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A flexible, modular route to cyclopentanols

Zhi Li, Samir Z. Zard *

Laboratoire de Synthèse Organique, UMR 7652 CNRS-École Polytechnique, Route de Saclay, 91128 Palaiseau Cedex, France

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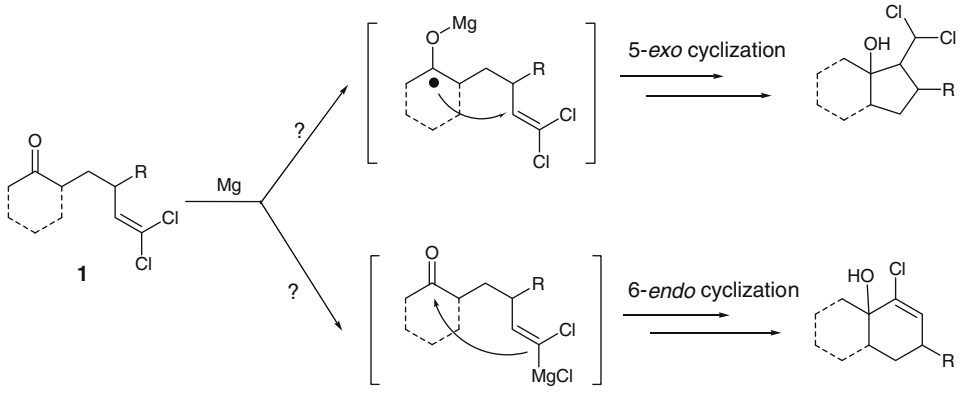
ABSTRACT

A flexible, modular route to cyclopentanols is devised based on a sequence of xanthate radical reactions followed by magnesium-mediated ketyl-olefin cyclization.

The intramolecular ketyl-olefin cyclization has proved to be a useful tool in organic synthesis.[1] In contrast to the numerous studies on the intramolecular ring closure of ketyl radicals to simple,[2] or activated olefins such as α,β-unsaturated esters,[3] nitriles,[4] and sulfides,[4b,5] little attention has been paid to the cyclization of ketyl radicals to halogenated alkenes. The presence of both the halide and the ketone group introduces an uncertainty as to which group could then undergo a 5-*exo* cyclization onto the vinyl group, or whether an organomagnesium species would form first followed by an ionic ring closure onto the ketone to furnish a chlorocyclohexenol or a product derived there from, Scheme 1.

As part of our work on the degenerative xanthate transfer reaction,[6] we conjectured that the requisite linear γ-dichlorovinyl-substituted ketone **1** could be obtained rapidly from readily



Scheme 1. Possible modes of cyclization of γ-dichlorovinyl-substituted ketone **1** in the presence of magnesium.

is reduced first. For instance, in the case of γ-dichlorovinyl-substituted ketone **1**, it is not obvious whether reduction with metallic magnesium would result in the creation of a ketyl radical, which available xanthate **2** via a xanthate transfer addition, followed by exchange of the xanthate group with a dichlorovinyl motif through reaction with dichlorovinyl ethyl sulfone, as indicated in Scheme 2.[7]

We started our study by preparing a series of xanthate derivatives **3** via radical addition of xanthates **2a–c** to various alkenes.

* Corresponding author. Tel.: +33 0 1 69335971; fax: +33 0 1 69335972.
E-mail address: zard@poly.polytechnique.fr (S.Z. Zard).

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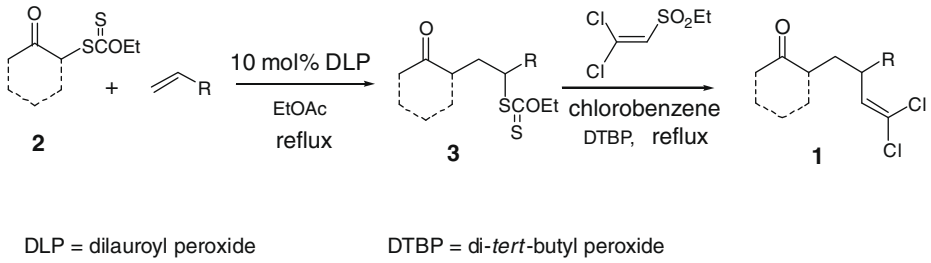


Scheme 2. Synthesis of γ-dichlorovinyl-substituted ketone **1**.

