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Synthesis of [*n*,5]-Spiroketals by Ring Enlargement of Donor-Acceptor-Substituted Cyclopropane Derivatives

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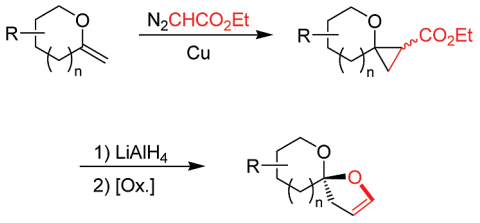

Exocyclic enol ethers served as starting materials for the synthesis of [*n*,5]-spiroketals (n = 5, 6). A metal-mediated cyclopropanation using ethyl diazoacetate afforded spiroannelated cyclopropane derivatives bearing an ester group. A reduction of the corresponding ester by $LiAlH_4$, followed by subsequent oxidation using hypervalent iodine reagents, produced [*n*,5]-spiroketals in moderate to good yields. The key step within this three-step sequence is the ring enlargement of the three-membered ring with an oxygen donor and a carbonyl acceptor group into the five-membered enol ether system. Catalytic amounts of the Lewis acid $Yb(OTf)_3$ facilitate the ring enlargement and increase the yield of the corresponding spiroketal in many cases. When $Yb(OTf)_3$ was used, our experiments revealed an open transition state rather than a concerted mechanism because the stereochemistry of the spirocenter was not conserved during the ring enlargement. As a result, the thermodynamically more favored anomeric [*n*,5]-spiroketal was observed as the major product. All the structures were established unambiguously by NOESY experiments.

Introduction

The semirigid spiroketal moiety forms a characteristic architectural feature in a plethora of simple as well as complex natural products including insect pheromones and marine and fungal toxins.[1] A number of different ring arrangements are observed in Nature; however the most abundant are [6,6]-, [6,5]-, and [5,5]-spiroketals. The conformational and geometric features of these frameworks have rendered spiroketals as preferred targets in diversity-oriented synthesis.[2]

The classical route for the preparation of the spiroketal motif is the Brønsted or Lewis acid mediated dehydrative spirocyclization[3] of the corresponding oxo diol **1** (Scheme 1). This rather flexible method that can afford different ring sizes is a thermodynamically driven process and commonly results in a diaxial spiroketal arrangement **3**. In such an arrangement two anomeric effects are in operation leading to a significant net energy stabilization.[4] However, in the case of acid-labile compounds (e.g., enol ethers) or in the case the less thermodynamically stable isomer is required, this methodology commonly fails.

Accordingly, other spiroketal syntheses have attracted considerable interest, and numerous elegant methods have

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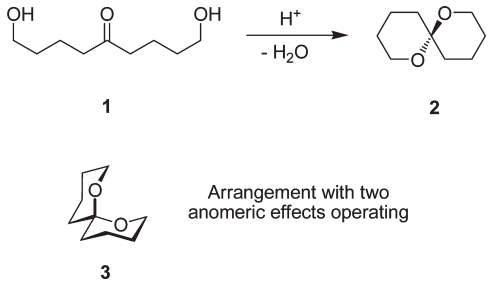
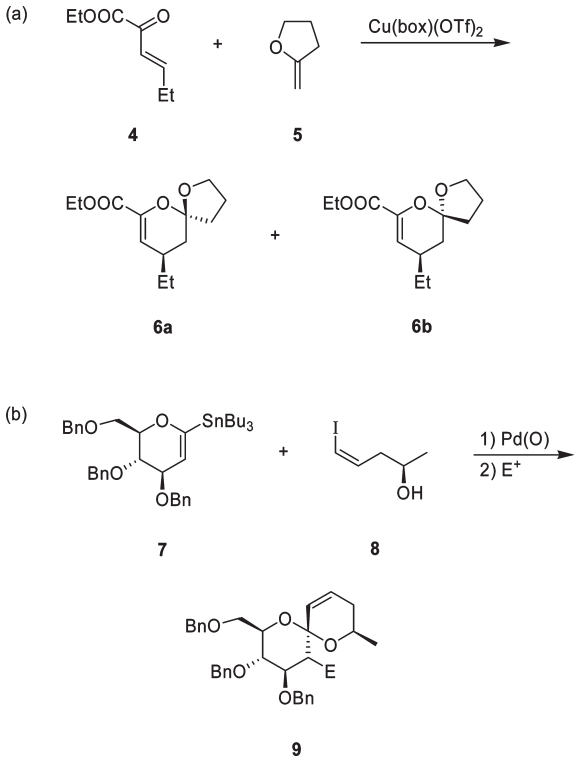
SCHEME 1. Dehydrative Spirocyclization of Oxo Diol 1 as the Classical Route to Spiroketals 2 (top) and the Most Favored Conformation 3 of a [6,6]-Spiroketal (bottom)



been developed.[5−7] The most popular approaches include hetero-Diels−Alder reactions (e.g., in the synthesis of **6a/6b**),[1f,8] acetylide anion additions to lactones,[9] and the use of organometallic reactions such as metathesis[10] or Pd-catalyzed cross-coupling reactions (e.g., for the preparation of **9**).[11] Two examples are illustrated in Scheme 2.

