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First example of Diels–Alder reaction in the 2,3,4,4a-tetrahydroquinoline series. Synthesis of hydrogenated 5,8-ethanoquinolines

Eugeniya V. Nikitina [a], Victor N. Khrustalev [b], Dmitry G. Grudinin [c], Flavien A.A. Toze [d], Vladimir V. Kouznetsov [e], Fedor I. Zubkov [a,*]

[a] Organic Chemistry Department, Russian Peoples Friendship University, 6 Miklukho-Maklaya St., Moscow 117198, Russian Federation
[b] Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 Vavilov St., Moscow 119991, Russian Federation
[c] Valeant Canada Ltd, 1956 Bourdon St., Montréal, QC H4M 1V1, Canada
[d] Department of Chemistry, University of Douala, Faculty of Sciences, PO Box 24157, Douala, Cameroon
[e] Laboratorio de Química Orgánica y Biomolecular, CIBIMOL, Escuela de Química, Universidad Industrial de Santander, A.A. 678 Bucaramanga, Colombia

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ABSTRACT

Diels–Alder reactions in the 2,3,4,4a-tetrahydroquinolines series were studied for the first time. It was shown that these dienes demonstrate only moderate reactivity. [4+2] Cycloaddition occurs stereo- and regioselectively only for alkenes bearing an electron-withdrawing group (acrylonitrile, maleic anhydride, dimethyl acetylene dicarboxylate, methyl propiolate). In this case, *endo*-Diels–Alder adducts, spiroannelated 5,8-ethanoquinolines, are formed in a high yield. Cyclopentadiene, being a highly reactive diene component, reacts with 2,3,4,4a-tetrahydroquinolines as the dienophile. Electron-rich unsaturated compounds (*N*-vinylpyrrolidone, vinylethyl ether, phenylacetylene) are inert to this cycloaddition reaction.

1. Introduction

Methods of synthesis of 2,3,4,4a-tetrahydroquinolines are not currently well known. This is mostly due to their high affinity for aromatization both under heating and in an acidic medium. Only three examples of 2,3,4,4a-tetrahydroquinoline compounds[1–4] have been isolated and described (Chart 1). Their chemical properties have not been studied yet.

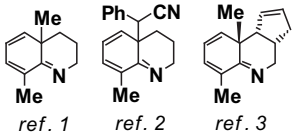
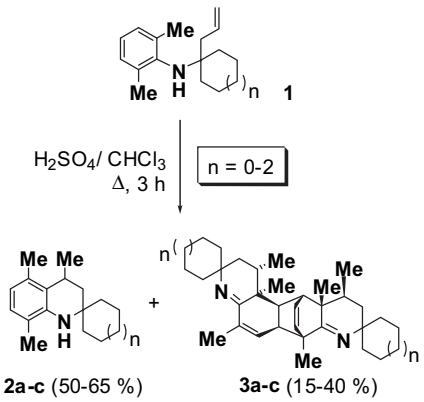


Chart 1.

In our earlier studies,[5,6] aimed at elaborating a new synthetic route to spiroannelated 1,2,3,4-tetrahydroquinolines (**2**) from homoallyl amines (**1**), we obtained and characterized some unusual annelated 7,12-ethenoquino[6,7-*f*]quinolines **3** as by-products (Scheme 1). In the current study we have investigated the reactivity of these uncommon heterocycles.



Scheme 1.

* Corresponding author. Tel.: +7 095 955 0729; fax: +7 095 952 2644.
E-mail address: fzubkov@sci.pfu.edu.ru (F.I. Zubkov).

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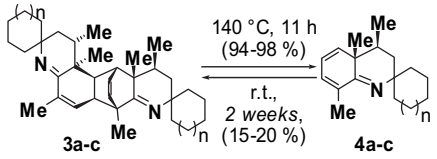
2. Results and discussion

The examination of chemical transformations of polycycles **3** revealed the surprisingly low reactivity of the endocyclic C=N bonds. We could not accomplish such common reactions for azomethines as reduction ($LiAlH_4$ in ether), Grignard reaction (MeMgI in ether or THF) and oxidation to the nitrone (Na_2WO_4/H_2O_2). The reduction in boiling alcohol (excess of $NaBH_4$ in methanol or ethanol) occurs slowly giving 4,4a,8-trimethyl-3,4,4a,8a-tetrahydro-1*H*-spiro[cycloalkane-2,1′-quinolines] as the main products. These facts could be probably explained by steric hindrances created by a rigid bicyclic framework and by cycloalkane substituents in α-positions to nitrogen atoms of the molecule.

Maleic anhydride does not interact with any imine moieties of spiranes **3**. Instead of ordinary products of nitrogen acylation,[7,8] the boiling of 7,12-ethenoquinolino[6,7-*f*]quinoline **3b** with an excess of maleic anhydride in *o*-xylene gives the previously unknown spirosystem—5,8-ethanoquinoline **5**—in a high yield (Scheme 3). Obviously, the reaction passes through the intermediate 2,3,4,4a-tetrahydroquinoline **4** (Scheme 2), which resulted from a retro-Diels–Alder reaction of the initial polycycles **3** under heating. Unstable diene **4b**, then being trapped by the dienophile, transforms to the [4+2] cycloaddition adduct **5**.



Scheme 2.

This assumption was confirmed experimentally. After prolonged heating of polycycles **3** in *o*-xylene the 2,3,4,4a-tetrahydroquinolines **4a–c** have been obtained in an almost quantitative yield.

The above-mentioned products are viscous, colourless liquids, highly soluble even in hexane. Quinolines **4**, left in hexane or ether solution for 1–2 weeks at ambient temperature, dimerize back to the starting quinolino[6,7-*f*]quinolines **3a–c** (Scheme 2). Heating to 50–60 °C increases the dimerization rate.

The relative stability of 2,3,4,4a-tetrahydroquinolines **4a–c** has allowed us to study their behaviour in the Diels–Alder reaction. As a model compound we chose the most accessible spirocyclohexylquinoline **4b**, which forms in situ from quinolinoquinoline **3b** during heating. All cycloaddition reactions were carried out under thermodynamic control until the reaction mixture's composition ceased to change (TLC or LC control).

