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Asymmetric Conjugate Addition for the Preparation of *syn*-1,3-Dimethyl Arrays: Synthesis and Structure Elucidation of Capensifuranone

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The synthesis of capensifuranone (**1**) has been achieved by the application of developments for asymmetric conjugate addition reactions of organocopper reagents with nonracemic *N*-enoyl-4-phenyl-1,3-oxazolidinones for the preparation of 1,3-*syn*-dimethyl arrays. The assignment of relative and absolute stereochemistry of **1** has been made following the high-field NMR characterizations of synthetic diol derivatives. The previously unassigned C_4 stereochemistry of **1** was determined to be of the (*S*)-configuration. The thermodynamic equilibration of capensifuranone and its C_4 diastereomer has been examined.

Introduction

Marine mollusks of the genus *Siphonaria* have yielded a number of structurally interesting secondary metabolites.[1] While it had been previously proposed that these metabolites were produced as a defense mechanism against natural predators,[1f] this concept is currently subject to debate.[1m] A common structural feature of this family of natural products is the occurrence of an aliphatic desoxygenated polypropionate side chain attached to either an unsaturated furanone, a pyranone, or a cyclic hemiacetal, in which the C_1 carboxylic acid headgroup of the biogenetic chain is embedded. Recently, the South African pulmonate mollusk *Siphonaria capensis* yielded three new polypropionates, capensifuranone **1**, capensinone **2**, and a biogentic precursor, (2*E*,4*S*,6*S*,8*S*)-2,4,6,8-tetramethyl-2-undecenoic acid **3** (Figure 1).[2] A related metabolite, pectinatone **4**, exhibits antibiotic activity.[1h,i,3] However, the biological activity of compounds **1** and **2** has yet to be fully investigated. Additional examples of interest include siphonarienfuranone (**5**)[1a,3] and siphonarienolone (**6**).[4]

An interesting structural feature shared by the metabolites of genus *Siphonaria* is the alternating 1,3-*syn* arrangement of methyl substituents in their respective aliphatic chains.[5] This structural motif offers a significant challenge for asymmetric synthesis and has inspired synthesis efforts toward members of the family.[6] Our previous efforts toward the syntheses of myxovirescin A_1,[7] sambutoxin,[8] and funiculosin[9] required the construction of an acyclic 1,3-*anti*-dimethyl array. The use of nonracemic 4-phenyl-1,3-oxazolidin-2-ones as chiral auxiliaries introduced by Hruby and co-workers[10] facilitated our studies. Thus, general methodology was developed for effecting facial selectivity in the asymmetric conjugate addition reactions of Yamamoto organocopper reagents[11] with enantiopure *N*-enoyl-1,3-oxazolidinones.[12] Our recent report of the conjugate additions of the Yamamoto

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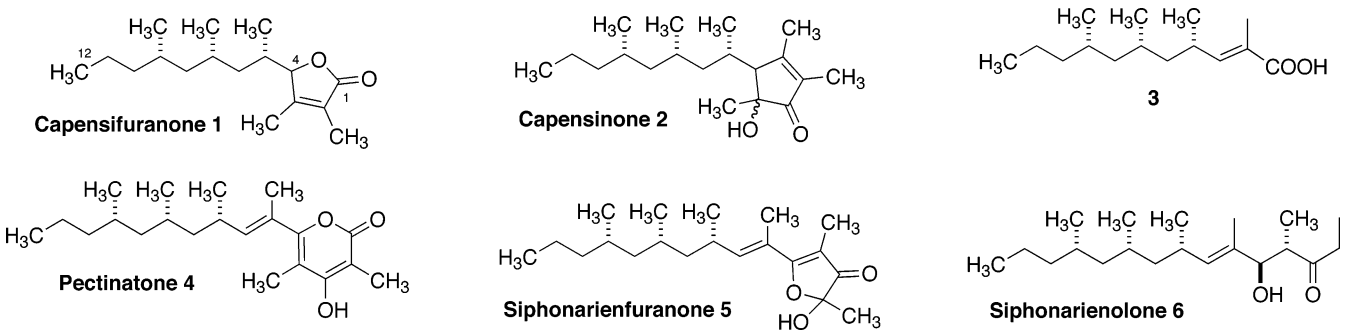
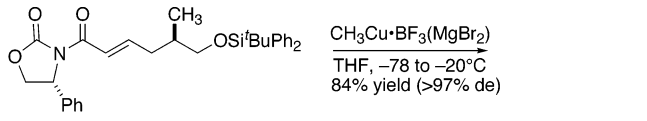
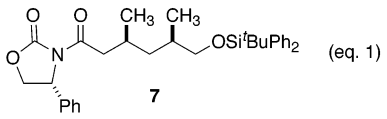


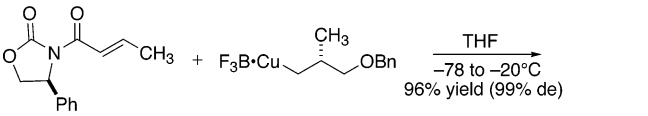
FIGURE 1. Secondary metabolites of marine mollusks of genus *Siphonaria*.

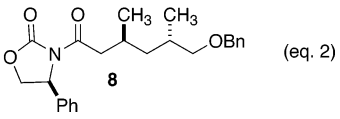
methylcopper reagent demonstrated features of double asymmetric induction, and provided accessibility to 1,3- and 1,2-*syn*- and *anti*-dimethyl arrays with excellent diastereoselectivity.[13] As illustrated in the production of *syn*-**7** (eq 1) and *anti*-**8** (eq 2), these results were particularly encouraging for the prospects of reiterative introduction of 1,3-asymmetry as posed in capensifuranone (**1**). Since the relative stereochemistry at C_4 of **1** could not be assigned in earlier isolation and characterization efforts, opportunities for establishing the relative and absolute configuration of **1** through synthesis provided further interest for these studies.





(eq. 1)





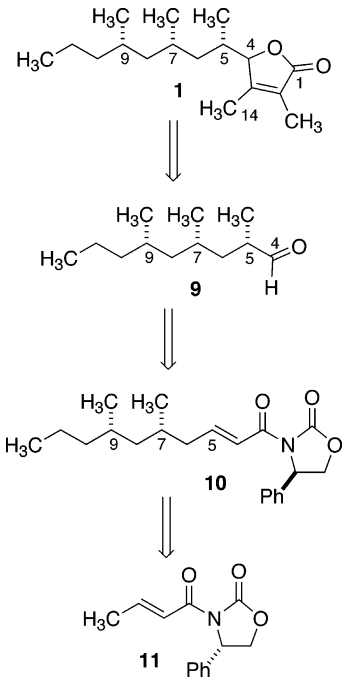
(eq. 2)

Herein, we describe our studies of asymmetric conjugate addition methodology which have led to the synthesis of (−)-capensifuranone (**1**). As summarized by the retrosynthetic analysis of Scheme 1, our plan would examine nucleophilic addition to the nonracemic aldehyde **9** to provide diastereomeric C_4 alcohols toward the assignment of relative stereochemistry in **1**. Conjugate addition to the enone **10** would establish the *all-syn* relationship in **9** and would require a one-carbon truncation of the aliphatic chain upon removal of the auxiliary. Thus, the iterative introduction of stereochemical features from **11** would provide a suitable starting point for these investigations.

Results and Discussion

The synthesis of the C_4-C_{12} carbon chain of capensifuranone (**1**) required the production of 1,3-asymmetry

SCHEME 1. Retrosynthetic Analysis of Capensifuranone



in an "*all-syn*" stereotriad. General strategies for the reiterative development of 1,3-stereorelationships are rare. However, recent findings by Negishi and co-workers[14] offer a noteworthy advancement via directed carbometalation of homoallylic alcohols. Asymmetric conjugate addition reactions play a central role in molecule constructions,[15–17] and previous efforts in our laboratories provided sufficient generality in the methodology to achieve this goal in an iterative fashion. This task was accomplished as shown in Scheme 2, beginning with the *N*-enoyl-4(*S*)-phenyl-1,3-oxazolidinon-2-one **11**.[18] Our stud-

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(14) Tan, Z.; Negishi, E. *Angew. Chem., Int. Ed.* **2004**, *43*, in press. Recently, Professor Negishi has informed us of adaptation of his enantioselective carboalumination methodology for synthesis of siphonarienolone and siphonarienone: Magnin-Lachaux, M.; Tan, Z.; Liang, B. Negishi, E. *Org. Lett.* **2004**, *6*, 1425.

(15) For a recent review of organocopper reagents: (a) Krause, N.; Gerold, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 283. (b) Krause, N. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 283.

