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Asymmetric Synthesis of Spiroketal, Spiroether, and Oxabicycle Building Blocks via Stereoselective Spiro- and Bicycloannulation of 2-Hydroxy Dihydropyrans

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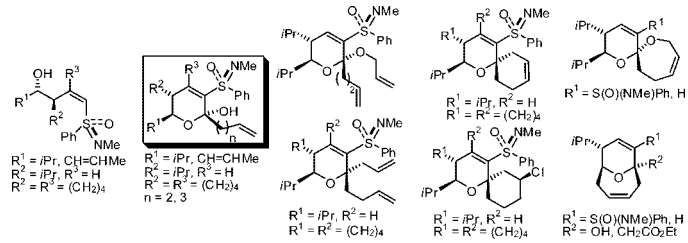
ABSTRACT



A modular asymmetric synthesis of spiroketal, spiroether, and oxabicycle building blocks is described based on the spiro- and bicycloannulation of α-hydroxy dihydropyrans, which were obtained from sulfoximine-substituted homoallylic alcohols. Key steps of the syntheses are stereoselective Ferrier-type O- and C-glycosidation, ring-closing metathesis, and stereoselective Prins cyclization.

The spiroketal structural motif is contained in a large number of natural products with diverse and interesting biological activities.[1] Because of the unremitting discovery of natural products of this type, the development of new methods for the asymmetric synthesis of spiroketal building blocks is a topic of current interest.[1,2] A promising but relatively little explored route to spiroketals is the spiroannulation of cyclic hemiacetals by the synthesis and ring-closing metathesis (RCM)[3] of the corresponding α,α-oxa-dienyl derivatives.[4] A particularly appealing aspect of this strategy is the possibility to also gain access to spiroethers by synthesis and RCM of the corresponding α,α-dienyl derivatives.[5] While the spiroether motif is found in a number of natural products, methods for the asymmetric synthesis of spiroether building blocks are scarce.[6] We describe in this paper a new modular asymmetric synthesis of highly substituted spiroketal and spiroether building blocks of type **I** and **II**, respectively, from the α-hydroxy pyrans **IX** (Scheme 1). Its key steps are the RCM of the sulfoximine-substituted α,α-oxa-dienyl and α,α-dienyl dihydropyrans **V** and **VI**, respectively, and their highly stereoselective synthesis through Ferrier-type glycosidation

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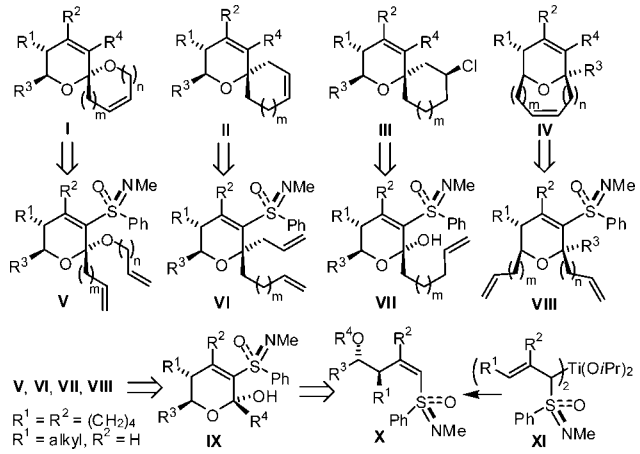
Scheme 1. Spiroketal, Spiroether, and Oxabicycle Building Blocks from α-Hydroxy Dihydropyrans

