Mercaptolysis of the E/F Rings of Steroidal Sapogenins: A Concise Synthesis of $\Delta^{20(22)}$-Furostene-26-thioethers†

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Lewis acid catalyzed mercaptolysis of steroidal sapogenins was reinvestigated. Besides obtaining the reported 26-thioacetals 5 under milder conditions, a new type of compounds $\Delta^{20(22)}$-furostene-26-thioethers 6 were also synthesized through the mercaptolysis of steroidal sapogenins, which can be used to the synthesis of the steroidal molecule with side chains.

Keywords $\Delta^{20(22)}$-furostene-26-thioethers, steroidal sapogenin, mercaptolysis, synthesis

Introduction

Steroidal sapogenins are well known natural resource compound, which have been used as important industrial material in the production of steroid drugs due to their easy availability in large scale. In general, the production of steroidal drugs as well as the synthesis of bioactive steroids from sapogenins needs firstly to degrade the latter into the corresponding Δ^{16}-pregnene or steroid-17-one derivatives.[1] However, these routine strategies are troublesome and resource wasteful for the synthesis of steroids with an eight-carbon side chains. Comparing the side chains of the certain bioactive steroidal compounds (such as vitamin D,[2] brassinolide,[3] ecodysone,[4] cephalostatin[5] and OSW-1[6]) with the imagined opening-chain type of the E/F spiroketal ring in steroidal sapogenin, it is easy to find that both possess very similar structural features. In order to explore more efficient ways of synthesizing steroids described above directly from sapogenins rather than their degraded products, we reinvestigate Lewis acid catalyzed mercaptolysis of steroidal sapogenins[7] in milder reaction conditions. In the course of our study, not only the previously reported 26-thioacetals **5** under milder reaction conditions were obtained, but also a concise method for the synthesis of a new type of steroidal compound, $\Delta^{20(22)}$-furostene-26-thioethers **6** was provided. $\Delta^{20(22)}$-Furostene-26-thioethers thus obtained have potential application in the synthesis of marine steroidal compounds with special bioactivities.

Results and discussion

The spiroketal ring system of steroidal sapogenin is usually stable to most reagents. However, the C-23-deuterium or bromine substitution,[9] Clemmensen reduction[10] and the isomerization of rings E/F[11] all indicated that there existed an equilibrium between the spiroketal **1** and their open side-chain tautomer **2** in acidic solution. On the basis of this hypothesis, it is possible to obtain **3** or **4** if the two hydroxyl groups at C-16 and C-26 or the carbonyl at C-22 are protected efficiently in this equilibrium (Scheme 1).

Being unable to convert sapogenin into **3**,[12] we turn our attention to the convertion of **1** into **4** although this reaction has been reported by Djerassis.[7] This is due to the fact that, firstly, the thioketals are generally more stable than ketals under acidic conditions; secondly, even some stable intramolecular ketals can also be converted into thioketals.[13] In order to find an approach for the conversion of rings E/F in sapogenin into the corresponding compound **4** with the open side-chains, the reaction of sapogenins **1a**—**1d** (**1a**, diosgenin; **1b**, diosgenin acetate; **1c**, tigogenin; **1d**, tigogenin acetate) with a variety of mercaptans (such as propane-1, 3-dithiol, ethyldithiol, benzyl mercaptan and thiophenol) in the presence of various acidic catalysts was studied. The results of the reaction of steroidal sapogenins and propane-1, 3-dithiol catalyzed by various acids are shown in Table 1.

As shown in Table 1, all Lewis acid catalyzed reaction can carry out at room temperature when using 3 equivalent of thiols in suitable solvents instead of thiols as reaction medium. This procedure remarkably differs from that reported by Djerassi. When Brønsted acid is used as catalyst, however, higher reaction temperature is required. According to our research result, boron trifluoride etherate seems to be the best Lewis acid catalyst for the mercaptolysis of sapogenins.

