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Mild Isomerative Opening of Tetrahydrofuranyl Subunits in Steroids Using TFAT (trifluoroacetyl trifluoromethanesulfonate): Application to Synthesis of C17-OH Rockogenin Acetate

Jong Seok Lee,* Byungsook Kim, Junho Shin, Yeon-Ju Lee, Hee Jae Shin, and Hyi-Seung Lee

Marine Natural Products Laboratory, Korea Ocean Research and Development Institute, Ansan 426-744, Korea
**E-mail: jslee@kordi.re.kr*
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A novel and efficient tetrahydrofuranyl ring opening method was developed using the highly reactive TFAT reagent in the presence of an acid scavenger, 2,6-di-*tert*-butyl-4-methylpyridine. Various acid sensitive groups are compatible with the reaction condition, making it generally applicable to many tetrahydrofuranyl steroids. Moreover, it is a synthetic equivalent of 'Marker degradation' affording an efficient synthesis of C17-OH rockogenin acetate.

Key Words : Steroid, TFAT (trifluoroacetyl trifluoromethanesulfonate), Ring opening, Dihydroxylation, Alkoxyl radical cyclization

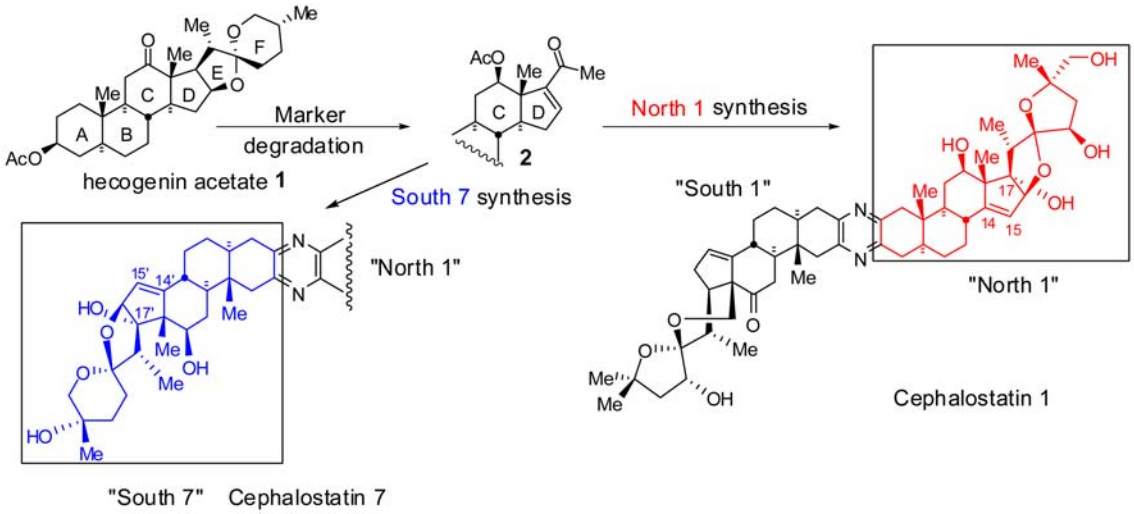
Introduction

In modern organic synthesis, the ether is one of the most frequently found features. It is commonly used as a protecting group for alcohols.[1] At the same time, its cyclic forms such as tetrahydrofurans and pyrans are found as core structures in many biologically active natural products. During the last few decades, many methods have been developed to manipulate the ethers, which are mainly focused on their introduction and cleavage.[1] Cleavage of cyclic ethers is an essential process in the syntheses of many natural products since it enables easy introduction of additional functionalities.[2]

Over many years, steroid sapogenins have been standing as steadfast starting materials for the synthesis of steroidal natural products. Thus, various reactions were developed and applied to chemically modify the steroid sapogenins.[2g,2h,3-5]

Since the historic report in 1938, 'Marker degradation' has been generally used for the synthesis of steroidal natural products including sex hormones such as progesterone, testosterone, estradiol and other steroid analogs.[4] Especially, it is the essential early process for introduction of C17-α-OH, which was successfully applied to the previous first generation synthesis of cephalostatin 1 and 7 (Scheme 1).[5]

But application of 'Marker degradation' in the synthesis of cephalostatins includes excision of the entire F-ring in the steroid sapogenin and subsequent reintroduction of the same atoms, which is not attractive on the strategic level (Scheme 1). To overcome this shortcoming, it is required to develop a novel synthetic tool retaining all carbon atoms of the starting steroid sapogenin and employ specific oxidation reactions



Scheme 1. The first generation synthesis of cephalostatins.

for introduction of the desired functional groups to the specific positions.

Experimental Section

All reactions were carried out under nitrogen unless otherwise indicated. Anhydrous methylene chloride (CH_2Cl_2), diethyl ether, and tetrahydrofuran (THF) were directly used from commercial source. Pyridine, cyclohexane, and triethylamine were used without further purification. All work-up, wash, and chromatographic solvents were distilled. Sodium sulfate (Na_2SO_4) was anhydrous.

Thin layer chromatography (TLC) was used to monitor the progress of reactions by co-spotting with the starting materials. *p*-Anisaldehyde (1350 mL absolute ethanol, 50 mL concentrated H_2SO_4, 37 mL *p*-anisaldehyde) was utilized as a common TLC visualizing solution.

Flash chromatographic purifications were performed using silica gel (230-400 mesh). ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded as solutions in chloroform-d_1 and are described in parts per million (ppm) from the residual chloroform (7.24 ppm and 77.23 ppm).

