Synthesis of Southern-Part Models of Soraphen A

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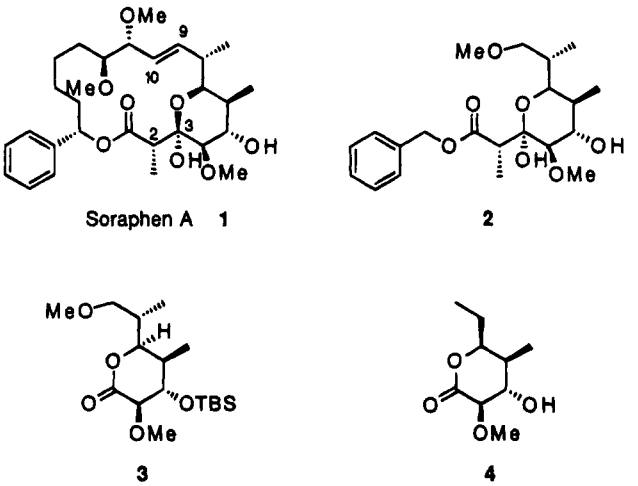
A number of model compounds corresponding to substructures of the fungicidal macrolide soraphen A were prepared from the lactone **3**. This lactone was obtained degradatively from soraphen A using the mild Japp–Klingemann variant of the retro-aldol reaction and ozonolysis of the double bond. Addition of ester enolates to the lactone **3** led to the isolation of unstable hemiacetals which were converted to their anomerically stabilized tautomers on chromatography or prolonged standing in solution. Because of the unusual stability of the initially formed hemiacetals it was possible to define the structures of the transition states of the addition of enolates to a lactone in unprecedented detail.

Introduction

Soraphen A (**1**) (Chart 1) is a macrolide isolated from the myxobacterium *Sorangium cellulosum* by Höfle *et al.* at the Gesellschaft für Biotechnologische Forschung in Germany.[1] It was shown to exhibit potent fungicidal activity against a variety of plant pathogenic fungi.[2] The synthesis of **1** is a complex and lengthy endeavor,[3] rendering it too expensive for a product of potential agricultural usage. However, it was considered interesting to attempt to reproduce the fungicidal activity of **1** with a simpler, more easily accessible, compound embodying a substructure of the soraphen A molecule. The choice of the substructure is clearly a matter of some importance. In aqueous solution the hemiacetal functionality in the bottom half of the molecule enters into an equilibrium with its hydroxy–ketone tautomer, which is a β-keto ester and in turn builds an equilibrium with its enol form. We chose to incorporate this moiety into our model structure together with the ester and phenyl groups. A series of compounds comprising such partial structures, but with less functionality on the tetrahydropyran ring, has already been described.[4] Now compounds containing the full functionality in this ring were of interest and thus **2** was selected as a target. By using Evans' aldol methodology the synthesis of compounds similar to **2** was completed[5] *via* an ester enolate condensation (Meinwald reaction[6]) on the lactone **4**. We now report the preparation of **2** by a similar strategy using **3** as intermediate, which was obtained by degradation of soraphen A (**1**).

Chart 1



Results

For the excision of the lactone **3** from soraphen A, the C(2)–C(3) bond and the C(9)–C(10) double bond have to be cleaved. The double bond can be cleaved by ozonolysis,[7] but for the C(2)–C(3) bond a more specific approach was required. This was achieved *via* a Japp–Klingemann[8] degradation of the enol **6**, which was simply derived from soraphen A. Persilylation of soraphen A with Me_3SiCl in DMF took place under conditions which activated the tautomerization to its hydroxy–ketone isomer. As the hydroxy groups of this tautomer are less sterically hindered, these were silylated preferentially, and **5**[9] was isolated in high yield (Scheme 1). Acid-catalyzed cleavage of the silyl groups led to the enol **6**. This enol is stable in mild acidic solution but is sensitive to base or chromatography. However, it was obtained in pure form after a simple aqueous workup and could be stored for weeks in the refrigerator without decomposition. Treatment of this compound with 4-(methoxyphenyl)diazonium tetrafluoroborate led to the product of

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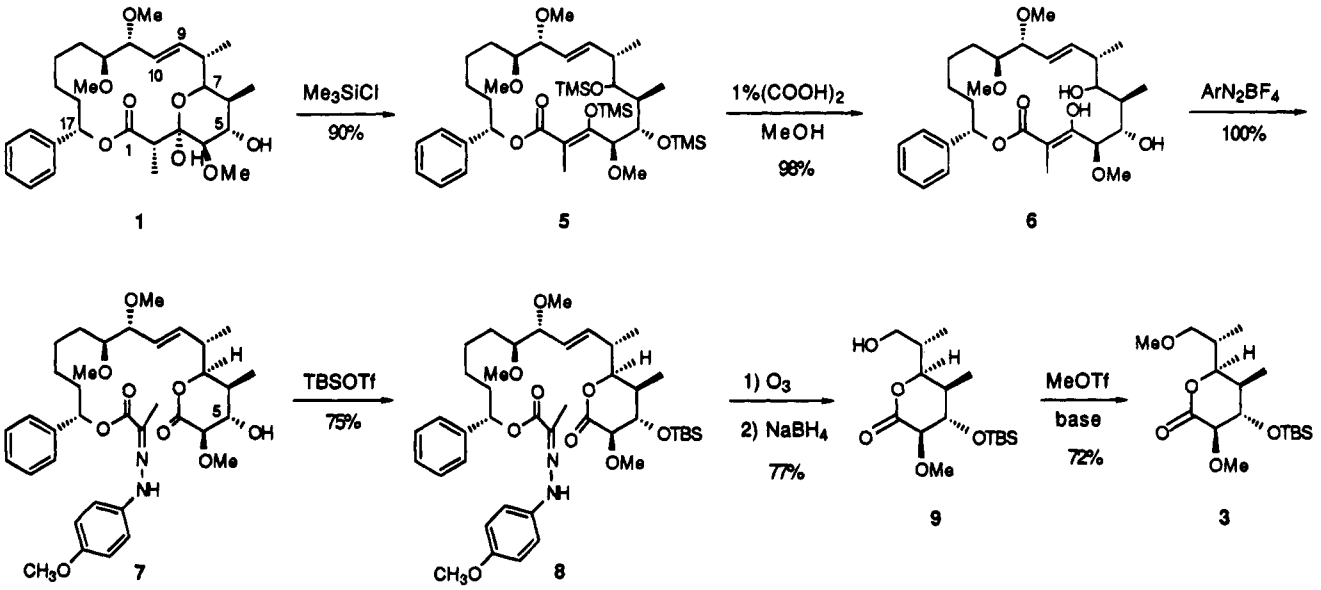
Scheme 1



