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Acid-Catalyzed Grob Fragmentation Reactions of Acetonides Derived from Terpenes

José Barluenga,* Mónica Álvarez-Pérez, Kirsten Wuerth, Félix Rodríguez, and Francisco J. Fañanás

Instituto Universitario de Química Organometálica "Enrique Moles", Unidad Asociada al C.S.I.C. Julián Clavería, 8, Universidad de Oviedo, 33006-Oviedo, Spain

barluenga@sauron.quimica.uniovi.es

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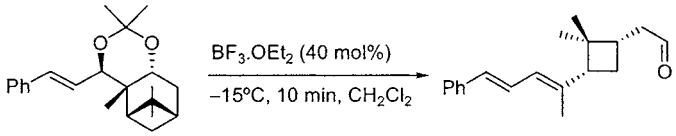
ABSTRACT



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Acetonides derived from different terpenes undergo Grob fragmentation by treatment with a catalytic amount of acid, triflic acid, or boron trifluoride, giving aldehydes containing a cyclopropane or cyclobutane ring with good yields and complete diastereoselectivity. The structure and the stereochemistry of the starting acetonide have a crucial influence on the reaction course.

Heterolytic Grob fragmentations have been widely studied since their discovery in the 1950s.[1] These processes may proceed through a concerted or a stepwise pathway, depending on stereochemical and stereoelectronic factors.[2] With regard to their application, there are numerous syntheses of natural products in which the key step involves a fragmentation reaction.[3]

Among Grob fragmentations, those of 1,3-diol derivatives are especially useful.[4] Although stoichiometric basic conditions are very common when 1,3-diol derivatives (especially 1,3-diol monosulfonate esters) are used as starting materials, 1,3-diols themselves may lead to the desired fragmentation product under certain acid conditions through the formation of a carbocation.[5] In this latter case, the process can be catalytic under strong acidity[5a] or when the structure of the diol contains groups that increase the stability of the carbocation formed.[5b] Nevertheless, Grob fragmentations under acid conditions have generally not been quite as studied and applied as those performed under nucleophilic or basic conditions.

(1) (a) Eschenmoser, A.; Frey, A. J. *Helv. Chim. Acta* **1952**, *35*, 1660. (b) Grob, C. A.; Schiess, P. W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1−15. (c) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535−546. (d) For a review of fragmentation reactions, see: Weyersthal, P.; Marschall, H. Fragmentation Reactions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Winterfeldt, E., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, pp 1041−1070.

(2) (a) Wharton, P. S.; Hiegel, G. A. *J. Org. Chem.* **1965**, *30*, 3254−3257. (b) Grob, C. A.; Bolleter, M.; Kunz, W. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 708−709. (c) Ochiai, M.; Ukita, T.; Iwaki, S.; Nagao, Y.; Fujita, E. *J. Org. Chem.* **1989**, *54*, 4832−4840. (d) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; pp 259−261.

(3) (a) Paquette, L. A.; Nakatani, S.; Zydowsky, T. M.; Edmondson, S. D.; Sun, L.-Q.; Skerlj, R. *J. Org. Chem.* **1999**, *64*, 3244−3254. (b) Paquette, L. A.; Edmondson, S. D.; Monck, N.; Rogers, R. D. *J. Org. Chem.* **1999**, *64*, 4, 3255−3265. (c) Koshimizu, H.; Baba, T.; Yoshimitsu, T.; Nagaoka, H. *Tetrahedron Lett.* **1999**, *40*, 2777−2780. (d) Mehta, G.; Mohal, N. *Tetrahedron Lett.* **1999**, *40*, 5791−5794. (e) Renneberg, D.; Pfander, H.; Leumann, C. J. *J. Org. Chem.* **2000**, *65*, 9069−9079. (f) Alonso, E. R.; Tehrani, K. A.; Boelens, M.; Knight, D. W.; Yu, V.; De Kimpe, N. *Tetrahedron Lett.* **2001**, *42*, 3921−3923. (g) Njardarson, J. T.; Wood, J. L. *Org. Lett.* **2001**, *3*, 2431−2434. (h) Evans, D. A.; Scheidt, K. A.; Downey, C. W. *Org. Lett.* **2001**, *3*, 3009−3012. See also ref 1d.

