Polyphosphoric Acid Trimethylsilyl Ester (PPSE) Promoted Intramolecular Acylation of an Olefin by a Carboxylic Acid: Convenient Construction of C-18 Functionalized D^{14}-Hecogenin Acetate

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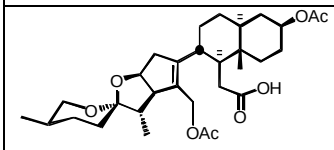
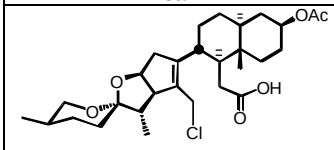
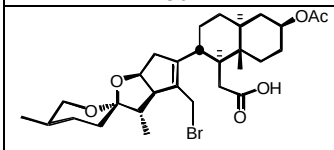
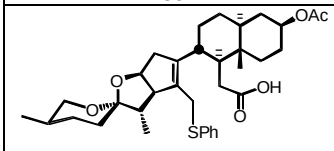
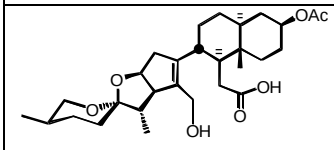
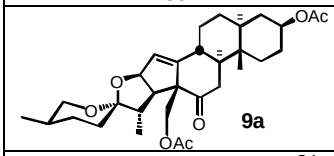
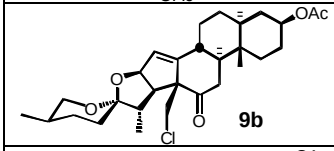
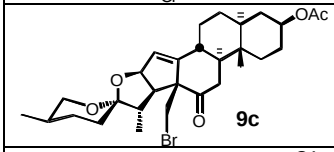
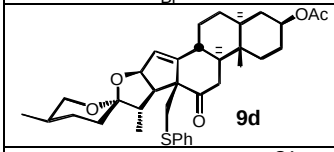
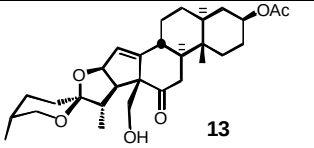
Contribution from the Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

SUPPORTING INFORMATION

Compound characterization checklist.

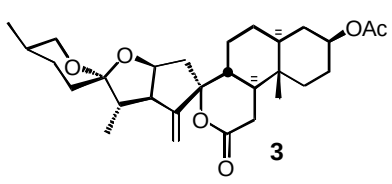
Structure and No.	Formula and MW	HRMS	$^{1}H/^{13}C$ NMR	Other
 **8a**	$C_{31}H_{46}O_8$ 546.7	(EI) *m/z* calcd 546.3193 found 546.3193	yes/yes	
 **8b**	$C_{29}H_{43}ClO_6$ 523.1	(ESI) *m/z* (M + H) calcd 523.2826 found 523.2820	yes/yes	
 **8c**	$C_{29}H_{43}BrO_6$ 567.6	(ESI) *m/z* (M + H) calcd 567.2321 found 567.2326	yes/yes	
 **8d**	$C_{35}H_{48}O_6S$ 596.8	(ESI) *m/z* (M + H) calcd 597.3250 found 597.3245	yes/yes	
 **8e**	$C_{29}H_{44}O_7$ 504.7	(ESI) *m/z* (M + Na) calcd 527.2985 found 527.2981	yes/yes	mp 108.0~112.0 ^{0}C
 **9a**	$C_{31}H_{44}O_7$ 528.7	(ESI) *m/z* (M + H) calcd 529.3165 found 529.3156	yes/yes	mp 192.0~193.8 ^{0}C
 **9b**	$C_{29}H_{41}ClO_5$ 505.1	(ESI) *m/z* $(M+H)^+$ calcd 505.2721 found 505.2721	yes/yes	mp 240.0~242.6 ^{0}C
 **9c**	$C_{29}H_{41}BrO_5$ 549.5	(ESI) *m/z* (M+H) calcd 549.2216 found 549.2213	yes/yes	mp 180.0~181.6 ^{0}C
 **9d**	$C_{35}H_{46}O_5S$ 578.8	(ESI) *m/z* (M + H) calcd 579.3144 found 579.3146	yes/yes	
 **13**	$C_{29}H_{42}O_6$ 484.62	(ESI) *m/z* (M + Na) calcd 509.2879 found 509.2883	yes/yes	Cosy, D_2O exchange NMR; mp 190.4~194.0 ^{0}C

Materials and general methods.

