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Synthetic studies on neoclerodane diterpenes from *Salvia splendens*: oxidative modifications of ring A

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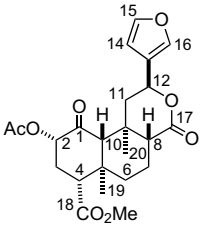
ABSTRACT

Salvinorin A (**1**), a neoclerodane diterpene from the hallucinogenic mint *Salvia divinorum*, is the only known naturally occurring non-nitrogenous and specific κ-opioid agonist. Some oxidative modifications of the A ring in the congeners of **1** isolated from *Salvia splendens* salviarin, splenolide B, splendidin, and in the non-natural 8-*epi*-salviarin gave new derivatives, some of which were tested as agonists at opioid receptors. However, none of these compounds was active. The presence of the C-18, C-19 lactone could be at the origin of the observed lack of binding affinity.

1. Introduction

Salvinorin A (**1**), isolated from the sage *Salvia divinorum* Epling & Játiva (Labiatae) is a potent and selective κ-opioid agonist.[1] Recently,[2] we screened other structurally related neoclerodane diterpenoids isolated from *Salvia splendens* Sellow ex Roem. & Schult, as well as several semisynthetic derivatives, for binding affinity and functional activity at opioid receptors. In this communication, we describe the preparation of a series of new derivatives starting from the major diterpene constituents of *S. splendens*, salviarin, splenolide B, and splendidin (**2**–**4**, respectively[3,4]) and from the derivative 8-*epi*-salviarin **5**[2,8] through several oxidative modifications of the ring A. The aim of this work was to obtain a series of new neoclerodanes (**6**–**24**) and to test their affinity to the opioid receptors and explore their structure–activity relationships. It is worth noting that the new derivative **24** possesses identical structural parts that those of salvinorin A (**1**) at the C-2 (α-acetoxyl group) and C-8 (β-hydrogen) positions, that have been reported[1,5–7] as some of the structural requirements for the psychoactivity of salvinorin **1**.



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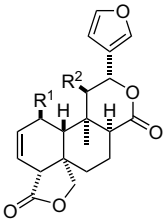
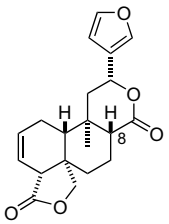


2 $R^1 = R^2 = H$
3 $R^1 = H$, $R^2 = OAc$
4 $R^1 = R^2 = OAc$



5

2. Results and discussion

Treatment of **2**–**5** with osmium tetroxide (see Section 4) stereoselectively yielded the cis dihydroxylated derivatives **6**–**9**, respectively. Partial acetylation of **6**–**8** with acetic anhydride–pyridine at room temperature for a short time gave the monoacetyl derivatives **10**–**14** (Scheme 1). Complete acetylation of **6**–**9** with an excess of Ac_2O–pyridine for 24 h produced peracetates **15**–**18**, respectively (Scheme 1).

The β-orientation of the C-2 and C-3 hydroxyl and/or acetoxyl groups in all these compounds (**6**–**18**) was supported by the following facts. The large vicinal coupling value (J=8.0–11.1 Hz)

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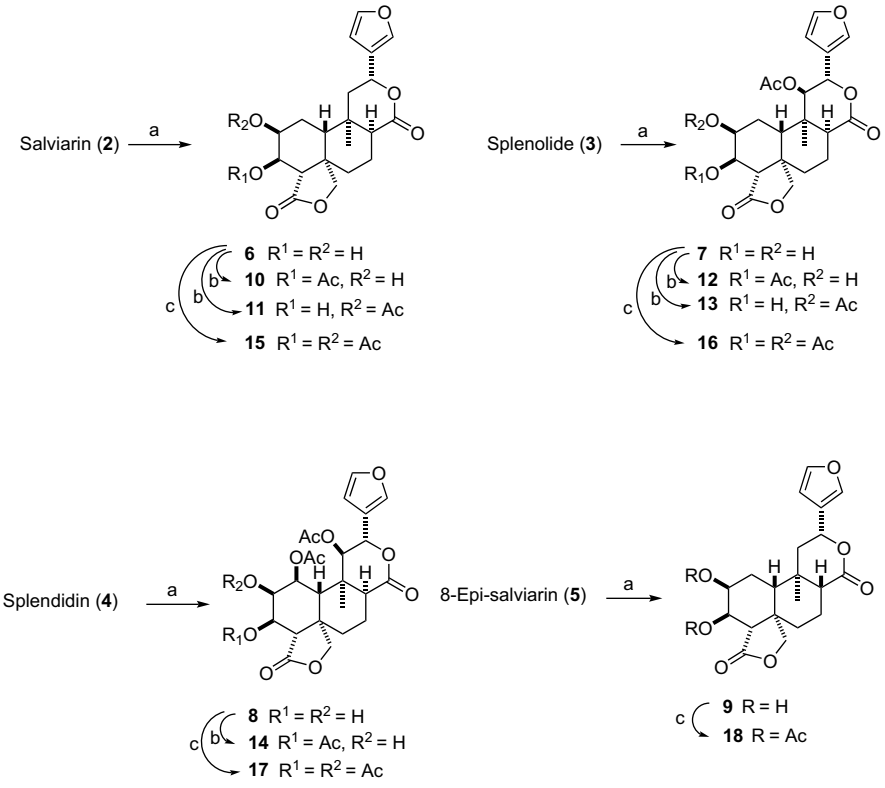
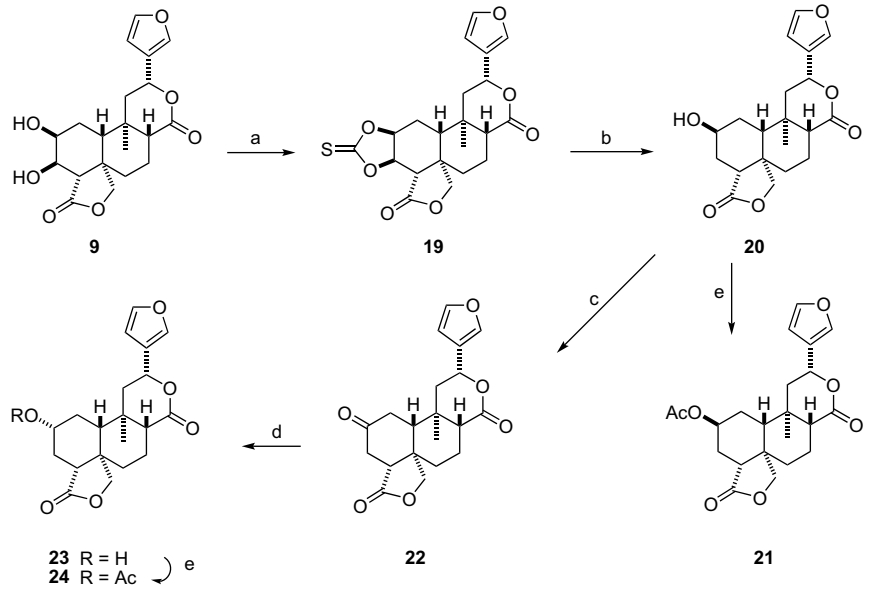


Scheme 1. Reagents and conditions: (a) OsO_4 (cat.), NMO, Me_2CO–H_2O 6:1, 24 h, rt, 70% (**7**), 72 h, 50 °C, 52% (**8**), 4 h, rt, 75% (**9**); (b) Ac_2O–Py 1:2, rt, 15 min, 38% (**10**), 15% (**11**), 2 min, 40% (**12**), 15% (**13**), 1.5 h, 50% (**14**); (c) Ac_2O–Py 1:2, 24 h, quant.

between the H-4β and H-3 protons, observed in the ^1H NMR spectra of **7**–**18**, established that the latter proton was α-oriented, and the H-2 proton must be also α-oriented not only by its vicinal coupling value with the H-3α proton ($J_{a,e}$=1.4–3.2 Hz) but also by the stereochemical requirements of a 1,2-dihydroxylation reaction with OsO_4. NOE experiments also supported this conclusion, because irradiation at the H-3α proton signal always caused an NOE enhancement in the H-19α (pro-*S*) proton, thus confirming that these protons are α-oriented. The location of the acetyl group in the regioisomeric acetates (**10**–**14**) was strongly supported by the HMBC spectra, which showed correlation between the carbonyl carbon of the acetate and the proton of the acetylated position. Moreover, comparison of the chemical shifts of the H-2α and H-3α protons in each one of these derivatives (**10**: δ 4.17 and 5.08, **11**: δ 5.20 and 3.92, **12**: δ 4.18 and 5.04, **13**: δ 5.29 and 3.89, **14**: δ 3.92 and 5.09, respectively) further confirmed the proposed structures.

Treatment of **9** (Scheme 2) with 1,1′-thiocarbonyldiimidazole and 4-dimethylaminopyridine (4-DMAP) yielded the cyclic



Scheme 2. Reagents and conditions: (a) $Im_2(CS)$, 4-DMAP, CH_2Cl_2, reflux, 3.5 h, 58%; (b) Bu_3SnH, AIBN, toluene, reflux, 4 h, 82%; (c) PCC, CH_2Cl_2, rt, 17 h, 89%; (d) $NaBH_4$, THF, 0 °C, 15 min, α/βOH 10:1, quant; (e) Ac_2O, pyridine, rt, 24 h, 100%.

thiocarbonate **19**, which was transformed into **20** by reaction with Bu_3SnH. Acetylation of **20** by standard procedures gave derivative **21**. The location of the hydroxyl (**20**) or acetoxyl (**21**) group at the C-2β position was deduced from the multiplicities of the H-2α and H-4β protons that appeared as a quintuplet (J=3.1 Hz in both **20** and **21**) and as a double doublet ($J_{4\beta,3\alpha}$=12.6 Hz and $J_{4\beta,3\beta}$=6.3 Hz in **20**, and J=12.2 and 6.3 Hz in **21**), respectively, in the ^{1}H NMR spectra of these substances.

An attempt to directly prepare the AcO-2α derivative **23**, using a Mitsunobu reaction, starting from compound **20**, unfortunately failed. However, compound **20** was transformed into **22** by oxidation with PCC (Scheme 2). Reduction of **22** with $NaBH_4$ at 0 °C gave a product, which showed only one spot on TLC with several eluents. The ^{1}H NMR spectrum of the reduction compound, however, revealed that it was a 10:1 mixture of the 2α-hydroxy derivative **23** and another minor constituent. Acetic anhydride–pyridine treatment of this mixture and subsequent chromatography allowed the isolation of the major acetyl derivative **24** together with a minor quantity of its C-2 epimer, the above described compound **21**. The α-orientation of the substituent at C-2 in **24** was in agreement[5] with the coupling values for the H-2β axial proton ($J_{a,a}=J_{a,a'}$=10.3 Hz, $J_{a,e}=J_{a,e'}$=4.3 Hz) observed in its ^{1}H NMR spectrum.

The structures of all the new neoclerodane derivatives were supported on a complete and unambiguous assignment of the ^{1}H and ^{13}C NMR spectra of **7**–**24** and by other spectroscopic and physicochemical data (see Section 4).

Compounds **7**–**10**, **12**, and **14**–**24** were then evaluated for opioid receptor affinity as described previously.[2] Unfortunately, none of these had affinity for opioid receptors (K_i>10,000 nM). These results would confirm the key role of the orientation of furan and the C-8 configuration in the binding of neoclerodanes, such as **1**, at opioid receptors. In addition, the lack of affinity by **23** and **24** would suggest that the additional lactone ring including C-18 and C-19 when compared to **1** is detrimental for binding.

To distinguish between the role of the C-18, C-19 lactone moiety and that of the absolute configuration at C-12 in inhibiting the binding to opioid receptors, the corresponding C-12 epimers of **23** and **24** would need to be prepared.

3. Conclusion

In summary, we have provided additional methodology for the selective oxidation of neoclerodanes isolated from *S. splendens*. The data collected in this work indicates that the presence of the C-18, C-19 lactone may be responsible for the lack of affinity at opioid receptors. However, additional work will be needed to confirm this finding. While none of the compounds examined possesses affinity for opioid receptors, it also provides valuable insight into the nature of the affinity and activity of **1** for opioid receptors.

