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Deoxygenation of aliphatic acetate derivatives using electrogenerated organic amalgams†

Lizeth M. Fragoso-Luna, Bernardo A. Frontana-Uribe* and Jorge Cárdenas

Instituto de Química de la Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, Coyoacán C.P. 04510, Mexico D.F.

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Abstract—An electrochemical deoxygenation reaction of aliphatic acetates has been developed, using electrogenerated organic amalgams (R_4N-Hg). This methodology led us to obtain the deoxygenated product and the alcohol in a 1:1 ratio with total transformation of the starting compound. Examples using the acetates of sarsasapogenin, diosgenin, 16-dehydro-pregnanolone and argentatine A, show the applications and some limitations of this electrochemical reaction.

1. Introduction

The reduction of aliphatic alcohols to the corresponding alkanes is of great interest, mainly in the field of the sugar derivatives, due to the enhancement of the biological activity of some deoxygenated antibiotics.[1] Radical processes have been developed to carry out this reductive transformation in the presence of sensitive functional groups. The possibility of producing rearranged products, frequently observed in ionic reactions, are considerably reduced in the radical reactions.[2,3] However, most of the radical reactions use tin hydrides as reducing agents and chain carriers.[4] The toxicity of tin derivatives and the difficulties of removing metal by-products from the reaction mixtures, has prompted the search for alternative deoxygenating methods and reagents in order to find suitable hydrogen sources.[5,6]

Quaternary ammonium amalgams have been known since the end of the 1960s.[7] Lately, Kariv-Miller and co-workers have demonstrated that during the electrochemical reduction of aromatic compounds on a mercury cathode, if tetraalkylammonium ions are present, organic amalgams (R_4N-Hg) are involved in the electron transfer.[8] These amalgams have been characterized both chemically and electrochemically, showing a stoichiometry of $R_4N(Hg)_5$ and a reversible electron transfer.[9,10] The reactivity of these organomercuric compounds is similar to the reductions using alkaline metals (Li, Na, K). The utility of these organic amalgams to achieve difficult reductions (aromatics, ketones, conjugated dienes and fluoroaromatic compounds for example) has been well documented as well,[11–13] but there are no references on their use in deoxygenation reactions. The quaternary ammonium amalgams are stable at room temperature in organic media in the presence of low quantities of water (8% or 4 M), which has been proposed as the source of protons in the reduction reactions.

We observed during our work that 3-acetyl-diosgenin (**1**) in the presence of electrogenerated tetrabutylammonium amalgam lost the acetoxy group, yielding the corresponding alkane and alcohol in a 1:1 ratio. The chemical equivalent to this deoxygenation reaction is carried out by a dissolving metal (Li or K) reduction of esters to alkanes at −60°C using a mixture of dry t-$BuNH_2$–THF or $EtNH_2$–THF as solvent and crown ethers to dissolve the metal ions.[14] We were interested in the electrochemical deoxygenation reaction, due to the easy access to the acetyl derivatives, the low cost of the reaction media compared with the chemical method, and the possibility of working with wet organic solvents. In the literature, some electrochemical deoxygenation methods are reported, but they are either performed in dry organic solvents[15–17] or they are useful for specific functions only.[18] In this communication we report our findings in the reductive deoxygenation reaction of aliphatic acetate derivatives, using electrogenerated tetrabutylammonium amalgams.

Keywords: deoxygenation; acetates; electrochemistry; organic amalgams; reduction.

* Corresponding author. Fax: +52 (55) 56162217; e-mail: bafrontu@servidor.unam.mx

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2. Results and discussion

The polarographic study of diosgenin acetate (**1**) and sarsasapogenin acetate (**4**) in THF–H_2O 93:7 with tetrabutylammonium tetrafluoroborate ($TBABF_4$) 0.1 M as electrolyte did not show a reduction signal, demonstrating that the reduction potential of the acetate group is higher than −2.5 V versus SCE. The lineal behavior observed in the polarogram at −2.2 V versus SCE is attributed to the production of the organic amalgam on the surface electrode as described previously (Fig. 1).[11]

