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TETRAHEDRON

First Total Synthesis of Cryptomisrine

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Abstract : The first total synthesis of cryptomisrine, a novel indolo[3,2-*b*]quinoline dimeric alkaloid from *Cryptolepis sanguinolenta*, is reported. The approach is based on a convergent methodology which involves a new halogen-dance reaction in quinoline series connected to a cross-coupling reaction.

Keywords : Halogen and compounds, metallation, polycyclic compounds, coupling reactions.

INTRODUCTION

Benzo-δ-carbolines[1] are very rare in nature, and the best representative of this family is cryptolepine **1** (scheme 1), a dark purple benzo-δ-carboline isolated in 1929 from a West African plant: *Cryptolepis sanguinolenta.*[2] Benzo-δ-carbolines are also found in another family of plants called *Sida.*[3] Very recently, minor alkaloids **2-4** (scheme 1) of this family were discovered,[4-5] and among them, cryptomisrine **2** (scheme 1). This latter compound, a bis-benzo-δ-carboline linked by a keto group, was isolated in 1996 by Martin *et al.*.[5] This is the first isolated dimeric indolo[3,2-*b*] quinoline and the biogenesis is unknown. Cryptolepine is known to have various biological properties such as antimuscarinic, antibacterial, antiviral, antiplasmodial and antihyperglycemic activities,[7-10] but the other minor alkaloids could not be studied, due to extremely low available quantities.

Up to now, and to our knowledge, no synthesis of cryptomisrine has been described. In 1997, we published[11] a new general synthesis to α-substituted δ-carbolines based on metallation[12] and cross-coupling reactions.[13-14] More recently, we discovered the first halogen-dance reaction in quinoline series which allowed us to efficiently prepare quindoline (the benzo-δ-carboline) according to an original and very short route.[15] We wish to report here on an extension of these fruitful methods to the total synthesis of cryptomisrine **2** starting from simple benzene and quinoline derivatives.

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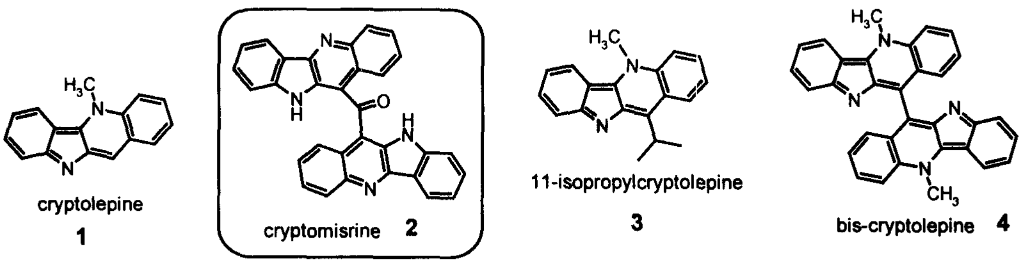
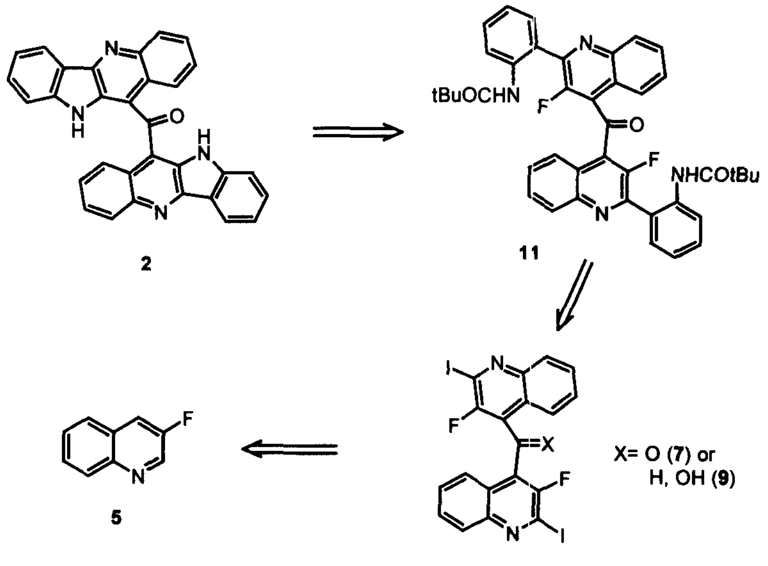