Herein, we report a novel methodology for the construction of [*n*,5]-spiroketals of type **10** ($n = 5, 6$) based on the unique properties of donor-acceptor-substituted three-membered rings.[12] The general idea of the retrosynthesis is depicted in Scheme 3. The key step involves the ring enlargement of a spiroannelated donor-acceptor-substituted cyclopropane derivative **11** that is easily accessible via the cyclopropanation of exocyclic enol ethers of type **13**. Ring

SCHEME 2. Diels−Alder (a) and Stille Approach (b) for the Synthesis of Spiroketals 6a/6b and 9, Respectively



openings and ring enlargements of cyclopropane derivatives bearing an electron-withdrawing and an electron-donating substituent have been intensively investigated[12−16] and have also been used in a variety of natural product syntheses.[12a,17] However, to the best of our knowledge donor-acceptor-substituted cyclopropanes have only rarely been used for spiroketal synthesis.[18]

Results and Discussion

As precursors for the formation of the spiroannelated cyclopropyl derivatives we prepared a series of five- and six-membered exocyclic enol ethers of type **13**. Whereas

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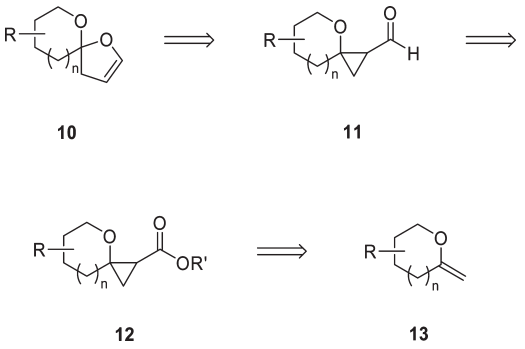
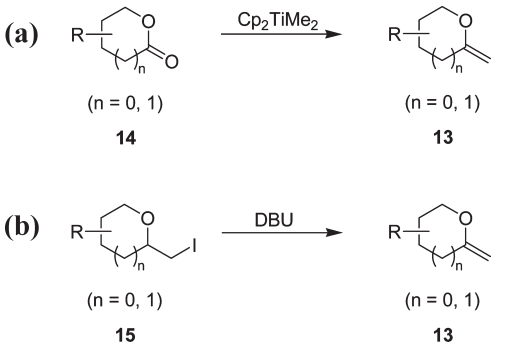
SCHEME 3. Retrosynthesis of [*n*,5]-Spiroketals 10 Using Exocyclic Enol Ethers 13 as Starting Materials



unsubstituted six-membered exocyclic enol ethers tend to rearrange to the endocyclic isomers, the five-membered counterparts are more stable in their exocyclic form. Because of this fact and a deeper interest in facile carbohydrate modification in our group,[19] mainly exocyclic glycals that are easily available by several routes were used for our methodological studies of the proposed sequence.[20] Either the corresponding fully protected lactones of type **14** were reacted with Petasis reagent,[21] or we eliminated HI from the exocyclic iodomethyl group next to the oxygen center in **15** by the action of DBU (Scheme 4).[20f] A high degree of substitution renders the six-membered cycles relatively stable in their exocyclic glycal form.

Exocyclic glycals of type **13** were treated with an excess of ethyl diazoacetate under rhodium or copper catalysis to afford the spiro-annelated cyclopropane derivatives of type **12** that were commonly obtained as a mixture of several (up to four) different stereoisomers (Table 2).[22] Figure 1 provides an assignment **a**−**d** for the different stereoisomers. In our cases, the best results for the cyclopropanation reaction were achieved by using elemental copper powder in hot toluene; the use of copper(I) catalysts such as Cu(OTf) generated in situ from $Cu(OTf)_2$ and phenyl hydrazine or the use of $Rh_2(OAc)_4$ at room temperature afforded lower yields. The resulting cyclopropyl esters **12a**−**12d** were reduced with $LiAlH_4$ in THF furnishing the corresponding

SCHEME 4. Two Ways To Generate Exocyclic Enol Ethers 13: (a) Petasis Olefination of Lactones 14, (b) Elimination of HI of Corresponding Primary Iodides 15



alcohols **16a**−**16d** in good to quantitative yield (for the assignment of the respective stereoisomers, see Figure 1).

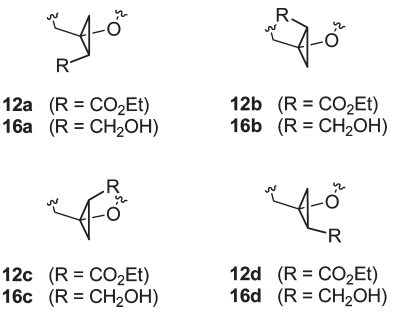


FIGURE 1. Assignment of the different stereoisomers of the cyclopropyl esters **12a**−**12d** and the corresponding alcohols **16a**−**16d**, respectively.

The generation of the donor-acceptor-substituted cyclopropane in **11** (by oxidation of the hydroxy methyl group of **16**) has to be performed in such a way that the oxidizing agent does not attack the newly generated enol ether system of **10** that is also prone to oxidation. Previous experiments in our group concerning the annelation of tetrahydrofuran units by performing a similar sequence using IBX as an oxidizing agent revealed an instantaneous ring enlargement of the three-membered to the five-membered ring; cyclopropanes bearing an aldehyde functionality were not observed.[16] In contrast to these results, the investigations with respect to spiroketal formation did not reveal such a clear-cut preference for the ring enlargement to the five-membered spiro compound when just IBX was used as an oxidizing agent. Therefore spirocyclopropyl derivative **19b** was chosen as a model compound to investigate a variety of different oxidation methods and conditions in order to optimize the transformation of **19b** to spiroketal **20** (Table 1). The Swern reaction afforded only traces of the desired spiroketal, whereas slightly better results were obtained when hypervalent iodine reagents such as Dess−Martin periodinane (DMP) or IBX, respectively, were employed. Hence, our attention focused toward the use of IBX in combination with different Lewis acids. It turned out that the choice of the Lewis acid is of utmost importance to increase the yield of the desired transformation. Whereas hard Lewis acids such as $Ti(O\textit{i}\text{-}Pr)_4$ and $SnCl_4$ lead only to traces of product (Table 2, entries 5 and 6) and Lewis acids

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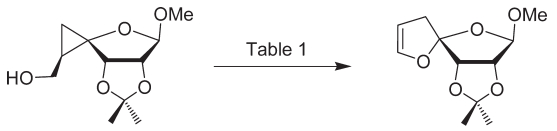
TABLE 1. Different Oxidations Methods/Conditions and Additives for the Conversion of the Cyclopropane Derivative 19b into the [5,5]-Spiroketal 20



