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SYNTHESIS OF HYBRID MOLECULES CONTAINING FRAGMENTS OF SESQUITERPENE LACTONES AND PLANT ALKALOIDS

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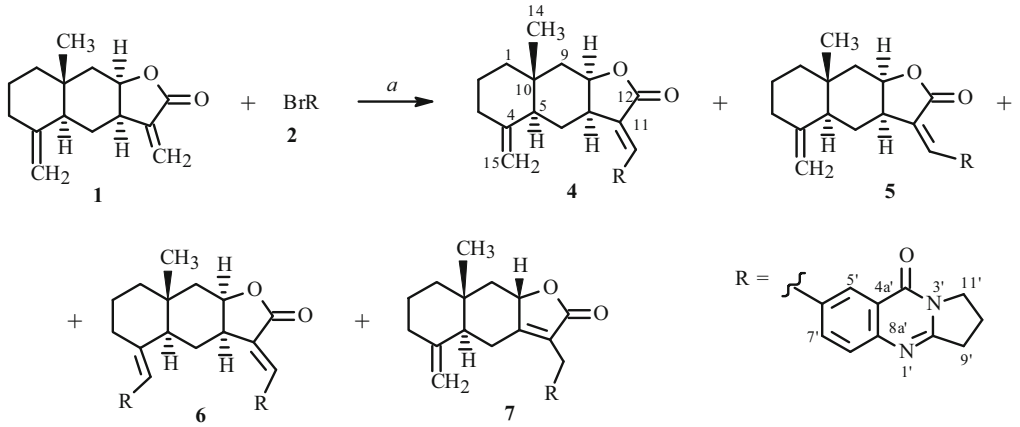
*The Pd-catalyzed arylation of isoalantolactone by deoxyvasicinone and lappaconitine halides occurred with formation mainly of cross-coupling products with the (*E*)-configuration of the double bond. Another three compounds were isolated from the reaction of isoalantolactone with 6-bromodeoxyvasicinone. These were the lactone diarylation product, a compound with the (Z)-configuration of the double bond, and a product with a shift of the C(11,13) double bond and configuration inversion at C(8). The new compounds are interesting as potential biologically active agents.*

Keywords: isoalantolactone, 5′-iodolappaconitine, 6-bromodeoxyvasicinone, Pd acetate, cross-coupling reaction.

Many compounds with a "hybrid" structure containing different fragments in their molecules were observed among natural plant and marine metabolites [1, 2]. In this respect the synthesis of conjugates designed by using structural analysis of natural metabolites seems logical for the discovery of pharmacologically promising agents [3]. Sesquiterpene methylenelactones exhibit various biological activities including antitumor [4], anti-inflammatory [5], and antiviral [6]. Recently interest in these natural compounds has risen sharply because of their ability to inhibit human tumor growth by activating the apoptosis mechanism that is associated with activation of the caspase cascade in such cells [7]. Therefore, the synthesis of new derivatives of α-methylene-γ-lactones of natural and synthetic origin is an active research area [8].

We showed previously that Pd-catalyzed cross-coupling is an efficient reaction for modifying sesquiterpene eudesmane-type α-methylene-γ-lactones because it occurs with retention of the *exo*-methylene bond [9, 10]. Herein we report results from the reaction of isoalantolactone (**1**) with plant alkaloid derivatives 6-bromodeoxyvasicinone (**2**) (Scheme 1) and 5′-iodolappaconitine (**3**) (Scheme 2).



