Cyclofunctionalization and Free-Radical-Based Hydrogen-Transfer Reactions. An Iterative Reaction Sequence Applied to the Synthesis of the C_7-C_{16} Subunit of Zincophorin

Yvan Guindon,* Lorraine Murtagh,† Valérie Caron, Serge R. Landry,† Grace Jung, Mohammed Bencheqroun, Anne-Marie Faucher,† and Brigitte Guérin

Institut de recherches cliniques de Montréal (IRCM), Bio-organic Chemistry Laboratory, 110 avenue des Pins Ouest, Montréal, Québec, Canada H2W 1R7, and Department of Chemistry and Department of Pharmacology, Université de Montréal, C.P. 6128, Succursale Centre-ville, Montréal, Québec, Canada H3C 3J7

guindoy@ircm.qc.ca

Received March 21, 2001

The strategy considered herein features an iodocyclofunctionalization/hydrogen-transfer reaction sequence for the elaboration of propionate motifs. Proceeding with excellent yield and diastereoselectivity, the synthetic sequence proposed gives access to the anti-anti dipropionate motif when the reduction step is performed under the control of the exocyclic effect. The tandem sequence is applied successfully to the synthesis of the C_7-C_{16} subunit of zincophorin, and iteration of the process gives the desired anti-anti-anti-anti polypropionate stereopentad. Modifications of the reaction sequence—including phenylselenocyclofunctionalization, carbonate hydrolysis, and chelation-controlled radical reduction reactions—lead to the formation of the anti-syn dipropionate motif with remarkable diastereocontrol.

Introduction

The need for diverse synthetic approaches leading to the anti-anti dipropionate motif has been well recognized by many research groups, and significant advances in this field of study have already been made.[1] The strategy considered herein features a cyclofunctionalization/hydrogen-transfer reaction sequence for the elaboration of this motif.[2] The first step of the sequence involves a stereoselective intramolecular addition of an oxygen, concomitant to the addition of an electrophilic iodine or phenylselenium, to a terminally disubstituted double bond (see Figure 1 depiction of the cyclofunctionalization reaction). The resultant tertiary halide or phenylselenide is then reduced under free-radical-based conditions in the second step of the sequence. We have already shown that a high degree of diastereoselectivity can be obtained in the hydrogen-transfer reaction of such substrates through the control of either the *exocyclic*[3] effect leading to the anti product or the *endocyclic*[4] effect leading to the syn product (Figure 1).

This reaction sequence should, in principle, allow for iteration. For instance, the first sequence involving the tandem cyclofunctionalization/hydrogen-transfer reactions (exocyclic effect) should lead to a 2,3-*anti*-3,4-*anti*-dipropionate stereotriad, and the repeated sequence should lead to the formation of a 2,3-*anti*-3,4-*anti*-4,5-*anti*-5,6-*anti*-polypropionate stereopentad. Alternatively, the syn motif could be introduced if a Lewis acid were added during the hydrogen-transfer step (endocyclic effect). A combination of both approaches with or without Lewis acid would lead to four of the eight isomers for a given stereopentad from a starting material bearing at the origin one stereocenter (Figure 1).

In this study, the iterative reaction sequence is applied to the synthesis of the C_7-C_{16} subunit of zincophorin (Figure 2), a synthon first realized by Danishefsky in the total synthesis of this natural product.[5] This C_7-C_{16} subunit has since been considered by other chemists interested in the synthesis of polypropionate motifs.[6] Experiments providing for a better understanding of cyclofunctionalization and hydrogen-transfer reactions involving exocyclic and endocyclic radicals and their mechanistic rationale are also discussed.

* To whom correspondence should be addressed. Tel: (514) 987-5786. Fax: (514) 987-5789.

† Boehringer Ingelheim (Canada) Ltd., Bio-Méga Research Division, 2100 rue Cunard, Laval, Québec, Canada H7S 2G5.

(1) Selected examples: (a) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487. (b) Hoffmann, R. W.; *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 489. (c) Hoffmann, R. W.; Dresely, S. *Chem. Ber.* **1989**, *122*, 903. (d) Paterson, I.; Channon, J. A. *Tetrahedron Lett.* **1992**, *33*, 797. (e) Paterson, I.; Cumming, J. G. *Tetrahedron Lett.* **1992**, *33*, 2847. (f) Harada, T.; Inoue, A.; Wada, I.; Uchimura, J.; Tanaka, S.; Oku, A. *J. Am. Chem. Soc.* **1993**, *115*, 7665. (g) Hoffmann, R. W.; Dahmann, G.; Andersen, M. W. *Synthesis* **1994**, 629. (h) Tanimoto, N.; Gerritz, S. W.; Sawabe, A.; Noda, T.; Filla, S. A.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 673. (i) Marshall, J. A.; Perkins, J. F.; Wolf, M. A. *J. Org. Chem.* **1995**, *60*, 5556. (j) Jain, N. F.; Takenaka, N.; Panek, J. S. *J. Am. Chem. Soc.* **1996**, *111*, 6429. (k) Roush, W. R.; Chemler, S. R. *J. Org. Chem.* **1998**, *63*, 3800.

(2) We have previously explored a combination of iodoetherification/hydrogen-transfer reactions leading to tetrahydrofurans that could be opened selectively by a Lewis acid (Me_2BBr) to offer acyclic counterparts with an anti-anti dipropionate motif. This approach was applied successfully to the synthesis of a $C_{17}-C_{22}$ subunit of ionomycin but did not have the potential for iteration. See: Guindon, Y.; Yoakim, C.; Gorys, V.; Ogilvie, W. W.; Delorme, D.; Renaud, J.; Robinson, G.; Lavallée, J.-F.; Slassi, A.; Jung, G.; Rancourt, J.; Durkin, K.; Liotta, D. *J. Org. Chem.* **1994**, *59*, 1166.

(3) Guindon, Y.; Faucher, A.-M.; Bourque, É.; Caron, V.; Jung, G.; Landry, S. R. *J. Org. Chem.* **1997**, *62*, 9276. See ref 2.

(4) (a) Guindon, Y.; Lavallée, J.-F.; Llinas-Brunet, M.; Horner, G.; Rancourt, J. *J. Am. Chem. Soc.* **1991**, *113*, 9701−9702. (b) Guindon, Y.; Rancourt, J. *J. Org. Chem.* **1998**, *63*, 6554.

(5) (a) Danishefsky, S. J.; Selnick, H. G.; Zelle, R. E.; DeNinno, M. P. *J. Am. Chem. Soc.* **1986**, *51*, 5032. (b) Danishefsky, S. J.; Selnick, H. G.; Zelle, R. E.; DeNinno, M. P. *J. Am. Chem. Soc.* **1987**, *109*, 1572. For the synthesis of the C_7-C_{16} subunit of zincophorin, see: (c) Danishefsky, S. J.; Selnick, H. G.; Zelle, R. E.; DeNinno, M. P. *J. Am. Chem. Soc.* **1988**, *110*, 4368.

(6) (a) Cywin, C. L.; Kallmerten, J. *Tetrahedron Lett.* **1993**, *34*, 1103. (b) Marshall, J. A.; Palovich, M. R. *J. Org. Chem.* **1998**, *63*, 3701. See ref 1k.

10.1021/jo010310f CCC: $20.00
Published on Web 07/07/2001

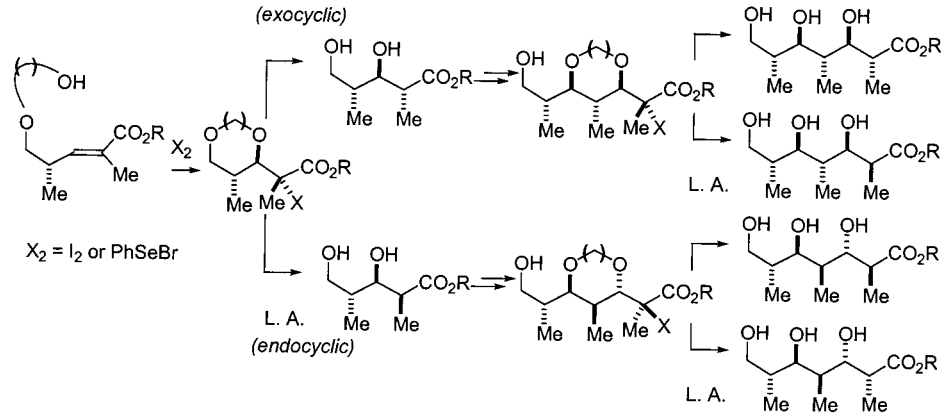


Figure 1. Tandem cyclofunctionalization/free-radical-based reduction reactions, iterative synthetic sequence.

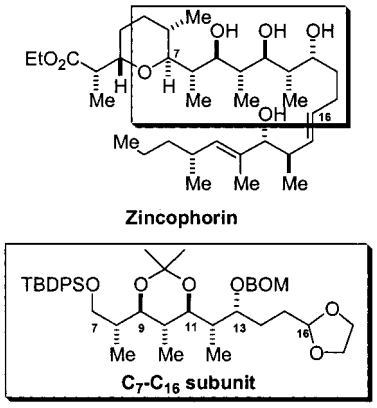
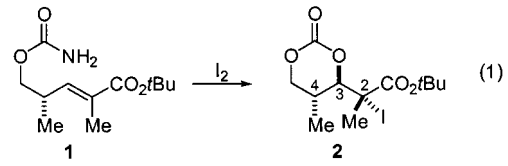


Figure 2. Structures of zincophorin and the C_7-C_{16} subunit of zincophorin.

Results and Discussion

Study of the Cyclofunctionalization Reaction. On the basis of results from previous studies,[7] the cyclofunctionalization reaction proposed herein involves the concomitant addition of an electrophilic iodine and a corresponding nucleophilic carbamate to a terminally disubstituted double bond (eq 1). This reaction is realized with



(1)

a primary homoallylic alcohol, the carrier of the nucleophilic carbamate. The substituent α to the double bond should impose at the transition-state level an allylic 1,3-strain[8] that will dictate the outcome of the reaction. One should note that only a few examples of cyclofunctionalization reactions involving electron-poor olefins have been reported to date.[9]

The kinetically controlled cyclofunctionalization reaction of olefins such as **1** should produce a six-membered ring in which the relative stereochemistry between C-3 and C-4 is trans. The rationale for such a prediction is evident from an analysis of possible transition states (Figure 3). Trans predictive transition state **A** seems to be the lowest in energy compared to the other transition states, where steric interactions should contribute to an increase in energy. Indeed, trans predictive transition state **B** is destabilized from 1,3-diaxial methyl−NH_2 interaction. Cis predictive transition state **C** is destabilized from a bisecting 1,3-allylic interaction, while **D** is destabilized from 1,3-allylic strain. Consequently, trans product **2** should predominate. Furthermore, the antiperiplanar addition of the oxygen to the double bond activated by the iodine (I_2) (i.e., through a π complex or an iodonium ion) in transition state **A** should result in a residual iodide that is anti to the newly formed C−O bond.

If the iodocyclofunctionalization reaction is successful, the resultant carbonate **2** should offer three elements that will be essential to the diastereocontrol of the subsequent free-radical hydrogen-transfer step: (1) the presence of an oxygen on the stereogenic center α to the iodide; (2) the presence of a ring on the stereogenic center α to the iodide; and (3) an anti relative stereochemistry between the C−O and C−I bonds. The effects of these key elements will be discussed in greater detail in the next section of this paper.

Study of the Free-Radical-Based Hydrogen-Transfer Reaction. The induction of new stereogenic centers on acyclic substrates has always been an interesting challenge in organic chemistry. In the past decade, free radicals were shown to be useful intermediates in reactions targeting such goals.[10] Of particular interest to our group has been the study of tertiary carbon-centered free radicals flanked by an ester and a stereogenic center bearing a heteroatom such as an oxygen.[11] As illustrated by Scheme 1, the hydrogen-transfer reaction of acyclic radicals gives a major product of anti relative stereochemistry. The level of diastereoselectivity in this kinetic process is dictated mainly by the presence of the ester, the steric bulk of R_1, the presence of a heteroatom at the

(7) Selected examples: (a) Cardillo, G.; Orena, M. *J. Org. Chem.* **1986**, *51*, 713. (b) Guindon, Y.; Slassi, A.; Ghiro, E.; Bantle, G.; Jung, G. *Tetrahedron Lett.* **1992**, *33*, 4257−4260. See ref 2.