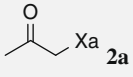
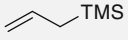
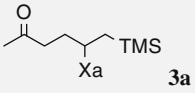
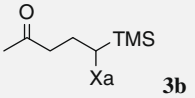
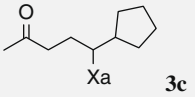
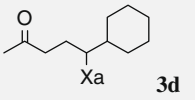
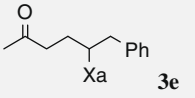
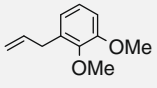
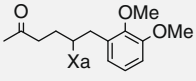
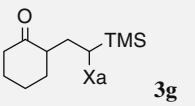
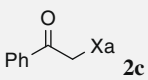
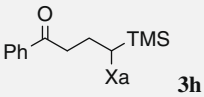
The reactions proceeded smoothly and in generally good yields, as shown by the results compiled in Table 1 (Xa = SC(S)OEt).

With xanthates **3** in hand, we set out to assemble the γ-dichlorovinyl-substituted ketones **1** via the radical reaction of **3** with 2,2-dichlorovinyl ethyl sulfone.[8] The desired key substrates **1** were obtained in moderate to good yields (Table 2). In the case of xanthate **3g**, the corresponding diastereoisomeric dichlorovinyl adducts **1g**/**1g′** could be separated by chromatography.

We elected to use magnesium[1c] to generate the ketyl radical in view of its convenience and low cost. In order to ascertain the viability of cyclization of ketones **1** in the presence of Mg, adduct **1a** was selected as a model substrate and various reaction conditions were screened as indicated in Table 3.

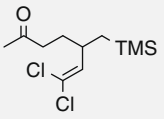
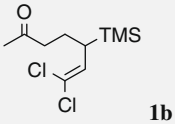
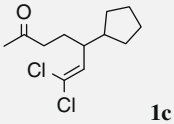
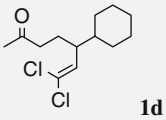
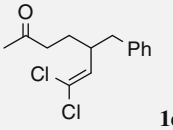
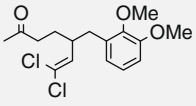
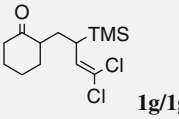
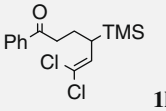
When the reaction was conducted in THF or Et_2O, no cyclization product was obtained and the starting material was recovered quantitatively (entries 1 and 2). The generation of either the ketyl or the Grignard intermediate did not seem straightforward under these conditions. In order to favor the creation of the former species, a protic solvent was employed. Indeed, when **1a** was treated with 4 equiv of Mg in methanol at room temperature, the 5-*exo* cyclization product **4a** was obtained in 20% yield as one major diastereoisomer (entry 3). Activation of the magnesium with a small amount of $HgCl_2$[10] caused an acceleration of the reaction but did not result in a significantly improved yield of **4a** (entry 4). When the reaction was conducted in methanol at reflux in the presence of 10 equiv of Mg, cyclopentanol **4a** was obtained

Table 1
Synthesis of xanthates **3**

Entry	Substrate	Alkene	Product	Yield[a] (%)
1	 **2a**		 **3a**	77
2	**2a**		 **3b**	86[b]
3	**2a**		 **3c**	81
4	**2a**		 **3d**	83
5	**2a**		 **3e**	81
6	**2a**		 **3f**	71
7	 **2b**		 **3g**	60[b,c]
8	 **2c**		 **3h**	87[b]

[a] Isolated yield.
[b] For syntheses of **3b**, **3g** and **3h**, see: Ref. 9.
[c] dr = 1:1.