a. $Pd(OAc)_2$, $(o\text{-Tol})_3P$, Et_3N, DMF, 120°C, 15 h

Scheme 1

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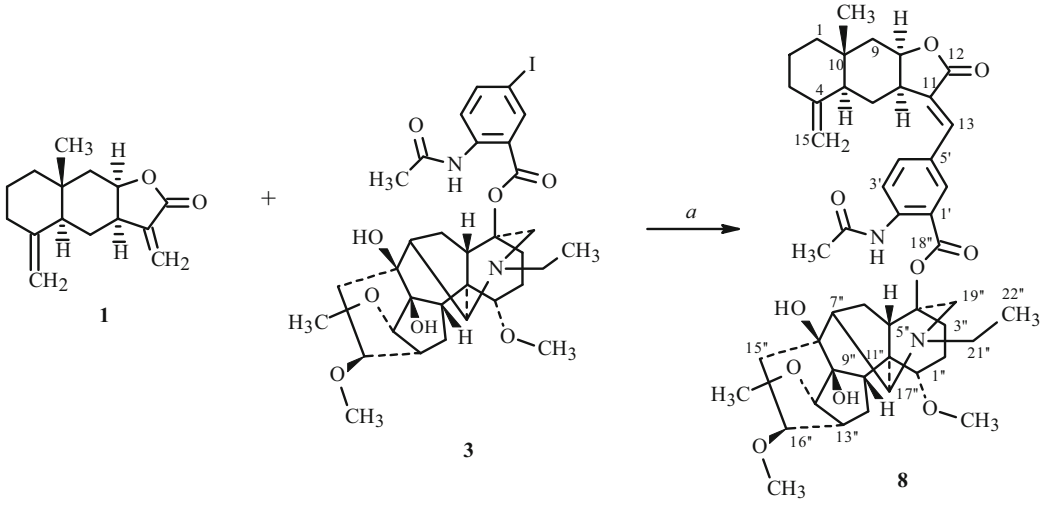


a. $Pd(OAc)_2$, $(o\text{-Tol})_3P$, Et_3N, DMF, 120°C, 15 h

Scheme 2

The cross-coupling of **1** with **2** catalyzed by $Pd(OAc)_2$-$(o\text{-Tol})_3P$ in DMF solution in the presence of Et_3N formed products of arylation at the C(11,13) *exo*-methylene bond with the (*E*)- and (*Z*)-configurations (**4**, **5**); *bis*-arylation at the C(11,13) and C(4,15) bonds (**6**); and C(8)-epimerization of isoalantolactone and isomerization of the C(11,13) double bond (**7**). It can be seen that the last compound contains fragments of the natural lactone asterolide [11] and the alkaloid vasicinone. Compounds **4**, **6**, and **7** were isolated pure (yields of 65%, 5, and 3, respectively). The content of the (*Z*)-isomer (**5**) in the reaction mixture was 5%. The structures of the products were established using spectral data. The (*E*)-configuration of the C(11,13) double bond in substituted lactone **4** was inferred from the presence in the ^{13}C NMR spectrum (single-resonance mode) of a C–H ^3J-*cis* coupling constant between the olefinic proton and the lactone carbonyl C atom [^3J = 7.0 Hz; the corresponding ^3J-*trans* constant for the (*Z*)-isomer (**5**) was 13.4 Hz]. The resonance for H(13) in the PMR spectrum of the (*E*)-isomer (**4**) appeared as a singlet at 7.44 ppm; for the (*Z*)-isomer (**5**), a singlet at 7.00 ppm.

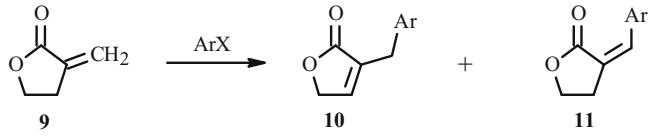
A characteristic feature of the PMR spectrum of **4** was a weak-field shift of the H(7) proton (δ 3.53 ppm) compared with the position of the corresponding proton in the spectrum of **5** (δ 3.01 ppm). A distinguishing feature of the PMR spectrum of diarylation product **6** was the presence of protons of the second aromatic substituent, the appearance of a 1H singlet for the resonance of H(15) at 6.04 ppm, and a weak-field shift of resonances for methyl and H(3) protons (Δδ 0.13 and 0.45 ppm, respectively). The structure of isomeric lactone **7** was confirmed by PMR spectral data that showed resonances for methylene protons on C(13) [δ 3.69 and 3.74 ppm (both doublets, J = 15.2 Hz)] and a significant increase in the difference between chemical shifts for the H(9) protons (Δδ ~ 1.2 ppm). Moreover, strong-field proton H(9a) (δ 1.12 ppm) had SSCC with the H(8) proton (J = 11.4 Hz) that corresponded to an axial–axial arrangement. The H(5′) proton of this dimeric compound experienced a characteristic strong-field shift (δ 8.03, d, J = 1.6 Hz) compared with its location in **4** (Δδ ~ 0.35 ppm) and **5** (Δδ ~ 0.34 ppm).