(8) For a review of the effects of 1,3-allylic strain on conformation and stereoselectivity see: (a) Johnson, F. *Chem. Rev.* **1968**, *68*, 375. (b) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

(9) Selected examples: (a) Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *Tetrahedron* **1987**, *43*, 4377. (b) Misiti, D.; Zappia, G. *Tetrahedron Lett.* **1990**, *31*, 7359. See ref 7b.

(10) (a) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296. (b) Liotta, D. C.; Durkin, K. A.; Soria, J. J. *Chemtracts* **1992**, *5*, 197. (c) Miracle, G. S.; Cannizzaro, S. M.; Porter, N. A. *Chemtracts* **1993**, *6*, 147. (d) Smadja, W. *Synlett* **1994**, 1. (e) Giese, B.; Damm, W.; Batra, R. *Chemtracts* **1994**, *7*, 355. (f) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions—Concepts, Guidelines and Synthetic Applications*; VCH: New York, 1996.

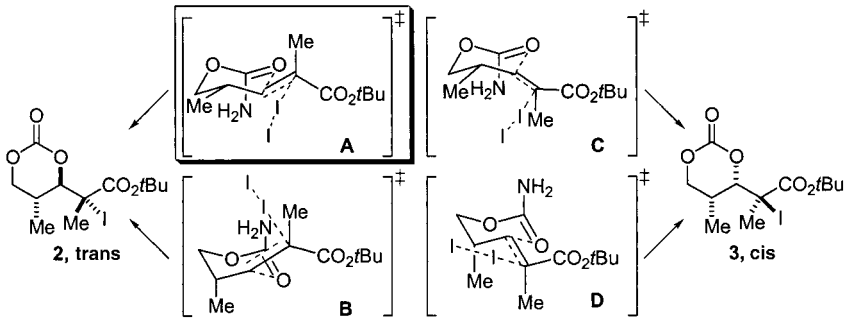


Figure 3. Trans and cis predictive transition states for the iodocyclization reaction.

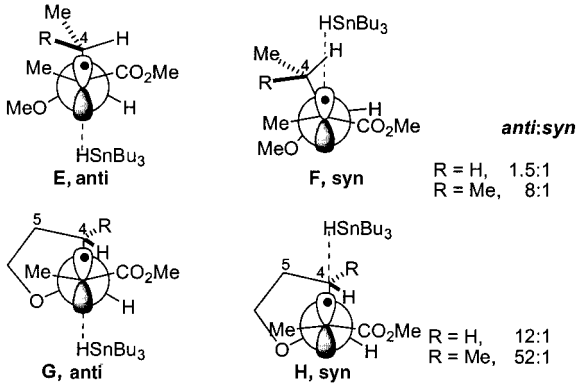
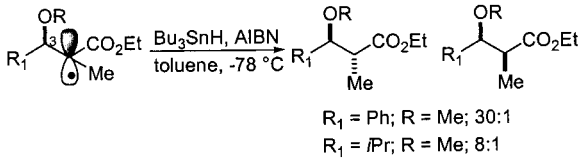


Figure 4. Anti and syn predictive transition states for the free-radical reduction reaction.

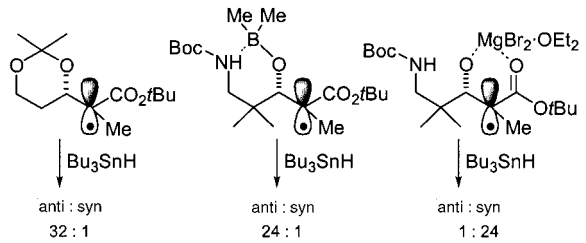
Scheme 1



C-3 position, and the temperature at which the reaction is performed.

Initially, our group began to evaluate the exocyclic effect as a means of circumventing the low diastereoselectivity observed for molecules bearing a small R_1.[2,4] This work was based on an observation illustrated in Figure 4,[2] where a comparison of cyclic and acyclic analogues shows that the ratio of anti products improves when R_1 and OR are embedded in a ring. Accounting for the high anti selectivity in the cyclic series is the increase in the difference in energy between transition states **G** and **H** brought on presumably by a forced alignment of the C_4-C_5 and C_3-O bonds.[2] For the acyclic series, the small difference in energy between transition states **E** and **F** precludes high stereocontrol. We have capitalized on the exocyclic effect in the design of different strategies involving the protection[4] or the in situ derivatization[12] of polyfunctionalized molecules such as diols and amino alcohols as seen in Scheme 2. In these approaches, either

Scheme 2



a permanent or a temporary cycle is formed α to the carbon-centered radical. These strategies have proven to be effective in controlling diastereoselectivity in favor of the anti reduced product. Considering that cyclofunctionalization product **2** bears an oxygen embedded in a ring α to the tertiary iodide, the anti preference should also be attainable in hydrogen-transfer reactions involving this compound.

Alternatively, chelation-controlled radical reduction of carbonate **2** should give access to the syn reduced product. Previous studies have shown that Lewis acids such as $MgBr_2 \cdot OEt_2$ can permit the formation of a stable preorganized chelate between the carbonyl of the ester and the oxygen adjacent to the iodide or the phenylselenide.[4,12] The resultant free-radical intermediate is embedded in a ring, which allows the reduction to proceed under the control of the endocyclic effect (Scheme 2). It is important to note that the Lewis acid can also generate other competing species that can influence the outcome of the reaction. In hydrogen-transfer reactions involving both monodentate[13] and chelate species, $MgBr_2 \cdot OEt_2$ has been shown to accelerate 10 times more than the monodentate species.[4b] From this observation, it is evident that the stability of the preorganized chelate is fundamentally important to the achievement of high syn diastereoselectivity in the endocyclic approach. We have shown in this regard that optimal selectivity can be realized with an excess of $MgBr_2 \cdot OEt_2$.[4b]

In principle, the stereochemistry of the radical precursor should not affect the free-radical process; however, under chelation control, anti isomers (at carbon C-2 and C-3) of halides or phenylselenides have generally led to better ratios than their corresponding syn isomers.[14] The anti motif between the C−O and C−I bonds offered by carbonate **2** will ensure a high ratio in favor of the syn product under chelation-controlled radical reduction.

Synthesis of the C_7-C_{16} Subunit of Zincophorin. The α,β-unsaturated ester **1** required for the cyclofunc-

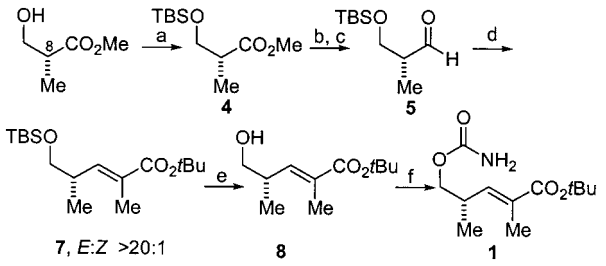
(11) (a) Guindon, Y.; Yoakim, C.; Lemieux, R.; Boisvert, L.; Delorme, D.; Lavallée, J.-F. *Tetrahedron Lett.* **1990**, *31*, 2845. (b) Guindon, Y.; Lavallée, J.-F.; Boisvert, L.; Chabot, C.; Delorme, D.; Yoakim, C.; Hall, D.; Lemieux, R.; Simoneau, B. *Tetrahedron Lett.* **1991**, *32*, 27. (c) Durkin, K.; Liotta, D.; Rancourt, J.; Lavallée, J.-F.; Boisvert, L.; Guindon, Y. *J. Am. Chem. Soc.* **1992**, *114*, 4912. (d) Guindon, Y.; Slassi, A.; Rancourt, J.; Bantle, G.; Bencheqroun, M.; Murtagh, L.; Ghiro, E.; Jung, G. *J. Org. Chem.* **1995**, *60*, 288.

(12) Guindon, Y.; Liu, Z., Jung, G. *J. Am. Chem. Soc.* **1997**, *119*, 9289.

(13) Lewis acid complexes to the carbonyl of the ester in the case of monodentate species.

(14) This observation has been made in chelation-controlled radical allylation and in the hydrogen-transfer reaction (see ref 4a).

Scheme 3[a]

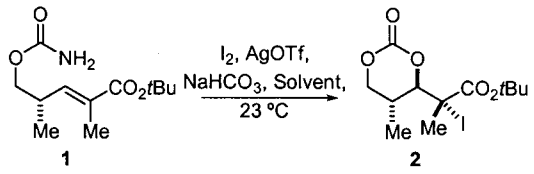


[a] Key: (a) TBSCl, imidazole, CH_2Cl_2, 85%; (b) DIBAL-H (1 M/Hex), CH_2Cl_2, −78 °C, 75%; (c) Py·SO_3 complex, DMSO, Et_3N, 80%; (d) $(Ph)_3P{=}C(Me)CO_2$-*t*-Bu (**6**), THF, 85%; (e) TBAF, CH_3CO_2H, THF, 78%; (f) (i) CCl_3CONCO, CH_2Cl_2, 0 °C; (ii) K_2CO_3 sat., *t*-BuOH reflux, 95%.

tionalization step was achieved in good yield following standard procedures as depicted in Scheme 3 starting from the (*R*)-3-hydroxy-2-methylpropionate. The first chiral center of the starting material corresponded to position-8 of the targeted zincophorin subunit. (To facilitate the recognition of the different carbon centers as they relate to the synthon in consideration, "zincophorin nomenclature" will be used.) The alcohol was protected under classical conditions,[15] and the resulting ester **4** was converted into aldehyde **5**, which was reacted with ylide **6**[16] to form the terminally disubstituted olefin **7** using a Wittig reaction. Primary alcohol **8** generated from the cleavage of silyl ether **7** was treated with trichloroacetylisocyanate (CCl_3CONCO) and potassium carbonate in refluxing *tert*-butyl alcohol[17] to ensure a complete conversion of the isocyanate intermediate into carbamate **1**, which was then used for the cyclofunctionalization reaction.

As seen in Table 1, treatment of carbamate **1** with I_2 in the presence of silver triflate (AgOTf) and $NaHCO_3$[7] led to a poor to mediocre recovery of cyclic carbonate **2**. Of interest were two experimental observations (Table 1, entry 1). First, an equal proportion of starting material and product **2** was found, as seen in entries 1 and 2 (Table 1), regardless of the solvent used. Second, the amount of starting material recovered contradicted TLC indication that the reaction was complete. These observations supported the involvement of an intermediate that seemed to have a tendency to revert back to the starting material through a retro-Michael reaction mechanism. The discrepancy with the TLC result suggested that an acidic workup could be beneficial to the reaction. To test this hypothesis, acidic buffer solution (NaH_2PO_4·H_2O) was added to the reaction mixture, but the yield of cyclofunctionalization product **2** was found to be variable. Finally, we resorted to reproducing the TLC conditions by adding to the reaction mixture 1 g of silica gel for every

Table 1. Synthesis of Carbonate 2 by Iodocyclization of Carbamate 1



entry	solvent (time)	ratio[b] **1**/**2**	yield (%)
1	THF (24 h)	1:1	55
2	MeCN	1:1	36
3	MeCN	1:3	70[c]

[a] All the reactions were carried out at a concentration of 0.2 M at 23 °C using 2.5 equiv of $NaHCO_3$ and AgOTf and 2 equiv of I_2. After 1 h, 1 equiv of each additive was added to the reaction mixture. [b] Ratios were determined for crude reaction isolates before chromatography. [c] When reaction was judged completed, 1 g of silica gel/0.5 mmol of substrate was added to the reaction at 0 °C.

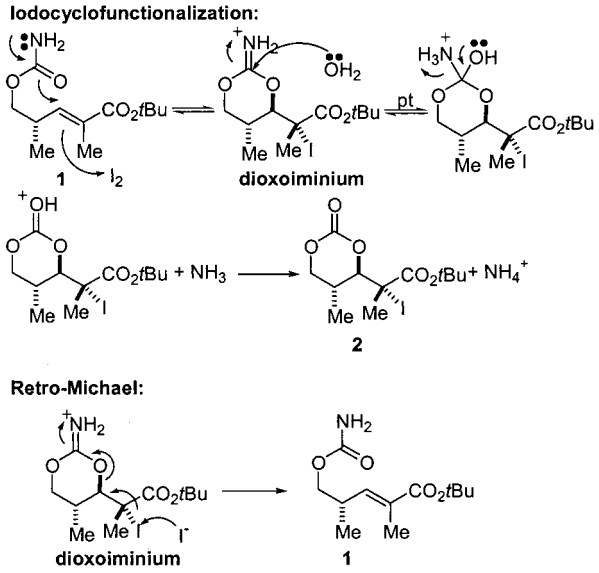


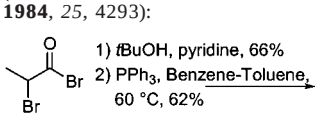
Figure 5. Proposed iodocyclofunctionalization and retro-Michael mechanisms.