Scheme 1

RETROSYNTHESIS

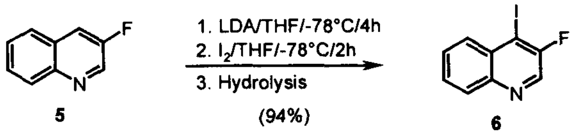
A retrosynthetic analysis (scheme 2) suggests that cryptomisrine **2** could be prepared by cyclization of the difluoropolyaromatic compound **11**. This latter could be obtained from either the diiodo alcohol **9** or the ketone **7** thanks to two coupling reactions. The key step of this retrosynthetic pathway is the very efficient synthesis of the bis-quinoline **7** or **9** which could be synthesize from 3-fluoroquinoline **5** by using metallation and halogen-dance reactions.



Scheme 2

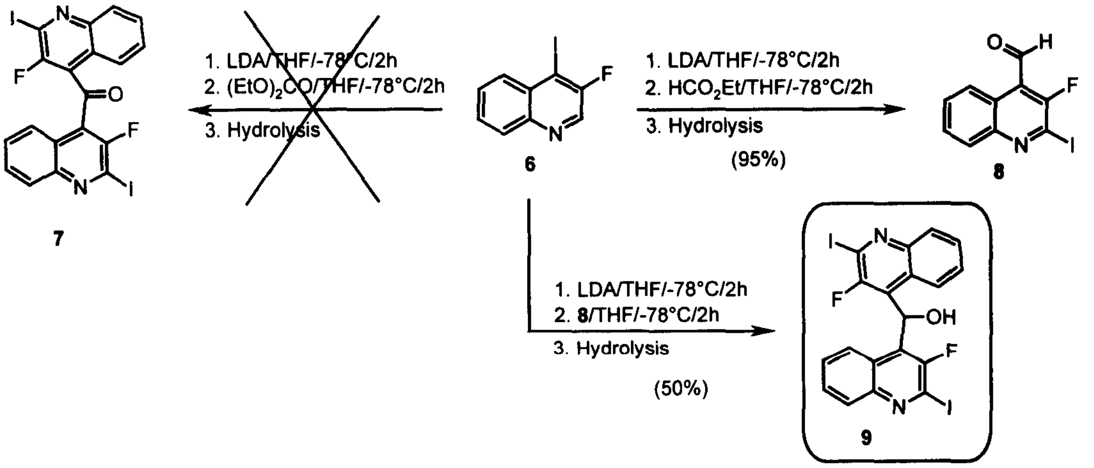
RESULTS AND DISCUSSION

3-Fluoroquinoline **5**[16] was metallated with LDA at low temperature to give the 3-fluoro-4-iodoquinoline **6** in a very good yield (scheme 3).