19b **20**

Entry	Conditions	Additives[a]	Yield [%]
1	$(COCl)_2$ (1.1 equiv), DMSO (2.2 equiv), NEt_3 (4.0 equiv), −78 °C, CH_2Cl_2, 30 min		5
2	DMP (1.2 equiv), CH2Cl2, rt, 2 h		22
3	IBX (1.2 equiv), DMSO, rt, 12 h		15
4	IBX (1.2 equiv), DMSO, rt, 8 h		26
5	IBX (1.2 equiv), DMSO, rt, 8 h	$Ti(O\textit{i}\text{-}Pr)_4$	-[b]
6	IBX (1.2 equiv), DMSO, rt, 8 h	$SnCl_4$	-[c]
7	IBX (1.2 equiv), DMSO, rt, 8 h	$BF_3 \cdot OEt_2$	15
8	IBX (1.2 equiv), DMSO, rt, 8 h	$MgCl_2$	18
9	IBX (1.2 equiv), DMSO, rt, 8 h	$ZnCl_2$	44
10	IBX (1.2 equiv), DMSO, rt, 8 h	$Yb(OTf)_3$	55
11	IBX (2.0 equiv), DMSO, rt, 8 h	$Yb(OTf)_3$	53
12	IBX (1.2 equiv), DMSO, 60 °C, 8 h	$Yb(OTf)_3$	24

[a]0.1 equiv of additive was used. [b]Traces of the product were observed. [c]Complete decomposition.

such as $BF_3 \cdot OEt_2$ and $MgCl_2$ have almost no influence on the reaction outcome (Table 2, entries 7 and 8), soft Lewis acids such as $ZnCl_2$ and $Yb(OTf)_3$ increase the yield to 44% and 55%, respectively (Table 1, entries 9 and 10). A larger excess of IBX did not result in better yield. Higher reaction temperatures led to worse results than those when performing the reaction at room temperature (Table 2, entries 11 and 12). We assume that the action of a Lewis acid is necessary in order to weaken the bond between the electron-donating and the electron-withdrawing substituent in the three-membered ring. However, after the ring enlargement the Lewis acid must not be allowed to attack the newly generated enol ether system. Thus, a successful outcome of the reaction results essentially as a compromise of two effects: an effective weakening of the push−pull-substituted bond in the three-membered ring by coordinating the in situ generated aldehyde moiety and the ability not to attack the enol ether system after its generation. Therefore, the kind of Lewis acid that has been added as a catalyst is crucial.

With a reliable procedure in our hands we examined the spiroketal formation of other cyclopropanated carbohydrate derivatives. As starting materials we used the exocyclic enol ether systems depicted in Table 2. Our choice comprises five- and six-membered exocyclic enol ethers as well as different protecting groups for hydroxyl functionalities such as isopropylidene, cyclohexylidene, and benzyl ethers. Also two examples of non-carbohydrate-derived enol ethers were chosen (entries 8 and 9). For all educts **13** cyclopropanation led to a mixture of cyclopropyl derivatives **12a**−**12d** that were reduced by $LiAlH_4$ to the corresponding alcohols **16a**−**16d**. In the case of enol ether **21** we observed a highly substrate-controlled product formation because one of the two faces of the double bond is shielded by bulky substituents. However, in general we were not interested in controlling the facial selectivity.[23] For an examination of the suggested sequence different stereoisomers were welcome. In some cases the product mixtures, either as ester or as alcohol, could be easily separated by silica gel column chromatography; in other cases a separation even by HPLC proved to be almost impossible.

We had a high degree of optimism that the ring enlargement reaction to afford the spiroketal would lead, even with mixtures of cyclopropyl derivatives, to one major product. We assumed that the push−pull-substituted three-membered ring generated in situ rearranges into the five-membered ring via an open-chain intermediate rather than via a concerted mechanism. The tendency to form such an open chain should even be greater when coordinating compounds are used such as Lewis acids. If the latter scenario were true, one would observe a product distribution of the corresponding spiroketals solely determined by the relative thermodynamic stability of the products.

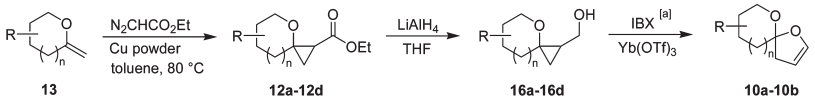
The ring enlargement reactions gave moderate to good yields of the corresponding spiroketals. In several cases trace amounts of the highly unstable donor-acceptor-substituted cyclopropane derivatives bearing aldehyde moieties could be found as side products. Entry 9 reveals that conjugation of the oxygen donor to an aromatic cycle does not destroy its ability to act as a donor in the push−pull system.