The current constant electroreduction of diosgenin acetate (**1**) was optimized, finding that the best yield (53%) of deoxygenated product **2** was obtained using a current density between 2 and 5 mA/cm^2 and 2.2 F/mol (Table 1, entries 1–4). The electrolysis of sarsasapogenin acetate (**4**) in these experimental conditions yielded the deoxygenated product **5** in 48%. Using this theoretical quantity of electricity, the sole by-product detected and isolated was the deacetylated product **3** for the first reaction, and **6** for the second one, with total transformation of the starting compound. The double bond and the ketal functions were not affected by the electrochemical reduction. In a typical experiment the electrolytic solution (THF–H_2O 93:7, 25 ml), $TBABF_4$ 0.1 M and mercury (6 ml = 12.5 cm^2 of surface electrode) were added into the divided cell (sintered glass number 4) with an electrical contact in the bottom cell. In the auxiliary compartment, a platinum grid was fitted and the electrolytic solution (10 ml) was added. Nitrogen was bubbled (15 min) through the working solution and a 5 min pre-electrolysis, at the selected current density to carry out the electrolysis, was performed before the addition of the starting product (1.2–0.5 mmol). After consumption of the required quantity of electricity, mercury was separated and the solvent was removed in a rotary evaporator. Water was added (10 ml) to the residue and the organic products were extracted with CH_2Cl_2 (4×25 ml). The organic phase was dried over $CaCl_2$, filtered, and concentrated; the mixture of products was separated using medium-pressure column chromatography (Silica gel–C_6H_{12}–EtOAc).

Our experimental results can be justified using the Barton and co-workers proposed mechanism for their alkaline metal deoxygenation reaction (Scheme 1).[19] This mechanism takes into account the two possibilities of cleavage for the anion radical produced after the first electron transfer (ET). In our case, the electron transfer is promoted by the electrogenerated organic amalgam. This proposed mechanism explains why the production of the alkane and the alcohol is done in a competitive way. The yields found for alkane and alcohol in the electrochemical reaction are similar to those found using the alkaline metal reduction of acetates, but the experimental procedure of the electrochemical method

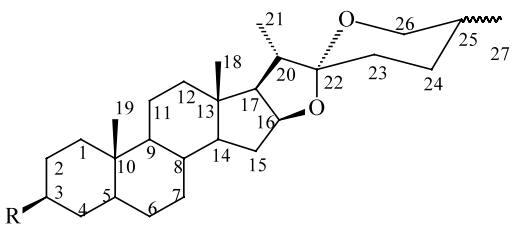
Table 1. Electrochemical deoxygenation of aliphatic acetates using organic amalgams

Entry	Starting product (scale)	Conditions	Products (%)
1	**1** (0.5 mmol)	**A** 2.2 F/mol 0.5 mA/cm^2	**1**: 28 **2**: 18 **3**: 54
2	**1** (0.5 mmol)	**A** 2.2 F/mol 2 mA/cm^2	**2**: 53 **3**: 47
3	**1** (0.5 mmol)	**A** 2.2 F/mol 5 mA/cm^2	**2**: 46 **3**: 50
4	**1** (0.5 mmol)	**A** 2.2 F/mol 10 mA/cm^2	**2**: 40 **3**: 58
5	**1**[a] (11 mmol)	**A** 2.2 F/mol 5 mA/cm^2	**2**: 45 **3**: 51
6	**4** (1.2 mmol)	**A** 2.2 F/mol 2 mA/cm^2	**5**: 48 **6**: 32
7	**10** (0.7 mmol)	**A** 2.2 F/mol 5 mA/cm^2	**11**: 7 **9**: 30 **12**+**13**: 14[b] **14**+**15**: 17[b]
8	**7** (0.6 mmol)	**A** 2.2 F/mol 5 mA/cm^2	Starting product >90
9	**7** (0.6 mmol)	**B** 2.2 F/mol 5 mA/cm^2	Starting product >90
10	**16** (0.7 mmol)	**A** 2.2 F/mol 5 mA/cm^2	**8**: 32 **16**: 57 **17**: 10
11	**18** (0.5 mmol)	**A** 2.2 F/mol 5 mA/cm^2	Complex mixture
12	**19** (1 mmol)	**A** 2.2 F/mol 5 mA/cm^2	**20**: 59 **21**: 41
13	**23** (0.5 mmol)	**A** 4.2 F/mol 5 mA/cm^2	Complex mixture

A: THF–H_2O 93:7+$TBABF_4$ 0.1 M working electrode: Hg, auxiliary electrode: Pt gauze, divided cell. **B**: diglime anhydr+$TBABF_4$ 0.1 M working electrode: Hg, auxiliary electrode: Pt gauze, divided cell.