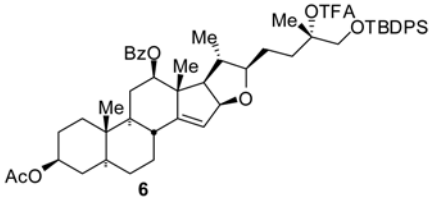
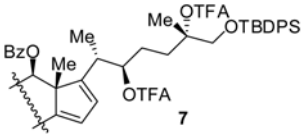
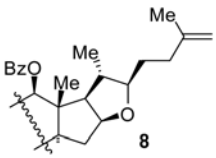
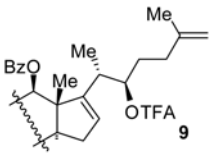
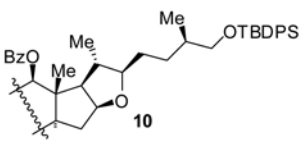
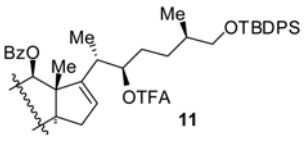
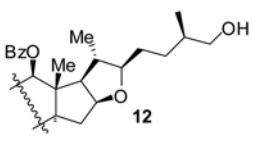
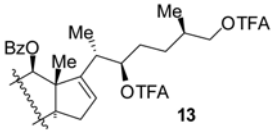
Peak multiplicates in ^{1}H NMR spectra are abbreviated as s (singlet), d (doublet), t (triplet), m (multiplet), dd (doublet of doublet), q (quartet), and dt (doublet of triplet).

General Procedure for the Preparation of Compounds 4, 5, 7, 9, 11, and 13. To a solution of a tetrahydrofuranyl steroid (compound **3**, **6**, **8**, **10**, **12**, **14**) and 2,6-di-*tert*-butyl-4-methylpyridine (indicated in the main text) in anhydrous CH_2Cl_2 (0.1-0.15 M) was added freshly prepared TFAT (3-5 equiv. as indicated in Table 1 of the main text) at −35 °C. The reaction was stirred at −35 °C until the starting material disappeared on TLC (normally 40 min. to 2 h), then quenched with sat. $NaHCO_3$. The reaction was extracted with EtOAc three times. The extract was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (EtOAc/*n*-Hexane 1:10 to 1:6) to give the corresponding product (compound **4**, **5**, **7**, **9**, **11**, and **13**).

Trifluoroacetate 4: Terminal olefin **3** (96 mg, 0.17 mmol) was used and the reaction was carried out with 3 equiv. of TFAT (0.52 mmol, 0.08 mL) alone to provide compound **4** (79 mg, 0.12 mmol, 70%, white floppy solid): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 7.2 Hz, 2H), 7.55 (t, J = 7.3 Hz, 1H), 7.41-7.46 (m, 2H), 6.15 (d, J = 1.8 Hz, 1H), 5.88 (s, 1H), 5.06 (q, J = 6.3 Hz, 1H), 4.96 (t, J = 7.10 Hz, 1H), 4.61-4.70 (m, 1H), 4.40 (dd, J = 11.4, 4.2 Hz, 1H), 2.86 (quintet, J = 7.0 Hz, 1H), 2.27-2.30 (m, 2H), 2.17 (t, J = 10.6 Hz, 1H), 1.97 (s, 3H), 1.60 (s, 3H), 1.47 (s, 3H), 1.23 (s, 3H), 0.89 (s, 3H), 0.85 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 165.4, 156.9, 156.5 (q, $^2J_{C\text{-}F}$ = 41.6 Hz, C=O), 155.7, 135.6, 133.0, 130.3, 129.3, 128.4, 125.9, 120.8, 118.4 (q, $^1J_{C\text{-}F}$ = 288.4 Hz, CF_3), 117.5, 82.1, 79.2, 73.2, 56.8, 53.1, 44.2, 36.9, 35.7, 35.4, 34.6, 33.7, 29.6, 29.0, 28.0, 27.2, 27.1, 25.6, 21.2, 18.5, 17.5, 13.6, 12.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.1; HRMS (ESI) for $C_{38}H_{47}F_3O_6Na$ $[M+Na]^+$ calcd. 679.3223, found 679.3233.

Trifluoroacetate 7: TBDPS ether **6** (166 mg, 0.18 mmol)

Table 1. Results of the TFAT-promoted E-ring opening of steroids

Entry[a]	Substrate	TFAT[b] (equiv.)	Acid scavenger[c] (equiv.)	Time (min.)	Product	Yield[d] (%)
1	 **6**	3	1.2	40	 **7**	91
2	 **8**	3	1.2	40	 **9**	61
3	 **10**	5	5	120	 **11**	68
4	 **12**	4.5	5	120	 **13**	42

[a]All the reactions were performed at −35 °C. [b]Freshly prepared TFAT was used. [c]2,6-di-*tert*-butyl-4-methylpyridine. [d]Separated yields.

was used and the reaction was carried out with 3 equiv. of TFAT (0.54 mmol, 0.08 mL) and 1.20 equiv. of 2,6-di-*tert*-butyl-4-methylpyridine (0.21 mmol, 44.0 mg) to provide compound **7** (167 mg, 0.16 mmol, 91%, white floppy solid): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 7.3 Hz, 2H), 7.58 (d, J = 7.0 Hz, 4H), 7.50 (t, J = 7.2 Hz, 1H), 7.34-7.45 (m, 8H), 6.13 (d, J = 1.6 Hz, 1H), 5.89 (s, 1H), 5.05-5.07 (m, 1H), 4.65-4.72 (m, 1H), 4.40 (dd, J = 11.2, 4.1 Hz, 1H), 3.78 (t, J = 11.0 Hz, 1H), 3.67 (t, J = 10.0 Hz, 1H), 2.86 (quintet, J = 6.9 Hz, 1H), 2.20 (br t, J = 10.1 Hz, 1H), 2.00 (s, 3H), 1.40 (s, 3H), 1.24 (s, 3H), 1.00 (s, 9H), 0.92 (s, 3H), 0.85 (d, J = 9.08 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 165.5, 156.6 (q, $^2J_{C\text{-}F}$ = 45.0 Hz, C=O), 156.2, 156.0, 155.8 (q, $^2J_{C\text{-}F}$ = 45.0 Hz, C=O), 135.5, 133.1, 132.6, 132.5, 130.2, 129.9, 129.3, 128.5, 127.8, 126.5, 120.8, 114.2 (q, $^1J_{C\text{-}F}$ = 277.8 Hz, C=O), 114.0 (q, $^1J_{C\text{-}F}$ = 277.8 Hz, C=O), 89.4, 89.3, 82.0, 79.3, 73.3, 66.3, 56.9, 53.2, 44.3, 37.0, 35.8, 35.5, 34.7, 33.8, 31.6, 30.8, 29.1, 28.1, 27.3, 27.2, 26.6, 25.3, 24.2, 22.6, 21.4, 20.3, 19.1, 18.1, 14.1, 13.6, 12.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ −74.9, −75.4; HRMS (ESI) for $C_{56}H_{66}F_6O_9SiNa$ $[M+Na]^+$ calcd. 1047.4278, found 1047.4280.

