Synthesis of a Polyhydroxyquinolizidine bearing a Polyhydroxylated Carbon Side-Chain

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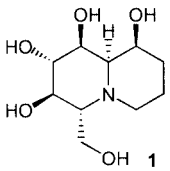
Received 26 April 1999

Abstract: The lithium enolate of (-)-6-*endo*-chloro-5-*exo*-(phenylseleno)-7-oxabicyclo[2.2.1]heptan-2-one ((-)-**4**) added to (+)-(3a*R*,4a*R*,7a*R*,7b*S*)-3a,4a,7a,7b-tetrahydro-6,6-dimethyl[1,3]dioxolo-[4,5]furo[2,3-*d*]isoxazole-3-carbaldehyde ((+)-**5**) giving a major aldol (+)-**6** in 90% yield that was converted into (+)-(1*R*,4*R*,5*R*,6*S*,7*R*)-4-*exo*-(4-bromobenzenesulfonyloxy)-6-*exo*-{(*S*)-[(*tert*-butyl)dimethylsilyloxy]-[(3a*R*,4a*R*,7a*R*,7b*S*)-3a,4a,7a,7b-tetrahydro-6,6-dimethyl[1,3]dioxolo[4,5]furo[2,3-*d*]isoxazol-3-yl]methyl}-7-*endo*-(methoxymethoxy)-2,8-dioxabicyclo[3.2.1]octan-3-one ((+)-**15**). Methanolysis of (+)-**15**, followed by reduction and protection steps provided (-)-1,4-anhydro-3-{6*S*-5-[(benzyloxy)carbonyl]amino-5-deoxy-β-L-idohexofuranos-6-C-yl}-3-deoxy-2,6-bis-O-(methoxymethyl)-α-D-galactopyranose ((-)-**21**). Acidic treatment of (-)-**21** followed by catalytical hydrogenation generated (-)-(1*R*,2*R*,3*S*,7*R*,8*S*,9*S*,9a*S*)-1,3,4,6,7,8,9, 9a-octahydro-8-[(1'*R*,2'*R*)-1',2',3'-trihydroxypropyl]-2*H*-quinolizine-1,2,3,7,9-pentol ((-)-**2**) characterized as its octaacetate (+)-**26**.

Key words: aldol condensation, "naked sugars", isoxazolines, aminodeoxysugars

Polyhydroxylated indolizidine alkaloids and their analogues, including ring contracted derivatives have shown interesting glycohydrolase inhibiting activities and as a consequence have a great potential as drugs against cancer and viruses.[1] Ring expanded analogues of polyhydroxyindolizidines, the polyhydroxyquinolizidines, emerge as a new class of potential glycohydrolase inhibitors, a few derivatives have been reported already.[2] Among them **1**, an analogue of α-homonojirimycin, is a potent inhibitor of α-glucosidase I from pig kidney (IC_{50} = 0.15 μM).[3]



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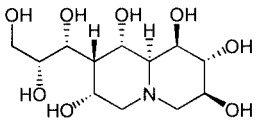

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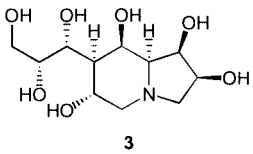

