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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 were active. The presence of the C-18, C-19 lactone could be at the origin of the observed lack of binding affinity.

Keywords

Salvia splendens; opioid receptors; neoclerodane diterpenes; semisynthetic derivatives

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**,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 noteworthy that the new derivative **24**

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possesses identical structural parts that those of salvinorin A (**1**) at the C-2 (α -acetoxy 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**.

Results and Discussion

Treatment of **2–5** with osmium tetroxide (see Experimental Section) 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 Ac₂O-pyridine for 24 hours produced the peracetates **15–18**, respectively (Scheme 1).

The β -orientation of the C-2 and C-3 hydroxyl and/or acetoxy groups in all these compounds (**6–18**) was supported by the following facts. The large vicinal coupling value ($J = 8.0\text{--}11.1$ Hz) between the H-4 β 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-3 α proton ($J_{\alpha,e} = 1.4\text{--}3.2$ Hz) but also by the stereochemical requirements of an 1,2-dihydroxylation reaction with OsO₄. NOE experiments also supported this conclusion, because irradiation at the H-3 α proton signal always caused an NOE enhancement in the H-19 α (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-2 α and H-3 α 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 thiocarbonate **19**, which was transformed into **20** by reaction with Bu₃SnH. Acetylation of **20** by standard procedures gave the derivative **21**. The location of the hydroxyl (**20**) or acetoxy (**21**) group at the C-2 β position was deduced from the multiplicities of the H-2 α and H-4 β 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 ¹H NMR spectra of these substances.

An attempt to directly prepare the AcO-2 α derivative **23**, using a Mitsunobu reaction, starting from the compound **20**, unfortunately failed. However, compound **20** was transformed into **22** by oxidation with PCC (Scheme 2). Reduction of **22** with NaBH₄ at 0 °C gave a product which showed only one spot on TLC with several eluents. The ¹H NMR spectrum of the reduction compound, however, revealed that it was a 10:1 mixture of the 2 α -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 agreement⁵ with the coupling values for the H-2 β axial proton ($J_{\alpha,a} = J_{\alpha,a'} = 10.3$ Hz, $J_{\alpha,e} = J_{\alpha,e'} = 4.3$ Hz) observed in its ¹H NMR spectrum.

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

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.

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.

Experimental Section

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 obtained on a Perkin-Elmer Spectrum One spectrophotometer. ¹H and ¹³C NMR spectra were recorded in CDCl₃ (**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 espectrumeter at 400 and 100 MHz, respectively. Chemical shifts are reported in the δ scale and are referenced to residual CHCl₃ (δ 7.25) or methanol (δ 3.30) signals for protons and to the solvent signals (δ_{CHCl_3} 77.00, $\delta_{\text{CH}_3\text{OH}}$ 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 LiChrorep 15-25/25-40 μm 1/1 was used for flash chromatography (elution under 0.7 psi of Ar). Merck 5554 Kieselgel 60 F₂₅₄ sheets were used for thin-layer chromatographic analysis. Petroleum ether (bp 50–70 °C) was used for column chromatography.

Starting Materials for Chemical Transformations

Compounds **2–4** were available from a previous work³ and **5** was obtained from **2** as described previously.²

General Procedure for the Osmylation of Compounds 2–5

0.5 mmol of the starting compounds were added to a solution of OsO₄ (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 Na₂S₂O₃ and the mixture was extracted with EtOAc (4×10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na₂SO₄. 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 CH₂Cl₂-acetone: 152 mg, 70%) compound **8** from **4** (elution with 7:3 CH₂Cl₂-acetone: 128 mg, 52%) and compound **9** from **5** (elution with 7:3 CH₂Cl₂-acetone: 163 mg, 75%).

Compound 7—colorless prisms (EtOAc-petroleum ether); mp 226–230 °C; $[\alpha]_D^{20}$ –46.8 (*c* 0.248, CHCl₃); *R*_f (3:1 CH₂Cl₂-acetone) 0.30; IR (KBr) $\nu_{\max}$ 3449, 2925, 1752, 1447, 1375, 1222, 1159, 1047, 1009, 875, 729, 603 cm^{–1}; ¹H NMR (400 MHz, CDCl₃) 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 β ,11 α} = 10.8 Hz, H-12 β), 5.16 (1H, d, *J*_{11 α ,12 β} = 10.8 Hz, H-11 α), 4.28 (1H, d, *J*_{19 a ,19 b} = 9.4 Hz, pro-*R* H-19 a), 4.24 (1H, dd, *J*_{19 b ,6 β} = 1.6 Hz, *J*_{19 b ,19 a} = 9.4 Hz, pro-*S* H-19 b), 4.16 (1H, ddd, *J*_{2 α ,1 α} = 2.0 Hz, *J*_{2 α ,1 β} = 3.0 Hz, *J*_{2 α ,3 α} = 2.8 Hz, H-2 α), 3.74 (1H, dd, *J*_{3 α ,2 α} = 2.8 Hz, *J*_{3 α ,4 β} = 10.0 Hz, H-3 α), 2.64 (1H, br dd, *J*_{8 α ,6 α} < 0.4 Hz, *J*_{8 α ,7 α} = 4.3 Hz, *J*_{8 α ,7 β} = 3.1 Hz, H-8 α), 2.61 (1H, dd, *J*_{10 β ,1 α} = 11.9 Hz, *J*_{10 β ,1 β} = 3.1 Hz, H-10 β), 2.49 (1H, m, H-1 β), 2.48 (1H, m, H-7 β), 2.31 (1H, d, *J*_{4 β ,3 α} = 10.0 Hz, H-4 β), 2.16 (3H, s, 11 β -OAc), 1.88 (1H, dddd, *J*_{7 α ,6 α} = 3.1 Hz, *J*_{7 α ,6 β} = 14.2 Hz, *J*_{7 α ,7 β} = 14.4 Hz, *J*_{7 α ,8 α} = 4.3 Hz, H-7 α), 1.69 (1H, br dt, *J*_{6 α ,6 β} = 14.0 Hz, *J*_{6 α ,7 α} = *J*_{6 α ,7 β} = 3.0 Hz, *J*_{6 α ,8 α} < 0.4 Hz, H-6 α), 1.55 (1H, ddd, *J*_{1 α ,1 β} = 14.8 Hz, *J*_{1 α ,2 α} = 2.0 Hz, *J*_{1 α ,10 β} = 11.9 Hz, H-1 α), 1.28 (1H, dddd, *J*_{6 β ,6 α} = 14.0 Hz, *J*_{6 β ,7 α} = 14.2 Hz, *J*_{6 β ,7 β} = 3.7 Hz, *J*_{6 β ,19 b} = 1.6 Hz, H-6 β), 0.89 (3H, s, Me-20); ¹³C NMR (100 MHz, CDCl₃) δ 177.8 (C, C-18), 169.9 (C, C-17), 169.2 (C, 11-O $\overline{\text{C}}\text{OCH}_3$), 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 (CH₂, 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 (CH₂, C-6), 27.2 (CH₂, C-1), 20.7 (CH₃, 11-OCO $\overline{\text{C}}\text{H}_3$), 19.7 (CH₂, C-7), 18.4 (CH₃, 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 C₂₂H₂₆O₉, C 60.82%, H 6.03%.

