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Mendeleev Commun., 2017, **27**, 93–94
Mendeleev Communications

Betulin esters with coumarin-3-carboxylic and 3,4,5-trimethoxybenzoic acids

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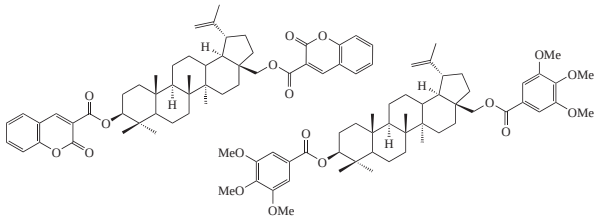
DOI: 10.1016/j.mencom.2017.01.030

Direct esterification of betulin with coumarin-3-carboxylic or 3,4,5-trimethoxybenzoic acid led to betulin-28-esters and betulin-3,28-diesters. The betulin-3-esters were synthesized through 28-O-protection, esterification and deprotection steps using betulin as a starting material.

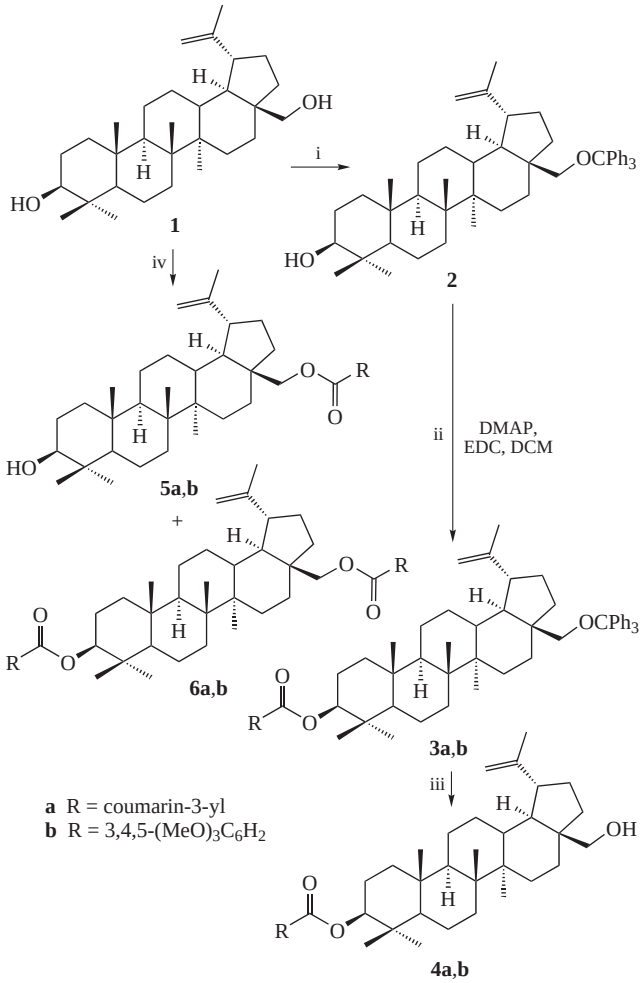


Recent studies have found that betulin derivatives exhibit a broad variety of bioactivities, including anti-HIV,[1,2] antitumor,[3,4] and anti-inflammatory.[5] More importantly, in antitumor and anti-AIDS, betulin derivatives have a different mechanism of action as compared to other drugs, a good targeting efficiency, and little or no adverse reaction.[6,7]

A 3D-QSAR study of several betulinic acid derivatives has been reported.[8] The result showed that the electron-withdrawing, hydrophilic and hydrogen bond donor substituents in C-3 and C-28 positions were essential for excellent anti-HIV-1 potency. On the basis of the above findings, we designed 3-OH and 28-OH structural modification of betulin with small molecular groups exhibiting anti-HIV,[9,10] antitumor,[11] and anti-inflammatory activities,[12,13] such as coumarin-3-carboxylic acid and 3,4,5-trimethoxybenzoic acid.

Betulin ester **5b** was synthesized through the esterification of betulin and acid chloride.[14] To simplify the procedure, in the present study we prepared betulin esters using direct reaction between betulin and acid (Scheme 1).† Because of the different activity of two hydroxyl groups, only esters **5** and diesters **6** were obtained. The reaction conditions were screened to find the optimal 2.5–3 equiv. acid in CH_2Cl_2 at room temperature.

