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Approaches to the C-B-A trisaccharide of dihydroaclacinomycin by extending the chain from either side*

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ABSTRACT

Selective benzylation of L-fucal (**1**) under phase-transfer conditions gave the 3- and 4-monoethers **2** and **3**, respectively. Two routes, the "tail" or the "head" addition are presented, both leading to the target molecule **9**, a mimic of the C-B-A trisaccharide component of dihydroaclacinomycin. Addition of glycals **2** and **3**, respectively, to the acetylated glycal (**7**) of amicetose used as glycosyl donor gave the disaccharide glycals **6** and **8**. Alternatively, glycosylation of the 4-acetate (**4**) of **2** with the benzyl hex-2-enopyranoside derivative **10** gave the disaccharide derivative **11**. In the first case, the final glycosylation step involves the addition of **10** to disaccharide glycal **8**. In the second procedure, the disaccharide alcohol **12** is obtained by *O*-deacetylation of **11**, and serves as the glycosyl acceptor for glycal derivative **7** to give the C-B-A precursor trisaccharide derivative **9**.

INTRODUCTION

Our rationale for the choice of synthetic targets among naturally occurring deoxy oligosaccharides of anthracycline glycosides is based upon the fact that pharmacological properties are attributable to both the aglycon and the oligosaccharide side-chain.

It has been emphasized in the literature[1] and in particular in our recent contributions[2] that the sugar side-chain evidently controls the drug transport and such factors as the bioavailability, selectivity, and pharmacokinetics of a given anthracycline glycoside.

The now well established "NIS-approach" for stereospecific glycosylations, affording deoxy sugars is of demonstrated utility for the systematic build-up of various deoxy sugar oligosaccharides, and has experienced a renaissance recently[3].

The synthetic strategy involves chain prolongation from either the reducing or non-reducing terminus. The differences between these and our earlier reported[4] approach is that of a batchwise method *vs.* the former "one-pot procedure".

* Dedicated to Professor Grant Buchanan in the year of his 65th birthday.
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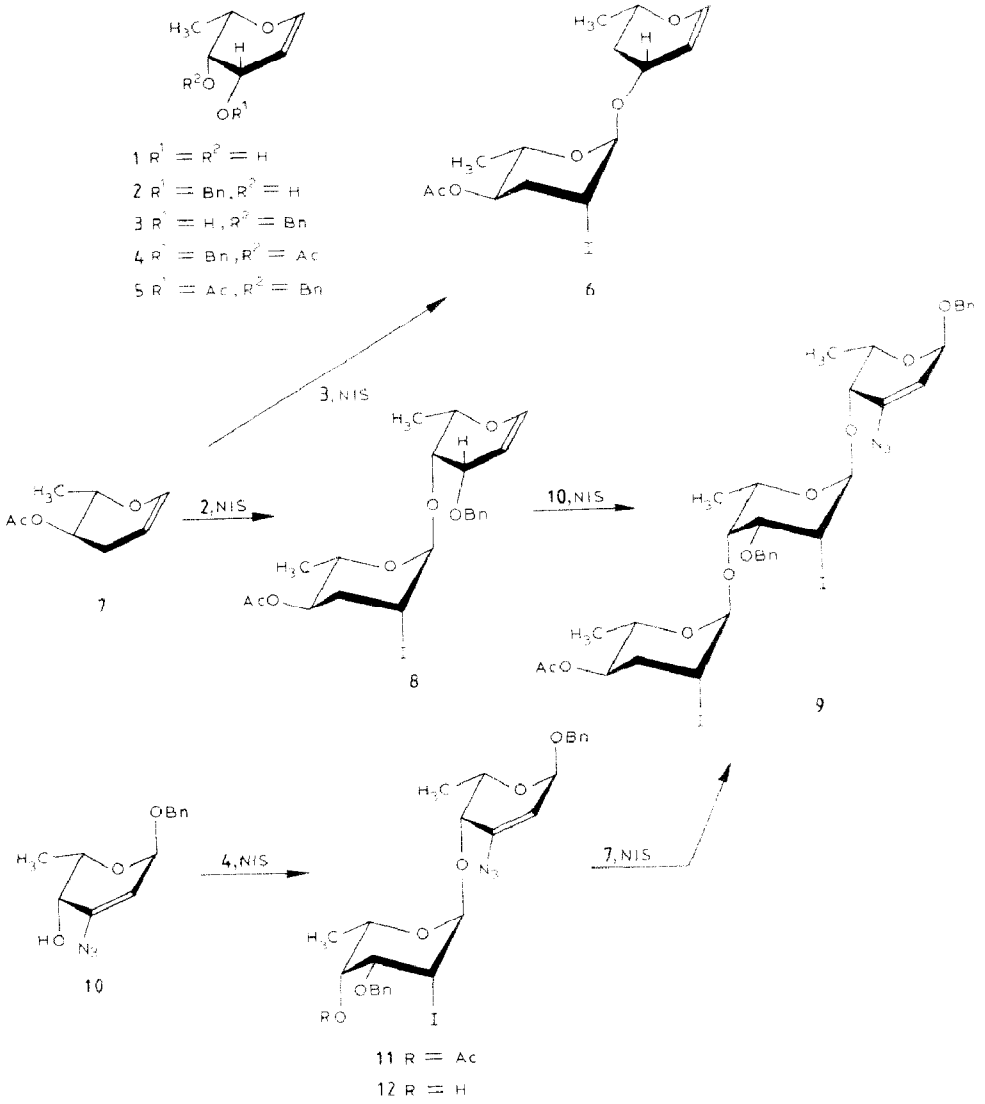
RESULTS AND DISCUSSION