The ratio of isomers could be determined from the clear differences in the PMR spectra of the reaction mixtures. Additional proof of the configuration inversion of asymmetric C(8) in **7** came from results of a NOESY experiment. The 2D proton nuclear Overhauser effect spectrum of **7** showed that the H(8) proton gave an NOE effect with protons of the angular methyl on C(10) and did not exhibit effects with the H(5) proton. An NOE effect was observed for the H(8) proton upon irradiation of the C(14)H3 protons. The H(8) proton in the proton 2D-NOESY spectrum of **4** exhibited an NOE effect with the H(5) proton and did not give effects with protons of the angular methyl. These results indicated that asymmetric C(8) in **7** had undergone configuration inversion.

The reaction of isoalantolactone (**1**) with 5′-iodolappaconitine (**3**) under the described conditions formed cross-coupling product **8**, which was isolated in 40% yield. It can be seen that the cross-coupling of **1** led to new possibilities for modifying the diterpene alkaloid lappaconitine at the acetylaminobenzoate substituent. The PMR and ^{13}C NMR spectra contained sets of resonances confirming the formation of (*E*)-11-[4-acetamido-3-(aconitan-4β-yloxycarbonyl)-

benzylidene]eudesma-4(15),11(13)-dien-8α,12-olide (**8**). Also, formation of the corresponding product from a shift of the double bond and configuration inversion at C(8) could be noticed from characteristic resonances in the PMR spectra (content about 5%). This compound could not be isolated pure.

The high stereoselectivity of the cross-coupling of **1** with halides **2** and **3** to produce mainly products **4**, **6**, and **8** with the (*E*)-configuration of the double bond is noteworthy. We observed previously an analogous result for arylation of **1** by various arylhalides [9, 10]. Therefore, it is interesting that arylation of α-methylene-γ-butyrolactone **9** occurred with formation of a mixture of 3-benzylfuran-2(5*H*)-one (**10**) and α-benzylidene-γ-butyrolactone (**11**) with the (*Z*)-configuration of the double bond (Scheme 3) [12]. However, exclusive (*E*)-stereoselectivity in the cross-coupling of sesquiterpene lactones parthenolide and 11,13-dehydrosantonin with arylhalides was recently communicated [13].



9 **10** **11**

Scheme 3

Thus, the Heck reaction of isoalantolactone and alkaloid derivatives produced conjugates of the terpenoid–alkaloid type. This cross-coupling reaction was characterized by (*E*)-stereoselectivity.

EXPERIMENTAL

NMR spectra were taken in $CDCl_3$ solutions on Bruker AM-400 [operating frequencies 400.13 (^{1}H) and 100.78 (^{13}C) MHz] and AV-600 [operating frequencies 600.30 (^{1}H) and 150.96 (^{13}C) MHz] spectrometers. Resonances were assigned and multiplicities were determined in NMR spectra using various modes of proton–proton and carbon–proton shift correlation spectroscopies (COSY, COXH, COLOC, NOESY). Mass spectra were recorded, molecular weights were determined, and elemental compositions were found using a DFS Thermo Scientific high-resolution mass spectrometer with ionizing-electron energy 70 eV (vaporizer temperature 270–300°C). The molecular weight of **8** was found by analyzing an acetonitrile solution of it using HPLC–MSD on a micrOTOF-Q103 instrument. IR spectra were recorded in KBr pellets on a Vector-22 instrument. UV absorption spectra were recorded in EtOH on an HP 8453 UV–Vis spectrometer. Specific rotation [α] was measured in $CHCl_3$ on a PolAAr3005 polarimeter.

