Synthesis of Five-, Six-, and Seven-Membered Heterocycles by Intramolecular Ring Opening Reactions of 3-Oxetanol Derivatives

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Intramolecular ring opening reactions of 2-phenyl-3-oxetanols have been studied. The starting materials were prepared by the photocycloaddition of benzaldehyde and various silyl enol ethers. The intramolecular nucleophile was either incorporated into the silyl enol ether prior to the Paternò−Büchi reaction (oxetanes **3**, **16**) or was later installed by functional group interconversion (oxetanes **5**, **12**). With anionic heteroatom nucleophiles (O, N, S) which were attached to the carbon atom C-3 of the trimethylsilyl-protected oxetanol via an alkyl chain, a substitution at the less substituted position C-4 was observed and the corresponding heterocycles (**6**, **8**, **13**, **19**) were obtained in moderate to good yields (52−91%). Upon acid catalysis a ring opening of the Boc-protected 3-oxetanol **23** to cyclic carbonates occurred. The reaction did not proceed stereospecifically and resulted in a mixture of diastereomeric products **24** and **25**.

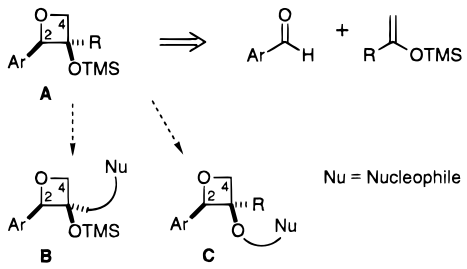
Introduction

Diastereomerically pure 2-aryl-3-silyloxyoxetanes **A** can be readily obtained by the photocycloaddition of aromatic aldehydes and β-unsubstituted silyl enol ethers (Scheme 1).[1] The synthetic relevance of this C−C bond-forming reaction rests to a considerable extent on the further use of the oxetanes by ring-opening processes.[2] Two positions (C-2 and C-4) in the oxetanes **A** (Scheme 1) are amenable to nucleophilic attack. Ring opening between O and C-4 leaves the relative configuration established in the photochemical step untouched, whereas a ring opening between O and C-2 may change the relative configuration depending on the mechanism of the nucleophilic displacement reaction. In terms of regioselectivity, the oxetanes should behave similarly to oxiranes (epoxides).[3] An S_N2 type nucleophilic substitution with an anionic nucleophile is expected to occur at the least substituted position (C-4).[4] Precoordination of the oxetane to a Lewis acid, however, may lead to a lengthening of the bond between O and C-2, the extreme being the formation of a carbenium ion (S_N1 type reaction). In such a distorted cyclic ether a nucleophile will attack the carbon atom which is more loosely bound to the oxygen atom (C-2).

In connection with our studies on 3-oxetanol derivatives such as **A,** we have found most intermolecular ring opening reactions not suited to facilitate a cleavage of the oxetane nucleus in satisfactory yields.[5] Only if an intramolecular assistance is provided either by a hydroxy or an amino group does a clean intermolecular reaction occur.[6] As an alternative one can apply fragmentation reactions which make use of an exocyclic substituent.[1] Finally, a protected heteroatom nucleophile can be attached to the oxetane and made to react intramolecularly after deprotection or activation. In this particular case the oxetane ring opening represents equally well a ring closure (cyclization) to a new heterocyclic ring system. We have attempted to realize the latter approach in order to prepare five-, six-, and seven-membered heterocycles stereoselectively by nucleophilic ring opening.[7] Previous work in this area has centered on the Brönsted or Lewis acid-catalyzed ring opening with oxygen nucleophiles[8] and on C−C bond-forming reactions.[9] Nitrogen and sulfur nucleophiles have not yet been used for an intramolecular attack.

Two different positions for the attachment of an intramolecular nucleophile are conceivable in oxetane **A**.

Scheme 1



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‡ Universität Münster
§ Undergraduate Research Participant (Summer 1997)

(1) Bach, T.; Jödicke, K.; Kather, K.; Fröhlich, R. *J. Am. Chem. Soc.* **1997**, *119*, 2437 and refs. cited therein.
(2) Reviews: (a) Bach, T. *Liebigs Ann.* **1997**, 1627. (b) Bach, T. *GIT Labor-Fachzeitschrift* **1997**, *41*, 299.
(3) Reviews: (a) Kropf, H.; Thiem, J.; Nimz, H. In *Methoden der Organischen Chemie (Houben-Weyl)*, 4th ed.; Kropf, H., Ed.; Thieme: Stuttgart, 1979; Vol. VI/1a, p 338. (b) Lewars, E. G. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Pergamon Press: Oxford 1984; Vol. 7, p 96.
(4) General reviews on oxetane ring opening: (a) Searles, S. In *The Chemistry of Heterocyclic Compounds;* Weissberger, A., Ed.; Wiley-Interscience: New York, 1964; Vol. 19−2, p 983. (b) Searles, S. In *Comprehensive Heterocyclic Chemistry;* Katritzky, A. R., Ed.; Pergamon Press: Oxford, 1984; Vol. 7, p 363.
(5) Bach, T.; Jödicke, K. *Chem. Ber.* **1993**, *126*, 2457.
(6) (a) Bach, T.; Kather, K. *J. Org. Chem.* **1996**, *61*, 3900. (b) Bach, T.; Schröder, J. *Tetrahedron Lett.* **1997**, *38*, 3707. (c) Bach, T.; Eilers, F.; Kather, K. *Liebigs Ann.* **1997**, 1529.
(7) Preliminary communication: Bach, T.; Kather, K. *J. Org. Chem.* **1996**, *61*, 7642.
(8) (a) Corey, E. J.; Raju, N. *Tetrahedron Lett.* **1983**, *24*, 5571. (b) Khan, N.; Morris, T. H.; Smith, E. H.; Walsh, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 865. (c) Itoh, A.; Hirose, Y.; Kashiwagi, H.; Masaki, Y. *Heterocycles* **1994**, *38*, 2165.
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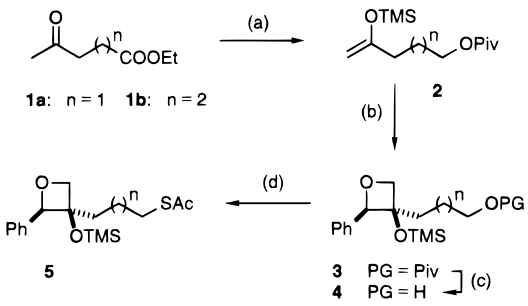
Scheme 2[a]

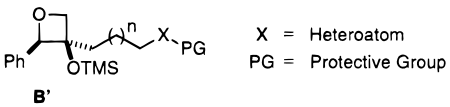


[a] Reagents, conditions, and yields: (a) five steps; see ref 11. **2a**: 68%; **2b**: 82%. (b) PhCHO, *hν*, 30 °C (PhH), **3a**: 65% (d.r. = 88/12); **3b**: 63% (d.r. = 84/16). (c) MeLi, 25 °C (Et_2O), >95%. (d) AcSH, PPh_3, DEAD, 0 °C → 25 °C (THF), **5a**: 87%; **5b**: 83%.

First, as depicted in Scheme 1, a nucleophile can be connected to the carbon atom C-3 of oxetane **B** by a carbon chain of variable length. Second, the oxetanol oxygen may serve as a site to which an intramolecular nucleophile can be attached. After deprotection of 3-silyloxyoxetane **A**, compounds **C** are available by *O*-alkylation or *O*-acylation of the intermediate oxetanol.[10] We have undertaken experiments related to both cases illustrated by **B** and **C** in Scheme 1. The results of this study are presented in the following account.

Results and Discussion

Compounds **B′** were identified as representative examples for oxetanes which contain an intramolecular nucleophile. We envisaged oxygen, sulfur, and nitrogen as synthetically relevant heteroatoms (X), the protective group (PG) of which was to be cleaved before a possible nucleophilic attack.



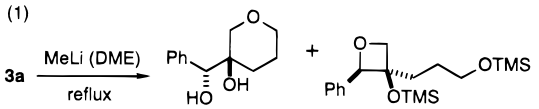
B′

For the preparation of compounds **B′** it appeared most feasible to start from a silyl enol ether which already bears a latent nucleophile in its side chain. In contrast to silyl enol ethers containing an amide or hydroxy moiety,[11] the corresponding derivatives from alkylcarbonyloxy-substituted alkylmethyl ketones can be readily synthesized. We selected the pivaloyl (Piv) substituted silyl enol ethers **2** which were prepared from the keto esters **1** and which reacted well in the photocycloaddition to benzaldehyde (Scheme 2). The oxetanes **3** were formed in decent yields with good diastereoselectivities. These compounds served as starting materials for the preparation of other oxetanes which carry a heteroatom in the side chain. The protected thiols **5** were obtained after selective deprotection of the pivaloyl esters **3** with methyllithium in ether and subsequent Mitsunobu reaction[12] of alcohols **4** with thiolacetic acid.[13]

The free alcohols **4** are not stable and they should be used immediately after they have been prepared. Intra- or intermolecular migration of the TMS group occurs upon standing. In the case of alcohol **4a,** its position isomers, i.e. the 3-trimethylsilyloxypropyl-substituted 3-oxetanol, and the disilylated diol were observed as degradation products.

