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Unified, Radical-Based Approach for the Synthesis of Spiroketals

Michiel de Greef and Samir Z. Zard*

Laboratoire de Synthèse Organique associé au C.N.R.S., Ecole Polytechnique,
91128 Palaiseau, France

zard@poly.polytechnique.fr

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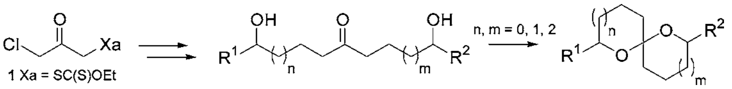
ABSTRACT



Functionalization of *S*-(3-chloro-2-oxo-propyl)-*O*-ethyl xanthate 1 by two consecutive xanthate transfer reactions, followed by spirocyclization of the resulting dihydroxy ketones, provides a flexible and highly convergent access to diversely substituted spiroketals, containing five-, six-, and seven-membered rings.

Spiroketals widely occur in nature and are an important class of secondary metabolites in many living organisms.[1] Those incorporating five- and six-membered rings are the most frequently encountered, as exemplified by the structures of reveromycin A,[2] broussonetine G,[3] and okadaic acid[4] (Figure 1). Many of the natural spiroketals exhibit an interesting biological activity. As a consequence, much attention has been given to their synthesis and several reviews have appeared.[1a,5,6] The most frequently employed strategy relies on the spirocyclization of properly functionalized dihydroxy ketones, themselves available by multistep procedures, involving common ionic processes.[7]

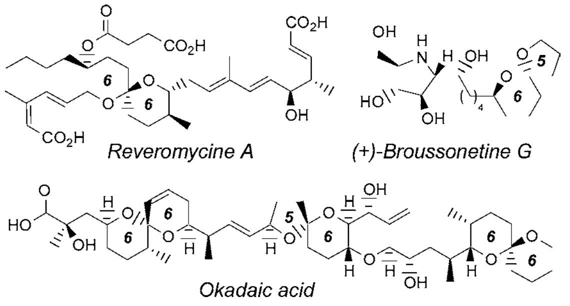


Figure 1. Examples of spiroketal natural products.

By contrast, radical chemistry has only played a very minor role in spiroketal synthesis, despite its mildness and functional group tolerance. Most examples involve a radical cyclization as a key step for the synthesis of the spiroketal moiety.[8] Strategies based on intermolecular radical reactions for the synthesis of dihydroxy ketones are even rarer. Only one example, by Giese et al., describes the symmetrical functionalization of divinyl ketone by stannane-mediated

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(1) (a) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617. (b) Fletcher, M. T.; Kitching, W. *Chem. Rev.* **1995**, *95*, 789. (c) Jacobs, M. F.; Kitching, W. *Curr. Org. Chem.* **1998**, *2*, 395. (d) Francke, W.; Kitching, W. *Curr. Org. Chem.* **2001**, *5*, 233.

(2) Drouet, K. E.; Ling, T.; Tran, H. V.; Theodorakis, E. A. *Org. Lett.* **2000**, *2*, 207.

(3) Trost, B. M.; Horne, D. B.; Woltering, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5987.

(4) Tachibana, K.; Scheuer, P. J.; Tsukitani, Y.; Kikuchi, H.; Van Engen, D.; Clardy, J.; Gopichand, Y.; Schmitz, F. J. *J. Am. Chem. Soc.* **1981**, *103*, 2469.

(5) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309.

(6) Mead, K. T.; Brewer, B. N. *Curr. Org. Chem.* **2003**, *7*, 227.

(7) For some representative examples, see: (a) Zinzalla, G.; Milroy, L.-G.; Ley, S. V. *Org. Biomol. Chem.* **2006**, *4*, 1977. (b) Lindsey, C. C.; Wu, K. L.; Pettus, T. R. R. *Org. Lett.* **2006**, *8*, 2365. (c) Waters, S. P.; Fennie, M. W.; Kozlowski, M. C. *Org. Lett.* **2006**, *8*, 3243. (d) Sörgel, S.; Azap, C.; Reissig, H.-U. *Org. Lett.* **2006**, *8*, 4875. (e) Zanatta, S. D.; White, J. M.; Rizzacasa, M. A. *Org. Lett.* **2004**, *6*, 1041. (f) Enders, D.; Lenzen, A. *Synlett* **2003**, 2185. (g) Panek, J. S.; Jain, N. F. *J. Org. Chem.* **2001**, *66*, 2747. (h) Brown, H. C.; Kulkarni, S. V.; Racherla, U. S.; Dhokte, U. P. *J. Org. Chem.* **1998**, *63*, 7030. (i) Barrett, A. G. M.; Edmunds, J. J.; Horita, K.; Parkinson, C. J. *J. Chem. Soc., Chem. Commun.* **1992**, 1236.

