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Efficient Protocol for Ring Opening of Spiroketals Using Trifluoroacetyl Trifluoromethanesulfonate (TFAT)[1]

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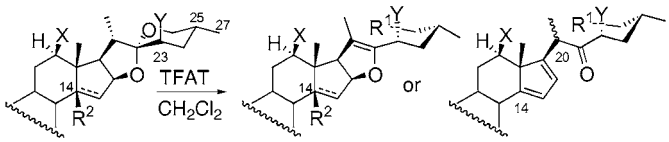
ABSTRACT



Ring opening of steroidal spiroketals under exceptionally mild conditions is smoothly achieved via reaction with trifluoroacetyl trifluoromethanesulfonate (TFAT). The new spiroketal ring-opening protocol provides ω-trifluoroacetyl vinyl ethers in good yield and avoids difficulties that attended previously employed vigorous reaction conditions.

Site-specific functionalization and isomerization of spiroketal subunits in common steroids are pivotal operations for the syntheses of steroidal natural products and their derivatives. With regard to the spiroketal subunits (E−F rings) in spirostans, normal-type structures **1** are the major class among the naturally occurring spirostans rather than iso-type structures **3** (Figure 1).[2] Several investigations have revealed that iso-type structures **3** are more stable to strong acid than normal-type structures **1**, and the transformation of normal- to iso-types proceeds via pseudospirostans **2**.[3] In addition, pseudospirostans **2** have proven to be useful intermediates for functionalization at C-25,26 to **5** and spiroketalization of terminal olefin **4** to **6** in our program for synthesis of cephalostatins[4] and ritterostatin G_N1_N.[6]

During the last few decades, a number of acid-catalyzed isomerative F-ring-opening protocols have been developed for obtaining pseudospirostans.[5] However, these suffer from several drawbacks. Although, in some cases, reaction temperatures were somewhat ameliorated (70∼140 °C),[7] the

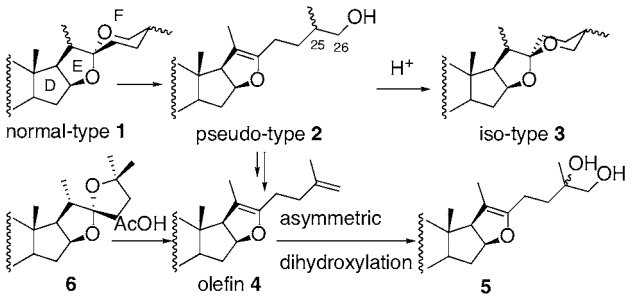


Figure 1.

(1) Cephalostatin support study no. 29. For paper no. 27, see: Li, W.; Fuchs, P. L. *Org. Lett.* **2003**, *5*, 2853.

(2) Tobari, A.; Teshima, M.; Koyanagi, J.; Kawase, M.; Miyamae, H.; Yoza, K.; Takasaki, A.; Nagamura, Y.; Saito, S. *Eur. J. Med. Chem.* **2000**, *35*, 511.

(3) (a) Marker, R. E.; Wagner, R. B.; Ulshafer, P. R.; Wittbecker, E. L.; Goldsmith, D. P. J.; Ruof, C. H. *J. Am. Chem. Soc.* **1947**, *69*, 2167. (b) Wall, M. E.; Eddy, C. R.; Serota, S. *J. Am. Chem. Soc.* **1954**, *76*, 2849. (c) Wall, M. E.; Eddy, C. R.; Serota, S. *J. Am. Chem. Soc.* **1954**, *76*, 2850. (d) Scheer, I.; Kostic, R. B.; Mosettig, E. *J. Am. Chem. Soc.* **1955**, *77*, 641. (e) Ziegler, J. B.; Rosen, W. E.; Shabica, A. C. *J. Am. Chem. Soc.* **1955**, *77*, 1223. (f) Wall, M. E.; Serota, S.; Eddy, C. R. *J. Am. Chem. Soc.* **1955**, *77*, 1230. (g) Wall, M. E.; Walens, H. A. *J. Am. Chem. Soc.* **1955**, *77*, 5661.