Japp–Klingemann[8] degradation **7** in quantitative yield. The cleavage of a C–C bond using the Japp–Klingemann reaction has not been described for the degradation or derivatization of a natural product, but in this case it is a mild high-yielding alternative to the retro-Claisen degradation in a molecule which is sensitive to strong acids or bases. The C(5) hydroxy group of **7** was silylated to give **8** and then subjected to ozonolysis with a reductive workup providing **9** in good yield. It was necessary to block the C(9) hydroxy group to prevent its involvement in full acetal formation during the deprotection of the C(5)–O silyl group in the target compound **2**, as had been seen with analogous compounds.[10] Methylation with methyl triflate[11] served this purpose leading to the desired methyl ether **3** in 72% yield, after MeI/Ag_2O[12] had proven unsuccessful in this reaction. That no change in stereochemistry had taken place during these transformations was evident from the similarity of the ^{1}H-NMR spectrum of **7**, **8**, **9**, and **3** to that of **4**, which was prepared synthetically using a series of stereoselective aldol reactions.[5]

With the availability of the lactone **3** assured, the Meinwald reaction was performed. Treatment of **3** with the lithium enolate of *tert*-butyl acetate at −78 °C for 4 h led to the adduct **10** (Scheme 2). This compound isomerized slowly but completely in $CDCl_3$ solution over several days to its epimer **11**, which is anomerically stabilized and has no 1,3 diaxial interaction between the ester side chain and the silyloxy group. Rapid chromatography on silica caused a partial conversion of **10** to **11**, after which they were isolated in 38% and 23% yield, respectively. Deprotection of either **10** or **11** led to the same anomerically stabilized hemiacetal **12** in high yield. The reaction of **3** with the enolate of benzyl acetate took a similar course. The kinetically formed product **13** anomerized completely on chromatography to **14**, which was isolated in 45% yield. Deprotection of **14** led to the hemiacetal **15** in high yield.

The addition of the (*E*)-enolate of benzyl propionate to **3** introduced an additional center of stereochemistry into the product. The reaction was slower in this case and required a higher temperature to reach completion. After 30 min. at 0 °C and quenching with NH_4Cl, **16** and **17** were formed in a 3:1 ratio in the crude product as determined by NMR (Scheme 3). Again chromatography induced tautomerisation to the anomerically stabilized isomers. After careful rapid chromatography **16**, **17**, **18**, and **19** were isolated in 26%, 2%, 8%, and 0.5% yields, respectively. Anomerization of the hemiacetal accompanied the deprotection of the C(5) hydroxy group of these compounds with HF/pyridine.[13] In each case **20** and **2** were isolated in the same 1:2 ratio. *tert*-Butyl propionate reacted similarly, and after chromatography, three of the possible four diastereomers were isolated. It was not possible to determine the stereochemistry of these compounds with certainty, but deprotection of each isomer led to **24** and **25** in a 1:6 ratio (Scheme 4).

Discussion

The addition of enolates to **3** all took a similar course. Axial attack took place on the *Si* face of the lactone **3**. Quenching of the reaction mixtures with NH_4Cl led to products **10**, **13**, **16**, and **17** with the hydroxy group in the equatorial position. Tautomerization of these compounds took place simply on standing over several days at room temperature or upon chromatography on silica. In each case they were converted cleanly into the C(2′) anomers with the hydroxy group occupying the axial position. The absence of anomerically stabilized products in the initially formed mixture indicates that no equilibration took place prior to quenching or during the workup procedure. Thus, knowing the stereochemistry of the initially formed products and assuming the Zimmermann–Traxler[14] mechanism of addition to the carbonyl group, it is possible to determine exactly the conformations (**a** and **b**) of the transition states of the reaction of **3** with the enolate of benzyl propionate, which are shown in Scheme 5. The definition of the transition states with such confidence and exactitude is only pos-

