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Reductive Cleavage of Tetrahydrofuryl Sulfur-Substituted Oxiranes: Application to the Formal Synthesis of Kumausyne and Kumausallene

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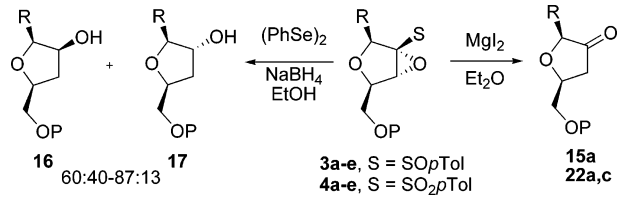
Received July 14, 2005



Readily available sulfinyl and sulfonyl tetrahydrofuran methanol derivatives have been transformed efficiently into a variety of substituted tetrahydrofuryl alcohols by treatment with $(PhSe)_2$ in the presence of an excess of $NaBH_4$. Alternatively, oxirane cleavage with MgI_2 produces the related ketones, amenable to stereocontrolled reduction. This reductive cleavage methodology has been applied to short formal syntheses of *trans*-Kumausyne and Kumausallene.

Introduction

Substituted tetrahydrofurans are ubiquitous structural motifs in bioactive natural products,[1] and this has motivated a sustained interest in the development of synthetic methods to prepare these heterocycles.[2] A few years ago, we reported an expedient route to 2,5-*cis* tetrahydrofuryl sulfur-substituted oxiranes, **B**, by the nucleophilic epoxidation of hydroxyl sulfinyl dienes **A** (Scheme 1).[3] The scope and limitations of this protocol were later disclosed along with an effective alternative stepwise methodology to access 2,5-*cis* and 2,5-*trans* sulfonyl derivatives, **B**.[4] In this article, we report in full our efforts to develop stereoselective routes to ketones **C** and alcohols **D** from precursors **B**, as well as the application of these methodologies to the formal syntheses of marine natural products Kumausyne, **1**, and Kumausallene, **2**.

Reductive Cleavage. Scheme 2 gathers the substrates chosen for the initial part of this study; these substrates (**3a**−**e**, **4a**−**e**, and **5a**,**c**,**d**) were selected to illustrate the influence of the oxidation state at sulfur, the nature of the R substituent, and the different stereochemistry at positions 2 and 5 on the outcome of the desired reductive oxirane cleavage. All substrates were prepared by our reported methodology.[4] Scheme 2 also shows some substrates used in the second part of this study (**10a**,**c** and **11a**,**c**) that were prepared from di-

(1) For reviews, see: (a) Westley, J. W. *Polyether Antibiotics: Naturally Occurring Acid Ionophores*; Marcel Dekker: New York, 1982; Vols. 1 and 2. (b) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407−2473. (c) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504−540. (d) Bermejo, A.; Figadère, B.; Zafra-Polo, M. C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269−303. (e) Hacksell, H.; Daves, G. D. The Chemistry and Biochemistry of C-Nucleosides and C-Aryl Glycosides. In *Progress in Medicinal Chemistry*; Ellis, G. P., West, G. B., Eds.; Elsevier: London, 1985; Vol 22, pp 1−65.

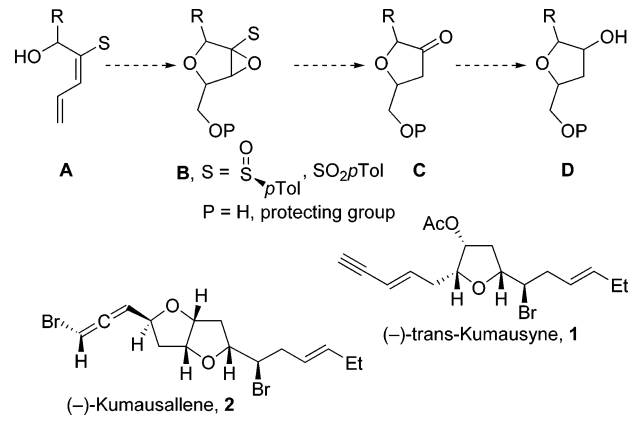
(2) For a review on synthetic approaches to tetrahydrofurans, see: (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309−3362. (b) Harmange, J.-C.; Figadère, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711−1754. (c) Elliot, M. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2301−2323. (d) Casiraghi, G.; Zanardi, F.; Battistini, G.; Rassu, G.; Appendino, G. *Chemtracts: Org. Chem.* **1998**, *11*, 803−828. (e) Jaramillo, C.; Knapp, S. *Synthesis* **1994**, 1−20. (f) Du, Y.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913−9959. For leading references, see: (g) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2000**, *2*, 461−464. (h) Pilli, R. A.; Riatto, V. B.; Vencato, I. *Org. Lett.* **2000**, *2*, 53−56. (i) Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 4831−4832. (j) Lei, A.; He, M.; Wu, S.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 3457−3460. (k) Kim, H. C.; Woo, S. W.; Seo, M. J.; Jeon, D. J.; No, Z.; Kim, H. R. *Synlett* **2002**, 1691−1693. (l) Smitrovich, J. H.; Woerpel, K. A. *Synthesis* **2002**, 2778−2785. (m) Ajamian, A.; Gleason, J. L. *Org. Lett.* **2001**, *3*, 4161−4164. (n) Evans, D. A.; Sweeney, Z. K.; Rovis, T.; Tedrow, J. S. *J. Am. Chem. Soc.* **2001**, *123*, 12095−12096. (o) Loh, T.-P.; Hu, Q.-Y.; Tan, K.-T.; Cheng, H.-S. *Org. Lett.* **2001**, *3*, 2669−2672. (p) Cohen, F.; MacMillan, D. W. C.; Overman, L. E.; Romero, A. *Org. Lett.* **2001**, *3*, 1225−1228. (q) Chakraborty, T. K.; Das, S.; Raju, T. V. *J. Org. Chem.* **2001**, *66*, 4091−4093. (r) Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 5374−5375. (s) Angle, S. R.; El-Said, N. A. *J. Am. Chem. Soc.* **2002**, *124*, 3608−3013.

(3) Fernández de la Pradilla, R.; Montero, C.; Priego, J.; Martínez-Cruz, L. A. *J. Org. Chem.* **1998**, *63*, 9612−9613.