It was established that even highly reactive dienophiles (maleic anhydride, dimethyl acetylene dicarboxylate (DMAD), methyl propiolate) do not react with dimer **3b** if the reaction temperature is lower than 80 °C. Probably, retrodiene degradation of **3b** (through intermediate 2,3,4,4a-tetrahydroquinoline **4b**) occurs with a noticeable rate only at a higher temperature. Thus, the reflux of polycycle **3b** in *o*-xylene (140 °C) in presence of twofold excess of dienophile during 3–7 h leads to Diels–Alder adducts **5–7** in a relatively good yield.

In all cases the Diels–Alder reaction represents an *endo*-cycloaddition. It was proved by X-ray diffraction analysis of adduct **5** (the monocrystal was obtained by slow recrystallization from ethyl acetate/hexane mixture).

Compound **5** comprises a tetracyclic system spiro-linked to a cyclohexyl fragment through the C2 carbon atom (Fig. 1). The tetracyclic system contains three six-membered rings (two cyclohexene and tetrahydropyridine) and one five-membered ring (dihydrofurandione). The cyclohexene rings of the bicyclic fragment have a regular *twist-boat* conformation, the central tetrahydropyridine ring adopts the *sofa* conformation, and the dihydrofurandione is planar. The molecules of **5** are diastereomers and possess six asymmetric centers at the C4, C4A, C5, C8, C9 and C10 carbon atoms. The relative configuration of the centers 4*S**,4a*S**,5*R**,8*S**,9*S**,10*S**.

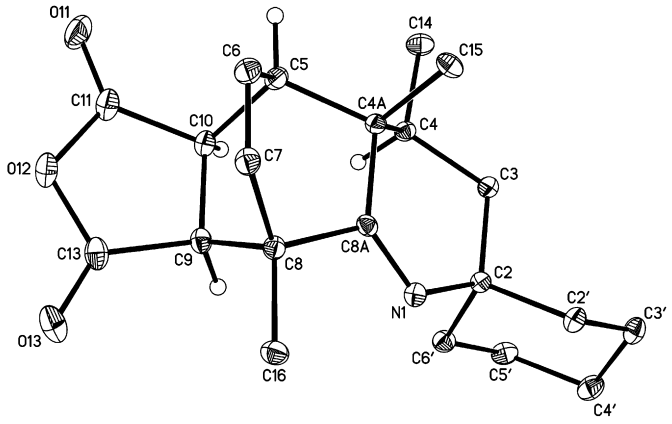
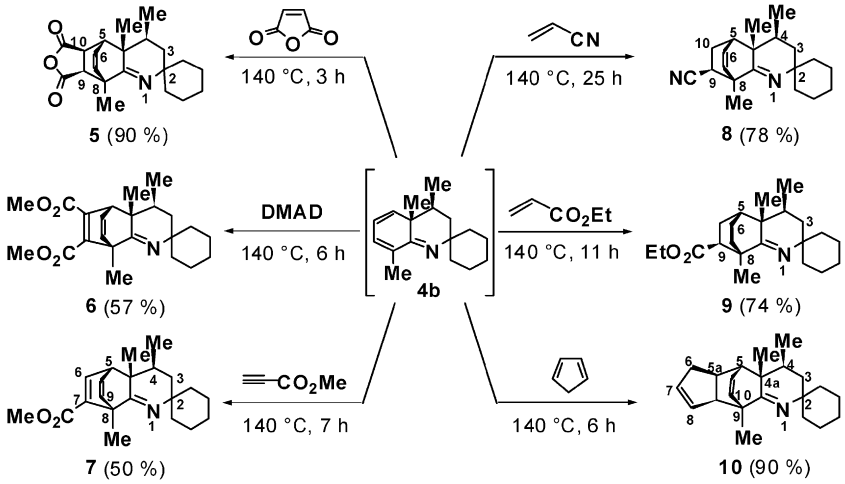


Figure 1. Molecular structure of **5** (only hydrogen atoms at the asymmetric centers are shown).



Scheme 3.

In the case of methyl propiolate, the reaction is stereoselective as well as regioselective; the single regioisomer of 7-carbomethoxy derivative **7** was isolated from the reaction mixture. That was confirmed by the presence of coupling constant $J_{5,6}$ 6.4 Hz in its ^{1}H NMR spectrum.

The configuration of bicyclo[2.2.2]octadiene fragment was established by analogy to anhydride **5** and based on NOE measurement (an increase in H_i proton signal's intensity during saturation of H_j proton signal (η_{Hi}{Hj}, %)). The high NOE value $\eta_{H\text{-}10}${Me-4a}=5.8% indicates that carbomethoxy group (CO_2Me-7) is oriented towards endocyclic double bond C_9=C_{10}; the C_4–H bond, in contrast, is *syn* to the carbomethoxy substituted bridge C_6=C_7, as shown by the corresponding NOE value $\eta_{H\text{-}6}${H-4}=5.1%.

It should be noted that the [4+2] cycloaddition of alkynes (methyl propiolate and DMAD) to diene **4b** (**3b**) is followed by the formation of numerous by-products, probably due to the polymerization of excess of alkynes at high temperature.

Heating of polycycle **3b** in toluene or in xylene with citraconic anhydride leads to a multicomponent mixture (TLC control), from which no individual product could be separated.

The Diels–Alder reaction of dienophiles possessing medium reactivity (acrylonitrile and ethyl acrylate) with polycycle **3b** (**4b**) in boiling xylene occurs much more slowly (11–25 h) and requires a 10-fold molar excess of alkene. But the yield of products is almost quantitative: the ^{1}H NMR spectrum of the crude reaction mass after the evaporation of solvents and excess of acrylonitrile (ethyl acrylate) revealed no by-products in adducts **8**, **9**. However, due to their exceptional solubility in hexane, we could separate preparatively the cycloaddition adducts **8** and **9** as crystals with only 70–80% yield.

Theoretically, the addition of acrylic acid derivatives to diene **4b** could generate four isomers: two from each of two regioisomers by position of nitrile (ethoxycarbonyl) moiety can exist as a pair of diastereomers. As was established experimentally, the cycloaddition is both a stereospecific and regiospecific process: in each case only one *endo*-9-*R*-stereoisomer was generated (Scheme 3).

The determination of the cyano group position in adduct **8** was based on ^{1}H NMR data. The signal of the bridgehead proton H-5 in the spectrum of nitrile **8** represents a complex multiplet ($^4J_{5,7}$ 1.5 Hz, $^3J_{5,10A}$ 2.1 Hz, $^3J_{5,10B}$ 3.4 Hz, $^3J_{5,6}$ 6.8 Hz). At the same time, the protons H-10A (δ 1.70) and H-10B (δ 1.19) appear as ddd and interact with H-9 (δ 2.08, $^3J_{10A,9}$ 9.8, $^3J_{10B,9}$ 4.1 Hz): this proves the presence of nitrile substituent at C_9.

