Synthesis of Novel 8,14-Secoursane Derivatives: Key Intermediates for the Preparation of Chiral Decalin Synthons from Ursolic Acid

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The novel 8,14-secoursatriene derivative **6** was synthesized starting from ursolic acid (**1**) *via* methyl esterification of the 17-carboxylic acid group and benzoylation of the 3-hydroxy group (→**2**; *Scheme 1*), ozone oxidation of the C(12)=C(13) bond (→**3**), dehydrogenation with Br_2/HBr (→**4**), enol acetylation of the resulting carbonyl group (→**5**; *Scheme 2*), and ring-*C* opening with the aid of UV light (→**6**). Ring-*C*-opened dienone derivative **7** of ursolic acid was also obtained *via* selective hydrolysis of **6** (*Scheme 2*). Both compounds **6** and **7** are key intermediates for the preparation of chiral decalin synthons from ursolic acid.

Introduction. – Ursolic acid (=(3β)-3-hydroxyurs-12-en-28-oic acid; **1**), a pentacyclic triterpene, is widely distributed in nature. Large available amounts and a low price allow its use as a suitable starting material for the semisynthesis of other biologically or chemically significant compounds [1]. Nowadays, a large number of ursane derivatives have been synthesized by transformations of ring *A* [2], ring *C* [3], and the 17-carboxylic acid group [4] of ursolic acid. However, very few ursane derivatives are used as pharmaceuticals, although their bioactivities can be improved to some extent *via* structure modifications [5]. Actually, most of the modifications are simple transformations based on the basic skeleton of ursolic acid. As far as bioactivity screening is concerned, it is interesting to get access to ursane derivatives with novel structures *via* synthesis or isolation of new natural products.

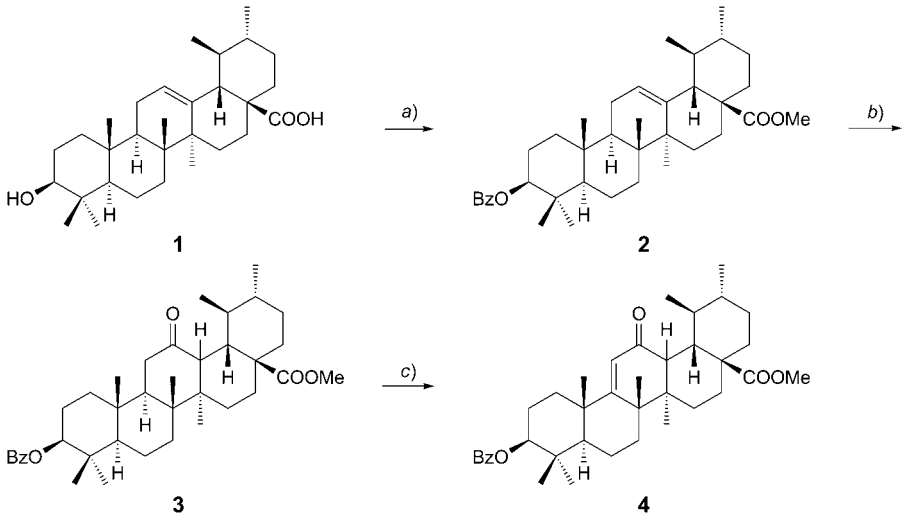
Decalin is one of the most prevalent structural units present in natural products that possess diverse and significant biological activities [6] and olfactory and fixative properties [7]. Generally, these compounds have complex structures with multiple chiral centers. Total syntheses of these compounds are usually rather inefficient in view of tedious synthetic routes, expensive chiral reagents, low yields, vigorous reaction conditions, and the low optical purities obtained [8]. To date, most of these syntheses are based on transformation of terpenes such as sclareolide [9], abietic acid [10], labdanolic acid [11], sclareol [12], manool [13], larixol [14], and communic acid [15] or well-established synthetic chiral materials such as the *Wieland–Miescher* ketone [6a][16]. Nevertheless, almost all these semisynthetic materials are comparatively rare and expensive, bearing no functional groups at ring *A* (C(1) to C(4)) and, therefore, may not be employed to synthesize compounds with functional groups at ring *A*. Interestingly, ursolic acid is characterized by a chiral *trans*-decalin framework of the rings *AB* and a chiral *cis*-decalin framework of the rings *DE*, which could be used as