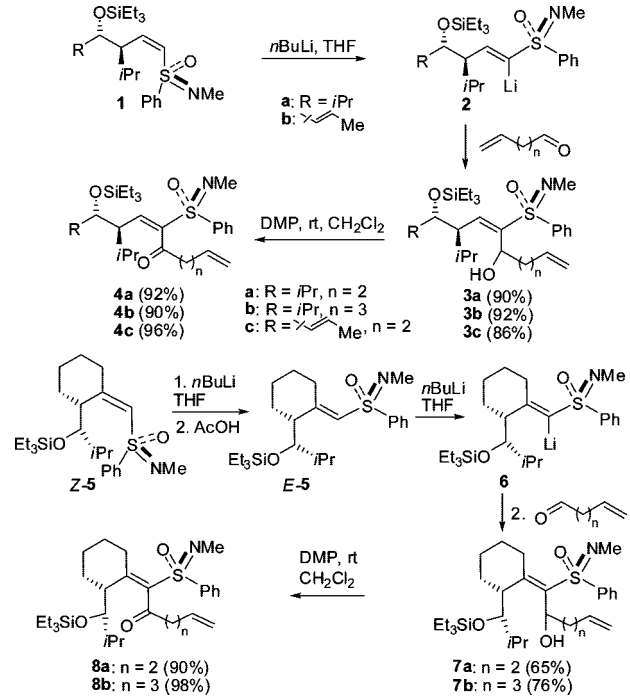


of **IX** with O- and C-nucleophiles. Pyrans **IX** in turn were synthesized in four steps from the enantio- and diastereopure mono- and bicyclic homoallylic alcohols **X**, which are readily available from the allyltitanium complexes **XI** and aldehydes.[7] The flexibility of the spiroannulation of **IX** is furthermore verified by the synthesis of Cl-substituted spiroethers of type **III** through a highly stereoselective Prins cyclization[8] of the α-hydroxy dihydropyrans **VII** that are also derived from **IX**. Although the Prins cyclization has already been used for the construction of spiroethers,[9] this type of an intramolecular trapping of a dihydropyranyl cation with the formation of a spiroether carrying a Cl atom at the carbocyclic ring is apparently unprecedented.[6b,8,10]

A final demonstration of the synthetic versatility of α-hydroxy dihydropyrans of type **IX** is provided by their α,α′-bicycloannulation through RCM of the corresponding α,α′-dienyl dihydropyrans **VIII**, which are also accessible from **IX**, with formation of the oxabicycle building block **IV**. While oxabicycles of type **IV** are found as core structures in natural products,[11,12] their asymmetric synthesis[12] by bicycloannulation using RCM has received only little attention.[13]

Lithiation of the enantio- and diastereopure *Z*-alkenyl sulfoximines **1a** and **1b**, which were obtained from the corresponding allyltitanium complexes **XI** and aldehydes,[7] with *n*BuLi at −78 to 0 °C, gave the *E*-configured α-lithioalkenyl sulfoximine **2a** and **2b**, respectively (Scheme 2).[7b,14] Treatment of **2a** and **2b** with pent-4-enal and hex-5-enal furnished the corresponding allylic alcohols **3a**−**c** as mixtures of diastereomers in 86−92% yield. Oxidation of alcohols **3a**−**c** with Dess-Martin periodinane (DMP) afforded the corresponding enones **4a**−**c** in 90−96% yield.

Scheme 2. Synthesis of Substituted δ-Hydroxy Enones



A similar route was followed for the synthesis of the cyclohexanoid enones **8a** and **8b**. Treatment of the enantio- and diastereopure *Z*-alkenyl sulfoximine *Z*-**5**, which was prepared from the corresponding allyltitanium complex **XI** and isobutyraldehyde,[7] with *n*BuLi at −78 to 0 °C followed by protonation gave the *E*-isomer *E*-**5** in practically quantitative yield. Lithiation of *E*-**5** furnished the *E*-configured α-lithioalkenyl sulfoximine **6** that upon reaction with pent-4-enal and hex-5-enal afforded the allylic alcohols **7a** and **7b**, respectively, as mixtures of epimers in good yield. The DMP oxidation of **7a** and **7b** gave the corresponding enones **8a** and **8b** in 90% and 98% yield, respectively.