The determination of the cyano group orientation was found to be a rather difficult task, requiring great thought regarding its solution.

The position of the 9-CN group relative to the C_6=C_7 double bond in the bicyclo[2.2.2]octene system was established taking into account the influence of the endocyclic double bond on the chemical shifts of geminal protons (H-10A and H-10B) in the neighbour bridge—these protons were shielded if oriented towards endocyclic double bond (C_6=C_7) and deshielded in the opposite orientation.[9,10] In compound **8** the proton H-10A (δ 1.70 ppm, $^3J_{10A,9}$ 9.8 Hz), one of two geminal protons at C_{10}, undergoes a slight downshift. In stereochemically similar 1-azabicyclo[2.2.2]octane systems such a situation corresponds to cis-position of this proton and of the unsaturated bridge.[9,10] Hence it appears that the C_9–H bond is oriented opposite to the C_6=C_7 double bond, and the cyano group towards this bond. This conclusion was confirmed by NOE measurements: a high vaue $\eta_{H\text{-}4}${H-10A}=9% indicates the spatial closeness between H-4 and H-10A atoms, and $\eta_{H\text{-}6}${Me-4a}=4.5%—the cis-orientation of C_6=C_7 bridge and Me-4a.

The spatial structure of ethyl acrylate cycloaddition product **9** was proved by analogy with nitrile **8**. For example, NOE measurements in adduct **9** indicated that H-10A is close to H-4 ($\eta_{H\text{-}10A}${H-4}=10%). At the same time H-10A and H-9 are both cis-oriented, which is testified to by a high value of coupling constant $^3J_{10A,9}$ 9.8 Hz as well as of NOE $\eta_{H\text{-}10A}${H-9}=5%. The orientation of Me-4a and C_6=C_7 bridge derives from $\eta_{H\text{-}6}${Me-4a}=5.3%.

All attempts to introduce electron-rich alkenes (phenylacetylene, vinyl ethyl ether, indene, *N*-vinylpirrolidone) in reaction with polycycle **3b** under heating up to 160 °C have led to 2,3,4,4a-tetrahydroquinoline **4b**, and acid catalysts (*p*-TSA, $BF_3\cdot OEt_2$, $AlCl_3$) have also been used to produce 1,2,3,4-tetrahydroquinoline **2a**.[6]

The cyclopentadiene, rather active in both roles of diene and dienophile, reacts with tetrahydroquinoline **4b** as dienophile. This reaction is highly regioselective as well as stereoselective; the adduct **10** having the central 1-aza-5,9-ethenocyclopenta[*g*]quinoline skeleton is formed in an almost quantitative yield.

To our regret, we were not able to grow a monocrystal of tetracycle **10**, because both the hydrochloride and oxalate of this azomethine turned out to be very hygroscopic.

The structure of *endo*-adduct **10** was assigned on the basis of 2D spectral data—ROESY, NOSY, HMQC and HMBC. In particular, the NOSY spectrum has cross-peaks conforming to the interaction of spatially close protons Me-9/10, Me-9/8a, and, which is more important—Me-9/8. This fact shows that the double bond in the cyclopentene fragment is in C_7=C_8 position. The *cisoid* position of C_6–C_7–C_8 and C_{10}–C_{11} bridges, as well as of Me-4a and Me-4 groups results from the presence of cross-peaks between Me-4/Me-4a, Me-4a/H-11, H-11/H-6B. This conclusion is confirmed also by the cross-peak H-4/H-5a. At first glance (Scheme 3) the existence of spatial interaction between H-4 and H-5a protons hardly looks probable, but, as was shown by molecular modeling (MM2 approximation; see also Fig. 1), the distance between them is less than 2.2 Å.

Thus, in the current study it was shown for the first time that the Diels–Alder reaction of difficult-to-access 2,3,4,4a-tetrahydroquinolines with activated dienophiles occurs as *endo*-addition both in the high regioselectivity and stereoselectivity. The cycloaddition described opens new opportunities for the construction of a 1-aza-5,8-ethanoquinoline system and represents an original approach to the synthesis of alkaloids possessing the bicyclo[2.2.2]octane core.[11]

3. Experimental

3.1. General

All alkenes and alkynes were purchased from Acros Chemical Co. Melting points of synthesized compounds were determined in a capillary tube using a SMP10 melting point apparatus and are uncorrected. IR spectra were obtained in KBr pellets for solids or in thin film for oils using an IR-Fourier spectrometer Infralum FT-801. NMR spectra ^{1}H (400 or 600 MHz) and ^{13}C (100.6 or 150.9 MHz) were recorded for 2–5% solutions in deuteriochloroform at 20 °C and traces of chloroform (^{1}H NMR δ 7.27 ppm and ^{13}C NMR 77.0 ppm) were used as the internal standard. The mixture of solvents $CDCl_3/C_6D_6$ (1:1 by volume) was used for nitrile **8**, which permitted the minimization of signal overlap, important for structure determination. In this case, the signals of deuterobenzene's residual protons (^{1}H NMR δ 7.16 ppm in C_6D_5H and ^{13}C NMR δ 128.0 ppm in C_6D_6) were used as an internal standard. The correlations in ^{1}H and ^{13}C NMR spectra of all synthesized compounds were made relying on ^{1}H–^{1}H COSY and HMQC dimeric spectral data; the assignment of quaternary carbon atoms was established on the basis of *J*-MOD pulse pattern, with the use of HMBC techniques. Mass spectra were obtained by electron impact at 70 eV on a Finnegan MAT95XL chromatomass spectrometer. The purity of the substances obtained and the composition of the

reaction mixtures were controlled by TLC Sorbfil plates. The purification of the final adducts was carried out by column chromatography on SiO_2 (eluent—hexane) or by fractional crystallization from hexane/ethyl acetate mixture.

