed furnishing pure syrupy **9** (575 mg, 98%), $[\alpha]_D$ -22.1° (c 0.95, $CHCl_3$), mass spectrum : m/z 864 (M^+ + Na).

Compound (10). A solution of **9** (181 mg, 0.21 mmol) in a mixture of AcOEt/H_2O (1 : 1) (5 ml) was heated to 100 °C for 24 h. After cooling, the organic layer was separated and the aqueous layer extracted with CH_2Cl_2. The united organic layers were dried over sodium sulfate and concentration furnished after crystallization pure **10** (169 mg, 99%); mp 154-155 °C, $[\alpha]_D$ -4.0° (c 1.0, $CHCl_3$), mass spectrum : *m/z* 816 (M^+ + Na), ^{1}H nmr (250 MHz, $CDCl_3$) δ 8.42 (s, 1H, H-2), 7.84 (d, 1H, $J_{5,F} = 14.2$ Hz, H-5), 7.06 (d, 1H, $J_{NH,6''} = 10.5$ Hz, CONH), 6.49 (d, 1H, $J_{8,F} = 6.7$ Hz, H-8), 5.58 (d, 1H, $J_{1'',2''} = 5.2$ Hz, H-1"), 5.32 (d, 1H, $J_{3'',4''} = 2.6$ Hz, H-4"), 5.23 (dd, 1H, $J_{2'',3''} = 10.8$ Hz, $J_{1'',2''} = 5.6$ Hz, H-2"), 5.03 (dd, 1H, $J_{2'',3''} = 10.8$ Hz, $J_{3'',4''} = 3.0$ Hz, H-3"), 4.83 (m, 1H, H-7"), 4.55 (m, 2H, H-2', 6"), 4.26 [m, 3H, CH_2(Et), H-5"], 3.88 (m, 1H, H-5'a), 3.01 (m, 1H, H-5'b), 2.33 (m, 2H, H-3'a, 4'), 2.16-1.82 (m, 16H, 4 x OAc, SMe, H-3'b), 1.53 [t, 3H, $J_{11,12} = 6.8$ Hz, Me(Et)], 1.44 [m, 4H, αCH_2(Pr), βCH_2(Pr)], 1.12 (d, 3H, $J_{7'',8''} = 6.8$ Hz, Me-8"), 0.94 [m, 3H, γMe(Pr)]; ^{13}C nmr (62.91 MHz, $CDCl_3$) δ 176.3 (C-4), 172.7 (CONH), 170.8-170.0 (4 x OAc), 167.4 (C-13), 150.3 (d, $J_{6,F} = 247.5$ Hz, C-6), 146.6 (C-2), 142.0 (d, $J_{7,F} = 11.5$ Hz, C-7), 137.5 (C-9), 117.4 (d, $J_{10,F} = 7.2$ Hz, C-10), 112.2 (d, $J_{5,F} = 23.3$ Hz, C-5), 107.5 (C-3), 100.0 (C-8), 84.9 (C-1"), 72.0

(C-7"), 68.7, 2 x 67.8, 67.2 (4C, C-2", 3", 4", 5"), 66.0 (d, $J_{2',F}$ = 7.2 Hz, C-2'), 56.8 (C-5'), 49.7 (C-6"), 49.6 [C-H_2(Et)], 37.3 (C-3'), 36.4 (C-4'), 35.1 [αCH_2(Pr)], 21.6-20.6 [4 x OAc + βCH_2(Pr)], 16.2 (C-8"), 14.3-13.7 [Me(Et), SMe, γMe(Pr)]. Anal. Calcd for $C_{37}H_{48}N_3O_{13}FS$: C, 55.97; H, 6.09; N, 5.29. Found : C, 56.03; H, 6.11; N, 5.11.

Compound (11). A solution of **9** (135 mg, 0.16 mmol) in a mixture of 1N sodium hydroxyde (960 µl) in ethanol to which absolute ethanol (1 ml) was added was refluxed for 45 min. After cooling, neutralization with 1N HCl in ethanol, the precipitate was collected, filtered and dissolved in ethanol. After concentration and purification on sephadex LH-20, crystalline **11** (92 mg, 92%) was obtained; mp 224 °C, $[\alpha]_D$ +9.8° (c 0.91, MeOH), mass spectrum : *m/z* 648 (M^+ + Na), ^{1}H nmr (200 MHz, MeOH-*d4*) δ 8.46 (s, 1H, H-2), 7.81 (d, 1H, $J_{5,F}$ = 14.2 Hz, H-5), 6.64 (d, 1H, $J_{8,F}$ = 6.5 Hz, H-8), 5.27 (d, 1H, $J_{1",2"}$ = 5.1 Hz, H-1"), 4.66-3.56 [m, 10H, H-2", 3", 4", 5", 6", 7", 2', 5', CH_2(Et)], 3.10 (m, 1H, H-5'a), 2.65-2.30 (m, 2H, H-3a', 4'), 2.06 (s, 3H, SMe), 1.92 (m, 1H, H-3b'), 1.47 [m, 7H, α, β CH_2(Pr), Me(Et)], 1.16 (d, 3H, $J_{7",8"}$ = 6.8 Hz, Me-8"), 1.00 [m, 3H, γMe(Pr)]; ^{13}C nmr (62.91 MHz, MeOH-d4) δ 176.7 and 176.4 (C-4 and CONH), 172.8 (C-13), 150.7 (d, $J_{6,F}$ = 248.9 Hz, C-6), 148.7 (C-2), 141.3 (d, $J_{7,F}$ = 11.8 Hz, C-7), 138.5 (C-9), 120.8 (C-10), 117.3 (C-3), 116.5 (d, $J_{5,F}$ = 22.3 Hz, C-5), 100.8 (C-8), 89.3 (C-1"), 71.8-68.5 (C-2", 3", 4", 5", 7"), 67.0 (d, $J_{2',F}$ = 8.8 Hz, C-2'), 58.4 (C-6"), 57.4 (C-5'), 38.9 (C-3'), 36.5 (C-4'), 36.5 (C-4'), 36.0 [αCH_2(Pr)], 22.7 [βCH_2(Pr)], 20.9 (C-8"), 14.6 and 13.0 [Me(Et), SMe, γMe(Pr)]. Anal. Calcd for $C_{29}H_{40}N_3O_9FS$: C, 55.66; H, 6.44; N, 6.71. Found : C, 55.72; H, 6.57; N, 6.53.