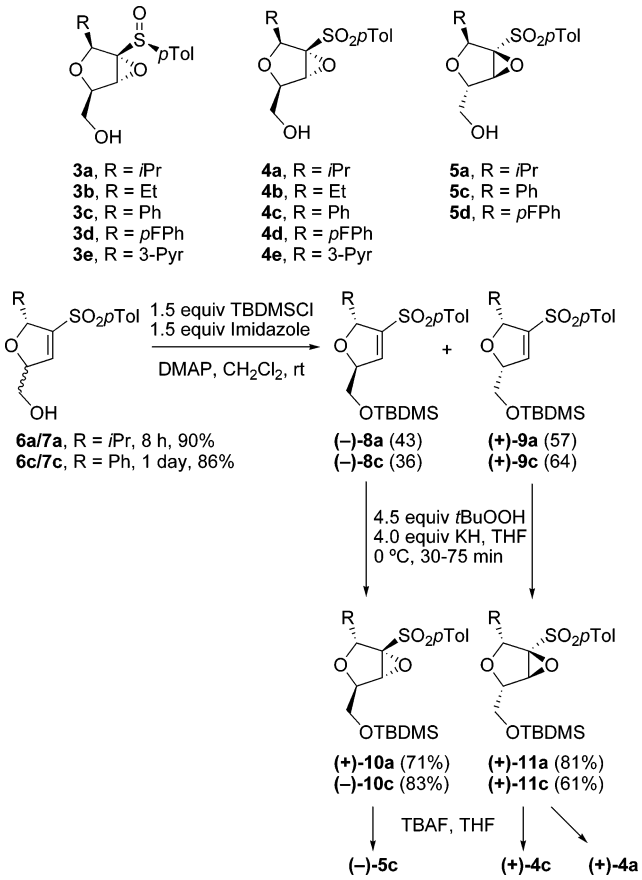
(4) Fernández de la Pradilla, R.; Manzano, P.; Montero, C.; Priego, J.; Martínez-Ripoll, M.; Martínez-Cruz, L. A. *J. Org. Chem.* **2003**, *68*, 7755−7767.

10.1021/jo051459k CCC: $30.25
Published on Web 11/18/2005

SCHEME 1



SCHEME 2



hydrofurans **6a/7a** and **6c/7c**,[4] by smooth silylation to afford protected sulfonyl dihydrofurans **8a**,**c** and **9a**,**c** that were easily separated by chromatography (Scheme 2). The stereoselective nucleophilic epoxidation of these substrates with *t*BuOOK gave the desired substrates **10a**,**c** and **11a**,**c** as single isomers and with good yields. It should be pointed out that these epoxidations are significantly more selective than those carried out on the related substrates with free primary alcohols.[4] Three of these silylated sulfonyl oxiranes were deprotected to the known alcohols **(+)-4a**, **(+)-4c**, and **(−)-5c** to allow for a firm structural assignment.

With regard to the oxirane cleavage protocol, we selected the one-step procedure entailing the use of a nucleophilic selenium species prepared from $(PhSe)_2$ and $NaBH_4$ since this species had been used before for the reductive cleavage of simple sulfinyl oxiranes.[5] The results obtained in this study are shown in Table 1. To obtain ketones **14** or **15**, we used conditions that avoided an excess of reducing agent, and we found that the treatment of substrate **3a** with a large excess of nucleophilic selenium species in EtOH gave ketone **12a** as a single isomer of undetermined stereochemistry, along with some recovered starting material (Table 1, entry 1). The use of a smaller excess of reagent on the less-reactive sulfone **4a** gave a complex mixture of products from which selenyl ketone **13a** (5%) and starting material **4a** (35%) were isolated, again in a very slow reaction (Table 1, entry 2). Resubmission of **13a** to the reaction conditions gave ketone **12a**. These experiments had been started under argon but without special precautions to secure an inert atmosphere until completion, and it was observed that the white suspension initially formed turned yellow after just a few hours. This observation was attributed to oxidative destruction of the reactive species to regenerate $(PhSe)_2$, and thus the remaining experiments were carried out under argon and with slow bubbling of argon through the reaction medium.

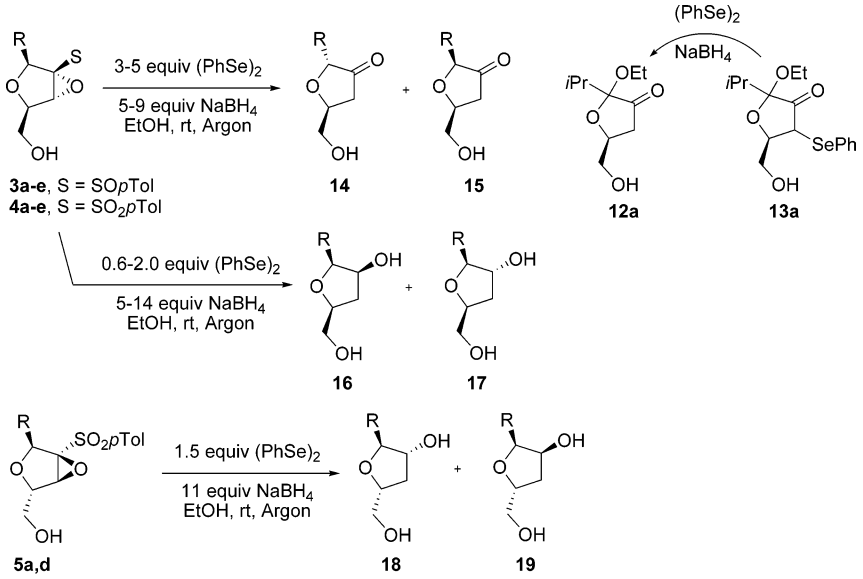
Sulfonyl oxiranes **4a** and **4b** and sulfinyl oxirane **3c**, under these optimized conditions, rendered good to excellent yields of the expected ketones but as practically nonselective mixtures of 2,5-trans and 2,5-cis isomers **14** and **15** (Table 1, entries 3−5). These results indicated that the nucleophilic selenium species was too basic to allow for the preservation of the stereochemistry of the starting material upon transformation to the desired ketone. At this stage, we hypothesized that the use of a large excess of $NaBH_4$, along with slow bubbling of argon through the reaction, could allow for the use of less $(PhSe)_2$ and, more importantly, perhaps reduce the carbonyl with useful stereocontrol, prior to epimerization.

The results obtained under these conditions are gathered in Table 1, entries 6−12. In these cases, the precise stoichiometry of the reaction was quite case-dependent, but a substantial reduction of the amount of $(PhSe)_2$ could be achieved, especially for the more reactive sulfinyl oxiranes. With regard to the selectivity of the process, in all cases the all-cis diols **16** were predominant but the selectivities ranged from low (Table 1, entry 7) to excellent (Table 1, entry 6). Unfortunately, these conditions were not effective for 2,5-trans isomers **5a** and **5d** that gave nonselective mixtures of the expected carbinols **18** and **19** (Table 1, entries 13 and 14).

The general structure of these products was derived primarily from their ^1H and ^{13}C NMR data, and the stereochemical assignments rely on detailed correlations particularly based on ^1H NMR spectra and comparison with literature values,[2s] as well as the completion of the formal syntheses described below. The difference in chemical shifts measured for both H-4 is particularly diagnostic, with $\Delta\delta = 0.4-0.6$ ppm for **16** and **18** and $\Delta\delta = 0-0.2$ ppm for **17** and **19**. On the other hand, isomers **16** had smaller values for J_{2-3} (2.4−2.8 Hz) than isomers **17** (4.4 Hz); this is in contrast with the measurements for 2,5-trans derivatives **18** ($J_{2-3} = 0-1.8$ Hz) and **19** ($J_{2-3} = 2.6-2.7$ Hz).

(5) Satoh, T.; Kaneko, Y.; Izawa, T.; Sakata, K. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1983−1990.