versatile precursors for a large number of natural products with similar chiral decalin units [17]. However, ursolic acid was rarely reported in the semisynthesis of the above targets due to the lack of suitable transformation methods. Thus, it would be highly advantageous to develop a simple method for the preparation of chiral decalin synthons derived from the rings *AB* and *DE* of ursolic acid. To the best of our knowledge, there are no reports about the preparation of chiral decalin synthons from ursolic acid. We have previously developed a novel method, which involved oxidative cleavage of a key 8,14-secooleanatriene derivative or its hydrolytic product, a dienone derivative, with peracid, to provide chiral decalin synthons derived from the rings *AB* and *DE* of oleanolic acid [18]. Application of this method to ursolic acid requires access to the 8,14-secoursatriene derivative or its hydrolytic dienone product.

In this article, the novel 8,14-secoursatriene derivative **6** was synthesized from ursolic acid (**1**) *via* a series of reactions. Ring-*C*-opened dienone derivative **7** of ursolic acid was also obtained *via* selective hydrolysis of **6**. Both of the ursane derivatives **6** and **7** have novel 8,14-seco structures, which could be used for bioactivity screening and/or preparation of chiral decalin synthons from ursolic acid.

Results and Discussion. – Methyl (3β)-3-(benzoyloxy)urs-12-en-28-oate (**2**) was prepared according to reported procedures starting from ursolic acid (**1**) *via* methyl esterification of the 17-carboxylic acid group [19], followed by benzoylation of the 3-hydroxy group [20] (*Scheme 1*). Oxidation of compound **2** with O_3 gave a 12-oxo compound **3**, which is actually the rearrangement product of the intermediate 12,13-fusedoxirane derivative in the presence of acid [21]. In the preparation of the α,β-unsaturated keto derivative **4**, a catalytic amount of HBr in AcOH (35%) was used as a

Scheme 1. *Synthesis of α,β-Unsaturated Keto Derivative* **4** *from Ursolic Acid* (**1**)

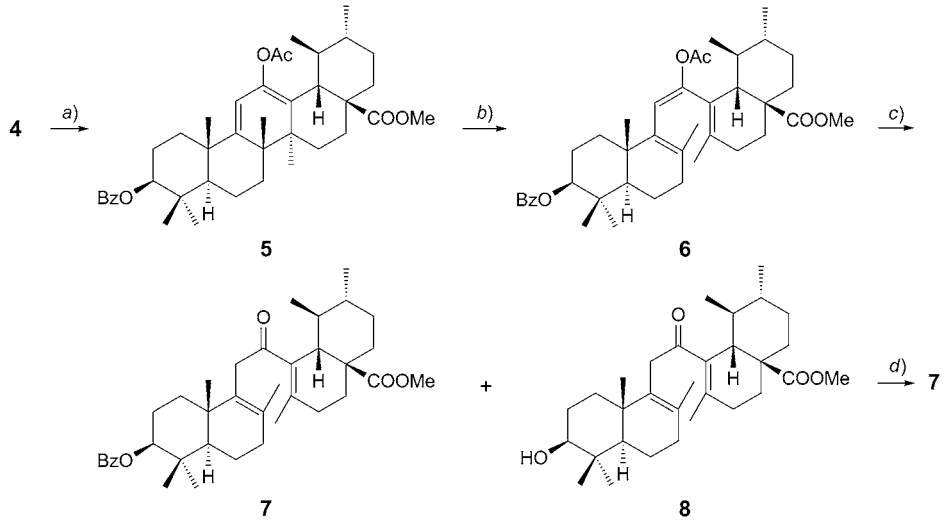


a) 1. CH_2N_2, THF, 0–5°; 2. BzCl, Py; total yield 75%. *b*) O_3, $CHCl_3$; 83%. *c*) Br_2, HBr in AcOH, AcOH, 70°; 47%.

catalyst, which could catalyze the dehydrogenation of 12-oxo compound **3** to **4** with Br_2, introducing a C(9)=C(11) bond [22] (*Scheme 1*). Without HBr in AcOH as catalyst, the dehydrogenation rate with Br_2 was very slow at the beginning. However, HBr was produced gradually while the reaction proceeded, and the reaction rate increased correspondingly.