Compound 8—colorless plates (EtOAc – *n*-pentane); mp 252–255 °C, $[\alpha]_D^{20}$ –19.3 (*c* 0.223, CHCl₃); *R*_f (3:1 CH₂Cl₂-acetone) 0.25; IR (KBr) $\nu_{\max}$ 3452, 2928, 1749, 1370, 1243, 1036, 969, 875, 737, 603 cm^{–1}; ¹H NMR (400 MHz, CDCl₃) 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 β ,11 α} = 10.9 Hz, H-12 β), 5.32 (1H, d, *J*_{11 α ,12 β} = 10.9 Hz, H-11 α), 5.09 (1H, dd, *J*_{1 α ,2 α} = 0.8 Hz, *J*_{1 α ,10 β} = 8.8 Hz, H-1 α), 4.58 (1H, dd, *J*_{19 a ,6 β} = 2.1 Hz, *J*_{19 a ,19 b} = 8.6 Hz, pro-*S* H-19 a), 4.25 (1H, ddd, *J*_{3 α ,2 α} = 1.4 Hz, *J*_{3 α ,4 β} = 8.0 Hz, *J*_{3 α ,3 β OH} = 6.8 Hz, H-3 α), 4.20 (1H, d, *J*_{19 b ,19 a} = 8.6 Hz, pro-*R* H-19 b), 4.12 (1H, d, *J*_{3 β OH,3 α} = 6.8 Hz, 3 β -OH), 3.85 (1H, dd, *J*_{2 α ,1 α} = 0.8 Hz, *J*_{2 α ,3 α} = 1.4 Hz, H-2 α), 2.71 (1H, br dd, *J*_{8 α ,6 α} < 0.4 Hz, *J*_{8 α ,7 α} = 4.0 Hz, *J*_{8 α ,7 β} = 3.2 Hz, H-8 α), 2.54 (1H, d, *J*_{4 β ,3 α} = 8.0 Hz, H-4 β), 2.45 (1H, ddt, *J*_{7 β ,6 α} = *J*_{7 β ,8 α} = 3.2 Hz, *J*_{7 β ,6 β} = 3.5 Hz, *J*_{7 β ,7 α} = 14.4 Hz, H-7 β), 2.27 (1H, d, *J*_{10 β ,1 α} = 8.8 Hz, H-10 β), 2.03 (3H, s, 1 β -OAc), 1.92 (1H, ddt, *J*_{7 α ,6 α} = *J*_{7 α ,8 α} = 4.0 Hz, *J*_{7 α ,6 β} = 14.0 Hz, *J*_{7 α ,7 β} = 14.4 Hz, H-7 α), 1.87 (3H, s, 11 β -OAc), 1.87 (1H, br ddd, *J*_{6 α ,6 β} = 14.1 Hz, *J*_{6 α ,7 α} = 4.0 Hz, *J*_{6 α ,7 β} = 3.2 Hz, *J*_{6 α ,8 α} < 0.4 Hz, H-6 α), 1.47 (1H, dddd, *J*_{6 β ,6 α} = 14.1 Hz, *J*_{6 β ,7 α} = 14.0 Hz, *J*_{6 β ,7 β} = 3.5 Hz, *J*_{6 β ,19 a} = 2.1 Hz, H-6 β), 1.06 (3H, s, Me-20); ¹³C NMR (100 MHz, CDCl₃) δ 178.5 (C, C-18), 170.1 (C, 1-O $\overline{\text{C}}\text{OCH}_3$), 169.7 (C, 11-O $\overline{\text{C}}\text{OCH}_3$), 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 (CH₂, 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 (CH₂, C-6), 21.6 (CH₃, 1-OCO $\overline{\text{C}}\text{H}_3$), 20.0 (CH₃, 11-OCO $\overline{\text{C}}\text{H}_3$), 19.4 (CH₂, C-7), 19.3 (CH₃, 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 C₂₄H₂₈O₁₁, C 58.53%, H 5.73%.