TABLE 1. Reductive Cleavage of Sulfur-Substituted Oxiranes with ($PhSe_2$)/$NaBH_4$



entry	substrate	conditions	products[a]	yield[b] %
1	**3a**	6.25 equiv of $(PhSe)_2$, 11.5 equiv of $NaBH_4$, 24 h	**12a**	54[c]
2	**4a**	3.0 equiv of $(PhSe)_2$, 5.5 equiv of $NaBH_4$, 48 h	**13a**	40[d]
3	**4a**	3.0 equiv of $(PhSe)_2$, 5.0 equiv of $NaBH_4$, 7 h, Ar	**14a** (70) **15a** (30)	81[e]
4	**4b**	3.0 equiv of $(PhSe)_2$, 5.0 equiv of $NaBH_4$, 7 h, Ar	**14b** (60) **15b** (40)	92[f]
5	**3c**	5.0 equiv of $(PhSe)_2$, 9.0 equiv of $NaBH_4$, 2 h, Ar	**14c** (60) **15c** (40)	57
6	**4a**	1.5 equiv of $(PhSe)_2$, 11.0 equiv of $NaBH_4$, 44 h, Ar	**16a**	73[g]
7	**4b**	1.0 equiv of $(PhSe)_2$, 8.0 equiv of $NaBH_4$, 7 h, Ar	**16b** (70) **17b** (30)	59
8	**3c**	0.6 equiv of $(PhSe)_2$, 5.0 equiv of $NaBH_4$, 1.5 h, Ar	**16c** (80) **17c** (20)	83
9	**4c**	1.5 equiv of $(PhSe)_2$, 11.0 equiv of $NaBH_4$, 17 h, Ar	**16c** (80) **17c** (20)	62
10	**3d**	0.6 equiv of $(PhSe)_2$, 5.0 equiv of $NaBH_4$, 1.5 h, Ar	**16d** (86) **17d** (14)	94
11	**4d**	1.5 equiv of $(PhSe)_2$, 11.0 equiv of $NaBH_4$, 2.5 h, Ar	**16d** (85) **17d** (15)	90
12	**4e**	2.0 equiv of $(PhSe)_2$, 14.0 equiv of $NaBH_4$, 7 h, Ar	**16e** (80) **17e** (20)	51
13	**5a**	3.0 equiv of $(PhSe)_2$, 14.0 equiv of $NaBH_4$, 96 h, Ar	**18a** (58) **19a** (42)	48
14	**5d**	1.5 equiv of $(PhSe)_2$, 11.0 equiv of $NaBH_4$, 8 h, Ar	**18d** (60) **19d** (40)	84

[a] Diastereomeric ratios are shown in parentheses. [b] Combined yields of pure products after column chromatography. [c] Reaction carried out without bubbling argon; starting material (16%) recovered. [d] Reaction carried out without bubbling argon; starting material (35%) recovered. [e] Traces of starting material and **12a** also isolated. [f] Starting material (9%) recovered. [g] Starting material (17%) recovered.

While this cleavage/reduction protocol could be useful, at least for 2,5-cis derivatives, we decided to explore alternative routes to access the ketones. After briefly evaluating the cleavage with $MgBr_2$,[6] which should be followed by a potentially troublesome reductive dehalogenation, we considered the use of an excess of MgI_2. It was envisioned that the iodoketone intermediate could react with iodide to generate I_2 (in analogy to the selenium protocol described above) and thus produce the desired dehalogenated ketone in a one-pot procedure and under acidic conditions. Scheme 3 gathers the results obtained for the reductive cleavage of sulfonyl oxiranes with freshly prepared magnesium halides. To test this idea, sulfonyl oxirane **5c** was treated with $MgBr_2$ to afford bromoketone **20** as a single isomer; then sulfonyl oxirane **4a** was treated with an excess of MgI_2 in Et_2O to produce in a rapid reaction 2,5-*cis* ketone **15a** as a single isomer and in excellent yield. Similarly, from protected substrates **10a**,**c** and **11a**,**c**, prepared as described above, diastereomerically pure ketones **(+)-21a**,**c** and **(+)-22a**,**c** were obtained uneventfully in excellent yields. Conditions to achieve the stereoselective reduction of these ketones were then explored briefly on **(+)-21c** and **(+)-22c**, and L-selectride gave excellent results to prepare 2,5-*trans* alcohol **(−)-23c** with complete selectivity, and $NaBH_4$ gave 2,5-*cis* alcohol **(−)-24c** with complete stereocontrol.

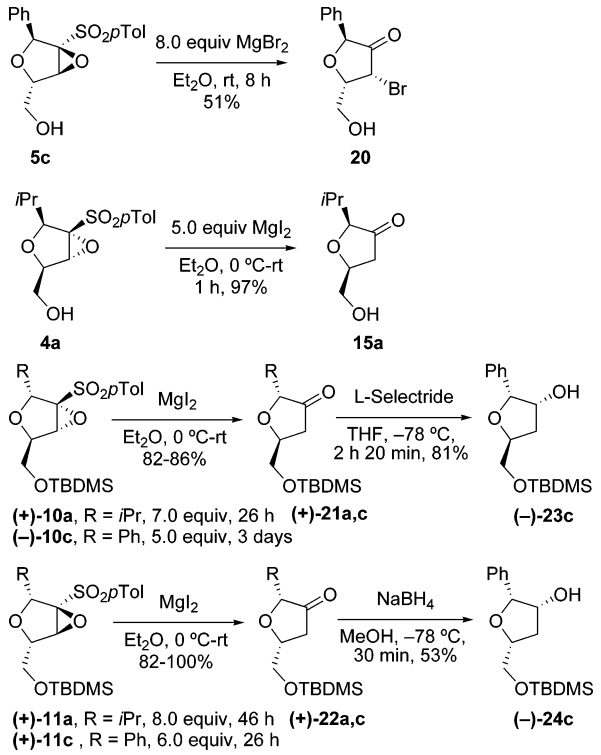
Formal Syntheses of Kumausyne and Kumausallene. The 2,5-disubstituted-3-oxygenated tetrahydrofuran unit is present in a variety of natural products. Among these, we focused our attention on halogenated metabolites isolated from the genus *Laurencia*, especially on (−)-*trans*-Kumausyne, **1**,[7] (Scheme 4) and (−)-Kumausallene, **2**,[8] which appeared as suitable targets for an application of our methodologies. These products have been synthesized before,[9,10] and upon inspection of the existing literature we envisioned that a unified approach to these targets could rely on lactol **25** (Scheme 4), notwithstanding the fact that since our efforts had begun with (−)-menthyl sulfinate, the unnatural enantiomer would be obtained. *trans*-Kumausyne had been prepared from lactol ***ent*-25** (P = TBDPS) in six steps,[9b] and (±)-

(6) Durst, T.; Tin, K.-C.; Reinach-Hirtzbach, F.; Decesare, J. M.; Ryan, M. D. *Can. J. Chem.* **1979**, *57*, 258−266.

(7) *cis*- and *trans*-Kumausyne: Suzuki, T.; Koizumi, K.; Suzuki, H.; Kurosawa, E. *Chem. Lett.* **1983**, 1643−1646.

(8) Kumausallene: Suzuki, T.; Koizumi, K.; Suzuki, H.; Kurosawa, E. *Chem. Lett.* **1983**, 1639−1642.

