1-Oxaspiro[4.4]nonan-6-ones. Synthetic Access via Oxonium Ion Technology, Optical Resolution, and Conversion into Enantiopure Spirocyclic α,β-Butenolides

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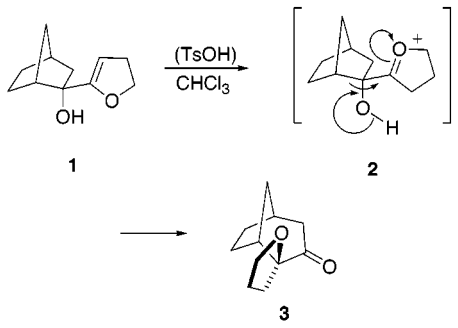
A general approach to the synthesis of enantiomerically pure spirocyclic α,β-butenolides is presented where the fundamental framework is rapidly elaborated by acid- or bromonium ion-induced rearrangement of the carbinol derived by addition of 2-lithio-4,5-dihydrofuran to cyclobutanone. Subsequent resolution of the resulting ketones by either sulfoximine or mandelate acetal technology has been applied effectively. The availability of these building blocks makes possible in turn the acquisition of the enantiomers of dihydrofurans typified by **17**, **35**, and **38** and lactones such as **25** and **31**, as well as the targeted title compounds. Complementary reductions of the early intermediates provide the added advantage that the α- and β-stereoisomeric carbinol series can be obtained on demand. These capabilities have been coordinated to allow the crafting of any member of the series in relatively few steps.

In 1990, we reported the first examples of the oxonium ion-initiated pinacolic ring expansion reaction.[1] This discovery, which constitutes an extension of the long established Wagner−Meerwein[2] and pinacolic rearrangements,[3] takes advantage of the fact that ketone adducts of metalated vinyl ethers represented by **1** are amenable under acid-catalyzed conditions to conversion to oxonium ions such as **2**. This first step triggers a subsequent 1,2-shift under steric and stereoelectronic control, resulting in diastereoselective ring expansion and spiro ketone formation as exemplified by **3**.[4] The migratory aptitudes



that come into play are predictably good,[5] and the differentiating elements that control product stereochemistry are reasonably well understood.[6] As a consequence, this process has seen serviceable application in the synthesis of spirocyclic bis-*C*,*C*-glycosides,[7] furanose and pyranose nucleosides,[8] *cis*- and *trans*-theaspirone,[9] dactyloxene-B and -C,[10] and (+)-grindelic acid.[11] In most of these studies, reliance was placed on double diastereoselection, the initial conjoining step involving optically active reaction partners either singly or as matched pairs.

Despite the latent potential of the parent oxa- and thia-substituted spiro[4.4]nonan-6-ones as useful building

(1) Paquette, L. A.; Lawhorn, D. E.; Teleha, C. A. *Heterocycles* **1990**, *30*, 765.
(2) *Molecular Rearrangements*; de Mayo, P.; Ed.: Interscience Publishers: New York, 1963; Part 1, Chapters 1 (Pocker, Y.), 3 (Berson, J.), and 4 (Breslow, R.).
(3) Collins, C. J. *Quart. Rev. (London)* **1960**, *14*, 357.
(4) Paquette, L. A. *Recent Res. Dev. Chem. Sci.* **1997**, *1*, 1.
(5) Paquette, L. A.; Andrews, J. F. P.; Vanucci, C.; Lawhorn, D. E.; Negri, J. T.; Rogers, R. D. *J. Org. Chem.* **1992**, *57*, 3956.
(6) Paquette, L. A.; Lanter, J. C.; Johnston, J. N. *J. Org. Chem.* **1997**, *62*, 1702.
(7) (a) Paquette, L. A.; Dullweber, U.; Cowgill, L. D. *Tetrahedron Lett.* **1993**, *34*, 8019. (b) Paquette, L. A.; Kinney, M. J.; Dullweber, U. *J. Org. Chem.* **1997**, *62*, 1713.
(8) Paquette, L. A.; Brand, S.; Behrens, C. *J. Org. Chem.* **1999**, *64*, 2010.
(9) Paquette, L. A.; Lanter, J. C.; Wang, H.-L. *J. Org. Chem.* **1996**, *61*, 1119.
(10) (a) Paquette, L. A.; Lord, M. D.; Negri, J. T. *Tetrahedron Lett.* **1993**, *34*, 5693. (b) Lord, M. D.; Negri, J. T.; Paquette, L. A. *J. Org. Chem.* **1995**, *60*, 191.
(11) (a) Paquette, L. A.; Wang, H.-L. *Tetrahedron Lett.* **1995**, *34*, 6005. (b) Paquette, L.A.; Wang, H.-L. *J. Org. Chem.* **1996**, *61*, 5352.
(12) Paquette, L. A. In *Science at the Turn of the Millenium*; Keinan, E.; Shechter, I., Eds.; Wiley/VCH: New York, 2001, in press.
(13) Trost, B. M.; Mao, M. K.-T.; Balkovec, J. M.; Buhlmayer, P. *J. Am. Chem. Soc.* **1986**, *108*, 4965.
(14) (a) Dimitroff, M.; Fallis, A. G. *Tetrahedron Lett.* **1998**, *39*, 2527. (b) Paquette, L. A.; Lobben P. C. *J. Am. Chem. Soc.* **1996**, *118*, 1917.
(15) For a preliminary report from this laboratory, consult Paquette, L. A.; Lanter, J. C.; Owen, D. R.; Fabris, F.; Bibart, R. T.; Corral, M. A. *Heterocycles* **2001**, *54*, 49.
(16) For representative examples, see: (a) Cram, D. J.; Steinberg, H. *J. Am. Chem. Soc.* **1954**, *76*, 2753. (b) Hardegger, E.; Maeder, E.; Semarne, H. M.; Cram, D. J. *J. Am. Chem. Soc.* **1959**, *81*, 2729. (c) Gerlach, H. *Helv. Chim. Acta* **1968**, *51*, 1587. (d) Gerlach, H.; Müller, W. *Helv. Chim. Acta* **1972**, *55*, 2277. (e) Gerlach, H.; Müller, W. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 1030. (f) Carruthers, W.; Orridge, A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2411. (g) Harada, N.; Ochiai, N.; Takada, K.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1977**, 495. (h) Harada, N.; Ai, T.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1982**, 232. (i) Naemura, K.; Furutani, A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2891. (j) Suemune, H.; Maeda, K.; Kato, K.; Sakai, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3441. (k) Nieman, J. A.; Parvez, M., Keay, B. A. *Tetrahedron: Asymmetry* **1993**, *4*, 1973. (l) Nieman, J. A., Keay, B. A. *Tetrahedron: Asymmetry* **1995**, *6*, 1575. (m) Nieman, J. A.; Keay, B. A.; Kubicki, M.; Yang, D.; Rauk, A.; Tsankov, D.; Wieser, J. *J. Org. Chem.* **1995**, *60*, 1918. (n) Nieman, J. A.; Keay, B. A. *Synth. Commun.* **1999**, *29*, 3829.