Compound 9—colorless rectangular plates (Me₂CO – *n*-pentane); mp 237–240 °C; $[\alpha]_D^{20}$ +28.7 (*c* 0.296, MeOH); *R*_f (3:1 CH₂Cl₂-acetone) 0.42; IR (KBr) $\nu_{\max}$ 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 (CD₃)₂CO – CD₃OD] 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-12 β), 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-2 α), 3.73 (1H, dd, $J_{3\alpha,2\alpha} = 2.9$ Hz, $J_{3\alpha,4\beta} = 10.1$ Hz, H-3 α), 2.91 (1H, dd, $J_{8\beta,7\alpha} = 10.3$ Hz, $J_{8\beta,7\beta} = 5.3$ Hz, H-8 β), 2.28 (1H, dd, $J_{10\beta,1\alpha} = 12.7$ Hz, $J_{10\beta,1\beta} = 3.7$ Hz, H-10 β), 2.15 (1H, d, $J_{4\beta,3\alpha} = 10.1$ Hz, H-4 β), 2.14 (1H, dd, $J_{11\beta,11\alpha} = 13.8$ Hz, $J_{11\beta,12\beta} = 6.6$ Hz, H-11 β), 1.85 (2H, m, H-7 α and H-7 β), 1.78 (2H, m, H-1 β and H-11 α), 1.75 (1H, m, H-6 α), 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-1 α), 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-6 β), 0.77 (3H, s, Me-20); ^{13}C NMR [100 MHz, 2:1 (CD₃)₂CO - CD₃OD] 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 (CH₂, 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 (CH₂, C-11), 43.5 (CH, C-10), 37.0 (C, C-9), 35.4 (CH₂, C-6), 27.7 (CH₂, C-1), 20.3 (CH₃, C-20), 19.5 (CH₂, 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 C₂₀H₂₄O₇, C 63.82%, H 6.43%.

General Procedure for Partial Acetylation: Compounds 10, 11, 12, 13, and 14

Treatment of **6** (50 mg, 0.133 mmol) with Ac₂O-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%).

Compound 10—FC eluent 97:3 CH₂Cl₂-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, CD₃OD) 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-12 β), 5.08 (1H, dd, $J_{3\alpha,2\alpha} = 2.8$ Hz, $J_{3\alpha,4\beta} = 10.8$ Hz, H-3 α), 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-2 α), 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-8 α), 2.40 (1H, d, $J_{4\beta,3\alpha} = 10.8$ Hz, H-4 β), 2.39 (1H, dd, $J_{10\beta,1\alpha} = 11.9$ Hz, $J_{10\beta,1\beta} = 3.7$ Hz, H-10 β), 2.38 (1H, m, H-7 β), 2.25 (1H, dd, $J_{11\beta,11\alpha} = 14.9$ Hz, $J_{11\beta,12\beta} = 3.3$ Hz, H-11 β), 2.08 (3H, s, 3 β -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-7 α), 1.84 (1H, dd, $J_{11\alpha,11\beta} = 14.9$ Hz, $J_{11\alpha,12\beta} = 12.5$ Hz, H-11 α), 1.83 (2H, m, H-1 α and H-1 β), 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-6 α), 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-6 β), 0.97 (3H, s, Me-20); ^{13}C NMR (100 MHz, CD₃OD) δ 178.2 (C, C-18), 174.8 (C, C-17), 171.8 (C, 3-O $\text{C}(=\text{O})\text{CH}_3$), 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 (CH₂, C-19), 67.2 (CH, C-2), 51.3 (CH, C-4), 49.9 (CH, C-8), 45.0 (C, C-5), 41.7 (CH₂, C-11), 36.1 (C, C-9), 35.7 (CH, C-10), 33.9 (CH₂, C-6), 27.7 (CH₂, C-1), 23.0 (CH₃, C-20), 20.8 (CH₃, 3-O $\text{C}(=\text{O})\text{CH}_3$), 20.1 (CH₂, 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 C₂₂H₂₆O₈, C 63.15%, H 6.26%.

Compound 11—FC eluent 97:3 CH₂Cl₂-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, CD₃OD) 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-2 α), 5.18 (1H, dd, $J_{12\beta,11\alpha} = 12.8$ Hz, $J_{12\beta,11\beta} = 3.2$ Hz, H-12 β), 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-3 α), 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-8 α), 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-7 β), 2.24 (1H, d, $J_{4\beta,3\alpha} = 10.0$ Hz, H-4 β), 2.20 (1H, dd, $J_{11\beta,11\alpha} = 15.0$ Hz, $J_{11\beta,12\beta} = 3.2$ Hz, H-11 β), 2.16 (1H, dd, $J_{10\beta,1\alpha} = 12.8$ Hz, $J_{10\beta,1\beta} = 3.4$ Hz, H-10 β), 2.13 (3H, s, 2 β -OAc), 2.08 (1H, m, H-1 β), 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-7 α), 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-1 α), 1.84 (1H, dd, $J_{11\alpha,11\beta} = 15.0$ Hz, $J_{11\alpha,12\beta} = 12.8$ Hz, H-11 α), 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-6 α), 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-6 β), 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-O C(=O)CH_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 (CH₂, C-19), 68.7 (CH, C-3), 55.1 (CH, C-4), 49.9 (CH, C-8), 44.6 (C, C-5), 41.6 (CH₂, C-11), 37.1 (CH, C-10), 36.1 (C, C-9), 34.2 (CH₂, C-6), 25.1 (CH₂, C-1), 22.8 (CH₃, C-20), 21.1 (CH₃, 2-O C(=O)CH_3), 20.1 (CH₂, 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 C₂₂H₂₆O₈, C 63.15%, H 6.26%.

