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Total Synthesis of an Aglycone of Spiramycin

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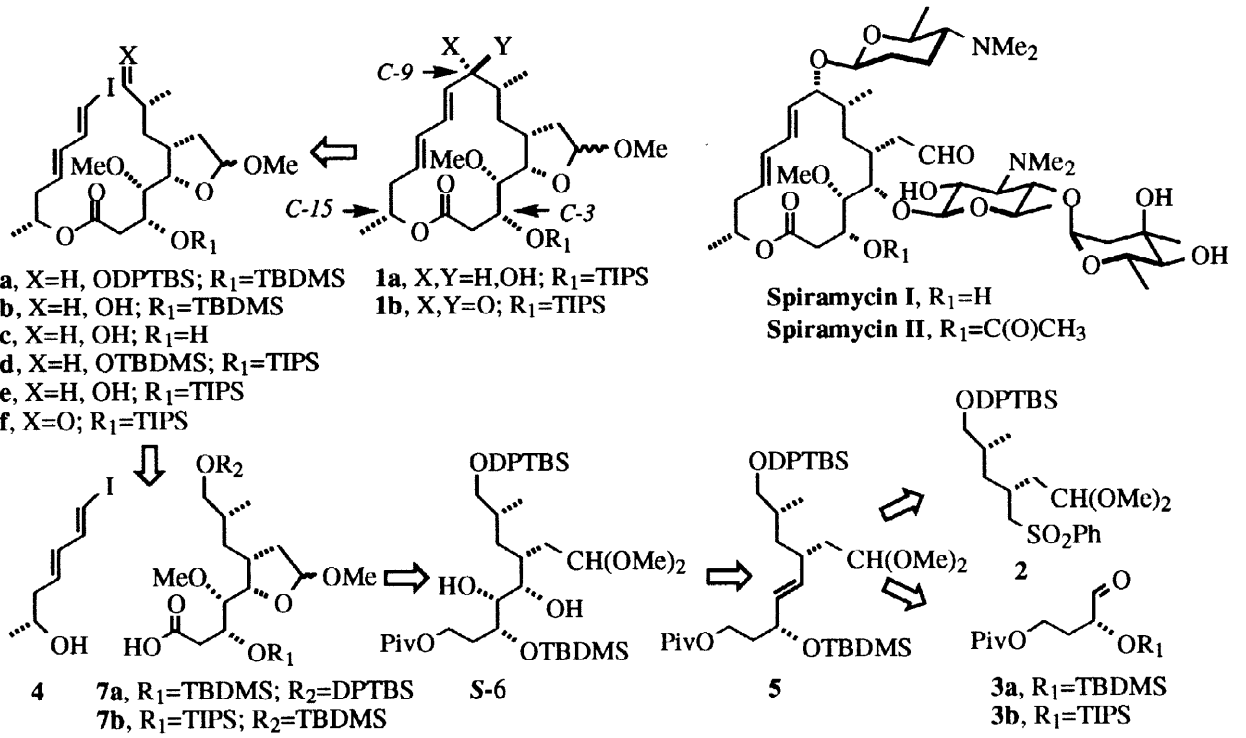
Abstract: The iodoaldehyde **β-8f** has been converted efficiently into the title aglycone by means of the Kishi-Nozaki-Takai coupling reaction.

In order to prepare the aglycone **1** of spiramycin, we considered the compounds **2**, **3** and **4** as possible synthetic precursors of this 16-membered macrolide and, accordingly, a stereo-controlled access to these building blocks was gained by means of chiron and enzyme methodologies, as detailed in previous communications.[1] After having verified, by using model substrates, that crucial steps of the indicated plan would be feasible,[1c] we next attempted to bring together these synthons in order to get the target aglycone.



8a, X=H, ODPTBS; R_1=TBDMS
8b, X=H, OH; R_1=TBDMS
8c, X=H, OH; R_1=H
8d, X=H, OTBDMS; R_1=TIPS
8e, X=H, OH; R_1=TIPS
8f, X=O; R_1=TIPS

1a, X,Y=H,OH; R_1=TIPS
1b, X,Y=O; R_1=TIPS

Spiramycin I, R_1=H
Spiramycin II, R_1=C(O)CH_3

4 **7a**, R_1=TBDMS; R_2=DPTBS
7b, R_1=TIPS; R_2=TBDMS

***S*-6**

5

3a, R_1=TBDMS
3b, R_1=TIPS

Though it appeared necessary, at an advanced stage of the synthesis, to modify the silyl groups favoured initially for protecting the oxygen atoms at the C-3 and C-9 positions, we are pleased to report herein that the above strategy proved to be efficient.

