

## Synthetic Studies of Antitumor Macrolide Rhizoxin: Stereoselective Syntheses of the C(1)–C(9) and C(12)–C(26) Subunits

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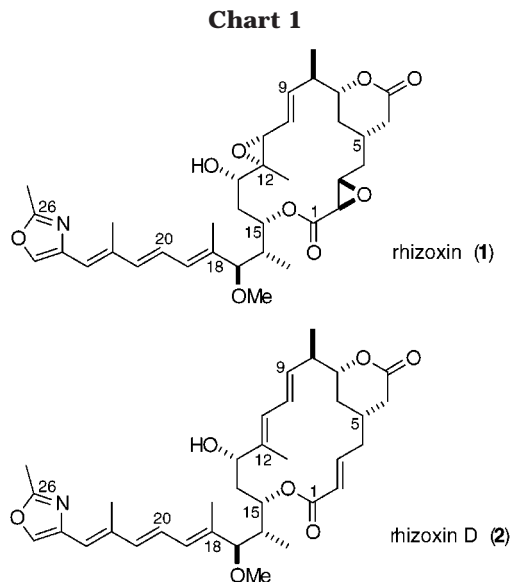
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A triply convergent synthetic approach which culminates in the enantioselective syntheses of the C(1)–C(9) and C(12)–C(26) subunits of the macrolide antitumor agent rhizoxin is described. The central C(12)–C(20) subunit **4** has been prepared efficiently via diastereoselective enzymatic acetate hydrolysis of **15** with porcine pancreatic lipase, a chelation-controlled Ireland–Claisen rearrangement (**10** → **12**) combined with kinetic bromolactonization (**12** → **14**), and Mitsunobu inversion (**23** → **26**) to introduce the three contiguous C(15)–C(17) stereocenters. Formation of the C(18)–C(19) trisubstituted (*E*)-olefin was achieved by a stereoselective Horner–Wadsworth–Emmons reaction. The central segment **4** and the oxazole chromophore side chain **3** were coupled using another highly stereoselective Horner–Wadsworth–Emmons reaction. Two different lactone subunits [C(1)–C(9) segment **5** and C(3)–C(10) segment **47**] were also prepared, employing a thermodynamically controlled diastereotopic group differentiation tactic for establishing the C(5) stereochemistry.

### Introduction

Rhizoxin (NSC-332598) and its congeners constitute a family of 16-membered macrolactones first isolated from the plant pathogenic fungus *Rhizopus chinensis* by Iwasaki and co-workers in 1984.<sup>1</sup> This pathogenic fungus causes a disease known as rice seedling blight. The characteristic symptom of this disease is abnormal swelling of the seedling roots, which is thought to be caused by inhibition of cell division. The relative and absolute configurations of rhizoxin and related compounds have been determined by single-crystal X-ray analysis and degradation studies.<sup>2</sup> The unprecedented structure of rhizoxin contains 11 stereogenic centers, 2 epoxides, a  $\delta$ -lactone, a 16-membered macrocyclic lactone, and an oxazole-terminated chromophore side chain. Interestingly, didesepoxyrhizoxin (rhizoxin D, **2**), a biosynthetic precursor to the bis-epoxide **1**, was isolated from the same fungus and has the same level of biological activity. Studies detailing the biosynthesis of rhizoxin have also been reported.<sup>3</sup>

Rhizoxin is a tubulin-interactive antimitotic agent which exhibits pronounced antimicrobial and antifungal activity as well as potent in vitro cytotoxicity and in vivo antitumor activity.<sup>4</sup> Moderate-to-good in vivo activities



have been demonstrated by rhizoxin in preclinical studies against murine tumors such as B16 melanoma, M5076 sarcoma, L1210 and P388 leukemias, and MH134 mouse hepatoma. It is also active against several human tumor xenografts, including LOX melanoma, MX-1 mammary carcinoma, A549 non-small-cell lung tumors, and LXFS605 and LXFS650 small-cell lung tumors. One impressive observation is that rhizoxin is effective against vincristine- and adriamycin-resistant tumor cells in vitro and in vivo, while other antimitotic agents such as maytansine have been found to be ineffective.<sup>5</sup> On the basis of these preclinical studies in the National Cancer Institute disease-oriented screening, rhizoxin has been selected for clinical evaluation. Rhizoxin has gone through

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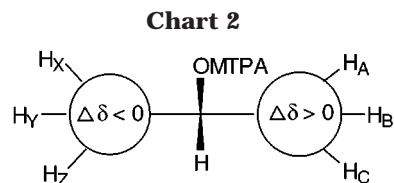
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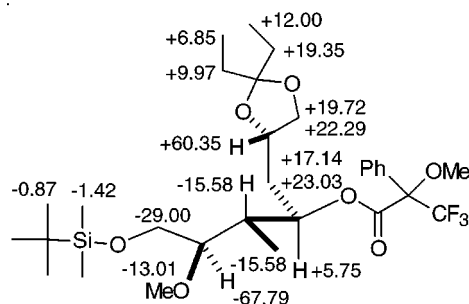
both Phase I and Phase II clinical trials for ovarian cancer, colorectal and renal cancer, breast cancer and melanoma, head and neck cancer, and non-small-cell lung cancer and is currently being evaluated in Phase III clinical trials.<sup>6,7</sup>

Rhizoxin binds to  $\beta$ -tubulin at the vinca domain.<sup>8a,b</sup> The mechanism of action is believed to be its complexation with tubulin to prevent tubulin polymerization, leading to the inhibition of microtubule formation and thereby blocking cell mitosis. The common binding site shared by rhizoxin and maytansine is different from the receptor for other tubulin inhibitors such as vinblastine and halichondrin B. Recently, rhizoxin was found to be a novel inhibitor of angiogenesis, thus suggesting another therapeutic mechanism of action.<sup>8c</sup> Limited structure-activity relationship (SAR) studies have been reported.<sup>9</sup> Classical antimitotic drugs such as vinblastine and vincristine have serious side effects, especially on the neurological system; thus it is highly desirable to discover and develop new antitumor drugs which are more effective and less toxic. Rhizoxin and its congeners represent a new class of very promising lead compounds for this purpose. Strongly promoted by rhizoxin's significant biological activity, great potential as a chemotherapeutic agent, and its unique structural features, total syntheses of rhizoxin and rhizoxin D, along with several synthetic efforts, have been reported.<sup>10-12</sup>

As part of a continuing synthetic program focused upon tubulin-binding natural products,<sup>13</sup> we now disclose our studies describing a convergent approach for the enan-



Model A  
( $\Delta\delta = \delta_S - \delta_R$ , in hertz)



tioselective synthesis of C(12)–C(26) subunit **35** and C(1)–C(9) subunit **5**, featuring a chelation-controlled Ireland–Claisen rearrangement, a highly stereoselective Horner–Wadsworth–Emmons reaction for incorporation of the oxazole chromophore side chain, and a diastereotopic group differentiation strategy for establishing the C(5) stereocenter.

## Results and Discussion

Outlined in Scheme 1 is our triply convergent approach to rhizoxin and its congeners, which includes a Horner–Wadsworth–Emmons coupling of phosphonate **3** and enal **4**, thereby leaving the protected diol moiety of **4** to be oxidized and homologated by two carbons to the corresponding terminal enal of the C(10)–C(26) subunit. Fragment coupling of the resultant C(10)–C(26) aldehyde with the C(1)–C(9) subunit **5** via a modified Julia procedure and macrolactonization was expected to complete the carbon skeleton of rhizoxin and its congeners. All three major segments, **3**, **4**, and **5**, which comprise most of the stereogenic centers and all but two backbone carbons of rhizoxin, were derivable from readily available starting materials.

On the basis of the analysis detailed in Scheme 1, our initial efforts on the synthesis of rhizoxin have focused on the preparation of the central C(12)–C(20) subunit **4** with control of the relative and absolute configuration of the three contiguous C(15)–C(17) stereocenters and introduction of the C(18)–C(19) trisubstituted (*E*)-olefin. We anticipated that appropriate functional and stereochemical elements for these purposes could be introduced via a sequence of chelation-controlled glycolate–enolate Claisen rearrangement and halolactonization, as detailed in Scheme 2. The synthesis began with protected D-glyceraldehyde **7**.<sup>14</sup> Addition of *trans*-propenyllithium in the presence of ZnBr<sub>2</sub> gave the *anti*-alcohol **9** with 8:1 diastereoselectivity.<sup>15</sup> Acylation with methoxyacetyl chlo-

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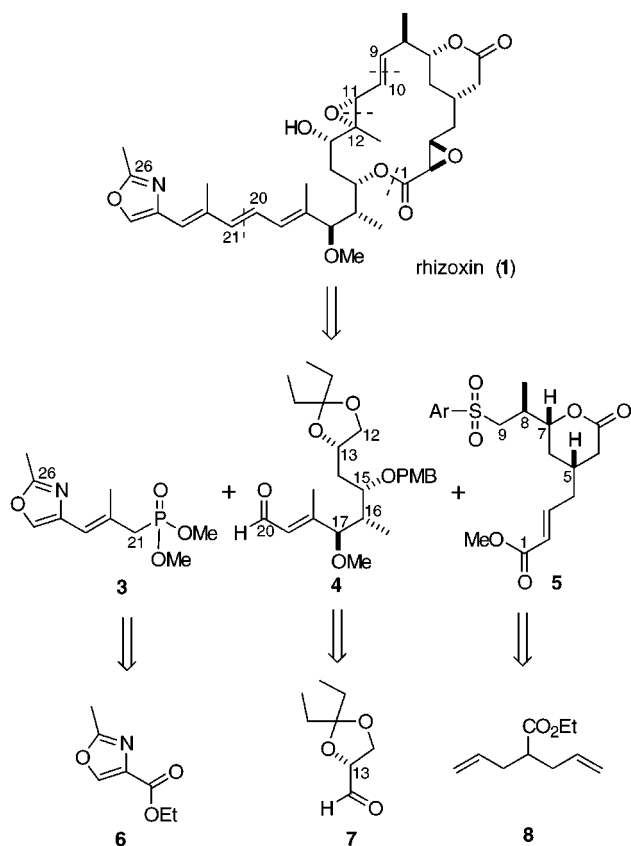
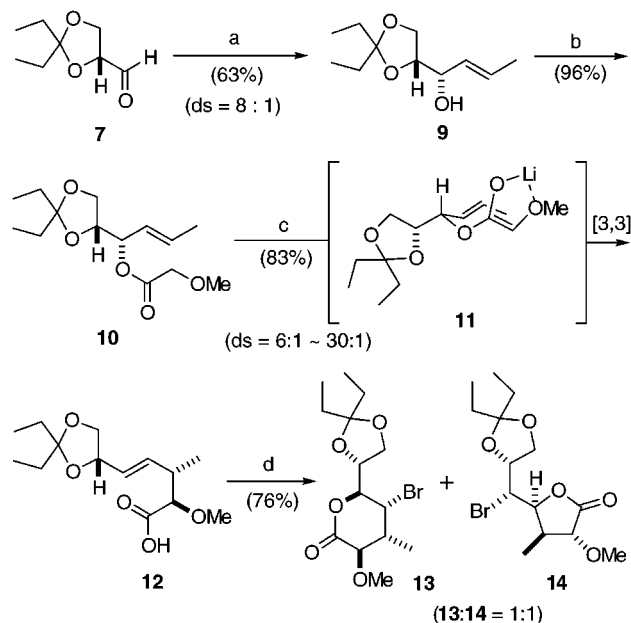
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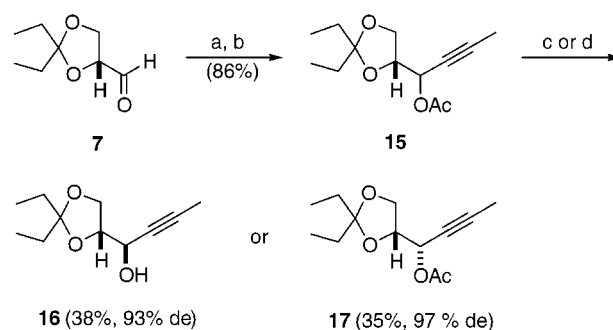
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## Scheme 1

Scheme 2<sup>a</sup>

<sup>a</sup> Reagents: (a) (*E*)-CH<sub>3</sub>CH=CHLi, ZnBr<sub>2</sub>, THF, 0 °C; (b) MeOCH<sub>2</sub>COCl, pyridine, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt; (c) LHMDS, THF, -100 °C; TMSCl-Et<sub>3</sub>N, -100 °C; -100 to 25 °C, 16 h; (d) NBS, NaHCO<sub>3</sub>, CCl<sub>4</sub>, rt, 20 h.

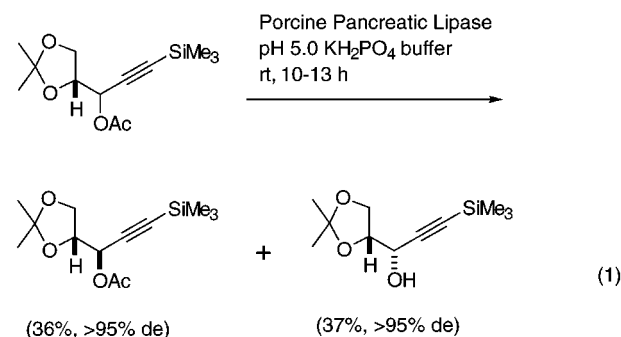
ride provided the allylic glycolate ester **10**. The crucial chelation-controlled Ireland–Claisen rearrangement<sup>16</sup> proceeded smoothly via the silyl ketene acetal derived from enolate **11**, affording acid **12** in 83% yield with 6:1 diastereoselectivity. Subsequent bromolactonization with NBS under kinetic conditions gave  $\delta$ - and  $\gamma$ -lactones **13**

Scheme 3<sup>a</sup>

<sup>a</sup> Reagents: (a) Propynylmagnesium bromide, THF, 0 °C to rt; (b) Ac<sub>2</sub>O, DMAP, Et<sub>3</sub>N, 0 °C to rt; (c) PPL, pH 5.1 KH<sub>2</sub>PO<sub>4</sub> buffer, rt, 3 h; (d) PPL, pH 6.0 KH<sub>2</sub>PO<sub>4</sub> buffer, rt, 6.5 h.

and **14** in an approximately 1:1 ratio.<sup>17</sup> These were separated by flash chromatography, and recycling of **13** via **12** can be accomplished by reductive fragmentation with zinc dust.<sup>18</sup> The structures of **13** and **14** were differentiated by complete assignment of all the protons via analysis of <sup>1</sup>H and 2D-COSY NMR spectra. The absolute configuration of the newly formed C(15) stereocenter was confirmed using the Kakisawa modification of Mosher's method (vide infra).<sup>19</sup>

An alternative route from glyceraldehyde **7** to alcohol **9** with high diastereomeric purity was also investigated in order to improve the diastereoselectivity of our crucial Ireland–Claisen rearrangement. Mulzer and co-workers have reported the selective enzymatic hydrolysis of a 1:1 diastereomeric mixture of propargylic acetates with greater than 95% de (eq 1).<sup>20a</sup> We have demonstrated



that the 1:1 diastereomeric mixture of acetates **15** (Scheme 3), structurally similar to Mulzer's substrate, can be selectively hydrolyzed with porcine pancreatic lipase (PPL) to afford either the *syn*-alcohol **16** or the

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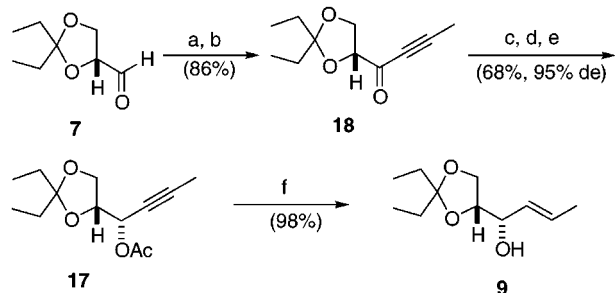
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Scheme 4<sup>a</sup>

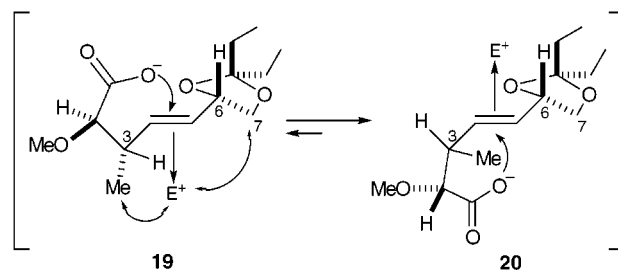
<sup>a</sup> Reagents: (a) Propynylmagnesium bromide, THF, 0°C to rt; (b) Dess–Martin Periodinane, CH<sub>2</sub>Cl<sub>2</sub> rt; (c) (*R*)-Alpine Borane, THF; (d) Ac<sub>2</sub>O, DMAP, Et<sub>3</sub>N, 0°C to rt; (e) PPL, pH 6.0 KH<sub>2</sub>PO<sub>4</sub> buffer; (f) LiAlH<sub>4</sub>, THF, reflux.

*anti*-acetate **17** in a highly stereoselective manner. Selective production of either **16** or **17** in high diastereomeric purity and high mass recovery from substrate **15** was accomplished by varying the pH and reaction time of the enzymatic hydrolysis.<sup>20b</sup> To obtain pure alcohol **16**, the hydrolysis was run to about 40% conversion; pure acetate **17** was obtained by running the reaction to about 60% conversion. When the reaction was performed in a pH 5.1 KH<sub>2</sub>PO<sub>4</sub> buffer solution for 3 h, the *syn*-alcohol **16** was isolated in 38% yield with 93% de. These conditions did not allow conversions over 50%, whereas PPL hydrolysis at pH 7 led to overhydrolysis. However, when the reaction was performed in a pH 6.0 KH<sub>2</sub>PO<sub>4</sub> buffer solution for 6.5 h, the acetate of *anti*-isomer **17** could be isolated in 35% yield with 97% de. These conditions afforded the intermediate hydrolysis rate needed for the production of **17** in high de.

Alcohol **16** and acetate **17** were readily separated by simple flash chromatography. The absolute stereochemical outcome of this reaction was determined by the Kakisawa modification of Mosher's method<sup>19</sup> and was found to be opposite to Mulzer's observed stereoselectivity at the carbinol center. Our rationale for the reversal in enzymatic stereochemical recognition is that the pentylidene group of our substrate **15** is larger than the propynyl group, but the acetonide group of Mulzer's substrate is relatively smaller than the trimethylsilyl acetylene group.

An optimized route to **9**, based upon the observation above, is detailed in Scheme 4. Addition of propynylmagnesium bromide to glycerinaldehyde **7** gave a 1:1 diastereomeric mixture of alcohols, which was oxidized to ketone **18** in 86% overall yield.<sup>21</sup> Asymmetric reduction and subsequent acylation led to a mixture of acetates **15** enriched with the desired *anti*-isomer in a 4.6:1 ratio.<sup>22</sup> PPL-mediated enzymatic hydrolysis of the minor component in this mixture afforded the desired *anti*-acetate **17** in 70% yield with 95% de. Acetate **17** was then reduced with LiAlH<sub>4</sub> to give *trans*-propenyl alcohol **9** with

Scheme 5



high purity (Scheme 4).<sup>23</sup> The diastereoselectivity of the Ireland–Claisen rearrangement (**10** to **12**) was improved to 30:1 by using diastereomerically pure substrate prepared from **9**.

Our result from kinetic bromolactonization of acid **12** implied that both substrate conformation and the nature of the electrophile influenced the stereoselectivity.<sup>24</sup> Both  $\gamma$ -lactone **14** and  $\delta$ -lactone **13** are the result of attack by the internal nucleophile on the same face of the *E* double bond. The diastereofacial selectivity of this reaction can be rationalized by the reactive intermediate structures shown in Scheme 5. The stereochemical outcome observed in the formation of **13** and **14** requires the  $\pi$ -facial attack depicted in structure **20**. The conformation **20** is likely to be favored over conformation **19** in the transition state because of the diminished unfavorable steric interactions of the C(3) methyl group and C(7) methylene group with the electrophile– $\pi$  complex. It should be noted that iodolactonization under kinetic conditions tended to give more  $\gamma$ -lactone over  $\delta$ -lactone than does bromolactonization, probably because the nature of the electrophile dictates a difference in rate-limiting steps.<sup>17,25</sup> Efforts to improve the regioselectivity of this reaction via the use of iodolactonization conditions are currently under investigation.