The 28-*O*-tritylbetulin **2** was prepared according to the reported procedure.[15] Reaction of compound **2** with the corresponding acid in the presence of 4-dimethylaminopyridine (DMAP) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide-HCl (EDC-HCl) produced betulin esters **3a** and **3b**, in moderate



Scheme 1 *Reagents and conditions*: i, Ph_3CCl, Py, DMAP, 90 °C, 18 h; ii, RC(O)OH, DMAP, EDC, CH_2Cl_2, room temperature, 24 h; iii, PPTS, CH_2Cl_2–EtOH, reflux, 24 h; iv, RC(O)OH, DMAP, EDC, CH_2Cl_2, room temperature, 24 h.

† *General procedure for the esterification of betulin derivatives*. DMAP (3.0–4.8 mmol), the corresponding acid (2.5–3.0 mmol) and EDC-HCl (3.0–4.8 mmol) were added to a solution of 28-tritylbetulin (or betulin) (1 mmol) in dry CH_2Cl_2 (20 ml). The mixture was stirred at room temperature. Reaction completion was monitored by TLC. The mixture was quenched by addition of water (20 ml). The organic layer was washed with saturated sodium bicarbonate (20 ml) and brine (20 ml), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography with ethyl acetate–light petroleum as an eluent to give compounds **3**, **5**, **6**.

3-O-*(Coumarin-3-ylcarbonyl)-28*-O-*tritylbetulin* **3a**. White solid, yield 90%, mp 159–160 °C. IR (KBr, ν/cm^{-1}): 3059, 2940, 1759, 1707, 1449, 1242. ^{1}H NMR ($CDCl_3$) δ: 8.45 (s, 1H, coumarinyl H-4), 7.20–7.70 (m, 19H), 4.71 (dd, 1H, H-3, *J* 10.2, 5.7 Hz), 4.58, 4.52 (2s, 2×1H, H-29), 3.13, 2.91 (2d, 2×1H, H-28, *J* 8.4 Hz), 2.16–2.22 (m, 3H, H-2 and H-19), 1.64 (s, 3H, Me), 0.98 (s, 3H, Me), 0.94 (s, 3H, Me), 0.91 (s, 3H, Me), 0.83 (s, 3H, Me), 0.52 (s, 3H, Me). MS (MALDI-TOF), *m*/*z*: 878.80 $[M+Na]^+$, 894.76 $[M+K]^+$.

to good yields. Products **4a** and **4b** were obtained through deprotection of trityl group in **3** using pyridinium *p*-toluenesulfonate (PPTS) in CH_2Cl_2–EtOH, in moderate to good yields.‡

The carbonyl absorption peaks in IR spectra of betulin esters were detected in the range of 1759–1693 cm^{-1}. The carbon signal of carbonyl groups appeared at 166.7–163.1 ppm in the ^{13}C NMR spectra. After the esterification, C-3 and C-28 protons showed a downfield shift of 1.6 and 0.8 ppm, respectively, in the ^1H NMR spectra. The MALDI-TOF mass spectra of betulin esters exhibit two peaks of sodium or potassium adduct ions.

In summary, synthesis of novel betulin esters of coumarin-3-caboxylic and 3,4,5-trimethoxybenzoic acids has been accomplished from a natural betulin in the presence of appropriate reagents. The prominent feature of these syntheses is the mutual connection of two active units with different skeleton using easy synthetic procedures.

This work was supported by the National Natural Science Foundation of China (grant no. 21362039) and the Science and Technology Development Plan of Jilin Province, China (grant no. 20130101025JC).