The Julia-Paris-Kocienski (JPK) condensation of the aldehyde **3a** with sulfone **2** in conditions defined earlier[1c] proceeded well, giving the olefin **5** in a fairly good yield (69%) and with a perfect *E* stereoselectivity, as judged by NMR. Bis-hydroxylation of **5** was then performed by using either AD-mix-α® or the OsO_4-NMO system.

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In both instances, the crude reaction product was composed of the diols ***S*-6** and ***A*-6** (NMR) and was immediately reacted with methanol and PPTS to afford a mixture of the mixed-acetals **α-9a**, **β-9a**, **α-10a** and **β-10a**, which were efficiently separated by chromatography and characterised by NMR.[2] As observed precedently in a related case,[1c] the all-*syn* product (*i.e.* ***S*-6**, in the present case) was indeed slightly favoured by using the former reagent. The latter was preferred however, the isolated yield in acetals **9a** being better in these conditions (44%).

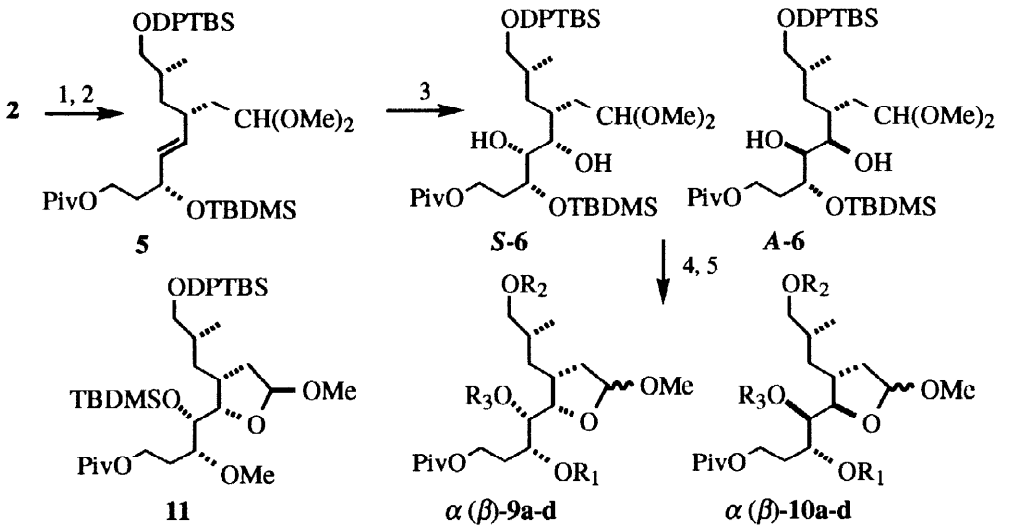
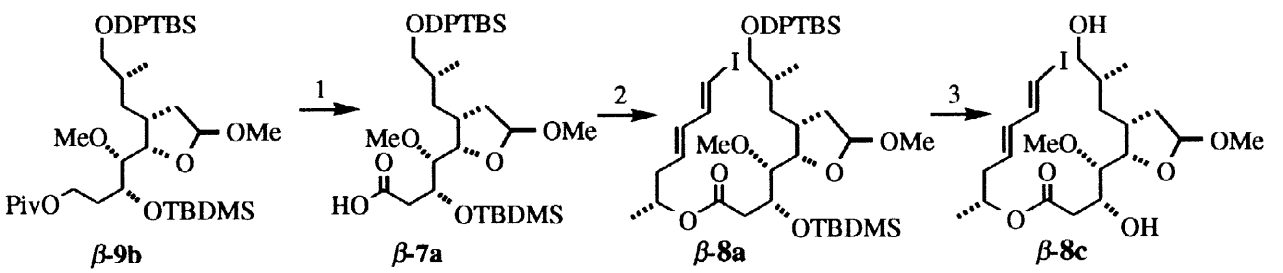


Table: Stereoselectivity of the **5-6** conversion		
reagent	***S*-6/*A*-6***	Yield (%)
OsO_4-NMO	50/50	89
AD-mix-α	45/55	62
** see ref. 2*		

a, R_1=*OTBDMS*; R_2=*DPTBS*; R_3=*H*
b, R_1=*OTBDMS*; R_2=*DPTBS*; R_3=*Me*
c, R_1=R_2=*H*; R_3=*Me*
d, R_1=*OTIPS*; R_2=*TBDMS*; R_3=*Me*