Radical dehalogenation<sup>26</sup> of bromolactone **14** gave lactone **21**, which was then reduced with lithium aluminum hydride.<sup>27</sup> The primary hydroxyl group of the resulting diol **22** was selectively protected as TBS ether **23** (Scheme 6), and the absolute stereochemistry at the C(15) stereocenter was determined by the Kakisawa modification of Mosher's method.<sup>19</sup> Treatment of alcohol **23** with both (*R*)-(+)- and (*S*)-(–)- $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetic (MTPA) acid under standard esterification conditions afforded Mosher esters **24** and **25**, respectively (Scheme 7).<sup>28</sup> On the basis of the data points from our analysis of the <sup>1</sup>H chemical shifts for these MTPA esters and according to Kakisawa's model A in Chart 2, the absolute configuration of the C(15) stereocenter was revealed to be *R*, which is opposite to the natural *S* configuration found in rhizoxin.

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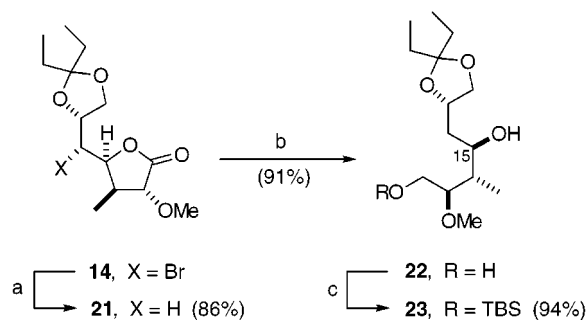
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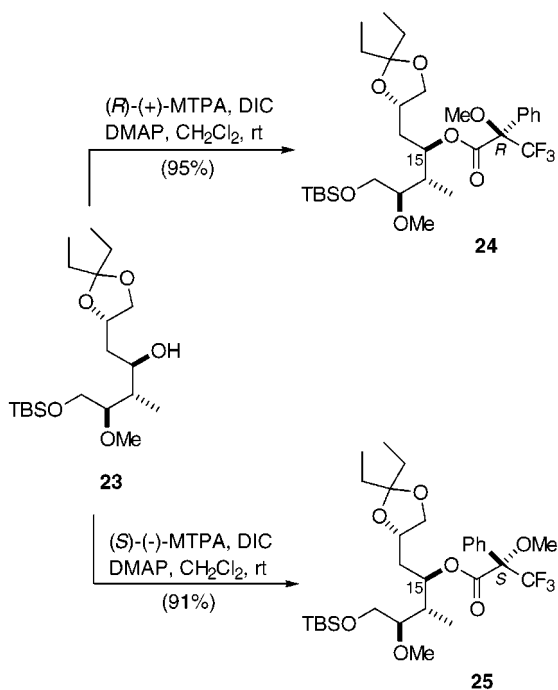
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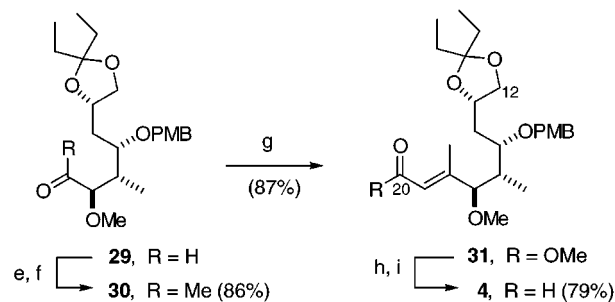
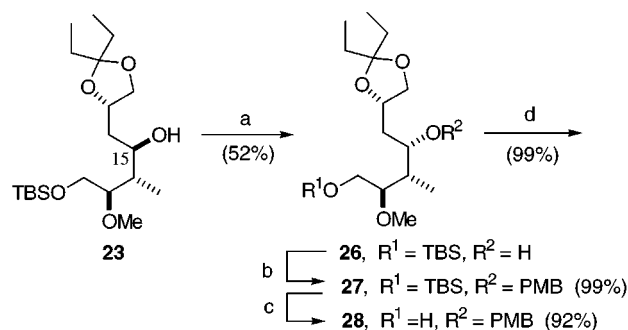
Scheme 6<sup>a</sup>

<sup>a</sup> Reagents: (a)  $\text{Bu}_3\text{SnH}$ , PhH, AIBN, reflux; (b)  $\text{LiAlH}_4$ , THF; (c) TBSCl,  $\text{Et}_3\text{N}$ , DMAP,  $\text{CH}_2\text{Cl}_2$ , rt, 18 h.

## Scheme 7



We examined many variations on the classical Mitsunobu reaction for inverting the C(15) stereogenic center of alcohol **23** (Scheme 8).<sup>29</sup> Since the C(15) hydroxyl group is in the middle of a long, highly branched chain, steric hindrance was expected to impede the reaction. It was decided that modified reaction conditions would have to be applied to achieve the inversion. The best conditions found were those described by Martin, utilizing *p*-nitrobenzoic acid as the nucleophile with 5 equiv of reagents and a reaction time of 72 h at ambient temperature.<sup>30</sup> This allowed us to obtain a 52% yield of the desired product **26** with a 34% yield of recovered starting material **23**. The resulting alcohol **26** was protected as its *p*-methoxybenzyl ether **27**,<sup>31</sup> and subsequent silyl group removal afforded primary alcohol **28**, which was

Scheme 8<sup>a</sup>

<sup>a</sup> Reagents: (a) DEAD,  $\text{Ph}_3\text{P}$ , PhH, *p*- $\text{O}_2\text{NC}_6\text{H}_4\text{CO}_2\text{H}$ ;  $\text{K}_2\text{CO}_3$ , MeOH; (b)  $\text{NaHMDS}$ , PMBBBr, THF-DMF (2:1), 0 °C to rt; (c) TBAF, THF, rt; (d)  $(\text{COCl})_2$ , DMSO,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , -78 °C; (e)  $\text{MeMgBr}$ , THF; (f) TPAP, NMO, 4 Å MS,  $\text{CH}_2\text{Cl}_2$ , rt; (g)  $\text{MeO}_2\text{CCH}_2\text{P}(\text{O})(\text{OMe})_2$ , NaH, THF, rt to 60 °C; (h) DIBALH,  $\text{Et}_2\text{O}$ , -78 °C; (i) TPAP, NMO, 4 Å MS,  $\text{CH}_2\text{Cl}_2$ , rt.

transformed to aldehyde **29** using the Swern oxidation.<sup>32</sup> Methyl ketone **30** was prepared by the addition of methylmagnesium bromide to aldehyde **29**, followed by TPAP oxidation.<sup>33</sup>

The key Horner–Wadsworth–Emmons chain extension for introduction of the C(18)–C(19) trisubstituted (*E*)-olefin was studied in detail.<sup>34</sup> Only trace amounts of the desired product **31** were formed when the reaction was performed using more than 10 equiv of the Wittig reagent at room temperature for 24 h. When the reaction mixture was heated to 60 °C for 3 h, a 64% yield of the desired product **31** was obtained. The yield of the desired (*E*)-trisubstituted olefin **31** was improved to 87% by heating the reaction at 60 °C for 24 h. The ester **31** was reduced with diisobutylaluminum hydride to the corresponding alcohol,<sup>35</sup> and subsequent TPAP oxidation<sup>33</sup> provided the C(12)–C(20) aldehyde **4**.

The preparation of the C(21)–C(26) phosphonate **3** from the known enal **32**<sup>12c</sup> is shown in Scheme 9. Reduction of **32** with diisobutylaluminum hydride<sup>35</sup> afforded allylic alcohol **33**, which was converted to allylic chloride **34** upon treatment with mesyl chloride.<sup>36</sup> Sub-

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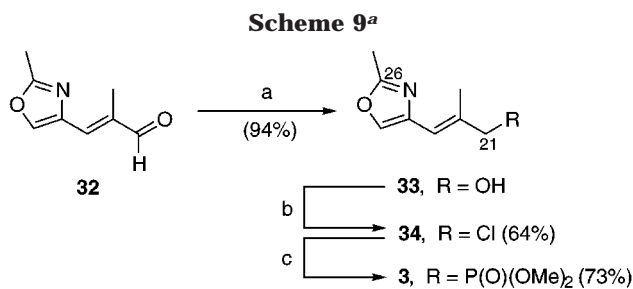
(32) (a) Omura, K.; Swern, D. *Tetrahedron* **1978**, 34, 1651. (b) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, 43, 2480.

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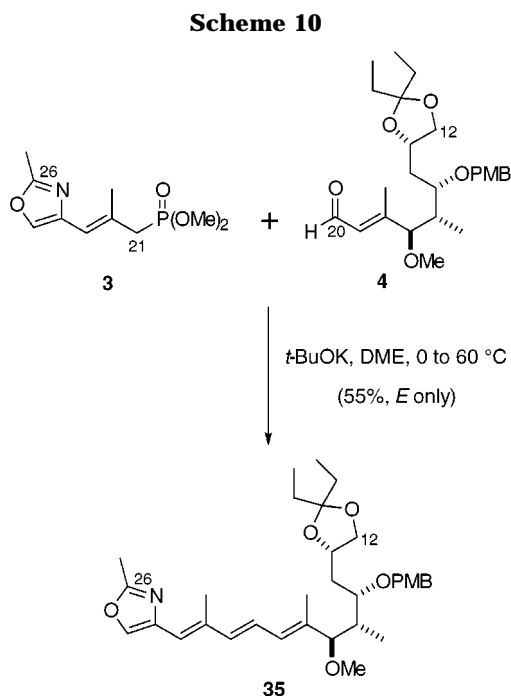
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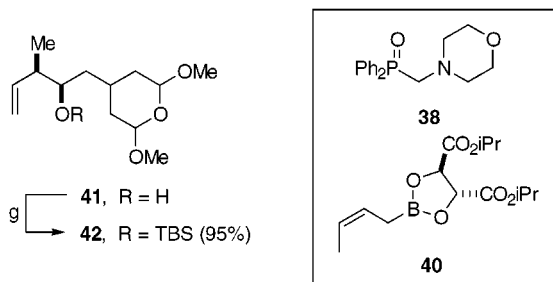
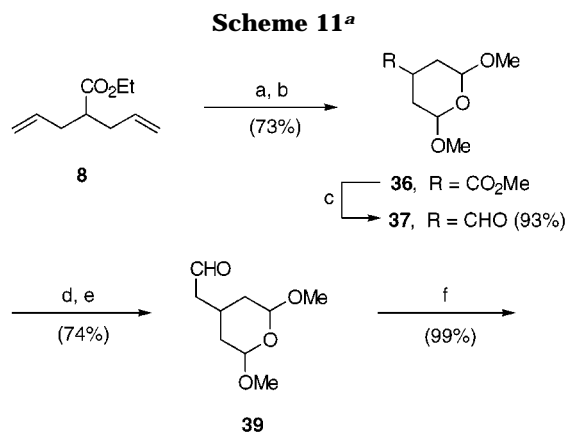
<sup>a</sup> Reagents: (a) DIBALH, Et<sub>2</sub>O, -78 °C, 2 h; (b) MsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, rt, 1 h; (c) NaH, HP(O)(OMe)<sub>2</sub>, THF, 45 °C, 1.5 h.



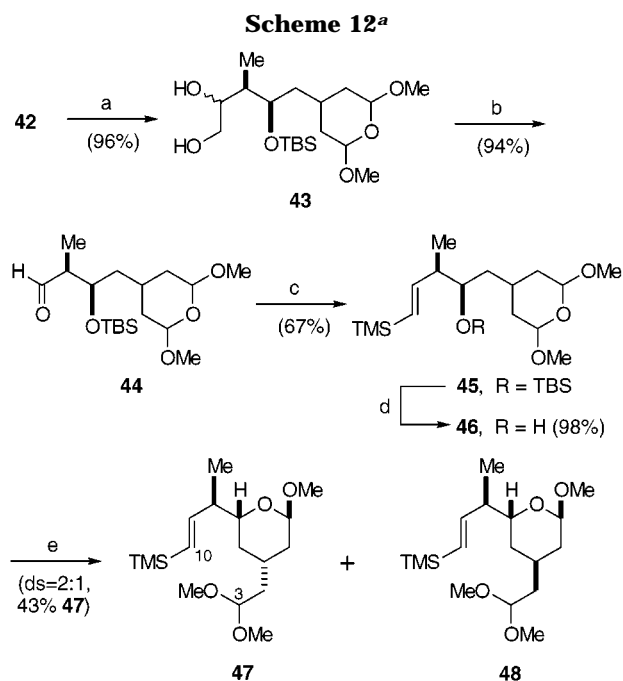
sequent displacement with sodium dimethyl phosphite provided phosphonate **3** in 73% yield.<sup>37</sup>

A second Horner–Wadsworth–Emmons coupling reaction completed the introduction of the (*E,E,E*)-triene to afford the desired C(12)–C(26) segment **35** (Scheme 10).<sup>38</sup> Treatment of aldehyde **4** and phosphonate **3** with *t*-BuOK in DME gave only triene stereoisomer **35**. The solvent employed for this coupling reaction proved to be important. For instance, when THF was used, a 1:1 mixture of alkene stereoisomers was formed.

Our preparations of the lactone subunits were mainly focused on a desymmetrization strategy to establish the C(5) stereocenter.<sup>39</sup> The initial synthetic studies of the C(3)–C(10) fragment are indicated in Schemes 11 and 12. The synthesis started with the known ethyl ester **8**.<sup>40</sup> Methanolic ozonolysis, acid-catalyzed degradation



<sup>a</sup> Reagents: (a) O<sub>3</sub>, MeOH, -78 °C; Me<sub>2</sub>S, TsOH, -78 °C to reflux; (b) MeCN (wet), rt; (c) DIBALH, 1.10 eq, 1:1 PhMe/Hexanes, -78 °C, 30 min; (d) **38**, BuLi, THF, 0 °C, then **37**; (e) KH, THF, 0 °C to rt; (f) **40**, PhMe, 4 Å sieves, -78 °C; (g) TBSCl, imidazole, DMF, 72 h.



<sup>a</sup> Reagents: (a) OsO<sub>4</sub> (cat.), NMO, Acetone, H<sub>2</sub>O, rt; (b) Pb(OAc)<sub>4</sub>, Na<sub>2</sub>CO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -5 to 0 °C; (c) TMSCHBr<sub>2</sub>, CrCl<sub>2</sub>, LiI, THF/DMF, NO LIGHT; (d) TBAF, THF, rt; (e) 2,2-Dimethoxypropane, CSA, PhH, 80 °C, 0.05 M.

of the intermediate ozonide,<sup>41</sup> and concomitant transesterification followed by a novel hydrolytic cyclization gave the mixed bis(acetal) **36** in an overall 73% yield. An efficient, selective reduction<sup>42</sup> of the methyl ester afforded

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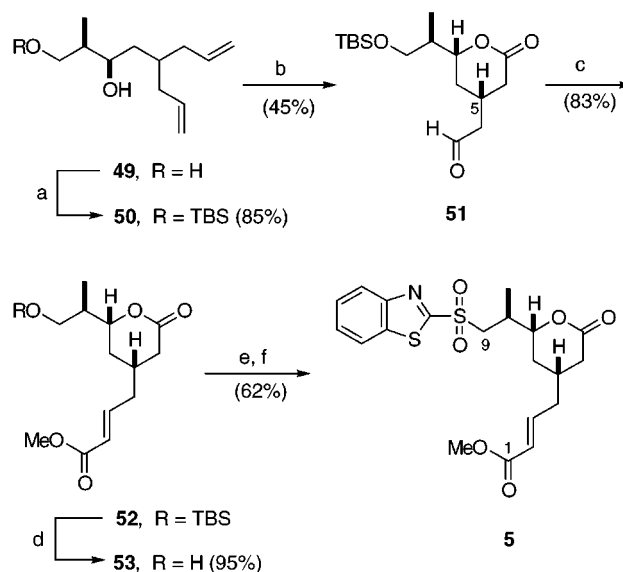
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aldehyde **37** in high yield. Condensation of the lithiated Horner–Wittig reagent **38**<sup>43</sup> with **37** produced a 1,2 adduct that underwent KH-facilitated elimination to the corresponding enamine, submission of which to flash chromatography on silica gel afforded the labile homologated aldehyde **39** in 74% yield. Treatment of **39** with the (*Z*)-crotylboronate **40**<sup>44</sup> gave **41** as a 1:1 mixture of the diastereomers.<sup>45</sup> The two methoxy groups of **41** have an *anti* relationship, thereby generating a pair of diastereomers due to the *R,R* and *S,S* configurations present in the mixed bis(acetal) ring system. Homoallylic alcohol **41** was then protected as the corresponding TBS ether **42**.

A two-step oxidation sequence applied to the olefin **42** provided aldehyde **44** via **43** (Scheme 12) in 90% yield.<sup>46</sup> Treatment of **44** with TMSCHBr<sub>2</sub> and CrCl<sub>2</sub> in the presence of LiI, followed by sonication, afforded vinylsilane **45**.<sup>47</sup> Deprotection of **45** using TBAF, followed by treatment of the resultant alcohol **46** with 2,2-dimethoxypropane under acidic conditions, produced a complex mixture of products, from which could be isolated the desired bis(acetal) **47** (43%) and its diastereomeric counterpart **48** in a 2:1 ratio.

Following our initial experience on the C(3)–C(10) lactone fragment, an alternative preparation of the C(1)–C(9) lactone subunit **5** was also investigated (Scheme 13). The synthesis of **5** began with the known diol **49**.<sup>12d</sup> The primary hydroxyl group of **49** was selectively protected as its TBS ether to afford the diene **50**. C(5) diastereotopic group differentiation was accomplished by one-pot ozonolysis and TPAP oxidation to provide lactone aldehyde **51** in 45% overall yield.<sup>48</sup> This tactic for establishing the C(5) stereocenter is analogous to those employed by Keck<sup>12d</sup> and Williams<sup>11d</sup> and relies upon thermodynamic diequatorial deployment of the side chains. The resultant lactone aldehyde **51** was subjected to a Wittig chain extension reaction to give ester **52**.<sup>49</sup> Removal of the TBS group with aqueous HF in acetonitrile<sup>50</sup> afforded primary alcohol **53**, which was converted to the corresponding benzothiazole sulfide under Mit-

Scheme 13<sup>a</sup>

<sup>a</sup> Reagents: (a) TBSCl, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, rt; (b) O<sub>3</sub>; Me<sub>2</sub>S, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C to rt; TPAP, NMO, 4 Å MS, CH<sub>2</sub>Cl<sub>2</sub>; (c) MeO<sub>2</sub>CCHPh<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt; (d) 5% aq HF, CH<sub>3</sub>CN, rt; (e) 2-mercaptobenzothiazole, Ph<sub>3</sub>P, DEAD, THF, rt; (f) *m*-CPBA, NaHCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt.

sunobu conditions.<sup>51</sup> Subsequent *m*-CPBA oxidation to the sulfone provided the C(1)–C(9) subunit **5** as a modified Julia coupling partner.<sup>52</sup>

## Conclusion

We have successfully achieved the stereoselective syntheses of the C(1)–C(9) and C(12)–C(26) subunits in our effort directed toward the total synthesis of rhizoxin. Studies for the extension of **35** to include the C(10)–C(11) carbons, fragment coupling with **5** via a modified Julia procedure,<sup>52</sup> and macrolactonization are being pursued actively in our laboratories to complete this synthetic route.

## Experimental Section

**General Methods.** Melting points (mp) are uncorrected. Optical rotations were measured on a digital polarimeter; concentrations (*c*) are reported in g/100 mL. Infrared (IR) spectra were recorded on an FT-IR spectrometer and are reported in wavenumbers (cm<sup>-1</sup>) with broad signals denoted by (br). Proton nuclear magnetic resonance (<sup>1</sup>H NMR) spectra were recorded in deuterated solvents at 300 or 400 MHz, as indicated. Carbon-13 nuclear magnetic resonance (<sup>13</sup>C NMR) spectra were recorded at 75 or 100 MHz, as indicated. Chemical shifts are reported in parts per million (ppm, δ) relative to Me<sub>4</sub>Si (δ 0.00). Mass spectra (MS) were obtained using electron impact (EI) at 70 eV. Fast atom bombardment

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mass spectra (FAB) were obtained using xenon carrier gas and an 8 kV ion acceptance voltage.