4. Experimental section

4.1. General experimental procedures

Melting points were determined on a Kofler block and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 MC polarimeter. IR spectra were recorded on a Perkin–Elmer Spectrum One spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (**7**, **8**, **12**–**18**, and **21**) or methanol-d_4 (**10**, **11**, **19**, and **20**) or 2:1 acetone-d_6–methanol-d_4 (**9**) solution on a Varian INOVA 400 spectrometer at 400 and 100 MHz, respectively. Chemical shifts are reported in the δ scale and are referenced to residual $CHCl_3$ (δ 7.25) or methanol (δ 3.30) signals for protons and to the solvent signals (δ_{CHCl3} 77.00, δ_{CH3OH} 49.00) for carbons. All the assignments for protons and carbons were in agreement with 2D COSY, gHSQC, gHMBC, and 1D NOESY spectra. Mass spectra were registered in the positive EI (70 eV) mode on a Hewlett–Packard 5973 instrument. Elemental analyses were conducted on a LECO CHNS-932 apparatus. Si gel Merck LiChroprep 15–25/25–40 μm 1/1 was used for flash chromatography (elution under 0.7 psi of Ar). Merck 5554 Kieselgel 60 F_{254} sheets were used for thin-layer chromatographic analysis. Petroleum ether (bp 50–70 °C) was used for column chromatography.

4.2. Starting materials for chemical transformations

Compounds **2**–**4** were available from a previous work[3] and **5** was obtained from **2** as described previously.[2]

4.3. General procedure for the osmylation of compounds 2–5

The starting compounds (0.5 mmol) were added to a solution of OsO_4 (1 mL of a 2.5 wt % solution in 2-methyl-2-propanol, 20.3 mg, 0.080 mmol) and 97% 4-methylmorpholine *N*-oxide (240 mg, 1.99 mmol) in 10 mL of acetone–water (6:1). The solution was stirred at room temperature for 4 h in the case of **2** and **5**, for 24 h in the case of **3**, and for 72 h at 50 °C in the case of **4**. Then, the reaction was quenched by adding 1 mL of saturated aqueous solution of $Na_2S_2O_3$ and the mixture was extracted with EtOAc (4×10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure and purification by flash column chromatography (FC) yielded compound **6**[9] from **2** (transformed, without characterization, into compounds **10**, **11**, and **15**, see below), compound **7** from **3** (elution with 3:1 CH_2Cl_2–acetone, 152 mg, 70%), compound **8** from **4** (elution with 7:3 CH_2Cl_2–acetone, 128 mg, 52%), and compound **9** from **5** (elution with 7:3 CH_2Cl_2–acetone, 163 mg, 75%).

4.3.1. Compound ***7***

Colorless prisms (EtOAc–petroleum ether); mp 226–230 °C; $[\alpha]_D^{20}$ −46.8 (*c* 0.248, $CHCl_3$); R_f (3:1 CH_2Cl_2–acetone) 0.30; IR (KBr) ν_{max} 3449, 2925, 1752, 1447, 1375, 1222, 1159, 1047, 1009, 875, 729, 603 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (1H, dd, $J_{16,14}$=0.8 Hz, $J_{16,15}$=1.8 Hz, H-16), 7.37 (1H, t, $J_{15,14}=J_{15,16}$=1.8 Hz, H-15), 6.39 (1H, dd, $J_{14,15}$=1.8 Hz, $J_{14,16}$=0.8 Hz, H-14), 5.42 (1H, d, $J_{12\beta,11\alpha}$=10.8 Hz, H-12β), 5.16 (1H, d, $J_{11\alpha,12\beta}$=10.8 Hz, H-11α), 4.28 (1H, d, $J_{19a,19b}$=9.4 Hz, pro-*R* H-19a), 4.24 (1H, dd, $J_{19b,6\beta}$=1.6 Hz, $J_{19b,19a}$=9.4 Hz, pro-*S* H-19b), 4.16 (1H, ddd, $J_{2\alpha,1\alpha}$=2.0 Hz, $J_{2\alpha,1\beta}$=3.0 Hz, $J_{2\alpha,3\alpha}$=2.8 Hz, H-2α), 3.74 (1H, dd, $J_{3\alpha,2\alpha}$=2.8 Hz, $J_{3\alpha,4\beta}$=10.0 Hz, H-3α), 2.64 (1H, br dd, $J_{8\alpha,6\alpha}$<0.4 Hz, $J_{8\alpha,7\alpha}$=4.3 Hz, $J_{8\alpha,7\beta}$=3.1 Hz, H-8α), 2.61 (1H, dd, $J_{10\beta,1\alpha}$=11.9 Hz, $J_{10\beta,1\beta}$=3.1 Hz, H-10β), 2.49 (1H, m, H-1β), 2.48 (1H, m, H-7β), 2.31 (1H, d, $J_{4\beta,3\alpha}$=10.0 Hz, H-4β), 2.16 (3H, s, 11β-OAc), 1.88 (1H, dddd, $J_{7\alpha,6\alpha}$=3.1 Hz, $J_{7\alpha,6\beta}$=14.2 Hz, $J_{7\alpha,7\beta}$=14.4 Hz, $J_{7\alpha,8\alpha}$=4.3 Hz, H-7α), 1.69 (1H, br dt, $J_{6\alpha,6\beta}$=14.0 Hz, $J_{6\alpha,7\alpha}=J_{6\alpha,7\beta}$=3.0 Hz, $J_{6\alpha,8\alpha}$<0.4 Hz, H-6α), 1.55 (1H, ddd, $J_{1\alpha,1\beta}$=14.8 Hz, $J_{1\alpha,2\alpha}$=2.0 Hz, $J_{1\alpha,10\beta}$=11.9 Hz, H-1α), 1.28 (1H, dddd, $J_{6\beta,6\alpha}$=14.0 Hz, $J_{6\beta,7\alpha}$=14.2 Hz, $J_{6\beta,7\beta}$=3.7 Hz, $J_{6\beta,19b}$=1.6 Hz, H-6β), 0.89 (3H, s, Me-20); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8 (C, C-18), 169.9 (C, C-17), 169.2 (C, 11-O*C*OCH$_3$), 143.9 (CH, C-15), 141.7 (CH, C-16), 121.4 (C, C-13), 108.5 (CH, C-14), 76.5 (CH, C-11), 71.3 (CH, C-12), 70.4 (CH_2, C-19), 69.0 (CH, C-3), 67.6 (CH, C-2), 53.1 (CH, C-4), 49.4 (CH, C-8), 43.5 (C, C-5), 38.9 (C, C-9), 34.2 (CH, C-10), 32.3 (CH_2, C-6), 27.2 (CH_2, C-1), 20.7 (CH_3, 11-OCO*C*H$_3$), 19.7 (CH_2, C-7), 18.4 (CH_3, C-20); EIMS *m*/*z* 434 $[M]^+$ (1), 392 (9), 374 (33), 325 (10), 279 (7), 203 (100), 189 (32), 176 (12), 161 (12), 110 (14), 95 (16), 81 (15). Anal.: C 60.69%, H 5.89%; calcd for $C_{22}H_{26}O_9$: C 60.82%, H 6.03%.

4.3.2. Compound ***8***

Colorless plates (EtOAc–*n*-pentane); mp 252–255 °C, $[\alpha]_D^{20}$ −19.3 (*c* 0.223, $CHCl_3$); R_f (3:1 CH_2Cl_2–acetone) 0.25; IR (KBr) ν_{max} 3452,

2928, 1749, 1370, 1243, 1036, 969, 875, 737, 603 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (1H, dd, $J_{16,14}$=0.8 Hz, $J_{16,15}$=1.8 Hz, H-16), 7.39 (1H, t, $J_{15,14}$=$J_{15,16}$=1.8 Hz, H-15), 6.38 (1H, dd, $J_{14,15}$=1.8 Hz, $J_{14,16}$=0.8 Hz, H-14), 5.82 (1H, d, $J_{12\beta,11\alpha}$=10.9 Hz, H-12β), 5.32 (1H, d, $J_{11\alpha,12\beta}$=10.9 Hz, H-11α), 5.09 (1H, dd, $J_{1\alpha,2\alpha}$=0.8 Hz, $J_{1\alpha,10\beta}$=8.8 Hz, H-1α), 4.58 (1H, dd, $J_{19a,6\beta}$=2.1 Hz, $J_{19a,19b}$=8.6 Hz, pro-*S* H-19a), 4.25 (1H, ddd, $J_{3\alpha,2\alpha}$=1.4 Hz, $J_{3\alpha,4\beta}$=8.0 Hz, $J_{3\alpha,3\beta OH}$=6.8 Hz, H-3α), 4.20 (1H, d, $J_{19b,19a}$=8.6 Hz, pro-*R* H-19b), 4.12 (1H, d, $J_{3\beta OH,3\alpha}$=6.8 Hz, 3β-OH), 3.85 (1H, dd, $J_{2\alpha,1\alpha}$=0.8 Hz, $J_{2\alpha,3\alpha}$=1.4 Hz, H-2α), 2.71 (1H, br dd, $J_{8\alpha,6\alpha}$<0.4 Hz, $J_{8\alpha,7\alpha}$=4.0 Hz, $J_{8\alpha,7\beta}$=3.2 Hz, H-8α), 2.54 (1H, d, $J_{4\beta,3\alpha}$=8.0 Hz, H-4β), 2.45 (1H, ddt, $J_{7\beta,6\alpha}$=$J_{7\beta,8\alpha}$=3.2 Hz, $J_{7\beta,6\beta}$=3.5 Hz, $J_{7\beta,7\alpha}$=14.4 Hz, H-7β), 2.27 (1H, d, $J_{10\beta,1\alpha}$=8.8 Hz, H-10β), 2.03 (3H, s, 1β-OAc), 1.92 (1H, ddt, $J_{7\alpha,6\alpha}$=$J_{7\alpha,8\alpha}$=4.0 Hz, $J_{7\alpha,6\beta}$=14.0 Hz, $J_{7\alpha,7\beta}$=14.4 Hz, H-7α), 1.87 (3H, s, 11β-OAc), 1.87 (1H, br ddd, $J_{6\alpha,6\beta}$=14.1 Hz, $J_{6\alpha,7\alpha}$=4.0 Hz, $J_{6\alpha,7\beta}$=3.2 Hz, $J_{6\alpha,8\alpha}$<0.4 Hz, H-6α), 1.47 (1H, dddd, $J_{6\beta,6\alpha}$=14.1 Hz, $J_{6\beta,7\alpha}$=14.0 Hz, $J_{6\beta,7\beta}$=3.5 Hz, $J_{6\beta,19a}$=2.1 Hz, H-6β), 1.06 (3H, s, Me-20); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5 (C, C-18), 170.1 (C, 1-$OCOCH_3$), 169.7 (C, 11-$OCOCH_3$), 169.3 (C, C-17), 144.2 (CH, C-15), 141.7 (CH, C-16), 121.4 (C, C-13), 108.6 (CH, C-14), 76.0 (CH, C-11), 74.4 (CH, C-2), 73.3 (CH, C-1), 73.0 (CH_2, C-19), 71.1 (CH, C-12), 67.0 (CH, C-3), 49.3 (CH, C-8), 48.2 (CH, C-4), 42.9 (C, C-5), 41.9 (CH, C-10), 40.4 (C, C-9), 36.3 (CH_2, C-6), 21.6 (CH_3, 1-$OCOCH_3$), 20.0 (CH_3, 11-$OCOCH_3$), 19.4 (CH_2, C-7), 19.3 (CH_3, C-20); EIMS *m*/*z* 492 $[M]^+$ (9), 474 (7), 450 (46), 432 (46), 408 (30), 390 (17), 378 (21), 354 (14), 335 (20), 203 (87), 189 (100), 176 (55), 161 (29), 110 (27), 95 (42), 81 (35). Anal.: C 58.20%, H 5.49%; calcd for $C_{24}H_{28}O_{11}$: C 58.53%, H 5.73%.