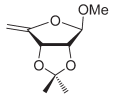
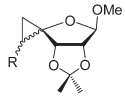
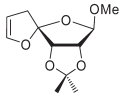
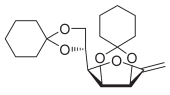
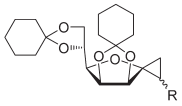
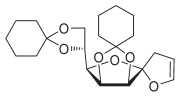
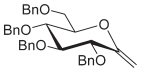
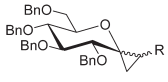
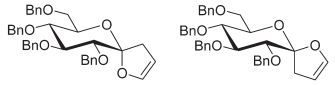
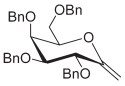
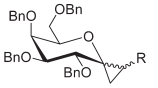
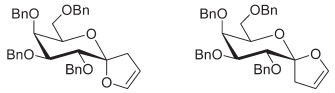
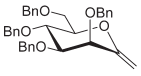
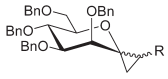
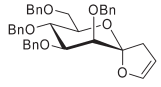
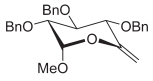
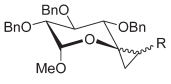
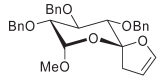
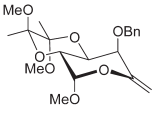
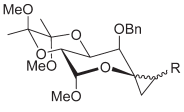
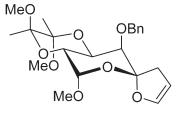
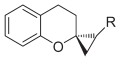
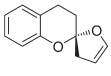
Our investigations of different diastereomers revealed that the configuration of the spirocenter is not conserved during the transformation when only IBX or IBX in the presence of $Yb(OTf)_3$ was used as oxidizing agent. As previously assumed, the creation of the thermodynamically more stable spiroketal is favored. Mechanistically, these results suggest that a concerted mechanism does not take place or only takes place to a minor extent (Scheme 5, left), whereas the main reaction pathway leads via a zwitterionic intermediate such as the open-chain compound **54** (Scheme 5, right). In the latter case, the stereochemistry at the spirocenter is not conserved. All four cyclopropyl stereoisomers would afford the same product or the same product ratio of spiroketals, respectively. To our surprise, a different outcome was observed when Dess−Martin periodinane was utilized to perform the ring enlargement. In general, the yields obtained with DMP were rather poor (see also Table 1); however, in two cases (entries 4 and 6) better results were obtained. As exemplified by entry 6, the oxidation of cyclopropyl derivative **39d** afforded only the less thermodynamically stable spiroketal without anomeric effect in operation. Such an outcome is only plausible if a concerted[24] rather than a zwitterionic mechanism takes place when DMP is employed. In contrast to the oxidation by IBX, different ratios of spiroketals **28a/28b** and **32a/32b**, respectively, were obtained when Dess−Martin periodinane was used. Whereas the 5:1 ratio of the corresponding spiroketals achieved by the action of IBX does not mirror the distribution of the starting material, the 2:1 ratio (after the oxidation using Dess−Martin periodinane) is similar to it. Experiments to equilibrate the different stereoisomeric spiroketals under the reaction conditions or with exposure to $Yb(OTf)_3$ were in vain.

(23) To the best of our knowledge, the highly diastereoselective cyclopropanation of exocyclic enol ethers is an unsolved problem. Initial experiments using bisoxazoline ligands did not reveal significant preferences for distinct stereoisomers.

(24) A concerted mechanism for the rearrangement of a vinylcyclopropylcarbaldehyde to afford a five-membered enol ether was discussed by DFT calculations: Sperling, D.; Reissig, H.-U.; Fabian, J. *Eur. J. Org. Chem.* **1999**, 1107–1114.

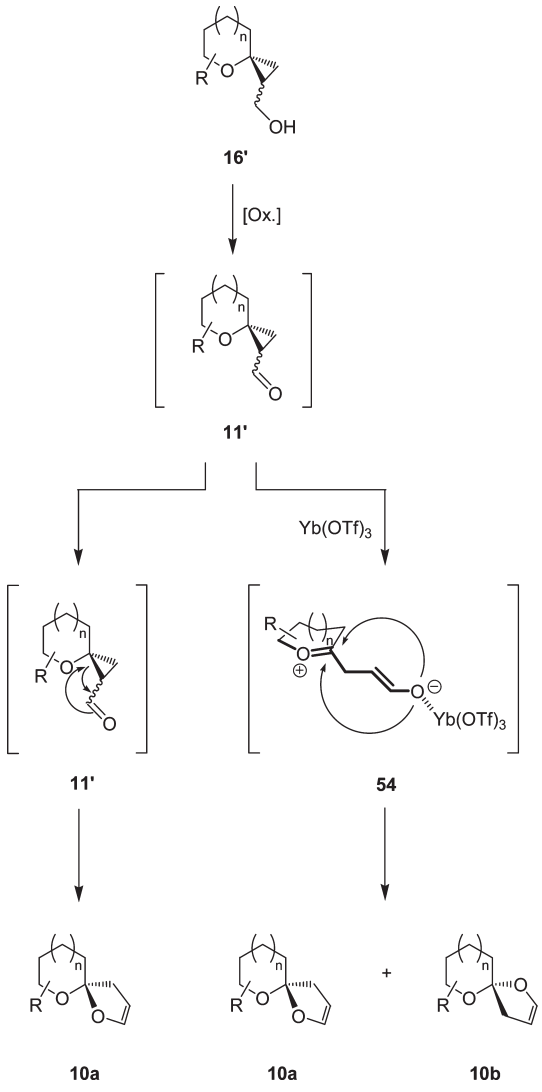
TABLE 2. Oxidative Spiroketal Formation



Entry	Enol Ether	Cyclopropyl Derivative[a]	[*n*,5]-Spiroketal	Yield [%][b]
1	 **17** [20n]	 **18a-18d** (R = CO_2Et) 83% **19a-19d** (R = CH_2OH) 81%	 **20**	55[c, f]
2	 **21** [20o]	 **22a-22b** (R = CO_2Et) 95% **23a-23b** (R = CH_2OH) 76%	 **24**	49[c, g]
3	 **25** [22]	 **26a-26d** (R = CO_2Et) 97% **27a-27d** (R = CH_2OH) 86%	 **28a** 5 : 1 **28b**	32[c, h, m]
4	 **29** [22]	 **30a-30d** (R = CO_2Et) 69% **31a-31d** (R = CH_2OH) 86%	 **32a** 5 : 1 **32b**	72[e, h, m]
5	 **33** [22]	 **34a-34d** (R = CO_2Et) 84% **35a-35d** (R = CH_2OH) 95%	 **36**	26[d, i]
6	 **37** [20p]	 **38a-38d** (R = CO_2Et) 70% **39a-39d** (R = CH_2OH) 94%	 **40**	87[e, j]
7	 **41** [20q]	 **42a-42c** (R = CO_2Et) **43a-43c** (R = CH_2OH) 31% (over 2 steps)	 **44**	35[c, k]
8	 **45** [20m]	 **46a-46b** (R = CO_2Et) **47a-47b** (R = CH_2OH) 38% (over 2 steps)	 **48**	35[d, l, n]
9	 **49** [20r]	 **50** (R = CO_2Et) 57% **51** (R = CH_2OH) 51%	 **52**	69[d, n]