3.2. X-ray crystal structure determination

The crystal of **5** ($C_{21}H_{27}NO_3$, M=341.44) is orthorhombic, space group $P2_12_12_1$, at T=100 K: a=6.5926(3), b=8.4328(4), c=31.6668(14) Å, V=1760.49(14) Å^3, Z=4, $D_{(calcd.)}$=1.288 g/cm^3, $F(000)$=736, μ=0.085 mm^{-1}. 23474 Total reflections (3087 unique reflections, R_{int}=0.042) were measured on a Bruker SMART APEX II CCD diffractometer (λ(Mo Kα)-radiation, graphite monochromator, ω and φ scan mode, $2\theta_{max}$=62°). The structure was determined by direct methods and refined by full-matrix least squares technique on F^2 with anisotropic displacement parameters for non-hydrogen atoms. The hydrogen atoms were placed in calculated positions and refined within a riding model with fixed isotropic displacement parameters (U_{iso}(H)=1.5 U_{eq}(C) for the CH_3-groups and U_{iso}(H)=1.2 U_{eq}(C) for the other groups). The final divergence factors were R_1=0.034 for 2772 independent reflections with $I>2\sigma(I)$ and wR_2=0.086 for all independent reflections, S=1.001. All calculations were carried out using the *SHELXTL* program.[12] Crystallographic data for compound **5** have been deposited with the Cambridge Crystallographic Data Centre. CCDC 745526 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk).

3.3. 1,2,3,6a,7,9,10,11,11a,12,12a,12b-Dodecahydro-1,5,7,11,11a,12b-hexamethyl-7,12-etheno dispiro[quino[6,7-*f*]quinoline-3,1′:9,1″-bis(cycloalkanes)] 3a–c

Synthesized earlier[6] with 15–40% yield.

3.4. (4*S**,4a*S**)-4,4a,8-Trimethyl-2,3,4,4a-tetrahydro spiro[quinoline-2,1′-cyclopentane] (4a), (4*S**,4a*S**)-4,4a,8-trimethyl-2,3,4,4a-tetrahydrospiro[quinoline-2,1′-cyclohexane] (4b), (4*S**,4a*S**)-4,4a,8-trimethyl-2,3,4,4a-tetrahydrospiro[quinoline-2,1′-cycloheptane] (4c). Typical procedure

Dimer **3a–c** (1 g, ~2.0 mmol) was heated to reflux in *o*-xylene (15 mL) over 11 h. After the solvent was removed under reduced pressure, the residual viscous oil was purified on silicagel (2×3 cm, eluted with hexane). The product **4a–c** was separated as a viscous oil; yield 0.94–0.98 g (~3.9 mmol). The additional washing of the column with chloroform gave 0.01–0.03 g of starting dimer **3a–c** (recovery 1–2%).

*3.4.1. Compound **4a**.* Colourless, viscous oil, slowly crystallizing at standing in to fine rhombus, 0.94 g (94%); ν_{max} (liquid film) 1655, 1609 (N=C, C=C) cm^{-1}; *m*/*z* (EI, 70 eV) 229 (14, M$^+$), 214 (23), 200 (2), 187 (17), 186 (14), 172 (7), 158 (43), 147 (27), 144 (45), 132 (47), 130 (19), 117 (10), 116 (10), 115 (10), 105 (20), 103 (16), 93 (15), 91 (23), 79 (26), 77 (34), 67 (19), 65 (14), 55 (15). δ_H (400 MHz, $CDCl_3$) 6.04–6.00 (2H, m, H-7 and H-5), 5.86 (1H, dd, $J_{5,6}$ 9.5 Hz, $J_{6,7}$ 5.7 Hz, H-6), 1.91 (3H, s, Me-8), 1.89–1.80 and 1.74–1.40 (8H, m, H-cyclopentyl), 1.82 (1H, ddq, $J_{3e,4}$ 4.3 Hz, $J_{Me\text{-}4,4}$ 6.9 Hz, $J_{3a,4}$ 13.5 Hz, H-4), 1.57 (1H, br t, $J_{3a,4}\approx{}^2J_{3,3}$ 13.5 Hz, H-3*a*), 1.50 (1H, dd, $^2J_{3,3}$ 13.5 Hz, $J_{3e,4}$ 4.3 Hz, H-3*e*), 1.00 (3H, s, Me-4a), 0.95 (3H, d, $J_{Me\text{-}4,4}$ 6.9 Hz, Me-4). δ_C (100.6 MHz, $CDCl_3$) 169.1 (C_{8a}), 136.7 (C_5), 134.9 (C_8), 125.1 (C_7), 121.5 (C_6), 56.0 ($C_{2(1')}$), 43.8 (C_3), 41.54 (C_{4a}), 41.70 and 39.4 (br s, $C_{2'}$ and $C_{5'}$), 30.0 (C_4), 24.6 and 24.4 ($C_{3'}$ and $C_{4'}$), 18.5 (Me-8), 18.3 (Me-4), 15.7 (Me-4a). Found: C, 83.22; H, 10.73; N, 5.97. $C_{16}H_{23}N$ requires C, 83.79; H, 10.11; N, 6.11%.

*3.4.2. Compound **4b**.* Colourless, viscous oil, 0.98 g (98%); ν_{max} (liquid film) 1658, 1615 (N=C, C=C) cm^{-1}; *m*/*z* (EI, 70 eV) 243 (37, M$^+$), 229 (19), 228 (100), 214 (6), 201 (30), 186 (10), 158 (45), 147 (44), 132 (46), 121 (8), 105 (11), 93 (10), 79 (8), 77 (10). δ_H (400 MHz, $CDCl_3$) 6.08 (1H, d, $J_{6,7}$ 5.7 Hz, H-7), 6.05 (1H, d, $J_{5,6}$ 9.5 Hz, H-5), 5.90 (1H, dd, $J_{5,6}$ 9.5 Hz, $J_{6,7}$ 5.7 Hz, H-6), 1.96 (3H, s, Me-8), 1.91–1.40 (10H, m, H-cyclohexyl), 1.87 (1H, ddq, $J_{3a,4}$ 14.0 Hz, $J_{Me\text{-}4,4}$ 7.0 Hz, $J_{3e,4}$ 3.2 Hz, H-4), 1.63 (1H, dd, $^2J_{3,3}$ 14.0 Hz, $J_{3e,4}$ 3.2 Hz, H-3*e*), 1.36 (1H, dd, $J_{3a,4}\approx{}^2J_{3,3}$ 14.0 Hz, H-3*a*), 1.01 (3H, s, Me-4a), 0.97 (3H, d, $J_{Me\text{-}4,4}$ 7.0 Hz, Me-4). δ_C (100.6 MHz, $CDCl_3$) 169.1 (C_{8a}), 136.7 (C_5), 134.9 (C_8), 125.2 (C_7), 121.3 (C_6), 56.5 ($C_{2(1')}$), 42.1 (C_3), 42.0 (C_{4a}), 38.96 and 38.92 (br s, $C_{2'}$ and $C_{6'}$), 28.3 (C_4), 26.5 ($C_{4'}$), 22.6 and 21.8 ($C_{3'}$ and $C_{5'}$), 18.8 (Me-8), 18.4 (Me-4), 15.7 (Me-4a). Found: C, 83.58; H, 10.49; N, 5.77. $C_{17}H_{25}N$ requires C, 83.89; H, 10.35; N, 5.75%.