(4) (a) Caine, D. *Org. Prep. Proced. Int.* **1988**, *20*, 3. (b) Corey, E. J.; Mitra. R. B.; Uda, H. *J. Am. Chem. Soc.* **1964**, *86*, 485−492. (c) Tietze, L.-F.; Reichert, U. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 830−831. (d) Olsen, R. J.; Lewis, T. A.; Mehta, M. A.; Stack, J. G. *J. Heterocycl. Chem.* **1986**, *23*, 1099−1102. (e) Iwata, C.; Takemoto, Y.; Doi, M.; Imanishi, T. *J. Org. Chem.* **1988**, *53*, 1623−1628. See also refs 2a,d and 3a−c,e,g.

(5) (a) Bucsi, I.; Molnár, A.; Bartók, M.; Olah, G. A. *Tetrahedron* **1995**, *51*, 3319−3326. (b) Kato, M.; Tooyama, Y.; Yoshikoshi, A. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 50−56.

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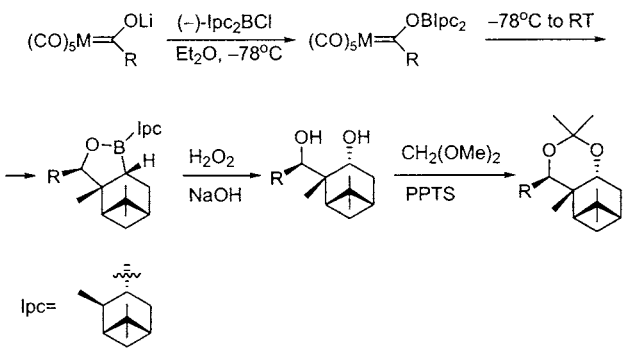
From previous work developed in our laboratories,[6] it is known that chiral 1,3-diols derived from terpenes are available in a diastereoselective manner by using group 6 metal boroxycarbene complexes (Scheme 1). The transformation of these 1,3-diols into the corresponding acetonides is possible under standard catalytic acid conditions without observing any fragmentation reaction.[7] However, the present work deals with the capability of these acetonides to undergo Grob fragmentation reactions under certain catalytic acid conditions. It was observed that the reaction course is influenced by different factors such as temperature, the nature of the acid, the stereochemistry of the acetonide, and the structure of the precursor terpene. On the other hand, the global sequence provides us with highly functionalized chiral aldehydes containing a cyclopropane[8] or a cyclobutane[9] ring and an alkene or a diene moiety. These structures are found in a wide variety of naturally occurring compounds.

Scheme 1



First of all, we tried the Grob fragmentation on compound **1a** (Scheme 2), easily obtained from α-pinene as a single diastereoisomer by means of molybdenum boroxycarbene complexes.[6] Thus, treatment of diol **1a** with different acids at several reaction conditions led to the aldehyde **2a** together with a variable amount of acetal **3a** (Scheme 2 and Table 1). Acetal **3a** was obtained as the main product when **1a** was treated with 20 mol % triflic acid at −15 °C for 10 min (Table 1, entry 1). The use of boron trifluoride diethyl ether complex[10] under the same reaction conditions led also to a mixture of **2a** and **3a**, but the amount of desired aldehyde **2a** was higher (Table 1, entry 2). An increase in the amount of boron trifluoride diethyl ether complex produced a considerable improvement in the yield of **2a** (Table 1, entries 2−4), and the best results were obtained with 60 mol % BF_3·OEt_2 (Table 1, entry 4). Although we have observed that the reaction is faster at room temperature, the yield of **2a** is lower and it is accompanied with the formation of unidentified products (Table 1, entry 5).