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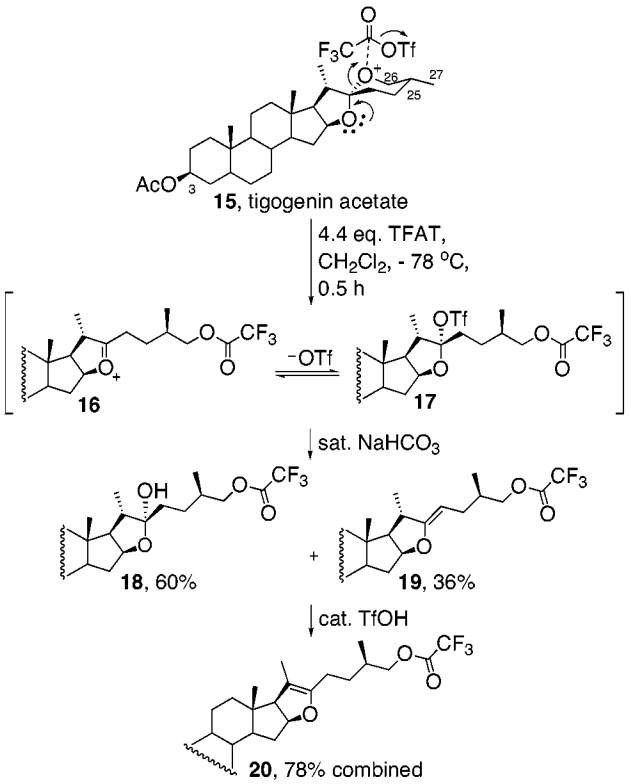
reaction conditions still require quite high temperatures, often resulting in moderate yields. No example of F ring opening with a double bond in the E ring has been reported, implying that such substrates may be problematic. Finally, differentiation of protecting groups at C-3 and C-26 (cf. Scheme 1) has been rarely realized.

Scheme 1



Previously, our group has reported a method resulting in F ring opening with differentiated protecting groups at C-3 and C-26 using $(Cl_2HCCO)_2O$ and NH_4Cl as a catalyst.[6] An alternative protocol featured F ring opening with concurrent halogenation.[7]

Herein, we wish to report a general and efficient tool for F ring opening of spiroketal rings in common steroids affording C-3, C-26 differentiated pseudospirostans. Reagents initially screened, including Tf_2O, TMSI, TMSOTf, $(F_3CO)_2O$, and p-$NO_2C_6H_4OTf$, were unrewarding.

Since the preparation and isolation of trifluoroacetyl trifluoromethanesulfonate (TFAT) from the dehydration of a 2:1 mixture of trifluoroacetic acid and trifluoromethanesulfonic acid by J. C. Martin et al.,[8a] only a few examples of its application in organic syntheses have been reported.[8] Due to its strong electrophilicity, the applications of TFAT are focused mainly on trifluoroacetylation of oxygen, nitrogen, carbon, or halogen centers (Figure 2).[8]

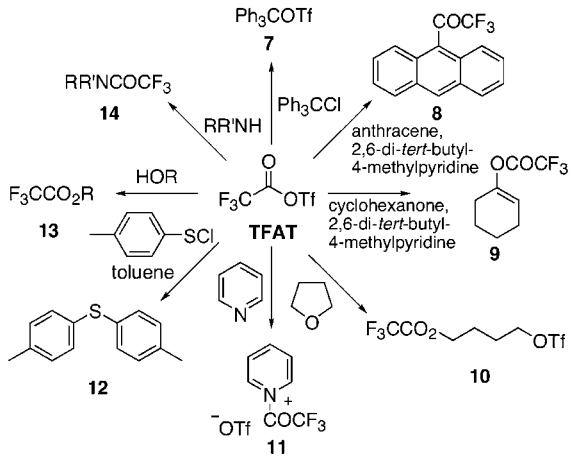
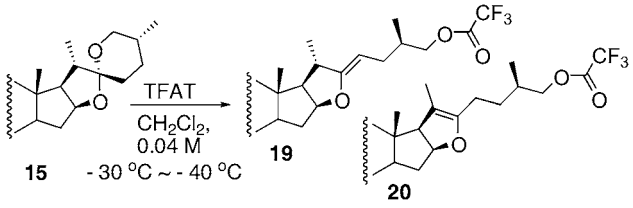


Figure 2.

