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New efficient and totally stereoselective copper allylic benzoyloxylation of sterol derivatives

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Abstract—A new efficient and totally stereoselective copper allylic benzoyloxylation of sterol derivatives has been developed. This methodology has been successfully applied to the synthesis of 7α-hydroxy DHEA and 7α-hydroxy cholesterol in a two-step synthesis with high chemical yields (77% and 61% overall yield, respectively). A mechanistic rationale justifying the total stereoselectivity encountered has been proposed.

1. Introduction

Stereoselective functionalization of unactivated olefins is a very active and challenging research area with many potential synthetic applications.[1] In this area, metal-induced allylic oxidation of alkenes appears to be one of the best methods of synthesis and has been the subject of several investigations.[2] Apart from radical-initiated reactions,[3] reactions based on selenium[4] or palladium[5] systems have attracted considerable interest. Among all these methods, Kharasch and Sosnovsky were the first to report in 1958, the allylic oxidation of olefins with *tert*-butyl perbenzoate and a catalytic amount of a copper(I) salt.[6] Since then, numerous systems have been proposed in order to improve the enantioselectivity of the copper catalyzed acetoxylation of cyclic alkenes using a *tert*-butyl hydroperoxide (TBHP)/acetic acid mixture as an oxidant.[7] Surprisingly, little research has been devoted to allylic sterol derivatives. 7α-Hydroxy derivatives of oxysterols are of considerable interest because of their possible involvement in the regulation of cholesterol metabolism.[8] Moreover, sterols bearing a hydroxyl group in position 7 have been shown to be selectively cytotoxic toward tumor cells cultured in vitro and possess immunosuppressive properties.[9] To date, no efficient and totally stereoselective methods have been reported for the synthesis of the corresponding pure 7α- or 7β-hydroxy derivatives. Among the most popular methods, the reduction of 7-ketosterol derivatives is achieved with L-selectride or sodium borohydride/cerium trichloride agents, respectively.[10] Nevertheless, the total stereoselectivity of such a reaction is difficult to achieve and the presence of the two diastereomers is always seen. In this context, allylic oxidation of olefins could constitute an interesting alternative. Herein, we report a new totally stereoselective copper allylic benzoyloxylation of sterol derivatives. A mechanistic rationale justifying the total stereoselectivity encountered and the synthesis of various important sterol compounds will be also discussed.

2. Results and discussion

In 1961, Starka reported the stereoselective oxidation of cholesteryl acetate in acetic acid with *tert*-butyl perbenzoate in the presence of a catalytic amount of cuprous bromide giving after treatment, 7α-hydroxycholesteryl-acetate in 65% yield.[11] In our hands, it was impossible to reproduce such results with only the starting material being recovered at the end of the reaction. Despite these surprising results, we examined the influence of solvents and reaction temperature on chemical yield by using cholesterylacetate **1a** as a test substrate and copper bromide (2 equiv) as copper source (Table 1).

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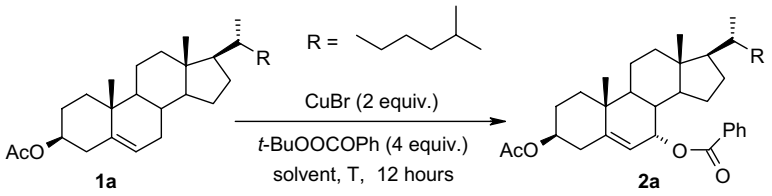
Table 1. Influence of the experimental conditions in the copper allylic benzoyloxylation of cholesterylacetate **1a**



Entry[a]	Solvent	Temperature (°C)	Yield (%)[d]	Diastereomeric ratio (α/β)[e]
1[b]	CH_3COOH	Reflux	0	—
2[c]	CH_3COOH	Reflux	0	—
3[b]	THF	Reflux	0	—
4[b]	Toluene	110	0	—
5[b]	CH_3COCH_3	Reflux	19	100/0
6[b]	CH_3CN	40	20	100/0
7[b]	CH_2Cl_2	40	76	100/0
8[c]	CH_2Cl_2	40	30	100/0
9[b]	CH_2Cl_2	20	18	100/0

[a] Reactions performed on 4.6 mmol scale during 12 h.
[b] Reactions carried out under argon atmosphere.
[c] Reaction performed under air atmosphere.
[d] Isolated yield.
[e] Diastereomeric ratio determined by ^1H and ^{13}C NMR spectroscopy.

