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Abnormal Beckmann rearrangement in 23-hydroxyiminodiosgenin acetate

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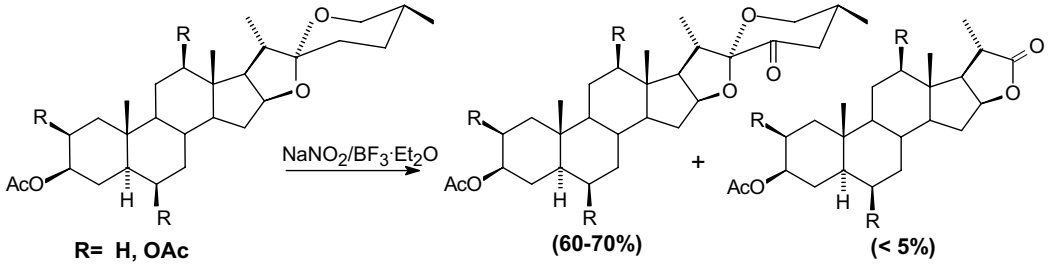
Abstract—A new transformation of the spiroketal side chain of diosgenin is reported: treatment of 23-hydroxyiminodiosgenin acetate with phosphorous oxychloride in pyridine produced an abnormal Beckmann rearrangement directing to the cleavage of the spiroketal side chain and generating 23,24-bisnorchol-5-enic skeletons: (2′*R*)-3′-cyano-2′-methylpropyl 3β-acetoxy-16α-chloro-23,24-bisnorchol-5-en-22-oate as the main product, and small amounts of (2′*R*)-3′-cyano-2′-methylpropyl 3β-acetoxy-16β-hydroxy-23,24-bisnorchol-5-en-22-oate and vespertilin acetate.

Steroidal sapogenins are widely spread in a variety of plants as glycosides.[1] Some members of this family of compounds has served as starting materials for the synthesis of steroid hormones,[2] ecdysteroids,[3] and more recently of plant growth stimulators[4a–f] and cephalostatines.[4g,h,i] The particular reactivity of the spirostanic side chain has been intensively studied.[5]

During our recently reported studies[4b,e,f] we observed that treatment of different steroidal sapogenins of the 25*R* series with $NaNO_2$ and $BF_3{\cdot}OEt_2$ produced the cleavage of their spirostanic side chain to a 23,24-bisnorcholanic 22→16 lactone, in small amounts (Eq. 1). A similar bisnorcholenic skeleton was reported on diosgenin acetate (**1**) when treated with fuming nitric acid,[6] but in this case a nitro group is introduced at C-6 (structure **2**, Eq. 2).

Owing to the interest in bisnorcholanic lactones as bioactive compounds,[7] we decided to study alternative



(1)

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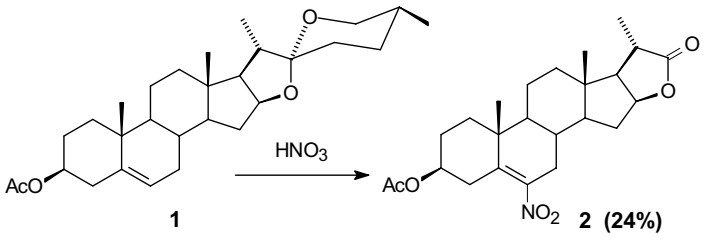
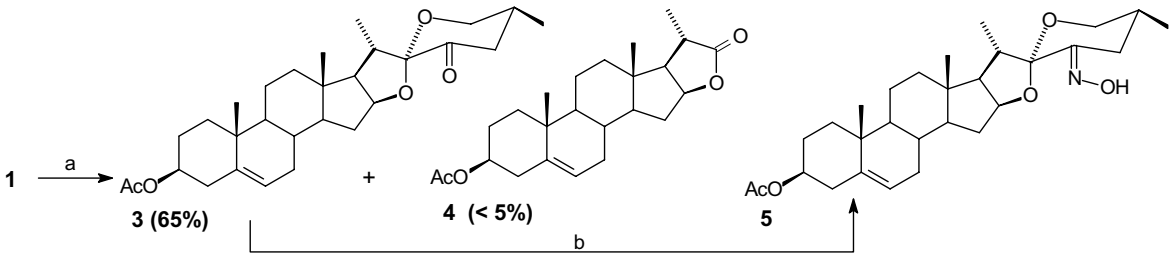


(2)



Scheme 1. Reagents and conditions: (a) $NaNO_2$, BF_3·OEt, AcOH; (b) NH_2OH·HCl, NaOAc, EtOH, reflux.