Intramolecular Attack of an Alkoxide. Alkoxides are formed as intermediates during the removal of the pivaloyl group as described above (Scheme 2). Upon treatment with methyllithium in ether, the cleavage of ester **3** occurs within 1 h at room temperature and an intramolecular oxygen nucleophile is generated. However, we did not detect any ring-expanded heterocycles even after extended periods of time at reflux in ether as solvent. Due to the lability of alcohols **4,** a deprotonation with base did not appear suited as an efficient way to form an alkoxide. Success was encountered in the case of oxetane **3a** after the solvent had been changed from ether to dimethoxyethane (DME). The deprotection was carried out with methyllithium at room temperature. Subsequent heating to reflux temperature (84 °C) yielded the desired tetrahydropyran **6a** after workup (eq 1). In

(1)



6a (54%) **7** (13%)

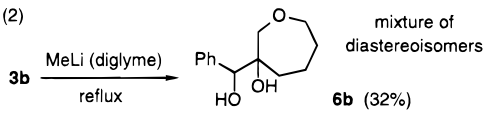
addition, an intermolecular silyl transfer took place. Consequently, a part of the intermediate alkoxide was captured by the formation of the unreactive product **7** losing its nucleophilicity.

The regioselectivity of the ring opening was deduced from the structure of tetrahydropyran **6a**. MS data revealed the expected α-cleavage of the PhCHOH fragment from the heterocycle. Indeed, both significant ions [$PhCHOH^+$] (37%) and [M^+ − PhCHOH] (19%) were detected. The putative regioisomeric product should readily lose a CH_2OH fragment ($m/z = 31$). The ion [M^+ − 31] was not observed. In addition, ^1H NMR spectra recorded in DMSO-d_6 exhibited a doublet and a singlet for the OH protons. This result correlates with structure **6a**, whereas the OH protons of the regioisomer would account for a triplet and a singlet.

For all other products described below, these two methods were routinely applied to secure the regioselectivity of the nucleophilic substitution. As already mentioned, an attack of the nucleophile at the more accessible, less substituted C-4 position was to be foreseen and was indeed observed. With all anionic heteroatom nucleophiles there were no hints pointing toward an attack at the oxetane's carbon atom C-2.

The ring opening of the homologue **3b** turned out to be less facile. Employing the very same conditions used for the reaction of oxetane **3a** (MeLi, DME, reflux) resulted only in the removal of the pivaloyl group, and alcohol **4b** was isolated in 68% yield together with the fully deprotected diol (15%). Replacing DME as solvent with the high boiling (162 °C) diethylene glycol dimethyl ether (diglyme) successfully induced a ring opening to the seven-membered oxepane **6b** (eq 2).

(2)



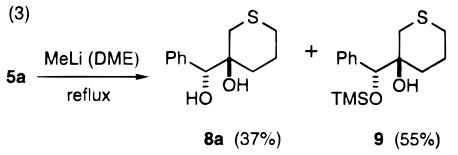
6b (32%)

Unfortunately, the drastic reaction conditions gave rise to an undesired epimerization. In view of earlier obser-

(10) Bach, T.; Kather, K. *J. Prakt. Chem.* **1996**, *338*, 750.
(11) Bach, T. *Liebigs Ann.* **1995**, 855.
(12) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 339.

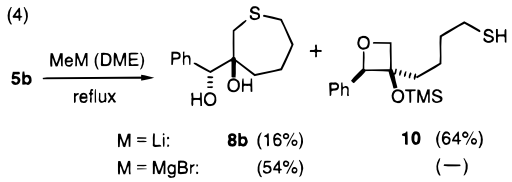
vations,[10] it is likely that a deprotonation/protonation sequence induced by the alkoxide is responsible for this phenomenon. We have not been able to find milder conditions which suppress an epimerization. A variation of the counterion (vide infra) was not successful, either.

Intramolecular Attack of a Thioalkoxide. The higher nucleophilicity of sulfur as compared to oxygen nucleophiles let us hope for a smooth ring opening of oxetanes **5**.[14] Compound **5a** fulfilled this hope without any complications. Its acetyl group was removed following the same protocol previously applied to the *O*-pivaloates **3**. Upon heating in DME, the resulting thioalkoxide underwent a smooth cyclization/ring opening to the desired thiotetrahydropyran (eq 3). After workup the heterocyclic products proved to be a mixture of diol **8a** and silyl ether **9**.

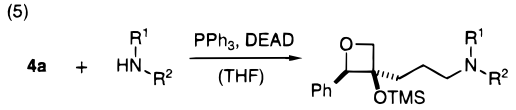


Both compounds were separated and characterized. On the basis of MS and NMR analyses, the silyl group in **9** is attached to the secondary and not to the tertiary alkoxy group. In the course of the reaction a migration must have occurred and the less congested silyl ether was formed. Preparatively, it proved most convenient to deprotect alcohol **9** by treating the crude product mixture with K_2CO_3 in methanol and to isolate only the diol **8a**. The total yield is not deteriorated by this minor modification and it remained high (91%).

Sulfur compound **5b** was less prone to the desired ring opening. The standard conditions (vide supra) yielded only minor amounts of the thiooxepane **8b** (16%) accompanied by the deprotected thiol **10** (64%). We were pleased to find that the counterion of the thioalkoxide can exert a beneficial influence on its nucleophilicity or, alternatively, on the electrophilicity of the oxetane. Methylmagnesium bromide turned out to be the reagent of choice for the sequence acetyl cleavage/thiooxepane formation. The yield of the desired heterocyclic product **8b** rose to 54%. Compound **8b** was isolated in diastereomerically pure form and no epimerized product was observed.



Intramolecular Attack of an Amide. In contrast to the chalkogen nucleophiles O and S, the nucleophilicity of amides depends on an additional substituent not located within the alkyl chain.[15] Due to this increase in the number of possible substitution patterns, we have synthesized several oxetanes which bear electronically different nitrogen atoms (eq 5). The idea was to install



11a	R^1 = Ac	R^2 = OBn	**12a**	(28%)	
11b	R^1 = Boc	R^2 = Ts	**12b**	(96%)	
11c	R^1 = Fmoc	R^2 = Ts	**12c**	(61%)	R^1 = H
11d	R^1 = Tf	R^2 = Bn	**12d**	(92%)	

one protective group (R^1) at nitrogen which is labile under basic or nucleophilic conditions. The second substituent R^2 should resist removal and remain at nitrogen in the consecutive substitution step.

Except for the hydroxamic acid derivative **11a,** which led partially to *O*-alkylation, the Mitsunobu reaction proceeded cleanly and in good yields.[16] To our surprise, the 9-fluorenylmethoxycarbonyl (Fmoc) protected toluenesulfonamide **11c** gave the free 3-tosylaminopropyl oxetane **12c,** which in contrast to alcohols **4** can be stored at room temperature for some time.

Following the protocol employed for the previous ring openings, we attempted to react the nitrogen-substituted oxetanes **12a** and **12d** after in situ deprotection. The acetyl group of **12a** was cleaved with methylmetal compounds (MeLi, MeMgBr). For the trifluormethansulfonyl (Tf) group of **12d,** $LiAlH_4$ was used as recommended in the literature.[17] Disappointingly, no ring-opened product was found in either case under a variety of conditions. Instead, the decomposition of the oxetanes was the major pathway. At elevated temperature oxetane **12a** was fully deprotected at the nitrogen atom and yielded the 3-aminopropyl-substituted product.

Next, we turned to the readily availble tosylated substrate **12c**. Deprotonation of this compound should generate an amide anion which can attack the oxetane nucleus. Originally, we had planned the synthesis of **12c** starting from the *N*-Boc derivative **12b** by thermal removal of the Boc group.[18] As problems were encountered for this particular substrate in this process, both in terms of yield (55% at best) and in terms of reproducibility, we used the Fmoc-protected sulfonamide **11c** for the preparation of **12c**. Sulfonamide **11c** was easily obtained from TsNCO and 9-fluorenylmethanol in analogy to Weinreb's procedure[16b] (93% yield). The attempted ring opening after deprotonation of amide **12c** with sodium (NaH) and lithium (MeLi, LDA) bases remained unsuccessful, and none of the desired piperidine was formed. As in the case of oxetane **5b,** magnesium as

(13) Volante, R. P. *Tetrahedron Lett.* **1981**, *22*, 3119.

(14) Intermolecular ring opening by sulfur nucleophiles: (a) Searles, S. *J. Am. Chem. Soc.* **1951**, *73*, 4515. (b) Whistler, R. L.; Luttenegger, T. J.; Powell, R. M. *J. Org. Chem.* **1968**, *33*, 396. (c) Godziela, G.; Tonker, T.; DuBois, M. R. *Organometallics* **1989**, *8*, 2220. (d) Xianming, H.; Kellogg, R. M. *Tetrahedron: Asymmetry* **1995**, *6*, 1399.

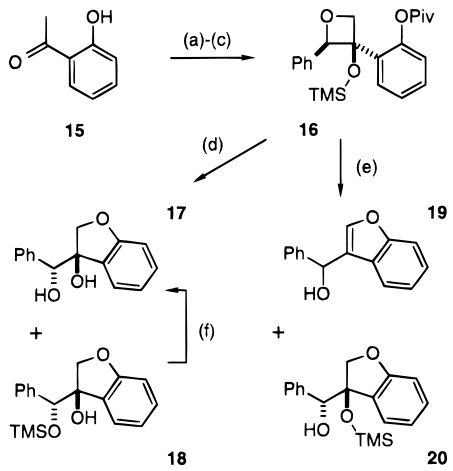
(15) Intermolecular ring opening by nitrogen nucleophiles: (a) Searles, S.; Gregory, V. P. *J. Am. Chem. Soc.* **1954**, *76*, 2789. (b) Mullis, J. C.; Weber, W. P. *J. Org. Chem.* **1982**, *47*, 2873. (c) Gassman, P. G.; Haberman, L. M. *Tetrahedron Lett.* **1985**, *26*, 4971. (d) Chini, M.; Crotti, P.; Favero, L.; Macchia, F. *Tetrahedron Lett.* **1994**, *35*, 761. (e) Crotti, P.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **1994**, *35*, 7089. (f) Meguro, M.; Asao, N.; Yamamoto, Y. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2597.