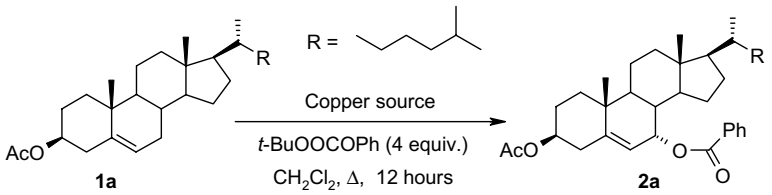
No reaction occurred in acetic acid, THF, or toluene with no clear relationship between the chemical yield encountered and polarity of the solvents being observed. Amongst the solvents examined, CH_2Cl_2 gave the best result decreasing from 76% to 18% yield as the reaction temperature was lowered (entries 7–9).

The influence of nature of the copper source was also taken into consideration (Table 2).

Copper sources such as $CuSO_4$, CuI, CuOTf, or $Cu(OTf)_2$, which are widely reported in the literature[7] to be efficient catalysts in copper allylic oxidation processes, were found to be ineffective for our reaction (entries 1–4). The best result was encountered using 2 equiv of CuBr as copper source and affording the expected compound in 76% yield (entry 7). It is noteworthy that the use of lower equivalents of copper source (1 and 0.5 equiv) does not improve the outcome of the reaction (65% and 46% yield, respectively, entries 8 and 9).

According to Kharasch and Sosnovsky's investigations, a mechanistic rationale may be envisioned involving the homolysis of the perester oxygen–oxygen bond by copper(I) to give a copper(II) benzoate intermediate and *tert*-butoxy radical.[2,6,12] This radical may abstract an allylic hydrogen atom to give *tert*-butanol and allylic radical **3**. Addition of copper(II) to allyl radical

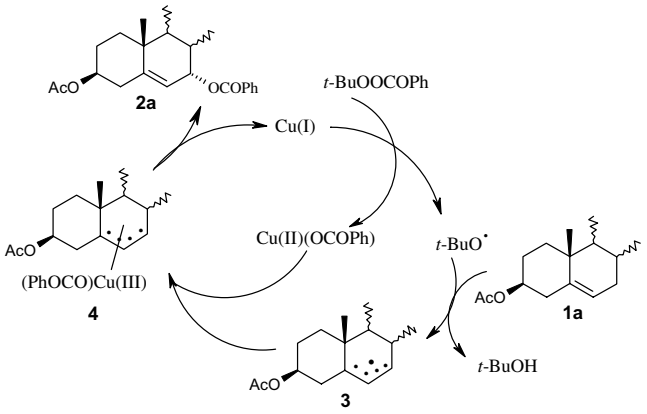
Table 2. Influence of the nature of copper source in allylic benzoyloxylation of cholesteryl acetate **1a**



Entry[a]	Copper source	Copper source amount[b] (equiv)	Yield (%)[c]	Diastereomeric ratio (α/β)[d]
1	$CuSO_4$	2	0	—
2	CuI	2	0	—
3	CuOTf	2	0	—
4	$Cu(OTf)_2$	2	0	—
5	CuCl	2	30	100/0
6	$CuCl_2$	2	42	100/0
7	**CuBr**	**2**	**76**	**100/0**
8	CuBr	1	65	100/0
9	CuBr	0.5	46	100/0

[a] Reactions performed on 4.6 mmol scale in refluxing CH_2Cl_2 during 12 h under argon atmosphere.
[b] Equivalents with respect of **1a**.
[c] Isolated yield.
[d] Diastereomeric ratio determined by ^1H and ^{13}C NMR spectroscopy.