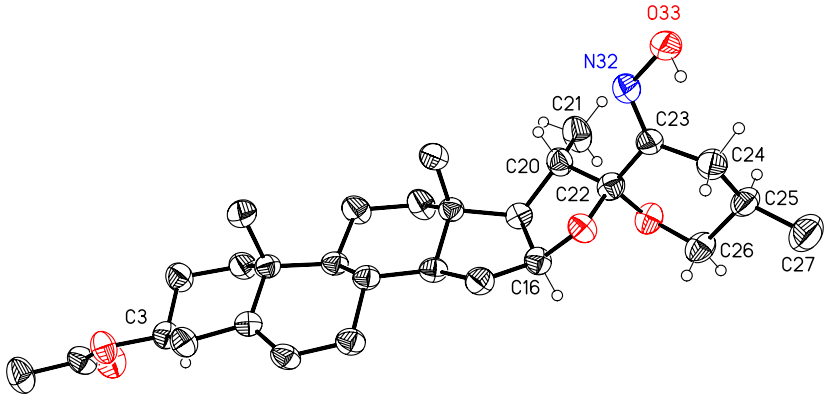


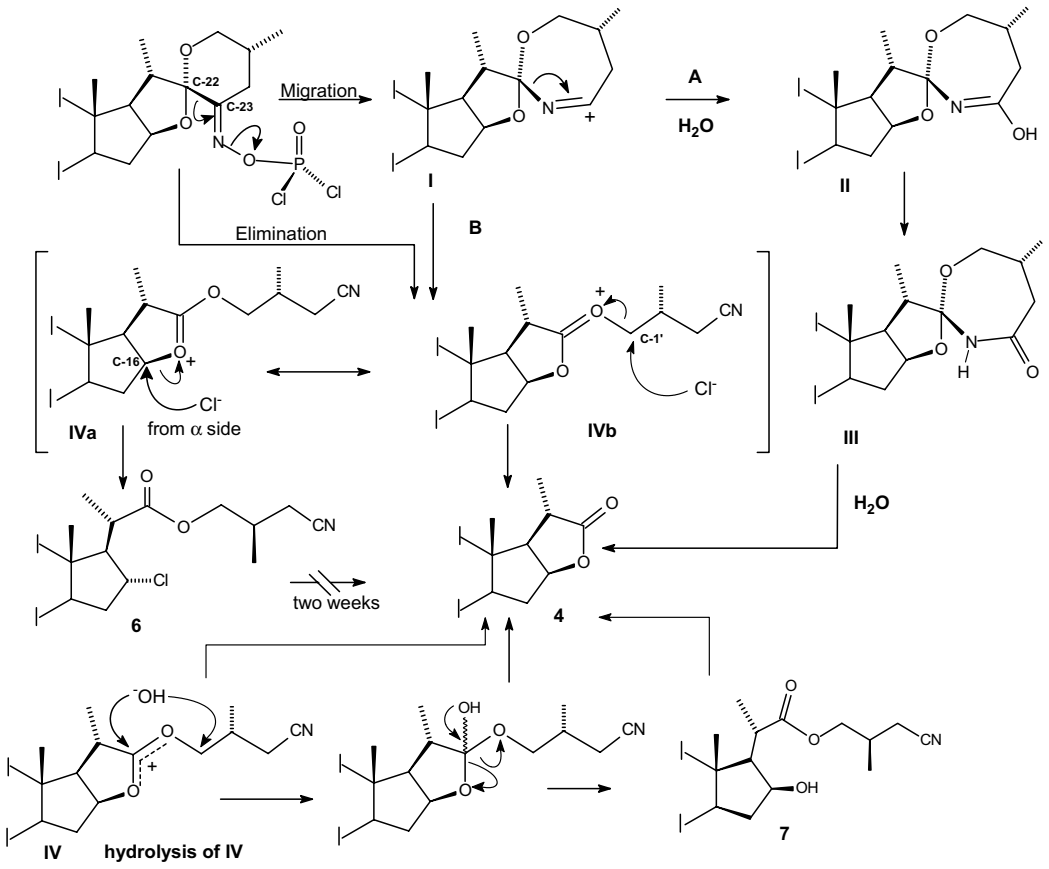
Figure 1. Crystal structure of oxime **5**.

procedures for increase the efficiency of this transformation. Herein, we report our observations on the transformation of 23-hydroxyiminodiosgenin acetate (**5**) under Beckmann rearrangement (BR) conditions.