Scheme 2

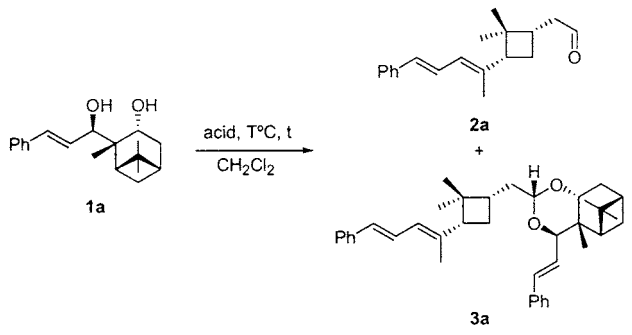


Table 1. Catalytic Grob Fragmentation of **1a** to Give Aldehyde **2a** and Acetal **3a**[a]

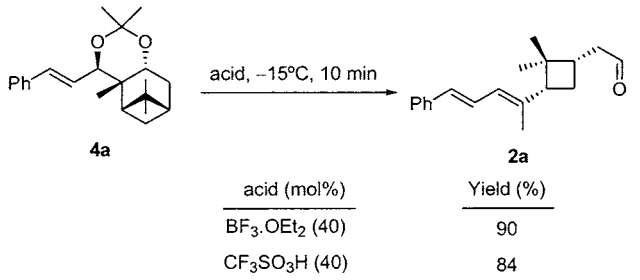
entry	mol % acid[b]	*T* (°C)/*t* (min)	yield of **2a** (%)[c]	yield of **3a** (%)[c]
1	20% CF_3SO_3H	−15/10	10	62
2	20% BF_3·OEt_2	−15/10	23	45
3	40% BF_3·OEt_2	−15/10	60	9
4	60% BF_3·OEt_2	−15/10	66	0
5	40% BF_3·OEt_2	rt/5	53	0

[a] Reactions were carried out in 0.10 M solutions of diol in dry CH_2Cl_2 under a nitrogen atmosphere. All starting diol was consumed. [b] A 0.02 M solution of acid in dry CH_2Cl_2 was freshly prepared before use under a nitrogen atmosphere. [c] Isolated yield based on the starting diol **1a**.

Taking into account that formation of **3a** implies reaction of the formed aldehyde **2a** with starting diol **1a**, we argued that the use of a protected diol (i.e., an acetonide) as a starting material would avoid the formation of **3a** and thus improve the yield of **2a**.

To our delight, treatment of acetonide **4a**[6] with 40% BF_3·OEt_2 or triflic acid at −15 °C for 10 min led to aldehyde **2a** in very high yield (Scheme 3).

Scheme 3



acid (mol%)	Yield (%)
BF_3.OEt_2 (40)	90
CF_3SO_3H (40)	84

In view of the excellent results obtained in the reaction with acetonide **4a**, we decided to extend the fragmentation

(6) (a) Barluenga, J.; Rodríguez, F.; Vadecard, J.; Bendix, M.; Fañanás, F. J.; López-Ortiz, F. *J. Am. Chem. Soc.* **1996**, *118*, 6090−6091. (b) Barluenga, J.; Rodríguez, F.; Vadecard, J.; Bendix, M.; Fañanás, F. J.; López-Ortiz, F.; Rodríguez, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 8776−8782.

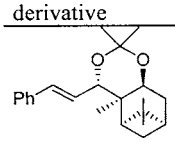
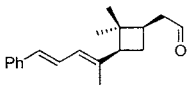
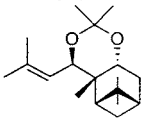
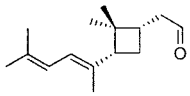
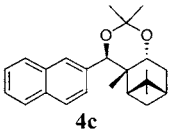
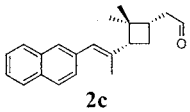
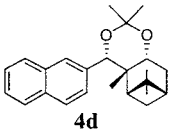
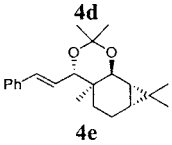
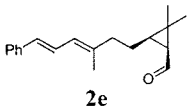
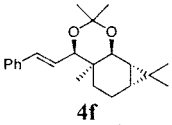
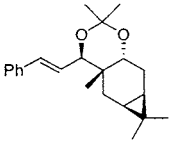
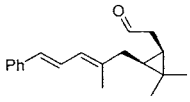
(7) Acetonides are prepared in 2,2-dimethoxypropane using catalytic PPTS. See ref 6.

(8) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589−8627 and references therein.

