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Efficient and Scalable One-Pot Synthesis of 2,4-Dienols from Cycloalkenones: Optimized Total Synthesis of Valerenic Acid

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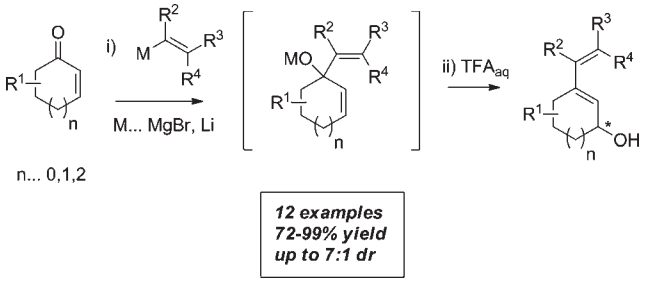
ABSTRACT



A mild and selective one-pot procedure to provide 2,4-dienols from simple cycloalkenones in high yields is described. This transformation is based on the in situ formation of acid-labile allylic alcohols, which on treatment with trifluoroacetic acid undergo a formal [1,3]-hydroxy migration to form diastereo- and enantiomerically enriched 2,4-dienols. The usefulness of this protocol is demonstrated in a short synthesis of valerenic acid.

2,4-Dienols are very important building blocks in natural product synthesis.[1] However, as even simple 2,4-dienols require several steps for their synthesis, a general and efficient access to these compounds would be welcome.

A straightforward access to 2,4-dienols is the [1,3]-hydroxy isomerization of tertiary allylic alcohols. This thermodynamically driven reaction has been known for several decades and has often been based on the use of metal−oxo catalysts,[2] although the pioneering investigations were carried out with sulfuric acid.[3] However, one of the disadvantages of this reaction type is the moderate stability of the required precursors. Therefore, we devised an effective and mild one-pot procedure that combines the preparation of the precursors with the [1,3]-hydroxy isomerization.[4,5]

As a proof of concept, 2-cyclopentenone (**1**) was chosen as a simple test substrate (see Table 1). After treatment with vinylmagnesium bromide, the in situ formed tertiary alkoxide **2** was treated with different aqueous Brønsted acids to trigger the transformation into 3-vinylcyclopent-2-enol (**3a**). The difference between sulfuric acid and hydrochloric acid was marginal, and at best, the isolated yields were only slightly higher than 40% (entries 1−3). After applying inorganic Brønsted acids, we switched to organic Brønsted acids instead (entries 4−6). Gratifyingly, when acetic acid or trifluoroacetic acid was used, decomposition and side reactions seemed to be much less competitive, in both cases, and much better results were obtained.

(1) For examples, see: (a) Corey, E. J.; Da Silva Jardine, P.; Rohloff, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 3672. (b) He, F.; Bo, Y.; Altom, J. D.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771. (c) Ramharter, J.; Mulzer, J. *Org. Lett.* **2009**, *11*, 1151.

(2) For a review, see: Bellemin-Laponnaz, S.; Le Ny, J.-P. *Compt. Rend. Chim.* **2002**, *5*, 217.

(3) For a review, see: Braude, E. A. *Q. Rev. Chem. Soc.* **1950**, *4*, 404.

(4) For reviews about one-pot reactions, see: (a) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831. (b) Albrecht, Ł.; Jiang, H.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* 2011, *50*, in press. (c) Vaxelaire, C.; Winter, P.; Christmann, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 3605.

(5) For a recent application of one-pot reactions in natural product synthesis from our group, see: Ramharter, J.; Weinstabl, H.; Mulzer, J. *J. Am. Chem. Soc.* **2010**, *132*, 14338.