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(12) Finch, N.; Fitt, J. J.; Hsu, I. H. S. *J. Org. Chem.* **1975**, *40*(2), 206.
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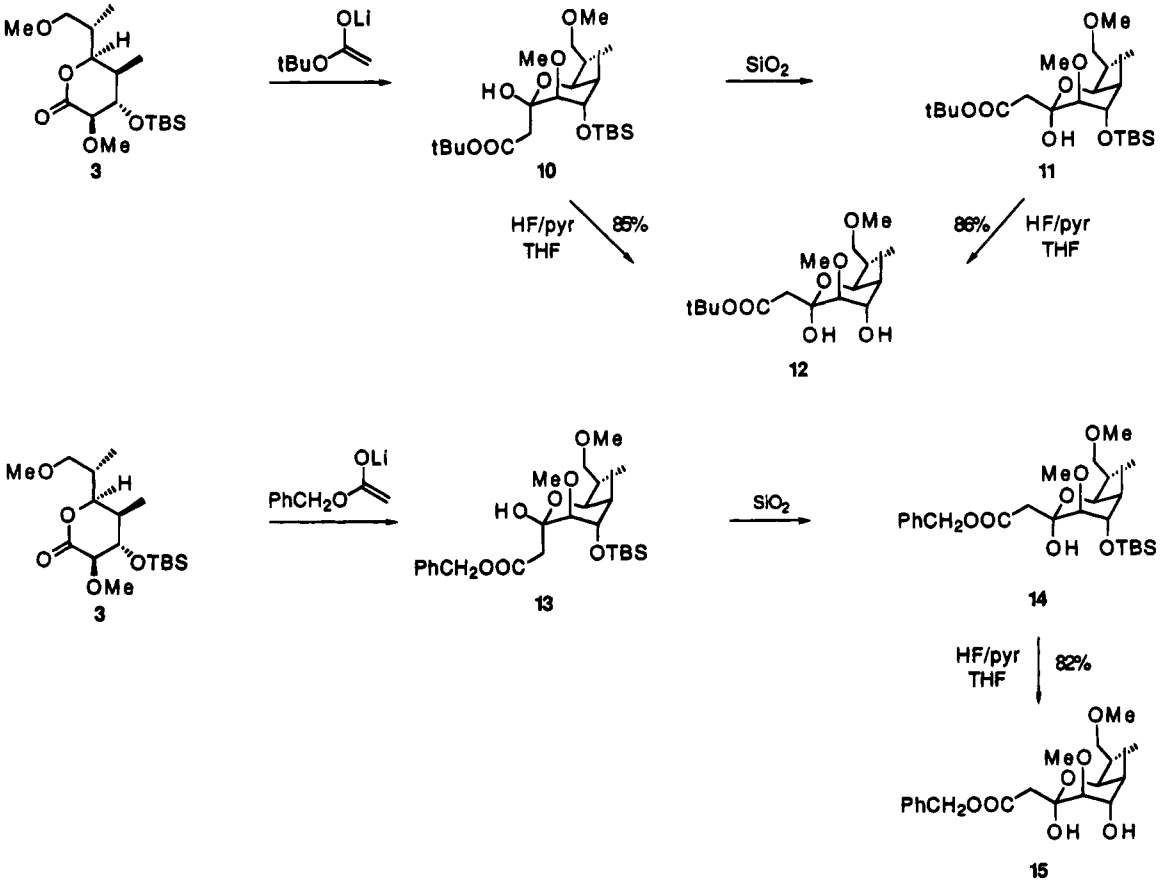
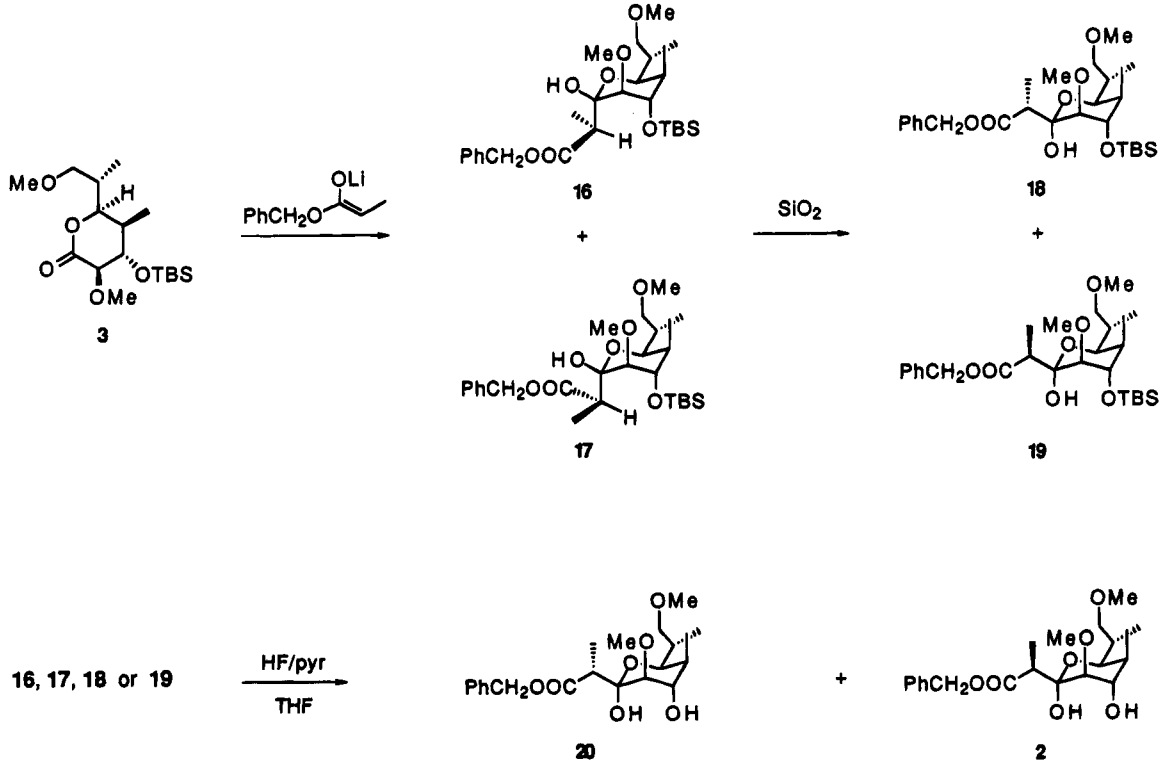
Scheme 2