Unless otherwise stated, reactions were performed in glassware recently removed from the oven and cooled under a nitrogen atmosphere. All reactions employed freshly distilled solvents. Methylene chloride, acetonitrile, toluene and benzene were distilled from calcium hydride. Tetrahydrofuran and diethyl ether were distilled from sodium with benzophenone. All other commercially obtained reagents were used as received. Ingredients are listed in the order of their addition. All reactions were magnetically stirred (unless otherwise stated) and monitored by thin-layer chromatography (TLC) using cut EM Si gel 60 F-254 (0.25 mm) plates, visualized with a UV lamp (254 nm) and p-anisaldehyde (for TLC colors, stain solution: EtOH, 1350 mL, H_2SO_4 50 mL, AcOH, 15 mL, p-anisaldehyde 37 mL; heat activated).

Standard work up: the reaction was diluted with organic solvent and washed with saturated $NaHCO_3$ or 5% HCl solution, then washed with brine, dried with anhydrous Na_2SO_4 and decanted. Solvent was removed under reduced pressure using a rotovap and then high vacuum ("concentrated" or "stripped"). Silica gel column chromatography ("sgc") with 230-400 mesh Si gel was based on the method of Still.[1]

All melting points were obtained on a MEL-TEMP and are uncorrected. ^1H and ^{13}C NMR spectra were determined on Varian INOVA-300 and Bruker DRX-500 spectrometers. High resolution mass spectra were performed by the Purdue Campus-wide Mass Spectrometry Facility. Single crystal X-ray analysis was performed by Dr. Fanwick at Purdue University.



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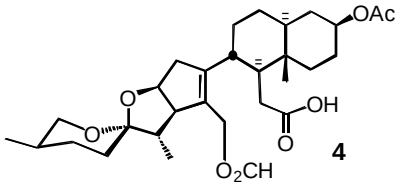
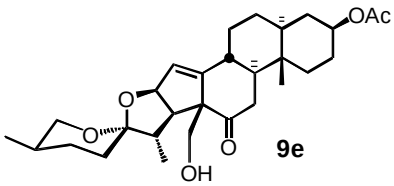
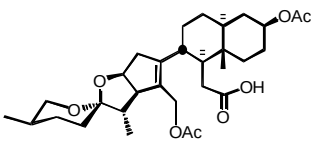


4



9e

Preparation of **8a**:



8a

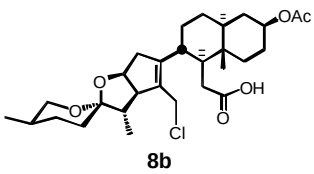
To a mixture of acetic acid (0.5 mL) and sulfuric acid (1 mL) was added compound **3** (100 mg, 0.206 mmol). The solution was stirred at room temperature for 10 hours. The reaction solution was then poured on ice and extracted with diethyl ether. The ether layers were combined and washed successively with water, cold aqueous bicarbonate, and brine. After drying over anhydrous sodium sulfate, the solvent was removed and the remainder was chromatographed (hexanes/ethyl acetate) to give a white solid (107 mg, y = 96%, containing 97% of **8a** and 3% of the starting material **3** by ^1H NMR). This material is directly used for the next step without further purification.