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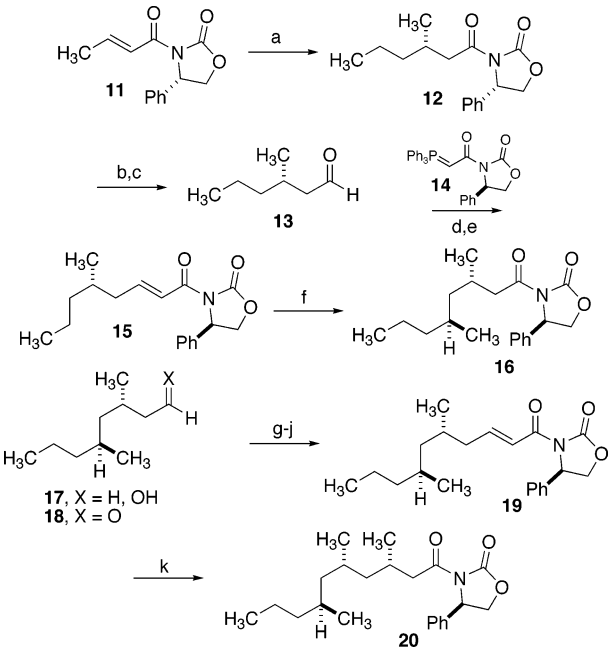
SCHEME 2. Iterative Stereocontrolled Synthesis of Polymethylated 20[a]



[a] Reagents and conditions: (a) ^{n}PrMgBr, CuBr·DMS, BF_3·OEt_2, THF, −78 °C, then oxazolidinone **11**, −78 → −20 °C, 16 h (95%, 91:9 dr); (b) $LiBH_4$, MeOH, Et_2O, 0 °C (86%); (c) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2, 1 h (98%); (d) ylide **14**, CH_2Cl_2, 16 h (99%, 2.5:1 *E*/*Z*); (e) I_2, *hν*, CH_2Cl_2. (95%, >20:1 *E*/*Z*); (f) MeMgBr, THF, CuBr·DMS, BF_3·OEt_2, −78 °C, then oxazolidinone **15**, −78 → −20 °C, 16 h (89%, >95:5 dr); (g) $LiBH_4$, MeOH, Et_2O, 0 °C (90%); (h) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2, 1 h (100%); (i) ylide **14**, CH_2Cl_2, 16 h (99%, 2.5:1 *E*/*Z*); (j) I_2, *hν*, CH_2Cl_2 (95%, >20:1 *E*/*Z*); (k) MeMgBr, THF, CuBr·DMS, BF_3·OEt_2, −78 °C, then oxazolidinone **19**, −78 → −20 °C, 16 h (86%).

ies[12] had shown that alkenyl and allylic Yamamoto reagents are more reactive than alkyl species, and the methyl reagent, generated in this manner, is the least reactive. In addition, stereochemical selectivity was generally enhanced in accord with increasing steric bulk of the carbon nucleophile. Thus, alkenyl and allyl conjugate additions are often completed at −78 °C, whereas alkyl and methyl reagents required warming to −20 °C. This temperature differential may contribute to the observed stereoselectivity in some cases. The Yamamoto organocopper reagent was prepared at −78 °C by the combination of equimolar proportions of *n*-propylmagnesium bromide, copper(I) bromide·dimethyl sulfide complex, and boron trifluoride etherate. Low-temperature addition of **11** with gradual warming to −20 °C resulted in formation of **12** with high yield and good diastereoselectivity (dr 91:9). Bis-coordination in the restricted conformer **A** (Figure 2) provides a predictive model for conjugate addition which avoids nonbonded interactions with the 4-phenyl substituent. Indeed, low-temperature NMR data have supported formation of a single species with bidentate Lewis acids.[19] While this viewpoint provides a consistent rationale for diastereoselectivity in the observed behavior of organocopper species, the model has a number of shortcomings. For example, homochiral 4-benzyl and 4-isopropyl analogues of **11** demonstrate the

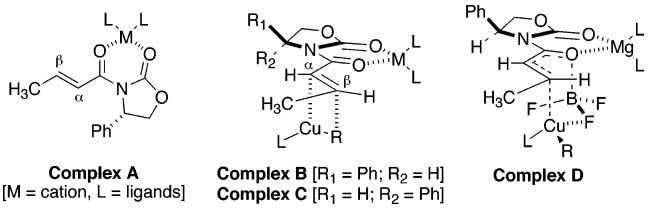


FIGURE 2. Chelation complexes of the *syn-S-cis* conformer of **11**.

conjugate addition of organocopper reagents under the same conditions with a general trend of a reversal of facial selectivity.[12] Furthermore, modeling indicates that the 4-phenyl substituent would not extend into the local environment of the β-carbon of the planar enone **11**. This suggests it would be more likely that the phenyl ring could sterically destabilize the initial synclinal metal complexation of copper reagent at the α-carbon as suggested in **C** of Figure 2 versus the diastereomeric arrangement in **B**. While these reactions may initially involve π-coordination, the four-centered mechanism in complex **B** is no longer favored in the case of lithium dialkylcuprate additions.[20] These studies feature a six-atom arrangement with lithium cation activation of the carbonyl oxygen. An analogous role could be proposed for BF_3 in complex **D**, in which a bridging fluoride provides for activation. The new C−C bond is made by reductive elimination from a Cu^{3+} intermediate. Indeed, this mechanistic picture is particularly challenging owing to the lack of structural information regarding the Yamamoto organocopper species.[21] Although we have not attempted a systematic study of cuprate reactivity, lithium dialkylcuprates appear to lead to substantial amounts of byproduct, some of which stems from attack at the C_2 carbonyl of the oxazolidinone system.[22] On the other hand, recent results from our laboratories have shown that bis-chelated **A** undergoes diastereocontrolled conjugate additions of allylstannanes with the opposite sense of facial selectivity compared to allyl Yamamoto reagents.[23]

The asymmetric conjugate addition was scaleable and produced multigram quantities of optically pure **12** (Scheme 2) after flash chromatography. Reductive removal of the chiral auxiliary and oxidation gave aldehyde **13** for chain elongation. Homologation was accomplished in an efficient manner utilizing ylide **14**[24] which afforded nearly quantitative conversion to the expected enone.

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(19) (a) Castellino, S.; Dwight, W. J. *J. Am. Chem. Soc.* **1993**, *115*, 2986. (b) Castellino, S. *J. Org. Chem.* **1990**, *55*, 5197. (c) Additionally, our low temeperature ^{13}C NMR studies of complexes of **11** with $ZrCl_4$, $Sc(OTf)_3$, and $Sm(OTf)_3$ confirm the presence of a single complex in complete agreement with the bidentate complexes described in ref 18a and 18b.

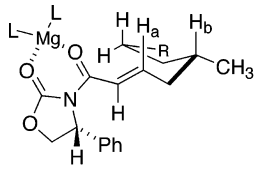
(20) For a review: Nakamura, E.; Mori, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3750.

(21) Neutral RCu species would be expected to behave as Lewis acids. However, polymeric complexes, dimers or tetramers could be involved in nucleophilic conjugate additions.

(22) We have noted that a study of conjugate addition reactions of vinylmagnesium bromide has led to a major correction of product structures demonstrating nucleophilic attack at the C_2 carbonyl of the oxazolidin-2-one system rather than the anticipated 1,4 addition. Han, Y.; Hruby, V. J. *Tetrahedron Lett.* **1997**, *38*, 7317 and Han, Y.; Hruby, V. J. *Tetrahedron Lett.* **1998**, *39*, 8561.

(23) Williams, D. R.; Mullins, R. J.; Miller, N. A. *Chem. Commun.* **2003**, 2220.

(24) Lee, K.; Cha, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 5590.



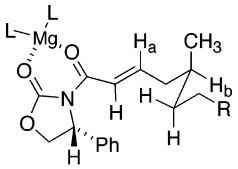


FIGURE 3. Conformations of γ-methyl substitution with bischelation.

However, inspection of the NMR data of crude product indicated the presence of a 2.5:1 mixture of *E*/*Z*-olefin isomers. Fortunately, a solution of the mixture containing a crystal of iodine was exposed to sunlight, which facilitated complete isomerization to the desired *E*-enone **15** (95% yield over these two steps).[25]

Conjugate 1,4-addition of methylcopper reagent to **15** proceeded with excellent diastereoselectivity (dr >95:5) in high overall yield (89%). The preexisting γ-stereogenecity at the homoallylic site in **15** led to a stereochemically reinforcing situation with respect to the chirality of the auxiliary. Our rationalization of the matched scenario is based upon a conformational analysis of 1,4-nonbonded interactions as summarized in Figure 3. Conformer **A** would minimize gauche interactions with a staggered butane geometry (alkenyl/methyl). This arrangement eliminates one gauche interaction compared to conformer **B** providing 0.6 kcal/mol of additional stability. As a result, the acyclic chain of **A** impedes nucleophilic attack to the α-face of the planar enoyl unit enhancing the role of the phenyl group of the chiral auxiliary. In conformer **B**, the acyclic chain is projected above the plane of the enoyl unit. Conformer **B** is mismatched in this regard and otherwise introduces the additional gauche butane interaction owing to the position of the homoallylic methyl group. In fact, the conjugate addition of methylcopper reagent in the case of the corresponding *tert*-butyldiphenylsilyl ethers (R = OSi-*t*-$C_4H_9Ph_2$) has led to greater than 97% diastereoselectivity via the synergy of the phenyl substituent and the bulk of the silyl ether.[13]

Installation of asymmetry at C_5 proceeded with the iterative introduction of the methyl substituent via reductive removal of the auxiliary in **16** (Scheme 2), followed by oxidation of the resulting primary alcohol **17** to yield aldehyde **18** and Wittig homologation to **19**. Once again, conjugate addition of the Yamamoto methylcopper species in enone **19** proceeded with reinforcing elements of stereochemistry and provided the single diastereomer **20** in 86% yield.