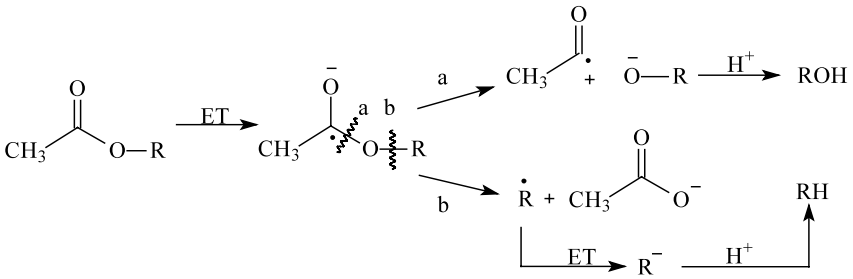
[a] This experiment was carried out using 5 g of diosgenin acetate in a bigger electrolysis cell with the same geometry.

[b] The products could not be separated by normal column chromatography due to the similar polarity.



1: (25*R*) Δ^{5-6}, R=OAc
2: (25*R*) Δ^{5-6}, R=H
3: (25*R*) Δ^{5-6}, R=OH
4: (5β, 25*S*) R=OAc
5: (5β, 25*S*) R=H
6: (5β, 25*S*) R=OH

Figure 1. Studied sapogenins and their electrolysis products.



Scheme 1. Proposed mechanism for the electrochemical deoxygenation of aliphatic acetates.

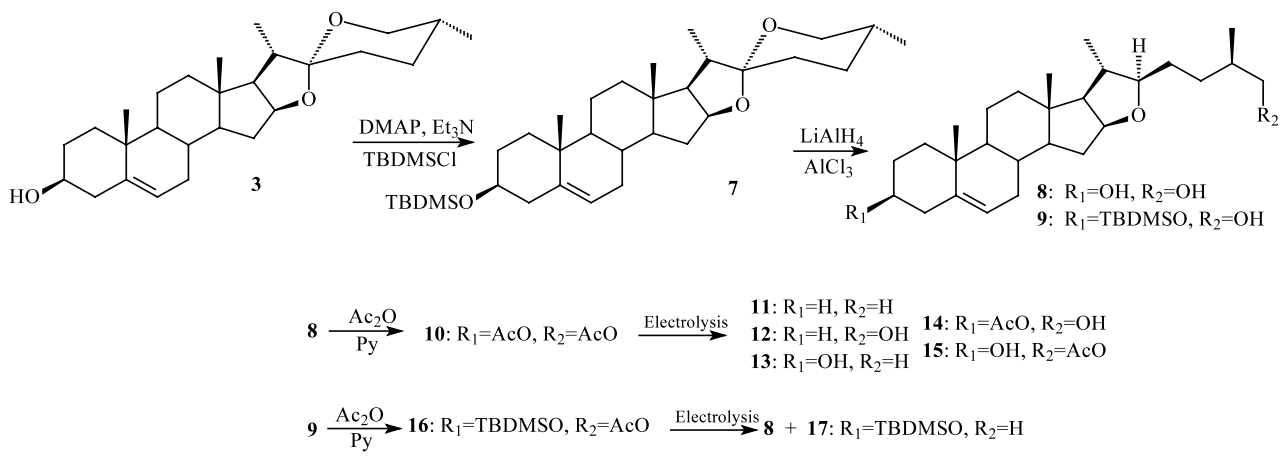
is more attractive, due to the use of wet solvents and a cheaper experimental set-up.

In order to study the behavior between a primary and a secondary alcohol, and following the protocol described in the literature, we reduced the ketal function of the diosgenin derivative **7** obtaining the diol **8** and the alcohol **9** (Scheme 2).[20] The acetylation of **8** gave **10**, which was electrolyzed in the same conditions, but at 2.2 and 4.2 F/mol. The TLC of the electrolyzed solutions showed a mixture of at least five products in both reactions, demonstrating that there is no selectivity between the acetates of the primary and the secondary alcohol. The isolated products after 2.2 F/mol electrolysis are summarized in Table 1.

