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Acetal−Vinyl Sulfide Cyclization on Sugar Substrates: Effect of Structure and Substituent

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A range of 2-deoxyfuranoside and -pyranoside derivatives were fashioned into derivatives that carry a vinyl or propenyl side chain. Extension of the alkene by a Suzuki cross-coupling reaction with 1-bromo-1-(phenylthio)ethene gave thioenol ethers as the cyclization substrates. The treatment of these substrates with $BF_3 \cdot Et_2O$ in *tert*-butylmethyl ether below 0 °C induced cyclization to optically active bicyclic ethers. If the cyclizations are carried out in toluene as the solvent, the isomerization of the terminal thioenol ether to the inner thioenol ether can take place prior to the cyclization. The cyclization reactions can be impeded by steric and electronic factors. The opening of the bicyclic ethers could be illustrated with the base-induced conversion of the ketone **53** to the cyclooctenone **54**.

Introduction

While less common in nature than bicyclic alkaloids, a range of natural products is known that feature oxabicyclo substructures. Examples include diterpenes such as sclerophytin A[1,2] and the eleutherobins.[3] Moreover, bicyclic ethers are used as synthetic intermediates for the synthesis of carbocyclic compounds with a distinct functional-group pattern. Among the bicyclic ethers, 8-oxabicyclo[3.2.1]octane derivatives are very easy to access by the [4 + 3] cycloaddition reactions of oxyallyl intermediates with furan.[4−6] In the latter case, the second carbon−carbon-bond formation usually corresponds to an attack of a nucleophile (enol ether or enolate) at a cyclic oxonium ion. Furthermore, [5 + 2] pyrone−alkene cycloaddition reactions provide access to such systems.[7−9] Another route is based on the annulation of bis-nucleophiles with suitable 1,4-dicarbonyl compounds.[10,11] In addition, transannular cyclization can provide access to bicyclic ethers.[12,13] We recently proposed an alternative strategy that utilizes acyclic hydroxyacetals containing C-nucleophilic groups as the substrates.[14] A tandem cyclization yielding initially a mixed acetal, followed by the generation of a cyclic oxonium ion and intramolecular trapping by the nucleophile, provides bicyclic oxacycles (Figure 1).

We could demonstrate this strategy in a stepwise fashion. Some isolated examples of this type of cyclization have been described in the literature.[15−19] Prior to our work, systematic studies have been carried out mainly by the Overman[20−24] and Rychnovsky[25] groups on the cyclization reactions of oxonium ions with nucleophiles directed at the formation of monocyclic ethers. An illustrative example of Overman's work is mentioned in

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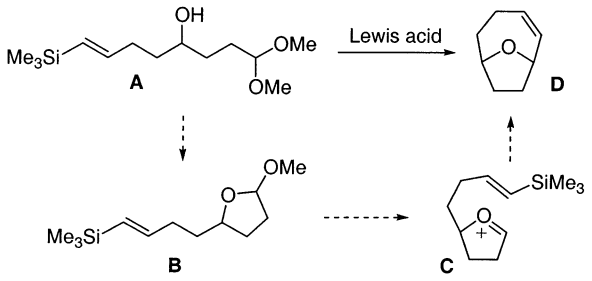


FIGURE 1. Tandem cyclization of hydroxyacetals containing a nucleophilic double bond.

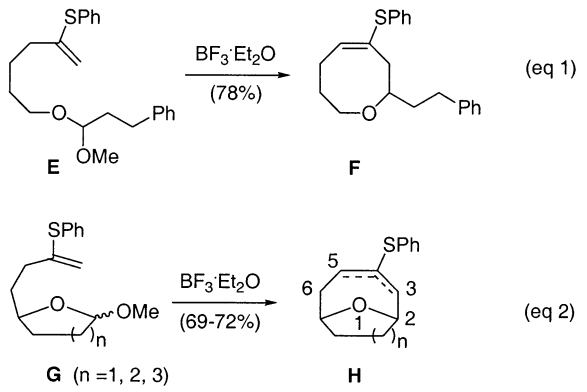


FIGURE 2. Representative examples for vinyl sulfide−oxonium ion cyclizations.

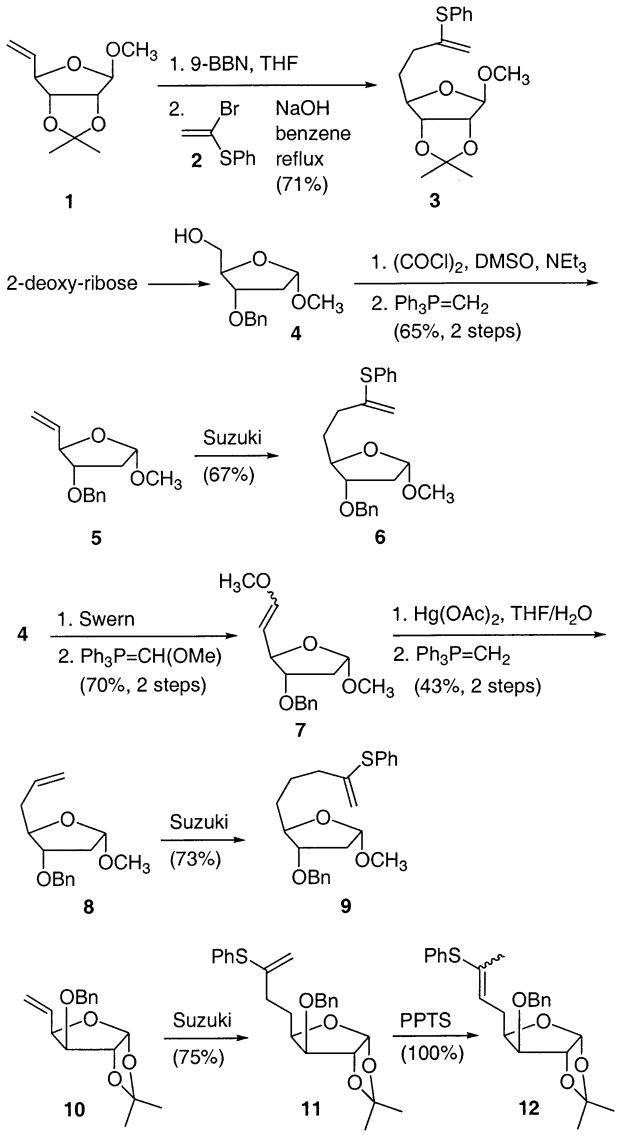
eq 1 (Figure 2). In the preparation of the substrates for the cyclization, the cyclic acetals served as the starting material whereby the nucleophilic group, usually a vinylsilane or thioenol ether, was introduced by a Suzuki cross-coupling reaction. In our earlier work, we described the intramolecular acetal−vinyl sulfide cyclization using five-, six-, and seven-membered oxonium ions (eq 2, Figure 2).[14] It was observed that the ring size of the cyclic oxonium ions plays an important role in the mechanism (ene vs Prins) of the cyclization process. The six-membered oxonium ion gave only the $^{\Delta}$4,5-bicyclic ether, whereas the seven-membered oxonium ion led mainly to the $^{\Delta}$3,4-bicyclic ether. In the case of five-membered oxonium ions, a mixture of two possible double-bond isomers was formed.