3.5. Anhydride of (4*S**,4a*S**,5*R**,8*S**,9*S**,10*S**)-4,4a,8-trimethyl-4,4a,5,8-tetrahydro-3*H*-spiro[1-aza-5,8-ethanoquinoline-2,1′-cyclohexane]-9,10-dicarboxylic acid (5)

Dimer **3b** (1.0 g, 2.05 mmol) and 0.42 g (4.30 mmol) of maleic anhydride were heated to reflux in *o*-xylene (15 mL) for 3 h. After the solvent was removed under reduced pressure, the residual slow-crystallizing oil was triturated with ether (10 mL). The crystals formed were filtered off, washed with ether (2×10 mL) and recrystallized from hexane/ethyl acetate mixture.

*3.5.1. Compound **5**.* Colourless clustered needles crystals; yield 1.22 g (90%); mp 189.5–191 °C; ν_{max} (KBr) 1661 (N=C, C=C), 1778, 1860 (C=O) cm^{-1}; *m*/*z* (EI, 70 eV) 342 (5), 341 (26, M$^+$), 243 (21), 229 (18), 228 (100), 202 (10), 201 (56), 200 (7), 162 (6), 158 (20), 145 (6), 144 (7), 105 (5), 91 (11), 81 (11), 67 (7). δ_H (400 MHz, $CDCl_3$) 6.38 (1H, dd, $J_{7,6}$ 8.2 Hz, $J_{6,5}$ 6.4 Hz, H-6), 6.15 (1H, dd, $J_{6,7}$ 8.2 Hz, $^4J_{7,5}$ 1.5 Hz, H-7), 3.34 (1H, dd, $J_{9,10}$ 8.6 Hz, $J_{5,10}$ 3.1 Hz, H-10), 3.23 (1H, ddd, $J_{5,6}$ 6.4 Hz, $J_{5,10}$ 3.1 Hz, $^4J_{7,5}$ 1.5 Hz, H-5), 2.76 (1H, d, $J_{9,10}$ 8.6 Hz, H-9), 1.61 (3H, s, Me-8), 1.56 (1H, dd, $^2J_{3,3}$ 13.5 Hz, $J_{3A,4}$ 4.2 Hz, H-3A), 1.46 (1H, ddq, $J_{4,3B}$ 12.4 Hz, $J_{4,Me\text{-}4}$ 6.5 Hz, $J_{3A,4}$ 4.2 Hz, H-4), 1.33 (1H, dd, $^2J_{3,3}$ 13.5 Hz, $J_{4,3B}$ 12.4 Hz, H-3B), 1.2–1.8 (10H, m, H-cyclohexyl), 0.92 (3H, d, $J_{4,Me\text{-}4}$ 6.5 Hz, Me-4), 0.77 (3H, s, Me-4a). δ_C (100.6 MHz, $CDCl_3$) 172.8 (C=O), 171.9 (C_{8a}), 170.1 (C=O), 135.2 (C_7), 132.9 (C_6), 57.2 ($C_{2(1')}$), 51.5 (C_9), 46.4 (C_8), 42.0 (C_5), 41.4 (C_{10}), 41.0 (C_{4a}), 38.3 (C_3), 30.3 (C_4), 40.2 and 39.9 ($C_{2'}$ and $C_{6'}$), 25.8 ($C_{4'}$), 22.2 and 22.0 ($C_{3'}$ and $C_{5'}$), 17.12 (Me-4a), 17.06 (Me-8), 14.5 (Me-4). Found: C, 73.58; H, 7.73; N, 4.18. $C_{21}H_{27}NO_3$ requires C, 73.87; H, 7.97; N, 4.10%.

3.6. Dimethyl (4*S**,4a*S**,5*S**,8*S**)-4,4a,8-trimethyl-4,4a,5,8-tetrahydro-3*H*-spiro[1-aza-5,8-ethenoquinoline-2,1′-cyclohexane]-6,7-dicarboxylate (6)

Dimer **3b** (1.5 g, 3.09 mmol) and 0.8 mL (6.5 mmol) of dimethyl acetylene dicarboxylate (DMAD) were heated to reflux in *o*-xylene (10 mL) over 6 h. After the solvent was removed under reduced pressure, the residual yellow crystals were recrystallized twice from a heptane/ethyl acetate mixture, yielding 1.35 g (3.51 mmol) of adduct **6**.

*3.6.1. Compound **6**.* White needles; yield 57%; mp 122–124 °C; ν_{max} (KBr) 1591, 1632, 1660 (N=C, C=C) and 1698, 1709 (C=O) cm^{-1}; *m*/*z* (EI, 70 eV) 385 (2, M$^+$), 178 (10), 177 (100), 118 (4), 96 (9), 81 (12), 67 (5). δ_H (400 MHz, $CDCl_3$) 6.51 (1H, dd, $J_{9,10}$ 7.1 Hz, $J_{5,10}$ 6.4 Hz, H-10), 6.15 (1H, dd, $J_{9,10}$ 7.1 Hz, $^4J_{9,5}$ 1.7 Hz,