(8) (a) Ferrier, R. J.; Hall, D. W. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3029. (b) Dorta, R. L.; Martin, A.; Salazar, J. A.; Suarez, E.; Prange, T. *J. Org. Chem.* **1998**, *63*, 2251. (c) Sharma, G. V. M.; Rakesh Chander, A. S.; Reddy, V. G.; Rao, M. H. V. R.; Kunwar, A. C. *Tetrahedron: Asymmetry* **2003**, *14*, 2991.

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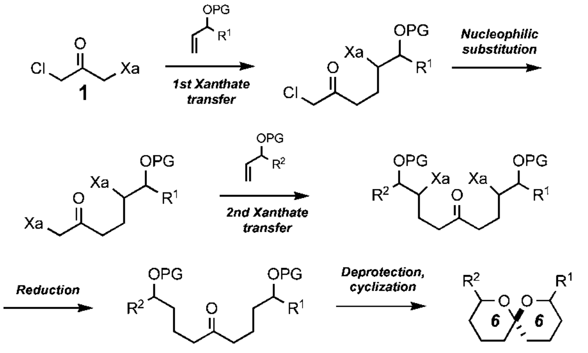
intermolecular addition of radicals generated from an excess of 2-acetoxypropyl mercuric acetate.[9]

We now describe a novel route to dihydroxy ketones and thence to spiroketals, which takes advantage of the powerful xanthate transfer reaction.[10] In contrast with other common C−C bond-forming radical processes, this method is characterized by the fact that the major undesired competing pathway is degenerate. As a consequence, the intermediate radicals acquire an extended effective lifetime and are able to undergo intermolecular addition even to unactivated olefin traps.

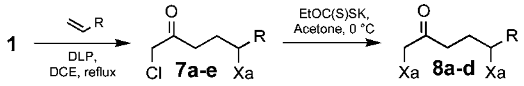
Scheme 1. Synthetic Route to Spiroketals

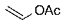
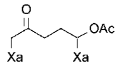
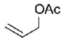
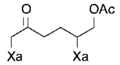
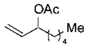
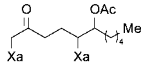
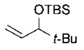
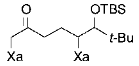
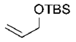
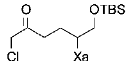


As outlined in Scheme 1 for the synthesis of [6,6]-spiroketal systems, rapid functionalization of *S*-(3-chloro-2-oxo-propyl)-*O*-ethyl xanthate **1**[11] should be possible by two consecutive xanthate transfer additions to two protected allylic alcohols (Xa = −SC(=S)OEt throughout). The resulting radical adducts are then reduced, deprotected, and cyclized to yield the corresponding spiroketals. By varying the chain length of the radical traps, this strategy would provide access to a large number of diversely substituted spiroketals, containing five-, six-, and seven-membered rings.

Xanthate **1** is accessible in one step from commercial 1,3-dichloroacetone.[11] It was reacted with a number of olefinic acetates and silyl ethers **2**−**6** in refluxing 1,2-dichloroethane (DCE) in the presence of a small amount of dilauroyl peroxide (DLP) (Table 1). Treatment of the resulting radical adducts **7a**−**d** with potassium *O*-ethyl xanthate in acetone then cleanly furnished the desired bis(xanthates) **8a**−**d** in good overall yields (52−80%).[12] Both vinyl (entry a) and allyl (entries b and c) acetates were successfully employed as radical traps, leading to precursors for spiroketals containing five- and six-membered rings, respectively. Allyl silyl ethers also proved to be efficient radical traps (entries d and e). It is worthy of note that a new carbon−carbon bond could be created, *despite the presence of the reactive chloroketone moiety*.