With the enones **4a**−**c**, **8a**, and **8b** in hand, their deprotection/cyclization was investigated. Treatment of **4a**, **8a**, and **8b** with Bu_4NF in THF afforded the corresponding mono- and bicyclic α-hydroxy dihydropyrans **9a**, **10a**, and **10b** as single diastereomers in 80−90% yield (Scheme 3).[15] In the case of enones **4b** and **4c**, the application of an acid instead of Bu_4NF gave better results in terms of yields. Thus, treatment of **4b** and **4c**

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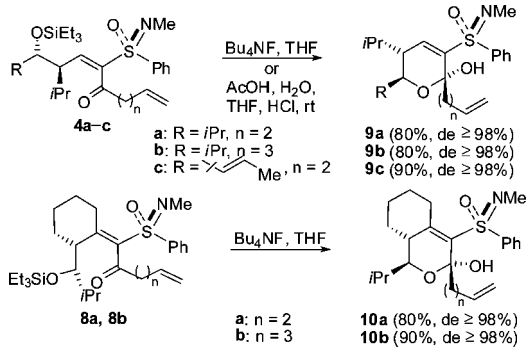
(15) The configurations of **9a**, **15**, **16**, **20**, **22**, **23**, and **24** at the newly created stereogenic center(s) established in the reactions starting from **4a**−**c** and **10b** were determined by ^1H NMR spectroscopy in combination with NOE experiments (Supporting Information), and those of **9b**, **9c**, **10a**, **10b**, **17**, and **25** were assigned by analogy based on their similar NMR data and mode of formation.

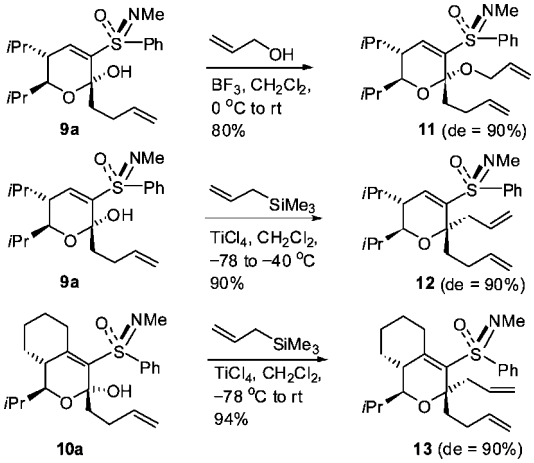
Scheme 3. Synthesis of α-Hydroxy Dihydropyrans



with HCl/AcOH/H_2O in THF furnished the corresponding α-hydroxy dihydropyrans **8b** and **9c** as single diastereomers in 80% and 90% yield, respectively.[15]

The synthesis of spiroketals and spiroethers of type **I** and **II**, respectively, from the corresponding mono- and bicyclic α-hydroxy dihydropyrans **9a**−**c** and **10a** required their stereoselective conversion to the corresponding α,α-dienyl derivatives **11**−**13** (Scheme 4). Thus, the unsaturated hemi-

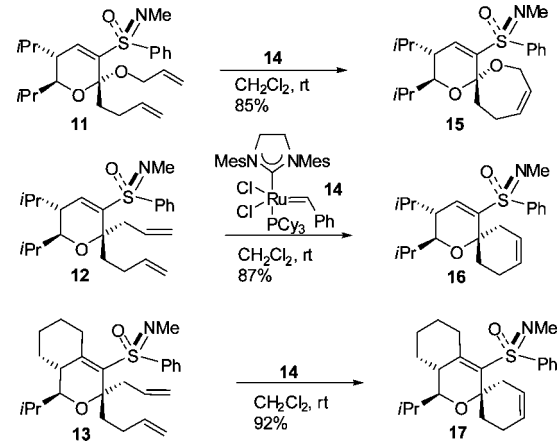
Scheme 4. Synthesis of α,α-Dienyl Dihydropyrans



acetal **9a** was treated with allyl alcohol in the presence of BF_3•Et_2O, which afforded the α,α-oxa-dienyl dihydropyran **11** with 90% de in 80% yield. The reaction of **9a** with allyltrimethylsilane in the presence of $TiCl_4$ furnished the α,α-dienyl dihydropyran **12** with 90% de in 90% yield. Similarly, the allylation of the bicyclic unsaturated hemiacetal **10a** afforded the bicyclic α,α-dienyl dihydropyran **13** with 90% de in 94% yield. Dienes **11**−**13** could be obtained in diastereopure form through column chromatography.