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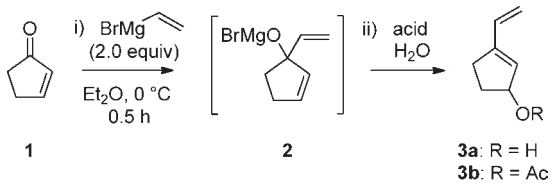
Table 1. Screening of Different Brønsted Acids



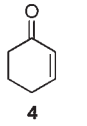
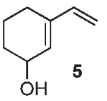
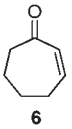
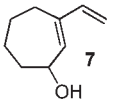
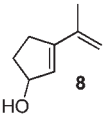
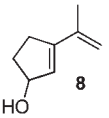
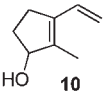
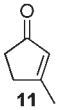
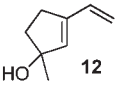
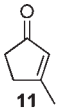
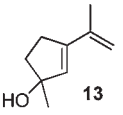
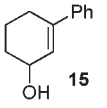
entry	acid (equiv)	temp (°C)	time (h)	product, yield (%)
1	H_2SO_4 (2.5)	25	1	**3a**, traces
2	H_2SO_4 (2.5)	0	1	**3a**, 45
3	HCl (2.5)	0	1	**3a**, 42
4	CH_3COOH (2.5)	25	24	**3a**, 68 + **3b**, 27
5	CF_3COOH (2.5)	0	1	**3a**, 78
6	CF_3COOH (2.5)	0	1.5	**3a**, 73 (gram scale)

Unfortunately, in the case of acetic acid, it took much longer to reach full conversion, and 1-acetoxy-2,4-dienol **3b** was isolated as side product (entry 4). Finally complete and selective isomerization to the desired 2,4-dienol **3a** was observed when trifluoroacetic acid was used (entry 5). The reaction was scalable, and nearly the same yield was obtained on a larger scale (entry 6).

After these initial results, the isomerization of other substrates was studied (see Table 2). The conversion of cycloalkenones with larger ring size was also highly selective (entries 1 and 2). Whereas treatment of 2-cyclopentenone (**1**) with 2-propenylmagnesium bromide led to the formation of considerable amounts of the 1,4-addition product, use of the corresponding organolithium compound and subsequent treatment with trifluoroacetic acid resulted in clean formation of the desired 2,4-dienol **8**. Scale up to gram scale did not reduce the yield (entry 4). Interestingly, while the substituent in 2-methylcyclopent-2-enone did not affect the transposition of the hydroxy group, the conversion of 3-methylcyclopent-2-enone was much more acid sensitive than most other substrates. As a consequence, better results were obtained when acetic acid was used instead of trifluoroacetic acid (entries 6 and 7). Remarkably, no other products were obtained in this case. Finally, also an aryl Grignard was used instead of an alkenyl Grignard (entry 8). Although the subsequent isomerization was much slower than before, a very selective formation of the expected 3-phenylhex-2-enol was observed in nearly quantitative yield.

Because metal−oxo-catalyzed 1,3-isomerizations of allylic alcohols often proceed stereoselectively,[6] the conversion of chiral substrates was investigated as well (see Table 3). According to our results, the limiting factor in the selectivity of the overall transformation appears to be the 1,2-addition. When a single intermediate was

Table 2. Conversion of Simple Substrates[a]

entry	substrate	nucleophile	cond.	product	yield
1	 **4**		TFA, 0 °C, 1.5 h	 **5**	79%
2	 **6**		TFA, 25 °C, 1.5 h	 **7**	80%
3	 **1**		TFA, 0 °C, 0.75 h	 **8**	81%
4	 **1**		TFA, 0 °C, 1 h	 **8**	72% (g-scale)
5	 **9**		TFA, 0 °C, 1 h	 **10**	79%
6	 **11**		AcOH, 0 °C, 0.75 h	 **12**	99%
7	 **11**		AcOH, 0 °C, 1 h	 **13**	78% (g-scale)
8	 **14**		TFA, 25 °C, 48 h	 **15**	94%

[a] Key: (i) 0.1 M in Et_2O at 0 °C or −78 °C, 2.0 equiv of nucleophile; (ii) 0 °C or rt, H_2O, 2.5 equiv of acid.

formed, high diastereomeric ratios were obtained for the resulting products (entries 2 and 3).[7] However, when the 1,2-addition was not selective, roughly the same diastereomeric ratio was observed for the rearranged dienols (entry 1).