Table 1. Radical Additions of Chloroketone Xanthate **1**[12]



entry	olefin		*8a-d, 7e yield (%)*	
a		2		**8a** (52%)
b		3		**8b** (80%)
c		4		**8c** (80%) dr = 1:1
d		5		**8d** (54%) dr = 1:3
e		6		**7e** (72%)

Further functionalization of ketones **8a**−**d** was achieved by a second xanthate transfer reaction with a range of olefins (Table 2). Although adducts **8a**−**d** bear two xanthate groups, all radical additions were completely regioselective. This selectivity results from the difference in stability between a secondary radical and a radical adjacent to a carbonyl group, the latter being the most stable and therefore much easier to generate. Radical adducts **15a**−**i** were obtained in good yields (56−88%) as mixtures of diastereomers that were used as such in the next step. The successful use of vinyl (entry g), allyl (entries a−e, h, and i), and homoallyl acetates (entry f) prepares for the incorporation of five-, six-, and seven-membered rings, respectively, into the spiroketal and illustrates the flexibility of our method.

Further structural diversity was achieved by changing the substituent at the carbon α to the oxygen substituent, as illustrated for a range of allyl acetates (entries a−e, h, and i). The latter are accessible from the corresponding aldehydes by reaction with vinylmagnesium bromide, followed by protection of the resulting racemic alcohols.

These might be transformed into optically active samples, either by kinetic[13] or by enzymatic[14] resolution. An equally efficient access to a library of homoallyl acetates is conceivable by using allyl- instead of vinylmagnesium bromide[15] or by applying Brown's asymmetric allylboration procedure, to obtain optically active homoallylic alcohols.[16]

Clean reduction of compounds **15a**−**i** was achieved with either DLP/2-propanol[17] or *n*-Bu$_3$SnH/AIBN. The choice of the reducing agent was dependent on the nature of the starting material. In most cases, our tin-free method gave satisfactory results (entries a and d−g). However, in one case, a slightly

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(9) Giese, B.; Bartmann, D.; Hasskerl, T. *Liebigs Ann. Chem.* **1987**, 427.

(10) (a) Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 672. (b) Quiclet-Sire, B.; Zard, S. Z. *Phosphorus, Sulfur Silicon Relat. Elem.* **1999**, *153−154*, 137. (c) Quiclet-Sire, B.; Zard, S. Z. *Chem.−Eur. J.* **2006**, *12*, 6002. (d) Quiclet-Sire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201. (e) Zard, S. Z. *Org. Biomol. Chem.* **2007**, *5*, 205.

(11) Bergeot, O.; Corsi, C.; El Qacemi, M.; Zard, S. Z. *Org. Biomol. Chem.* **2006**, *4*, 278.

(12) The reported yields are unoptimized.

(13) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; Chapter 4.

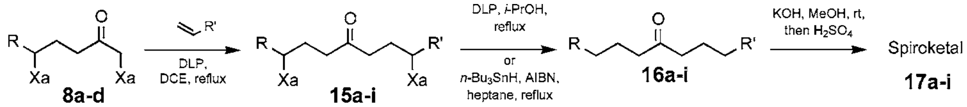
(14) Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon: Oxford, 1994; Chapter 2.

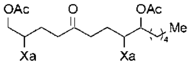
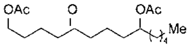
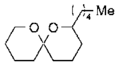
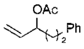
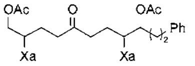
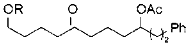
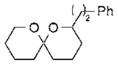
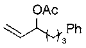
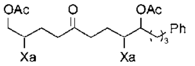
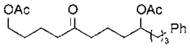
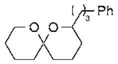
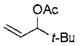
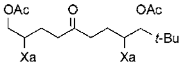
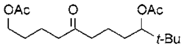
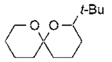
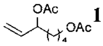
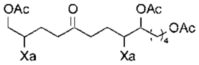
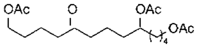
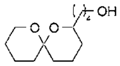
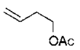
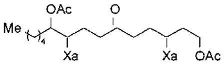
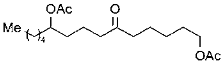
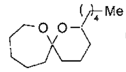
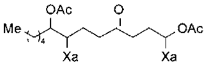
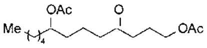
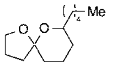
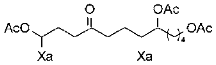
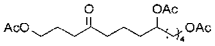
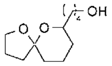
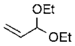
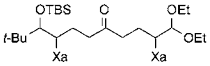
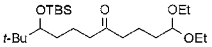
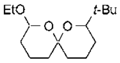
(15) For example, see: Barluenga, J.; Mateos, C.; Aznar, F.; Valdes, C. *J. Org. Chem.* **2004**, *69*, 7114.