All moisture-sensitive reactions were performed in flame-dried glassware under a stream of nitrogen, unless indicated otherwise. Bath temperatures were used to record the reaction temperature in all cases. All reactions were stirred magnetically unless otherwise indicated. Ozonolysis was performed using a commercial ozonator. Reactions requiring ultrasound facilitation were done using either an ultrasonic cell disrupter (50 W maximum output) or an ultrasonic bath (9.5 L, 115 V, 50/50 Hz; 29.2 cm w × 24.1 cm d × 15.2 cm h). When prolonged cooling was necessary, an immersion cooler was employed. Analytical thin-layer chromatography (TLC) was carried out on E. Merck (Darmstadt) TLC plates precoated with silica gel 60 F<sub>254</sub> (250- $\mu$ m layer thickness). Preparative TLC was carried out using 0.5 and 2.0 mm × 10 cm × 10 cm E. Merck precoated silica gel 60 F<sub>254</sub> plates. TLC visualization was accomplished using either a UV lamp, iodine adsorbed on silica gel or charring solution [*p*-anisaldehyde (PAA)/phosphomolybdic acid (PMA)]. Flash chromatography was performed according to the procedure by Still<sup>53</sup> on EM Science silica gel 60 (230–400 mesh) or Florisil (100–200 mesh) purchased from Aldrich. When indicated, further purification was effected using a Rainin Dynamax HPLC system.

Tetrahydrofuran (THF), diethyl ether (Et<sub>2</sub>O), and benzene (PhH) were distilled from sodium/benzophenone ketyl. Toluene (PhCH<sub>3</sub>) was distilled from sodium metal. Triethylamine (Et<sub>3</sub>N), diisopropylethylamine (*i*-Pr<sub>2</sub>NET, Hünig's base), pyridine, 1,2-dichloroethane, dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>), 1,2-dimethoxyethane (DME), and acetonitrile (CH<sub>3</sub>CN) were distilled from calcium hydride. Dimethyl sulfoxide (DMSO) and *N,N*-dimethylformamide (DMF) were distilled under reduced pressure from calcium hydride and stored over 4 Å molecular sieves. Deuteriochloroform (chloroform-*d*, CDCl<sub>3</sub>), deuterioacetone (acetone-*d*<sub>6</sub>), and deuteriobenzene (benzene-*d*<sub>6</sub>, C<sub>6</sub>D<sub>6</sub>) were stored over 4 Å molecular sieves before use. Deuteriomethanol (methanol-*d*<sub>4</sub>) was used as received from Aldrich in glass ampules. Chlorotrimethylsilane (Me<sub>3</sub>SiCl, TMSCl) was distilled from calcium hydride and stored over 4 Å molecular sieves prior to use. Methanesulfonyl chloride (MsCl) was distilled under reduced pressure prior to use. Methanol (MeOH) was distilled from magnesium methoxide. Hexanes were distilled at atmospheric pressure. 1,1,1,3,3,3-Hexamethyldisilazane (HMDS) was distilled from calcium hydride and stored over 4 Å molecular sieves. All other commercially obtained reagents and solvents were used as received without further purification unless indicated otherwise.

**(1*S*,2*E*)-1-[(1*R*)-3,3-Diethyl-2,4-dioxolanyl]but-2-en-1-ol (9).** To a cooled (0 °C) solution of ZnBr<sub>2</sub> in THF (31 mL) was added a solution of *trans*-propenyllithium (0.70 M solution in Et<sub>2</sub>O, 84.0 mL, 109 mmol). The mixture was stirred at 0 °C for 1 h. A solution of aldehyde **7** (8.7 g) in THF (18 mL) was added in a dropwise manner via cannula. The mixture was stirred at 0 °C for 48 h and then quenched with saturated aqueous NH<sub>4</sub>Cl (200 mL). The aqueous layer was separated and extracted with Et<sub>2</sub>O (3 × 200 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and filtered. The solvent was removed in vacuo, and the residue was purified by flash chromatography (silica gel, elution with 17% Et<sub>2</sub>O in hexanes) to give 6.80 g (34.0 mmol, 63%, ds = 8:1) of alcohol **9** as a yellowish oil.

An analytical sample was prepared from acetate **17** according to the following procedure. To a vigorously stirred slurry of LiAlH<sub>4</sub> (2.28 g, 60.0 mmol) in THF (150 mL) at 0 °C was added a solution of ester **17** (2.88 g, 12.0 mmol) in THF (21 mL) in a dropwise manner via cannula. The mixture was stirred at 0 °C for 0.5 h and then allowed to warm to ambient temperature and heated to reflux for 20 h. The gray slurry was then cooled to 0 °C and cautiously quenched by the sequential dropwise addition of H<sub>2</sub>O (2.3 mL), 15% aqueous NaOH solution (2.3 mL), and then H<sub>2</sub>O (6.9 mL). The resulting white suspension was stirred rapidly for 0.5 h,

filtered, and washed with Et<sub>2</sub>O. The filtrate was concentrated in vacuo. The residue was diluted in Et<sub>2</sub>O, dried (MgSO<sub>4</sub>), and filtered. The solvent was removed in vacuo, and the residue was purified by Kugelrohr distillation to give 2.37 g (11.8 mmol, 98%) of alcohol **9** as a colorless oil. Data for **9**: *R*<sub>f</sub> 0.31 (50% Et<sub>2</sub>O in hexanes/PMA); [α]<sub>D</sub><sup>20</sup> +20.7 (*c* 1.77, CH<sub>2</sub>Cl<sub>2</sub>); IR (thin film) 3435 (br) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 5.78 (ddq, 1H, *J* = 15.4, 6.6, 1.1 Hz), 5.39 (ddq, 1H, *J* = 15.1, 6.6, 1.5 Hz), 4.24 (m, 1H), 4.04 (ddd, 1H, *J* = 7.4, 6.3, 4.0 Hz), 3.94 (A portion of ABX, 1H, *J*<sub>AB</sub> = 8.1 Hz, *J*<sub>AX</sub> = 6.3 Hz), 3.84 (B portion of ABX, 1H, *J*<sub>AB</sub> = 8.1 Hz, *J*<sub>BX</sub> = 7.7 Hz), 2.11 (bs, 1H), 1.69 (m, 3H), 1.65 (m, 2H), 1.59 (q, 2H, *J* = 7.4 Hz), 0.90 (t, 3H, *J* = 7.4 Hz), 0.86 (t, 3H, *J* = 7.4 Hz); <sup>13</sup>C NMR (C<sub>6</sub>D<sub>6</sub>, 75 MHz) δ 130.4, 127.5, 113.1, 79.2, 72.2, 66.0, 29.9, 29.4, 17.8, 8.4, 8.2; HRMS (EI) exact mass calcd for C<sub>11</sub>H<sub>21</sub>O<sub>3</sub> (M<sup>+</sup> + H) requires 201.1491, found 201.1469.

**(1*S*,2*E*)-[(1*R*)-3,3-Diethyl-2,4-dioxolanyl]but-2-enyl 2-methoxyacetate (10).** To a cooled (0 °C) solution of alcohol **9** (2.0 g, 10.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (36.2 mL) and pyridine (1.62 mL, 20.0 mmol) was added 2-methoxyacetyl chloride (1.1 mL, 12.0 mmol) in a dropwise fashion via syringe. After the reaction mixture had been stirred at 0 °C for 1 h and 25 °C for 16 h, the solvent was removed in vacuo. The residue was dissolved in Et<sub>2</sub>O (100 mL). The ether layer was washed with a saturated CuSO<sub>4</sub> solution (2 × 50 mL), dried (MgSO<sub>4</sub>), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, elution with 17% Et<sub>2</sub>O in hexanes) to give 2.61 g (9.6 mmol, 96%) of **10** as a colorless oil. Data for **10**: *R*<sub>f</sub> 0.42 (50% Et<sub>2</sub>O in hexanes/PMA); [α]<sub>D</sub><sup>20</sup> +32.4 (*c* 2.07, CH<sub>2</sub>Cl<sub>2</sub>); IR (thin film) 1759 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 5.83 (m, 1H), 5.40 (m, 2H), 4.17 (dt, 1H, *J* = 6.6, 4.4 Hz), 4.03 (dd, 1H, *J* = 8.1, 6.6 Hz), 4.02 (s, 2H), 3.73 (dd, 1H, *J* = 8.1, 7.4 Hz), 3.43 (s, 3H), 1.70 (m, 2H), 1.59 (q, 2H, *J* = 7.4 Hz), 0.88 (t, 3H, *J* = 7.4 Hz), 0.86 (t, 3H, *J* = 7.4 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ 169.1, 132.0, 124.8, 113.5, 76.7, 74.2, 69.6, 65.9, 59.2, 29.3, 28.8, 17.7, 7.9, 7.8; HRMS (EI) exact mass calcd for C<sub>12</sub>H<sub>19</sub>O<sub>5</sub> (M<sup>+</sup> - C<sub>2</sub>H<sub>5</sub>) requires 243.1233, found 243.1239.

**(2*R*,3*S*,4*E*)-5-[(1*S*)-3,3-Diethyl-2,4-dioxolanyl]-2-methoxy-3-methylpent-4-enoic Acid (12).** To a solution of ester **10** (88.4 mg, 0.325 mmol) in THF (2.6 mL) at -100 °C (Et<sub>2</sub>O/dry ice bath) was added LHMDS solution (1.0 M in THF, 0.65 mL, 0.65 mmol) in a dropwise fashion. After the mixture had been stirred at -100 °C for 0.5 h, 0.4 mL of the supernatant from the centrifugation of a 1:1 (v/v) mixture of Me<sub>3</sub>SiCl and Et<sub>3</sub>N was added. The mixture was stirred at -100 °C for 1 h, allowed to warm to 25 °C, and stirred for 16 h. A 2.5% aqueous HCl solution (5.0 mL) was added. The mixture was stirred for 5 min. The aqueous layer was separated and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried (MgSO<sub>4</sub>), filtered, and concentrated in vacuo. Purification by flash column chromatography (silica gel, elution with 50% Et<sub>2</sub>O in hexanes, followed by 50% EtOAc and 1% HOAc in hexane) and azeotropic removal of HOAc with benzene afforded 73.6 mg (0.271 mmol, 83%, ds = 6:1) of the desired acid **12** as a yellowish oil. An analytical sample was prepared from diastereomerically pure **10** using the same procedure. Data for acid **12**: *R*<sub>f</sub> 0.18 (6.0 mL of 50% EtOAc in hexanes with 3 drops of AcOH/PMA); [α]<sub>D</sub><sup>20</sup> +21.4 (*c* 2.57, CH<sub>2</sub>Cl<sub>2</sub>); IR (thin film) 3195, 1753 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 8.51 (bs, 1H), 5.76 (dd, 1H, *J* = 15.4, 7.7 Hz), 5.52 (dd, 1H, *J* = 15.4, 7.7 Hz), 4.46 (dd, 1H, *J* = 14.3, 8.1 Hz), 4.06 (dd, 1H, *J* = 8.1, 6.3 Hz), 3.56 (d, 1H, *J* = 4.8 Hz), 3.49 (t, 1H, *J* = 8.1 Hz), 3.42 (s, 3H), 2.68 (m, 1H), 1.64 (q, 2H, *J* = 7.7 Hz), 1.62 (q, 2H, *J* = 7.4 Hz), 1.08 (d, 3H, *J* = 6.8 Hz), 0.89 (t, 3H, *J* = 7.4 Hz), 0.88 (t, 3H, *J* = 7.7 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ 176.1, 135.2, 128.5, 113.1, 83.9, 76.4, 69.7, 58.7, 39.5, 29.7, 29.6, 14.8, 7.9, 7.8; HRMS (EI) exact mass calcd for C<sub>12</sub>H<sub>19</sub>O<sub>5</sub> (M<sup>+</sup> - C<sub>2</sub>H<sub>5</sub>) requires 243.1233, found 243.1228.

To a solution of bromolactone **13** (1.14 g, 3.25 mmol) in THF (54 mL) was added Zn dust (6.37 g, 97.5 mmol). To this rapidly stirred solution was added aqueous 1 M NH<sub>4</sub>OAc (11 mL) slowly. The resulting solution was stirred at 25 °C for 5 h, EtOAc (20 mL) and an aqueous pH 4 buffer solution (50 mL, a 48:2 (v/v) mixture of 1 M NaH<sub>2</sub>PO<sub>4</sub> and 1 M NaHSO<sub>4</sub>) were

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



added. The mixture was filtered through Celite with EtOAc. The aqueous layer was separated and adjusted to pH 4 with the slow addition of 1 M NaHSO<sub>4</sub> solution. The resultant aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried (MgSO<sub>4</sub>), filtered, and concentrated in vacuo. Purification by flash chromatography (silica gel, elution with 50% EtOAc and 1% HOAc in hexanes), followed by azeotropic removal of HOAc with PhH, afforded 0.77 g (2.83 mmol, 87%) of acid **12** as a colorless oil. Data for the acid **12** match that of the previous procedure.

**(3R,4S,5R,6R)-6-[(1R)-3,3-Diethyl-2,4-dioxolanyl]-5-bromo-3-methoxy-4-methyloxolan-2-one (13) and (3R,4S,5S)-5-[(1S)-3,3-Diethyl-2,4-dioxolanyl]bromomethyl-3-methoxy-4-methyloxolan-2-one (14).** To a solution of acid **12** (3.02 g, 11.1 mmol) in CCl<sub>4</sub> (44.4 mL) were added NaHCO<sub>3</sub> (1.87 g, 22.2 mmol) and NBS (3.95 g, 22.2 mmol) at room temperature. The reaction solution was protected from light and stirred for 20 h. The mixture was diluted with hexanes, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, gradient elution with 11% and 20% Et<sub>2</sub>O in hexanes) to afford 1.48 g (4.20 mmol, 38%) of **13** and 1.49 g (4.23 mmol, 38%) of **14** as a colorless oil. Data for bromolactone **13**: *R*<sub>f</sub> 0.40 (50% Et<sub>2</sub>O in hexanes/PMA); [α]<sub>D</sub><sup>22</sup> +36.6 (*c* 1.37, CH<sub>2</sub>Cl<sub>2</sub>); IR (thin film) 1791 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 4.36 (ddd, 1H, *J* = 7.4, 6.6, 2.9 Hz), 4.30 (dd, 1H, *J* = 9.6, 4.8 Hz), 4.07 (dd, 1H, *J* = 8.1, 6.6 Hz), 4.04 (dd, 1H, *J* = 9.6, 2.9 Hz), 3.81 (dd, 1H, *J* = 8.1, 7.7 Hz), 3.57 (s, 3H), 3.56 (d, 1H, *J* = 5.1 Hz), 2.59 (m, 1H), 1.72 (dq, 2H, *J* = 7.4, 1.5 Hz), 1.61 (q, 2H, *J* = 7.4 Hz), 1.32 (d, 3H, *J* = 7.0 Hz), 0.89 (t, 3H, *J* = 7.4 Hz), 0.88 (t, 3H, *J* = 7.7 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ 173.0, 113.6, 83.4, 82.0, 73.6, 67.9, 58.5, 55.4, 40.6, 29.2, 28.6, 17.5, 8.0, 7.9; MS (FAB) *m/e* (relative intensity, assignment) 352.0 (25, M<sup>+</sup>), 350.0 (25, M<sup>+</sup> - 2), 323.0 (100, M<sup>+</sup> - C<sub>2</sub>H<sub>5</sub>), 321.0 (100, (M<sup>+</sup> - 2) - C<sub>2</sub>H<sub>5</sub>); experimental isotope pattern calculated for C<sub>14</sub>H<sub>25</sub>O<sub>5</sub>Br matches that observed; HRMS (EI) exact mass calcd for C<sub>12</sub>H<sub>18</sub>O<sub>5</sub>Br (M<sup>+</sup> - C<sub>2</sub>H<sub>5</sub>) requires 323.0320, found 323.0343. Data for bromolactone **14**: *R*<sub>f</sub> 0.60 (50% Et<sub>2</sub>O in hexanes/PMA); [α]<sub>D</sub><sup>22</sup> +68.4 (*c* 1.80, CH<sub>2</sub>Cl<sub>2</sub>); IR (thin film) 1792 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 4.69 (dd, 1H, *J* = 8.8, 5.5 Hz), 4.41 (ddd, 1H, *J* = 7.0, 6.3, 5.5 Hz), 4.18 (dd, 1H, *J* = 8.8, 5.2 Hz), 4.13 (dd, 1H, *J* = 8.1, 6.3 Hz), 3.85 (dd, 1H, *J* = 8.1, 7.4 Hz), 3.71 (d, 1H, *J* = 3.7 Hz), 3.52 (s, 3H), 2.69 (ddq, 1H, *J* = 7.4, 5.9, 3.7 Hz), 1.70 (dq, 2H, *J* = 7.7, 1.8 Hz), 1.60 (q, 2H, *J* = 7.4 Hz), 1.13 (d, 3H, *J* = 7.4 Hz), 0.92 (t, 3H, *J* = 7.4 Hz), 0.87 (t, 3H, *J* = 7.7 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ 172.9, 114.2, 81.7, 80.3, 74.8, 67.3, 58.2, 51.3, 39.3, 39.8, 29.4, 28.7, 10.1, 8.0, 7.9; MS (FAB) *m/e* (relative intensity, assignment) 352.0 (25, M<sup>+</sup>), 350.0 (26, M<sup>+</sup> - 2), 323.0 (100, M<sup>+</sup> - C<sub>2</sub>H<sub>5</sub>), 321.0 (100, (M<sup>+</sup> - 2) - C<sub>2</sub>H<sub>5</sub>); experimental isotope pattern calculated for C<sub>14</sub>H<sub>23</sub>O<sub>5</sub>Br matches that observed; HRMS (EI) exact mass calcd for C<sub>12</sub>H<sub>18</sub>O<sub>5</sub>Br (M<sup>+</sup> - C<sub>2</sub>H<sub>5</sub>) requires 323.0320, found 323.0305.

**1-[(1R)-3,3-Diethyl-2,4-dioxolanyl]but-2-ynyl Acetate (15).** To a cooled (0 °C) solution of 1-propynylmagnesium bromide (0.5 M solution in THF, 182 mL, 91.2 mmol) was added a solution of aldehyde (9.73 g, 60.8 mmol) in THF (21 mL) slowly over a period of 30 min. The solution was then allowed to warm to 25 °C and stirred for 6 h. The reaction was quenched by the slow addition of saturated aqueous NH<sub>4</sub>-Cl (150 mL). The aqueous layer was separated and extracted with Et<sub>2</sub>O (3 × 100 mL), and the combined organic extracts were dried (MgSO<sub>4</sub>), filtered, and concentrated in vacuo. Purification by Kugelrohr distillation afforded 10.8 g (54.5 mmol, 88%) of a 1:1 diastereomeric mixture of propargyl alcohols as a colorless oil.

To a cooled (0 °C) 1:1 diastereomeric mixture of the propargyl alcohols (8.84 g, 44.7 mmol), DMAP (0.55 g, 4.47 mmol), and Et<sub>3</sub>N (9.32 mL, 67.0 mmol) was added Ac<sub>2</sub>O (6.33 mL, 67.0 mmol) in a dropwise manner. The mixture was stirred at 0 °C for 0.5 h, allowed to warm to ambient temperature, and stirred for 18 h. The reaction mixture was diluted with Et<sub>2</sub>O (200 mL) and quenched with H<sub>2</sub>O (100 mL). The aqueous layer was separated and extracted with Et<sub>2</sub>O (3 × 100 mL). The combined organic extracts were dried

(MgSO<sub>4</sub>), filtered, and concentrated in vacuo. Purification by Kugelrohr distillation afforded 9.99 g (41.6 mmol, 93%) of ester **15** (1:1 diastereomeric mixture) as a colorless oil. Data for **15**: *R*<sub>f</sub> 0.52 (50% Et<sub>2</sub>O in hexanes/PMA); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 5.49–5.31 (m, 1H), 4.23 (m, 1H), 4.09 (m, 1H), 3.88 (m, 1H), 2.09 (m, 3H), 1.81 (m, 3H), 1.62 (m, 4H), 0.87 (m, 6H).