4.3.3. Compound **9**

Colorless rectangular plates (Me_2CO–*n*-pentane); mp 237–240 °C; $[\alpha]_D^{20}$ +28.7 (*c* 0.296, MeOH); R_f (3:1 CH_2Cl_2–acetone) 0.42; IR (KBr) ν_{max} 3470, 3152, 3135, 2952, 1749, 1507, 1446, 1392, 1292, 1230, 1152, 1072, 1049, 1027, 991, 878, 789, 667, 604 cm^{-1}; ^1H NMR [400 MHz, 2:1 $(CD_3)_2CO$–CD_3OD] δ 7.61 (1H, dd, $J_{16,14}$=0.8 Hz, $J_{16,15}$=1.6 Hz, H-16), 7.53 (1H, t, $J_{15,14}$=$J_{15,16}$=1.6 Hz, H-15), 6.51 (1H, dd, $J_{14,15}$=1.6 Hz, $J_{14,16}$=0.8 Hz, H-14), 5.54 (1H, dd, $J_{12\beta,11\alpha}$=10.9 Hz, $J_{12\beta,11\beta}$=6.6 Hz, H-12β), 4.37 (1H, dd, $J_{19a,6\beta}$=2.0 Hz, $J_{19a,19b}$=9.4 Hz, pro-*S* H-19a), 4.24 (1H, d, $J_{19b,19a}$=9.4 Hz, pro-*R* H-19b), 4.02 (1H, ddd, $J_{2\alpha,1\alpha}$=2.7 Hz, $J_{2\alpha,1\beta}$=4.7 Hz, $J_{2\alpha,3\alpha}$=2.9 Hz, H-2α), 3.73 (1H, dd, $J_{3\alpha,2\alpha}$=2.9 Hz, $J_{3\alpha,4\beta}$=10.1 Hz, H-3α), 2.91 (1H, dd, $J_{8\beta,7\alpha}$=10.3 Hz, $J_{8\beta,7\beta}$=5.3 Hz, H-8β), 2.28 (1H, dd, $J_{10\beta,1\alpha}$=12.7 Hz, $J_{10\beta,1\beta}$=3.7 Hz, H-10β), 2.15 (1H, d, $J_{4\beta,3\alpha}$=10.1 Hz, H-4β), 2.14 (1H, dd, $J_{11\beta,11\alpha}$=13.8 Hz, $J_{11\beta,12\beta}$=6.6 Hz, H-11β), 1.85 (2H, m, H-7α and H-7β), 1.78 (2H, m, H-1β and H-11α), 1.75 (1H, m, H-6α), 1.74 (1H, ddd, $J_{1\alpha,1\beta}$=14.2 Hz, $J_{1\alpha,2\alpha}$=2.7 Hz, $J_{1\alpha,10\beta}$=12.7 Hz, H-1α), 1.34 (1H, dddd, $J_{6\beta,6\alpha}$=13.5 Hz, $J_{6\beta,7\alpha}$=14.0 Hz, $J_{6\beta,7\beta}$=4.0 Hz, $J_{6\beta,19a}$=2.0 Hz, H-6β), 0.77 (3H, s, Me-20); ^{13}C NMR [100 MHz, 2:1 $(CD_3)_2CO$–CD_3OD] δ 178.0 (C, C-18), 175.2 (C, C-17), 144.9 (CH, C-15), 141.1 (CH, C-16), 126.2 (C, C-13), 109.9 (CH, C-14), 70.8 (CH, C-12), 70.6 (CH_2, C-19), 70.1 (CH, C-3), 69.5 (CH, C-2), 54.2 (CH, C-4), 47.8 (CH, C-8), 44.4 (C, C-5), 43.9 (CH_2, C-11), 43.5 (CH, C-10), 37.0 (C, C-9), 35.4 (CH_2, C-6), 27.7 (CH_2, C-1), 20.3 (CH_3, C-20), 19.5 (CH_2, C-7); EIMS *m*/*z* 376 $[M]^+$ (49), 361 (1), 265 (8), 252 (3), 238 (9), 216 (6), 171 (9), 143 (11), 131 (10), 121 (11), 105 (13), 94 (100), 81 (16), 55 (16). Anal.: C 63.61%, H 6.54%; calcd for $C_{20}H_{24}O_7$: C 63.82%, H 6.43%.

4.4. General procedure for partial acetylation: compounds 10–14

Treatment of **6** (50 mg, 0.133 mmol) with Ac_2O–pyridine (1:2, 1 mL) for 15 min at room temperature followed by standard workup and purification by FC yielded compounds **10** (21 mg, 38%) and **11** (8 mg, 15%). Treatment of **7** (50 mg, 0.115 mmol) in the same conditions as for compound **6** gave, after 2 min, compounds **12** (22 mg, 40%) and **13** (8 mg, 15%). Finally, acetylation of **8** (40 mg, 0.081 mmol) for 1.5 h yielded **14** (22 mg, 50%).

4.4.1. Compound **10**

FC eluent 97:3 CH_2Cl_2–acetone, R_f 0.22; colorless fine needles (EtOAc); mp 264–267 °C (decomp.); $[\alpha]_D^{20}$ +19.7 (*c* 0.076, MeOH); IR (KBr) ν_{max} 3575, 3440, 3003, 2925, 1785, 1742, 1721, 1455, 1372, 1237, 1202, 1183, 1131, 1075, 1028, 932, 876, 784, 691, 603 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.60 (1H, dd, $J_{16,14}$=0.8 Hz, $J_{16,15}$=1.8 Hz, H-16), 7.50 (1H, t, $J_{15,14}$=$J_{15,16}$=1.8 Hz, H-15), 6.54 (1H, dd, $J_{14,15}$=1.8 Hz, $J_{14,16}$=0.8 Hz, H-14), 5.47 (1H, dd, $J_{12\beta,11\alpha}$=12.5 Hz, $J_{12\beta,11\beta}$=3.3 Hz, H-12β), 5.08 (1H, dd, $J_{3\alpha,2\alpha}$=2.8 Hz, $J_{3\alpha,4\beta}$=10.8 Hz, H-3α), 4.55 (1H, dd, $J_{19a,6\beta}$=1.8 Hz, $J_{19a,19b}$=9.5 Hz, pro-*S* H-19a), 4.47 (1H, d, $J_{19b,19a}$=9.5 Hz, pro-*R* H-19b), 4.17 (1H, dt, $J_{2\alpha,1\alpha}$=$J_{2\alpha,3\alpha}$=2.8 Hz, $J_{2\alpha,1\beta}$=3.6 Hz, H-2α), 2.58 (1H, br dd, $J_{8\alpha,6\alpha}$<0.3 Hz, $J_{8\alpha,7\alpha}$=4.6 Hz, $J_{8\alpha,7\beta}$=2.2 Hz, H-8α), 2.40 (1H, d, $J_{4\beta,3\alpha}$=10.8 Hz, H-4β), 2.39 (1H, dd, $J_{10\beta,1\alpha}$=11.9 Hz, $J_{10\beta,1\beta}$=3.7 Hz, H-10β), 2.38 (1H, m, H-7β), 2.25 (1H, dd, $J_{11\beta,11\alpha}$=14.9 Hz, $J_{11\beta,12\beta}$=3.3 Hz, H-11β), 2.08 (3H, s, 3β-OAc), 2.06 (1H, dddd, $J_{7\alpha,6\alpha}$=3.2 Hz, $J_{7\alpha,6\beta}$=14.2 Hz, $J_{7\alpha,7\beta}$=14.7 Hz, $J_{7\alpha,8\alpha}$=4.6 Hz, H-7α), 1.84 (1H, dd, $J_{11\alpha,11\beta}$=14.9 Hz, $J_{11\alpha,12\beta}$=12.5 Hz, H-11α), 1.83 (2H, m, H-1α and H-1β), 1.66 (1H, br ddd, $J_{6\alpha,6\beta}$=13.7 Hz, $J_{6\alpha,7\alpha}$=3.2 Hz, $J_{6\alpha,7\beta}$=2.9 Hz, $J_{6\alpha,8\alpha}$<0.3 Hz, H-6α), 1.25 (1H, dddd, $J_{6\beta,6\alpha}$=13.7 Hz, $J_{6\beta,7\alpha}$=14.2 Hz, $J_{6\beta,7\beta}$=3.6 Hz, $J_{6\beta,19a}$=1.8 Hz, H-6β), 0.97 (3H, s, Me-20); ^{13}C NMR (100 MHz, CD_3OD) δ 178.2 (C, C-18), 174.8 (C, C-17), 171.8 (C, 3-$OCOCH_3$), 145.0 (CH, C-15), 141.3 (CH, C-16), 126.7 (C, C-13), 109.5 (CH, C-14), 72.2 (CH, C-12), 72.0 (CH, C-3), 71.4 (CH_2, C-19), 67.2 (CH, C-2), 51.3 (CH, C-4), 49.9 (CH, C-8), 45.0 (C, C-5), 41.7 (CH_2, C-11), 36.1 (C, C-9), 35.7 (CH, C-10), 33.9 (CH_2, C-6), 27.7 (CH_2, C-1), 23.0 (CH_3, C-20), 20.8 (CH_3, 3-$OCOCH_3$), 20.1 (CH_2, C-7); EIMS *m*/*z* 418 $[M]^+$ (92), 400 (2), 376 (14), 375 (14), 341 (25), 265 (8), 247 (30), 203 (14), 161 (18), 145 (18), 105 (20), 94 (100), 81 (22), 55 (15). Anal.: C 63.31%, H 6.09%; calcd for $C_{22}H_{26}O_8$: C 63.15%, H 6.26%.

4.4.2. Compound **11**

FC eluent 97:3 CH_2Cl_2–acetone, R_f 0.28; colorless prisms (MeOH); mp 197–200 °C; $[\alpha]_D^{20}$ +28.1 (*c* 0.032, MeOH); IR (KBr) ν_{max} 3448, 3145, 3115, 2929, 1779, 1738, 1694, 1505, 1449, 1372, 1295, 1246, 1181, 1131, 1074, 1015, 875, 787, 693, 601 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.56 (1H, dd, $J_{16,14}$=0.8 Hz, $J_{16,15}$=1.9 Hz, H-16), 7.51 (1H, t, $J_{15,14}$=$J_{15,16}$=1.9 Hz, H-15), 6.51 (1H, dd, $J_{14,15}$=1.9 Hz, $J_{14,16}$=0.8 Hz, H-14), 5.20 (1H, td, $J_{2\alpha,1\alpha}$=2.1 Hz, $J_{2\alpha,1\beta}$=$J_{2\alpha,3\alpha}$=3.2 Hz, H-2α), 5.18 (1H, dd, $J_{12\beta,11\alpha}$=12.8 Hz, $J_{12\beta,11\beta}$=3.2 Hz, H-12β), 4.47 (1H, dd, $J_{19a,6\beta}$=1.8 Hz, $J_{19a,19b}$=9.6 Hz, pro-*S* H-19a), 4.43 (1H, d, $J_{19b,19a}$=9.6 Hz, pro-*R* H-19b), 3.92 (1H, dd, $J_{3\alpha,2\alpha}$=3.2 Hz, $J_{3\alpha,4\beta}$=10.0 Hz, H-3α), 2.59 (1H, ddd, $J_{8\alpha,6\alpha}$=0.6 Hz, $J_{8\alpha,7\alpha}$=4.8 Hz, $J_{8\alpha,7\beta}$=3.5 Hz, H-8α), 2.38 (1H, dddd, $J_{7\beta,6\alpha}$=2.8 Hz, $J_{7\beta,6\beta}$=3.2 Hz, $J_{7\beta,7\alpha}$=14.0 Hz, $J_{7\beta,8\alpha}$=3.5 Hz, H-7β), 2.24 (1H, d, $J_{4\beta,3\alpha}$=10.0 Hz, H-4β), 2.20 (1H, dd, $J_{11\beta,11\alpha}$=15.0 Hz, $J_{11\beta,12\beta}$=3.2 Hz, H-11β), 2.16 (1H, dd, $J_{10\beta,1\alpha}$=12.8 Hz, $J_{10\beta,1\beta}$=3.4 Hz, H-10β), 2.13 (3H, s, 2β-OAc), 2.08 (1H, m, H-1β), 2.01 (1H, dddd, $J_{7\alpha,6\alpha}$=3.6 Hz, $J_{7\alpha,6\beta}$=14.8 Hz, $J_{7\alpha,7\beta}$=14.0 Hz, $J_{7\alpha,8\alpha}$=4.8 Hz, H-7α), 1.85 (1H, ddd, $J_{1\alpha,1\beta}$=14.8 Hz, $J_{1\alpha,2\alpha}$=2.1 Hz, $J_{1\alpha,10\beta}$=12.8 Hz, H-1α), 1.84 (1H, dd, $J_{11\alpha,11\beta}$=15.0 Hz, $J_{11\alpha,12\beta}$=12.8 Hz, H-11α), 1.70 (1H, dddd, $J_{6\alpha,6\beta}$=14.0 Hz, $J_{6\alpha,7\alpha}$=3.6 Hz, $J_{6\alpha,7\beta}$=2.8 Hz, $J_{6\alpha,8\alpha}$=0.6 Hz, H-6α), 1.24 (1H, dddd, $J_{6\beta,6\alpha}$=14.0 Hz, $J_{6\beta,7\alpha}$=14.8 Hz, $J_{6\beta,7\beta}$=3.2 Hz, $J_{6\beta,19a}$=1.8 Hz, H-6β), 0.96 (3H, s, Me-20); ^{13}C NMR (100 MHz, CD_3OD) δ 178.1 (C, C-18), 174.5 (C, C-17), 172.2 (C, 2-$OCOCH_3$), 145.2 (CH, C-15), 141.2 (CH, C-16), 126.4 (C, C-13), 109.4 (CH, C-14), 73.3 (CH, C-2), 72.3 (CH, C-12), 71.3 (CH_2, C-19), 68.7 (CH, C-3), 55.1 (CH, C-4), 49.9 (CH, C-8), 44.6 (C, C-5), 41.6 (CH_2, C-11), 37.1 (CH, C-10), 36.1 (C, C-9), 34.2 (CH_2, C-6), 25.1 (CH_2, C-1), 22.8 (CH_3, C-20), 21.1 (CH_3, 2-$OCOCH_3$), 20.1 (CH_2, C-7); EIMS *m*/*z* 418 $[M]^+$ (59), 400 (1), 376 (7), 375 (7), 358 (11), 341 (13), 247 (22), 203 (12), 161 (18), 143 (17), 105 (20), 94 (100), 81 (26), 55 (21). Anal.: C 63.01%, H 6.18%; calcd for $C_{22}H_{26}O_8$: C 63.15%, H 6.26%.