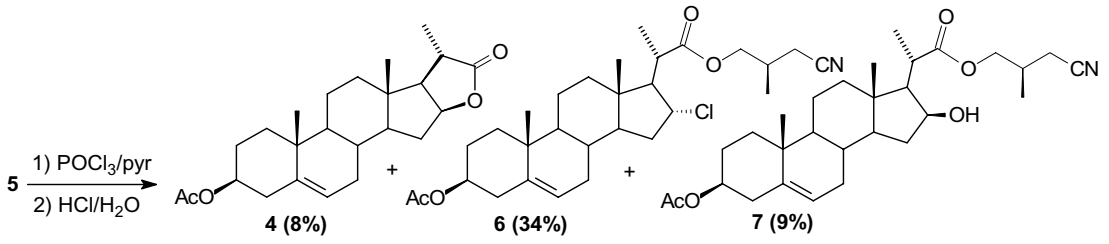
(25*R*)-3β-Acetoxyspirost-5-en-23-one (**3**)[8] was prepared modifying a previous report.[9] As above mentioned, formation of a small amount of vespertilin acetate (**4**) was observed. Treatment of the ketone **3** with H_2NOH·HCl and AcONa in refluxing EtOH led to the 23-hydroxyiminodiosgenin acetate (**5**) in nearly quantitative yield (Scheme 1).

The *anti* configuration of the oxime **5** results in spatial proximity of the hydroxyimino function to H-24_{eq} that should led to a strong deshielding due to van der Waals compression, which also should produce the shielding of C-24. The deshielding of H-24_{eq} (from 2.44 ppm in **3** to 3.33 ppm in **5**) and the shielding of C-24 (compare C-24 at 27.77 ppm and C-22 at 108.50 ppm in the oxime **5** to C-24 at 45.29 ppm and C-22 at 109.68 ppm in the ketone **3**) accounts for the *anti* configuration of the 23-hydroxyimino moiety. Satisfactory crystals of the oxime **5**[10] were grown on slow evaporation of an ethyl acetate solution; Figure 1 displays one of the two independent molecules in the asymmetric unit, with displacement ellipsoids at the 30% probability level. For clarity, most of the H atoms for the steroidal nucleus have been omitted.

Treatment of **5** with $POCl_3$ in anhydrous pyridine produced a minor amount (8%) of **4**—a derivative of the lactone first isolated by González et al.[11a] and synthesized by Sato and Ikekawa—,[11b] and the hitherto unreported nitriles (2′*R*)-3′-cyano-2′-methylpropyl 3β-acetoxy-16α-chloro-23,24-bisnorchol-5-en-22-oate (**6**) (34%) and (2′*R*)-3′-cyano-2′-methylpropyl 3β-acetoxy-16β-hydroxy-23,24-bisnorchol-5-en-22-oate (**7**) (9%) (Eq. 3).



Scheme 2.



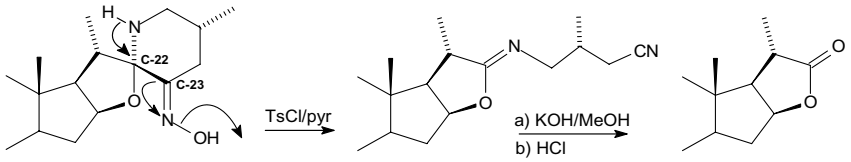
(3)

It has been postulated that the first step for normal and abnormal Beckmann rearrangements (NBR or ABR) is the same (intermediate **I**, Scheme 2), and as a consequence, the nature of the product is determinated in the second step.[12] At this point, two different pathways should be considered: *Pathway A* (NBR), hydrolysis to the iminol **II** would lead to the unstable lactam **III**, which could be hydrolyzed to **4**, or *Pathway B* (ABR or second-order BR),[13] cleavage to oxonium **IV** (Scheme 2).

As accepted, an unshared electron pair at the α position is able to stabilize a cation and directs the course of the reaction to cleavage rather than hydrolysis.[14] Direct elimination to the oxonium cation **IV** assisted by electron pairs at O-16 and O-26 should be also considered. Hence, participation of electron pairs at O-16 and O-26 favors the formation of the stabilized oxonium cation **IV**. Attack of chloride at C-16 in mesomeric structure **IVa** would produce the 16α-chloro ester **6** or the lactone **4** when attack occurs at C-1′ in mesomeric structure **IVb**.