(9) Johnston, D.; McCusker, C. F.; Muir, K.; Procter, D. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 681−695 and references therein.

reaction to other acetonides. At this point, we turned our attention to our previous work describing the easy preparation of highly functionalized acetonides from simple terpenes. The results of the fragmentation reactions from these terpene-derived acetonides **4** are summarized in Table 2.

Table 2. Catalytic BF_3·OEt_2-Mediated Grob Fragmentation of Terpene Acetonide Derivatives **4** to Give Aldehydes **2**[a]

acetonide derivative	mol % acid[b]	T(°C)/ t(min)	product	yield (%)[c]
 ***ent*-4a**	40	−15/10	 ***ent*-2a**	88
 **4b**	40	−15/10	 **2b**	95
 **4c**	100[d]	RT/110	 **2c**	64[e]
 **4d**	40	RT/60	**2c**	68
 **4e**	40[d]	−78[f]/10	 **2e**	81
 **4f**	20	−78[f]/10	**2e**	84[g]
 **4g**	40	−78[f]/10	 **2g**	54[h]

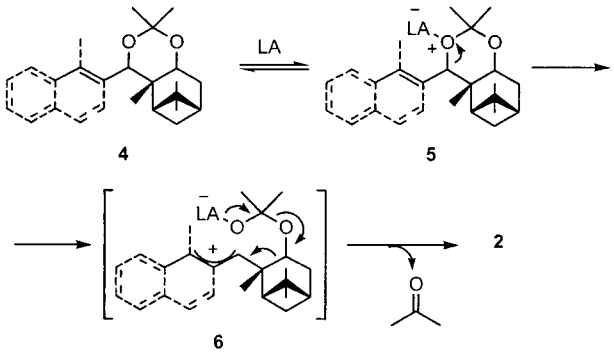
[a] All reactions were carried out in 0.10 M solutions of acetonide in dry CH_2Cl_2 and under a nitrogen atmosphere. Total conversions were achieved. [b] A 0.02 M solution of BF_3·OEt_2 in dried CH_2Cl_2 was freshly prepared before use under a nitrogen atmosphere.Unless noted, the same amounts of CF_3SO_3H can be used. [c] Isolated yield based on the starting acetonide **4**. [d] Use of CF_3SO_3H provides the acetal formed between the precursor diol of **4** and the final aldehyde. [e] Traces of 2-naphthylaldehyde have also been detected in the reaction crude. [f] Lower temperature was required to avoid side products or decomposition of the product. [g] Smaller amounts of acid (<10 mol %) gave a mixture of (*E*,*E*)- and (*E*,*Z*)-aldehydes. [h] Decomposition of the product was fast even at this temperature.

The first example in Table 2 indicates that it is possible to obtain a pair of aldehydes enantiomers (**2a** and *ent*-**2a**) from the two enantiomers of α-pinene and by following a sequence of reactions involving our previously reported C−H insertion[6] reaction and the fragmentation here described. Considering the acid, both CF_3SO_3H and BF_3·OEt_2 can be used except for **4c** and **4e**. In these cases, only BF_3·OEt_2 provided us with the desired aldehydes, while with CF_3SO_3H, acetals analogous to **3a** were obtained at some extension. Apparently, small variations in the structure of the acetonide can play an important role in the reaction course. For example, carene derivatives **4e**−**g** react in shorter times at lower temperatures than α-pinene derivatives **4a**−**d**. On the other hand, the structural changes between **4a** and **4b** hardly have an effect on their reactivity. More remarkable is the difference in reactivity between **4a**,**b** and **4c**,**d**, which indicates that acetonides containing an oxygen atom in a benzylic position react slower than those containing an oxygen atom in an allylic position (**4c** and **4d** required room temperature, longer reaction times, and larger amounts of acid to undergo a complete transformation).

In those cases in which two diastereoisomers of the same diol are available (**4c** vs **4d** and **4e** vs **4f**), we have observed that the fragmentation reaction is easier on the 1,3-*cis*-acetonide (**4d** and **4f**) than on the corresponding 1,3-*trans*-acetonide (**4c** and **4e**). The most striking difference in behavior was detected by using CF_3SO_3H as the acid. Thus, 1,3-*trans*-acetonide **4c** gave rise to an acetal analogous to **3a** and **4e** gave rise to a mixture of decomposition products in which the corresponding acetal analogous to **3a** could also be detected; in contrast, 1,3-*cis*-acetonides **4d** and **4f** led to the desired aldehydes in good yields. In general, it can be said that 1,3-*cis*-acetonides give the fragmentation reaction under milder conditions than 1,3-*trans*-acetonides.