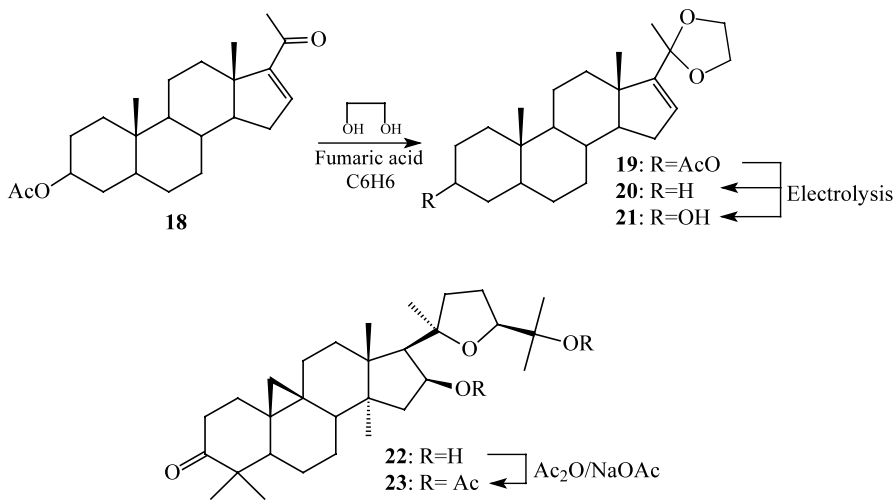
The electrolysis of **7** did not produce a change in the starting compound, indicating that the TBDMS group is stable in the electrochemical reaction conditions (Table 1, entry 8); the change of solvent to anhydrous diglime in order to increase the applied reduction potential did not affect the starting product, and it was recovered in more than a 90% (Table 1, entry 9). The electroreduction of **16** showed an atypical behavior, being slower than the previous experiments. With the theoretical amount of electricity only a 40% of product was transformed (Table 1, entry 10). We propose to explain this behavior by the fact that the TBDMS group has some negative influence over the electroreduction reaction.

The electrolysis of 16-dehydropregnanolone acetate (**18**) produced a complex mixture of products. The α,β-unsaturated ketone function was protected with the ketal function[21] and this derivative (**19**) was electrolyzed. After the work-up, we obtained 59% of the deoxygenated product **20** and 41% of the alcohol **21** (Scheme 3). The electrolysis of argentatine A diacetate (**23**), which contains a ketone function and two acetates, one from a secondary alcohol and another one from a tertiary alcohol, produced also a complex mixture of products. The ^{1}H NMR spectra of some purified fractions showed, that both acetate groups were affected by the organic amalgam without selectivity, yielding the corresponding alkane and alcohol.

The complex mixtures observed after electrolysis of products containing ketone groups (**18** and **23**) are attributed to the reduction of the ketone function. It is well known that ketones are reduced by electron transfer to the radical anion which can follow other chemical reactions, e.g. dimerization.[22] Studies to clarify and optimize this reaction are currently been carried out. The spectroscopic data of the key compound are included in Ref. 23.



Scheme 2. Diosgenin derivatives and their electrolysis products.



Scheme 3. Studied compounds containing the ketone function.