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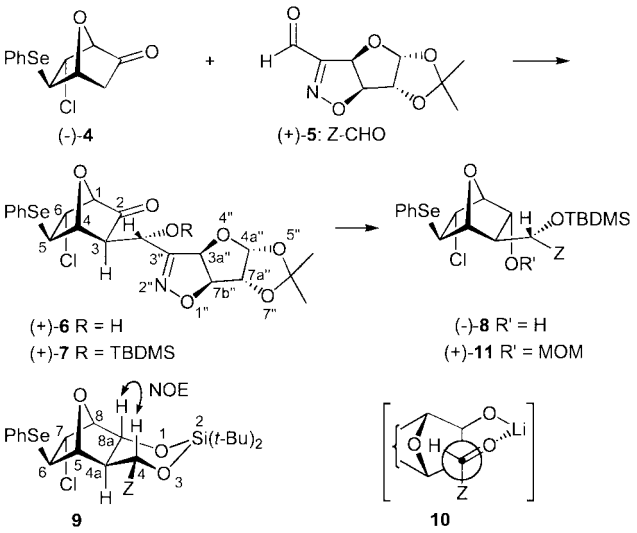
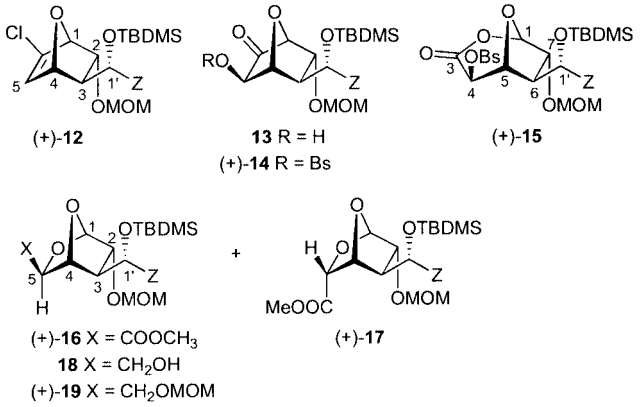
We report here the synthesis of (-)-(1*R*,2*R*,3*S*,7*R*,8*S*,9*S*,9a*S*)-1,3,4,6,7,8,9,9a-octahydro-8-[(1'*R*,2'*R*)-1',2',3'-trihydroxypropyl]-2*H*-quinolizine-1,2,3,7,9-pentol ((-)-**2**) the first example of a new kind of polyhydroxyquinolizidines bearing a polyhydroxylated side-chain. Our synthetic approach has been inspired from that we had used to prepare **3**, the first example a 7-(1,2,3-trihydroxypropyl)-octahydroindolizine-1,2,6,8-tetrol.[4] It features the diastereoselective cross-aldolization[5] of the enantiomerically pure 7-oxabicyclo[2.2.1]heptan-2-one (-)-**4** derived from a "naked sugar of the first generation"[6] with (+)-(3a*R*,4a*R*,7a*R*,7b*S*)-3a,4a,7a,7b-tetrahydro-6,6-dimethyl-[1,3]dioxolo-[4,5]furo[2,3-*d*]isoxazole-3-carbaldehyde ((+)-**5**) that has been obtained recently enantiomerically pure.[8]