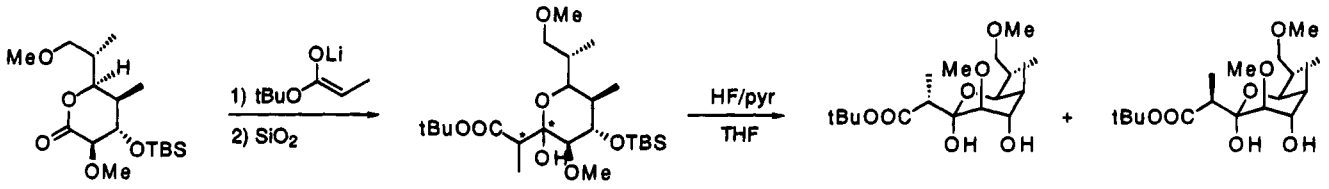


Scheme 3

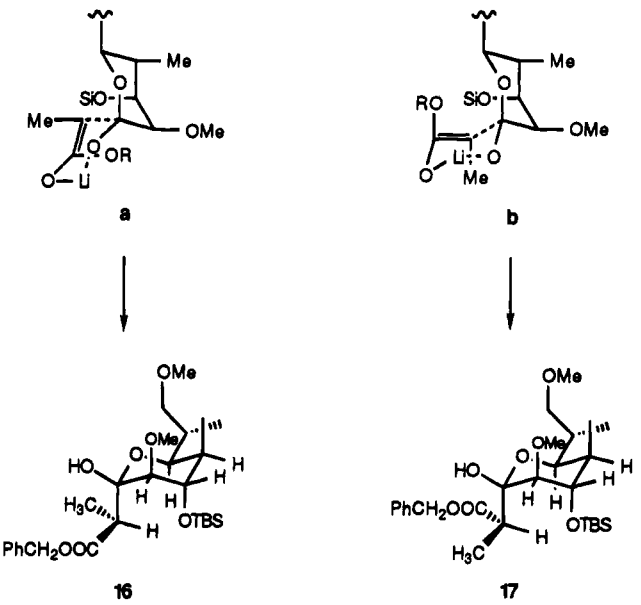


sible in this case because of the stability of the kinetically formed tetrahedral intermediates.[15] Certainly the hydrogen bond between the anomeric hydroxy group and the 3′-methoxy group stabilizes the structures and slows the equilibration. In addition, the *gem*-dimethyl effect exerted by the various ring substituents slows the ring opening.[16] The formation of the unstable anomers is interesting for another reason. According to Deslong-

Scheme 4



Scheme 5



champs' stereoelectronic theory,[17] the attack of a nucleophile on a lactone should take place axially to allow overlap of the newly forming bond with the axial lone pair on the ether oxygen next to the reaction site. It was not possible for Deslongchamps to study the selectivity of attack on simple lactones because rapid equilibration of the products camouflaged the initial face of attack. All of the reactions described here take place through axial attack on the lactone **3** in accord with Deslongchamps' theory. However the stereoselectivity of the reaction may be ascribed to other causes. For example, the 3′-methoxy group may hinder the attack on the equatorial face, although the 1,3 interaction with the 4′-O-silyl group appears to be more unfavorable.

Characterization of the Products. The stereochemistry of the hemiacetals prepared in this paper as target compounds was determined by ^{1}H-NMR spectroscopy. It was clear that the tetrahydropyran rings of all the products **10**–**25** have the same configuration and conformation, because the signals of the ring protons of every compound show similar chemical shifts and the same coupling constants. In fact, these chemical shifts and coupling constants were similar to those in the natural product soraphen A (**1**) itself, the structure of which is well characterized.[1] On the basis of an X-ray structure analysis and NOE investigations,[1] it is known that the substituents at C(3′), C(4′), and C(5′) occupy the axial position and the substituent at C(6′) the equatorial position. From the close similarity of the ring coupling constants in our compounds and in soraphen A, it is concluded that the substituents possess the same orientation as in soraphen A. Therefore, the configurational isomerism of our compounds must be located at the C(2′) and C(2) centers. The isomerism at C(2′) is easily assigned in all compounds by an NOE between the axial proton H–C(6′) and a proton on the axial substituent at C(2′), namely the hydroxy proton in **2**, **11**, **18**–**20**, and **25** or an H–C(2) in **10**, **16**, and **17** (Scheme 6).

The configuration at C(2) is less easily deduced, since an assignment of this configuration requires the knowledge of the preferred conformation around the C(2)–C(2′) single bond. In **10**, **11**, **16**, **18**, and **19** a long range ^4J_w coupling between the OH and H-C(2) is observed. This coupling constant is only then large enough to be observed directly, when the four intervening bonds assume a planar zig–zag conformation (the so called W conformation).[18] In these compounds, therefore, the preferred conformation around the C(2)–C(2′) bond is that in which the OH group and an H-C(2) possess an antiperiplanar orientation. NOEs (indicated by arrows in the formulas) between the CH_3–C(2) or the benzylic CH_2 protons and H-C(3′), H-C(6′) or H-C(1″) determine then the configurational assignment at C(2). In all cases, the observation of an NOE with one side of the molecule, i.e., with either H-C(3′) or with H-C(6′)/H-C(1″), is complemented by the absence of NOEs from CH_3-C(2) (or from the benzylic CH_2 group or from the *tert*-butyl group) to the other side of the molecule. This indicates that the conformation in which H-C(2) is antiperiplanar to HO-C(2′) is also the preferred one in those cases where no long range coupling is observed. This conformation—with the smallest substituents antiperiplanar to each other—is of course also the most stable one. In conclusion, compounds **17**, **18**, and **20** possess the *R* configuration at C(2) and compounds **16**, **19**, **2**, and **25** the *S* configuration.

Conclusion

In this work we describe the specific degradation of soraphen A to the useful synthon **3**. In addition to ozonolysis to cleave the double bond, the C(2)–C(3) bond was cleaved under mild conditions using a Japp–Klingemann[8] protocol. Because we were able to isolate the initial products of attack of enolates on this lactone **3** and to separate all four diastereomers of the product of attack of benzyl propionate and characterize them, it was possible to examine the mechanism of this reaction in unprecedented definition.