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23. Characterization data of key compounds: Compound **2**. White crystals (CH_2Cl_2/EtOAc) mp 185–187°C. IR ($CHCl_3$) ν cm^{-1}: 2952, 2930, 2874, 2852, 1729, 1456, 1376, 1173, 1050, 980, 896. ^1H NMR δ ppm, J=Hz: 5.26 (1H, d, J=5.2, H-6), 4.4 (1H, c, J=6.12, H-16), 3.48 (1H, m, H-26), 3.40 (1H, dd, J=21, 10.7, H-26), 1.01 (3H, s, CH_3), 0.96 (3H, d, J=6.78, CH_3), 0.78 (3H, s, CH_3), 0.78 (3H, d, J=6.02, CH_3). ^{13}C NMR δ ppm: 143.7, 118.7. 109.2, 80.8, 66.8, 62.1, 56.6, 50.5, 41.6, 40.2, 39.8, 37.6, 32.8, 32.0, 31.8, 31.4, 30.3, 29.7, 28.8, 28.0, 22.5, 20.5, 19.4. 17.1, 16.3, 14.5. HRMS EI m/z (rel. int.): M^+ 398.3165 (14), 339 (7), 326 (17), 284 (100), 269 (30), 255 (46), 139 (85), 115 (16), 69 (13). $C_{27}H_{42}O_2$ requires M^+ at 398.3185. Compound **5**: Cream solid mp 203–206°C. IR ($CHCl_3$) ν cm^{-1}: 2931, 2863, 1602, 1451, 1378, 1174, 1064, 918. ^1H NMR δ ppm, J=Hz: 4.40 (1H, m, H-16), 3.95 (1H, dd, J=11, 2.4, H-26), 3.3 (1H, d, J=11, H-26), 1.07 (3H, d, J=7, CH_3), 1.0 (3H, d, J=6.6, CH_3), 0.93 (3H, s, CH_3), 0.75 (3H, s, CH_3). ^{13}C NMR δ ppm: 109.7, 81.10, 65.1, 62.2, 56.5, 43.7, 42.2, 40.7, 40.6, 37.6, 35.5, 35.2, 31.8, 30.3, 29.7, 27.4, 27.2, 27.0, 26.8, 26.0, 25.8, 24.3, 21.3, 20.66, 16.5, 16.0, 14.3. HRMS EI m/z (rel. int.): M^+ 400.3354 (18), 331 (13), 328 (20), 313 (12), 286 (53), 271 (38), 257 (74), 255 (22), 139 (100), 122 (13), 69 (15). $C_{27}H_{44}O_2$ requires M^+ at 400.3341. Compound **10**: White crystals, mp 112–115°C. IR ($CHCl_3$) ν cm^{-1}: 2953, 2904,