3 generates copper(III) benzoate **4**, which rapidly rearranges to give the expected product **2a** with regeneration of copper(I) source (Scheme 1).



Scheme 1. Mechanism for the copper allylic benzoyloxylation of cholesteryl acetate **1a**.

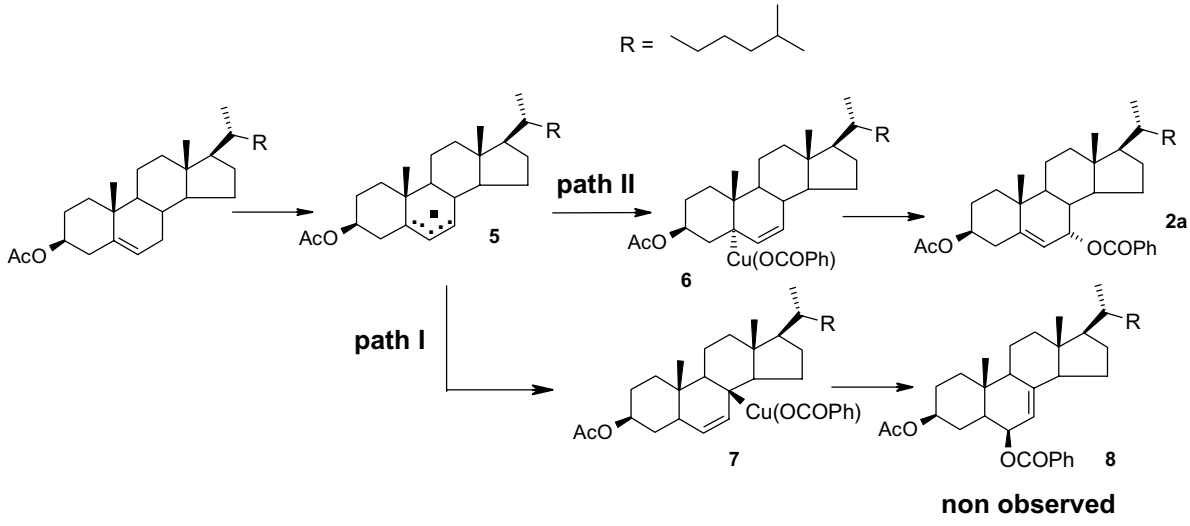
The total 7α stereoselectivity encountered can be rationalized through the three different pathways underlined in Scheme 2.

Path I is reasonable from a chemical point of view, but we have never been able to observe traces of the formation of derivative **8**. Path II involving the formation of 5α-copper(III) derivative **6**, which rearranges to the expected 7α-benzoate product **2a**, via a seven-membered intermediate, constitutes the unique possible reaction pathway proposal. A transition state model is proposed to account for the stereoinduction in the reaction (Scheme 3).

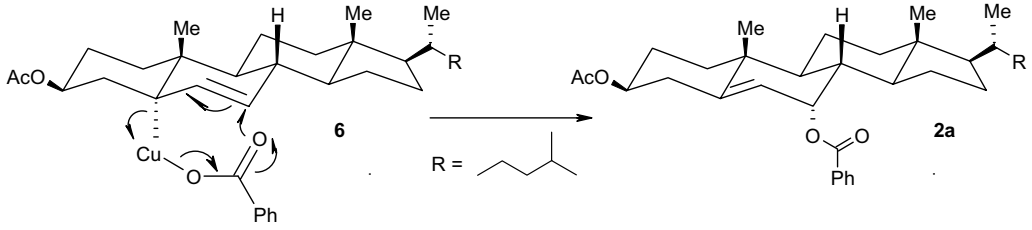
In this favorable transition state assembly, copper benzoate attains an orientation in such a way that the benzoate oxygen attacks the allylic carbon, which is electrophilic in nature due to the coordination of the incipient double bond with Cu species, in an α-position generating exclusively 7α-benzoate cholesteryl derivative **2a**. Moreover, this transition state allows us to justify that the formation of 7β-parent derivative is totally excluded and will never be encountered whatever the experimental conditions applied since only attack in an α-position occurs.