Siddiqui et al. [23] found that the 12-oxo group was to 100% in the enol form in the synthesis of a (3β)-3-hydroxy-11,12-dioxoursan-28-oic acid derivative, indicating that enol acetylation of the 12-oxo group should be possible. With Ac_2O as acylation reagent, different acids or bases such as pyridine, AcONa, H_2SO_4, TsOH, and H_2SO_4/TsOH were tried as catalyst for the enol acetylation of **4** to **5**. When a base such as pyridine or AcONa was used as catalyst, a low conversion rate was observed even at a high temperature during a long reaction time. However, H_2SO_4/TsOH was a very effective catalyst, and the enol acetate **5** was obtained from **4** in 78% yield (*Scheme 2*). Ring *C* of **5** is a cyclohexadiene system and has a *trans*-disposition between Me–C(8) and Me–C(14). The specific structure of ring *C* could undergo a photochemically allowed six-electron-system antarafacial reaction [24], which could lead to ring-*C* opening between C(8) and C(14); this process would take place *via* a photochemical electrocyclic conrotatory reaction similar to that evidenced in the preparation of previtamin D [25]. Thus, irradiation of **5** in different solvents such as CH_2Cl_2, $CHCl_3$, EtOH, or AcOEt in a *Pyrex* flask under Ar with a 500-W high-pressure Hg lamp gave an (acetyloxy)-substituted triene derivative **6** in 85% yield (*Scheme 2*). Interestingly, when compound **5** was irradiated in a quartz flask, another product **9** was also observed gradually after triene **6** was produced. A mixture **6**/**9** was hydrolyzed with KOH/MeOH/H_2O and then benzoylated with benzoyl chloride, giving dienone derivative **7** as

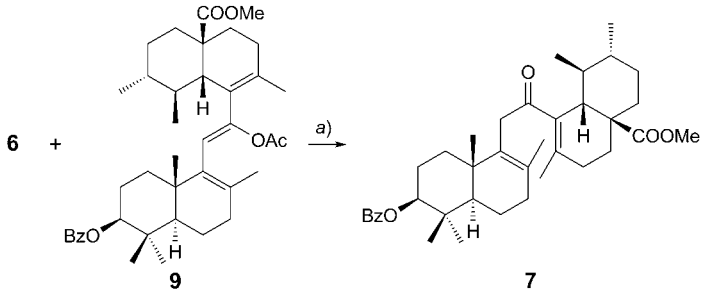
Scheme 2. *Synthesis of Novel 8,14-Secoursatriene Derivative* **6** *and Dienone Derivative* **7**



a) Ac_2O, H_2SO_4/TsOH; 78%. *b*) *hv*, *Pyrex*, AcOEt; 85%. *c*) KOH, MeOH, H_2O; 82% (**7**) and 4% (**8**). *d*) BzCl, Py; 87%.

the only product (*Scheme 3*). Moreover, the two products **6** and **9** interconverted, when irradiated in a quartz flask. These results indicate that compound **9** is the (11*Z*)-isomer of **6** [26]. The different results obtained in the *Pyrex* and quartz flasks must be due to light of different wavelengths and, therefore, energy entering the reaction vessel.

Scheme 3. *Hydrolysis and Benzoylation of the Mixture of* **6**/**9**



a) 1. KOH, MeOH, H_2O; 2. BzCl, Py; total yield 85%.

The (acetyloxy)-substituted triene derivative **6** could be used as a key precursor for the preparation of chiral decalin synthons by means of the oxidative cleavage method reported previously [18]. The three ester groups present in **6** have different reactivities, the 12-enol ester being the most reactive, allowing for its chemoselective hydrolysis. Different amounts of KOH were tried to hydrolyze compound **6**. When 0.8 equiv. of KOH was used, **6** was not consumed completely and dienone derivative **7** was the only product. When 1.2 equiv. of KOH was used, **7** and 3-hydroxydienone derivative **8** were produced in 82% and 4% yields, respectively. Treatment of the mixture **7**/**8** with benzoyl chloride gave as a sole product **7** in high yield (*Scheme 2*). Dienone derivative **7** has an oxo group at C(12), which could undergo a *Baeyer–Villiger* reaction to give the desired chiral decalin synthons derived from ursolic acid.