The advantage in our approach lies in the fact that it should be easy to prepare optically active substrates starting from carbohydrate precursors or by asymmetric synthesis. In this paper, we present studies that employ carbohydrate precursors with a vinyl sulfide as the nucleophile. In the course of these studies, some interesting effects of the stereocenters in the cyclic hemiacetals were observed.

Results and Discussion

Preparation of the Cyclization Substrates. For this study, a range of five- and six-membered sugars were used as starting materials. Considering the fact that an alkoxy group next to the acetal makes the formation of the oxonium ion more difficult, mainly 2-deoxyglycosides were used as starting materials. Further variations that were considered were different ring sizes (five- vs six-membered acetals), the length of the chain connecting

SCHEME 1. Synthesis of the Thioenol Ethers in the Furanoside Series



the acetals with the thioenol ether, and the configuration of the secondary alcohols in the starting sugar. All the vinyl sulfides described in the study were prepared by the Suzuki cross-coupling reaction of 1-bromo-1-(phenylthio)ethene[26] (**2**) with sugar-derived alkenes. Thus, the vinyl sulfide **3** was obtained from the alkene **1**, which in turn can be prepared from D-ribose (Scheme 1).[27] The Suzuki coupling was done under standard conditions.[21,28,29] Thus, the hydroboration of the alkene **1** with 9-BBN (1.2 equiv) in THF, followed by the addition of benzene and aqueous NaOH and the heating of the mixture in the presence of tetrakis(triphenylphosphine)palladium [$(Ph_3P)_4Pd$], furnished the vinyl sulfide **3** in good yield. The thioenol ethers can be chromatographed on silica gel, but they tend to hydrolyze to the corresponding methyl ketones in acidic solvents.

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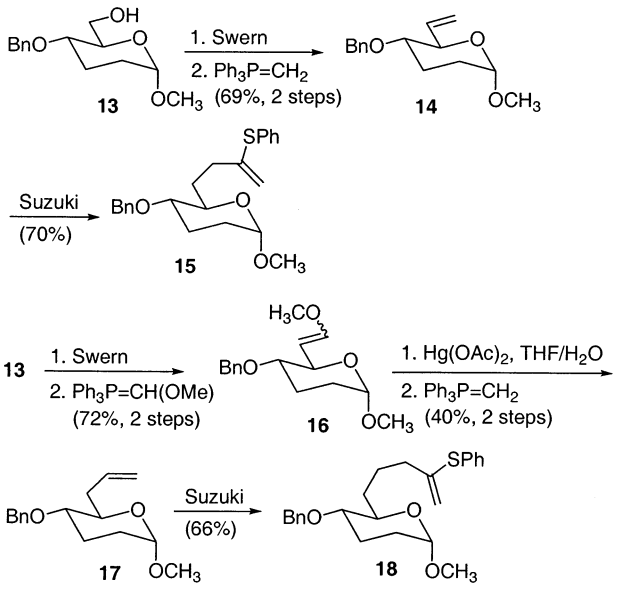
Likewise, the glycoside **4**, which is available from 2-deoxyribose,[30] was oxidized to the aldehyde using Swern conditions and subjected to a Wittig olefination, providing the vinyl derivative **5**. Chain extension by Suzuki coupling gave rise to the vinyl sulfide **6**. A classical one-carbon homologation of the primary alcohol by the Wittig reaction of the derived aldehyde with (methoxymethyl)triphenylphosphonium chloride−KO-*t*-Bu gave the enol ether **7** (*E*/*Z* 3:1).[31] The hydrolysis of **7** in the presence of mercuric acetate led to an aldehyde that was directly subjected to a Wittig olefination, providing the alkene **8**. As before, the Suzuki coupling of **8** with **2** via the intermediate borane delivered substrate **9**. As a final substrate in the furanoside series, the alkene **10**, which is available from diacetone−D-glucose,[32] was extended by Suzuki coupling to the vinyl sulfide **11**. In this context, it was discovered that catalytic amounts of pyridinium *p*-toluenesulfonate in CH_2Cl_2 induced the quantitative isomerization of the terminal vinyl sulfide to the internal isomer.

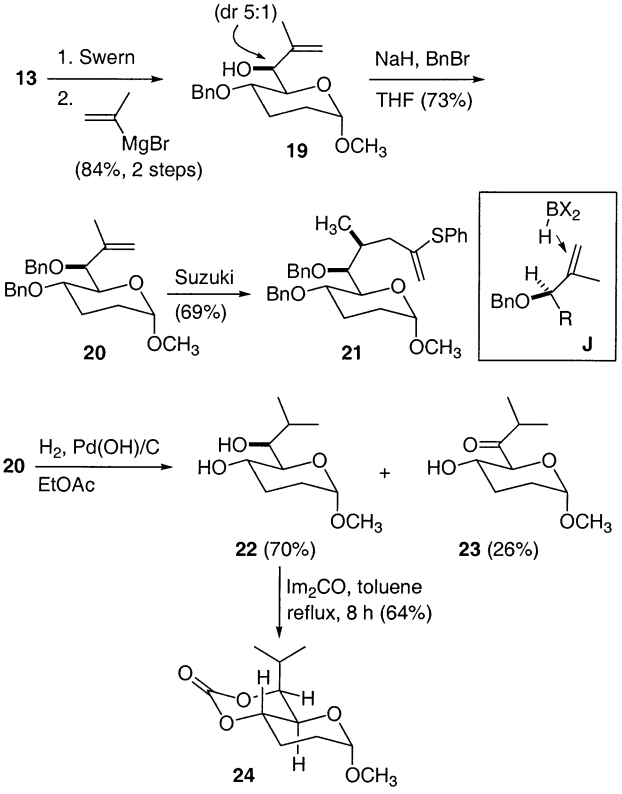
In the pyranoside series, the choice of substrates, on the one hand, was guided by the ease of availability. On the other hand, we sought to choose substrates with few enough stereocenters to allow for a clear-cut interpretation of the results in the cyclization reaction. Accordingly, the pyranosylmethyl alcohol **13**, available from 3,4,6-tri-*O*-acetyl-D-glucal,[33] was subjected to Swern oxidation and the Wittig reaction to afford the vinyl compound **14**. The synthesis continued with a Suzuki extension to deliver the vinyl sulfide **15**. As a related substrate in this series, the homologated vinyl sulfide **18** could be reached by the same strategy as that described for compound **9**. Thus, the conversion of the sugar alcohol to the enol ether **16** via the corresponding aldehyde, hydrolysis, and methylenation led to the allyl derivative **17**. The Suzuki reaction of **17** proceeded uneventfully and provided the thioenol ether **18** (Scheme 2).