Reagents and conditions: 1- *i*) 1.55 M (in hexane) n-BuLi (1 eq.), THF (10 ml/mmol); -78 °C, 45 mn; *ii*) **3a** (1 eq.); -78 °C, 1 hour; *iii*) Ac_2O (2.1 eq.), DMAP (0.1 eq.); r.t., 4 hours; 2- 6% HgNa (3x5 eq.), 1/1 MeOH/AcOEt (20 ml/mmol); -50 °C, 6 hours (69% overall, from **2**); 3- OsO_4 (0.08 eq.), NMO (2 eq.), 9/1 acetone/water (5 ml/mmol); r.t., 2 hours, or AD-mix-α (1.4 g/mmol), $CH_3SO_2NH_2$ (1.5 eq.), $K_2OsO_4.2H_2O$ (0.001 eq.), $(DHQ)_2$-PHAL (0.06 eq.), 1/1 *t*-BuOH/H_2O (10 ml/mmol); r.t., 2 weeks; 4- PPTS (0.2 eq.), 1/1 MeOH/CH_2Cl_2 (14 ml/mmol); r.t., 2 days; 5- NaH (1.2 eq.), 1/1 MeI/DMF (3.3 ml/mmol); r.t., overnight (81%).

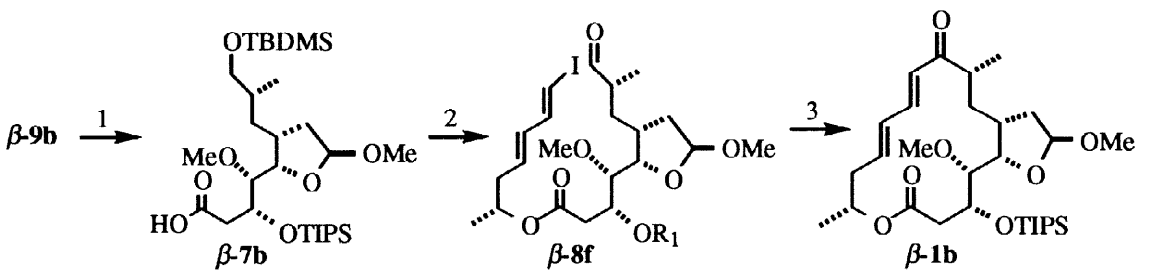
The ensuing methylation of the C-5 hydroxy group in the compound **β-9a** was not straightforward, the use of the more prevalent methylation conditions leading invariably to a mixture of **β–9b** with the isomeric ether **11**.[3] This side trans-silylation reaction was minimised however by performing that methylation with NaH in DMF and methyl iodide, used both as reagent and as cosolvent, the small amount (ca 7%) of ether **11** still formed being separated easily by chromatography from the desired methoxy compound **β–9b** (81%).



Reagents and conditions: 1- *i*) 1M (in hexane) DIBA-H (2.5 eq.), CH_2Cl_2; -78 °C, 0.5 hour, then pH 5-6 tartaric buffer (96%); *ii*) $(COCl)_2$ (1.5 eq.), DMSO (2 eq.), Hünig base (4 eq.), CH_2Cl_2; -78 °C to -20°C, 2 hours (76%); *iii*) 3/2/1 0.4 M aqueous $KMnO_4$/1.3 M KH_2PO_4/*t*-BuOH (30 ml/mmol); 0°C, 15 mn, then $NaHSO_3$ (100%); 2- *i*) NEt_3 (1.3 eq.), 2,4,6-trichlorobenzoyl chloride (1.2 eq.), THF; r.t., 1 hour, then filtration; *ii*) DMAP (6 eq.), **4** (1.05 eq.), toluene; r.t., 3 hours (92%); 3- TBAF.H_2O (1 eq.), pyridine.HF (1 eq.), THF; r.t., 2 hours (94%).

Conversion of **β–9b** into the acid **β–7a** (73% overall) and ensuing condensation of **β–7a** with the alcohol **4** to give the ester **β–8a** (92%) were then performed by using protocols previously designed.[1d] Somewhat unexpectedly, attempted selective hydrolysis of the O-DPTBS group at C-9 in **β–8a**, in order to form **β–8b**, proved unfeasible, the only detectable product being the diol **β–8c** whatever the used reagent (*e.g.* TBAF, alone or buffered with HF.pyridine) was. It is worth noting that any mono-deprotected compound failed to be detected. After numerous unsuccessful trials, implementation of the TIPS protection of the C-3 oxygen atom was decided.