Reaction products were isolated using column chromatography over silica gel (Acros, 0.035-0.070 mm, pore diameter 6 nm) (C_6H_6:EtOAc and $CHCl_3$:EtOH eluents). Preparative TLC on a layer of silica gel (thickness 1 mm) containing K-35 luminophore (1%) on plates (20 × 20 cm) was also used as necessary.

Freshly distilled solvents and "pure" reagents were used.

$Pd(OAc)_2$ was synthesized by the literature method [14]. Lactone **1** was isolated by extraction from *Inula helenium* roots with subsequent separation as morpholine adducts by the literature method [15]. 6-Bromodeoxyvasicinone (**2**) was prepared by a modified method. Its analytical characteristics agreed with those published [16]. 5′-Iodolappaconitine (**3**) was prepared as before [17].

6-Bromodeoxyvasicinone (2). A mixture of 5-bromoanthranylic acid (8.64 g, 40 mmol) and γ-butyrolactam (5.44 g, 64 mmol) was treated dropwise with $POCl_3$ (26 mL), heated on a water bath for 1.5 h, cooled, decomposed with ice and stirring, and treated with aqueous ammonia (1:1) until the pH was 9-10. The resulting crystals were filtered off, washed several times with water, dried, and recrystallized from alcohol to afford **2** (9.15 g, 82%), mp 159–160°C (EtOH).

PMR spectrum (400.13 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.29 (2H, q, J = 7.2, H-10a, H-10b), 3.15 (2H, t, J = 8.0, H-9a, H-9b), 4.19 (2H, t, J = 7.3, H-11a, H-11b), 7.49 (1H, d, J = 8.6, H-8), 7.77 (1H, dd, J = 8.6, 2.2, H-7), 8.37 (1H, d, J = 2.2, H-5).

^{13}C NMR spectrum (100.61 MHz, $CDCl_3$): 19.37 (t, C-10), 32.43 (t, C-9), 46.50 (t, C-11), 119.50 (s, C-6), 121.80 (s, C-4a), 128.49 (s, C-8), 128.77 (s, C-5), 137.11 (s, C-7), 147.85 (s, C-8a), 159.62 (s, C-4), 159.79 (s, C-2).

Heck Reaction. A two-necked glass ampul was filled with Ar. Isoalantolactone (**1**, 440 mg, 1.19 mmol), 6-bromodeoxyvasicinone (500 mg, 1.19 mmol), $Pd(OAc)_2$ (0.113 mmol, 6 mol%), *tris*-(*o*-tolyl)phosphine (0.34 mmol, 18 mol%), DMF (7 mL), and Et_3N (267 mg, 2.64 mmol) were placed into the ampul under a stream of Ar. The ampul was sealed (small excess of Ar pressure). The reaction mixture was heated for 15 h at 120°C in the presence of 3-Å molecular sieves. When the reaction was finished the system was cooled. The ampul was opened. The contents were poured into a Petri dish and chromatographed over silica gel (eluent $CHCl_3$:EtOH, 100:0→10:1). *trans*-(*o*-Tolyl)phosphine, starting lactone ($CHCl_3$ eluent), the product **4** ($CHCl_3$:EtOH 100:1), a mixture of products (**4**, **5**, **7**), and compound **6** ($CHCl_3$:EtOH 10:1) eluted successively. The main fraction of **4** (50%) was a pure compound after chromatography. Recrystallization of the fractions isolated another 15% of **4**. The diarylation product **6** and compound **7** were isolated by preparative TLC of separate fractions (eluents $CHCl_3$:EtOH 100:1 for **6** and petroleum ether:EtOAc:EtOH 20:5:1 for **7**).