Certainly, the outcome of the cyclization is dependent on substituents in the side chain connecting the nucleophile and the cyclic acetal. To gain insight into this issue, the aldehyde derived from the alcohol **13** was reacted with isopropenylmagnesium bromide in THF (0−23 °C), which gave the secondary alcohol **19** as the major product (dr = 5:1; Scheme 3). The protection of the alcohol with benzyl bromide and chromatography gave the diastereomerically pure alkene **20**. The subsequent hydroboration and Suzuki coupling delivered the vinyl sulfide **21** (dr = 12:1). The stereochemistry at C-2′ was assigned based on the Houk model for diastereoselective hydroboration.[34,35] According to this model, an alkyl group occupies the anti position because it can stabilize the transition state of the hydroboration. The alkoxy group will be in the outside position (see structure **J**, Scheme 3). While the stereochemistry at C-2′ was difficult to ascertain by

SCHEME 2. Synthesis of the Thioenol Ethers 15 and 18 of the Pyranoside Series



SCHEME 3. Synthesis of the Thioenol Ether 21 from the 2,3-Deoxyglucoside 13



spectroscopic means, the configuration at C-3′ could be inferred from the NMR data of the cyclic carbonate **24**. This compound was prepared by the hydrogenation of the benzyl ether **20** using palladium hydroxide on charcoal. Besides the alcohol **22**, some ketone **23** was also formed in this reaction. The ketone **23** is the major product even if the hydrogenation is carried out on the alcohol **19**. Treatment of the diol **22** with carbonyldiimidazole produced the carbonate **24**. As an indicator for the configuration in the side chain, H-5 of the sugar could be used.

(30) Giuliano, R. M.; Villani, F. J., Jr. *J. Org. Chem.* **1995**, *60*, 202−211.
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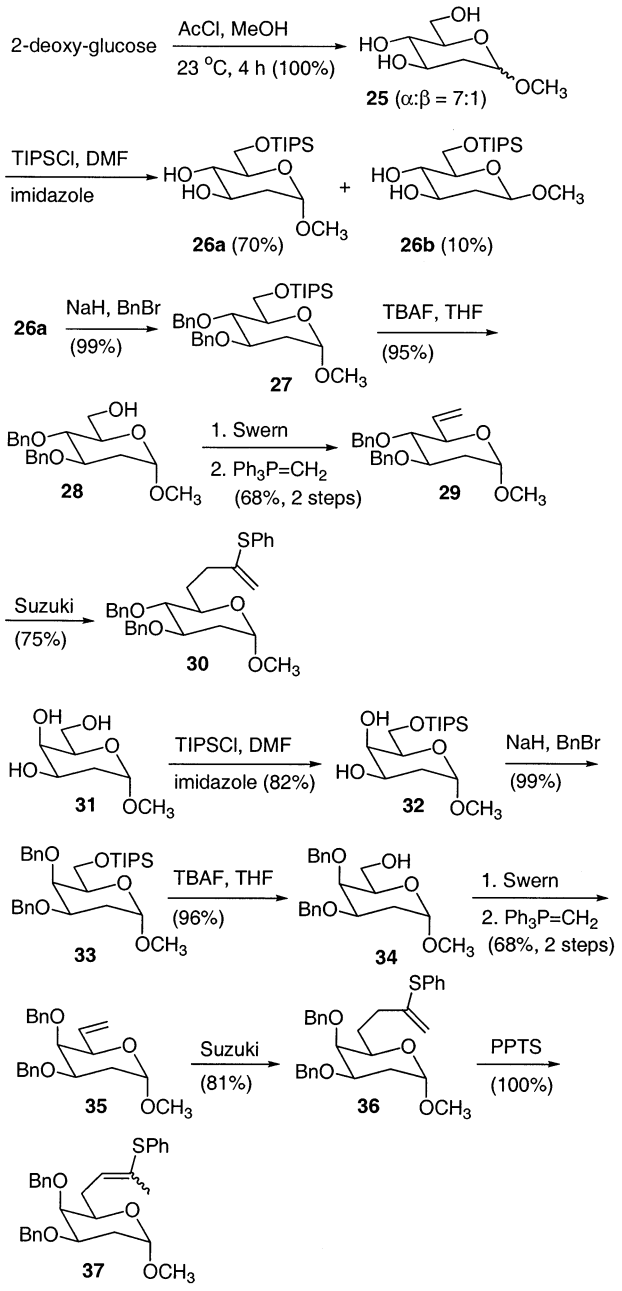
This proton appears as a doublet of doublets with coupling constants of 10.5 and 6.5 Hz, respectively, which is in agreement with a pseudoaxial position for the isopropyl group. The observed stereoselectivity is in accordance with the results observed on Grignard reactions on similar 2-deoxyglucopyranoside aldehydes.[36]

Further substrates were prepared from 2-deoxyglucose and 2-deoxygalactose. The methyl glucoside **25**[37,38] was obtained as mixture of α and β isomers (α/β 7:1) by the treatment of 2-deoxyglucose with AcCl−MeOH at room temperature. Selective protection of the primary hydroxyl group gave the anomeric TIPS ethers **26a** and **26b**, which could be separated by flash column chromatography. The major α anomer was benzylated and converted to the known primary alcohol **28**[39] by TBAF treatment. The oxidation of **28** to the aldehyde and Wittig methylenation provided the 2-methoxyvinyloxacycle **29**. The attachment of the thioenol ether moiety according to the Suzuki protocol made compound **30** available. Following the same sequence of reactions, α-methyl 2-deoxy-D-galactopyranoside[40] (**31**) was converted to the dibenzyl compound **33**. The removal of the TIPS protecting group, Swern oxidation, and Wittig reaction gave rise to the alkene **35**. To complete the synthesis of the cyclization substrate **36**, Suzuki coupling was utilized as before (Scheme 4).

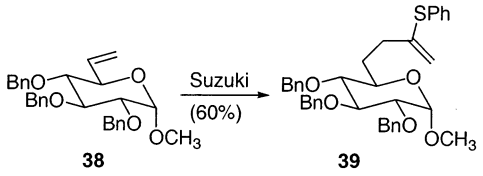
To complete the range of substrates, the glucoside **38**[41] was extended to the thioenol ether **39** via the standard Suzuki protocol. This substrate can be considered an extreme case because oxonium ion formation as well as ring flipping are disfavored in comparison to the other pyranoside substrates (Scheme 5).

Cyclization Reactions. As became evident in the course of these investigations, the oxacycles carrying a thioenol ether side chain can enter into several reaction channels. Thus, depending on the reaction conditions (Lewis acid, solvent, temperature) and the substrate, direct cyclization, isomerization, isomerization followed by cyclization, and also hydrolysis can take place. The cyclization reactions were carried out with a substrate concentration of 0.02 M in the required solvent. Using $SnCl_4$ in CH_2Cl_2 between −78 and 0 °C led to the decomposition of the starting material. Changing the promoter to TMSOTf resulted in hydrolysis to the corresponding ketone. The Lewis acid $BF_3{\cdot}Et_2O$ induced cyclization in various solvents (toluene, Et_2O, THF, CH_2Cl_2), but the reactions were most clean and proceeded with the highest yields in *t*-BuOMe. Thus, these acetal−vinyl sulfide cyclizations were best performed in *tert*-butylmethyl ether using borontrifluoride etherate ($BF_3{\cdot}Et_2O$, 2 equiv) as the Lewis acid. It is noteworthy that the isomerization of the terminal vinyl sulfide under these conditions is very slow below 0 °C. The results of the cyclization reactions are summarized in Table 1.