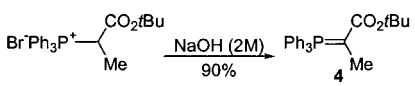
0.5 mmol of substrate used and a few equivalents of water, a treatment that effectively decreased the amount of starting material recovered and increased the amount of desired product (Table 1, entry 3).

Figure 5 illustrates proposed mechanisms for the iodocyclofunctionalization and the retro-Michael reactions. In the first case, intramolecular addition of the oxygen to the double bond activated by the I_2 should result in the formation of a dioxoiminium intermediate. During workup, the dioxoiminium species can be attacked by a water molecule to generate a tetrahedral intermediate that, after proton transfer and elimination of ammonia, can provide protonated carbonate **2**. A final proton transfer of this species to the ammonia should give cyclofunctionalization product **2**. Partitioning of the dioxoiminium intermediate between the formation of product **2** and the reversion to the starting material can be affected by the presence of different salts in the reaction mixture as well as by the amount of water added during workup. These salts could lead, if dissolved, to the release of nucleophiles such as an iodide ion, which can attack the iodide α to the ester resulting in a competing retro-Michael-type reaction, thus recovering the starting material (Figure 5).

(15) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

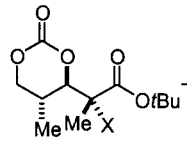
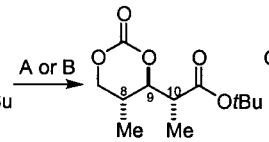
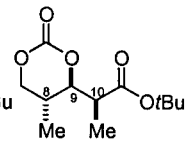
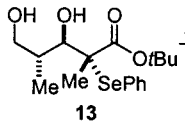
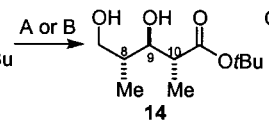
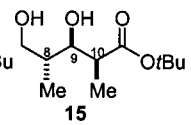
(16) **4** was prepared in three steps using the following procedure (see: Dauben, W. G.; Gerdes, J. M.; Bunce, R. A. *Tetrahedron Lett.* **1984**, *25*, 4293):





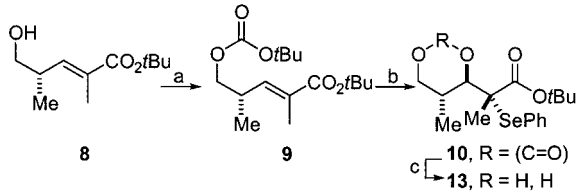
(17) Hirama, M.; Hioki, H.; Itô, S. *Tetrahedron Lett.* **1988**, *29*, 3125.

Table 2. Radical Reductions of Substrates 2, 10, and 13[a]

Entry	Substrate	Conditions[a]	Ratio[b] 9,10-(anti:syn)	Yield (%)
	 X = I, **2**; X = PhSe, **10**	 **11**	 **12**	
1	**2**	A	>30 : 1	80
2	**2**	B	– –	–[c]
3	**10**	A	>30 : 1	90
4	**10**	B	1 : 1	25[d]
	 **13**	 **14**	 **15**	
5	**13**	B	1 : >30	94

[a] Conditions: (A) 2 equiv of Bu_3SnH, 0.2 equiv of Et_3B, THF, −78 °C; (B) 5 equiv of $MgBr_2 \cdot OEt_2$, 2 equiv of Bu_3SnH, 0.2 equiv of Et_3B, CH_2Cl_2, 0 °C. All the reactions were carried out at a concentration of 0.1 M. [b] Ratios were determined for crude reaction isolates before chromatography. [c] Only olefin **8** was observed. [d] 55% of olefin **8** was obtained.

Scheme 4[a]



[a] Key: (a) BOC_2O, DMAP, Et_3N, THF, 91%; (b) PhSeBr, AgOTf, $NaHCO_3$, MeCN, 50%; (c) LiOH, H_2O-THF (1:3), 50%.

For the second step of the sequence, iodide **2** was reduced under radical-based conditions giving an impressive ratio >30:1 in favor of the 9,10-anti isomer (Table 2, entry 1). Attempts to obtain the syn motif in the reduction of **2** under chelation-controlled conditions were unfortunately unsuccessful (Table 2, entry 2). The presence of a very significant amount (55%) of olefin **8** suggested that a retro-Michael reaction followed by a decarboxylation had occurred during the formation of the chelate prior to reduction.

An approach involving the synthesis of an α-phenylselenocarbonate was considered in the hopes that this compound would be more stable than iodocarbonate **2** under chelation-controlled reduction conditions. Unfortunately, carbamate **1** did not react under the phenylselenocyclofunctionalization conditions, and the starting material was recovered. The carbamate function was replaced by a BOC group on primary alcohol **8**, and the resultant carbonate **9** was cyclized efficiently in acetonitrile in the presence of phenylselenyl bromide, silver triflate, and sodium bicarbonate (Scheme 4). As was the case with iodide **2**, phenylselenide **10** gave an excellent ratio >30:1 in favor of anti product **11** (Table 2, entry 3) when reduced under free-radical-based conditions but gave poor yield and ratio of reduced products under chelation-controlled conditions (Table 2, entry 4). In the latter reaction, olefin **8** was still the major component in the mixture. Fortunately, it was possible to hydrolyze α-phenylselenocarbonate **10** into diol **13** using LiOH in H_2O-THF, and the reduction of **13** under chelation-controlled radical conditions proved to be very effective giving syn product **15** in good yield and with high diastereoselectivity (Table 2, entry 5).

The proof of structure of the cyclofunctionalization reaction product was then considered. NMR analyses of **2** and **10** were inconclusive since the coupling constants of H_8-H_9 (J = 6.6 Hz) were lower than those normally seen for axial hydrogen atoms in a six-membered ring.[18] Therefore, the common reduced product **11** was chosen to be transformed into isopropylidene ketal **16** for further analysis (Scheme 5). The coupling constant value of **16** was 10.3 Hz between H_8-H_9, which confirmed the anti motif between the two protons and the trans relative stereochemistry between the Me-C_8 and C_9-O bonds. This result corroborated our predictions for the cyclofunctionalization reaction.

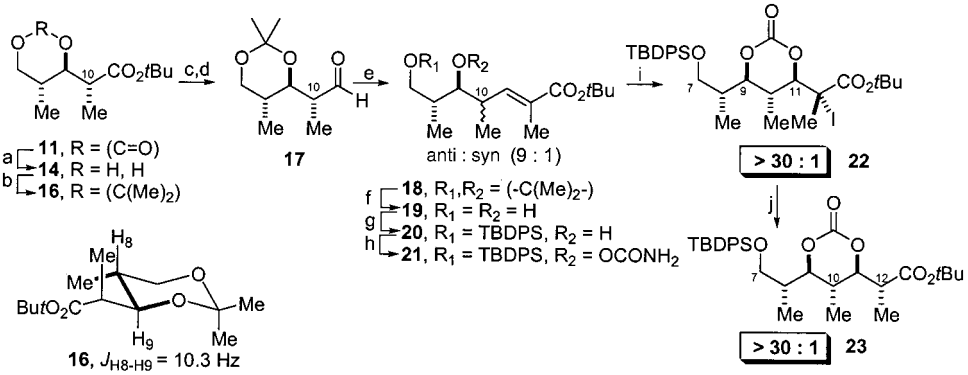
Ester **16** was then converted into α,β-unsaturated ester **18** to test the iterative quality of the synthetic sequence in Scheme 5. The Wittig reaction proved to be much more difficult to realize for the sterically encumbered aldehyde **17**, and conditions involving reflux of toluene had to be maintained over 6 h for completion of the reaction. This led to a mixture of olefins in a ratio of 9:1 in favor of the desired product **18** (8,9-anti-9,10-anti). The transformations leading to **22**, including hydrolysis of acetonide **18**, selective protection of the primary alcohol of **19** to afford silyl derivative **20**, and the formation and subsequent iodocyclofunctionalization of secondary carbamate **21** were performed with mixtures of inseparable olefins. Fortunately, only the major isomer **21** (8,9-anti-9,10-anti) reacted under iodocyclofunctionalization conditions to afford carbonate **22** in good yield and in an excellent ratio >30:1. The resulting iodide **22**, under free-radical-based reduction conditions, gave a ratio >30:1 favoring product **23** with a relative anti diastereoselectivity between C_{12} and C_{11}.

As seen in Figure 6, the large values of J_{H9-H10} (10.6 HZ) and $J_{H10-H11}$ (10.4 Hz) determined from NMR analysis of carbonate **23** confirmed the anti relative stereochemistry between the C_9-O and $C_{10}-Me$ bonds achieved during the hydrogen-transfer reaction in the first sequence. The analysis also showed that the orientation of the $C_{10}-Me$ and $C_{11}-O$ bonds was trans, confirming that the second iodocyclofunctionalization reaction was similar to the first, despite the presence of a secondary homoallylic alcohol.

The hydrolysis of cyclic carbonate **23** by LiOH gave a mixture of the corresponding diol and lactone **24**. The mixture was treated with acidic conditions (*p*-toluenesulfonic acid in THF) to complete the conversion of the diol to lactone **24** (Scheme 6). Analysis of this lactone provided spectral evidence of the relative stereochemistry between the C_{11} and C_{12} centers (Figure 6). The low value of $J_{H11-H12}$ (2.9 Hz) indicated a gauche orientation between the protons and confirmed consequently that the second free-radical reduction reaction had given the anti

(18) The low J_{H8-H9} value can be attributed to the imposed planarity of the carbonate.

Scheme 5[a]



[a] Key: (a) LiOH, H_2O−THF (1:3), 63%; (b) $(CH_3)_2C(OMe)_2$, *p*-TsOH, 85%; (c) DIBAL-H (1 M/Hex), CH_2Cl_2, −78 °C, 75%; (d) (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, (ii) Et_3N, 1 h, −78 to +23 °C, 81% (crude); (e) $(Ph)_3P{=}C(Me)CO_2$-*t*-Bu (**6**), toluene, reflux, 6 h, 60%; (f) THF/HCl (1 M) (1:1), 92%; (g) TBDPSCl, imidazole, CH_2Cl_2, 89%; (h) (i) CCl_3CONCO, CH_2Cl_2, 0 °C, (ii) K_2CO_3 sat., (aq), *t*-BuOH reflux, 86%; (i) I_2, AgOTf, $NaHCO_3$, CH_3CN, 70%; (j) Bu_3SnH, Et_3B, THF, −78 °C, 80%.

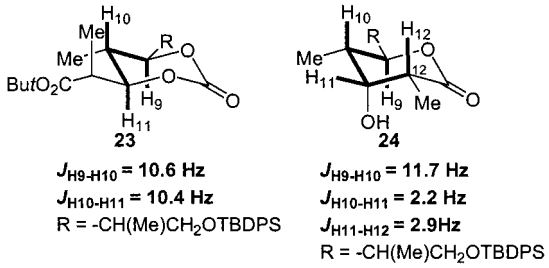


Figure 6. NMR analysis of compounds **23** and **24**.

product **23**. Furthermore, the J_{H9-H10} (11.7 Hz) and $J_{H10-H11}$ (2.2 Hz) values observed for **24** were consistent with the stereochemical outcomes of the first free-radical hydrogen-transfer reaction and the second iodocyclofunctionalization reaction. These results were also consistent with the NMR analysis of carbonate **23** (Figure 6). Therefore, iteration of the tandem sequence proposed herein was successful in the elaboration of the anti-anti-anti polypropionate motif, as found on carbonate **23**.