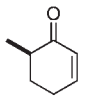
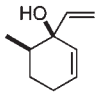
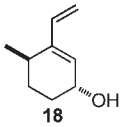
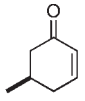
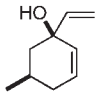
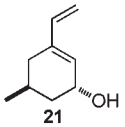
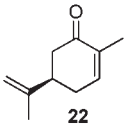
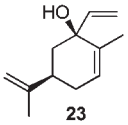
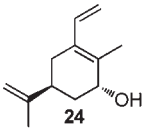
Interestingly, *cis* intermediates led to the formation of *trans* products, indicating that a different mechanism is operating than for metal−oxo catalyst mediated reactions.[8] To account for the observed stereoselectivity, we propose that trifluoroacetic acid does not only protonate the tertiary alcohol but also blocks the site of the molecule *syn* to the alcohol (see Figure 1). The interaction of acid and hydroxyl group may result either in the formation of an instable trifluoroacetate followed by S_N2 hydrolysis or

(6) (a) Matsubara, S.; Okazoe, T.; Oshima, K.; Takai, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 844. (b) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 11262. (c) Morrill, C.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 2842.

(7) Diastereomers were separated by means of HPLC. *cis*- and *trans*-configurations were assigned by NOE experiments.

(8) Bellemin-Laponnaz, S.; Le Ny, J.-P.; Dedieu, A. *Chem.—Eur. J.* **1999**, *5*, 57.

Table 3. Selective Conversion of Chiral Substrates[a]

entry	substrate	intermediate[b] (*cis* / *trans*)	product[b] (*trans* / *cis*)	yield[c]
1	 **16**	 **17** 2.2 / 1	 **18** 2.3 / 1	83%
2	 **19**	 **20** > 10 / 1	 **21** 7 / 1	82%
3[d]	 **22**	 **23** > 10 / 1	 **24** 6 / 1	79%

[a] Key: (i) 0.1 M in Et_2O at 0 °C, 2.0 equiv of vinylmagnesium bromide; (ii) rt, H_2O, 2.5 equiv of CF_3COOH. [b] Only the major isomer is depicted. [c] Combined yield of *cis* and *trans* products. [d] A 5-fold excess of CF_3COOH is used to speed up the reaction.

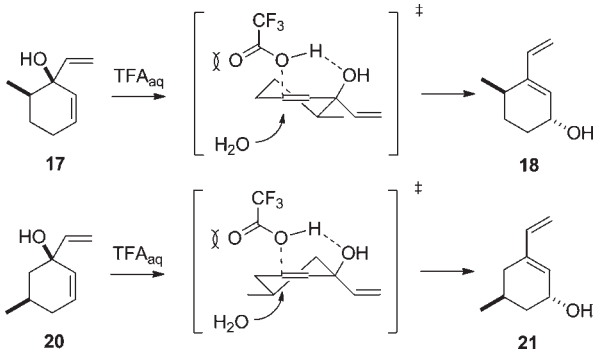
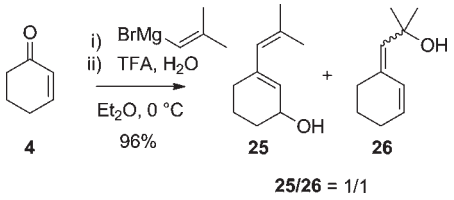


Figure 1. Proposed reaction mechanism for the diastereoselective [1,3]-hydroxy isomerization.

in the formation of a contact ion pair, which immediately is attacked by water from the opposite ring face.

Although, so far, all isomerizations have proven regioselective, some limitations must be taken into account. As outlined in Scheme 1, treatment of 2-cyclohexenone (**4**) with 2-methyl-1-propenylmagnesium bromide and subsequent addition of aqueous trifluoroacetic acid led to compounds **25** and **26** as a 1:1 mixture. This can be rationalized by assuming a significant carbenium character in the isomerization. Normally, a stereoelectronic preference for the endocyclic position is observed. If, however, the exocyclic position can stabilize a positive charge, nucleophilic attack can occur there too. A pronounced carbenium character also supports the proposed formation of a contact ion pair as intermediate (see discussion above).