[a]Combined yield for the different stereoisomers; the first value gives the yield of the cyclopropanation reaction; the second the yield of the reduction. For detailed information on cyclopropanation yields and product distribution, as well as yields of reduction, see Supporting Information. [b]Yield of spiroketal formation (see also Supporting Information for details). [c]IBX (1.2 equiv), $Yb(OTf)_3$ (0.1 equiv), DMSO, rt, 8 h. [d]IBX (1.2 equiv), DMSO, rt, 8 h. [e]Dess−Martin periodinane (1.1 equiv), CH_2Cl_2, rt, 12 h. [f]**19b** was oxidized. [g]**23a** and **23b** were oxidized as a mixture and separately with the same yield. [h]A mixture of all four diastereomers was oxidized. [i]**35a** was oxidized. [j]**39a** as well as **39d** was oxidized with the same yield. [k]**43c** was oxidized; there was a poorer yield with **43d**. [l]**47a** and **47b** were oxidized separately with the same yield. [m]5:1 ratio (**a**:**b**) when IBX was used, 2:1 ratio (**a**:**b**) when Dess−Martin periodinane was used. [n]Obtained as racemic mixture of both enantiomers.

SCHEME 5. Potential Mechanism of Spiroketal Formation via a Concerted Mechanism (left) and an Open-Chain Intermediate 54 (right)



The identity of all diastereomers was unequivocally determined by extensive 2D-NMR spectroscopic techniques as well as NOESY investigations. The major NOE correlation effects for the determination of the configuration at the spirocenter of spiroketals is exemplarily depicted in Figure 2 for **28a** and **28b**. In the case of **28b** we found a strong NOE correlation between H-2 and one hydrogen of the methylene unit in the five-membered ring, whereas such NOE correlation could not be observed in the case of the other diastereomer **28a**, but for H-3.

For three of the cyclopropane derivatives, the ester **38d** and the alcohols **43b** and **51**, we were able to grow single crystals suitable for X-ray crystallography to elucidate their molecular structures[25,26] and to confirm the stereochemistry at the spirocenter also assigned by NOESY investigations. Two structures are depicted in Figure 3. An elucidation of the geometrical properties within the cyclopropane moiety shows an almost perpendicular arrangement (74.4°) of the ester group to the plane of the three-membered ring. Such a behavior is suggested by the Walsh model of cyclopropane.[27] Also the bond lengths are in accordance with this model: the shortest bond (1.488 Å compared to 1.523 and 1.508 Å) is found opposite to the electron-withdrawing ester group. The longest bond (1.523 Å) is located between the donor- and the acceptor-substituted carbon atoms. As anticipated by the Walsh model, such geometrical features were not observed for the cyclopropyl alcohols **43** and **51** bearing the hydroxy methyl instead of the ester moiety.

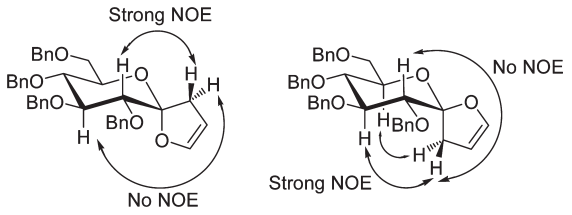


FIGURE 2. Most important NOE effects for determination of stereochemistry of **28a** (left) and **28b** (right).

Finally, we subjected the benzyl-protected [6,5]-spiroketals **28**, **32**, **36**, and **40** to hydrogenolysis using Pearlman's catalyst (Table 3). Cleavage of all benzyl groups and the reduction of the enol ether double bond was achieved, affording the fully deprotected spiroketals **57a**−**60** in very good to quantitative yield.

A proper analysis of the ^{13}C NMR spectra of protected and deprotected [6,5]-spiroketals revealed an interesting tendency of the chemical shift of the spiro carbon atom. All spiroketals that are anomerically favored (in our nomenclature in Table 4 assigned as **a**) showed a lower-frequency resonance than the corresponding stereoisomers that are not stabilized by the anomeric affect (assigned in Table 4 as **b**).[4] In general, we found resonance frequencies of 109−111 ppm when anomeric effects are operating and resonance frequencies of 111−112 ppm without this effect in operation. We assume that this slight difference in chemical shift may be attributed to the $n_p(O) \rightarrow \sigma^*(C-O)$ interaction that increases the electron density around the spiro carbon atom, whereas such an interaction cannot take place in the other anomer. As a result of the increased electron density the spiro carbon atoms are more shielded. This observation, which has also been demonstrated in recent literature,[28] may be also useful for the elucidation of the stereochemistry of unknown spiroketal structures and may give a further indication of their geometrical feature besides extensive spectroscopic investigations such as NOE spectroscopy.

(25) The diffractometer was equipped with a molybdenum microsource. Diffraction data also allowed an invariom refinement using the XDLSM program, which led to significant improvements in the figures of merit, bond lengths, and the physical significance of the anisotropic displacement parameters (ADPs). For the method of invariom refinement, see: (a) Dittrich, B.; Koritsánszky, T.; Luger, P. *Angew. Chem.* **2004**, *116*, 2773–2776. *Angew. Chem., Int. Ed.* **2004**, *43*, 2718−2721. (b) Dittrich, B.; Hübschle, C. B.; Messerschmidt, M.; Kalinowski, R.; Girnt, D.; Luger, P. *Acta Crystallogr.* **2005**, *A61*, 314–320.