Trifluoroacetate 9:. Terminal olefin **8** (103 mg, 0.18 mmol) was used and the reaction was carried out with 3 equiv. of TFAT (0.55 mmol, 0.08 mL) and 1.20 equiv. of 2,6-di-*tert*-butyl-4-methylpyridine (0.22 mmol, 45 mg) to provide compound **9** (73 mg, 0.11 mmol, 61%, white floppy solid): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 7.2 Hz, 2H), 7.56 (t, J = 7.3 Hz, 1H), 7.43-7.48 (m, 2H), 5.41 (s, 1H), 5.09-5.16 (m, 2H), 4.63-4.70 (m, 2H), 4.49 (s, 1H), 2.64 (quintet, J = 7.7 Hz, 1H), 1.99 (s, 3H), 1.56 (s, 3H), 0.98 (s, 3H), 0.98 (s, 3H), 0.83 (s, 3H), 0.82 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 165.7, 157.0 (q, $^2J_{C\text{-}F}$ = 39.0 Hz, C=O), 154.2, 144.1, 133.1, 130.4, 129.4, 128.5, 123.5, 118.6 (q, $^1J_{C\text{-}F}$ = 288.0 Hz, CF_3), 110.5, 81.1, 78.7, 73.4, 54.2, 53.1, 50.5, 44.7, 36.4, 35.7, 35.6, 33.8, 33.1, 31.9, 31.2, 30.7, 29.4, 28.3, 27.4, 27.2, 22.3, 21.4, 18.2, 12.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.0; HRMS (ESI) for $C_{38}H_{49}F_3O_6Na$ $[M+Na]^+$ calcd. 681.3379, found 681.3375.

Trifluoroacetate 11: TBDPS ether **10** (522 mg, 0.64 mmol) was used and the reaction was carried out with 5 equiv. of TFAT (3.19 mmol, 0.49 mL) and 5 equiv. of 2,6-di-*tert*-butyl-4-methylpyridine (3.19 mmol, 655 mg) to provide compound **11** (396 mg, 0.43 mmol, 68%, white floppy solid): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 8.1 Hz, 2H), 7.72 (d, J = 7.6 Hz, 1H), 7.63 (t, J = 7.7 Hz, 4H), 7.33-7.43 (m, 9H), 5.40 (s, 1H), 5.11-5.16 (m, 2H), 4.66-4.71 (m, 1H), 3.30 (t, J = 5.0 Hz, 1H), 3.30 (q, J = 10.0 Hz, 1H), 2.64 (quintet, J = 7.4 Hz, 1H), 2.05-2.15 (m, 2H), 2.00 (d, J = 1.2 Hz, 3H), 1.06 (s, 3H), 1.02 (s, 9H), 0.99 (s, 3H), 0.85 (s, 3H), 0.81 (d, J = 6.6 Hz, 3H), 0.71 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 165.9, 157.3 (q, $^2J_{C\text{-}F}$ = 41.6 Hz, C=O), 154.5, 135.7, 135.5, 135.0, 134.02, 134.0, 133.2, 130.5, 129.8, 129.5, 128.7, 127.9, 127.8, 123.4, 114.8 (q, $^1J_{C\text{-}F}$ = 285.0 Hz, CF_3), 81.6, 78.9, 73.6, 68.8, 54.3, 53.3, 50.7, 44.8, 36.6, 35.9, 35.7, 35.6, 34.0, 33.3, 31.4, 30.9, 29.9, 29.1, 28.5, 27.6, 27.4, 27.2, 26.9, 26.7, 21.6, 19.4, 19.2, 18.4, 16.5, 12.2, 12.1; ^{19}F NMR (470 MHz, CDC_{l3}) δ −75.0; HRMS (ESI) for $C_{54}H_{69}F_3O_7SiNa$ $[M+Na]^+$ calcd. 937.4662, found 937.4657.

Trifluoroacetate 13: Primary alcohol **12** (101 mg, 0.17 mmol) was used and the reaction was carried out with 4.50 equiv. of TFAT (0.78 mmol, 0.12 mL) and 5 equiv. of 2,6-di-*tert*-butyl-4-methylpyridine (0.87 mmol, 178 mg) to provide compound **13** (55 mg, 0.07 mmol, 42%, white floppy solid): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 8.0 Hz, 2H), 7.56 (t, J = 7.3 Hz, 1H), 7.44 (t, J = 7.7 Hz, 2H), 5.38 (s, 1H), 5.14 (dd, J = 10.6, 5.2 Hz, 1H), 5.07-5.10 (m, 1H), 4.65 (m, 1H), 3.99 (dd, J = 10.7, 6.6 Hz, 1H), 3.94 (dd, J = 10.8, 6.6 Hz, 1H), 2.61 (dt, J = 15.9, 7.1 Hz, 1H), 2.07-2.12 (m, 1H), 2.00-2.05 (m, 1H), 1.97 (s, 3H), 0.97 (s, 3H), 0.83 (s, 3H), 0.81 (d, J = 7.0 Hz, 3H), 0.75 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 165.8, 157.6 (q, $^2J_{C\text{-}F}$ = 39.4 Hz, C=O), 157.2 (q, $^2J_{C\text{-}F}$ = 42.2 Hz, C=O), 154.4, 133.3, 130.6, 129.6, 128.7, 123.63, 123.61, 114.7 (q, $^1J_{C\text{-}F}$ = 285.0 Hz, CF_3), 114.6 (q, $^1J_{C\text{-}F}$ = 284.5 Hz, CF_3), 80.9, 78.7, 73.6, 72.2, 54.4, 53.3, 50.6, 44.8, 36.6, 35.9, 35.4, 34.0, 33.3, 32.1, 31.4, 30.9, 29.9, 28.5, 28.4, 27.6, 27.4, 26.8, 21.6, 18.4, 16.1, 12.2, 12.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ −75.18, −75.20; HRMS (ESI) for $C_{40}H_{52}F_6O_9$ $[M+H_2O]^+$ calcd. 790.3516, found 790.3761.

