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Allylic bromination of anhydrodihydroartemisinin and of its 10-trifluoromethyl analogue: a new access to 16-substituted artemisinin derivatives

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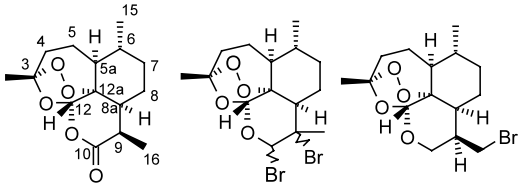
Abstract—The reactivity of the anhydrodihydroartemisinin **2** and of its 10-trifluoromethyl analogue **3** toward brominating reagents was explored with the aim of preparing the new corresponding C-16 allylic bromides **5** and **7**. Both glycals **2** and **3** react with NBS to provide compounds **5** and **7**, respectively. From the 10-CF_3 anhydrodihydroartemisinin **3**, the allylic bromination also occurred in high yield with Br_2 in CCl_4. Products **5** and **7** react with N-, O- and C-nucleophiles. From **5**, products of S_N and S'_N were obtained in low to moderate yield, while the CF_3-substituted allylic bromide **7** only underwent nucleophilic substitution. New fluorinated 16-substituted artemisinin derivatives **14a–c** could be obtained in high yield.

Since the discovery of artemisinin **1**, great efforts have been made to modify its structure in order to improve both its activity and its bioavailability. In this connection, introduction of a fluoroalkyl substituent onto artemisinin has been proved to enhance antimalarial efficacy and metabolic stability.[1] We now pursue our investigations on the comparison of the reactivity of the anhydrodihydroartemisinin **2**[2] and of its 10-trifluoromethyl analogue **3**[3] in order to introduce new functionalities onto these molecules. Reaction of anhydrodihydroartemisinin **2** with Br_2 has been already studied and led to the dibrominated product **4**. Lin et al. reported the condensation of dibromide **4** with different aromatic amines,[4] whereas Venugopalan et al. showed that its hydrolysis led to the 9-bromodihydroartemisinin[5] which is the precursor of various 9-bromo derivatives and different artemisinin based novel skeletons.[6] Surprisingly, despite the synthetic interest of bromides derived from artemisinin, allylic bromination of glycal **2** had never been reported, while it could directly provide the bromide **5** which could itself be a good precursor of 16-substituted derivatives. Very recently, the interesting 16-bromodeoxoartemisitene **6** has been reported through a six step sequence from the artemisinic acid,[7] but no application has been described so far. We report here our investigations on the reactivity of glycals **2** and **3** toward radical bromination, and some preliminary results of their 16-bromo derivatives **5** and **7** regarding their reactivity toward representative nucleophiles.



1 **4** **6**

Allylic bromination of glycals **2**[2] and **3**[3] was investigated under the usual Wohl–Ziegler conditions in the presence of an initiator.[8] When glycal **2** in CCl_4 (0.5 M) reacted with *N*-bromosuccinimide (1.5 equiv.) at reflux in the presence of a catalytic amount of 2,2′-azobisisobutyronitrile (AIBN, 0.1 equiv.), a complex mixture was formed. However, when concentration of glycal **2** was 0.1 M in CCl_4, and when the mixture was heated to reflux very quickly (in less than 2 minutes), the reaction was efficient and after 20 minutes at reflux the 16-bromoanhydrodihydroartemisinin **5**[9] was obtained as the only product (Table 1). Nevertheless, because of its instability, it could not be purified (dismutation reaction rapidly occurred leading to dibromoallylic compound which is itself unstable). Under the same conditions

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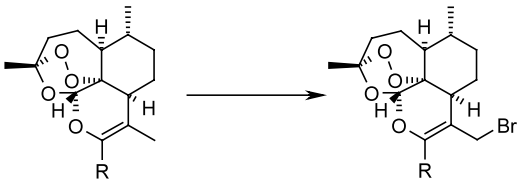
Table 1. Allylic bromination of glycals **2** and **3**



2 R = H
3 R = CF_3

5 R = H
7 R = CF_3

	Starting material	Conditions (0.1 M in CCl_4)	Product (yield)
2	R = H	NBS (1.5 equiv.), AIBN (0.1 equiv.), reflux, 20 min	**5** >95%[a]
3	R = CF_3	NBS (1.1 equiv.), reflux, 20 min	**7** (90%)[b]
3		Br_2 (1.5 equiv.), 0°C, 1 h	**7** (70%)[b]

[a] Non purified. Yield based on NMR.
[b] Isolated yield.