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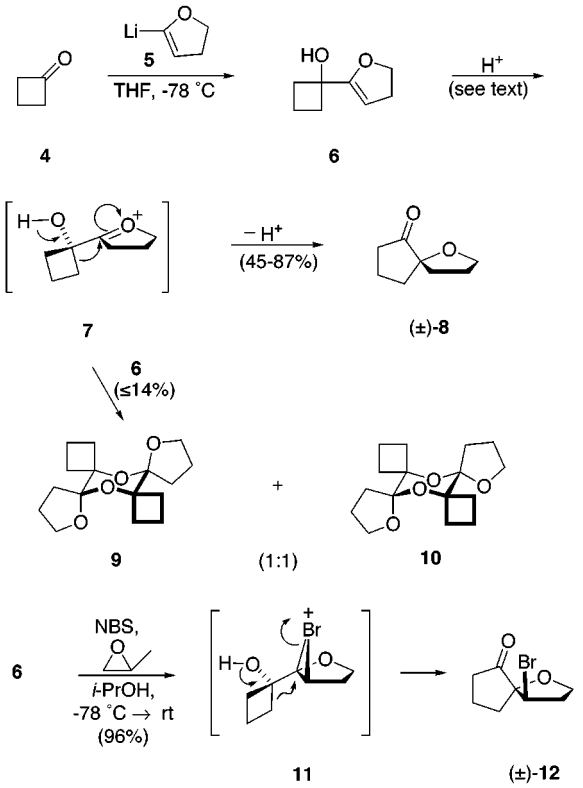
blocks[12,13] and molecular probes,[14] no attention has previously been directed to their acquisition in optically active condition.[15] That this concept has not been reduced to practice contrasts with the frequency with which their functionalized carbocyclic equivalents, the spiro[4.4]-nonanes, have been resolved.[16] These efforts have seemingly been spurred on by the occurrence of the spirane platform in nature (gloiosiphone A,[17] fredericamycin,[18] etc), by the applicability of designed derivatives to asymmetric synthesis,[19,20] and the like.

In an effort to remedy the deficiency existent in the heterocyclic series, we have explored direct oxonium ion-based routes to the 1-oxaspiro[4.4]nonan-4-one class, established a notably feasible means for effecting their optical resolution, unequivocally established absolute configuration of the antipodes, and defined a selection of regio- and stereocontrolled transformations within this structural series.

Ring Expansion Process. The addition of 2-lithio-4,5-dihydrofuran (**5**)[21a] to cyclobutanone (**4**) in THF at −78 °C provided the highly sensitive carbinol **6** in excellent yield (Scheme 1). The elevated reactivity of **6** toward traces of acid precludes its attempted storage. The fate of **6** in the presence of different acidic ion-exchange resins was such as to give a preponderance of the racemic spiro ketone **8** (45−87%) alongside variable quantities of the highly crystalline 1,4-dioxanes **9** and **10** (0−14% in a 1:1 ratio). Although dimerization in this fashion had been observed in higher homologues,[1] it was not anticipated at an appreciable level in the present example because of very favorable strain release energetics in oxonium ion **7**. Since **8** and **9**/**10** do not interconvert under the reaction conditions, they are evidently formed under kinetic control. We speculate that the capture of intermediate **7** by unrearranged **6** likely operates in the early stages of this process when the concentration gradient of the carbinol is high. However, the possibility cannot be ruled out that the intermolecular reaction can compete favorably as a consequence of multipoint coordinative binding to the acidic resin.

Alternative initiation of the oxonium ion-promoted rearrangement with *N*-bromosuccinimide requires the presence of an acid scavenger to be effective, and propylene oxide was found to serve well in this role.[21b] The exclusive formation of (±)-**12** under conditions of proper temperature control is consistent with initial formation of bromonium ion **11**, followed by the depicted concerted

Scheme 1



electronic shift or a stepwise process with the identical stereochemical alignment.[6,7b] The presence of a syn-directed bromine atom in **12** can be projected to play several obvious key roles. Of these, the more advanced regioselective functionalization of the tetrahydrofuran ring and the steric control potential for guiding nucleophilic attack at the carbonyl site were considered to be the most serviceable.

Resolution Studies and Absolute Configurational Assignments. The structural features inherent to (±)-**12** alluded to above prompted us initially to examine its coupling to Johnson's (*S*)-(+)-sulfoximine[22] for the purpose of optical resolution. When the lithiated anion **13** was added to racemic **12** in THF at −78 °C, the three chromatographically separable diastereomers **14**, **15**, and **16** were formed in a 2:1:1 ratio (Scheme 2). Determination of the stereochemical relationships present in major adduct **14** was accomplished by X-ray crystallographic analysis. Thermal activation of **14** by overnight heating in xylene resulted in recovery of the chiral auxiliary and smooth conversion to dextrorotatory **12**, whose absolute configuration could now be reliably depicted as shown. Entirely comparable processing of **15** and **16** led to formation of the enantiomeric bromo ketone (−)-**12** in both cases. The detailed stereochemistry of all three compounds here involved was thereby directly elucidated.

Beyond this, **16** was found to undergo dehydrobromination in the presence of DBU to furnish **18**. Thermal fragmentation of the latter delivered (+)-**17**, but with lowered efficiency because of the thermal sensitivity of this enone product. X-ray analysis of **18** provided the necessary evidence to confirm the indicated configurations. The lability to heat exhibited by **17** was also

(17) (a) Chen, J. L.; Moghaddam, M. F.; Gerwick, W. H. *J. Nat. Prod.* **1993**, *56*, 1205 (b) Paquette, L. A.; Sturino, C. F.; Doussot, P. *J. Am. Chem. Soc.* **1996**, *118*, 9456. (c) Sturino, C. F.; Doussot, P.; Paquette, L. A. *Tetrahedron* **1997**, *53*, 8913.

(18) (a) Pandey, R. C.; Toussaint, M. W.; Stroshane, R. M. Kalita, C. C.; Aszalos, A. A.; Garretson, A. L.; Wei, T. T.; Byrne, K. M.; Geoghegan, R. F. Jr.; White, R. J. *J. Antibiot.* **1981**, *34*, 1389 (b) Kita, Y.; Higuchi, K.; Yoshida, Y.; Iio, K. Kitagaki. S.; Akai, S.; Fujioka, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 683.

