A TBAF-mediated Chemoselective Method for Synthesis of 4-Methylbutenolides and 4-Hydroxy-4-methylbutenolides from 3-Hydroxy-4-(*tert*-butyldimethylsilyloxy)pentanoates

Chunhong Li, Jijun Xue, Baiyan Xu, Zhixiang Xie, and Ying Li*
State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, Gansu 730000, P. R. China

(Received May 10, 2007; CL-070508; E-mail: liying@lzu.du.cn)

A chemoselective synthesis of butenolides was found based on TBAF-mediated deprotection, cyclization, dehydration, and oxidation of 3-hydroxy-4-(*tert*-butyldimethylsilyloxy)-pentanoates, which yielded either 4-methylbutenolides or 4-hydroxy-4-methylbutenolides in moderate to good yields. The selectivity depends on the quantity of TBAF. This method was applied to the synthesis of several 4-butenolide compounds.

Annonaceous acetogenins belong to the family of natural polyketides, which contain either 4-methylbutenolides or 4-hydroxy-4-methylbutenolides at one terminal of the linear structure.[1] A broadened spectrum of activities caused by annonaceous acetogenins has been reported, including anticancer, immunosuppressant, anti-malarial, pestitcidal, and so on. Many acetogenins present good to excellent toxicity against various tumor cells. For example, asiminacin, a 4-methylbutenolide acetogenin, showed IC_{50} in the 10^{-12} μg/mL range against KB cell.[2a] And anmontanins B, C have highly potent anti-influenza and anti-insomnia activities.[2b]

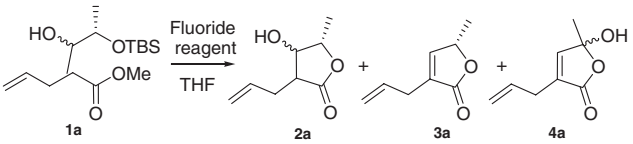
Although there are many strategies established for the construction of 4-methylbutenolides[3] and 4-hydroxy-4-methylbutenolides,[4] to our knowledge, chemoselective synthesis of 4-methylbutenolide and 4-hydroxy-4-methylbutenolides from the same substrate based on one-pot reactions has not been reported.

When we investigated the deprotection of TBS on **1a** by TBAF,[5] interestingly, besides the desired lactone **2a**, two unexpected products **3a** and **4a** were also isolated. After a detail exploration on this discovery, we will report a new method to chemoselectively synthesize 4-methylbutenolides and 4-hydroxy-4-methylbutenolides based on a TBAF-mediated one-pot reaction.

Using compound **1a** as substrate, we examined the effects of different temperature, fluoride reagents and their quantities on the yield of 4-methylbutenolide **3a** and 4-hydroxy-4-methyl-butenolides **4a** (Table 1). The chemo-selectivity depends on the quantity of TBAF. **2a** was the main product when less than 2 equiv. of TBAF was used (Entries 1 and 2, Table 1). **3a** was obtained in more than 50% yield when **1a** was treated with more than 2 equiv. of TBAF (Entries 3 and 4, Table 1). And more than 4 equiv. of TBAF caused mainly the formation of **4a** (Entry 5, Table 1). Different from TBAF, $BF_3 \cdot Et_2O$,[6] and Py·HF[7] only gave cyclization product **2a** in moderate to good yields when the amounts of reagents were varied from 1 to 4 equiv. (Entries 6–9, Table 1).

To further demonstrate the application of this reaction, more substrates were examined under the modified reaction condition. Very good results were obtained (Table 2). Using 1.5 equiv. of

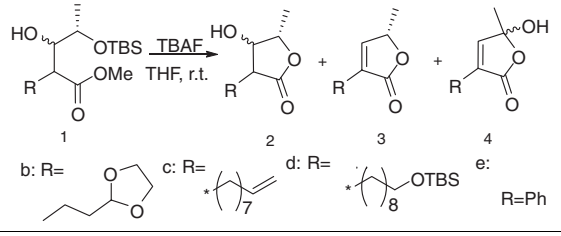
Table 1. Investigation of chemoselectivity of the reaction



Entry	Fluoride reagents	Amount /equiv.	Temp /°C	Time /min	Main product (yield[a]/%)
1	TBAF	1.2	20[b]	30	**2a** (75)
2	TBAF	1.2	0[b]	55	**2a** (75)
3	TBAF	2.0	20	30	**3a** (59)
4	TBAF	2.5	20	30	**3a** (70)
5	TBAF	4.0	20	30	**4a** (67)
6	$BF_3 \cdot Et_2O$	1.0	20	30	**2a** (56)
7	$BF_3 \cdot Et_2O$	4.0	20	30	**2a** (78)
8	Py·HF	1.0	20	30	**2a** (56)
9	Py·HF	4.0	20	30	**2a** (87)

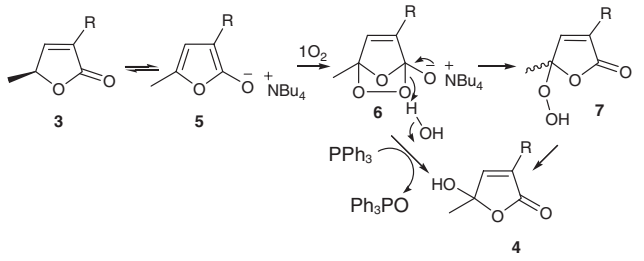
[a]Isolated yield. [b]Reaction temperature has no obvious influence on the selectivity and yield, but the reaction rate increased with the raising of temperature.