SCHEME 3



Kumausallene had been prepared from dioxabicyclic derivative **27** in 13 steps.[10a] Alternatively, Evans et al. reported a synthesis of Kumausallene that entailed a 10-step sequence to access benzylated lactol ***ent*-25** (P = Bn) from commercially available *cis*-4-benzyloxy-2-buten-1-ol, followed by a three-step sequence to produce bromoallene ***ent*-28** that was transformed in four additional steps to Kumausallene.[10c] It was envisioned that Overman's intermediate **27** could arise from **25** by a Wittig reaction followed by intramolecular Michael cyclization. In turn, **25** would be obtained from monoprotected diol **26** by a Wacker protocol,[11] and **26** could arise from sulfur-substituted oxiranes **3f** and **4f** by the reductive oxirane cleavage followed by selective carbonyl reduction described in this article. Furthermore, we considered that benzylated lactol **25** (P = Bn) could be prepared expediently by our methodology and result in a further improvement of Evans' route. Finally, if viable, the use of unprotected lactol **25** (P = H), in principle available in just five steps from (−)-menthyl sulfinate, could result in further shortening of both Overman's and Evans' routes. Therefore, we decided to examine the preparation of these lactols **25** (P = TBDPS, Bn, H) from our sulfinyl and sulfonyl oxiranes.

Scheme 5 gathers the preparation of suitably protected derivatives from the known oxiranes **(+)-3f** and **(+)-4f**, available in three steps from (−)-menthyl sulfinate.[4] Silylation under standard conditions proceeded smoothly to afford silyl ethers **(+)-28a**, **(+)-28b**, and **(−)-29b** in good yield. In contrast, formation of benzyl ethers **28c** and **(+)-29c** required more experimentation and gave just fair yields of the desired products. Initially, we focused our attention on the stepwise oxirane cleavage and carbonyl reduction; however, the treatment of sulfonyl oxirane **(−)-29b** with MgI_2 led to complex mixtures of products under different experimental conditions. This led us to reexamine the one-pot selenium-based protocol to prepare the desired target **26**.

Table 2 summarizes our results on the reductive cleavage of these synthetic precursors. Not too unexpectedly, when the cleavage was carried out in the absence of excess $NaBH_4$, α,β-unsaturated ketone **(−)-31b** was obtained by a facile double bond migration under these basic conditions (Table 2, entry 1). Ketone **(−)-31b** was produced as a single isomer, but the stereochemistry of the exocyclic alkene has not been studied in detail. Entries 2 and 3 show that the use of a large excess of $NaBH_4$ affords mixtures of the desired alcohols **(+)-26b** and **(−)-32b** in good yields and with reasonable selectivities. Unprotected precursors **(+)-3f** and **(+)-4f** were also transformed into diols **(+)-26d** and **(−)-32d**, albeit with reduced selectivity (Table 2, entries 4 and 5).

SCHEME 4

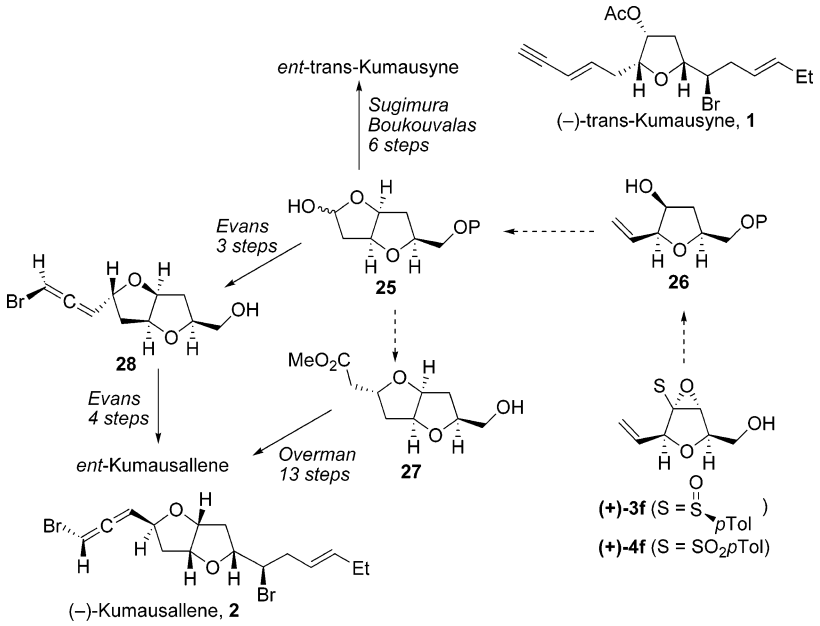
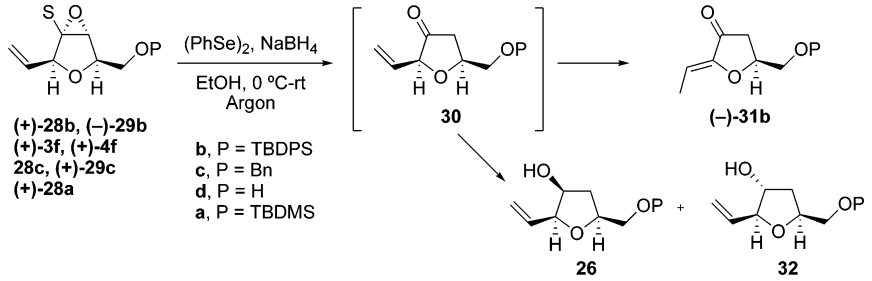


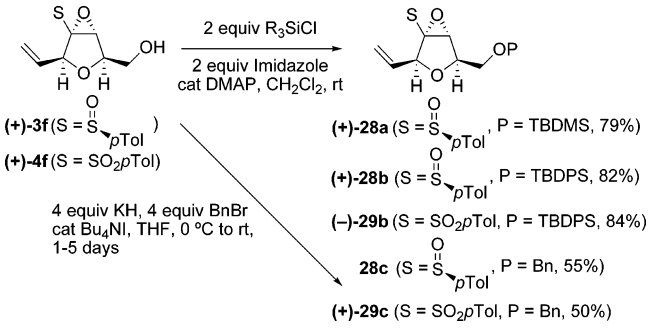
TABLE 2. Reductive Cleavage of Precursors for *trans*-Kumausyne and Kumausallene



entry	substrate	conditions	P	products[a]	yield[b] %
1	(+)-**28b**	5.0 equiv of $(PhSe)_2$, 9.0 equiv of $NaBH_4$, 0 °C, 1 h	TBDPS	(−)-**31b**	73
2	(+)-**28b**	3.0 equiv of $(PhSe)_2$, 26.0 equiv of $NaBH_4$, 0 °C, 3 h	TBDPS	(+)-**26b** (87) (−)-**32b** (13)	77
3	(−)-**29b**	4.0 equiv of $(PhSe)_2$, 28.0 equiv of $NaBH_4$, 28 h	TBDPS	(+)-**26b** (87) (−)-**32b** (13)	69
4	(+)-**3f**	3.0 equiv of $(PhSe)_2$, 26.0 equiv of $NaBH_4$, 0 °C, 4 h	H	(+)-**26d** (76) (−)-**32d** (24)	69
5	(+)-**4f**	3.0 equiv of $(PhSe)_2$, 26.0 equiv of $NaBH_4$, rt, 19 h	H	(+)-**26d** (76) (−)-**32d** (24)	60
6	**28c**	3.0 equiv of $(PhSe)_2$, 16.0 equiv of $NaBH_4$, 1 equiv of AcOH, 0 °C, 2 h	Bn	(+)-**26c** (76) **32c** (24)	70
7	(+)-**29c**	4.5 equiv of $(PhSe)_2$, 30.0 equiv of $NaBH_4$, 3 equiv of AcOH, rt, 4 days	Bn	(+)-**26c** (76) **32c** (24)	80[c]
8	(+)-**28a**	3.0 equiv of $(PhSe)_2$, 12.0 equiv of $NaBH_4$, 1 equiv of AcOH, 0 °C to rt, 1.5 h	TBDMS	(+)-**26a** (83) (−)-**32a** (17)	80

[a] Diastereomeric ratios are shown in parentheses. [b] Combined yields of pure products after column chromatography. [c] Starting material (50%) recovered, included in the yield.

