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Pestalotiopsin A. Enantioselective Construction of Potential Building Blocks Derived from Antipodal Cyclobutanol Intermediates

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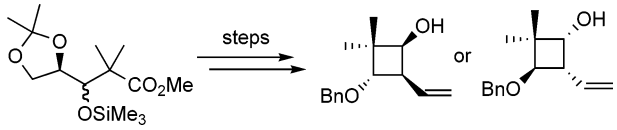
Received April 24, 2007



D-Glyceraldehyde acetonide has been used as the starting point for accessing the enantiomeric cyclobutanols **11** in optically pure condition. The dextrorotatory enantiomer has been transformed in five steps into the [3.2.0] bicyclic lactone **22**. While the deoxygenation of **22** proved to be problematical, the uncyclized variant **25** underwent the Barton process smoothly. These findings guided the related conversion of (−)-**11** into **34**. Use was also made of ring-closing metathesis to bring about the conversion of (+)-**11** into [4.2.0] bicyclic lactone building blocks. In general, all three pathways are efficient and offer the prospect of practical side-chain appendage for the purpose of installing the nine-membered ring of pestalotiopsin A (**1**).

Introduction

Fungal metabolites have become recognized to be a prolific source of structurally novel and pharmacologically active substances. In 1996, Sugawara and co-workers reported the isolation from strains of *Pestalotiopsis* species several new caryophyllene sesquiterpenes, among which was pestalotiopsin A (**1**), a powerful immunosuppressant ($IC_{50} = 3-4$ μg/mL) of the mixed lymphocyte reaction.[1] This genus was being scrutinized because of its endophytic relationship with *Taxus brevifolia*, the Pacific yew tree responsible for the generation of Taxol. The producing strain could be grown in still culture to provide adequate material for biological evaluation and structural definition. By virtue of 2D NMR techniques capped by an X-ray crystallographic analysis, **1** was shown to contain several unique structural features including an unprecedented oxatricyclic system, a δ-lactol, a highly oxygenated (*E*)-cyclononene ring, and a geminally methylated cyclobutane that defines its classification. While the absolute configuration of **1** has not yet been determined, its intriguing architecture was considered to serve as an excellent target with which to showcase new synthetic methodology. Also provided was an opportunity for defining the detailed stereochemistry of the naturally occurring dextrorotatory form.

In addition to our own synthetic efforts in this field,[2] other groups have explored creative approaches to pestalotiopsin A. The route being developed by the Procter group consists of a samarium(II)-mediated 4-*exo*-*trig* ketyl-olefin cyclization for forming the central 2-oxabicyclo[3.2.0]heptane subunit.[3] The distinctively different protocol disclosed by Tadano and co-workers is based on a Lewis acid catalyzed asymmetric [2 + 2] cycloaddition involving a camphor sultam and a ketene acetal.[4] Described here and in the following paper[5] is a detailed account of the several strategies based on a zirconocene-mediated ring contraction that we have investigated to realize an enantioselective synthesis of **1**.[2]

Results and Discussion

Retrosynthetic Analysis. Although the specific enantiomer **1** was initially targeted for exploration, our goal was to develop an approach that would prove amenable to branching at a midway point in order to produce the antipode if necessary.[5]

(1) Pulici, M.; Sugawara, F.; Koshino, H.; Uzawa, J.; Yoshida, S.; Lobkovsky, E.; Clardy, J. *J. Org. Chem.* **1996**, *61*, 2122.

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(3) (a) Johnston, D.; Francon, N.; Edmonds, D. J.; Procter, D. J. *Org. Lett.* **2001**, *3*, 2001. (b) Edmonds, D. J.; Muir, K. W.; Procter, D. J. *J. Org. Chem.* **2003**, *68*, 3190. (c) Johnston, D.; Couché, E.; Edmonds, D. J.; Muir, K. W.; Procter, D. J. *Org. Biomol. Chem.* **2003**, 328.

(4) Takao, K.; Saegusa, H.; Tsujita, T.; Washizawa, T.; Tadano, K. *Tetrahedron Lett.* **2005**, *46*, 5815.

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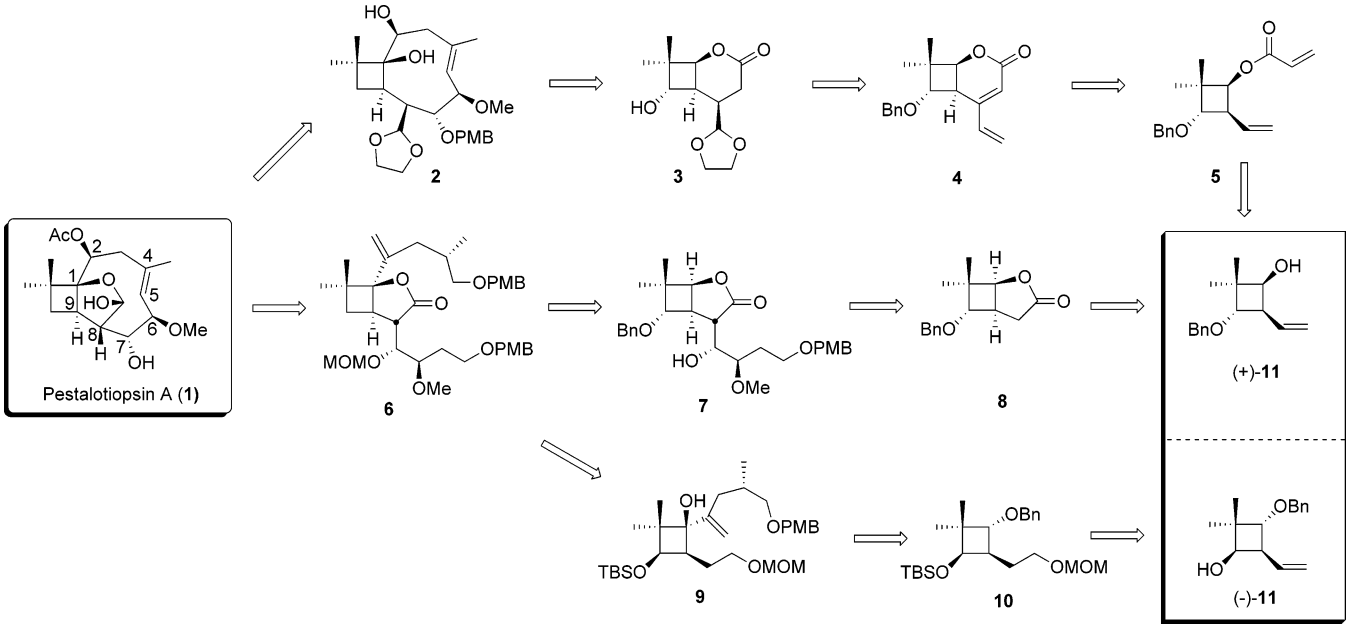
10.1021/jo070861r CCC: $37.00
Published on Web 08/15/2007

SCHEME 1



Beyond that, several possible disconnections of the nine-membered ring from the western sector suggested themselves, and three of these were given serious consideration (Scheme 1). It is widely recognized that the formation of medium-sized rings is plagued by steric and strain factors nonconducive to C−C bond installation. For this reason, recourse must be made to a special type of process with the power to bind together two reluctant partners having these structural parameters. Ring-closing metathesis has been shown to have this capability under a range of circumstances.[6] A tactic commonly employed to facilitate this type of transformation is the incorporation of some form of conformational constraint into the cyclization precursor.[7]

As shown in Scheme 1, we settled on three scenarios. The first of these involves a [4.2.0] bicyclic lactone core such as defined in **3** or **4** as a prelude to increasing molecular complexity like that resident in **2**. Dissection in a manner involving a [3.2.0] bicyclic lactone subunit as exemplified by **6** also offers convergency. Intriguingly, the lower side chain may be introduced first (see **7**) or last (onward from **9**). In every instance, the termini of these chains are forced into reasonable proximity.

Another set of variables involves the nature of the protecting groups and their likely impact on the *E*/*Z* ratio[7] (see **2**). The inherent flexibility of these modifications was to be accompanied by molecular modeling studies so as to maximize the opportunity for success.

Synthesis of the Enantiopure Core Cyclobutanols. Enantiomeric Relationships. In accord with the preceding plan of action, D-glyceraldehyde acetonide was brought into ZnI_2-promoted condensation with the silyl ketene acetal derived from methyl isobutyrate according to Kita.[8] The resulting β-siloxy ester **12** was deprotected quantitatively with potassium carbonate in methanol, thereby allowing for the ready chromatographic separation of **13** from **14** (9:1) on preparative scale (Scheme 2). We note that **14** can be directly generated as the major product via an uncatalyzed aldol reaction that involves prohibitively expensive reagents in stoichiometric amounts.[9] For this reason, inversion of the epimeric ratio to 1:8 was alternatively effected by sequential catalytic perruthenate oxidation[10] followed by low-temperature (−100 to −40 °C) reduction of the keto ester with zinc borohydride in ether.[11] The next task was to mask the OH group in both **13** and **14** as benzyl ethers, a transformation that was ultimately made efficient (92%) by adding benzyl bromide at a very slow rate. Subsequent reduction with lithium aluminum hydride provided primary carbinols whose oxidation to the aldehyde level by the Swern process was followed by treatment with *p*-toluenesulfonic acid in methanol to effect ring closure and make available the methyl furanosides **15** and **16**. Subsequently, advantage was taken of the capability of IBX in hot acetonitrile[12] to provide the chemically sensitive aldehydes which were directly olefinated under Wittig conditions. In both series, we found it possible to minimize the level of competing β-elimination, although lower yields invariably accompanied the production of **17** (53%) relative to **18** (71%). We attribute this phenomenon in part to the enhanced steric crowding present when proceeding from **15** to **17** and the availability of a *trans* E_2 pathway, which is otherwise lacking when the benzyloxy group is α-oriented. To address this discrepancy in efficiency, recourse was made to the titanium-based nonbasic methylenation reagents. Although

(6) *Handbook of Metathesis*; Grubbs, R. H., Ed.: Wiley-VCH: Weinheim, 2003; Vols. 1−3.