The formation of 16β-hydroxylated ester **7** is explained by hydrolysis of the oxonium intermediary **IV**, which is stable enough to remain in solution until work up (additional stabilization provided by chloride as counter-ion should be also considered). Since no conversion of the chlorinated nitrile ester **6** into the lactone **4** was observed after prolonged standing (2 weeks) of the NMR probe solution ($CDCl_3$), internal nucleophilic substitution of chloride due to attack of carboxylic oxygen to C-16 should be discarded as a possibility for the production of **4**. On the other hand, **4** can also arise from acid catalyzed transesterification of the C-16 hydroxylated nitrile **7**.

Sato and Ikekawa reported that the BR of 23-hydroxyiminospirosolanes (solasodine and tomatidine)



Scheme 3.

produced an iminolactone, which could be hydrolyzed to the corresponding bisnorcholanic lactone (Scheme 3).[15]

Although the nature of the processes is essentially the same, the possibility of elimination of the proton attached to the nitrogen, not present in sapogenins, produces the two different pathways followed by 23-hydroxyiminospirosolanes and 23-oxyiminospirostanes through BR conditions (compare Schemes 2 and 3).

In summary we have found that BR of 23-hydroxyiminodiosgenin acetate (**5**) follows the ABR to produce vespertilin acetate (**4**) and two new compounds, (2′*R*)-3′-cyano-2′-methylpropyl 3β-acetoxy-16α-chloro-23,24-bisnorchol-5-en-22-oate (**6**) and (2′*R*)-3′-cyano-2′-methylpropyl 3β-acetoxy-16β-hydroxy-23,24-bisnorchol-5-en-22-oate (**7**). Although NBR rearrangement could led to vespertilin acetate (**4**) and cannot be totally discarded, the production of the chlorinated nitrile ester **6** evidences the intermediacy of the oxonium cation **IV**. Moreover the occurrence of the hydroxylated nitrile **7** accounts for the stability of **IV**.

NBR and ABR have been extensively explored and applied to steroid chemistry,[16] but to the best of our knowledge, this is the first report on the ABR of a 23-hydroxyiminosapogenin (*an oxime bearing a ketal moiety at the α position*). This reaction opens a new pathway to 23,24-bisnorcholanes from the readily available steroid sapogenins. The application of this method to different steroid sapogenins or their derivatives, would lead to the noncommon 5α- and Δ^5-23,24-bisnorcholanes. The chlorine or hydroxyl group present at C-16 add synthetic potentialities to the products of the described reaction.

NMR spectra were registered in $CDCl_3$ on a Varian Mercury spectrometer at 400 MHz for ^1H or 100 MHz for ^{13}C. Chemical shifts are expressed on ppm downfield from TMS. Melting points were obtained on a Gallenkamp MFB 595 apparatus and were not corrected. Optical rotations were measured at room temperature in a Perkin–Elmer polarimeter 241, using the sodium D-line (589 nm).

(25R)-3β-Acetoxyspirost-5-en-23-one (**3**): mp 191–192.5 °C (*from ethyl acetate/hexane*), lit.[8] 184.5–186.5. NMR ^1H (δ, ppm): 5.36 (1H, m, H-6), 4.61 (1H, m, H-3), 4.60 (1H, m, H-16), 3.78 (1H, dd, $J_{26a-26e,26a-25a} = 11$ Hz, H-26a), 3.59 (1H, ddd, $J_{26a-26e} = 11$ Hz, $J_{26e-25a} = 5$ Hz, $J_{26e-24e} = 1.8$ Hz, H-26e), 2.88 (1H, q, $J_{20-21 \text{ and } 20-17} = 7$ Hz, H-20), 2.44 (2H, m, H-24), 2.32 (2H, m, H-4), 2.27 (1H, m, H-25), 2.03 (3H, s, C*H*$_3$–COO-3), 1.03 (3H, s, H-19), 0.94 (3H, d, $J_{21-20} = 7$ Hz, CH_3-21), 0.94 (3H, d, $J_{25-27} = 7$ Hz, H_3-27), 0.79 (3H, s, CH_3-18). NMR ^{13}C (δ, ppm): 36.97 (C-1), 27.77 (C-2), 73.78 (C-3), 38.10 (C-4), 139.54 (C-5), 122.01 (C-6), 32.02 (C-7), 31.40 (C-8), 49.89 (C-9), 36.74 (C-10), 20.79 (C-11), 39.52 (C-12), 40.75 (C-13), 56.52 (C-14), 31.82 (C-15), 83.21 (C-16), 61.58 (C-17), 16.11 (C-18), 19.42 (C-19), 34.78 (C-20), 14.50 (C-21), 109.68 (C-22), 201.51 (C-23), 45.29 (C-24), 35.88 (C-25), 65.57 (C-26), 17.19 (C-27), 170.27 (CH_3*C*OO-3), 21.52 (*C*H$_3$COO-3).