H-9), 4.13 (1H, dd, $J_{5,10}$ 6.4 Hz, $^4J_{9,5}$ 1.7 Hz, H-5), 1.52 (3H, s, Me-8), 1.43 (1H, dd, $^2J_{3,3}$ 14.0 Hz, $J_{3e,4}$ 4.6 Hz, H-3*e*), 1.25 (1H, dd, $^2J_{3,3}$ 14.0 Hz, $J_{3a,4}$ 12.8 Hz, H-3*a*), 1.1–1.8 (10H, m, H-cyclohexyl), 1.08 (1H, ddq, $J_{3a,4}$ 12.8 Hz, $J_{4,Me}$ 6.6 Hz, $J_{3e,4}$ 4.6 Hz, H-4), 0.92 (3H, d, $J_{4,Me}$ 6.6 Hz, Me-4), 0.78 (3H, s, Me-4a). δ_C (100.6 MHz, $CDCl_3$) 168.8 (C_{8a}), 166.7 and 164.1 (CO_2Me-6 and CO_2Me-7), 151.4 (C_7), 135.9 (C_{10}), 134.9 (C_6), 134.7 (C_9), 57.9 ($C_{2(1')}$), 54.5 (C_8), 51.9 and 51.8 (CO_2*Me*-6 and CO_2*Me*-7), 45.4 (C_5), 39.86 (C_3), 39.90 (C_{4a}), 35.1 (C_4), 39.78 and 38.94 ($C_{6'}$ and $C_{2'}$), 25.8 ($C_{4'}$), 22.4 and 22.1 ($C_{3'}$ and $C_{5'}$), 18.1 (Me-4a), 15.1 (Me-4), 14.4 (Me-8). Found: C, 71.85; H, 8.13; N, 3.47. $C_{23}H_{31}NO_4$ requires C, 71.66; H, 8.11; N, 3.63%.

3.7. Methyl (4*S**,4a*S**,5*S**,8*S**)-4,4a,8-trimethyl-4,4a,5,8-tetrahydro-3*H*-spiro[1-aza-5,8-ethenoquinoline-2,1′-cyclohexane]-7-carboxylate (7)

Dimer **3b** (1.5 g, 3.09 mmol) and 1.1 mL (13.0 mmol) of methyl propiolate were heated to reflux in *o*-xylene (15 mL) over 7 h. After the solvent and the methyl propiolate excess were removed under reduced pressure, the residual yellow crystals were recrystallized twice from hexane, yielding adduct **7**—1.01 g (3.09 mmol).

3.7.1. Compound ***7***. Light-cream prisms; yield 50%; mp 81.5–82 °C; ν_{max} (KBr) 1715 (CO_2), 1648 (C=C) cm^{-1}; *m*/*z* (EI, 70 eV) 327 (19, M^+), 312 (9), 296 (8), 284 (3), 268 (5), 214 (3), 203 (5), 177 (6), 162 (10), 151 (100), 144 (4), 119 (36), 96 (88), 81 (63), 67 (20), 55 (9). δ_H (400 MHz, $CDCl_3$) 7.09 (1H, d, $J_{5,6}$ 6.4 Hz, H-6), 6.38 (1H, dd, $J_{9,10}$ 7.2 Hz, $J_{5,10}$ 6.1 Hz, H-10), 6.17 (1H, dd, $J_{9,10}$ 7.2 Hz, $^4J_{9,5}$ 1.8 Hz, H-9), 3.63 (1H, ddd, $J_{5,6}$ 6.4 Hz, $J_{5,10}$ 6.1 Hz, $^4J_{9,5}$ 1.8 Hz, H-5), 3.62 (3H, s, CO_2Me), 1.05–1.80 (10H, m, H-cyclohexyl), 1.75 (3H, s, Me-8), 1.41 (1H, dd, $^2J_{4,4}$ 13.9 Hz, $J_{4,3e}$ 4.6 Hz, H-3*e*), 1.25 (1H, dd, $^2J_{4,4}$ 13.9 Hz, $J_{4,3a}$ 12.9 Hz, H-3*a*), 1.13 (1H, ddq, $J_{4,3a}$ 12.9 Hz, $J_{4,Me}$ 6.4 Hz, $J_{4,3e}$ 4.6 Hz, H-4), 0.87 (3H, d, $J_{4,Me}$ 6.4 Hz, Me-4), 0.79 (3H, s, Me-4a). δ_C (100.6 MHz, $CDCl_3$) 170.9 (s, C_{8a}), 164.8 (s, C=O), 145.2 (d, *J* 170.5 Hz, C_6), 140.9 (s, C_7), 137.3 (d, *J* 170.0 Hz, C_9), 134.4 (d, *J* 171.0 Hz, C_{10}), 57.1 (s, $C_{2(1')}$), 53.4 (s, C_8), 51.1 (q, *J* 146.8 Hz, CO_2*Me*), 45.9 (d, *J* 141.0 Hz, C_5), 40.7 (s, C_{4a}), 40.1 and 38.9 (br t, *J* 127.5 Hz and br t, *J* 126.5 Hz, $C_{2'}$ and $C_{6'}$), 39.8 (t, *J* 126.0 Hz, C_3), 35.8 (d, *J* 128 Hz, C_4), 25.8 (t, *J* 126.0 Hz, $C_{4'}$), 22.4 and 22.2 (t, *J* 126.0 Hz and t, *J* 126.0 Hz, $C_{3'}$ and $C_{5'}$), 18.2 (q, *J* 127.2 Hz, Me-4a), 16.3 (q, *J* 128.5 Hz, Me-8), 15.0 (q, *J* 125.0 Hz, Me-4). Found: C, 77.11; H, 8.84; N, 4.35. $C_{21}H_{29}NO_2$ requires C, 77.02; H, 8.93; N, 4.28%.

3.8. (4*S**,4a*S**,5*S**,8*S**,9*S**)-4,4a,8-Trimethyl-4,4a,5,8-tetrahydro-3*H*-spiro[1-aza-5,8-ethanoquinoline-2,1′-cyclohexane]-9-carbonitrile (8)

Dimer **3b** (1.5 g, 3.09 mmol) and 2.0 mL (31 mmol) of acrylonitrile were heated to reflux in *o*-xylene (10 mL) over 25 h. After the solvent and the alkene excess were removed under reduced pressure, hexane (3 mL) was added to the residual viscous brown chromatographically individual oil and left for two days at −3 °C. Separated pale-brown crystals were filtered off, dissolved in hexane (3 mL) and left for one day at −3 °C. Separated white-snow crystals were filtered and air-dried; yield of adduct **8** is 1.42 g (4.8 mmol).