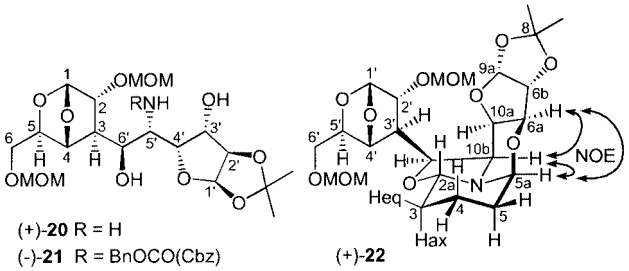


The lithium enolate of (-)-**4**[6c,9] obtained by reaction of (-)-**4** with $(Me_3Si)_2NLi$ in THF at –5 °C was cooled to –78 °C and a solution of aldehyde (+)-**5**[8] in THF was added to it. After stirring at –78 °C for 3 h, acidic quenching with AcOH/MeOH and flash chromatography on silica gel provided pure aldol (+)-**6** in 90% yield[10] which was silylated into (+)-**7** (92%)[11] with (*t*-Bu)$Me_2SiOSO_2CF_3$ and 2,6-lutidine (CH_2Cl_2, 0°C for 1 h, then 25 °C for 5 h). Reduction of ketone (+)-**7** with $NaBH_4$ in MeOH (5°C) was highly *exo* face selective[6c] giving the corresponding *endo* alcohol (-)-**8** (91%).[12] The structures of (+)-**6**, (+)-**7** and (-)-**8** were deduced from their spectral data including 2D (NOESY, COSY) ^{1}H-NMR spectra and were confirmed by the formation of the 5,8-epoxy-4*H*-1,3,2-benzodioxasiline **9**[13,14] for which ^3J(H-8,H-8a) = 4.2 Hz,[15] ^3J(H-4a,H-5) ≅ 0 Hz,[15] ^3J(H-4,H-4a) = 10.8 Hz and ^3J(H-4a,H-8a) = 3.5 Hz were measured in its ^{1}H-NMR spectrum. Furthermore, a strong NOE was observed between the signals at δ_H = 4.78 and 4.48 ppm assigned to protons H*exo*-8a and H-4, respec-

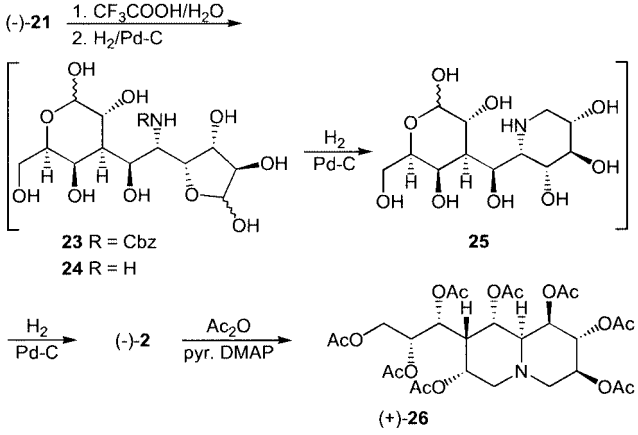
tively. Compound **9** was obtained in 36% yield on treatment of (-)-**8** first with $(n\text{-Bu})_4NF$ in THF, then with $(t\text{-Bu})_2Si(OSO_2CF_3)_2$ and 2,6-lutidine in CH_2Cl_2 (0-20 °C, 4 h). The data reported above confirm that the cross-aldolization (-)-**4** + (+)-**5** → (+)-**6** adopts a Zimmerman-Traxler transition state[16] of type **10** in which the *exo* face of the lithium enolate is preferred for the aldehyde attack by its *Si* face.



Conversion of the 7-oxabicyclo[2.2.1]heptane moiety of (-)-**8** into a uronic moiety followed a procedure similar to that developed by us earlier for the synthesis of (±)-**3**.[4] The *endo* alcohol (-)-**8** was protected as a methoxymethyl ether on treatment with CH_3OCH_2Cl and $(i\text{-Pr})_2NEt$ in CH_2Cl_2 (0-25 °C, 20 h) giving (+)-**11** (86% yield) which underwent oxidative elimination of the benzeneselenyl group on treatment with *meta*-chloroperbenzoic acid (*m*CPBA 70%) in CH_2Cl_2/THF (-78 °C for 2 h, then 25 °C for 14 h) to furnish the chloroalkene (+)-**12** in 95% yield.[17] Double hydroxylation of (+)-**12** with $Me_3NO{\cdot}2\ H_2O$ in THF/H_2O catalyzed with OsO_4 ($NaHCO_3$, 25 °C, 2 h) was highly *exo* face selective giving the corresponding α hydroxyketone **13** that was not isolated, but esterified directly with *para*-bromobenzenesulfonyl chloride and Et_3N (0°C for 1 h, then 25°C for 2 h) into the brosylate (+)-**14** (88%).[18] Baeyer-Villiger oxidation of ketone (+)-**14** with *m*CPBA/$NaHCO_3$ in CH_2Cl_2 (0 °C for 5 h, then 25 °C for 15 h) was, as expected,[19] highly regioselective providing uronolactone (+)-**15** (92%).[20] Methanolysis (MeOH, K_2CO_3, DMF, 5 °C for 30 min, then 25 °C for 90 min) led to a 5:1 mixture (90%) of methyl 1,5-anhydro-α-D-galactofuranuronate (+)-**16** and methyl 1,5-anhydro-β-L-altrofuranuronate (+)-**17** that could be separated by column chromatography on silica gel.[21] Reduction of (+)-**16** with $LiAlH_4$ in THF at 0 °C (10 min) provided the 1,5-anhydro-α-D-galactofuranose **18** which was not isolated but directly treated with $MeOCH_2Cl$ and $(i\text{-Pr})_2NEt$ to give (+)-**19** (92%).[22] Under these conditions the reduction of the isoxazoline moiety does not occur. The latter reaction requires ether as solvent, higher temperature (25 °C) and prolonged exposure (5 days) to a concentrated solution of $LiAlH_4$. This generated the aminodiol (+)-**20** (desilylation occurs concomitantly with the imine reduction) which was selectively protected as the N-benzylcarbamate (-)-**21** (88%)[23] following a modified Oku's procedure.[24]