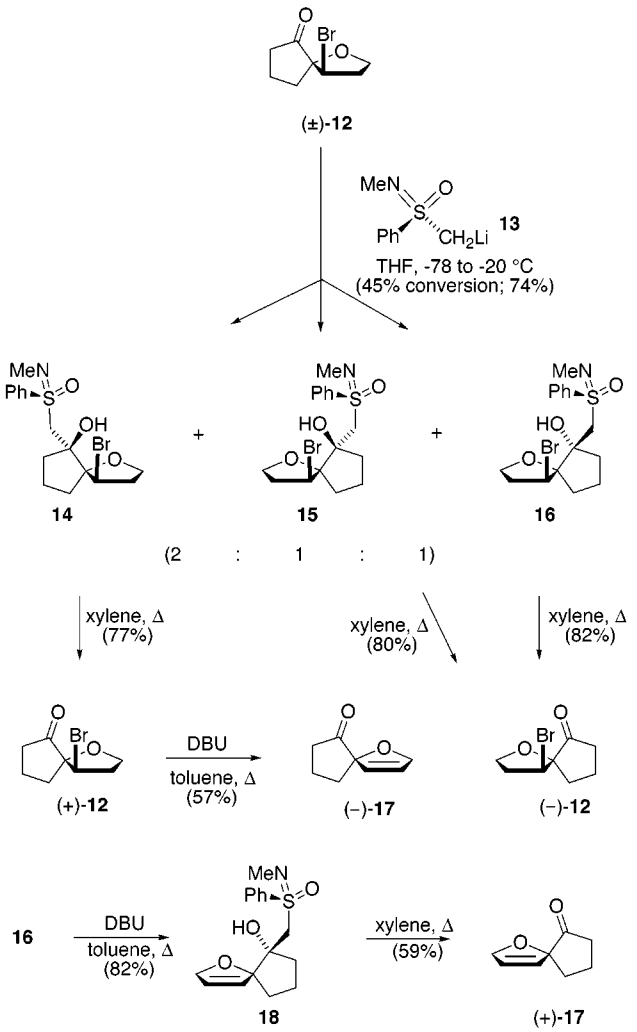
(19) (a) Nieman, J. A.; Keay, B. A. *Tetrahedron: Asymmetry* **1996**, *7*, 3521. (b) Keay, B. A.; Maddaford, S. P.; Cristofoli, W. A.; Andersen, N. G.; Passafaro, M. S.; Wilson, N. S.; Nieman, J. A. *Can. J. Chem.* **1997**, *75*, 1163.

(20) (a) Chan, A. S. C.; Hu, W.; Pai, C.-C.; Lau, C.-P.; Jiang, Y.; Mi, A.; Yan, M.; Sun, J.; Lou, R.; Deng. J. *J. Am. Chem. Soc.* **1997**, *119*, 9570. (b) Seebach, D.; Beck, A. K.; Dahinden, R.; Hoffmann, M.; Kühnle, F. N. M. *Croatica Chem. Acta* **1996**, *69*, 459. (c) Srivastava, N.; Mital, A.; Kumar, A. *J. Chem. Soc., Chem. Commun.* **1992**, 493.

(21) (a) Paquette, L. A.; Oplinger, J. A. *Tetrahedron* **1989**, *45*, 107 and relevant references therein. (b) Koppenhoefer, B.; Lohmiller, K.; Schurig, F. V. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley and Sons: Chichester, 1995; Volume 6, pp 4331−4336.

(22) (a) Johnson, C. R. *Aldrichimica Acta* **1985**, *18*, 3. (b) Johnson, C. R.; Zeller, J. R. *J. Am. Chem. Soc.* **1982**, *104*, 4021.

Scheme 2



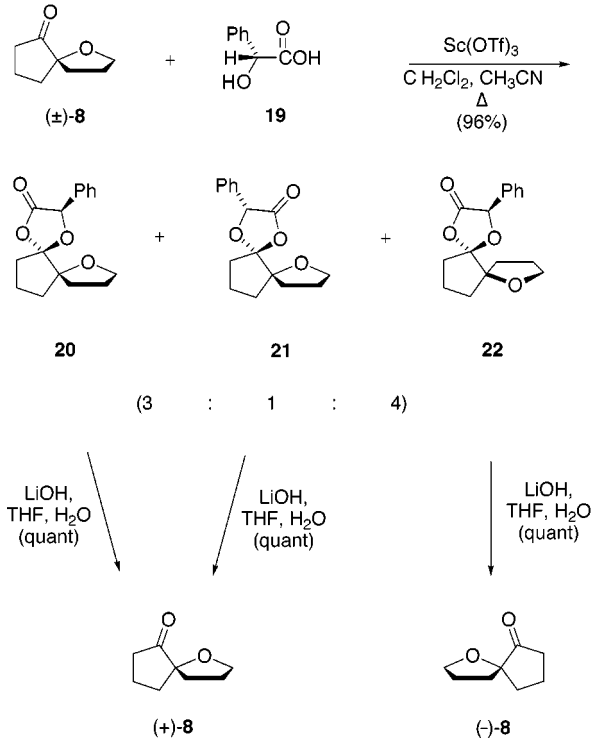
manifested during the generation of its levorotatory enantiomer by dehydrobromination of (+)-**12** with DBU in hot toluene.

The stereoselectivity with which **13** undergoes 1,2-addition to (±)-**12** predominantly from the direction anti to bromine can be viewed as a serviceable feature of the chemistry of this spirocyclic ketone. Nonetheless, the addition of **13** to (±)-**12** could not be forced beyond the level of 45% conversion due presumably to competing enolization. Our inability to resolve this dilemma despite considerable experimentation prompted the search for an improved method of resolution that would facilitate the throughput of enantiomerically pure spirocyclic intermediates on a reasonable scale.

After a number of unproductive starts, recourse was made to the acetalization of racemic **8** with (*R*)-(−)-mandelic acid (**19**) under catalysis by scandium triflate[23] (Scheme 3). Optimal conditions involving the use of a 13:1 solvent mixture of CH_2Cl_2 and acetonitrile under overnight reflux in the presence of 4 Å molecular sieves to remove the liberated water furnished a chromatographically separable mixture of **20**, **21**, and **22** (ratio of 3:1:4, 96% combined yield). Although acid-catalyzed methanolysis has been touted as a means for the degradation

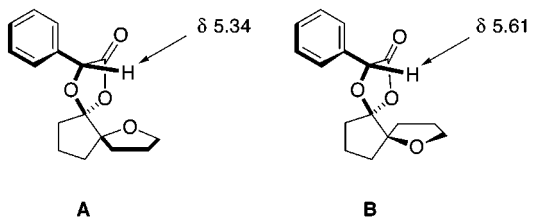
(23) Ishihara, K.; Karumi, Y.; Kubota, M.; Yamamoto, H. *Synlett.* **1996**, 839.

Scheme 3



of mandelate acetals,[24] this method failed in the present circumstances. However, hydrolysis with lithium hydroxide[25] was uniformly advantageous and notably efficient in returning the enantiopure spiro ketones quantitatively.