(16) (a) **11a**: Lee, B. H.; Miller, M. J. *J. Org. Chem.* **1983**, *48*, 24. (b) **11b**: Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D., Jr.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709. (c) **11d**: Bell, K. E.; Knight, D. W.; Gravestock, M. B. *Tetrahedron Lett.* **1995**, *36*, 8681.

(17) Hendrickson, J. B.; Bergeron, R.; Sternbach, D. D. *Tetrahedron* **1975**, *31*, 2517.

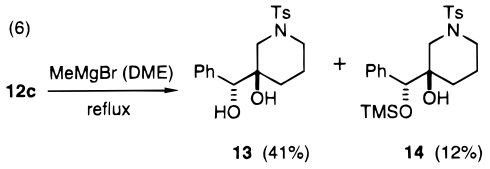
(18) Rawal, V. H.; Jones, R. J.; Cava, M. P. *J. Org. Chem.* **1987**, *52*, 19.

Scheme 3[a]



[a] Reagents, conditions, and yields: (a) PivCl, NEt_3, DMAP, 25 °C (CH_2Cl_2), 99%. (b) LDA, TMSCl, −78 °C → 25 °C (THF), 99%. (c) PhCHO, *hν*, 30 °C (PhH), 37%. (d) MeLi, 25 °C → 85 °C (DME), **17**: 70%; **18**: 21%. (e) MeMgBr, 25 °C → 85 °C (DME), **19**: 83%; MeMgBr, 25 °C (Et_2O), **19**: 32%; **20**: 24%. (f) K_2CO_3, 25 °C (MeOH), quant.

counterion proved to be a more fortitious choice. Upon treatment of **12c** with MeMgBr at ambient temperature in DME and after subsequent heating the heterocycle **13** was generated (eq 6).

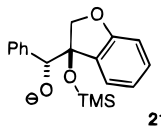


As some silylated product **14** was also detected, the crude product mixture was completely desilylated (K_2CO_3, MeOH). With this modification the yield of piperidine **13** was improved to 52%. Still, the nitrogen nucleophiles under scrutiny cannot compete with the sulfur nucleophile with regard to nucleophilicity and we therefore did not attempt a ring opening/cyclization to a seven-membered azepane.

Intramolecular Attack of a Phenoxide. As a prototypical substrate with a protected intramolecular phenoxide we selected oxetane **16**. This compound is obtained readily from 2-hydroxyacetophenone (**15**) in three steps (Scheme 3): pivaloyl protection,[11] silyl enol ether formation,[5] and photocycloaddition.[5] The sequence proceeded uneventfully but, as observed earlier with related α-aryl silyl enol ethers, the Paternò−Büchi reaction is sluggish. A possible reason may be a triplet energy transfer from the photoexcited aldehyde to the alkene.

The ring opening of oxetane **16** occurred without any problems. Indeed, due to the cis-arrangement of the enolate in the aromatic side chain, this substrate is predisposed toward an effective ring expansion. Treatment of compound **16** with MeLi in DME and subsequent reflux yielded the desired diol **17** in combination with its monosilylated derivative **18** (Scheme 3). In analogy to what had happened during thiotetrahydropyran formation (**8a**/**9**), the TMS group migrated to the less congested secondary alkoxy group. Desilylation (K_2CO_3, MeOH) to diol **17** is facile, but it should be noted that **17** is prone to an elimination to benzofuran **19**. The dehydration occurred for example upon drying in vacuo. Diol **17** was therefore always slightly contaminated with some benzofuran **19**. The tendency to eliminate water was less pronounced in the silyl ether **18,** which could be obtained in analytically pure form.

If magnesium was used as the counterion for the intramolecular phenoxide nucleophile, the direct formation of benzofuran **19** was the major reaction pathway. A reasonable explanation for the different behavior of the lithium and magnesium reagents can be based on the migratory aptitudes of the silyl group. Silyl ether **20** was isolated from the MeMgBr-induced ring opening at lower temperature (rt) in ether. It is indicative of the fact that there is no silyl migration in the intermediate alkoxide **21** if magnesium is the counterion. For lithium as



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counterion, the migration takes place and an elimination to benzofuran **19** is prevented. As shown in a control experiment, diol **17** does not undergo an elimination if subjected to the reaction conditions of the MeMgBr-initiated ring opening. Silyl ether **20** or the alkoxide **21**, however, are forced to undergo an elimination with excess base by an E2 or E1cB pathway.

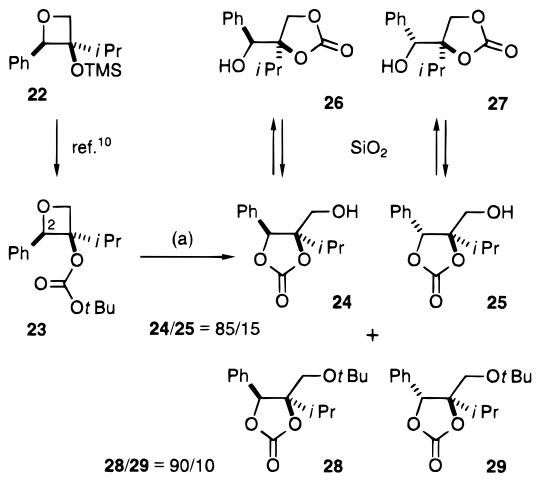
An interesting observation was made running the reaction with MeMgBr in ether at room temperature. The oxetane **16** used was not diastereomerically pure (diastereomeric ratio d.r. = 87/13) and the ring expansion remained incomplete. Besides the already mentioned silyl ether **20** (24%) and benzofuran **19** (32%), starting material (17%) was isolated whose diastereomeric composition was determined to be d.r. = 69/31. Obviously, the major diastereoisomer **16** had reacted much faster in the ring opening than its epimer. Indeed, since no silyl ether diastereomeric to **20** was isolated, it appears as if the diastereoisomer of **16** is not reactive at all. Clearly, the phenoxide derived from **16** can react intramolecularly in an S_N2 type reaction whereas S_N2 attack is hindered in its diastereomer.

Intramolecular Attack of a Carbonate. In the context of recent work on the ring opening of 3-aminooxetanes, it was observed that *N*-Boc-protected 3-amino-2-aryloxetanes undergo a stereospecific ring opening at the C-2 position.[6b] Acid catalysis led to the formation of oxazolidinones in which the configuration of the oxetane's former C-2 atom was inverted. The latter result suggests a reaction course via a protonated oxetane which is attacked by the weak intramolecular nucleophile fast enough to avoid epimerization.

In analogy to these experiments, we hoped for an acid-catalyzed intramolecular ring opening of oxetane **23** to a cyclic carbonate with complete inversion of configuration at C-2 (Scheme 4).[19] This method, together with ring opening reactions which occur at C-4 (retention of configuration at C-2),[6] would enable access to 1,2-diols with either relative configuration starting from readily avail-

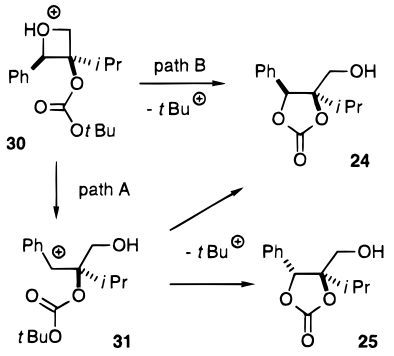
(19) For related epoxide ring opening reactions, see: (a) Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109. (b) Corey, E. J.; Hopkins, P. B.; Munroe, J. E.; Marfat, A.; Hashimoto, S.-i. *J. Am. Chem. Soc.* **1980**, *102*, 7986. (c) Roush, W. R.; Brown, R. J.; DiMare, M. *J. Org. Chem.* **1983**, *48*, 5083.

Scheme 4[a]



[a] Reagents, conditions, and yields: (a) TFA, −20 °C → 25 °C (CH_2Cl_2), mixture of **24**−**27**: 62% (ratios: **24**/**26** = 46/56; **25**/**27** = 16/84); mixture of **28** and **29**: 20% (**28**/**29** = 90/10).

Scheme 5

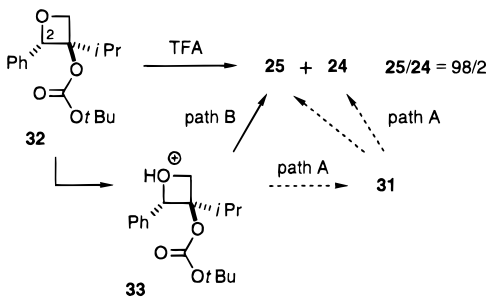


able diastereomerically pure 3-silyloxyoxetanes, such as **22**. Unfortunately, it turned out that the reaction is *not* stereospecific. Upon treatment of oxetane **23** with trifluoroacetic acid (TFA) the two diastereomeric cyclic carbonates **24** and **25** were isolated in a ratio (d.r.) of 85/15. The relative configuration of the dioxolanones was deduced from ^{1}H NOE studies.

Upon attempted purification by chromatography, a rearrangement to the less substituted heterocyclic compounds **26** and **27** occurred which we were not able to suppress. Flash chromatography[20] therefore delivered a 46/54 mixture of the two products **24**/**26** and a 16/84 mixture of **25**/**27** in an unseparable mixture of all four compounds. The total yield amounted to 62%. In addition, the *tert*-butyl ethers **28** and **29** of alcohols **24** and **25** were isolated in a ratio which correlates roughly to that of the parent compounds (20%, d.r. = 90/10). Mechanistically, one can envisage a protonated oxetane **30** as a likely intermediate (Scheme 5). Two explanations for the observed product ratio appear plausible. If the bond cleavage between O and C-2 is fast (path A), the product ratio reflects the facial diastereoselection exerted by the chiral substituent in carbenium ion **31**. If the attack of the oxygen nucleophile (path B) can compete with the O−C bond cleavage, the product arises partially from a direct nucleophilic displacement and partially from an S_N1 type reaction of carbenium ion **31**.