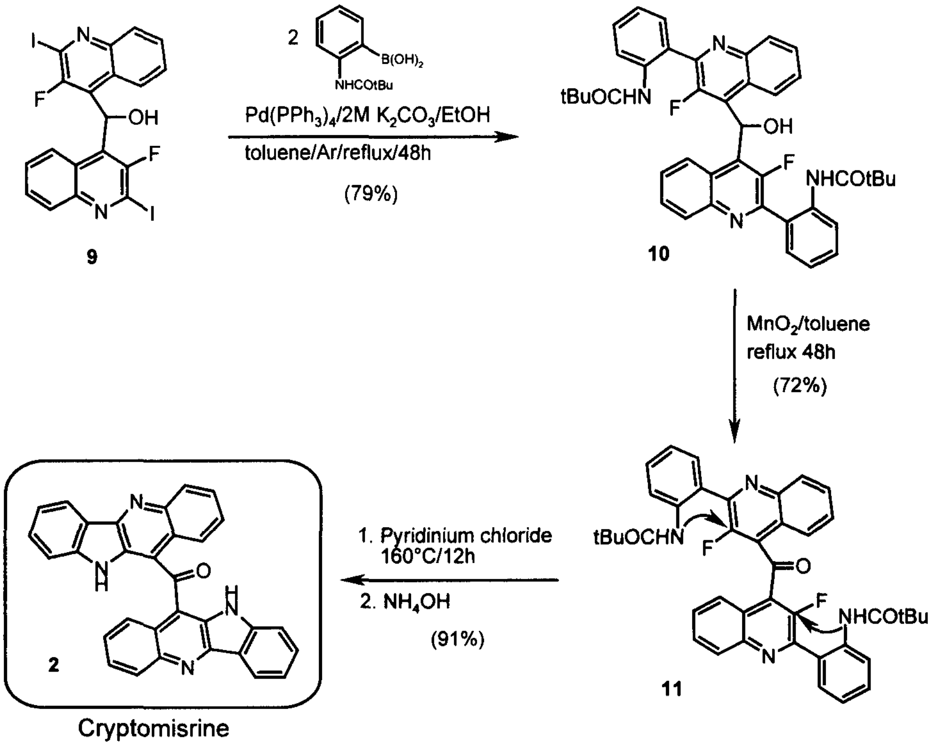
Scheme 3

Treatment of **6** with LDA at –75°C and reaction of the resulting lithio species with half equivalent of diethyl carbonate (or triphosgene) never afforded the expected product **7** (scheme 4) whereas the same reaction, carried out with 3-fluoro-4-iodopyridine, lead to the corresponding ketone. These results lead us to study the second pathway in order to obtain the alcohol **9**. Thus, treatment of **6** with LDA at –75°C followed by reaction with freshly distilled ethyl formate afforded the aldehyde **8** in 95% isolated yield (scheme 4). An halogen-dance reaction[15,17] occurred and the most stable 4-lithioquinoline was formed during this metallation (mechanistic studies of this new reaction in quinoline series are under investigations). Another metallation-isomerisation process was carried out to prepare alcohol **9** by using the previously prepared aldehyde **8** as electrophile (scheme 4).



Scheme 4

Palladium-catalyzed cross-coupling reaction between 2-pivaloylaminophenylboronic acid[18] and alcohol **9** using the Suzuki procedure[13] gave the expected diamide **10** in good yield. Oxidation of **10** by manganese oxide in refluxed toluene[18] led to the corresponding ketone **11**. Ultimately, cyclization of **11** to the orange cryptomisrine **2** was best achieved (yield: 91%) by treatment with pyridinium chloride at 160°C followed by a basic workup (scheme 5).[19] It can be noted that no degradation occurred during the cyclization step, due to a careful control of the temperature. Indeed, above 180°C, a rapid decomposition occurred in pyridinium chloride. The main physical data of compound **2** are identical to those of the natural product described in literature, see experimental section.



Scheme 5

CONCLUSION

The first reported total synthesis of cryptomisrine **2** relies on such key steps as metallation, halogen-dance and cross-coupling. It is fully convergent and regioselective. Moreover, it allows an interesting 24% overall yield (6 steps) starting from 3-fluoroquinoline and several grams of this material can be easily made. The strategy is currently being extended to the preparation of other alkaloids in this family for biological tests.

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EXPERIMENTAL

General Data

The ^{1}H, ^{19}F and ^{13}C were obtained on a Brücker Advance 300 (300 MHz) spectrometer. The IR spectra were taken on a Perkin Elmer Paragon 500 FT-IR spectrometer, main absorption frequencies (NH, CH, C=O, C=C, C=N) are given in cm^{-1}. Mass spectra were obtained on a Jeol D700 instrument. Elemental analyses were performed on a CE instrument apparatus EA 1110 CHNS-O. Tetrahydrofuran was distilled from sodium/benzophenone. The water content of the solvent was estimated lower than 25 ppm by the Karl-Fischer method.[20] Commercial diisopropylamine was distilled from calcium hydride under a dry nitrogen atmosphere. Commercial 2.5 M solution of *n*-butyllithium in hexane used and all reactions involving organometallic compounds were carried out under a dry nitrogen atmosphere. 3-Fluoroquinoline **5** was prepared by the method of Roe and Hawkins[16] starting from 3-aminoquinoline.

3-Fluoro-4-iodoquinoline (6)