(16) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401.

(17) Liard, A.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 5877.

Table 2. Formation of Spiroketals[12]



entry	di-xanthate	olefin	15a-i yield (%)[a]	16a-i yield (%)	17a-i yield (%)[b]
a	8b	4	 **15a** (88%)	 **16a** (79%)	 **17a** (71%)
b	8b	 **9**	 **15b** (70%)	 **16b**[c] (R=Ac, 60%) + **16b'** (R=H, 25%)	 **17b** (75%)
c	8b	 **10**	 **15c** (82%)	 **16c**[c] (R=Ac, 75%) + **16c'** (R=H, 15%)	 **17c** (74%)
d	8b	 **11**	 **15d** (69%)	 **16d** (76%)	 **17d**[d] (61%)
e	8b	 **12**	 **15e** (78%)	 **16e** (84%)	 **17e** (72%)
f	8c	 **13**	 **15f**[e]	 **16f**[f] (58%)	 **17f** (75%)
g	8c	2	 **15g**[e]	 **16g**[f] (50%)	 **17g** (68%)
h	8a	12	 **15h** (57%)	 **16h** (57%)	 **17h** (92%)
i	8d	 **14**	 **15i** (56%)	 **16i**[c] (85%)	 **17i**[f,g] (57%)

[a] Mixtures of diastereomers were obtained that were used as such in the next step. [b] All spiroketals were obtained as single diastereomers. [c] Reduction was achieved by Bu_3SnH/AIBN in refluxing heptane. [d] An aqueous solution of NaOH in MeOH was used for hydrolysis. [e] Crude reaction product was used as such in the next step. [f] Yield over two steps. [g] Spirocyclization was achieved by deprotection of the secondary alcohol with TBAF in refluxing THF, followed by exposure of the crude alcohol to Amberlyst-15 in CH_2Cl_2 at rt.

lower yield was observed (entry h). This might be ascribed to the hydrolysis of the *O*,*S*-acetal moiety in **15h**, induced by small amounts of lauric acid, derived from the peroxide. The use of 2-propanol, a slow hydrogen donor, is excluded when the intermediate radical can undergo reactions other than simple reduction (entries b and c). As a consequence of the presence of favorably positioned phenyl groups, **15b**,**c** may undergo benzylic hydrogen abstraction or cyclization onto the aromatic ring, if the intermediate radicals are too long-lived. Thus, a faster reducing agent such as n-Bu_3SnH becomes preferable. However, in some cases, stannane-mediated reduction led to partial hydrolysis of the primary acetate group, and **16b**,**c** were obtained as mixtures of mono- and bisacetylated dihydroxy ketones. Fortunately, this was of no consequence because the mixtures could be used as such in the next reaction, involving saponification of the acetate groups, prior to acid-catalyzed cyclization. This two-step procedure was therefore carried out in a one-pot fashion. In all cases, the desired spiroketals **17a**−**h** were isolated in good yields (61−92%) as single diastereomers. As observed previously,[1a] the latter are likely to have adopted the thermodynamically most favorable and naturally most widely occurring configuration, in which the two oxygens are in axial positions, whereas the side chain occupies an equatorial position.

It is interesting to note that nonracemic spiroketal **17h** was used previously by Trost et al.[3] in the first total synthesis of (+)-Broussonetine G, a potential antitumor and anti-HIV agent pictured in Figure 1.[18] The present route represents an interesting alternative that can easily be made enantioselective by starting with the known optically pure allylic acetate **12**.[19]

Spiroketals bearing an oxygen substituent at the 2-position were recently employed by Brimble et al. for the synthesis of a number of nucleoside analogues, displaying interesting antiviral activity.[20] Our method could easily be extended to the synthesis of such bisspiroketals, by using protected acrolein **14** as a radical trap (entry i). Attempts to simultaneously deprotect and cyclize spiroketal precursor **16i** were all in vain. However, fluoride-induced deprotection of the secondary alcohol, followed by acid-catalyzed cyclization, furnished the desired spiroketal **17i** in 57% yield over two

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(18) Shibano, M.; Nakamura, S.; Akazawa, N.; Kusano, G. *Chem. Pharm. Bull.* **1998**, *46*, 1048.