Compound 12—FC eluent 90:10 CH₂Cl₂-acetone, R_f 0.33; colorless prisms (EtOAc – *n*-pentane); mp 157–160 °C; $[\alpha]_D^{20}$ –48.6 (*c* 0.111, CHCl₃); 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, CDCl₃) 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-12 β), 5.18 (1H, d, $J_{11\alpha,12\beta} = 10.7$ Hz, H-11 α), 5.04 (1H, dd, $J_{3\alpha,2\alpha} = 2.8$ Hz, $J_{3\alpha,4\beta} = 10.8$ Hz, H-3 α), 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-2 α), 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-8 α), 2.64 (1H, dd, $J_{10\beta,1\alpha} = 10.0$ Hz, $J_{10\beta,1\beta} = 2.8$ Hz, H-10 β), 2.48 (2H, m, H-1 β and H-7 β), 2.44 (1H, d, $J_{4\beta,3\alpha} = 10.8$ Hz, H-4 β), 2.16 (3H, s, 3 β -OAc), 1.96 (3H, s, 11 β -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-7 α), 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-6 α), 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-1 α), 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-6 β), 0.92 (3H, s, Me-20); ^{13}C NMR (100 MHz, CDCl₃) δ 174.8 (C, C-18), 169.8 (C, 3-O C(=O)CH_3), 169.7 (C, C-17), 169.1 (C, 11-O C(=O)CH_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 (CH₂, 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 (CH₂, C-6), 27.5 (CH₂, C-1), 20.9 (C, 3-O C(=O)CH_3), 20.7 (CH₃, 11-O C(=O)CH_3), 19.7 (CH₂, C-7), 18.4 (CH₃, 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 C₂₄H₂₈O₁₀, C 60.50%, H 5.92%.

Compound 13—FC eluent 90:10 CH₂Cl₂-acetone, R_f 0.40; amorphous, white solid; $[\alpha]_D^{20}$ –38.9 (*c* 0.072, CHCl₃); ^1H NMR (400 MHz, CDCl₃) 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-2 α), 5.15 (1H, d, $J_{11\alpha,12\beta} = 10.9$ Hz, H-11 α), 5.10 (1H, d, $J_{12\beta,11\alpha} = 10.9$ Hz, H-12 β), 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, $J_{3\alpha,3\beta\text{OH}} = 4.3$ Hz, H-3 α), 2.70

(2H, m, H-1 β and H-7 β), 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-8 α), 2.44 (1H, d, $J_{3\beta\text{OH},3\alpha} = 4.3$ Hz, 3 β -OH), 2.42 (1H, dd, $J_{10\beta,1\alpha} = 12.9$ Hz, $J_{10\beta,1\beta} = 3.9$ Hz, H-10 β), 2.31 (1H, d, $J_{4\beta,3\alpha} = 9.4$ Hz, H-4 β), 2.19 (3H, s, 2 β -OAc), 1.96 (3H, s, 11 β -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-7 α), 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-6 α), 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-1 α), 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-6 β), 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); C₂₄H₂₈O₁₀, M_r 476.

Compound 14—FC eluent 90:10 CH₂Cl₂-acetone, R_f 0.25; colorless prisms (EtOAc – *n*-pentane); mp 190–193 °C, [α]_D²⁰ –20.5 (*c* 0.341, CHCl₃); 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, CDCl₃) 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-12 β), 5.34 (1H, d, $J_{11\alpha,12\beta} = 10.9$ Hz, H-11 α), 5.13 (1H, dd, $J_{1\alpha,2\alpha} = 0.8$ Hz, $J_{1\alpha,10\beta} = 8.8$ Hz, H-1 α), 5.09 (1H, dd, $J_{3\alpha,2\alpha} = 1.9$ Hz, $J_{3\alpha,4\beta} = 8.7$ Hz, H-3 α), 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, $J_{2\alpha,2\beta\text{OH}} = 3.7$ Hz, H-2 α), 3.68 (1H, d, $J_{2\beta\text{OH},2\alpha} = 3.7$ Hz, 3 β -OH), 2.90 (1H, d, $J_{4\beta,3\alpha} = 8.7$ Hz, H-4 β), 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-8 α), 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-7 β), 2.36 (1H, d, $J_{10\beta,1\alpha} = 8.8$ Hz, H-10 β), 2.14 (3H, s, 3 β -OAc), 2.04 (3H, s, 1 β -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-7 α), 1.88 (3H, s, 11 β -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-6 α), 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-6 β), 1.08 (3H, s, Me-20); ¹³C NMR (100 MHz, CDCl₃) δ 174.4 (C, C-18), 170.5 (C, 3-O $\text{C}(=\text{O})\text{CH}_3$), 169.8 (C, 1-O $\text{C}(=\text{O})\text{CH}_3$), 169.6 (C, 11-O $\text{C}(=\text{O})\text{CH}_3$), 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 (CH₂, 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 (CH₂, C-6), 21.5 (CH₃, 1-OCOCH₃), 20.8 (CH₃, 3-OCOCH₃), 20.0 (CH₃, 11-OCOCH₃), 19.5 (CH₃, C-20), 19.3 (CH₂, 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 C₂₆H₃₀O₁₂, C 58.42%, H 5.66%.

General Procedure for Complete Acetylation: Compounds 15, 16, 17 and 18

Treatment of compounds **6–9** (0.05 mmol) with Ac₂O-pyridine (1:2, 400 μ L) for 24 h at room temperature followed by standard workup and purification by FC yielded quantitatively the acetyl derivatives **15–18**, respectively.