(7) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490.

(8) (a) Kita, Y.; Tamura, O.; Itoh, F.; Yasuda, H.; Kishino, H.; Ke, Y. Y.; Tamura, Y. *J. Org. Chem.* **1988**, *53*, 554. (b) Kita, Y.; Yasuda, H.; Tamura, O.; Itoh, F.; Ke, Y. Y.; Tamura, Y. *Tetrahedron Lett.* **1985**, *26*, 5777.

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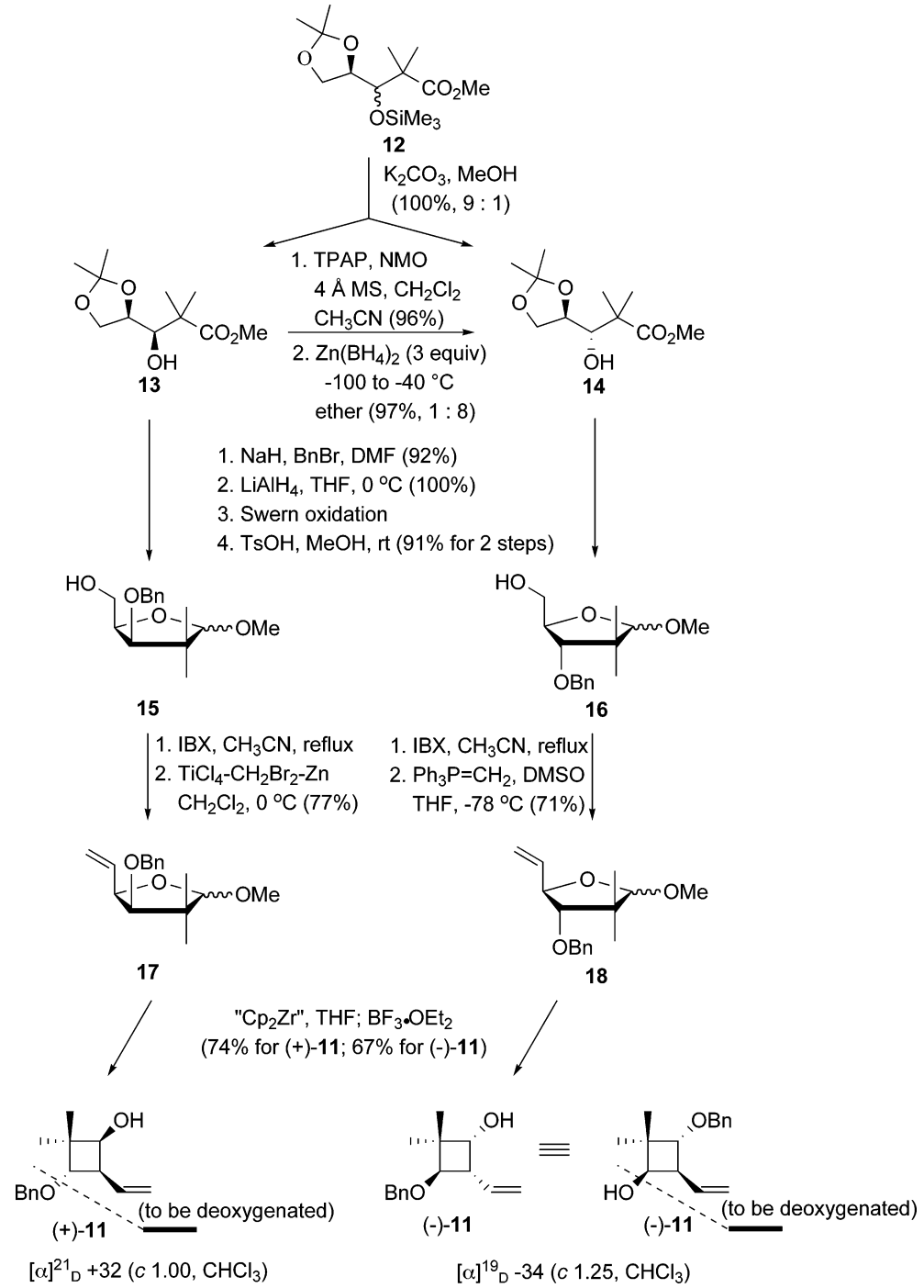
(10) (a) Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13. (b) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

(11) (a) Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1983**, *24*, 2653. (b) Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338. (c) Kobayashi, Y.; Nakano, M.; Kumar, G. B.; Kishihara, K. *J. Org. Chem.* **1998**, *63*, 7505.

(12) (a) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019. (b) Yang, J.; Long, Y. O.; Paquette, L. A. *J. Am. Chem. Soc.* **2003**, *125*, 1567. (c) More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001.

SCHEME 2. Synthesis of Cyclobutanols (+)-11 and (−)-11



the Petasis reagent[13] only delivered **17** in a 31% yield, treatment of the sensitive aldehyde derived from **15** with the Lombardo reagent[14] resulted in a 77% yield of **17**.

In the spirit of our orienting paradigm, the responsiveness of all four vinylfuranosides to the zirconocene reagent developed by Negishi[15] was probed.[16,17] In so doing, we discovered **17** and its anomer to be appropriately responsive to conditions that included the co-addition of boron trifluoride etherate as a promoter. The ring contraction performed in this manner gave rise to dextrorotatory cyclobutanol **11** (74%). Analogous treatment of **18** afforded the enantiomeric (−)-**11** with approximately comparable efficiency. At this point, some commentary concerning certain key structural interrelationships present in these antipodes is warranted. Thus, reductive removal of the benzy-

(13) (a) For the Petasis reagent: Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392. (b) For the preparation of dimethyltitanocene, see: Payack, J. F.; Hughes, D. L.; Cai, D.; Cottrell, I. F.; Verhoeven, T. R. *Org. Synth.* **2002**, *79*, 19.

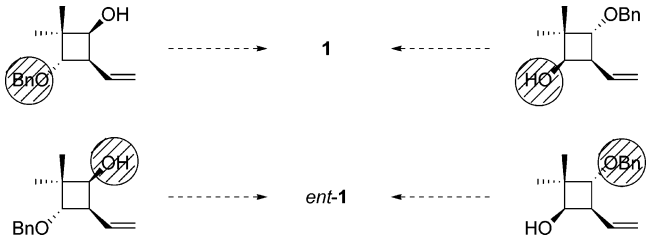
(14) For the Lombardo reagent, consult: (a) Hibino, J.-I.; Okazoe, T.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 5579. (b) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, *19*, 2417. (c) Lombardo, L. *Tetrahedron Lett.* **1982**, *23*, 4293. (d) Lombardo, L. *Org. Synth.* **1987**, *65*, 81.

(15) Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829.

(16) Review: Hanzawa, Y.; Ito, H.; Taguchi, T. *Synlett* **1995**, 299.

(17) Review: Paquette, L. A. *J. Organomet. Chem.* **2006**, *691*, 2083.

SCHEME 3. Consequences of Regiocontrolled Deoxygenation of the Enantiomers of Cyclobutanol 11



loxy group in (+)-**11** or of the hydroxyl substituent in (-)-**11** permits targeting of the same enantiomer of pestalotiopsin A, viz. **1** (Scheme 3). Furthermore, deoxygenation of (+)-**11** and (-)-**11** in the reverse fashion would result in the acquisition of *ent*-**1**. The progressions required to realize these objectives have been pursued.

More Advanced Functionalization of the Enantiomeric Cyclobutanols. In a first series of experiments, (+)-**11** was transformed into its TBS ether **19** (Scheme 4). In light of the prevailing steric congestion in this region of the cyclobutane ring, it was imperative that TBS triflate be used to achieve a reasonable reaction rate and chemical yield. The hydroboration of **19** with the borane·THF complex followed. When the oxidative workup was performed with alkaline hydrogen peroxide, the yield realized for **20** was 94%. The use of sodium perborate[18] fared less well (27%). Treatment of **20** with 2 M HCl in methanol resulted in efficient desilylation, thereby setting the stage for perruthenate oxidation[10] of the resulting diol **21** to afford bicyclic lactone **8**, whose hydrogenolysis made available the desired functionalized subtarget. Subsequent attempts to remove the hydroxyl group in this bicyclic lactone failed. Neither 1,1′-thiocarbonyldiimidazole[19] nor *O*-*p*-tolyl chlorothionoformate[20] enabled recognizable conversion to **23** subsequent to treatment with tri-*n*-butyltin hydride.

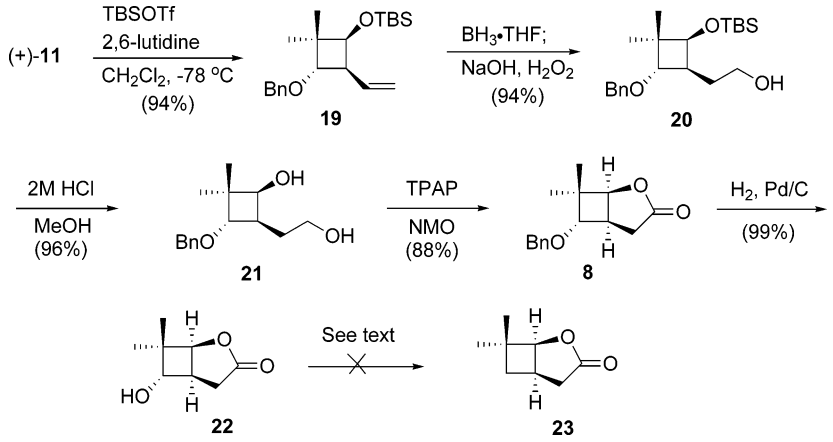
More interesting results were secured when generation of the butyrolactone ring was deferred to a later stage. To illustrate this point, alcohol **20** was transformed quantitatively into the MOM ether **24** and subsequently debenzylated (Scheme 5). To complete the deoxygenation process, **25** was coupled successfully with the chlorothionoformate and subjected in turn to reduction with tributylstannane to give **27**.