(25) As an alternative, the use of the corresponding phosphonate reagent *i* was explored in an attempt to secure the *E*−enone in a single operation. The phosphonate was prepared in accordance with published procedure: Broka, C. A.; Ehrler, J. *Tetrahedron Lett.* **1991**, *32*, 5907. While these efforts led to exclusive *E*−olefin selectivity, poor yields (~30%) were obtained in gram-scale reactions.

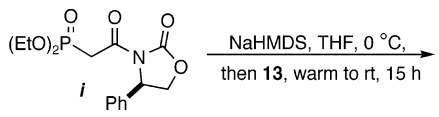
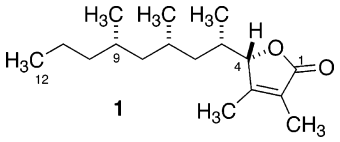


TABLE 1. Comparison of ^{13}C NMR Data for Synthetic and Natural Capensifuranone 1 and 27[a]



carbon	natural **1** δ_C (ppm)	synthetic **1** δ_C[a] (ppm)	synthetic **27** δ_C[a] (ppm)
1	174.8	174.7	175.0
2	124.6	124.5	124.1
3	158.0	158.1	158.5
4	87.8	87.8	85.0
5	32.1	32.0	31.5
6	36.6	36.5	39.0
7	29.8	29.7	29.6
8	44.5	44.3	45.3
9	27.7	27.5	27.3
10	38.4	38.2	41.3
11	19.8	19.8	20.0
12	14.4	14.4	14.4
13	8.4	8.4	8.4
14	12.4	12.4	12.3
15	17.5	17.4	11.9
16	21.2	21.2	20.4
17	20.7	20.7	20.3

[a] Spectra recorded at 100 MHz

While a number of alternatives were considered to address the issue of stereochemistry at C_4 of **1**, we have found that oxidation of the enolate of **20** with the Davis oxaziridine **21**[26,27] led to the α-hydroxyimide **22** with high diastereoselectivity (dr 10:1). Purification and $LiBH_4$ reduction gave the optically active diol **23** which was assigned as the C_4-(*R*)-isomer for subsequent comparisons. To ensure formation of both C_4 diastereomers of **1**, sodium periodate cleavage of diol **23** gave aldehyde **24** which was then utilized for direct assembly of the butyrolactone via nucleophilic addition of the dianion derived from (*E*)-3-bromo-2-methyl-2-propenoic acid.[28] The reaction cleanly provided a 4:1 mixture of separable C_4 diastereomers **25** and **26**, wherein product **25**, corresponding to the expected result of Felkin−Anh addition, was assumed to predominate. Each isomeric lactone was independently subjected to the conditions of Negishi coupling[29] using dimethylzinc in the presence of palladium catalyst to replace the C_3 bromide with a methyl substituent without epimerization of the labile C_4 position. In the event, synthetic capensifuranone (**1**) was exclusively formed from the minor condensation product **26** while the major butyrolactone **25** gave rise to the diastereomer **27**. Spectral characterization of synthetic **1** was in agreement with the NMR spectra and published physical data for natural capensifuranone.[2] Table 1 provides a listing of carbon assignments from our ^{13}C NMR data for synthetic **1** and the C_4 diastereomer **27** as

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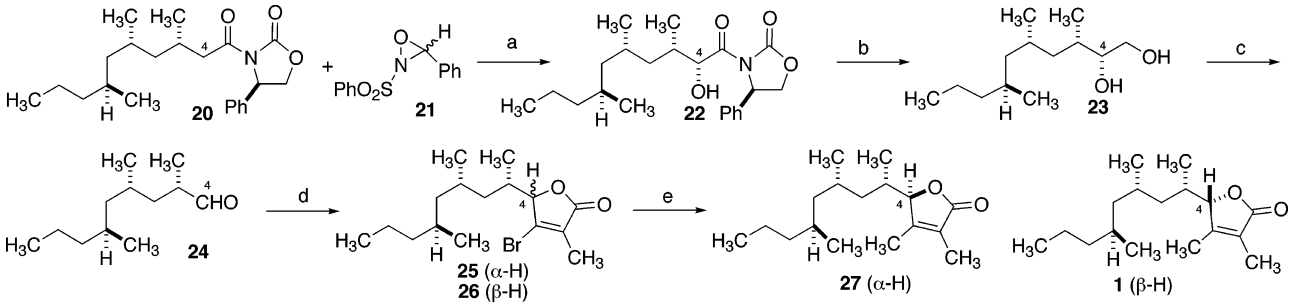
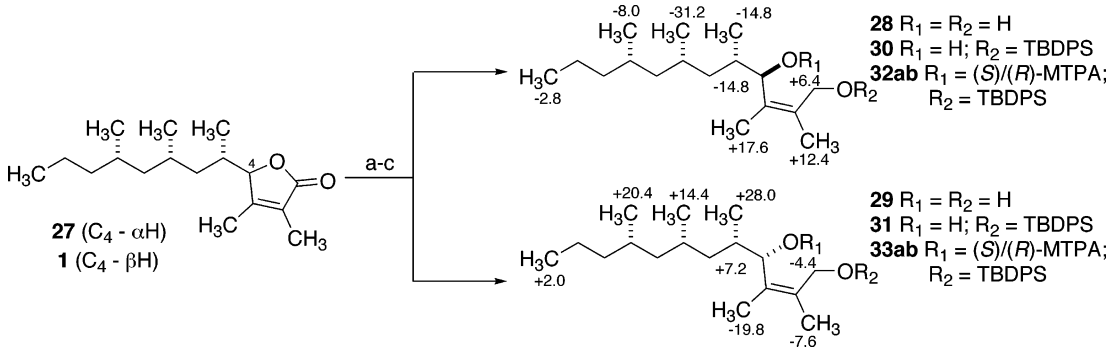
(27) Evans, D. A.; Morissey, M. M.; Dorrow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346.
(28) (a) Caine, D.; Samuels, W. D. *Tetrahedron Lett.* **1980**, *21*, 4057. (b) Caine, D.; Ukachukwu, V. C. *J. Org. Chem.* **1985**, *50*, 2195 (c) Caine, D.; Ukachukwu, V. C. *Tetrahedron Lett.* **1983**, *24*, 3959. (d) Caine, D.; Frobese, A. S. *Tetrahedron Lett.* **1978**, 5167.
(29) (a) Wipf, P.; Soth, M. J. *Org. Lett.* **2002**, *4*, 1787 (b) Tamara, Y.; Kagotani, M.; Yushida, Z. I. *J. Org. Chem.* **1980**, *45*, 5223 (c) Negishi, E. I.; Luo, F. T.; Frisbee, R.; Matsushita, H. *Heterocycles* **1982**, *18*, 117.

SCHEME 3. Completion of the Total Synthesis[a]



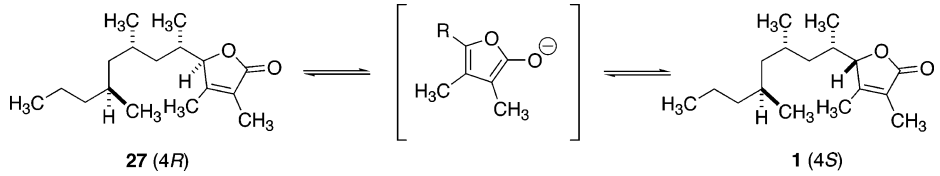
[a] Reagents and conditions employed: (a) NaHMDS, THF, −78 °C, then Davis oxaziridine, 15 s, then CSA, THF (10:1 dr); (b) $LiBH_4$, MeOH, Et_2O, 0 °C, 1 h (93% from **20**); (c) $NaIO_4$, THF, pH 7 buffer, 2 h (84%); (d) (*E*)-3-bromo-2-methyl-2-propenoic acid, BuLi (2 equiv), THF, 30 min, −78 °C, then aldehyde **24**, −78 → rt, 16 h, H_3O^+ (97%, 4:1 dr); (e) Me_2Zn, $Pd(PPh_3)_4$, THF, −78 °C, 16 h (99%).

SCHEME 4. Absolute Stereochemistry Determination of Lactones 1 and 27 by the Mosher Method[a,b]



[a] Δδ values ((*S*)-MTPA − (*R*)-MTPA) obtained for the MTPA esters of **1** and **27**. Δδ values are expressed in hertz (400 MHz). [b]Reagents and conditions employed: (a) $LiAlH_4$, Et_2O, 0 °C , **1**/**27**, 0 °C → rt, 16 h, (98%); (b) Imid, TBDPSCl, CH_2Cl_2, 1 h, (95%); (c) DMAP, Et_3N, Mosher acid chloride, CH_2Cl_2, 45 min.