The L-*ido* configuration of the 5-amino-5-deoxy-aldose moiety of (+)-**20** was expected by analogy with the $LiAlH_4$ reductions of simpler isoxazolines that favor hydride delivery on the less sterically hindered face of the imine functions.[7,8,25] Definitive proof for that configuration was given by ^{1}H-NMR spectra of the 1*H*,6a*H*,8*H*-2,6,7,9,10-pentaoxa-10c-azapentaleno[2,3-*d*]acenaphthylene derivative (+)-**22** obtained by reaction of (+)-**20** (65%) with glutaraldehyde in MeOH[26] (25 °C, 12 h). For steric reasons and because of the conformational anomeric effect expected[27] for the aminoacetal moiety in (+)-**22**, this compound is the most stable stereomer resulting from the reversible condensation (+)-**20** + glutaraldehyde. The ^{1}H-NMR spectra of the crude product showed the presence of 6-10% only of stereomers of (+)-**22**.[28] The vicinal coupling constants observed in the ^{1}H-NMR spectrum of (+)-**22** were consistent with a "*cis*-decalin" type of conformation for its 1-aza-5-oxabicyclo[4.4.0]decane moiety (^3J(H-2a,Hax-3) = 9.7 Hz, ^3J(H-2a,Heq-3) = 2.5 Hz, ^3J(H-5a,H-5) = 2.9, 2.4 Hz, ^3J(H-10a,H-10b) = 3.3 Hz, ^3J(H-6a,H-10a) = 1.8 Hz). The 2D-NOESY ^{1}H-NMR spectrum of (+)-**22** showed correlation peaks confirming the structure and conformation shown for (+)-**22**.[14]



Treatment of (-)-**21** with CF_3COOH/H_2O (25 °C, 10 h) gave a complex mixture of dialdoses **23** that was hydrogenated over 10% Pd on charcoal (25 °C, H_2O, 15 h) to give the polyhydroxylated quinolizidine (-)-**2** as unique prod-

uct. Debenzylation was expected to generate **24**. The primary amine of **24** equilibrates with imines resulting from its reaction with the aldose moieties, imines that are reduced into the corresponding piperidines under our hydrogenation conditions. A possible piperidine intermediate is **25** which undergoes formation of an intermediate iminium salt with the second aldose moiety that is reduced into **2**. This polyol was fully characterized as its octaacetate (+)-**26** obtained in 40% yield (based on (-)-**21**) on treating crude **2** with Ac_2O/pyridine and 4-dimethylaminopyridine as catalyst (25°C, 15 h).[29]

This work demonstrates that the cross-aldolization of aldehydes such as (+)-**5** with 7-oxabicyclo[2.2.1]heptanones can be highly stereoselective, thus allowing one to construct complicated long-chain amino-deoxysugars via the stereoselective hydride reductions of the isoxazolines so-obtained. Deprotection under hydrogenation conditions converts these systems into quinolizidines. The first example (**2**) of a 8-(1',2',3'-trihydroxypropyl)-2*H*-quinolizine-1,2,3,7,9-pentol has been reached by this method. Further efforts should make possible the obtention of stereomers of **2** and of unprotected long-chain amino-deoxycarbohydrates and analogues.