In comparable fashion, the levorotatory cyclobutanol **11** lent itself in a highly efficient manner to conversion to **34** (Scheme 6). The first two steps involved protection as the TBS ether and anti-Markovnikov hydration. The road to **34** was paved by formation of the MOM ether **30** in advance of desilylation. Interestingly, functionalization of the hydroxyl group in **31** with *O*-*p*-tolyl chlorothionoformate gave rise quantitatively to isomers **32** and **33** in a 1:2.5 ratio. Structural assignment to the major constituent rests soundly on the downfield shift exhibited by H-1 (5.32 ppm) relative to the location of that in **32** (4.75 ppm). Beyond that, the stereochemical assignments are convincingly based on NOESY studies that clearly revealed strong correlations between the 1,3-related cyclobutane protons and the different components of the *gem*-dimethyl group. In line with our goals, **33** underwent efficient reductive conversion to **34**.

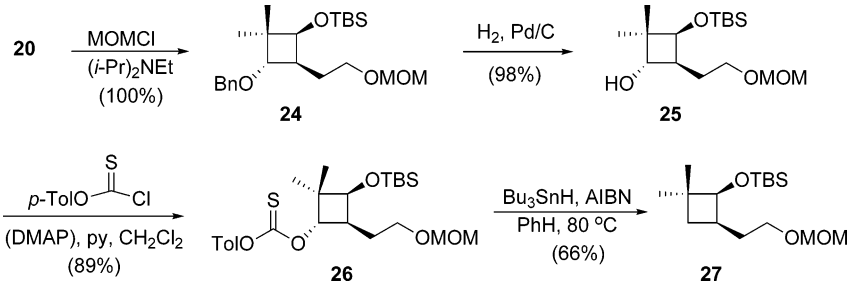
The pathways that form the basis of Schemes 5 and 6 demonstrate the workability of a key deoxygenative step. Not yet defined is the timing of this event. The sacrifice of an asymmetric center in this maneuver could prove premature if the resident stereogenicity were of value in controlling the introduction of other chiral sites. These issues are dealt with in the sequel.[5]

Crafting of [4.2.0] Bicyclic Lactone Building Blocks. A third possible approach to pestalotiopsin A that has been pursued involves the intervention of bicyclic lactones exemplified by **3** and **4** (Scheme 1). Scaffolds of this type were viewed to offer the fascinating prospect of allowing extensive stereocontrolled

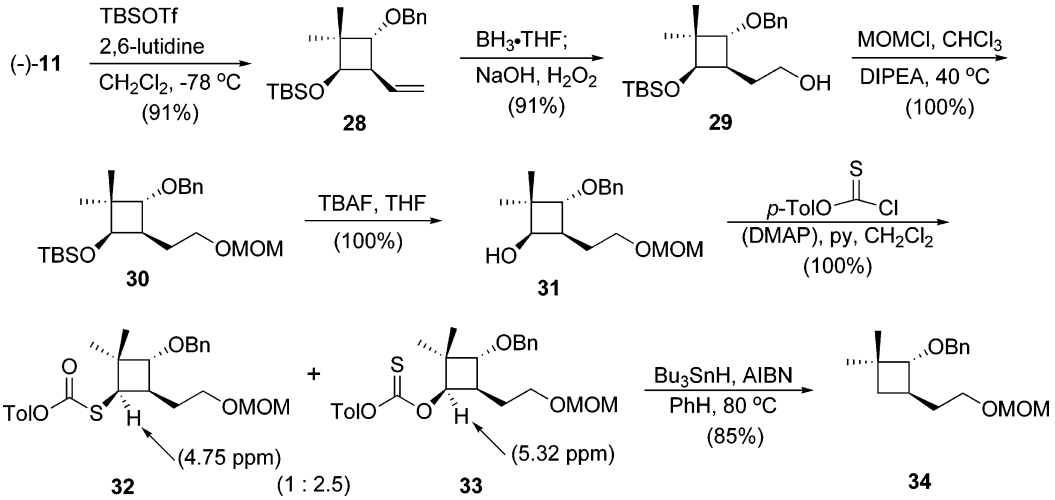
SCHEME 4. Syntheis of Hydroxy Lactone 22



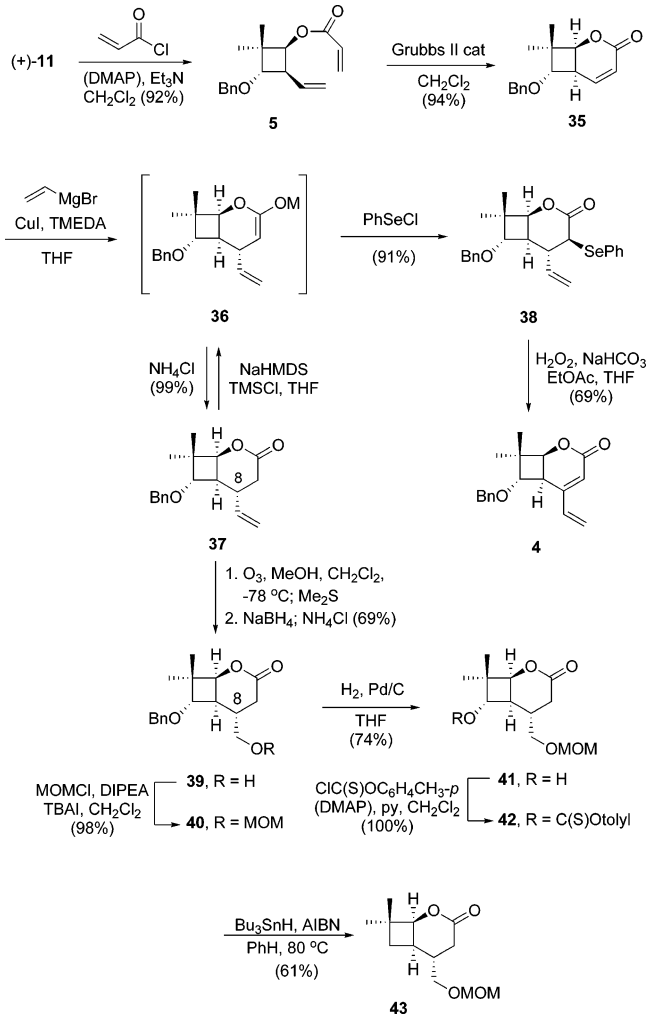
SCHEME 5. Pursuit of an "Open-Chain" Alternative



SCHEME 6. Functional Group Manipulations Involving (−)-11



SCHEME 7. Ring-Closing Metathesis-Based Approach



oxygenation to be brought about in an expedient fashion, with the six-membered ring serving as the template. To this end, (+)-**11** was esterified with acryloyl chloride in order to secure **5** (Scheme 7). An excess of both the acid chloride and triethylamine proved necessary to drive this reaction to completion. Moreover, very slow addition of either component was mandatory in order to avoid polymerization and decomposition of the cyclobutanols. When these precautions were taken, the desired ester was obtained in 92% yield. In the presence of the second-generation Grubbs catalyst,[21] the ring-closing metathesis of **5** proved very effective, delivering **35** with near-quantitative efficiency.

Copper(I) iodide-promoted conjugate addition of freshly prepared vinylmagnesium bromide to **35** proceeded stereoselectively from the less sterically hindered α-surface of the six-membered ring as in **37**. The intermediate enolate (**36**; M = Cu) could be regenerated (as M = Na) by the deprotonation of **37** with sodium hexamethyldisilazide. This particular transformation holds importance because of our need to ultimately invert configuration at C-8 in order to reach the target. Reintroduction of the double bond via organoselenium chemistry as in the sequence **36** → **38** → **4** illustrates a step in this direction.

A number of alternative synthetic sequences can be envisioned. For example, the double bond in **37** may be subjected to ozonolytic cleavage with a reductive ($NaBH_4$) workup. This conversion to **39** followed by MOM protection of the primary alcohol set the stage for removal of the benzyloxy group by sequential hydrogenolysis and application of the Barton reaction to deliver **43**.

The rationale for pursuing a synthesis of **1** via one of the three routes, whose foundations were established herein, is discussed in the following paper in this issue.[5]

Conclusion

In summary, the capability of transforming D-glyceraldehyde acetonide into either pure enantiomer of cyclobutanol **11** has been defined. This protocol takes advantage of the chemical reactivity of zirconocene in a manner that enables the diastereocontrolled ring contraction of **17** and **18**. These studies have revealed that the structural features resident in these antipodal

(18) (a) Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *Tetrahedron Lett.* **1989**, *30*, 1483. (b) Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *J. Org. Chem.* **1989**, *54*, 5930.

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(21) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

intermediates can be used to advantage in situations preparatory to the attachment of side chains for appendage of the medium-sized ring.