SCHEME 5. Equilibration of Capensifuranone 1 and *epi*-Capensifuranone 27



well as the reported data for natural **1**. Proton NMR spectra of natural and synthetic **1** were identical in all respects.[30]

To confirm our assumptions regarding the assignment of C_4 stereochemistry, a series of chemical conversions were undertaken. First, the lithium aluminum hydride reduction of the major diastereomer **25** gave the expected alkenyl diol which was treated with ozone (O_3, CH_2Cl_2, −78 °C) followed by a lithium borohydride quench. This procedure yielded a diol which proved to be identical with **23** (Scheme 3) in all respects. Thus, substantial literature precedent[26,27] for the stereocontrolled hydroxylation of the *Z*(O)-enolate leading to **22** coincides with the stereochemistry of Felkin−Anh addition in **25**. Second, lactones **1** and **27** were independently subjected to lithium aluminum hydride reductions to yield a pair of nonracemic diols **28** and **29** (Scheme 4). Protection of the primary alcohol and acylation of the secondary allylic alcohol led to four products **32ab** and **33ab** for modified Mosher analysis.[31] Chemical shift differences (Δδ) for the ^1H NMR data ((*S*)-MTPA − (*R*)-MTPA) were obtained for the pairs of α-methoxy-α-trifluromethyl phenylacetic acid (MTPA) esters **32ab** and **33ab** as summarized in Scheme 4. The treatment unambiguously validated our assignment of (*S*)-stereochemistry at C_4 in **33** and (*R*)-**32**. This corroborating evidence also established the absolute stereochemistry of **1**.

Finally, we considered the possibility that facile C_4 epimerization of the butyrolactone moiety of capensifuranone in the marine environment could account for the observed stereochemistry in **1** as a result of its thermodynamic stability. Thus, methanol solutions of synthetic **1** and 4-*epi*-capensifuranone **27** were individually equilibrated in the presence of DBU (Scheme 5). In each case, this study gave rise to a 2.5:1 mixture of diastereomers favoring the epimeric C_4 isomer **27**, a derivative which has not been found to date as a naturally occurring metabolite.

(30) We are indebted to Professor Mike Davies-Coleman, Rhodes University (Grahamstown, South Africa) for providing ^1H, ^{13}C and DEPT spectra of authentic capensifuranone which were used to confirm the identity of our synthetic **1**.

(31) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

Conclusion

The synthesis of capensifuranone has been completed leading to the assignment of C_4 stereochemistry and the absolute configuration of **1**. We have demonstrated the applicability of asymmetric 1,4-conjugate additions of organocopper reagents using nonracemic 4-phenyl-1,3-oxazolidin-2-ones for the reiterative generation of 1,3-*syn*-dimethyl arrays. The generality of the process offers promise for widespread applications in natural products synthesis.

Experimental Section

(4*S*)-3-((3*S*)-3-Methylhexanoyl)-4-phenyloxazolidin-2-one (12). A solution of propylmagnesium bromide (2.0 M solution in Et_2O, 61.0 mL, 122 mmol) was added dropwise to a suspension of recrystallized CuBr·DMS (24.9 g, 121 mmol) in THF (400 mL) at −40 °C. After 1 h, the mixture was cooled to −78 °C for the dropwise addition of freshly distilled BF_3·OEt_2 (15.3 mL, 121 mmol), and a precooled solution of oxazolidinone **11**[17] (12.7 g, 54.9 mmol) in THF (100 mL) was added 5 min later. The suspension was stirred for 3 h at −78 °C and was then transferred with its dry ice/acetone bath to a freezer where it was stirred for 18 h while warming to −20 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl (500 mL) and diluted with Et_2O (500 mL). The phases were separated, and the aqueous layer was extracted with Et_2O (2 × 500 mL). Combined organic phases were washed with H_2O (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (4:1 hexanes/EtOAc) to afford 14.4 g (95%, 91:9 dr) of **12** as a white solid: R_f = 0.6 (hexanes/EtOAc 2:1); $[\alpha]^{20}_D$ +32.2 (*c* 0.90, $CHCl_3$); ^{1}H NMR (400 MHz) δ 7.40−7.28 (m, 5H), 5.43 (dd, J = 8.9, 3.8 Hz, 1H), 4.68 (t, J = 8.9 Hz, 1H), 4.27 (dd, J = 8.9, 3.8 Hz, 1H), 2.98 (A of ABX, J_{AB} = 16.0 Hz, J_{AX} = 5.3 Hz, 1H), 2.67 (B of ABX, J_{AB} = 16.0 Hz, J_{BX} = 8.6 Hz, 1H), 2.06−1.96 (m, 1H), 1.34−1.14 (m, 4H), 0.85 (d, J = 6.6 Hz, 3H), 0.84 (t, J = 6.2 Hz, 3H); ^{13}C NMR (100 MHz) δ 172.2, 153.6, 139.2, 129.0, 128.5, 125.8, 69.7, 57.5, 42.4, 39.0, 29.3, 19.8, 19.4, 14.0; IR (thin film) 3031, 2958, 2929, 2872, 1783, 1705, 1457, 1384, 1321, 1198, 1081, 1045, 761, 707 cm^{-1}; HRMS (DEI) calcd for $C_{16}H_{21}O_3N$ (M^+) 275.1521, found 275.1513.

(3*S*)-3-Methylhexanal (13). Lithium borohydride (0.59 g, 27 mmol) was added in one portion to a solution of imide **12** (5.0 g, 18 mmol) in Et_2O (180 mL) at −20 °C. Methanol (1.1 mL, 27 mmol) was then added dropwise to this reaction mixture at −20 °C, and the reaction was stirred for 1 h while warming to room temperature. The reaction was carefully diluted with saturated aqueous $NaHCO_3$ (100 mL), and the phases were separated with additional extractions of the aqueous layer with Et_2O (3 × 200 mL). The combined organic phases were washed with H_2O (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (4:1 pentane/Et_2O) to afford 1.8 g (86%) of (3*S*)-3-methylhexanol as a clear oil: R_f = 0.5 (hexanes/EtOAc 2:1); $[\alpha]^{20}_D$ = −0.94 (*c* 0.91, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73−3.63 (m, 2H), 1.64−1.51 (m, 2H), 1.43−1.34 (m, 2H), 1.33−1.24 (m, 2H), 1.16−1.08 (m, 1H), 0.89 (d, J = 6.6 Hz, 3H), 0.88 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 61.2, 40.0, 39.4, 29.2, 20.0, 19.6, 14.3; IR (thin film): 3327, 2957, 2929, 2873, 1456, 1056 cm^{-1}; HRMS (DEI) calcd for C_7H_{14} ($M^+ - H_2O$) 98.1096, found 98.1092.

Solid $NaHCO_3$ (10.2 g, 122 mmol) was added in one portion to a solution of (3*S*)-3-methylhexanol (1.0 g, 8.1 mmol) in dry methylene chloride (41 mL) at rt and was followed by the addition of Dess−Martin periodinane (6.9 g, 16 mmol). The mixture was stirred for 2.5 h, and the contents of the reaction were then poured into a solution comprised of saturated aq $NaHCO_3$ (150 mL), pH 7 buffer (150 mL), and saturated aq $Na_2S_2O_3$ (150 mL). After vigorously stirring for 2.5 h, the phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 0.91 g (98%) of **13** as a clear oil, which was used in the next step without further purification. This product was characterized as follows: R_f = 0.5 (hexanes/EtOAc 6:1); $[\alpha]^{20}_D$ −7.9 (*c* 0.09, $CHCl_3$); ^{1}H NMR (400 MHz) δ 9.76 (t, J = 2.4 Hz, 1H), 2.39 (ddd, J = 17.0, 5.6, 2.4 Hz, 1H), 2.22 (ddd, J = 17.0, 7.8, 2.4 Hz, 1H), 2.13−2.02 (m, 1H), 1.42−1.18 (m, 4H), 0.96 (d, J = 6.7 Hz, 3H), 0.90 (t, J = 7.1 Hz, 3H); ^{13}C NMR: 203.1, 51.1, 39.2, 27.9, 20.0, 19.9, 14.1; IR (thin film) 2958, 2929, 2715, 1726, 1151, 1115 cm^{-1}; HRMS (DEI) calcd for $C_7H_{15}O$ (M^+ + H) 115.1123, found 115.1122.

(*R*)-4-Phenyl-3-[(triphenylphosphoranylidene)acetyl]-oxazolidin-2-one (14).[24] Phosphonium ylide **14** was prepared by standard methods and was characterized according to the following spectral data: R_f = 0.3 (hexanes/EtOAc 1:2); mp 170−174 °C; $[\alpha]^{21}_D$ = −80.1 (*c* 1.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 7.59−7.47 (m, 8H), 7.39−7.29 (m, 12H), 5.57 (dd, J = 8.6, 3.5 Hz, 1H), 4.73 (d, J = 23.5 Hz, 1H), 4.58 (t, J = 8.6 Hz, 1H), 4.12 (dd, J = 8.6, 3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 155.2, 141.4, 132.9, 131.9, 128.6, 127.5, 127.0, 126.1, 125.7, 68.9, 40.8, 39.7; IR (thin film): 3057, 2905, 1751, 1587, 1434, 1359, 1137 cm^{-1}; HRMS (EI) calcd for $C_{29}H_{24}O_3NP$ (M^+) 465.1494, found 465.1497.

(4*R*)-3-((5*S*)-(2*E*)-Methyl-oct-2-enoyl)-4-phenyloxazolidin-2-one (15). Phosphonium ylide **14** (23 g, 49 mmol) was added to a solution of aldehyde **13** (3.7 g, 32 mmol) in CH_2Cl_2 (65 mL). The reaction mixture was stirred for 24 h and subsequently concentrated in vacuo. The residue was purified by flash silica gel chromatography (8:1 hexanes/EtOAc → 3:1 hexanes/EtOAc) to afford a 2.5:1 mixture (*E*/*Z*) of olefin isomers which were used directly as described below**.** Characteristic ^{1}H NMR signals for the olefin isomers are as follows: *E*-isomer [β-H: δ 7.03 (dt, J = 15.3, 7.3 Hz, 1H)], *Z*-isomer [β-H: δ 6.29 (dt, J = 11.7, 7.3 Hz, 1H)].