Stepwise construction of the C-B-A trisaccharide from its non-reducing sugar terminus required two glycals and an amino sugar glycoside. These were subsequently attached to the enol-ether double bond of an intermediate disaccharide glycal to serve as the "reducing" sugar terminus in the resulting trisaccharide.

Whereas the amino sugar precursor was readily prepared following a procedure described earlier[5], the monosubstituted glycals had to be synthesized from L-fucal[6]. Alkylation by a phase-transfer catalysis procedure[7,8] gave the monoethers **2** and **3** in 7:4 ratio, respectively. No other products were detected, and column chromatography



readily gave the pure compounds, which were both also characterized as their respective 4- (**4**) and 3-acetates (**5**). The use of two compounds, L-amicetal[9] (**7**) and one of the disaccharide glycals **6** and **8** presented several problems in directing the reaction towards a homogenous product, as the two starting materials are similarly functionalized, and both compete for the electrophilic iodonium ion.

This central question has been addressed in recent contributions concerning the *endo*-[10] and *exo*-[11] iodoalkoxylation procedures, and may be expressed by such terms as "armed" and "disarmed" donors. When this concept was merely a laboratory hypothesis we overcame the similarities in reactivity by simply saturating the nucleophile with a large excess of glycosyl acceptor. Yields of the coupling reaction were diminished because of the similar reactivities of the double bonds as well as by the low reactivity of the axial hydroxy group of the nucleophilic alcohol component. This problem has also been previously addressed and solved in anthracycline oligosaccharide synthesis[12].