7-{(*E*)-[(3a*R*,4a*S*,8a*R*,9a*R*)-8a-Methyl-5-methylene-2-oxodecahydronaphtho[2,3-*b*]furan-3(2*H*)-ylidene]methyl}-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (4). Yield 65%, $[\alpha]_D$ +435° (*c* 0.74, $CHCl_3$), mp 237–238°C (EtOH). UV spectrum (EtOH, λ_{max}, nm): 200, 225, 247, 317, 327sh, 341sh (log ε 4.21, 4.23, 4.26, 4.32, 4.31, 4.09). IR spectrum (KBr, ν, cm^{-1}): 835, 908, 1002, 1169, 1488, 1607, 1647, 1687, 1736, 2987.

PMR spectrum (600.30 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.84 (3H, s, 14-CH_3), 1.24 (1H, ddd, J = 12.7, 12.5, 4.7, H-1a), 1.38 (1H, ddd, J = 13.1, 12.6, 12.3, H-6a), 1.52-1.59 (4H, m, H-1, H-2a, H-2b, H-9a), 1.93-2.02 (3H, m, H-3, H-5, H-6b), 2.23 (1H, d, J = 15.5, H-9b), 2.28-2.32 (3H, m, H-3, H-10′a, H-10′b), 3.22 (2H, t, J = 7.9, H-9′a, H-9′b), 3.53 (1H, ddd, J = 11.7, 6.0, 5.6, H-7), 4.20 (2H, t, J = 7.3, H-11′a, H-11′b), 4.36 (1H, s, H-15), 4.51 (1H, dd, J = 4.2, 3.7, H-8), 4.71 (1H, s, H-15), 7.44 (1H, s, H-13), 7.67 (1H, d, J = 8.5, H-8′), 7.80 (1H, dd, J = 8.5, 1.6, H-7′), 8.38 (1H, s, H-5′).

^{13}C NMR spectrum (150.96 MHz, $CDCl_3$): 17.54 (q, C-14), 19.26 (t, C-10′), 22.56 (t, C-2), 24.40 (t, C-6), 32.41 (t, C-9′), 34.29 (s, C-10), 36.70 (t, C-3), 39.31 (d, C-7), 41.17 (t, C-9), 42.04 (t, C-1), 46.12 (d, C-5), 46.65 (t, C-11′), 76.83 (d, C-8), 106.60 (t, C-15), 120.62 (s, C-4′a), 127.06 (d, C-8′), 127.44 (d, C-5′), 132.34 (s, C-6′), 133.15 (d, C-13), 133.63 (s, C-11), 134.84 (d, C-7′), 148.73 (s, C-4, C-8′a), 160.09 (s, C-4′), 160.83 (s, C-2′), 171.85 (s, C-12). $C_{26}H_{28}N_2O_3$.

7-{(*Z*)-[(3a*R*,4a*S*,8a*R*,9a*R*)-8a-Methyl-5-methylene-2-oxodecahydronaphtho[2,3-*b*]furan-3(2*H*)-ylidene]methyl}-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (5) was characterized from a mixture with **4**, content 50%, characteristic resonances are given.

PMR spectrum (400.13 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.88 (3H, s, 14-CH_3), 2.32 (2H, t, H-10′a, H-10′b), 3.22 (2H, t, J = 7.9, H-9′a, H-9′b), 3.01 (1H, ddd, J = 11.4, 6.4, 5.6, H-7), 4.22 (2H, t, J = 7.3, H-11′a, H-11′b), 4.49 (1H, d, J = 1.0, H-15), 4.63 (1H, ddd, J = 4.7, 4.6, 1.1, H-8), 4.79 (1H, d, J = 1.0, H-15), 7.00 (1H, s, H-13), 7.63 (1H, d, J = 8.6, H-8′), 8.37 (1H, d, J = 1.6, H-5′), 8.64 (1H, dd, J = 8.6, 1.6, H-7′).

7,7′-(1*E*,1′*E*)-[(3a*R*,4a*R*,8a*R*,9a*R*)-8a-Methyl-2-oxooctahydronaphtho[2,3-*b*]furan-3,5(2*H*,3a*H*)-diylidene]*bis*(methan-1-yl-1-ylidene)*bis*-{2,3-dihydropyrrolo[2,1-*b*]-quinazolin-9(1*H*)-one} (6). Yield 9%. UV spectrum (EtOH, λ_{max}, nm): 202, 228, 236sh, 312, 343sh (log ε 4.68, 4.66, 4.40, 4.05, 3.26).