3.8.1. Compound ***8***. White powder, easily soluble in hexane; yield 78%; R_f (Silufol, 15% ethyl acetate/hexane) 0.70; mp 92.5–93.5 °C (hexane); ν_{max} (KBr) 2234 (C≡N), 1668 (N=C, C=C) cm^{-1}; *m*/*z* (EI, 70 eV) 297 (3), 296 (17, M^+), 243 (16), 229 (18), 228 (100), 202 (10), 201 (54), 172 (5), 158 (21), 146 (8), 145 (9), 144 (7), 132 (4), 105 (5), 91 (5), 77 (4). δ_H (400 MHz, $CDCl_3/C_6D_6$ (1:1)) 6.19 (1H, dd, $J_{6,7}$ 8.2 Hz, $J_{5,6}$ 6.8 Hz, H-6), 5.93 (1H, dd, $J_{6,7}$ 8.2 Hz, $^4J_{5,7}$ 1.5 Hz H-7), 2.21 (1H, m, $J_{5,6}$ 6.8 Hz, $J_{5,10B}$ 3.4 Hz, $J_{5,10A}$ 2.1 Hz, $^4J_{5,7}$ 1.5 Hz, H-5), 2.08 (1H, dd, $J_{9,10A}$ 9.8 Hz, $J_{9,10B}$ 4.1 Hz, H-9), 1.78 (1H, m, H-cyclohexyl), 1.70 (1H, ddd, $^2J_{10,10}$ 13.8 Hz, $J_{9,10A}$ 9.8 Hz, $J_{5,10A}$ 2.1 Hz, H-10A), 1.67 (1H, m, H-cyclohexyl), 1.47 (3H, s, Me-8), 1.35–1.45 (5H, m, H-cyclohexyl), 1.30 (1H, dd, $^2J_{3,3}$ 13.0 Hz, $J_{3A,4}$ 4.2 Hz, H-3A), 1.25 (1H, ddq, $J_{3B,4}$ 12.8 Hz, $J_{4,Me}$ 6.5 Hz, $J_{3A,4}$ 4.2 Hz, H-4), 1.20–1.30 (2H, m, H-cyclohexyl), 1.19 (1H, ddd, $^2J_{10,10}$ 13.8 Hz, $J_{10B,9}$ 4.1 Hz, $J_{10B,5}$ 3.4 Hz, H-10B), 1.10 (1H, m, H-cyclohexyl), 1.08 (1H, dd, $^2J_{3,3}$ 13.0 Hz, $J_{3B,4}$ 12.8 Hz, H-3B), 0.55 (3H, d, $J_{4,Me}$ 6.5 Hz, Me-4), 0.50 (3H, s, Me-4a). δ_C (100.6 MHz, $CDCl_3+C_6D_6$ (1:1)) 174.0 (s, C_{8a}), 136.4 (d, *J* 166.7 Hz, C_6), 133.4 (d, *J* 167.3 Hz, C_7), 121.8 (s, CN), 57.2 (s, $C_{2(1')}$), 46.0 (s, C_8), 42.1 (s, C_{4a}), 40.8 and 40.5 (t, *J* 126.0 Hz and t, *J* 128.0 Hz, $C_{2'}$ and $C_{6'}$), 39.5 (d, *J* 135.0 Hz, C_5), 38.9 (t, *J* 127.0 Hz, C_3), 29.9 (d, *J* 125.0 Hz, C_4), 26.6 (t, *J* 134.3 Hz, C_{10}), 26.4 (t, *J* 127.0 Hz, $C_{4'}$), 22.8 and 22.5 (t, *J* 126.5 Hz and t, *J* 126.5 Hz, $C_{3'}$ and $C_{5'}$), 18.7 (q, *J* 127.7 Hz, Me-8), 17.7 (q, *J* 127.2 Hz, Me-4a), 14.7 (q, *J* 125.2 Hz, Me-4). Found: C, 80.98; H, 9.54; N, 9.61. $C_{20}H_{28}N_2$ requires C, 81.04; H, 9.52; N, 9.45%.

3.9. Ethyl (4*S**,4a*S**,5*S**,8*S**,9*S**)-4,4a,8-trimethyl-4,4a,5,8-tetrahydro-3*H*-spiro[1-aza-5,8-ethanoquinoline-2,1′-cyclohexane]-9-carboxylate (9)

Dimer **3b** (1.0 g, 2.05 mmol) and 2.2 mL (20.5 mmol) of ethyl acrylate were heated to reflux in *o*-xylene (15 mL) over 11 h. After the solvent and the excess of ethyl acrylate were removed under reduced pressure, the residue, viscous, yellow, chromatographically individual oil, slowly crystallized upon standing. Double recrystallization of the crude product from hexane (see procedure for adduct **8**) gave 1.04 g (3.02 mmol) of adduct **9** as colourless crystals.

3.9.1. Compound ***9***. Transparent fine needles, crumbling on exposure to air to white powder, easily soluble in hexane; yield 74%; R_f (Silufol, 15% ethyl acetate/hexane) 0.43; mp 62–63.5 °C (hexane); ν_{max} (KBr) 1735 (CO_2), 1660 (N=C, C=C) cm^{-1}; *m*/*z* (EI, 70 eV) 344 (7), 343 (39, M^+), 328 (7), 298 (10), 270 (5), 243 (18), 228 (100), 201 (36), 158 (15), 146 (14), 132 (8), 105 (6), 93 (13), 81 (10), 55 (8). δ_H (400 MHz, $CDCl_3$) 6.43 (1H, dd, $J_{6,7}$ 8.2 Hz, $J_{5,6}$ 6.8 Hz, H-6), 5.93 (1H, d, $J_{6,7}$ 8.2 Hz, H-7), 4.06 (2H, m, $CO_2CH_2CH_3$), 2.65 (1H, ddd, $J_{5,6}$ 6.8 Hz, $J_{10B,5}$ 3.1 Hz, $J_{5,10A}$ 2.5 Hz, H-5), 2.34 (1H, dd, $J_{9,10A}$ 9.8 Hz, $J_{9,10B}$ 5.3 Hz, H-9), 2.03 (1H, ddd, $^2J_{10,10}$ 13.5 Hz, $J_{9,10A}$ 9.8 Hz, $J_{5,10A}$ 2.5 Hz, H-10A), 1.2–1.8 (10H, m, H-cyclohexyl), 1.60 (1H, ddq, $J_{3B,4}$ 13.0 Hz, $J_{4,Me}$ 6.6 Hz, $J_{3A,4}$ 4.5 Hz, H-4), 1.51 (1H, dd, $^2J_{3,3}$ 13.8 Hz, $J_{3A,4}$ 4.5 Hz, H-3A), 1.44 (1H, ddd, $^2J_{10,10}$ 13.5 Hz, $J_{10B,9}$ 5.3 Hz, $J_{10B,5}$ 3.1 Hz, H-10B), 1.32 (3H, s, Me-8), 1.30 (1H, dd, $^2J_{3,3}$ 13.8 Hz, $J_{3B,4}$ 13.0 Hz, H-3B), 1.21 (3H, t, *J* 7.2 Hz, $CO_2CH_2CH_3$), 0.81 (3H, d, $J_{4,Me}$ 6.6 Hz, Me-4), 0.72 (3H, s, Me-4a). δ_C (100.6 MHz, $CDCl_3$) 176.1 (s, C=O), 174.4 (s, C_{8a}), 134.6 (d, *J* 166.0 Hz, C_6), 132.3 (d, *J* 166.0 Hz, C_7), 60.5 (t, *J* 147.5 Hz, $CO_2CH_2CH_3$), 56.8 (s, $C_{2(1')}$), 50.5 (d, *J* 136.0 Hz, C_9), 46.4 (s, C_8), 41.6 (s, C_{4a}), 40.4 (t, *J* 127.0 Hz, C_3), 39.9 (d, *J* 137.0 Hz, C_5), 40.1 and 38.5 (br t, *J* 127.5 Hz and br t, *J* 126.5 Hz, $C_{2'}$ and $C_{6'}$), 30.4 (d, *J* 125.0 Hz, C_4), 26.1 (t, *J* 132.0 Hz, C_{10}), 25.9 (t, *J* 127.0 Hz, $C_{4'}$), 22.5 and 22.2 (t, *J* 127.0 Hz and t, *J* 127.0 Hz, $C_{3'}$ and $C_{5'}$), 18.4 (q, *J* 127.4 Hz, Me-8), 17.7 (q, *J* 127.0 Hz, Me-4a), 14.6 (q, *J* 125.7 Hz, Me-4), 14.2 (q, *J* 127.0 Hz, $CO_2CH_2CH_3$). Found: C, 76.78; H, 9.58; N, 9.59. $C_{22}H_{33}NO_2$ requires C, 76.92; H, 9.68; N, 9.32%.