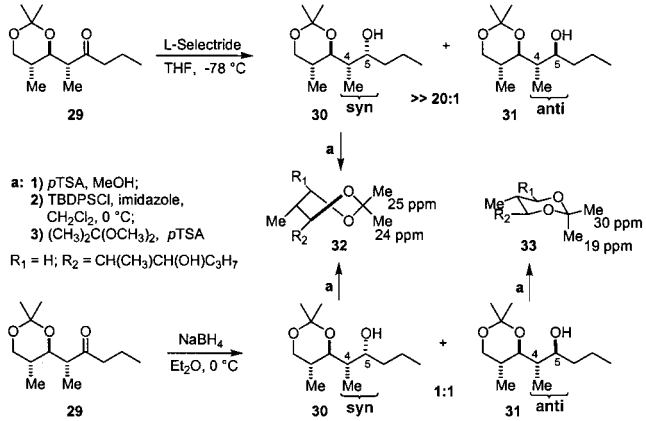
To complete the synthesis of the C_7−C_{16} subunit of zincophorin, lactone **24** was opened to generate an *N*-methoxy-*N*-methylamide. Weinreb conditions[19] involving *N*,*O*-dimethylhydroxyamine hydrochloride and Me_3-Al gave only 50% of the desired compound **25** after 8 h of reaction. A 95% yield of the desired amide **25** was obtained when a stronger Lewis acid such as Me_2AlCl was used (Scheme 6).[20] The diol function of amide **25** was protected with 2,2-dimethoxypropane and *p*-TsOH to form acetonide **26**, but the formation of lactone **24** was still noted during the reaction. Other conditions were tested, but the yield of **26** did not improve and lactone **24** continued to be present in the reaction mixture. On the basis of these results, the former condition was maintained. The addition of organolithium compound **27** to amide **26** gave in good yield the corresponding ketone **28**,[21] which was reduced using L-Selectride to give the major syn alcohol **29** in a ratio of 7:1 through a mechanism involving a putative chelated lithium intermediate.[22] The desired synthon was obtained by protection of alcohol **29** using conditions originally applied by Roush for the synthesis of the same fragment.[1k] Additional confirmation of stereochemistry was provided by a comparison of our spectral data and optical rotation of the benzyloxymethyl (BOM) ether to the published values.[5c]

Conclusions

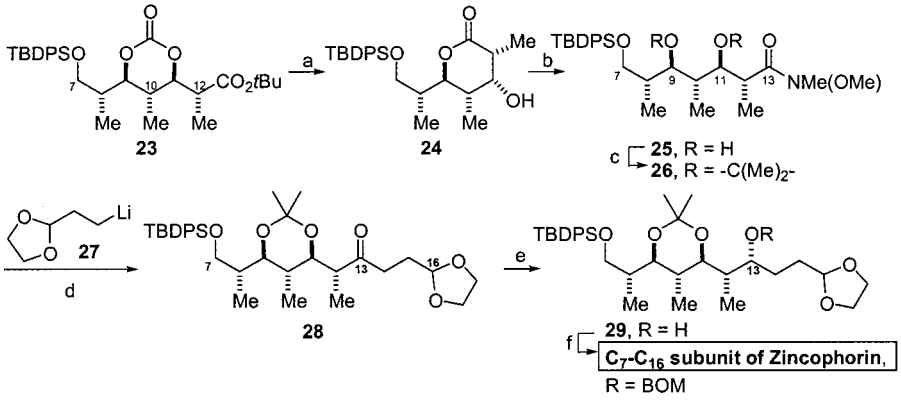
The iterative reaction sequence involving cyclofunctionalization/free-radical-based hydrogen-transfer reactions leading to the anti-anti-anti-anti polypropionate motif was applied successfully to the synthesis of the C_7−C_{16} subunit of zincophorin. Excellent yield and diastereoselectivity were obtained for key steps throughout the tandem process. The anti-syn dipropionate motif was also realized with excellent diastereocontrol using the reaction sequence of phenylselenocyclofunctionalization, carbonate hydrolysis, and chelation-controlled reduction. We have further shown that trans-selective cyclofunctionalization combined with free-radical reduction, under the

(19) Weinreb, S. M.; Basha, A.; Lipton, M. *Tetrahedron Lett.* **1977**, *18*, 4171.
(20) Shimizu, T.; Osako, K.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 2685.
(21) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

(22) A study was done on model compound **29** to determine the best reducing agent for the desired syn stereochemistry. L-Selectride has proven to be the most effective, giving a ratio >20:1 in favor of **30**; see: Arai, Y.; Suzuki, A.; Masuda, T.; Masaki, Y.; Shiro, M. *Chem. Pharm. Bull.* **1996**, *44*, 1765. Faucher, A.-M.; Brochu, C.; Landry, S. R.; Duchesne, I.; Hantos, S.; Roy, A.; Myles, A.; Legault, C. *Tetrahedron Lett.* **1998**, *39*, 8425. Alcohols **30** and **31** were transformed into corresponding acetonides **32** and **33** following the steps illustrated below in order to verify their C_4−C_5 stereochemistries. The ^{13}C resonances of ketal carbons for acetonide **32** were 25 and 24 ppm, indicating that the two hydroxy groups were trans. Consequently, alcohol **30** had to be syn. For **33**, the ^{13}C resonances were 19 and 30 ppm, indicating that the two hydroxyl groups were cis. Consequently, alcohol **31** had to be anti. See Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511.



Scheme 6[a]



[a] Key: (a) (i) LiOH, H_2O−THF (1:3), (ii) *p*-TsOH, THF, 77%; (b) HNMe(OMe)·HCl, Me_2ALCl, THF, −78 °C, 95%; (c) $(CH_3)_2C(OMe)_2$, *p*-TsOH, 65%; (d) (i) **27**, Et_2N, (ii) NH_4Cl aq sat. 75%; (e) L-Selectride, THF, −78 °C, 72%; (f) BOM-Cl, iPr_2NEt, CH_2Cl_2, reflux, 24 h, 84%.

control of either the exocyclic or the endocyclic effect, can offer a powerful approach to the formation of a variety of polypropionate motifs.

Experimental Section

General Methods. All reactions requiring anhydrous conditions were conducted under a positive nitrogen atmosphere in oven-dried glassware using standard syringe techniques. Tetrahydrofuran (THF) and ether were distilled from sodium/benzophenone under N_2 atmosphere immediately prior to use. The anhydrous THF used for radical reduction was purchased from Aldrich and was used as received. Dichloromethane (CH_2Cl_2), DMSO, and Et_3N were freshly distilled from CaH_2 under N_2 atmosphere. Methyl (*R*)-3-hydroxy-2-methylpropionate, DIBAL-H (1 M solution in hexane), tributyltin hydride, triethylborane (1 M solution in hexane), and 2,2-dimethoxypropane were also purchased from Aldrich and used as received. Oxalyl chloride was purchased from Aldrich and distilled prior to use. Flash chromatography was performed on Merck silica gel 60 (0.040−0.063 mm) using air pressure. Analytical thin-layer chromatography (TLC) was carried out on precoated (0.25 mm) Merck silica gel F-254 plates. Melting points were determined on an electrothermal melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian VXR-400S spectrometer and are referenced to the residual pic of the solvent as internal standard. IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer. CI and EI mass spectra were recorded on a MF 50 TATC instrument operating at 70 eV. FAB mass spectra were performed on a VG AutospecQ. Optical rotations were measured on a Perkin-Elmer 343 polarimeter at the sodium D line with a 1 dm path length, 1 mL cell.

Methyl (*R*)-2-Methyl-3-[(*tert*-butyldimethylsilyl)oxy]-propionate (4). To a stirred solution of (*R*)-3-hydroxy-2-methylpropionate (15.08 g, 128 mmol) in CH_2Cl_2 (130 mL) at 0 °C were added sequentially imidazole (19.12 g, 281 mmol) and *tert*-butyldimethylsilyl chloride (26.94 g, 179 mmol). The mixture was allowed to warm to room temperature. After 1 h at room temperature, the mixture was filtered through Celite, and the organic layer was washed with 10% HCl (35 mL), water (35 mL), saturated aqueous $NaHCO_3$ (35 mL), and brine (35 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude oil by Kugelrohr distillation (59 °C/0.2 mmHg) afforded silyl ester **4** (25.4 g, 85%) as a colorless oil: R_f 0.9 (hexanes−EtOAc, 4:1); $[\alpha]^{20}_D$ −20 (*c* 1.1, $CHCl_3$); IR (neat) ν_{max} 2900, 1750, 1460, 1430, 1380, 1360, 1250, 1180, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.87 (s, 9H), 1.13 (d, J = 7.1 Hz, 3H), 2.62−2.67 (m, 1H), 3.64 (dd, J = 6.0, 9.7 Hz, 1H), 3.67 (s, 3H), 3.77 (dd, J = 6.8, 9.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.6, 13.3, 18.1, 25.7, 42.4, 51.4, 65.1, 175.4 (C=O) ppm; MS (FAB) 233 (MH, 30), 217 (25), 201 (6), 175 (2), 91 (100); HRMS calcd for $C_{11}H_{25}O_3Si$ (MH) 233.1573, found 233.1566 (2.8 ppm). Anal. Calcd for $C_{11}H_{24}O_3Si$: C, 56.85; H, 10.41. Found: C, 56.49; H, 10.39.

(*R*)-2-Methyl-3-[(*tert*-butyldimethylsilyl)oxy]propanal. (5) To a cold (−78 °C) stirred solution of ester **4** (9.48 g, 41 mmol) in CH_2Cl_2 (200 mL) under nitrogen atmosphere was added dropwise DIBAL (1 M in hexane) (82 mL, 82 mmol). The resultant mixture was stirred for 15 min at −78 °C and then allowed to warm to room temperature over 1 h (TLC analysis indicated that no starting material or aldehyde remained after this time). The mixture was then cooled to −78 °C, quenched with pH 7.2 buffer solution (100 mL), and allowed to warm to room temperature over 1.5 h. The mixture was then filtered through Celite, and the organic layer was washed with water (50 mL) and saturated aqueous NaCl (50 mL). The aluminum salts were washed with EtOAc (50 mL), and the aqueous layers were re-extracted with EtOAc (2 × 25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification of the crude oil by distillation (60 °C/0.8 mmHg) afforded the alcohol (6.25 g, 75%) as a colorless oil: R_f 0.48 (hexanes−EtOAc, 4:1); $[\alpha]^{20}_D$ −7.5 (*c* 1, $CHCl_3$); IR (neat) ν_{max} 3350, 2900, 1470, 1380, 1360, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.82 (d, J = 6.9 Hz, 3H), 0.88 (s, 9H), 1.88−1.95 (m, 1H), 2.90 (dd, J = 4.2, 6.6 Hz, 1H), 3.53 (dd, J = 8.1, 9.7 Hz, 1H), 3.58−3.62 (m, 2H), 3.71 (dd, J = 4.4, 9.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.5, 13.1, 18.2, 25.9, 37.0, 68.4, 68.8 ppm; MS (FAB) 205 (MH, 36%), 147 (22), 89 (31), 73 (100); HRMS calcd for $C_{10}H_{25}O_2Si$ (MH) 205.1624, found 205.1624 (0.2 ppm). To a cold (10 °C) stirred solution of the silyl alcohol (11.08 g, 54 mmol) in DMSO (270 mL) under nitrogen atmosphere were added triethylamine (18 mL, 130 mmol) and pyridine sulfur trioxide complex (17.26 g, 108 mmol). The mixture was stirred for 3 h at room temperature, after which time TLC analysis indicated no remaining alcohol. The mixture was then cooled to 10 °C and quenched with water (100 mL). The mixture was diluted with hexane (3 × 100 mL), and the organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by distillation (60 °C/0.9 mmHg) afforded aldehyde **5** (8.69 g, 80%) as a colorless oil: R_f 0.82 (hexanes−EtOAc, 4:1); $[\alpha]^{20}_D$ −36.6 (*c* 1.1, $CHCl_3$); IR (neat) ν_{max} 2900, 1720, 1460, 1250, 1100, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.87 (s, 9H), 1.08 (d, J = 7.1 Hz, 3H), 2.49−2.58 (m, 1H), 3.80 (dd, J = 6.1, 10.2 Hz, 1H), 3.86 (dd, J = 5.2, 10.2 Hz, 1H), 9.74 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.5, 10.3, 18.2, 25.8, 48.8, 63.4, 204.7 (C=O) ppm; MS (CI, isobutane) *m/e* 203 (MH^+, 100), 185 (5), 145 (35), 115 (2).