(NBS 1.5 equiv., AIBN), the glycal **3**, 10-CF_3 analogue of glycal **2**, led to the 10-CF_3-16-bromo derivative **7**[10] which is more stable than the allylic bromide **5**. It could be purified by recrystallization, isolated in 72%, and can be stored for several weeks at 0°C. Clearly the electron withdrawing character of the CF_3 group makes the allylic bromine less labile.

A search for improving the preparation of the interesting synthon **7** has been performed: (i) the number of equivalents of NBS could be reduced to 1.1, (ii) the presence of the initiator AIBN is not necessary, and when the reaction was performed without AIBN, the yield was improved to 90% (Table 1), and (iii) the reaction of glycal **3** with bromine in CCl_4 at 0°C also led to the allylic bromide **7** (80%)[11] but optimal conditions are more delicate to be obtained (Table 1). The dibromo adduct analogue of **4** was never observed.

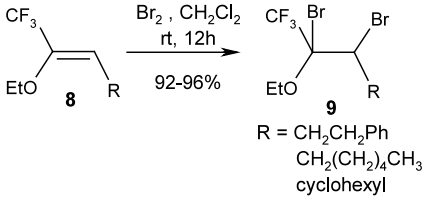
The reactivity of glycal **3** with Br_2 was unexpected, since it is different from that of glycal **2** and also from that of trifluoromethyl substituted parent enol ethers **8** (Scheme 1). Bromination of enol ethers **8**, which results from electrophilic bromination of the double bond, despite the electron-withdrawing character of CF_3 group, provides the stable dibromoadducts **9** (Scheme 1).[12]

Since the β-disubstitution of glycal **3** should increase the electron density of the double bond, and since the addition of bromine is not so much affected by steric effects,[13] the prevailed radical allylic bromination over electrophilic reaction could not be rationalised. Another surprising result is the success of the allylic bromination of glycal **3** with NBS or Br_2 in the absence of any initiator.

Allylic bromination with NBS can be initiated by heating; however this factor cannot be put forward for the radical reaction with Br_2, which takes place at 0°C. A radical reaction can also be initiated by daylight or the endoperoxide itself. When the glycal **3** was allowed to react with bromine in the absence of light, allylic bromination still occurred but the reaction was considerably slower (33% of recovered starting material after 24 h at rt). In order to check the role of the endoperoxide bridge as initiator, the deoxytrifluoromethylglycal **10** was prepared from the trifluoromethyl glycal **3**, by reduction with Zn in acetic acid, according to the procedure described for non fluorinated artemisinin derivatives[14] (Scheme 2). After purification, the deoxy glycal **10** was isolated in high yield (91%). Treatment of **10** with Br_2 in daylight led to a mixture of products after 24 hours of reaction. Conversely, in the dark, the reaction of CF_3-deoxy glycal **10** with Br_2 provided the 4-bromo derivative **11** as a single product, which was isolated in a high yield (81%) (Scheme 2). Its structure was determined by complete assignment of protons and carbons by NMR (characteristic δH-4 = 4.04 ppm (d) and δC-4 = 50.9 ppm). The small coupling constant ($^3J_{5ax,4}$ = 4 Hz) suggests the equatorial position of H-4, and, hence, the axial configuration of the bromine atom (addition through the α face). So, when the endoperoxide and any other initiator are lacking, bromination occurs on the α position of the ketalic function, and this reaction is known to be acido-catalyzed.[15] It is worth noting that this new bromo compound **11**, is unstable and rapidly decomposed into a mixture of compounds containing ketone functions (ν_{CO} = 1697 cm^{-1}, ^{13}C NMR δ = 197, 202, 208 ppm).

This comparative study on reactivity of glycals **2** and **3** toward NBS and Br_2 clearly shows that the trifluoroartemisinin glycal **3** is its own initiator for radical reaction,[16] and allylic bromination is always favoured, while radical bromination of non fluorinated glycal **2** requires an external initiator (for example, heating, AIBN).