SCHEME 4. Synthesis of the Thioenol Ethers 30 and 36 from 2-Deoxyglycosides



SCHEME 5. Synthesis of the Thioenol Ethers 39 from the Alkene 38



The treatment of substrate **6** with $BF_3{\cdot}Et_2O$ (2 equiv) in *tert*-butylmethyl ether between −30 and 0 °C (standard conditions) gave a mixture of the $^{\Delta}$3,4- and $^{\Delta}$4,5-bicyclic ethers **40a** and **40b** (Figure 3). The homologue of **6**, vinyl sulfide **9**, cyclized selectively to the ene-type isomer **41**. The part containing the ether oxygen is an oxocene ring. Under the same conditions (−30 to 0 °C), the vinyl sulfide

(36) van Delft, F. L.; van der Marel, G. A.; van Boom, J. H. *Synlett* **1995**, 1069−1070.
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TABLE 1. Results of the Treatment of Various Thioenol Ethers with Lewis Acid

entry	substrate	conditions[a]	products/results
1	**6**	A	**40a**, **40b** (3.5:1, 71%)
2	**9**	A	**41** (51%)
3	**3**	A	no reaction
4	**3**	A[b]	**43** (100%)[c]
5	**3**	B	**42** (63%)
6	**11**	A	no reaction
7	**11**	C	**44** (38%)
8	**12**	C	**44** (42%)
9	**15**	A	**45** (70%)
10	**18**	A	**46** (48%)
11	**39**	A	no reaction
12	**39**	B	**47** (71%)
13	**21**	A	**48** (41%)
14	**30**	A	no reaction
15	**30**	C	**49** (2 isomers, 25%, 16%)
16	**36**	A	**50** (60%)[d]
17	**36**	C	**52a** (69%), **52b** (4%)
18	**37**	C	**52a** (70%)

[a] Conditions A: $BF_3{\cdot}Et_2O$ (2 equiv), *t*-BuOMe, −30 to 0 °C. Conditions B: TMSOTf (1.5 equiv), CH_2Cl_2, −78 to 0 °C. Conditions C: $BF_3{\cdot}Et_2O$ (2 equiv), toluene, −30 to 10 °C. [b] Conditions A with $BF_3{\cdot}Et_2O$ (6 equiv), *t*-BuOMe, 23 °C, 2 d. [c] Quantitative conversion by analyzing the crude reaction mixture. [d] A pure compound was not obtained, and the structure and yield (∼60%) were confirmed by converting **50** to the ketone **51** (Figure 3).

3 was recovered unchanged. Stirring the mixture for 2 d at room temperature with additional $BF_3{\cdot}Et_2O$ (6 equiv) induced complete isomerization to the internal vinyl sulfide **43**. Changing the promoter and the solvent [TMSOTf, 1.5 equiv; CH_2Cl_2, −78 to 0 °C] produced the known ketone **42**.[42] Thus, it can be concluded that compounds **3** and **43** are difficult to convert to the corresponding oxonium ions. The 1,2-di-*O*-isopropylidene substrate **11** also remained unchanged under the standard conditions. Changing the solvent to toluene resulted in the formation of the bicyclic ether **44**. The formation of this compound can be explained by invoking the cyclization of the internal vinyl sulfide **12** followed by a 1,2 shift of the thiophenyl group and the trapping of the more stable carbocation with water. The same product was obtained by subjecting the internal vinyl sulfide **12** to the same reaction conditions.

In line with the expectations, the 2,3-deoxypyranoside derivatives **15** and **18** could be induced to cyclize under standard conditions. While the yield for the formation of the seven-membered unsaturated ether **45** was reasonable (70%), the corresponding eight-membered ether **46** formed with less efficiency (48%). Both compounds correspond to the ene-type cyclization product. The substrate **39**, with three benzyloxy substituents in equatorial positions, could not be forced to cyclize. While the standard conditions left **39** unchanged, TMSOTf in CH_2Cl_2 (−78 to 0 °C) produced the methyl ketone **47**. With four equatorial substituents, the ring flipping that is required for cyclization is clearly strongly disfavored. Substrate **21**, which features two stereocenters in the nucleophilic side chain, also did not cyclize. Instead, the enol ether (glycal) **48** was isolated in 41% yield. This can be rationalized by looking at the prospective product. It features a gauche-type arrangement of the methyl and benzyloxy groups. Plus, there is an unfavorable *syn*-pentane-type interaction between the two alkoxy groups. Thus, while the oxonium ion is formed, the geometry that enables the cyclization cannot be reached.

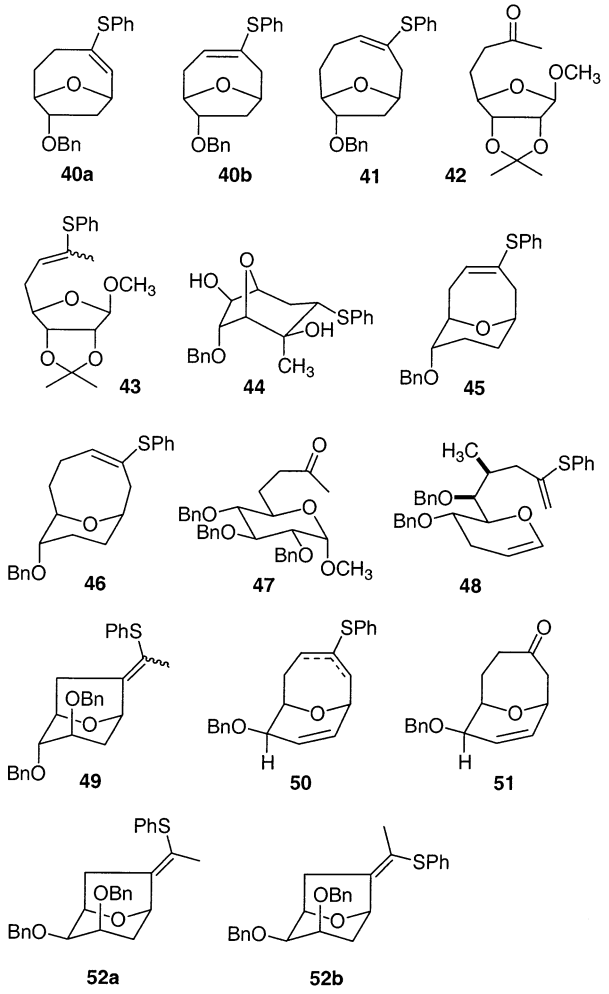


FIGURE 3. Structures of the compounds obtained in the cyclization reactions (for conditions, see Table 1).

In a substrate with benzyloxy groups at positions 3 and 4, cis- and trans-relative configurations are, in principle, possible. The 2-deoxyglucose-derived vinyl sulfide **30** should flip more easily than compound **39**. Furthermore, the oxonium ion should form faster. Nevertheless, the reaction of **30** under standard conditions left the starting material unchanged. However, when the solvent *tert*-butylmethyl ether was replaced by toluene, a solvent that favors isomerization of the thioenol ether, the oxabicyclo-[3.2.1]octane **49** was isolated as a mixture of double-bond isomers. As compared to **30**, the galactose-derived substrate **36** should be able to occupy the other chair conformation more easily because of the axial substituent at C-4. This is indeed reflected in the outcome of the cyclization experiments. Thus, **36** cyclized under the standard conditions to the bicyclic compound **50**. Because the Prins- and ene-type isomers could not be separated, the mixture was hydrolyzed to the ketone **51** with HCl in THF. The yield for the two steps amounted to 50%. Most likely, after the cyclization, the axial-positioned C-3 benzyloxy group is expelled by elimination. If the cyclization is run in toluene as the solvent, the cyclization is preceded by the isomerization of the thioenol ether. This

(42) Kim, K. S.; Szarek, W. A. *Carbohydr. Res.* **1982**, *100*, 169−176.