***tert*-Butyl (4*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-2,4-dimethylpent-2-enoate (7).** To a stirred solution of *tert*-butoxycarbonylethylidenetriphenylphosphorane **6**[16] (23.15 g, 60 mmol) was added dropwise a solution of aldehyde **5** (6.0 g, 30 mmol) in THF (150 mL). The mixture was stirred at room

temperature over 24 h. The THF was evaporated, and ether (100 mL) was added to the crude mixture. The solution was filtered through Celite and concentrated under reduced pressure. Purification by flash column chromatography (hexanes−EtOAc 95:5) afforded **7** (6.75 g, 72%) as a colorless oil (32:1 mixture of olefin *E*/*Z*): R_f 0.96 (hexanes−EtOAc, 4:1); $[\alpha]^{20}_D$ −3.9 (*c* 1, $CHCl_3$); IR (neat) ν_{max} 2900, 1715, 1470, 1370 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.88 (s, 9H), 0.99 (d, J = 6.7 Hz, 3H), 1.48 (s, 9H), 1.81 (s, 3H), 2.64−2.68 (m, 1H), 3.48 (d, J = 6.2 Hz, 2H), 6.44 (d, J = 9.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$)) δ −5.4, 12.7, 16.3, 18.3, 25.9, 28.1, 36.2, 67.2, 79.9, 129.3, 143.5, 167.6 (C═O) ppm; MS (FAB) 315.5 (MH, 40), 259 (100), 241 (80), 201 (54), 127 (38). Anal. Calcd for $C_{17}H_{34}O_3Si$: C, 64.92; H, 10.90. Found: C, 64.65; H, 10.81.

***tert*-Butyl (4*S*)-5-Hydroxy-2,4-dimethyl-2-pentenoate (8).** To a cold (0 °C) stirred solution of silyl ester **7** (9.95 g, 32 mmol) in THF (160 mL) under nitrogen atmosphere were added sequentially acetic acid (3.6 mL, 63 mmol) and tetrabutylammonium fluoride (1.0 M in THF, 64 mL, 64 mmol). After 3 h at room temperature, the mixture was diluted with a pH 7.2 buffer solution (100 mL), and the aqueous layer was washed with EtOAc (3 × 75 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes−EtOAc, 4:1) afforded **8** (5.0 g, 78%) as a colorless oil: R_f 0.5 (hexanes−EtOAc, 1:1); $[\alpha]^{20}_D$ −21° (*c* 1, $CHCl_3$); IR (neat) ν_{max} 3450, 2990, 2940, 2880, 1700, 1650, 1460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (d, J = 6.8 Hz, 3H), 1.46 (s, 9H), 1.81 (s, 3H), 1.99 (s, 1H), 2.70 (ddd, J = 3.5, 6.8, 9.9 Hz, 1H), 3.45−3.51 (m, 2H), 6.41 (ddd, J = 1.5, 2.7, 9.9 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 16.0, 28.0, 36.1, 67.0, 80.2, 130.3, 142.8, 167.5 (C═O) ppm; MS (FAB) 201 (MH, 29), 145 (100), 127 (82), 57 (84); HRMS calcd for $C_{11}H_{21}O_3$ (MH) 201.1491, found 201.1497 (−3.2 ppm).

***tert*-Butyl (4*S*)-5-Carbamoyloxy-2,4-dimethylpent-2-enoate (1).** To a cold (0 °C) stirred solution of alcohol **8** (4.74 g, 24 mmol) in CH_2Cl_2 (120 mL) was added dropwise trichloroacetylisocyanate (3.7 mL, 31 mmol). The mixture was stirred for 1 h at room temperature (or until the TLC analysis indicated that no starting material remained). The solvent was then removed under reduced pressure, and the substrate was dissolved in *tert*-butyl alcohol (60 mL). Saturated aqueous K_2CO_3 (30 mL) was added, and the mixture was stirred at reflux for 6 h. The solution was cooled to 0 °C and acidified to pH 7 by adding aqueous 5 M HCl, and the resulting mixture was diluted with EtOAc (75 mL). The organic layer was washed with water (2 × 50 mL) and saturated aqueous NaCl (2 × 50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes−EtOAc 3:1) afforded carbamate **1** (5.7 g, 98%) as a colorless oil: R_f 0.45 (hexanes−EtOAc, 1:1); $[\alpha]^{20}_D$ −14.1 (*c* 1, $CHCl_3$); IR (neat) ν_{max} 3450, 3370, 3200, 2990, 1720, 1600, 1460, 1370, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (d, J = 6.8 Hz, 3H), 1.49 (s, 9H), 1.82 (s, 3H), 2.84−2.88 (m, 1H), 3.92 (dd, J = 7.3, 10.0 Hz, 1H), 4.02 (dd, J = 6.2, 10.0 Hz, 1H), 4.59 (bs, 2H), 6.44 (dd, J = 1, 9.5 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 16.3, 28.0, 33.0, 68.5, 80.2, 130.3, 141.7, 156.9, 167.3 ppm; MS (FAB) *m*/*z* 244 (MH^+, 9), 188 (27), 133 (100), 127 (52), 109 (9); HRMS calcd for $C_{12}H_{22}NO_4$ (MH) 244.1549, found 244.1556 (−3.0 ppm). Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.06; H, 8.97; N, 5.81.

***tert*-Butyl 2*R*-2-Iodo-[(4*R*,5*R*)-5-methyl-2-oxo[1,3]dioxan-4-yl)propionate (2).** To a solution of carbamate **1** (1.70 g 7 mmol) in acetonitrile (30 mL) under nitrogen atmosphere were added sequentially $NaHCO_3$ (1.46 g, 17 mmol), silver triflate (4.48 g, 17 mmol), and iodine (3.54 g, 14 mmol). The mixture was stirred at room temperature in the dark. One equivalent of each reactive species ($NaHCO_3$, silver triflate, and iodine) was added after 30 min and then again after another 30 min until the TLC analysis indicated that no starting material remained. The reaction mixture was then cooled to 0 °C and quenched by the addition of silica gel (50 g), EtOAc (100 mL), and water (5 mL). The resultant suspension was filtered through a Celite pad, which had been rinsed well with EtOAc. The filtrate was washed with water (50 mL), saturated aqueous NaCl (50 mL), and saturated aqueous NaS_2O_3 (3 × 50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes−EtOAc, 3:1) afforded **2** (1.81 g, 70%) as a yellow oil: R_f 0.79 (hexanes−EtOAc, 5:1); $[\alpha]_D^{20}$ −15 (*c* 1.1, $CHCl_3$); IR ($CDCl_3$) ν_{max} 2995, 2270, 1750, 1400, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (d, J = 7.0 Hz, 2H), 1.50 (s, 9H), 2.09 (s, 3H), 2.45−2.51 (m, 1H), 4.03 (dd, J = 7.7, 11.0 Hz, 1H), 4.28 (dd, J = 4.8, 11.0 Hz, 1H), 4.53 (d, J = 6.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 25.6, 27.5, 31.2, 41.6, 70.8, 83.5, 87.4, 149.1, 169.0 ppm; MS (FAB) *m*/*z* 371 (MH^+, 72), 315 (100), 253 (22), 225 (36), 154 (8); HRMS calcd for $C_{12}H_{20}O_5I$ 371.0356, found 371.0339 (4.5 ppm). Anal. Calcd for $C_{12}H_{19}O_5I$: C, 38.93; H, 5.17. Found: C, 38.93; H, 5.22.

***tert*-Butyl 2*R*-(5*R*-Methyl-2-oxo[1,3]dioxan-4*R*-yl)propionate (11).** To a −78 °C solution of iodide **2** (1.53 g, 4.13 mmol) in THF (21 mL) were added tributyltin hydride (2.2 mL, 8.25 mmol) and triethylborane (1 M in hexane, 0.82 mL, 0.82 mmol). The solution was stirred for 40 min at −78 °C, and 0.2 equiv of 1,3-dinitrobenzene (radical inhibitor) was added to terminate the reaction. The mixture was concentrated under vacuum, and the resultant crude oil was partitioned between acetonitrile (25 mL) and hexane (25 mL). The acetonitrile layer was washed with hexane (2 × 25 mL) and then concentrated under reduced pressure. Purification of the crude oil by flash column chromatography (hexane 200 mL, then EtOAc−hexane, 1:2) gave the reduced product **11** (1.0 g, 99%) as a white solid: mp = 80.5 °C; R_f 0.51 (hexanes−EtOAc, 1:1); $[\alpha]^{20}_D$ −19.5 (*c* 1.07, $CHCl_3$); IR ($CDCl_3$) ν_{max} 2995, 2260, 1750, 1410, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (d, J = 6.8 Hz, 3H), 1.27 (d, J = 7.1 Hz, 3H), 1.47 (s, 9H), 2.33−2.41 (m, 1H), 2.79 (qd, J = 3.2, 7.0 Hz, 1H), 3.98 (t, J = 10.6 Hz, 1H), 4.27 (dd, J = 4.6, 10.8 Hz, 1H), 4.34 (dd, J = 3.7, 9.5 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 12.2, 27.5, 28.4, 42.3, 71.1, 81.2, 85.3, 148.5, 170.4 ppm; MS (FAB) *m*/*z* 245 (MH^+, 9), 189 (100), 133 (20); HRMS calcd for $C_{12}H_{21}O_5$ 245.1389, found 245.1379 (4.1 ppm). Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.78; H, 8.37.

***tert*-Butyl-(4*S*)-5-*tert*-butoxycarbonyloxy-2,4-dimethylpent-2-enoate (9).** To a cold (0 °C) stirred solution of alcohol **8** (1.63 g, 8.1 mmol) in THF (20 mL) were added triethylamine (2.3 mL, 16.3 mmol), di-*tert*-butyl dicarbonate (3.55 g, 16.3 mmol), and *N*, *N*-(dimethylamino)pyridine (198 mg, 1.6 mmol). The mixture was stirred for 2 h at room temperature (or until the TLC analysis indicated that no starting material remained). The solvent was then removed under reduced pressure, and the substrate was purified by flash column chromatography (hexanes−EtOAc 9:1) to afford as a colorless oil carbonate **9** containing ∼5% of impurities (2.0 g, 81%). R_f 0.34 (hexanes−EtOAc, 9:1); IR (neat) ν_{max} 2979, 1811, 1707, 1652, 1458 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, J = 7.0 Hz, 3H), 1.44 (s, 18H), 1.78 (s, 3H), 2.84−2.88 (m, 1H), 3.90 (d, J = 7 Hz, 2H), 6.39 (dd, J = 1.5, 9.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.0, 16.7, 27.7, 28.0, 28.1, 28.3, 33.2, 70.4, 80.5, 82.2, 85.4, 130.8, 141.6, 147.0, 153.8, 167.5 ppm.

***tert*-Butyl 2*R*-2-Phenylseleno[(4*R*,5*R*)-5-methyl-2-oxo-[1,3]dioxan-4-yl)propionate (10).** To a solution of carbonate **9** (722 mg, 2.4 mmol) in acetonitrile (12 mL) under nitrogen atmosphere were added sequentially $NaHCO_3$ (605 mg, 7.2 mmol), silver triflate (1.85 g, 7.2 mmol), and PhSeBr (1.70 g, 7.2 mmol). The mixture was stirred at room temperature in the dark. One equivalent of each reactive species was added after 30 min and then again after another 30 min until TLC analysis indicated that no starting material remained. The reaction mixture was then cooled to 0 °C and quenched by the addition of silica gel (50 g), EtOAc (100 mL), and water (5 mL). The resultant suspension was filtered through a Celite pad, which had been rinsed well with EtOAc. The filtrate was washed with water (50 mL), saturated aqueous NaCl (50 mL), and saturated aqueous NaS_2O_3 (3 × 50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes−EtOAc, 3:1) afforded **10** (0.48 mg, 50%) as a yellow oil: R_f 0.31 (hexanes−

EtOAc, 3:7); $[\alpha]^{20}_D$ −6.3 (*c* 1.1, $CHCl_3$); IR ($CDCl_3$) ν_{max} 2990, 1760, 1260, 1140 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, J = 7.0 Hz, 2H), 1.41 (s, 9H), 1.45 (s, 3H), 2.47−2.54 (m, 1H), 4.04 (dd, J = 7.7, 11.0 Hz, 1H), 4.24 (dd, J = 4.5, 11.0 Hz, 1H), 4.70 (d, J = 6.7 Hz, 1H), 7.26−7.42 (m, 3H), 7.62 (d, J = 8 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0, 18.6, 29.2, 52.8, 70.9, 82.7, 87.6, 129.1, 129.8, 138.2, 149.5, 153.5, 170.1 ppm; MS (FAB) *m*/*z* 401 (MH^+, 32), 345 (100), 283 (8), 255 (6), 154 (56); HRMS calcd for $C_{18}H_{25}O_5{}^{80}Se$ 401.0867, found 401.0880 (−3.2 ppm). Anal. Calcd for $C_{18}H_{24}O_5Se$: C, 54.14; H, 6.66. Found: C, 54.48; H, 6.37.