Having in hand the 16-bromoanhydrodihydroartemisinin **5** and its 10-trifluoromethyl analogue **7**, we submitted them to N-, O- and C-nucleophiles (Tables 2 and 3).



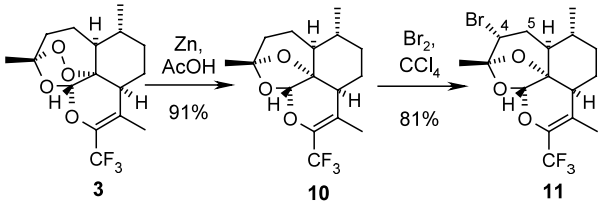
8

Br_2, CH_2Cl_2, rt, 12h; 92-96%

9

R = CH_2CH_2Ph
$CH_2(CH_2)_4CH_3$
cyclohexyl

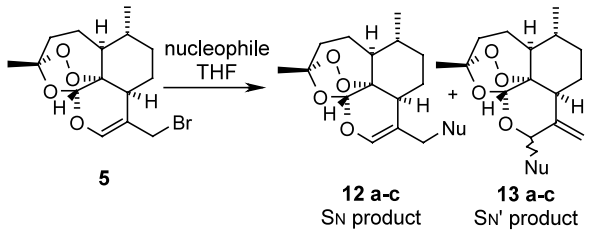
Scheme 1. Reaction of α-CF_3 enol ethers **8** with bromine.



3 → (Zn, AcOH; 91%) → **10** → (Br_2, CCl_4; 81%) → **11**

Scheme 2. Reaction of CF_3-deoxy glycal **10** with bromine.

Table 2. Reaction of allylic bromide **5** with nucleophiles

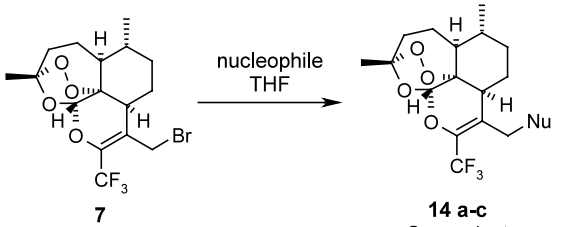


5 **12 a-c** SN product **13 a-c** SN' product

Conditions	Ratio S_N/S'_N	Yield[a,b] (%)
Morpholine (4 equiv.), 1.5 h	**12a**/**13a** 50:50	82
EtOH (2 equiv.), NaH (2 equiv.), 1 h	**12b**/**13b** 10:90	36
$MeCH(CO_2Et)_2$ (1.5 equiv.), NaH (1.5 equiv.), 1.5 h	**12c**/**13c** 100:0	28[c]

[a] Yield given from the anhydrodihydroartemisinin **2**.
[b] Total isolated yield of **12**+**13**.
[c] Low yield due to purification procedure.

Table 3. Reaction of allylic bromide **7** with nucleophiles



7 **14 a-c** SN product

Conditions	Product (yield)[a]
Morpholine (4 equiv.), 5 h	**14a** (79%)
EtOH (2 equiv.), NaH (2 equiv.), KI (cat.), 18 h	**14b** (97%)
$MeCH(CO_2Et)_2$ (1.5 equiv.), NaH (1.5 equiv.), KI (cat.), 18 h	**14c** (67%)

[a] Isolated yield.

The crude allylic bromide **5** reacted smoothly with morpholine (4 equiv.) in THF, within 1.5 h, to give a 1:1 mixture of products **12a** and **13a**[17] resulting from S_N and S'_N reactions, respectively (Table 2). After purification by chromatography, each product was isolated in a 41% yield (from glycal **2**). Ethoxide ion could also react with allylic bromide **5** within 1 h but led to a mixture of compounds, among them **12b** and **13b** could be isolated in a 10:90 ratio but could not be separated (36% yield from glycal **2**). In the reaction of allylic bromide **5** with diethyl methyl malonate sodium salt (1.5 equiv.) the major compound was **12c** resulting from the S_N reaction (>60% in the crude mixture), and **13c** could not be detected. However **12c** could be isolated only in 28% yield. Interestingly, with morpholine and ethoxide ion as nucleophiles, the artemisitene-type compounds **13a** and **13b** (S'_N products) were obtained as single isomers. However, their configuration at C-10 could not be determined by NMR, in particular homo NOE experiments gave no indications.