4.4.3. Compound **12**

FC eluent 90:10 CH_2Cl_2–acetone, R_f 0.33; colorless prisms (EtOAc–*n*-pentane); mp 157–160 °C; $[\alpha]_D^{20}$ −48.6 (*c* 0.111, $CHCl_3$); IR

(KBr) ν_{max} 3463, 3145, 2927, 1779, 1745, 1506, 1447, 1376, 1223, 1161, 1040, 1012, 933, 875, 729, 603 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (1H, dd, $J_{16,14}$=0.8 Hz, $J_{16,15}$=1.9 Hz, H-16), 7.39 (1H, t, $J_{15,14}$=$J_{15,16}$=1.9 Hz, H-15), 6.39 (1H, dd, $J_{14,15}$=1.9 Hz, $J_{14,16}$=0.8 Hz, H-14), 5.39 (1H, d, $J_{12\beta,11\alpha}$=10.7 Hz, H-12β), 5.18 (1H, d, $J_{11\alpha,12\beta}$=10.7 Hz, H-11α), 5.04 (1H, dd, $J_{3\alpha,2\alpha}$=2.8 Hz, $J_{3\alpha,4\beta}$=10.8 Hz, H-3α), 4.32 (1H, dd, $J_{19a,6\beta}$=1.9 Hz, $J_{19a,19b}$=9.6 Hz, pro-*S* H-19a), 4.27 (1H, d, $J_{19b,19a}$=9.6 Hz, pro-*R* H-19b), 4.18 (1H, ddd, $J_{2\alpha,1\alpha}$=3.0 Hz, $J_{2\alpha,1\beta}$=4.6 Hz, $J_{2\alpha,3\alpha}$=2.8 Hz, H-2α), 2.66 (1H, br dd, $J_{8\alpha,6\alpha}$<0.5 Hz, $J_{8\alpha,7\alpha}$=4.1 Hz, $J_{8\alpha,7\beta}$=2.4 Hz, H-8α), 2.64 (1H, dd, $J_{10\beta,1\alpha}$=10.0 Hz, $J_{10\beta,1\beta}$=2.8 Hz, H-10β), 2.48 (2H, m, H-1β and H-7β), 2.44 (1H, d, $J_{4\beta,3\alpha}$=10.8 Hz, H-4β), 2.16 (3H, s, 3β-OAc), 1.96 (3H, s, 11β-OAc), 1.90 (1H, ddt, $J_{7\alpha,6\alpha}$=$J_{7\alpha,8\alpha}$=4.1 Hz, $J_{7\alpha,6\beta}$=14.2 Hz, $J_{7\alpha,7\beta}$=14.6 Hz, H-7α), 1.75 (1H, br ddd, $J_{6\alpha,6\beta}$=14.0 Hz, $J_{6\alpha,7\alpha}$=4.0 Hz, $J_{6\alpha,7\beta}$=3.1 Hz, $J_{6\alpha,8\alpha}$<0.5 Hz, H-6α), 1.66 (1H, ddd, $J_{1\alpha,1\beta}$=13.8 Hz, $J_{1\alpha,2\alpha}$=3.0 Hz, $J_{1\alpha,10\beta}$=10.0 Hz, H-1α), 1.32 (1H, dddd, $J_{6\beta,6\alpha}$=14.0 Hz, $J_{6\beta,7\alpha}$=14.2 Hz, $J_{6\beta,7\beta}$=3.9 Hz, $J_{6\beta,19a}$=1.9 Hz, H-6β), 0.92 (3H, s, Me-20); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8 (C, C-18), 169.8 (C, 3-O*C*OCH$_3$), 169.7 (C, C-17), 169.1 (C, 11-O*C*OCH$_3$), 143.9 (CH, C-15), 141.5 (CH, C-16), 121.4 (C, C-13), 108.5 (CH, C-14), 76.4 (CH, C-11), 71.4 (CH, C-12), 69.9 (CH, C-3), 69.6 (CH_2, C-19), 66.6 (CH, C-2), 49.6 (CH, C-4), 49.3 (CH, C-8), 43.9 (C, C-5), 38.9 (C, C-9), 34.0 (CH, C-10), 32.1 (CH_2, C-6), 27.5 (CH_2, C-1), 20.9 (C, 3-OCO*C*H$_3$), 20.7 (CH_3, 11-OCO*C*H$_3$), 19.7 (CH_2, C-7), 18.4 (CH_3, C-20); EIMS *m*/*z* 476 $[M]^+$ (5), 458 (4), 434 (9), 416 (45), 398 (17), 374 (14), 356 (16), 338 (16), 325 (18), 203 (100), 189 (44), 110 (16), 95 (19), 81 (17). Anal.: C 60.29%, H 5.78%; calcd for $C_{24}H_{28}O_{10}$: C 60.50%, H 5.92%.

4.4.4. Compound **13**

FC eluent 90:10 CH_2Cl_2–acetone, R_f 0.40; amorphous, white solid; $[\alpha]_D^{20}$ −38.9 (*c* 0.072, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (1H, dd, $J_{16,14}$=1.0 Hz, $J_{16,15}$=1.9 Hz, H-16), 7.40 (1H, t, $J_{15,14}$=$J_{15,16}$=1.9 Hz, H-15), 6.36 (1H, dd, $J_{14,15}$=1.9 Hz, $J_{14,16}$=1.0 Hz, H-14), 5.29 (1H, ddd, $J_{2\alpha,1\alpha}$=2.7 Hz, $J_{2\alpha,1\beta}$=4.8 Hz, $J_{2\alpha,3\alpha}$=3.1 Hz, H-2α), 5.15 (1H, d, $J_{11\alpha,12\beta}$=10.9 Hz, H-11α), 5.10 (1H, d, $J_{12\beta,11\alpha}$=10.9 Hz, H-12β), 4.30 (1H, d, $J_{19a,19b}$=9.4 Hz, pro-*R* H-19a), 4.23 (1H, dd, $J_{19b,6\beta}$=1.9 Hz, $J_{19b,19a}$=9.4 Hz, pro-*S* H-19b), 3.89 (1H, ddd, $J_{3\alpha,2\alpha}$=3.1 Hz, $J_{3\alpha,4\beta}$=9.4 Hz, $J_{3\alpha,3\beta OH}$=4.3 Hz, H-3α), 2.70 (2H, m, H-1β and H-7β), 2.67 (1H, br dd, $J_{8\alpha,6\alpha}$<0.5 Hz, $J_{8\alpha,7\alpha}$=4.7 Hz, $J_{8\alpha,7\beta}$=2.5 Hz, H-8α), 2.44 (1H, d, $J_{3\beta OH,3\alpha}$=4.3 Hz, 3β-OH), 2.42 (1H, dd, $J_{10\beta,1\alpha}$=12.9 Hz, $J_{10\beta,1\beta}$=3.9 Hz, H-10β), 2.31 (1H, d, $J_{4\beta,3\alpha}$=9.4 Hz, H-4β), 2.19 (3H, s, 2β-OAc), 1.96 (3H, s, 11β-OAc), 1.92 (1H, dddd, $J_{7\alpha,6\alpha}$=4.1 Hz, $J_{7\alpha,6\beta}$=14.2 Hz, $J_{7\alpha,7\beta}$=14.4 Hz, $J_{7\alpha,8\alpha}$=4.7 Hz, H-7α), 1.80 (1H, br ddd, $J_{6\alpha,6\beta}$=14.2 Hz, $J_{6\alpha,7\alpha}$=4.1 Hz, $J_{6\alpha,7\beta}$=3.2 Hz, $J_{6\alpha,8\alpha}$<0.5 Hz, H-6α), 1.72 (1H, ddd, $J_{1\alpha,1\beta}$=15.2 Hz, $J_{1\alpha,2\alpha}$=2.7 Hz, $J_{1\alpha,10\beta}$=12.9 Hz, H-1α), 1.35 (1H, tdd, $J_{6\beta,6\alpha}$=$J_{6\beta,7\alpha}$=14.2 Hz, $J_{6\beta,7\beta}$=3.8 Hz, $J_{6\beta,19b}$=1.9 Hz, H-6β), 0.92 (3H, s, Me-20); EIMS *m*/*z* 476 $[M]^+$ (17), 434 (16), 416 (32), 398 (17), 374 (11), 338 (11), 325 (22), 203 (100), 189 (33), 176 (14), 110 (16), 95 (22), 81 (18); $C_{24}H_{28}O_{10}$, M_r 476.