Acknowledgement

We thank the *Swiss National Science Foundation* (Bern) and the *Fonds Herbette* (Lausanne) for financial support.

References and Notes

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(10) Data for (+)-**6**: m.p. 111-112 °C; $[\alpha]^{25}_D$ +50 (c=1.0, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 7.61-7-65 (m, 2H), 7.35-7.32 (m, 3H), 5.77 (d, ^3J=3.6, H-4a"), 5.68 (d, ^3J=6.4, H-3a"), 4.96 (d, ^3J=6.4, H-7b"), 4.84 (dd, ^3J=8.3, 2.6, H-1'), 4.78-4.76 (m, H-7a", H-4), 4.54 (d, ^3J=5.6, H-1), 4.29 (ddd, ^3J=5.6, 2.8, ^4J=1.0, H-6), 3.65 (d, ^3J=2.8, H-5), 3.35 (d, ^3J=2.6, HO-C(1')), 2.78 (d, ^3J=8.3, H-3), 1.50, 1.37 (2s, 2 Me).

(11) Data for (+)-**7**: $[\alpha]^{25}_D$ +28 (c=1.1, $CHCl_3$).

(12) Data for (-)-**8**: $[\alpha]^{25}_D$ -10 (c=0.43, $CHCl_3$).

(13) Data for **9**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 7.59-7.57 (m, 2H), 7.34-7.31 (m, 3H), 5.70 (d, ^3J=3.5, H-4a'), 5.51 (d, ^3J=6.4, H-3a'), 4.83 (d, ^3J=6.4, H-7b'), 4.78 (dd, ^3J=4.2, 3.8, H-8a), 4.76 (d, ^3J=3.5, H-7a'), 4.49-4.47 (m, H-4, H-8), 4.30 (s, H-5), 4.15 (dd, ^3J=5.3, 3.5, H-7), 3.51 (d, ^3J=5.3, H-6), 2.23 (dd, ^3J=10.8, 3.3, H-4a), 1.49, 1.37 (2s, 2 Me), 1.05 (s, 2 *t*-Bu); ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ_C: 158.6 (s), 134.0 (d, 2C), 133.9 (s), 129.2 (2d), 127.8, 113.9 (s), 106.1, 87.1, 86.8, 86.5, 84.6, 79.4, 77.1, 68.6, 60.4, 56.6, 51.5 (11d), 27.7, 27.3, 27.1, 26.8 (4q), 24.3, 20.8 (2s).

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(17) Data for (+)-**12**: colorless oil; $[\alpha]^{25}_D$ = +129 (c=1.1, $CHCl_3$); UV (MeCN) λ_{max}: 209 nm (ε=7000); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 6.37 (d, ^3J=2.2, H-5), 5.87 (d, ^3J=3.6, H-4a"), 5.44 (d, ^3J=5.8, H-3a"), 4.97 (d, ^3J=2.2, H-4), 4.92 (d, ^3J=6.5, H-1'), 4.84 (d, ^3J=5.8, H-7b"), 4.82 (d, ^3J=3.6, H-7a"), 4.70-4.68 (m, H-1), 4.69, 4.66 (AB, ^2J=6.7, CH_2(MOM)), 4.17 (dd, ^3J=4.4, 2.4, H-2), 3.39 (s, MeO), 2.02 (dd, ^3J=6.5, 2.4, H-3), 1.49, 1.36 (2s, 2 Me), 0.92 (s, *t*-Bu), 0.11, 0.10 (2s, Me_2Si).