Trifluroacetates 15, 16, and 17: TBDPS ether **14** (94 mg, 0.13 mmol) was used and the reaction was carried out for 1 h with 3 equiv. of TFAT (0.40 mmol, 0.06 mL) and 1.20 equiv. of 2,6-di-*tert*-butyl-4-methylpyridine (0.16 mmol, 33 mg). The reaction was purified by HPLC (Silica column, 250 × 10 mm ID, 98% *n*-Hexane/2% EtOAc, 2.0 mL/min, RI detector) to provide compound **15** (29 mg, 0.04 mmol, 27%, white floppy solid), compound **16** (30 mg, 0.04 mmol, 28%, white floppy solid), and compound **17** (5.4 mg, 0.01 mmol, 5%, white floppy solid):

Trifluoroacetate 15: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J = 6.6 Hz, 4H), 7.35-7.42 (m, 6H), 5.42 (s, 1H), 5.18 (dd, J = 11.5, 5.6 Hz, 1H), 4.67-4.70 (m, 1H), 3.45 (t, J = 3.9 Hz, 1H), 3.45 (t, J = 8.6 Hz, 1H), 2.44 (quintet, J = 6.6 Hz, 1H), 2.01 (s, 3H), 1.04 (s, 9H), 1.01 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 6.4 Hz, 3H), 0.85 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 157.5 (q, $^2J_{C\text{-}F}$ = 42.0 Hz, C=O), 155.8, 135.8, 135.7, 134.04, 134.01, 129.7, 127.8, 123.6, 114.9 (q, $^1J_{C\text{-}F}$ = 285.0 Hz, CF_3), 82.0, 73.8, 68.8, 57.4, 55.0, 47.3, 45.1, 36.8, 36.0, 35.9, 35.7, 35.6, 34.8, 34.3, 34.2, 32.0, 31.3, 29.9, 28.7, 28.6, 28.3, 27.6, 27.0, 21.6, 21.2, 19.4, 17.5, 16.6, 16.1, 12.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ −75.0; HRMS (ESI) for $C_{47}H_{66}F_3O_5Si$ $[M+H]^+$ calcd. 795.4632, found 795.4641.

Trifluoroacetate 16: ^{1}H NMR (500 MHz, $CDCl_3$) d 7.65 (d, J = 7.1 Hz, 4H), 7.35-7.42 (m, 6H), 5.26 (d, J = 11.0 Hz, 1H), 4.68-4.71 (m, 1H), 3.47 (t, J = 2.4 Hz, 1H), 3.46 (t, J = 2.7 Hz, 1H), 2.21-2.23 (m, 1H), 2.09-2.11 (m, 1H), 2.02 (s, 3H), 1.06 (s, 3H), 1.05 (s, 9H), 0.92 (d, J = 6.6 Hz, 3H), 0.82 (d, J = 7.1 Hz, 3H), 0.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 157.3 (q, $^2J_{C\text{-}F}$ = 41.5 Hz, C=O), 139.2, 138.3, 135.8, 135.76, 134.0, 133.9, 129.7, 127.8, 127.7, 114.9 (q, $^1J_{C\text{-}F}$ = 285.0 Hz, CF_3), 82.2, 77.0, 73.9, 68.7, 51.8, 51.81, 44.7, 42.2, 37.1, 36.6, 35.6, 35.63, 34.0, 32.9, 31.6,

31.3, 29.9, 29.5, 29.1, 27.5, 27.0, 26.9, 25.3, 23.2, 23.1, 21.6, 19.4, 16.8, 11.9, 9.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ −75.2; HRMS (ESI) for $C_{47}H_{66}F_3O_5Si$ $[M+H]^+$ calcd. 795.4632, found 795.4640.

Trifluoroacetate 17: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, J = 6.3 Hz, 4H), 7.34-7.40 (m, 6H), 5.24-5.26 (m, 2H), 4.62-4.70 (m, 1H), 3.43 (d, J = 5.9 Hz, 1H), 2.01 (s, 3H), 1.04 (s, 3H), 1.02 (s, 9H), 0.88 (d, J = 6.9 Hz, 3H), 0.85 (d, J = 7.1 Hz, 3H), 0.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 157.3 (q, $^2J_{C\text{-}F}$ = 41.0 Hz, C=O), 150.8, 135.81, 135.79, 134.1, 134.0, 129.8, 127.81, 127.80, 116.3, 114.9 (q, $^1J_{C\text{-}F}$ = 285.0 Hz, CF_3), 82.1, 73.8, 68.8, 50.1, 48.4, 46.6, 45.0, 44.5, 39.0, 37.0, 35.65, 35.61, 35.3, 34.3, 32.7, 29.9, 29.5, 29.4, 28.1, 27.4, 27.0, 26.97, 25.6, 21.7, 19.5, 16.8, 12.3, 9.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ −75.2; HRMS (ESI) for $C_{47}H_{66}F_3O_5Si$ $[M+H]^+$ calcd. 795.4632, found 795.4644.

Secondary Alcohol 18: Trifluoroacetate **11** (305 mg, 0.33 mmol) was stirred with K_2CO_3 (92 mg, 0.67 mmol, 2 equiv.) and thiourea (63 mg, 0.83 mmol, 2.50 equiv.) in 6.70 mL of EtOH at room temperature for 4.5 h. The reaction was quenched with EtOAc/H_2O, extracted with EtOAc three times. The extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (EtOAc/*n*-Hexane = 1:6 to 1:3) to give secondary alcohol **18** (271 mg, 0.33 mmol, 99%) as white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 7.6 Hz, 2H), 7.64 (d, J = 6.6 Hz, 4H), 7.34-7.43 (m, 9H), 5.49 (s, 1H), 5.15 (dd, J = 5.7, 4.5 Hz, 1H), 4.66-4.71 (m, 1H), 3.54 (t, J = 7.6 Hz, 1H), 3.44 (dt, J = 5.3, 4.4 Hz, 1H), 3.29 (t, J = 8.0 Hz, 1H), 2.3 (quintet, J = 7.4 Hz, 1H), 2.15-2.18 (m, 1H), 2.01-2.09 (m, 1H), 2.00 (s, 3H), 1.04 (s, 3H), 1.02 (s, 9H), 0.85 (s, 3H), 0.80 (d, J = 6.4 Hz, 3H), 0.75 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 165.9, 157.5, 135.8, 134.24, 134.22, 133.2, 130.6, 129.65, 129.60, 128.6, 127.7, 123.0, 78.6, 73.7, 73.6, 69.2, 54.6, 53.3, 50.7, 44.8, 39.8, 36.7, 36.1, 35.9, 34.0, 33.4, 31.4, 30.9, 30.6, 28.5, 28.4, 27.6, 27.5, 27.0, 21.6, 19.4, 18.1, 17.0, 13.0, 12.3; HRMS (ESI) for $C_{52}H_{70}O_6SiNa$ $[M+Na]^+$ calcd. 841.4839, found 841.4815.