Experimental Section

(*S*)-3-((*R*)-2,2-Dimethyl[1,3]dioxolan-4-yl)-3-hydroxy-2,2-dimethylpropionic Acid Methyl Ester (14). To a solution of the ketone intermediate derived from **13** (100 mg, 0.43 mmol) in Et_2O (2 mL) at −100 °C was added an ethereal solution of $Zn(BH_4)_2$ (7.2 mL, 0.18 M, 1.30 mmol) in three equal portions over 2 h. The mixture was gradually warmed to −40 °C over 1 h and poured into brine. The resulting mixture was stirred at room temperature for 1 h and then extracted with Et_2O several times. The combined ethereal solutions were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (5−20% ethyl acetate/hexanes) to furnish **14**/**13** (98 mg, 97%), whose diastereomeric selectivity was determined to be 8:1 (**14**/**13**) by ^{1}H NMR spectroscopy. For **14**: IR (film, cm^{-1}) 3518, 1735, 1371; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20−4.17 (m, 1H), 4.02 (dd, J = 8.0, 6.5 Hz, 1H), 3.86 (t, J = 7.8 Hz, 1H), 3.69 (s, 3H), 3.53 (dd, J = 9.5, 2.5 Hz, 1 H), 2.98 (d, J = 9.5 Hz, 1H), 1.39 (s, 3H), 1.35 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 98.7, 76.7, 76.1, 66.8, 52.0, 46.0, 26.4, 25.3, 21.7, 21.4; $[\alpha]_D^{16}$ −2.4 (*c* 1.33, $CHCl_3$).

((2*R*,3*S*,5*S*)- and ((2*R*,3*S*,5*R*)-3-Benzyloxy-5-methoxy-4,4-dimethyltetrahydrofuran-2-yl)methanol (15α and 15*β*). A stirred solution of oxalyl chloride (60.32 mL, 0.69 mol) in anhydrous CH_2Cl_2 (1.6 L) was cooled to −78 °C under N_2 and treated dropwise with a solution of dimethyl sulfoxide (98.48 mL, 1.39 mol) in anhydrous CH_2Cl_2 (100 mL). After 45 min, a solution of the alcohol intermediate derived from **13** (102 g, 0.35 mol) in anhydrous CH_2Cl_2 (300 mL) was added dropwise. After 1 h, triethylamine (387 mL, 2.78 mol) was added dropwise, and the reaction mixture was stirred at −78 °C for a further 2 h until complete by TLC analysis and quenched with water (2 L). The aqueous layer was extracted with CH_2Cl_2 (3 × 1 L). The combined organic extracts were washed with water (2 × 750 mL) and brine (500 mL) and then dried. The solvent was evaporated under reduced pressure to yield the aldehyde (106.45 g) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.50 (s, 1H), 7.38−7.27 (m, 5H), 4.77 (d, J = 11.2 Hz, 1H), 4.64 (d, J = 11.2 Hz, 1H), 4.16 (m, 1H), 4.01 (dd, J = 8.1, 6.4 Hz, 1H), 3.92 (dd, J = 8.1, 6.7 Hz, 1H), 3.80 (d, J = 5.1 Hz, 1H), 1.41 (s, 3H), 1.32 (s, 3H), 1.13 (s, 3H), 1.11 (s, 3H).

A stirred solution of the crude aldehyde (106.45 g) in methanol (750 mL) was treated with anhydrous *p*-toluenesulfonic acid (5.97 g, 34.7 mmol) at rt under N_2. The reaction mixture was stirred overnight, and the solvent was evaporated under reduced pressure. The residue was partitioned between ethyl acetate (1 L) and water (250 mL). The aqueous layer was extracted with ethyl acetate (2 × 1 L), and the combined organic extracts were washed with saturated $NaHCO_3$ solution (500 mL) and brine (500 mL) and then dried. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (elution with 15% ethyl acetate in hexanes) to yield **15**α and **15***β* (3:1) (89.81 g, 91%) as colorless oils.

For **15**α: IR (film, cm^{-1}) 3457, 1603, 1585; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.25 (m, 5H), 4.63 (d, J = 11.8 Hz, 1H), 4.54 (d, J = 11.8 Hz, 1H), 4.40 (s, 1H), 4.09 (ddd, J = 6.9, 4.6, 3.0 Hz, 1H), 3.91 (d, J = 6.9 Hz, 1H), 3.73 (ddd, J = 11.8, 3.9, 3.0 Hz, 1H), 3.54 (ddd, J = 11.8, 7.2, 4.6 Hz, 1H), 3.37 (s, 3H), 2.50 (br s, OH), 1.11 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 128.4, 127.8, 127.6, 111.9, 84.2, 83.3, 73.3, 63.9, 55.6, 46.3, 21.0, 20.1; HRMS (ES) *m*/*z* (M + Na)$^+$ calcd 289.1426, obsd 289.1409; $[\alpha]_D^{20}$ −62.1 (*c* 1.0, $CHCl_3$).

For **15***β*: IR (film, cm^{-1}) 3457, 1603, 1585; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.25 (m, 5H), 4.63 (d, J = 12.1 Hz, 1H), 4.51 (d, J = 12.1 Hz, 1H), 4.46 (s, 1H), 4.05 (m, 1H), 3.72 (ddd, J = 11.8, 5.2, 3.5 Hz, 1H), 3.53 (ddd, J = 11.8, 6.6, 5.2 Hz, 1H), 3.41 (d, J = 5.5 Hz, 1H), 3.38 (s, 3H), 1.28 (d, J = 11.1 Hz, OH), 1.11 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 128.4, 127.8, 111.5, 84.9, 83.5, 73.0, 63.1, 55.6, 45.8, 26.8, 16.7; HRMS (ES) *m*/*z* (M + Na)$^+$ calcd 289.1426, obsd 289.1411; $[\alpha]_D^{22}$ +42.7 (*c* 2.02, $CHCl_3$).

((2*R*,3*R*,5*S*)- and ((2*R*,3*R*,5*R*)-3-Benzyloxy-5-methoxy-4,4-dimethyltetrahydrofuran-2-yl)methanol (16α and 16*β*). Swern oxidation of the alcohol intermediate derived from **14** (5.44 g, 18.5 mmol), following the previous example, afforded the crude aldehyde: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.64 (s, 1H), 7.35−7.28 (m, 5H), 4.78 (d, J = 11.1 Hz, 1H), 4.64 (d, J = 11.1 Hz, 1H), 4.33−4.26 (m, 1H), 3.98 (dd, J = 8.0, 6.3 Hz, 1H), 3.76 (t, J = 8.0 Hz, 1H), 3.53 (d, J = 4.8 Hz, 1H), 1.41 (s, 3H), 1.34 (s, 3H), 1.16 (s, 3H), 1.12 (s, 3H).

Cyclization of the preceding crude aldehyde, following the previous example, afforded **16**α and **16***β* (1:3) (4.53 g, 92%) as colorless oils.

For **16**α: IR (film, cm^{-1}) 3424, 1103, 1031; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.30 (m, 5H), 4.70 (d, J = 11.9 Hz, 1H), 4.47 (d, J = 11.9 Hz, 1H), 4.42 (s, 1H), 4.32 (dd, J = 11.0, 5.0 Hz, 1H), 3.76 (dd, J = 4.9, 2.2 Hz, 2H), 3.67 (d, J = 6.1 Hz, 1H), 3.39 (s, 3H), 2.17 (br s, 1H), 1.14 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7, 128.6, 128.2 (2 C), 128.0 (2 C), 111.0, 86.7, 81.4, 74.7, 62.8, 55.5, 47.7, 26.0, 17.2; $[\alpha]_D^{20}$ −105.4 (*c* 1.14, $CHCl_3$).

For **16***β*: IR (film, cm^{-1}) 3440, 1100, 1053; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.28 (m, 5H), 4.67 (d, J = 11.5 Hz, 1H), 4.50 (d, J = 11.5 Hz, 1H), 4.49 (s, 1H), 4.27−4.21 (m, 1H), 4.05 (d, J = 7.4 Hz, 1H), 3.81−3.78 (m, 2H), 3.34 (s, 3H), 2.14 (br s, 1H), 1.14 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 128.6 (2 C), 128.0 (2 C), 127.6, 110.5, 86.9, 78.3, 74.1, 62.6, 55.3, 46.2, 22.0, 20.4; $[\alpha]_D^{20}$ +54.5 (*c* 1.33, $CHCl_3$).

(2*S*,4*S*,5*R*)- and (2*R*,4*S*,5*R*)-4-Benzyloxy-2-methoxy-3,3-dimethyl-5-vinyltetrahydrofuran (17α and 17*β*). A stirred solution of acetals **15** (2.5 g, 9.4 mmol) in anhydrous MeCN (100 mL) was treated with IBX (2.98 g, 11.28 mmol) and heated to reflux for 90 min. The reaction mixture was allowed to cool, filtered through a pad of Celite, and washed with ether (100 mL). The solvent was evaporated under reduced pressure and the residue was treated with ether (100 mL), filtered through a fresh pad of Celite, and washed with ether (100 mL). The filtrate was dried and the solvent evaporated under reduced pressure to yield the aldehydes as a colorless oil which was used directly in the next reaction.

To a stirred suspension of activated Zn powder (5.24 g, 80.3 mmol) and CH_2Br_2 (1.84 mL, 26.3 mmol) in THF (45 mL) was added dropwise neat $TiCl_4$ (2.06 mL, 18.8 mmol) at −40 °C under N_2. The mixture was then allowed to warm to 5 °C and stirred for 3 days to produce a thick gray slurry of the active reagent. To the $Zn-CH_2Br_2-TiCl_4$ mixed methylenation reagent was added dropwise a CH_2Cl_2 (20 mL) solution of unpurified aldehydes (9.4 mmol) at 5 °C. After being stirred for 2 h, the reaction mixture was quenched with cold saturated $NaHCO_3$ solution (20 mL) cautiously. The aqueous layer was extracted with ether (3 × 20 mL), and the combined organic extracts were washed with brine (20 mL), then dried. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (elution with 40% CH_2Cl_2 in hexanes) to yield **17**α and **17***β* (3:1) (1.90 g, 77%) as colorless oils.