Conclusions. – An (acetyloxy)-substituted triene derivative **6**, which has a novel 8,14-seco structure, was prepared from ursolic acid in six reaction steps. Selective hydrolysis of **6** gave a novel 8,14-secoursadienone derivative **7**. Both compounds **6** and **7** are key intermediates for the preparation of chiral decalin synthons derived from ursolic acid. Bearing the novel 8,14-seco structures, they could also be used for bioactivity screening. Compounds **3**–**7** were characterized by spectral data (^{1}H- and ^{13}C-NMR, IR, and MS; see *Exper. Part*).

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Experimental Part

General. All materials were of commercial reagent grade and used without further purification. Column chromatography (CC): silica gel (SiO_2, 200–300 mesh). TLC: precoated plates (SiO_2 *GF*$_{254}$, 38–48 μm) activated at 110° for 2 h, detection by UV light, I_2, and/or an 8% EtOH soln. of phosphomolybdic acid. M.p.: *X-T4* melting-point apparatus; uncorrected. IR Spectra: *Nicolet-5700* FT-IR spectrometer; $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Bruker-Advance-600* spectrometer; in $CDCl_3$; δ in ppm rel. to

Me_4Si as internal standard, *J* in Hz. ESI-MS: *Varian 1200* LC/MS spectrometers; in *m*/*z*. HR-ESI-MS: *BioTOF-Q* mass spectrometer; in *m*/*z*.

Methyl (3β,13ζ)-3-(Benzoyloxy)-12-oxoursan-28-oate (**3**). A soln. of **2** (1 g, 1.7 mmol) in $CHCl_3$ (30 ml) was treated with ozone at r.t. until **2** disappeared (TLC monitoring). The soln. was concentrated, and the residue purified by CC(SiO_2, petroleum ether/AcOEt 20:1): **3** (0.85g, 83%). Colorless crystals. M.p. 242–244°. IR (KBr): 2930, 2873, 1718, 1662, 1452, 1275, 1114, 713. ^{1}H-NMR (600 MHz, $CDCl_3$): 8.04 (*d*, *J* = 7.3, 2 arom. H); 7.55 (*dd*, *J* = 7.4, 7.4, 1 arom. H); 7.44 (*dd*, *J* = 7.7, 7.7, 2 arom. H); 4.75 (*ddd*, *J* = 12.1, 4.8, 4.8, H–C(3)); 3.72 (*s*, MeOOC–C(17)); 2.88–2.75 (*m*, H–C(18)); 2.61 (*d*, *J* = 4.1, H–C(13)); 1.36 (*s*, Me); 1.04 (*s*, Me); 1.01 (*s*, Me), 0.95 (*s*, 2 Me); 0.77 (*d*, *J* = 6.2, Me); 0.70 (*d*, *J* = 6.3, Me). ^{13}C-NMR (150 MHz, $CDCl_3$): 215.8; 179.0; 166.2; 132.8; 130.9; 129.5; 128.3; 81.1; 59.1; 55.4; 52.1; 50.6; 46.8; 43.5; 43.1; 40.4; 39.7; 38.2; 38.1; 37.2; 36.6; 34.0; 32.0; 31.8; 29.3; 28.1; 27.7; 25.9; 24.7; 23.6; 20.3; 20.1; 18.1; 17.6; 16.9; 16.1. ESI-MS: 613 ($[M+Na]^+$). HR-ESI-MS: 613.3863($[M+Na]^+$, $C_{38}H_{54}NaO_5^+$; calc. 613.3869).