(20) Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

Scheme 6



To clarify this question, we prepared the diastereomeric Boc-protected oxetanol **32** from the corresponding 3-silyloxyoxetane.[10] By applying conditions identical to those which induced the rearrangement of compound **23**, oxetanol **32** yielded the cyclic carbonate **25** almost exclusively. The diastereomeric ratio of **25**/**24** in the crude reaction mixture was determined to be 98/2 by ^{1}H NMR. This result is in accord with a reaction which occurs via a direct nucleophilic substitution (path B in Scheme 6). Only a small amount of protonated oxetane **33** undergoes ring opening to a free carbenium ion **31**. A facial diastereoselection via the carbeniumion **31** can be ruled out as **23** and **32** yield different product ratios. Apparently, the Boc group in **32** is situated in a way which enables rapid attack at C-2 after protonation. Contrary to that, the trajectory in intermediate **30** is less favored and a ring opening to carbenium ion **31** takes place to a larger extent.

Conclusion and Outlook

In summary, two major routes for the ring opening of 3-oxetanols have been described. One route employs an intramolecular heteroatom substituent attached to the C-3 carbon atom of the oxetanol via an alkyl or aryl chain. The ring opening is induced by formation of the anionic heteroatom nucleophile which attacks the oxetane in an S_N2 type process at the less substituted C-4 position. By this means tetrahydropyran **6a**, thiotetrahydropyran **8a**, thiooxepane **8b**, piperidine **13**, and dihydrobenzofuran **17** are accessible. The stereochemistry of the stereogenic centers at the oxetanol's C-2 and C-3 is retained. The second ring opening route proceeds at the phenyl-substituted carbon atom C-2 upon activation by acid. The Boc-protected 3-oxetanols **23** and **32** were transformed to the corresponding cyclic carbonates **24** and **25**. As the reaction is not stereospecific, a mixture of diastereoisomers was obtained. In the case of oxetane **23,** the major product was diastereoisomer **24** (d.r. = 85/15), whereas oxetane **32** produced predominantly **25** (d.r. = 98/2). Although inversion of configuration is favored, there is obviously a reaction pathway via a carbenium ion **31** which is responsible for partial retention. If the corresponding intramolecular nucleophile was more nucleophilic, the partial epimerization could possibly be prohibited.

Experimental Section

General. For general remarks, see ref 1. ^{13}C NMR multiplicities were obtained by DEPT experiments.

Preparation of Silyl Enol Ethers 2. The silyl enol ethers were prepared according to a known procedure from the keto

esters **1**.[11] The analytical data for silyl enol ether **2a** are given in the reference.[11]

2,2-Dimethylpropanoic Acid 5-[(Trimethylsilyl)oxy]-5-hexenyl Ester (2b). R_f = 0.64 (CH/EtOAc = 70/30). IR (film): 1720 cm^{-1} (vs, C=O), 1245 (s, $SiMe_3$), 840 (vs, $SiMe_3$). ^1H NMR (acetone-d_6): δ 0.19 (s, 9 H), 1.17 (s, 9 H), 1.48−1.70 (m, 4 H), 2.03−2.08 (m, 2 H), 4.00−4.06 (m, 4 H). ^{13}C NMR (acetone-d_6): δ 0.3 (q), 24.1 (t), 27.6 (q), 28.9 (t), 36.8 (t), 39.3 (s), 64.6 (t), 90.5 (t), 159.9 (s), 178.2 (s). Anal. Calcd for $C_{14}H_{28}O_3Si$ (272.459): C, 61.72; H 10.36. Found: C, 61.87; H, 10.29.

Preparation of Oxetanes 3. The oxetanes were prepared from benzaldehyde and the corresponding silyl enol ether **2** as previously described.[5,11] The analytical data for oxetane **3a** are given in the reference.[11]

(2*RS*,3*RS*)-3-[4-(2,2-Dimethylpropanoyl)oxybutyl]-2-phenyl-3-[(trimethylsilyl)oxy]oxetane (3b). R_f = 0.32 (CH/EtOAc = 90/10). IR (film): 1715 cm^{-1} (vs, C=O), 1240 (s, $SiMe_3$), 980 (m, COC), 830 (s, $SiMe_3$). ^1H NMR ($CDCl_3$): δ −0.16 (s, 9 H), 1.22 (s, 9 H), 1.51−1.79 (m, 4 H), 1.88−1.98 (m, 1 H), 2.06−2.16 (m, 1 H), 4.13 (t, J = 6.4 Hz, 2 H), 4.53 (d, J = 6.5 Hz, 1 H), 4.71 (d, J = 6.5 Hz, 1 H), 5.45 (s, 1 H), 7.23−7.38 (m, 5 H). ^{13}C NMR ($CDCl_3$): δ 1.3 (q), 19.9 (t), 27.2 (q), 28.8 (t), 38.7 (s), 40.4 (t), 64.0 (t), 77.4 (s), 81.8 (t), 92.8 (d), 126.4 (d), 127.2 (d), 127.6 (d), 138.5 (s), 178.4 (s). Anal. Calcd for $C_{21}H_{34}O_4Si$ (378.583): C, 66.63; H, 9.05. Found: C, 66.64; H, 9.17.

General Procedure for the Deprotection of Pivaloates 3 (General Procedure A). A solution of 2.3 mmol of MeLi (1.4 mL of a 1.6 M solution) in ether was added dropwise to a stirred solution of 1.0 mmol of oxetane in 10 mL of ether at room temperature. After complete addition, the solution was stirred for another hour and subsequently quenched with 0.3 mL of a saturated aqueous NH_4Cl solution. The resulting mixture was diluted with ether, and Na_2SO_4 was added. After stirring for 15 min the mixture was filtered by suction through a glass filter. The filtrate was collected and the solvent was removed in vacuo. The crude product (yield > 95%) can be used for further transformations without purification. If desired, it can be purified by flash chromatography.

(2*RS*,3*RS*)-3-(3-Hydroxypropyl)-2-phenyl-3-[(trimethylsilyl)oxy]oxetane (4a) was prepared according to general procedure A. R_f = 0.32 (CH/EtOAc = 50/50). IR (film): 1245 cm^{-1} (vs, $SiMe_3$), 975 (s, COC), 835 (vs, $SiMe_3$). ^1H NMR (DMSO-d_6): δ −0.18 (s, 9 H), 1.47−1.64 (m, 2 H), 1.87 (ddd, J = 14.1 Hz, J = 10.5 Hz, J = 5.5 Hz, 1 H), 2.02 (ddd, J = 14.1 Hz, J = 11.1 Hz, J = 5.2 Hz, 1 H), 3.47 (virt q, $J \approx$ 5.7 Hz, 2 H), 4.45 (t, J = 5.3 Hz, 1 H), 4.49 (d, J = 6.7 Hz, 1 H), 4.61 (d, J = 6.7 Hz, 1 H), 5.41 (s, 1 H), 7.23−7.38 (m, 5 H). ^{13}C NMR (DMSO-d_6): δ 1.6 (q), 26.7 (t), 36.7 (t), 61.0 (t), 77.6 (s), 81.2 (t), 91.9 (d), 126.8 (d), 127.3 (d), 127.7 (d), 138.9 (s). Anal. Calcd for $C_{15}H_{24}O_3Si$ (280.438): C, 64.24; H, 8.63. Found: C, 64.35; H, 8.52.

(2*RS*,3*RS*)-3-(4-Hydroxybutyl)-2-phenyl-3-[(trimethylsilyl)oxy]oxetane (4b) was prepared according to general procedure A. R_f = 0.30 (CH/EtOAc = 50/50). IR (film): 1245 cm^{-1} (vs, $SiMe_3$), 975 (s, COC), 835 (vs, $SiMe_3$). ^1H NMR ($CDCl_3$): δ −0.16 (s, 9 H), 1.49−1.70 (m, 4 H), 1.85−1.95 (m, 1 H), 2.03−2.14 (m, 1 H), 2.57 (s, b, 1 H), 3.67 (t, J = 6.3 Hz, 2 H), 4.53 (d, J = 6.3 Hz, 1 H), 4.70 (d, J = 6.3 Hz, 1 H), 5.46 (s, 1 H), 7.19−7.38 (m, 5 H). ^{13}C NMR ($CDCl_3$): δ 1.3 (q), 19.6 (t), 32.8 (t), 40.5 (t), 62.5 (t), 77.5 (s), 81.9 (t), 92.8 (d), 126.5 (d), 127.2 (d), 127.6 (d), 138.4 (s). Anal. Calcd for $C_{16}H_{26}O_3Si$ (294.465): C, 65.26; H, 8.90. Found: C, 65.32; H, 8.83.

General Procedure for the Mitsunobu Reaction with Thiolacetic Acid (General Procedure B). An 8 mmol (1.39 g, 1.2 mL) portion of diethyl azodicarboxylate (DEAD) was added at 0 °C to a solution of 8 mmol of triphenylphosphine (2.10 g) in 20 mL of THF. After some time (5−50 min) the mixture spontanously turned into a solid. (It is essential for the success of the reaction to wait until the solidification has occurred.) Upon warming (to 5−10 °C) the mixture could be stirred and stirring was continued after cooling to 0 °C. At this temperature a solution of 4 mmol of crude alcohol **4** (prepared according to procedure A) and 8 mmol of thiolacetic acid (609 mg, 0.6 mL) in 10 mL of THF was added dropwise. The resulting clear solution was stirred for 1 h at 0 °C and subsequently warmed to room temperature. After complete consumption of the alcohol (24−48 h), the solvent was removed in vacuo and the resulting solid was thoroughly triturated with a 10/1 (v/v) mixture of pentane/ether. The combined organic layers were concentrated in vacuo and the residual oil was purified by flash chromatography (FC).