In order to clarify the scope of the present reaction, we examined the oxidation of a series of cholesterol derivatives by using the best experimental conditions previously encountered. The results are summarized in Table 3.

Whatever be the nature of sterol derivative under consideration, the reaction proceeds in moderate to excellent chemical yields varying from 31% to 95% but always with a total stereoselectivity. This methodology

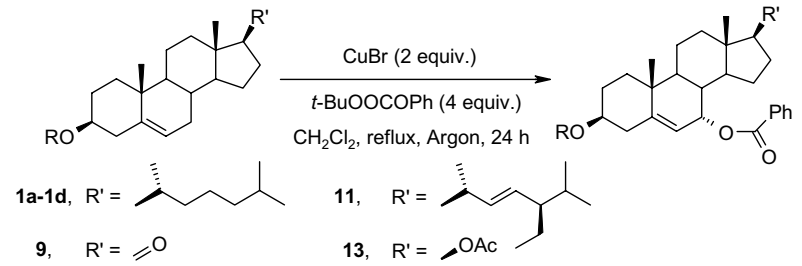


Scheme 2. Possible mechanisms for the stereoselective copper allylic benzoyloxylation of cholesteryl acetate **1**.



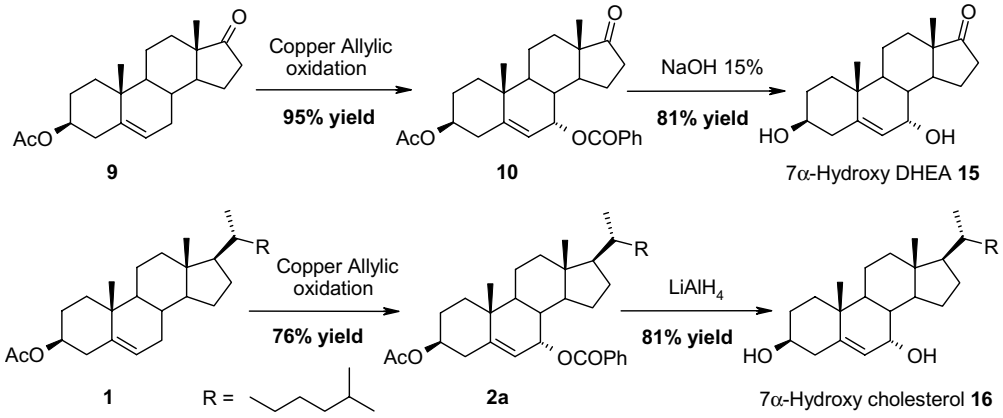
Scheme 3. Possible transition state for the total stereoselective benzoyloxylation of cholesteryl acetate **1**.

Table 3. Stereoselective copper allylic benzoyloxylation of various sterol derivatives



Entry[a]	Sterol derivative	R, Product	Yield (%)[b]	Diastereomeric ratio (α/β)[c]
1	**1a**	Ac, **2a**	76	100/0
2	**1b**	COPh, **2b**	69	100/0
3	**1c**	*tert*-Bu(Me)$_2$Si, **2c**	66	100/0
4	**1d**	H, **2d**	31	100/0
5	**9**	Ac, **10**	95	100/0
6[d]	**11**	Ac, **12**	76	100/0
7	**13**	Ac, **14**	88	100/0

[a] Reactions performed on 4.6 mmol scale in refluxing CH_2Cl_2 over 12 h under an argon atmosphere.
[b] Isolated yield after column chromatography.
[c] Diastereomeric ratio α/β determined by ^{1}H and ^{13}C NMR spectroscopy.
[d] Reaction performed over 48 h.



Scheme 4. Synthesis of 7α-hydroxy DHEA **16** and 7α-hydroxy cholesterol **17**.

has been successfully applied to the synthesis of two important oxygenated cholesterol derivatives, namely 7α-hydroxy DHEA[13] and 7α-hydroxy cholesterol[10] in a two-step synthesis with high chemical yields (77% and 61% overall yield, respectively) (Scheme 4).