Vespertilin acetate (**4**): mp 213–214.5 °C (*from acetone/hexane*), lit.[11b] 212–215 °C. NMR ^1H (δ, ppm): 5.37 (1H, m, H-6), 4.60 (1H, m, H-3), 4.96 (1H, m, H-16), 2.59 (1H, q, $J_{20-21,20-17} = 6.6$ Hz, H-20), 2.04 (3H, s, C*H*$_3$–COO-3), 1.32 (3H, d, $J_{21-20} = 7$ Hz, CH_3-21), 1.04 (3H, s, H-19), 0.77 (3H, s, CH_3-18). NMR ^{13}C (δ, ppm): 36.97 (C-1), 27.73 (C-2), 73.66 (C-3), 38.05 (C-4), 139.57 (C-5), 121.75 (C-6), 31.90 (C-7), 31.23 (C-8), 49.96 (C-9), 36.70 (C-10), 20.36 (C-11), 38.15 (C-12), 41.46 (C-13), 54.70 (C-14), 33.13 (C-15), 82.65 (C-16), 58.86 (C-17), 13.80 (C-18), 19.41 (C-19), 36.07 (C-20), 18.09 (C-21), 181.05 (C-22), 170.28 (CH_3*C*OO-3), 21.52 (*C*H$_3$COO-3).

23-Hydroxyiminodiosgenin acetate (**5**): mp 208.5–211 °C (*from ethyl acetate/hexane*). $[\alpha]_D^{25} - 105.83$ (*c* 1.2, $CHCl_3$). NMR ^1H (δ, ppm): 8.36 (1H, s, C=N–O*H*), 5.37 (1H, m, H-6), 4.60 (1H, m, H-3), 4.48 (1H, ddd, $J = 7$ Hz, H-16), 3.62 (1H, dd, $J_{26a-26e,26a-25a} = 11$ Hz, H-26a), 3.53 (1H, ddd, $J_{26a-26e} = 11$ Hz, $J_{26e-25a} = 4.5$ Hz, $J_{26e-24e} = 1.5$ Hz, H-26e), 3.33 (1H, ddd, $J_{24a-24e} = 14$ Hz, $J_{24e-25a} = 4.4$ Hz, $J_{26e-24e} = 1.5$ Hz, H-24e), 2.80 (1H, q, $J_{20-21,20-17} = 6.6$ Hz, H-20), 2.32 (2H, m, H-4), 2.04 (3H, s, C*H*$_3$–COO-3), 1.03 (3H, s, H-19), 1.00 (3H, d, $J_{21-20} = 7$ Hz, CH_3-21), 0.91 (3H, d, $J_{25-27} = 6.2$ Hz, H_3-27), 0.81 (3H, s, CH_3-18). NMR ^{13}C (δ, ppm): 36.76 (C-1), 28.33 (C-2), 73.87 (C-3), 38.11 (C-4), 139.50 (C-5), 122.13 (C-6), 32.08 (C-7), 31.90 (C-8), 49.90 (C-9), 36.97 (C-10), 20.88 (C-11), 39.75 (C-12), 40.66 (C-13), 56.43 (C-14), 31.72 (C-15), 81.48 (C-16), 61.06 (C-17), 16.40 (C-18), 19.44 (C-19), 36.03 (C-20), 14.55 (C-21), 108.50 (C-22), 154.36 (C-23), 27.77 (C-24), 31.38 (C-25), 65.71 (C-26), 17.13 (C-27), 170.41 (CH_3*C*OO-3), 21.56 (*C*H$_3$COO-3). HRMS (FAB), *observed* 486.3216; *estimated for* $C_{29}H_{44}O_5N$, 486.3219.