(2*RS*,3*RS*)-3-(3-Ethanoylthiapropyl)-2-phenyl-3-[(trimethylsilyl)oxy]oxetane (5a) was prepared from oxetane **3a** according to general procedure B. Eluent (FC): CH/EtOAc = 97/3. Yield: 1.18 g (87%). R_f = 0.54 (CH/EtOAc = 70/30). IR (film): 1680 cm^{-1} (vs, C=O), 1245 (s, $SiMe_3$), 980 (s, COC), 835 (vs, $SiMe_3$). ^1H NMR ($CDCl_3$): δ −0.16 (s, 9 H), 1.72−1.84 (m, 2 H), 1.89−2.01 (m, 1 H), 2.07−2.22 (m, 1 H), 2.35 (s, 3 H), 2.97 (t, J = 7.0 Hz, 2 H), 4.51 (d, J = 6.4 Hz, 1 H), 4.70 (d, J = 6.4 Hz, 1 H), 5.43 (s, 1 H), 7.23−7.38 (m, 5 H). ^{13}C NMR ($CDCl_3$): δ 1.3 (q), 23.7 (t), 29.1 (t), 30.6 (q), 39.7 (t), 77.2 (s), 81.8 (t), 92.7 (d), 126.4 (d), 127.3 (d), 127.7 (d), 138.3 (s), 195.5 (s). Anal. Calcd for $C_{17}H_{26}O_3SSi$ (338.536): C, 60.31; H, 7.74. Found: C, 60.48; H, 7.66.

(2*RS*,3*RS*)-3-(4-Ethanoylthiabutyl)-2-phenyl-3-[(trimethylsilyl)oxy]oxetane (5b) was prepared from oxetane **3b** according to general procedure B. Eluent (FC): CH/EtOAc = 94/6. Yield: 1.17 g (83%). R_f = 0.65 (CH/EtOAc = 50/50). IR (film): 1680 cm^{-1} (vs, C=O), 1245 (s, $SiMe_3$), 975 (m, COC), 835 (s, $SiMe_3$). ^1H NMR ($CDCl_3$): δ −0.23 (s, 9 H), 1.41−1.66 (m, 4 H), 1.78−1.88 (m, 1 H), 1.96−2.06 (m, 1 H), 2.26 (s, 3 H), 2.87 (t, J = 7.1 Hz, 2 H), 4.45 (d, J = 6.2 Hz, 1 H), 4.63 (d, J = 6.2 Hz, 1 H), 5.37 (s, 1 H), 7.16−7.34 (m, 5 H). ^{13}C NMR ($CDCl_3$): δ 1.3 (q), 22.5 (t), 28.9 (t), 29.7 (t), 30.5 (q), 40.2 (t), 77.4 (s), 81.8 (t), 92.7 (d), 126.5 (d), 127.2 (d), 127.6 (d), 138.5 (s), 195.6 (s). Anal. Calcd for $C_{18}H_{28}O_3SSi$ (352.563): C, 61.32; H, 8.01. Found: C, 61.31; H, 7.90.

General Procedure for the Intramolecular Ring Opening (General Procedure C). A solution of 2.4 mmol of MeLi or MeMgBr (1.5 mL of a 1.6 M solution) in ether was added dropwise to a stirred solution of 1.0 mmol of oxetane in 15 mL of DME at room temperature. After complete addition the solution was stirred for another hour and subsequently heated to reflux for the period of time indicated below. Into the hot solution was injected 0.3 mL of a saturated aqueous NH_4Cl solution. The resulting mixture was diluted with ether and Na_2SO_4 was added. After stirring for 15 min the mixture was filtered by suction through a glass filter. The filtrate was collected and the solvent was removed in vacuo. The crude material was purified by flash chromatography (FC).

(3*RS*,1′*RS*)-3-Hydroxy-3-(1-hydroxyphenylmethyl)tetrahydropyran (6a). Tetrahydropyran **6a** was prepared from oxetane **4a** with MeLi in DME according to general procedure C (reflux for 6 h). Eluent (FC): CH/EtOAc = 90/10 → 55/45. Yield: 112 mg (54%). Mp: 130−131 °C. R_f = 0.18 (CH/EtOAc = 50/50). IR (KBr): 3430 cm^{-1} (s, OH), 3300 (s, b, OH), 1070 (vs, COC). ^1H NMR ($CDCl_3$): δ 1.32−1.55 (m, 3 H), 1.70−1.84 (m, 1 H), 2.71 (s, b, 1 H), 2.76 (s, b, 1 H), 3.42 (ddd, J = 10.2 Hz, J = 10.2 Hz, J = 2.7 Hz, 1 H), 3.55 (d, J = 11.7 Hz, 1 H), 3.72−3.81 (m, 1 H), 3.75 (d, J = 11.7 Hz, 1 H,), 4.55 (s, 1 H), 7.26−7.38 (m, 5 H). ^1H NMR (DMSO-d_6): δ 1.13−1.21 (m, 1 H), 1.36−1.48 (m, 2 H), 1.58−1.71 (m, 1 H), 3.29−3.40 (m, 1 H), 3.38 (d, J = 10.7 Hz, 1 H), 3.53−3.59 (m, 1 H), 3.55 (d, J = 10.7 Hz, 1 H), 4.20 (s, 1 H), 4.41 (d, J = 4.9 Hz, 1 H), 5.21 (d, J = 4.9 Hz, 1 H), 7.18−7.36 (m, 5 H). ^{13}C NMR ($CDCl_3$): δ 21.9 (t), 30.3 (t), 68.1 (t), 71.4 (s), 74.0 (t), 76.7 (d), 127.6 (d), 128.0 (d), 128.2 (d), 139.7 (s). Anal. Calcd for $C_{12}H_{16}O_3$ (208.257): C, 69.21; H, 7.74. Found: C, 69.16; H 7.69.

(3*SR*,1′*RS*)-3-Hydroxy-3-(1-hydroxyphenylmethyl)thiotetrahydropyran (8a). Compound **8a** was obtained together with its silyl derivative **9** from oxetane **5a** with MeLi in DME according to general procedure C (reflux for 3 h). After complete desilylation,[10] pure thiotetrahydropyran **8a** was isolated. Eluent (FC): CH/EtOAc = 85/15. Yield: 204 mg (91%). Mp: 94−95 °C. R_f = 0.47 (CH/EtOAc = 50/50). IR (KBr): 3370 cm^{-1} (vs, OH), 3300 (b, sh, OH). ^1H NMR ($CDCl_3$): δ 1.21 (ddd, J = 13.8 Hz, J = 8.8 Hz, J = 7.4 Hz, 1

H,), 1.57 (ddt, J = 13.8 Hz, J = 4.1 Hz, J = 2.1 Hz, 1 H), 1.80−1.89 (m, 2 H), 2.40−2.44 (m, 2 H), 2.69 (d, J = 13.5 Hz, 1 H), 2.78 (d, J = 13.5 Hz, 1 H), 4.59 (s, 1 H), 7.29−7.41 (m, 5 H). ^{13}C NMR ($CDCl_3$): δ 23.5 (t), 28.0 (t), 31.9 (t), 37.5 (t), 69.9 (s), 79.4 (d), 127.7 (d), 127.9 (d), 128.0 (d), 139.6 (s). Anal. Calcd for $C_{12}H_{16}O_2S$ (224.317): C, 64.25; H, 7.19. Found: C, 64.31; H, 7.20.

(3*SR*,1′*RS*)-3-Hydroxy-3-(1-hydroxyphenylmethyl)thiooxepane (8b). Thiooxepane **8b** was prepared from oxetane **5b** with MeMgBr in DME according to general procedure C (reflux for 5 h). Eluent (FC): CH/EtOAc = 95/5 → 85/15. Yield: 129 mg (54%). Mp: 111−112 °C. R_f = 0.44 (CH/EtOAc = 50/50). IR (KBr): 3380 cm^{-1} (vs, OH), 3250 (b, OH). ^{1}H NMR ($CDCl_3$): δ 1.40−1.47 (m, 2 H), 1.54 (s, 1 H), 1.57−1.71 (m, 3 H), 1.92−2.04 (m, 1 H), 2.57−2.74 (m, 2 H), 2.61 (d, J = 4.3 Hz, 1 H), 2.74 (d, J = 14.9 Hz, 1 H), 3.09 (d, J = 14.9 Hz, 1 H), 4.59 (d, J = 4.3 Hz, 1 H), 7.29−7.42 (m, 5 H). ^{13}C NMR ($CDCl_3$): δ 21.8 (t), 31.9 (t), 34.7 (t), 36.7 (t), 40.9 (t), 78.0 (s), 78.3 (d), 127.8 (d), 127.9 (d), 128.1 (d), 140.0 (s). Anal. Calcd for $C_{13}H_{18}O_2S$ (238.344): C, 65.51; H, 7.61. Found: C, 65.37; H, 7.79.