References

1 I.-C. Sun, J.-K. Shen, H.-K. Wang, L. M. Cosentino and K.-H. Lee, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 1267.
2 K. Qian, D. Yu, C.-H. Chen, L. Huang, S. L. Morris-Natschke, T. J. Nitz, K. Salzwedel, M. Reddick, G. P. Allaway and K.-H. Lee, *J. Med. Chem.*, 2009, **52**, 3248.
3 J.-Y. Kim, H.-M. Koo and D. S. H. L. Kim, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 2405.
4 B. B. Saxena, L. Zhu, M. Hao, E. Kisilis, M. Katdare, O. Oktem, A. Bomshteyn and P. Rathnam, *Bioorg. Med. Chem*., 2006, **14**, 6349.
5 T. Honda, K. T. Liby, X. Su, C. Sundararajan, Y. Honda, N. Suh, R. Risingsong, C. R. Williams, D. B. Royce, M. B. Sporn and G. W. Gribble, *Bioorg. Med. Chem. Lett*., 2006, **16**, 6306.
6 J. Zhou, L. Huang, D. L. Hachey, C.-H. Chen and C. Aiken, *J. Biol. Chem.*, 2005, **280**, 42149.
7 Z. Wen, D. E. Martin, P. Bullock, K.-H. Lee and P. C. Smith, *Drug Metab. Dispos*., 2007, **35**, 440.
8 P. Lan, W.-N. Chen, Z.-J. Huang, P.-H. Sun and W.-M. Chen, *J. Mol. Model.*, 2011, **17**, 1643.
9 T. O. Olomola, R. Klein, K. A. Lobb, Y. Sayed and P. T. Kaye, *Tetrahedron Lett.*, 2010, **51**, 6325.
10 R.-R. Wang, Q. Gu, Y.-H. Wang, X.-M. Zhang, L.-M. Yang, J. Zhou, J.-J. Chen and Y.-T. Zheng, *J. Ethnopharmacol.*, 2008, **117**, 249.
11 D. García-Rivera, R. Delgado, N. Bougarne, G. Haegeman and W. V. Berghe, *Cancer Lett*., 2011, **305**, 21.
12 G. Melagraki, A. Afantitis, O. Igglessi-Markopoulou, A. Detsi, M. Koufaki, C. Kontogiorgis and D. J. Hadjipavlou-Litina, *Eur. J. Med. Chem.*, 2009, **44**, 3020.
13 C. Pal, S. Bindu, S. Dey, A. Alam, M. Goyal, M. S. Iqbal, P. Maity, S. S. Adhikari and U. Bandyopadhyay, *Free Radical Biol. Med*., 2010, **49**, 258.
14 K.-T. Chue, M.-S. Chang and L. N. Ten, *Chem. Nat. Compd*., 2011, **47**, 583.
15 G. Zhao and W. Yan, *J. Carbohydr. Chem*., 2009, **28**, 234.

Received: 8th June 2016; Com. 16/4952

3-O-*(3,4,5-Trimethoxybenzoyl)-28*-O-*tritylbetulin* **3b**. White solid, yield 51%, mp 120–121 °C. IR (KBr, ν/cm^{-1}): 3063, 2936, 1713, 1458, 1227. ^1H NMR ($CDCl_3$) δ: 7.48 (d, 6H, trityl H-2, H-6, *J* 7.2 Hz), 7.19–7.35 (m, 11H, H_{Ar}), 4.67 (dd, 1H, H-3, *J* 9.0, 6.0 Hz), 4.58, 4.52 (2s, 2×1H, H-29), 3.90 (s, 9H, 3OMe), 3.12, 2.91 (2d, 2×1H, H-28, *J* 8.4 Hz), 2.16–2.21 (m, 3H, H-2 and H-19), 1.64 (s, 3H, Me), 0.97 (s, 3H, Me), 0.91 (s, 3H, Me), 0.90 (s, 3H, Me), 0.83 (s, 3H, Me), 0.53 (s, 3H, Me). MS (MALDI-TOF), *m*/*z*: 900.89 $[M+Na]^+$.

28-O-*(Coumarin-3-ylcarbonyl)betulin* **5a**. White solid, yield 78%, mp 228–229 °C. IR (KBr, ν/cm^{-1}): 3524, 3069, 2940, 1759, 1713, 1454, 1240. ^1H NMR ($CDCl_3$) δ: 8.50 (s, 1H, coumarinyl H-4), 7.60–7.68 (m, 2H, coumarinyl H-5, H-7), 7.30–7.38 (m, 2H, coumarinyl H-6, H-8), 4.72, 4.61 (2s, 2×1H, H-29), 4.57, 4.14 (2d, 2×1H, H-28, *J* 11.4 Hz), 3.19 (dd, 1H, H-3, *J* 10.2, 4.8 Hz), 2.46–2.54 (m, 1H, H-19), 1.71 (s, 3H, Me), 1.06 (s, 3H, Me), 1.00 (s, 3H, Me), 0.97 (s, 3H, Me), 0.84 (s, 3H, Me), 0.76 (s, 3H, Me). ^{13}C NMR ($CDCl_3$) δ: 163.7, 156.8, 155.4, 150.3, 148.6, 134.6, 129.7, 125.0, 118.6, 118.1, 117.0, 110.2, 79.2, 64.6, 55.5, 50.6, 49.1, 48.0, 46.9, 43.0, 41.1, 39.1, 38.9, 37.9, 37.4, 34.9, 34.4, 30.0, 29.8, 28.2, 27.6, 27.3, 25.4, 21.0, 19.4, 18.5, 16.3, 16.3, 15.6, 15.0. MS (MALDI-TOF), *m*/*z*: 637.09 $[M+Na]^+$, 653.07 $[M+K]^+$.