For **17**α: IR (film, cm^{-1}) 1644, 1604, 1585; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.23 (m, 5H), 5.90 (ddd, J = 17.1, 10.2, 7.8 Hz, 1H), 5.32 (ddd, J = 17.1, 1.6, 1.0 Hz, 1H), 5.16 (ddd, J = 10.2, 1.6, 1.0 Hz, 1H), 4.62 (d, J = 11.8 Hz, 1H), 4.55 (d, J = 11.8 Hz, 1H), 4.41 (s, 1H), 4.35 (m, 1H), 3.74 (d, J = 7.2 Hz, 1H), 3.35 (s, 3H), 1.11 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.6, 138.5, 128.3, 127.6, 127.5, 116.7, 111.3, 88.8, 83.6, 73.0, 55.0, 46.0, 20.7, 19.7; HRMS (ES) *m*/*z* (M + Na)$^+$ calcd 285.1461, obsd 285.1448; $[\alpha]_D^{21}$ −89.7 (*c* 1.25, $CHCl_3$).

For **17***β*: IR (film, cm^{-1}) 1645, 1606, 1497; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.26 (m, 5H), 5.84 (ddd, J = 17.0, 10.2, 6.8 Hz,

1H), 5.32 (ddd, J = 17.0, 1.3, 1.2 Hz, 1H), 5.14 (ddd, J = 10.2, 1.3, 1.2 Hz, 1H), 4.57 (s, 2H), 4.50 (s, 1H), 4.46 (m, 1H), 3.41 (s, 3H), 3.28 (d, J = 4.9 Hz, 1H), 1.11 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 128.3, 127.7, 127.6, 116.3, 111.4, 89.2, 84.4, 72.6, 55.5, 46.2, 26.9, 16.7; HRMS (ES) m/z $(M + Na)^+$ calcd 285.1461, obsd 285.1448; $[\alpha]_D^{21}$ +45.0 (c 1.0, $CHCl_3$).

(2*S*,4*R*,5*R*)- and (2*R*,4*R*,5*R*)-4-Benzyloxy-2-methoxy-3,3-dimethyl-5-vinyltetrahydrofuran (18α and 18β). IBX oxidation of **16**α and **16**β (1.00 g, 3.76 mmol), following the previous example, afforded the crude aldehyde, which was used directly in the next reaction.

A suspension of methyltriphenylphosphonium bromide (2.02 g, 5.64 mmol) in anhydrous THF (10 mL) was cooled to 0 °C under N_2 and treated with *n*-butyllithium (3.3 mL, 1.6 M in hexanes, 5.26 mmol). The orange mixture was stirred at rt for 1 h, agitation was stopped, and the solids were allowed to settle. A solution of unpurified aldehydes in anhydrous THF (10 mL) and DMSO (1 mL) was cooled to −78 °C under N_2 and treated slowly with the supernatant ylide solution via cannula. The reaction mixture was allowed to warm slowly to rt over 4 h. The reaction mixture was treated with saturated NH_4Cl solution (20 mL) and extracted with ether (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), then dried. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (elution with 2−10% ethyl acetate in hexanes) to yield **18**α and **18**β (1:3) (699 mg, 71%) as colorless oils.

For **18**α: IR (film, cm^{-1}) 1468, 1363, 1102, 1030; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5H), 6.14−6.07 (m, 1H), 5.33−5.29 (m, 1H), 5.25−5.23 (m, 1H), 4.64−4.58 (m, 2H), 4.44 (d, J = 12.9 Hz, 1H), 4.42 (s, 1H), 3.52 (d, J = 5.5 Hz, 1H), 3.41 (s, 3H), 1.09 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 136.5, 128.1 (3 C), 127.6 (2 C), 117.5, 111.4, 86.0, 83.6, 73.4, 55.7, 47.4, 26.1, 17.4; $[\alpha]_D^{20}$ −18.3 (c 1.63, $CHCl_3$).

For **18**β: IR (film, cm^{-1}) 1467, 1362, 1097, 1028; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.27 (m, 5H), 6.10−6.03 (m, 1H), 5.38−5.34 (m, 1H), 5.27−5.25 (m, 1H), 4.63−4.58 (m, 2H), 4.54 (s, 1H), 4.46 (d, J = 11.8 Hz, 1H), 3.91 (d, J = 7.8 Hz, 1H), 3.37 (s, 3H), 1.11 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 135.6, 128.3 (2 C), 127.5 (3 C), 118.0, 110.5, 86.4, 80.4, 73.1, 55.5, 46.2, 21.2, 20.6; $[\alpha]_D^{20}$ +112.6 (c 2.61, $CHCl_3$).

(1*S*,3*S*,4*R*)-3-Benzyloxy-2,2-dimethyl-4-vinylcyclobutanol ((+)-11). A stirred solution of Cp_2ZrCl_2 (0.7 g, 2.39 mmol) in anhydrous THF (7.5 mL) was cooled to −78 °C under N_2 and treated with *n*-butyllithium (2.5 mL, 1.9 M in hexanes, 4.77 mmol). The yellow solution was stirred for 2 h and transferred via cannula into a stirred solution of **17** (250 mg, 0.95 mmol) and Cp_2ZrCl_2 (28 mg, 95 μmol) at −78 °C under N_2. After the addition was complete, the reaction mixture was allowed to warm slowly to rt overnight, and $BF_3 \cdot OEt_2$ (0.12 mL, 0.95 mmol) was slowly introduced. The stirring was continued for 2 h, and the reaction mixture was filtered through a short pad of silica gel which was rinsed with ether (50 mL). The filtrate was passed through another fresh pad of silica gel which was washed with ether (50 mL). The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (elution with an increasing proportion of ethyl acetate in hexanes from 5 to 10%) to yield (+)-**11** (163 mg, 74%) as a colorless oil: IR (film, cm^{-1}) 3458, 1637, 1498; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.25 (m, 5H), 5.93 (ddd, J = 17.5, 10.5, 7.2 Hz, 1H), 5.24 (ddd, J = 10.5, 1.6, 1.0 Hz, 1H), 5.17 (ddd, J = 17.5, 1.6, 1.0 Hz, 1H), 4.48 (s, 2H), 3.84 (d, J = 6.9 Hz, 1H), 3.82 (d, J = 8.0 Hz, 1H), 3.05 (ddt, J = 15.3, 7.2, 1.0 Hz, 1H), 1.52 (br s, OH), 1.15 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 134.6, 128.3 (2 C), 127.5 (3 C), 117.9, 82.1, 72.2, 71.4, 47.4, 42.3, 21.4, 20.9; HRMS (ES) m/z $(M + Na)^+$ calcd 255.1356, obsd 255.1360; $[\alpha]_D^{21}$ +32 (c 1.00, $CHCl_3$).

(1*R*,3*R*,4*S*)-3-Benzyloxy-2,2-dimethyl-4-vinylcyclobutanol ((−)-11). Zirconocene ring contraction of **18** (800 mg, 3.05 mmol), following the previous example, afforded (−)-**11** (474 mg, 67%) as a colorless oil: IR (film, cm^{-1}) 3458, 1637, 1498; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.25 (m, 5H), 5.93 (ddd, J = 17.5, 10.5, 7.2 Hz, 1H), 5.24 (ddd, J = 10.5, 1.6, 1.0 Hz, 1H), 5.17 (ddd, J = 17.5, 1.6, 1.0 Hz, 1H), 4.48 (s, 2H), 3.84 (d, J = 6.9 Hz, 1H), 3.82 (d, J = 8.0 Hz, 1H), 3.05 (ddt, J = 15.3, 7.2, 1.0 Hz, 1H), 1.52 (br s, OH), 1.15 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 134.6, 128.3 (2 C), 127.5 (3 C), 117.9, 82.1, 72.2, 71.4, 47.4, 42.3, 21.4, 20.9; $[\alpha]_D^{19}$ −34 (c 1.25, $CHCl_3$).

(1*S*,5*S*,6*S*)-6-Benzyloxy-7,7-dimethyl-2-oxabicyclo[3.2.0]heptan-3-one (8). A stirred solution of **21** (100 mg, 0.4 mmol) and *N*-methylmorpholine *N*-oxide monohydrate (216 mg, 1.6 mmol) in 10% $MeCN/CH_2Cl_2$ (5 mL) was treated with 4 Å molecular sieves (200 mg) under N_2. After 10 min, TPAP (14 mg, 40 μmol) was added, and the reaction mixture was stirred for a further hour and evaporated under reduced pressure to leave a residue that was diluted with CH_2Cl_2 (10 mL) and passed through a pad of silica gel. The latter was washed with ethyl acetate (20 mL) to provide **8** (96 mg, 98%) as a colorless oil: IR (film, cm^{-1}) 1778, 1605, 1413; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.27 (m, 5H), 4.51 (d, J = 11.8 Hz, 1H), 4.41 (d, J = 6.2 Hz, 1H), 4.40 (d, J = 11.8 Hz, 1H), 3.49 (d, J = 5.7 Hz, 1H), 2.98 (m, 1H), 2.60 (dd, J = 18.3, 8.9 Hz, 1H), 2.36 (dd, J = 18.3, 1.1 Hz, 1H), 1.19 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 137.8, 128.5, 128.0 (2 C), 127.6 (2 C), 84.8, 82.0, 71.9, 43.9, 38.9, 33.5, 21.5, 19.8; HRMS (ES) m/z $(M + Na)^+$ calcd 269.1154, obsd 269.1163; $[\alpha]_D^{19}$ −13.0 (c 0.3, $CHCl_3$).

(1*S*,5*S*,6*S*)-7,7-Dimethyl-6-hydroxy-2-oxabicyclo[3.2.0]heptan-3-one (22). A stirred solution of **8** (120 mg, 0.49 mmol) in anhydrous THF (2 mL) was treated with 5% Pd on carbon (20 mg, excess) and placed under 500 psi of hydrogen for 48 h. The reaction mixture was filtered through a pad of Celite which was washed with ethyl acetate (10 mL). The solvent was evaporated under reduced pressure to yield the crude product which was purified by column chromatography on silica gel (elution with 1:1 ethyl acetate/hexanes) to afford **22** (75 mg, 99%) as a white solid: mp 68−69 °C; IR (film, cm^{-1}) 3438, 1754, 1466; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.43 (d, J = 6.6 Hz, 1H), 3.76 (d, J = 5.6 Hz, 1H), 2.94 (m, 1H), 2.68 (dd, J = 18.5, 8.5 Hz, 1H), 2.56 (dd, J = 18.5, 1.6 Hz, 1H), 1.90 (br s, OH), 1.13 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 81.8, 78.8, 44.1, 40.8, 33.4, 20.6, 19.2; HRMS (ES) m/z $(M + Na)^+$ calcd 179.0684, obsd 179.0685; $[\alpha]_D^{19}$ −72.8 (c 1.15, $CHCl_3$).