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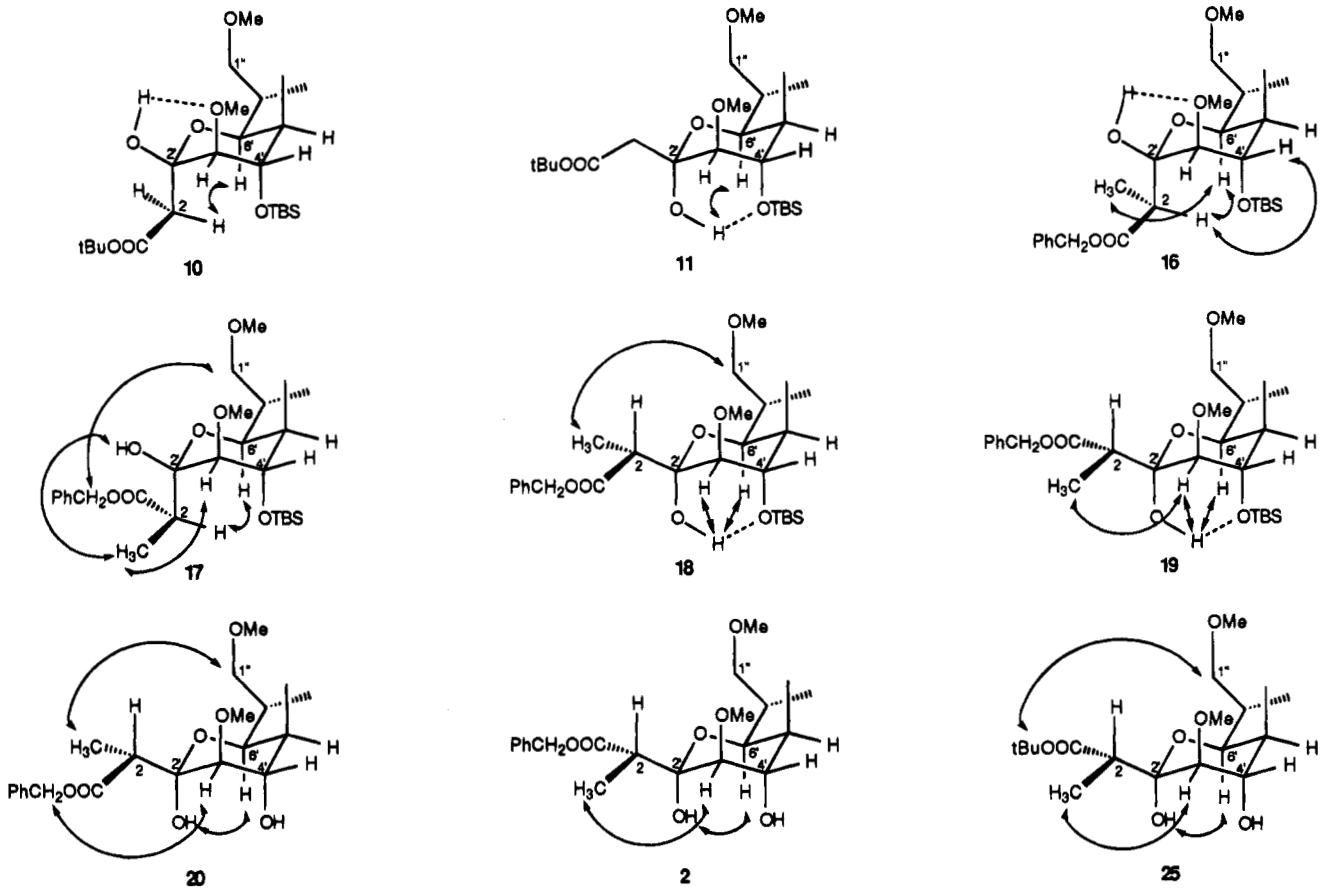
Scheme 6



These compounds exibited no fungicidal activity when tested against a series of fungal pathogens in greenhouse trials. Neither did they inhibit acetyl coenzyme A carboxylase[19] at concentrations up to 300 × the IC_{50} of soraphen A.

Experimental Section

Materials and Apparatus. Solvents (Fluka or Merck "puriss") were used without further distillation. THF was freshly distilled from sodium/benzophenone under argon. Glassware was dried with a flame and cooled under nitrogen. NMR spectra were recorded with tetramethylsilane as internal standard on a Varian Unity 500 (500 MHz ^{1}H), a Bruker ACF 250 (250 MHz ^{1}H), or a Brücker AM 400 (400 MHz ^{1}H) spectrometer. Chemical shifts are given in ppm. IR spectra were recorded on a Perkin-Elmer 1420 spectrophotometer. Mass spectra (MS) were recorded with electron impact (EI, 8 keV), chemical ionization (CI, NH_3), or field desorption (FD). Melting points were determined with a Büchi 535 apparatus and are not corrected. Ozone was generated with a Fisher Model 502 apparatus. Flash chromatography was performed by use of Merck silica gel 60 (230–400 mesh).

3,5,7-*O*-Tris(trimethylsilyl)soraphen-2-ene (5). Imidazole (45.8 g, 673 mmol) and trimethylsilyl chloride (TMSCl) (85.32 mL, 673 mmol) were successively added to a solution of soraphen A (**1**) (35 g, 67.3 mmol) in DMF (130 mL) at 0 °C. The mixture was stirred for 16 h at rt, and then the excess of TMSCl was removed by evaporation under reduced pressure. The mixture was cooled to 0 °C, and ice was added. The mixture allowed to warm to rt, shaken between CH_2Cl_2/hexane 1:10 with H_2O, and the organic phase dried over $MgSO_4$ yielding 44.5 g (90%) of **5**. ^{1}H NMR (250 MHz, $CDCl_3$) δ: −0.91–0.19 (m, 9H), 0.75 (d, J = 7 Hz, 3H), 1.01 (d, J = 7 Hz, 3H), 1.92 (s, 3H), 2.45 (m, 1H), 3.15–3.38 (m, 2H), 3.20 (s, 3H), 3.21 (s, 3H), 3.29 (s, 3H), 3.55 (m, 1H), 3.75 (m, 1H), 3.89 (m, 1H), 5.28 (m, 1H), 5.65–5.82 (m, 2H), 7.21 (m, 5H). MS (EI): 771 (1.7, (M + Cl)$^-$), 736 (8.5, M$^-$), 665 (78), 663 (100), 321 (42.4), 249 (20.3), 215 (32.2), 171 (15.2), 139 (71.2). Anal. Calcd for $C_{38}H_{68}O_8Si_3$: C, 61.91; H, 9.30. Found: C, 61.80; H, 8.9.