(2′R)-3′-Cyano-2′-methylpropyl 3β-acetoxy-16α-chloro-23,24-bisnorchol-5-enoate (**6**): mp 116.5–118 °C (*from acetone/hexane*). $[\alpha]_D^{25} - 69.29$ (*c* 1.4, $CHCl_3$). NMR ^1H (δ, ppm): 5.37 (1H, m, H-6), 4.60 (1H, m, H-3), 4.19 (1H, dc, $J = 6.2$ Hz, H-16), 4.12 (2H, dd, $J_{1'-2'} = 4.4$ Hz, $J_{1'-1'} = 11$ Hz, H-1′), 3.89 (2H,dd, $J_{3'-2'} = 7.7$ Hz, $J_{3'-3'} = 11$ Hz, H-3′), 2.03 (3H, s, *C*H$_3$–COO-3),

1.24 (3H, d, $J_{20-21} = 7$ Hz, CH_3-21), 1.15 (3H, d, $J_{2'-2'} = 6.6$ Hz, CH_3-2″), 1.02 (3H, s, H-19), 0.73 (3H, s, H-18). NMR ^{13}C (δ, ppm): 37.96 (C-1), 31.49 (C-2), 73.60 (C-3), 37.99 (C-4), 139.38 (C-5), 121.77 (C-6), 36.78 (C-7), 30.90 (C-8), 49.46 (C-9), 36.45 (C-10), 21.68 (C-11), 39.16 (C-12), 44.71 (C-13), 52.91 (C-14), 27.63 (C-15), 61.52 (C-16), 64.57 (C-17), 12.80 (C-18), 19.27 (C-19), 40.95 (C-20), 16.29 (C-21), 174.85 (C-22), 118.03 (C≡N), 20.59 (C-3′), 30.03 (C-2′), 67.39 (C-1′), 16.66 (C-2″), 170.15 (CH_3COO-3), 21.43 (CH_3COO-3). HRMS (FAB), *observed* 504.2882; *estimated for* $C_{29}H_{43}O_4NCl$, 504.2881.

(2′R)-3′-Cyano-2′-methylpropyl 3β-acetoxy-16β-hydroxy-23,24-bisnorchol-5-eno-ate (**7**): mp 138–140 °C (*from acetone/hexane*). $[\alpha]_D^{25} - 24.62$ (*c* 1.3, $CHCl_3$). NMR ^1H (δ, ppm): 5.36 (1H, m, H-6), 4.59 (1H, m, H-3), 4.40 (1H, H-16), 4.11 (1H, dd, $J_{1'-2'} = 5.1$ Hz, $J_{1'-1'} = 11.3$ Hz, H-1′), 3.87 (1H, dd, $J_{3'-2'} = 7.3$ Hz, $J_{3'-3'} = 11.3$ Hz, H-3′), 2.82 (1H, q, $J = 6.6$ Hz, H-20), 2.49 (1H, dd, $J = 5.5$ Hz, $J = 16.2$ Hz, H-3), 2.37 (1H, dd, $J = 7.33$ Hz, $J = 16.5$ Hz, H-3), 2.03 (3H, s, CH_3–COO-3), 1.29 (3H, d, $J = 6.6$ Hz, CH_3-21), 1.15 (3H, d, $J_{2'-2'} = 6.6$ Hz, CH_3-2″), 1.02 (3H, s, H-19), 0.93 (3H, s, H-18). NMR ^{13}C (δ, ppm): 37.21 (C-1), 31.76 (C-2), 73.83 (C-3), 37.97 (C-4), 139.63 (C-5), 122.01 (C-6), 36.92 (C-7), 31.50 (C-8), 49.93 (C-9), 36.65 (C-10), 20.54 (C-11), 38.11 (C-12), 41.80 (C-13), 54.29 (C-14), 27.75 (C-15), 71.70 (C-16), 58.70 (C-17), 13.38 (C-18), 19.41 (C-19), 36.35 (C-20), 17.34 (C-21), 174.25 (C-22), 117.82 (C≡N), 21.67 (C-3′), 30.30 (C-2′), 66.63 (C-1′), 16.46 (C-2″), 170.34 (CH_3COO-3), 21.55 (CH_3COO-3). HRMS (FAB), *observed* 486.3218; *estimated for* $C_{29}H_{44}O_5N$, 486.3219.

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