(26) For the XDLSM program see: Koritsánszky, T.; Richter, T.; Macchi, P.; Volkov, A.; Gatti, C.; Howard, S.; Mallinson, P. R.; Farrugia, L.; Su, Z.; Hansen, N. K. *XD—A Computer Program Package for Multipole Refinement and Analysis of Electron Densities from Diffraction Data* (*Handbook*), Freie Universität: Berlin, 2003.

(27) (a) Walsh, A. D. *Nature* (*London*) **1947**, *159*, 712–713. (b) Sugden, T. M. *Nature* (*London*) **1947**, *160*, 367–368. (c) Walsh, A. D. *Trans. Faraday Soc.* **1949**, *45*, 179–190.

(28) (a) Pothier, N.; Goldstein, S.; Deslongchamps, P. *Helv. Chim. Acta* **1992**, *75*, 604–620. (b) Zanatta, S. D.; White, J. M.; Rizzacasa, M. A. *Org. Lett.* **2004**, *6*, 1041–1044. (c) de Oliveira, L. G.; Dias, L. C.; Sakauchi, H.; Kiyota, H. *Tetrahedron Lett.* **2006**, *47*, 2413–2418.

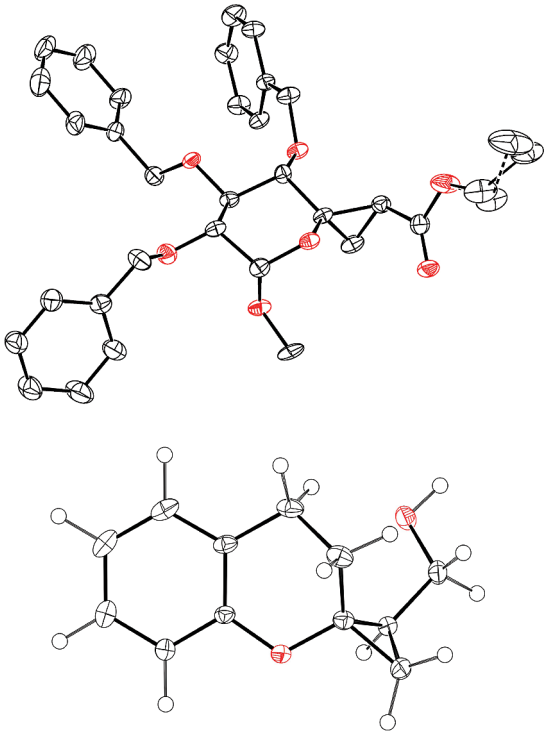


FIGURE 3. ORTEP plots (50% ellipsoid probability) of the molecular structures of **38d** (top) and **51** (bottom). Oxygen atoms are shown in red. In the case of **38d** hydrogen atoms are omitted for the sake of clarity.

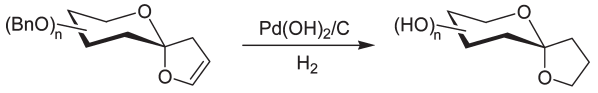
Conclusions

In summary, we have developed a concise and original method for the formation of [*n*,5]-spiroketals ($n = 5, 6$). The key step of the synthetic sequence is the ring enlargement of donor-acceptor-substituted cyclopropane derivatives into five-membered enol ether systems. Starting materials are easily available exocyclic enol ethers that are converted by a sequence of cyclopropanation using ethyl diazoacetate and subsequent reduction with $LiAlH_4$ into the corresponding alcohols. The hydroxy functionality was oxidized by hypervalent iodine reagents to the cyclopropyl aldehyde that underwent ring enlargement to the desired compounds. In most cases best results were achieved by the use of IBX. The soft Lewis acid $Yb(OTf)_3$ proved to be a useful additive to increase the yield of the desired transformation. In general, stereoisomeric mixtures of cyclopropyl derivatives could be employed because of a zwitterionic mechanism leading to the corresponding products via an open-chain intermediate. Surprisingly, the use of Dess−Martin periodinane conserved the stereochemistry of the spirocenter during the transformation. This method for spiroketal formation proves to be an elegant way to access [*n*,5]-spiroketals with an enol ether double bond in the five-membered ring that are difficult to obtain by common methods of spiroketal formation. The versatility of our three-step approach has been demonstrated by the preparation of several monosaccharide-derived spiroketals.

Experimental Section

Formation of the Cyclopropyl Ester 18a−18d. Compound **17**[20n] (1.57 g, 8.43 mmol, 1.0 equiv) was dissolved in anhydrous toluene (12 mL). Cu powder (0.269 g, 4.22 mmol, 0.5 equiv) was added and heated to 70 °C. Over a period of 12 h a solution of ethyl diazoacetate (4.29 g, 35.9 mmol, 4.0 equiv) in anhydrous toluene (10 mL) was added via syringe pump. After completed addition, the solution was stirred for 30 min at 70 °C.

TABLE 3. Hydrogenolysis of Protected [6,5]-Spiroketals of Type 55 To Afford Deprotected Spiroketals of Type 56



55 **56**

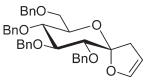
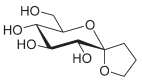
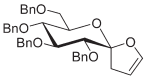
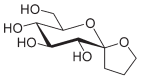
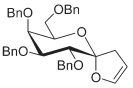
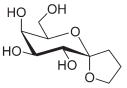
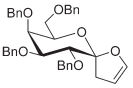
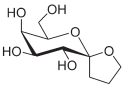
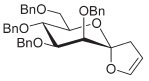
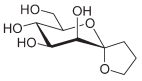
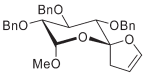
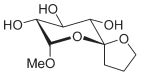
Entry	Protected [6,5]-Spiroketal	Deprotected [6,5]-Spiroketal	Yield [%]
1	 **28a**	 **57a**	quant.
2	 **28b**	 **57b**	quant.
3	 **32a**	 **58a**	99
4	 **32b**	 **58b**	99
5	 **36**	 **59**	95
6	 **40**	 **60**	91

TABLE 4. Comparison of the Chemical Shift of Spiro Carbon Atom $\delta(C_{spiro})$ [ppm] in [6,5]-Spiroketals with and without Anomeric Stabilization

Spiroketal	$\delta(C_{spiro})$ With Anomeric Stabilization (**a**)	$\delta(C_{spiro})$ Without Anomeric Stabilization (**b**)
28[a]	109.1	111.4
32[a]	109.3	112.0
36[a]	109.7	-
40[a]	109.6	111.9
44[a]	110.9	-
57[b]	108.9	111.1
58[b]	109.3	111.8
59[b]	109.3	-
60[b]	-	111.9

[a]Relative to $\delta(CDCl_3) = 77.0$ ppm; measured in $CDCl_3$. [b]Relative to $\delta(CD_3OD) = 49.2$ ppm; measured in CD_3OD.