**(1R)-1-[(1R)-3,3-Diethyl-2,4-dioxolanyl]but-2-yn-1-ol (16) and (1S)-1-[(1R)-3,3-Diethyl-2,4-dioxolanyl]but-2-ynyl Acetate (17).** Preparation of pure **16** via diastereoselective saponification reaction of **15** (120 mg, 0.5 mmol, 1:1 diastereomeric mixture) with porcine pancreatic lipase (PPL, EC 3.1.1.3, Type II, Sigma, 40 mg) was carried out at 23 °C with KH<sub>2</sub>PO<sub>4</sub> buffer (0.2 M, pH 5.1, 10 mL) under air. The mixture was stirred for 3 h and quenched by the addition of Et<sub>2</sub>O. The aqueous layer was separated and extracted with Et<sub>2</sub>O (3 × 20 mL). The combined organic layers were dried (MgSO<sub>4</sub>), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, gradient elution with 13% Et<sub>2</sub>O in hexanes and 20% Et<sub>2</sub>O in hexanes) to afford 38 mg (0.192 mmol, 38%, 93% de) of pure alcohol **16** and recovered acetate **17** as a colorless oil. Data for **16**: *R*<sub>f</sub> 0.31 (50% Et<sub>2</sub>O in hexanes/PMA); [α]<sub>D</sub><sup>22</sup> +27.9 (*c* 0.85, CH<sub>2</sub>Cl<sub>2</sub>); IR (thin film) 3435 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 4.23 (m, 1H), 4.12 (dd, 1H, *J* = 7.4, 6.6 Hz), 4.07 (dd, 1H, *J* = 12.9, 9.5 Hz), 3.77 (ddd, 1H, *J* = 13.2, 6.6, 5.2 Hz), 2.42 (bs, 1H), 1.81 (d, 3H, *J* = 2.2 Hz), 1.64 (q, 2H, *J* = 7.7 Hz), 1.60 (q, 2H, *J* = 7.4 Hz), 0.88 (t, 3H, *J* = 7.4 Hz), 0.87 (t, 3H, *J* = 7.4 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ 114.1, 82.5, 79.0, 76.0, 66.4, 29.3, 29.0, 7.87, 7.61, 3.30; HRMS (EI) exact mass calcd for C<sub>11</sub>H<sub>19</sub>O<sub>3</sub> (M<sup>+</sup> + H) requires 199.1335, found 199.1333.

Preparation of pure **17** via diastereoselective saponification of **15** was accomplished similarly. To a suspension of **15** (9.99 g, 41.6 mmol, 1:1 diastereomeric mixture) in KH<sub>2</sub>PO<sub>4</sub> buffer (0.2 M, pH 6.0, 420 mL) and H<sub>2</sub>O (420 mL) was added porcine pancreatic lipase (PPL, EC 3.1.1.3, Type II, Sigma, 5.0 g). The mixture was stirred under air at 23 °C for 6.5 h and quenched by the addition of Et<sub>2</sub>O. The mixture was filtered through a Buchner funnel and extracted with Et<sub>2</sub>O (4 × 200 mL). The combined organic layers were dried (MgSO<sub>4</sub>), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, gradient elution with 13% Et<sub>2</sub>O in hexanes and 20% Et<sub>2</sub>O in hexanes) to afford 3.49 g (14.5 mmol, 35%, 97% de) of pure acetate **17** and recovered alcohol **16** as a colorless oil. Data for **17**: *R*<sub>f</sub> 0.52 (50% Et<sub>2</sub>O in hexanes/PMA); [α]<sub>D</sub><sup>22</sup> +86.4 (*c* 3.16, CH<sub>2</sub>Cl<sub>2</sub>); IR (thin film) 2244, 1748 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 5.48 (dq, 1H, *J* = 4.4, 2.2 Hz), 4.25 (dt, 1H, *J* = 6.6, 4.1 Hz), 4.08 (dd, 1H, *J* = 8.5, 6.6 Hz), 3.89 (dd, 1H, *J* = 8.1, 7.0 Hz), 2.08 (s, 3H), 1.82 (d, 3H, *J* = 2.2 Hz), 1.62 (m, 4H), 0.88 (t, 3H, *J* = 7.4 Hz), 0.87 (t, 3H, *J* = 7.4 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ 169.6, 114.0, 83.1, 76.7, 73.3, 65.7, 63.4, 29.3, 28.9, 20.8, 7.8, 7.7, 3.5; HRMS (EI) exact mass calcd for C<sub>13</sub>H<sub>20</sub>O<sub>4</sub> (M<sup>+</sup>) requires 240.1362, found 240.1389.

**1-[(1R)-3,3-Diethyl-2,4-dioxolanyl]but-2-yn-1-one (18).** To a cooled (0 °C) solution of 1-propynylmagnesium bromide (0.5 M solution in THF, 182 mL, 91.2 mmol) was added a solution of aldehyde (9.73 g, 60.8 mmol) in THF (21 mL) slowly over a period of 30 min. The solution was then allowed to warm to 25 °C and stirred for 6 h. The reaction was quenched by the slow addition of saturated aqueous NH<sub>4</sub>Cl (150 mL). The aqueous layer was separated and extracted with Et<sub>2</sub>O (3 × 100 mL), and the combined organic extracts were dried (MgSO<sub>4</sub>), filtered, and concentrated in vacuo. Purification by Kugelrohr distillation afforded 10.8 g (54.5 mmol, 88%) of a 1:1 diastereomeric mixture of propargyl alcohols as a colorless oil.

To a suspension of Dess–Martin periodinane (321 mg, 0.758 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL) was added a solution of the above propargyl alcohol diastereomeric mixture (100 mg, 0.505 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) in a dropwise fashion via cannula at 25 °C. The reaction mixture was stirred at 25 °C for 2 h and was quenched with a saturated aqueous NaHCO<sub>3</sub> solution (50 mL). The aqueous layer was separated and extracted with Et<sub>2</sub>O (3 × 50 mL). The combined organic layers were dried (MgSO<sub>4</sub>),

filtered, and concentrated in vacuo. The residue was purified by Kugelrohr distillation to afford 97 mg (0.496 mmol, 98%) of ketone **18** as a colorless oil. Data for ketone **18**:  $R_f$  0.53 (50% Et<sub>2</sub>O in hexanes/PMA);  $[\alpha]_D^{25} +49.5$  (*c* 2.53, CH<sub>2</sub>Cl<sub>2</sub>); IR (thin film) 2216, 1674 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  4.50 (dd, 1H, *J* = 7.7, 6.3 Hz), 4.23 (dd, 1H, *J* = 8.5, 7.7 Hz), 4.05 (dd, 1H, *J* = 8.5, 5.9 Hz), 2.05 (s, 3H), 1.72 (q, 2H, *J* = 7.4 Hz), 1.65 (q, 2H, *J* = 7.4 Hz), 0.95 (t, 3H, *J* = 7.4 Hz), 0.89 (t, 3H, *J* = 7.4 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  186.0, 115.5, 94.8, 80.9, 78.1, 66.6, 29.1, 28.5, 7.86, 7.68, 4.09; HRMS (EI) exact mass calcd for C<sub>11</sub>H<sub>17</sub>O<sub>3</sub> (M<sup>+</sup> + H) requires 197.1178, found 197.1175.

**(1S)-1-[(1R)-3,3-Diethyl-2,4-dioxolanyl]but-2-ynyl Acetate (17)**. To a 25-mL round-bottom flask were added ketone **18** (288 mg, 1.46 mmol) and (*R*)-Alpine borane (5.82 mL, 0.5 M in THF, 2.91 mmol). The mixture was stirred at room temperature for 40 h. Acetaldehyde (0.5 mL) was added to this solution, and the mixture was allowed to stir for 30 min. Et<sub>2</sub>O (10 mL) was then added. This solution was cooled in an ice bath and treated with ethanolamine (0.66 mL), which caused a white precipitate to form. The mixture was stirred for 1 h at 0 °C, suction filtered, and washed with pentane. The filtrate was concentrated in vacuo. The residue was purified by Kugelrohr distillation to give 389 mg ( $\alpha/\beta$  = 4.6:1) of crude alcohol mixture.

To the crude mixture of alcohols (389 mg), Et<sub>3</sub>N (1.0 mL, 2.91 mmol), and DMAP (17.8 mg) was added Ac<sub>2</sub>O (0.69 mL, 2.91 mmol) at 0 °C. The mixture was stirred for 20 min, warmed to room temperature, and stirred for 18 h. The reaction mixture was diluted with Et<sub>2</sub>O (50 mL) and H<sub>2</sub>O (50 mL). The aqueous layer was separated and extracted with Et<sub>2</sub>O (3 × 50 mL). The combined organic layers were dried (MgSO<sub>4</sub>), filtered, and concentrated in vacuo. The residue was purified by Kugelrohr distillation to afford 339 mg (1.41 mmol, 97%,  $\alpha/\beta$  = 4.6:1 diastereomeric mixture) of acetates as a colorless oil.  $R_f$  0.52 (50% Et<sub>2</sub>O in hexanes/PMA).

To a suspension of the above diastereomeric mixture of acetates (50 mg, 0.208 mmol, 4.6:1 diastereomeric mixture) in KH<sub>2</sub>PO<sub>4</sub> buffer (0.1 M, pH 6.0, 4.0 mL) was added porcine pancreatic lipase (PPL, EC 3.1.1.3, Type II, Sigma, 20 mg). The mixture was stirred under air at 23 °C for 6.5 h and quenched by the addition of Et<sub>2</sub>O (30 mL). The mixture was extracted with Et<sub>2</sub>O (3 × 30 mL). The combined organic layers were dried (MgSO<sub>4</sub>), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, gradient elution with 13% Et<sub>2</sub>O in hexanes and 20% Et<sub>2</sub>O in hexanes) to afford 35 mg (0.146 mmol, 70%, 95% de) of pure acetate **17** and recovered alcohol **16** as a colorless oil. All data for the acetate **17** are identical to those of the previous procedure.

**(3R,4S,5R)-5-[[1(S)-3,3-Diethyl-2,4-dioxolanyl]methyl]-3-methoxy-4-methyloxolan-2-one (21)**. To a solution of bromolactone **14** (2.16 g, 6.15 mmol) in PhH (41 mL) were added <sup>n</sup>Bu<sub>3</sub>SnH (3.31 mL, 12.3 mmol) and AIBN (51 mg, 0.31 mmol). The solution was heated to reflux for 16 h and cooled to room temperature. The solvent was removed in vacuo. The residue was diluted in Et<sub>2</sub>O (50 mL) and treated with excess aqueous KF solution (5 g of KF in 50 mL of H<sub>2</sub>O). The resulting white precipitate was removed by filtration with Et<sub>2</sub>O wash. The aqueous layer was extracted with Et<sub>2</sub>O (3 × 100 mL). The combined organic layers were dried (MgSO<sub>4</sub>), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 33% Et<sub>2</sub>O in hexanes) to give 1.75 g (5.29 mmol, 86%) of lactone **21** as a colorless oil. Data for **21**:  $R_f$  0.23 (50% Et<sub>2</sub>O in hexanes/PMA);  $[\alpha]_D^{25} +118.9$  (*c* 1.0, CH<sub>2</sub>Cl<sub>2</sub>); IR (thin film) 1779 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  4.61 (ddd, 1H, *J* = 10.7, 6.3, 4.4 Hz), 4.23 (tt, 1H, *J* = 7.7, 5.9 Hz), 4.11 (dd, 1H, *J* = 7.7, 5.9 Hz), 3.60 (d, 1H, *J* = 5.5 Hz), 3.56 (s, 3H), 3.55 (t, 1H, *J* = 7.7 Hz), 2.53 (m, 1H), 2.00 (ddd, 1H, *J* = 14.3, 9.9, 5.5 Hz), 1.75 (ddd, 1H, *J* = 14.3, 7.4, 4.4 Hz), 1.63 (q, 2H, *J* = 7.7 Hz), 1.59 (q, 2H, *J* = 7.4 Hz), 1.06 (d, 3H, *J* = 7.4 Hz), 0.89 (t, 3H, *J* = 7.4 Hz), 0.87 (t, 3H, *J* = 7.4 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  173.7, 112.8, 83.4, 81.6, 77.8, 72.5, 69.2, 58.2, 39.3, 33.5, 29.6, 29.3,

11.3, 8.0, 7.8; HRMS (EI) exact mass calcd for C<sub>14</sub>H<sub>24</sub>O<sub>5</sub> (M<sup>+</sup>) requires 272.1624, found 272.1641.

**(2R,3S,4R)-5-[(1S)-3,3-Diethyl-2,4-dioxolanyl]-2-methoxy-3-methylpentane-1,4-diol (22)**. LiAlH<sub>4</sub> (35 mg, 0.92 mmol) was suspended in THF (0.84 mL) at -78 °C, and a solution of the lactone **21** (50 mg, 0.184 mmol) in THF (1.0 mL) was added via cannula. The mixture was stirred at -78 °C for 0.5 h and 0 °C for 2 h, and stirring was then continued for 20 h, while the temperature was allowed to rise to room temperature. The reaction was quenched by the addition of a saturated aqueous potassium sodium tartrate solution (Rochelle's salt solution, 20 mL) and EtOAc (20 mL). The mixture was vigorously stirred until two clear layers formed. The aqueous layer was separated and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried (MgSO<sub>4</sub>), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 50% EtOAc in hexanes) to give 46 mg (0.167 mmol, 91%) of diol **22** as a colorless oil. Data for **22**:  $R_f$  0.27 (17% EtOAc in hexanes/PMA);  $[\alpha]_D^{25} -1.26$  (*c* 6.1, CH<sub>2</sub>Cl<sub>2</sub>); IR (thin film) 3417 (br) cm<sup>-1</sup>; <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>, 300 MHz)  $\delta$  4.10 (dt, 1H, *J* = 9.6, 2.6 Hz), 3.99 (m, 1H), 3.81 (bs, 1H), 3.80 (dd, 1H, *J* = 8.1, 6.3 Hz), 3.72 (bm, 2H), 3.28 (t, 1H, *J* = 8.1 Hz), 3.19 (bs, 1H), 3.16 (s, 3H), 3.08 (dt, 1H, *J* = 5.9, 4.0 Hz), 1.79 (m, 1H), 1.73 (m, 1H), 1.57 (q, 1H, *J* = 7.7 Hz), 1.54 (q, 1H, *J* = 7.4 Hz), 1.24 (ddd, 1H, *J* = 13.6, 4.0, 2.6 Hz), 0.99 (d, 3H, *J* = 7.4 Hz), 0.90 (t, 3H, *J* = 7.4 Hz), 0.85 (t, 3H, *J* = 7.4 Hz); <sup>13</sup>C NMR (C<sub>6</sub>D<sub>6</sub>, 75 MHz)  $\delta$  113.2, 84.3, 76.3, 70.4, 69.9, 60.4, 57.1, 40.4, 38.5, 30.3, 29.9, 9.6, 8.4, 8.2; HRMS (EI) exact mass calcd for C<sub>12</sub>H<sub>23</sub>O<sub>5</sub> (M<sup>+</sup>) requires 247.1546, found 247.1542.

**(1R,2S,3R)-1-[(1S)-3,3-Diethyl-2,4-dioxolanyl]-4-methoxy-3-methyl-5-(1,1,2-tetramethyl-1-silapropoxy)pentan-2-ol (23)**. To a solution of diol **22** (0.882 g, 3.19 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (24.5 mL) were added DMAP (0.195 g, 1.60 mmol) and Et<sub>3</sub>N (0.89 mL, 6.38 mmol). The resulting solution was cooled to 0 °C and treated with TBSCl (0.721 g, 4.79 mmol). The mixture was allowed to warm to room temperature and stirred for 18 h. H<sub>2</sub>O (50 mL) was added to the reaction mixture. The aqueous phase was separated and extracted with Et<sub>2</sub>O (3 × 100 mL). The combined organic layers were dried (MgSO<sub>4</sub>), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, gradient elution with 13% Et<sub>2</sub>O in hexanes and 17% Et<sub>2</sub>O in hexanes) to give 1.17 g (3.0 mmol, 94%) of alcohol **23** as a colorless oil. Data for **23**:  $R_f$  0.45 (50% Et<sub>2</sub>O in hexanes/PMA);  $[\alpha]_D^{25} +19.7$  (*c* 1.91, CH<sub>2</sub>Cl<sub>2</sub>); IR (thin film) 3519 (br) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  4.22 (m, 1H), 4.09 (dd, 1H, *J* = 7.4, 5.9 Hz), 3.90 (dt, 1H, *J* = 9.6, 3.3 Hz), 3.74 (A portion of ABX, 1H, *J*<sub>AB</sub> = 10.7 Hz, *J*<sub>AX</sub> = 5.0 Hz), 3.63 (B portion of ABX, 1H, *J*<sub>AB</sub> = 10.7 Hz, *J*<sub>BX</sub> = 5.3 Hz), 3.51 (t, 1H, *J* = 7.7 Hz), 3.48 (bs, 1H), 3.41 (s, 3H), 3.30 (q, 1H, *J* = 5.2 Hz), 1.85 (ddd, 1H, *J* = 14.0, 9.6, 7.7 Hz), 1.75 (m, 1H), 1.62 (q, 1H, *J* = 7.4 Hz), 1.59 (q, 1H, *J* = 7.4 Hz), 1.56 (ddd, 1H, *J* = 7.4, 5.5, 3.7 Hz), 0.90 (d, 3H, *J* = 7.4 Hz), 0.88 (t, 3H, *J* = 7.4 Hz), 0.87 (s, 9H), 0.86 (t, 3H, *J* = 7.7 Hz), 0.047 (s, 6H); <sup>13</sup>C NMR (C<sub>6</sub>D<sub>6</sub>, 75 MHz)  $\delta$  112.6, 84.8, 74.9, 71.2, 70.0, 62.5, 58.0, 39.2, 37.7, 29.7, 29.5, 25.6, 18.0, 8.0, 7.8, 7.5, -5.7; HRMS (EI) exact mass calcd for C<sub>18</sub>H<sub>39</sub>O<sub>5</sub>Si (M<sup>+</sup> - C<sub>2</sub>H<sub>5</sub>) requires 361.2410, found 361.2411.