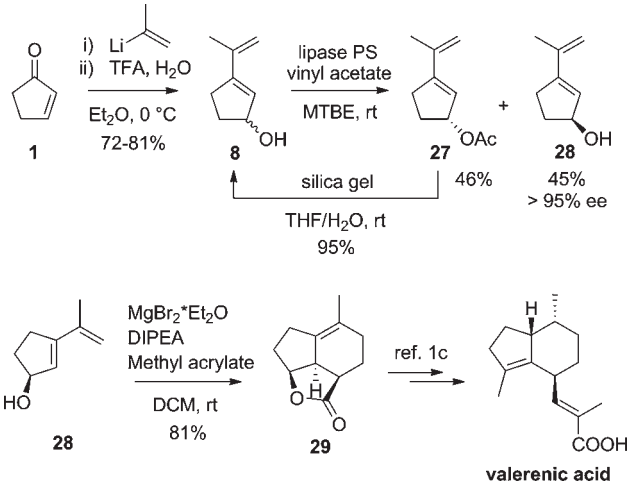
Scheme 1. Limitations[a]



[a] Key: (i) 0.1 M in Et_2O at 0 °C, 2.0 equiv of 2-methyl-1-propenylmagnesium bromide; (ii) 0 °C, H_2O, 2.5 equiv of CF_3COOH.

Finally, we highlight the usefulness of the described one-pot procedure by improving our previous synthesis of valerenic acid (see Scheme 2).[1c,9] We began with the one-pot synthesis of racemic dienol **8** (see Table 2, entries 3 and 4). Chiral resolution provided the optically enriched alcohol **28** and ester **27**.[10] The ester could easily be recycled to racemic dienol **8** by treatment with silica gel. Interestingly, during this reaction, the optical activity was completely lost,[11] indicating an S_N1 displacement of the acetate was occurring by water. With enantioenriched alcohol **28** in hand, a hydroxy-directed Diels–Alder reaction (HDDA), according to a modified protocol by the group of Barriault and co-workers, was conducted to provide tricyclic lactone **29**.[12] This compound is a

Scheme 2. Optimized Synthesis of Valerenic Acid[a]



[a] Abbreviations: TFA, trifluoroacetic acid; MTBE, methyl *tert*-butyl ether; DIPEA, diisopropylethylamine.

(9) For a different total synthesis of valerenic acid, see: Kopp, S.; Schweizer, W. B.; Altmann, K.-H. *Synlett* **2009**, *11*, 1769.

(10) Sumi, S.; Matsumoto, K.; Tokuyama, H.; Fukuyama, T. *Tetrahedron* **2003**, *59*, 8571.

(11) Proven by optical rotation: $[\alpha]^{20}_D = 0.000$.

(12) Barriault, L.; Thomas, J. D. O.; Clement, R. *J. Org. Chem.* **2003**, *68*, 2317.

key intermediate in our recently published synthesis of valerenic acid and only seven steps away from the target. The simplified access to dienol **8** shortens the route by five steps and increases the overall yield from 8% to 13% (25% if compound **27** is fully recycled).

In conclusion, we have developed a selective, flexible, and scalable one-pot synthesis of optically enriched 2,4-dienols from simple cycloalkenones. The underlying [1,3]-hydroxy isomerization is simple and stereoselective. Stereochemically, it complements the well-known oxo-metal-catalyzed [1,3]-hydroxy isomerization. An application in the synthesis of valerenic acid has led to a significant reduction in the overall number of steps.

Acknowledgment. We thank H. P. Kählig and S. Felsinger for NMR analysis as well as A. Körner and F. Nasufi for HPLC analysis, all at the University of Vienna, and the Austrian Science Fund (FWF) for financial support (projects P21241-N19 and TRP 107-B11).

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