SCHEME 5



At this stage of the project, we ran out of $(PhSe)_2$, and a new bottle of reagent was purchased. Surprisingly, this batch of reagent provided inferior results in related transformations examined concurrently in the group, with low conversions being observed even for reactions that had been already examined by us with the old batch of reagent. After extensive experimentation and examining the purity of the new reagent, we found that addition of 1−3 equiv of AcOH had very significant beneficial effects on the rates and conversions of these reactions.[12] We tentatively attribute this profound difference in reactivity to the presence of very small amounts of acidic contaminants in the "old" bottle of $(PhSe)_2$, and therefore we now routinely add AcOH in these cleavages.

Under these conditions, sulfinyl benzyl ether **28c** gave a good yield of the expected diol derivatives (+)-**26c** and **32c** with fair selectivity. In contrast, the related sulfone (+)-**29c** was much less reactive and 50% starting material was recovered (Table 2, entries 6 and 7). Finally TBDMS ether (+)-**28a** was also examined with results that largely paralleled the TBDPS analogue (Table 2, entries 2 and 8).

Our formal synthesis of *trans*-Kumausyne was completed by a regiocontrolled Wacker protocol, well-documented by Mereyala for related systems, on alcohol (+)-**26b** that afforded a good yield of lactol (−)-**25b** as a 74:26 mixture of anomers with spectral features identical to those in the literature.[9e,13] These conditions were also shown to be viable for unprotected diol (+)-**26d**, but in this case, the use of $Cu(OAc)_2$ gave slightly better results of unprotected lactol (−)-**25d** (53%), along with ketone (−)-**33** (21%) (Scheme 6).

Our efforts toward a formal synthesis of Kumausallene are shown in Scheme 7. The transformation of (−)-**25d**

(9) For a review, see: Fernández de la Pradilla, R.; Viso, A. *Recent Res. Dev. Org. Bioorg. Chem.* **2001**, *4*, 123−132. For syntheses of Kumausyne, see: (a) Brown, M. J.; Harrison, T.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5378−5384. (b) Osumi, K.; Sugimura, H. *Tetrahedron Lett.* **1995**, *36*, 5789−5792. (c) Martín, T.; Soler, M. A.; Betancort, J. M.; Martín, V. S. *J. Org. Chem.* **1997**, *62*, 1570−1571. (d) Lee, E.; Yoo, S.-K.; Cho, Y.-S.; Cheon, H.-S.; Chong, Y. H. *Tetrahedron Lett.* **1997**, *38*, 7757−7758. (e) Boukouvalas, J.; Fortier, G.; Radu, I.-I. *J. Org. Chem.* **1998**, *63*, 916−917. (f) Mereyala, H. B.; Gadikota, R. R. *Tetrahedron: Asymmetry* **2000**, *11*, 743−751. (g) García, C.; Martín, T.; Martín, V. S. *J. Org. Chem.* **2001**, *66*, 1420−1428. (h) Gadikota, R. R.; Callam, C. S.; Lowary, T. L. *J. Org. Chem.* **2001**, *66*, 9046−9051. (i) Chandler, C. L.; Phillips, A. J. *Org. Lett.* **2005**, *7*, 3493−3495.

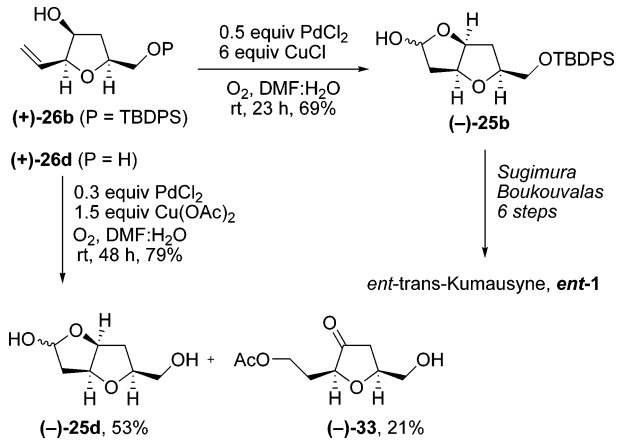
(10) For syntheses of Kumausallene, see: (a) Grese, T. A.; Hutchinson, K. D.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 2468−2477. (b) Lee, E.; Yoo, S.-K.; Choo, H.; Song, H. Y. *Tetrahedron Lett.* **1998**, *39*, 317−318. (c) Evans, P. A.; Murthy, V. S.; Roseman, J. D.; Rheingold, A. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 3175−3177. (d) For a review, see: Hoffmann-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196−1216.

(11) (a) Mereyala, H. B.; Gadikota, R. R.; Krishnan, R. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3567−3571. (b) Krishnudu, K.; Krishna, P. R.; Mereyala, H. B. *Tetrahedron Lett.* **1996**, *37*, 6007−6010. See also: (c) Mereyala, H. B.; Gadikota, R. R.; Sunder, K. S.; Shailaja, S. *Tetrahedron* **2000**, *56*, 3021−3026.

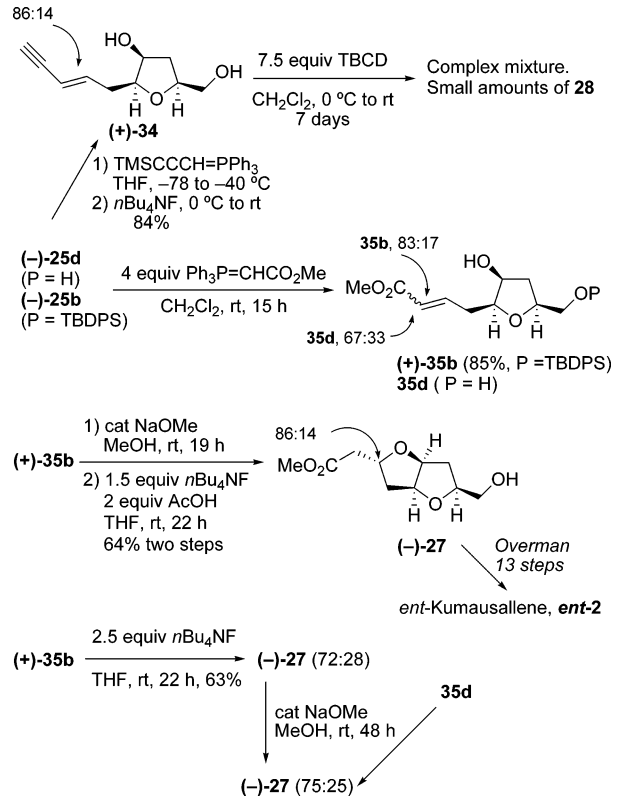
(12) The beneficial effect of weak acids on related selenide cleavages has been noted before. See: Miyashita, M.; Suzuki, T.; Hoshino, M.; Yoshikoshi, A. *Tetrahedron* **1997**, *53*, 12469−12486.