4.4.5. Compound **14**

FC eluent 90:10 CH_2Cl_2–acetone, R_f 0.25; colorless prisms (EtOAc–*n*-pentane); mp 190–193 °C, $[\alpha]_D^{20}$ −20.5 (*c* 0.341, $CHCl_3$); IR (KBr) ν_{max} 3451, 3015, 2943, 1745, 1506, 1444, 1370, 1239, 1143, 1039, 970, 899, 875, 737, 603 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (1H, dd, $J_{16,14}$=1.0 Hz, $J_{16,15}$=1.8 Hz, H-16), 7.39 (1H, t, $J_{15,14}$=$J_{15,16}$=1.8 Hz, H-15), 6.38 (1H, dd, $J_{14,15}$=1.8 Hz, $J_{14,16}$=1.0 Hz, H-14), 5.81 (1H, d, $J_{12\beta,11\alpha}$=10.9 Hz, H-12β), 5.34 (1H, d, $J_{11\alpha,12\beta}$=10.9 Hz, H-11α), 5.13 (1H, dd, $J_{1\alpha,2\alpha}$=0.8 Hz, $J_{1\alpha,10\beta}$=8.8 Hz, H-1α), 5.09 (1H, dd, $J_{3\alpha,2\alpha}$=1.9 Hz, $J_{3\alpha,4\beta}$=8.7 Hz, H-3α), 4.63 (1H, dd, $J_{19a,6\beta}$=2.1 Hz, $J_{19a,19b}$=8.7 Hz, pro-*S* H-19a), 4.14 (1H, d, $J_{19b,19a}$=8.7 Hz, pro-*R* H-19b), 3.92 (1H, ddd, $J_{2\alpha,1\alpha}$=0.8 Hz, $J_{2\alpha,3\alpha}$=1.9 Hz, $J_{2\alpha,2\beta OH}$=3.7 Hz, H-2α), 3.68 (1H, d, $J_{2\beta OH,2\alpha}$=3.7 Hz, 3β-OH), 2.90 (1H, d, $J_{4\beta,3\alpha}$=8.7 Hz, H-4β), 2.71 (1H, ddd, $J_{8\alpha,6\alpha}$=1.0 Hz, $J_{8\alpha,7\alpha}$=4.2 Hz, $J_{8\alpha,7\beta}$=3.3 Hz, H-8α), 2.45 (1H, ddt, $J_{7\beta,6\alpha}$=$J_{7\beta,8\alpha}$=3.3 Hz, $J_{7\beta,6\beta}$=3.7 Hz, $J_{7\beta,7\alpha}$=14.6 Hz, H-7β), 2.36 (1H, d, $J_{10\beta,1\alpha}$=8.8 Hz, H-10β), 2.14 (3H, s, 3β-OAc), 2.04 (3H, s, 1β-OAc), 1.92 (1H, ddt, $J_{7\alpha,6\alpha}$=$J_{7\alpha,8\alpha}$=4.2 Hz, $J_{7\alpha,6\beta}$=14.0 Hz, $J_{7\alpha,7\beta}$=14.6 Hz, H-7α), 1.88 (3H, s, 11β-OAc), 1.83 (1H, dddd, $J_{6\alpha,6\beta}$=14.2 Hz, $J_{6\alpha,7\alpha}$=4.1 Hz, $J_{6\alpha,7\beta}$=3.3 Hz, $J_{6\alpha,8\alpha}$=1.0 Hz, H-6α), 1.47 (1H, dddd, $J_{6\beta,6\alpha}$=14.2 Hz, $J_{6\beta,7\alpha}$=14.0 Hz, $J_{6\beta,7\beta}$=3.7 Hz, $J_{6\beta,19a}$=2.1 Hz, H-6β), 1.08 (3H, s, Me-20); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4 (C, C-18), 170.5 (C, 3-O*C*OCH$_3$), 169.8 (C, 1-O*C*OCH$_3$), 169.6 (C, 11-O*C*OCH$_3$), 169.0 (C, C-17), 144.2 (CH, C-15), 141.7 (CH, C-16), 121.4 (C, C-13), 108.6 (CH, C-14), 76.0 (CH, C-11), 73.0 (CH, C-1), 72.5 (CH, C-2), 72.0 (CH_2, C-19), 71.0 (CH, C-12), 68.5 (CH, C-3), 49.2 (CH, C-8), 45.4 (CH, C-4), 42.9 (CH, C-10), 41.9 (C, C-5), 40.4 (C, C-9), 36.2 (CH_2, C-6), 21.5 (CH_3, 1-OCO*C*H$_3$), 20.8 (CH_3, 3-OCO*C*H$_3$), 20.0 (CH_3, 11-OCO*C*H$_3$), 19.5 (CH_3, C-20), 19.3 (CH_2, C-7); EIMS *m*/*z* 534 $[M]^+$ (4), 516 (1), 492 (32), 474 (48), 450 (19), 432 (18), 415 (19), 372 (16), 354 (23), 337 (24), 277 (16), 219 (17), 204 (100), 203 (97), 202 (46), 189 (100), 176 (68), 161 (31), 110 (28), 95 (43), 81 (38). Anal.: C 58.19%, H 5.41%; calcd for $C_{26}H_{30}O_{12}$: C 58.42%, H 5.66%.

4.5. General procedure for complete acetylation: compounds 15–18

Treatment of compounds **6**–**9** (0.05 mmol) with Ac_2O–pyridine (1:2, 400 μL) for 24 h at room temperature followed by standard workup and purification by FC yielded quantitatively the acetyl derivatives **15**–**18**, respectively.

4.5.1. Compound **15**

FC eluent 97:3 CH_2Cl_2–acetone, R_f 0.45; colorless prisms (EtOAc–*n*-pentane); mp 283–286 °C; $[\alpha]_D^{20}$ +25.7 (*c* 0.167, $CHCl_3$); IR (KBr) ν_{max} 3139, 2926, 1784, 1746, 1726, 1449, 1366, 1293, 1247, 1179, 1132, 1054, 1028, 1008, 923, 875, 802, 785, 691, 604 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (2H, m, H-15 and H-16), 6.38 (1H, dd, $J_{14,15}$=1.8 Hz, $J_{14,16}$=1.0 Hz, H-14), 5.43 (1H, ddd, $J_{2\alpha,1\alpha}$=2.4 Hz, $J_{2\alpha,1\beta}$=4.8 Hz, $J_{2\alpha,3\alpha}$=3.1 Hz, H-2α), 5.17 (1H, dd, $J_{12\beta,11\alpha}$=12.7 Hz, $J_{12\beta,11\beta}$=3.2 Hz, H-12β), 5.05 (1H, dd, $J_{3\alpha,2\alpha}$=3.1 Hz, $J_{3\alpha,4\beta}$=11.1 Hz, H-3α), 4.33 (2H, s, H_2-19), 2.53 (1H, ddt, $J_{7\beta,6\alpha}$=$J_{7\beta,8\alpha}$=2.6 Hz, $J_{7\beta,6\beta}$=3.4 Hz, $J_{7\beta,7\alpha}$=14.7 Hz, H-7β), 2.47 (1H, br dd, $J_{8\alpha,6\alpha}$<0.4 Hz, $J_{8\alpha,7\alpha}$=4.5 Hz, $J_{8\alpha,7\beta}$=2.6 Hz, H-8α), 2.38 (1H, d, $J_{4\beta,3\alpha}$=11.1 Hz, H-4β), 2.22 (1H, dd, $J_{10\beta,1\alpha}$=13.6 Hz, $J_{10\beta,1\beta}$=2.9 Hz, H-10β), 2.17 (1H, dd, $J_{11\beta,11\alpha}$=15.0 Hz, $J_{11\beta,12\beta}$=3.2 Hz, H-11β), 2.13 (3H, s, 2β-OAc), 2.04 (3H, s, 3β-OAc), 1.93 (1H, ddd, $J_{1\beta,1\alpha}$=15.2 Hz, $J_{1\beta,2\alpha}$=4.8 Hz, $J_{1\beta,10\beta}$=2.9 Hz, H-1β), 1.91 (1H, dddd, $J_{7\alpha,6\alpha}$=2.8 Hz, $J_{7\alpha,6\beta}$=14.3 Hz, $J_{7\alpha,7\beta}$=14.7 Hz, $J_{7\alpha,8\alpha}$=4.5 Hz, H-7α), 1.78 (1H, m, H-6α), 1.75 (1H, dd, $J_{11\alpha,11\beta}$=15.0 Hz, $J_{11\alpha,12\beta}$=12.7 Hz, H-11α), 1.74 (1H, ddd, $J_{1\alpha,1\beta}$=15.2 Hz, $J_{1\alpha,2\alpha}$=2.4 Hz, $J_{1\alpha,10\beta}$=13.6 Hz, H-1α), 1.36 (1H, ddd, $J_{6\beta,6\alpha}$=13.8 Hz, $J_{6\beta,7\alpha}$=14.3 Hz, $J_{6\beta,7\beta}$=3.4 Hz, H-6β), 0.95 (3H, s, Me-20); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0 (C, C-18), 171.4 (C, C-17), 170.0 (C, 3-O*C*OCH$_3$), 169.9 (C, 2-O*C*OCH$_3$), 144.0 (CH, C-15), 139.5 (CH, C-16), 124.5 (C, C-13), 108.1 (CH, C-14), 70.4 (CH, C-12), 69.5 (CH_2, C-19), 67.9 (CH, C-3), 67.8 (CH, C-2), 49.8 (CH, C-4), 48.8 (CH, C-8), 43.5 (C, C-5), 40.9 (CH_2, C-11), 35.7 (CH, C-10), 35.0 (C, C-9), 32.5 (CH_2, C-6), 24.6 (CH_2, C-1), 22.9 (CH_3, C-20), 21.1 (CH_3, 2-OCO*C*H$_3$), 20.6 (CH_3, 3-OCO*C*H$_3$), 19.1 (CH_2, C-7); EIMS *m*/*z* 460 $[M]^+$ (100), 418 (46), 400 (5), 375 (6), 357 (62), 341 (52), 247 (31), 203 (15), 145 (14), 94 (47), 81 (14). Anal.: C 62.81%, H 6.20%; calcd for $C_{24}H_{28}O_9$: C 62.60%, H 6.13%.

4.5.2. Compound **16**

FC eluent 95:5 CH_2Cl_2–acetone, R_f 0.35; colorless quadrangular plaques (EtOAc–petroleum ether); mp 260–263 °C; $[\alpha]_D^{20}$ −37.9 (*c* 0.269, $CHCl_3$); IR (KBr) ν_{max} 3145, 2936, 1776, 1750, 1747, 1447, 1373, 1229, 1186, 1161, 1139, 1057, 876, 735, 603 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (1H, dd, $J_{16,14}$=0.9 Hz, $J_{16,15}$=1.8 Hz, H-16), 7.39 (1H, t, $J_{15,14}$=$J_{15,16}$=1.8 Hz, H-15), 6.35 (1H, dd, $J_{14,15}$=1.8 Hz, $J_{14,16}$=0.9 Hz, H-14), 5.44 (1H, dt, $J_{2\alpha,1\alpha}$=$J_{2\alpha,3\alpha}$=3.1 Hz, $J_{2\alpha,1\beta}$=4.8 Hz, H-2α), 5.16

(1xH, d, $J_{11\alpha,12\beta}$=10.8 Hz, H-11α), 5.10 (1H, d, $J_{12\beta,11\alpha}$=10.8 Hz, H-12β), 5.02 (1H, dd, $J_{3\alpha,2\alpha}$=3.1 Hz, $J_{3\alpha,4\beta}$=11.0 Hz, H-3α), 4.33 (1H, dd, $J_{19a,6\beta}$=1.6 Hz, $J_{19a,19b}$=9.5 Hz, pro-*S* H-19a), 4.28 (1H, d, $J_{19b,19a}$=9.5 Hz, pro-*R* H-19b), 2.68 (1H, br dd, $J_{8\alpha,6\alpha}$<0.5 Hz, $J_{8\alpha,7\alpha}$=4.1 Hz, $J_{8\alpha,7\beta}$=2.8 Hz, H-8α), 2.41 (1H, dd, $J_{10\beta,1\alpha}$=13.2 Hz, $J_{10\beta,1\beta}$=3.3 Hz, H-10β), 2.50 (2H, m, H-1β and H-7β), 2.40 (1H, d, $J_{4\beta,3\alpha}$=11.0 Hz, H-4β), 2.17 (3H, s, 3β- or 2β-OAc), 2.03 (3H, s, 2β- or 3β-OAc), 1.95 (3H, s, 11β-OAc), 1.92 (1H, dddd, $J_{7\alpha,6\alpha}$=3.9 Hz, $J_{7\alpha,6\beta}$=13.8 Hz, $J_{7\alpha,7\beta}$=14.4 Hz, $J_{7\alpha,8\alpha}$=4.1 Hz, H-7α), 1.78 (2H, m, H-1α and H-6α), 1.34 (1H, dddd, $J_{6\beta,6\alpha}$=14.0 Hz, $J_{6\beta,7\alpha}$=13.8 Hz, $J_{6\beta,7\beta}$=4.0 Hz, $J_{6\beta,19a}$=1.6 Hz, H-6β), 0.92 (3H, s, Me-20); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8 (C, C-18), 170.1 (C, 3-O*C*OCH$_3$), 170.0 (C, 2-O*C*OCH$_3$), 169.5 (C, C-17), 168.9 (C, 11-O*C*OCH$_3$), 144.1 (CH, C-15), 141.2 (CH, C-16), 121.2 (C, C-13), 108.3 (CH, C-14), 76.1 (CH, C-11), 71.5 (CH, C-12), 69.4 (CH_2, C-19), 67.9 (CH, C-2), 67.5 (CH, C-3), 49.8 (CH, C-4), 49.2 (CH, C-8), 43.9 (C, C-5), 38.9 (C, C-9), 35.6 (CH, C-10), 32.1 (CH_2, C-6), 25.9 (CH_2, C-1), 21.1 (C, 2- or 3-OCO*C*H$_3$), 20.7 (CH_3, 3- or 2-OCO*C*H$_3$), 20.6 (CH_3, 11-OCO*C*H$_3$), 19.7 (CH_2, C-7), 18.2 (CH_3, C-20); EIMS *m*/*z* 518 $[M]^+$ (9), 476 (46), 458 (60), 434 (18), 416 (18), 398 (50), 374 (21), 357 (22), 338 (29), 325 (18), 203 (100), 202 (99), 189 (84), 161 (22), 110 (25), 95 (31), 81 (29). Anal.: C 60.41%, H 5.62%; calcd for $C_{26}H_{30}O_{11}$: C 60.23%, H 5.83%.