3. Conclusion

In conclusion, a new efficient and totally stereoselective copper allylic benzoyloxylation of sterol derivatives has been developed. Additional studies dealing with the scope and limitations of such a reaction are under current investigation.

4. Experimental

4.1. Materials and methods

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC300 spectrometer in $CDCl_3$ as solvent. The chemical shifts (ppm) were determined relative to Me_4Si (^{1}H and ^{13}C). Toluene, tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl immediately prior to use. Ethyl acetate and petroleum ether (35–60 °C) were purchased from SDS and used without any previous purification. Column chromatography were performed on SDS silica gel (70–230 mesh).

4.2. General procedure for stereoselective copper allylic benzoyloxylation of cholesteryl acetate 1a

To a 50 mL two-necked round flask under argon were placed 2 g (4.6×10^{-3} mol) of cholesteryl acetate **1a** dissolved in 25 mL of dry CH_2Cl_2. Copper bromide (1.3 g, 9.2×10^{-3} mol) was subsequently added and the solution heated to reflux for 15 min. *tert*-Butyl peroxybenzoate (3.4 mL, 18.4×10^{-3} mol) was added dropwise and the reaction heated overnight. After completion of the reaction, the mixture was filtered through a pad of Celite. The solvents were removed in vacuo and the resulting yellow oil subjected to chromatography on silica gel column (petroleum ether/ethyl acetate = 9/1) to give the

expected 7α-benzoyloxycholesterylacetate **2a** in 76% yield. White solid; mp 74 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.01–7.42 (m, 5H), 5.73–5.21 (m, 2H), 4.68–4.57 (m, 1H), 2.38–0.66 (m, 44H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.73, 166.49, 147.35, 133.10, 131.41, 129.96, 128.74, 121.18, 73.57, 69.30, 56.42, 49.99, 43.88, 42.73, 39.83, 38.22, 37.82, 37.40, 36.60, 36.19, 28.38, 28.01, 24.46, 24.32, 23.20, 22.91, 21.71, 21.20, 19.13, 18.61, 11.88. MS *m*/*z*: 549.3 [M+1] for $C_{36}H_{52}O_4$.

4.3. Synthesis of 7α-benzoyloxycholesteryl-3β benzoate 2b

69% yield; white solid; mp 92 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.01–7.37 (m, 10H), 5.53 (m, 1H), 5.42 (m, 1H), 4.85 (m, 1H), 2.77–0.70 (m, 41H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.57, 165.10, 141.47, 132.17, 131.30, 129.84, 129.12, 124.02, 73.35, 73.01, 56.45, 55.91, 47.21, 39.90, 39.83, 37.98, 37.71, 37.36, 36.64, 28.58, 28.25, 28.10, 25.62, 24.25, 22.70, 21.90, 19.08, 11.92. MS *m*/*z*: 611.8 [M+1] for $C_{41}H_{54}O_4$.

4.4. Synthesis of 7α-benzoyloxycholesteryl-3β-*tert*-butyldimethylsilyloxy 2c

66% yield; white solid; mp 71 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.08–7.44 (m, 5H), 5.71–5.21 (m, 1H), 3.54–3.47 (m, 1H), 2.35 to −0.05 (m, 57H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.98, 166.52, 149.21, 133.28, 131.60, 130.51, 130.02, 128.71, 119.81, 72.30, 69.81, 56.49, 50.11, 43.96, 42.75, 39.85, 37.84, 38.23, 36.67, 36.21, 32.20, 30.11, 28.38, 26.29, 26.09, 24.35, 23.23, 22.94, 21.10, 19.17, 18.53, 18.24, 11.87, −4.19, −4.35. MS *m*/*z*: 621.4 [M+1] for $C_{40}H_{64}O_3Si$.