(13) This reaction required substantial optimization. Early experiments with less $PdCl_2$ gave important amounts of byproducts of undetermined structure, tentatively attributed to transient buildup of HCl through the catalytic cycle. Unfortunately, the use of $Pd(OAc)_2$ and $Cu(OAc)_2$ (Smith, A. B.; Cho, Y. S.; Friestad, G. K. *Tetrahedron Lett.* **1998**, *39*, 8765−8768.) did not give better results. Finally the conditions shown in Scheme 7, with continuous slow bubbling of oxygen through the reaction medium, gave good results.

SCHEME 6



SCHEME 7



into **28** in two steps following the route disclosed by Evans et al.[10c] would result in an expedient route to Kumausallene (11 steps). Thus, the one-pot Wittig desilylation protocol was tested on **(−)-25d** to afford an excellent yield of enyne diol **(+)-34** as an 86:14 *E*/*Z* mixture. To our dismay, the treatment of **(+)-34** with an excess of TBCD in a very slow reaction gave a complex mixture of allenes in which **28** and its bromoallene epimer were just minor constituents. In view of these disappointing results, and considering that the initial steps of our route to the benzylated lactol, originally used by Evans, occurred with fair yields and moderate selectivities (Scheme 5 and Table 2, entries 6 and 7), we decided to shift our efforts to Overman's intermediate **27**. Thus, a Wittig reaction on lactol **(−)-25b** gave unsaturated ester **(+)-35b** as a separable 83:17 mixture of *E*/*Z* isomers in excellent yield. Treatment of **(+)-35b** with a catalytic amount of NaOMe in MeOH gave an 86:14 mixture of dioxabicyclic derivatives that were deprotected with nBu$_4$NF buffered with AcOH to produce Kumausallene precursor **(−)-27** (64% two steps, 86:14 mixture) with spectral features identical to those in the literature.[10a] To shorten the sequence, **(+)-35b** was treated with nBu$_4$NF that smoothly effected desilylation and cyclization in a single step with comparable yield but slightly lower selectivity (72:28). This mixture was treated with catalytic NaOMe/MeOH without a significant change in the isomeric ratio. Finally, to further shorten our synthetic sequence, we examined briefly the Wittig reaction on unprotected lactol **(−)-25d** that cleanly led to unsaturated ester **35d** (67:33, *E*/*Z* mixture) and the smooth base-catalyzed cyclization of **35d** that led to a 75:25 mixture of epimers of **27**.[14]

Conclusions

An expedient route to a variety of substituted tetrahydrofurans from readily available sulfur-substituted oxiranes has been outlined. This reductive cleavage methodology has been applied to short formal syntheses of *trans*-Kumausyne and Kumausallene.

Experimental Section

General Procedure for the Preparation of Silyl Ethers. To a solution of the substrate in anhydrous CH_2Cl_2 (0.4 mL/mmol) at room temperature was added imidazole (1.5 equiv) and DMAP (0.05 equiv). The solution was cooled to 0 °C and TBDMSCl or TBDPSCl (1.5 equiv) was added. The mixture was allowed to warm to room temperature and monitored by TLC. Upon completion, the reaction was quenched with H_2O (5 mL/mmol) and saturated NH_4Cl solution (5 mL/mmol). The layers were separated, the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL/mmol), and the combined organic extracts were washed with a saturated solution of NaCl (5 mL/mmol), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a crude product that was purified by column chromatography on silica gel using a gradient of the appropriate solvents.

Synthesis of the *tert*-Butyldimethylsilyl Ethers of (2*R*,5*R*)-5-Isopropyl-4-(*p*-tolylsulfonyl)-2,5-dihydrofuran-2-methanol, (−)-8a, and (2*S*,5*R*)-5-Isopropyl-4-(*p*-tolylsulfonyl)-2,5-dihydrofuran-2-methanol, (+)-9a. From a mixture of sulfonyl dihydrofurans **6a** and **7a**[4] (189 mg, 0.64 mmol, 1.0 equiv) with TBDMSCl (152 mg, 0.96 mmol, 1.5 equiv), according to the general procedure (8 h), a 43:57 mixture of silyl ethers **(−)-8a** and **(+)-9a** was obtained. Purification by chromatography (30−70% CH_2Cl_2/hexane) gave **(−)-8a** (76 mg, 29%) and **(+)-9a** (137 mg, 61%) as colorless oils. Data for **(−)-8a**: R_f 0.25 (CH_2Cl_2). $[\alpha]^{20}_D$ −105.1 (*c* 1.39). ^{1}H NMR (300 MHz) δ −0.04 (s, 3 H), −0.01 (s, 3 H), 0.69 (d, 3 H, J = 6.8 Hz), 0.81 (s, 9 H), 0.98 (d, 3 H, J = 6.9 Hz), 2.06 (hept d, 1 H, J = 6.9, 1.5 Hz), 2.43 (s, 3 H), 3.56 (dd, 1 H, J = 10.4, 5.6 Hz), 3.71 (dd, 1 H, J = 10.4, 3.8 Hz), 4.80 (ap tt, 1 H, J = 6.8, 6.1, 1.6 Hz), 4.84 (dd, 1 H, J = 6.1,1.4 Hz), 6.72 (ap t, 1 H, J = 1.5 Hz), 7.32 (d, 2 H, J = 8.5 Hz), 7.76 (d, 2 H, J = 8.6 Hz). ^{13}C NMR (75 MHz) δ −5.5, −5.5, 14.3, 18.2, 19.9, 21.6, 25.8 (3 C), 31.8, 64.9, 86.1, 89.4, 128.1 (2 C), 129.9 (2 C), 136.7, 140.6, 144.1, 144.9. IR (film): 3355, 2956, 2929, 2855, 1597, 1463, 1322, 1158, 836, 666 cm^{-1}. MS (ES): 843 [2M + Na]$^+$, 433 [M + Na]$^+$ (100%), 411 [M + 1]$^+$. Anal. Calcd for $C_{21}H_{34}O_4SSi$: C, 61.42; H, 8.35; S, 7.81. Found: C, 61.75; H,

(14) It should be mentioned that these last experiments were carried out on a small scale and the yields were not determined.