TBS Ether 19: To a solution of secondary alcohol **18** (268 mg, 0.33 mmol), triethylamine (0.09 mL, 0.65 mmol, 2 equiv.) in CH_2Cl_2 (6.5 mL) was added TBSOTf (0.11 mL, 0.49 mmol, 1.50 equiv.) at room temperature. The reaction was stirred for 0.5 h. The reaction was diluted with CH_2Cl_2, worked up with sat. $NaHCO_3$. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (EtOAc/*n*-Hexane = 1:15 to 1:10) to give TBS ether **19** (287 mg, 0.31 mmol, 94%) as white floppy solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J = 7.5 Hz, 2H), 7.68 (d, J = 5.9 Hz, 4H), 7.40-7.45 (m, 6H), 7.26-7.34 (m, 4H), 5.54 (s, 1H), 5.15 (dd, J = 10.2, 4.9 Hz, 1H), 4.69-4.73 (m, 1H), 3.59 (d, J = 4.4 Hz, 1H), 3.43 (dd, J = 9.5, 5.7 Hz, 1H), 3.23 (t, J = 7.8 Hz, 1H), 2.35 (quintet, J = 6.4 Hz, 1H), 2.02 (s, 3H), 1.06 (s, 9H), 0.98 (s, 3H), 0.87 (s, 3H), 0.84 (s, 9H), 0.80 (d, J = 5.6 Hz, 3H), 0.79 (d, J = 6.1 Hz, 3H), −0.02 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 166.0, 156.1, 135.8, 134.3, 133.0, 130.8, 129.7, 129.6, 128.5, 127.8, 123.1, 79.1, 76.1, 73.7, 69.5, 54.3, 53.4, 50.8, 44.9, 36.8, 36.7, 36.5, 35.9, 34.1, 33.4, 32.4, 31.5, 31.0, 28.6, 27.7, 27.6, 27.5, 27.1, 27.05, 26.2, 26.1, 21.6, 19.5, 19.1, 18.2, 17.0, 12.54, 12.48, 12.3, 12.2; HRMS (ESI) for $C_{58}H_{84}O_6Si_2$ $[M+H_2O]^+$ calcd. 950.5912, found 950.6161.

Diol 20: To a solution of TBS ether **19** (128 mg, 0.14 mmol) in pyridine/THF (1.4 mL/2.8 mL) was added OsO_4 (2.5 wt % in tBuOH, 3.10 mL, 0.30 mmol, 2.20 equiv.) at -78 °C. The reaction was stirred for 26 h with temperature allowed to reach room temperature. After dilution with EtOAc, the reaction was treated with 1 N aq. HCl solution to remove pyridine. The resulting solution was neutralized with sat. $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. To the concentrate was added sat. $NaHSO_3$/THF (1:1) and the solution was heated for 3.5 h at 60 °C. The reaction was diluted with EtOAc, worked up with water. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (EtOAc/*n*-Hexane = 1:6) to give diol **20** (129 mg, 0.13 mmol, 98%) as white floppy solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 7.4 Hz, 2H), 7.64 (d, J = 6.6 Hz, 4H), 7.53 (t, J = 7.4 Hz, 1H), 7.34-7.42 (m, 8H), 5.31 (dd, J = 10.9, 4.8 Hz, 1H), 4.65-4.69 (m, 1H), 4.30 (t, J = 6.1 Hz, 1H), 3.74 (s, 1H), 7.03 (d, J = 5.2 Hz, 1H), 3.47 (dd, J = 9.8, 5.6 Hz, 1H), 3.42 (dd, J = 9.6, 6.2 Hz, 1H), 3.09 (s, 1H), 1.99 (s, 3H), 1.04 (s, 9H), 0.95 (s, 3H), 0.88 (d, J = 6.6 Hz, 3H), 0.82 (s, 9H), 0.817 (s, 3H), 0.74 (d, J = 6.9 Hz, 3H), 0.00 (s, 3H), −0.003 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 166.7, 135.82, 135.81, 134.24, 134.22, 133.2, 131.0, 129.8, 129.7, 128.6, 127.8, 84.4, 78.0, 74.9, 74.7, 73.6, 69.2, 53.4, 52.0, 47.7, 44.6, 42.5, 36.7, 36.1, 35.6, 34.5, 34.0, 32.9, 31.5, 30.9, 29.9, 28.6, 27.8, 27.4, 27.1, 26.1, 21.6, 19.5, 18.2, 17.0, 12.4, 12.2, 11.2, -4.1; HRMS (EI) for $C_{58}H_{87}O_8Si_2$ $[M+H]^+$ calcd. 967.5939, found 967.5940.