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Scheme 1

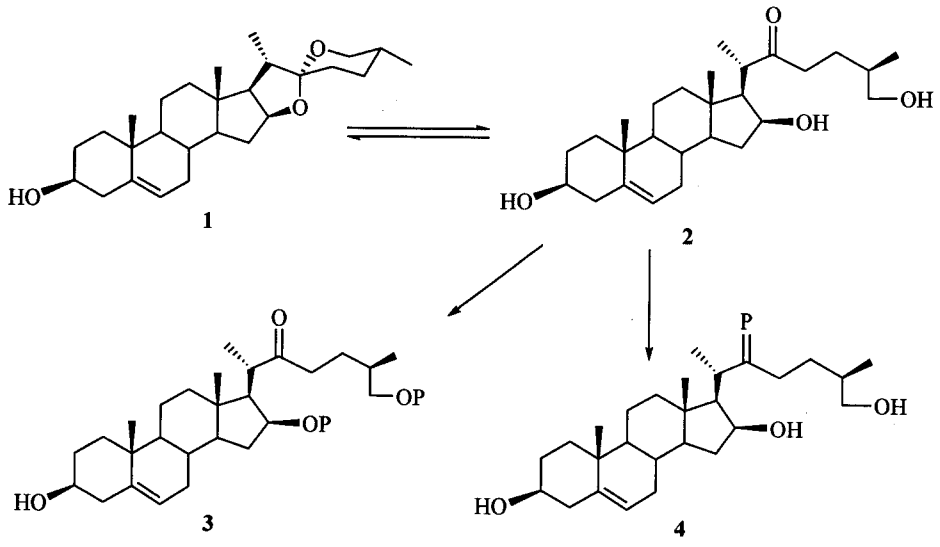
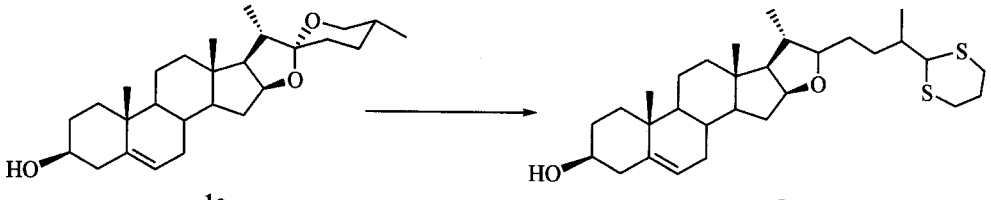


Table 1 Reaction of steroidal sapogenins and propanadithiol catalyzed by various acids



Acid catalyst	$TiCl_4$	$ZnCl_2$	$SnCl_4$	$BF_3 \cdot Et_2O$	HCl	CF_3COOH
Temperature (℃)	25	25	25	25	97	110
Time (h)	48	96	72	33	10	96
Yield (%)	75	40	20	90	37	34

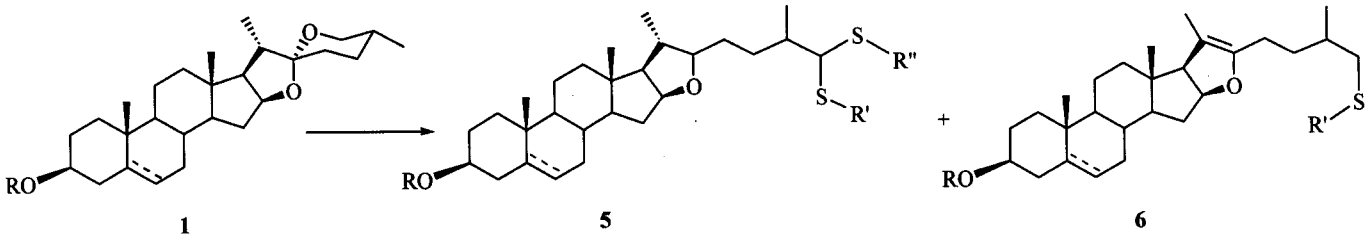
Further studies indicated that mercaptolysis of sapogenins depended on not only the used mercaptans but also the substrate/mercaptan ratio used in the reaction. When dithiols, such as propane-1,3-dithiol and ethyldithiol were used, 26-thioacetal **5** was obtained as the sole product and the result was not affected by the amount of mercaptans used. 26-Thioacetal **5** is a single isomer and its configuration at C-22 was preferably assigned as *R* according to its ^1H NMR spectrum.[15] For the mercaptolysis of sapogenins with thiophenol or benzyl mercaptan, product 26-thioacetal **5** was always accompanied by a new type of compound $\Delta^{20(22)}$-furostene-26-thioethers **6**. The yield of **6** is related to the substrate/mercaptan ratio. Increasing the amount of thiophenol or benzyl mercaptan used in reaction favored the formation of 26-acetal **5**, decreasing the amount of thiophenol or benzyl mercaptan resulted in $\Delta^{20(22)}$-furostene-26-thioethers **6** as main product. The results of the reaction of sapogenins with a variety of mercaptans are listed in Table 2.