(18) Data for (+)-**14**: mp 55-56 °C, $[\alpha]^{25}_D$ +13 (c=1.0, $CHCl_3$).

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(20) Data for (+)-**15**: mp 67-68 °C, $[\alpha]^{25}_D$ +18 (c=1.0, $CHCl_3$); IR (KBr) ν: 2930, 1770, 1575, 1390, 1375, 1205, 1190, 1105, 1060, 1010, 840 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 7.83, 7.73 (2d, ^3J=8.8, 4H), 5.82 (d, ^3J=3.5, H-1), 5.79 (d, ^3J=3.5, H-4a"), 5.56 (d, ^3J=6.7, H-3a"), 4.95 (d, ^3J=6.7, H-7b"), 4.78 (d, ^3J=5.7, H-1'), 4.74 (d, ^3J=3.5, H-7a"), 4.73 (s, H-4), 4.64, 4.50 (AB, ^2J=7.0, CH_2(MOM)), 4.55 (br. s, H-5), 4.19 (dd, ^3J=4.5, 3.5, H-7), 3.32 (s, MeO), 2.36 (ddd, ^3J=5.7, 4.5, 1.9, H-6), 1.44, 1.32 (2s, 2 Me), 0.84 (s, *t*-Bu), 0.06, 0.05 (2s, Me_2Si).

(21) Data for (+)-**16**: oil, $[\alpha]^{25}_D$ +64 (c=0.36, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): ^3J(H-4,H-3) = ^3J(H-4,H-5) ≅ 0, ^3J(H-1,H-2) = 2.3. Data for (+)-**17**: oil, $[\alpha]^{25}_D$ +75 (c=0.25, $CHCl_3$); ^3J(H-3,H-4) ≅ 0, ^3J(H-4,H-5) = 4, ^3J(H-1,H-2) = 2.0.

(22) Data for (+)-**19**: oil, $[\alpha]_D^{25}$+54 (c=0.65, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 5.86 (d, ^3J=3.6, H-4a"), 5.55 (d, ^3J=6.0, H-3a"), 5.47 (d, ^3J=2.4, H-1), 4.89 (d, ^3J=6.0, H-7b"), 4.82 (d, ^3J=3.6, H-7a"), 4.72 (d, ^3J=7.0, H-1'), 4.71 (AB, ^2J=6.8, 1H, CH_2(MOM)), 4.64-4.60 (m, 4H, H-4, MOM), 3.93 (dd, ^3J=8.0, 5.2, H-5), 3.81 (dd, ^3J=2.8, 2.4, H-2), 3.46 (dd, ^2J=10.3, ^3J=5.2, H-6), 3.41-3.39 (m, H'-6), 3.40, 3.35 (2s, 2 MeO), 2.05 (dd, ^3J=7.0, 2.8, H-3), 1.51, 1.36 (2s, Me_2C), 0.91 (s, *t*-Bu), 0.11, 0.09 (2s, Me_2Si).

(23) Data for (+)-**20**: $[\alpha]_D^{25}$+ 37 (c=1.1, $CHCl_3$); Data for (-)-**21**: m.p. 49-50°C, $[\alpha]_D^{25}$-2.0 (c=0.5, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 7.34-7.30 (m, 5 H), 5.89 (d, ^3J=3.7, H-1'), 5.53 (d, ^3J=2.5, H-1), 5.42 (d, ^3J(H-N,H-5')=9.0, HN), 5.12, 5.08 (AB, ^2J=12.4), 4.72, 4.66 (AB, ^2J=6.9), 4.60, 4.58 (AB, ^2J=6.4), 4.54 (s, H-4), 4.50 (d, ^3J=3.7, H-2'), 4.38 (dd, ^3J=5.0, 2.7, H-4'), 4.24 (d, ^3J=2.7, H-3'), 4.12 (m, H-5'), 3.98 (dd, ^3J=2.8, 2.5, H-2), 3.91 (dd, ^3J=7.7, 5.3, H-5), 3.80 (dd, ^3J=8.1, 5.8, H-6'), 3.55 (br. s, 2 HO), 3.45 (dd, ^3J=10.3, 5.3, H-6), 3.41 (s, MeO), 3.38-3.34 (m, H'-6), 3.34 (s, MeO), 2.01 (dd, ^3J=8.1, 2.8, H-3), 1.47, 1.30 (2s, Me_2C).