Compound 15—FC eluent 97:3 CH₂Cl₂-acetone, R_f 0.45; colorless prisms (EtOAc – *n*-pentane); mp 283–286 °C; [α]_D²⁰ +25.7 (*c* 0.167, CHCl₃); 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, CDCl₃) 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-2 α), 5.17 (1H, dd, $J_{12\beta,11\alpha} = 12.7$ Hz, $J_{12\beta,11\beta} = 3.2$ Hz, H-12 β), 5.05 (1H, dd, $J_{3\alpha,2\alpha} = 3.1$ Hz, $J_{3\alpha,4\beta} = 11.1$ Hz, H-3 α), 4.33 (2H, s, H₂-19), 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-7 β), 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-8 α), 2.38 (1H, d, $J_{4\beta,3\alpha} = 11.1$ Hz, H-4 β), 2.22 (1H, dd, $J_{10\beta,1\alpha} = 13.6$ Hz, $J_{10\beta,1\beta} = 2.9$ Hz, H-10 β), 2.17 (1H, dd, $J_{11\beta,11\alpha} = 15.0$ Hz, $J_{11\beta,12\beta} = 3.2$ Hz, H-11 β), 2.13 (3H, s, 2 β -OAc), 2.04 (3H, s, 3 β -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-1 β), 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-7 α), 1.78 (1H, m, H-6 α), 1.75 (1H, dd, $J_{11\alpha,11\beta} = 15.0$ Hz, $J_{11\alpha,12\beta} = 12.7$ Hz, H-11 α), 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-1 α), 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-6 β), 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-OCOCH₃), 169.9 (C, 2-OCOCH₃), 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 (CH₂, 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 (CH₂, C-11), 35.7 (CH, C-10), 35.0 (C, C-9), 32.5 (CH₂, C-6), 24.6 (CH₂, C-1), 22.9 (CH₃, C-20), 21.1 (CH₃, 2-OCOCH₃), 20.6 (CH₃, 3-OCOCH₃), 19.1 (CH₂, 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 C₂₄H₂₈O₉, C 62.60%, H 6.13%.

Compound 16—FC eluent 95:5 CH₂Cl₂-acetone, R_f 0.35; colorless quadrangular plaques (EtOAc-petroleum ether); mp 260–263 °C; $[\alpha]_{\text{D}}^{20} -37.9$ (c 0.269, CHCl₃); 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-2 α), 5.16 (1H, d, $J_{11\alpha,12\beta} = 10.8$ Hz, H-11 α), 5.10 (1H, d, $J_{12\beta,11\alpha} = 10.8$ Hz, H-12 β), 5.02 (1H, dd, $J_{3\alpha,2\alpha} = 3.1$ Hz, $J_{3\alpha,4\beta} = 11.0$ Hz, H-3 α), 4.33 (1H, dd, $J_{19\alpha,6\beta} = 1.6$ Hz, $J_{19\alpha,19\beta} = 9.5$ Hz, pro-S H-19 α), 4.28 (1H, d, $J_{19\beta,19\alpha} = 9.5$ Hz, pro-R H-19 β), 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-8 α), 2.41 (1H, dd, $J_{10\beta,1\alpha} = 13.2$ Hz, $J_{10\beta,1\beta} = 3.3$ Hz, H-10 β), 2.50 (2H, m, H-1 β and H-7 β), 2.40 (1H, d, $J_{4\beta,3\alpha} = 11.0$ Hz, H-4 β), 2.17 (3H, s, 3 β - or 2 β -OAc), 2.03 (3H, s, 2 β - or 3 β -OAc), 1.95 (3H, s, 11 β -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-7 α), 1.78 (2H, m, H-1 α and H-6 α), 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, $J_{6\beta,19\alpha} = 1.6$ Hz, H-6 β), 0.92 (3H, s, Me-20); ^{13}C NMR (100 MHz, CDCl_3) δ 173.8 (C, C-18), 170.1 (C, 3-OCOCH₃), 170.0 (C, 2-OCOCH₃), 169.5 (C, C-17), 168.9 (C, 11-OCOCH₃), 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 (CH₂, 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 (CH₂, C-6), 25.9 (CH₂, C-1), 21.1 (C, 2- or 3-OCOCH₃), 20.7 (CH₃, 3- or 2-OCOCH₃), 20.6 (CH₃, 11-OCOCH₃), 19.7 (CH₂, C-7), 18.2 (CH₃, 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 C₂₆H₃₀O₁₁, C 60.23%, H 5.83%.

Compound 17—FC eluent 95:5 CH₂Cl₂-acetone, R_f 0.27; colorless fine plates (EtOAc – *n*-pentane); mp 285–287 °C, $[\alpha]_{\text{D}}^{20} -29.9$ (c 0.267, CHCl₃); IR (KBr) ν_{max} 3145, 2932, 1752, 1436, 1371, 1233, 1162, 1043, 958, 875, 738, 603 cm⁻¹; ^1H 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-12 β), 5.34 (1H, d, $J_{11\alpha,12\beta} = 11.0$ Hz, H-11 α), 5.22 (2H, m, H-2 α and H-3 α), 5.09 (1H, br d, $J_{1\alpha,2\alpha} < 0.4$ Hz, $J_{1\alpha,10\beta} = 8.8$ Hz, H-1 α), 4.45 (1H, dd, $J_{19\alpha,6\beta} = 2.1$ Hz, $J_{19\alpha,19\beta} = 9.1$ Hz, pro-S H-19 α), 4.21 (1H, d, $J_{19\beta,19\alpha} = 9.1$ Hz, pro-R H-19 β), 2.88 (1H, d, $J_{4\beta,3\alpha} = 8.7$ Hz, H-4 β), 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-8 α), 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-7 β), 2.42 (1H, d, $J_{10\beta,1\alpha} = 8.8$ Hz, H-10 β), 2.09 (6H, s, 2 β -OAc and 3 β -OAc), 2.06 (3H, s, 1 β -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-7 α), 1.87 (3H, s, 11 β -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-6 α), 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, $J_{6\beta,19\alpha} = 2.1$ Hz, H-6 β), 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-OCOCH₃), 169.6 (C, 11-OCOCH₃), 169.1 (C, C-17), 168.7 (C, 1-OCOCH₃), 168.1 (C, 2- or 3-OCOCH₃), 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 (CH₂, 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 (CH₂, C-6), 21.4 (CH₃, 1-OCOCH₃), 20.7 (CH₃, 3- or 2-OCOCH₃), 20.4 (CH₃, 2- or 3-OCOCH₃), 20.0 (CH₃, 11-OCOCH₃), 19.4 (CH₃, C-20), 19.2 (CH₂, 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 C₂₈H₃₂O₁₃, C 58.33%, H 5.59%.