Methyl (3β,13ζ)-3-(Benzoyloxy)-12-oxours-9(11)-en-28-oate (**4**) To a soln. of **3** (500 mg, 0.85 mmol) in AcOH (25 ml) were added a soln. of Br_2 (0.06 ml, 1.17 mmol) in AcOH (2 ml) and a drop of HBr in AcOH (35%). The mixture was maintained at 70° for 12 h, and then at 25° for 24 h. The resulting soln. was poured into ice/H_2O. The formed light yellow precipitate was washed with sat. aq. $NaHSO_3$ soln., sat. aq. $NaHCO_3$ soln., and H_2O, dried *in vacuo*, and separated by CC(SiO_2, petroleum ether/AcOEt 15:1): **4** (223mg, 47%). Colorless cubic crystals. M.p. 252–254°. IR (KBr): 2930, 2873, 1720, 1660, 1452, 1275, 1114, 713. ^{1}H-NMR (600 MHz, $CDCl_3$): 8.04 (*d*, *J* = 8.2, 2 arom. H); 7.56 (*dd*, *J* = 7.4, 7.4, 1 arom. H); 7.44 (*dd*, *J* = 7.6, 7.6, 2 arom. H); 5.82 (*s*, H–C(11)); 4.72 (*ddd*, *J* = 11.8, 4.4, 4.4, H–C(3)); 3.67 (*s*, MeOOC–C(17)); 3.01–3.05 (*m*, H–C(18)); 2.64 (*d*, *J* = 9.9, H–C(13)); 1.59 (*s*, Me); 1.43 (*s*, Me); 1.32 (*s*, Me); 1.23 (*s*, Me); 1.07 (*d*, *J* = 9.9, Me); 0.97 (*s*, Me); 0.86 (*s*, Me). ^{13}C-NMR (150 MHz, $CDCl_3$): 200.4; 179.1; 175.8; 166.1; 132.9; 130.7; 129.5; 128.4; 121.8; 80.2; 51.5; 50.4; 48.7; 45.2; 44.8; 44.3; 41.5; 40.3; 38.7; 38.0; 36.9; 32.7; 31.8; 28.0; 27.9; 26.6; 25.1; 23.9; 23.8; 21.9; 20.8; 19.7; 17.9; 17.3; 16.9; 16.4. ESI-MS: 611 ($[M+Na]^+$). HR-ESI-MS: 611.3707 ($[M+Na]^+$, $C_{38}H_{52}NaO_5^+$; calc. 611.3712).

Methyl (3β)-12-(Acetyloxy)-3-(benzoyloxy)ursa-9(11),12-dien-28-oate (**5**). To a soln. of **4** (1 g, 1.7 mmol) in Ac_2O (10 ml) were added a drop of conc. H_2SO_4 soln. and a catalytic amount of TsOH (20 mg). The reddish mixture was stirred at r.t. for 10 h and then poured into ice/H_2O. The precipitate was filtered, washed with sat. aq. $NaHCO_3$ soln. and H_2O, dried, and purified by CC(SiO_2, petroleum ether/AcOEt 20:1): **5** (0.84g, 78%). Colorless needle crystals. M.p. 257–260°. IR (KBr): 2976, 2949, 2924, 2875, 1755, 1716, 1452, 1274, 1116, 711. ^{1}H-NMR ($CDCl_3$, 600 MHz): 8.04 (*d*, *J* = 7.4, 2 arom. H); 7.55 (*dd*, *J* = 7.4, 7.4, 1 arom. H); 7.44 (*dd*, *J* = 7.7, 7.7, 2 arom. H); 5.45 (*s*, H–C(11)); 4.75 (*ddd*, *J* = 10.9, 4.7, 4.7, H–C(3)); 3.57 (*s*, MeOOC–C(17)); 2.80 (*d*, *J* = 12.5, H–C(18)); 2.15 (*s*, MeCOO–C(12)); 1.29 (*s*, Me); 1.13 (*s*, Me); 1.04 (*s*, Me); 1.03 (*s*, Me); 0.97 (*s*, Me); 0.96 (*d*, *J* = 6.5, Me); 0.93 (*d*, *J* = 6.6, Me). ^{13}C-NMR (150 MHz, $CDCl_3$): 177.5; 169.0; 166.3; 156.0; 142.6; 132.8; 130.9; 129.5; 128.3; 125.3; 115.2; 81.1; 51.6; 51.1; 47.0; 43.6; 42.9; 40.1; 39.6; 39.0; 38.7; 38.3; 36.8; 36.3; 31.9; 30.6; 28.3; 27.1; 25.1; 24.2; 24.0; 21.1; 21.0; 20.9; 18.6; 18.1; 17.0; 16.5. ESI-MS: 653 ($[M+Na]^+$). HR-ESI-MS: 653.3813 ($[M+Na]^+$, $C_{40}H_{54}NaO_6^+$; calc. 653.3818).