4.5. Synthesis of 7α-benzoyloxycholesteryl-3β ol 2d

31% yield; viscous oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.02–7.26 (m, 5H), 6.13–4.86 (m, 4H), 2.53–0.81 (m, 41H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.34, 142.92, 134.77, 131.06, 130.92, 129.91, 129.76, 124.76, 78.48, 75.80, 57.28, 54.69, 51.94, 51.36, 46.74, 44.67, 43.87, 40.81, 40.74, 39.01, 37.37, 37.33, 37.03, 29.42, 29.26, 29.20, 25.09, 24.07, 23.81, 21.93, 19.91, 17.54, 13.14, 13.05. MS *m*/*z*: 507.4 [M+1] for $C_{34}H_{50}O_3$.

4.6. Synthesis of 7α-benzoyloxy DHEA-acetate 10

95% yield; white solid; mp 100 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.01–7.42 (m, 5H), 5.65 (m, 1H), 5.42 (m, 1H), 4.57 (m, 1H), 2.20–0.86 (m, 26H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 220.11, 170.40, 166.80, 141.42, 132.17, 129.87, 129.12, 124.02, 74.80, 72.39, 49.59, 48.70, 46.54, 37.95, 37.71, 36.55, 35.77, 31.50, 27.70, 21.75, 21.58, 21.27, 19.04, 14.03. MS *m*/*z*: 451.1 [M+1] for $C_{28}H_{446}O_5$.

4.7. Synthesis of 7α-benzoyloxystigmasteryl-3β acetate 12

76% yield; viscous oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.20–7.48 (m, 5H), 5.75–5.25 (m, 2H), 4.55–4.75 (m, 1H), 2.49–0.63 (m, 46H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.80, 166.46, 147.34, 138.48, 133.11, 131.35, 129.98, 128.74, 121.18, 73.59, 69.27, 56.06, 51.59, 50.10, 43.89, 42.59, 40.94, 39.53, 38.22, 37.82, 36.91, 36.57, 32.23, 29.20, 27.87, 25.76, 24.52, 24.24, 21.72, 21.47, 21.19, 19.36, 18.61, 17.88, 17.68, 12.62, 12.08. MS *m*/*z*: 575.3 [M+1] for $C_{38}H_{54}O_4$.

4.8. Synthesis of 7α-benzoyloxy-5-androstene-3β,17β diacetate 14

88% yield; viscous oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.05–7.45 (m, 5H), 5.75–5.73 (m, 1H), 4.69–4.55 (m, 1H), 2.41–0.80 (m, 31H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.00, 171.09, 166.78, 147.85, 133.68, 131.38, 130.27, 129.23, 121.30, 83.15, 73.80, 68.92, 44.96, 44.55, 43.11, 38.57, 38.22, 37.13, 37.05, 36.83, 28.20, 28.04, 24.08, 22.08, 21.92, 21.05, 19.01, 12.23. MS *m*/*z*: 495.6 [M+1] for $C_{36}H_{38}O_6$.

4.9. Synthesis of 7α-hydroxy DHEA 15

77% overall yield (two steps); white solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.55 (m, 1H), 4.78 (m, 1H), 3.54 (m, 1H), 2.72–0.86 (m, 25H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 220.11, 141.00, 127.39, 74.69, 71.96, 50.13, 49.62, 48.95, 42.39, 39.40, 38.58, 32.12, 31.45, 21.90, 21.57, 19.04, 14.15. MS *m*/*z*: 305.4 [M+1] for $C_{19}H_{28}O_3$.

4.10. Synthesis of 7α-hydroxycholesteryl-3β ol 16

61% overall yield (two steps); white solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.63–5.61 (m, 1H), 3.88–3.83 (m, 1H), 3.65–3.55 (m, 1H), 2.35–0.70 (m, 43H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.65, 124.25, 71.71, 65.75, 56.25, 49.81, 42.65, 42.54, 39.92, 39.70, 37.91, 37.79, 37.50, 36.51, 36.16, 31.75, 28.67, 28.40, 24.69, 24.11, 23.20, 22.96, 21.10, 19.13, 18.64, 12.03. MS *m*/*z*: 403.3 [M+1] for $C_{27}H_{46}O_2$.

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