**(2R)-[(1R,2S,3R)-1-[(1S)-3,3-Diethyl-2,4-dioxolanyl]-methyl]-3-methoxy-2-methyl-4-(1,1,2,2-tetramethyl-1-silapropoxy)butyl] 3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate (24)**. To a solution of alcohol **23** (20 mg, 0.051 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.7 mL) at 23 °C were added DMAP (14.3 mg, 0.117 mmol), (*R*)-(+)-MTPA (55.5 mg, 0.234 mmol), and DIC (18.3  $\mu$ L, 0.117 mmol). The resulting mixture was stirred at 23 °C for 18 h and then diluted with Et<sub>2</sub>O (30 mL) and H<sub>2</sub>O (30 mL). The aqueous layer was separated and extracted with Et<sub>2</sub>O (3 × 30 mL). The combined organic layers were dried (MgSO<sub>4</sub>), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 9% Et<sub>2</sub>O in hexanes) to give 29 mg (0.048 mmol, 95%) of ester **24** as a colorless oil. Data for **24**:  $R_f$  0.62 (50% Et<sub>2</sub>O in hexanes/PMA);  $[\alpha]_D^{25} -5.46$  (*c* 1.87, CH<sub>2</sub>Cl<sub>2</sub>); IR (thin film) 1745 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  7.55 (m, 2H), 7.37 (m, 3H), 5.17 (dt, 1H, *J* = 8.1, 4.4 Hz), 3.97 (dd, 1H, *J* = 7.7, 5.9 Hz), 3.82 (quin, 1H,



$J = 6.3$  Hz), 3.66 (A portion of ABX, 1H,  $J_{AB} = 10.7$  Hz,  $J_{AX} = 5.1$  Hz), 3.54 (B portion of ABX, 1H,  $J_{AB} = 10.7$  Hz,  $J_{BX} = 5.5$  Hz), 3.54 (d, 3H,  $J = 1.1$  Hz), 3.35 (t, 1H,  $J = 7.7$  Hz), 3.32 (s, 3H), 3.20 (q, 1H,  $J = 5.2$  Hz), 2.05 (m, 1H), 2.03 (ddd, 1H,  $J = 14.3, 6.3, 4.4$  Hz), 1.72 (ddd, 1H,  $J = 14.3, 7.0, 4.4$  Hz), 1.56 (q, 2H,  $J = 7.7$  Hz), 1.47 (q, 2H,  $J = 7.7$  Hz), 0.91 (d, 3H,  $J = 7.0$  Hz), 0.86 (s, 9H), 0.84 (t, 3H,  $J = 7.7$  Hz), 0.79 (t, 3H,  $J = 7.4$  Hz), 0.032 (s, 3H), 0.026 (s, 3H);  $^{13}\text{C}$  NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  166.0, 131.9, 129.4, 128.2, 127.2, 112.6, 81.9, 72.6, 69.9, 62.1, 58.0, 55.3, 37.1, 35.3, 29.7, 29.5, 18.0, 8.8, 8.0, 7.7, -5.6, -5.7; HRMS (EI) exact mass calcd for C<sub>28</sub>H<sub>44</sub>O<sub>7</sub>F<sub>3</sub>Si (M<sup>+</sup> - C<sub>2</sub>H<sub>5</sub>) requires 577.2809, found 577.2860.

**(2S)-[(1R,2S,3R)-1-[(1S)-3,3-Diethyl-2,4-dioxolanyl]-methyl]-3-methoxy-2-methyl-4-(1,1,2,2-tetramethyl-1-silapropoxy)butyl] 3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate (25).** To a solution of alcohol **23** (20 mg, 0.051 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.7 mL) at 23 °C were added DMAP (14.3 mg, 0.117 mmol), (S)-(-)-MTPA (55.5 mg, 0.234 mmol), and DIC (18.3  $\mu\text{L}$ , 0.117 mmol). The resulting mixture was stirred at 23 °C for 18 h and then diluted with Et<sub>2</sub>O (30 mL) and H<sub>2</sub>O (30 mL). The aqueous layer was separated and extracted with Et<sub>2</sub>O (3  $\times$  30 mL). The combined organic layers were dried (MgSO<sub>4</sub>), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 9% Et<sub>2</sub>O in hexanes) to give 28 mg (0.046 mmol, 91%) of ester **25** as a colorless oil. Data for **25**:  $R_f$  0.62 (50% Et<sub>2</sub>O in hexanes/PMA);  $[\alpha]_D^{22} +36.2$  (c 1.8, CH<sub>2</sub>Cl<sub>2</sub>); IR (thin film) 1743 cm<sup>-1</sup>;  $^1\text{H}$  NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  7.55 (m, 2H), 7.38 (m, 3H), 5.19 (dt, 1H,  $J = 8.1, 4.4$  Hz), 4.05 (t, 1H,  $J = 5.9$  Hz), 4.03 (m, 1H), 3.57 (A portion of ABX, 1H,  $J_{AB} = 11.1$  Hz,  $J_{AX} = 5.2$  Hz), 3.53 (B portion of ABX, 1H,  $J_{AB} = 11.1$  Hz,  $J_{BX} = 4.1$  Hz), 3.54 (d, 3H,  $J = 1.1$  Hz), 3.42 (t, 1H,  $J = 6.6$  Hz), 3.28 (s, 3H), 2.98 (q, 1H,  $J = 4.8$  Hz), 2.09 (ddd, 1H,  $J = 14.3, 7.7, 6.3$  Hz), 2.00 (m, 1H), 1.80 (ddd, 1H,  $J = 14.3, 6.3, 4.4$  Hz), 1.59 (q, 2H,  $J = 7.0$  Hz), 1.53 (q, 2H,  $J = 7.4$  Hz), 0.87 (t, 3H,  $J = 8.1$  Hz), 0.86 (s, 9H), 0.85 (d, 3H,  $J = 5.5$  Hz), 0.83 (t, 3H,  $J = 7.4$  Hz), 0.028 (s, 3H), 0.021 (s, 3H);  $^{13}\text{C}$  NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  165.7, 131.8, 129.3, 128.1, 127.0, 112.7, 81.5, 76.0, 72.9, 69.9, 62.0, 57.9, 55.1, 37.2, 35.4, 29.7, 29.6, 29.4, 25.5, 17.9, 9.0, 7.8, 7.6, -5.9; HRMS (EI) exact mass calcd for C<sub>28</sub>H<sub>44</sub>O<sub>7</sub>F<sub>3</sub>Si (M<sup>+</sup> - C<sub>2</sub>H<sub>5</sub>) requires 577.2809, found 577.2813.

**(1S,2S,3R)-1-[(1S)-3,3-Diethyl-2,4-dioxolanyl]-4-methoxy-3-methyl-5-(1,1,2,2-tetramethyl-1-silapropoxy)pentan-2-ol (26).** To a stirred solution of alcohol **23** (64.4 mg, 0.165 mmol), Ph<sub>3</sub>P (217 mg, 0.826 mmol), and *p*-nitrobenzoic acid (138 mg, 0.826 mmol) in dry benzene (1.0 mL) at room temperature was added diethylazodicarboxylate (DEAD) dropwise (0.13 mL, 0.826 mmol). The resulting solution was stirred at room temperature for 72 h. The solvent was removed in vacuo. The residue was diluted in Et<sub>2</sub>O (10 mL), and the white solid that formed was filtered off. The filtrate was concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 10% and 20% Et<sub>2</sub>O in hexanes) to afford 48 mg (0.891 mmol, 54%) of the desired *p*-nitrobenzoate and 22 mg (0.0564 mmol, 34%) of the recovered starting alcohol **23**.

To a solution of the *p*-nitrobenzoate (48 mg, 0.0891 mmol) in MeOH (1.5 mL) and Et<sub>2</sub>O (0.5 mL) was added saturated aqueous K<sub>2</sub>CO<sub>3</sub> solution (1.0 mL). The mixture was stirred at room temperature for 18 h and diluted with a saturated aqueous NH<sub>4</sub>Cl solution (50 mL) and Et<sub>2</sub>O (50 mL). The aqueous layer was separated and extracted with Et<sub>2</sub>O (3  $\times$  50 mL). The combined organic layers were dried (MgSO<sub>4</sub>), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 17% Et<sub>2</sub>O in hexanes) to give 33 mg (0.085 mmol, 96%) of alcohol **22** as a yellowish oil. Data for **26**:  $R_f$  0.41 (50% Et<sub>2</sub>O in hexanes/PMA);  $[\alpha]_D^{22} +0.6$  (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>); IR (thin film) 3496 (br) cm<sup>-1</sup>;  $^1\text{H}$  NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  4.28 (m, 1H), 4.11 (dd, 1H,  $J = 8.1, 6.3$  Hz), 3.76 (dd, 1H,  $J = 10.3, 5.9$  Hz), 3.72 (m, 1H), 3.62 (dd, 1H,  $J = 10.7, 5.2$  Hz), 3.53 (dd, 1H,  $J = 8.5, 5.5$  Hz), 3.52 (t, 1H,  $J = 8.1$  Hz), 3.44 (s, 3H), 1.83 (m, 2H), 1.64 (q, 2H,  $J = 7.0$  Hz), 1.63 (m, 1H), 1.59 (q, 2H,  $J = 7.4$  Hz), 0.90 (d, 3H,  $J = 7.4$  Hz), 0.89 (t, 3H,  $J = 7.4$  Hz), 0.88 (t, 3H,  $J = 7.4$  Hz), 0.88 (s, 9H), 0.05 (s, 6H);  $^{13}\text{C}$  NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  120.0, 83.3,

74.1, 71.8, 70.5, 62.6, 58.2, 39.1, 38.9, 29.7, 29.5, 25.6, 17.9, 11.7, 8.0, 7.7, -5.7, -5.8; HRMS (EI) exact mass calcd for C<sub>20</sub>H<sub>43</sub>O<sub>5</sub>Si (M<sup>+</sup> + H) requires 391.2880, found 391.2854; exact mass calcd for C<sub>18</sub>H<sub>37</sub>O<sub>5</sub>Si (M<sup>+</sup> - C<sub>2</sub>H<sub>5</sub>) requires 361.2410, found 361.2375.

**(1S,2S,3R)-1-[(1S)-3,3-Diethyl-2,4-dioxolanyl]methyl]-3-methoxy-1-[(4-methoxyphenyl)methoxy]-2-methyl-4-(1,1,2,2-tetramethyl-1-silapropoxy)butane (27).** Preparation of *p*-methoxybenzyl bromide (PMBBr) was as follows. Anisyl alcohol (3.0 g, 21.9 mmol) in Et<sub>2</sub>O (4.7 mL) was added slowly to 48% aqueous HBr (5.0 g) in Et<sub>2</sub>O (4.7 mL) and stirred for 1 h. The reaction mixture was then quenched with a saturated aqueous NaHCO<sub>3</sub> solution. The aqueous layer was separated and extracted with Et<sub>2</sub>O (3  $\times$  50 mL). The combined organic layers were washed with H<sub>2</sub>O and saturated NaBr solution and then dried (MgSO<sub>4</sub>). The solvent was removed in vacuo (<30 °C bath temperature). The crude *p*-methoxybenzyl bromide was essentially pure and could be used directly.

To a cooled (0 °C) solution of the alcohol **26** (236 mg, 0.605 mmol) and PMBBr (243 mg, 1.21 mmol) in THF (1.21 mL) and DMF (0.605 mL) was added NaHMDS (1.21 mL, 1.0 M in THF, 1.21 mmol). The mixture was allowed to warm to room temperature and stirred for 3 h. A saturated aqueous NH<sub>4</sub>Cl solution and Et<sub>2</sub>O were added. The aqueous layer was separated and extracted with Et<sub>2</sub>O (3  $\times$  50 mL). The combined organic layers were washed with H<sub>2</sub>O (80 mL), dried (MgSO<sub>4</sub>), and filtered. The solvent was removed in vacuo. The residue was purified by flash chromatography (silica gel, elution with 6% Et<sub>2</sub>O in hexanes) to afford 305 mg (0.598 mmol, 99%) of **27** as a colorless oil. Data for **27**:  $R_f$  0.64 (50% Et<sub>2</sub>O in hexanes/PMA);  $[\alpha]_D^{22} -31.1$  (c 1.68, CH<sub>2</sub>Cl<sub>2</sub>); IR (thin film) 2930, 2882, 1614, 1514, 1078, 837 cm<sup>-1</sup>;  $^1\text{H}$  NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  7.25 (m, 2H), 6.85 (m, 2H), 4.44 (ABq, 2H,  $J_{AB} = 10.7$  Hz,  $\Delta\nu_{AB} = 42.2$  Hz), 4.22 (m, 1H), 4.01 (dd, 1H,  $J = 5.9, 8.1$  Hz), 3.78 (s, 3H), 3.69 (A portion of ABX, 1H,  $J_{AB} = 10.7$  Hz,  $J_{AX} = 5.1$  Hz), 3.62 (B portion of ABX, 1H,  $J_{AB} = 10.7$  Hz,  $J_{BX} = 5.5$  Hz), 3.68 (m, 1H), 3.43 (t, 1H,  $J = 8.1$  Hz), 3.40 (s, 3H), 3.18 (q, 1H,  $J = 5.2$  Hz), 2.13 (m, 1H), 1.66 (m, 2H), 1.61 (q, 2H,  $J = 7.4$  Hz), 1.59 (q, 2H,  $J = 7.4$  Hz), 0.89 (s, 9H), 0.88 (d, 3H,  $J = 7.0$  Hz), 0.87 (t, 3H,  $J = 7.7$  Hz), 0.06 (s, 6H);  $^{13}\text{C}$  NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  158.9, 130.7, 129.2, 113.6, 112.0, 82.6, 77.8, 73.7, 71.2, 70.6, 62.4, 58.2, 55.1, 36.5, 35.2, 29.7, 25.7, 18.1, 8.5, 8.1, 7.8, -5.6; HRMS (EI) exact mass calcd for C<sub>28</sub>H<sub>50</sub>O<sub>6</sub>Si (M<sup>+</sup>) requires 510.3377, found 510.3374.

**(2R,3S,4S)-5-[(1S)-3,3-Diethyl-2,4-dioxolanyl]-2-methoxy-4-[(4-methoxyphenyl)methoxy]-3-methylpentan-1-ol (28).** To a solution of TBS ether **27** (510 mg, 1.0 mmol) in THF (15.6 mL) was added TBAF·3H<sub>2</sub>O (784 mg, 3.0 mmol). The mixture was stirred at room temperature for 1 h. The solvent was removed in vacuo. The residue was purified by flash chromatography (silica gel, elution with 25% EtOAc in hexanes) to give 363 mg (0.92 mmol, 92%) of alcohol **28** as a colorless oil. Data for alcohol **28**:  $R_f$  0.28 (50% EtOAc in hexanes/PMA);  $[\alpha]_D^{22} -46.6$  (c 1.71, CH<sub>2</sub>Cl<sub>2</sub>); IR (thin film) 3480 (br) cm<sup>-1</sup>;  $^1\text{H}$  NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  7.23 (m, 2H), 6.84 (m, 2H), 4.44 (ABq, 2H,  $J_{AB} = 11.0$  Hz,  $\Delta\nu_{AB} = 35.5$  Hz), 4.18 (m, 1H), 4.01 (dd, 1H,  $J = 7.7, 5.9$  Hz), 3.77 (s, 3H), 3.73 (A portion of ABX, 1H,  $J_{AB} = 11.8$  Hz,  $J_{AX} = 4.0$  Hz), 3.59 (B portion of ABX, 1H,  $J_{AB} = 11.8$  Hz,  $J_{BX} = 4.8$  Hz), 3.67 (ddd, 1H,  $J = 9.9, 4.4, 2.6$  Hz), 3.42 (t, 1H,  $J = 8.1$  Hz), 3.41 (s, 3H), 3.12 (dt, 1H,  $J = 6.6, 4.8$  Hz), 2.12 (tq, 1H,  $J = 7.0, 4.4$  Hz), 2.04 (bs, 1H), 1.63 (q, 2H), 1.60 (q, 2H,  $J = 7.4$  Hz), 1.57 (q, 2H,  $J = 7.4$  Hz), 0.96 (d, 3H,  $J = 7.0$  Hz), 0.86 (t, 3H,  $J = 7.4$  Hz), 0.85 (t, 3H,  $J = 7.4$  Hz);  $^{13}\text{C}$  NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  158.9, 130.3, 129.1, 113.5, 112.0, 83.0, 76.6, 73.4, 71.1, 70.3, 61.3, 58.0, 54.9, 36.8, 34.9, 29.7, 29.5, 9.9, 8.0, 7.6; HRMS (EI) exact mass calcd for C<sub>22</sub>H<sub>36</sub>O<sub>6</sub> (M<sup>+</sup>) requires 396.2512, found 396.2529.

**(2R,3S,4S)-5-[(1S)-3,3-Diethyl-2,4-dioxolanyl]-2-methoxy-4-[(4-methoxyphenyl)methoxy]-3-methylpentanal (29).** To a cooled (-78 °C) solution of oxalyl chloride (0.51 mL, 2.0 M in CH<sub>2</sub>Cl<sub>2</sub>, 1.01 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.4 mL) was added DMSO (0.16 mL, 2.02 mmol). The mixture was stirred at -78 °C for 10 min before a solution of alcohol **28** (100 mg, 0.253 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.4 mL) was added. The resulting mixture was



stirred at  $-78\text{ }^{\circ}\text{C}$  for 30 min before  $\text{Et}_3\text{N}$  (0.422 mL, 3.03 mmol) was added. The mixture was then allowed to warm to room temperature and stirred for 10 min.  $\text{Et}_2\text{O}$  (50 mL) and  $\text{H}_2\text{O}$  (50 mL) were added. The aqueous layer was separated and extracted with  $\text{Et}_2\text{O}$  ( $3 \times 50$  mL). The combined organic layers were washed with a saturated aqueous NaCl solution and dried ( $\text{MgSO}_4$ ). The solvent was removed in vacuo. The residue was purified by flash chromatography (silica gel, elution with 17%  $\text{Et}_2\text{O}$  in hexanes) to give 98 mg (0.249 mmol, 99%) of aldehyde **29** as a colorless oil. Data for **29**:  $R_f$  0.33 (50%  $\text{Et}_2\text{O}$  in hexanes/PMA);  $[\alpha]_D^{22} -13.4$  ( $c$  1.45,  $\text{CH}_2\text{Cl}_2$ ); IR (thin film)  $1733\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  9.63 (d, 1H,  $J = 1.1$  Hz), 7.25 (m, 2H), 6.86 (m, 2H), 4.50 (AB<sub>q</sub>, 2H,  $J_{AB} = 11.0$  Hz,  $\Delta\nu_{AB} = 24.5$  Hz), 4.28 (m, 1H), 4.04 (dd, 1H,  $J = 7.7, 5.9$  Hz), 3.81 (dd, 1H,  $J = 3.3, 1.1$  Hz), 3.78 (s, 3H), 3.64 (ddd, 1H,  $J = 9.9, 7.4, 2.6$  Hz), 3.46 (t, 1H,  $J = 7.7$  Hz), 3.40 (s, 3H), 2.13 (tq, 1H,  $J = 7.0, 3.3$  Hz), 1.84 (ddd, 1H,  $J = 14.0, 8.5, 2.6$  Hz), 1.66 (m, 1H), 1.62 (q, 1H,  $J = 7.7$  Hz), 1.61 (q, 1H,  $J = 7.4$  Hz), 0.89 (t, 6H,  $J = 7.7$  Hz), 0.88 (d, 3H,  $J = 7.4$  Hz);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  203.6, 159.3, 130.5, 129.3, 113.9, 112.6, 86.5, 77.6, 73.1, 72.7, 70.6, 58.4, 55.3, 39.2, 36.9, 30.0, 29.9, 29.5, 10.5, 8.4, 7.9; HRMS (EI) exact mass calcd for  $\text{C}_{22}\text{H}_{34}\text{O}_6$  ( $\text{M}^+$ ) requires 394.2355, found 394.2355.

**(3R,4S,5S)-6-[(1S)-3,3-Diethyl-2,4-dioxolanyl]-3-methoxy-5-[(4-methoxyphenyl)methoxy]-4-methylhexan-2-one (30)**. To a cooled ( $-78\text{ }^{\circ}\text{C}$ ) solution of  $\text{MeMgBr}$  (0.42 mL, 3.0 M in  $\text{Et}_2\text{O}$ , 1.24 mmol) in  $\text{Et}_2\text{O}$  (1.0 mL) was added a solution of aldehyde **29** (98 mg, 0.249 mmol) in  $\text{Et}_2\text{O}$  (1.4 mL) in a dropwise fashion via cannula. The mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 0.5 h, allowed to warm to  $25\text{ }^{\circ}\text{C}$ , and stirred for 1.5 h. A saturated aqueous  $\text{NH}_4\text{Cl}$  solution (50 mL) and  $\text{Et}_2\text{O}$  (50 mL) were added. The aqueous layer was separated and extracted with  $\text{Et}_2\text{O}$  ( $3 \times 50$  mL). The combined organic layers were dried ( $\text{MgSO}_4$ ), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 50%  $\text{Et}_2\text{O}$  in hexanes) to afford 94 mg (0.229 mmol, 92%) of the desired secondary alcohol as a colorless oil.