The mixture of olefin isomers was dissolved in CH_2Cl_2 (30 mL) and treated with iodine (two crystals). After being stirred in sunlight for 2 d, the reaction mixture was quenched with saturated aq $Na_2S_2O_3$ (30 mL) and diluted with EtOAc (50 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (9:1 hexanes/EtOAc) to afford 8.0 g (82%, two steps from **13**) of **15** as a white solid: R_f = 0.5 (hexanes/EtOAc 2:1); mp 48−49 °C; $[\alpha]^{20}_D$ = −84.0 (*c* 0.63, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 7.36−7.24 (m, 5H), 7.20 (d, J = 15.3 Hz, 1H), 7.03 (dt, J = 15.3, 7.3 Hz, 1H), 5.43 (dd, J = 8.9, 3.7 Hz, 1H), 4.65 (t, J = 8.9 Hz, 1H), 4.23 (dd, J = 8.9, 3.7 Hz, 1H), 2.24−2.16 (m, 1H), 2.09−2.01 (m, 1H), 1.62−1.52 (m, 1H), 1.26−1.20 (m, 3H), 1.11−1.05 (m, 1H), 0.82 (d, J = 6.7 Hz, 3H), 0.84−0.79 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 153.7, 151.3, 139.1, 129.1, 128.6, 125.9, 121.1, 69.9, 57.7, 40.1, 38.9, 32.3, 20.0, 19.6, 14.2; IR (thin film) 2958, 2927, 2872, 1780, 1688, 1634, 1457, 1284, 1102 cm^{-1}; HRMS (DEI) calcd for $C_{18}H_{23}O_3N$ (M^+) 301.1678, found 301.1678.

(4*R*)-3-((3*S*,5*S*)-3,5-Dimethyloctanoyl)-4-phenyloxazolidin-2-one (16). A solution of methylmagnesium bromide (3.0 M solution in Et_2O, 35.6 mL, 107 mmol) was added dropwise to a suspension of recrystallized CuBr·DMS (22.0 g, 107 mmol) in THF (150 mL) at −40 °C. After 1 h, the mixture was cooled to −78 °C, and freshly distilled BF_3·OEt_2 (13.6 mL, 107 mmol) was added dropwise. After the mixture was stirred at −78 °C, oxazolidinone **15** (6.44 g, 21.4 mmol) in THF (60 mL) was slowly added. The suspension was stirred for 3 h at −78 °C and was then transferred with its dry ice/acetone bath to a freezer where it was allowed to slowly warm to −20 °C with stirring for 18 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (100 mL) and saturated aqueous

$NaHCO_3$ (50 mL) and then diluted with Et_2O (200 mL). The phases were separated, and the aqueous layer extracted with Et_2O (2 × 200 mL). The combined organic phases were washed with H_2O (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (4:1 hexanes/EtOAc) to afford 5.2 g (89%, >20:1 dr) of **16** as a white solid: $R_f = 0.5$ (hexanes/EtOAc 2:1); mp 76−78 °C; $[\alpha]^{20}_D = -51.0$ (*c* 0.63, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.22 (m, 5H), 5.39 (dd, $J = 8.9$, 3.7 Hz, 1H), 4.63 (t, $J = 8.9$ Hz, 1H), 4.21 (dd, $J = 8.9$, 3.7 Hz, 1H), 2.77 (app d, $J = 6.7$ Hz, 2H), 2.10−2.00 (m, 1H), 1.44−1.36 (m, 1H), 1.22−1.12 (m, 2H), 0.98−0.90 (m, 2H), 0.80 (d, $J = 6.4$ Hz, 3H), 0.77 (d, $J = 6.7$ Hz, 3H), 0.82−0.72 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 153.7, 139.2, 129.1, 128.6, 125.9, 69.8, 57.6, 44.6, 42.5, 38.6, 29.7, 27.2, 20.2, 20.1, 19.9, 14.3; IR (thin film) 2956, 2928, 2872, 1784, 1704, 1457, 1196, 1060 cm^{-1}; HRMS (DEI) calcd for $C_{19}H_{27}O_3N$ (M^+) 317.1991, found 317.1990.

(3*S*,5*S*)-3,5-Dimethyloctanol (17). Lithium borohydride (0.23 g, 11 mmol) was added in one portion to a solution of imide **16** (1.7 g, 5.3 mmol) in Et_2O (53 mL) at −10 °C. Methanol (0.43 mL, 11 mmol) was added dropwise to this mixture at −10 °C, and the reaction was stirred for 1 h while slowly warming to room temperature. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (50 mL), phases were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic phases were washed with H_2O (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (4:1 pentane/Et_2O) to afford 0.77 g (90%) of **17** as a clear oil: $R_f = 0.5$ (hexanes/EtOAc 2:1); $[\alpha]^{20}_D = -3.85$ (*c* 0.68, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74−3.62 (m, 2H), 1.70−1.56 (m, 2H), 1.55−1.46 (m, 1H), 1.36−1.28 (m, 2H), 1.27−1.18 (m, 3H), 1.10−0.95 (m, 2H), 0.88 (d, $J = 6.7$ Hz, 3H), 0.85 (t, $J = 6.6$ Hz, 3H), 0.84 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 61.2, 45.3, 39.8, 39.1, 29.7, 26.9, 20.2, 20.2, 20.0, 14.4; IR (thin film) 3328, 2957, 2927, 2872, 1458, 1379, 1058 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{20}O$ ($M^+ - H$) 157.1592, found 157.1594.

(3*S*,5*S*)-3,5-Dimethyloctanal (18). Solid $NaHCO_3$ (5.4 g, 64 mmol) was added in one portion to a solution of alcohol **17** (0.68 g, 4.3 mmol) in dry methylene chloride (21 mL) at rt, followed immediately by the addition of Dess−Martin periodinane (3.6 g, 8.6 mmol). The mixture was stirred for 2.5 h, at which point the contents of the reaction were poured into a solution containing saturated aq $NaHCO_3$ (75 mL), pH 7 buffer (75 mL), and saturated aq $Na_2S_2O_3$ (75 mL). After the mixture was stirred vigorously for 2.5 h, the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 0.67 g (100%) of **18** as a clear oil, which could be used in the next step without further purification. Characterization of aldehyde **18** is described as follows: $R_f = 0.9$ (hexanes/EtOAc 2:1); $[\alpha]^{20}_D = -3.26$ (*c* 3.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (d, $J = 2.1$ Hz, 1H), 2.41−2.33 (m, 1H), 2.20−2.10 (m, 2H), 1.50−1.41 (m, 1H), 1.36−1.27 (m, 2H), 1.27−1.19 (m, 2H), 1.09−1.00 (m, 2H), 0.94 (d, $J = 6.3$ Hz, 3H), 0.86 (t, $J = 6.8$ Hz, 3H), 0.84 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.2, 50.9, 44.8, 39.0, 31.6, 29.7, 25.7, 22.6, 19.9, 14.3; IR (thin film) 2947, 2926, 2873, 1723, 1375 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{20}O$ (M^+) 156.1514, found 156.1514.

(4*R*)-3-((5*S*,7*S*)(2*E*)-5,7-Dimethyldec-2-enoyl)-4-phenyloxazolidin-2-one (19). Phosphonium ylide **14** (3.0 g, 6.4 mmol) was added in one portion to a solution of aldehyde **18** (0.67 g, 4.3 mmol) in CH_2Cl_2 (9.0 mL). The reaction mixture was stirred for 24 h and then was concentrated in vacuo. The residue was purified by flash silica gel chromatography using a solvent gradient of 8:1 hexanes/EtOAc to 3:1 hexanes/EtOAc affording a 2.5:1 mixture (*E*/*Z*) olefin isomers**.** Characteristic ^{1}H NMR signals for the olefin isomers are described as follows: *E*-isomer [β-H: δ 7.04 (dt, $J = 15.3$, 7.3 Hz, 1H)], *Z*-isomer [β-H: δ 6.33 (dt, $J = 11.7$, 7.3 Hz, 1H)].

This mixture of olefin isomers was dissolved in CH_2Cl_2 (9 mL) and treated with iodine (two crystals). After being stirred in sunlight for 2 d, the reaction mixture was quenched with saturated aq $Na_2S_2O_3$ (25 mL) and diluted with EtOAc (25 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL). Combined organic phases were washed with brine (25 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (9:1 hexanes/EtOAc) to afford 1.2 g (82%, two steps from **18**) of **19** (dr > 20:1) as a white solid: $R_f = 0.4$ (hexanes/EtOAc 4:1); mp 60−64 °C; $[\alpha]^{20}_D = -71.8$ (*c* 2.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5H), 7.22 (d, $J = 15.3$ Hz, 1H), 7.04 (dt, $J = 15.3$, 7.3 Hz, 1H), 5.44 (dd, $J = 8.9$, 4.0 Hz, 1H), 4.64 (t, $J = 8.9$ Hz, 1H), 4.22 (dd, $J = 8.9$, 4.0 Hz, 1H), 2.27−2.19 (m, 1H), 2.05−1.97 (m, 1H), 1.72−1.64 (m, 1H), 1.48−1.40 (m, 1H), 1.30−1.24 (m, 1H), 1.24−1.14 (m, 3H), 1.08−1.00 (m, 1H), 0.96−0.88 (m, 1H), 0.82 (d, $J = 6.4$ Hz, 3H), 0.79 (d, $J = 6.7$ Hz, 3H), 0.77 (t, $J = 6.7$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 153.7, 151.1, 139.1, 129.1, 128.6, 125.9, 121.1, 69.9, 57.7, 44.5, 39.8, 39.0, 29.9, 29.6, 20.1, 20.0, 19.9, 14.3; IR (thin film) 2957, 2918, 1780, 1690, 1634, 1197, 1061 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{29}O_3N$ (M^+) 343.2147, found 343.2147.