3-Hydroxysoraphen-2-ene (6). **5** (63 g, 85.6 mmol) was dissolved in 1 L of a 1% solution of oxalic acid in methanol. The mixture was stirred for 1 h at rt, extracted with Et_2O, washed with H_2O, and dried over $MgSO_4$ yielding 43.7 g (98%) of **6**. Mp: 50–52 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.10 (d. J = 7 Hz, 3H), 1.17 (d, J = 7 Hz, 3H), 1.25–1.85 (m, 10H), 1.92 (s, 3H), 2.10 (m, 1H), 2.84 (m, 1H), 3.23 (m, 1H), 3.28 (s, 3H), 3.37 (s, 3H), 3.38 (s, 3H), 3.50 (m, 2H), 4.16 (m, 2H), 5.43 (dd, J = 17.5, 7.5 Hz, 1H), 5.63 (dd, J = 16, 5 Hz, 1H), 6.19 (dd, J = 12, 3 Hz, 1H), 7.30–7.40 (m, 5H), 12.82 (s, 1H). MS (EI): 543 (7.4, (M + Na)$^+$), 520 (3.7, M$^+$), 503 (46.3), 471 (50), 439 (37), 255 (37), 225 (81.5), 215 (57.4), 157 (68.5), 149 (100), 129 (42.6), 121 (59.3).

2,3-Dioxo-2,3-*seco*-soraphen-2-(4′-methoxyphenyl)hydrazone (7). Under argon diisopropylethylamine (11.5 mL, 65.5 mmol) and 4-methoxybenzenediazonium tetrafluoroborate (8 g, 36 mmol) were successively added to a solution of **6** (17 g, 32.7 mmol) in dry CH_2Cl_2 (350 mL). The mixture was stirred 4.5 h at rt and washed with HCl (1 M), sodium bicarbonate (saturated), and H_2O and then dried over Na_2SO_4 yielding 21.4 g (100%) of **7**. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.03 (d, J = 7 Hz, 3H), 1.05 (d, J = 7 Hz, 3H), 1.20–2.20 (m, 8H), 2.22 (s, 3H), 2.51 (m, 2H), 3.16 (m, 1H), 3.29 (s, 3H), 3.40 (s, 3H), 3.53 (dd, J = 8, 4 Hz, 1H), 3.60 (m, 1H), 3.63 (s, 3H), 3.78 (s, 3H), 3.86 (d, J = 8 Hz, 1H), 4.19 (dd, J = 10, 3 Hz, 1H), 5.49 (dd, J = 16, 8 Hz, 1H), 5.68 (dd, J = 16, 8 Hz, 1H), 5.80 (dd, J = 8, 6 Hz, 1H), 6.84 (d, J = 9 Hz, 2H), 7.09 (d, J = 9 Hz, 2H), 7.28–7.38 (m, 5H), 11.97 (s, 1H). IR ($CHCl_3$): 3580, 1760 cm^{-1}.

5-*O*-(*tert*-Butyldimethylsilyl)-2,3-dioxo-2,3-*seco*-soraphen-2-(4′-methoxyphenyl)hydrazone (8). Under argon

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2,6-lutidine (0.12 mL, 1.07 mmol) and *tert*-butyldimethylsilyl triflate (0.21 mL, 0.91 mmol) were added successively to a solution of **7** (500 mg, 0.76 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C. The mixture was stirred for 2 h at 0 °C and poured into a mixture of aqueous sodium bicarbonate and CH_2Cl_2. The organic layer was separated, the aqueous one was reextracted with CH_2Cl_2, and the combinated organic layers were dried over Na_2SO_4. Evaporation of the solvent followed by chromatography (EtOAc/hexane 1:3) yielded 440 mg (75%) of **8**. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.1 (d, J = 5 Hz, 6H), 0.91 (s, 9H), 0.93 (d, J = 7.5 Hz, 3H), 1.0 (d, J = 7.5 Hz, 3H), 1.17–2.05 (m, 9H), 2.21 (s, 3H), 2.53 (m, 1H), 3.15 (m, 1H), 3.26 (s, 3H), 3.40 (s, 3H), 3.53 (m, 1H), 3.56 (s, 3H), 3.58 (m, 1H), 3.75 (d, J = 6 Hz, 1H), 3.78 (s, 3H), 4.20 (dd, J = 10, 2.5 Hz, 1H), 5.49 (dd, J = 15, 7.5 Hz, 1H), 5.71 (dd, J = 15, 7.5 Hz, 1H), 5.80 (dd, J = 9, 6 Hz, 1H), 6.83 (d, J = 9 Hz, 2H), 7.07 (d, J = 9 Hz, 2H), 7.27–7.40 (m, 5H), 11.95 (s, 1H). IR ($CHCl_3$): 1760 cm^{-1}. MS (FD): 769 $(M + H)^+$.

(3*R*,4*S*,5*R*,6*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-6-(1′-hydroxy-2′(*S*)-methylethyl)-3-methoxy-5-methyltetrahydropyran-2-one (9). Ozone was bubbled through a solution of the hydrazone **8** (20 g, 260 mmol) in CH_2Cl_2 (300 mL) and methanol (300 mL) at −70 °C until a persistant pale blue color appeared. $NaBH_4$ (4.5 g, 120 mmol) was then added and the mixture allowed to warm to rt. The solvent was evaporated, the residue shaken between H_2O and CH_2Cl_2, and the organic phase dried over Na_2SO_4 and evaporated. Chromatography (EtOAc/hexane 1:1) yielded 6.61 g (77%) of **9**. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.1 (d, J = 5 Hz, 6H), 0.90 (s, 9H), 0.92 (d, J = 7.5 Hz, 3H), 0.96 (d, J = 7.5 Hz, 3H), 1.59 (dd, J = 7.5, 5 Hz, 1H), 1.95 (m, 2H), 3.58 (s, 3H), 3.59 (m, 1H), 3.76 (m, 2H), 2.81 (d, J = 6 Hz, 1H), 4.45 (dd, J = 10, 2.5 Hz, 1H). IR ($CHCl_3$): 3460, 1750 cm^{-1}. MS (FD): 333 $[M + H]^+$, 275 $[M - tBu]^+$.