Methyl (3β)-12-(Acetyloxy)-3-(benzoyloxy)-8,14-secoursa-8,11,13-trien-28-oate (**6**). A soln. of **5** (100 mg, 0.16 mmol) in AcOEt (20 ml) in a *Pyrex* flask under Ar was irradiated with a 500-W high-pressure Hg lamp at r.t. until **5** disappeared (TLC monitoring). Then, the soln. was concentrated and the resluting syrup purified by CC(SiO_2, petroleum ether/AcOEt 25:1): **6** (85mg, 85%). Colorless amorphous powder. IR (KBr): 2948, 2873, 1719, 1646, 1453, 1368, 1275, 1203, 1115, 712. ^{1}H-NMR ($CDCl_3$, 600 MHz): 8.05 (*d*, *J* = 7.6, 2 arom. H); 7.55 (*dd*, *J* = 7.3, 7.3, 1 arom. H); 7.44 (*dd*, *J* = 7.7, 7.7, 2 arom. H); 5.84 (*s*, H–C(11)); 4.78 (*ddd*, *J* = 11.7, 4.4, 4.4, H–C(3)); 3.63 (*s*, MeOOC–C(17)); 2.30 (*d*, *J* = 9.3, H–C(18)); 2.13 (*s*, MeCOO–C(12)); 1.53 (*s*, Me); 1.43 (*s*, Me); 1.17 (*s*, 2 Me): 1.08 (*s*, Me); 0.98 (*d*, *J* = 5.4, Me); 0.92 (*d*, *J* = 5.1, Me). ^{13}C-NMR (150 MHz, $CDCl_3$): 177.5; 169.3; 166.3; 148.3; 136.9; 133.3; 132.7; 132.0; 131.1; 129.5; 128.3; 119.2; 111.9; 81.6; 51.5; 46.9; 42.4; 39.0; 38.8; 38.7; 38.2; 36.9; 36.2; 34.7; 30.8; 30.0; 28.6; 26.9; 24.3; 23.1; 21.8; 21.6; 21.5; 20.6; 18.9; 18.7; 17.1; 14.1. ESI-MS: 653 ($[M+Na]^+$). HR-ESI-MS: 653.3813 ($[M+Na]^+$, $C_{40}H_{54}NaO_6^+$; calc. 653.3818).

Methyl (3β)-3-(Benzoyloxy)-12-oxo-8,14-secoursa-8,13-dien-28-oate (**7**) *and Methyl (3β)-3-(Hydroxy)-12-oxo-8,14-secoursa-8,13-dien-28-oate* (**8**). *Method A:* To a soln. of **6** (500 mg, 0.79 mmol) in

MeOH (25 ml) were added KOH (52 mg, 0.93 mmol) and H_2O (1.0 ml). The mixture was stirred at r.t. until **6** disappeared (TLC monitoring). Then, H_2O (25 ml) was added, and the mixture was extracted three times with CH_2Cl_2. The combined org. phase was washed with H_2O and brine, dried ($MgSO_4$), and concentrated and the residue purified by CC(SiO_2, petroleum ether/AcOEt 10 : 1): **7** (384mg, 82%) and **8** (18mg, 4%).

Method B: As described in *Method A* with **6** (500 mg, 0.79 mmol), MeOH (25 ml), KOH (52 mg, 0.93 mmol), and H_2O (1.0 ml). The combined org. phase was washed with H_2O and brine and dried ($MgSO_4$). To this CH_2Cl_2 soln. were added pyridine (5 ml) and benzoyl chloride (0.12 ml). The resulting soln. was stirred at r.t. until **8** was consumed completely, which was then washed with H_2O, 5% aq. HCl soln., sat. aq. $NaHCO_3$ soln., and brine, dried ($MgSO_4$), and concentrated. The resulting residue, was purified by CC(SiO_2, petroleum ether/AcOEt 10 : 1): **7** (407 mg, 87%). Colorless crystals. M.p. 202 – 204°. IR (KBr): 2965, 2933, 2875, 1718, 1685, 1630, 1455, 1280, 1117, 972, 713. ^{1}H-NMR (600 MHz, $CDCl_3$): 8.05 (*d*, *J* = 7.6, 2 arom. H); 7.54 (*dd*, *J* = 7.4, 7.4, 1 arom. H); 7.43 (*dd*, *J* = 7.7, 7.7, 2 arom. H); 4.79 (*ddd*, *J* = 11.5, 5.5, 5.5, H–C(3)); 3.66 (*s*, MeOOC–C(17)); 3.46 (*d*, *J* = 18.7, 1 H–C(11)); 3.25 (*d*, *J* = 18.6, 1 H–C(11)); 2.74 (*d*, *J* = 10.4, H–C(18)); 1.69 (*s*, Me); 1.34 (*s*, Me); 1.04 (*s*, Me); 0.97 (*s*, 2 Me); 0.91 (*d*, *J* = 6.1, Me); 0.88 (*d*, *J* = 6.2, Me).^{13}C-NMR (150 MHz, $CDCl_3$): 205.3; 177.7; 166.2; 146.2; 139.0; 138.2; 132.6; 131.1; 129.5; 128.8; 128.3; 81.4; 51.7; 50.4; 46.8; 44.5; 42.5; 39.9; 38.8; 38.1; 37.9; 35.4; 34.2; 33.3; 30.8; 30.0; 29.7; 28.1; 24.1; 23.0; 20.8; 20.2; 19.9; 18.7; 17.1; 16.8. ESI-MS: 611 ($[M + Na]^+$). HR-ESI-MS: 611.3707 ($[M + Na]^+$, $C_{38}H_{52}NaO_5^+$; calc. 611. 3712).