To a solution of the secondary alcohol (94 mg, 0.229 mmol) in  $\text{CH}_2\text{Cl}_2$  (2.55 mL) was added crushed 4 Å molecular sieves (100 mg). The resulting slurry was stirred at  $25\text{ }^{\circ}\text{C}$  for 10 min before the addition of NMO (73 mg, 0.619 mmol). After 10 min, TPAP (16.1 mg, 0.0459 mmol) was added and the greenish black slurry was stirred at  $25\text{ }^{\circ}\text{C}$  for 20 min. The black suspension was then filtered through a short plug of silica gel and washed with  $\text{Et}_2\text{O}$ . The filtrate was concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 25%  $\text{Et}_2\text{O}$  in hexanes) to give 87 mg (0.213 mmol, 93%) of ketone **30** as a colorless oil. Data for **30**:  $R_f$  0.30 (50%  $\text{Et}_2\text{O}$  in hexanes/PMA);  $[\alpha]_D^{22} -23.3$  ( $c$  1.53,  $\text{CH}_2\text{Cl}_2$ ); IR (thin film)  $1723\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  7.25 (m, 2H), 6.86 (m, 2H), 4.49 (AB<sub>q</sub>, 2H,  $J_{AB} = 10.7$  Hz,  $\Delta\nu_{AB} = 21.8$  Hz), 4.27 (m, 1H), 4.04 (dd, 1H,  $J = 7.7, 5.9$  Hz), 3.84 (d, 1H,  $J = 3.3$  Hz), 3.78 (s, 3H), 3.61 (ddd, 1H,  $J = 9.9, 7.4, 2.6$  Hz), 3.46 (t, 1H,  $J = 7.7$  Hz), 3.32 (s, 3H), 2.10 (s, 3H), 2.03 (tq, 1H,  $J = 7.0, 3.7$  Hz), 1.84 (ddd, 1H,  $J = 14.0, 8.5, 2.6$  Hz), 1.63 (q, 2H,  $J = 7.4$  Hz), 1.60 (q, 2H,  $J = 7.7$  Hz), 1.58 (m, 1H), 0.88 (t, 6H,  $J = 7.4$  Hz), 0.83 (d, 3H,  $J = 7.0$  Hz);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  210.3, 159.0, 130.4, 129.1, 113.7, 112.3, 87.4, 77.4, 73.0, 72.3, 70.5, 58.2, 55.1, 40.0, 36.4, 30.0, 29.7, 26.2, 9.9, 8.2, 7.8; HRMS (EI) exact mass calcd for  $\text{C}_{23}\text{H}_{36}\text{O}_6$  ( $\text{M}^+$ ) requires 408.2512, found 408.2525.

**(4R,5S,6S)-Methyl 7-[(1S)-3,3-Diethyl-2,4-dioxolanyl]-4-methoxy-6-[(4-methoxyphenyl)methoxy]-3,5-dimethylhept-2-enoate (31)**. To a solution of trimethyl phosphonoacetate (968 mg, 5.32 mmol) in THF (12.5 mL) was added NaH (112 mg, 95%, 4.43 mmol). The mixture was stirred at  $25\text{ }^{\circ}\text{C}$  for 0.5 h. A solution of ketone **30** (181 mg, 4.43 mmol) in THF (2.3 mL) was added dropwise via cannula. The mixture was stirred at  $25\text{ }^{\circ}\text{C}$  for 1 h and allowed to warm to  $60\text{ }^{\circ}\text{C}$  for 24 h. A saturated aqueous  $\text{NH}_4\text{Cl}$  solution (100 mL) was added to quench the reaction. The aqueous layer was separated and extracted with  $\text{Et}_2\text{O}$  ( $3 \times 100$  mL). The combined organic layers were dried ( $\text{MgSO}_4$ ), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 14% and 25%  $\text{Et}_2\text{O}$  in hexanes) to give 180 mg

(0.388 mmol, 87%) of the desired methyl ester **31** and 22 mg (0.054 mmol, 12%) of the recovered ketone **26** as colorless oils. Data for **31**:  $R_f$  0.45 (50%  $\text{Et}_2\text{O}$  in hexanes/PMA);  $[\alpha]_D^{22} -13.4$  ( $c$  1.28,  $\text{CH}_2\text{Cl}_2$ ); IR (thin film)  $1720, 1653, 1612\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{C}_6\text{D}_6$ , 300 MHz)  $\delta$  7.25 (m, 2H), 6.80 (m, 2H), 6.02 (s, 1H), 4.42 (AB<sub>q</sub>, 2H,  $J_{AB} = 11.0$  Hz,  $\Delta\nu_{AB} = 7.4$  Hz), 4.30 (m, 1H), 3.88 (dd, 1H,  $J = 7.7, 5.9$  Hz), 3.64 (ddd, 1H,  $J = 10.3, 5.9, 2.6$  Hz), 3.44 (s, 3H), 3.43 (d, 1H,  $J = 4.8$  Hz), 3.37 (t, 1H,  $J = 8.1$  Hz), 3.29 (s, 3H), 2.95 (s, 3H), 2.18 (d, 3H,  $J = 1.5$  Hz), 1.98 (m, 1H), 1.69 (q, 2H,  $J = 7.4$  Hz), 1.66 (q, 2H,  $J = 7.7$  Hz), 1.63 (m, 1H), 1.49 (m, 1H), 1.00 (t, 3H,  $J = 7.4$  Hz), 0.98 (d, 3H,  $J = 7.0$  Hz), 0.97 (t, 3H,  $J = 7.4$  Hz);  $^{13}\text{C NMR}$  ( $\text{C}_6\text{D}_6$ , 75 MHz)  $\delta$  166.4, 159.7, 156.9, 131.4, 129.4, 117.5, 114.1, 112.5, 87.1, 77.6, 73.9, 72.0, 70.9, 56.6, 54.8, 50.5, 39.1, 36.0, 30.5, 30.3, 15.3, 9.4, 8.6, 8.3; HRMS (EI) exact mass calcd for  $\text{C}_{26}\text{H}_{40}\text{O}_7$  ( $\text{M}^+$ ) requires 464.2774, found 464.2751.

**(4R,5S,6S)-7-[(1S)-3,3-Diethyl-2,4-dioxolanyl]-4-methoxy-6-[(4-methoxyphenyl)methoxy]-3,5-dimethylhept-2-enal (4)**. To a cooled solution ( $-78\text{ }^{\circ}\text{C}$ ) of ester **31** (67 mg, 0.144 mmol) in  $\text{Et}_2\text{O}$  (4.8 mL) was added DIBAL-H (0.722 mL, 1.0 M in hexane, 0.722 mmol) in a dropwise fashion. The mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 1 h and  $0\text{ }^{\circ}\text{C}$  for 1.5 h. A saturated aqueous potassium sodium tartrate solution (50 mL) and  $\text{Et}_2\text{O}$  (30 mL) were added. The mixture was stirred for 2 h until two clear layers formed. The aqueous layer was separated and extracted with  $\text{Et}_2\text{O}$  ( $3 \times 50$  mL). The combined organic layers were dried ( $\text{MgSO}_4$ ), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 33%  $\text{Et}_2\text{O}$  in hexanes) to give 60 mg (0.138 mmol, 96%) of the desired allylic alcohol as a colorless oil.  $R_f$  0.39 (50%  $\text{EtOAc}$  in hexanes).

To a solution of the allylic alcohol (60 mg, 0.318 mmol) in  $\text{CH}_2\text{Cl}_2$  (1.5 mL) was added crushed 4 Å molecular sieves (90 mg). The slurry was stirred at  $25\text{ }^{\circ}\text{C}$  for 10 min before the addition of NMO (32 mg, 0.275 mmol). After 10 min, TPAP (9.7 mg, 0.0275 mmol) was added and the greenish black slurry was stirred at  $25\text{ }^{\circ}\text{C}$  for 20 min. The black suspension was then filtered through a short plug of silica gel and washed with  $\text{Et}_2\text{O}$ . The filtrate was concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 25%  $\text{Et}_2\text{O}$  in hexanes) to afford 48.4 mg (0.112 mmol, 82%) of aldehyde **4** as a colorless oil. Data for aldehyde **4**:  $R_f$  0.37 (50%  $\text{Et}_2\text{O}$  in hexanes/PMA);  $[\alpha]_D^{22} +6.62$  ( $c$  1.36,  $\text{CH}_2\text{Cl}_2$ ); IR (thin film)  $1676, 1612\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{C}_6\text{D}_6$ , 300 MHz)  $\delta$  9.91 (d, 1H,  $J = 7.7$  Hz), 7.24 (m, 2H), 6.81 (m, 2H), 6.03 (d, 1H,  $J = 7.7$  Hz), 4.45 (AB<sub>q</sub>, 2H,  $J_{AB} = 11.4$  Hz,  $\Delta\nu_{AB} = 13.4$  Hz), 4.30 (m, 1H), 3.87 (dd, 1H,  $J = 7.7, 5.9$  Hz), 3.60 (ddd, 1H,  $J = 9.9, 5.9, 2.2$  Hz), 3.37 (d, 1H,  $J = 5.5$  Hz), 3.36 (t, 1H,  $J = 7.7$  Hz), 2.87 (s, 3H), 1.83 (m, 1H), 1.70 (q, 2H,  $J = 7.4$  Hz), 1.65 (q, 2H,  $J = 7.4$  Hz), 1.60 (m, 1H), 1.56 (d, 3H,  $J = 1.5$  Hz), 1.47 (m, 1H), 1.01 (t, 3H,  $J = 7.4$  Hz), 0.96 (t, 3H,  $J = 7.7$  Hz), 0.89 (d, 3H,  $J = 7.0$  Hz);  $^{13}\text{C NMR}$  ( $\text{C}_6\text{D}_6$ , 75 MHz)  $\delta$  189.5, 159.8, 158.4, 131.3, 129.3, 128.2, 114.1, 112.6, 86.5, 77.5, 73.6, 72.2, 70.8, 56.7, 54.8, 39.5, 36.1, 30.5, 30.3, 13.4, 9.4, 8.6, 8.4; HRMS (EI) exact mass calcd for  $\text{C}_{25}\text{H}_{38}\text{O}_6$  ( $\text{M}^+$ ) requires 434.2668, found 434.2683.

**2-Methyl-3-[4-methyl(3,5-oxazolyl)]prop-2-en-1-ol (33)**. To a cooled ( $-78\text{ }^{\circ}\text{C}$ ) solution of aldehyde **32** (286 mg, 1.89 mmol) in  $\text{Et}_2\text{O}$  (6.4 mL) was added DIBAL-H (1.0 M in hexane, 5.68 mL, 5.68 mmol) in a dropwise manner over 10 min. The mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 2 h and treated with MeOH (2.0 mL). A saturated aqueous potassium sodium tartrate solution (10 mL) was added. The mixture was stirred until two clear layers formed. The aqueous phase was separated and extracted with  $\text{EtOAc}$  ( $3 \times 30$  mL). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography (silica gel, elution with 50%  $\text{EtOAc}$  in hexanes) afforded 272 mg (1.78 mmol, 94%) of allylic alcohol **33** as a colorless oil. Data for **33**:  $R_f$  0.14 (50%  $\text{EtOAc}$  in hexanes/PMA); IR (thin film)  $3324$  (br),  $1583\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  7.43 (s, 1H), 6.27 (m, 1H), 3.59 (bs, 1H), 2.42 (s, 3H), 1.86 (s, 3H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  160.7, 140.0, 137.4, 134.9, 113.5, 67.5, 15.9, 13.5; HRMS (EI) exact mass calcd for  $\text{C}_8\text{H}_{11}\text{NO}_2$  ( $\text{M}^+$ ) requires 153.0790, found 153.0793.

**4-(3-Chloro-2-methylprop-1-enyl)-2-methyl-1,3-oxazole (34).** To a cooled (0 °C) solution of allylic alcohol **33** (570 mg, 3.73 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (18.0 mL) was added Et<sub>3</sub>N (1.04 mL, 7.45 mmol), followed by methanesulfonyl chloride (0.433 mL, 5.59 mmol). The reaction mixture was warmed to room temperature and allowed to stir for 8 h. The reaction mixture was quenched with a saturated aqueous NaCl solution (50 mL). The aqueous layer was extracted with Et<sub>2</sub>O (3 × 50 mL). The combined organic layers were dried (MgSO<sub>4</sub>), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, elution with 14% and 20% Et<sub>2</sub>O in hexanes) to afford 410 mg (2.39 mmol, 64%) of chloride **34** as a colorless solid. Data for chloride **34**: *R*<sub>f</sub> 0.41 (50% Et<sub>2</sub>O in hexanes); IR (thin film) 1585 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.49 (s, 1H), 6.30 (s, 1H), 4.12 (s, 2H), 2.43 (s, 3H), 2.04 (d, 3H, *J* = 1.1 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ 161.0, 137.4, 136.2, 135.3, 118.9, 52.3, 16.8, 13.8, 13.7; HRMS (EI) exact mass calcd for C<sub>8</sub>H<sub>10</sub>NOCl (M<sup>+</sup>) requires 171.0451, found 171.0454.

**Dimethoxy[2-methyl-3-(4-methyl(3,5-oxazolyl)prop-2-enyl]phosphine 1-Oxide (3).** Dimethyl phosphite (0.89 mL, 9.69 mmol) was added slowly to a suspension of NaH (245 mg, 95%, 9.69 mmol) in THF (16.0 mL). This mixture was stirred at room temperature for 2 h to give a clear solution, which was transferred via cannula into a solution of chloride **34** (373 mg, 2.18 mmol) in THF (1.75 mL). The resulting mixture was heated to 45 °C for 1.5 h. A saturated aqueous NH<sub>4</sub>Cl (50 mL) solution was added to quench the reaction. The aqueous layer was separated and extracted with Et<sub>2</sub>O (3 × 50 mL). The combined organic layers were dried (MgSO<sub>4</sub>), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, gradient elution with 50% Et<sub>2</sub>O in hexanes and 50% acetone in hexanes) to give 386 mg (1.58 mmol, 73%) of the phosphonate **3** as a yellow oil. Data for **3**: *R*<sub>f</sub> 0.42 (acetone/PMA); IR (thin film) 1586, 1250, 1105, 1030 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.39 (d, 1H, *J* = 1.8 Hz), 6.08 (d, 1H, *J* = 5.9 Hz), 3.68 (d, 6H, *J* = 11.0 Hz), 2.66 (d, 2H, *J* = 22.8 Hz), 2.37 (s, 3H), 2.02 (dd, 3H, *J* = 4.0, 0.7 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ 160.6, 137.3, 135.2, 130.7, 130.5, 119.0, 118.7, 52.6, 52.5, 37.7, 35.9, 19.8, 13.5; HRMS (EI) exact mass calcd for C<sub>10</sub>H<sub>16</sub>NO<sub>4</sub>P (M<sup>+</sup>) requires 245.0817, found 245.0807.

**(4*S*,2*S*,3*R*)-1-[[1*S*]-3,3-Diethyl-2,4-dioxolanyl]methyl]-3-methoxy-1-[(4-methoxyphenyl)methoxy]-2,4,8-trimethyl-9-[4-methyl(3,5-oxazolyl)]nona-4,6,8-triene (35).** To a solution of <sup>t</sup>BuOK (30 mg, 0.266 mmol) in DME (0.21 mL) was added a solution of phosphonate **3** (33 mg, 0.133 mmol) and aldehyde **4** (19.2 mg, 0.0442 mmol) in DME (0.3 mL) in a dropwise fashion at 0 °C. The mixture was stirred at 0 °C for 2 h, allowed to warm to 60 °C, and stirred for 0.5 h. A saturated aqueous NH<sub>4</sub>Cl solution (50 mL) was added, and the mixture was extracted with Et<sub>2</sub>O (3 × 50 mL). The combined organic layers were dried (MgSO<sub>4</sub>), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 20% Et<sub>2</sub>O in hexanes) to give 13.5 mg (0.0244 mmol, 55%) of the desired triene **35** as a colorless oil. Data for triene **35**: *R*<sub>f</sub> 0.31 (50% Et<sub>2</sub>O in hexanes/PMA); [α]<sub>D</sub><sup>20</sup> +36.2 (*c* 0.90, CH<sub>2</sub>Cl<sub>2</sub>); IR (thin film) 1612, 1514 cm<sup>-1</sup>; <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>, 300 MHz) δ 7.25 (m, 2H), 7.07 (s, 1H), 6.79 (m, 2H), 6.68 (dd, 1H, *J* = 15.1, 10.7 Hz), 6.45 (d, 1H, *J* = 15.4 Hz), 6.40 (s, 1H), 6.17 (d, 1H, *J* = 10.7 Hz), 4.42 (AB<sub>q</sub>, 2H, *J*<sub>AB</sub> = 11.0 Hz, Δ*v*<sub>AB</sub> = 48.4 Hz), 4.32 (m, 1H), 3.93 (dd, 1H, *J* = 8.1, 6.3 Hz), 3.65 (dt, 1H, *J* = 8.1, 4.0 Hz), 3.46 (t, 1H, *J* = 8.1 Hz), 3.35 (d, 1H, *J* = 7.7 Hz), 3.29 (s, 3H), 3.13 (s, 3H), 2.32 (s, 3H), 2.29 (m, 1H), 1.97 (s, 3H), 1.72 (d, 3H, *J* = 0.7 Hz), 1.70 (q, 2H, *J* = 7.7 Hz), 1.69 (m, 2H), 1.62 (q, 2H, *J* = 7.4 Hz), 1.22 (d, 3H, *J* = 7.0 Hz), 1.01 (t, 3H, *J* = 7.4 Hz), 0.94 (t, 3H, *J* = 7.4 Hz); <sup>13</sup>C NMR (C<sub>6</sub>D<sub>6</sub>, 75 MHz) δ 161.0, 159.8, 140.0, 138.4, 137.2, 13.6, 136.2, 131.6, 129.6, 124.4, 120.8, 114.2, 112.4, 89.1, 77.3, 74.4, 71.7, 71.2, 56.2, 54.7, 38.6, 35.1, 30.8, 30.5, 30.3, 14.5, 13.5, 12.5, 10.5, 8.8, 8.6; HRMS (EI) exact mass calcd for C<sub>33</sub>H<sub>47</sub>NO<sub>6</sub> (M<sup>+</sup>) requires 553.3403, found 553.3382; exact mass calcd for C<sub>33</sub>H<sub>48</sub>NO<sub>6</sub> (M<sup>+</sup> + H) requires 554.3481, found 554.3437; exact mass calcd for C<sub>31</sub>H<sub>42</sub>NO<sub>6</sub> (M<sup>+</sup> - C<sub>2</sub>H<sub>5</sub>) requires 524.3012, found 524.3047.

**trans-2,6-Dimethoxytetrahydropyran-4-carboxylic Acid Methyl Ester (36).** Through a homogeneous solution of 1,6-hexadiene-4-carboxylic acid ethyl ester (**8**) (12.5 mL, *d* 0.86 g/cm<sup>3</sup>, 66.5 mmol) and anhydrous MeOH (500 mL) in a two-necked 1-L round-bottom flask fitted with a gas dispersion tube and drying tube was bubbled ozone (pressure 8 psig, flow 1.6–1.8 L/min, potential 100V) at -78 °C until the solution turned blue. Ozonation was ceased, and the solution was purged with dry nitrogen for 20 min, whereupon DMS (20 mL, 272 mmol) and *p*-TsOH (3.16 g, 16.6 mmol) were added consecutively. The reaction mixture was then warmed to room temperature, stirred for 12 h, and then heated to reflux for 17 h. All MeOH was removed by rotary evaporation and was replaced with MeCN (750 mL) having a 0.02% water content as determined by Karl Fisher analysis. The resultant mixture was stirred for 12 h, concentrated by rotary evaporation, taken up in toluene (750 mL), and then concentrated to an oil, which was submitted immediately to flash chromatography (elution with 20% ether in hexanes) to yield 9.88 g (73%) of the dimethoxytetrahydropyran **36** as a clear, colorless oil. Data for **36**: *R*<sub>f</sub> 0.24 (40% ether in hexanes/PAA); IR (thin film) 1737 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.93 (dd, 1H, *J* = 5.7, 2.9 Hz), 4.72 (dd, 1H, *J* = 9.2, 2.6 Hz), 3.69 (s, 3H), 3.49 (s, 3H), 3.44 (s, 3H), 2.94 (tt, 1H, *J* = 11.7, 4.1 Hz), 2.07–2.14 (m, 1H), 1.90–1.97 (m, 1H), 1.76–1.86 (m, 1H), 1.58–1.69 (m, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 174.40, 98.29, 96.50, 55.95, 54.82, 51.85, 34.82, 32.83, 31.51; HRMS (FAB) exact mass calcd for C<sub>9</sub>H<sub>16</sub>O<sub>5</sub>Na (M<sup>+</sup> + Na) requires 227.0896, found 227.0903.