Compound (15). To a solution of **8** (176 mg, 0.58 mmol) and dihydroconessimine **14** (301 mg, 0.87 mmol) in DMSO (7 ml), was added triethylamine (123 µl, 0.87 mmol). The mixture was stirred overnight at room temperature and then concentrated. The residue was dissolved in CH_2Cl_2 and the organic layer washed with water, dried and concentrated. Flash chromatography of the residue (CH_2Cl_2 : MeOH : NH_4OH 8 : 1 : 0.5%) gave pure syrupy **15** (358 mg, 98%), $[\alpha]_D$ -169.1° (c 1.1, $CHCl_3$), mass spectrum : m/z 648 (M^+ + Na). Anal. Calcd for $C_{35}H_{47}N_3O_3BF_3$: C, 64.86; H, 7.30; N, 6.48; B, 1.66; F, 8.79. Found : C, 64.76; H, 7.38; N, 6.54; B, 1.33; F, 8.50.

Compound (16). In a mixture (1 : 1) of $CHCl_3$ and H_2O (4 ml) was dissolved **15** (150 mg, 0.24 mmol). After refluxing it for 22 h, cooling, extraction with CH_2Cl_2, the organic layer was dried over sodium sulfate and evaporated. Flash chromatography (CH_2Cl_2 : MeOH : NH_4OH 8 : 2 : 0.5%) gave **16** (97 mg, 70%) and starting material **15** (40 mg). A sample of **16** was crystallized from acetone-heptane : mp 130 °C, $[\alpha]_D$ -95.2° (c 1.05, $CHCl_3$), mass spectrum : *m/z* 600 (M^+ + Na), ^{1}H nmr (300 MHz, $CDCl_3$) δ 8.62 (s, 1H, H-2), 8.00 (d, 1H, $J_{5,F}$ = 13.2 Hz, H-5), 6.53 (d, 1H, $J_{8,F}$ = 6.8 Hz, H-8), 4.28 [m, 2H, CH_2(Et)], 4.08 (m, 1H, H-20'), 3.63 (m, 1H, H-18'a), 3.07 (m, 1H, H-18'b), 2.40 [m, 7H, N(Me)2 + H-3'], 2.18 (m, 1H, H-17'), 1.60 [t, 3H, $J_{11,12}$ = 7.1 Hz, Me(Et)], 1.25 (d, 3H, $J_{20',21'}$ = 7 Hz, Me-21'), 0.76 (s, 3H, Me-19'); ^{13}C nmr (62.91 MHz, $CDCl_3$) δ 176.5 (C-4), 167.5 (C-13), 152.1 (d, $J_{6,F}$ = 249.8 Hz, C-6), 146.6 (C-2), 143.7 (d, $J_{7,F}$ = 12.3 Hz, C-7), 137.4 (C-9), 117.5 (C-10), 112.0 (d, $J_{5,F}$ = 22.6 Hz, C-5), 107.6 (C-3), 100.7 (C-8), 64.2 (C-3'), 55.9 (C-18'), 55.7 (C-20'), 53.7 (C-9', 14'), 53.1 (C-17'), 52.3 (C-13'), 49.5 [CH_2(Et)], 45.3 (C-5'),

40.9 [N(Me)2], 38.1 (C-8'), 37.4 (C-1'), 35.6 (C-10'), 34.1 (C-16'), 32.0 (C-7'), 30.6 (C-4'), 28.4 (C-6'), 24.5, 23.7, 23.0 (C-2', 12', 15'), 21.8 (C-11'), 15.1 (C-21'), 14.4 [Me(Et)], 12.3 (C-19'). Anal. Calcd for $C_{35}H_{48}N_3O_3F$: C, 72.75; H, 8.37; N, 7.27. Found : C, 72.79; H, 8.41; N, 7.18.

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