(**8a**) ^1H NMR (300 Hz, $CDCl_3$): d 4.68-4.64 (2H, m, H_{18a} and H_{16}), 4.52-4.46 (2H, m, H_{18b} and H_3), 3.42 (1H, dd, J = 9.9 Hz, 3.8 Hz, H_{26b}), 3.34 (1H, apt, J = 10.7 Hz, H_{26a}), 2.91 (1H, apt, J = 7.3 Hz, H_{17}), 2.58 (1H, dd, J = 17.9, 7.5 Hz, H_{11b}), 2.54-2.45 (1H, m), 2.35 (1H, d, J = 17.7 Hz, H_{11a}), 2.21 (1H, dd, J = 17.0, 6.3 Hz), 2.01 (3H, s, H_{18OAc} 1.97 (3H, s, H_{3OAc}), 1.01 (3H, d, J = 6.9 Hz, H_{21}), 0.80 (3H, s, H_{19}), 0.75 (3H, d, J = 6.3 Hz, H_{27}); ^{13}C NMR (500 Hz, $CDCl_3$): d 179.4, 171.1, 170.6, 142.8, 133.4, 106.1, 77.5, 73.1, 66.8, 59.2, 58.4, 48.6, 46.3, 43.7, 37.7, 37.6,

[1] Still, W. C., Kahn, M., Mitra, A. *J. Org. Chem.* **1978**, 43, 2923.

36.6, 36.4, 33.8, 33.3, 31.1, 31.0, 30.2, 28.6, 27.8, 27.0, 21.3, 20.8, 17.0, 13.6, 11.8; HRMS (EI) *m/z*: calcd 546.3193, found 546.3193.

Preparation of **8b**:

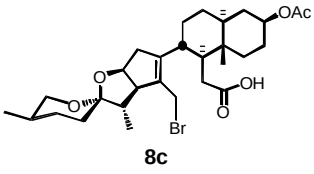


8b

To a solution of compound **3** (100 mg, 0.206 mmol) in dichloromethane (1.0 mL) was added hydrogen chloride etherate (0.6 mL, 0.6 mmol). After stirring at room temperature for 2 hours, the solution was quenched with saturated aqueous sodium bicarbonate and diluted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed and the residue was chromatographed (hexanes/ethyl acetate 2:1, 1:1) to give compound **8b** (106 mg, y = 98%) as a white solid.

^{1}H NMR (300 Hz, $CDCl_3$): d 4.68-4.66 (1H, m, H_3), 4.52 (1H, apt, J = 6.7 Hz, H_{16}), 4.16 (1H, d, J = 11.5 Hz, H_{18a}), 4.01 (1H, d, J = 11.5 Hz, H_{18b}), 3.46 (1H, dd, J = 10.1 Hz, 3.2 Hz, H_{26b}), 3.37 (1H, apt, J = 10.7 Hz, H_{26a}), 3.06 (1H, apt, J = 7.3 Hz, H_{17}), 2.62 (1H, dd, J = 18.2, 7.5 Hz, H_{11b}), 2.46-2.41 (1H, m), 2.38 (1H, d, J = 18.2 Hz, H_{11a}), 2.25 (1H, dd, J = 17.1, 6.9 Hz), 1.99 (3H, s, H_{3OAc}), 1.01 (3H, d, J = 6.9 Hz, H_{21}), 0.84 (3H, s, H_{19}), 0.77 (3H, d, J = 6.1 Hz, H_{27}); ^{13}C NMR (300 Hz, $CDCl_3$): d 179.4, 170.6, 143.4, 135.0, 106.2, 77.3, 73.1, 66.9, 58.0, 48.6, 46.4, 43.7, 38.9, 37.9, 37.6, 36.8, 36.4, 33.9, 33.3, 31.1, 30.3, 28.7, 27.8, 27.1, 21.4, 17.1, 13.9, 11.9; HRMS (ESI) *m/z*: calcd 523.2826 $(M+H)^+$, found 523.2820.

Preparation of **8c**:

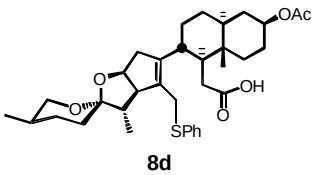


8c

To a solution of compound **3** (100 mg, 0.206 mmol) in dichloromethane (1.0 mL) was added HBr (30% in AcOH, 82 mL, 0.41 mmol) at 0 ^{0}C. After stirring at 0-5 ^{0}C for 2 hours, the solution was quenched with saturated aqueous sodium bicarbonate and diluted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed to give a colorless foam (117 mg, containing 90% of compound **8c** by ^{1}H NMR).