PMR spectrum (400.13 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.97 (3H, s, 14-CH_3), 1.37 (1H, ddd, J = 12.9, 12.6, 4.9, H-1a), 1.55 (1H, ddd, J = 13.2, 12.6, 12.6, H-6a), 1.63–1.70 (4H, m, H-1, H-2a, H-2b, H-9a), 1.85 (1H, ddd, J = 13.6, 11.9, 4.6, H-3), 2.18 (1H, d, J = 13.8, H-9b), 2.25–2.35 (6H, m, H-5, H-6, H-10′a, H-10′b, H-10″a, H-10″b), 2.94 (1H, br.d, J = 13.3, $W_{1/2}$ = 6.7, H-3), 3.15 (2H, t, J = 7.5, H-9′a, H-9′b), 3.20 (2H, t, J = 7.5, H-9″a, H-9″b), 3.67 (1H, ddd, J = 11.4, 5.7, 5.2, H-7), 4.18 (2H, t, J = 7.6, H-11′a, H-11′b), 4.22 (2H, t, J = 7.6, H-11″a, H-11″b), 4.59 (1H, ddd, J = 4.6, 4.6, 1.2, H-8), 6.04 (1H, s, H-15), 7.89 (1H, dd, J = 8.3, 2.0, H-7″), 7.54 (1H, s, H-13), 7.55 (1H, d, J = 8.3, H-8″), 7.70 (1H, d, J = 8.5, H-8′), 7.87 (1H, dd, J = 8.5, 1.9, H-7′), 8.01 (1H, d, J = 2.0, H-5″), 8.49 (1H, d, J = 1.9, H-5′).

^{13}C NMR spectrum (100.61 MHz, $CDCl_3$): 17.90 (q, C-14), 19.33 (t, C-10′), 19.44 (t, C-10″), 22.54 (t, C-2), 24.41 (t, C-6), 30.41 (s, C-3), 32.33 (t, C-9″), 32.53 (t, C-9′), 35.33 (t, C-10), 39.39 (d, C-7), 41.48 (t, C-9), 42.30 (t, C-1), 46.35 (t, C-11″), 46.53 (t, C-11′), 47.10 (d, C-5), 76.65 (d, C-8), 120.02 (s, C-4′a), 120.57 (d, C-15), 120.83 (s, C-4″a), 125.86 (d, C-5′), 126.28 (d, C-5″), 127.34 (d, C-8′), 127.66 (d, C-8″), 132.09 (s, C-6′), 133.33 (s, C-11), 133.60 (d, C-13), 135.04 (d, C-7′), 135.18 (d, C-7″), 136.43 (s, C-6″), 143.89 (s, C-4), 147.18 (s, C-8″a), 149.67 (s, C-8′a), 158.82 (s, C-2′), 160.44 (s, C-4′), 160.66 (s, C-2″), 160.84 (s, C-4″), 171.98 (s, C-12).

Mass spectrum (*m*/*z*, I_{rel}, %): 600 (29) $[M]^+$, 413 (10), 399 (34), 362 (28), 239 (10), 213 (10), 199 (42), 149 (32), 147 (20), 125 (20), 111 (24), 97 (43), 85 (58), 83 (91), 57 (100), 43 (90). Found $[M]^+$ 600.2728. $C_{37}H_{36}N_4O_4$, calcd. MW 600.2731.

7-{[(4a*S*,8a*R*,9a*S*)-8a-Methyl-5-methylene-2-oxo-2,4,4a,5,6,7,8,8a,9,9a-decahydronaphtho[2,3-*b*]furan-3-yl]methyl}-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (7). Amorphous solid. Yield 3%. UV spectrum (EtOH, λ_{max}, nm): 200, 227, 269, 308, 320 (log ε 4.33 ,4.28, 3.74, 3.49, 3.43).