Thiocarbonic Acid [(1*S*,3*S*,4*S*)-3-(*tert*-Butyldimethylsiloxy)-4-(2′-methoxymethoxyethyl)-2,2-dimethylcyclobutyl] Ester *p*-Tolyl Ester (26). A stirred solution of **25** (20 mg, 63 μmol) in anhydrous CH_2Cl_2 (0.5 mL) was treated with freshly distilled pyridine (0.5 mL), *O*-*p*-tolyl thiochloroformate (29 μL, 0.19 mmol), and DMAP (cat) under N_2. The reaction mixture was stirred for 16 h, quenched with water (2 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with water (2 × 2 mL), then dried. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel (elution with 5% ethyl acetate in hexanes) to afford **26** (26.2 mg, 89%) as a pale yellow oil: IR (film, cm^{-1}) 1730, 1612, 1506; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, J = 8.3 Hz, 2H), 6.97 (d, J = 8.3 Hz, 2H), 5.19 (d, J = 7.7 Hz, 1H), 4.62 (s, 2H), 3.91 (d, J = 7.7 Hz, 1H), 3.54 (tq, J = 6.4, 2.8 Hz, 2H), 3.37 (s, 3H), 2.78 (tt, J = 15.1, 7.5 Hz, 1H), 2.37 (s, 3H), 1.88 (qd, J = 6.4, 3.3 Hz, 2H), 1.16 (s, 3H), 1.14 (s, 3H), 0.92 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.2, 151.4, 136.2, 130.0 (2 C), 121.5 (2 C), 96.5, 87.7, 72.0, 65.9, 55.2, 44.6, 40.8, 27.5, 25.8 (3 C), 22.1, 21.6, 20.9, 18.3, −4.7, −5.1; HRMS (ES) m/z $(M + Na)^+$ calcd 491.2263, obsd 491.2276; $[\alpha]_D^{19}$ +20.7 (c 0.3, $CHCl_3$).

***tert*-Butyl((1*S*,4*R*)-4-(2-(methoxymethoxy)ethyl)-2,2-dimethylcyclobutoxy)dimethylsilane (27).** A solution of **26** (15 mg, 0.032 mmol), tributyltin hydride (69 μL, 0.25 mmol), and AIBN (4.2 mg, 0.025 mmol) in freshly distilled benzene (6 mL) was deoxygenated thoroughly with argon. The reaction mixture was heated at 80 °C

for 3 h, cooled, and purified by column chromatography on silica gel (elution with an increasing proportion of ethyl acetate in hexanes from 0 to 20%) to furnish **27** (6.4 mg, 66%) as a colorless oil: IR (film, cm^{-1}) 1463, 1259, 1111; ^1H NMR (500 MHz, $CDCl_3$) δ 4.60 (s, 2H), 3.90 (dd, $J = 7.3$, 1.2 Hz, 1H), 3.46 (t, $J = 6.8$ Hz, 2H), 3.35 (s, 3H), 2.49−2.41 (m, 1H), 1.92−1.86 (m, 1H), 1.69−1.62 (m, 2H), 1.42−1.38 (m, 1H), 1.06 (s, 3H), 0.99 (s, 3H), 0.91 (s, 9H), 0.011 (s, 3H), 0.008 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 96.4, 75.7, 66.4, 55.1, 39.1, 36.4, 29.7, 28.7, 25.9 (3 C), 23.8, 22.7, 18.3, −4.7, −5.0; HRMS (ES) *m*/*z* $(M + Na)^+$ calcd 325.2175, obsd 325.2169; $[\alpha]_D^{23}$ −2.4 (*c* 0.21, $CHCl_3$).

***O*-(1*R*,3*R*,4*R*)-3-(Benzyloxy)-4-(2-(methoxymethoxy)ethyl)-2,2-dimethylcyclobutyl *O*-*p*-Tolyl Carbonothioate (32) and *S*-(1*S*,3*R*,4*R*)-3-(Benzyloxy)-4-(2-(methoxymethoxy)ethyl)-2,2-dimethylcyclobutyl *O*-*p*-Tolyl Carbonothioate (33).** A stirred solution of **31** (25 mg, 0.085 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was treated with freshly distilled pyridine (0.5 mL), *O*-*p*-tolyl chlorothionoformate (52 μL, 0.34 mmol), and DMAP (cat) under N_2. The reaction mixture was stirred for 24 h, and more *O*-*p*-tolyl chlorothionoformate (52 μL, 0.34 mmol) was added. After a further day, the reaction mixture was quenched with water (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine (5 mL) and then dried. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel (elution with 5−10% ethyl acetate in hexanes) to afford **32** (27 mg, 71.6%) and **33** (10.7 mg, 28.4%) as pale yellow oils.

For **32**: IR (film, cm^{-1}) 1506, 1291, 1220, 1196; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39−7.27 (m, 5H), 7.21 (d, $J = 8.4$ Hz, 1H), 6.97 (d, $J = 8.4$ Hz, 1H), 5.32 (d, $J = 7.4$ Hz, 1H), 4.60 (s, 2H), 4.54 (d, $J = 11.8$ Hz, 1H), 4.45 (d, $J = 11.8$ Hz, 1H), 3.64 (d, $J = 8.1$ Hz, 1H), 3.52 (dt, $J = 6.7$, 1.4 Hz, 2H), 3.34 (s, 3H), 2.80−2.70 (m, 1H), 2.37 (s, 3H), 1.96−1.75 (m, 2H), 1.27 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.7, 151.3, 138.2, 136.3, 130.1 (2 C), 128.4 (2 C), 127.7, 127.6 (2C), 121.5 (2 C), 96.4, 83.9, 83.5, 72.0, 65.7, 55.2, 44.1, 40.5, 28.1, 22.5, 21.0, 20.7; HRMS (ES) *m*/*z* $(M + Na)^+$ calcd 467.1868, obsd 467.1851; $[\alpha]_D^{24}$ −42.9 (*c* 0.76, $CHCl_3$).

For **33**: IR (film, cm^{-1}) 1761, 1253, 1111; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.28 (m, 5H), 7.17 (d, $J = 8.4$ Hz, 1H), 7.03 (d, $J = 8.4$ Hz, 1H), 4.75 (d, $J = 7.4$ Hz, 1H), 4.59 (s, 2H), 4.53 (d, $J = 11.8$ Hz, 1H), 4.44 (d, $J = 11.8$ Hz, 1H), 3.62 (d, $J = 8.2$ Hz, 1H), 3.52 (t, $J = 6.6$ Hz, 2H), 3.34 (s, 3H), 2.73−2.62 (m, 1H), 2.34 (s, 3H), 1.96−1.68 (m, 2H), 1.22 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 149.0, 138.3, 135.7, 130.0 (2 C), 128.4 (2 C), 127.7, 127.6 (2C), 120.7 (2 C), 96.4, 83.8, 78.5, 72.0, 65.7, 55.1, 43.4, 40.2, 29.7, 27.8, 22.0, 20.9, 20.6; HRMS (ES) *m*/*z* $(M + Na)^+$ calcd 467.1868, obsd 467.1851; $[\alpha]_D^{24}$ −32.7 (*c* 0.15, $CHCl_3$).

(((1*R*,4*R*)-4-(2-(Methoxymethoxy)ethyl)-2,2-dimethylcyclobutoxy)methyl)benzene (34). A solution of tributyltin hydride (67 μL, 0.25 mmol) and AIBN (4 mg, 0.025 mmol) in freshly distilled benzene (5 mL) was deoxygenated thoroughly with argon. Thiocarbonate **32** (22 mg, 0.050 mmol) was dissolved in 1 mL of the above solution and brought to reflux. The rest of the above solution was added via syringe pump (0.24 mL/h), and the reaction mixture was heated for 2 d, cooled, diluted with ether (10 mL) and brine (10 mL), and extracted with ether (2 × 10 mL). The combined organic extracts were dried, and the solvent was evaporated under reduced pressure to leave a residue that was purified by column chromatography on silica gel (elution with an increasing proportion of ethyl acetate in hexanes from 0 to 20%) to furnish **34** (11.7 mg, 85%) as a colorless oil: IR (film, cm^{-1}) 1455, 1260, 1112, 1048; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.26 (m, 5H), 4.59 (s, 2H), 4.53 (d, $J = 11.8$ Hz, 1H), 4.42 (d, $J = 11.8$ Hz, 1H), 3.47 (t, $J = 7.0$ Hz, 2H), 3.34 (s, 3H), 3.31 (d, $J = 8.2$ Hz, 1H), 2.30−2.22 (m, 1H), 1.89−1.78 (m, 1H), 1.69−1.56 (m, 3H), 1.18 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 128.3 (2 C), 127.6 (2 C), 127.5, 96.4, 85.9, 71.4, 66.1, 55.1, 38.4, 35.6, 35.0, 33.9, 29.8, 21.7; HRMS (ES) *m*/*z* $(M + Na)^+$ calcd 301.1780, obsd 301.1769; $[\alpha]_D^{21}$ −38.3 (*c* 0.46, $CHCl_3$).