We were initially pleased to note that addition of 4.4 equiv of TFAT to tigogenin acetate **15** in CH_2Cl_2 at −78 °C for 0.5 h, followed by quenching with $NaHCO_3$, provided hemiketal **18** and exocyclic olefin **19** in 60 and 36% yields, respectively (Scheme 1). Interestingly, further treatment of either hemiketal **18** or olefin **19** with catalytic triflic acid gave the desired endocyclic ω-trifluoroacetyl enol ether **20**

Table 1. Optimization of the Reaction Conditions



entry[a]	TFAT[b] (equiv)	time (h)	**15**[c] (%)	**19**[c] (%)	**20**[c] (%)
1	2.0	1	0	0	100
2	1.5	1	17	45	38
3	1.5	2	0	0	100
4	1.2	2	32	0	68
5	1.2	3	30	0	70

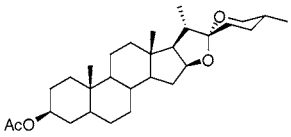
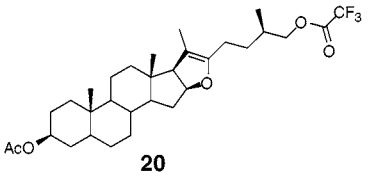
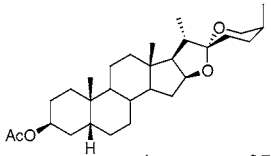
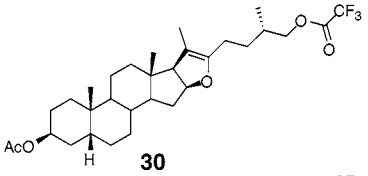
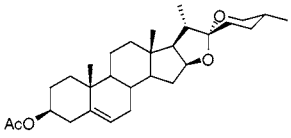
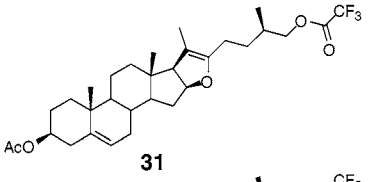
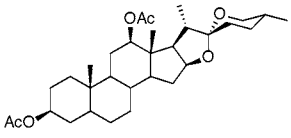
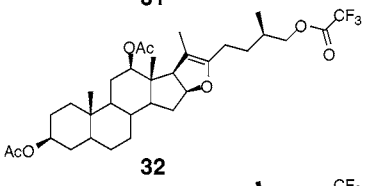
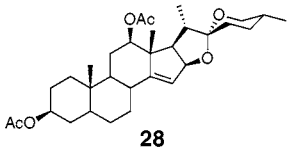
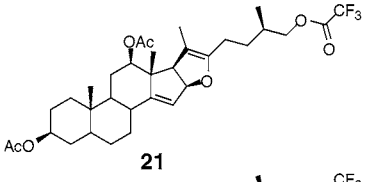
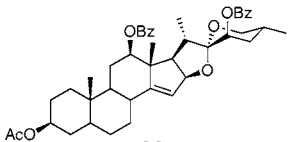
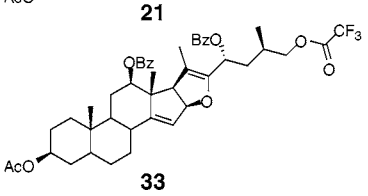
[a] Procedure A was used. [b] Freshly prepared TFAT was used. [c] Yields of the products were calculated from the integration of ^1H NMR peaks.

