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SYNTHESIS OF CONJUGATE ESTERS OF 5-(4-HYDROXYPHENYL)-3*H*-1,2-DITHIOLE-3-THIONE AND URSOLIC ACID 3-*O*-ACYL DERIVATIVES

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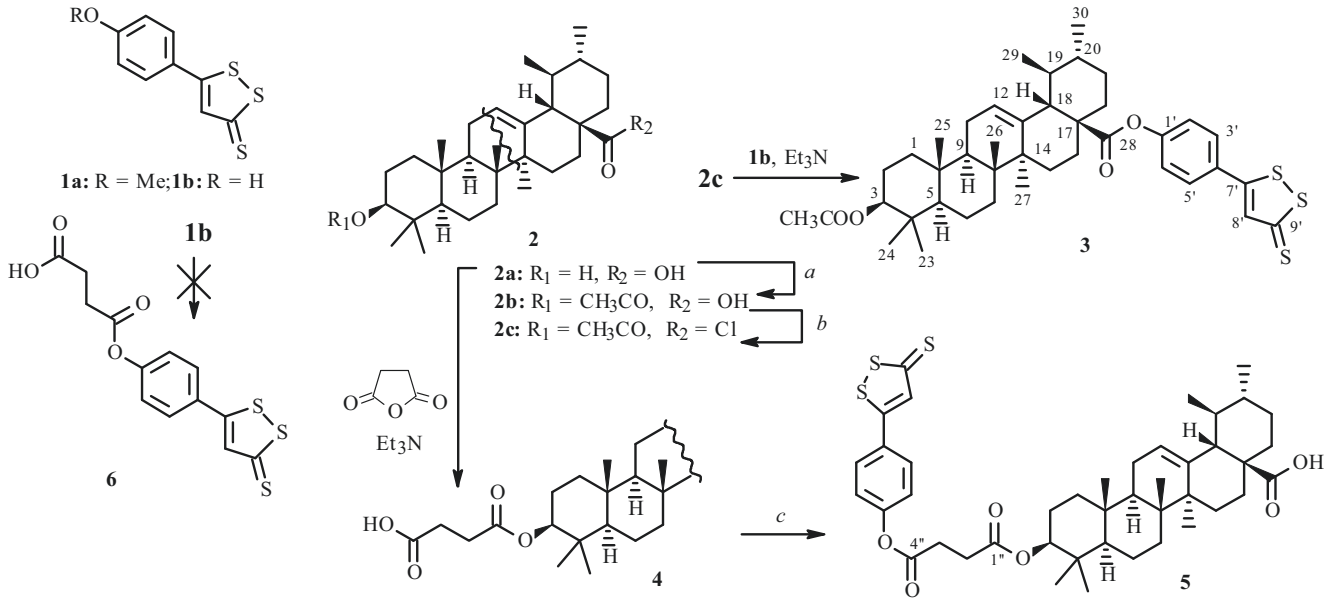
Chemical conjugates of H_2S-donors and non-steroidal anti-inflammatory drugs (NSAIDs) are being investigated as anti-inflammatory and chemoprevention agents [1]. Dithiolethiones, in particular 5-(4-methoxyphenyl)-3*H*-1,2-dithiole-3-thione (**1a**, ADT), are H_2S donors and exhibit marked antioxidant activity (free-radical binding, lipid peroxidation inhibition) [2]. Desmethylanethol trithione (**1b**, ADTOH) is a known ADT metabolite and is used as a synthon to prepare new promising NSAID conjugate derivatives [3]. Available triterpenoids such as ursolic acid (UA, **2a**) and its synthetic derivatives were also reported to have anti-inflammatory, antioxidant, and antitumor activity [4].



a. Py, Ac_2O; *b*. $SOCl_2$; *c*. **1b**, DCC, DMAP

Triterpenoid conjugate derivatives were reported to have a higher level of chemoprotection and lower toxicity than the precursor compounds [5]. Therefore, it seemed interesting to prepare molecules combining the natural compound **2a** and **1b** as the H_2S donor. For this, we synthesized conjugate esters of UA 3-*O*-acyl derivatives with 5-(4-hydroxyphenyl)-3*H*-1,2-dithiole-3-thione (**1b**) with the *S*-containing substituent in different positions relative to the triterpenoid scaffold.