2870, 2851, 1725, 1456, 1371, 1033. ^{1}H NMR δ ppm, J=Hz: 5.36 (1H, d, J=5.1, H-6), 4.6 (1H, m, H-3), 4.29 (1H, dt, J=5.4, 7.8, H-16), 3.96 (1H, dd, J=10.8, 5.7, H-26), 3.84 (1H, dd, J=10.8, 6.9, H-26), 3.3 (1H, dt, J=3.9, 7.2, H-22), 2.04 (3H, s, CH_3CO), 2.02 (3H, s, CH_3CO), 1.03 (3H, s, CH_3), 0.99 (3H, d, J=6.6, CH_3), 0.93 (3H, d, J=7, CH_3), 0.80 (3H, s, CH_3). ^{13}C NMR δ ppm: 171.2, 170.5, 139.7, 122.3, 90.2, 83.2, 73.9, 69.4, 65.2, 56.9, 50.0, 40.7, 39.4, 38.1, 37.9, 37.0, 36.7, 32.8, 32.2, 31.6, 30.8, 30.4, 27.7, 21.4, 21.3, 20.9, 20.6, 19.3, 18.9, 16.7, 16.4. HRMS EI m/z (rel. int.): M^+ 500 (1), 441 (32), 440 (100), 380 (49), 253 (61), 213 (10), 145 (14), 99 (18), 81 (12). $C_{31}H_{48}O_5$ requires M^+ at 500. Compound **11**: Cream solid mp 120–123°C. IR ($CHCl_3$) ν cm^{-1}: 2956, 2958, 2854, 1721, 1602, 1461, 1377, 1163, 1094, 1048. ^{1}H NMR δ ppm, J=Hz: 5.25 (1H, d, J=5.1, H-6), 4.3 (1H, dt, J=7.5, 5.1, H-16), 3.3 (1H, m, H-22), 1.0 (3H, s, CH_3), 0.99 (3H, d, J=6.5, CH_3), 0.99 (6H, d, J=7, i-Pr), 0.80 (3H, s, CH_3). ^{13}C NMR δ ppm: 125.4, 118.7, 90.4, 83.1, 65.3, 57.1, 50.6, 40.6, 39.8, 39.5, 37.8, 37.6, 35.8, 32.8, 32.2, 31.9, 31.5, 31.4, 30.31, 28.2, 28.0, 22.4, 20.4, 19.4, 19.0, 16.4, 14.0. HRMS EI m/z (rel. int.): M^+ 384.3384 (40), 369 (19), 313 (67), 269 (15), 255 (100), 230 (12), 219 (20), 159 (20), 145 (17), 109 (17). $C_{27}H_{44}O$ requires M^+ at 384.3392. Compound **16**: White crystals (CH_2Cl_2/MeOH) mp 85–86°C. IR ($CHCl_3$) ν cm^{-1}: 2955, 2934, 2901, 2855, 1725, 1465, 1374, 1090, 1047, 889, 868, 837. ^{1}H NMR δ ppm, J=Hz: 5.3 (1H, broad s, H-6), 4.3 (1H, c, J=5.49, H-16), 3.9 (2H, m, H-26), 3.5 (1H, m, H-3), 3.3 (1H, m, H-22), 2.05 (3H, s, CH_3CO), 1.1 (3H, s, CH_3), 0.95 (3H, d, J=7, CH_3), 0.9 (9H, s, t-butyl), 0.8 (3H, s, CH_3), 0.05 (6H, s, dimethyl-Si). ^{13}C NMR δ ppm: 171.3, 141.6, 120.9, 90.2, 83.2, 72.6, 69.4, 65.1, 57.03, 50.2, 42.7, 39.5, 37.9, 37.4, 32.7, 32.2, 32.06, 31.6, 30.81, 30.8, 30.4, 25.9, 19.45, 19.02, 18.9, 18.2, 16.76, 16.7, 16.4, –4.5. HRMS EI m/z (rel. int.): 572 (2), 515 (100), 455 (4), 381 (12), 253 (31), 99 (15). $C_{35}H_{60}O_4Si$ requires M^+ at 572. Compound **17**: Cream solid mp 106–110°C. IR ($CHCl_3$) ν cm^{-1}: 2956, 2932, 2902, 2855, 1466, 1382, 1253, 1090, 964, 889, 837. ^{1}H NMR δ ppm, J=Hz: 5.3 (1H, d, J=3.6, H-6), 4.3 (1H, dt, J=5.1, 3.8 H-16), 3.49 (1H, m, H-3), 3.30 (1H, dd, J=15.9, 6.39, H-22), 1.01 (3H, s, CH_3), 1.0 (3H, d, J=7.2, CH_3), 0.88 (9H, s, t-butyl), 0.87 (6H, d, J=i-Pr), 0.80 (3H, s, CH_3), 0.05 (6H, s, dimethyl-Si). ^{13}C NMR δ ppm: 141.6, 120.9, 90.5, 83.1, 65.3, 72.5, 65.3, 57.03, 50.2, 42.8, 40.7, 39.5, 37.9, 37.4, 36.7, 35.8, 32.3, 32.0, 31.6, 31.4, 29.7, 28.25, 25.9, 22.55, 22.5, 20.7, 19.4, 19.0, 18.2, 16.4, –4.5. HRMS EI m/z (rel. int.): 514 (1), 499 (3), 471 (4), 457 (100), 439 (3), 381 (7), 365 (4), 253 (7), 213 (3), 193 (4), 171 (5), 164 (8). $C_{33}H_{58}O_2Si$ requires M^+ at 514. Compound **20**: Cream solid 70–72°C. IR ($CHCl_3$) ν cm^{-1}: 2974, 2933, 2859, 1448, 1373, 1104, 1043, 949, 861. ^{1}H NMR δ ppm, J=Hz: 5.74 (1H, dd, J=3.3, 1.5, H-16), 3.92–4.0 (4H, m, CH_2-ketal), 2.05 (1H, ddd, J=15, 6.3, 3.3, H-15), 1.50 (3H, s, CH_3), 0.95 (3H, s, CH_3), 0.9 (3H, s, CH_3). ^{13}C NMR δ ppm: 126.7, 108.5, 64.26, 64.24, 58.3, 46.3, 43.8, 40.9, 37.6, 35.9, 35.5, 34.4, 30.8, 27.5, 27.2, 27.1, 26.5, 25.9, 24.2, 21.3, 20.7, 17.1, 15.9. HRMS EI m/z (rel. int.): M^+ 344.2731 (4), 329 (92), 300 (69), 285 (32), 267 (15), 257 (86), 189 (12), 161 (15), 135 (17), 126 (19), 107 (17), 93 (22), 87 (100), 43 (59). $C_{23}H_{36}O_2$ requires M^+ at 344.2715.