(3*R*,4*S*,5*R*,6*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-3-methoxy-6-(1′-methoxy-2′(*S*)-methylethyl)-5-methyltetrahydropyran-2-one (3). Methyl triflate (3.47 mL, 31.62 mmol) was slowly added to a solution of 2,6-di-*tert*-butyl-4-methylpyridine (8.66 g, 42.17 mmol) and **9** (3.5 g, 10.54 mmol) in dry CH_2Cl_2 (140 mL) at 0 °C. After 15 min at 0 °C and 24 h at rt, pyridine (1 mL) was added, and the solution was washed successively with HCl (1 M) and sodium bicarbonate (dilute), dried over Na_2SO_4, and evaporated. Chromatography (EtOAc/hexane 1:3) yielded 2.62 g (72%) of **3**. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.1 (d, J = 5 Hz, 6H), 0.90 (s, 9H), 0.91 (d, J = 7.5 Hz, 3H), 0.96 (d, J = 7.5 Hz, 3H), 1.97 (m, 2H), 3.35 (s, 3H), 3.44 (dd, J = 9, 3 Hz, 1H), 3.54 (dd, J = 9, 5 Hz, 1H), 3.58 (m, 4H), 3.81 (d, J = 6 Hz, 1H), 4.42 (dd, J = 10, 2.5 Hz, 1H). MS (FD): 347 $(M + H)^+$, 289 $(M - tBu)^+$.

(3′*R*,4′*S*,5′*R*,6′*S*)-[4′-[(*tert*-Butyldimethylsilyl)oxy]-2′-hydroxy-3′-methoxy-6′-(1″-methoxy-2″(*S*)-methylethyl)-5′-methyltetrahydropyran-2′-yl]acetic Acid *tert*-Butyl Ester (10 and 11). Under argon *n*-BuLi (1.6 M in hexane, 1.08 mL, 1.73 mmol) was added slowly to a solution of diisopropylamine (0.245 mL, 1.73 mmol) in dry THF (2.5 mL) at 0 °C. The solution was stirred for 45 min at 0 °C and cooled to −78 °C, and a solution of *tert*-butyl acetate (0.233 mL, 1.73 mmol) in dry THF (1 mL) was added slowly. The mixture was stirred for 45 min at −78 °C, and then a solution of lactone **3** (600 mg, 1.73 mmol) in dry THF (1 mL) was added slowly. The mixture was stirred for 4 h at −78 °C, and the reaction was quenched with ammonium chloride (saturated, 1.5 mL). The mixture was allowed to warm to rt, extracted with Et_2O, and washed with H_2O. The aqueous layer was reextracted with EtOAc, and the combined organic layers were dried over Na_2SO_4 and evaporated yielding crude **10**, the NMR of which showed no **11**. Chromatography (EtOAc/hexane 1:4) yielded **10** (185 mg, 23%) and **11** (304 mg, 38%).

10. ^1H NMR (400 MHz, C_6D_6) δ: 0.03 (s, 3H), 0.12 (s, 3H), 0.97 (s, 9H), 0.98 (d, J = 7 Hz, 3H), 1.10 (d, J = 7 Hz, 3H), 1.43 (s, 9H), 1.63 (m, 1H), 1.74–2.02 (m, 1H), 2.97 (d, J = 15 Hz, 1H), 3.13 (s, 3H), 3.14 (s, 3H), 3.53 (m, 2H), 3.65 (dd, J = 2, 15 Hz, 1H), 3.90 (dd, J = 3, 10 Hz, 1H), 3.95 (dd, J = 1, 3 Hz, 1H), 4.07 (dd, J = 3 Hz, 1H), 4.49 (d, J = 2.5 Hz, 1H). MS (EI): 461 (74.5, $(M - H)^-$), 427 (14.5), 405 (12.7), 321 (45.5), 215 (69), 141 (18.2), 139 (61.8), 131 (100), 127 (30.9).

11. ^1H NMR (400 MHz, C_6D_6) δ: 0.00 (s, 3H), 0.02 (s, 3H), 0.90 (s, 9H), 1.02 (d, J = 7 Hz, 3H), 1.11 (d, J = 7 Hz, 3H), 1.40 (s, 9H), 1.78 (m, 1H), 2.10 (m, 1H), 2.95 (d, J = 15 Hz, 1H), 3.05 (dd, J = 2, 15 Hz, 1H), 3.23 (s, 3H), 3.30 (s, 3H), 3.42 (dd, J = 7, 9 Hz, 1H), 3.60 (m, 1H), 3.80 (dd, J = 3, 9 Hz, 1H), 4.00 (dd, J = 3 Hz, 1H), 4.30 (dd, J = 3, 10 Hz, 1H), 5.59 (d, J = 2 Hz, 1H). MS (EI): 461 (30.5, $(M - H)^-$), 347 (17), 321 (54.2), 229 (17), 215 (100), 171 (20.3), 141 (25.4), 131 (98.3), 127 (50.8). Anal. Calcd for $C_{23}H_{46}O_7$ Si: C, 59.70; H, 10.02. Found: C, 60.10; H, 10.0.

(3′*R*,4′*S*,5′*R*,6′*S*)-[2′,4′-Dihydroxy-3′-methoxy-6′-(1″-methoxy-2″(*S*)-methylethyl)-5′-methyltetrahydropyran-2′-yl]-acetic Acid *tert*-Butyl Ester (12). Compound **10** (100 mg, 0.216 mmol) was dissolved in a solution of HF/pyr/THF[13] (1 mL). After 16 h at rt, the solution was diluted with CH_2Cl_2, washed with HCl (1 M) and H_2O, dried over Na_2SO_4, and evaporated. Chromatography (EtOAc/hexane 1:4) yielded 64 mg (85%) of **12**. Similar treatment of **11** (50 mg, 0.108 mmol) yielded 32 mg (86%) of **12**. Mp = 60–61 °C. ^1H NMR (360 MHz, $CDCl_3$) δ: 0.09 (d, J = 7 Hz, 3H), 1.00 (d, J = 7 Hz, 3H), 1.50 (s, 9H), 1.90 (m, 2H), 2.41 (d, J = 15 Hz, 1H), 2.85 (d, J = 15 Hz, 1H), 3.11 (d, J = 3 Hz, 1H), 3.25 (dd, J = 7, 8 Hz, 1H), 3.30 (s, 3H), 3.40 (s, 3H), 3.50 (dd, J = 3.5, 8 Hz, 1H), 3.78 (d, J = 10 Hz, 1H), 3.90 (ddd, J = 3, 10 Hz, 1H), 4.05 (dd, J = 3.5, 10 Hz, 1H), 5.95 (s, 1H). MS (EI): 349 (10, $(M + H)^+$), 331 (90), 313 (56), 275 (100), 257 (69), 239 (24), 225 (22), 214 (22), 185 (64), 143 (59), 125 (29), 111 (31). Anal. Calcd for $C_{17}H_{32}O_7$: C, 58.60; H, 9.26. Found: C, 58.70; H, 9.40.