***tert*-Butyl (2*R*,3*R*,4*R*)-3,5-Dihydroxy-2-phenylseleno-2,4-dimethylpentanoate (13).** To carbonate **10** (180 mg, 0.45 mmol) in THF−H_2O (3:1, 8 mL) at 0 °C was added lithium hydroxide (20 mg, 0.90 mmol). The solution was stirred for 2 h at the same temperature. The mixture was diluted with EtOAc (50 mL), washed with brine (3 × 50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude oil by flash column chromatography (hexanes−EtOAc, 7:3) gave diol **13** (84 mg, 50%) as a yellow oil: R_f 0.33 (hexanes−EtOAc, 4:6); $[\alpha]^{20}_D$ 40.1 (*c* 1.0, $CHCl_3$); IR ($CDCl_3$) ν_{max} 3419, 2975, 2932, 1715, 1577 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.12 (d, J = 7.0 Hz, 3H), 1.37 (s, 3H), 1.44 (s, 9H), 2.04−2.06 (m, 1H), 3.59 (dd, J = 5.0, 11.0 Hz, 1H), 3.77 (dd, J = 4.7, 11.0 Hz, 1H), 3.84 (d, J = 4.3 Hz, 1H), 7.25−7.61 (m, 3H), 7.60 (d, J = 7 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 20.3, 27.9, 36.9, 55.7, 65.5, 80.8, 82.6, 126.8, 128.8, 129.4, 138.3, 173.6 ppm.

***tert*-Butyl (2*R*,3*R*,4*R*)-3,5-Dihydroxy-2,4-dimethylpentanoate (14).** To carbonate **11** (1.43 g, 5.8 mmol) in THF−H_2O (3:1, 120 mL) at 0 °C was added lithium hydroxide (0.28 g, 11.7 mmol). The solution was stirred for 2 h at the same temperature. The mixture was diluted with EtOAc (50 mL), washed with brine (3 × 50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude oil by flash column chromatography (hexanes−EtOAc, 1:1) gave diol **14** (1.2 g, 95%) as a white solid: mp = 56 °C: R_f 0.34 (hexanes−EtOAc, 1:1); $[\alpha]^{20}_D$ −21.6° (*c* 1.0, $CHCl_3$); IR ($CDCl_3$) ν_{max} 3580, 3490, 2900, 1700, 1460, 1370, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (d, J = 7.0 Hz, 3H), 1.25 (d, J = 7.1 Hz, 3H), 1.47 (s, 9H), 1.76−1.83 (m, 1H), 2.65 (qd, J = 4.2, 7.2 Hz, 1H), 3.01 (dd, J = 4.2, 7.1 Hz, 1H), 3.47 (td, J = 4.2, 8.1 Hz, 1H), 3.59 (d, J = 8.1 Hz, 1H), 3.63−3.76 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.6, 27.9, 38.1, 42.7, 66.7, 78.8, 81.2, 175.5 ppm; MS (FAB) 219 (MH, 31), 163 (100), 145 (40), 127 (10); HRMS calcd for $C_{11}H_{23}O_4$ (MH) 219.1596, found 219.1589 (3.4 ppm). Anal. Calcd for $C_{11}H_{22}O_4$: C, 60.52; H, 10.16. Found: C, 60.26; H, 10.51.

***tert*-Butyl (2*S*,3*R*,4*R*)-3,5-Dihydroxy-2,4-dimethylpentanoate (15).** To a 0 °C solution of phenylselenide **13** (60 mg, 0.16 mmol) in CH_2Cl_2 (2 mL) was added $MgBr_2{\cdot}OEt_2$ (125 mg, 0.48 mmol). The solution was stirred for 5 min before the addition of tributyltin hydride (87 μL, 0.32 mmol) and triethylborane (1 M in hexane, 32 μL, 0.03 mmol). The resulting solution was stirred for 40 min at 0 °C, and 0.2 equiv of 1,3-dinitrobenzene was added. The mixture was diluted with EtOAc (15 mL), washed with brine (3 × 50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude oil by flash column chromatography (hexanes−EtOAc, 1:1) gave diol **15** (33 mg, 94%) as a colorless oil: R_f 0.42 (hexanes−EtOAc, 3:7); $[\alpha]^{20}_D$ −29.8° (*c* 0.92, $CHCl_3$); IR ($CDCl_3$) ν_{max} 3500, 2990, 2970, 2240, 1715, 1440 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.79 (d, J = 7.1 Hz, 3H), 1.18 (d, J = 7.0 Hz, 3H), 1.46 (s, 9H), 1.82−1.86 (m, 1H), 2.51 (qd, J = 2.3, 7.1 Hz, 1H), 3.65 (dd, J = 3.8, 10.8 Hz, 1H), 3.71 (dd, J = 7.5, 10.8 Hz, 1H), 3.86 (dd, J = 2.3, 9.5 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.0, 13.3, 29.7, 36.6, 41.9, 68.7, 81.4, 173.4 ppm.

***tert*-Butyl (2*R*)-2-[(4*R*,5*R*)-2,2,5-Trimethyl[1,3]dioxan-4-yl)]propionate (16).** To a solution of diol **14** (0.3 g, 1.4 mmol) in 2,2-dimethoxypropane (20 mL) was added *p*-toluenesulfonic acid (78 mg, 0.4 mmol). The mixture was stirred for 2 h at room temperature, diluted with CH_2Cl_2 (30 mL), washed with saturated aqueous $NaHCO_3$ (3 × 25 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes−EtOAc 6:1) gave acetonide **16** (0.3 g, 85%) as a colorless oil: R_f 0.57 (hexanes−EtOAc, 4:1); $[\alpha]^{20}_D$ −28 (*c* 1.2, $CHCl_3$); IR ($CDCl_3$) ν_{max} 2980, 1740, 1460, 1370, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.78 (d, J = 6.8 Hz, 3H), 1.14 (d, J = 7.1 Hz, 3H), 1.35 (s, 3H), 1.41 (s, 3H), 1.46 (s, 9H), 1.96−2.04 (m, 1H), 2.58 (qd, J = 3.3, 7.1 Hz, 1H), 3.46 (dd, J = 10.6, 11.5 Hz, 1H), 3.63−3.70 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8, 12.9, 19.1, 28.1, 29.3, 31.9, 42.9, 66.0, 80.1, 98.4, 172.6 ppm; MS (FAB) 259 (MH, 60), 243 (14), 203 (52), 149 (100), 91 (46), 57 (34). Anal. Calcd for $C_{14}H_{26}O_4$: C, 65.09; H, 10.14. Found: C, 64.75; H, 10.49.

(2*R*)-2-[(4*R*,5*R*)-2,2,5-trimethyl[1,3]dioxan-4-yl]propionaldehyde (17). To a −78 °C solution of ester **16** (1.84 g, 7.1 mmol) in THF (36 mL) under nitrogen atmosphere was added dropwise DIBAL (1 M in hexane, 18 mL, 18 mmol). The mixture was allowed to warm to room temperature over 24 h and was then recooled to −78 °C and quenched with MeOH (20 mL). The mixture was again allowed to warm to room temperature over 1.5 h before being diluted with EtOAc (20 mL). The organic layer was washed with brine (50 mL), and the aqueous layer was washed with EtOAc (2 × 25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes−EtOAc, 3:1) gave the alcohol (0.84 g, 63%) as a colorless oil: R_f 0.26 (hexanes−EtOAc, 4:1); $[\alpha]^{20}_D$ −23 (*c* 1, $CHCl_3$); IR ($CDCl_3$) ν_{max} 3520, 2980, 1460, 1380, 1200 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.74 (d, J = 6.6 Hz, 3H), 1.11 (d, J = 7.1 Hz, 3H), 1.37 (s, 3H), 1.40 (s, 3H), 1.81−1.86 (m, 1H), 1.94−2.02 (m, 1H), 2.81 (d, J = 8.0 Hz, 1H), 3.46−3.56 (m, 3H), 3.72 (dd, J = 5.1, 11.5 Hz, 1H), 3.94 (d, J = 11 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6, 14.9, 18.6, 29.5, 31.7, 34.7, 63.6, 66.0, 80.4, 98.5 ppm; MS (CI, isobutane) *m*/*e* 189 (MH^+, 97), 173 (15), 131 (100), 113 (69). To a −78 °C solution of oxalyl chloride (0.55 mL, 6.3 mmol) in CH_2Cl_2 (10 mL) was added dropwise dimethylsulfoxide (0.8 mL, 11.1 mmol). The mixture was stirred for 15 min at −78 °C, and a solution of the alcohol (0.70 g, 3.7 mmol) in CH_2Cl_2 (10 mL) was added dropwise with stirring. After 1 h at −78 °C, Et_3N (3.2 mL, 18 mmol) was added, and stirring continued for 15 min at the same temperature. The mixture was allowed to warm to room temperature while being stirred and was then diluted with CH_2Cl_2 (10 mL). The organic layer was washed with water (2 × 25 mL) and saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give aldehyde **17** (0.69 g, 99%) as a colorless oil, R_f 0.43 (hexanes−EtOAc, 4:1). The crude aldehyde **17** was used immediately for the next step without further purification: ^1H NMR (400 MHz, $CDCl_3$) δ 0.78 (d, J = 6.7 Hz, 3H), 1.19 (d, J = 7.1 Hz, 3H), 1.37 (s, 3H), 1.43 (s, 3H), 1.89−1.98 (m, 1H), 2.50−2.54 (m, 1H), 3.49 (t, J = 11.0 Hz, 1H), 3.68−3.74 (m, 2H), 9.77 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.2, 12.5, 18.7, 29.4, 31.9, 47.6, 65.8, 77.2, 98.5, 204.6 ppm.

***tert*-Butyl (4*S*)-4-[(4*S*,5*R*)-2,2,5-Trimethyl[1,3]dioxan-4-yl)]-2-methylpent-2-enoate (18).** To a solution of aldehyde **17** (0.69 g, 3.7 mmol) in toluene (19 mL) was added (*tert*-butoxycarbonylethylidene)triphenylphosphorane **6** (2.89 g, 7.4 mmol). The mixture was heated at reflux for 6 h. The solvent was then removed under reduced pressure, and the resultant yellow solid was suspended in ether (20 mL), filtered through Celite, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (hexanes−EtOAc 95:5) to afford ester **18** (0.66 g, 60%) as an 8:1 mixture of epimerized products (at C_4, C_{10} in zincophorin as shown in Scheme 5): R_f 0.70 (hexanes−EtOAc, 8:2); $[\alpha]^{20}_D$ −10.9 (*c* 1.5, $CHCl_3$); IR ($CDCl_3$) ν_{max} 2980, 1700, 1450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) major epimer: δ 0.69 (d, J = 6.6 Hz, 3H), 1.04 (d, J = 6.1 Hz, 3H), 1.39 (s, 3H), 1.42 (s, 3H), 1.49 (s, 9H), 1.56−1.66 (m, 1H), 1.80 (s, 3H), 2.70−2.78 (m, 1H), 3.43 (dd, J = 2.4, 10.3 Hz, 1H), 3.47 (t, J = 11.3 Hz, 1H), 3.65 (dd, J = 5.1, 11.5 Hz, 1H), 6.80 (dd, J = 1.5, 10.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) major epimer: δ 12.4, 16.6, 18.9, 28.1, 29.5, 31.9, 34.4, 66.0, 78.0, 79.9, 98.1, 128.9, 141.6, 168.0 ppm; MS (FAB) 299 (MH, 18), 283 (65), 243 (50), 185

(68), 167 (65), 129 (80); HRMS calcd for $C_{17}H_{31}O_4$ (MH) 299.2222, found 299.2236 (−4.6 ppm). Anal. Calcd for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13. Found: C, 68.50; H, 10.32.

***tert*-Butyl (4*S*,5*S*,6*R*)-5,7-dihydroxy-2,4,6-trimethyl-2-heptenoate (19).** Acetonide **18** (0.66 g, 2.2 mmol), in a 1:1 mixture of THF and HCl (1 M) (44 mL), was stirred for 2 h at room temperature under nitrogen atmosphere. The mixture was then diluted with CH_2Cl_2 (40 mL) and washed with saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was washed with CH_2Cl_2 (2 × 20 mL) and EtOAc (20 mL). The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes−EtOAc, 1:1) gave diol **19** (0.53 g, 92%) as a colorless oil: R_f 0.53 (hexanes−EtOAc, 1:1); $[\alpha]^{25}_D$ −23.2 (*c* 1, $CHCl_3$); IR (neat) ν_{max} 3620, 3500, 2980, 1700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, J = 7.0 Hz, 3H), 1.06 (d, J = 7.0 Hz, 3H), 1.49 (s, 9H), 1.76 (qd, J = 3.5, 7.1 Hz, 1H), 1.83 (s, 3H), 2.63 (t, J = 5.1 Hz, 1H), 2.71−2.76 (m, 1H), 2.87 (d, J = 3.1 Hz, 1H), 3.49−3.52 (m, 1H), 3.61−3.67 (m, 1H), 3.78−3.83 (m, 1H), 6.71 (dd, J = 1.3, 10.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8, 14.1, 16.8, 28.2, 36.8, 37.5, 67.6, 80.8, 84.6, 130.0, 141.1, 167.5 ppm; MS (FAB) 259 (MH, 30), 203 (95), 185 (100), 167 (32) 154 (36); HRMS calcd for $C_{14}H_{27}O_4$ (MH) 259.1910, found 259.1897 (4.8 ppm).