Careful optimization and portionwise addition of NIS over several days gave **8** in 20% yield. Synthesis of the isomeric α-(1→3)-linked disaccharide **6** proceeded with somewhat higher yield (33%), because of the higher reactivity of the allylic hydroxy group. The α-glycosidic linkage was established by a typically small $J_{1',2'}$ coupling of 1.6 Hz. Finally, the disaccharide glycal **8** was condensed with the amino sugar benzyl glycoside **10** and *N*-iodosuccinimide to give the trisaccharide **9** in 27% yield. Because of these moderate yields, the idea of an oligosaccharide synthesis *via* a growing glycosyl acceptor was abandoned in favor of the reverse approach, where the reducing sugar is glycosylated first. Thus the vinyl azide **10** reacted with the acetylated glycal **4** to give the α-linked disaccharide **11** in 50% yield. The yields were poorly reproducible, probably because of a side-reaction of **10** with NIS, as observed similarly with simpler vinyl azides[13]. To overcome this instability of the starting material, a satisfactory procedure was established by maintaining a low stationary concentration of NIS and an excess of the acceptor glycal through portionwise addition of the iodonium donor during a period of one week. This procedure afforded, in reproducible yield, the fully blocked disaccharide **11**, whose structure was assigned completely by two-dimensional ^{1}H-n.m.r. spectroscopy. Characteristic signals, such as the 6 and 6′ methyl resonances are readily detected, as is the narrow H-1′ signal ($J_{1',2'}$ <0.5 Hz) attributable to the α-glycosidic linkage. For further chain extension, the 4′-acetate **11** was readily deprotected by the Zemplén method to give alcohol **12**. The literature reports and our experience confirms the considerably lower nucleophilicity of certain alcohol functions in oligosaccharide derivatives. Nevertheless addition of the acetylated glycal **7**, again promoted by NIS, proceeded successfully with moderate yields; trisaccharide **9** was obtained in 58% yield and identified by n.m.r. spectroscopy.

These experiments demonstrate that the route to the target molecule **9** via the disaccharide alcohol is superior to the "growing glycal" route.

EXPERIMENTAL

General procedures. — *A* (*Acetylation*). A solution of the sugar (1 mmol) in anhydrous pyridine (5 mL) plus Ac_2O (6 mmol) was stirred for 4–25 h at room temperature, whereupon volatiles were removed by distillation of toluene (twice) from the mixture and the residue was purified by chromatography.

B (*Work-up of N-iodosuccinimide-mediated glycosylations*). The mixture was filtered, the filtrate evaporated, and the residue diluted with CH_2Cl_2. This solution was washed subsequently with 10% aq. $Na_2S_2O_3$ and water, dried ($MgSO_4$), and the solvent finally removed by evaporation. The residue was then purified by chromatography.

C (*Deacetylation*). To a solution of the ester (1 mmol) in dry MeOH (5 mL) was added 0.1M methanolic NaOMe until the mixture became alkaline. The reaction was quenched, after t.l.c. monitoring, by addition of Amberlite IR-120 (H^+) ion-exchange resin. Upon neutralization, the resin was removed and the mixture either filtered through silica, purified by column chromatography, or crystallized directly.

1,5-Anhydro-3-O-benzyl-2,6-dideoxy-L-lyxo-*hex-1-enitol* (**2**) *and 1,5-anhydro-4-O-benzyl-2,6-dideoxy*-L-lyxo-*hex-1-enitol* (**3**). — To a solution of **1** (600 mg, 4.60 mmol) in CH_2Cl_2 (20 mL) was added α-bromotoluene (550 μL, 4.60 mmol), Bu_4NBr (160 mg), and 20% aq. KOH (10 mL). After vigorous stirring for 2 days, the organic layer was separated, washed with water, dried ($MgSO_4$), and the solvent evaporated. The syrupy residue was subjected to chromatography (15:1 toluene–EtOAc) to give as the first fraction, compound **3** (332 mg, 33%) as a colourless syrup: $[\alpha]_D^{20}$ +13.1° (*c* 2.0, $CHCl_3$); ^{1}H-n.m.r. (300 MHz, $CDCl_3$): δ 7.27–7.37 (m, 5 H, aryl-H), 6.38 (dd, H-1), 4.67 (ddd ~ dt, H-2), 4.62 and 4.65 (AB, 2 H, Ph-CH_2), 4.22 (dddd, H-3), 3.87 (m, H-4), 3.95 (dq, H-5), 2.48 (d, O*H*), and 1.41 (d, 3 H, H-6); $J_{1,2}$ 6.3, $J_{1,3}$ 1.7, $J_{2,3}$ 1.9, $J_{3,4}$ 4.7, $J_{3,5}$ 0.7, $J_{4,5}$ 1.0, $J_{5,6}$ 6.5, J_{AB} 11.7, and $J_{4,OH}$ 3.5 Hz.