(5) (a) Marker, R. E.; Rohrmann, E. *J. Am. Chem. Soc.* **1939**, *61*, 3592. (b) Marker, R. E.; Rohrmann, E. *J. Am. Chem. Soc.* **1940**, *62*, 518. (c) Dauben, W. G.; Fonken, G. J. *J. Am. Chem. Soc.* **1954**, *76*, 4618. (d) Cameron, A. F. B.; Evans, R. M.; Hamlet, J. C.; Hunt, J. S.; Jones, P. G.; Long, A. G. *J. Chem. Soc.* **1955**, 2807. (e) Gould, D. H.; Staeudle, H.; Hershberg, E. B. *J. Am. Chem. Soc.* **1952**, *74*, 3685. (f) Danievski, A. R.; Kinowski, A. Poland Patent 119829, 1984. (g) Khuyen, H. N.; Dan, N. V. *Tap. Chi. Hoa. Hoc.* **1976**, *14*, 37. (h) Honda, K. L.; Rao, P. R. *Res. Ind.* **1970**, *15*, 165. (i) Micovic, I. V.; Invanovic, M. D.; Piatak, D. M. *Synthesis* **1990**, 591. (j) Brown, L.; Koreeda, M. *J. Org. Chem.* **1984**, *49*, 3875. (k) Tavares, R.; Randoux, T.; Braekman, J.; Daloze, D. *Tetrahedron* **1993**, *49*, 5079. (l) Borah, P.; Chowdhury, P. *Indian J. Chem., Section B: Org. Chem. Incl. Med. Chem.* **1998**, *37B*, 408. (m) Haeuser, H. German Patent DE 19635418, 1997. (n) Chowdhury, P. K.; Bordoloi, M.; Baraua, N. C.; Sarmah, H. P.; Goswami, P. K.; Saharma, Baruah, A. P.; Mathur, R. K.; Chandra, A. U.S. Patent 5808117, 1998.

(6) LaCour, T. G.; Guo, C.; Bhandaru, S.; Boyd, M. R.; Fuchs, P. L. *J. Am. Chem. Soc.* **1998**, *120*, 692.

(7) (a) LaCour, T. G.; Fuchs, P. L. *Tetrahedron Lett.* **1999**, *40*, 4655. (b) LaCour, T. G.; Tong, Z.; Fuchs, P. L. *Org. Lett.* **1999**, *1*, 1815.

Table 2. Reactions of TFAT with Common Steroids

entry	substrate	TFAT (equivalent)	time (h)	product	yield (%)[c]
1[a]	 tigogenin acetate **15**	1.5	2	 **20**	94
2[a]	 sarsasapogenin acetate **25**	1.5	2	 **30**	95
3[a]	 diosgenin acetate **26**	1.5	2	 **31**	96
4[a]	 diacetate **27**	1.5	2	 **32**	95
5[b]	 **28**	3.25	14[d]	 **21**	73
6[b]	 **29**	3.25	20[e]	 **33**	83

[a] Procedure A was used at −30 to −40 °C. [b] Procedure B was used at −78 °C. [c] Isolated yield. [d] TFAT reaction to hemiketal (2 h) and dehydration (12 h). [e] TFAT reaction to hemiketal (4 h) and dehydration (16 h).

in 90 and 67% yields, respectively (Scheme 1). In search of an optimized procedure, a series of test reactions at higher temperature with reduced amounts of TFAT revealed that the conversion could be completed with 1.5 equiv of TFAT at −30 to −40 °C (Table 1, entry 3). The final procedure involves low-temperature (−30 to −40 °C) treatment of tigogenin acetate **15** with 1.5 equiv of TFAT for 2 h, followed by water workup to give a mixture of hemiketal **18** and olefin **19**. Evaporation of the reaction mixture in a warm water bath and subsequent basic workup (**Procedure A**) furnished the ω-trifluoroacetyl enol ether **20** in 94% yield (Table 2, entry 1).

Expanded application of the TFAT-assisted spiroketal ring opening to the other common steroids was also successful. In the case of sarsasapogenin acetate **25**, compound **30** was obtained in 95% via the general reaction procedure (Table 2, entry 2). Diosgenin acetate **26** and diacetate **27** provided compounds **31** and **32** in 96 and 95% yields, respectively (Table 2, entries 3 and 4).

In contrast, the 14,15-olefinic steroid **28** (Table 2, entry 5) gave a mixture of cyclopentadienes **23** and **24** in 78% yield (**23**/**24** = 1:6.1) from acid-promoted subsequent E ring opening (Figure 3). This can be explained by β-elimination of oxonium ion **22**, generated from protonation of ω-trifluoroacetyl enol ether **21**, to give a thermodynamically more stable cyclopentadiene along with some acid-catalyzed epimerization at C-20 (Figure 3).