4.5.3. Compound ***17***

FC eluent 95:5 CH_2Cl_2–acetone, R_f 0.27; colorless fine plates (EtOAc–*n*-pentane); mp 285–287 °C, $[\alpha]_D^{20}$ −29.9 (*c* 0.267, $CHCl_3$); IR (KBr) ν_{max} 3145, 2932, 1752, 1436, 1371, 1233, 1162, 1043, 958, 875, 738, 603 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (1H, dd, $J_{16,14}$=1.0 Hz, $J_{16,15}$=1.8 Hz, H-16), 7.40 (1H, t, $J_{15,14}$=$J_{15,16}$=1.8 Hz, H-15), 6.39 (1H, dd, $J_{14,15}$=1.8 Hz, $J_{14,16}$=1.0 Hz, H-14), 5.80 (1H, d, $J_{12\beta,11\alpha}$=11.0 Hz, H-12β), 5.34 (1H, d, $J_{11\alpha,12\beta}$=11.0 Hz, H-11α), 5.22 (2H, m, H-2α and H-3α), 5.09 (1H, br d, $J_{1\alpha,2\alpha}$<0.4 Hz, $J_{1\alpha,10\beta}$=8.8 Hz, H-1α), 4.45 (1H, dd, $J_{19a,6\beta}$=2.1 Hz, $J_{19a,19b}$=9.1 Hz, pro-*S* H-19a), 4.21 (1H, d, $J_{19b,19a}$=9.1 Hz, pro-*R* H-19b), 2.88 (1H, d, $J_{4\beta,3\alpha}$=8.7 Hz, H-4β), 2.73 (1H, ddd, $J_{8\alpha,6\alpha}$=1.2 Hz, $J_{8\alpha,7\alpha}$=4.0 Hz, $J_{8\alpha,7\beta}$=3.4 Hz, H-8α), 2.48 (1H, dddd, $J_{7\beta,6\alpha}$=2.9 Hz, $J_{7\beta,6\beta}$=3.8 Hz, $J_{7\beta,7\alpha}$=14.4 Hz, $J_{7\beta,8\alpha}$=3.4 Hz, H-7β), 2.42 (1H, d, $J_{10\beta,1\alpha}$=8.8 Hz, H-10β), 2.09 (6H, s, 2β-OAc and 3β-OAc), 2.06 (3H, s, 1β-OAc), 1.93 (1H, ddt, $J_{7\alpha,6\alpha}$=$J_{7\alpha,8\alpha}$=4.0 Hz, $J_{7\alpha,6\beta}$=14.0 Hz, $J_{7\alpha,7\beta}$=14.4 Hz, H-7α), 1.87 (3H, s, 11β-OAc), 1.85 (1H, dddd, $J_{6\alpha,6\beta}$=14.7 Hz, $J_{6\alpha,7\alpha}$=4.1 Hz, $J_{6\alpha,7\beta}$=2.9 Hz, $J_{6\alpha,8\alpha}$=1.2 Hz, H-6α), 1.52 (1H, dddd, $J_{6\beta,6\alpha}$=14.2 Hz, $J_{6\beta,7\alpha}$=14.0 Hz, $J_{6\beta,7\beta}$=3.8 Hz, $J_{6\beta,19a}$=2.1 Hz, H-6β), 1.07 (3H, s, Me-20); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3 (C, C-18), 170.4 (C, 3- or 2-O*C*OCH$_3$), 169.6 (C, 11-O*C*OCH$_3$), 169.1 (C, C-17), 168.7 (C, 1-O*C*OCH$_3$), 168.1 (C, 2- or 3-O*C*OCH$_3$), 144.3 (CH, C-15), 141.7 (CH, C-16), 121.3 (C, C-13), 108.5 (CH, C-14), 75.9 (CH, C-11), 71.7 (CH_2, C-19), 71.36 (2CH, C-1 and C-2), 71.0 (CH, C-12), 66.5 (CH, C-3), 49.3 (CH, C-8), 45.7 (CH, C-4), 43.0 (C, C-5), 41.7 (CH, C-10), 40.4 (C, C-9), 36.3 (CH_2, C-6), 21.4 (CH_3, 1-OCO*C*H$_3$), 20.7 (CH_3, 3- or 2-OCO*C*H$_3$), 20.4 (CH_3, 2- or 3-OCO*C*H$_3$), 20.0 (CH_3, 11-OCO*C*H$_3$), 19.4 (CH_3, C-20), 19.2 (CH_2, C-7); EIMS *m*/*z* 576 $[M]^+$ (2), 534 (23), 516 (52), 492 (24), 474 (35), 456 (25), 431 (18), 371 (22), 354 (28), 337 (32), 204 (94), 203 (96), 202 (53), 189 (100), 176 (50), 161 (26), 110 (23), 95 (33), 81 (27). Anal.: C 58.29%, H 5.73%; calcd for $C_{28}H_{32}O_{13}$: C 58.33%, H 5.59%.

4.5.4. Compound ***18***

FC eluent 95:5 CH_2Cl_2–acetone, R_f 0.47; amorphous, vitreous solid; $[\alpha]_D^{20}$ +32.0 (*c* 0.147, $CHCl_3$); IR (KBr) ν_{max} 3148, 2948, 1781, 1746, 1506, 1373, 1227, 1180, 1155, 1060, 1020, 875, 805, 738, 602 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (1H, dd, $J_{16,14}$=0.8 Hz, $J_{16,15}$=1.7 Hz, H-16), 7.42 (1H, t, $J_{15,14}$=$J_{15,16}$=1.7 Hz, H-15), 6.40 (1H, dd, $J_{14,15}$=1.7 Hz, $J_{14,16}$=0.8 Hz, H-14), 5.46 (1H, ddd, $J_{2\alpha,1\alpha}$=2.3 Hz, $J_{2\alpha,1\beta}$=4.8 Hz, $J_{2\alpha,3\alpha}$=3.1 Hz, H-2α), 5.37 (1H, dd, $J_{12\beta,11\alpha}$=10.4 Hz, $J_{12\beta,11\beta}$=7.1 Hz, H-12β), 5.05 (1H, dd, $J_{3\alpha,2\alpha}$=3.1 Hz, $J_{3\alpha,4\beta}$=11.0 Hz, H-3α), 4.31 (1H, dd, $J_{19a,6\beta}$=2.0 Hz, $J_{19a,19b}$=9.5 Hz, pro-*S* H-19a), 4.24 (1H, d, $J_{19b,19a}$=9.5 Hz, pro-*R* H-19b), 2.66 (1H, dd, $J_{8\beta,7\alpha}$=11.9 Hz, $J_{8\beta,7\beta}$=3.9 Hz, H-8β), 2.41 (1H, d, $J_{4\beta,3\alpha}$=11.0 Hz, H-4β), 2.13 (3H, s, 2β-OAc), 2.04 (1H, m, H-7β), 2.03 (3H, s, 3β-OAc), 2.02 (1H, m, H-7α), 2.00 (1H, m, H-6α), 1.95 (1H, dd, $J_{10\beta,1\alpha}$=13.5 Hz, $J_{10\beta,1\beta}$=2.8 Hz, H-10β), 1.88 (3H, m, H-1β, H-11α, and H-11β), 1.76 (1H, ddd, $J_{1\alpha,1\beta}$=15.2 Hz, $J_{1\alpha,2\alpha}$=2.3 Hz, $J_{1\alpha,10\beta}$=13.5 Hz, H-1α), 1.38 (1H, tdd, $J_{6\beta,6\alpha}$=$J_{6\beta,7\alpha}$=13.6 Hz, $J_{6\beta,7\beta}$=3.8 Hz, $J_{6\beta,19a}$=2.0 Hz, H-6β), 0.82 (3H, s, Me-20); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1 (C, C-18), 172.9 (C, C-17), 169.9 (C, 3-O*C*OCH$_3$), 169.7 (C, 2-O*C*OCH$_3$), 144.0 (CH, C-15), 139.7 (CH, C-16), 124.0 (C, C-13), 108.5 (CH, C-14), 69.8 (CH, C-12), 69.5 (CH_2, C-19), 68.0 (CH, C-3), 67.6 (CH, C-2), 49.7 (CH, C-4), 47.2 (CH, C-8), 44.3 (CH, C-10), 43.6 (C, C-5), 43.2 (CH_2, C-11), 36.2 (C, C-9), 34.3 (CH_2, C-6), 25.1 (CH_2, C-1), 21.0 (CH_3, 2-OCO*C*H$_3$), 20.6 (CH_3, 3-OCO*C*H$_3$), 19.7 (CH_3, C-20), 18.5 (CH_2, C-7); EIMS *m*/*z* 460 $[M]^+$ (34), 445 (1), 418 (14), 400 (4), 376 (6), 358 (19), 234 (15), 220 (15), 188 (20), 143 (15), 94 (100), 81 (14). Anal. C 62.33%, H 5.97%; calcd for $C_{24}H_{28}O_9$: C 62.60%, H 6.13%.

4.6. Preparation of thiocarbonate 19 from compound 9

A solution of compound **9** (100 mg, 0.266 mmol), 95% 1,1′-thiocarbonyldiimidazole (165 mg, 0.879 mmol), and 4-DMAP (6 mg, 0.049 mmol) in dry CH_2Cl_2 (10 mL) was heated to reflux under Ar for 3.5 h. Then, the solvent was removed in vacuo and the solid residue was purified by FC (90:10 CH_2Cl_2–acetone as eluent) to give pure **19** (64 mg, 58%): colorless quadrangular plates (MeOH); mp 277–280 °C; $[\alpha]_D^{20}$ +76.2 (*c* 0.021, pyridine); IR (KBr) ν_{max} 3153, 3126, 2939, 1774, 1750, 1509, 1445, 1354, 1222, 1185, 1155, 1143, 1068, 1030, 876, 823, 603 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.60 (1H, dd, $J_{16,14}$=0.9 Hz, $J_{16,15}$=1.9 Hz, H-16), 7.51 (1H, t, $J_{15,14}$=$J_{15,16}$=1.9 Hz, H-15), 6.51 (1H, dd, $J_{14,15}$=1.9 Hz, $J_{14,16}$=0.9 Hz, H-14), 5.52 (1H, dd, $J_{12\beta,11\alpha}$=11.0 Hz, $J_{12\beta,11\beta}$=6.5 Hz, H-12β), 4.91 (1H, ddd, $J_{2\alpha,1\alpha}$=3.0 Hz, $J_{2\alpha,1\beta}$=2.7 Hz, $J_{2\alpha,3\alpha}$=4.7 Hz, H-2α), 4.47 (1H, dd, $J_{19a,6\beta}$=2.0 Hz, $J_{19a,19b}$=9.6 Hz, pro-*S* H-19a), 4.37 (1H, d, $J_{19b,19a}$=9.6 Hz, pro-*R* H-19b), 3.99 (1H, dd, $J_{3\alpha,2\alpha}$=4.7 Hz, $J_{3\alpha,4\beta}$=9.8 Hz, H-3α), 2.96 (1H, dd, $J_{8\beta,7\alpha}$=11.4 Hz, $J_{8\beta,7\beta}$=4.4 Hz, H-8β), 2.53 (1H, d, $J_{4\beta,3\alpha}$=9.8 Hz, H-4β), 2.30 (1H, dt, $J_{1\beta,1\alpha}$=15.3, $J_{1\beta2\alpha}$=$J_{1\beta,10\beta}$=2.7 Hz, H-1β), 2.18 (1H, dd, $J_{10\beta,1\alpha}$=13.8 Hz, $J_{10\beta,1\beta}$=2.7 Hz, H-10β), 2.13 (1H, dd, $J_{11\beta,11\alpha}$=13.8 Hz, $J_{11\beta,12\beta}$=6.5 Hz, H-11β), 1.98 (1H, ddd, $J_{1\alpha,1\beta}$=15.3 Hz, $J_{1\alpha,2\alpha}$=3.0 Hz, $J_{1\alpha,10\beta}$=13.8 Hz, H-1α), 1.93 (1H, m, H-6α), 1.90 (1H, dd, $J_{11\alpha,11\beta}$=13.8 Hz, $J_{11\alpha,12\beta}$=11.0 Hz, H-11α), 1.88 (2H, m, H-7α and H-7β), 1.43 (1H, dddd, $J_{6\beta,6\alpha}$=13.6 Hz, $J_{6\beta,7\alpha}$=13.9 Hz, $J_{6\beta,7\beta}$=4.7 Hz, $J_{6\beta,19a}$=2.0 Hz, H-6β), 0.83 (3H, s, Me-20); ^{13}C NMR (100 MHz, CD_3OD) δ 183.4 (C, C=S), 177.9 (C, C-18), 176.4 (C, C-17), 145.2 (CH, C-15), 141.4 (CH, C-16), 125.9 (C, C-13), 109.8 (CH, C-14), 82.2 (CH, C-2), 79.5 (CH, C-3), 71.6 (CH_2, C-19), 71.0 (CH, C-12), 57.4 (CH, C-4), 47.7 (CH, C-8), 44.2 (C, C-5), 43.9 (CH_2, C-11), 43.3 (CH, C-10), 37.2 (C, C-9), 35.6 (CH_2, C-6), 24.4 (CH_2, C-1), 20.1 (CH_3, C-20), 19.6 (CH_2, C-7); EIMS *m*/*z* 418 $[M]^+$ (47), 403 (1), 374 (4), 358 (3), 322 (4), 307 (4), 280 (9), 217 (6), 105 (13), 94 (100), 81 (14), 55 (15). Anal.: C 60.01%, H 5.43%, S 7.31%; calcd for $C_{21}H_{22}O_7S$: C 60.28%, H 5.30%, S 7.66%.