(4*R*)-3-((3*S*,5*S*,7*S*)-3,5,7-Trimethyldecanoyl)-4-phenyloxazolidin-2-one (20). A solution of methylmagnesium bromide (3.0 M solution in Et_2O, 5.9 mL, 18 mmol) was added dropwise to a suspension of recrystallized CuBr·DMS (3.6 g, 18 mmol) in THF (35 mL) at −40 °C. After 1 h, the mixture was cooled to −78 °C, and freshly distilled BF_3·OEt_2 (2.2 mL, 18 mmol) was added dropwise. Upon stirring at −78 °C, the oxazolidinone **19** (1.2 g, 3.5 mmol) in THF (35 mL) was slowly introduced. This suspension was stirred for 3 h at −78 °C and was then transferred with its dry ice/acetone bath to a freezer where it was allowed to slowly warm to −20 °C with continuous stirring for 18 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (50 mL) and saturated aqueous $NaHCO_3$ (25 mL) and diluted with Et_2O (100 mL). The phases were separated and the aqueous layer extracted with Et_2O (2 × 100 mL). The combined organic phases were washed with H_2O (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (4:1 hexanes/EtOAc) to afford 1.1 g (86%, >20:1 dr) of **20** as a white solid: $R_f = 0.4$ (hexanes/EtOAc 4:1); mp 63−65 °C; $[\alpha]^{24}_D = -41.7$ (*c* 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.22 (m, 5H), 5.39 (dd, $J = 8.9$, 3.7 Hz, 1H), 4.63 (t, $J = 8.9$ Hz, 1H), 4.21 (dd, $J = 8.9$, 3.7 Hz, 1H), 2.80−2.74 (m, 2H), 2.11−2.02 (m, 1H), 1.52−1.44 (m, 1H), 1.46−1.38 (m, 1H), 1.30−1.24 (m, 1H), 1.24−1.10 (m, 5H), 0.97−0.90 (m, 2H), 0.81 (d, $J = 6.4$ Hz, 3H), 0.77 (d, $J = 6.7$ Hz, 3H), 0.77 (d, $J = 6.7$ Hz, 3H), 0.84−0.73 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 139.2, 129.1, 128.6, 125.9, 125.6, 69.8, 57.6, 44.8, 44.7, 42.3, 38.6, 29.6, 27.3, 27.1, 20.6, 20.5, 20.3, 19.9, 14.4; IR (thin film) 2957, 2925, 2871, 1784, 1703, 1456, 1193, 1060 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{33}O_3N$ (M^+) 359.2460, found 359.2460.

(4*R*)-3-((2*R*,3*S*,5*S*,7*S*)-2-Hydroxy-3,5,7-trimethyldecanoyl)-4-phenyloxazolidin-2-one (22). Sodium bis(trimethylsilyl)amide (1.0 M solution in THF, 6.1 mL, 6.1 mmol) was added to a solution of **20** (2.0 g, 5.6 mmol) in THF (22 mL) at −78 °C. After the mixture was stirred for 30 min, a solution of Davis oxaziridine[25] **21** (2.2 g, 8.3 mmol) in THF (11 mL) was added rapidly via cannula. A solution of CSA (6.5 g, 28 mmol) in THF (56 mL) was cannulated into the flask after 15 s. Upon completion, the reaction mixture was diluted with Et_2O (200 mL) and washed with water (100 mL). The phases were separated, and the organic layer was washed with saturated aq $NaHCO_3$ (2 × 100 mL) and brine (100 mL). The aqueous phases were combined and extracted with Et_2O (3 × 150 mL), and organic phases were then combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was

purified by flash silica gel chromatography (75:24:1 hexanes/EtOAc/MeOH) to afford **22**, which contained small amounts of imine impurities, suitable for use in the subsequent step. A sample of **22** was purified by flash silica gel chromatography (8:1 hexanes/EtOAc) for extensive characterization of the major product: $R_f = 0.7$ (hexanes/EtOAc 2:1); $[\alpha]^{20}_D = -68.4$ (*c* 0.81, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.22 (m, 5H), 5.39 (dd, $J = 8.9$, 2.7 Hz, 1H), 5.10 (d, $J = 5.1$ Hz, 1H), 4.77 (t, $J = 8.9$ Hz, 1H), 4.36 (dd, $J = 8.9$, 2.7 Hz, 1H), 3.05 (d, $J = 7.8$ Hz, 1H), 2.14−2.06 (m, 1H), 1.74−1.64 (m, 1H), 1.61−1.50 (m, 2H), 1.40−1.28 (m, 1H), 1.30−1.18 (m, 3H), 1.07−0.99 (m, 3H), 0.92 (d, $J = 6.4$ Hz, 3H), 0.88 (t, $J = 7.0$ Hz, 3H), 0.86 (d, $J = 6.6$ Hz, 3H), 0.77 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 153.0, 138.5, 129.3, 129.0, 125.7, 73.0, 70.8, 58.1, 45.1, 41.5, 39.0, 33.1, 29.7, 27.1, 20.7, 20.3, 20.0, 14.4, 13.7; IR (thin film) 3518, 2957, 2926, 2871, 1788, 1696, 1381, 1324, 1198 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{33}O_4N$ (M^+) 375.2410, found 375.2410.

(2*R*,3*S*,5*S*,7*S*)-3,5,7-Trimethyldecane-1,2-diol (23). Methanol (1.95 mL, 48.2 mmol) and lithium borohydride (1.05 g, 48.2 mmol) were added to a solution of **22** in Et_2O (100 mL) at 0 °C. The reaction was stirred for 3 h at 0 °C, and the reaction was then quenched by the slow dropwise addition of saturated aq $NaHCO_3$ (50 mL). After the mixture was stirred for 12 h, the phases were separated and the aqueous layer extracted with Et_2O (3 × 100 mL). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (4:1 hexanes/EtOAc, 1% MeOH) to afford 1.1 g (93% over two steps) of **23** as a clear oil: $R_f = 0.3$ (hexanes/EtOAc 2:1); $[\alpha]^{24}_D = -30.6$ (*c* 0.78, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63−3.50 (m, 3H), 2.73 (br s, 2H), 1.67−1.60 (m, 1H), 1.62−1.54 (m, 1H), 1.52−1.45 (m, 1H), 1.38−1.28 (m, 2H), 1.26−1.16 (m, 4H), 1.01−0.91 (m, 2H), 0.88 (d, $J = 6.8$ Hz, 3H), 0.86 (t, $J = 7.0$ Hz, 3H), 0.84 (d, $J = 6.4$ Hz, 3H), 0.83 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.3, 65.4, 44.8, 41.2, 38.6, 32.8, 29.7, 27.4, 20.9, 20.5, 19.9, 14.9, 14.4; IR (thin film) 3382, 2957, 2841, 1709, 1641, 1456, 1379, 1261, 1017 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{28}O_2Na$ ($M + Na^+$) 239.1987, found 239.1997.

(2*S*,4*S*,6*S*)-2,4,6-Trimethylnonanal (24). Sodium *m*-periodate (191 mg, 0.893 mmol) was added to a solution of **23** (129 mg, 0.595 mmol) in THF (1.5 mL) containing pH 7 buffer (1.5 mL) at rt. The reaction mixture was stirred for 2 h at rt and was then diluted with Et_2O (10 mL) and H_2O (10 mL). The phases were separated and the aqueous layer was extracted with Et_2O (4 × 20 mL). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (40:1 hexanes/EtOAc) to afford 91.7 mg (84%) of **24** as a clear oil: $R_f = 0.8$ (hexanes/EtOAc 6:1); $[\alpha]^{21}_D = +6.70$ (*c* 0.88, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (d, $J = 2.6$ Hz, 1H), 2.50−2.40 (m, 1H), 1.75−1.67 (m, 1H), 1.62−1.54 (m, 1H), 1.53−1.46 (m, 1H), 1.39−1.32 (m, 1H), 1.32−1.27 (m, 1H), 1.27−1.22 (m, 1H), 1.24−1.16 (m, 2H), 1.08 (d, $J = 7.0$ Hz, 3H), 1.06−1.00 (m, 1H), 0.98−0.92 (m, 1H), 0.88 (d, $J = 6.4$ Hz, 3H), 0.87 (t, $J = 7.2$ Hz, 3H), 0.84 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.5, 45.1, 44.1, 38.9, 38.4, 29.7, 27.9, 20.4, 20.2, 19.9, 14.4, 14.3; IR (thin film) 2958, 2924, 2874, 1730, 1453, 1261 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{24}O$ (M^+) 184.1827, found 184.1827.