Ketone 22: Solid TPAP, tetrapropylammonium perruthenate (12 mg, 0.03 mmol, 0.25 equiv.) was added in one portion to a stirred solution of diol **20** (129 mg, 0.13 mmol), NMO, 4-methylmorpholine *N*-oxide (47 mg, 0.40 mmol, 3 equiv.) and powdered molecular sieves (13 mg, 4 Å, activated) in CH_2Cl_2 (2.7 mL) at room temperature. On completion, the reaction was filtered through a short celite pad (5 cm), and the filtrate was concentrated *in vacuo*. The crude residue was purified by flash chromatography (EtOAc/*n*-Hexane = 1:6 to 1:4) to provide ketone **22** (94 mg, 0.10 mmol, 71% overall from TBS ether **19**) as white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J = 7.8 Hz, 2H), 7.64 (d, J = 6.4 Hz, 4H), 7.51 (t, J = 7.0 Hz, 1H), 7.34-7.40 (m, 8H), 5.41 (dd, J = 10.7, 4.6 Hz, 1H), 4.66-4.70 (m, 1H), 4.12 (s, 1H), 3.42-3.46 (m, 2H), 3.35 (dd, J = 9.5, 6.9 Hz, 1H), 2.35 (dd, J = 17.2, 6.6 Hz, 1H), 2.29 (t, J = 6.6 Hz, 1H), 1.99 (s, 3H), 1.24 (s, 3H), 1.12 (s, 3H), 1.02 (s, 9H), 0.84 (s, 3H), 0.82 (d, J = 10.5 Hz, 3H), 0.81 (s, 9H), 0.77 (d, J = 6.8 Hz, 3H), −0.03 (s, 3H), -0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.1, 170.8, 165.8, 135.8, 134.2, 133.2, 130.8, 129.7, 129.6, 128.6, 127.7, 84.3, 74.0, 73.53, 73.52, 69.5, 51.7, 51.2, 44.5,

44.0, 40.5, 37.2, 36.5, 36.3, 35.7, 33.9, 33.7, 32.2, 31.6, 29.9, 28.5, 28.4, 27.4, 27.1, 27.0, 26.1, 21.6, 19.5, 18.2, 16.7, 12.2, 12.0, 11.2, −3.8, −4.3; HRMS (EI) for $C_{58}H_{85}O_8Si_2$ $[M+H]^+$ calcd. 965.5783, found 965.5803.

Aldehyde 21: To a solution of diol **20** (12 mg, 0.01 mmol) in CH_2Cl_2 (0.25 mL) was added Dess-Martin periodinane (11 mg, 0.03 mmol, 2 equiv.) and stirred for 2 h at room temperature. The reaction was diluted with CH_2Cl_2, worked up with sat. $NaHCO_3$. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (EtOAc/*n*-Hexane = 1:6) to give aldehyde **21** (12 mg, 0.01 mmol, 95%) as white floppy solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.69 (d, *J* = 1.7 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.60-7.62 (m, 4H), 7.35-7.42 (m, 7H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.18-7.24 (m, 2H), 5.21 (dd, *J* = 11.2, 4.2 Hz, 1H), 4.66-4.71 (m, 1H), 3.60-3.62 (m, 1H), 3.51 (t, *J* = 6.3 Hz, 1H), 3.20 (dd, *J* = 9.4, 5.3 Hz, 1H), 3.04 (dd, *J* = 9.4, 7.0 Hz, 1H), 2.45 (t, *J* = 9.4 Hz, 1H), 2.20-2.30 (m, 2H), 1.99 (s, 3H), 1.32 (s, 3H), 1.00 (s, 9H), 0.84 (s, 9H), 0.79 (s, 3H), 0.78 (d, *J* = 8.5 Hz, 3H), 0.70 (d, *J* = 6.6 Hz, 3H), 0.12 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.2, 200.9, 170.8, 165.4, 135.8, 134.2, 133.4, 130.0, 129.7, 129.65, 129.5, 128.6, 127.76, 127.74, 77.4, 77.0, 73.4, 72.5, 69.5, 57.4, 50.4, 46.8, 45.9, 44.0, 40.4, 37.4, 36.7, 36.1, 35.7, 33.8, 31.7, 29.1, 28.7, 28.4, 27.3, 27.0, 26.1, 26.0, 21.6, 19.5, 18.3, 16.4, 12.3, 12.2, 10.8, −3.7, −4.4; HRMS (ESI) for $C_{58}H_{85}O_8Si_2$ $[M+H]^+$ calcd. 965.5783, found 965.5792.

Hemiketal 23: TBAF, tetrabutylammonium fluoride, 1.0 M solution in THF (0.29 mL, 0.29 mmol, 7.50 equiv.) was added to a stirred solution of ketone **22** (37 mg, 0.04 mmol) in THF (3.8 mL). The reaction was stirred at room temperature for 24 h. On completion the reaction mixture was worked up with sat. $NaHCO_3$/EtOAc, washed with brine, dried over Na_2SO_4. After removal of solvent under reduced pressure, the reaction mixture was purified by flash column chromatography (EtOAc/*n*-Hexane = 1:1) to provide hemiketal **21** (23 mg, 0.04 mmol, 100%) as white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.8 Hz, 2H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 7.0 Hz, 2H), 5.25 (dd, *J* = 11.2, 2.9 Hz, 1H), 4.64-4.68 (m, 1H), 4.47 (s, 1H), 4.19 (s, 1H), 3.68 (t, *J* = 7.8 Hz, 1H), 3.43 (dd, *J* = 16.4, 9.8 Hz, 1H), 3.39 (dd, *J* = 15.8, 11.0 Hz, 1H), 1.99 (s, 3H), 1.23 (s, 3H), 1.00 (s, 3H), 0.86 (s, 3H), 0.85 (d, *J* = 7.8 Hz, 3H), 0.58 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 167.7, 133.7, 130.0, 129.9, 128.8, 112.0, 89.1, 87.8, 75.8, 73.5, 68.3, 52.3, 50.9, 50.7, 44.6, 40.9, 39.1, 36.7, 35.8, 35.7, 34.4, 34.0, 31.4, 30.5, 29.9, 29.86, 28.5, 27.5, 27.2, 21.6, 16.7, 12.3, 12.1, 12.0; HRMS (ESI) for $C_{36}H_{51}O_7$[M-OH]$^+$ calcd. 595.3634, found 595.3636.