***N*-9-Fluorenylmethyloxycarbonyl-*N*-*p*-toluenesulfonamide (11c)**. At ambient temperature, 6 mmol of solid 9-fluorenylmethanol (1.18 g) was added in portions to a stirred solution of 6 mmol of toluenesulfonyl isocyanate (1.18 g, 0.9 mL) in 6 mL of toluene. The addition was accompanied by a moderate exotherm and a solid precipitated. After the addition was complete, the mixture was stirred for another 10 min and it was subsequently filtered by suction through a glass filter. The solid collected in the filter was washed thoroughly with pentane and dried in vacuo. Yield: 2.20 g (93%). Mp: 170−171 °C. IR (KBr): 3170 cm^{-1} (m, b, NH), 1705 (vs, C═O). ^{1}H NMR (acetone-d_6): δ 2.42 (s, 3 H), 4.18 (t, J = 6.7 Hz, 1 H), 4.39 (d, J = 6.7 Hz, 2 H), 7.26 (dt, J = 7.4 Hz, J = 1.0 Hz, 2 H), 7.38 (t, J = 7.4 Hz, 2 H), 7.41 (d, J = 8.2 Hz, 2 H), 7.61 (d, J = 7.4 Hz, 2 H), 7.82 (d, J = 7.4 Hz, 2 H), 7.89 (d, J = 8.2 Hz, 2 H), 10.49 (s, b, 1 H). ^{13}C NMR (acetone-d_6): δ 21.5 (q), 47.4 (d), 68.4 (t), 120.8 (d), 125.9 (d), 127.9 (d), 128.6 (d), 128.8 (d), 130.4 (d), 137.7 (s), 142.0 (s), 144.3 (s), 145.5 (s), 151.7 (s). Anal. Calcd for $C_{22}H_{19}NO_4S$ (393.456): C, 67.16; H, 4.87; N, 3.56. Found: C, 67.22; H, 4.85; N, 3.72.

General Procedure for the Mitsunobu Reaction with Amides 11 (General Procedure D). Triphenylphosphine and the corresponding amide **11** were dissolved in THF, and the solution was cooled to 0 °C. At this temperature the alcohol **4a** (prepared according to general procedure A) was added to the stirred solution followed by dropwise addition of DEAD. The mixture was subsequently warmed to room temperature. After complete consumption of the alcohol (24−48 h), the solvent was removed in vacuo and the resulting solid was purified by flash chromatography (FC).

(2*RS*,3*RS*)-*N*-Benzyloxy-*N*-[3-[2-phenyl-3-[(trimethylsilyl)oxy]oxetan-3-yl]propyl]acetylamide (12a). Compound **12a** was prepared from 6 mmol of alcohol **4a** (1.68 g), 7.8 mmol of triphenylphosphine (2.05 g), 7.2 mmol of amide **11a** (1.19 g), and 7.8 mmol of DEAD (1.36 g, 1.2 mL) in 60 mL of THF according to general procedure D. Eluent (FC): CH/EtOAc = 85/15 → 80/20. Yield: 724 mg (28%). Mp: 54−56 °C. R_f = 0.28 (CH/EtOAc = 70/30). IR (KBr): 1635 cm^{-1} (m, C═O), 1245 (s, $SiMe_3$), 980 (m, COC), 840 (s, $SiMe_3$). ^{1}H NMR ($CDCl_3$): δ −0.16 (s, 9 H), 1.76−1.89 (m, 2 H), 1.91−2.00 (m, 1 H), 1.97 (s, 3 H), 2.12−2.22 (m, 1 H), 4.04 (dt, J = 6.2 Hz, J = 1.4 Hz, 2 H), 4.52 (d, J = 6.5 Hz, 1 H), 4.71 (d, J = 6.5 Hz, 1 H), 4.94 (s, 2 H), 5.44 (s, 1 H), 7.23−7.38 (m, 10 H). ^{13}C NMR ($CDCl_3$): δ 1.3 (q), 13.7 (q), 23.0 (t), 37.2 (t), 66.3 (t), 75.7 (t), 77.3 (s), 81.8 (t), 92.8 (d), 126.5 (d), 126.5 (d), 127.3 (d), 127.6 (d), 128.2 (d), 128.2 (d), 138.4 (s), 138.4 (s), 162.6 (s). Anal. Calcd for $C_{24}H_{33}NO_4Si$ (427.615): C, 67.41; H, 7.78; N, 3.28. Found: C, 67.31; H, 8.07; N, 3.30.

(2*RS*,3*RS*)-*N*-[3-[2-Phenyl-3-[(trimethylsilyl)oxy]oxetan-3-yl]propyl]-4-toluenesulfonamide (12c). Compound **12c** was prepared from 2.5 mmol of alcohol **4a** (0.70 g), 7.5 mmol of triphenylphosphine (1.97 g), 3.75 mmol of amide **11c** (1.48 g), and 7.8 mmol of DEAD (1.09 g, 1.0 mL) in 35 mL of THF according to general procedure D. Eluent (FC): CH/EtOAc = 80/20 → 70/30. Yield: 661 mg (61%). Mp: 78−80 °C. R_f = 0.27 (CH/EtOAc = 70/30). IR (KBr): 1240 cm^{-1} (s, $SiMe_3$), 955 (m, COC), 835 (s, $SiMe_3$). ^{1}H NMR ($CDCl_3$): δ −0.21 (s, 9 H), 1.57−1.67 (m, 2 H), 1.78−1.88 (m, 1 H), 2.00−2.08 (m, 1 H), 2.40 (s, 3 H), 3.03 (virt dq, $J \approx$ 6.9 Hz, J = 2.8 Hz, 2 H), 4.44 (d, J = 6.4 Hz, 1 H), 4.66 (d, J = 6.4 Hz, 1 H), 5.06 (t, J = 6.2 Hz, 1 H), 5.31 (s, 1 H), 7.22−7.36 (m, 7 H), 7.78 (d, J = 8.3 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ 1.3 (q), 21.4 (q), 23.9 (t), 37.8 (t), 43.3 (t), 77.0 (s), 81.5 (t), 92.5 (d), 126.3 (d), 127.1 (d), 127.3 (d), 127.7 (d), 129.7 (d), 137.2 (s), 138.2 (s), 143.4 (s). Anal. Calcd for $C_{22}H_{31}NO_4SSi$ (433.637): C, 60.94; H, 7.21; N, 3.23. Found: C, 60.86; H, 7.10; N, 3.47.

(2*RS*,3*RS*)-*N*-Phenylmethyl-*N*-[3-[2-phenyl-3-[(trimethylsilyl)oxy]oxetan-3-yl]propyl]trifluoromethanesulfonamide (12d). Compound **12d** was prepared from 5 mmol of alcohol **4a** (1.40 g), 5.5 mmol of triphenylphosphine (1.44 g), 5 mmol of amide **11d** (1.20 g), and 5.5 mmol of DEAD (0.96 g, 0.90 mL) in 10 mL of THF according to general procedure D. Eluent (FC): CH/EtOAc = 90/10 → 80/20. Yield: 2.31 g (92%). Mp: 89−90 °C. R_f = 0.52 (CH/EtOAc = 90/10). IR (KBr): 1245 cm^{-1} (s, $SiMe_3$), 975 (m, COC), 830 (s, $SiMe_3$). ^{1}H NMR ($CDCl_3$): δ −0.22 (s, 9 H), 1.53−1.75 (m, 3 H), 1.88−1.98 (m, 1 H), 3.39 (t, J = 7.5 Hz, 2 H), 4.34 (d, J = 6.4 Hz, 1 H), 4.56 (s, b, 2 H), 4.63 (d, J = 6.4 Hz, 1 H), 5.16 (s, 1 H), 7.18 (dd, J = 7.6 Hz, J = 1.4 Hz, 2 H), 7.23−7.43 (m, 8 H). ^{13}C NMR ($CDCl_3$): δ 1.2 (q), 22.6 (t), 37.6 (t), 49.0 (t), 52.8 (t), 76.8 (s), 81.4 (t), 92.4 (d), 126.3 (d), 127.4 (d), 127.7 (d), 128.5 (d), 128.8 (d), 129.0 (s), 129.1 (d), 134.6 (s), 138.1 (s). Anal. Calcd for $C_{23}H_{30}F_3NO_4SSi$ (501.635): C, 55.07; H, 6.03; N, 2.79. Found: C, 55.03; H, 5.84; N, 2.99.

(3*RS*,1′*RS*)-3-Hydroxy-3-(1-hydroxyphenylmethyl)-*N*-4-toluenesulfonylpiperidine (13). Compound **13** was prepared according to general procedure C except for the fact that 3 mmol of MeMgBr (1 mL of a 3 M solution in ether) was used (reflux for 5 h). After complete desilylation,[10] pure piperidine **13** was isolated. Eluent (FC): CH/EtOAc = 80/20 → 65/35. Yield: 188 mg (52%). Mp: 155−156 °C. R_f = 0.37 (CH/EtOAc = 50/50). IR (KBr): 3500 cm^{-1} (s, OH), 3390 (b, OH). ^{1}H NMR ($CDCl_3$): δ 1.16 (ddd, J = 13.7 Hz, J = 9.8 Hz, J = 4.5 Hz, 1 H), 1.30 (dt, J = 13.7 Hz, J = 5.2 Hz, 1 H), 1.54−1.66 (m, 1 H), 1.70−1.84 (m, 1 H), 2.44 (s, 3 H), 2.65 (ddd, J = 12.0 Hz, J = 9.1 Hz, J = 3.6 Hz, 1 H), 2.83 (s, 1 H), 2.84 (d, J = 11.6 Hz, 1 H), 2.88 (d, J = 5.3 Hz, 1 H), 3.30 (dt, J = 12.0 Hz, J = 4.8 Hz, 1 H), 3.37 (d, J = 11.6 Hz, 1 H), 4.58 (d, J = 5.3 Hz, 1 H), 7.27−7.36 (m, 7 H), 7.66 (d, J = 8.1 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ 20.9 (t), 21.5 (q), 31.0 (t), 46.4 (t), 53.9 (t), 71.9 (s), 76.6 (d), 127.6 (d), 127.6 (d), 128.1 (d), 128.2 (d), 129.7 (d), 133.2 (s), 139.3 (s), 143.7 (s). Anal. Calcd for $C_{19}H_{23}NO_4S$ (361.455): C, 63.14; H, 6.41; N, 3.88. Found: C, 63.21; H, 6.50; N, 4.09.