This was first tried by preparing the O-TIPS derivative **3b** but attempted JPK condensation of this aldehyde with sulfone **2** proved unfeasible, probably as a result of the large size of the OTIPS group. Accordingly, the planned exchange of protection was realised at a more advanced stage by treating the pivalate **β-9b** with TBAF.H_2O to form the diol **β-9c** (96%), which, by sequential treatment with TBDMSCl and TIPSTf as above afforded the compound **β-9d** in good overall yield (89%, from **β-9b**). Conversion of **β-9d** into the acid **β–7b** (84%) was then realised by means of the sequence used precedently. Ensuing esterification of **4** by **β–7b** (61% yield), followed by treatment of the resulting ester **β–8d** with AcOH/THF/H_2O delivered the alcohol **β–8e** (67%). Finally, oxidation of **β–8e** by SO_3.pyridine and DMSO furnished the iodoaldehyde **β–8f** in good yield (89%).



Reagents and conditions: 1- *i*) TBAF.3 H_2O (4 eq.), THF; r.t., 7 hours (96%); *ii*) TBDMSCl (1 eq.), NEt_3 (1.2 eq.), CH_2Cl_2; 1 day (98%); *iii*) TIPSTf (1.2 eq.), 2,6-lutidine (1 eq.), CH_2Cl_2; 0 °C, 5 hours (95%); *iv*) same conditions as for the **β-9b-7a** conversion (84%, overall); 2- *i*) same conditions as for the **7a-8a** conversion (61%); *ii*) 3/1/1 AcOH/THF/H_2O (13 ml/mmol); r.t., 2 days (67%); *iii*) SO_3.pyridine (4 eq.), NEt_3 (8 eq.), DMSO (large excess), CH_2Cl_2; O °C to r.t., 1 hour (89%); 3- *i*) $CrCl_2$ (100 eq.), $NiCl_2$ (1 eq.), DMSO; r.t., 5 hours (76%); *ii*) DDQ (1.2 eq.), CH_2Cl_2; r.t., 12 hours (40%).

The final problem we had to solve was to convert the iodoaldehyde **β-8f** into the aglycone **β-1a**. In a first experiment, a solution of **β-8f** in DMSO was added slowly to a slurry of excess (ca 4 eq.) $CrCl_2$ and $NiCl_2$ (Cr(II)/Ni(II)=100/1) in the same solvent, the final concentration being approximately 0.01 M. Unfortunately, almost no reaction took place after two days at room temperature, obviously a result of the high dilution of both the substrate and the reducing agent. Indeed, by using a very large excess (ca 100 eq.) of reducing species, the other conditions being unchanged, the hydroxy compound **β-1a** was formed in good yield (76%) as a 9/1 mixture of two diastereomers (NMR). In order to facilitate the characterisation of the product, that mixture was reacted with DDQ to give a ketone (40%), whose the structure was firmly established as being **β-1b** by NMR (^1H, ^{13}C, COSY, TOCSY, NOESY, $^1H/^{13}C$ correlation, HMBC), mass, IR and UV spectroscopies.[4]

In conclusion, the scheme we used for synthesizing the aglycone **1** suffers from the lack of stereoselectivity of the step by which the olefin **5** was converted into the bis-hydroxy compound ***S*-6** and, to a lesser extent, from the sensitivity of dienyl iodides **4** and **8d-f** to light, which forced us to protect carefully from daylight all the vessels we used at any stage of the **4-8f** conversion. A few rewarding points emerge however. Besides being highly convergent, the synthesis of **β-1b** presented herein[5] appears relatively short, the longer sequence comprising 36 steps (average yield by step: 82%). Moreover, the strategy retained permitted to control efficiently the configuration at the C-3, C-4, C-5, C-6, C-8 and C-15 chiral centers .

Acknowledgement: Thanks are due to Rhône-Poulenc Rorer for a grant (to G. O.).

References and Notes

1- a) Oddon, G.; Uguen, D. *Tetrahedron Lett.* **1997**, *38*, 4411-4414; b) Breuilles, P.; Oddon, G.; Uguen, D. *Tetrahedron Lett.* **1997**, *38*, 6607-6610; c) Oddon, G.; Uguen, D. *Tetrahedron Lett.* **1998**, *39*, 1153-1156. The results presented herein are taken from the thesis dissertation of Gilles Oddon (Strasbourg, 1996).