Based on the facts mentioned above, a plausible mechanism for such reaction is proposed (Scheme 2). According to Pearson's principle of hard and soft acids and bases (HSAB principle),[14] the initial attack of softer sulfur could be considered to occur at the softer C-26 instead of C-22 to give an intermediate **7**, which might be in equilibrium with **8** via 1, 5-proton shift. For the reaction of steroidal sapogenin with dithiols or an excess of thiophenol or benzyl mercaptan, the further reaction of intermediate **8** with another sulfur through intramolecular (for dithiols) or intermolecular (for thiophenol or benzyl mercaptan) resulted in the formation of 26-thioacetal **5**. In the case of lacking enough mercaptans, the leave of the proton at C-20 of intermediate **7** afforded $\Delta^{20(22)}$-furostene-26-thioethers **6** as main product. Another important reason for only obtaining **5** and **6** rather than the expected C-22 thioketal in this reaction could be attributed to the steric hindrance at C-22 of sapogenins.

Experimental

All melting points are uncorrected. ^1H NMR spectra were obtained on a Varian XL-200 instrument with $CDCl_3$ as solvent and internal TMS as standard. IR spectra were recorded as KCl plate on a Shimadzu IR-440 Spectrometer.

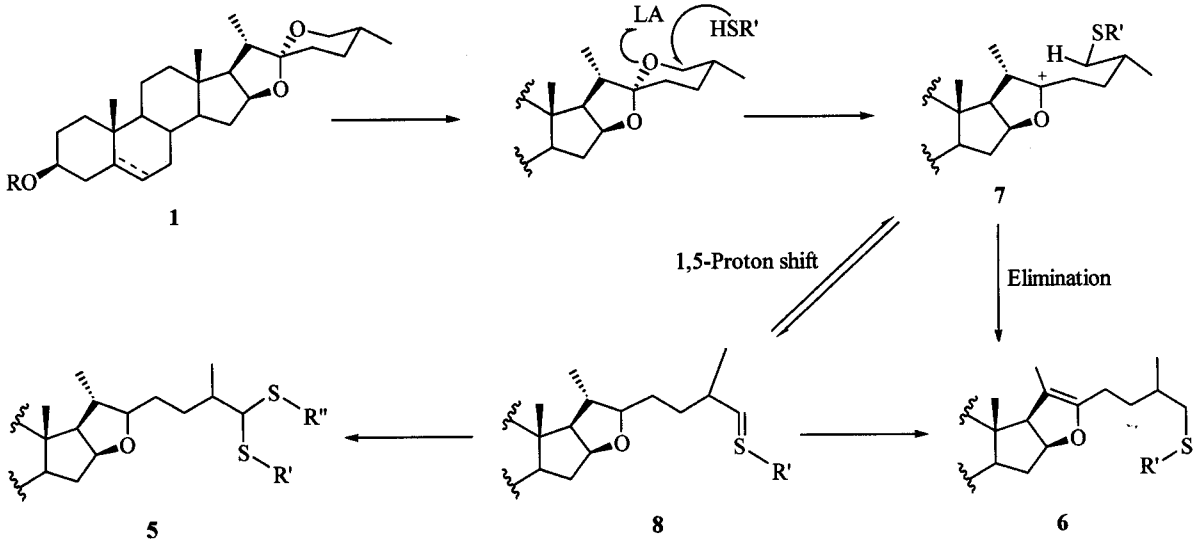
Table 2 Reaction of sapogenins with a variety of mercaptans