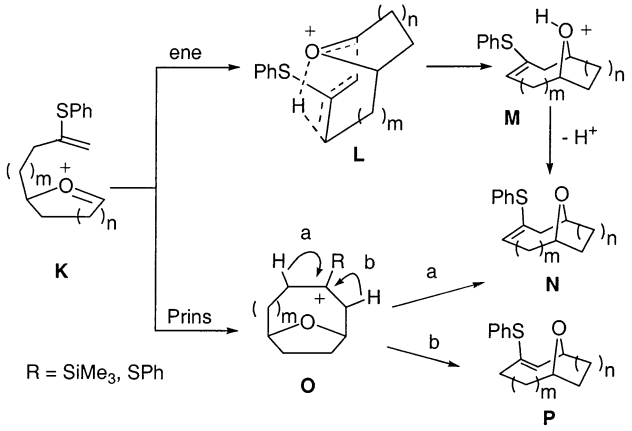
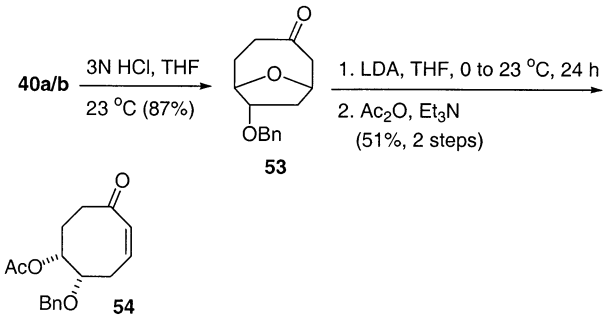


FIGURE 4. Mechanistic pathways (ene vs Prins) for the reaction of cyclic oxonium ions with vinyl sulfides.

SCHEME 6. Ring Opening of the Bicyclic Ketone under the Influence of LDA To Yield the Cyclooctenone 54



led mainly to the bicyclic ether **52a** together with a small amount of the isomer **52b**. Support for this came from the cyclization of the inner thioenol ether **37** to afford **52a** in 70% yield. The position of the Me group was confirmed by a NOESY spectrum of **52a**, which is characterized by the appearance of a strong cross-peak between H-5 and the methyl group.

On the basis of our previous and current experimental observations, it can be ascribed that both the existing and newly formed rings influence the cyclization pathway. If the steric and stereoelectronic factors fit the formation of a six-membered, cyclic, boatlike transition state L, the cyclization will proceed through the ene pathway; otherwise, the Prins pathway will prevail (Figure 4).

The utility of the bicyclic ethers was demonstrated by the base-induced ring opening of the ketone **53**, which is available in 71% yield from the alkenyl sulfides **40a** and **40b**. The treatment of **53** with LDA (3 equiv) in THF followed by the acetylation of the hydroxyl group with acetic anhydride gave rise to the optically active cyclooctenone **54** (Scheme 6). One of many applications for such compounds could be to utilize them as higher homologues of inositols and precursors to protein β-turn mimetics.[43] This method complements other methods for the synthesis of polyhydroxylated carbocycles such as the ring-closing metathesis strategy.[44,45]

Conclusion

Particularly, 2-deoxypyranoside derivatives are suitable substrates for vinyl sulfide−oxonium ion cyclizations. These kinds of cyclizations are best performed in *tert*-butylmethyl ether with $BF_3{\cdot}Et_2O$ as the promoter at temperatures below 0 °C. Under these conditions, the isomerization of the thioenol ether is repressed. The combination of $BF_3{\cdot}Et_2O$ in toluene promotes a relatively fast isomerization of the thioenol ether to the thermodynamically more stable isomer. These conditions are then recommended for the synthesis of the smaller bicyclic ether. In one instance, the chiral bicyclic ether (ketone **53**) was opened by base treatment to the cyclooctenone **54**. In general, the overall strategy is very concise and delivers the bicyclic compounds in good yields, provided that the steric and electronic situation in the substrate is suitable. On the basis of our study, appropriate substrates can now be easily identified.

Experimental Section

General Procedure for Suzuki Reaction. A stirred solution of the olefin (1 equiv) in THF (2 mL per 1 mmol) was treated with 9-BBN (0.5 M in THF, 1.2 equiv) at 0 °C under nitrogen. Stirring was continued at the same temperature for 1 h and then at room temperature for 3 h. The excess borane reagent was quenched with degassed water (1 equiv) and the mixture diluted with benzene (twice the total volume of THF). To the mixture were added an aqueous 3 N NaOH solution (4 equiv), $Pd(PPh_3)_3$ (3 mol %), and **2**[26] (1 equiv), and the reaction mixture was refluxed for 4 h. After cooling to room temperature, the organic layer was separated and the aqueous layer extracted with ether twice. The combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash chromatography (ethyl acetate−petroleum ether) afforded the desired vinyl sulfide.

General Procedure for Bicyclic Ether Formation. To a stirred solution of the acetal−vinyl sulfide derivative (0.02 M in *t*-BuOMe or toluene) was added $BF_3{\cdot}Et_2O$ (2.0 equiv) at −30 °C. After stirring for 1 h at the same temperature, the reaction mixture was slowly warmed to 0 °C (reaction in *t*-BuOMe) or 10 °C (reaction in toluene) over a period of 4 h and then quenched with an aqueous 2 N NaOH solution. The organic layer was separated and the aqueous layer extracted with dichloromethane twice. The combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo using a rotavapor. The crude products were subjected to flash chromatography (ethyl acetate−petroleum ether), yielding the bicyclic ethers.

(2*R*,3*S*,5*S*)-3-(Benzyloxy)-5-methoxy-2-vinyltetrahydrofuran (5). A solution of DMSO (0.9 mL, 12.9 mmol) in CH_2Cl_2 (5 mL) was added dropwise at −78 °C to a solution of oxalyl chloride (0.6 mL, 6.878 mmol) in CH_2Cl_2 (40 mL). After 5 min, a solution of **4** (1.36 g, 5.71 mmol) in CH_2Cl_2 (5 mL) was added dropwise to the reaction mixture. Stirring was continued for 20 min at −78 °C, before Et_3N (4.0 mL, 28.7 mmol) was added in a dropwise fashion. Thereafter, the reaction mixture was allowed to warm to 0 °C over a period of 3 h. The reaction mixture was quenched by the addition of water and diluted with ether (150 mL). The organic layer was separated and the aqueous layer extracted with additional ether (2 × 50 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated to give the crude aldehyde (1.27 g), which was immediately used in the next step without further purification. A solution of this