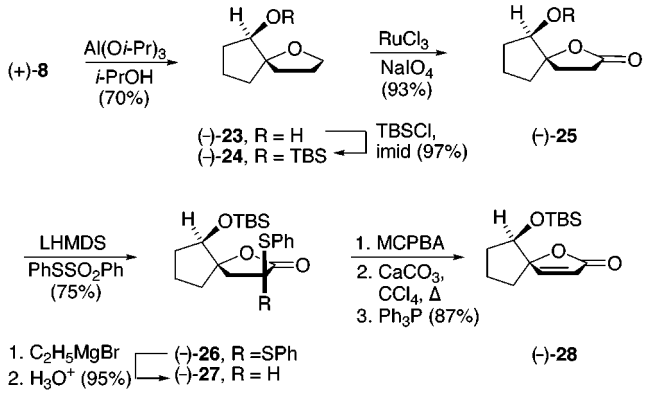
The structural assignment to **20** is based on direct spectral comparison with the tetrahydrothiophene congener for which crystallographic proof of structure is available.[26] Beyond this, the absolute configuration of (+)-**8** was independently derived by a chemical correlation to be delineated below. The parallel conversion of **21** to (+)-**8** and of **22** to (−)-**8** holds similar relevance for stereochemical assignment. In our view, the preferred generation of acetals **20** and **22** stems from the avoidance of nonbonded steric interactions involving the phenyl substituent. These features are clearly apparent in projections **A** and **B**, which depict additionally the deshielding consequences on chemical shift when the benzylic proton is projected above the tetrahydrofuranyl oxygen atom.



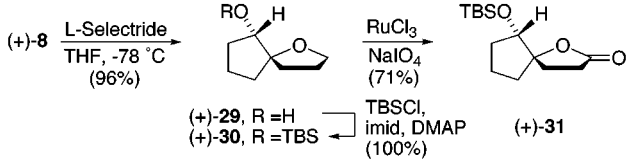
Stereoselectivity of Carbonyl Group Reduction. The spirocyclic ketones **8**, **12**, and **17** constitute a subset

(24) Kellogg, R. M.; Hof, R. P. *J. Org. Chem.* **1996**, *61*, 3423.
(25) Bigi, F.; Bocelli, G.; Maggi, R.; Sartori, G. *J. Org. Chem.* **1999**, *64*, 5004.
(26) Fabris, F.; Rogers, R. D. Unpublished results.

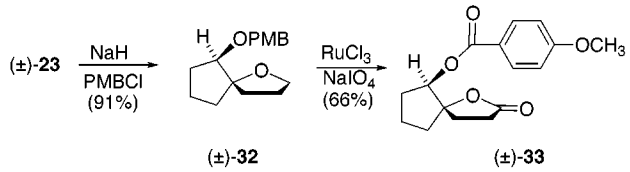
Scheme 4



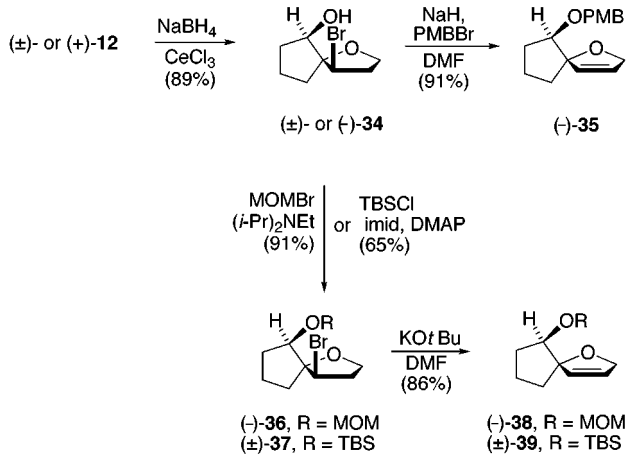
Scheme 5



Scheme 6



Scheme 7



of related structures that hold interest with regard to the diastereofacial selectivity of nucleophilic attack at their carbonyl groups. This general topic has been widely scrutinized and diverse rationalizations have been offered.[27] The addition of methyllithium, methyl Gringnard reagents, and several hydride sources to racemic **8** has been independently explored by Dimitroff and Fallis.[28] The Canadian group recognized that the controlling factors operational in such reactions are subtle. Since our purposes in the present context were preparative, clean controlled conversion to the β- and α-carbinols on a preparative scale was targeted. Recourse to Meerwein−Ponndorf−Verley conditions was found to be particularly well suited to the predominant formation of **23** in high yield (β/α = 85:15) (Scheme 4). No other reagent examined by us gave rise in useful amounts to the β-carbinol.

Following protection of the hydroxyl group in **23** as the TBS derivative **24**, the oxidation to lactone **25** was examined. Ruthenium tetroxide[29] gave **25** as the sole product, thereby setting the stage for introduction of the double bond as in **28**. When attempts to introduce an α-phenylselenenyl substituent into **25** were invariably met with bisfunctionalization, advantage was taken of this heightened nucleophilic reactivity for the generation of **26** by comparable treatment with phenyl benzenethiosulfonate.[30] With arrival at **26** in this manner, direct conversion to **27** as a 1:1 diastereomeric mixture was realized by reaction with ethylmagnesum bromide.[13] The Grignard reagent attacks at sulfur and cleanly produces a solution of the enolate that is amenable to protonation with delivery of the diastereomeric monosulfenylated end-products in equivalent amounts. The route to **28** was completed by formation of the sulfoxide and thermal extrusion of phenylsulfenic acid.[31] The levorotatory properties of **28** generated from (+)-**8** in this manner correlate perfectly with the optical rotations exhibited by **43** and **45** as synthesized in the sequel, thus establishing its absolute configuration to be as shown.

The problem of generating the α-carbinol was resolved when L-Selectride was discovered to produce **29** exclusively in 96% yield (Scheme 5). As before, this carbinol could be sequentially silylated and oxidized to give (+)-**31**, a lactone previously reported in racemic form.[13,32]

In other studies, the serviceability of the PMB protecting group is somewhat compromised in these RuO_4-promoted conversions because of concomitant oxidation of the benzylic methylene group. The smooth transformation of **32** to **33** is illustrative of this chemistry (Scheme 6).

The stereoselectivity of the reduction of bromo ketone **12** is overwhelmingly controlled by the relative position of the halogen atom. As a result, sodium borohydride can be called upon to generate the β-carbinol **34** via approach from the open α-surface (Scheme 7). A significant added advantage associated with the bromine substituent is the option that it offers for the introduction of a double bond regioselectively by dehydrobromination. Dihydrofuran **35** is the sole product of the action on **34** of excess sodium hydride and *p*-methoxybenzyl bromide in DMF (91% yield). Thus, it is entirely feasible to protect the hydroxyl group and bring about the loss of HBr in a single

(27) (a) Houk, K. N.; Paddon-Row: M. N.; Rondan, G. N.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108. (b) Wu, Y.-D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018. (c) Wu, Y.; Houk, K. N.; *J. Am. Chem. Soc.* **1993**, *115*, 10992. (d) Fraser, R. R.; Kong, F.; Stanciulescu, M.; Wu, Y.-D.; Houk, K. N. *J. Org. Chem.* **1993**, *58*, 4431. (e) Gung, B. W. *Tetrahedron* **1996**, *52*, 5263. (f) Fraser, R. R.; Faibish, N. C.; Kong, F.; Bednarski, K. *J. Org. Chem.* **1997**, *62*, 6164.

(28) Dimitroff, M.; Fallis, A. G. *Tetrahedron Lett.* **1998**, *39*, 2531.