28-O-*(3,4,5-Trimethoxybenzoyl)betulin* **5b**. White solid, yield 64%, mp 235–236 °C. IR (KBr, ν/cm^{-1}): 3545, 3071, 2943, 1713, 1458, 1227. ^1H NMR ($CDCl_3$) δ: 7.31 (s, 2H, H_{Ar}), 4.73, 4.61 (2s, 2×1H, H-29), 4.53, 4.09 (2d, 2×1H, H-28, *J* 11.1 Hz), 3.91 (s, 9H, 3OMe), 3.16–3.22 (m, 1H, H-3), 2.50–2.55 (m, 1H, H-19), 1.71 (s, 3H, Me), 1.07 (s, 3H, Me), 1.01 (s, 3H, Me), 0.97 (s, 3H, Me), 0.84 (s, 3H, Me), 0.76 (s, 3H, Me). ^{13}C NMR ($CDCl_3$) δ: 166.1, 153.1, 150.7, 142.2, 126.2, 109.9, 106.9, 81.9, 61.1, 60.7, 56.4, 55.6, 50.5, 48.9, 48.0, 42.9, 41.1, 38.6, 38.4, 37.5, 37.3, 34.3, 34.2, 29.9, 29.4, 28.4, 27.2, 25.4, 24.0, 21.1, 19.3, 18.4, 17.0, 16.4, 16.2, 15.0. MS (MALDI-TOF), *m*/*z*: 659.28 $[M+Na]^+$, 675.86 $[M+K]^+$.

3,28-Bis-O-*(coumarin-3-ylcarbonyl)betulin* **6a**. White solid, yield 21%, mp 267–268 °C. IR (KBr, ν/cm^{-1}): 3069, 2928, 1757, 1707, 1454, 1242. ^1H NMR ($CDCl_3$) δ: 8.51, 8.46 (2s, 2×1H, coumarinyl H-4, H-4′), 7.61–7.69 (m, 4H, coumarinyl H-5, H-5′, H-7, H-7′), 7.27–7.37 (m, 4H, coumarinyl H-6, H-6′, H-8, H-8′), 4.68–4.80 (m, 2H, H-29, H-3), 4.54–4.66 (m, 2H, H-29, H-28), 4.10 (d, 1H, H-28, *J* 11.1 Hz), 2.45–2.49 (m, 1H, H-19), 1.72 (s, 3H, Me), 1.08 (s, 3H, Me), 1.02 (s, 3H, Me), 1.00 (s, 3H, Me), 0.96 (s, 3H, Me), 0.91 (s, 3H, Me). ^{13}C NMR ($CDCl_3$) δ: 163.7, 163.1, 156.8, 156.8, 155.4, 155.4, 150.3, 148.6, 148.2, 134.6, 134.4, 129.7, 129.7, 125.0, 124.9, 119.1, 118.6, 118.1, 118.1, 117.0, 117.0, 110.2, 83.3, 64.6, 55.6, 50.5, 49.1, 48.0, 46.9, 43.0, 41.2, 38.6, 38.4, 37.9, 37.3, 34.9, 34.3, 30.0, 29.8, 28.3, 27.3, 25.4, 23.9, 21.0, 19.4, 18.4, 16.9, 16.4, 16.3, 15.0. MS (MALDI-TOF), *m*/*z*: 809.08 $[M+Na]^+$, 825.04 $[M+K]^+$.