Compound **8**: Colorless cubic crystals. IR: 3448, 2945, 2864, 1728, 1692, 1631, 1455. ESI-MS: 507($[M + Na]^+$).

REFERENCES

[1] G. Chadalapaka, I. Jutooru, A. McAless, T. Stefanac, S. Safe, *Bioorg. Med. Chem. Lett*. **2008**, *18*, 2633; H. Sheng, H. Sun, *Nat. Prod. Rep.* **2011**, *28*, 543.

[2] H.-Y. Tu, A.-M. Huang, B.-L. Wei, K.-H. Gan, T.-C. Hour, S.-C. Yang, Y.-S. Pu, C.-N. Lin, *Bioorg. Med. Chem*. **2009**, *17*, 7265; S. C. B. Gnoatto, A. Dassonville-Klimpt, S. D. Nascimento, P. Galéra, K. Boumediene, G. Gosmann, P. Sonnet, S. Moslemi, *Eur. J. Med. Chem*. **2008**, *43*, 1865; H. J. Finlay, T. Honda, G. W. Gribble, D. Danielpour, N. E. Benoit, N. Suh, C. Williams, M. B. Spom, *Bioorg. Med. Chem. Lett*. **1997**, *7*, 1769.

[3] T. Honda, H. J. Finlay, G. W. Gribble, *J. Nat. Prod*. **1997**, *60*, 1174.

[4] Y.-Q. Meng, D.Liu, L.-L. Cai, H. Chen, B. Cao, Y.-Z. Wang, *Bioorg. Med. Chem*. **2009**, *17*, 848.

[5] X. Liu, B. Shi, B. Yu, *Tetrahedron* **2004**, *60*, 11647; J. D. Connolly, R. A. Hill, *Nat. Prod. Rep.* **2010**, *27*, 79; A. V. Tkachev, A. Y. Densiov, Y. V. Gatilov, I. Y. Bagryanskaya, S. A. Shevsov, T. V. Rybalova, *Tetrahedron* **1994**, *50*, 11459.

[6] a) C. Caballero, P. Castañera, F. Ortego, G. Fontana, P. Pierro, G. Savona, B. Rodríguez, *Phytochemistry* **2001**, *58*, 249; b) D. Demeke, C. J. Forsyth, *Tetrahedron* **2002**, *58*, 6531; c) M. Scheck, M. A. Koch, H. Waldmann, *Tetrahedron* **2008**, *64*, 4792; d) C. Dufresen, D. Cretney, C. K. Lau, V. Mascitti, N. Tsou, *Tetrahedron: Asymmetry* **2002**, *13*, 1965.

[7] G. Ohloff, W. Giersch, W. Pickenhagen, A. Furrer, B. Frei, *Helv. Chim. Acta* **1985**, *68*, 2022.

[8] A. F. Barrero, E. J. Alvarez-Manzaneda, R. Alvarez-Manzaneda, R. Chahboun, R. Meneses, J. M. Cuerva, M. Aparicio, J. L. Romera, *Org. Lett*. **2001**, *3*, 647.