8.04; S, 7.60. Data for **(+)-9a**: R_f 0.16 (CH_2Cl_2). $[\alpha]^{20}_D$ +63.0 (*c* 1.55). ^{1}H NMR (300 MHz) δ 0.02 (s, 3 H), 0.03 (s, 3 H), 0.63 (d, 3 H, J = 6.7 Hz), 0.85 (s, 9 H), 0.96 (d, 3 H, J = 7.0 Hz), 2.08 (hept d, 1H, J = 6.9, 1.4 Hz), 2.43 (s, 3 H), 3.55 (dd, 1 H, J = 10.0, 6.9 Hz), 3.76 (dd, 1 H, J = 10.1, 5.2 Hz), 4.78−4.83 (m, 2 H), 6.74 (s, 1 H), 7.33 (d, 2 H, J = 9.0 Hz), 7.76 (d, 2 H, J = 8.3 Hz). ^{13}C NMR (75 MHz) δ −5.4, 14.9, 18.3, 19.8, 21.7, 25.8 (3 C), 30.4, 64.9, 85.1, 89.1, 128.1 (2 C), 129.9 (2 C), 136.6, 140.9, 144.2, 144.9. IR (film): 3500, 2956, 2932, 2876, 1786, 1757, 1597, 1558, 1464, 1323, 1154, 667 cm^{-1}. MS (ES): 843 $[2M + Na]^+$, 433 $[M + Na]^+$, 411 $[M + 1]^+$ (100%). Anal. Calcd for $C_{21}H_{34}O_4SSi$: C, 61.42; H, 8.35; S, 7.81. Found: C, 61.57; H, 8.42; S, 7.89.

General Procedure for Nucleophilic Epoxidation of Vinyl Sulfoxides and Sulfones with *t*BuOOK. A two-necked round-bottomed flask fitted with a tube in T for entrance and exit of argon and a polyethylene stopper was charged with anhydrous THF (5 mL/mmol) and 2−4 equiv of oil-free KH (washed with hexane and dried). The mixture was cooled to 0 °C, and then 2−4.5 equiv of *t*BuOOH (80% in *t*BuOO*t*Bu) was added. After being stirred at room temperature for 10 min, the resulting solution was cooled to 0 °C and a solution of 1 equiv of the corresponding vinyl sulfoxide in THF (7 mL/mmol), previously dried over 4 Å sieves, was added dropwise. The reaction mixture was stirred at 0 °C until the starting material disappearance, monitored by TLC. The reaction was then quenched with a 10% solution of $Na_2S_2O_4$ (4 mL/mmol), diluted with EtOAc (10 mL/mmol), and the layers were separated. The aqueous layer was extracted with EtOAc (3 times, 10 mL/mmol), and the combined organic extracts were washed with a saturated solution of NaCl (4 mL/mmol), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give a crude product, which was purified by column chromatography on silica gel, using a gradient of mixtures of EtOAc/hexane or EtOAc/CH_2Cl_2. Product ratios were determined by integration of well-resolved signals in the ^{1}H NMR of the crude reaction mixtures.

Synthesis of (+)-(2*S*,3*S*,4*S*,5*R*)-2(*tert*-Butyldimethylsilyloxymethyl)-3,4-epoxy-5-isopropyl-4-(*p*-tolylsulfonyl)-tetrahydrofuran, (+)-11a. From a solution of sulfonyl dihydrofuran **(+)-9a** (62 mg, 0.151 mmol, 1.0 equiv) in 1.1 mL of THF, with *t*BuOOK (4.0 equiv, in THF), according to the general procedure (0 °C, 30 min), sulfonyl oxirane **(+)-11a** was obtained as a single isomer. Purification by chromatography (2−10% EtOAc/hexane) gave **(+)-11a** (52 mg, 81%) as a colorless oil. Data for **(+)-11a**: R_f 0.32 (100% CH_2Cl_2). $[\alpha]^{20}_D$ +14.5 (*c* 2.57). ^{1}H NMR (300 MHz) δ 0.05 (s, 3 H), 0.06 (s, 3 H), 0.87 (s, 9 H), 1.01 (t, 6 H, J = 6.9 Hz), 2.37 (ap hept d, 1 H, J = 6.7, 3.2 Hz), 2.45 (s, 3 H), 3.61−3.73 (m, 2 H), 3.96 (ap t, 1 H, J = 5.1, 3.8 Hz), 4.01 (d, 1 H, J = 3.4 Hz), 4.02 (s, 1 H), 7.35 (d, 2 H, J = 8.0 Hz), 7.80 (d, 2 H, J = 8.3 Hz). ^{13}C NMR (75 MHz) δ −5.5, −5.4, 17.8, 18.2, 21.3, 21.7, 25.8 (3 C), 29.5, 62.4, 66.9, 77.7, 78.0, 84.5, 129.3 (2 C), 129.8 (2 C), 133.6, 145.9. IR (film): 3384, 2956, 2930, 2876, 2855, 1597, 1471, 1332, 1257, 1150, 1086, 838 cm^{-1}. MS (ES): 427 $[M + 1]^+$, 449 $[M + Na]^+$(100%). Anal. Calcd for $C_{21}H_{34}O_5SSi$: C, 59.12; H, 8.03; S, 7.52. Found: C, 59.36; H, 8.29; S, 7.73.

General Procedure for Reductive Cleavage of Sulfinyl and Sulfonyl Oxiranes with $(PhSe)_2$ and $NaBH_4$. A two-necked round-bottomed flask was charged with a solution of $(PhSe)_2$ (0.6−5.0 equiv) in EtOH (3.5−6 mL/mmol of diselenide), and argon was slowly bubbled through the solution with a pipet. To this solution was added powdered $NaBH_4$ (5−14 equiv) portionwise at room temperature, and the mixture was stirred until evolution of H_2 subsided (ca. 1 h). In many cases, AcOH (1 equiv) was added to ensure reproducibility and faster reaction rate. Then, a solution of 1 equiv of sulfinyl or sulfonyl oxirane in EtOH (2−5 mL/mmol) was added, and the reaction was monitored by TLC until disappearance of the starting material. The reaction was then quenched with a saturated NH_4Cl solution (3 drops/mmol), the solvent was removed under reduced pressure, and the residue was taken up in EtOAc, filtered through a cotton plug, and washed carefully with additional EtOAc. The solution was concentrated under reduced pressure to produce a crude product that was purified by chromatography on silica gel using the appropriate mixture of eluents, to produce substantial amounts (70−80%) of the nonpolar $(PhSe)_2$ and the reaction products.