1 5 6

Entry	Substrate	Mercaptans (the ratio of substrate to mercaptan)	Product & yield (%)[b]
1	1a, R = H; $\Delta^{5(6)}$	Propane-1,3-dithiol (1:3)	5a (90.2), R = H; R', R" = 1,3-propylen; $\Delta^{5(6)}$
2	1a, R = H; $\Delta^{5(6)}$	Thiophenol (1:5)	5b (87), R = H; R', R" = Phenylthio; $\Delta^{5(6)}$
			6a (10) R = H; R', R" = Phenylthio; $\Delta^{5(6)}$, $^{20(22)}$
3	1a, R = H; $\Delta^{5(6)}$	Benzyl mercaptan (1:5)	5c (70.2), R = H; R', R" = Benzylthio; $\Delta^{5(6)}$
			6b(16), R = H; R' = Benzylthio; $\Delta^{5(6)}$, $\Delta^{20(22)}$
4	1a, R = Ac; $\Delta^{5(6)}$	Propane-1,3-dithiol (1:3)	5d (94), R = H; R', R" = 1,3-propylen; $\Delta^{5(6)}$
5	1a, R = Ac; $\Delta^{5(6)}$	Ethanedithiol (1:3)	5e (92), R = H; R', R" = 1,2-ethanelen; $\Delta^{5(6)}$
6	1a, R = Ac; $\Delta^{5(6)}$	Benzyl mercaptan (1:6)	5f (81), R = H; R', R" = Benzylthio; $\Delta^{5(6)}$
			6c (10), R = H; R' = Benzylthio; $\Delta^{5(6)}$, $\Delta^{20(22)}$
7	1a, R = Ac; $\Delta^{5(6)}$	Benzyl mercaptan (1:3)	5f (43), R = H; R', R" = Benzylthio; $\Delta^{5(6)}$
			6c (41), R = H; R' = Benzylthio; $\Delta^{5(6)}$, $\Delta^{20(22)}$
8	1a, R = Ac; $\Delta^{5(6)}$	Benzyl mercaptan (1:1.2)	5f (10), R = H; R', R" = Benzylthio; $\Delta^{5(6)}$
			6c (80), R = H; R' = Benzylthio; $\Delta^{5(6)}$, $\Delta^{20(22)}$

Scheme 2 A plausible mechanism for the mercaptolysis of sapogenins



when R' = dithiols, or an excess of thiols used when R' ≠ dithiols, no excess of thiols used

Mass spectra were recorded on a Finnigan 4021 mass spectrometer. All new products are fully characterized by ^{1}H NMR, IR, MS and elemental analyses.

Typical procedure for the reaction of steroidal sapogenins **1** *with mercaptans*

To a mixture of steroidal sapogenin **1** (1 mmol) and mercaptan (1.2—5 mmol) in dichloromethane (5 mL) at 0 ℃, boron trifluoride ethereal was added dropwise. The reaction mixture was allowed to stirred at room temperature until the complete conversion of the starting marterial as indicated by TLC. Work-up in the usual way then provided the pure products **5** or **6**.

3β-Hydroxyl-$\Delta^{5(6)}$-furostene-26-propylenethioacetal (**5a**) Yield 90.2%, m.p. 124—125 ℃; [α]^{20}

-38.30 (c 0.55, $CHCl_3$); ^1H NMR (90 MHz) δ: 5.30 (s, 1H, 6-H), 4.20—4.32 (m, 1H, 16-H), 4.17 (d, J = 3.8 Hz, 1H, 26-H), 3.45 (m, 1H, 3-H), 3.20—3.40 (m, 1H, 22-H), 2.80—3.00 (m, 4H, RS-CH_2), 1.62 (s, 1H, OH), 1.02—0.8 (m, 12H, 4 × CH_3); IR ν_{max}: 3400 (OH), 3010 (C = CH), 2900 (C—H), 1450, 1380 (C—C), 1060 (C—O) cm^{-1}; MS m/z (%): 504 (M^+, 40), 487 (M^+ - OH, 38), 429 [M^+ - $(CH_2)_3SH$, 20], 411 [M^+ - $(CH_2)_3SH$ - H_2O], 396 [M^+ - $(CH_2)_3SH$ - SH], 355 (16), 271 (30), 120 (100). Anal. calcd for $C_{30}H_{48}O_2S_2$: C 71.42, H 9.52, S 12.66; found C 70.77, H 9.33, S 12.67.

3β-Hydroxyl-Δ$^{5(6)}$-furostene-26-diphenylthioacetal (**5b**) Yield 87%, m.p. 140—143 ℃; $[\alpha]^{20}$ - 40.5 (c 0.69, $CHCl_3$); ^1H NMR (200 MHz) δ: 7.39, 7.25 (m, 10H, Ar-H), 5.30—5.40 (m, 1H, 6-H), 4.50 (d, J = 4.0 Hz, 1H, 26-H), 4.20—4.30 (m, 1H, 16-H), 3.42—3.58 (m, 1H, 3-H), 3.19—3.29 (m, 1H, 22-H), 1.14—0.78 (m, 12H, 4 × CH_3); IR ν_{max}: 3500, 3010, 2900, 1600, 1500, 1450, 1380, 1050 cm^{-1}; MS m/z (%): 616 (FAB, M^+), 615 (M^+ - 1), 507 (M^+ - SPh, 100), 489 (M^+ - SPh - H_2O), 355 [M^+ - $CH_3CHCH(SPh)_2$], 253. Anal. calcd for $C_{39}H_{52}O_2S_2$: C 75.70, H 8.76, S 10.04; found C 75.44, H 8.71, S 10.92.