**trans-2,6-Dimethoxytetrahydropyran-4-carboxaldehyde (37).** To a 500-mL round-bottom flask (to obtain optimal selectivity in this reaction, it was absolutely imperative to ensure maximum cooling by using a round-bottom flask which was at least four times the volume of the total reaction mixture) charged with methyl ester **36** (5.00 mL, *d* 1.12 g/cm<sup>3</sup>, 27.5 mmol), anhydrous hexanes (29 mL), and anhydrous toluene (58 mL) at -78 °C was added over 25 min via syringe pump 1.0 M DIBAL-H (29 mL, 29.0 mmol) in hexanes. The cold reaction mixture was quenched with 2-propanol (2.5 mL) immediately following the completed addition (addition time should be restricted to no more than 30 min, followed by immediate quench, to avoid the formation of an unsymmetrical dimeric product), whereupon the cold bath was removed, and a 30% aqueous sodium-potassium tartrate solution (120 mL) was added. The resultant mixture was stirred vigorously for 30 min, poured into a separatory funnel, and extracted with EtOAc (200 mL). The aqueous phase was saturated with solid NaCl and then extracted further with EtOAc (3 × 200 mL). The combined organic extracts were washed with brine (200 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to an oil. The crude aldehyde was taken up in 50% ether in petroleum ether (200 mL) and passed through a short pad of silica gel via vacuum filtration directly into an oven-dried round-bottom flask. The pad was then eluted with 50% ether/petroleum ether (200 mL), and the resultant solution (alcohol-free) was concentrated to afford 4.447 g (93%) of the aldehyde **37** as a pale yellow oil which was used without further purification. Data for **37**: *R*<sub>f</sub> 0.17 (40% ether-hexanes/PAA); IR (thin film) 1725 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.61 (s, 1H), 4.85–4.87 (m, 1H), 4.77 (dd, 1H, *J* = 7.4, 2.8 Hz), 3.44 (s, 3H), 3.43 (s, 3H), 2.76–2.84 (m, 1H), 2.09 (1H, ddd, *J* = 13.2, 4.7, 2.7 Hz), 1.83–1.85 (m, 2H), 1.63 (ddd, 1H, *J* = 13.2, 9.7, 7.3 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 201.82, 97.25, 96.89, 55.59, 55.11, 42.33, 29.95, 28.82; HRMS (FAB) exact mass calcd for C<sub>8</sub>H<sub>14</sub>O<sub>4</sub>Na (M<sup>+</sup> + Na) requires 197.0790, found 197.0814.

**trans-(2,6-Dimethoxytetrahydropyran-4-yl)acetaldehyde (39).** To a 250-mL round-bottom flask (argon atmosphere) charged with a thick slurry of *N*-(morpholino)methylidiphenylphosphine oxide (**38**) (8.22 g, 27.3 mmol) and THF (60 mL) at 0 °C was added via syringe pump over 20 min 2.5 M *n*-butyllithium (10.5 mL, 26.1 mmol) in hexanes. The resultant orange anion, which became less heterogeneous upon continued addition, was stirred an additional 30 min upon completed addition. The temperature of the resultant dark red homogeneous solution was lowered to -10 °C, and then the aldehyde **37** (3.48 g, 20.0 mmol) was added as a



homogeneous solution in THF (10 mL) via syringe over 25 min. Upon completed addition, the reaction mixture was stirred for 1 h at  $-5^{\circ}\text{C}$ , whereupon it was concentrated and then partitioned between  $\text{CH}_2\text{Cl}_2$  (150 mL) and saturated  $\text{NH}_4\text{Cl}$  (100 mL). The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (150 mL), and the combined organic extracts were washed with brine (100 mL) and dried over  $\text{Na}_2\text{SO}_4$  and Norit. This solution was filtered through Celite directly into an oven-dried round-bottom flask, concentrated to an amorphous solid, taken up in ether (300 mL), and finally concentrated to a foam. Following residual solvent removal under high vacuum, the intermediate 1,2-adduct was dissolved in THF (25 mL) (on a larger scale, a solution of the 1,2-adduct in THF sometimes forms a precipitate of the pure compound during addition) and added to a 250-mL round-bottom flask containing a heterogeneous mixture of potassium hydride (3.13 g, 27.3 mmol), as a 25% suspension in mineral oil (prewashed,  $3 \times 20$  mL anhydrous hexane), in THF (75 mL) at  $0^{\circ}\text{C}$ . The resultant mixture was warmed to room temperature and then stirred for 12 h, whereupon it was diluted to 250 mL with THF and vacuum filtered through a short pad of silica gel. The pad was eluted with THF (100 mL), and the resultant solution was concentrated to a solid material which was adsorbed onto silica gel and then submitted to flash chromatography (solid load, gradient elution, 30–35–40% ether in petroleum ether) to afford 3.17 g (74%) of the homologated aldehyde **39** (the homologated aldehyde must be used immediately or frozen in a benzene matrix to prevent decomposition) as a clear, colorless oil. Data for **39**:  $R_f$  0.18 (50% ether–hexanes/PAA); IR (thin film)  $1723\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.73 (t, 1H, 3.51, 1.76 Hz), 4.86 (dd, 1H,  $J = 3.3$ , 1.3 Hz), 4.71 (dd, 1H,  $J = 9.6$ , 2.5 Hz), 3.47 (s, 3H), 3.41 (s, 3H), 2.53–2.57 (m, 1H), 2.34–2.36 (m, 2H), 1.87–1.93 (m, 1H), 1.72–1.77 (m, 1H), 1.32–1.39 (m, 1H), 1.15–1.23 (m, 1H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  200.96, 98.78, 96.71, 56.07, 54.73, 49.99, 36.89, 35.44, 24.03; HRMS (FAB) exact mass calcd for  $\text{C}_9\text{H}_{16}\text{O}_4\text{Na}$  ( $\text{M}^+ + \text{Na}$ ) requires 211.0947, found 211.0913.

**trans-(2R,3R)-1-(2,6-Dimethoxytetrahydropyran-4-yl)-3-methylpent-4-en-2-ol (41)**. To a 500-mL round-bottom flask charged with 0.84 M (*Z*)-crotylboronate (**40**) in toluene (29 mL, 24.3 mmol), activated 4 Å molecular sieves (2.50 g), and toluene (30 mL) was added via syringe pump over 1 h a solution of aldehyde **39** (3.52 g, 18.7 mmol) in toluene (12 mL) at  $-78^{\circ}\text{C}$ . Upon completed addition, the reaction mixture was transferred to a  $-78^{\circ}\text{C}$  CyroCool for 6 h, whereupon it was quenched with 2.5 M NaOH (21 mL). The resultant mixture was warmed to room temperature, stirred vigorously for 1 h, and vacuum filtered through a short pad of Celite, which was washed with EtOAc (100 mL). The biphasic mixture was partitioned with EtOAc (100 mL) and then the aqueous phase was extracted with EtOAc ( $2 \times 100$  mL). The combined organic extracts were washed with brine (50 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered through Celite, and concentrated to a viscous residue which was submitted to flash chromatography (elution with 40% ether in petroleum ether), yielding 4.51 g (99%) of the homoallyl alcohol **41** as a clear, colorless oil. Note: The following NMR spectra are representative of ring diastereomers *R,R* and *S,S* which are manifest via complex overlapping resonances in the  $^1\text{H NMR}$  and by doubling of signals in the  $^{13}\text{C NMR}$ . Data for **41**:  $R_f$  0.13 (50% ether in hexanes/PAA);  $[\alpha]_D^{25} + 17.4^{\circ}$  ( $c$  1.42,  $\text{CH}_2\text{Cl}_2$ ); IR (thin film)  $3447$ ,  $1639\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.69–5.79 (m, 1H), 5.07–5.08 (m, 1H), 5.03–5.07 (m, 1H), 4.85–4.87 (m, 1H), 4.68 (ddd, 1H,  $J = 9.7$ , 3.8, 2.1 Hz), 3.54–3.62 (m, 1H), 3.47 (s, 3H), 3.40 (s, 3H), 2.14–2.27 (m, 2H), 1.02–1.98 (m, 7H), 1.00 (d, 3H,  $J = 6.9$  Hz);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  140.71/140.57, 115.60/115.44, 99.30/99.25, 97.22/97.17, 71.55/71.50, 56.08/56.03, 54.68/54.66, 43.87/43.75, 40.74/40.49, 38.08, 36.80/36.68, 35.42, 26.07/25.99; HRMS (FAB) exact mass calcd for  $\text{C}_{13}\text{H}_{24}\text{O}_4\text{Na}$  ( $\text{M}^+ + \text{Na}$ ) requires 267.1573, found 267.1619.

**trans-(2R,3R)-4-[2-(tert-Butyldimethylsiloxy)-3-methylpent-4-enyl]-2,6-dimethoxytetrahydropyran (42)**. To a 100-mL round-bottom flask charged with TBDMSCl (9.53 g, 63.2 mmol), imidazole (6.46 g, 94.8 mmol), and DMF (22 mL), was added the alcohol **41** (7.72 g, 31.6 mmol) as a solution in

DMF (10 mL). The reaction mixture was stirred at room temperature for 72 h, poured into water (250 mL), and partitioned with EtOAc (500 mL). The organic phase was extracted further with water ( $3 \times 250$  mL), diluted with hexanes (100 mL), washed consecutively with water (100 mL) and brine (100 mL), dried over  $\text{Na}_2\text{SO}_4$ , and finally filtered through Celite. Subjected to flash chromatography (gradient elution, 7.5–10% ether in petroleum ether) afforded 10.72 g (95%) of TBS ether **42** as a clear, colorless oil. Note: The following NMR spectra are representative of ring diastereomers *R,R* and *S,S* which are manifest via complex overlapping resonances in the  $^1\text{H NMR}$  and by doubling of signals in the  $^{13}\text{C NMR}$ . Data for **42**:  $R_f$  0.50 (40% ether in hexanes/PAA);  $[\alpha]_D^{25} + 23.2^{\circ}$  ( $c$  1.91,  $\text{CH}_2\text{Cl}_2$ ); IR (film)  $1640\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.83–5.92 (m, 1H), 4.96–5.02 (m, 2H), 4.84–4.86 (m, 1H), 4.62–4.67 (m, 1H), 3.63–3.67 (m, 1H), 3.49 (s, 3H), 3.40 (s, 3H), 2.27–2.33 (m, 1H), 1.91–2.10 (m, 1H), 1.63–1.89 (m, 2H), 0.98–1.34 (m, 4H), 0.93 (d, 3H,  $J = 6.8$  Hz), 0.88 (s, 9H), 0.03–0.04 (m, 6H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  141.28/140.98, 113.95/113.88, 99.32/99.29, 97.05, 72.91/72.83, 55.96, 54.62/54.60, 42.58/42.32, 40.57/40.19, 37.95/37.32, 36.61/36.07, 25.87, 25.41/25.20, 14.11/13.94, -4.28, -4.36, -4.38; HRMS (FAB) exact mass calcd for  $\text{C}_{19}\text{H}_{37}\text{O}_4\text{Si}$  ( $\text{M}^+ - \text{H}$ ) requires 357.2461, found 357.2520.

**(2R,3R,4R)-4-(tert-Butyldimethylsiloxy)-5-(trans-2,6-dimethoxytetrahydropyran-4-yl)-3-methylpentane-1,2-diol (43)**. To a 25-mL round-bottom flask charged with NMO (182 mg, 1.55 mmol) was added consecutively acetone (10.0 mL), 4% aqueous  $\text{OsO}_4$  (432  $\mu\text{L}$ , 0.071 mmol), and water (331  $\mu\text{L}$ , 18.4 mmol) at  $0^{\circ}\text{C}$ . This mixture was cooled to  $-5^{\circ}\text{C}$  and then treated with a solution of the olefin **42** (507 mg, 1.41 mmol) in acetone (4.0 mL). The reaction mixture was stirred at  $-5^{\circ}\text{C}$  for 15 min, warmed to room temperature, and stirred for 12 h. It was then diluted with EtOAc (200 mL), treated with saturated  $\text{Na}_2\text{S}_2\text{O}_3$  (28 mL), and stirred vigorously for approximately 15 min. The phases were separated, and the aqueous phase was stirred vigorously with EtOAc (100 mL) for 15 min. The phases were separated, and the combined organic extracts were brine washed and dried over  $\text{Na}_2\text{SO}_4$ . Vacuum filtration through a short pad of silica gel followed by concentration provided 533 mg (96%) of the diol **43** as a light tan viscous oil, which was used without further purification. Note: The following NMR spectra are representative of ring diastereomers *R,R* and *S,S* which are manifest via complex overlapping resonances in the  $^1\text{H NMR}$  and by doubling of signals in the  $^{13}\text{C NMR}$ . In addition, there is a 1:1 ratio of alcohol diastereomers. Data for **43**:  $R_f$  0.28 (ether/PAA);  $[\alpha]_D^{25} + 4.62^{\circ}$  ( $c$  1.73,  $\text{CH}_2\text{Cl}_2$ ); IR (thin film)  $3446\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.85 (br s, 1H), 4.62–4.69 (m, 1H), 4.28 (d, 1H,  $J = 20.8$  Hz), 3.85–3.90 (m, 1H), 3.56–3.70 (m, 2H), 3.47 (s, 3H), 3.38–3.39 (m, 3H), 1.00–2.32 (m, 10H), 0.88 (s, 9H), 0.75 (dd, 3H,  $J = 7.0$ , 1.3 Hz), 0.06–0.11 (m, 6H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  99.12, 97.03, 96.89, 73.85, 73.77, 73.73, 73.55, 64.81, 55.98, 54.66, 54.62, 54.58, 38.77, 38.67, 38.31, 38.11, 36.95, 36.67, 35.66, 25.73, 25.37, 25.19, 17.85, 12.76, 12.59, -4.39, -4.69, -4.80; HRMS (FAB) exact mass calcd for  $\text{C}_{19}\text{H}_{40}\text{O}_6\text{SiNa}$  ( $\text{M}^+ + \text{Na}$ ) requires 415.2492, found 415.2487.

**(2R,3R)-3-(tert-Butyldimethylsiloxy)-4-(trans-2,6-dimethoxytetrahydropyran-4-yl)-2-methylbutyraldehyde (44)**. To a 50-mL round-bottom flask charged with  $\text{Pb}(\text{OAc})_4$  (944 mg, 2.13 mmol),  $\text{Na}_2\text{CO}_3$  (414 mg, 3.90 mmol), activated 4 Å molecular sieves (1.0 g), and  $\text{CH}_2\text{Cl}_2$  (13 mL) at  $-10^{\circ}\text{C}$  was added dropwise diol **43** (519 mg, 1.77 mmol) as a solution in  $\text{CH}_2\text{Cl}_2$  (5 mL). The reaction mixture was stirred between  $-10$  and  $0^{\circ}\text{C}$  for 1 h, diluted to 50 mL with ether, and poured into a rapidly stirring mixture of EtOAc (50 mL) and pH 7 phosphate buffer (75 mL). The resultant brown heterogeneous mixture was stirred for 15 min, vacuum filtered through a short pad of Celite, and washed with EtOAc (100 mL) and then ether (100 mL). The two phases were separated, and the aqueous phase was extracted by vigorous stirring with EtOAc ( $2 \times 100$  mL). The combined organic extracts were brine washed, dried over  $\text{Na}_2\text{SO}_4$ , vacuum filtered through a short pad of Florisil, and then concentrated to give 433 mg (94%) of the aldehyde **44** as a yellow oil, which was used



without further purification. Note: The following NMR spectra are representative of ring diastereomers *R,R* and *S,S* which are manifest via complex overlapping resonances in the  $^1\text{H}$  NMR and by doubling of signals in the  $^{13}\text{C}$  NMR. Data for **44**:  $R_f$  0.34 (50% ether in hexanes/PAA);  $[\alpha]_D^{25} + 24.8^\circ$  ( $c$  2.18,  $\text{CH}_2\text{Cl}_2$ ); IR (thin film)  $1727\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.74/9.75 (d, 1H,  $J = 3.29$  Hz), 4.86 (br s, 1H), 4.65 (dt, 1H,  $J = 9.66, 2.64$  Hz), 4.20–4.23 (m, 1H), 3.48 (s, 3H), 3.40 (s, 3H), 2.38–2.47 (m, 1H), 1.70–2.06 (m, 3H), 1.03–1.47 (m, 8H), 0.84/0.85 (s, 9H), 0.06 (s, 3H), 0.01/0.03 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  205.04/205.00, 99.09/99.07, 96.87/96.84, 69.04/68.89, 56.09/56.04, 54.70/54.68, 51.03/50.91, 41.30/41.13, 37.50/37.36, 36.16/36.04, 25.72, 25.64/25.53, 17.97, –4.25, –4.34/–4.58, –4.64; HRMS (FAB) exact mass calcd for  $\text{C}_{18}\text{H}_{36}\text{O}_5\text{SiNa}$  ( $\text{M}^+ + \text{Na}$ ) requires 383.2230, found 383.2273.

**(E)-(2*R*,3*R*)-4-[2-(*tert*-Butyldimethylsilyloxy)-3-methyl-5-trimethylsilylpent-4-enyl]-*trans*-2,6-dimethoxytetrahydropyran (45).** To a 200-mL round-bottom flask charged with anhydrous  $\text{CrCl}_2$  (6.19 g, 50.3 mmol) was added THF (36 mL) at room temperature, resulting in an exotherm. This heterogeneous mixture was stirred for 1 h and then treated with DMF (3.90 mL, 50.3 mmol), resulting in the formation of an extremely thick mixture which thinned out after 45 min, whereupon a solution of  $\text{Me}_3\text{SiCHBr}_2$  (1.50 mL,  $d$  1.57  $\text{g}/\text{cm}^3$ , 9.59 mmol) and aldehyde **44** (1.73 g, 4.79 mmol) in THF (18 mL) was added dropwise. The flask was then covered completely with aluminum foil, and anhydrous LiI (2.57 g, 19.2 mmol) as a solution in THF (18 mL) was added at room temperature over 5 min. The reaction mixture was then stirred in the dark for 18 h, whereupon TLC analysis of the reaction mixture indicated the presence of some remaining starting material. The flask was, therefore, immersed in an ultrasound bath for 2 h (sonication of the reaction mixture should be limited to a maximum of 2 h to avoid excessive loss of product due to  $\beta$ -elimination of the OTBS group) over which time the water temperature increased from 24.1 to 35.0  $^\circ\text{C}$ . The mixture was then diluted with ether (200 mL) and poured into a vigorously stirring mixture of ether (400 mL) and water (400 mL). The aqueous phase was extracted further with ether ( $2 \times 400$  mL) by vigorous "stir-partitioning". The combined organic extracts were diluted with hexanes (200 mL), washed with water (200 mL) followed by brine (200 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered through Celite, and concentrated to a light tan oil, which was submitted to flash chromatography (elution with 5% ether in petroleum ether), affording 1.2125 g (67%) of (*E*)-vinylsilane **45** as a clear, colorless oil. Note: The following NMR spectra are representative of ring diastereomers *R,R* and *S,S* which are manifest via complex overlapping resonances in the  $^1\text{H}$  NMR and by doubling of signals in the  $^{13}\text{C}$  NMR. Data for **45**:  $R_f$  0.35 (20% ether in hexanes/PAA);  $[\alpha]_D^{25} + 22.4^\circ$  ( $c$  0.891,  $\text{CH}_2\text{Cl}_2$ ); IR (thin film) 2953, 2896, 1155, 1097, 1021, 1006  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.02–6.09 (m, 1H), 5.58–5.63 (m, 1H), 4.85–4.86 (m, 1H), 4.62–4.67 (m, 1H), 3.67–3.71 (m, 1H), 3.49 (d, 3H,  $J = 2.9$  Hz), 3.40 (s, 3H), 2.24–2.29 (m, 1H), 2.02–2.06 (m, 1H), 1.67–1.77 (m, 1H), 0.96–1.38 (m, 2H), 0.92 (d, 3H,  $J = 6.8$  Hz), 0.87 (d, 9H,  $J = 2.4$  Hz), 0.00–0.45 (m, 18H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  150.07/149.68, 128.91/128.82, 99.36/99.34, 97.10/97.04, 72.78/72.74, 56.06/56.04, 54.67, 44.70/44.40, 41.26/40.88, 37.75/37.53, 36.52/36.31, 25.92, 25.56/25.34, 18.12, –1.19, –4.20, –4.26, –4.35; HRMS (FAB) exact mass calcd for  $\text{C}_{22}\text{H}_{45}\text{O}_4\text{Si}_2$  ( $\text{M}^+ - \text{H}$ ) requires 429.2856, found 429.2986.