Acrylic Acid (1*S*,3*S*,4*S*)-3-Benzyloxy-2,2-dimethyl-4-vinylcyclobutyl Ester (5). A stirred solution of (+)-**11** (290 mg, 1.25 mmol) in anhydrous CH_2Cl_2 (5 mL) was treated with triethylamine (0.35 mL, 2.5 mmol) and DMAP (cat) under N_2. A solution of acryloyl chloride (0.12 mL, 1.50 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise over 2.5 h. The reaction mixture was stirred for a further 4 h and treated with triethylamine (0.17 mL, 1.25 mmol). A solution of acryloyl chloride (0.05 mL, 0.63 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dropwise over 1 h, and the reaction mixture was stirred for a further hour. The reaction mixture was quenched with water (5 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were washed with saturated NH_4Cl solution (10 mL), saturated $NaHCO_3$ solution (10 mL), water (10 mL), and brine (10 mL) then dried. The solution was passed through a short pad of silica gel which was washed with ether (25 mL), and the solvent was evaporated under reduced pressure to provide **5** (328 mg, 92%) as a colorless oil: IR (film, cm^{-1}) 1727, 1637, 1497; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5H), 6.41 (d, $J = 17.3$ Hz, 1H), 6.13 (dd, $J = 17.3$, 10.4 Hz, 1H), 5.84 (m, 1H), 5.83 (d, $J = 10.4$ Hz, 1H), 5.16−5.06 (m, 2H), 4.88 (d, $J = 7.5$ Hz, 1H), 4.51 (s, 2H), 3.83 (d, $J = 8.1$ Hz, 1H), 3.19 (dd, $J = 15.6$, 7.5 Hz, 1H), 1.25 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 138.4, 134.2, 130.7, 128.3, 127.6, 127.5, 117.0, 82.5, 74.9, 71.4, 46.9, 42.7, 22.0, 20.7; HRMS (ES) *m*/*z* $(M + Na)^+$ calcd 309.1461, obsd 309.1453; $[\alpha]_D^{21}$ −10.7 (*c* 1.0, $CHCl_3$).

(1*S*,6*S*,7*S*)-7-Benzyloxy-8,8-dimethyl-2-oxabicyclo[4.2.0]oct-4-en-3-one (35). A stirred solution of **5** (130 mg, 0.45 mmol) in anhydrous CH_2Cl_2 (45 mL) was treated with Grubb's second-generation catalyst (19 mg, 23 μmol) under N_2. After 18 h, the reaction mixture was quenched with water (1 drop), and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with 20% ethyl acetate in hexanes) to afford **35** (110 mg, 94%) as white crystals: mp 50−51 °C; IR ($CHCl_3$, cm^{-1}) 1724, 1498, 1455; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39−7.29 (m, 5H), 6.53 (dd, $J = 10.0$, 5.4 Hz, 1H), 5.82 (dd, $J = 10.0$, 1.2 Hz, 1H), 4.57 (d, $J = 12.5$ Hz, 1H), 4.56 (d, $J = 7.7$ Hz, 1H), 4.42 (d, $J = 12.5$ Hz, 1H), 3.72 (d, $J = 6.3$ Hz, 1H), 2.96 (m, 1H), 1.22 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1, 144.4, 137.6, 128.6, 128.1, 127.7, 118.9, 86.6, 78.2, 72.6, 46.5, 37.4, 21.6, 21.0; HRMS (ES) *m*/*z* $(M + Na)^+$ calcd 281.1148, obsd 281.1151; $[\alpha]_D^{20}$ +255 (*c* 1.0, $CHCl_3$).

(1*S*,5*R*,6*S*,7*S*)-7-Benzyloxy-8,8-dimethyl-5-vinyl-2-oxabicyclo-[4.2.0]octan-3-one (37). A stirred suspension of copper(I) iodide (15 mg, 0.08 mmol) in anhydrous THF (20 mL) was cooled to −78 °C under N_2 and treated with TMEDA (0.53 mL, 3.49 mmol). After 5 min, vinylmagnesium bromide (3.1 mL, 0.75 M in THF, 2.33 mmol) was added dropwise, and stirring was continued for 10 min. A solution of **35** (200 mg, 0.78 mmol) in anhydrous THF (10 mL) was added dropwise, and stirring was continued for 1 h. The reaction mixture was quenched with saturated NH_4Cl solution (10 mL), warmed to rt, and extracted with ether (3 × 25 mL). The combined extracts were washed with water (20 mL) and brine (20 mL). The combined extracts were dried, and the solvent was evaporated under reduced pressure to leave a residue that was purified by column chromatography on silica gel (elution with an increasing proportion of ethyl acetate in hexanes from 10 to 20%) to furnish **37** (219 mg, 99%) as a colorless oil: IR (film, cm^{-1}) 1751, 1641, 1497; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39−7.27 (m, 5H), 5.74 (ddd, $J = 16.9$, 10.1, 6.4 Hz, 1H), 5.14 (m, 1H), 5.10 (m, 1H), 4.44 (s, 2H), 4.33 (d, $J = 7.3$ Hz, 1H), 3.65 (d, $J = 5.8$ Hz, 1H), 2.59−2.45 (m, 3H), 2.18 (m, 1H), 1.20 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 138.5, 137.9, 128.4, 127.7, 127.3, 115.6, 84.4, 78.3, 71.5, 43.0, 42.1, 35.0, 21.8, 21.0;

HRMS (ES) *m*/*z* (M + Na)$^+$ calcd 309.1461, obsd 309.1462; $[\alpha]_D^{20}$ −47.8 (*c* 1.0, $CHCl_3$).

(1*S*,4*S*,5*R*,6*S*,7*S*)-7-Benzyloxy-8,8-dimethyl-4-phenylselanyl-5-vinyl-2-oxabicyclo[4.2.0]octan-3-one (38). A stirred solution of **37** (15 mg, 52.4 μmol) in anhydrous THF (1 mL) was cooled to −78 °C under N_2 and treated with TMS chloride (33 μL, 0.26 mmol) and then NaHMDS (84 μL, 1.0 M in THF, 0.08 mmol). After 20 min, a solution of PhSeCl (12 mg, 63 μmol) in anhydrous THF (1 mL) was added. The reaction mixture was stirred for 4 h, quenched with saturated $NaHCO_3$ solution (5 mL), warmed to rt, and extracted with ethyl acetate (2 × 10 mL). The combined organic extracts were washed with brine (10 mL) and then dried. The solvent was evaporated under reduced pressure to leave a residue that was purified by column chromatography on silica gel (elution with an increasing proportion of ethyl acetate in hexanes from 0 to 10%) to yield **38** (21 mg, 91%) as a colorless oil: IR (film, cm^{-1}) 1734, 1637, 1578; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64−7.57 (m, 2H), 7.38−7.25 (m, 8H), 5.99 (ddd, *J* = 17.1, 10.0, 7.0 Hz, 1H), 5.31−5.25 (m, 2H), 4.57 (d, *J* = 7.8 Hz, 1H), 4.46 (d, *J* = 12.1 Hz, 1H), 4.39 (d, *J* = 12.1 Hz, 1H), 3.79 (d, *J* = 3.3 Hz, 1H), 3.60 (d, *J* = 6.1 Hz, 1H), 2.83 (m, 1H), 2.62 (m, 1H), 1.23 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 137.9, 136.6, 135.2 (2 C), 129.4 (2 C), 128.8, 128.4 (2 C), 127.7, 127.3 (2 C), 127.1, 117.9, 85.1, 78.3, 71.5, 45.2, 44.7, 42.9, 40.1, 21.9, 21.2; HRMS (ES) *m*/*z* (M + Na)$^+$ calcd 465.0939, obsd 465.0924; $[\alpha]_D^{21}$ −81.9 (*c* 1.3, $CHCl_3$).

(1*S*,6*S*,7*S*)-7-Benzyloxy-8,8-dimethyl-5-vinyl-2-oxabicyclo-[4.2.0]oct-4-en-3-one (4). A stirred solution of **38** (18 mg, 0.04 mmol) in ethyl acetate/THF (2:1) (1 mL) was cooled to 0 °C and treated with sodium hydrogen carbonate (30 mg, 0.35 mmol) and 30% hydrogen peroxide solution (15 μL). After complete oxidation (35 min), the ice bath was removed, and stirring was continued for 3 h. The reaction mixture was diluted with ethyl acetate (10 mL) and water (10 mL) and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried, and freed of solvent under reduced pressure to leave a residue that was purified by column chromatography on silica gel (elution with an increasing proportion of ethyl acetate in hexanes from 0 to 20%) to afford **4** (8 mg, 69%) as a colorless oil: IR (film, cm^{-1}) 1716, 1497, 1455; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.26 (m, 5H), 6.43 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.85 (d, *J* = 17.5 Hz, 1H), 5.77 (s, 1H), 5.56 (d, *J* = 8.2 Hz, 1H), 4.56 (d, *J* = 8.2 Hz, 1H), 4.50 (d, *J* = 11.7 Hz, 1H), 4.43 (d, *J* = 11.7 Hz, 1H), 3.70 (d, *J* = 7.0 Hz, 1H), 3.31 (t, *J* = 7.6 Hz, 1H), 1.25 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 152.5, 137.6, 134.6, 128.5 (2 C), 128.4, 128.0, 127.7 (2 C), 123.6, 115.4, 86.2, 77.8, 72.8, 46.4, 36.1, 21.8, 20.9; HRMS (ES) *m*/*z* (M + Na)$^+$ calcd 307.1305, obsd 307.1312; $[\alpha]_D^{20}$ +88.8 (*c* 0.7, $CHCl_3$).