Compound 18—FC eluent 95:5 CH₂Cl₂-acetone, R_f 0.47; amorphous, vitreous solid; [α]_D²⁰ +32.0 (*c* 0.147, CHCl₃); IR (KBr) ν_{max} 3148, 2948, 1781, 1746, 1506, 1373, 1227, 1180, 1155, 1060, 1020, 875, 805, 738, 602 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 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*_{2α,1α} = 2.3 Hz, *J*_{2α,1β} = 4.8 Hz, *J*_{2α,3α} = 3.1 Hz, H-2α), 5.37 (1H, dd, *J*_{12β,11α} = 10.4 Hz, *J*_{12β,11β} = 7.1 Hz, H-12β), 5.05 (1H, dd, *J*_{3α,2α} = 3.1 Hz, *J*_{3α,4β} = 11.0 Hz, H-3α), 4.31 (1H, dd, *J*_{19a,6β} = 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*_{8β,7α} = 11.9 Hz, *J*_{8β,7β} = 3.9 Hz, H-8β), 2.41 (1H, d, *J*_{4β,3α} = 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*_{10β,1α} = 13.5 Hz, *J*_{10β,1β} = 2.8 Hz, H-10β), 1.88 (3H, m, H-1β, H-11α, and H-11β), 1.76 (1H, ddd, *J*_{1α,1β} = 15.2 Hz, *J*_{1α,2α} = 2.3 Hz, *J*_{1α,10β} = 13.5 Hz, H-1α), 1.38 (1H, tdd, *J*_{6β,6α} = *J*_{6β,7α} = 13.6 Hz, *J*_{6β,7β} = 3.8 Hz, *J*_{6β,19a} = 2.0 Hz, H-6β), 0.82 (3H, s, Me-20); ¹³C NMR (100 MHz, CDCl₃) δ 174.1 (C, C-18), 172.9 (C, C-17), 169.9 (C, 3-OCOCH₃), 169.7 (C, 2-OCOCH₃), 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 (CH₂, 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 (CH₂, C-11), 36.2 (C, C-9), 34.3 (CH₂, C-6), 25.1 (CH₂, C-1), 21.0 (CH₃, 2-OCOCH₃), 20.6 (CH₃, 3-OCOCH₃), 19.7 (CH₃, C-20), 18.5 (CH₂, 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 C₂₄H₂₈O₉, C 62.60%, H 6.13%.

Preparation of the 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 CH₂Cl₂ (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 CH₂Cl₂-acetone as eluent) to give pure **19** (64 mg, 58%): colorless quadrangular plates (MeOH); mp 277–280 °C; [α]_D²⁰ +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; ¹H NMR (400 MHz, CD₃OD) 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*_{12β,11α} = 11.0 Hz, *J*_{12β,11β} = 6.5 Hz, H-12β), 4.91 (1H, ddd, *J*_{2α,1α} = 3.0 Hz, *J*_{2α,1β} = 2.7 Hz, *J*_{2α,3α} = 4.7 Hz, H-2α), 4.47 (1H, dd, *J*_{19a,6β} = 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*_{3α,2α} = 4.7 Hz, *J*_{3α,4β} = 9.8 Hz, H-3α), 2.96 (1H, dd, *J*_{8β,7α} = 11.4 Hz, *J*_{8β,7β} = 4.4 Hz, H-8β), 2.53 (1H, d, *J*_{4β,3α} = 9.8 Hz, H-4β), 2.30 (1H, dt, *J*_{1β,1α} = 15.3, *J*_{1β,2α} = *J*_{1β,10β} = 2.7 Hz, H-1β), 2.18 (1H, dd, *J*_{10β,1α} = 13.8 Hz, *J*_{10β,1β} = 2.7 Hz, H-10β), 2.13 (1H, dd, *J*_{11β,11α} = 13.8 Hz, *J*_{11β,12β} = 6.5 Hz, H-11β), 1.98 (1H, ddd, *J*_{1α,1β} = 15.3 Hz, *J*_{1α,2α} = 3.0 Hz, *J*_{1α,10β} = 13.8 Hz, H-1α), 1.93 (1H, m, H-6α), 1.90 (1H, dd, *J*_{11α,11β} = 13.8 Hz, *J*_{11α,12β} = 11.0 Hz, H-11α), 1.88 (2H, m, H-7α and H-7β), 1.43 (1H, dddd, *J*_{6β,6α} = 13.6 Hz, *J*_{6β,7α} = 13.9 Hz, *J*_{6β,7β} = 4.7 Hz, *J*_{6β,19a} = 2.0 Hz, H-6β), 0.83 (3H, s, Me-20); ¹³C NMR (100 MHz, CD₃OD) 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 (CH₂, C-19), 71.0 (CH, C-12), 57.4 (CH, C-4), 47.7 (CH, C-8), 44.2 (C, C-5), 43.9 (CH₂, C-11), 43.3 (CH, C-10), 37.2 (C, C-9), 35.6 (CH₂, C-6), 24.4 (CH₂, C-1), 20.1 (CH₃, C-20), 19.6 (CH₂, 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 C₂₁H₂₂O₇S, C 60.28%, H 5.30%, S 7.66%.