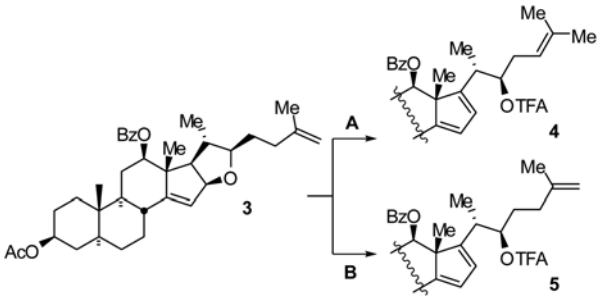
Primary Alcohol 24: To a solution of hemiketal **23** (18 mg, 0.03 mmol) and Et_3SiH (0.03 mL, 0.18 mmol, 6 equiv.) in CH_2Cl_2 (0.59 mL) was added $BF_3.OEt_2$ (0.01 mL, 0.06 mmol, 2 equiv.) at 0 °C and stirred for 1.3 h at the same temperature. The reaction was diluted with CH_2Cl_2, worked up with sat. $NaHCO_3$. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (EtOAc/*n*-Hexane = 1:1) to give primary alcohol **24** (10 mg, 0.02 mmol, 55%) as white floppy solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.8 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 5.22 (dd, *J* = 11.3, 4.4 Hz, 1H), 4.64-4.68 (m, 1H), 3.91 (t, *J* = 5.6 Hz, 1H), 3.37-3.45 (m, 4H), 2.13 (quintet, *J* = 6.7 Hz, 1H), 1.99 (s, 3H), 0.94 (s, 3H), 0.88 (s, 3H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.59 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 167.8, 133.7, 130.1, 129.9, 128.8, 90.4, 89.9, 75.7, 73.6, 68.3, 52.5, 51.7, 50.6, 44.6, 41.7, 36.8, 35.8, 35.7, 34.8, 34.0, 31.5, 30.9, 30.6, 29.9, 28.5, 27.5, 27.4, 21.6, 16.7, 12.4, 11.8, 11.5; HRMS (ESI) for $C_{36}H_{53}O_7$ $[M+H]^+$ calcd. 597.3791, found 597.3788.

C12-β-OBz, C17-α-OH Rockogenin Acetate 25: Primary alcohol **22** (10 mg, 0.02 mmol) was stirred with diacetoxy iodobenzene (11 mg, 0.04 mmol, 2.20 equiv.) and iodine (4 mg, 0.02 mmol, 1 equiv.) in 3.3 mL of cyclohexane/CH_2Cl_2 (1:1 mixture) for 6 h at 0 °C. The reaction was diluted with CH_2Cl_2, and quenched with sat. $Na_2S_2O_3$. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (EtOAc/*n*-Hexane = 1:3) to give secondary alcohol **23** (9 mg, 0.01 mmol, 90%) as white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.9 Hz, 2H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 5.34 (dd, *J* = 11.1, 4.5 Hz, 1H), 4.61-4.66 (m, 1H), 4.01 (t, *J* = 6.8 Hz, 1H), 3.45 (d, *J* = 11.0 Hz, 1H), 3.31 (t, *J* = 11.4 Hz, 1H), 2.65 (s, 1H), 2.10-2.15 (m, 1H), 1.99 (s, 3H), 0.98 (s, 3H), 0.85 (s, 3H), 0.75 (d, *J* = 5.8 Hz, 3H), 0.60 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 166.5, 133.2, 130.8, 129.9, 128.6, 110.0, 89.8, 89.4, 74.9, 73.6, 67.0, 52.4, 51.6, 49.5, 44.9, 44.6, 36.8, 35.8, 34.6, 34.0, 31.6, 31.4, 30.8, 30.2, 28.5, 28.4, 27.5, 27.2, 21.6, 17.3, 12.3, 12.2, 7.8; HRMS (ESI) for $C_{36}H_{51}O_7$ $[M+H]^+$ calcd. 595.3635, found 595.3632.

Results and Discussion

Herein we describe an efficient method to open tetrahydrofuranyl subunits in steroids using TFAT (trifluoroacetyl trifluoromethanesulfonate) and an efficient synthesis of C12-β-OBz, C17-α-OH rockogenin acetate.

Since the C17 position is placed in a sterically demanding environment, it is envisaged that access to the C17 position can be realized by E-ring opening of steroids. During preliminary studies under various reaction conditions for tetrahydrofuran ring opening, it was discovered that treatment of **3** with TFAT alone in CH_2Cl_2 at −35 °C afforded an E-ring opened compound **4** in 70% yield, but the product also indicated that acid-promoted subsequent double bond migration to the thermodynamically more stable tri-substituted position occurred owing to the triflic acid generated during the reaction (Scheme 2). It was, therefore, anticipated that addition of a TFAT-compatible acid scavenger, 2,6-di-*tert*-butyl-4-methylpyridine would prevent the unwanted double bond migration following E-ring cleavage (Scheme 2).[6]



Scheme 2. Acid-promoted double bond migration.

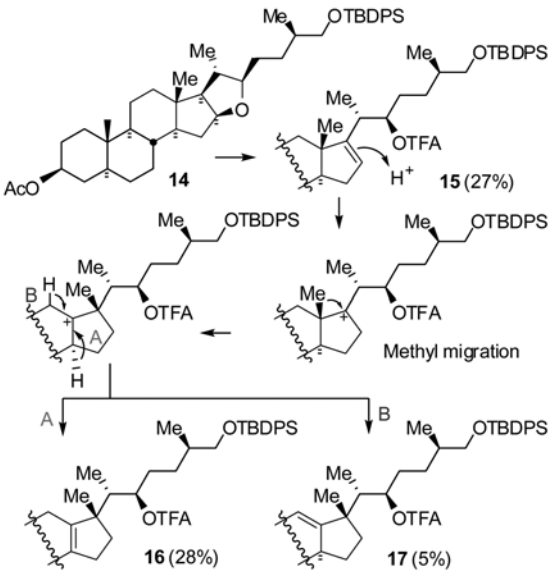
Hence, the reaction of TFAT in combination with an acid scavenger, 2,6-di-*tert*-butyl-4-methylpyridine prevents the unwanted double bond migration providing the desired product **5** in 97% yield (Scheme 2).

This method was also applied to other acid sensitive substrates. Thus, the above reaction condition readily transformed TBDPS ether **6** to the corresponding diene **7** in 91% yield (entry 1, Table 1).[7]

Surprisingly, application of the same reaction condition to the non-allylic C14,15-dihydro steroid **8** with TFAT and 2,6-di-*tert*-butyl-4-methylpyridine gave compound **9** in 61% yield (entry 2, Table 1). Likewise, reaction of TBDPS ether **10** provided the corresponding E-ring opened compound **11** in 68% yield (entry 3, Table 1).[8]

Furthermore, di-trifluoroacetate **13** was obtained by consecutive transformations of trifluoroacetylation of primary alcohol **12** to mono-trifluoroacetate, followed by E-ring opening (entry 4, Table 1).