PMR spectrum (600.30 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.88 (3H, s, 14-CH_3), 1.18 (1H, dd, J = 12.1, 11.4, H-9), 1.33 (1H, ddd, J = 13.6, 13.6, 5.3, H-1), 1.53–1.63 (3H, m, H-1, H-2a, H-2b), 1.87 (1H, dd, J = 13.6, 2.4, H-5), 2.25 (2H, q, J = 7.6, H-10′a, H-10′b), 2.31–2.36 (3H, m, H-3, H-6, H-9), 2.75 (1H, dd, J = 13.6, 3.0, H-6), 3.15 (2H, t, J = 7.5, H-9′a, H-9′b), 3.69 (1H, d, J = 15.2, H-13a), 3.74 (1H, d, J = 15.2, H-13b), 4.18 (2H, t, J = 7.9, H-11′a, H-11′b), 4.53 (1H, s, H-15a), 4.83 (1H, s, H-15b), 4.88 (1H, dd, J = 11.4, 6.8, H-8), 7.56 (1H, d, J = 8.3, H-8′), 7.66 (1H, dd, J = 8.3, 1.6, H-7′), 8.03 (1H, d, J = 1.6, H-5′).

^{13}C NMR spectrum (150.96 MHz, $CDCl_3$): 16.31 (q, C-14), 19.38 (t, C-10′), 22.16 (t, C-2), 25.77 (t, C-6), 28.79 (t, C-13), 32.28 (t, C-9′), 36.07 (t, C-3), 36.79 (s, C-10), 40.63 (t, C-1), 46.31 (t, C-11′), 47.53 (t, C-9), 49.93 (d, C-5), 77.93 (d, C-8), 106.92 (t, C-15), 120.29 (s, C-4′a), 122.64 (s, C-11), 125.05 (d, C-5′), 127.05 (d, C-8′), 134.82 (d, C-7′), 136.49 (s, C-6′), 147.77 (s, C-8′a), 147.98 (s, C-4), 158.91 (s, C-2′), 160.67 (s, C-4′), 164.34 (s, C-7), 173.65 (s, C-12). $C_{26}H_{28}N_2O_3$.

(3a*R*,4a*S*,8a*R*,9a*R*,*E*)-3-{4′′β-3-[4′-Acetamido-3′-(8′′,9′′-dihydroxy-1′′α,14′′α,16′′β-trimethoxy-20′′-ethylaconitan-4β-yl)oxycarbonyl)]benzylidene}-8a-methyl-5-methylenedecahydronaphtho[2,3-*b*]furan-2(3*H*)-one (8). A two-necked glass ampul was filled with Ar. Isoalantolactone (**1**, 150 mg, 0.65 mmol), 5′-iodolappaconitine (**3**, 375 mg, 0.54 mmol), $Pd(OAc)_2$ (0.03 mmol, 6 mol%), *tris*-(*o*-tolyl)phosphine (0.13 mmol, 24 mol%), DMF (4 mL), and Et_3N (77 mg, 0.76 mmol) were placed successively into the ampul under a stream of Ar. The ampul was sealed (small excess of Ar pressure). The reaction mixture was heated for 15 h at 120°C in the presence of 3Å molecular sieves. When the reaction was finished the system was cooled. The ampul was opened. The contents were poured into a Petri dish and chromatographed over silica gel (eluent $CHCl_3$:EtOH 100:0→10:1). Unreacted lactone (**1**) and product **8** ($CHCl_3$:EtOH 50:1) eluted successively. The fraction containing the product was also purified by preparative TLC ($CHCl_3$:EtOH 10:1). Yield of **8**, 40%, $[\alpha]_D$ +235° (*c* 0.50, $CHCl_3$), mp 148–152°C ($CHCl_3$). UV spectrum (EtOH, λ_{max}, nm): 200, 226, 247, 314 (log ε 4.38, 4.25, 4.23, 4.40). IR spectrum (KBr, ν, cm^{-1}): 1088, 1169, 1230, 1247, 1293, 1513, 1588, 1689, 1705, 1754.