Table 2
Synthesis of ketones **1** from xanthates **3** and dichlorovinyl ethyl sulfone

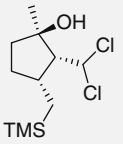
Entry	Substrate	Product	Yield[a] (%)
1	**3a**	 **1a**	70
2	**3b**	 **1b**	55[b]
3	**3c**	 **1c**	63
4	**3d**	 **1d**	33
5	**3e**	 **1e**	65
6	**3f**	 **1f**	75
7	**3g**	 **1g/1g'**	54[b,c]
8	**3h**	 **1h**	60[b]

[a] Isolated yield.
[b] For syntheses of **1b**, **1g/1g'** and **1h**, see: Ref. 10.
[c] dr = 1:1, **1g** (R_f = 0.6, petroleum ether/EtOAc = 30:1), **1g'** (R_f = 0.5, petroleum ether/EtOAc = 30:1). The ratio of **1g** and **1g'** was determined from the ^{1}H NMR spectrum of the crude product.

along with unidentified impurities in 46% yield (entry 5). Increasing the load of Mg but operating at room temperature did improve the yield of **4a** to 40% (entry 6) with respect to the same reaction conducted with only 4 equiv of magnesium (entry 3). Switching the solvent from methanol to ethanol, or to a mixture of methanol and hexane (v/v = 2:1) did not result in any noticeable improvement in yield (entries 7 and 8). Addition of NH_4Cl to the reaction mixture as a weak acid had no effect on the yield. However, when the reaction temperature was lowered to −23 °C, compound **4a** was obtained in 50% yield (entry 10). This improved result may be due to fewer side reactions at the lower temperature. Eventually, **4a** was obtained in 55% yield when the reaction was conducted in methanol at −23 °C in the presence of 40 equiv of Mg (entry 11).

With reasonably optimized reaction conditions in hand, we examined the cyclization of the remaining substrates (Table 4).

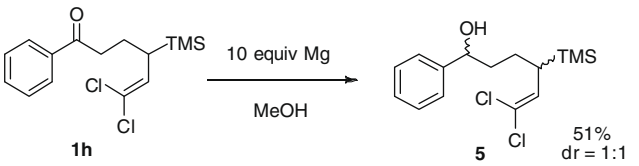
Table 3
Reactions of ketone **1a** in the presence of Mg

Entry	Solvent	Mg/catalyst	Product (yield)[a]
1	THF (rt)	4 equiv	None[b]
2	Et_2O (rt)	4 equiv	None[b]
3	MeOH (rt)	4 equiv	 **4a** (20%)[c]
4	MeOH (rt)	4 equiv /$HgCl_2$	**4a** (20%)[c]
5	MeOH (reflux)	10 equiv	**4a** (46%)[c,d]
6	MeOH (rt)	20 equiv/$HgCl_2$	**4a** (40%)[c]
7	EtOH (rt)	20 equiv/$HgCl_2$	**4a** (42%)[c]
8	MeOH/hexane (rt)	20 equiv/$HgCl_2$	**4a** (45%)[c,e]
9	MeOH/hexane (rt)	20 equiv/$HgCl_2$ NH_4Cl	**4a** (45%)[c,f]
10	MeOH (−23 °C)	20 equiv/$HgCl_2$	**4a** (50%)[c]
11	**MeOH** (**−23 °C**)	**40 equiv/$HgCl_2$**	**4a** (55%)[c,g]

[a] Isolated yield.
[b] Starting material recovered.
[c] dr = 5:1 was determined from the ^{1}H NMR spectrum of the crude product. Cyclopentanol **4a** was isolated as the major isomer.
[d] The product was contaminated by small amounts of unidentified impurities which could not be removed by flash column chromatography.
[e] MeOH/hexane (v/v = 2:1).
[f] 40 equiv of NH_4Cl were added.
[g] For reaction details, see: Supplementary data.