***tert*-Butyl (4*S*,5*S*,6*R*)-7-[(*tert*-Butyldiphenylsilyl)oxy]-5-hydroxy-2,4,6-trimethylhept-2-enoate (20).** To a solution of diol **19** (0.44 g, 1.72 mmol) in CH_2Cl_2 (17 mL) at 0 °C under nitrogen atmosphere were added sequentially imidazole (0.23 g, 3.4 mmol) and *tert*-butyldiphenylsilyl chloride (0.45 mL, 1.74 mmol). The mixture was stirred at the same temperature for 2 h before being diluted with CH_2Cl_2 (20 mL) and washed with HCl (1 M, 20 mL), water (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL). The mixture was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude oil by flash column chromatography (hexanes−EtOAc 93:7) gave silyl alcohol **20** (0.76 g, 89%) as a colorless oil: R_f 0.76 (hexanes−EtOAc, 4:1); $[\alpha]^{20}_D$ −36.4 (*c* 1.5, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3450, 2980, 1700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.72 (d, J = 7.0 Hz, 3H), 1.06 (s, 9H), 1.09 (d, J = 7.0 Hz, 3H), 1.50 (s, 9H), 1.72−1.80 (m, 1H), 1.81 (s, 3H), 2.66−2.71 (m, 1H), 3.53 (dd, J = 3.6, 8.1 Hz, 1 H), 3.67 (dd, J = 4.0, 10.3 Hz, 1H), 3.69 (dd, J = 7.9, 10.3 Hz, 1H), 6.86 (dd, J = 1.3, 10.0 Hz, 1H), 7.38−7.73 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) 12.6, 13.7, 17.0, 19.1, 26.8, 28.2, 36.7, 37.9, 69.1, 79.9, 80.1, 127.8, 129.9, 135.6, 142.0, 167.0; MS (FAB) *m*/*z* 497 (MH^+, 15), 441 (51), 199 (100), 135 (93). Anal. Calcd for $C_{30}H_{44}O_4Si$: C, 72.54; H, 8.93. Found: C, 72.56; H, 8.78.

***tert*-Butyl (4*S*,5*S*,6*R*)-7-[(*tert*-Butyldiphenylsilyl)oxy]-5-carbamoyloxy-2,4,6-trimethylhept-2-enoate (21).** To a 0 °C solution of alcohol **20** (0.56 g, 1.1 mmol) in CH_2Cl_2 (6 mL) was added dropwise trichloroacetylisocyanate (147 μL, 1.2 mmol). The mixture was stirred for 30 min at the same temperature, and the solvent was then removed under reduced pressure. The resultant viscous oil was dissolved in *tert*-butyl alcohol (3 mL), and saturated aqueous K_2CO_3 (1.5 mL) was added. The mixture was heated at reflux for 6 h, cooled to 0 °C, acidified to pH 7, diluted with EtOAc (10 mL), and washed with water (10 mL) and brine (10 mL) before being dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude oil by flash column chromatography (hexanes−EtOAc 2:1) gave carbamate **21** (0.53 g, 86%) as a colorless oil: R_f 0.43 (hexanes−EtOAc, 4:1); $[\alpha]^{25}_D$ +20.4 (*c* 1.4, $CHCl_3$); IR ($CHCl_3$) $\nu_{max.}$ 4530, 3420, 2980, 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (d, J = 7.0 Hz, 3H), 0.99 (d, J = 7.0 Hz, 3H), 1.05 (s, 9H), 1.49 (s, 9H), 1.78 (s, 3H), 1.86−1.90 (m, 1H), 2.82−2.87 (m, 1H), 3.48 (dd, J = 6.8, 10.1 Hz, 1H), 3.63 (dd, J = 4.6, 10.1 Hz, 1H), 4.40 (bs, 2H), 4.74 (dd, J = 4.4, 8.0 Hz, 1H), 6.61 (dd, J = 1.4, 10.1 Hz, 1H) 7.35−7.42 (m, 6H), 7.64−7.67 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5, 14.1, 16.8, 19.2, 26.8, 28.1, 35.1, 38.2, 65.0, 78.4, 80.0, 127.5, 129.3, 129.5, 133.7, 135.6, 141.2, 156.9, 167.4 ppm; MS (FAB) *m*/*z* 540 (MH^+, 20), 484 (52), 426 (48), 345 (64), 242 (100), 199 (78), 135 (100); HRMS calcd for $C_{31}H_{46}O_5SiN$ (MH) 540.3145, found 540.3123 (4.1 ppm).

***tert*-Butyl (2*R*)-2-[(4*R*,5*R*,6*R*)-6-[(1*R*)-2-*tert*-Butyldiphenylsilyloxy-1-methylethyl]-5-methyl-2-oxo[1,3]dioxan-4-yl]-2-iodopropionoate (22).** To a solution of carbamate **21** (0.21 g, 0.39 mmol) in dry acetonitrile (4 mL) under nitrogen atmosphere at room temperature were added sequentially $NaHCO_3$ (81.7 mg, 0.97 mmol), silver triflate (0.25 g, 0.97 mmol), and iodine (0.20 g, 0.78 mmol). The mixture was stirred at room temperature in the dark. After 3 h, 1 equiv of each reactive species was added until TLC analysis indicated no remaining carbamate (5 h). The reaction mixture was then cooled to 0 °C and quenched by the addition of SiO_2 (5 g), EtOAc (5 mL), and water (1 mL). The resultant suspension was filtered through a Celite pad, which had been rinsed well with EtOAc. The organic layer was washed with water (20 mL), brine (2 × 25 mL), and saturated aqueous NaS_2O_3 (3 × 25 mL) before being dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes−EtOAc, 4:1) afforded the iodocarbonate **22** (0.16 g, 60%) as a yellow oil: R_f 0.68 (hexanes−EtOAc, 4:1); $[\alpha]^{20}_D$ +3.4 (*c* 1.6, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2940, 1750, 1450, 1370, 1300, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, J = 7.1 Hz, 3H), 1.06 (s, 9H), 1.32 (d, J = 6.6 Hz, 3H), 1.50 (s, 9H), 2.04 (s, 3H), 2.20−2.24 (m, 1H), 2.70−2.77 (m, 1H), 3.50 (dd, J = 4.8, 10.8 Hz, 1H), 3.87 (dd, J = 8.0, 10.9 Hz, 1H), 4.06 (dd, J = 1.8, 10.8 Hz, 1H), 4.53 (d, J = 8.4 Hz, 1H) 7.37−7.46 (m, 6H), 7.63−7.67 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 17.5, 19.2, 25.9, 27.0, 27.5, 33.9, 36.2, 41.2, 63.9, 83.5, 85.2, 86.8, 127.8, 129.8, 133.1, 135.5, 150.0, 169.2 ppm. Anal. Calcd for $C_{31}H_{43}O_6SiI$: C, 55.85; H, 6.50. Found: C, 55.48; H, 6.21.

***tert*-Butyl (2*R*)-2-[(4*R*,5*R*,6*R*)-6-[(1*R*)-2-*tert*-Butyldiphenylsilyloxy-1-methylethyl]-5-methyl-2-oxo[1,3]dioxan-4-yl]propionoate (23).** To a −78 °C solution of iodocarbonate **22** (0.34 g, 0.51 mmol) in THF (3 mL) were added tributyltin hydride (275 μL, 1.02 mmol) and triethylborane (1 M in hexane, 100 μL, 0.1 mmol). The temperature was maintained, and the reaction mixture was stirred for 3 h before 0.2 equiv of 1,3-dinitrobenzene was added. After an additional 15 min at −78 °C, the mixture was warmed and concentrated under reduced pressure. The crude oil was then partitioned between acetonitrile (4 mL) and hexane (4 mL). The acetonitrile layer was washed with hexane (3 × 4 mL) and concentrated under reduced pressure. The resultant crude oil was purified by flash column chromatography (100 mL hexane, then hexanes−EtOAc, 5:1) to give the reduced product **23** (0.24 g, 89%) as a colorless oil: R_f 0.33 (hexanes−EtOAc, 1:1); $[\alpha]^{25}_D$ −31.2 (*c* 0.5, $CHCl_3$); IR (neat) ν_{max} 2950, 1700, 1440, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (d, J = 6.6 Hz, 3H), 1.03 (d, J = 7.1 Hz, 3H), 1.04 (s, 9H), 1.22 (d, J = 7.1 Hz, 3H), 1.41 (s, 9H), 2.14−2.19 (m, 1H), 2.44−2.51 (m, 1H), 2.78 (qd, J = 2.5, 7.1 Hz, 1H), 3.52 (dd, J = 5.7, 10.5 Hz, 1H), 3.80 (dd, J = 7.5, 10.5 Hz, 1H), 4.04 (dd, J = 1.9, 10.5 Hz, 1H), 4.25 (dd, J = 2.7, 10.4 Hz, 1H) 7.36−7.45 (m, 6H), 7.62−7.65 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 12.5, 14.7, 19.1, 26.9, 28.0, 31.8, 36.6, 42.8, 63.7, 81.7, 84.9, 85.7, 127.8, 129.8, 133.2, 135.5, 149.8, 170.8 ppm; MS (FAB) *m*/*z* 563 ($M^+ + Na^+$, 84), (483, 40), 407 (100), 199 (70), 135 (84); HRMS calcd for $C_{31}H_{44}O_6SiNa$ 563.2805, found 563.2780 (4.4 ppm).

(3*R*,4*R*,5*S*,6*R*)-6-[(1*R*)-2-(*tert*-Butyldiphenylsilyloxy-1-methylethyl)]-4-hydroxy-3,5-dimethyltetrahydropyran-2-one (24). To carbonate **23** (0.10 g, 0.193 mmol) in THF−H_2O (1:1, 4 mL) at 0 °C was added lithium hydroxide (9.2 mg, 0.39 mmol). The mixture was stirred for 2 h at the same temperature, and an additional 1 equiv of lithium hydroxide was added. After 3 h, the mixture was concentrated under reduced pressure, diluted with EtOAc (4 mL), and washed with brine (2 × 4 mL). The aqueous layer was washed with EtOAc (2 × 4 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude diol was then diluted in THF (4 mL), and *p*-toluenesulfonic acid (7.3 mg, 0.039 mmol) was added. The reaction mixture was stirred 24 h, diluted with CH_2Cl_2 (2 mL), and washed with saturated aqueous $NaHCO_3$ (2 × 4 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum to give lactone **24** (0.065 g, 77%) as a colorless

oil: R_f 0.75 (hexanes−EtOAc, 1:1); $[\alpha]^{20}_D$ 6.9 (*c* 1.3, $CHCl_3$); IR (neat) ν_{max} 3450, 2900, 1700, 1470, 1360 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (s, 9H), 1.03−1.07 (m, 6H), 1.28 (d, J = 7.3 Hz, 3H), 1.76 (d, J = 3.7 Hz, 1H), 2.06−2.12 (m, 1H), 2.29−2.34 (m, 1H), 2.34−2.38 (m, 1H), 3.52 (dd, J = 5.7, 10.4 Hz, 1H), 3.76 (dd, J = 2.2, 2.9 Hz, 1H), 3.83 (dd, J = 7.5, 10.4 Hz, 1H), 4.37 (dd, J = 1.6, 11.0 Hz, 1H), 7.36−7.45 (m, 6H), 7.62−7.65 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDC1_3$) δ 12.8, 14.5, 15.5, 19.1, 26.9, 36.0, 36.9, 42.3, 64.3, 73.4, 76.7, 84.0, 127.8, 129.8, 133.4, 133.5, 135.5, 173.8 ppm; MS (FAB) 363 ($M-C_6H_5$, 96), 307 (18), 239 (44), 199 (74), 135 (100); HRMS calcd for $C_{26}H_{37}O_4Si$ 441.2461, found 441.2439 (5.0 ppm).