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(28) Data for (+)-**22**: mp 54-55 °C, $[\alpha]_D^{25}$+17 (c=0.35, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 5.82 (d, ^3J=3.6, H-9a), 5.53 (d, ^3J=2.4, H-1'), 4.87, 4.67 (AB, ^2J=6.6, 2H), 4.84 (dd, ^3J=9.7, 2.5, H-2a), 4.69 (dd, ^3J=2.9, 2.4, H-5a), 4.55 (s, 2H), 4.48 (d, ^3J=3.6, H-6b), 4.28 (s, H-4'), 4.21 (dd, ^3J=11.6, 6.5, H-1), 4.17 (br. s, H-6a), 4.03 (dd, ^3J=2.6, 2.4, H-6'), 4.01 (dd, ^3J=8.8, 4.8, H-3'), 3.98 (dd, ^3J=3.3, 1.8, H-10a), 3.73 (dd, ^3J=6.5, 3.3, H-10b), 3.46 (dd, ^3J=9.7, 4.8, H-8'), 3.41, 3.31 (2s, 2 MeO), 3.32-3.29 (m, H'-8'), 2.78 (dd, ^3J=11.6, 2.6, H-5'), 1.96-1.92 (m, H-3), 1.75-1.70 (m, 2H, H-4), 1.69-1.55 (m, 2H, H-5), 1.44, 1.31 (2s, Me_2C), 1.29-1.23 (m, H'-3).

(29) Data for (+)-**26**: oil, $[\alpha]_D^{25}$ +40 (c=0.3, $CHCl_3$); UV (MeCN): 199 (8500); IR (film) ν: 2920, 2850, 1750, 1435, 1375, 1230, 1045, 740 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 5.51 (dd, ^3J=7.8, 4.1, H-1'), 5.33 (ddd, ^3J=6.8, 4.1, 4.0, H-2'), 5.25 (ddd, ^3J=9.7, 4.9, 4.8, H-7), 5.07 (dd, ^3J=4.8, 4.7, H-9), 5.03 (br. s, H-2), 4.98 (br. s, H-1), 4.76 (br. s, H-3), 4.28 (dd, ^2J=11.9, ^3J=4.0, H-3'), 3.93 (dd, ^2J=11.9, ^3J=6.8, H'-3'), 3.37-3.33 (m, Heq-6), 3.01 (dm, ^2J=13.5, Heq-4), 2.95 (m, H-9a), 2.85 (dm, ^2J=13.5, Hax-4), 2.67-2.60 (m, 2H, Hax-6, H-8), 2.15, 2.11, 2.10, 2.09, 2.07, 2.03 (6s, 8 AcO). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ_H: 170.5, 170.3, 170.0, 169.8, 169.5, 169.2, 168.2 (7s, 8 COO), 70.0, 68.2 (2C), 67.8 (2C), 66.8, 66.3 (5d), 62.6 (t), 57.1 (d), 54.0, 52.7 (2t), 37.8 (d), 21.2, 21.0, 20.9, 20.8, 20.5 (5q, 8 CH_3); CI-MS (NH_3) m/z: 647 (M+1, 7), 646 ($M^{\bullet+}$, 5). Anal. calcd. for $C_{28}H_{39}NO_{16}$ (645.61): C 52.09, H 6.09, N 2.17; found: C 52.09, H 6.42, N 2.30.

Article Identifier:
1437-2096,E;1999,0,08,1219,1222,ftx,en;G12899ST.pdf