Synthesis of (±)-(2*S*,3*S*,5*S*)-2-(*p*-Fluorophenyl)-5-hydroxymethyltetrahydrofuran-3-ol, 16d, and (±)-(2*S*,3*R*,5*S*)-2-(*p*-Fluorophenyl)-5-hydroxymethyltetrahydrofuran-3-ol, 17d. From a solution of epoxy sulfoxide **3d**[2] (52 mg, 0.15 mmol, 1.0 equiv) in 0.6 mL of EtOH and a suspension generated from $(PhSe)_2$ (28 mg, 0.09 mmol, 0.6 equiv) in 0.75 mL of EtOH and $NaBH_4$ (29 mg, 0.75 mmol, 5 equiv), according to the general procedure (1.5 h), an 86:14 mixture of diols **16d** and **17d** was obtained. Purification by chromatography (20−80% EtOAc/hexane) gave **16d** (26 mg, 81%) and **17d** (4 mg, 13%) as colorless oils. In a related experiment from a solution of epoxy sulfone **4d**[4] (1.57 g, 4.3 mmol, 1.0 equiv) in 8.0 mL of EtOH and a suspension generated from $(PhSe)_2$ (2.01 g, 6.45 mmol, 1.5 equiv) in 26 mL of EtOH and $NaBH_4$ (1.80 g, 47.3 mmol, 11 equiv), according to the general procedure (2.5 h), an 85:15 mixture of diols **16d** and **17d** was obtained. Purification by chromatography (40−80% EtOAc/hexane) gave **16d** (698 mg, 77%) and **17d** (123 mg, 13%) as colorless oils. Data for **16d**: R_f 0.13 (50% EtOAc/CH_2Cl_2). ^{1}H NMR (300 MHz) δ 2.04 (ddd, 1 H, J = 14.0, 3.4, 0.9 Hz), 2.47 (ddd, 1 H, J = 14.0, 9.4, 5.2 Hz), 2.90 (br s, 2 H), 3.60 (dd, 1 H, J = 11.5, 3.0 Hz), 3.91 (dd, 1 H, J = 11.5, 2.4 Hz), 4.21 (dd, 1 H, J = 4.9, 2.9 Hz), 4.33 (ddd, 1 H, J = 9.9, 5.7, 3.1 Hz), 4.80 (d, 1 H, J = 2.7 Hz), 7.00−7.07 (m, 2 H), 7.32−7.37 (m, 2 H). ^{13}C NMR (75 MHz) δ 36.7, 64.5, 73.0, 77.8, 85.1, 115.2 (2 C, J_{C-F} = 21.2 Hz), 128.5 (2 C, J_{C-F} = 8.1 Hz), 132.4, 162.3 (J_{C-F} = 245.8 Hz). IR (film): 3350, 2938, 1606, 1512, 1445, 1294, 1222, 1157, 1118, 1059, 927, 877, 850, 808, 777 cm^{-1}. MS (ES): 235 $[M + Na]^+$ (100%), 230, 213 $[M + 1]^+$. Anal. Calcd for $C_{11}H_{13}FO_3$: C, 62.26; H, 6.17. Found: C, 62.45; H, 6.46. Data for **17d**: R_f 0.08 (50% EtOAc/CH_2Cl_2). ^{1}H NMR (200 MHz) δ 1.92 (ddd, 1 H, J = 13.0, 6.8, 3.8 Hz), 1.94 (br s, 2 H), 2.09 (ddd, 1 H, J = 13.2, 8.4, 6.8 Hz), 3.64 (dd, 1 H, J = 11.9, 5.3 Hz), 3.86 (dd, 1 H, J = 11.9, 2.9 Hz), 4.20 (ap dt, 1 H, J = 7.0, 4.1 Hz), 4.37 (m, 1 H), 4.69 (d, 1 H, J = 4.4 Hz), 7.02 (ap t, 2 H, J = 8.7 Hz), 7.32 (ap dd, 2 H, J = 8.4, 5.3 Hz). ^{13}C NMR (50 MHz) δ 36.3, 64.7, 78.6, 77.8, 87.5, 115.4 (2 C, J_{C-F} = 21.5 Hz), 127.6 (2 C, J_{C-F} = 8.0 Hz), 136.0, 162.5 (J_{C-F} = 246.0 Hz). IR (film): 3368, 2928, 1606, 1511, 1225, 1045, 832, 757 cm^{-1}. MS (ES): 235 $[M + Na]^+$ (100%), 213 $[M + 1]^+$. Anal. Calcd for $C_{11}H_{13}FO_3$: C, 62.26; H, 6.17. Found: C, 62.54; H, 6.33.

General Procedure for Cleavage of Sulfonyl Oxiranes with $MgBr_2$ and MgI_2. A two-necked round-bottomed flask fitted with a condenser was charged with a suspension of dry Mg turnings (stored in an oven overnight) in anhydrous Et_2O (5 mL/mmol of Mg). Then, 1,2-diiodoethane or 1,2-dibromoethane (1.2 equiv relative to Mg) was added at room temperature, and the mixture was stirred for about 30 min or until disappearance of Mg was observed, to produce a ca. 0.2 M solution of MgX_2 in Et_2O that could be stored in a refrigerator under argon for a few days. To a cold (0 °C) solution of epoxy sulfone, previously azeotroped with anhydrous cyclohexane, in anhydrous Et_2O (5 mL/mmol of sulfone) was added MgX_2 (5−9 equiv of the above solution), and the reaction mixture was allowed to warm to room temperature and monitored by TLC until disappearance of starting material was observed. The reaction was then quenched with 5% $NaHCO_3$ solution (10 mL/mmol) and 1 M $Na_2S_2O_4$ solution (10 mL/mmol), the layers were separated, the aqueous layer was extracted with EtOAc (3 × 10 mL/mmol), and the combined organic layers were washed with a saturated solution of NaCl and dried over anhydrous $MgSO_4$. Removal of the drying agent and concentration of the solution under reduced pressure gave a crude product that was purified by column chromatography on silica gel using the appropriate mixture of eluents.

Synthesis of (+)-(2*R*,5*R*)-5-(*tert*-Butyldimethylsilyloxymethyl)-2-isopropyl-3-oxotetrahydrofuran, (+)-22a. From sulfonyl oxirane **(+)-11a** (31 mg, 0.073 mmol, 1.0 equiv) in 0.4 mL of Et_2O, with MgI_2 (2.9 mL from a ca. 0.2 M solution in Et_2O, 8.0 equiv) according to the general procedure (0 °C to room temperature, 46 h), and after chromatography (10−20% CH_2Cl_2/hexane), ketone **(+)-22a** (16.3 mg, 82%) was obtained. Data for **(+)-22a**: R_f 0.31 (CH_2Cl_2). $[\alpha]^{20}_D$ +64.4 (*c* 0.64). ^{1}H NMR (300 MHz) δ 0.07 (s, 6 H), 0.88 (s, 9 H), 0.89 (d, 3 H, J = 6.1 Hz), 1.01 (d, 3 H, J = 7.0 Hz), 2.03 (hept d, 1H, J = 6.9, 3.9 Hz), 2.39 (s, 1 H), 2.41 (d, 1 H, J = 2.3 Hz), 3.64 (d, 1 H, J = 3.9 Hz), 3.77 (dd, 1 H, J = 11.1, 4.0 Hz), 3.85 (dd, 1 H, J = 11.1, 3.8 Hz), 4.14−4.22 (m, 1 H, J = 7.4, 3.8 Hz). ^{13}C NMR (75 MHz) δ −5.4, −5.3, 16.9, 18.4, 18.8, 25.9 (3 C), 30.3, 40.0, 64.4, 75.8, 85.6, 216.4. IR (film): 2926, 2855, 1741, 1710, 1436, 1269, 1162 cm^{-1}. MS (ES): 295 $[M + Na]^+$ (100%), 273 $[M + 1]^+$. Anal. Calcd for $C_{14}H_{28}O_3Si$: C, 61.72; H, 10.36. Found: C, 61.37; H, 10.53.

Acknowledgment. This research was supported by DGICYT (BQU2003-02921) and CAM (GR/SAL/0823/2004). We thank JANSSEN-CILAG for generous additional support. We thank CAM, CSIC, and MEC for doctoral fellowships to C.M. and A.C. and M.U.

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

JO051459K