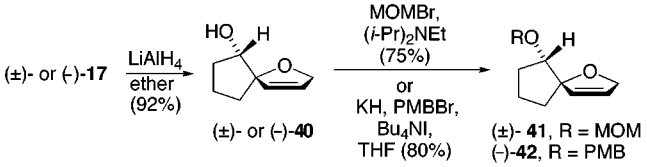
(29) Smith, A, B., III.; Scarborough, R. M. *Synth. Commun.* **1980**, *10*, 205.

(30) Takeuchi, K. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley and Sons: Chichester; 1995; Volume 6, pp 3957−3960.

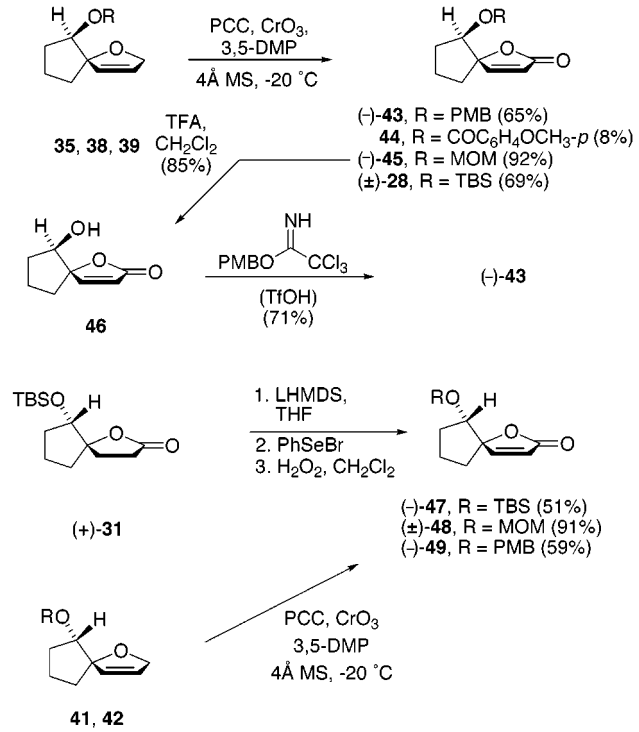
(31) The phenylsulfenic acid subsequently enters into dimerization and generates phenyl benzenethiosulfinate, an end-product that co-elutes with **28**. To skirt this difficult separation, the reaction mixture was stirred with triphenylphosphine prior to workup in order to effect reduction as recommended elsewhere [Horner, L.; Hoffmann, H. *Angew. Chem.* **1956**, *68*, 473].

(32) The assignment defined earlier by Trost and co-workers[13] as (±)-**31** should be changed. Direct spectral comparisons show that the intermediates prepared by them are in reality the anti diastereomers **25** and **26**.

Scheme 8



Scheme 9



laboratory operation. It is, of course, also possible to effect this overall structural change in stepwise fashion. The formation of **36** and **37** can be realized with a somewhat weaker base as a prelude to reaction with potassium *tert*-butoxide. Advancement by way of either route does not erode the configurational integrity of the vicinal stereogenic centers.

Further insight into reduction stereoselectivity was realized by subjecting **17** to the action of lithium aluminum hydride. The presence of a double bond so modifies the conformational and steric shielding within the spirocyclic structure that nucleophilic attack syn to this site of unsaturation is now overwhelmingly favored. The isolated yield of **40** was consistently above the 90% level (Scheme 8). Protection of the hydroxyl as in **41** and **42** proved expectedly to be a routine operation.

Allylic Oxidation. At this stage, the prospect of allylic oxidation of the dihydrofurans occupied our attention. When attempts to bring about this process by means of selenium dioxide, pyridinium chlorochromate (PCC), or *N*-bromosuccinimide under photochemical conditions were to no avail, we developed a protocol involving the combined action of PCC (5 equiv), chromium trioxide (5 equiv), and 3,5-dimethylpyrazole (10 equiv). As shown in Scheme 9, conversion of the OCH_2 residue to the lactone segment of a spirocyclic α,β-butenolide occurs regioselectively with very reasonable efficiency irrespective of the configuration of the RO-substituted carbon. The general workability of this tactic is superior to other alternatives starting from the lactone. Note that the OPMB group survives this oxidative protocol quite well (e.g., **35** → **43**). The difficulties associated with the phenylselenenylation−oxidation of **25** have already been pointed out. While the less sterically congested features of its invertomer **31** allow for reasonable control of the monofunctionalization step,[33] the efficiency with which **47** could be produced never exceeded 51%.

In a companion study, the β-OMOM derivative **45** was deprotected and **46** so generated could be transformed into the OPMB analogue **43** via the trichloroacetimidate in a functional group exchange. This operation proved to be difficult to reproduce, principally because of the susceptibility of **46** to retrograde vinylogous aldol fragmentation.

Summary

The notable aspects of this synthetic exercise are several in number. π-Facial diastereoselection in both directions was realized during reduction of the parent spiro ketone **8**, with the Meerwein−Ponndorf−Verley protocol delivering the β-carbinol and L-Selectide the α-epimer. Alternative control of this important step can be accomplished by reduction of readily available bromo ketone **12** (β-specific) or dihydrofuranyl ketone **17** (α-specific). The first of these regimens advances to the butenolide level via the intermediate lactone, with introduction of the double bond by way of α-substituted organosulfur or selenium intermediates. Alternatively, the presence of the bromine atom allows for the implementation of an elimination process and ultimate allylic oxidation with high level regiocontrol. If preference is given to overall yields, then the first option should be viewed as the more serviceable synthetic entry.

Both **8** and **12** have been resolved and their absolute configurations reliably defined. Many of the transformations reported herein have been carried out on enantiopure samples of the numerous intermediates. The ulterior motive of this aspect of the investigation was to set a solid foundation for the synthesis of an entirely new class of structurally restricted nucleosides whose unprecedented spirocyclic nature was contemplated to provide several unique and interesting properties. Some of the early progress realized in this arena will form the subject of future submissions.

Experimental Section

General Information. THF and ether were distilled from sodium benzophenone ketyl under nitrogen just prior to use. For CH_2Cl_2, the drying agent was calcium hydride. Isopropyl alcohol was freshly distilled from calcium oxide. All reactions were performed under a nitrogen atmosphere. Analytical thin-layer chromatography was carried out on E. Merck silica gel 60 F_{254} aluminum-backed plates. The 230−400 mesh size of the same absorbent was utilized for all chromatographic purifications. The organic extracts were dried over anhydrous $MgSO_4$ or Na_2SO_4. ^1H and ^{13}C NMR spectra were recorded at the indicated field strengths. The high-resolution mass spectra were recorded at The Ohio State University Campus Chemical Instrumentation Center.