[9] D. H. Hua, X. Huang, Y. Chen, S. K. Battina, M. Tamura, S. K. Noh, S. I. Koo, I. Namatame, H. Tomoda, E. M. Perchellet, J.-P. Perchellet, *J. Org. Chem*. **2004**, *69*, 6065; S. Chackalamannil, Y. Wang, Y. Xia, M. Czarniecki, *Tetrahedron Lett*. **1995**, *36*, 5315.

[10] M. Arnó, M. A. González, R. J. Zaragozá, *J. Org. Chem*. **2003**, *68*, 1242.

[11] M. G. Bolster, B. J. M. Jansen, A. de Groot, *Tetrahedron* **2001**, *57*, 5657.

[12] A. F. Barrero, M. Cortés, E. A. Manzaneda, E. Cabrera, R. Chahboun, M. Lara, A. R. Rivas, *J. Nat. Prod.* **1999**, *62*, 1488.

[13] A. W. W. van Wyk, M. T. Davies-Coleman, *Tetrahedron* **2007**, *63*, 12179.

[14] M. G. Bolster, B. J. M. Jansen, A. de Groot, *Tetrahedron* **2001**, *57*, 5663; J. Aslaoui, H. Li, C. Morin, *Tetrahedron Lett*. **2005**, *46*, 1713.
[15] E. J. Alvarez-Manzaneda, J. L. Romera, A. F. Barrero, R. Alvarez-Manzaneda, R.Chahboun, R. Meneses, M. Aparicio, *Tetrahedron* **2005**, *61*, 837.
[16] W.-P. Deng, M. Zhong, X.-C. Guo, A. S. Kende, *J. Org. Chem*. **2003**, *68*, 7422.
[17] J. R. Hanson, *Nat. Prod. Rep.* **2009**, *26*, 1156.
[18] H.-J. Yang, B.-G. Li, X.-H. Cai, H.-Y. Qi, Y.-G. Luo, G.-L. Zhang, *J. Nat. Prod*. **2006**, *69*, 1531.
[19] M. Gil, A. Haïdour, J. L. Ramos, *J. Agric. Food. Chem*. **1997**, *45*, 4490.
[20] J. Mclean, G. A. Silverstone, F. S. Spring, *J. Chem. Soc*. **1951**, 935.
[21] S. Kim, E. Ma, *Molecules* **2009**, *14*, 4655; K. Gamoh, M. Hirayama, N. Lkekawa, *J. Chem. Soc., Perkin Trans. 1* **1984**, 449; J. Mclean, S. U. Ruff, F. S. Spring, *J. Chem. Soc*. **1951**, 1093.
[22] D. E. Seymour, K. S. Sharples, F. S. Spring, *J. Chem. Soc*. **1939**, 1075; D. E. Seymour, F. S. Spring, *J. Chem. Soc*. **1941**, 319; W. Manson, F. S. Spring, *J. Chem. Soc*. **1951**, 3332; C. W. Picard, K. S. Sharples, F. S. Spring, *J. Chem. Soc*. **1939**, 1045; G. G. Allan, F. S. Spring, *J. Chem. Soc*. **1955**, 2125.
[23] A. Siddiqui, S. Begum, F. Hafeez, B. S. Siddiqui, *Phytochemistry* **1989**, *28*, 1187.
[24] S. Manna, P. Yadagiri, J. R. Falck, *J. Chem. Soc., Chem. Commun*. **1987**, 1324; R. L. Autrey, D. H. R. Barton, A. K. Ganguly, W. H. Reusch, *J. Chem. Soc*. **1961**, 3313.
[25] E. Havinga, R. J. de Kock, M. P. Rappoldt, *Tetrahedron* **1960**, *11*, 276.
[26] A. García-Granados, P. E. López, E. Melguizo, A. Parra, Y. Simeó, *Tetrahedron* **2004**, *60*, 1491; A. García-Granados, P. E. López, E. Melguizo, A. Parra, Y. Simeó, *Tetrahedron* **2004**, *60*, 3831; W. Nerinckx, P. J. de Clercq, *Tetrahedron* **1991**, *47*, 9419; L. Vanmaele, P. J. de Clercq, M. Vandewalle, *Tetrahedron* **1985**, *41*, 141.

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