Preparation of Compound 20 from Compound 19

A solution of **19** (60 mg, 0.143 mmol), 120 μ L (126 mg, 0.433 mmol) of 97% *n*-Bu₃SnH, 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 $\times$ 5 mL) to remove the residual tin compounds. The acetonitrile phase was distilled in vacuo and the residue was purified by FC (80:20 CH₂Cl₂-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 CH₂Cl₂-acetone) 0.32; IR (KBr) $\nu_{\max}$ 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, CD₃OD) 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-12 β), 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-2 α), 2.91 (1H, dd, $J_{8\beta,7\alpha}$ = 10.8 Hz, $J_{8\beta,7\beta}$ = 5.0 Hz, H-8 β), 2.35 (1H, dd, $J_{4\beta,3\alpha}$ = 12.6 Hz, $J_{4\beta,3\beta}$ = 6.3 Hz, H-4 β), 2.26 (1H, dd, $J_{10\beta,1\alpha}$ = 11.7 Hz, $J_{10\beta,1\beta}$ = 4.7 Hz, H-10 β), 2.15 (1H, dd, $J_{11\beta,11\alpha}$ = 14.0 Hz, $J_{11\beta,12\beta}$ = 6.6 Hz, H-11 β), 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-3 β), 1.90 (2H, m, H-7 α and H-7 β), 1.85 (1H, m, H-6 α), 1.81 (1H, dd, $J_{11\alpha,11\beta}$ = 14.0 Hz, $J_{11\alpha,12\beta}$ = 11.0 Hz, H-11 α), 1.71 (1H, m, H-1 β), 1.68 (2H, m, H-1 α and H-3 α), 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-6 β), 0.80 (3H, s, Me-20); ¹³C NMR (100 MHz, CD₃OD) 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 (CH₂, 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 (CH₂, C-11), 37.4 (C, C-9), 35.6 (CH₂, C-6), 32.4 (CH₂, C-3), 29.0 (CH₂, C-1), 20.4 (CH₃, C-20), 19.8 (CH₂, 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 C₂₀H₂₄O₆, C 66.65%, H 6.71%.

Acetylation of Compound 20 to Give Compound 21

Treatment of **20** (0.05 mmol) with Ac₂O-pyridine (1:2, 400 μ L) for 24 h at room temperature followed by standard workup and purification by FC (95:5 CH₂Cl₂-acetone as eluent) yielded quantitatively the acetyl derivative **21**: amorphous, white solid; $[\alpha]_D^{20}$ -9.1 (*c* 0.033, CHCl₃); *R*_f (95:5 CH₂Cl₂-acetone) 0.27; IR (KBr) $\nu_{\max}$ 3146, 2950, 1776, 1738, 1505, 1377, 1244, 1229, 1179, 1155, 1026, 875, 805, 602 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 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-12 β), 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-2 α), 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-8 β), 2.32 (1H, dd, $J_{4\beta,3\alpha}$ = 12.2 Hz, $J_{4\beta,3\beta}$ = 6.3 Hz, H-4 β), 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-3 β), 2.09 (3H, s, 2 β -OAc), 2.05 (1H, m, H-1 β), 2.01 (1H, m, H-10 β), 2.00 (1H, m, H-6 α), 1.91 (1H, dd, $J_{11\beta,11\alpha}$ = 14.0 Hz, $J_{11\beta,12\beta}$ = 7.0 Hz, H-11 β), 1.87 (2H, m, H-7 α and H-7 β), 1.84 (1H, dd, $J_{11\alpha,11\beta}$ = 14.0 Hz, $J_{11\alpha,12\beta}$ = 10.5 Hz, H-11 α), 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-3 α), 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-1 α), 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-6 β), 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-OCOCH₃), 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 (CH₂, C-19), 67.6 (CH, C-2), 47.4 (CH, C-8), 45.6 (CH, C-4), 44.6 (CH, C-10), 43.2 (CH₂, C-11), 42.4 (C, C-5), 36.3 (C, C-9), 34.6 (CH₂, C-6), 28.6 (CH₂, C-3), 25.8 (CH₂, C-1), 21.3 (CH₃, 2-OCOCH₃), 19.8 (CH₃, C-20), 18.7 (CH₂, 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 C₂₂H₂₆O₇, C 65.66%, H 6.51%.