Some nucleophiles were allowed to react with the allylic bromide **7**, trifluoromethyl analogue of **5** (Table 3). With morpholine, **7** reacted within 5 hours to provide the product **14a**[18] in a 79% yield. With ethoxide ion and diethyl methyl malonate sodium salt, the reaction required an addition of catalytic amount of KI, and provided after 18 hours 97% and 67% of products **14b** and **14c**, respectively. In all cases, reaction times were longer than for the allylic bromide **5**, indicating the lower reactivity of the allylic bromide **7**. However the reaction with **7** was much more selective leading to only one product which is the result of SN substitution (Table 3). No trace of the allylic rearrangement products was detected by ^{19}F NMR in the crude mixtures.

The major product of the allylic rearrangement reaction of the non fluorinated allylic bromide **5** can be explained by a cationic process with formation of the stabilised alkoxy carbenium ion. From the allylic bromide **7**, the alkoxy carbenium ion is not so stabilised because of the CF_3 group, and the substitution takes place at the less hindered allylic carbon.[19]

In conclusion, this study shows the difference of reactivity of the anhydrodihydroartemisinin **2** and its trifluoromethyl analogue **3** toward brominating reagents: **2** reacts with NBS in the presence of AIBN to provide the new allylic bromide **5**, while the new parent 10-CF_3 allylic bromide **7** could be prepared in high yield by reaction of glycal **3** with either NBS alone or Br_2 in CCl_4. In these reactions the radical process seems to be induced by the presence of the endoperoxide bridge. Both allylic bromides **5** and **7** are key synthons for the preparation of new artemisinin derivatives. For example, **5** and **7** could undergo nucleophilic substitutions with N-, O- and C-nucleophiles. From **5**, products of S_N and S'_N were obtained, while from the CF_3-substituted allylic bromide **7** the reaction was very selective in favour of nucleophilic substitution. The yield in S_N product is much higher from **7** than from **5**. New fluorinated artemisinin derivatives **14a**–**c** with a functionality at C-16 could be obtained in high yield, and their physico-chemical and antimalarial properties are under investigation.