Table 2. Chemoselectivity investigation with different substrates[a]



Entry	Substrate	TBAF /equiv.	Main product (yield[b]/%)
1	**1b**	1.5	**2b** (72) and **3b** (9)
2	**1b**	2.5	**3b** (66)
3	**1b**	4.0	**4b** (60)
4	**1c**	2.5	**3c** (78)
5	**1c**	4.0	**4c** (76)
6	**1d**	3.5	**3d** (85)
7	**1d**	5.0	**4d** (69)
8	**1e**	1.2	**3e** (83)
9	**1e**	3.0	**4e** (72)

[a]Reaction temperature is 20 °C and reaction time is 30 min. [b]Isolated yield.



Scheme 1. Supposed mechanism of the formation of **4a**–**4e**.

TBAF, **1b** was mainly converted to **2b** along with a little of **3b** (Entry 1, Table 2). When 2.5 equiv. of TBAF was used, **3b** and **3c** were found in 66 and 78%, respectively (Entries 2 and 4, Table 2). **3c** has been isolated from the leaves of all three species of Hortonia[8] (Family Monimiaceae) and synthesized by Yao.[9] And **4b**, **4c** were synthesized from **1b** and **1c** in 60 and 76% yield by 4.0 equiv. of TBAF, respectively (Entries 3 and 5, Table 2). But one exception was found. **3e** yielded from **1e** directly by treatment with only 1.2 equiv. of TBAF (Entry 8, Table 2) and no **2e** was found. This means that **2e** was not stable and was converted to **3e** easily. This is due to the phenyl group of **3e**. In **3e**, the phenyl group conjugated with a carbonyl group and a double bond, which pushed the dehydration of **2e** forward. Similarly, **4e** yielded by 3.0 equiv., not 4.0 equiv. of TBAF. For there is one more TBS ether in R group of **1d**, one more equiv. of TBAF was used when **1d** was converted to the corresponding products, compared with the reactions of **1a**, **1b**, and **1c**.

We reasoned that TBS ether of **1a** was cleaved by TBAF and the released free hydroxy group attacked the ester group intramolecularly to established lactone **2a**. Subsequently, the new formed 3-hydroxy lactone was dehydrated by excess TBAF. The role of TBAF played in the elimination of 3-hydroxy could be a Lewis base.[10]

When total 4.5 equiv. of TBAF were used to treat compound **1a** in three portions (1.5 equiv. Every 30 min), **2a**, **3a**, and **4a** were observed as major products in turn by TLC. This showed that compound **3a** came from **2a** and converted to **4a**. So the mechanism of the formation of **4a** was supposed as following (Scheme 1): **3a** was enolized by TBAF[11] to form a furan intermediate **5**,[12] which sensitized O_2 as that Hart and Young[13] observed and a [4 + 2] cycloaddition occurred between **3** and singlet-oxygen to form an intermediate **6**, which was converted to **7** and then to **4**.[14] Friedrichsen reported[15] the [4 + 2] cycloaddition between singlet oxygen and furan proceeded in the light. There are several cases supporting our hypothesis of the mechanism. Firstly, when PPh_3 was added to the reaction mixture of **1a** and 4 equivalents of TBAF, Ph_3PO was observed.[16] During this process, PPh_3 converted compound **6** directly to **4**. Secondly, there is no compound **4** obtained under argon without oxygen atmosphere. Under dark to avoid light, also no **4** obtained. These cases showed the reaction is concerned with oxygen and light. And TBAF, as a Lewis base,[10] enolized compound **3** to **5**.

In conclusion, a cost-effective and convenient method was found for chemoselectivity form the corresponding products: 3-hydroxy-4-methylbutanolides, 4-methylbutenolides, and 4-hydroxy-4-methylbutenolides, respectively depending on the amounts of TBAF. The mechanism was also suggested and TBAF functionalized as both desilylative reagents and Lewis base. This method will serve as a complement to the existing methodologies and find wide applications in organic synthesis.

Project 20672050 supported by the National Natural Science Foundation of China.