(5*R*)- and (5*S*)-4-Bromo-3-methyl-5-((1′*S*,3′*S*,5′*S*)-1,3,5-trimethyloctyl)-5*H*-furan-2-one (25) and (26). A solution of *n*-butyllithium (2.5 M solution in THF, 352 μL, 0.88 mmol) was added to a solution of (*E*)-3-bromo-2-methyl-2-propenoic acid (72.5 mg, 0.439 mmol) in THF (8.8 mL) at −78 °C, and the reaction was stirred for 3 h. Aldehyde **24** (81.0 mg, 0.439 mmol) in a solution of THF (3.0 mL) was introduced dropwise via syringe. The reaction was stirred for 2 h at −78 °C and then allowed to warm to room temperature over 16 h. The reaction was quenched with H_2O (10 mL), acidified with a 1.0 M solution of HCl (10 mL), and diluted with Et_2O (20 mL). The phases were separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (6:1 hexanes/EtOAc) to afford 131 mg (97%) of **25** and **26** (**25**:**26** 4:1) as a clear oil. The major product, **(5*R*)-4-bromo-3-methyl-5-((1′*S*,3′*S*,5′*S*)-1,3,5-trimethyloctyl)-5*H*-furan-2-one (25)**, was characterized as follows: $R_f = 0.5$ (hexanes/EtOAc 8:1); $[\alpha]^{21}_D = +32.6$ (*c* 0.82, $CHCl_3$); ^{1}H NMR (400 MHz) δ 4.89 (t, $J = 1.9$ Hz, 1H), 2.27−2.17 (m, 1H), 1.91 (d, $J = 1.9$ Hz, 3H), 1.70−1.55 (m, 2H), 1.55−1.45 (m, 2H), 1.40−1.20 (m, 3H), 1.20−1.05 (m, 2H), 1.00−0.95 (m, 1H), 0.90 (d, $J = 6.6$ Hz, 3H), 0.86 (d, $J = 6.2$ Hz, 3H), 0.86 (t, $J = 6.6$ Hz, 3H), 0.66 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz) δ 171.5, 143.9, 129.4, 85.1, 45.2, 40.7, 40.0, 31.7, 29.6, 27.2, 20.2, 20.2, 20.0, 14.4, 12.0, 10.1; IR (thin film) 2958, 2925, 1771, 1664, 1380, 1272, 1083 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{27}O_2Br$ (M^+) 330.1194, found 330.1193.

The minor adduct, **(5*S*)-4-bromo-3-methyl-5-((1′*S*,3′*S*,5′*S*)-1,3,5-trimethyloctyl)-5*H*-furan-2-one (26)**, was characterized by the following spectral information: $R_f = 0.50$ (hexanes/EtOAc 8:1); $[\alpha]^{21}_D = -29.9$ (*c* 0.77, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (t, $J = 1.9$ Hz, 1H), 2.26−2.17 (m, 1H), 1.90 (d, $J = 1.9$ Hz, 3H), 1.54−1.42 (m, 2H), 1.35−1.15 (m, 5H), 1.12 (d, $J = 7.0$ Hz, 3H), 1.02−0.90 (m, 3H), 0.87 (t, $J = 7.0$ Hz, 3H), 0.84 (d, $J = 6.8$ Hz, 3H) 0.82 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 143.2, 129.8, 87.7, 44.2, 38.4, 36.1, 32.2, 29.7, 27.5, 21.2, 20.6, 19.8, 17.1, 14.4, 10.1; IR (thin film): 2957, 2925, 1770, 1663, 1380, 1274, 1089 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{28}O_2Br$ ($M^+ + H$) 331.1273, found 331.1272.

Capensifuranone (1) and *epi*-Capensifuranone (27). A general procedure was used to prepare capensifuranone **1** and *epi*-capensifuranone **27**. A solution of 3-bromo-2-butenolide **26** (24.1 mg, 0.073 mmol) and $Pd(PPh_3)_4$ (8.4 mg, 7.3×10^{-3} mmol) in THF (1 mL) was subjected to three freeze−pump−thaw cycles to remove traces of oxygen. After cooling to 0 °C, Me_2-Zn (2.0 M solution in toluene, 0.18 mL, 0.36 mmol) was added. The reaction mixture was then stirred for 16 h at rt and was subsequently poured into Et_2O (5 mL) and quenched by the addition of H_2O (1 mL). The phases were separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (20:1 hexanes/EtOAc) to afford 19.2 mg (99%) of **capensifuranone (1)**, which was characterized as follows: $R_f = 0.50$ (hexanes/EtOAc 4:1); $[\alpha]^{22}_D = -14.5$ (*c* 0.29, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.68 (app s, 1H), 2.06−2.00 (m, 1H), 1.93−1.92 (m, 3H), 1.82−1.81 (m, 3H), 1.51−1.42 (m, 2H), 1.35−1.28 (m, 1H), 1.28−1.23 (m, 2H), 1.21−1.12 (m, 2H), 1.10 (d, $J = 7.0$ Hz, 3H), 1.00−0.91 (m, 3H), 0.87 (t, $J = 7.0$ Hz, 3H), 0.83 (d, $J = 6.6$ Hz, 3H), 0.82 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 157.9, 124.7, 87.7, 44.6, 38.5, 36.7, 32.2, 29.8, 27.8, 21.2, 20.7, 19.9, 17.5, 14.4, 12.3, 8.4; IR (thin film) 2958, 2925, 2866, 1756, 1381 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{30}O_2Na$ ($M^+ + Na$) 289.2143, found 289.2143.[30]

The reaction was repeated with the bromide **25** to yield (97%) the diastereomer described as ***Epi*-capensifuranone (27)**, which was characterized as follows: $R_f = 0.50$ (hexanes/EtOAc 4:1); $[\alpha]^{21}_D = +37.6$ (*c* 0.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (app s, 1H), 2.04−1.96 (m, 1H), 1.92 (s, 3H), 1.81 (s, 3H), 1.70−1.56 (m, 2H), 1.56−1.48 (m, 2H), 1.38−1.32 (m, 1H), 1.32−1.27 (m, 1H), 1.27−1.19 (m, 2H), 1.17−1.10 (m, 1H), 1.06−0.92 (m, 1H), 0.89 (d, $J = 6.3$ Hz, 3H), 0.87 (t, $J = 6.9$ Hz, 3H), 0.85 (d, $J = 6.4$ Hz, 3H), 0.61 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 158.5, 124.1, 85.0, 45.3, 41.3, 39.0, 31.5, 29.6, 27.3, 20.4, 20.3, 20.0, 14.4, 12.3, 11.9, 8.4; IR (thin film): 2958, 2925, 1755, 1685, 1089 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{30}O_2$ (M^+) 266.2246, found 266.2247.

***2Z*-(4*R*,5*S*,7*S*,9*S*)-2,3,5,7,9-Pentamethyl-dodec-2-ene-1,4-diol (28) and *2Z*-(4*S*,5*S*,7*S*,9*S*)-2,3,5,7,9-Pentamethyl-dodec-2-ene-1,4-diol (29).** A general procedure was used to prepare diols **28** and **29**. A solution of *epi*-capensifuranone **27**

(17.8 mg, 67.0 μmol) in Et_2O (0.15 mL) was added to a solution of LAH (1.0 M in Et_2O, 60.0 μL, 60.0 μmol) in Et_2O (0.45 mL) at 0 °C. After being stirred at 0 °C for 10 min, the reaction was warmed to rt, allowed to stir for 16 h prior to dilution with Et_2O (5 mL), and quenched of excess reagent by the slow addition of H_2O (1 mL) and 2 M NaOH (1 mL). The phases were separated, and the aqueous layer was extracted with Et_2O (6 × 5 mL). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (2:1 hexanes/EtOAc) to afford 17.7 mg (98%) of ***2Z*-(4*R*,5*S*,7*S*,9*S*)-2,3,5,7,9-pentamethyl-dodec-2-ene-1,4-diol (28),** which was characterized as follows: $R_f = 0.5$ (hexanes/EtOAc 1:1); $[\alpha]^{21}_D = -33.9$ (*c* 0.87, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (A of AB, $J_{AB} = 11.5$ Hz, 1H), 4.20 (d, $J = 9.0$ Hz, 1H), 3.95 (B of AB, $J_{AB} = 11.5$ Hz, 1H), 2.15−1.95 (br s, 2H), 1.79 (s, 3H), 1.70−1.65 (m, 1H), 1.64 (s, 3H), 1.55−1.50 (m, 1H), 1.48−1.43 (m, 1H), 1.38−1.33 (m, 1H), 1.33−1.24 (m, 2H), 1.23−1.16 (m, 2H), 1.00 (d, $J = 6.4$ Hz, 3H), 0.97−0.92 (m, 1H), 0.87 (t, $J = 7.0$ Hz, 3H), 0.83 (d, $J = 6.6$ Hz, 3H), 0.83 (d, $J = 6.6$ Hz, 3H), 0.80−0.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.4, 131.6, 75.8, 62.7, 44.3, 41.6, 38.4, 34.3, 29.9, 27.6, 21.5, 20.8, 19.9, 17.6, 16.6, 14.4, 13.1; IR (thin film): 3353, 2957, 2926, 2871, 2839, 1459 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{34}O_2$ (M^+) 270.2559, found 270.2567.