4.7. Preparation of compound 20 from compound 19

A solution of **19** (60 mg, 0.143 mmol), 120 μL (126 mg, 0.433 mmol) of 97% *n*-Bu_3SnH, and 2,2′-azobis(2-methylpropionitrile) (AIBN, 5 mg, 0.03 mmol) in toluene (5 mL) was heated to reflux under Ar for 4 h. Then, the mixture was evaporated to a small volume and partitioned between acetonitrile and *n*-hexane (5 mL each). The acetonitrile layer was washed with *n*-hexane (4×5 mL) to remove the residual tin compounds. The acetonitrile phase was distilled in vacuo and the residue was purified by FC (80:20 CH_2Cl_2–acetone as eluent) to give pure **20** (42 mg, 82%): colorless fine needles (EtOAc–petroleum ether); mp 224–227 °C; $[\alpha]_D^{20}$ +9.6 (*c* 0.146, MeOH); R_f (80:20 CH_2Cl_2–acetone) 0.32; IR (KBr) ν_{max} 3474,

3152, 3136, 2950, 2574, 1745, 1507, 1445, 1379, 1293, 1230, 1165, 1152, 1053, 1027, 986, 878, 790, 672, 602 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.58 (1H, dd, $J_{16,14}$=1.0 Hz, $J_{16,15}$=2.0 Hz, H-16), 7.51 (1H, t, $J_{15,14}$=$J_{15,16}$=2.0 Hz, H-15), 6.49 (1H, dd, $J_{14,15}$=2.0 Hz, $J_{14,16}$=1.0 Hz, H-14), 5.51 (1H, dd, $J_{12\beta,11\alpha}$=11.0 Hz, $J_{12\beta,11\beta}$=6.6 Hz, H-12β), 4.49 (1H, dd, $J_{19a,6\beta}$=2.0 Hz, $J_{19a,19b}$=9.4 Hz, pro-*S* H-19a), 4.32 (1H, d, $J_{19b,19a}$=9.4 Hz, pro-*R* H-19b), 4.21 (1H, quint, $J_{2\alpha,1\alpha}$=$J_{2\alpha,1\beta}$=$J_{2\alpha,3\alpha}$=$J_{2\alpha,3\beta}$=3.1 Hz, H-2α), 2.91 (1H, dd, $J_{8\beta,7\alpha}$=10.8 Hz, $J_{8\beta,7\beta}$=5.0 Hz, H-8β), 2.35 (1H, dd, $J_{4\beta,3\alpha}$=12.6 Hz, $J_{4\beta,3\beta}$=6.3 Hz, H-4β), 2.26 (1H, dd, $J_{10\beta,1\alpha}$=11.7 Hz, $J_{10\beta,1\beta}$=4.7 Hz, H-10β), 2.15 (1H, dd, $J_{11\beta,11\alpha}$=14.0 Hz, $J_{11\beta,12\beta}$=6.6 Hz, H-11β), 2.00 (1H, dddd, $J_{3\beta,1\beta}$=1.8 Hz, $J_{3\beta,2\alpha}$=3.1 Hz, $J_{3\beta,3\alpha}$=14.4 Hz, $J_{3\beta,4\beta}$=6.3 Hz, H-3β), 1.90 (2H, m, H-7α and H-7β), 1.85 (1H, m, H-6α), 1.81 (1H, dd, $J_{11\alpha,11\beta}$=14.0 Hz, $J_{11\alpha,12\beta}$=11.0 Hz, H-11α), 1.71 (1H, m, H-1β), 1.68 (2H, m, H-1α and H-3α), 1.36 (1H, dddd, $J_{6\beta,6\alpha}$=13.8 Hz, $J_{6\beta,7\alpha}$=13.3 Hz, $J_{6\beta,7\beta}$=4.2 Hz, $J_{6\beta,19a}$=2.0 Hz, H-6β), 0.80 (3H, s, Me-20); ^{13}C NMR (100 MHz, CD_3OD) δ 181.3 (C, C-18), 176.8 (C, C-17), 145.2 (CH, C-15), 141.3 (CH, C-16), 126.2 (C, C-13), 109.8 (CH, C-14), 71.6 (CH, C-12), 71.2 (CH_2, C-19), 65.7 (CH, C-2), 48.3 (CH, C-8), 47.1 (CH, C-4), 44.2 (CH, C-10), 44.1 (C, C-5), 43.9 (CH_2, C-11), 37.4 (C, C-9), 35.6 (CH_2, C-6), 32.4 (CH_2, C-3), 29.0 (CH_2, C-1), 20.4 (CH_3, C-20), 19.8 (CH_2, C-7); EIMS *m*/*z* 360 $[M]^+$ (48), 342 (3), 332 (2), 264 (4), 236 (11), 204 (13), 176 (12), 131 (25), 94 (100), 79 (14), 55 (14). Anal.: C 66.79%, H 6.48%; calcd for $C_{20}H_{24}O_6$: C 66.65%, H 6.71%.

4.8. Acetylation of compound 20 to give compound 21

Treatment of **20** (0.05 mmol) with Ac_2O–pyridine (1:2, 400 μL) for 24 h at room temperature followed by standard workup and purification by FC (95:5 CH_2Cl_2–acetone as eluent) yielded quantitatively the acetyl derivative **21**: amorphous, white solid; $[\alpha]_D^{20}$ −9.1 (*c* 0.033, $CHCl_3$); R_f (95:5 CH_2Cl_2–acetone) 0.27; IR (KBr) ν_{max} 3146, 2950, 1776, 1738, 1505, 1377, 1244, 1229, 1179, 1155, 1026, 875, 805, 602 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (1H, dd, $J_{16,14}$=0.8 Hz, $J_{16,15}$=1.8 Hz, H-16), 7.43 (1H, t, $J_{15,14}$=$J_{15,16}$=1.8 Hz, H-15), 6.40 (1H, dd, $J_{14,15}$=1.8 Hz, $J_{14,16}$=0.8 Hz, H-14), 5.36 (1H, dd, $J_{12\beta,11\alpha}$=10.5 Hz, $J_{12\beta,11\beta}$=7.0 Hz, H-12β), 5.24 (1H, quint, $J_{2\alpha,1\alpha}$=$J_{2\alpha,1\beta}$=$J_{2\alpha,3\alpha}$=$J_{2\alpha,3\beta}$=3.1 Hz, H-2α), 4.32 (1H, dd, $J_{19a,6\beta}$=2.0 Hz, $J_{19a,19b}$=9.4 Hz, pro-*S* H-19a), 4.23 (1H, d, $J_{19b,19a}$=9.4 Hz, pro-*R* H-19b), 2.65 (1H, dd, $J_{8\beta,7\alpha}$=12.0 Hz, $J_{8\beta,7\beta}$=4.0 Hz, H-8β), 2.32 (1H, dd, $J_{4\beta,3\alpha}$=12.2 Hz, $J_{4\beta,3\beta}$=6.3 Hz, H-4β), 2.24 (1H, dddd, $J_{3\beta,1\beta}$=2.1 Hz, $J_{3\beta,2\alpha}$=3.1 Hz, $J_{3\beta,3\alpha}$=14.8 Hz, $J_{3\beta,4\beta}$=6.3 Hz, H-3β), 2.09 (3H, s, 2β-OAc), 2.05 (1H, m, H-1β), 2.01 (1H, m, H-10β), 2.00 (1H, m, H-6α), 1.91 (1H, dd, $J_{11\beta,11\alpha}$=14.0 Hz, $J_{11\beta,12\beta}$=7.0 Hz, H-11β), 1.87 (2H, m, H-7α and H-7β), 1.84 (1H, dd, $J_{11\alpha,11\beta}$=14.0 Hz, $J_{11\alpha,12\beta}$=10.5 Hz, H-11α), 1.65 (1H, ddd, $J_{3\alpha,2\alpha}$=3.1 Hz, $J_{3\alpha,3\beta}$=14.8 Hz, $J_{3\alpha,4\beta}$=12.2 Hz, H-3α), 1.62 (1H, ddd, $J_{1\alpha,1\beta}$=14.4 Hz, $J_{1\alpha,2\alpha}$=3.1 Hz, $J_{1\alpha,10\beta}$=12.6 Hz, H-1α), 1.31 (1H, dddd, $J_{6\beta,6\alpha}$=13.6 Hz, $J_{6\beta,7\alpha}$=13.3 Hz, $J_{6\beta,7\beta}$=3.7 Hz, $J_{6\beta,19a}$=2.0 Hz, H-6β), 0.82 (3H, s, Me-20); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2 (C, C-18), 173.1 (C, C-17), 169.9 (C, 2-O*C*OCH$_3$), 144.0 (CH, C-15), 139.7 (CH, C-16), 124.1 (C, C-13), 108.5 (CH, C-14), 69.8 (CH, C-12), 69.3 (CH_2, C-19), 67.6 (CH, C-2), 47.4 (CH, C-8), 45.6 (CH, C-4), 44.6 (CH, C-10), 43.2 (CH_2, C-11), 42.4 (C, C-5), 36.3 (C, C-9), 34.6 (CH_2, C-6), 28.6 (CH_2, C-3), 25.8 (CH_2, C-1), 21.3 (CH_3, 2-OCO*C*H$_3$), 19.8 (CH_3, C-20), 18.7 (CH_2, C-7); EIMS *m*/*z* 402 $[M]^+$ (44), 342 (15), 218 (32), 204 (16), 176 (20), 145 (20), 131 (33), 94 (100), 91 (27), 81 (14), 55 (11). Anal.: C 65.41%, H 6.48%; calcd for $C_{22}H_{26}O_7$: C 65.66%, H 6.51%.