Compound **2** was eluted last and was obtained, after recrystallization, as colourless needles (191 mg, 19%): m.p. 74–75°, $[\alpha]_D^{20}$ +12.5° (*c* 2.0, $CHCl_3$); ^{1}H-n.m.r. (300 MHz, $CDCl_3$): δ 7.31–7.43 (m, 5 H, aryl-H), 6.35 (dd, H-1), 4.79 (mc, 2 H, Ph-CH_2), 4.70 (ddd, H-2), 4.40 (m, H-3), 4.09 (ddq, H-5), 3.67 (ddd, H-4), 2.21 (d, OH), and 1.34 (d, 3 H, H-6); $J_{1,2}$ 6.2, $J_{1,3}$ 1.3, $J_{2,3}$ 2.5, $J_{2,4}$ 1.3, $J_{3,4}$ 5.0, $J_{3,5}$ 0.6, $J_{4,5}$ 1.2, $J_{5,6}$ 6.7, and $J_{3,OH}$ 9.0 Hz.

Anal. Calc. for $C_{13}H_{16}O_3$ (220.3): C 70.88; H, 7.32; Found for **2**: C, 70.20; H, 7.44; **3**: C, 70.79; H, 7.31.

4-O-Acetyl-1,5-anhydro-3-O-benzyl-2,6-dideoxy-L-lyxo-*hex-1-enitol* (**4**). — Compound **2** (480 mg, 2.18 mmol) was acetylated by the general procedure *A* to give **4** (after recrystallization from EtOAc–*n*-hexane) as colourless needles (540 mg, 94%): m.p. 55°, $[\alpha]_D^{20}$ −44.0° (*c* 1.2, $CHCl_3$); ^{1}H-n.m.r. (300 MHz, $CDCl_3$): δ 7.28–7.34 (m, 5 H, aryl-H), 6.40 (dd, H-1), 5.39 (ddd, H-4), 4.48 and 4.66 (AB, 2H, Ph-CH_2), 4.26 (dddd, H-3), 4.12 (ddq, H-5), 2.18 (s, 3 H, OAc), 1.27 (d, 3 H, H-6), and 4.73 (ddd ~ dt, H-2); $J_{1,2}$ 6.4, $J_{1,3}$ 1.8, $J_{2,3}$ 2.0, $J_{2,4}$ 1.8, $J_{3,4}$ 4.8, $J_{3,5}$ 1.0, $J_{4,5}$ 1.2, $J_{5,6}$ 6.6, and J_{AB} 11.8 Hz.

Anal. Calc. for $C_{15}H_{18}O_4$ (262.3): C, 68.68; H, 6.92; Found: C, 68.25; H, 6.96.

3-O-Acetyl-1,5-anhydro-4-O-benzyl-2,6-dideoxy-L-lyxo-*hex-1-enitol* (**5**). — Compound **3** (210 mg, 0.95 mmol) was acetylated following the general procedure; filtration

through silica gel gave **5** as a colourless syrup (238 mg, 95%), $[\alpha]_D^{20}$ +65.3° (*c* 0.6, $CHCl_3$); ^{1}H-n.m.r. (300 MHz, $CDCl_3$): δ 7.14–7.28 (m, 5 H, aryl-H), 6.29 (dd, H-1), 5.39 (ddd, H-3), 4.60 (ddd, H-2), 4.58 (m, 2 H, Ph-CH_2), 4.04 (dq, H-5), 3.72 (ddd, H-4), 1.96 (s, 3 H, OAc), and 1.19 (d, 3 H, H-6); $J_{1,2}$ 6.3, $J_{1,2}$ 1.5, $J_{2,3}$ 3.1, $J_{2,4}$ 1.1, $J_{3,4}$ 5.5, $J_{4,5}$ 2.1, $J_{5,6}$ 6.7, and J_{AB} 11.8 Hz.