^{1}H NMR (300 Hz, $CDCl_3$): d 4.65 (1H, m, H_3), 4.49 (1H, apt, J = 6.8 Hz, H_{16}), 4.05 (1H, d, J = 10.1 Hz, H_{18a}), 3.89 (1H, d, J = 10.1 Hz, H_{18b}), 3.46-3.43 (1H, m, H_{26b}), 3.35 (1H, apt, J = 10.6 Hz, H_{26a}), 3.06 (1H, apt, J = 7.2 Hz, H_{17}), 2.60 (1H, dd, J = 18.3, 7.3 Hz, H_{11b}), 2.47-2.38 (1H, m), 2.34 (1H, d, J = 18.5 Hz, H_{11a}), 2.24 (1H, dd, J = 17.1, 7.0 Hz), 1.97 (3H, s, H_{3OAc}), 1.09 (3H, d, J = 6.9 Hz, H_{21}), 0.84 (3H, s, H_{19}), 0.75 (3H, d, J = 6.1 Hz, H_{27}); ^{13}C NMR (300 Hz, $CDCl_3$): d 179.8, 170.6, 143.8, 135.1, 106.2, 77.2, 73.0, 66.8, 58.1, 48.5, 46.5, 43.7, 37.9, 37.6, 36.8, 36.3, 33.8, 33.3, 31.0, 30.8, 30.2, 28.7, 27.8, 27.0, 26.8, 21.3, 17.1, 13.96, 11.9; HRMS (ESI) *m/z*: calcd 567.2321 $(M+H)^+$, found 567.2326.

Preparation of **8d**:



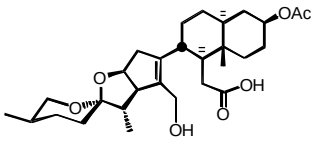
8d

To a solution of compound **3** (60 mg, 0.12 mmol) in dichloromethane (1.0 mL) was added benzene thiol (39 mL, 0.36 mmol) and *p*-toluenesulfonic acid monohydrate (2.4 mg, 0.012 mmol). After stirring at room temperature for 76 hours, the solution was quenched with saturated aqueous sodium bicarbonate and diluted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed and the residue was chromatographed (hexanes/ethyl acetate 4:1, 2:1, 1:1) to give compound **8d** (54 mg, y = 73%) and starting material **3** (5 mg).

^{1}H NMR (300 Hz, $CDCl_3$): d 7.41-7.14 (5H, m), 4.68-4.67 (1H, m, H_3), 4.55 (1H, apt, J = 7.2 Hz, H_{16}), 3.71 (1H, d, J = 12.3 Hz, H_{18a}), 3.52-3.38 (3H, m, H_{18b}, H_{26a}, H_{26b}), 3.11 (1H, apt, J

= 7.2 Hz, H_{17}), 2.56 (1H, dd, J = 17.7 Hz, 7.3 Hz, H_{11b}), 2.39-2.24 (2H, m, H_{11a} and H_{20}), 2.02 (3H, s, H_{OAc}), 1.12 (3H, d, J = 6.9 Hz, H_{21}), 0.81 (3H, d, J = 6.2 Hz, H_{27}), 0.78 (3H, s, H_{19}); ^{13}C NMR (300 Hz, $CDCl_3$): d 179.6, 170.6, 140.9, 136.7, 134.1, 130.8, 128.98, 126.7, 106.2, 77.5, 73.1, 66.9, 58.9, 48.7, 46.4, 43.7, 37.6, 37.4, 36.7, 36.4, 33.9, 33.0, 32.1, 31.2, 30.3, 28.8, 27.9, 27.1, 21.4, 17.1, 14.1, 11.9; HRMS (ESI) *m/z*: calcd 597.3250 $(M+H)^+$, found 597.3245.

Preparation of **8e**:



8e

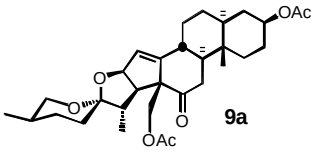
To a solution of **4** (65 mg, 0.12 mmol) in methanol (1 mL) was added $KHCO_3$ (12 mg, 0.12 mmol). After stirring at room temperature for 12 hours, the reaction was diluted with dichloromethane and washed with brine, and dried over anhydrous sodium sulfate. The solvent was removed and the residue was chromatographed to give **8e** (55 mg, y = 91%) as a white solid. mp 108.0~112.0 ^0C.