(1*S*,5*S*,6*S*,7*S*)-7-Benzyloxy-5-hydroxymethyl-8,8-dimethyl-2-oxabicyclo[4.2.0]octan-3-one (39). A stirred solution of **37** (200 mg, 0.70 mmol) in methanol/CH_2Cl_2 (5:1) (24 mL) was cooled to −78 °C and treated with ozone for 5 min. N_2 gas was bubbled through the reaction mixture until the blue color had dispersed. Dimethyl sulfide (4 mL) was added. The reaction mixture was warmed to rt, stirred for 2 h, and cooled to 0 °C. Sodium borohydride (26 mg, 0.70 mmol) was added in one portion with vigorous stirring. After 5 min, a further portion of sodium borohydride (26 mg, 0.70 mmol) was added. After 5 min, the reaction mixture was quenched with saturated NH_4Cl solution (10 mL) and ether (20 mL), warmed to rt, and extracted with ether (3 × 25 mL). The combined extracts were washed with water (20 mL) and brine (20 mL). The combined extracts were dried, and the solvent was evaporated under reduced pressure to leave a residue that was purified by column chromatography on silica gel (elution with 50% ethyl acetate in hexanes) to furnish **39** (135 mg, 67%) as a colorless oil: IR (film, cm^{-1}) 3618, 1772, 1496; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.27 (m, 5H), 4.52 (d, *J* = 11.5 Hz, 1H), 4.34 (d, *J* = 11.5 Hz, 1H), 4.31 (m, 1H), 4.15 (dd, *J* = 9.0, 6.5 Hz, 1H), 3.82 (d, *J* = 7.2 Hz, 1H), 3.62 (d, *J* = 8.4 Hz, 1H), 2.81 (m, 1H), 2.62 (dd, *J* = 17.5, 8.4 Hz, 1H), 2.36 (m, 1H), 2.20 (dd, *J* = 17.5, 7.2 Hz, 1H), 1.25 (br s, 1H), 1.11 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 137.9, 129.6, 128.5 (2 C), 127.9, 127.8, 82.5, 72.0, 71.6, 71.1, 45.8, 42.7, 33.9, 33.4, 21.7, 20.5; HRMS (ES) *m*/*z* (M + Na)$^+$ calcd 313.1410, obsd 313.1407; $[\alpha]_D^{20}$ +46.7 (*c* 0.9, $CHCl_3$).

(1*S*,5*S*,6*S*,7*S*)-7-Benzyloxy-5-methoxymethoxymethyl-8,8-dimethyl-2-oxabicyclo[4.2.0]octan-3-one (40). A stirred solution of **39** (40 mg, 0.14 mmol) in anhydrous CH_2Cl_2 (5 mL) was treated with MOM chloride (31 μL, 0.41 mmol) and tetrabutylammonium iodide (cat.) under N_2. Diisopropylethylamine (0.14 mL, 0.83 mmol) was added dropwise and the reaction mixture was stirred for 48 h, quenched with water (5 mL) and extracted with ether (3 × 10 mL). The combined organic extracts were washed with saturated NH_4Cl solution (10 mL), water (10 mL), and brine (10 mL) and then dried. The solvent was evaporated under reduced pressure to leave a residue that was purified by column chromatography on silica gel (elution with 30% ethyl acetate in hexanes) to provide **40** (45.1 mg, 98%) as a colorless oil: IR (film, cm^{-1}) 1772, 1717, 1463; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.27 (m, 5H), 4.54 (AB_q, *J* = 8.6, 6.6 Hz, 2H), 4.51 (s, 1H), 4.39−4.26 (m, 2H), 4.15 (dd, *J* = 8.9, 6.6 Hz, 1H), 3.76 (d, *J* = 7.6 Hz, 1H), 3.59 (d, *J* = 8.5 Hz, 1H), 3.34 (s, 3H), 2.81 (m, 1H), 2.58 (dd, *J* = 17.4, 8.5 Hz, 1H), 2.43 (td, *J* = 9.8, 7.6 Hz, 1H), 2.21 (dd, *J* = 17.4, 7.3 Hz, 1H), 1.15 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 137.9, 128.5 (2 C), 127.9, 127.8 (2 C), 96.8, 82.0, 76.4, 72.0, 71.4, 55.8, 45.6, 43.5, 34.1, 33.5, 22.8, 20.9; HRMS (ES) *m*/*z* (M + Na)$^+$ calcd 357.1672, obsd 357.1673; $[\alpha]_D^{21}$ +93.0 (*c* 0.47, $CHCl_3$).

(1*S*,5*S*,6*S*,7*S*)-7-Hydroxy-5-methoxymethoxymethyl-8,8-dimethyl-2-oxabicyclo[4.2.0]octan-3-one (41). A stirred solution of **40** (35 mg, 0.10 mmol) in anhydrous THF (5 mL) was treated with 5% Pd on carbon (20 mg) and placed under 500 psi of H_2 for 24 h. The reaction mixture was filtered through a pad of Celite which was washed with ethyl acetate (10 mL). The solvent was evaporated under reduced pressure to leave a residue that was purified by column chromatography on silica gel (elution with 1:1 ethyl acetate/hexanes) to provide **41** (19 mg, 74%) as a colorless oil: IR (film, cm^{-1}) 3607, 1772, 1465; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.56 (AB_q, *J* = 8.4, 6.6 Hz, 2H), 4.44 (dd, *J* = 9.2, 7.2 Hz, 1H), 4.25 (dd, *J* = 9.2, 5.7 Hz, 1H), 3.79 (dd, *J* = 7.4, 4.3 Hz, 2H), 3.34 (s, 3H), 2.86 (m, 1H), 2.62 (dd, *J* = 17.5, 8.4 Hz, 1H), 2.28 (m, 1H), 2.17 (s, 1H), 1.92 (br s, 1H), 1.06 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.5, 96.7, 76.3, 75.9, 71.5, 55.8, 48.0, 43.4, 34.1, 33.5, 21.2, 20.2; HRMS (ES) *m*/*z* (M + Na)$^+$ calcd 267.1203, obsd 267.1193; $[\alpha]_D^{20}$ +87.7 (*c* 0.26, $CHCl_3$).

Thiocarbonic Acid ((1*S*,5*S*,6*R*,7*S*)-5-Methoxymethoxymethyl-8,8-dimethyl-3-oxo-2-oxabicyclo[4.2.0]oct-7-yl) Ester *p*-Tolyl Ester (42). A stirred solution of **41** (10 mg, 41 μmol) in anhydrous CH_2Cl_2 (1 mL) was treated with freshly distilled pyridine (1 mL), *O*-*p*-tolyl thiochloroformate (0.1 mL, 0.65 mmol), and DMAP (cat) under N_2. The reaction mixture was stirred for 16 h, quenched with saturated NH_4Cl solution (5 mL), and extracted with ether (3 × 10 mL). The combined extracts were washed with water (10 mL) and brine (10 mL), then dried and evaporated under reduced pressure to leave a residue that was purified by column chromatography on silica gel (elution with an increasing proportion of ethyl acetate in hexanes from 10 to 30%). Ester **42** was isolated as a colorless oil (17 mg, 100%): IR (film, cm^{-1}) 2341, 1778, 1683, 1628; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25−7.17 (m, 2H), 7.05−6.95 (m, 2H), 5.31 (d, *J* = 7.8 Hz, 1H) 4.66−4.55 (m, 2H), 4.47 (dd, *J* = 9.2, 7.3 Hz, 1H), 4.10 (dd, *J* = 9.2, 6.0 Hz, 1H), 3.94 (d, *J* = 6.0 Hz, 1H), 3.38 (s, 3H), 2.98 (m, 1H), 2.83−2.62 (m, 2H), 2.37 (s, 3H), 2.30 (m, 1H), 1.23 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.9, 176.9, 151.2, 136.5, 130.0 (2 C), 121.3 (2 C), 96.9, 84.8, 76.1, 71.3, 56.1, 45.1, 44.4, 33.7, 33.2, 21.9, 21.6, 20.9; HRMS

(ES) *m*/*z* (M + Na)$^+$ calcd 417.1342, obsd 417.1326; $[\alpha]_D^{21}$ +38.0 (*c* 1.5, $CHCl_3$).

(1*S*,5*S*,6*R*)-5-Methoxymethoxymethyl-8,8-dimethyl-2-oxabicyclo[4.2.0]octan-3-one (43). A solution of **42** (20 mg, 50.8 μmol) in freshly distilled dioxane (10 mL) was treated with tributyltin hydride (0.28 mL, 1.02 mmol) and deoxygenated thoroughly with argon. A catalytic amount of AIBN was added, and the reaction mixture was heated to reflux for 14h under argon. The cooled reaction mixture was diluted with ether (10 mL) and brine (10 mL) and extracted with ether (2 × 10 mL). The combined organic extracts were dried and the solvent was evaporated under reduced pressure to leave a residue that was purified by column chromatography on silica gel (elution with an increasing proportion of ethyl acetate in hexanes from 0 to 25%) to afford **43** (7.1 mg, 61%) as a colorless oil: IR (film, cm^{-1}) 1744, 1460, 1376; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.58 (dd, *J* = 10.0, 6.5 Hz, 2H), 4.41 (dd, *J* = 9.0, 7.3 Hz, 1H), 3.95−3.89 (m, 2H), 3.36 (s, 3H), 2.91 (m, 1H), 2.71 (d, *J* = 17.7, 8.4 Hz, 1H), 2.53 (m, 1H), 2.20 (dd, *J* = 17.7, 6.8 Hz, 1H), 1.73 (m, 1H), 1.46 (dd, *J* = 11.6, 6.9 Hz, 1H), 1.14 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.6, 96.3, 79.5, 71.5, 55.8, 38.7, 37.3, 36.1, 34.5, 34.2, 29.0, 23.8; HRMS (ES) *m*/*z* (M + Na)$^+$ calcd 251.1254, obsd 251.1249; $[\alpha]_D^{20}$ +8.4 (*c* 0.3, $CHCl_3$).

Acknowledgment. This work was supported in part by the Astellas USA Foundation for which we are appreciative. S.D. thanks The Ohio State University for the award of a Presidential Fellowship.

Supporting Information Available: Selected experimental procedures and ^{1}H/^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070861R