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9. Spectral data for **5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (d, $^3J_{H15-H6}=6$ Hz, 3H, CH_3-15), 1.15 (m, 1H, H-7ax), 1.20 (m, 1H, H-8), 1.42 (s, 3H, CH_3-14), 1.45 (m, 1H, H-6), 1.50 (m, 2H, H-5a, H-5), 1.68 (qd, $^2J=13$ Hz, $^3J_{H7eq-H6}=$ $^3J_{H7eq-H8}=$ $^3J_{H7eq-H8'}=3$ Hz, 1H, H-7eq), 2.00 (m, 1H, H-5′), 2.10 (m, 1H, H-4eq), 2.15 (m, 1H, H-8a), 2.20 (m, 1H, H-8′), 2.42 (ddd, $^2J=15$ Hz, $^3J_{H4ax-H5ax}=13.5$ Hz, $^3J_{H4ax-H5eq}=4$ Hz, 1H, H-4ax), 4.03 (d, $^2J=10.5$ Hz, 1H, H-16a), 4.13 (d, $^2J=10.5$ Hz, 1H, H-16b), 5.61 (s, 1H, H-12), 6.66 (s, 1H, H-10); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.2 (C-15), 24.4 (C-5), 25.7 (C-14), 30.2 (C-8), 33.8 (C-7), 35.0 (C-16), 36.0 (C-4), 37.4 (C-6), 41.6 (C-8a), 51.1 (C-5a), 78.2 (C-12a), 90.6 (C-12), 105.0 (C-3), 110.1 (C-9), 141.5 (C-10).
10. Spectral data for **7**: ^{19}F NMR (188 MHz, $CDCl_3$) δ −65.9 (s, 3F, CF_3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (d, $^3J_{H15-H6}=6$ Hz, 3H, CH_3-15), 1.16 (m, 1H, H-7ax), 1.30 (qd, $^2J=$ $^3J_{H8ax-H7ax}=$ $^3J_{H8ax-H8a}=13.5$ Hz, $^3J_{H8ax-H7eq}=$ 3.5 Hz, 1H, H-8ax), 1.40 (m, 1H, H-6), 1.41 (s, 3H, CH_3-14), 1.50 (m, 2H, H-5, H-5a), 1.72 (qd, $^2J=13$ Hz, $^3J_{H7eq-H8ax}=$ $^3J_{H7eq-H8eq}=$ $^3J_{H7eq-H6}=3.5$ Hz, 1H, H-7eq), 1.96 (m, 1H, H-5′), 2.04 (ddd, $^2J=14$ Hz, $^3J_{H4eq-H5eq}=4.5$ Hz, $^3J_{H4eq-H5ax}=3$ Hz, 1H, H-4eq), 2.11 (tdd, $^2J=13.5$ Hz, $^3J_{H8eq-H7eq}=$ $^3J_{H8eq-H7ax}=3.5$ Hz, $^3J_{H8eq-H8a}=4.5$ Hz, 1H, H-8eq), 2.19 (qdd, $^3J_{H8a-H8ax}=13$ Hz, $^3J_{H8a-H8eq}=4.5$ Hz, $^5J_{H8a-F}=1.5$ Hz, 1H, H-8a), 2.40 (td, $^2J=$ $^3J_{H4ax-H5ax}=14$ Hz, $^3J_{H4ax-H5eq}=4$ Hz, 1H, H-4ax), 4.00 (dq, $^2J=11$ Hz, $^5J_{H16a-F}=1.5$ Hz, 1H, H-16a), 4.28 (dq, $^2J=11$ Hz, $^5J_{H16b-F}=1$ Hz, 1H, H-16b), 5.70 (s, 1H, H-12); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.9 (C-15), 24.2 (C-5), 25.3 (C-14), 28.2 (C-16), 29.1 (C-8), 33.7 (C-7), 35.8 (C-4), 37.4 (C-6), 44.0 (C-8a), 50.2 (C-5a), 77.3 (C-12a), 91.3 (C-12), 105.2 (C-3), 112.1 (C-9), 125.5 (q, $^1J_{C-F}=275$ Hz, CF_3), 139.8 (q, $^2J_{C-F}=35$ Hz, C-10). Anal. calcd for $C_{16}H_{20}BrF_3O_4$: C, 46.39; H, 4.97. Found: C, 46.55; H, 4.98.
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17. Spectral data for **12a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, $^3J_{H15-H6}=6$ Hz, 3H, CH_3-15), 1.19 (m, 2H, H-8, H-7), 1.40 (m, 1H, H-6), 1.41 (s, 3H, CH_3-14), 1.47 (m, 1H, H-5a), 1.56 (m, 1H, H-5), 1.63 (m, 1H, H-7′), 1.92 (m, 1H, H-5′), 2.05 (m, 3H, H-4eq, H-8a, H-8′), 2.26 (m, 2H, 2 CH_aH$_b$N), 2.39 (td, $^2J=$ $^3J_{H4ax-H5ax}=13$ Hz, $^3J_{H4ax-H5eq}=$ 3 Hz, 1H, H-4ax), 2.50 (m, 2H, 2 CH$_a$$H_b$N), 2.52 (d, $^2J=$ 12.5 Hz, 1H, H-16a), 3.04 (d, $^2J=12.5$ Hz, 1H, H-16b), 3.67 (m, 4H, 2 CH_2O), 5.59 (s, 1H, H-12), 6.31 (s, 1H, H-10); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.2 (C-15), 24.4 (C-5), 25.8 (C-14), 29.9 (C-8), 34.0 (C-7), 36.2 (C-4), 37.5 (C-6), 40.6 (C-8a), 51.2 (C-5a), 53.2 (2 CH_2N), 58.7 (C-16), 67.0 (2 CH_2O), 79.0 (C-12a), 90.5 (C-12), 104.6 (C-3), 109.1 (C-9), 138.7 (C-10). Anal. calcd for $C_{19}H_{29}NO_5$: C, 64.93; H, 8.32; N, 3.99. Found: C, 64.67; H, 8.48; N, 3.95. For **13a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, $^3J_{H15-H6}=6$ Hz, 3H, CH_3-15), 1.10 (qd, $^2J=$ $^3J_{H7ax-H8ax}=$ $^3J_{H7ax-H6}=13.5$ Hz, $^3J_{H7ax-H8eq}=3$ Hz, 1H, H-7ax), 1.23 (ddd, $^3J_{H5a-H6}=11$ Hz or 14.5 Hz, $^3J_{H5a-H5ax}=11$ Hz or 14.5 Hz, $^3J_{H5a-H5eq}=6$ Hz, 1H, H-5a), 1.30 (m, 1H, H-6), 1.38 (s, 3H, CH_3-14), 1.45 (m, 1H, H-5ax), 1.62 (dq, $^2J=13.5$ Hz, $^3J_{H8eq-H7ax}=$ $^3J_{H8eq-H7eq}=$ $^3J_{H8eq-H8a}=3$ Hz, 1H, H-8eq), 1.70 (m, 1H, H-7eq), 1.82 (qd, $^2J=$ $^3J_{H8ax-H7ax}=$ $^3J_{H8ax-H8a}=13.5$ Hz, $^3J_{H8ax-H7eq}=3$ Hz, 1H, H-8ax), 1.91 (dddd, $^2J=13.5$ Hz, $^3J_{H5eq-H5a}=6$ Hz, $^3J_{H5eq-H4ax}=4$ Hz, $^3J_{H5eq-H4eq}=3$ Hz, 1H, H-5eq), 2.00 (dt, $^2J=14$ Hz, $^3J_{H4eq-H5eq}=$ $^3J_{H4eq-H5ax}=$ 3 Hz, 1H, H-4eq), 2.30 (m, 2H, H-4ax, H-8a), 2.52 (m, 2H, 2 CH_aH$_b$N), 2.87 (m, 2H, 2 CH$_a$$H_b$N), 3.70 (m, 4H, 2 CH_2O), 5.00 (s, 1H, H-10), 5.05 (s, 1H, H-16a), 5.22 (s, 1H, H-16b), 5.53 (s, 1H, H-12); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.9 (C-15), 24.7 (C-5), 25.1 (C-14), 31.3 (C-8), 34.0 (C-7), 36.5 (C-4), 37.5 (C-6), 48.0 (C-8a), 48.5 (2 CH_2N), 51.1 (C-5a), 67.1 (2 CH_2O), 80.4 (C-12a), 89.4 (C-12), 91.0 (C-10), 102.9 (C-3), 114.6 (C-16), 143.6 (C-9).
18. Spectral data for **14a**: ^{19}F NMR (188 MHz, $CDCl_3$) δ −63.0 (s, 3F, CF_3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (d, $^3J_{H15-H6}=6$ Hz, 3H, CH_3-15), 1.20 (m, 2H, H-8, H-7), 1.41 (s, 3H, CH_3-14), 1.50 (m, 3H, H-5, H-5a, H-6), 1.69 (m, 1H, H-7), 1.95 (m, 1H, H-5′), 2.03 (m, 1H, H-4, H-8′), 2.31 (bs, 2H, 2 CHaHbN), 2.40 (m, 2H, H-4′, H-8a), 2.53 (bs, 2H, 2 CHaHbN), 3.02 (d, $^2J=13.5$ Hz, 1H, H-16a), 3.10 (d, $^2J=$ 13.5 Hz, 1H, H-16b), 3.67 (m, 4H, 2 CH_2O), 5.71 (s, 1H, H-12); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.0 (C-15), 24.3 (C-5), 25.4 (C-14), 28.6 (C-8), 33.9 (C-7), 35.9 (C-4), 37.5 (C-6), 41.9 (C-8a), 50.3 (C-5a), 53.0 (2 CH_2N), 54.4 (C-16), 67.0 (2 CH_2O), 77.8 (C-12a), 90.8 (C-12), 104.8 (C-3), 113.1 (C-9), 120.5 (q, $^1J_{C-F}=278$ Hz, CF_3), 137.6 (q, $^2J_{C-F}=34$ Hz, C-10). Anal. calcd for $C_{20}H_{28}F_3NO_5$: C, 57.27; H, 6.73; N, 3.34. Found: C, 57.20; H, 6.89; N, 3.28.
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