^1H NMR (300 Hz, $CDCl_3$): d 4.69-4.63 (1H, m, H_3), 4.46-4.39 (2H, m, H_{18a} and H_{16}), 3.92 (1H, d, J = 12.0 Hz, H_{18b}), 3.55-3.53 (1H, m, H_{26b}), 3.34 (1H, apt, J = 10.8 Hz, H_{26a}), 2.97 (1H, apt, J = 7.5 Hz, H_{17}), 2.62-2.27 (4H, m), 1.98 (3H, s, H_{3OAc}), 1.07 (3H, d, J = 6.9 Hz, H_{21}), 0.78 (3H, s, H_{19}), 0.76 (3H, d, J = 6.5 Hz, H_{27}); ^{13}C NMR (300 Hz, $CDCl_3$): d 176.4, 170.7, 140.2, 137.1, 106.7, 77.5, 73.1, 66.6, 57.1, 56.7, 48.2, 46.9, 43.6, 38.3, 38.2, 36.7, 36.3, 35.1, 33.7, 31.04, 31.0, 30.1, 28.6, 27.9, 27.2, 21.3, 17.0, 13.8, 11.9; HRMS (ESI) *m/z*: calcd 527.2985 $(M+Na)^+$, found 527.2981.

Standard procedure for PPSE promoted Friedel-Crafts reaction:

A solution of P_2O_5 (25 equivalent) and hexamethyldisiloxane (37.5 equivalent) in dichloroethane (1.8 x volume of hexamethyldisiloxane, dried over K_2CO_3) was heated at reflux for 1.5 hours. Acid (1 equivalent) in dichloroethane (0.2 M) was added in a small stream to the above clear, colorless solution while keeping the solution at reflux. The reaction mixture was heated at reflux for another 1 to 2 hours. The solution was cooled to room temperature using an ice bath and was then diluted with dichloromethane, washed with cold 10% NaOH, brine, and dried over anhydrous sodium sulfate. The solvent was removed and the residue was chromatographed to give the desired cyclized product.

Preparation of **9a**:

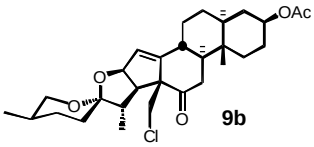


9a

Following the above procedure, 66 mg of **9a** (y = 70%), 6.5 mg of **7** (y = 8%), and 5 mg of **3** (y = 5%) were obtained starting from 100 mg of acid **8a** (containing 3% of compound **3**) after silica gel chromatography (toluene/ethyl acetate 10:1 to 2:1).

Compound **9a**: mp 192.0~193.8 ^0C. ^1H NMR (300 Hz, $CDCl_3$): d 5.52 (1H, s, H_{15}), 4.75-4.71 (1H, m, H_{16}), 4.72 (1H, d, J = 12.0 Hz, H_{18a}), 4.68-4.57 (1H, m, H_3), 4.03 (1H, d, J = 12.0 Hz, H_{18b}), 3.50-3.46 (1H, m, H_{26a}), 3.40-3.32 (2H, m, H_{26b} and H_{17}), 2.53 (1H, apt, J = 14.2 Hz), 2.41-2.34 (2H, m), 1.983 (3H, s, H_{3Ac}), 1.977 (3H, s, H_{18OAc}), 1.03 (3H, d, J = 6.7 Hz, H_{21}), 0.91 (3H, s, H_{19}), 0.76 (3H, d, J = 6.3 Hz, H_{27}); ^{13}C NMR (300 Hz, $CDCl_3$): d 207.6, 170.53, 170.51, 150.9, 123.8, 107.4, 83.7, 72.9, 67.0, 66.8, 65.1, 53.7, 49.1, 44.4, 43.9, 38.0, 36.3, 36.1, 35.4, 33.6, 31.3, 30.2, 29.5, 28.7, 27.7, 27.1, 21.3, 20.7, 17.1, 13.5, 11.7; HRMS (ESI) *m/z*: calcd 529.3165 $(M+H)^+$, found 529.3156.