3,28-Bis-O-*(3,4,5-trimethoxybenzoyl)betulin* **6b**. White solid, yield 30%, mp 150–151 °C. IR (KBr, ν/cm^{-1}): 3071, 2940, 1713, 1460, 1225. ^1H NMR ($CDCl_3$) δ: 7.31 (s, 4H, H_{Ar}), 4.67–4.77 (m, 2H, H-3, H-29), 4.62 (s, 1H, H-29), 4.54, 4.08 (2d, 2×1H, H-28, *J* 10.8 Hz), 3.91 (s, 18H, 6OMe), 2.52–2.56 (m, 1H, H-19), 1.72 (s, 3H, Me), 1.09 (s, 3H, Me), 1.03 (s, 3H, Me), 0.99 (s, 3H, Me), 0.92 (s, 6H, 2Me). ^{13}C NMR ($CDCl_3$) δ: 166.7, 166.1, 153.2, 153.1, 150.3, 142.4, 142.2, 126.2, 125.7, 110.2, 107.0, 106.9, 81.9, 63.8, 61.3, 61.1, 56.4, 56.4, 55.6, 50.5, 49.0, 48.1, 47.0, 43.0, 41.2, 38.6, 38.4, 37.9, 37.3, 35.0, 34.3, 30.4, 29.6, 28.4, 27.4, 25.4, 24.0, 21.1, 19.3, 18.4, 17.0, 16.4, 16.3, 15.0. MS (MALDI-TOF), *m*/*z*: 853.23 $[M+Na]^+$.

‡ *Betulin esters* **4a**,**b** *(general procedure)*. PPTS (3.0 mmol) was added to a solution of **3** (0.6 mmol) in 1:1 CH_2Cl_2–EtOH (20 ml) and the mixture was refluxed for 24 h. The mixture was cooled to ~20 °C and the organic solvent was removed by rotary evaporation under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 ml), and the solution was washed with brine (20 ml), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography with ethyl acetate–light petroleum as an eluent to give compounds **4**.

3-O-*(Coumarin-3-ylcarbonyl)betulin* **4a**. White solid, yield 51%, mp 223–224 °C. IR (KBr, ν/cm^{-1}): 3555, 3065, 2940, 1759, 1449, 1242. ^1H NMR ($CDCl_3$) δ: 8.46 (s, 1H, coumarinyl H-4), 7.58–7.67 (m, 2H, coumarinyl H-5, H-7), 7.27–7.37 (m, 2H, coumarinyl H-6, H-8), 4.72–4.78 (m, 1H, H-3), 4.69, 4.59 (2s, 2×1H, H-29), 3.81, 3.34 (2d, 2×1H, H-28, *J* 9.6 Hz), 2.34–2.41 (s, 1H, H-19), 1.69 (s, 3H, Me), 1.04 (s, 3H, Me), 1.00 (s, 6H, 2Me), 0.96 (s, 3H, Me), 0.90 (s, 3H, Me). ^{13}C NMR ($CDCl_3$) δ: 163.1, 156.8, 155.4, 150.2, 148.2, 134.4, 129.7, 125.0, 119.1, 118.1, 117.0, 110.2, 83.2, 64.6, 55.6, 50.5, 49.1, 48.0, 46.9, 43.0, 41.1, 38.6, 38.4, 37.9, 37.3, 34.9, 34.3, 30.0, 29.9, 29.8, 28.3, 27.3, 25.4, 23.9, 19.4, 18.4, 16.9, 16.4, 16.3, 15.0. MS (MALDI-TOF), *m*/*z*: 637.42 $[M+Na]^+$, 653.44 $[M+K]^+$.

3-O-*(3,4,5-Trimethoxybenzoyl)betulin* **4b**. White solid, yield 58%, mp 125–126 °C. IR (KBr, ν/cm^{-1}): 3545, 3071, 2943, 1713, 1458, 1227. ^1H NMR ($CDCl_3$) δ: 7.31 (s, 2H, H_{Ar}), 4.68–4.75 (m, 2H, H-3, H-29), 4.59 (s, 1H, H-29), 3.91 (s, 6H, 2OMe), 3.90 (s, 3H, OMe), 3.81, 3.34 (2d, 2×1H, H-28, *J* 10.8 Hz), 2.34–2.45 (m, 1H, H-19), 1.69 (s, 3H, Me), 1.06 (s, 3H, Me), 1.04 (s, 3H, Me), 1.00 (s, 3H, Me), 0.98 (s, 3H, Me), 0.92 (s, 3H, Me), 0.90 (s, 3H, Me). ^{13}C NMR ($CDCl_3$) δ: 166.7, 153.2, 150.3, 142.4, 125.7, 110.2, 107.0, 79.2, 63.8, 61.2, 56.5, 55.5, 50.6, 49.0, 48.0, 47.0, 43.0, 41.1, 39.1, 38.9, 37.9, 37.4, 35.0, 34.4, 30.4, 29.9, 28.2, 27.6, 27.4, 25.4, 21.0, 19.4, 18.5, 16.3, 15.6, 15.0. MS (MALDI-TOF), *m*/*z*: 659.20 $[M+Na]^+$, 675.09 $[M+K]^+$.