PMR spectrum (600.30 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.83 (3H, s, 14-CH_3), 1.11 (3H, t, J = 7, 22′′-CH_3), 1.29-1.36 (2H, m, H-1a, H-6a), 1.48-1.60 (5H, m, H-1b, H-2a, H-2b, H-6′′a, H-9a), 1.79 (1H, dd, J = 11.9, 11.6, $W_{1/2}$ = 9, H-3′′a), 1.97–2.10 (6H, m, H-2′′a, H-3a, H-5, H-6b, H-10′′, H-15′′a), 2.12 (1H, d, J = 7.8, H-5′′), 2.15–2.23 (3H, m, H-9b, H-12′′a, H-12′′b), 2.21 (3H, s, CH_3CO), 2.29-2.37 (4H, m, H-3b, H-7′′, H-13′′, H-15′′b), 2.42 (1H, dd, J = 14.8, 4.2, H-2′′b), 2.50-2.58 (4H, m, H-3′′b, H-19′′a, H-21′′a, H-21′′b), 2.68 (1H, dd, J = 14.6, 7.5, H-6′′b), 2.99 (1H, s, H-17′′), 3.13 (1H, dd, J = 9.9, 6.3, H-1′′), 3.27 (3H, s, CH_3OC-1′′), 3.28 (3H, s, CH_3OC-16′′), 3.28 (1H, m, H-16′′), 3.38 (3H, s, CH_3OC-14′′), 3.39-3.43 (2H, m, H-7, H-14′′), 3.54 (1H, d, J = 11.5, C-19′′b), 4.36 (1H, s, H-15), 4.51 (1H, dd, J = 4.6, 4.0, H-8), 4.73 (1H, s, H-15), 7.33 (1H, $W_{1/2}$ = 3.3, H-13), 7.63 (1H, dd, J = 8.7, 1.5, H-4′), 8.15 (1H, d, J = 1.5, H-6′), 8.71 (1H, d, J = 8.8, H-3′), 11.13 (1H, s, NH).

^{13}C NMR spectrum (150.96 MHz, $CDCl_3$): 13.27 (q, C-22′′), 17.49 (q, C-14), 22.57 (t, C-2), 23.99 (t, C-6,6′′), 25.38 (q, CH_3CONH), 26.12 (t, C-2′′), 26.47 (t, C-12′′), 31.69 (t, C-3′′), 34.32 (s, C-10), 36.17 (d, C-13′′), 36.68 (t, C-3), 39.25 (d, C-7), 41.13 (t, C-9), 41.64 (t, C-1), 44.52 (t, C-15′′), 45.66 (d, C-5), 47.49 (d, C-5′′), 48.14 (d, C-7′′), 48.83 (t, C-21′′), 49.78 (d, C-10′′), 50.94 (s, C-11′′), 55.36 (t, C-19′′), 55.96 (q, OCH_3), 56.39 (q, OCH_3), 57.80 (q, $\underline{C}H_3$OC-14′′), 61.30 (d, C-17′′), 75.38 (s, C-8′′), 76.77 (d, C-8), 78.42 (s, C-9′′), 82.71 (d, C-16′′), 83.94 (d, C-1′′), 85.03 (s, C-4′′), 90.03 (d, C-14′′), 106.63 (t, C-15), 115.81 (s, C-1′), 120.53 (d, C-3′), 127.96 (s, C-11), 131.47 (s, C-5′), 132.45 (d, C-6′), 133.56 (d, C-13), 135.41 (d, C-4′), 142.39 (s, C-2′), 148.83 (s, C-4), 166.52 (s, COO), 169.15 (s, CONH), 172.27 (s, C-12). $C_{47}H_{62}N_2O_{10}$. Ions with *m*/*z* 815.47 $[M + H]^+$ and 849.418 $[M + Cl]^-$ were detected by scanning positive ions of **8** (micrOTOF 103 instrument) in the *m*/*z* range 500-2500. Found $[M + Cl]^-$ 849.418 (MW 814.45). $C_{47}H_{62}N_2O_{10}$, calcd. MW 814.44.

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