Cyclopentanols **4** with various substituents were obtained in moderate to good yields according to this protocol. In all of these derivatives, the 2-position was substituted with a dichloromethyl group. No products bearing a monochloromethyl or a methyl group in the 2-position were observed. This indicated that the dichloromethyl group was inert to the presence of excess Mg under our reaction conditions. The substituent at the 3-position of cyclopentanols **4** can be alkyl (entries 1, 5, and 6), TMS (entry 2), or cycloalkyl (entries 3 and 4). Bicyclic alcohols such as **4g** and **4g'** can also be prepared efficiently by this method (entries 7 and 8). In all cases, the major diastereoisomer was the 1,2-*trans* alcohol and the diastereomeric ratio was 5:1 to 4:1. Interestingly, the two separated diastereoisomers **1g** and **1g'** afforded the same cyclization products in the same diastereomeric ratios (entries 7 and 8). This indicated that epimerization via the enolate of the ketone was faster than ketyl generation. Indeed, thin layer chromatography indicated the equilibration of **1g** and **1g'** under the reaction conditions.

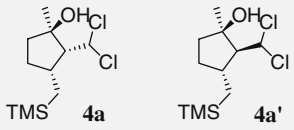
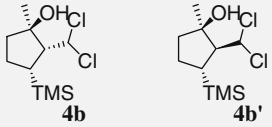
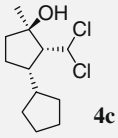
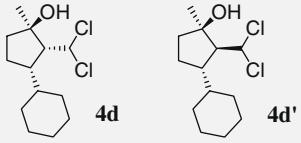
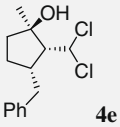
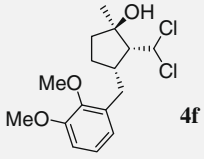
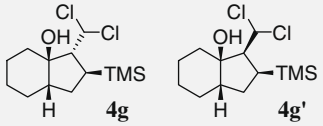
We next explored the cyclization of γ-dichlorovinyl-substituted phenyl ketone **1h**. Unfortunately, only the simple ketone reduction product **5** was obtained in 51% yield (Eq. 1). The ketyl radical is clearly not sufficiently reactive with respect to cyclization while further reduction is facilitated by the aromatic ring.



(1)

In summary, we have developed a flexible, modular route to cyclopentanols based on a sequence of three radical reactions. The first two exploit the unique ability of xanthates to mediate intermolecular additions while the last is a magnesium-induced ketyl-olefin cyclization. Various polyfunctional cyclopentanols can be rapidly and efficiently assembled by simply modifying the xanthate and olefinic partners in the first step.

Table 4
Syntheses of cyclopentanols **4**

Entry	Substrate	Product	Yield[a] (%)
1	**1a**	 **4a** **4a'**	65[b] (99) [c] **4a**/**4a′** = 5:1
2	**1b**	 **4b** **4b'**	60[b] **4b**/**4b′** = 5:1
3	**1c**	 **4c**	56[d] (85)[c]
4	**1d**	 **4d** **4d'**	66[b] (74)[c] **4d**/**4d′** = 5:1
5	**1e**	 **4e**	76[d] (81)[c]
6	**1f**	 **4f**	55[d] (78)[c]
7	**1g**	 **4g** **4g'**	52[b] (82)[c] **4g**/**4g′** = 5:1
8	**1g′**	**4g** and **4g′**	41[b] (63)[c] **4g**/**4g′** = 5:1

[a] Isolated yield.
[b] Total yield of the two diastereoisomers.
[c] Yield based on recovered of starting material.
[d] dr = 4:1 was determined from the ^{1}H NMR spectrum of the crude product. The product was isolated as the major isomer.

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Supplementary data

Supplementary data (detailed experimental procedures and characterization data for new compounds are provided) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.157.

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