Gratifyingly, RCM of the oxa-dienyl dihydropyran **11** with 5 mol % of the ruthenium catalyst **14**[3b] in CH_2Cl_2 at room temperature gave spiroketal **15** in 85% yield (Scheme 5). A similar RCM of the dienyl dihydropyran **12** with **14** afforded spiroether **16** in 87% yield. The tricyclic spiroether **17** was

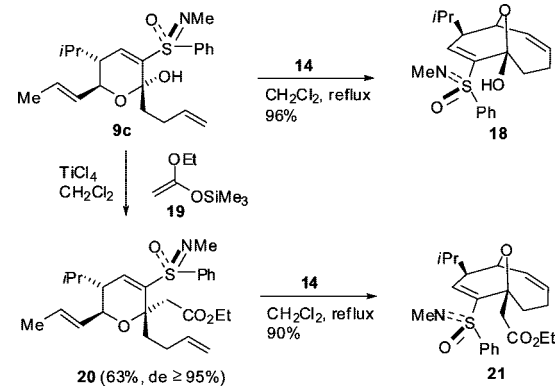
Scheme 5. Synthesis of Spiroketals and Spiroethers by RCM



isolated in 92% yield from the RCM reaction of the bicyclic dienyl derivative **13** with **14**.[15] It is noteworthy that the RCM reaction of **11**−**13** was not noticeably affected by the Lewis basic sulfoximine group being perhaps in close structural proximity to the Ru atom of intermediates of the catalytic cycle leading to **15**−**17**.[16]

Because of the high modularity of the synthesis of enones of type **4** and **8**, both α,α-dienyl dihydropyrans of type **V**−**VII** and α,α′-dienyl dihydropyrans of type **VIII** are easily accessible. Such dienyl dihydropyrans could give access to oxabicycles of type **IV**. Therefore, the α,α′-dienyl dihydropyran **9c** was subjected to a treatment with catalyst **14** in CH_2Cl_2 at reflux, which afforded oxabicycle **18** in 96% yield (Scheme 6). The

Scheme 6. Synthesis of Oxabicycles by RCM



possibility of a synthesis of a bridgehead-functionalized derivative of **18** was also investigated. Thus, reaction of the unsaturated hemiacetal **9c** with the ketene acetal **19** gave the α,α′-dienyl dihydropyran **20** with ≥95% de in 63% yield.[15] The RCM of **20** with **14** proceeded with high yield and furnished the bridgehead-substituted oxabicycle **21**.

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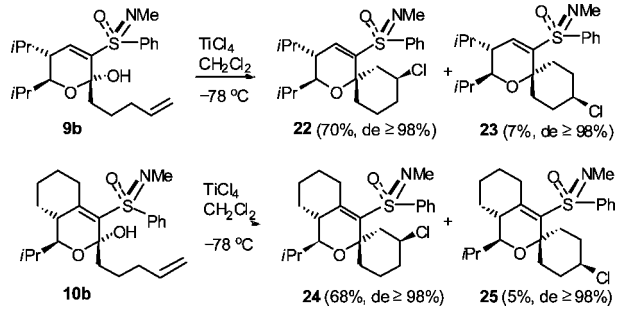
The facile synthesis of the α-hydroxy dihydropyrans **9b** and **10b** carrying a pent-4-enyl group at the Cα atom prompted a study of their Prins cyclization (Scheme 7).