A plausible mechanism that accounts for the formation of aldehydes **2** is outlined in Scheme 4 and involves a

Scheme 4



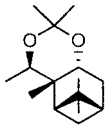
coordination of the Lewis acid to the allylic (or benzylic) oxygen of acetonides **4** to give, in the first place, the oxonium ion **5** and, finally, the formal allylic carbocation **6**,[11,12] which rapidly affords aldehyde **2** by simultaneous breaking of a

(10) The capability of BF_3·OEt_2 to favor Grob fragmentations can also be found in previous works. (a) Nagumo, S.; Matsukuma, A.; Inoue, F.; Yamamoto, T.; Suemune, H.; Sakai, K. *Chem. Commun.* **1990**, 1538−1539. (b) Yamamoto, T.; Suemune, H.; Sakai, K. *Tetrahedron* **1991**, *47*, 8523−8528. (c) Kabalka, G. W.; Tejedor, D.; Li, N.-S.; Malladi, R. R.; Trotman, S. *Tetrahedron Lett.* **1998**, *39*, 8071−8072. (d) Kabalka, G. W.; Tejedor, D.; Li, N.-S.; Malladi, R. R.; Trotman, S. *J. Org. Chem.* **1998**, *63*, 6438−6439. (e) Kabalka, G. W.; Li, N.-S.; Tejedor, D.; Malladi, R. R.; Trotman, S. *J. Org. Chem.* **1999**, *64*, 3157−3161. See also refs 2c and 4e.

(11) De Giacomo, M.; Bettolo, R. M.; Scarpelli, R. *Tetrahedron Lett.* **1997**, *38*, 3469−3470. See also refs 10b−e.

carbon−carbon bond, formation of a carbon−carbon double bond, and loss of acetone. Synchronous fragmentation of **5** as proposed by Grob in his initial studies[1c] is not possible in our case, because the rigidity of the structures avoids the necessary through-bond coupling alignment in the transition state.

The stepwise mechanism here proposed is supported by an experiment carried out with the acetonide **4h** (Figure 1).



4h

Figure 1.

This compound did not lead to the desired aldehyde in any of the conditions attempted, probably because the formation of a cationic intermediate like **6** is not favored in this case.

More proof for the stepwise mechanism could be that a mixture of (*E*,*E*)- and (*E*,*Z*)-aldehydes is obtained from the reaction of **4f** under certain conditions (see Table 2). The formation of such a mixture is consistent with the proposed intermediate **6**, while a concerted mechanism would explain the formation of only one diastereoisomer.

(12) To read about recent calculations on cations in Grob fragmentations, see: Alder, R. W.; Harvey, J. N.; Oakley, M. T. *J. Am. Chem. Soc.* **2002**, *124*, 4960−4961.

The generation of small amounts of 1-naphthalenecarbaldehyde starting from acetonide **4c** (Table 2) can also be explained with the proposed mechanism by considering first the coordination of the acid to the other oxygen atom followed by fragmentation reaction.

Finally, the reason for the difference in reactivity between 1,3-*cis*- and 1,3-*trans*-acetonides is not clear, but it could be due to steric factors. Tentatively, it can be proposed that the steric relief associated with a more crowded environment in the 1,3-*cis*-acetonide can accelerate the rate of the fragmentation reaction.

In summary, acetonides derived from 1,3-diols undergo Grob fragmentation reactions under milder conditions than the diols themselves. As far as we know, these are the first examples of Grob fragmentations performed on acetonides. The influence of different factors on the reaction pathway has been widely studied, and a stepwise mechanism has been proposed. Moreover, highly functionalized chiral aldehydes containing a diene or alkene moiety and a cyclobutane or cyclopropane ring have been obtained as single enantiomers in high yields.

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Supporting Information Available: Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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