2- The ***A*-6/*S*-6** ratio (table) was determined by HPLC (C-18 column; 1/9 isopropanol/hexane). Column chromatography of the crude methanolysis product of the ***S*-6/*A*-6** mixture was performed efficiently on silica gel (Rf values (eluant: 9/1 hexane/AcOEt; 2 elutions): *α*-**9a**: 0.56; *β*-**10a**: 0.54; *β*-***9a***: 0.42; *α*-**10a**: 0.19). Structure assignment to each individual mixed-acetal was performed unambiguously by NMR, *i.a.* NOE experiments (see ref. 1c).

3- The **9a/11** ratio reached 2/1 by using KH and CH_3I (1 eq. each) in THF.

4- Selected data: **5**: ^1H NMR (200 MHz): 0.03 (s, 3H), 0.05 (s, 3H), 0.86-0.92 (m, 12H), 1.04 (s, 9H), 1.2 (s, 9H), 1.32-1.85 (m, 7H), 2.15-2.38 (m, 1H), 3.28 (s, 3H), 3.29 (s, 3H), 3.43 (d, J=6 Hz, 2H), 4.08-4.3 (m, 3H), 4.34 (dd, J=7.6, 4.1 Hz, 1H), 5.24 (dd, J=15.5, 9 Hz, 1H), 5.46 (dd, J=15.5, 6.7 Hz, 1H), 7.45-7.55 (m, 6H), 7.6-7.7 (m, 4H); ^{13}C NMR: -4.83, -4.13, 16.09, 18.24, 19.41, 25.92, 26.95, 27.34, 32.07, 33.31, 37.85, 38.89, 38.98, 52.72, 52.8, 61.22, 69.51, 70.3, 103, 127.64, 129.56, 133.99, 134.1, 134.13, 135.69, 178.44; $[\alpha]_D^{21}$ +5 (c=1, CH_2Cl_2); *β*-**9a**: ^1H NMR (400 MHz): 0.08 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 1.05 (s, 9H), 0.97 (d, J=6.5 Hz, 3H), 1.19 (s, 9H), 1.22-1.4 (m, 1H), 1.62-1.95 (m, 6H), 2.32 (d, J=7.5 Hz, 1H; O*H*); 2.5-2.6 (m, 1H), 3.32 (s, 3H), 3.42-3.56 (m, 3H), 3.85-3.91 (m, 1H), 4.03-4.1 (m, 1H), 4.2-4.26 (m, 1H), 4.14 (d, J=8.2 Hz, 1H), 4.9 (d, J=4.5 Hz, 1H), 7.35-7.45 (m, 6H), 7.6-7.7 (m, 4H); ^{13}C NMR (50 MHz): -4.49, -4.38, 18.13, 19.38, 25.96, 26.99, 27.32, 32.57, 33.29, 34.82, 36.95, 38.8, 39.24, 54.81, 61.06, 68.43, 70.87, 72.03, 78.7, 104.94, 127.69, 129.63, 133.95, 135.72, 178.52; $[\alpha]_D$ +50 (c=0.7, CH_2Cl_2); *α*–**9a**: ^1H NMR (200 MHz): 0.06 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 1.05 (s, 9H), 0.98 (d, J=6.2 Hz, 3H), 1.2 (s, 9H), 1.33-2.5 (m, 8H), 3.38-3.57 (m, 6H), 3.77-3.9 (m, 1H), 3.98-4.37 (m, 2H), 4.36 (d, J=7.7 Hz, 1H), 4.99 (t, J=5.3 Hz, 1H), 7.35-7.45 (m, 6H), 7.6-7.7 (m, 4H); ^{13}C NMR (50 MHz): -4.84, -3.9, 18, 18.17, 19.38, 25.99, 26.98, 27.34, 31.82, 33.07, 34.62, 38.8, 39.01, 39.15, 56.29, 61.58, 68.38, 71.54, 72.06, 79.91, 106.61, 127.7, 129.66, 133.89, 135.7, 178.53; $[\alpha]_D$ +7 (c=1, CH_2Cl_2); *β*-**7b**: ^1H NMR (200 MHz): 0.02 (s, 6H), 0.88 (s, 9H), 0.91 (d, J=6.5 Hz, 3H), 1-1.1 (m, 21H), 1.11-1.2 (m, 2H), 1.5-1.92 (m, 3H), 2.52-2.77 (m, 2H), 3 (dd, J=14, 8 Hz, 1H), 3.3-3.5 (m, 9H), 4.54 (d, J=8.2 Hz, 1H), 4.5-4.6 (m, 1H), 5.05 (d, J=4.2 Hz, 1H); ^{13}C NMR (50 MHz): -5.38, 12.54, 18.03, 18.2, 18.4, 26.01, 29.76, 33.51. 