Evaporation of the solvent and purification by column chromatography (SiO_2, pentane/EtOAc, 5:1) afforded four diastereoisomers **18a**−**18d** as colorless oils with an overall yield of 1.90 g (83%). HPLC (hexane/isopropyl alcohol 98:2, 3 mL/min) afforded pure samples of **18c** and **18d**.

Analytical Data of Mixture of 18a and 18b. Yield: 54%. R_f: 0.30 (hexane/EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, J = 7.1 Hz, 3.6 H), 1.47−1.55 (m, 2.4 H), 1.89 (dd, J = 9.5, 7.3 Hz, 1 H), 2.15 (dd, J = 9.4, 6.8 Hz, 0.2 H), 3.28 (s, 0.6 H), 3.31 (s, 3 H), 4.03−4.23 (m, 2.6 H), 4.56 (d, J = 5.9 Hz, 1 H), 4.62 (d, J = 5.9 Hz, 0.2 H), 4.70 (d, J = 5.9 Hz, 0.2 H), 4.77 (d, J = 5.9 Hz, 1 H), 4.91 (s, 0.2 H), 4.94 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.2, 13.2, 14.2, 14.4, 20.1, 20.9, 25.5, 25.7, 26.4, 26.5, 26.9, 54.9, 55.0, 60.7, 60.8, 72.2, 73.0, 79.0, 82.0, 84.8, 107.8, 107.9, 112.4, 112.5, 170.8, 171.1. IR (film): $\tilde{\nu}$ (cm^{-1}) = 2986, 2939, 2836, 1722, 1447, 1383. UV (CH_3CN): λ_{max} [nm] (log ε) = no absorption in the range of 190−350 nm. HRMS (ESI): m/z calcd for $C_{13}H_{20}O_6Na$: 295.11521; found 295.11521.

Analytical Data of 18c. Yield: 16%. R_f: 0.18 (hexane/EtOAc, 5:1). [α] = 107.5° (c 0.20, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.18 (dd, J = 9.2, 5.9 Hz, 1 H), 1.24 (t, J = 7.2 Hz, 3 H), 1.32 (s, 3 H), 1.46 (s, 3 H), 1.66 (dd, J = 7.0, 5.9 Hz, 1 H), 2.08 (dd, J = 9.1, 7.0 Hz, 1 H), 3.33 (s, 3 H), 4.18 (q, J = 7.2 Hz, 2 H), 4.38 (d, J = 5.8 Hz, 1 H), 4.62 (d, J = 5.8 Hz, 1 H), 5.00 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3, 19.1, 20.5, 26.1, 26.6, 54.8, 60.8, 71.6, 83.7, 84.7, 107.4, 113.1, 169.3. IR (film): $\tilde{\nu}$ (cm^{-1}) = 2986, 2836, 1736, 1449, 1384, 1330. UV (CH_3CN): λ_{max} [nm] (log ε) = no absorption in the range of 190−350 nm. HPLC: t_R (hexane/isopropyl alcohol 98:2, 3 mL/min) = 12.2 min. HRMS (ESI): m/z calcd for $C_{13}H_{20}O_6Na$: 295.1152; found 295.1158.

Analytical Data of 18d. Yield: 13%. R_f: 0.18 (hexane/EtOAc, 5:1). [α] = 90.0° (c 0.22, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.26 (t, J = 6.9 Hz, 3 H), 1.30 (s, 3 H), 1.37 (dd, J = 8.6, 6.3 Hz, 1 H), 1.47 (s, 3 H), 1.78−1.89 (m, 2 H), 3.20 (s, 3 H), 4.01−4.23 (m, 2 H), 4.40 (d, J = 6.0 Hz, 1 H), 4.63 (d, J = 6.0 Hz, 1 H), 4.95 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.6, 14.4, 25.7, 26.4, 27.2, 55.7, 60.6, 72.9, 84.3, 84.7, 108.8, 112.9, 169.1. IR (film): $\tilde{\nu}$ (cm^{-1}) = 2985, 2938, 2838, 1731, 1455, 1402, 1383. UV (CH_3CN): λ_{max} [nm] (log ε) = no absorption in the range of 190−350 nm. HPLC: t_R (hexane/isopropyl alcohol 98:2, 3 mL/min) = 13.3 min. HRMS (ESI): m/z calcd for $C_{13}H_{20}O_6Na$: 295.1152; found 295.1163.

Formation of the Cyclopropyl Alcohols 19a and 19b. To a solution of $LiAlH_4$ (0.045 g, 1.2 mmol, 1.2 equiv) in dry THF (8 mL) was slowly added a solution of a mixture of **18a** and **18b** (0.27 g, 0.99 mmol, 1.0 equiv) in dry THF (5 mL), and the mixture was stirred at room temperature for 2 h. The reaction was stopped by addition of MeOH. Evaporation of the solvent and purification by column chromatography (SiO_2, pentane/EtOAc, 2:1) afforded **19a** and **19b** as colorless oils with an overall yield of (0.184 g, 81%).