4.9. Oxidation of compound 20 to give ketone 22

Pyridinium chlorochromate (PCC) (45 mg, 0.209 mmol) was added in one portion to a solution of **20** (45 mg, 0.083 mmol) in dry CH_2Cl_2 (1 mL). The resulting suspension was stirred under Ar at room temperature for 17 h. Then the mixture was filtered through a short pad of Celite and the solvent was removed under reduced pressure. The residue was purified by FC (90:10 CH_2Cl_2–acetone as eluent) to give pure **22** (40 mg, 89%): amorphous, white solid; $[\alpha]_D^{20}$ +28.4 (*c* 0.208, $CHCl_3$); R_f (90:10 CH_2Cl_2–acetone) 0.35; IR (KBr) ν_{max} 3145, 2924, 1773, 1742, 1718, 1505, 1384, 1217, 1154, 1025, 998, 875, 807, 734, 602 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (1H, dd, $J_{16,14}$=1.0 Hz, $J_{16,15}$=1.9 Hz, H-16), 7.42 (1H, t, $J_{15,14}$=$J_{15,16}$=1.9 Hz, H-15), 6.38 (1H, dd, $J_{14,15}$=1.9 Hz, $J_{14,16}$=1.0 Hz, H-14), 5.36 (1H, dd, $J_{12\beta,11\alpha}$=11.1 Hz, $J_{12\beta,11\beta}$=6.4 Hz, H-12β), 4.37 (1H, dd, $J_{19a,6\beta}$=2.1 Hz, $J_{19a,19b}$=9.8 Hz, pro-*S* H-19a), 4.28 (1H, d, $J_{19b,19a}$=9.8 Hz, pro-*R* H-19b), 2.79 (1H, m, H-3β), 2.63 (1H, dd, $J_{8\beta,7\alpha}$=11.9 Hz, $J_{8\beta,7\beta}$=3.7 Hz, H-8β), 2.57 (2H, m, H-3α and H-4β), 2.42 (2H, m, H-1α and H-1β), 2.16 (2H, m, H-6α and H-10β), 2.11 (1H, m, H-7β), 2.06 (1H, dd, $J_{11\beta,11\alpha}$=13.9 Hz, $J_{11\beta,12\beta}$=6.4 Hz, H-11β), 1.86 (1H, dddd, $J_{7\alpha,6\alpha}$=3.4 Hz, $J_{7\alpha,6\beta}$=13.7 Hz, $J_{7\alpha,7\beta}$=14.8 Hz, $J_{7\alpha,8\beta}$=11.9 Hz, H-7α), 1.85 (1H, dd, $J_{11\alpha,11\beta}$=13.9 Hz, $J_{11\alpha,12\beta}$=11.1 Hz, H-11α), 1.41 (1H, tdd, $J_{6\beta,6\alpha}$=$J_{6\beta,7\alpha}$=13.7 Hz, $J_{6\beta,7\beta}$=3.8 Hz, $J_{6\beta,19a}$=2.1 Hz, H-6β), 0.88 (3H, s, Me-20); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.8 (C, C-2), 176.1 (C, C-18), 172.7 (C, C-17), 144.0 (CH, C-15), 139.6 (CH, C-16), 123.8 (C, C-13), 108.3 (CH, C-14), 70.0 (CH_2, C-19), 69.9 (CH, C-12), 49.7 (CH, C-10), 48.0 (CH, C-4), 46.8 (CH, C-8), 42.9 (CH_2, C-11), 42.1 (C, C-5), 38.6 (CH_2, C-3), 37.4 (CH_2, C-1), 36.7 (C, C-9), 35.9 (CH_2, C-6), 19.9 (CH_3, C-20), 18.6 (CH_2, C-7); EIMS *m*/*z* 358 $[M]^+$ (53), 343 (2), 330 (1), 262 (3), 247 (9), 220 (15), 192 (13), 176 (7), 147 (6), 133 (7), 94 (100), 91 (14), 79 (12), 55 (8). Anal.: C 67.31%, H 6.02%; calcd for $C_{20}H_{22}O_6$: C 67.02%, H 6.19%.

4.10. Sodium borohydride reduction of compound 22: mixture of epimers 20 and 23

To a solution of **22** (30 mg, 0.084 mmol) in THF (800 μL), $NaBH_4$ (1.2 mg, 0.0315 mmol) was added while keeping the temperature below 0 °C. The mixture was stirred at 0 °C for 15 min. Then, the reaction was quenched by adding few drops of 0.1 N HCl. The solvent was removed under reduced pressure and the solid residue was recovered with CH_2Cl_2 and purified by FC (80:20 CH_2Cl_2–acetone as eluent). A mixture of the C-2 epimers **20** and **23** (single TLC spot) was obtained (30 mg, 100%). The ^1H NMR spectrum (400 MHz, $CDCl_3$) showed that the product of reaction was a 10:1 mixture of two compounds, in which **23** was the major constituent: δ 7.45 (1H, dd, $J_{16,14}$=1.0 Hz, $J_{16,15}$=1.9 Hz, H-16), 7.43 (1H, t, $J_{15,14}$=$J_{15,16}$=1.9 Hz, H-15), 6.40 (1H, dd, $J_{14,15}$=1.9 Hz, $J_{14,16}$=1.0 Hz, H-14), 5.34 (1H, dd, $J_{12\beta,11\alpha}$=10.8 Hz, $J_{12\beta,11\beta}$=6.7 Hz, H-12β), 4.35 (1H, dd, $J_{19a,6\beta}$=2.1 Hz, $J_{19a,19b}$=9.4 Hz, pro-*S* H-19a), 4.18 (1H, d, $J_{19b,19a}$=9.4 Hz, pro-*R* H-19b), 3.76 (1H, br t, *J*=11 Hz, H-2β), 2.57 (1H, dd, $J_{8\beta,7\alpha}$=12.0 Hz, $J_{8\beta,7\beta}$=3.8 Hz, H-8β), 2.27 (1H, dddd, $J_{3\beta,1\beta}$=2.0 Hz, $J_{3\beta,2\beta}$=4.1 Hz, $J_{3\beta,3\alpha}$=13.0 Hz, $J_{3\beta,4\beta}$=6.4 Hz, H-3β), 2.20 (1H, dd, $J_{4\beta,3\alpha}$=11.7 Hz, $J_{4\beta,3\beta}$=6.4 Hz, H-4β), 2.07 (1H, dd, $J_{11\beta,11\alpha}$=13.9 Hz, $J_{11\beta,12\beta}$=6.7 Hz, H-11β), 2.03 (2H, m, H-6α and H-7β), 1.95 (1H, dddd, $J_{1\beta,1\alpha}$=12.9 Hz, $J_{1\beta,2\beta}$=4.5 Hz, $J_{1\beta,3\beta}$=2.0 Hz, $J_{1\beta,10\beta}$=2.7 Hz, H-1β), 1.88 (1H, dd, $J_{11\alpha,11\beta}$=13.9 Hz, $J_{11\alpha,12\beta}$=10.8 Hz, H-11α), 1.84 (1H, m, H-7α), 1.64 (1H, dd, $J_{10\beta,1\alpha}$=12.9 Hz, $J_{10\beta,1\beta}$=2.7 Hz, H-10β), 1.48 (1H, td, $J_{3\alpha,2\beta}$=$J_{3\alpha,4\beta}$=11.6 Hz, $J_{3\alpha,3\beta}$=13.0 Hz, H-3α), 1.40 (1H, td, $J_{1\alpha,1\beta}$=$J_{1\alpha,10\beta}$=12.9 Hz, $J_{1\alpha,2\beta}$=10.2 Hz, H-1α), 1.19 (1H, dddd, $J_{6\beta,6\alpha}$=13.2 Hz, $J_{6\beta,7\alpha}$=14.0 Hz, $J_{6\beta,7\beta}$=4.7 Hz, $J_{6\beta,19a}$=2.1 Hz, H-6β), 0.83 (3H, s, Me-20).

4.11. Acetylation of the mixture of 20 and 23 to give compounds 21 and 24

Treatment of the mixture described above with Ac_2O–pyridine (1:2, 500 μL) for 24 h at room temperature, followed by standard workup and purification by FC (95:5 CH_2Cl_2–acetone as eluent), yielded the acetyl derivatives **21** (3 mg, 8%) and **24** (30 mg, 90%).

*4.11.1. Compound **24***

Colorless quadrangular plates (EtOAc–petroleum ether); mp 217–219 °C; $[\alpha]_D^{20}$ +8.2 (*c* 0.182, $CHCl_3$); R_f (95:5 CH_2Cl_2–acetone)

0.29; IR (KBr) ν_{max} 3143, 3115, 2921, 1781, 1756, 1706, 1502, 1372, 1264, 1227, 1174, 1152, 1054, 1031, 1016, 876, 825, 609 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (1H, dd, $J_{16,14}$=0.8 Hz, $J_{16,15}$=1.8 Hz, H-16), 7.42 (1H, t, $J_{15,14}$=$J_{15,16}$=1.8 Hz, H-15), 6.39 (1H, dd, $J_{14,15}$=1.8 Hz, $J_{14,16}$=0.8 Hz, H-14), 5.35 (1H, dd, $J_{12\beta,11\alpha}$=10.8 Hz, $J_{12\beta,11\beta}$=6.7 Hz, H-12β), 4.79 (1H, tt, $J_{2\beta,1\alpha}$=$J_{2\beta,3\alpha}$=10.3 Hz, $J_{2\beta,1\beta}$=$J_{2\beta,3\beta}$=4.3 Hz, H-2β), 4.35 (1H, dd, $J_{19a,6\beta}$=2.0 Hz, $J_{19a,19b}$=9.5 Hz, pro-*S* H-19a), 4.20 (1H, d, $J_{19b,19a}$=9.5 Hz, pro-*R* H-19b), 2.59 (1H, dd, $J_{8\beta,7\alpha}$=11.9 Hz, $J_{8\beta,7\beta}$=3.8 Hz, H-8β), 2.27 (1H, dddd, $J_{3\beta,1\beta}$=1.9 Hz, $J_{3\beta,2\beta}$=4.3 Hz, $J_{3\beta,3\alpha}$=12.1 Hz, $J_{3\beta,4\beta}$=6.4 Hz, H-3β), 2.24 (1H, dd, $J_{4\beta,3\alpha}$=12.1 Hz, $J_{4\beta,3\beta}$=6.4 Hz, H-4β), 2.07 (1H, dd, $J_{11\beta,11\alpha}$=13.9 Hz, $J_{11\beta,12\beta}$=6.7 Hz, H-11β), 2.04 (2H, m, H-6α and H-7β), 2.04 (3H, s, 2α-OAc), 1.99 (1H, dddd, $J_{1\beta,1\alpha}$=12.9 Hz, $J_{1\beta,2\beta}$=4.3 Hz, $J_{1\beta,3\beta}$=1.9 Hz, $J_{1\beta,10\beta}$=2.7 Hz, H-1β), 1.85 (1H, dd, $J_{11\alpha,11\beta}$=13.9 Hz, $J_{11\alpha,12\beta}$=10.8 Hz, H-11α), 1.84 (1H, dddd, $J_{7\alpha,6\alpha}$=3.3 Hz, $J_{7\alpha,6\beta}$=13.3 Hz, $J_{7\alpha,7\beta}$=15.1 Hz, $J_{7\alpha,8\beta}$=11.9 Hz, H-7α), 1.72 (1H, dd, $J_{10\beta,1\alpha}$=12.9 Hz, $J_{10\beta,1\beta}$=2.7 Hz, H-10β), 1.58 (1H, td, $J_{3\alpha,2\beta}$=10.3 Hz, $J_{3\alpha,3\beta}$=$J_{3\alpha,4\beta}$=12.1 Hz, H-3α), 1.46 (1H, td, $J_{1\alpha,1\beta}$=$J_{1\alpha,10\beta}$=12.9 Hz, $J_{1\alpha,2\beta}$=10.3 Hz, H-1α), 1.21 (1H, dddd, $J_{6\beta,6\alpha}$=13.5 Hz, $J_{6\beta,7\alpha}$=13.3 Hz, $J_{6\beta,7\beta}$=3.7 Hz, $J_{6\beta,19a}$=2.0 Hz, H-6β), 0.83 (3H, s, Me-20); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4 (C, C-18), 173.0 (C, C-17), 170.2 (C, 2-$OCOCH_3$), 143.9 (CH, C-15), 139.6 (CH, C-16), 124.0 (C, C-13), 108.4 (CH, C-14), 70.6 (CH, C-2), 69.9 (CH, C-12), 69.5 (CH_2, C-19), 49.7 (CH, C-10), 48.0 (CH, C-4), 47.2 (CH, C-8), 43.3 (CH_2, C-11), 42.3 (C, C-5), 36.7 (C, C-9), 34.6 (CH_2, C-6), 29.9 (CH_2, C-3), 27.7 (CH_2, C-1), 21.1 (CH_3, 2-$OCOCH_3$), 20.1 (CH_3, C-20), 18.7 (CH_2, C-7); EIMS *m*/*z* 402 $[M]^+$ (42), 342 (17), 264 (26), 218 (18), 204 (15), 176 (18), 145 (18), 131 (29), 94 (100), 91 (23), 81 (14), 55 (13). Anal.: C 65.71%, H 6.43%; calcd for $C_{22}H_{26}O_7$: C 65.66%, H 6.51%.

4.12. Biological assays

The new neoclerodane derivatives were assayed for affinity at human opioid receptors, except for **6**, **11**, and **13**, which were not tested due to the scarcity of the sample available. Cell culture and opioid binding assays proceeded as described elsewhere[2] using [^{3}H]DAMGO, [^{3}H]DADLE, and [^{3}H]U69,593 as radioligands. Recombinant CHO cells (hMOR-CHO, hDOR-CHO, and hKOR-CHO) were produced by stable transfection with the respective human opioid receptor cDNA and provided by Dr. Larry Toll (SRI International, CA).

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9. Compound **6** is sparingly soluble in many solvents. However, it can be extracted from the reaction mixture with EtOAc, in which this compound forms a stable opaque dispersion.