Application of the procedure described above to capensifuranone (**1**) gave ***2Z*-(4*S*,5*S*,7*S*,9*S*)-2,3,5,7,9-pentamethyl-dodec-2-ene-1,4-diol (29)**, which was characterized as follows: $R_f = 0.5$ (hexanes/EtOAc 1:1); $[\alpha]^{21}_D = -21.0$ (*c* 0.30, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 (A of AB, $J_{AB} = 11.5$ Hz, 1H), 4.22 (d, $J = 9.1$ Hz, 1H), 4.06 (B of AB, $J_{AB} = 11.5$ Hz, 1H), 1.80 (d, $J = 0.8$ Hz, 3H), 1.72−1.62 (m, 3H), 1.67 (s, 3H), 1.61−1.57 (m, 2H), 1.40−1.20 (m, 3H), 1.02−0.92 (m, 1H), 0.90 (d, $J = 6.2$ Hz, 3H), 0.88 (t, $J = 7.1$ Hz, 3H), 0.86 (d, $J = 6.6$ Hz, 3H), 0.85−0.80 (m, 3H), 0.77−0.70 (m, 1H), 0.67 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.5, 131.6, 76.1, 62.8, 44.2, 42.2, 38.2, 34.1, 29.7, 28.0, 21.6, 20.9, 19.9, 17.4, 16.4, 14.4, 12.8; IR (thin film): 3403, 2957, 2925, 2871, 1460, 1375 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{34}O_2Na$ ($M^+ + Na$) 293.2457, found 293.2465.

***2Z*-(4*R*,5*S*,7*S*,9*S*)-1-*tert*-Butyldiphenylsilyloxy-2,3,5,7,9-pentamethyldodec-2-ene-4-ol (30) and *2Z*-(4*S*,5*S*,7*S*,9*S*)-1-*tert*-Butyldiphenylsilyloxy-2,3,5,7,9-pentamethyldodec-2-ene-4-ol (31).** A general procedure was used to prepare the alcohols **30** and **31**. Imidazole (11.1 mg, 0.163 mmol) and *tert*-butyldiphenylsilyl chloride (16 μL, 0.060 mmol) were added to a solution of diol **28** (15 mg, 0.054 mmol) in methylene chloride (200 μL). The reaction mixture was stirred at ambient temperature for 1.25 h and diluted with Et_2O (5 mL). The organic layer was washed with H_2O (3 mL) and the resulting aqueous layer was then extracted with Et_2O (4 × 5 mL). Organic phases were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (20:1 hexanes/EtOAc) to afford 26.3 mg (95%) of ***2Z*-(4*R*,5*S*,7*S*,9*S*)-1-*tert*-butyldiphenylsilyloxy-2,3,5,7,9-pentamethyl-dodec-2-ene-4-ol (30)**, which was characterized as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72−7.66 (m, 4H), 7.46−7.36 (m, 6H), 4.29 (A of AB, $J_{AB} = 11.8$ Hz, 1H), 4.04 (B of AB, $J_{AB} = 11.8$ Hz, 1H), 3.86 (d, $J = 8.7$ Hz, 1H), 1.78 (s, 3H), 1.55 (s, 3H), 1.34−1.24 (m, 3H), 1.20−1.10 (m, 4H), 1.04 (s, 9H), 0.87 (d, $J = 6.8$ Hz, 3H), 0.86 (t, $J = 7.3$ Hz, 3H), 0.80 (d, $J = 6.6$ Hz, 3H), 0.75 (d, $J = 6.6$ Hz, 3H), 0.72−0.66 (m, 1H), 0.62−0.54 (m, 2H).

The procedure was also applied to diol **29** yielding (91%) of ***2Z*-(4*S*,5*S*,7*S*,9*S*)-1-*tert*-butyldiphenylsilyloxy-2,3,5,7,9-pentamethyl-dodec-2-ene-4-ol (31)**, which was characterized as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72−7.66 (m, 4H), 7.46−7.36 (m, 6H), 4.31 (A of AB, $J_{AB} = 11.7$ Hz, 1H), 4.04 (B of AB, $J_{AB} = 11.7$ Hz, 1H), 3.86 (d, $J = 8.9$ Hz, 1H), 1.78 (s, 3H), 1.58 (s, 3H), 1.34−1.24 (m, 3H), 1.24−1.17 (m, 4H), 1.04 (s, 9H), 0.96−0.90 (m, 1H), 0.86 (t, $J = 6.9$ Hz, 3H), 0.84 (d, $J = 6.0$ Hz, 3H), 0.83 (d, $J = 6.7$ Hz, 3H), 0.80−0.74 (m, 2H), 0.52 (d, $J = 6.8$ Hz, 3H).

General Procedure for the Formation of Mosher Esters of 32 and 33. A methylene chloride (0.20 mL) solution containing 4-(dimethylamino)pyridine (16.8 mg, 0.138 mmol) and (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride (20.0 mg, 0.079 mmol) was added to allylic alcohol **30** (3.5 mg, 0.0069 mmol) in dry Et_3N (0.040 mL) at ambient temperature. The solution was stirred for 45 min at rt and applied directly for preparative thin-layer chromatography (10:1 hexanes/EtOAc). Recovery and identification of the purified Mosher ester derivative was undertaken.

The (*S*)-Mosher ester derivative **32a**, prepared from alcohol **30**, was characterized as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74−7.68 (m, 4H), 7.46−7.34 (m, 11H), 5.39 (d, $J = 9.7$ Hz, 1H), 4.49 (d, $J = 11.5$ Hz, 1H), 4.23 (d, $J = 11.7$ Hz, 1H), 3.54 (s, 3H), 1.88−1.80 (m, 1H), 1.72 (s, 3H), 1.50−1.40 (m, 2H), 1.31 (s, 3H), 1.34−1.20 (m, 4H), 1.20−1.14 (m, 2H), 1.06 (s, 9H), 1.04−0.98 (m, 1H), 0.94−0.86 (m, 2H), 0.87 (d, $J = 6.3$ Hz, 3H), 0.86 (t, $J = 7.1$ Hz, 3H), 0.80 (d, $J = 6.6$ Hz, 3H), 0.77 (d, $J = 6.3$ Hz, 3H).

The corresponding (*R*)-Mosher ester derivative **32b**, prepared from alcohol **30**, was characterized as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74−7.67 (m, 4H), 7.46−7.34 (m, 11H), 5.48 (d, $J = 9.7$ Hz, 1H), 4.50 (d, $J = 11.7$ Hz, 1H), 4.22 (d, $J = 11.7$ Hz, 1H), 3.49 (s, 3H), 1.86−1.80 (m, 1H), 1.76 (s, 3H), 1.57 (s, 3H), 1.50−1.40 (m, 1H), 1.34−1.20 (m, 4H), 1.20−1.14 (m, 2H), 1.05 (s, 9H), 1.04−0.98 (m, 1H), 0.94−0.86 (m, 2H), 0.85 (t, $J = 7.1$ Hz, 3H), 0.80 (d, $J = 6.6$ Hz, 3H), 0.76 (d, $J = 6.6$ Hz, 3H), 0.71 (d, $J = 6.3$ Hz, 3H).

The (*S*)-Mosher ester derivative **33a** obtained from **31** was characterized as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74−7.68 (m, 4H), 7.48−7.34 (m, 11H), 5.43 (d, $J = 9.8$ Hz, 1H), 4.51 (d, $J = 11.7$ Hz, 1H), 4.24 (d, $J = 11.5$ Hz, 1H), 3.49 (s, 3H), 1.84−1.76 (m, 1H), 1.77 (s, 3H), 1.59 (s, 3H), 1.44−1.34 (m, 1H), 1.34−1.20 (m, 4H), 1.20−1.14 (m, 2H), 1.05 (s, 9H), 1.04−0.98 (m, 1H), 0.90−0.86 (m, 2H), 0.86 (t, $J = 7.0$ Hz, 3H), 0.78 (d, $J = 6.6$ Hz, 3H), 0.74 (d, $J = 6.6$ Hz, 3H), 0.63 (d, $J = 6.7$ Hz, 3H).

The (*R*)-Mosher ester derivative **33b**, prepared from alcohol **31**, using the same procedure, was characterized by the following data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, 4H), 7.48−7.34 (m, 11H), 5.36 (d, $J = 9.8$ Hz, 1H), 4.54−4.46 (m, 1H), 4.24 (d, $J = 11.5$ Hz, 1H), 3.50 (s, 3H), 1.88−1.80 (m, 1H), 1.72 (s, 3H), 1.54−1.44 (m, 1H), 1.35 (s, 3H), 1.34−1.20 (m, 4H), 1.20−1.14 (m, 2H), 1.06 (s, 9H), 1.04−0.98 (m, 1H), 0.94−0.86 (m, 2H), 0.86 (t, $J = 7.0$ Hz, 3H), 0.81 (d, $J = 6.6$ Hz, 3H), 0.81 (d, $J = 6.6$ Hz, 3H), 0.65 (d, $J = 6.7$ Hz, 3H).

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Supporting Information Available: General experimental information and proton and carbon NMR spectra for compounds **11**−**27** of the synthesis pathway and synthetic capensifuranone (**1**). This material is available free of charge via the Internet at http://pubs.acs.org.

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