3.10. (4*S**,4a*S**,5*R**,5a*S**,8a*S**,9*S**)-4,4a,9-Trimethyl-3,4,4a,5,5a,6,8a,9-octahydrospiro[1-aza-5,9-ethenocyclopenta[*g*]quinoline-2,1′-cyclohexane] (10)

Dimer **3b** (0.5 g, 1.02 mmol) and 2.6 mL (40 mmol) of freshly distilled cyclopentadiene were heated to reflux in *o*-xylene (15 mL)

over 6 h. After the solvent and the excess of dienophile were removed under reduced pressure, the residual yellow oil was purified on silicagel (2×3 cm, eluted with hexane). The adduct **10** represents a glassy oil; yield 0.65 g (1.8 mmol).

*3.10.1. Compound **10**.* Viscous colourless oil; yield 90%; ν_{max} (liquid film) 1661, 1617 (N=C, C=C) cm^{-1}; *m/z* (EI, 70 eV) 309 (7, M^+), 243 (31), 228 (100), 214 (3), 201 (27), 186 (14), 172 (6), 158 (41), 147 (27), 132 (36), 117 (17), 105 (21), 93 (14), 91 (25), 79 (22), 77 (19), 66 (62), 55 (23), 41 (31). δ_H (600 MHz, $CDCl_3$) 6.23 (1H, dd, $J_{10,11}$ 8.2 Hz, $J_{11,5}$ 6.4 Hz, H-11), 5.89 (1H, dd, $J_{10,11}$ 8.2, $^4J_{10,5}$ 1.5 Hz, H-10), 5.65 (1H, dq, $J_{7,8}$ 5.7 Hz, $J_{7,6A}\approx J_{7,6B}\approx {}^4J_{7,8a}$ 2.2 Hz, H-7), 5.59 (1H, dq, $J_{7,8}$ 5.7 Hz, $^4J_{8,6A}\approx {}^4J_{8,6B}\approx J_{8,8a}$ 2.2 Hz, H-8), 2.73–2.67 (2H, m, H-5 and H-5a), 2.56 (1H, m, $J_{5a,8a}$ 8.6 Hz, $^4J_{8a,7}\approx J_{8a,8}$ 2.2 Hz, H-8a), 2.46 (1H, m, $^2J_{6,6}$ 17.2 Hz, $J_{6A,5a}$ 9.9 Hz, $J_{6A,7}\approx {}^4J_{6A,8}$ 2.2 Hz, H-6A), 1.93 (1H, m, $^2J_{6,6}$ 17.2 Hz, $J_{6B,7}\approx J_{6B,8}$ 2.2 Hz, H-6B), 1.73–1.84 (2H, m, H-3′A, H-5′A), 1.77 (1H, ddq, $J_{4,3a}$ 13.4 Hz, $J_{4,Me\text{-}4}$ 6.6 Hz, $J_{3e,4}$ 4.8 Hz, H-4), 1.58 (1H, dd, $^2J_{3,3}$ 13.4 Hz, $J_{3e,4}$ 4.8 Hz, H-3*e*), 1.56–1.48 (3H, m, H-2′A, H-4′A, H-6′A), 1.47–1.35 (4H, m, H-2′B, H-3′B, H-4′B, H-5′B), 1.36 (1H, t, $^2J_{3,3}\approx J_{4,3a}$ 13.4 Hz, H-3*a*), 1.34 (3H, s, Me-9), 1.29 (1H, m, H-6′B), 0.89 (3H, d, $J_{4,Me\text{-}4}$ 6.6 Hz, Me-4), 0.78 (3H, s, Me-4a). δ_C (150.6 MHz, $CDCl_3$) 177.3 (C_{9a}), 135.1 (C_{10}), 132.7 (C_7), 132.1 (C_{11}), 130.8 (C_8), 61.4 (C_{8a}), 56.9 ($C_{2(1')}$), 47.4 (C_9), 45.8 (C_5), 42.0 (C_{4a}), 40.6 ($C_{6'}$), 40.2 ($C_{2'}$, br d), 39.3 (C_6), 38.4 (C_3, br d), 34.8 (C_{5a}), 29.8 (C_4), 26.1 ($C_{4'}$), 22.8 and 22.3 ($C_{3'}$ and $C_{5'}$), 18.6 (Me-9), 18.0 (Me-4a), 15.0 (Me-4). Found: C, 85.12; H, 9.93; N, 4.71. $C_{22}H_{31}N$ requires C, 85.38; H, 10.10; N, 4.53%.

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