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 CH₂Cl₂ (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 CH₂Cl₂-acetone as eluent) to give pure **22** (40 mg, 89%): amorphous, white solid; $[\alpha]_D^{20} +28.4$ (*c* 0.208, CHCl₃); *R*_f (90:10 CH₂Cl₂-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-12 β), 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-3 β), 2.63 (1H, dd, $J_{8\beta,7\alpha} = 11.9$ Hz, $J_{8\beta,7\beta} = 3.7$ Hz, H-8 β), 2.57 (2H, m, H-3 α and H-4 β), 2.42 (2H, m, H-1 α and H-1 β), 2.16 (2H, m, H-6 α and H-10 β), 2.11 (1H, m, H-7 β), 2.06 (1H, dd, $J_{11\beta,11\alpha} = 13.9$ Hz, $J_{11\beta,12\beta} = 6.4$ Hz, H-11 β), 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-7 α), 1.85 (1H, dd, $J_{11\alpha,11\beta} = 13.9$ Hz, $J_{11\alpha,12\beta} = 11.1$ Hz, H-11 α), 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-6 β), 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 (CH₂, C-19), 69.9 (CH, C-12), 49.7 (CH, C-10), 48.0 (CH, C-4), 46.8 (CH, C-8), 42.9 (CH₂, C-11), 42.1 (C, C-5), 38.6 (CH₂, C-3), 37.4 (CH₂, C-1), 36.7 (C, C-9), 35.9 (CH₂, C-6), 19.9 (CH₃, C-20), 18.6 (CH₂, 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 C₂₀H₂₂O₆, C 67.02%, H 6.19%.

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), NaBH₄ (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 a few drops of 0.1 N HCl. The solvent was removed under reduced pressure and the solid residue was recovered with CH₂Cl₂ and purified by FC (80:20 CH₂Cl₂-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-12 β), 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-2 β), 2.57 (1H, dd, $J_{8\beta,7\alpha} = 12.0$ Hz, $J_{8\beta,7\beta} = 3.8$ Hz, H-8 β), 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-3 β), 2.20 (1H, dd, $J_{4\beta,3\alpha} = 11.7$ Hz, $J_{4\beta,3\beta} = 6.4$ Hz, H-4 β), 2.07 (1H, dd, $J_{11\beta,11\alpha} = 13.9$ Hz, $J_{11\beta,12\beta} = 6.7$ Hz, H-11 β), 2.03 (2H, m, H-6 α and H-7 β), 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-1 β), 1.88 (1H, dd, $J_{11\alpha,11\beta} = 13.9$ Hz, $J_{11\alpha,12\beta} = 10.8$ Hz,

H-11 α), 1.84 (1H, m, H-7 α), 1.64 (1H, dd, $J_{10\beta,1\alpha} = 12.9$ Hz, $J_{10\beta,1\beta} = 2.7$ Hz, H-10 β), 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-3 α), 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-1 α), 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-6 β), 0.83 (3H, s, Me-20).

Acetylation of the Mixture of 20 and 23 to Give Compounds 21 and 24

Treatment of the mixture described above with Ac₂O-pyridine (1:2, 500 μ L) for 24 h at room temperature, followed by standard workup and purification by FC (95:5 CH₂Cl₂-acetone as eluent), yielded the acetyl derivatives **21** (3 mg, 8%) and **24** (30 mg, 90%).

Compound 24—colorless quadrangular plates (EtOAc-petroleum ether); mp 217–219 °C; $[\alpha]_D^{20} +8.2$ (*c* 0.182, CHCl₃); R_f (95:5 CH₂Cl₂-acetone) 0.29; IR (KBr) $\nu_{\max}$ 3143, 3115, 2921, 1781, 1756, 1706, 1502, 1372, 1264, 1227, 1174, 1152, 1054, 1031, 1016, 876, 825, 609 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 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-12 β), 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-2 β), 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-8 β), 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-3 β), 2.24 (1H, dd, $J_{4\beta,3\alpha} = 12.1$ Hz, $J_{4\beta,3\beta} = 6.4$ Hz, H-4 β), 2.07 (1H, dd, $J_{11\beta,11\alpha} = 13.9$ Hz, $J_{11\beta,12\beta} = 6.7$ Hz, H-11 β), 2.04 (2H, m, H-6 α and H-7 β), 2.04 (3H, s, 2 α -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-1 β), 1.85 (1H, dd, $J_{11\alpha,11\beta} = 13.9$ Hz, $J_{11\alpha,12\beta} = 10.8$ Hz, H-11 α), 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-7 α), 1.72 (1H, dd, $J_{10\beta,1\alpha} = 12.9$ Hz, $J_{10\beta,1\beta} = 2.7$ Hz, H-10 β), 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-3 α), 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-1 α), 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-6 β), 0.83 (3H, s, Me-20); ¹³C NMR (100 MHz, CDCl₃) δ 176.4 (C, C-18), 173.0 (C, C-17), 170.2 (C, 2-OOCOCH₃), 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 (CH₂, C-19), 49.7 (CH, C-10), 48.0 (CH, C-4), 47.2 (CH, C-8), 43.3 (CH₂, C-11), 42.3 (C, C-5), 36.7 (C, C-9), 34.6 (CH₂, C-6), 29.9 (CH₂, C-3), 27.7 (CH₂, C-1), 21.1 (CH₃, 2-OOCOCH₃), 20.1 (CH₃, C-20), 18.7 (CH₂, 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 C₂₂H₂₆O₇, C 65.66%, H 6.51%.

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 elsewhere² using [³H]DAMGO, [³H]DADLE, and [³H]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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- 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.

Scheme 1.

Reagents and conditions: (a) OsO₄ (cat.), NMO, Me₂CO/H₂O 6:1, 24 h rt 70% (**7**), 72h 50°C 52% (**8**), 4 h rt 75% (**9**); (b) Ac₂O/Py 1:2, rt, 15 min. 38% (**10**), 15% (**11**), 2 min. 40% (**12**), 15% (**13**), 1.5 h 50% (**14**); (c) Ac₂O/Py 1:2, 24 h, quant.

Scheme 2.

Reagents and conditions: (a) $\text{Im}_2(\text{CS})$, 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, $\alpha/\beta\text{OH}$ 10/1, quant; (e) Ac_2O , pyridine, rt, 24 h, 100 %.