n-Butyllithium in hexane (100.0 mmoles, 40.0 mL, 2.5 M) was added to diisopropylamine (100.0 mmoles, 14.0 mL) in THF (400.0 mL) at –78°C. After 20 min, a solution of 3-fluoroquinoline (100.0 mmoles, 14.7 g) in 80.0 mL of THF was slowly added to the solution of LDA. The resulting solution was stirred for 4h at –78°C, and iodine (105.0 mmoles, 26.67 g) in 100.0 mL of THF was slowly added. Stirring was continued for 2h at –78°C before hydrolysis by 100.0 mL of THF/H_2O 9/1. Extraction with ethyl acetate, drying over $MgSO_4$, filtration and solvent removal afforded a crude product which was purified by flash chromatography on silica gel (light petroleum/ethyl acetate: 7/3) to give 94% (25.66 g) of **6** as a pale yellow powder, mp 114°C; ^{1}H NMR ($CDCl_3$): 8.62 (s, 1H, H2), 8.12-8.01 (m, $2H_{arom}$), 7.78-7.64 (m, $2H_{arom}$); ^{19}F NMR ($CDCl_3$): -104.82 (s, 1F); ^{13}C NMR ($CDCl_3$): 157.71 (d, 1C, C3, J= 254.3 Hz), 145.00 (d, 1C, C8', J = 2.2 Hz), 139.50 (d, 1C, C2, J= 30.50 Hz), 130.57 (s, $2C_{arom}$), 130.28 (d, 1C, C5', J = 0.8 Hz), 129.57 (s, $1C_{arom}$), 128.82 (s, $1C_{arom}$), 94.97 (d, 1C, C4, J = 22.06 Hz); IR (KBr): 1492, 1338, 1306, 1262, 1144, 922, 798, 757, 724, 632, 508 cm^{-1}; MS: EI [M+] 273. *Anal.* Calcd. for C_9H_5FIN (273,05): C, 39.59; H, 1.84; N, 5.12. Found : C, 39.53; H, 1.84; N, 5.22.

General procedure: metallation-isomerisation of the 3-fluoro-4-iodoquinoline

n-Butyllithium in hexane (10.0 mmoles, 4.0 mL, 2.5 M) was added to diisopropylamine (10.0 mmoles, 1.4 mL) in THF (40.00 mL) at –78°C. After 20 min, a solution of 3-fluoro-4-iodoquinoline **6** (10.0 mmoles, 2.73 g) in 8.0 mL of THF was slowly added to the solution of LDA. The resulting solution was stirred for 2h at –78°C and the electrophile (10.0 mmoles) in 10.0 mL of THF was slowly added. Stirring was continued for 2 h at –78°C before hydrolysis at 0°C by 10.0 mL of THF/H_2O 9/1. Extraction with ethyl acetate, drying over $MgSO_4$, filtration and solvent removal afforded to a crude product which was purified by flash chromatography on silica gel.

3-Fluoro-4-iodo-4-quinolinecarboxaldehyde (8)

General procedure, using **ethyl formate** as electrophile, gave 2.85 g (95%) of **8**, mp 106°C; ^{1}H NMR ($CDCl_3$): 10.79 (s, 1H, CHO), 8.98 (comp, 1H, H5 or H8), 8.14 (comp, 1H, H8 or H5), 7.77 (m, 2H, H6 and H7); ^{19}F NMR ($CDCl_3$): -111.95 (s, 1F); ^{13}C NMR ($CDCl_3$): 188.15 (d, 1C, CHO, J = 9.4 Hz), 157.20 (d, 1C, C3, J = 271.4 Hz), 147.56 (d, 1C, C8a, J = 3.9 Hz), 130.83 (s, 1C_{arom}), 129.95 (d, 1C_{arom}, J = 2.2 Hz), 129.32 (s, 1C_{arom}), 125.14 (d, 1C_{arom}, J = 5.5 Hz), 123.14 (s, 1C_{arom}), 120,28 (d, 1C_{arom}, J= 5,5 Hz), 110.70 (d, 1C, C2, J = 32.5 Hz; IR (KBr): 2925, 1693, 1542, 1494, 1396, 1315, 1181, 1071, 765, 706 cm^{-1}; MS: EI [M+] 301. *Anal.* Calcd. for $C_{10}H_5FINO$ (301,06): C, 39.90; H, 1.67; N, 4.65. Found: C, 40.02; H, 1.85; N, 4.87.

Bis-(3-fluoro-2-iodoquinol-4-yl)methanol (9)