2,2-Dimethylpropanoic Acid (2-Acetylphenyl) Ester. This compound was prepared from phenol **15** on a 50 mmol scale according to a published acylation procedure.[11] Yield: 10.9 g (99%). R_f = 0.23 (CH/EtOAc = 90/10). IR (film): 1740 cm^{-1} (vs, OC═O), 1680 (vs, C═O), 1590 (s, C═C). ^{1}H NMR ($CDCl_3$): δ 1.38 (s, 9 H), 2.54 (s, 3 H), 7.04 (dd, J = 8.1 Hz, J = 1.2 Hz, 1 H), 7.29 (virt dt, $J \approx$ 7.6 Hz, J = 1.2 Hz, 1 H), 7.50 (ddd, J = 8.1 Hz, J = 7.4 Hz, J = 1.7 Hz, 1 H), 7.75 (dd, J = 7.6 Hz, J = 1.7 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 27.0 (q), 29.4 (q), 39.0 (s), 123.4 (d), 125.7 (d), 129.7 (d), 131.6 (s), 132.9 (d), 149.2 (s), 176.7 (s), 197.6 (s). Anal. Calcd for $C_{13}H_{16}O_3$ (220.268): C, 70.89; H, 7.32. Found: C, 70.76; H, 7.43.

2,2-Dimethylpropanoic Acid 2-[1-[(Trimethylsilyl)oxy]-ethenyl]phenyl Ester. This compound was prepared from the corresponding ketone on a 44 mmol scale according to a published procedure.[5] Yield: 12.8 g (99%). R_f = 0.58 (CH/EtOAc = 90/10). IR (film): 1740 cm^{-1} (vs, C═O), 1620 (m, C═C), 1245 (s, $SiMe_3$), 840 (vs, $SiMe_3$). ^{1}H NMR (acetone-d_6): δ 0.17 (s, 9 H), 1.34 (s, 9 H), 4.61 (d, J = 0.8 Hz, 1 H), 4.62 (d, J = 0.8 Hz, 1 H), 7.02 (dd, J = 7.9 Hz, J = 1.4 Hz, 1 H), 7.23 (dt, J = 7.6 Hz, J = 1.4 Hz, 1 H), 7.33 (dt, J = 7.9 Hz, J = 1.9 Hz, 1 H), 7.50 (dd, J = 7.6 Hz, J = 1.9 Hz, 1 H). ^{13}C NMR (acetone-d_6): δ 0.5 (q), 27.8 (q), 39.8 (s), 97.4 (t), 124.4 (d), 126.7 (d), 130.2 (d), 130.3 (d), 133.5 (s), 149.6 (s), 153.9 (s), 177.1 (s).

Anal. Calcd for $C_{16}H_{24}O_3Si$ (292.449): C, 65.71; H, 8.27. Found: C, 65.57; H 8.54.

(2*RS*,3*RS*)-3-[2-(2,2-Dimethylpropanoyl)oxyphenyl]-2-phenyl-3-[(trimethylsilyl)oxy]oxetane (16). Oxetane **16** was prepared from benzaldehyde and the corresponding silyl enol ether on a 1.5 mmol scale according to a published procedure[5] (irradiation time: 7 h). Yield: 221 mg (37%). Diastereomeric ratio (d.r.) = 87:13. Mp: 88−89 °C. R_f = 0.21 (CH/EtOAc = 95/5). IR (KBr): 1740 cm^{-1} (vs, C=O), 1240 (s, $SiMe_3$), 980 (s, COC), 835 (vs, $SiMe_3$). ^{1}H NMR ($CDCl_3$): δ −0.44 (s, 9 H), 1.40 (s, 9 H), 4.89 (d, J = 6.7 Hz, 1 H), 5.11 (d, J = 6.7 Hz, 1 H), 6.19 (s, 1 H), 7.14 (dd, J = 8.1 Hz, J = 1.0 Hz, 1 H), 7.27 (dt, J = 7.6 Hz, J = 1.0 Hz, 1 H), 7.36−7.49 (m, 5 H), 7.64−7.68 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 0.9 (q), 27.1 (q), 39.2 (s), 79.4 (s), 82.9 (t), 91.8 (d), 123.1 (d), 125.2 (d), 127.9 (d), 128.1 (d), 128.6 (d), 128.9 (d), 129.3 (d), 133.5 (s), 137.6 (s), 149.6 (s), 176.5 (s). Anal. Calcd for $C_{23}H_{30}O_4Si$ (398.573): C, 69.31; H, 7.59. Found: C, 69.60; H, 7.78.

(3*RS*,1′*RS*)-3-Hydroxy-3-(1-hydroxyphenylmethyl)dihydrobenzofuran (17). Compound **17** was prepared from oxetane **16** with MeLi according to general procedure C. Eluent (FC): CH/EtOAc = 80/20. The compound was not stable (see narrative) and was not obtained in analytically pure form. Yield: 170 mg (70%). R_f = 0.23 (CH/EtOAc = 70/30). IR (film): 3400 cm^{-1} (s, b, OH). ^{1}H NMR ($CDCl_3$): δ 2.47 (d, J = 3.2 Hz, 1 H), 2.65 (s, 1 H), 4.28 (d, J = 10.5 Hz, 1 H), 4.74 (d, J = 10.5 Hz, 1 H), 4.98 (d, J = 3.2 Hz, 1 H), 6.78 (d, J = 8.1 Hz, 1 H), 6.85 (dt, J = 7.4 Hz, J = 1.0 Hz, 1 H), 7.01 (ddd, J = 7.4 Hz, J = 1.4 Hz, J = 0.5 Hz, 1 H), 7.23 (ddd, J = 8.1 Hz, J = 7.4 Hz, J = 1.4 Hz, 1 H), 7.28−7.33 (m, 5 H). ^{13}C NMR ($CDCl_3$): δ 77.6 (d), 79.8 (t), 83.3 (s), 110.4 (d), 120.6 (d), 124.9 (d), 127.8 (d), 128.1 (d), 128.2 (s), 128.4 (d), 130.7 (d), 138.5 (s), 160.9 (s). $C_{15}H_{14}O_3$ (HRMS) Calcd.: 242.0943. Found: 242.0937.

(3*RS*,1′*RS*)-3-Hydroxy-3-[1-[(trimethylsilyl)oxy]phenylmethyl]dihydrobenzofuran (18). In addition to benzofuran **17**, compound **18** was obtained from treatment of oxetane **16** with MeLi according to general procedure C. Eluent (FC): CH/EtOAc = 80/20. Yield: 66 mg (21%). R_f = 0.52 (CH/EtOAc = 70/30). IR (film): 3440 cm^{-1} (m, b, OH), 1240 (s, $SiMe_3$), 835 (vs, $SiMe_3$). ^{1}H NMR ($CDCl_3$): δ −0.03 (s, 9 H), 3.01 (s, 1 H), 4.26 (d, J = 10.0 Hz, 1 H), 4.68 (d, J = 10.0 Hz, 1 H), 4.88 (s, 1 H), 6.76 (dt, J = 8.1 Hz, J = 0.7 Hz, 1 H), 6.79 (virt dt, $J \approx$ 7.2 Hz, J = 1.0 Hz, 1 H,), 6.84 (ddd, J = 7.4 Hz, J = 1.9 Hz, J = 0.7 Hz, 1 H), 7.18 (ddd, J = 8.1 Hz, J = 6.9 Hz, J = 1.9 Hz, 1 H), 7.24−7.30 (m, 5 H). ^{13}C NMR ($CDCl_3$): δ 0.0 (q), 78.9 (d), 80.0 (t), 83.5 (s), 110.1 (d), 120.3 (d), 125.2 (d), 127.7 (d), 127.9 (s), 128.1 (d), 128.1 (d), 130.2 (d), 139.2 (s), 161.0 (s). Anal. Calcd for $C_{18}H_{22}O_3Si$ (314.456): C, 68.75; H, 7.05. Found: C, 69.06; H, 7.12.

(1′*RS*)-3-(1-Hydroxyphenylmethyl)benzofuran (19). Compound **17** was prepared from oxetane **16** with MeMgBr according to general procedure C. Eluent (FC): CH/EtOAc = 95/5 → 90/10. Yield: 186 mg (83%). Mp: 58−59 °C. R_f = 0.43 (CH/EtOAc = 70/30). IR (KBr): 3350 cm^{-1} (m, b, OH). ^{1}H NMR ($CDCl_3$): δ 2.37 (s, b, 1 H), 6.00 (s, 1 H), 7.14 (t, J = 7.6 Hz, 1 H), 7.25 (dt, J = 7.6 Hz, J = 1.4 Hz, 1 H), 7.29−7.38 (m, 3 H), 7.40−7.48 (m, 5 H). ^{13}C NMR ($CDCl_3$): δ 69.5 (d), 111.5 (d), 120.6 (d), 122.6 (d), 123.8 (s), 124.5 (d), 126.1 (s), 126.6 (d), 128.1 (d), 128.6 (d), 142.1 (s), 142.4 (d), 155.8 (s). Anal. Calcd for $C_{15}H_{12}O_2$ (224.259): C, 80.34; H 5.39. Found: C, 80.10; H, 5.49.