Scheme 7. Synthesis of Spiroethers by Prins Cyclization



Treatment of **9b** with $TiCl_4$ in CH_2Cl_2 at −78 °C resulted in a cyclization and furnished with high diastereoselectivities the Cl-substituted spiroethers **22** and **23** in a ratio of 8:1 in a combined yield of 92%. Separation of **22** and **23** by chromatography afforded the spiroethers in 70% and 7% yield, respectively.[15] A similar cyclization of the bicyclic α-hydroxy dihydropyran **10b** also occurred with high diastereoselectivities and gave a mixture of the tricyclic Cl-substituted spiroethers **24** and **25** in a ratio of 8:1 in a combined yield of 84%. Separation of **24** and **25** by chromatography afforded the spiroethers in 68% and 5% yield, respectively.[15] It seems remarkable that both new stereocenters of **22**−**25** were established with high diastereoselectivities.

The high diastereoselectivity of the O- and C-glycosidation of **9a**−**c**, **10a**, and **10b** with formation of **11**−**13**, **20**, **22**, and **24**, respectively, is noteworthy. Its rationalization recognizes the intermediate allyloxy-carbenium ions **XII** as the most stable and reactive conformer (Figure 1). Inter- and

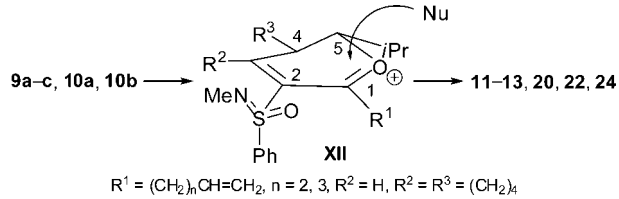
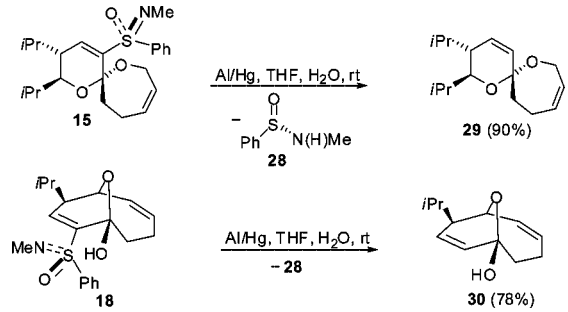


Figure 1. Model for the stereoselective glycosidation.

intramolecular attack of the O- and C-nucleophiles at C-1 of **XII** *anti* to the isopropyl group at C-5 should be favored. A similar stereochemical directing effect of the substituent at C-5 had also been observed in the O- and C-glycosidation of glycals.[17] Whether the sulfoximine group exerts an additional directing effect is yet unknown.

Because of the alkenyl sulfoximine moiety of **15**−**18**, and **21**−**24**, a number of useful synthetic transformations such as for example Michael addition, cross-coupling reaction, and reduction can be envisioned.[18] First, the reductive removal of the sulfoximine group was studied. Therefore, the spirocyclic alkenyl sulfoximine **15** was treated with Al/Hg in THF/H_2O, which afforded spiroketal **29** in 90% yield (Scheme 8). A similar reduction of the bicyclic alkenyl

Scheme 8. Reduction of Alkenyl Sulfoximines



sulfoximine **18** delivered oxabicycle **30** in 78% yield. In addition, the enantiopure sulfinamide **28** was obtained in good yield. The conversion of **28** into enantiopure (*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine, the starting material for the synthesis of **1** and **5**, has already been described.[19]

In summary, we have devised a modular asymmetric synthesis of the spiroketal, spiroether, and oxabicycle building blocks of type **I**−**IV** featuring stereoselective Ferrier-type glycosidation, RCM, and Prins reaction as key steps. Highly substituted derivatives of this type containing a removable electron-withdrawing group at the double bond are not easily available by existing methods. Because of the mode of the synthesis of **X**, derivatives of **I**−**IV** carrying groups R^1 and R^3 other than isopropyl should also be accessible.

Acknowledgment. Financial support of this work by the DFG (GK 440) is gratefully acknowledged.

Supporting Information Available: Experimental procedures, characterization data, and copies of NMR spectra for all new compounds, and NOE data of **9a**, **15**, **16**, **20**, **22**, **23**, and **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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