(±)-1-Oxaspiro[4.4]nonan-6-one (8). A. Use of Dowex-50 for the Rearrangement of 6. A solution of 2,3-dihydrofuran (9.0 mL, 0.12 mol) in dry THF (90 mL) was blanketed with N_2, cooled to −78 °C, and treated dropwise with *tert*-

(33) Hanessian, S.; Murray, P. J.; Sahoo, S. P. *Tetrahedron Lett.* **1985**, *26*, 5627.

butyllithium (80 mL of 1.61 M in pentane, 0.13 mol). Upon completion of the addition, the reaction mixture was stirred at this temperature for 30 min, warmed to 0 °C for 1 h, and returned to −78 °C, at which point cyclobutanone (7.5 mL, 0.10 mol) was introduced over 2 h by means of a syringe pump. The reaction mixture was maintained at −78 °C for 6 h, allowed to warm to room temperature overnight, returned to −78 °C, and treated with a saturated aqueous solution of $NaHCO_3$ (115 mL). The separated aqueous phase was extracted with ether (3 × 25 mL), and the combined organic layers were washed with brine, dried, and concentrated. The resultant colorless oil (15.5 g) was dissolved in CH_2Cl_2 (1.25 L), treated with Dowex-50 (0.42 g), and stirred for 24 h prior to filtration through a pad of Celite and solvent evaporation. The residual light yellow oil/solid mixture was vacuum filtered to remove the precipitated dimer. Washing with hexanes gave **9** and **10** as a 1:1 mixture (1.93 g, 14%): white powder, mp 178−188 °C; IR ($CHCl_3$, cm^{-1}) 1057; ^1H NMR (300 MHz, $CDCl_3$) δ 4.15−4.06 (m, 2 H), 3.96−3.86 (m, 2 H), 2.47−1.68 (series of m, 18 H), 1.60−1.44 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.0, 107.6, 78.8, 77.4, 68.5, 68.3, 33.9, 33.1, 32.8, 32.2, 31.3, 31.1, 24.3, 24.0, 14.5, 14.3; EI MS *m*/*z* (M^+) calcd 280.1675, obsd 280.1728. Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.45; H, 8.61.

The oily fraction was purified by chromatography on silica gel (elution with 8:1 hexanes/ethyl acetate) to furnish 6.31 g (45%) of **8** as a clear, volatile, colorless oil: IR ($CHCl_3$, cm^{-1}) 1744; ^1H NMR (300 MHz, $CDCl_3$) δ 3.90 (t, J = 6.4 Hz, 2 H), 2.35−2.15 (m, 2 H), 2.15−1.60 (series of m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.3, 86.3, 68.6, 35.7, 35.0, 32.2, 25.8, 18.0; EI MS *m*/*z* (M^+) calcd 140.0837, obsd 140.0838.

A different synthetic approach to this ketone has been reported.[28]

B. Use of Amberlyst-15 as the Acidic Catalyst. A 18.0 mL (0.24 mol) sample of 2,3-dihydrofuran was metalated and combined with cyclobutanone (15.0 mL, 0.20 mol) as described above to leave 32 g of unpurified **6**. This alcohol was dissolved in CH_2Cl_2 (3 L), Amberlyst-15 (7.0 g) was introduced, and the mixture was stirred for 2 h. The preceding workup afforded 24.34 g (87%) of **8** without any evidence for the formation of **9** and **10**.

(±)-4-Bromo-1-oxaspiro[4.4]nonan-6-one (12). A 15.3 mL (0.20 mol) sample of 2,3-dihydrofuran was metalated with *tert*-butyllithium (80.0 mL of 1.7 M in pentane, 0.135 mol) in the predescribed manner and reacted with 7.5 mL (0.10 mol) of cyclobutanone to give 14.0 g of unpurified **6**. This carbinol (14.0 g, 0.10 mol) and propylene oxide (230 mL) were dissolved in isopropyl alcohol (230 mL), cooled to −78 °C under N_2, and treated with *N*-bromosuccinimide (17.8 g, 0.10 mol) in one portion. The reaction mixture was stirred overnight with warming to room temperature. Concentration of the solution followed by dilution with 300 mL of 2:1 ether/hexanes allowed for the removal of succimide by filtration after standing for 1 h. The filtrate was washed with saturated $NaHCO_3$ solution, and the aqueous phase was back-extracted with ether. The combined organic layers were washed with brine, dried, and evaporated to give 21.0 g (96%) of diastereomerically pure **12** as a colorless oil: IR ($CHCl_3$, cm^{-1}) 1745; ^1H NMR (300 MHz, C_6D_6) δ 3.99 (ddd, J = 9.3, 8.3, 4.0 Hz, 1 H), 3.48−3.36 (m, 2 H), 2.61−2.48 (m, 1 H), 1.93−1.66 (series of m, 5 H), 1.53−1.43 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.0, 87.4, 66.9, 46.9, 37.0, 35.3, 33.7, 18.2; EI MS *m*/*z* (M^+) calcd 217.9942, obsd 217.9942. Anal. Calcd for $C_8H_{11}BrO_2$: C, 43.86; H, 5.06. Found: C, 44.02; H, 5.18.

Dehydrobromination of 16. A solution of **16** (230 mg, 0.76 mmol) and DBU (0.92 g, 6.0 mmol) in toluene (50 mL) was stirred under N_2 at the reflux temperature overnight. The reaction mixture was cooled, diluted with ether (200 mL), and washed with saturated NH_4Cl solution, 1 M $NaHCO_3$ solution, and brine prior to drying and solvent evaporation. The residue was chromatographed on silica gel (elution with 1:1 hexanes/ethyl acetate) to give **18** (170 mg, 82%) as a colorless crystalline solid: mp 129−132 °C; IR ($CHCl_3$, cm^{-1}) 1446, 1246; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90−7.84 (m, 2 H), 7.64−7.52 (m, 3 H), 6.60 (br s, 1 H), 5.87 (dt, J = 6.1, 1.5 Hz, 1 H), 5.59 (dt, J = 6.1, 2.4 Hz, 1 H), 4.62 (dt, J = 13.6, 2.0 Hz, 1 H), 4.55 (dt, J = 13.5, 2.0 Hz, 1 H), 3.38 (d, J = 13.7 Hz, 1 H), 2.88 (d, J = 13.7 Hz, 1 H), 2.87 (s, 3 H), 2.41−2.32 (m, 1 H), 2.28−2.15 (m, 1 H), 2.11−1.88 (m, 2 H), 1.68−1.57 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 133.1, 129.5 (2C), 129.2, 129.1 (2C), 127.8, 100.9, 80.0, 75.4, 60.7, 33.9, 33.0, 28.8, 18.1; EI MS *m*/*z* (M^+) calcd 307.1242, obsd 307.1255. Anal. calcd for $C_{16}H_{21}NO_3S$: C, 62.51; H, 6.89. Found: C, 62.47; H, 6.99.