Anal. Calc. for $C_{15}H_{18}O_4$ (262.3): C, 68.68; H, 6.92. Found: C, 68.16; H, 6.77.

*4-O-(4-O-Acetyl-2,3,6-trideoxy-2-iodo-α-*L*-arabino-hexopyranosyl)-1,5-anhydro-3-O-benzyl-2,6-dideoxy-*L*-lyxo-hex-1-enitol* (**8**). — A solution of **7** (510 mg, 3.27 mmol) and **2** (2.16 mg, 0.98 mmol) in dry MeCN (7 mL) was equilibrated over molecular sieves (4 Å) and aliquots of *N*-iodosuccinimide (229 mg, 1.01 mmol) were added during one week. The reaction was monitored by t.l.c. (1:4 EtOAc–*n*-hexane). The reaction was then processed by the general procedure *B* with purification by chromatography (1:10 EtOAc–petroleum ether). Compound **8** was eluted first and obtained after evaporation of the solvent as a colourless syrup (71 mg, 21% based on **2**); $[\alpha]_D^{20}$ −68.6° (*c* 1.0, $CHCl_3$); ^{1}H-n.m.r. (400 MHz, $CDCl_3$): δ 7.25–5.35 (m, 5 H, aryl-H), 6.15 (dd, H-1), 5.11 (d, H-1′), 4.91 (ddd, H-4′), 4.79 (ddd, H-2), 4.62 (m, 2 H, Ph-CH_2), 4.42 (ddd, H-2′), 4.28 (dq, H-5′), 4.13 (dddd, H-3), 4.09 (ddq, H-5), 3.96 (ddd, H-4), 2.26 (ddd, H-3a′), 2.24 (ddd, H-3e′), 2.01 (s, 3 H, OAc), 1.34 (d, 3 H, H-6), and 1.04 (d, 3 H, H-6′); $J_{1,2}$ 6.2, $J_{1,3}$ 1.6, $J_{2,3}$ 2.7, $J_{2,4}$ 1.2, $J_{3,4}$ 4.4, $J_{3,5}$ 1.4, $J_{4,5}$ 1.8, $J_{5,6}$ 6.7, $J_{1',2'}$ 1.6, $J_{2',3a'}$ 3.9, $J_{2',3e'}$ 3.6, $J_{3a',3e'}$ 14.2, $J_{3a',4'}$ 9.5, 5.6, $J_{4',5'}$ 9.3, and $J_{5',6'}$ 6.2 Hz.

Anal. Calc. for $C_{21}H_{27}IO_3$ (502.3): C, 50.21; H, 5.42. Found: C, 50.40; H, 5.56.