(43) Olson, G.; Voss, M. E.; Hill, D. E.; Kahn, M.; Madison, V. S.; Cook, C. M. *J. Am. Chem. Soc.* **1990**, *112*, 323−333.
(44) Hanna, I.; Ricard, L. *Org. Lett.* **2000**, *2*, 2651−2654.
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aldehyde in THF (5 mL) was added dropwise to a cold solution (−78 °C) of methylene(triphenyl)phosphorane (3 equiv) in THF [generated by the addition of *n*-BuLi (6.8 mL, 2.5 M solution in hexane, 17.0 mmol) to methyltriphenylphosphonium bromide (6.1 g, 17.1 mmol) and dissolution in THF (40 mL) at 0 °C, followed by stirring at 0 °C for 30 min and then at room temperature for 30 min]. The reaction mixture was stirred at −78 °C for 30 min and then allowed to warm to room temperature over a period of 4 h. Subsequently, the mixture was treated with acetone (10 mL) and stirred for 30 min. Sufficient ether (∼200 mL) was added and the mixture stirred for 1 h. The solid was filtered through a pad of Celite and washed with ether twice. The combined filtrate and washings were concentrated under vacuum, and the crude product was flash chromatographed using 10% ethyl acetate in petroleum ether to afford **5** (869 mg, 65% yield in two steps) as a colorless, thin liquid. $[\alpha]^{25}_{D}$: +103.6° (*c* 0.84, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26−7.16 (m, 10H), 5.74 (ddd, J = 6.5, 10.0, 17.0 Hz, 1H), 5.28 (ddd, J = 1.3, 1.3, 17.0 Hz, 1H), 5.10 (ddd, J = 1.3, 1.3, 10.0 Hz, 1H), 4.96 (dd, J = 1.7, 5.5 Hz, 1H), 4.47 (AB q, J = 12.4 Hz, $\Delta\nu$ = 8.3 Hz, 2H), 4.41 (br dd, J = 5.3, 6.6 Hz, 1H), 3.72 (ddd, J = 3.5, 5.0, 8.0 Hz, 1H), 3.16 (s, 3H), 2.20 (ddd, J = 5.5, 8.0, 14.0 Hz, 1H), 1.92 (ddd, J = 1.7, 3.8, 14.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 136.3, 128.3, 127.63, 127.57, 116.8, 104.6, 83.1, 81.7, 71.6, 55.1, 38.6. IR (neat): 2905, 1496, 1454, 1360, 1210, 1094, 1040 cm^{-1}. API-ES MS (90 V) *m*/*z* (%): 257 (27) $[M + Na]^+$, 203 (12) $[M - OMe]^+$, 185 (12), 167 (13), 159 (36), 131 (100), 91 (53). HRMS (FT-ICR): calcd for $C_{14}H_{18}O_3Na$, 257.1148; found, 257.1149.

(2*R*,3*S*,5*S*)-3-(Benzyloxy)-5-methoxy-2-[3-(phenylthio)-but-3-enyl]tetrahydrofuran (6). Following the general procedure for the Suzuki coupling, alkene **5** (525 mg, 2.24 mmol) was converted to compound **6** (556 mg, 67% yield), a pale yellow, viscous oil. $[\alpha]^{25}_{D}$: +92.5° (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50−7.28 (m, 10H), 5.23 (s, 1H), 5.01 (dd, J = 1.5, 5.5 Hz, 1H), 4.97 (s, 1H), 4.54 (AB q, J = 12.0 Hz, $\Delta\nu$ = 36.6 Hz, 2H), 4.07 (ddd, J = 5.0, 5.0, 8.0 Hz, 1H), 3.71 (ddd, J = 3.5, 5.0, 8.0 Hz, 1H), 3.40 (s, 3H), 2.48−2.32 (m, 2H), 2.26 (ddd, J = 5.5, 8.0, 14.0 Hz, 1H), 2.01 (ddd, J = 1.5, 3.5, 14.0 Hz, 1H), 1.97−1.89 (m, 1H), 1.83−1.74 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.1, 137.9, 133.0, 132.9, 129.0, 128.3, 127.7, 127.5, 113.2, 104.1, 81.5, 80.9, 71.5, 54.7, 38.7, 32.7, 32.5. IR (neat): 2912, 1583, 1476, 1454, 1439 cm^{-1}. EIMS *m*/*z* (%): 370 (3) $[M]^+$, 339 (5) $[M - OMe]^+$, 312 (11), 279 (14), 203 (17), 150 (100), 135 (23), 91 (76). HRMS (EI): calcd for $C_{22}H_{26}O_3S$, 370.1603; found, 370.1610.

Methyl (5*E*,*Z*)-3-*O*-Benzyl-2,5-dideoxy-6-*O*-methyl-α-D-*erythro*-hex-5-enofuranoside (7). A solution of DMSO (1.6 mL, 22.6 mmol) in CH_2Cl_2 (5 mL) was added dropwise at −78 °C to a solution of oxalyl chloride (1.0 mL, 11.5 mmol) in CH_2Cl_2 (50 mL). After 5 min, a solution of the alcohol **4** (2.40 g, 5.71 mmol) in CH_2Cl_2 (5 mL) was added dropwise to the reaction mixture. Stirring was continued for 20 min at −78 °C, before Et_3N (7.0 mL, 50.2 mmol) was added dropwise. Thereafter, the reaction mixture was allowed to warm to 0 °C over a period of 3 h. Workup was initiated by the addition of water and ether (200 mL). The organic layer was separated and the aqueous layer extracted with additional ether (2 × 75 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated to give the crude aldehyde (1.86 g), which was immediately used in the next step without further purification. In a different flask, (methoxymethyl)triphenylphosphonium chloride (10.36 g, 30.22 mmol) was suspended in THF (60 mL). The slurry was treated at 0 °C, in portions, with potassium *tert*-butoxide (2.26 g, 20.14 mmol) over a period of 15 min. After 1 h at 0 °C, a solution of the above crude aldehyde in THF (10 mL) was added dropwise to the ylide solution. After being stirred for 30 min at the same temperature, the mixture was treated with water and extracted with ether three times. The combined organic extracts were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated. Purification of the crude product by flash chromatography (using 20% ethyl acetate in petroleum ether) afforded the enol ether **7** (1.86 g, *E*/*Z* 3.5:1, 70% yield in two steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): (*E* isomer) δ 7.30−7.18 (m, 5H), 6.57 (d, J = 12.6 Hz, 1H), 4.91 (dd, J = 2.0, 5.8 Hz, 1H), 4.63 (dd, J = 9.0, 12.6 Hz, 1H, olefin), 4.48 (AB q, J = 12.4 Hz, $\Delta\nu$ = 10.7 Hz, 2H), 4.31 (dd, J = 5.8, 9.0 Hz, 1H), 3.75−3.68 (m, 1H), 3.48 (s, 3H), 3.32 (s, 3H), 2.31 (ddd, J = 5.8, 8.3, 14.0 Hz, 1H), 1.95−1.88 (ddd, J = 2.0, 4.5, 14.0 Hz, 1H); (*Z* isomer) δ 7.30−7.18 (m, 5H), 5.99 (br d, J = 6.3 Hz, 1H), 4.96−4.93 (m, 2H), 4.51 (AB q, J = 12.4 Hz, $\Delta\nu$ = 41.2 Hz, 2H), 4.34 (dd, J = 6.3, 9.0 Hz, 1H), 3.75−3.68 (m, 1H), 3.48 (s, 3H), 3.33 (s, 3H), 2.24 (ddd, J = 5.5, 8.0, 14.0 Hz, 1H), 1.95−1.88 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): (*E* isomer) δ 151.4, 138.0, 128.2, 127.6, 127.5, 103.8, 100.9, 82.4, 80.4, 71.7, 55.9, 55.0, 39.0; (*Z* isomer) δ 149.2, 138.3, 128.1, 127.6, 127.3, 104.9, 104.2, 82.4, 76.1, 71.2, 60.0, 54.9, 39.3. IR (neat): 2933, 1692, 1454, 1363, 1211 cm^{-1}. EIMS *m*/*z* (%): 264 (5) $[M]^+$, 232 (7) $[M - MeOH]^+$, 200 (17), 178 (67), 146 (28), 91 (100). HRMS (EI): calcd for $C_{15}H_{20}O_4$, 264.1361; found, 264.1352.