ADTOH was prepared from anethole as before [6]. 3-*O*-Acyl derivatives **2b** and **4** were prepared by treating UA with Ac_2O and succinic anhydride in the presence of Et_3N, respectively. The triterpenoid C-28 ester was synthesized via the reaction of 3-*O*-acetylursolyl chloride (**2c**) with ADTOH. A solution of **2b** (0.45 g, 0.9 mmol) in thionylchloride (3.3 g, 27 mmol) was held for 6 h at 20–25°C and concentrated *in vacuo* at ≤40°C to afford **2c** as a yellow glassy substance that was used immediately without further purification to produce ester **3**. A solution of **2c** in CH_2Cl_2 (5 mL) was treated over 15 min

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with a solution of **1b** (0.20 g, 0.9 mmol), 4-dimethylaminopyridine (1 mg), and Et_3N (2 mL) in CH_2Cl_2 (5 mL) at 15–25°C, stirred for 4–6 h, and concentrated *in vacuo*. The residue was dissolved in MTBE, washed with HCl (2 N, 10 mL) and NaOH (2 N, 10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was chromatographed (SiO_2, CH_2Cl_2) to afford 28-[4-(3*H*-1,2-dithiole-3-thione-5-yl)phenyl]-3β-acetoxyurs-12-en-28-oate (**3**) as a red powder (0.52 g, 81%), mp 142°C. Mass spectrum *m/z* (I_{rel}, %): 706 (M^+, 1), 582 (4), 554 (5), 525 (2), 496 (1), 466 (4), 453 (18), 438 (4), 393 (6), 303 (6), 301 (4), 276 (4), 262 (7), 248 (87), 216 (23), 203 (100), 189 (59), 133 (60), 119 (39), 107 (36), 81 (42), 69 (53), 55 (47), 43 (68). Found [M] 706.3171, $C_{41}H_{54}O_4S_3$, calcd 706.3179. IR spectrum (KBr, ν, cm^{-1}): 3435, 2968, 2947, 2926, 2872, 1734, 1659, 1639, 1601, 1526, 1493, 1456, 1412, 1389, 1369, 1308, 1248, 1211, 1180, 1167, 1144, 1130, 1109, 1090, 1074, 1028, 984, 966, 951, 941, 897, 856, 839, 808, 791, 733, 696, 677. UV spectrum (MeOH, λ_{max}, nm) (log ε): 433 (3.9), 321 (4.23), 275 (3.92), 229 (4.07). ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.83 (3H, s, H-26[§]), 0.83 (3H, s, H-25[§]), 0.84 (3H, s, H-24[§]), 0.87 (3H, d, $J_{29,19}$ = 6.4, H-29), 0.92 (3H, s, H-23[§]), 0.95 (3H, d, $J_{A,B}$ = 6.3, H-30), 1.10 (3H, s, H-27), 2.02 (3H, s, OCOC$\underline{H}_3$), 2.31 (1H, br.d, $J_{18,19}$ = 11.3, H-18), 4.47 (1H, dd, $J_{3,2ax} = J_{3,2eq}$ = 8.0, H-3), 5.30 (1H, dd, $J_{12,11ax} = J_{12,11eq}$ = 3.5, H-12), 7.12 (2H, d, $J_{2',3'} = J_{6',5'}$ = 8.7, H-2′, 6′), 7.35 (1H, s, H-8′), 7.62 (2H, d, $J_{3',2'} = J_{5',6'}$ = 8.7, H-3′, 5′). ^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 15.4 (q, C-25), 16.6 (q, C-24[§]), 16.8 (q, C-26[§]), 17.4 (q, C-29), 18.0 (t, C-6), 21.0 (q, C-30[#]), 21.1 (q, OCO$\underline{C}H_3$[#]), 23.2 (t, C-11[‡]), 23.3 (q, C-27), 23.4 (t, C-2[‡]), 24.1 (t, C-16[‡]), 26.8 (q, C-23), 27.9 (t, C-15), 30.4 (t, C-21), 32.9 (t, C-7), 36.4 (t, C-22), 36.7 (s, C-10[¶]), 37.5 (s, C-4[¶]), 38.2 (t, C-1), 38.7 (d, C-20[†]), 38.9 (d, C-19[†]), 39.6 (s, C-8), 42.0 (s, C-14), 47.3 (d, C-9), 48.6 (s, C-17), 52.8 (d, C-18), 55.1 (d, C-5), 80.7 (d, C-3), 122.8 (dd, C-2′, 6′), 125.9 (d, C-12), 127.9 (dd, C-3′, 5′), 128.7 (s, C-4′), 135.7 (d, C-8′), 137.5 (s, C-13), 154.0 (s, C-1′), 170.6 (s, O$\underline{C}OCH_3$[*]), 171.7 (s, C-7′[*]), 175.3 (s, C-28[*]), 215.2 (s, C-9′) (assignments for atoms in PMR and ^{13}C NMR spectra marked with the same symbols [§,#,‡,¶,†,*] may be interchanged).