*3-O-(4-O-Acetyl-2,3,6-trideoxy-2-iodo-α-*L*-arabino-hexopyranosyl)-1,5-anhydro-4-O-benzyl-2,6-dideoxy-*L*-lyxo-hex-1-enitol* (**6**). — A solution of **7** (245 mg, 1.57 mmol) and **3** (80 mg, 0.36 mmol) in MeCN (5 mL) was stirred under strict exclusion of light and moisture over molecular sieves (4 Å) and aliquots of *N*-iodosuccinimide (107 mg, 0.48 mmol) were added over a period of one week. Isolation by procedure *B* and subsequent chromatography (1:10 EtOAc–petroleum ether) gave **6** as a colourless oil (46 mg, 32% based on **3**); $[\alpha]_D^{20}$ −21.5° (*c* 2.0, $CHCl_3$); ^{1}H-n.m.r. (400 MHz, $CDCl_3$): δ 7.25–7.35 (m, 5 H, aryl-H), 6.32 (dd, H-1), 5.10 (d, H-1′), 4.94 (dddd, H-4′), 4.73 (ddd, H-2), 4.62 and 4.74 (AB, 2 H, Ph-CH_2), 4.36 (dddd, H-3), 4.22 (dddd, H-2′), 4.17 (ddq, H-5), 3.99 (dq, H-5′), 3.71 (ddd, H-4), 2.19–2.22 (m, 2 H, H-3a′, H-3e′), 2.08 (s, 3 H, OAc), 1.30 (d, 3 H, H-6), and 1.20 (d, 3 H, H-6′); $J_{1,2}$ 6.2, $J_{1,3}$ 1.4, $J_{2,3}$ 3.6, $J_{2,4}$ 0.8, $J_{3,4}$ 4.2, $J_{3,5}$ 1.0, $J_{4,5}$ 2.7, $J_{5,6}$ 6.5, $J_{1',2'}$ 1.3, $J_{2',3a'}$ 3.8, $J_{2',3e'}$ 3.6, $J_{2',4'}$ 0.3, $J_{3a',4'}$ 8.5, $J_{3e',4'}$ 6.5, $J_{4',5'}$ 9.5, $J_{5',6'}$ 6.2 and J_{AB} 11.7 Hz.

Anal. Calc. for $C_{21}H_{27}IO_3$ (502.3): C, 50.21; H, 5.42. Found: C, 50.10; H, 5.50.

*Benzyl 4-O-(4-O-acetyl-3-O-benzyl-2,6-dideoxy-2-iodo-α-*L*-talopyranosyl)-3-azido-2,3,6-trideoxy-α-*L*-threo-hex-2-enopyranoside* (**11**). — Compounds **10** (50 mg, 0.19 mmol) and **4** (100 mg, 0.38 mmol) were dissolved in dry MeCN, 4 Å molecular sieves (500 mg) were added and the mixture was stirred for 1 h at room temperature. Under strict exclusion of moisture and light, aliquots of *N*-iodosuccinimide (90 mg, 0.4 mmol) were added during a period of 3 days. Isolation by general procedure *B*, and purification by column chromatography (1:12 EtOAc–petroleum ether) gave pure **11** as a colourless oil (28 mg, 49% based on **10**); $[\alpha]_D^{20}$ −21.6° (*c* 2.0, $CHCl_3$); ^{1}H-n.m.r. (300

MHz, C_6D_6): δ 7.04–7.38 (m, 10 H, aryl-H), 5.43 (d ~ s, H-1'), 5.30 (dd, H-4'), 5.23 (d, H-2), 5.00 (d, H-1), 4.42 (~ d, H-2'), 4.36 and 4.61 (AB, 2 H, Ph-CH_2), 4.22 (dq, H-5'), 4.12 and 4.46 (AB, 2 H, Ph-CH_2), 3.83 (dq, H-5), 3.24 (dd ~ t, H-3'), 3.08 (d, H-4), 1.95 (s, 3 H, OAc), 1.23 (d, 3 H, H-6'), and 0.98 (d, 3 H, H-6); $J_{1,2}$ 3.2, $J_{4,5}$ 1.9, $J_{5,6}$ 6.6, $J_{1,2'}$ <0.6, $J_{2',3'}$ 4.5, $J_{3',4'}$ 3.5, $J_{4',5'}$ 1.5, $J_{5',6'}$ 6.5, J_{AB} 11.6, and J_{AB} 12.0 Hz.

Anal. Calc. for $C_{28}H_{32}IN_3O$ (649.5): C, 51.78; H, 4.97; N, 6.47. Found: C, 51.95; H, 5.12; N, 6.27.