(2*R*,3*R*,4*R*,5*R*,6*R*)-7-(*tert*-Butyldiphenylsilyloxy)-3,5-dihydroxy-*N*,*N*-methoxymethyl-2,4,6-trimethylheptanamide (25). To a suspension of *N*,*O*-methoxymethylhydroxylamine hydrochloride (56 mg, 0.57 mM) in CH_2Cl_2 (2 mL) at 0 °C was added trimethylaluminum (1 M in hexane, 0.58 mL, 0.57 mM) (CAUTION: *vigorous gas evolution*). The cooling bath was then removed, and the clear solution was stirred for 1 h at room temperature. The solution of lactone **24** (75 mg, 0.17 mM) in CH_2Cl_2 (4 mL) was added dropwise. The solution was stirred at room temperature for 30 min (*vigorous gas evolution*), and a buffer solution at pH 7.2 (1.7 mL) was added. The reaction mixture was then stirred for an additional 10 min. The resultant gel was filtered through a Celite pad, which had been rinsed well with $CHCl_3$ (10 mL). The organic layer was washed with brine (2 × 10 mL), and the aqueous layer was extracted with $CHCl_3$ (10 mL) and EtOAc (10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum to give hydroxyamide **25** (81 mg, 95%) as a yellow oil: R_f 0.43 (hexanes−EtOAc, 1:1); IR (neat) ν_{max} 3450, 3070, 2960, 2860, 1740, 1630, 1470 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, J = 7 Hz, 3H), 0.98 (d, J = 7 Hz, 3H), 1.04 (s, 9H), 1.33 (d, J = 7.1 Hz, 3H), 1.92 (q, J = 7.1 Hz, 1H), 2.06−2.12 (m, 1H), 3.15 (s, 3H), 3.30 (bd, J = 4.2, 1H), 3.56 (t, J = 5.5 Hz, 1H), 3.66−3.76 (m, 3H), 3.71 (s, 3H), 4.60 (bs, 1H), 4.83 (bs, 1H), 7.36−7.45 (m, 6H), 7.66−7.69 (m, 4H); ^{13}C (100 MHz, $CDCl_3$) 14.8, 15.2, 16.1, 19.1, 26.9, 29.3, 31.7, 36.0, 37.8, 40.2, 53.9, 61.6, 66.9, 69.5, 79.1, 80.5, 127.7, 129.7, 133.3, 135.6, 178.2, 211.0; MS (FAB) 502 (MH, 42), 239 (20), 199 (100); HRMS calcd for $C_{28}H_{44}O_5NSi$ 502.2989, found 502.3001 (−2.4 ppm).

(2*R*)-2-[(4*R*,5*R*,6*R*)-6-[(1*R*)-2-*tert*-Butyldiphenylsilyloxy-1-methylethyl]-2,2,5-trimethyl[1,3]dioxan-4-yl]-*N*,*N*-methoxymethylpropanamide (26). To diol **25** (30 mg, 0.60 mM) were added *p*-toluenesulfonic acid (1.1 mg, 0.006 mM) and 2,2-dimethoxypropane (0.9 mL). The mixture was stirred for 1 h at room temperature and concentrated under vacuum. Purification by flash column chromatography (hexanes−EtOAc, 7:3) gave a 2:1 mixture of acetonide **26** (20 mg, 63%) and lactone **24** (10.8 mg, 37%): R_f 0.65 (hexanes−EtOAc, 1:1); $[\alpha]^{20}_D$ −7.0 (*c* 1.4, $CHCl_3$); IR (neat) ν_{max} 3050, 2960, 1740, 1670, 1460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.78 (d, J = 6.4 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H), 1.05 (s, 9H), 1.12 (d, J = 7.1 Hz, 3H), 1.29 (s, 3H), 1.35 (s, 3H), 1.81−1.88 (m, 1H), 2.04−2.09 (m, 1H), 2.99 (bs, 1H), 3.16 (s, 3H), 3.38 (dd, J = 1.6, 10.4 Hz, 1H), 3.44 (dd, J = 6.6, 10.3 Hz, 1H), 3.64 (s, 3H), 3.71 (dd, J = 5.4, 10.0 Hz, 1H), 3.86 (dd, J = 6.4, 10.0 Hz, 1H), 7.36−7.43 (m, 6H), 7.67−7.72 (m, 4H); ^{13}C (100 MHz, $CDCl_3$) δ 8.8, 9.3, 11.5, 14.9, 15.0, 22.6, 25.5, 25.7, 29.8, 32.0, 37.2, 50.1, 56.9, 60.4, 71.7, 72.9, 73.2, 93.5, 102.2, 123.3, 123.4, 125.3, 129.8, 131.4, 133.4, 211.0; MS (FAB) *m*/*z* 542 (MH^+, 32), 484 (50), 199 (50), 146 (42), 135 (100); HRMS calcd for $C_{31}H_{48}O_5NSi$ 542.3302, found 542.3329 (−5.0 ppm). Anal. Calcd for $C_{31}H_{47}O_5NSi$: C, 68.72; H, 8.74; N, 2.59. Found: C, 68.95; H, 8.83; N, 2.59.

(2*R*)-2-[(4*R*,5*R*,6*R*)-6-[(1*R*)-2-*tert*-Butyldiphenylsilyloxy-1-methylethyl]-2,2,5-trimethyl[1,3]dioxan-4-yl]-5-[1,3]dioxolanepentan-3-one (28). Bromo-2-(2-ethyl)dioxolane (48 μL, 0.41 mmol) was dissolved in Et_2O (0.7 mL) and cooled to −78 °C in a two-necked round-bottom flask fitted with a condenser. The *tert*-butyllithium (1.7 M in pentane, 0.4 mL, 0.68 mmol) was added dropwise, and the mixture was stirred at −78 °C for 30 min. The solution was allowed to warm to 0 °C. Amide **26** (37 mg, 0.68 mmol) in solution with Et_2O (0.7 mL) was cannuled to organolithium **27**, and the resultant solution was stirred at room temperature for 20 min. The mixture was then poured into a solution of 5% HCl in EtOH (10 mL), cooled to 0 °C, and diluted with $Et_2O-CH_2Cl_2$ (1:1, 10 mL). The organic layer was washed with brine (2 × 10 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash column chromatography (hexanes−EtOAc, 4:1) gave ketone **28** (26 mg, 65%) as a yellow oil: R_f 0.43 (hexanes−Et_2O, 3:2); $[\alpha]^{20}_D$ −1.0 (*c* 1.8, $CHCl_3$); IR (neat) ν_{max} 3070, 3030, 2960, 2930, 2880, 1710, 1595, 1470, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.69 (d, J = 6.6 Hz, 3H), 0.94 (d, J = 7.1 Hz, 3H), 1.04 (s, 9H), 1.14 (d, J = 7.1 Hz, 3H), 1.30 (s, 3H), 1.35 (s, 3H), 1.63−1.72 (m, 2H), 1.88 (td, J = 4.6, 7.5 Hz, 2H), 1.99−2.18 (m, 1H), 2.56−2.62 (m, 2H), 2.65−2.69 (m, 1H), 3.38 (d, J = 10.4 Hz, 1H), 3.43 (dd, J = 6.8, 10.0 Hz, 1H), 3.57 (dd, J = 3.6, 10.2 Hz, 1H), 3.75−3.91 (m, 4H), 4.83 (t, J = 4.6 Hz, 1H), 7.36−7.44 (m, 6H), 7.65−7.70 (m, 4H); ^{13}C (100 MHz, $CDCl_3$) δ 12.2, 13.5, 15.5, 19.1, 26.9, 27.5, 29.9, 34.5, 35.3, 36.5, 50.2, 64.5, 64.9, 77.4, 98.0, 103.6, 127.6, 129.5, 133.9, 135.6, 211.8. Anal. Calcd for $C_{34}H_{50}O_6Si$: C, 70.06; H, 8.65. Found: C, 69.75; H, 8.99.

(2*R*,3*R*)-2-[(4*R*,5*R*,6*R*)-6-[(1*R*)-2-*tert*-Butyldiphenylsilyloxy-1-methylethyl]-2,2,5-trimethyl[1,3]dioxan-4-yl]-5-[1,3]dioxolanepentan-3-ol (29).[1k] To ketone **28** (0.23 mg, 0.04 mmol) in THF (0.8 mL) at −78 °C was added dropwise L-Selectride (1 M in THF, 79 μL, 0.08 mmol). The mixture was stirred at the same temperature for 1 h, and an additional 1 equiv of L-Selectride was added to the solution, which was then allowed to warm to −50 °C. After 2 h, the mixture was warmed to 0 °C over 30 min and quenched by the addition of MeOH (0.5 mL) and a small amount of SiO_2. The resultant suspension was filtered through a Celite pad, which had been rinsed well with EtOAc. The organic layer was washed with brine (2 × 1 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The two diastereoisomers, in a 7:1 ratio, were separated by flash column chromatography (hexanes−EtOAc, 4:1) to give the major alcohol **29** (17 mg, 72%) as a yellow oil: R_f 0.38 (hexanes−EtOAc, 4:1); $[\alpha]^{20}_D$ 1.07 (*c* 0.98, $CHCl_3$) [lit.[1k] $[\alpha]^{28}_D$ 1.19 (*c* 1.01, $CHCl_3$)]; ^1H NMR (400 MHz, $CDCl_3$) δ 0.68 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H), 0.99 (d, J = 7.1 Hz, 3H), 1.04 (s, 9H), 1.33 (s, 3H), 1.34 (s, 3H), 1.47−1.83 (m, 5H), 2.00−2.09 (m, 2H), 3.39−3.44 (m, 2H), 3.47 (dd, J = 1.3, 10.4 Hz, 1H), 3.60 (bs, 1H), 3.79−3.95 (m, 6H), 4.85 (t, J = 4.8 Hz, 1H), 7.36−7.45 (m, 6H), 7.67−7.71 (m, 4H); ^{13}C (100 MHz, $CDCl_3$) δ 11.0, 11.8, 15.5, 18.8, 19.1, 26.9, 29.2, 30.1, 30.7, 33.2, 36.0, 36.4, 64.4, 64.9, 69.6, 77.6, 81.5, 98.5, 104.6, 127.7, 129.6, 133.8, 135.7.

(2*R*,3*R*)-3-Benzyloxymethoxy-2-[(4*R*,5*R*,6*R*)-6-[(1*R*)-2-*tert*-butyldiphenylsilyloxy-1-methylethyl]-2,2,5-trimethyl-[1,3]dioxan-4-yl]-5-[1,3]dioxolanepentane:[5c] R_f 0.43 (hexanes−EtOAc, 4:1); $[\alpha]^{20}_D$ 24.5 (*c* 1.6, $CHCl_3$) [lit.[5c] $[\alpha]^{28}_D$ 26.2 (*c* 1.75, $CHCl_3$)]; ^1H NMR (400 MHz, $CDCl_3$) δ 0.68 (d, J = 6.2 Hz, 3H), 0.96 (d, J = 6.7 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H), 1.04 (s, 9H), 1.28 (s, 3H), 1.31 (s, 3H), 1.58−1.80 (m, 6H), 1.99−2.04 (m, 1H), 3.31−3.38 (m, 2H), 3.46 (dd, J = 6.8, 10.1 Hz, 1H), 3.77−3.93 (m, 6H), 4.60 (q AB, J = 11.9 Hz, $\Delta\nu_{AB}$ = 89 Hz, 2H), 4.78 (q AB, J = 6.4 Hz, $\Delta\nu_{AB}$ = 65.3 Hz, 2H), 4.84 (t, J = 4.6 Hz, 1H), 7.27−7.41 (m, 11H), 7.66−7.69 (m, 4H); ^{13}C (100 MHz, $CDCl_3$) δ 12.7, 12.8, 15.6, 19.2, 26.9, 29.1, 30.0, 30.2, 33.5, 36.8, 38.8, 64.6, 64.9, 69.7, 77.2, 77.6, 77.9, 95.0, 97.9, 104.6, 127.4, 127.6, 127.8, 128.3, 129.5, 134.0, 135.6, 138.4.

Acknowledgment. This work was supported financially by NSERC. We thank LaVonne Dlouhy for her assistance in the preparation of this manuscript.

Supporting Information Available: NMR spectra for compounds **5**, **8**, **9**, **13**, **15**, **17**, **19**, **21**, **23**, **24, 25**, and the C_7-C_{16} subunit of zincophorin. This material is available free of charge via the Internet at http://pubs.acs.org.

JO010310F