34.41, 37.02, 39.23, 54.92, 57.03, 66.75, 67.61, 77.34, 81.15, 105.02, 175.51; $[\alpha]_D$ +53 (c=0.6, CH_2Cl_2); *β*-**8f**: ^1H NMR (200 MHz): 1-1.1 (m, 21H), 1.18 (d, J=7,1 Hz, 3H), 1.21 (d, J=6.3 Hz, 3H), 1.3-1.9 (2m, 4H), 2.22-2.6 (m, 5H), 2.95 (dd, J=16.7, 3.8 Hz, 1H), 3.25 (d, J=4.6 Hz, 1H), 3.34 (s, 3H), 3.39 (s, 3H), 4.48 (dd, J=7.9 Hz, 1H), 4.67-4.76 (m, 1H), 4.9-5.04 (m, 2H), 5.66 (dt, J=14.8, 7.3 Hz, 1H), 6.01 (dd, J=15.1, 10.5 Hz, 1H), 6.21 (d, J=14.3 Hz, 1H), 6.97 (dd, J=14.4, 10.5 Hz, 1H), 9.62 (d, J=2 Hz, 1H); ^{13}C NMR (50 Mhz): 12.6, 14.63, 18.25, 19.58, 31.22, 37.37, 38.64, 38.86, 38.99, 45.28, 54.8, 57.19, 66.79, 69.78, 76.74, 77.29, 81.01, 104.58, 130.55, 132.98, 145.11, 172.58, 204.3; *β*-**1b**: ^1H NMR (600 MHz): 1-1.1 (m, 21H), 1.2 (d, J=6.5 Hz, 3H), 1.3 (d, J=6.5 Hz, 3H), 1.3-1.4 (m, 1H), 1.78-1.85 (m, 1H), 1.88-1.95 (m, 2H), 2.1-2.16 (m, 1H), 2.2-2.28 (m, 1H), 2.42 (dd, J=18, 6.5 Hz, 1H), 2.43-2.5 (m, 1H), 2.7 (dd, J=18, 3.5 Hz, 1H), 2.6-2.68 (m, 1H), 2.93 (t, J=4 Hz, 1H), 3.31 (s, 3H), 3.43 (s, 3H), 3.97 (dd, J=6.5, 4 Hz, 1H), 4.4-4.46 (m, 1H), 4.98 (dd, J=5.5, 2 Hz, 1H), 5.1-5.16 (m, 1H), 6.05 (ddd, J=16, 9.5, 5 Hz, 1H), 6.15 (dd, J= 16, 11 Hz, 1H), 6.25 (d, J=15 Hz, 1H), 7 (dd, J=15, 11 Hz, 1H); ^{13}C NMR (150 MHz): 12.3, 17.2, 19.8, 21.1, 35.2, 39.5, 40.5, 41.5, 44, 46, 55.3, 59.9, 69.5, 70, 81.1, 83.9, 104.8, 127.5, 131.8, 140.1, 143, 171.3, 204.9; Mass (NH_3): m/z: 553 (MH^+), 570 ($M+NH_4^+$), 575 ($M+Na^+$); 591 ($M+K^+$); 157 (TIPS); UV: λ_{max}=278nm (MeOH); IR ($CHCl_3$): 2929, 2867, 2833, 1734, 1690, 1675 cm^{-1}. ^1H and ^{13}C NMR spectra: on $CDCl_3$ solutions; $[\alpha]_D$ values: 21 °C.

5- For previous syntheses of related aglycones, see: *i*) Tatsuta, K.; Amemiya, Y.; Maniwa, S.; Kinoshita, M. *Tetrahedron Lett.* **1980**, *21*, 2837-2840; *ii*) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 1224-1226; *iii*) Nakajima, N.; Uoto, K.; Yonemitsu, O.; Hata, T. *Chem. Pharm. Bull.* **1991**, *39*, 64-74; *iv*) Keck, G. E.; Palani, S. F.; Hardy, F. M. *J. Org. Chem.* **1994**, *59*, 3113-3122.