*Benzyl 4-O-[(4-O-acetyl-2,3,6-trideoxy-2-iodo-α-*L*-arabino-hexopyranosyl)-3-O-benzyl-2,6-dideoxy-2-iodo-α-*L*-talo-hexopyranosyl]-3-azido-2,3,6-trideoxy-α-*L*-threo-hex-2-enopyranoside* (**9**). — *Route* A. Compound **11** (28 mg, 0.04 mmol) was deacetylated by the general procedure *C*. From the crude benzyl 3-azido-(3-*O*-benzyl-2,6-dideoxy-2-iodo-α-L-*talo*pyranosyl)-2,3,6-trideoxy-α-L-*threo*-hex-2-enopyranoside (**12**) was distilled toluene (twice), and the residue, dried *in vacuo*, was dissolved in dry MeCN (4 mL). To this solution was added **7** (17 mg, 0.11 mmol) and the mixture was stirred over molecular sieves (4 Å). After 1 h, *N*-iodocuccinimide (22 mg, 0.10 mmol) was added and the mixture was stirred for 4 days with strict exclusion of light and moisture. Isolation by general procedure *B* and subsequent preparative t.l.c. (1:5 EtOAc *n*-hexane; developed twice) gave starting material from the polar zone and, from the apolar zone after evaporation of the solvent, compound **9** as a colourless syrup (12 mg, 58%).

Route B. A solution of **8** (20 mg, 0.04 mmol) and **10** (10 mg, 0.04 mmol) in dry MeCN (4 ml) was stirred over molecular sieves (4 Å). Under exclusion of moisture and light *N*-iodosuccinimide (9 mg, 0.04 mmol) was added and the mixture was stirred for 7 days at room temperature. The crude mixture was treated by general procedure *B* and purified by preparative t.l.c. (1:5 EtOAc–*n*-hexane; developed twice). Together with starting material **10** (4 mg), compound **9** (5 mg, 27%) was obtained as a colourless syrup; $[\alpha]_D^{20}$ −27.0° (*c* 0.5, $CHCl_3$); ^{1}H-n.m.r. (360 MHz, $CDCl_3$): δ 7.10–7.40 (m, 10 H, aryl-H), 5.41 (d ~ s, H-1'), 5.40 (ddd, H-4'), 5.21 (d, H-2), 4.97 (d, H-1), 4.93 (d ~ s, H-1''), 4.71 (dq, H-5''), 4.38 (dd ~ d, H-2'), 4.34 and 4.60 (AB, 2 H, Ph-CH_2), 4.29 (ddd ~ t, H-2''), 4.08 and 4.23 (AB, 2 H, Ph-CH_2), 3.96 (dq, H-5'), 3.83 (dq, H-5), 3.50 (dd, H-4'), 3.16 (dd ~ t, H-3'), 3.08 (d, H-4), 2.67 (ddd, H-3''), 2.27 (ddd, H-3e''), 1.62 (s, 3 H, OAc), 1.00 and 1.04 (each d, each 3 H, H-6, H-6'), and 0.99 (d, 3 H, H-6''); $J_{1,2}$ 3.3, $J_{4,5}$ 1.9, $J_{5,6}$ 6.5, $J_{1,2'}$ <0.5, $J_{2,3'}$ 4.8, $J_{3',4'}$ 3.3, $J_{4',5'}$ 0.7, $J_{5',6'}$ 6.5, $J_{1'',2''}$ 0.8, $J_{2'',3a''}$ 3.8, $J_{2'',3e''}$ 3.3, $J_{3a'',3e''}$ 14.0, $J_{3a'',4''}$ 10.5, $J_{3e'',4''}$ 4.5, $J_{4'',5''}$ 10.0, $J_{5'',6''}$ 6.3, J_{AB} 12.1, and J_{AB} 11.3 Hz.

Anal. Calc. for $C_{34}H_{41}I_2N_3O_9$ (889.5): C, 45.91; H, 4.65; N, 4.72. Found: C, 46.38; H, 4.69; N, 4.94.

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