3β-Hydroxyl-Δ$^{5(6)}$-furostena-26-dibenzylthioacetal (**5c**) Yield 70.2%, m.p. 125—127 ℃; $[\alpha]^{20}$ - 46.5 (c 0.70, $CHCl_3$); ^1H NMR (200 MHz) δ: 7.10—7.40 (m, 10H), 5.36 (m, 1H), 4.27—4.37 (m, 1H, 16-H), 3.70 (d, J = 4.0 Hz, 4H, SCH_2Ph), 3.54 (m, 1H, 3-H), 3.46 (d, J = 4.0 Hz, 1H, 26-H), 3.10—3.30 (m, 1H, 22-H), 1.04—0.8 (m, 12H, 4 × CH_3); IR ν_{max}: 3350, 2900, 1460, 1380, 1050 cm^{-1}; MS m/z (%): 644 (M^+, 2.4), 553 (M^+ - CH_2Ph, 1.9), 521 (M^+ - SCH_2Ph, 63.8), 503 (M^+ - SCH_2Ph - H_2O, 100), 355 (27.7), 397 (15.0), 271, 253. Anal. calcd for $C_{41}H_{56}O_2S_2$: C 76.40, H 8.70, S 9.94; found C 76.01, H 8.55, S 9.40.

3β-Acetoxyl-Δ$^{5(6)}$-furostena-26-propylenethioacetal (**5d**) Yield 94%, m.p. 153—154 ℃; $[\alpha]^{20}$ - 42.90 (c 0.978, $CHCl_3$); ^1H NMR (90 MHz) δ: 5.35 (s, 1H), 4.40—4.60 (m, 1H), 4.20—4.30 (m, H), 4.15 (d, J = 3.8 Hz, 1H), 3.20—3.40 (m, 1H), 2.02 (s, 3H, $OCCH_3$), 2.80—3.00 (m, 4H), 1.02—0.8 (m, 12H, 4 × CH_3); IR ν_{max}: 2900 (C—H), 1700, 1245 (COOR), 1450, 1380 (C—C), 1040 (C—O) cm^{-1}; MS m/z (%): 547 (M^+ + 1, 14), 546 (M^+, 32), 531 (M^+ - CH_3), 486 (M^+ - AcOH, 9.5), 471 [M^+ - $(CH_2)_3SH$, 15.6], 397 (9.1), 313 (11.2), 120 (100). Anal. calcd for $C_{32}H_{50}O_3S_2$: C 70.33, H 9.16, S 11.77; found C 70.33, H 9.27, S 11.77.

3β-Acetoxyl-Δ$^{5(6)}$-furostena-26-ethylenethioketal (**5e**) Yield 92%, m.p. 140—141 ℃; $[\alpha]^{20}$ - 30.80 (c 0.65, $CHCl_3$); ^1H NMR (90 MHz) δ: 5.40 (s, 1H), 4.50—4.70 (m, 1H), 4.55 (d, J = 6.2 Hz, 1H), 4.20—4.30 (m, 1H), 3.29—3.39 (m, 1H), 2.02 (s, 3H), 3.10—3.30 (m, 4H, $RSCH_2$), 1.02—0.8 (m, 12H, 4 × CH_3); IR ν_{max}: 2940, 1720, 1450, 1380, 1240, 1040 cm^{-1}; MS m/z (%): 533 (M^+ + 1, 1.0), 473 (M^+ - OAc), 457 (M^+ - HOAc - CH_3, 7.5), 411 [M^+ - $(CH_2)_2SH$, 34], 313 (24), 105 [$CH_2(SCH_2)_2^+$, 100]. Anal. calcd for $C_{31}H_{48}O_3S_2$: C 69.92, H 9.02, S 12.03; found C 70.34, H 8.95, S 12.18.