General procedure, using **8** as electrophile, gave 2.87g (50%) of **9**, mp 248°C; ^{1}H NMR (DMSO-d6): 8.80 (d, 2H, H8, J = 8.3 Hz), 8.12 (d, 2H, H5, J = 8.3 Hz), 7.87 (t, 2H, H6 or H7, J = 8.3 Hz), 7.80 (t, 2H, H7 or H6, J = 8.3 Hz), 7.44 (d, 1H, CH, J = 5.3 Hz), 7.26 (d, 1H, OH, J = 5.3 Hz); ^{19}F NMR (DMSO-d6): -103.7 (s, 2F); ^{13}C NMR (DMSO-d6): 151.34 (2C, C3, J = 255.0 Hz), 146.65 (s, 2C, C8a), 130.01 (d, 2C, C4, J = 12.1 Hz), 129.44 (s, 2C_{arom}), 129.01 (s, 2C_{arom}), 128.18 (s, 2C_{arom}), 126.09 (s, 2C_{arom}), 125.33 (s, 2C_{arom}), 112.72 (d, 2C, C2, J = 34.6 Hz), 64.04 (s, 1C, CH(OH)); IR (KBr): 3119, 1581, 1328, 1160, 761 cm^{-1}; MS: EI [M+] 574. *Anal.* Calcd. for $C_{19}H_{10}F_2I_2N_2O$ (574,11): C, 39.75; H, 1.75; N, 4.87. Found: C, 40.08; H, 1.90; N, 5.03.

Bis-(3-fluoro-2-(2-pivaloylaminophen-1-yl)quinol-4-yl)methanol (10)

Compound **9** (2.0 mmoles, 1.148 g) and 2-pivaloylaminophenylboronic acid[18] (4.4 mmoles, 972.0 mg) were added to an aqueous solution of potassium carbonate (4.4 mL, 2.0 M) and ethanol (2.2 mL) in deoxygenated toluene (40.0 mL). The resulting mixture was stirred during 1h under a nitrogen atmosphere. Tetrakis(triphenylphosphine)palladium (0) (0.1 mmole, 250.0 mg) was added and the solution was refluxed for 48h. Cooling, filtration, extraction with toluene, drying over $MgSO_4$, filtration and solvent removal afforded to a crude product which was purified by flash chromatography on silica gel (light petroleum/ethyl acetate: 8/2). After purification, we obtained 1.063 g (79%) of **10**, mp >260°C ; ^{1}H NMR (DMSO-d6): 9.97 (s, 2H, NH), 8.89 (d, 2H_{arom}, J= 8.4 Hz), 8.08 (dd, 2H, H6, J = 1.1/8.4 Hz), 7.87 (d, 2H_{arom}, J = 8.4 Hz), 7.81 (td, 2H_{arom}, J = 1.1/8.4 Hz), 7.70 (td, 2H_{arom}, J = 1.1/8.4 Hz), 7.46-7.39 (m, 5H, 4H_{arom} and CH), 7.17 (m, 3H, 2H_{arom} and OH), 0.90 (s, 18H, tBu); ^{19}F NMR (DMSO-d6): -122.14 (s, 2F); ^{13}C NMR (DMSO-d6): 175.74 (s, 2C, CO(NH)), 152.05 (d, 2C, C3', J = 260.9 Hz), 148.10 (d, 2C, C2', J = 17.7 Hz), 144.00 (s, 2C_{arom}), 136.59 (s, 2C_{arom}), 132.12 (d, 2C, C4', J = 12.1 Hz), 130.70 (s, 2C_{arom}), 129.75 (s, 2C, CH_{arom}), 129.19 (s, 2C, CH_{arom}), 128.95 (s, 2C, CH_{arom}), 127.54 (s, 2C, CH_{arom}), 126.61 (s, 2C_{arom}), 126.35 (s, 2C_{arom}), 125.53 (s, 2C_{arom}), 123.98 (s, 2C, CH_{arom}), 123.79 (s, 2C, CH_{arom}), 63.95 (s, 1C, CH(OH)), 40.03 (s, 2C, *t*Bu), 26.99 (s, 6C, CH_3); IR (KBr): 3312, 3062, 2961, 2869, 1686, 1664, 1584, 1522, 1458, 764 cm^{-1}; MS: EI [M+] 673. *Anal.* Calcd. for $C_{41}H_{38}F_2N_4O_3$ (672,78): C, 73.20; H, 5.69; N, 8.32. Found: C, 72.96; H, 5.92; N, 8.18.