(2*R*,3*S*,5*S*)-2-Allyl-3-(benzyloxy)-5-methoxytetrahydrofuran (8). To a solution of **7** (1.31 g, 4.96 mmol) in a mixture of THF−H_2O (10:1, 60 mL) was added mercuric acetate (4.74 g, 14.87 mmol) at room temperature. After vigorous stirring for 1 h at the same temperature, a freshly prepared saturated aqueous KI solution (100 mL) was added to the mixture. After stirring for 20 min, the reaction mixture was extracted with ether three times. The combined extracts were washed with saturated KI solution, dried (Na_2SO_4), filtered, and concentrated with a rotavapor to give the crude aldehyde (870 mg) as a pale yellow viscous oil, which was used in the next step without further purification. A solution of this aldehyde in THF (5 mL) was added dropwise to a cold solution (−78 °C) of methylene(triphenyl)phosphorane in THF [generated by the treatment of *n*-BuLi (5.9 mL, 2.5 M solution in hexane, 14.75 mmol) to a solution of methyltriphenylphosphonium bromide (5.32 g, 14.89 mmol) in THF (40 mL) at 0 °C for 30 min and then at room temperature for 30 min]. The reaction mixture was stirred at −78 °C for 30 min and then warmed to room temperature over a period of 4 h. Then it was treated with acetone (10 mL) and stirred for 30 min. Sufficient ether (∼200 mL) was added, and it was stirred for 1 h. The solid was filtered through a pad of Celite and washed with ether twice. The combined filtrate and washings were concentrated under vacuum, and the crude product was flash chromatographed using 10% ethyl acetate in petroleum ether to afford **8** (529 mg, 43% yield in two steps) as a colorless, thin liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28−7.18 (m, 5H), 5.72 (dddd, J = 6.8, 6.8, 10.4, 17.2 Hz, 1H), 5.03−4.91 (m, 3H), 4.44 (AB q, J = 12.0 Hz, $\Delta\nu$ = 38.5 Hz, 2H), 4.05 (ddd, J = 5.8, 5.8, 5.8 Hz, 1H), 3.66 (ddd, J = 3.0, 4.8, 8.0 Hz, 1H), 3.30 (s, 3H), 2.80−2.17 (m, 2H), 2.12 (ddd, J = 5.6, 8.0, 14.0 Hz, 1H), 1.92 (ddd, J = 1.3, 3.0, 14.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.0, 134.0, 128.3, 127.8, 127.6, 117.3, 104.5, 81.5, 80.6, 71.6, 54.9, 38.6, 37.6. IR (neat): 2919, 1497, 1454, 1205, 1058 cm^{-1}.

(2*R*,3*S*,5*S*)-3-(Benzyloxy)-5-methoxy-2-[4-(phenylthio)-pent-4-enyl]tetrahydrofuran (9). Following the general procedure, alkene **8** (170 mg, 0.68 mmol) was extended to the vinyl sulfide **9** (192 mg, 73% yield), a pale yellow, viscous oil. $[\alpha]^{23}_{D}$: +89.2° (*c* 0.75, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32−7.27 (m, 2H), 7.22−7.13 (m, 8H), 5.02 (s, 1H), 4.86 (dd, J = 1.5, 5.5 Hz, 1H), 4.77 (s, 1H), 4.45 (A of AB q, J = 12.0 Hz, 1H), 4.35 (B of AB q, J = 12.0 Hz, 1H), 3.88 (ddd, J = 5.3, 5.3, 7.0 Hz, 1H), 3.56 (ddd, J = 3.5, 5.0, 8.0 Hz, 1H), 3.24 (s, 3H), 2.16−2.06 (m, 3H), 1.85 (ddd, J = 1.5, 3.0, 14.0 Hz, 1H), 1.58−1.33 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.5, 138.1, 133.1, 129.1, 128.4, 127.8, 127.7, 113.1, 104.3, 81.7, 81.6, 71.7, 54.9, 38.8, 36.3, 32.8, 24.6. IR (neat): 2926, 1607, 1439, 1364, 1208, 1091, 1043 cm^{-1}. EIMS *m*/*z* (%): 384 (3) $[M]^+$, 353 (6) $[M - OMe]^+$, 293 (3) $[M - 91]^+$, 277 (7), 235 (12), 217 (20), 167 (69), 91 (100). HRMS (EI): calcd for $C_{23}H_{28}O_3S$, 384.1759; found, 384.1752.

(1*R*,6*R*,7*S*)-7-(Benzyloxy)-3-(phenylthio)-9-oxabicyclo-[4.2.1]non-2-ene (40a) and (1*R*,6*R*,7*S*)-7-(Benzyloxy)-3-(phenylthio)-9-oxabicyclo[4.2.1]non-3-ene (40b). Following the general procedure, compound **6** (200 mg, 0.54 mmol) was cyclized to an inseparable mixture of compounds **40a** and **40b** (3.5:1, 129 mg, 71% yield), a pale yellow, viscous oil. All data reported are for **40a**. ^{1}H NMR (400 MHz, C_6D_6): δ 7.40−6.93 (m, 10H), 5.91 (d, J = 5.5 Hz, 1H), 4.56 (ddd, J = 2.5, 5.5, 8.0 Hz, 1H), 4.42 (dd, J = 5.0, 5.0 Hz, 1H), 4.17 (AB q, J = 12.0 Hz, $\Delta\nu$ = 6.8 Hz, 2H), 3.71 (dd, J = 2.5, 7.0 Hz, 1H), 2.57 (ddd, J = 3.5, 8.0, 16.4 Hz, 1H), 2.09−1.98 (m, 2H), 1.80−1.70 (m, 2H), 1.25 (dddd, J = 3.5, 4.5, 8.0, 14.0 Hz, 1H). ^{13}C NMR (100 MHz, C_6D_6): δ 138.9, 136.8, 136.7, 131.6, 129.4, 129.5−127.2 (several lines), 84.9, 81.8, 76.6, 71.0, 39.9, 33.3, 30.8. IR (neat): 3030, 2935, 1582, 1475, 1439, 1360, 1208 cm^{-1}. HRMS (FT-ICR): calcd for $C_{21}H_{22}O_2SNa$, 361.1233; found, 361.1231.