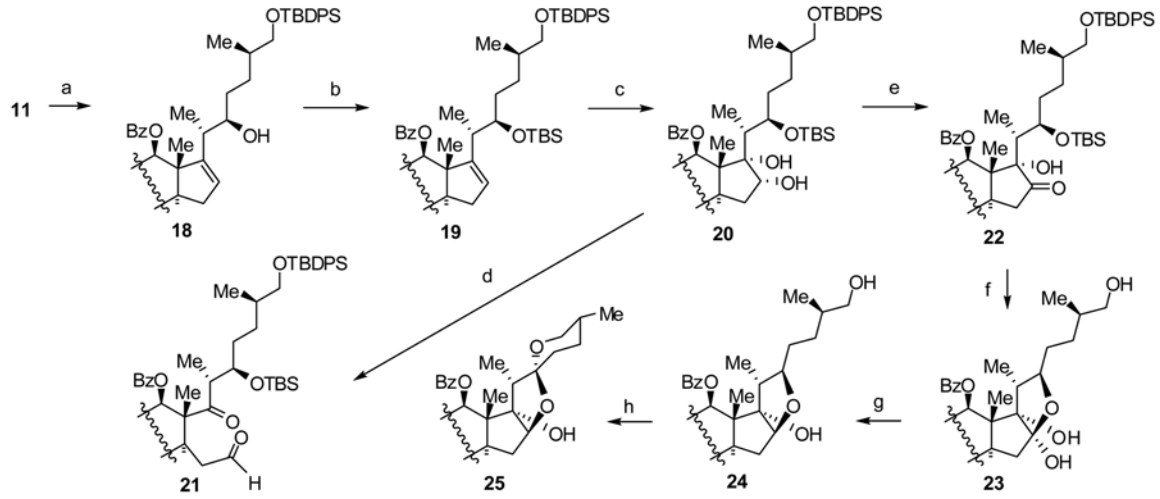
In stark contrast, the above reaction condition triggered Wagner-Meerwein rearrangement in the reaction of TBDPS ether **14** which doesn't have C12-β-OBz (Scheme 3).[9] Thus, the C18 angular methyl group migrated to the adjacent C17-β position providing the corresponding olefinic steroids **16** (28%), and **17** (5%), accompanied by the E-ring opened product **15** in 27% yield (Scheme 3).[10,11]



Scheme 3. Wagner-Meerwein rearrangement of C18 methyl group.

Inspired by the results, synthesis of C12-β-OBz, C17-α-OH rockogenin acetate was attempted as a synthetic application of the newly developed TFAT-promoted E-ring opening method to install a hydroxyl group into the C17 position (Scheme 4).

Mild deprotection of trifluoroacetate **11** with K_2CO_3 and thiourea, followed by TBS protection provided compound **19** in 93% overall yield.[12] After stoichiometric dihydroxylation with OsO_4, oxidation of the resulting diol **20** to the



a. 2 equiv. K_2CO_3, 2.5 equiv. thiourea, EtOH, rt, 4.5 h; b. 1.5 equiv. TBSOTf, 2 equiv. TEA, CH_2Cl_2, rt, 0.5 h; c. 1.3 equiv. OsO_4, pyridine, THF, -78 °C to rt, 20 h; d. 2 equiv. Dess-Martin, CH_2Cl_2, rt, 2 h; e. 0.25 equiv. TPAP, 3 equiv. NMO, Molecular Sieves, CH_2Cl_2, rt, 20 h; f. 7.5 equiv. TBAF, THF, rt, 21 h; g. 2 equiv. BF_3OEt_2, 6 equiv. Et_3SiH, CH_2Cl_2, 0 °C, 1.3 h; h. 2.2 equiv. $PhI(OAc)_2$, 1 equiv. I_2, Cyclohexane/CH_2Cl_2 (1:1), 0 °C, 6 h.

Scheme 4. Synthesis of C12-β-OBz, C17-α-OH rockogenin acetate.

corresponding C16-oxo compound **22** was initially attempted with Dess-Martin periodinane. Instead of the desired C16-oxo compound **22**, aldehyde **21** was obtained as a sole product (95% yield) in consequence of C-C bond cleavage of spirobicyclic periodinane intermediate.[13] To overcome this unwanted C-C bond cleavage between C16 and C17 position, the diol was subjected to TPAP (tetrapropylammonium perruthenate)-catalyzed oxidation condition to provide the desired C16-oxo compound **22** in 71% yield over 2 steps (Scheme 4).[14]

Concomitant deprotection of the two silyl ether protecting groups at C22 and C27 with TBAF (tetrabutylammonium fluoride) provided hemiketal **23** quantitatively, which was further treated with 2 equiv. of $BF_3{\cdot}OEt_2$ and 6 equiv. Et_3SiH to afford primary alcohol **24** in 55% yield (Scheme 4).[15]

Alkoxyl radical is an electrophilic intermediate which is an efficient tool for hydrogen atom abstraction from non-activated C–H bonds.[16] Especially, alkoxyl radical 1,5-hydrogen transfer has been intensively used for spiroketalization in syntheses of many biologically active natural products.[17]

In the final step, therefore, the primary alcohol **24** was subjected to Suarez alkoxyl radical cyclization condition to give C12-β-OBz, C17-α-OH rockogenin acetate **25** in 90% yield.

In conclusion, we have developed a novel and efficient method to smoothly open tetrahydrofuranyl rings of steroids to provide either cyclopentadienes or cyclopentenes depending upon the bond order between C14 and C15 positions, using freshly prepared TFAT (trifluoroacetyl trifluoromethanesulfonate) in the presence of an acid scavenger (2,6-di-*tert*-butyl-4-methylpyridine).

Additionally, this method was applied to the synthesis of C12-β-OBz, C17-α-OH rockogenin acetate (12 steps from hecogenin acetate **1**) where the C17-α-OH group was successfully introduced without using 'Marker degradation'.

Thus, from the synthetic point of view, the above reaction affords an attractive synthesis to introduce a hydroxyl group to highly hindered C17 position without excision of the entire F-ring in the steroid sapogenin.

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