Analytical Data of 19a. Yield: 66%. R_f: 0.18 (hexane/EtOAc, 2:1). [α] = 19.0° (c 0.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.78 (t, J = 7.0 Hz, 1 H), 1.22 (dd, J = 10.0, 6.9 Hz, 1 H), 1.32 (s, 3 H), 1.35−1.46 (m, 1 H), 1.49 (s, 3 H), 1.65 (bs, 1 H), 3.21 (t, J = 10.6 Hz, 1 H), 3.32 (s, 3 H), 3.90 (dd, J = 11.3, 5.7 Hz, 1 H), 4.57 (d, J = 5.9 Hz, 1 H), 4.66 (d, J = 5.9 Hz, 1 H), 4.91 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 9.9, 25.4, 26.3, 26.4, 55.0, 62.9, 69.2, 79.9, 85.3, 107.4, 112.4. IR (film): $\tilde{\nu}$ (cm^{-1}) = 3435, 2935, 1729, 1454, 1373. UV (CH_3CN): λ_{max} [nm] (log ε) = 228.5 (3.482). HRMS (ESI): m/z calcd for $C_{11}H_{18}O_5Na$: 253.1046; found 253.1045.

Analytical Data of 19b. Yield: 15%. R_f: 0.28 (hexane/EtOAc, 2:1). [α] = −37.9° (c 0.39, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.63 (t, J = 6.5 Hz, 1 H), 0.95 (dd, J = 10.1, 6.0 Hz, 1 H), 1.31 (s, 3 H), 1.52 (s, 3 H), 1.67−1.77 (m, 1 H), 2.99−3.16 (m, 2 H), 3.27 (s, 3 H), 3.98 (dt, J = 12.0, 5.1 Hz, 1 H), 4.59 (d, J = 6.0 Hz, 1 H), 4.70 (d, J = 6.0 Hz, 1 H), 4.91 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.8, 20.5, 25.0, 26.3, 54.8, 64.2, 70.1, 83.1, 85.6, 107.8, 112.6. IR (film): $\tilde{\nu}$ (cm^{-1}) = 3338, 2992, 1374, 1264. UV (CH_3CN): λ_{max} [nm] (log ε) = 194.0 (2.767). HRMS (ESI): m/z calcd for $C_{11}H_{18}O_5Na$: 253.10464; found 253.10459.

Formation of Spiroketal 20. A 10 mL flask was charged with a solution of **19b** (60 mg, 0.26 mmol, 1.0 equiv) in dry DMSO (3 mL). IBX (88 mg, 0.31 mmol, 1.2 equiv) and $Yb(OTf)_3$ (16 mg, 0.03 mmol, 0.1 equiv) were sequentially added, and the resulting mixture was stirred at room temperature for 8 h. The reaction was stopped by addition of water (5 mL). Et_2O (10 mL) was added, and the layers were separated. The water layer was extracted with Et_2O (3 × 5 mL), and the combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, filtrated, and concentrated in vacuo. Purification by column chromatography (SiO_2, pentane/Et_2O, 6:1) afforded **20** (33 mg, 55%) as a colorless oil: R_f: 0.30 (hexane/Et_2O, 6:1). [α] = 4.0° (c 1.05, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.29 (s, 3 H), 1.40 (s, 3 H), 2.54 (dt, J = 17.5, 2.4 Hz, 1 H), 3.06 (dt, J = 17.5, 2.5 Hz, 1 H), 3.35 (s, 3 H), 4.65 (d, J = 5.8 Hz, 1 H), 4.69 (d, J = 5.8 Hz, 1 H), 4.96 (dd, J = 5.3, 2.8 Hz, 1 H), 4.98 (s, 1 H), 6.27 (dt, J = 2.8, 2.0 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.2, 26.4, 35.5, 55.0, 84.1, 84.7, 99.5, 108.9, 112.6, 119.1, 143.3. IR (film): $\tilde{\nu}$ (cm^{-1}) = 2989, 1623, 1374, 1198. UV (CH_3CN): λ_{max} [nm] (log ε) = no absorption in the range of 190 − 350 nm. HRMS (ESI): m/z calcd for $C_{11}H_{16}O_5Na$: 251.08899; found 251.08904.

Hydrogenation and Deprotection of Spiroketal 28a To Afford 57a. To a solution of **28a** (32.0 mg, 0.055 mmol, 1.0 equiv) in a mixture of MeOH/CH_2Cl_2 (3:1, 3 mL) was added $Pd(OH)_2/C$ (Pearlman's catalyst, 25 mg). The reaction mixture was stirred under a hydrogen atmosphere of 1 bar for 16 h at room temperature. Filtration over Celite afforded **57a** (12.1 mg, quant) as a colorless solid: [α] = 58.1° (c 1.46, MeOH). ^{1}H NMR (300 MHz, CD_3OD): δ 1.79−2.23 (m, 4 H), 3.26−3.38 (m, 2 H), 3.53−3.67 (m, 3 H), 3.76 (dd, J = 11.5, 2.4 Hz, 1 H), 3.90−3.97 (m, 2 H). ^{13}C NMR (125 MHz, CD_3OD): δ 24.8, 34.6, 62.8, 69.4, 71.9, 74.1, 74.3, 76.6, 108.9. IR (film): $\tilde{\nu}$ (cm^{-1}) = 3423, 2933, 2509, 1647, 1441, 1195, 1165. UV (CH_3CN): λ_{max} [nm] (log ε) = no absorption in the range of 190−350 nm. HRMS (ESI): m/z calcd for $C_9H_{16}O_6Na$: 243.08391; found 243.08408.

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Supporting Information Available: Experimental procedures and analytical data for all new compounds. ^{1}H and ^{13}C NMR spectra of all new compounds. CIF files of **38d**, **43b**, and **51**.[29] This material is available free of charge via the Internet at http://pubs.acs.org.

(29) Cif files have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC-746262 (**38d**), CCDC-746263 (**43b**), and CCDC-746264 (**51**). Copies can be obtained via email: data_request@ccdc.cam.ac.uk.