3β-Acetoxyl-Δ$^{5(6)}$-furostene-26-dibenzylthioketal (**5f**) Yield 81%, m.p. 92.6—95.8 ℃; $[\alpha]^{20}$ - 73.9 (c 0.75, $CHCl_3$); ^1H NMR (200 MHz) δ: 7.10—7.40 (m, 10H, Ar-H), 5.35—5.45 (m, 1H, 6-H), 4.50—4.70 (m, 1H, 3H), 4.27—4.37 (m, 1H, 16-H), 3.70 (d, 4H, SCH_2Ph), 3.46 (d, 1H, J = 4.0 Hz, 26-H), 3.10—3.30 (m, 1H, 22-H), 2.02 (s, 3H, CH_3COO), 1.04—0.8 (m, 12H, 4 × CH_3); IR ν_{max}: 3050, 1600, 1500, 1450 (Ar-H), 1760, 1240 (COOR), 2950, 1460, 1380, 1040 cm^{-1}; MS m/z (%): 686 (FAB, M^+), 685 (M^+ - 1), 595 (M^+ - CH_2Ph, 5.2), 563 (M^+ - SCH_2Ph, 60), 503 (M^+ - SCH_2Ph - HOAc, 2.0), 471 [M^+ - CH_2Ph, 17.6], 397 (15.0), 313, 253. Anal. calcd for $C_{43}H_{58}O_3S_2$: C 75.20, H 8.48, S 9.22; found C 74.78, H 9.34, S 9.37.

3β-Hydroxy-Δ$^{5(6),20(22)}$-furostene-26-phenylthioether (**6a**) m.p. 106—108 ℃; $[\alpha]^{20}$ - 26.8 (c 0.85, $CHCl_3$); ^1H NMR (200 MHz) δ: 7.10—7.40 (m, 5H), 4.20—4.30 (m, 1H, 16-H), 3.52—3.68 (m, 1H, 3-H), 3.0, 2.84 (2d, J = 4.0, 2.0 Hz, 2H, 26-H), 1.60 (s, 3H, 21-H), 1.10—0.7 (m, 9H, 3 × CH_3); IR ν_{max}: 3400, 2950, 1380, 1050 cm^{-1}; MS m/z (%): 508 (M^+, 10), 398 (M^+ - SPh, 1.0), 355 (M^+ - $CH_3CH_2CH_2SPh$, 1.4), 343 (5.0), 273 (3.6).

3β-Hydroxy-Δ$^{5(6),20(22)}$-furostenae-26-benzylthioether (**6b**) m.p. 105—108 ℃; $[\alpha]^{20}$ - 30.3 (c 0.63, $CHCl_3$); ^1H NMR (200 MHz) δ: 7.10—7.40 (m, 5H,) 5.32—5.40 (m, 1H, 5-H), 4.66—4.82 (m, 1H, 16-H), 3.70 (s, 2H), 3.40—3.60 (m, 1H, 3-H), 1.56 (s, 3H, 21-H), 1.02—0.7 (m, 9H, 3 × CH_3); IR ν_{max}: 3400, 2950, 1450, 1380, 1050 cm^{-1}; MS m/z (%): 521 (M^+ + 1, 25.0), 429 (M^+ - CH_2Ph, 100), 411 (M^+ - CH_2Ph - H_2O, 15.3), 341, 195, 91 (98.5). Anal. calcd for $C_{34}H_{48}O_2S$: C 78.46, H 9.23, S 6.15; found C 77.98, H 9.73, S 6.67.

3β-Acetoxyl-Δ$^{5(6),20(22)}$-furostene-26-benzylthioether (**6c**) Yield 87%, m.p. 101—104 ℃; $[\alpha]^{20}$ - 38.8 (c 0.75, $CHCl_3$); ^1H NMR (200 MHz) δ: 7.10—7.40 (5H, Ar-H), 5.33—5.63 (m, 1H, 6-H), 4.66—4.82 (m, 1H, 3-H), 4.50—4.70 (m, 1H, 16-H), 3.70 (s, 2H, SCH_2Ph), 2.02 (s, 3H, $OCCH_3$), 1.56 (s, 3H, 21-H), 1.02—0.7 (m, 9H, 3 × CH_3); IR ν_{max}: 3050, 1600, 1500, 1450 (Ar-H), 1760, 1240 (COOR), 2950, 1460, 1380, 1040 cm^{-1}; MS m/z (%): 562 (M^+, 10.0), 519 (M^+ - CH_3CO, 2.3), 502 (M^+ - AcOH, 4.1), 487 (M^+ - AcOH - CH_3, 2.0), 471 (M^+ - Ph, 20.6), 438 (M^+ - HSPh), 411 (M^+ - Ph - HOAc, 17.6), 313 (13.0), 253. Anal. calcd for $C_{36}H_{50}O_3S$: C 76.86, H 8.89, S 5.69; found C 76.30, H 8.91, S 6.13.

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