(−)-1-Oxaspiro[4.4]non-3-en-6-one (17). A solution of (+)-**12** (1.33 g, 6.08 mmol) and DBU (9.13 g, 60.0 mmol) in toluene (50 mL) was refluxed overnight under N_2. The reaction mixture was cooled, diluted with ether (200 mL), and washed with saturated NH_4Cl solution, 1 M $NaHCO_3$ solution, and brine. The organic phase was dried and carefully evaporated. The residue was chromatographed on silica gel (elution with hexanes/ethyl acetate 7:1) to afford 480 mg (57%) of **17** as a colorless oil: IR ($CHCl_3$, cm^{-1}) 1748; ^1H NMR (300 MHz, C_6D_6) δ 5.58 (dt, J = 6.1, 1.5 Hz, 1 H), 5.25 (dt, J = 6.1, 2.4 Hz, 1 H), 4.64 (ddd, J = 12.8, 2.4, 1.6 Hz, 1 H), 4.41 (dt, J = 12.9, 1.9 Hz, 1 H), 1.98−1.69 (m, 3 H), 1.65−1.50 (m, 2 H), 1.33−1.19 (m, 1 H); ^{13}C NMR (75 MHz, C_6D_6) δ 214.1, 129.5, 127.3, 94.2, 75.9, 35.4, 35.1, 18.3; EI MS *m*/*z* (M^+) calcd 138.0681, obsd 138.0681.

Meerwein−Ponndorf−Verley Reduction of (+)-8. A solution of (+)-**8** (300 mg, 2.14 mmol) in isopropyl alcohol (2.5 mL) was treated with aluminum isopropoxide (310 mg, 1.51 mmol), refluxed for 1 h, and distilled at atmospheric pressure until 1.5 mL of distillate was collected. The distillation flask was cooled in ice and diluted with 40 mL of 1 M hydrochloric acid. The products were extracted into ether (3 × 50 mL), and the combined organic solutions were dried and concentrated. The residue was chromatographed on silica gel (elution with 10:1 hexanes/ethyl acetate) to give 211 mg (70%) of (−)-**23** and 46 mg (15%) of the epimeric carbinol (+)-**29**, independently prepared below.

For (−)-**23**: colorless oil; IR ($CHCl_3$, cm^{-1}) 3534; ^1H NMR (300 MHz, $CDCl_3$) δ 3.92 (dd, J = 4.7, 1.4 Hz, 1 H), 3.80 (t, J = 7.1 Hz, 2 H), 2.19−1.76 (series of m, 5 H), 1.72−1.63 (series of m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 92.1, 77.1, 67.3, 31.7, 31.3, 29.3, 25.8, 19.2; $[\alpha]^{20}_D$ −4.8 (*c* 3.0, $CHCl_3$).

The racemic form of this alcohol has been reported.[28]

For (+)-**29**: IR ($CHCl_3$, cm^{-1}) 3534; ^1H NMR (300 MHz, $CDCl_3$) δ 3.71 (m, 2 H), 3.56 (t, J = 7.0 Hz, 1 H), 2.87 (s, 1 H), 1.87−1.67 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 90.0, 76.5, 67.7, 34.7, 34.3, 31.6, 26.0, 19.3; $[\alpha]^{20}_D$ −3.4 (*c* 1.5, $CHCl_3$).

The racemic form of this alcohol has been reported.[28]

Compound 25. To a vigorously stirred mixture of (−)-**24** (2.60 g, 10.1 mmol), sodium periodate (8.64 g, 40.4 mmol), carbon tetrachloride (30 mL), acetonitrile (25 mL), and water (19 mL) was added ruthenium trichloride (640 mg, 3.0 mmol). After 30 min, the reaction mixture was diluted with ether (100 mL) and filtered through a pad of silica gel (ether elution). The filtrate was evaporated, and the residue was chromatographed on silica gel (elution with 6:1 petroleum ether/ether) to furnish 2.55 g (93%) of (−)-**25** as a colorless oil: IR ($CHCl_3$, cm^{-1}) 1765; ^1H NMR (300 MHz, $CDCl_3$) δ 4.00 (t, J = 6.0 Hz, 1 H), 2.56−2.43 (m, 3 H), 1.98−1.63 (m, 6 H), 1.57−1.50 (m, 1 H), 0.84 (s, 9 H), 0.02 (s, 3 H), −0.03 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 94.9, 77.4, 34.5, 31.6, 29.2, 26.9, 25.6 (3C), 18.8, 17.8, −4.7, −5.1; ES MS *m*/*z* ($M + H)^+$ calcd 271.1729 obsd 271.1726; $[\alpha]^{20}_D$ −30.4 (*c* 1.10, $CHCl_3$). Anal. Calcd for $C_{14}H_{26}O_3Si$: C, 62.18; H, 9.69. Found: C, 61.79; H, 9.26.

The racemic form of this lactone has previously been incorrectly assigned.[13,32]

Compound 28. The diastereomers of **27** (3.60 g, 9.50 mmol) were dissolved in CH_2Cl_2 (40 mL), cooled to −78 °C, treated with *m*-chloroperbenzoic acid (2.07 g, 12.0 mmol), and warmed to 0 °C for 2 h. Saturated $NaHSO_3$ solution (100 mL) was added, and the separated aqueous layer was extracted with CH_2Cl_2 (150 mL). The organic phases were combined, dried, and evaporated, leaving the sulfoxide, which was dissolved in CCl_4 (400 mL) containing calcium carbonate (3.17 g, 50 mmol). This mixture was refluxed for 3 h, cooled, filtered, and evaporated. The residue was dissolved in THF (200 mL),

triphenylphosphine (6.56 g, 25 mmol) was introduced, stirring was maintained for 2 h, and the solvent was evaporated. Chromatography of the residue on silica gel (elution with 20:1 petroleum ether/ether) afforded 2.23 g (87%) of (−)-**28** as a colorless oil: IR (neat, cm^{-1}) 1766; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, $J = 5.7$ Hz, 1 H), 6.06 (d, $J = 5.7$ Hz, 1 H), 4.04 (dd, $J = 4.8$, 2.5 Hz, 1 H), 2.24−2.09 (m, 2 H), 1.98−1.91 (m, 2 H), 1.82−1.68 (m, 2 H), 0.86 (s, 9 H), 0.00 (s, 3 H), −0.01 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 158.0, 121.0, 98.3, 80.6, 34.2, 33.0, 25.6 (3C), 21.6, 17.9, −4.7, −5.1; EI MS *m*/*z* (M^+) calcd 268.1495, obsd 268.1495; $[\alpha]^{20}_D$ −174.4 (*c* 0.47, $CHCl_3$). Anal. Calcd for $C_{14}H_{24}O_3Si$: C, 62.64; H, 9.01. Found: C, 62.70; H, 9.02.