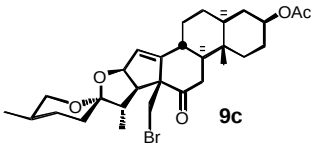
Preparation of **9b**:



Starting from 100 mg of acid **8b**, following the same procedure, 81 mg of **9b** (y = 84%) was obtained as a white solid after silica gel chromatography (hexanes/ethyl acetate 5:1 to 3:1). mp 240.0~242.6 ^{0}C.

^{1}H NMR (300 Hz, $CDCl_3$): d 5.54 (1H, s, H_{15}), 4.70 (1H, dd, J = 8.1 Hz, 2.1 Hz, H_{16}), 4.67-4.58 (1H, m, H_3), 3.96 (1H, d, J = 12.2 Hz, H_{18a}), 3.62 (1H, d, J = 12.2 Hz, H_{18b}), 3.48 (1H, dd, J = 10.7 Hz, 2.3 Hz, H_{26a}), 3.41-3.32 (2H, m, H_{26b} and H_{17}), 2.46-2.33 (3H, m), 1.98 (3H, s, H_{3OAc}), 1.13 (3H, d, J = 6.7 Hz, H_{21}), 0.91 (3H, s, H_{19}), 0.76 (3H, d, J = 6.3 Hz, H_{27}); ^{13}C NMR (300 Hz, $CDCl_3$): d 206.3, 170.5, 151.7, 124.0, 107.6, 83.3, 72.8, 68.4, 66.96, 53.6, 49.2, 45.4, 44.2, 43.8, 37.97, 36.3, 36.1, 35.3, 33.6, 31.3, 30.1, 29.4, 28.7, 27.7, 27.0, 21.3, 17.0, 14.0, 11.7; HRMS (ESI) *m/z*: calcd 505.2721 $(M+H)^+$, found 505.2721.

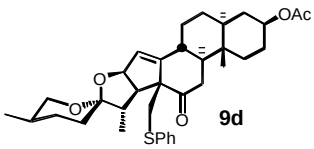
Preparation of **9c**:



Starting from 117 mg of acid **8c** (90% purity based on ^{1}H NMR), following the same procedure, 79 mg of **9c** (y = 78%) was obtained as a white solid after silica gel chromatography (hexanes/ethyl acetate 5:1 to 3:1). mp 180.0~181.6 ^{0}C.

^{1}H NMR (300 Hz, $CDCl_3$): d 5.55 (1H, s, H_{15}), 4.69 (1H, dd, J = 8.1 Hz, 2.2 Hz, H_{16}), 4.67-4.57 (1H, m, H_3), 3.77 (1H, d, J = 11.4 Hz, H_{18a}), 3.50-3.31 (4H, m, H_{26b}, H_{26a}, H_{18b} and H_{17}), 2.45-2.34 (3H, m), 1.98 (3H, s, H_{3Ac}), 1.15 (3H, d, J = 6.9 Hz, H_{21}), 0.91 (3H, s, H_{19}), 0.75 (3H, d, J = 6.3 Hz, H_{27}); ^{13}C NMR (300 Hz, $CDCl_3$): d 206.5, 170.5, 152.5, 123.9, 107.7, 83.2, 72.8, 67.6, 66.98, 53.5, 49.5, 44.0, 43.8, 37.9, 36.3, 36.1, 35.3, 33.63, 33.60, 31.4, 30.1, 29.4, 28.7, 27.7, 27.1, 21.3, 17.1, 14.4, 11.7; HRMS (ESI) *m/z*: calcd 549.2216 $(M+H)^+$, found 549.2213.

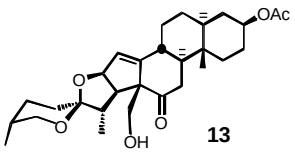
Preparation of **9d**:



Starting from 90 mg of acid **8d**, following the same procedure, 65 mg of **9d** (y = 74%) was obtained as a white fluffy solid after silica gel chromatography (hexanes/ethyl acetate 6:1, 5:1).