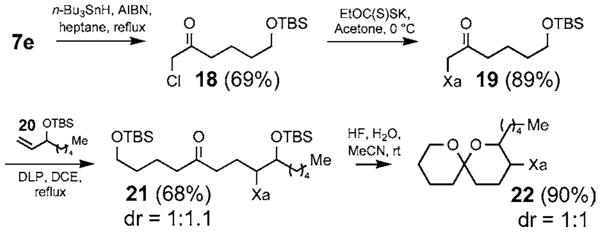
(19) Enders, D.; Nguyen, D. *Synthesis* **2000**, 2092.

(20) Brimble, M. A.; Robinson, J. E.; Choi, K. W.; Woodgate, P. D. *Aust. J. Chem.* **2004**, *57*, 665.

steps as a single diastereomer. This example illustrates the potential of this approach for constructing the more complex bisspiroketals.

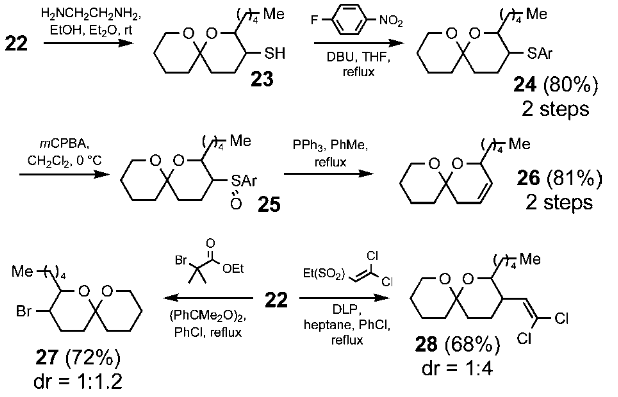
The use of olefinic silyl ethers as radical traps allows deprotection to be carried out under conditions compatible with the presence of base-sensitive functionalities, such as the xanthate group.[21] The latter being a versatile synthetic handle, we envisaged to keep at least one xanthate in the final spiroketal, by starting with compound **7e**. To reduce the number of stereocenters and to simplify characterization of the intermediates, we decided to remove the first xanthate group while keeping the second. Thus, selective tin-mediated reduction of the xanthate group, followed by treatment of the resulting chloride **18** with potassium *O*-ethyl xanthate cleanly furnished the desired xanthate **19** in good overall yield (Scheme 2). Compound **19** was further functionalized by a second xanthate transfer reaction. Thus, reaction with **20** in refluxing DCE using small amounts of DLP gave the corresponding radical adduct **21** in 68% yield as a mixture of inseparable diastereomers. The latter was exposed to aqueous HF, leading to simultaneous deprotection and cyclization. To our satisfaction, the corresponding spiroketal **22** was obtained in excellent yield (90%) as a 1:1 mixture of inseparable epimers.

Scheme 2. Synthesis of a Xanthate-Containing Spiroketal[12]



The xanthate group is indeed a useful handle for further functionalization of the spirocyclic core. Thus, oxidation of **22** and thermal decomposition of the intermediate sulfoxide **25** resulted in the clean, regioselective formation of alkene **26** (Scheme 3). Alternatively, following radical processes we developed recently, we were able to transform **22** into the corresponding bromide **27**[22] or to introduce a vinyl substituent[23] (Scheme 3). In the latter case, a modest diastereoselectivity was observed, which is due to the bulkiness of the vinyl donor and its preferred approach of the less hindered side of the radical center. The newly introduced vinyl group might be transformed into the corresponding alkyne, by taking advantage of the Corey–Fuchs reaction.[24]

Scheme 3. Modifications of the Xanthate Group[12]



This approach offers an attractive alternative to existing ionic methods. It is modular, is tolerant of many of the functional groups commonly encountered in modern synthesis, and allows the concise assembly of spiroketals with various combinations of ring sizes. Furthermore, xanthate **1** is the simplest member of a family of conjunctive radical-based reagents; substituted analogues should open access to yet more complex derivatives.

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

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(21) Greene, T. W.; Wuts, P. G. M. *Protecting Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999.

(22) Barbier, F.; Pautrat, F.; Quiclet-Sire, B.; Zard, S. Z. *Synlett* **2002**, 811.

(23) Bertrand, F.; Quiclet-Sire, B.; Zard, S. Z. *Angew. Chem., Int. Ed.* **1999**, *38*, 1943.

(24) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.