UA succinate (**4**) reacted regioselectively with ADTOH in the presence of dicyclohexylcarbodiimide (DCC) to form a disubstituted succinic acid ester with a free C-28 carboxylic acid. A mixture of **4** (0.2 g, 0.36 mmol), **1b** (0.081 g, 36 mmol), and 4-dimethylaminopyridine (1 mg) in CH_2Cl_2 (10 mL) at 0°C was treated with a solution of DCC (0.078 g, 0.38 mmol) in CH_2Cl_2 (2 mL), stirred for 6 h at 0–20°C, washed with HCl solution (1 N, 10 mL) and H_2O (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The concentrate was chromatographed (SiO_2, CH_2Cl_2) to afford 3β-*O*-{4-oxo-4-[4-(3*H*-1,2-dithiole-3-thione-5-yl)phenoxy]butanoyl}ursolic acid (**5**, 0.21 g, 75%) as a red powder, mp 231–233°C. Mass spectrum *m/z* (I_{rel}, %): 764 (M^+, 0.1), 510 (1), 440 (1), 438 (6), 423 (3), 395 (1), 390 (2), 377 (1), 369 (1), 327 (1), 308 (1), 307 (4), 300 (4), 248 (100), 226 (82), 203 (79), 200 (55), 190 (49), 161 (90), 133 (82), 118 (36), 107 (23), 101 (43), 95 (23), 81 (23), 69 (31), 55 (24). Found [M] 764.3259, $C_{43}H_{56}O_6S_3$, calcd 764.3234. IR spectrum (KBr, ν, cm^{-1}): 3325, 2968, 2926, 2872, 2855, 1763, 1730, 1692, 1626, 1601, 1580, 1526, 1491, 1456, 1412, 1387, 1369, 1313, 1275, 1254, 1211, 1182, 1169, 1128, 1028, 986, 966, 949, 924, 910, 895, 833, 806, 789, 756, 694, 662, 629, 571, 538, 515. UV spectrum (MeOH, λ_{max}, nm) (log ε): 433 (3.73), 321 (4.0), 274 (3.69), 230 (3.85), 203 (4.09). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.73 (3H, s, H-26[§]), 0.84 (3H, s, H-25[§]), 0.84 (3H, s, H-24[§]), 0.84 (3H, d, $J_{29,19}$ = 6.5, H-29), 0.92 (3H, d, $J_{A,B}$ = 6.1, H-30), 0.93 (3H, s, H-23[§]), 1.04 (3H, s, H-27), 2.15 (1H, br.d, $J_{18,19}$ = 11.3, H-18), 2.73 (2H, m, H-2″[#]), 2.89 (2H, m, H-3″[#]), 4.54 (1H, dd, $J_{3,2ax} = J_{3,2eq}$ = 7.6, H-3), 5.20 (1H, m, H-12), 7.21 (2H, d, $J_{2',3'} = J_{6',5'}$ = 8.5, H-2′, 6′), 7.37 (1H, s, H-8′), 7.65 (2H, d, $J_{3',2'} = J_{5',6'}$ = 8.5, H-3′, 5′), 11.67 (1H, br.s, COO$\underline{H}$). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 15.4 (q, C-25), 16.6 (q, C-24[§]), 16.9 (q, C-26[§]), 16.9 (q, C-29[§]), 18.0 (t, C-6), 21.0 (q, C-30), 23.1 (t, C-11[#]), 23.4 (t, C-2[#]), 23.4 (q, C-27), 23.8 (t, C-16[#]), 27.8 (t, C-15), 28.0 (q, C-23), 29.2 (t, C-3″), 29.3 (t, C-2″), 30.4 (t, C-21), 32.6 (t, C-7), 36.5 (t, C-22), 36.7 (s, C-10[‡]), 37.6 (s, C-4[‡]), 38.0 (t, C-1), 38.6 (d, C-20[¶]), 38.8 (d, C-19[¶]), 39.3 (s, C-8), 41.7 (s, C-14), 47.3 (d, C-9), 47.8 (s, C-17), 52.3 (d, C-18), 55.1 (d, C-5), 81.5 (d, C-3), 122.7 (dd, C-2′, 6′), 125.5 (d, C-12), 128.1 (dd, C-3′, 5′), 129.1 (s, C-4′), 135.9 (d, C-8′), 137.8 (s, C-13), 153.4 (s, C-1″), 170.4 (s, C-4″[†]), 171.5 (s, C-7′[†]), 171.6 (s, C-1″[†]), 184.0 (s, C-28), 215.3 (s, C-9′) (assignments for atoms in PMR and ^{13}C NMR spectra marked with the same symbols [§,#,‡,¶,†] may be interchanged).

An attempt to prepare monosubstituted succinate **6** by acylation of **1b** was unsuccessful. Compound **6** was exclusively easily hydrolyzed and always gave quantitative yields of starting **1b**. The acetyl protection was removed from **3** using NaOH–MeOH–dioxane. However, several products from partial destruction of the *S*-containing heterocycle by the base were apparently formed. Hydrolysis of succinate **5** in this system gave UA succinate (**4**), ADTOH (**1b**), and a small amount of UA (**2a**).

The synthesized ursolic acid conjugate derivatives with *S*-containing substituents in different positions relative to the terpene scaffold are interesting as potential anti-inflammatory and chemoprevention agents.

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