**(E)-(2*R*,3*R*)-1-(*trans*-2,6-Dimethoxytetrahydropyran-4-yl)-3-methyl-5-trimethylsilylpent-4-en-2-ol (46).** To a 50-mL round-bottom flask containing TBS ether **45** (1.28 g, 3.00 mmol) was added 1.0 M TBAF (20.8 mL, 20.8 mmol) in THF at 0  $^\circ\text{C}$ , whereupon the mixture was slowly warmed to room temperature and stirred for 12 h. The reaction mixture was diluted with ether (20 mL) and then poured into a rapidly stirring mixture of 33%  $\text{CH}_2\text{Cl}_2$ -ether (400 mL) and saturated  $\text{NH}_4\text{Cl}$  (100 mL). The two phases were separated, and the aqueous phase was again "stir-partitioned" with 33%  $\text{CH}_2\text{Cl}_2$ -ether ( $3 \times 400$  mL). The combined organic extracts were washed with brine (100 mL), dried over  $\text{Na}_2\text{SO}_4$ , concentrated to a solid-oil mixture, taken up in benzene (100 mL), passed

through a short pad of  $\text{Na}_2\text{SO}_4$ , concentrated to a light tan oil, filtered through Celite, and submitted to flash chromatography (elution with 50% ether in petroleum ether) to provide 917 mg (98%) of homoallyl alcohol **46** as a pale yellow viscous oil. Data for **46**:  $R_f$  0.19 (50% ether in hexanes/PAA);  $[\alpha]_D^{25} + 22.2^\circ$  ( $c$  0.898,  $\text{CH}_2\text{Cl}_2$ ); IR (thin film) 3450, 1613  $\text{cm}^{-1}$ . Note: The following NMR spectra are representative of ring diastereomers *R,R* and *S,S* which are manifest via complex overlapping resonances in the  $^1\text{H}$  NMR and by doubling of signals in the  $^{13}\text{C}$  NMR.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.90–5.98 (m, 1H), 5.68–5.73 (m, 1H), 4.86–4.88 (m, 1H), 4.66–4.70 (m, 1H), 3.58–3.61 (m, 1H), 3.48 (s, 3H), 3.41 (s, 3H), 2.15–2.25 (m, 2H), 1.95–1.97 (m, 1H), 1.72–1.89 (m, 2H), 1.54 (br s, 1H), 1.05–1.38 (m, 4H), 0.99 (d, 3H,  $J = 6.8$  Hz), 0.04 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  148.62/148.44, 131.33/131.08, 99.31/99.26, 97.22/97.20, 71.39/71.37, 56.09/56.03, 54.69/54.67, 46.05/45.83, 40.94/40.70, 38.08, 36.87/36.68, 35.51, 26.10/26.02, 13.87/13.64, –1.20; HRMS (FAB) exact mass calcd for  $\text{C}_{16}\text{H}_{32}\text{O}_4\text{SiNa}$  ( $\text{M}^+ + \text{Na}$ ) requires 339.1968, found 339.1933.

**(E)-(2*R*,4*S*,6*R*)-6-[(*R*)-3-But-1-enyltrimethylsilyl-4-(2,2-dimethoxyethyl)]-2-methoxytetrahydropyran (47).** To a 100-mL round-bottom flask fitted with a reflux condenser and charged with homoallyl alcohol **46** (702 mg, 2.22 mmol), CSA (51.5 mg, 0.222 mmol), and benzene (44 mL) at room temperature was added 2,2-dimethoxypropane (2.73 mL, 22.2 mmol). The resultant mixture was heated to 80  $^\circ\text{C}$  and stirred for a total of 22 h, whereupon it was concentrated to a dark brown residue which was treated with hexanes (200 mL) and then filtered through a plug of glass wool. The filtrate was concentrated via rotary evaporation, and the crude product was submitted to flash chromatography (elution with 10% ether-hexanes) to give 507 mg of a mixture of stereoisomers. The stereoisomerically impure mixture was dissolved in hexanes (2.0 mL) and injected onto a 41.4-mm i.d. Dynamax Si 83-141-C HPLC column fitted with a Si 83-141-G guard module (elution with 4% EtOAc in hexanes) running at 30 mL/min, using two channels of UV (254 and 280 nm), and collecting 144 fractions at a rate of 1 fraction per min. Concentration of the desired fractions and removal of residual solvent in vacuo afforded 304 mg (41%) of the rearrangement product **47** as a pale yellow oil. Data for **47**:  $R_f$  0.29 (15% EtOAc in hexanes/PAA);  $[\alpha]_D^{25} - 45.0^\circ$  ( $c$  1.00,  $\text{CH}_2\text{Cl}_2$ ); IR (thin film) 2944, 2827, 1612, 1126, 1057  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.94 (dd, 1H,  $J = 18.9, 7.5$  Hz), 5.67 (dd, 1H,  $J = 18.7, 1.1$  Hz), 4.74 (d, 1H,  $J = 3.1$  Hz), 4.43 (t, 1H,  $J = 5.7$  Hz), 3.52 (ddd, 1H,  $J = 11.4, 6.8, 2.0$  Hz), 3.32 (s, 3H), 3.30 (s, 3H), 3.28 (s, 3H), 2.15–2.20 (m, 1H), 1.84–2.04 (m, 1H), 1.63–1.78 (m, 2H), 1.45–1.49 (m, 1H), 1.22–1.30 (m, 1H), 1.05 (d, 3H,  $J = 6.6$  Hz), 0.94 (q, 2H,  $J = 11.9$  Hz), 0.04 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  149.14, 129.80, 102.52, 98.45, 71.53, 54.28, 52.79, 52.27, 45.58, 39.69, 36.61, 35.66, 26.15, 15.37, –1.15; HRMS (FAB) exact mass calcd for  $\text{C}_{17}\text{H}_{34}\text{O}_4\text{SiNa}$  ( $\text{M}^+ + \text{Na}$ ) requires 353.2124, found 353.2194.

**(2*R*,3*R*)-2-Methyl-5-(prop-2-enyl)-1-(1,1,2,2-tetramethyl-1-silapropoxy)oct-7-en-3-ol (50).** To a solution of diol **49**<sup>2d</sup> (2.01 g, 10.2 mmol) in  $\text{CH}_2\text{Cl}_2$  (127 mL) were added DMAP (0.62 g, 5.1 mmol) and  $\text{Et}_3\text{N}$  (2.83 mL, 20.3 mmol). The resulting solution was cooled to 0  $^\circ\text{C}$  and treated with TBSCl (3.07 g, 20.3 mmol). The mixture was allowed to warm to room temperature and stirred for 18 h.  $\text{H}_2\text{O}$  (150 mL) was added to the reaction mixture. The aqueous phase was separated and extracted with  $\text{Et}_2\text{O}$  ( $3 \times 100$  mL). The combined organic layers were dried ( $\text{MgSO}_4$ ), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 6%  $\text{Et}_2\text{O}$  in hexanes) to give 2.71 g (8.68 mmol, 85%) of alcohol **50** as a colorless oil. Data for **50**:  $R_f$  0.44 (17%  $\text{Et}_2\text{O}$  in hexanes/PMA);  $[\alpha]_D^{25} + 9.64^\circ$  ( $c$  2.53,  $\text{CH}_2\text{Cl}_2$ ); IR (thin film) 3471 (br), 1639  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  5.76 (m, 2H), 5.02–4.97 (m, 4H), 3.72 (A portion of ABX, 1H,  $J_{\text{AB}} = 9.9$  Hz,  $J_{\text{AX}} = 3.7$  Hz), 3.64 (B portion of ABX, 1H,  $J_{\text{AB}} = 9.9$  Hz,  $J_{\text{BX}} = 5.9$  Hz), 2.98 (d, 1H,  $J = 4.4$  Hz), 2.08 (m, 4H), 1.74 (m, 2H), 1.48 (ddd, 1H,  $J = 14.0, 9.6, 5.2$  Hz), 1.23 (ddd, 1H,  $J = 13.6, 8.5, 3.7$  Hz), 0.88 (s, 9H), 0.86 (d, 3H,  $J = 7.0$  Hz), 0.05 (s, 6H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  137.0, 136.6, 116.1, 115.9, 72.0, 67.9, 39.0, 38.3, 37.1, 33.5, 25.6, 17.9, 10.3, –5.8,

–5.9; HRMS (EI) exact mass calcd for  $C_{18}H_{36}O_2Si$  ( $M^+$ ) requires 312.2485, found 312.2490.

**2-[(1*S*,5*R*)-5-[(1*R*)-1-Methyl-2-(1,1,2,2-tetramethyl-1-silapropoxy)ethyl]-3-oxo-4-oxanyl]ethanal (51).** A solution of diene **50** (50 mg, 0.160 mmol) in  $CH_2Cl_2$  (6.0 mL) was cooled to  $-78^\circ C$ . Ozone was bubbled through the solution until a distinct blue color persisted for 5 min. Nitrogen was bubbled through the solution to dissipate the excess ozone until the solution became colorless.  $Me_2S$  (0.3 mL) was added. The mixture was allowed to warm to room temperature and stirred for 3 h. The solvent and excess  $Me_2S$  were removed in vacuo. The resulting colorless residue was dissolved in  $CH_2Cl_2$  (15.4 mL) and heated at reflux (oil bath temperature  $45^\circ C$ ) for 6 h. The mixture was cooled to  $25^\circ C$  and concentrated in vacuo. The resulting colorless residue was dissolved in  $CH_2Cl_2$  (2.5 mL). Crushed 4 Å molecular sieves (156 mg) were added, and the slurry was stirred at  $25^\circ C$  for 10 min before the addition of NMO (52 mg, 0.444 mmol). After 10 min, TPAP (18.8 mg, 0.0535 mmol) was added and the greenish black slurry was stirred for 20 min at  $25^\circ C$ . The black suspension was then filtered through a short plug of silica gel and washed with EtOAc. The filtrate was concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 20% EtOAc in hexanes) to afford 23 mg (0.027 mmol, 45% for 2 steps) of aldehyde **51** as a colorless oil. Data for **51**:  $R_f$  0.30 (50% EtOAc in hexanes/PMA);  $[\alpha]^{22}_D -23.9$  ( $c$  0.93,  $CH_2Cl_2$ ); IR (thin film) 2929, 2856, 1732  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ , 300 MHz)  $\delta$  9.75 (s, 1H), 4.47 (ddd, 1H,  $J = 12.1, 3.7, 2.9$  Hz), 3.59 (A portion of ABX, 1H,  $J_{AB} = 9.9$  Hz,  $J_{AX} = 7.4$  Hz), 3.52 (B portion of ABX, 1H,  $J_{AB} = 9.9$  Hz,  $J_{BX} = 5.1$  Hz), 2.76 (ddd, 1H,  $J = 17.3, 5.9, 1.8$  Hz), 2.55 (m, 2H), 2.09 (dd, 1H,  $J = 17.3, 9.9$  Hz), 1.92 (m, 1H), 1.78 (m, 1H), 1.39 (ddd, 1H,  $J = 13.2, 11.4, 11.0$  Hz), 0.91 (d, 3H,  $J = 7.0$  Hz), 0.86 (s, 9H), 0.85 (m, 1H), 0.02 (s, 6H);  $^{13}C$  NMR ( $CDCl_3$ , 75 MHz)  $\delta$  199.4, 170.4, 79.7, 64.4, 49.8, 40.0, 35.7, 32.1, 26.0, 25.7, 18.1, 10.6, –5.7; HRMS (EI) exact mass calcd for  $C_{16}H_{31}O_4Si$  ( $M^+ + H$ ) requires 315.1992, found 315.2014.

**Methyl 4-[(1*S*,5*R*)-5-[(1*R*)-1-Methyl-2-(1,1,2,2-tetramethyl-1-silapropoxy)ethyl]-3-oxo-4-oxanyl]but-2-enoate (52).** To a solution of aldehyde **51** (178 mg, 0.567 mmol) in  $CH_2Cl_2$  (5.0 mL) was added methyl (triphenylphosphoranylidene)acetate (569 mg, 1.7 mmol) at room temperature. The resulting mixture was stirred at room temperature for 24 h. The solvent was removed in vacuo. The residue was subjected to flash column chromatography (silica gel, elution with 50% Et<sub>2</sub>O in hexanes) to afford 174 mg (0.471 mmol, 83%) of methyl ester **52** as a colorless oil. Data for **52**:  $R_f$  0.49 (50% EtOAc in hexanes/PMA);  $[\alpha]^{22}_D -27.3$  ( $c$  0.80,  $CH_2Cl_2$ ); IR (thin film) 1728, 1659  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ , 300 MHz)  $\delta$  6.86 (dt, 1H,  $J = 15.8, 7.0$  Hz), 5.86 (d, 1H,  $J = 15.8$  Hz), 4.42 (dt, 1H,  $J = 12.1, 3.3$  Hz), 3.72 (s, 3H), 3.59 (A portion of ABX, 1H,  $J_{AB} = 9.9$  Hz,  $J_{AX} = 7.5$  Hz), 3.53 (B portion of ABX, 1H,  $J_{AB} = 9.9$  Hz,  $J_{BX} = 5.0$  Hz), 2.69 (m, 1H), 2.26–2.04 (m, 4H), 1.87 (m, 1H), 1.79 (m, 1H), 1.36 (m, 1H), 0.94 (d, 3H,  $J = 9.6$  Hz), 0.86 (s, 9H), 0.02 (s, 6H);  $^{13}C$  NMR ( $CDCl_3$ , 75 MHz)  $\delta$  170.7, 166.3, 144.6, 123.5, 79.8, 64.0, 51.4, 40.0, 38.5, 35.9, 32.1, 31.0, 25.7, 18.1, 10.7, –5.7; HRMS (EI) exact mass calcd for  $C_{19}H_{35}NO_5Si$  ( $M^+ + H$ ) requires 371.2254, found 371.2243.

**Methyl 4-[(1*S*,5*R*)-5-[(1*R*)-2-Hydroxyisopropyl]-3-oxo-4-oxanyl]but-2-enoate (53).** To a solution of TBS ether **52** (39.4 mg, 0.107 mmol) in  $CH_3CN$  (3.94 mL) was added HF (52% aqueous solution, 0.394 mL). The mixture was stirred at room temperature for 1 h. A saturated aqueous  $NaHCO_3$  solution was added slowly, and the mixture was extracted with EtOAc (3  $\times$  50 mL). The combined organic phases were dried ( $MgSO_4$ ), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, elution

with 20% hexanes in EtOAc) to give 26 mg (0.101 mmol, 95%) of alcohol **53** as a colorless oil. Data for alcohol **53**:  $R_f$  0.18 (17% hexanes in EtOAc/PMA);  $[\alpha]^{22}_D 19.4$  ( $c$  0.80,  $CH_2Cl_2$ ); IR (thin film) 3446 (br), 1716, 1653  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ , 300 MHz)  $\delta$  6.85 (dt, 1H,  $J = 15.4, 7.4$  Hz), 5.86 (dt, 1H,  $J = 15.8, 2.9$  Hz), 4.50 (dt, 1H,  $J = 12.1, 2.9$  Hz), 3.72 (s, 3H), 3.68 (A portion of ABX, 1H,  $J_{AB} = 11.0$  Hz,  $J_{AX} = 7.7$  Hz), 3.59 (B portion of ABX, 1H,  $J_{AB} = 11.0$  Hz,  $J_{BX} = 5.5$  Hz), 2.69 (m, 1H), 2.26–2.04 (m, 4H), 1.86 (m, 2H), 1.38 (m, 1H), 0.93 (d, 3H,  $J = 7.0$  Hz);  $^{13}C$  NMR ( $CDCl_3$ , 75 MHz)  $\delta$  170.6, 166.3, 144.5, 123.5, 79.9, 64.0, 51.4, 39.6, 38.4, 35.8, 31.8, 31.0, 10.3; HRMS (EI) exact mass calcd for  $C_{13}H_{20}NO_5$  ( $M^+$ ) requires 256.1311, found 256.1287; exact mass calcd for  $C_{13}H_{21}NO_5$  ( $M^+ + H$ ) requires 257.1389, found 257.1416.

**Methyl 4-[(1*S*,5*R*)-5-[(1*R*)-2-(Benzothiazol-2-ylsulfonyl)isopropyl]-3-oxo-4-oxanyl]but-2-enoate (5).** To a solution of alcohol **53** (16.4 mg, 0.0641 mmol),  $Ph_3P$  (25.2 mg, 0.0961 mmol), and 2-mercaptobenzothiazole (16.1 mg, 0.0961 mmol) in THF (0.825 mL) was added DEAD (0.0151 mL, 0.0961 mmol) dropwise at room temperature. The solution was stirred at room temperature for 18 h and then concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, elution with 17% EtOAc in hexanes) to give 21.3 mg (0.0526 mmol, 82%) of the desired thioether as a colorless oil:  $R_f$  0.35 (50% EtOAc in hexanes/PMA).

To a solution of the thioether (21.3 mg, 0.0526 mmol) in  $CH_2Cl_2$  (0.0862 mL) was added  $NaHCO_3$  (22.1 mg, 0.263 mmol), followed by *m*-CPBA (22.7 mg, 0.132 mmol). The mixture was stirred at room temperature for 18 h and then poured into a mixture of saturated aqueous  $NaHCO_3$  (10 mL) and saturated aqueous sodium thiosulfate (10 mL). The aqueous layer was separated and extracted with  $CH_2Cl_2$  (3  $\times$  15 mL). The combined organic extracts were dried ( $MgSO_4$ ), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, elution with 33% EtOAc in hexanes) to give 16.8 mg (0.0386 mmol, 75%) of sulfone **5** as a colorless oil. Data for sulfone **5**:  $R_f$  0.23 (50% EtOAc in hexanes/PMA);  $[\alpha]^{22}_D -24.6$  ( $c$  1.12,  $CH_2Cl_2$ ); IR (thin film) 1723, 1657, 1237, 1147, 1082  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ , 300 MHz)  $\delta$  8.19 (m, 1H), 8.00 (m, 1H), 7.61 (dq, 2H,  $J = 7.4, 1.5$  Hz), 6.82 (dt, 1H,  $J = 15.8, 6.6$  Hz), 5.86 (d, 1H,  $J = 15.8$  Hz), 4.60 (dt, 1H,  $J = 11.8, 2.6$  Hz), 3.81 (dd, 1H,  $J = 14.3, 6.3$  Hz), 3.72 (s, 3H), 3.47 (dd, 1H,  $J = 14.3, 6.3$  Hz), 2.70 (m, 1H), 2.62 (m, 1H), 2.17 (m, 1H), 1.88 (m, 1H), 1.33 (m, 1H), 1.16 (d, 3H,  $J = 7.0$  Hz);  $^{13}C$  NMR ( $CDCl_3$ , 75 MHz)  $\delta$  169.7, 166.1, 165.7, 152.3, 144.0, 136.4, 127.9, 127.5, 123.7, 122.1, 80.6, 57.1, 51.4, 38.2, 35.6, 32.3, 31.3, 30.6, 13.4; HRMS (EI) exact mass calcd for  $C_{20}H_{23}NO_6S_2$  ( $M^+$ ) requires 437.0967, found 437.0978.

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**Supporting Information Available:** Characterization data including  $^1H$  and  $^{13}C$  NMR spectra of all new compounds (81 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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