(1*R*,7*R*,8*S*)-8-(Benzyloxy)-3-(phenylthio)-10-oxabicyclo-[5.2.1]dec-3-ene (41). Following the general procedure, compound **9** (525 mg, 2.24 mmol) was cyclized to compound **41** (556 mg, 67% yield), a pale yellow, viscous oil. $[\alpha]^{25}_D$: −114.0° (c 0.15, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.26 (m, 10H, aromatic), 5.71 (t, J = 8.6 Hz, 1H, H-4), 4.61 (ddd, J = 2.0, 4.0, 7.0 Hz, 1H, H-1), 4.45 (AB q, J = 11.6 Hz, $\Delta\nu$ = 29.8 Hz, 2H, benzylic), 4.25 (dd, J = 4.8, 7.0 Hz, 1H, H-7), 4.14 (ddd, J = 4.8, 7.6, 7.6 Hz, 1H, H-8), 2.70 (d, J = 15.0 Hz, 1H, H-2), 2.55 (dd, J = 7.6, 12.5 Hz, 1H, H-9), 2.48 (ddd, J = 3.5, 3.5, 12.5 Hz, 1H, H-5), 2.22−2.14 (m, 1H, H-6), 2.11−1.93 (m, 3H, H-2, H-5, and H-9), 1.68 (ddd, J = 3.5, 13.5, 13.5 Hz, 1H, H-6). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 134.5, 133.7, 132.4 (C-4), 132.1, 129.2, 128.4, 127.7, 127.4, 85.6 (C-8), 83.0 (C-7), 81.6 (C-1), 71.6 (benzylic), 39.4 (C-2), 36.9 (C-9), 35.2 (C-6), 23.8 (C-5). IR (neat): 2922, 1583, 1496, 1439, 1363 cm^{-1}. EIMS m/z (%): 352 (6) $[M]^+$, 261 (4) $[M - 91]^+$, 243 (32), 165 (44), 151 (69), 91 (100). HRMS (EI): calcd for $C_{22}H_{24}O_2S$, 352.1497; found, 352.1517.

(1*R*,6*R*,7*S*)-7-(Benzyloxy)-9-oxabicyclo[4.2.1]nonan-3-one (53). To a stirred solution of the bicyclic vinyl sulfide **40** (100 mg, 0.30 mmol) in THF (10 mL) was added an aqueous 3 N HCl solution (3 mL) at 0 °C, and the reaction mixture was stirred overnight at room temperature. Solid $NaHCO_3$ was added to neutralize the acid. The mixture was treated with water and extracted with ether three times. The combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Chromatographic purification (30% ethyl acetate in petroleum ether) furnished the ketone **53** as a colorless oil (63 mg, 87% yield). $[\alpha]^{28}_D$: +35.9° (c 0.90, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34−7.22 (m, 5H, aromatic), 4.64 (dddd, J = 1.3, 4.0, 5.3, 9.4 Hz, 1H, H-1), 4.48 (dd, J = 2.3, 5.0 Hz, 1H, H-6), 4.44 (s, 2H, benzylic), 3.99 (dd, J = 1.5, 6.8 Hz, 1H, H-7), 2.87 (dd, J = 6.0, 16.0 Hz, 1H, H-2), 2.55 (ddd, J = 4.8, 7.0, 12.6 Hz, 1H, H-4), 2.40−2.28 (m, 3H, H-2, H-4, and H-8), 2.07 (ddd, J = 3.8, 6.8, 14.5 Hz, 1H, H-8), 1.93 (dddd, J = 5.0, 5.0, 10.6, 14.5 Hz, 1H, H-5), 1.51 (dddd, J = 3.0, 4.3, 7.0, 14.5 Hz, 1H, H-5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.5 (C-3), 137.7, 128.5, 127.8, 127.7, 84.1 (C-7), 82.2 (C-6), 72.9 (C-1), 71.0 (benzylic), 51.6 (C-2), 40.2 (C-4), 38.5 (C-8), 28.1 (C-5). IR (neat): 2941, 1699, 1496, 1455, 1365, 1248, 1196, 1091 cm^{-1}. API-ES MS (70 V) m/z (%): 269 (28) $[M + Na]^+$, 247 (26) $[M + H]^+$, 155 (8) $[M - 91]^+$, 139 (17), 91 (100). HRMS (FT-ICR): calcd for $C_{15}H_{18}O_3$-Na, 269.1148; found, 269.1147.

(1*R*,2*S*)-2-(Benzyloxy)-6-oxocyclooct-4-en-1-yl Acetate (54). To a solution of LDA (0.366 mmol) in THF (3 mL) [generated from n-BuLi (122 μL, 2.5 M solution, 0.305 mmol) and i-Pr_2NH (50 μL, 0.357 mmol) at −10 °C] was added a solution of the ketone **53** (30 mg, 0.122 mmol) in THF (1 mL) dropwise at 0 °C. The reaction mixture was allowed to reach room temperature and was stirred for 16 h before it was quenched with an aqueous NH_4Cl solution and extracted with ether three times. The combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was dissolved in dichloromethane (4 mL) and treated with DMAP (15 mg, 0.123 mmol), triethylamine (102 μL, 0.732 mmol), and acetic anhydride (46 μL, 0.487 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. Then it was quenched with an aqueous $NaHCO_3$ solution and extracted with dichloromethane. The dichloromethane layer was washed with water and brine, dried (Na_2SO_4), and filtered. Concentration and chromatographic purification (25% ethyl acetate in petroleum ether) afforded the cyclooctenone **54** as a colorless, viscous oil (18 mg, 51% yield). $[\alpha]^{24}_D$: −14.7° (c 0.28, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.27 (m, 5H, aromatic), 6.32 (ddd, J = 6.8, 7.6, 12.6 Hz, 1H, H-4), 5.98 (d, J = 12.6 Hz, 1H, H-5), 5.20 (ddd, J = 3.0, 3.0, 9.8 Hz, 1H, H-1), 4.55 (AB q, J = 12.0 Hz, $\Delta\nu$ = 16.0 Hz, 2H, benzylic), 3.76 (ddd, J = 3.0, 3.0, 9.0 Hz, 1H, H-2), 3.03−2.86 (m, 2H), 2.69−2.50 (m, 2H), 2.30−2.21 (m, 1H), 2.06 (s, 3H, OCOMe), 1.97−1.90 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.1, 170.2, 137.8, 128.5, 127.9, 127.7, 74.6, 72.5, 71.8, 39.1, 31.7, 24.2, 21.2. IR (neat): 2925, 1735, 1684, 1668, 1369, 1242 cm^{-1}. EIMS m/z (%): 288 (0.3) $[M]^+$, 228 (7), 181 (10), 137 (42), 122 (67), 91 (100). HRMS (FT-ICR): calcd for $C_{17}H_{20}O_4Na$, 311.1254; found, 311.1256.

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Supporting Information Available: Experimental procedures for the synthesis of all new compounds and the NMR spectra for these compounds (^{1}H, ^{13}C). This material is available free of charge via the Internet at http://pubs.acs.org.

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