^{1}H NMR (300 Hz, $CDCl_3$): d 7.35-7.19 95H, m), 5.58 (1H, s, H_{15}), 4.76 (1H, dd, J = 7.9 Hz, 2.1 Hz, H_{16}), 4.71-4.60 (1H, m, H_3), 3.55-3.51 (1H, m, H_{26b}), 3.48-3.33 (3H, m, H_{26a}, H_{18a} and H_{17}), 3.21 (1H, d, J = 12.6 Hz, H_{18b}), 2.43-2.28 (3H, m), 2.02 (3H, s, H_{OAc}), 1.19 (3H, d, J = 6.9 Hz, H_{21}), 0.81 (3H, d, J = 6.3 Hz, H_{27}), 0.78 (3H, s, H_{19}); ^{13}C NMR (300 Hz, $CDCl_3$): d 208.3, 170.5, 153.4, 136.8, 129.7, 129.1, 126.5, 122.9, 107.7, 83.6, 72.9, 66.98, 66.9, 53.2, 50.1, 44.3, 43.8, 39.1, 38.1, 36.2, 36.1, 35.2, 33.6, 31.4, 30.2, 29.3, 28.7, 27.8, 27.1, 21.3, 17.1, 14.3, 11.5; HRMS (ESI) *m/z*: calcd 579.3144 $(M+H)^+$, found 579.3146.

Weak acid catalyzed equilibrium, preparation of **13**:



To a solution of **9e** (100 mg, 0.21 mmol) in dichloromethane was added PPTS (3 mg, 0.01 mmol). After stirring at room temperature for 5 hours, the reaction was quenched with saturated sodium bicarbonate and washed with brine once. The organic layers were dried over anhydrous sodium sulfate. The solvent was removed to give a white solid. ^{1}H NMR showed that the ratio of **9e**:**12**:**13** was 67:28:5. Several reactions were performed following the same procedure but used different solvents (CH_3OH, or CH_3OH/CH_2Cl_2, or 75% aqueous $AcOH/CH_2Cl_2$). More experiments were performed using **12** as starting material to get the ^{1}H NMR ratios. Some of the recovered products were combined and chromatographed (hexanes/ethyl acetate, 3:1, 1.5:1, 100% ethyl acetate) to give 20 mg of **13**. mp 190.4~194.0 ^{0}C.

^{1}H NMR (300 Hz, $CDCl_3$): d 5.53 (1H, s, H_{15}), 5.14 (1H, d, J = 10.7 Hz, $H_{18\text{-}OH}$), 5.03 (1H, dd, J = 8.4 Hz, 1.9 Hz, H_{16}), 4.69-4.59 (1H, m, H_3), 3.97-3.90 (2H, m, H_{18a} and H_{26a}), 3.68 (1H, d, J = 11.2 Hz, H_{18b}), 3.35 (1H, d, J = 8.4 Hz, H_{17}), 3.13 (1H, bd, J = 11.1 Hz, H_{26b}), 2.60-2.51 (2H, m), 2.36 (1H, dd, J = 15.4 Hz, 5.0 Hz, H_{11a}), 2.27 (1H, apq, J = 7.3 Hz, H_{20}), 1.99 (3H, s, $H_{3\text{-}OAc}$), 1.06 (3H, d, J = 7.3 Hz, H_{21}) , 1.01 (3H, d, J = 7.0 Hz, H_{27}), 0.91 (3H, s, H_{19}); ^{13}C NMR (300 Hz, $CDCl_3$): d 208.8, 170.6, 150.9, 124.5, 108.8, 86.7, 73.1, 71.7, 65.4, 62.9, 53.4, 49.8, 44.4, 44.1, 37.7, 36.3, 36.2, 34.97, 33.7, 29.6, 27.7, 27.2, 27.0, 25.7, 25.6, 21.4, 18.4, 16.3, 11.7; HRMS (ESI) *m/z*: calcd 509.2879 $(M+Na)^+$, found 509.2883.