Bis-(3-fluoro-2-(2-pivaloylaminophen-1-yl)quinol-4-yl)oxomethane (11)

Compound **10** (0.5 mmole, 336 mg) was added to a solution of manganese dioxide (5.0 mmoles, 435 mg), in 25.0 mL of toluene. This solution was refluxed for 48h. Filtration on celite®, washing with 3x10.0 mL of toluene, drying over $MgSO_4$, filtration and solvent removal afforded to a crude product which was purified by flash chromatography (light petroleum/ethyl acetate: 7/3). After purification, we obtained 240 mg (72%) of **11**, mp 241°C; ^1H NMR ($CDCl_3$): 10.77 (s, 2H, NH), 8.40 (dd, $2H_{arom}$, J = 1.1/8.4 Hz), 8.15 (m, $4H_{arom}$), 7.83 (td, $2H_{arom}$, J = 1.5/7.0 Hz), 7.73 (td, $2H_{arom}$, J = 1.1/8.0 Hz), 7.49 (comp, 2H, H3), 7.41 (td, $2H_{arom}$, J = 1.5/8.8 Hz), 7.06 (td, $2H_{arom}$, J = 1.2/7.7 Hz), 1.23 (s, 18H, CH3); ^{19}F NMR ($CDCl_3$): -121.63 (d, 2F, J = 4.5 Hz); ^{13}C NMR ($CDCl_3$): 190.60 (s, 1C, CO), 177.00 (s, 2C, CO(NH)), 151.65 (d, 2C, C3', J = 265.4 Hz), 148.95 (d, 2C, C2', J = 14.8 Hz), 144.16 (s, $2C_{arom}$), 137.00 (s, $4C_{arom}$), 130.93 (s, $2C_{arom}$), 130.64 (d, 2C, C4', J = 9.9 Hz), 130.16 (s, $2C_{arom}$), 129.69 (s, $2C_{arom}$), 129.18 (s, $2C_{arom}$), 124.62 (s, $2C_{arom}$), 123.87 (s, $2C_{arom}$), 123.11 (s, $2C_{arom}$), 123.05 (s, $2C_{arom}$), 122.18 (s, $2C_{arom}$), 39.90 (s, 2C, *t*Bu), 27.64 (s, 6C, CH3); IR (KBr): 3307, 3063, 2965, 2870, 1682, 1582, 1523, 1290,1162, 767, 748 cm^{-1}; MS: EI [M+] 671. *Anal.* Calcd. for $C_{41}H_{36}F_2N_4O_3$ (670,77): C, 73.42; H, 5.41; N, 8.35. Found: C, 73.46; H, 5.25; N, 8.09.

Cryptomisrine (2)

Anhydrous pyridinium chloride (5.0 g) was added at 160°C to the diamide **11** (0.25 mmole, 167 mg) and the solution mixture was refluxed for 12h at 160°C. The resulting solution was poured into a 2M ammonia solution (10.0 mL). Extraction of the aqueous layer with ethyl acetate, drying over $MgSO_4$, filtration and solvent removal afforded to a crude product which was purified by flash chromatography on silica gel (light petroleum/ethyl acetate: 7/3). After purification, we obtained 105 mg (91%) of **2**, mp >260°C; ^1H NMR (DMSO-d6): 11.71 (s, 2H, H10/H10'), 8.42 (d, 2H, H6/H6', J = 8.0 Hz), 8.29 (d, 2H, H4/H4', J = 8.4 Hz), 7.66 (comp, 2H, H8/H8'), 7.63 (comp, 2H, H9/H9'), 7.57 (comp, 2H, H1/H1'), 7.55 (comp, 2H, H3/H3'), 7.37 (td, 2H, H7/H7', J = 1.8/6.6 Hz), 7.22 (td, 2H, H2/H2', J = 1.1/6.9 Hz); ^{13}C NMR (DMSO-d6): 195.69 (s, 1C, C=O), 148.36 (s, 2C, C 5a/C5a'), 145.34 (s, 2C, C9a/C9a'), 143.58 (s, 2C, C4a/C4a'), 130.95 (s, 2C , C8/C8' or C10a/C10a'), 130.81 (s, 2C, C10a/C10a' or C8/C8'), 130.19 (s, 2C, C4/C4'), 127.11 (s, 2C, C2/C2'), 126.58 (s, 2C, C3/C3'), 123.27 (s, 2C, C1/C1'), 122.57 (s, 2C, C11a/C11a'), 121.87 (s, 2C, C6/C6'), 121.04 (s, 2C, C5b/C5b' or C11/C11'), 120.99 (s, 4C, C11/C11' or C5b/5b'and C7/C7'), 112.81 (s, 2C, C9/C9'); IR (KBr): 3411, 3064, 2962, 2925, 1693, 1613, 1467, 1168, 1116, 764, 752 cm^{-1}. MS: EI [M+] 463. *Anal.* Calcd. for $C_{31}H_{18}N_4O$ (462,52): C, 80.50; H, 3.92; N, 12.11. Found: C, 80.62; H, 3.85; N, 11.96.

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