(8) (a) Forbus, T. R., Jr.; Martin, J. C. *J. Org. Chem.* **1979**, *44*, 313. (b) Michalak, R. S.; Martin, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 5921. (c) Maas, G.; Stang, P. J. *J. Org. Chem.* **1981**, *46*, 1606. (d) Taylor, S. L.; Forbus, T. R., Jr.; Martin, J. C. *Org. Synth.* **1986**, *64*, 217. (e) Forbus, Jr., T. R.; Taylor, S. L.; Martin, J. C. *J. Org. Chem.* **1987**, *52*, 4156. (f) Sagl, D. J.; Martin, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 5827. (g) Kiselyov, A. S.; Harvey, R. G. *Tetrahedron Lett.* **1995**, *36*, 4005. (h) Umemoto, T.; Adachi, K.; Ishihara, S. *Jpn. Kodai Tokkyo Koho* **1993**, 8.

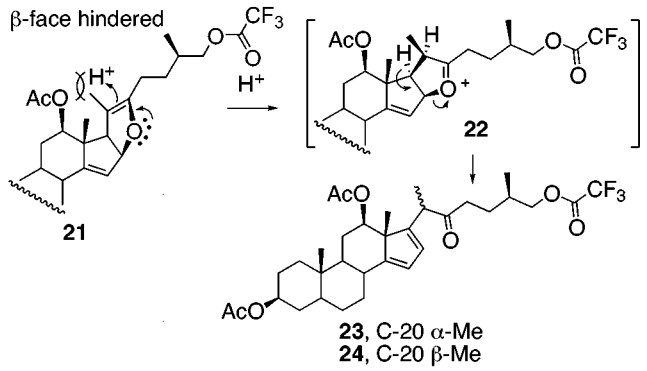


Figure 3.

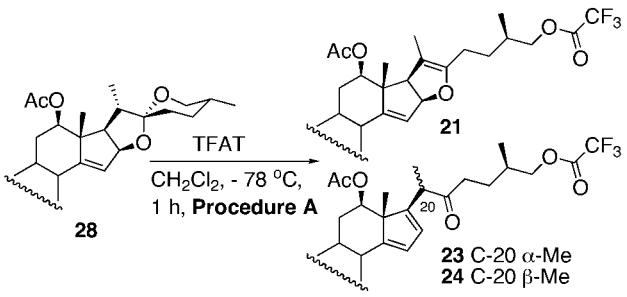
Careful investigation on the relationship between the amount of TFAT and the products from spiroketal **28** indicated that 3.25 equiv of TFAT gave the best result (Table 3).[9]

To avoid the consequences of protonation at C-20, the reaction mixture was given a basic workup with saturated $NaHCO_3$ followed by subjecting the reaction mixture of hemiketal and exocyclic olefin to a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) in dichloromethane at reflux for 12 h (**Procedure B**) to provide the desired compound **21** in 73% yield (Table 2, entry 5). This was also applicable to compound **29**, which has a C-23 axial benzoate to furnish compound **33** in 83% (Table 2, entry 6).

In conclusion, we have demonstrated an efficient and useful synthetic method for opening spiroketal rings in various steroids by addition of TFAT, which is commercially available and also easily prepared from inexpensive reagents.

(9) Same reaction using 1.5∼2.0 equiv of TFAT at −30 to −40 °C, followed by basic workup, led to conversion, during evaporation, to cyclopentadienes **23** and **24** (75%, **23**/**24** = 1:3.8) along with 25% of pseudo compound **21**. No hemiketal was observed.

Table 3. Relationship between TFAT and the Products



entry[a]	TFAT (equiv)[b]	**21** (%)	**23** (%)	**24** (%)	**28** (%)
1	1	0	0	0	100
2	2	5	0	6	89
3	3	24	0	2	74
4	**3.25**	**47**	**4**	**32**	**17**
5	3.5	5	21	69	5
6	4	0	17	59	17

[a] Yields of the products were calculated from the integration of ^{1}H NMR peaks. [b] Freshly prepared TFAT was used.

Furthermore, trifluoroacetyl trifluoromethanesulfonate (TFAT) has advantages of providing acid-stable trifluoroacetyl esters, which are selectively deprotected in the presence of the C-3 acetate or other ester groups, which is very advantageous for subsequent reactions.

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Supporting Information Available: Experimental procedures and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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