Acid-Catalyzed Ring Opening of Oxetane 23. At −20 °C a solution of 1 mmol (292 mg) of oxetane **23**[10] in 1 mL of CH_2Cl_2 was added dropwise to a solution of 2 mmol (228 mg, 160 μL) of TFA in 4 mL of CH_2Cl_2. After the addition was complete the mixture was stirred at −20 °C for another 30 min and was subsequently warmed to room temperature. According to TLC the reaction was complete after an additional 3 h. The mixture was azeotroped three times with toluene (10 mL) in vacuo. The diastereomeric ratios **24**/**25** (d.r. = 85/15) and **28**/**29** (d.r. = 90/10) were determined by ^{1}H NMR spectroscopy of the crude product mixture. The material was purified by FC (Eluent: CH/EtOAc = 95/5 → 60/40).

The dioxolanones **24**−**27** were obtained as a mixture of products. Their ratio (**24**/**25**/**26**/**27** = 37/3/43/17) was determined by ^{1}H NMR. The total yield amounted to 146 mg (62%). Mp: 111−113 °C. R_f = 0.19 and 0.15 (CH/EtOAc = 70/30). IR (KBr): 3490 cm^{-1} (vs, OH), 3260 (m, b, OH), 2950 (m, $C_{al}H$), 1780 (vs, C=O). Anal. Calcd for $C_{13}H_{16}O_4$ (236.267): C, 66.09; H, 6.83. Found: C, 66.14; H, 6.95.

(4*RS*,5*SR*)-4-Hydroxymethyl-4-(methylethyl)-5-phenyl-[1,3]dioxolan-2-one (24). ^{1}H NMR ($CDCl_3$): δ 1.13 (d, J = 6.9 Hz, 3 H), 1.13 (d, J = 6.9 Hz, 3 H), 1.47 (virt t, $J \approx$ 6.7 Hz, 1 H), 2.47 (sept, J = 6.9 Hz, 1 H), 3.37 (dd, J = 12.6 Hz, J = 7.1 Hz, 1 H), 3.43 (dd, J = 12.6 Hz, J = 5.7 Hz, 1 H), 5.55 (s, 1 H), 7.32−7.45 (m, 5 H). ^{1}H NOE ($CDCl_3$): H (5.55): H_{ar} [2.4%], C*H*Me_2 [3.2%], CH_3 [1.3%]; CH_2 (3.37 and 3.43): H_{ar} [0.8%], $H_{\delta 5.55}$ [0.6%], C*H*Me_2 [2.1%], OH [4.4%], CH_3 [0.9%]; C*H*Me_2 (2.47): $H_{\delta 5.55}$ [2.1%], CH_3 [1.3%]. ^{13}C NMR ($CDCl_3$): δ 15.9 (q), 16.5 (q), 31.5 (d), 62.7 (t), 80.7 (d), 89.9 (s), 126.3 (d), 128.8 (d), 129.3 (d), 133.4 (s), 154.2 (s).

(4*RS*,5*RS*)-4-Hydroxymethyl-4-(methylethyl)-5-phenyl-[1,3]dioxolan-2-one (25). ^{1}H NMR ($CDCl_3$): δ 0.52 (d, J = 6.9 Hz, 3 H), 0.93 (d, J = 6.9 Hz, 3 H), 1.93 (sept, ^3J = 6.9 Hz, 1 H), 3.79 (d, ^2J = 12.6 Hz, 1 H), 4.10 (d, ^2J = 12.6 Hz, 1 H), 5.89 (s, 1 H), 7.17−7.45 (m, 5 H).

(4*RS*,1′*SR*)-4-(1-Hydroxyphenylmethyl)-4-(methylethyl)-[1,3]dioxolan-2-one (26). ^{1}H NMR ($CDCl_3$): δ 0.98 (d, J = 6.9 Hz, 3 H), 1.09 (d, J = 6.9 Hz, 3 H), 2.12 (sept, J = 6.9 Hz, 1 H,), 2.66 (d, J = 4.3 Hz, 1 H), 4.10 (d, J = 8.6 Hz, 1 H), 4.56 (d, J = 8.6 Hz, 1 H), 5.00 (d, J = 4.3 Hz, 1 H), 7.32−7.45 (m, 5 H). ^{13}C NMR ($CDCl_3$): δ 16.3 (q), 16.3 (q), 31.2 (d), 66.4 (t), 74.0 (d), 89.5 (s), 127.4 (d), 128.8 (d), 129.0 (d), 137.2 (s), 154.9 (s).

(4*RS*,1′*RS*)-4-(1-Hydroxyphenylmethyl)-4-(methylethyl)-[1,3]dioxolan-2-one (27). ^{1}H NMR ($CDCl_3$): δ 0.92 (d, J = 6.9 Hz, 3 H), 1.00 (d, J = 6.9 Hz, 3 H), 1.92 (sept, J = 6.9 Hz, 1 H,), 2.37 (d, J = 4.5 Hz, 1 H), 4.25 (d, J = 8.6 Hz, 1 H), 4.55 (d, J = 8.6 Hz, 1 H), 4.82 (d, J = 4.5 Hz, 1 H), 7.30−7.47 (m, 5 H). ^{13}C NMR ($CDCl_3$): δ 15.9 (q), 16.0 (q), 31.2 (d), 67.1 (t), 74.8 (d), 88.5 (s), 127.8 (d), 128.6 (d), 128.7 (d), 138.1 (s), 155.1 (s).

The *tert*-butyl derivatives **28** and **29** were obtained as a mixture of diastereoisomers (d.r. = 90/10). The total yield amounted to 56 mg (20%). R_f = 0.55 (CH/EtOAc = 70/30). IR (film): 1800 cm^{-1} (vs, C=O). Anal. Calcd for $C_{17}H_{24}O_4$ (292.374): C, 69.84; H, 8.27. Found: C, 70.11; H, 7.98.

(4*RS*,5*SR*)-4-(1,1-Dimethylethyloxymethyl)-4-(methylethyl)-5-phenyl[1,3]dioxolan-2-one (28). ^{1}H NMR ($CDCl_3$): δ 0.86 (s, 9 H), 1.10 (d, J = 6.9 Hz, 3 H), 1.13 (d, J = 6.9 Hz, 3 H), 2.35 (sept, J = 6.9 Hz, 1 H), 3.11 (d, J = 9.5 Hz, 1 H), 3.18 (d, J = 9.5 Hz, 1 H), 5.50 (s, 1 H), 7.32−7.39 (m, 5 H). ^{13}C NMR ($CDCl_3$): δ 16.2 (q), 16.3 (q), 26.7 (q), 32.7 (d), 60.7 (t), 73.2 (s), 82.3 (d), 88.9 (s), 127.0 (d), 128.1 (d), 128.8 (d), 134.3 (s,), 154.5 (s).

(4*RS*,5*RS*)-4-(1,1-Dimethylethyloxymethyl)-4-(methylethyl)-5-phenyl[1,3]dioxolan-2-one (29). ^{1}H NMR ($CDCl_3$): δ 0.65 (d, J = 6.9 Hz, 3 H), 0.88 (d, J = 6.9 Hz, 3 H), 1.28 (s, 9 H), 1.88 (sept, J = 6.9 Hz, 1 H), 3.63 (d, J = 9.9 Hz, 1 H), 3.69 (d, J = 9.9 Hz, 1 H), 5.75 (s, 1 H), 7.32−7.39 (m, 5 H).

(2*SR*,3*RS*)-3-[(1,1-Dimethylethyloxy)carbonyloxy]-3-(methylethyl)-2-phenyloxetane (32). Oxetane **32** was prepared on a 0.95 mmol scale from the corresponding oxetanol (182 mg) in full analogy to a previously published procedure.[10] Purification (FC) with CH/EtOAc (99/1). Yield: 271 mg (97%). R_f = 0.72 (CH/EtOAc = 70/30). IR (film): 1740 cm^{-1} (vs, C=O), 990 (s, COC). ^{1}H NMR ($CDCl_3$): δ 0.49 (d, J = 6.8 Hz, 3 H), 0.82 (d, J = 7.0 Hz, 3 H), 1.53 (s, 9 H), 2.28 (virt sept, $J \approx$ 6.9 Hz, 1 H), 4.60 (d, J = 7.6 Hz, 1 H), 4.89 (d, J = 7.6 Hz, 1 H), 6.01 (s, 1 H), 7.30−7.60 (m, 5 H). ^{13}C NMR ($CDCl_3$): δ 16.1 (q), 16.7 (q,), 27.7 (q), 30.6 (d), 75.7 (t,), 82.2 (s), 87.6 (s), 89.8 (d), 126.9 (d), 127.9 (d), 128.0 (d), 137.7 (s), 152.0 (s). Anal. Calcd for $C_{17}H_{24}O_4$ (292.374): C, 69.84; H, 8.27. Found: C, 69.44; H, 8.66.

Acid-Catalyzed Ring Opening of Oxetane 32. The reaction was conducted as desribed for the diastereomeric oxetane **23**. The diastereomeric ratio **24**/**25** (d.r. = 2/98) was

determined by ^{1}H NMR spectroscopy of the crude product mixture. The material was purified by flash chromatography (FC) eluting with CH/EtOAc (95/5 → 70/30). The dioxolanones **25** and **27** were obtained as a mixture of products. Their ratio (**25**/**27** = 34/66) was determined by ^{1}H NMR. The total yield amounted to 133 mg (56%). The *tert*-butyl derivative **29** was obtained diastereomerically pure (d.r. > 98/2). Yield: 26 mg (9%).

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Supporting Information Available: Further analytical data (NMR assignments, IR, MS) for compounds **2b**, **3b**, **4**-**6**, **8**, **11c**, **12**, **13**, and **16**−**19** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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