L-Selectride Reduction of (+)-8. A N_2-blanketed solution of (+)-**8** (0.25 g, 1.8 mmol) in dry THF (1.0 mL) was cooled to −78 °C and treated dropwise with a solution of L-Selectride in THF (5.4 mL of 1.0 M, 5.4 mmol), stirred at this temperature for 1 h, and quenched with 3 M NaOH solution (10 mL) and 30% hydrogen peroxide (8 mL). The reaction mixture was allowed to warm to 20 °C, transferred to a separatory funnel with a CH_2Cl_2 rinse (15 mL), and neutralized to pH 7 by the addition of 2 M sulfuric acid. The separated aqueous phase was extracted with CH_2Cl_2 (4 × 15 mL), and the combined organic layers were dried and concentrated. Purification of the residue by chromatography on silica gel (elution with 7:1 hexanes/ethyl acetate) yielded (+)-**29** as a colorless oil (0.24 g, 96%): IR (neat, cm^{-1}) 3454; ^1H NMR (300 MHz, $CDCl_3$) δ 3.87−3.74 (m, 2 H), 3.62 (t, $J = 7.0$ Hz, 1 H), 2.59 (s, 1 H), 1.99−1.41 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 91.0, 77.4, 68.7, 35.7, 35.3, 32.6, 27.0, 20.2; ES MS *m*/*z* $(M + Na)^+$ calcd 165.0891, obsd 165.0887; $[\alpha]^{20}_D$ +3.4 (*c* 1.5, $CHCl_3$).

The racemic form of **29** is a known compound.[13,32]

Compound 31. To a solution of (+)-**30** (1.30 g, 5.06 mmol) in CCl_4 (19 mL), water (9.5 mL), and acetonitrile (15 mL) was added sodium periodate (4.60 g, 21 mmol) and ruthenium trichloride (0.23 g, 1.1 mmol). The reaction mixture was stirred for 1.5 h, diluted with ether (10 mL), and filtered through a pad of silica gel. Chromatographic purification on the same adsorbent (elution with 11:1 hexanes/ethyl acetate afforded (+)-**31** as a colorless solid: mp 39.5−42.0 °C, (0.98 g, 71%); IR (neat, cm^{-1}) 1775; ^1H NMR (300 MHz, $CDCl_3$) δ 3.86 (dd, $J =$ 7.9, 2.1 Hz, 1 H), 2.70 (dt, $J = 17.5$, 10.2 Hz, 1 H), 2.49−2.39 (m, 1 H), 2.22−2.10 (m, 2 H), 2.04−1.57 (series of m, 6 H), 0.88 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 92.7, 79.7, 33.5, 30.8, 29.5, 29.2, 25.7 (3C), 18.5, 17.9, −4.3, −5.1; EI MS *m*/*z* calcd 270.1651, obsd 270.1655; $[\alpha]^{20}_D$ +18.4 (*c* 1.18, $CHCl_3$). Anal. Calcd for $C_{14}H_{26}O_3Si$: C, 62.18; H, 9.69. Found: C, 62.11; H, 9.73.

This racemic lactone, prepared in a rather different manner, has previously been incorrectly assigned.[13,32]

Allylic Oxidation of the Spirodihydrofurans. General Procedure. A mixture of pyridinium chlorochromate (16.06 g, 73 mmol), chromium trioxide (7.30 g, 73 mmol) and powdered 3 Å molecular sieves (45.6 g) were suspended in CH_2Cl_2 (500 mL) and cooled to −25 °C. After 3,5-dimethypyrazole (14.25 g, 146 mmol) had been added and stirring maintained at this temperature for 30 min, (−)-**35** (3.80 g, 14.6 mmol) dissolved in CH_2Cl_2 (40 mL) was introduced. After 1 h at −20 °C, the reaction mixture was filtered through a pad of silica gel (washing with ethyl acetate), the filtrate was concentrated, and the residue was immediately chromatographed on silica gel (elution with hexanes/ether 3:2) to give 2.6 g (65%) of (−)-**43** and 350 mg (8%) of **44**.

For **43**: colorless oil; IR (neat, cm^{-1}) 1769; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, $J = 5.7$ Hz, 1 H), 7.19−7.15 (m, 2 H), 6.88−6.84 (m, 2 H), 6.06 (d, $J = 5.7$ Hz, 1 H), 4.44 (d, $J = 11.5$ Hz, 1 H), 4.31 (d, $J = 11.5$ Hz, 1 H), 3.87−3.84 (m, 1 H), 3.79 (s, 3 H), 2.20−2.11 (m, 2 H), 1.99−1.75 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 159.3, 157.5, 129.7, 129.1 (2C) 121.0, 113.8 (2C), 97.5, 86.3, 71.1, 55.2, 33.9, 30.8, 30.5; EI MS *m*/*z* (M^+) calcd 274.1205, obsd 274.1180; $[\alpha]^{23}_D$ −223.8 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 69.87; H, 6.74.

For **44**: IR ($CHCl_3$, cm^{-1}) 1755, 1713; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, $J = 9.0$ Hz, 2 H), 7.33 (d, $J = 5.6$ Hz, 1 H), 6.88 (d, $J = 9.0$ Hz, 2 H), 6.01 (d, $J = 5.6$ Hz, 1 H), 5.39 (dd, $J = 8.1$, 1.7 Hz, 1 H), 3.84 (s, 3 H), 2.40−1.63 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 165.7, 163.7, 155.7, 131.8 (2C), 122.2, 121.5, 113.8 (2C), 94.5, 75.1, 55.4, 32.6, 28.3, 19.1.

Compound 47. Lithium hexamethyldisilazide (0.80 mL of 0.93 M in THF, 0.73 mmol) was cooled to −78 °C and treated via cannula with a solution of (+)-**31** (50 mg, 0.19 mmol) in dry THF (5 mL). After 30 min, a solution of phenylselenenyl bromide (2.0 mL of 0.25 M in THF, 0.5 mmol) was introduced. After 1 h at this temperature, the reaction mixture was quenched with 1 M hydrochloric acid (10 mL), and the separated aqueous phase was extracted with ether (2 × 20 mL). The combined organic solutions were evaporated, and the resulting selenide was dissolved in CH_2Cl_2 (10 mL), cooled to 0 °C, and treated with 30% hydrogen peroxide (15 mL). After an hour of vigorous stirring, the separated aqueous layer was extracted with CH_2Cl_2 (15 mL), and the combined organic phases were washed with water (10 mL) and brine (10 mL) prior to drying and evaporation. Purification of the residue by chromatography on silica gel (elution with hexanes/ethyl acetate 8:1) afforded 26 mg (51%) of (−)-**47** as a colorless oil: IR ($CHCl_3$, cm^{-1}) 1750; ^1H NMR (300 MHz, C_6D_6) δ 6.23 (d, $J =$ 5.6 Hz, 1 H), 5.67 (d, $J = 5.6$ Hz, 1 H), 3.53 (dd, $J = 7.1$, 2.5 Hz, 1 H), 1.91−1.75 (m, 1 H), 1.70−1.48 (series of m, 2 H), 1.40−1.10 (series of m, 3 H), 0.89 (s, 9 H) −0.06 (s, 3 H), −0.09 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 171.6, 155.4, 123.1, 94.7, 76.5, 32.3, 31.9, 26.2 (3C), 19.5, 18.6, −4.2, −4.4; EI MS *m*/*z* (M^+) calcd 268.1495, obsd 268.1501; $[\alpha]^{20}_D$ −91.1 (*c* 1.4, $CHCl_3$).

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Supporting Information Available: Experimental procedures and spectroscopic data for all compounds not described in the printed format. This material is available free of charge via the Internet at http://pubs.acs.org.

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