References

1 a) Z. Jiang, Y. Chen, R.-Y. Chen, D.-Q. Yu, *Phytochemistry* **1997**, *46*, 327. b) Z. Jiang, D.-Q. Yu, *J. Nat. Prod.* **1997**, *60*, 122. c) Z. Jiang, Y. Chen, R. Y. Chen, D. Q. Yu, *Phytochemistry* **1998**, *49*, 769. d) Y. Chen, R. Y. Chen, Z. Jiang, D. Q. Yu, D. Q. Yu, *Planta Med.* **1998**, *64*, 242. e) Z. Jiang, R.-Y. Chen, Y. Chen, D.-Q. Yu, *Planta Med.* **1998**, *64*, 362. f) B. S. Mootoo, A. Ali, A. Khan, W. F. Reynolds, S. McLean, *J. Nat. Prod.* **2000**, *63*, 807.

2 a) G.-X. Zhao, L. R. Miesbauer, D. L. Smith, J. L. McLaughlin, *J. Med. Chem.* **1994**, *37*, 1971. b) D. Cortes, B. Figadere, A. Cavé, *Phytochemistry* **1993**, *32*, 1467.

3 a) T. R. Hoye, P. R. Hanson, A. C. Kovelesky, T. D. Ocain, Z. Zhang, *J. Am. Chem. Soc.* **1991**, *113*, 9369. b) J. D. White, T. C. Somers, G. N. Reddy, *J. Org. Chem.* **1992**, *57*, 4991. c) Z.-J. Yao, Y.-L. Wu, *Tetrahedron Lett.* **1994**, *35*, 157. d) T. R. Hoye, P. E. Humpal, J. I. Jiménez, M. J. Mayer, L. Tan, Z. Ye, *Tetrahedron Lett.* **1994**, *35*, 7517. e) U. Koert, *Tetrahedron Lett.* **1994**, *35*, 2517. f) B. M. Trost, Z. Shi, *J. Am. Chem. Soc.* **1994**, *116*, 7459. g) Z.-J. Yao, Y.-L. Wu, *J. Org. Chem.* **1995**, *60*, 1170. h) J. A. Marshall, K. W. Hinkle, *J. Org. Chem.* **1997**, *62*, 5989. i) T.-T. He, H.-N. Yang, Z.-J. Yao, *Tetrahedron* **2002**, *58*, 8805.

4 a) H. Arzoumanian, M. Jean, D. Nuel, A. Cabrera, J. L. G. Guiterrez, N. Rosas, *Organometallics* **1995**, *14*, 5438. b) R. Shiraki, Y. Shiraga, K. Tadano, *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu.* **1997**, *39*, 415.

5 a) M. Kimura, A. Ezoe, M. Mori, K. Iwata, Y. Tamaru, *J. Am. Chem. Soc.* **2006**, *128*, 8559. b) T. Řezanka, V. M. Dembitsky, *Tetrahedron* **2001**, *57*, 8743. c) J. A. Marshall, H. Jiang, *J. Org. Chem.* **1999**, *64*, 971.

6 S. A. King, B. Pipik, A. S. Thompson, A. DeCamp, T. R. Verhoeven, *Tetrahedron Lett.* **1995**, *36*, 4563.

7 K. C. Nicolaou, S. E. Webber, *Synthesis* **1986**, 453.

8 R. Ratnayake, V. Karunaratne, B. M. R. Bandara, V. Kumar, J. K. MacLeod, P. Simmonds, *J. Nat. Prod.* **2001**, *64*, 376.

9 J. Sheng, Y. L. Wu, Z. J. Yao, *Chin. J. Chem.* **2002**, *20*, 692.

10 A. B. Smith, III, G. R. Ott, *J. Am. Chem. Soc.* **1996**, *118*, 13095.

11 a) J. H. Clark, *Chem. Rev.* **1980**, *80*, 429. b) P. C. Montevecchi, M. L. Navacchi, *Tetrahedron* **2000**, *56*, 9339.

12 G. Rassu, F. Zanardi, L. Battistinib, G. Casiraghi, *Chem. Soc. Rev.* **2000**, *29*, 109.

13 R. H. Young, H. Hart, *Chem. Commun. (London)* **1967**, 827.

14 a) D. L. Boger, C. M. Baldino, *J. Am. Chem. Soc.* **1993**, *115*, 11418. b) H. H. Wasserman, R. W. Desimone, D. L. Boger, C. M. Baldino, *J. Am. Chem. Soc.* **1993**, *115*, 8457.

15 W. Friedrichsen, *Adv. Heterocycl. Chem.* **1981**, *26*, 135.

16 a) B. W. Greatrex, D. K. Taylor, *J. Org. Chem.* **2004**, *69*, 2577. b) E. L. Clennan, P. C. Heah, *J. Org. Chem.* **1981**, *46*, 4105.

Published on the web (Advance View) July 21, 2007; doi:10.1246/cl.2007.1058