(3′*R*,4′*S*,5′*R*,6′*S*)-[4′-[(*tert*-Butyldimethylsilyl)oxy]-2′-hydroxy-3′-methoxy-6′-(1″-methoxy-2″(*S*)-methylethyl)-5′-methyltetrahydropyran-2′-yl]acetic Acid Benzyl Ester (14). The reaction was carried out with benzyl acetate (217 mg, 1.44 mmol) and the lactone **3** (500 mg, 1.44 mmol) using the procedure described for **10** and **11**, with the exceptions that LTMP was used as the base and time of reaction was 21 h at −78 °C. After workup **13** was obtained. Chromatography (EtOAc/hexane 1:5) yielded 320 mg (45%) of **14**.

13. ^1H NMR (250 MHz, $CDCl_3$) δ: 0.09 (m, 6H), 0.83–094 (m, 12H), 0.98 (d, J = 7 Hz, 3H), 1.62 (m, 1H), 1.87 (m, 1H), 2.85 (d, J = 15 Hz, 1H), 3.27–3.66 (m, 5H), 3.30 (s, 3H), 3.48 (s, 3H), 4.05 (dd, J = 3 Hz, 1H), 4.70 (s, 1H), 5.10 (m, 2H), 7.25–7.38 (m, 5H).

14. ^1H NMR (360 MHz, $CDCl_3$) δ: 0.12 (d, J = 3 Hz, 6H), 0.87 (d, J = 7 Hz, 3H), 0.90 (s, 9H), 1.00 (d, J = 7 Hz, 3H), 1.70 (m, 1H), 1.92 (m, 1H), 2.70 (d, J = 15 Hz, 1H), 2.94 (d, J = 15 Hz, 1H), 3.20 (t, J = 9 Hz, 1H), 3.30 (s, 3H), 3.32 (m, 1H), 3.34 (s, 3H), 3.65 (dd, J = 3, 9 Hz, 1H), 3.88 (dd, J = 3, 10 Hz, 1H), 4.02 (dd, J = 3 Hz, 1H), 5.10 (m, 2H), 5.40 (d, J = 1 Hz, 1H), 7.31 (m, 5H). MS (EI): 497 (2, $(M + H)^+$), 479 (71.2), 377 (18.6), 348 (22), 347 (100), 257 (81.4), 239 (27.1), 185 (23.7), 170 (23.7), 143 (28.8), 131 (28.8), 125 (45.7), 115 (35.6). Anal. Calcd for $C_{26}H_{44}O_7Si$: C, 62.87; H, 8.93. Found: C, 63.10; H, 8.90.

(3′*R*,4′*S*,5′*R*,6′*S*)-[2′,4′-Dihydroxy-3′-methoxy-6′-(1″-methoxy-2″(*S*)-methylethyl)-5′-methyltetrahydropyran-2′-yl]-acetic Acid Benzyl Ester (15). The cleavage of the silyl ether of **14** (100 mg, 0.2 mmol) using the conditions described for **12** yielded 62 mg (82%) of **15**. ^1H NMR (360 MHz, $CDCl_3$) δ: 0.09 (d, J = 7 Hz, 3H), 1.00 (d, J = 7 Hz, 3H), 1.85 (m, 2H), 2.55 (d, J = 15 Hz, 1H), 3.01 (d, J = 15 Hz, 1H), 3.15 (d, J = 3 Hz, 1H), 3.25 (dd, J = 7, 8 Hz, 1H), 3.30 (s, 3H), 3.42 (m, 4H), 3.65 (d, J = 10 Hz, 1H), 3.90 (ddd, J = 3, 10 Hz, 1H), 4.05 (dd, J = 3.5, 10 Hz, 1H), 5.20 (s, 2H), 5.49 (s, 1H), 7.38 (s, 5H). MS (CI): 400 (27.1, $M^+ + 18$), 382 (100, M^+), 366 (15.2), 347 (40.7), 248 (13.6), 231 (22), 213 (28.8), 178 (11.9). Anal. Calcd for $C_{20}H_{30}O_7$: C, 62.81; H, 7.91. Found: C, 63.10; H, 8.20.

(3′*R*,4′*S*,5′*R*,6′*S*)-2′-[4′-[(*tert*-Butyldimethylsilyl)oxy]-2′-hydroxy-3′-methoxy-6′-(1″-methoxy-2″(*S*)-methylethyl)-5′-methyltetrahydropyran-2′-yl]propionic Acid Benzyl Ester (16–19). The reaction was carried out with benzyl propionate (237.3 mg, 1.44 mmol) and the lactone **3** (500 mg, 1.44 mmol) using the procedure described for **14**, but the mixture was stirred for 5 h at −78 °C and 30 min at 0 °C. In the crude product only the isomers **16** and **17** were present according to ^1H NMR. Chromatography (EtOAc/hexane 1:5)

yielded **16** (195 mg, 26%), **17** (13.6 mg, 2%), **18** (56 mg, 8%) and **19** (3 mg, 0.5%).

16. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.02 (s, 3H), 0.05 (s, 3H), 0.85 (s, 9H), 0.86 (d, J = 7 Hz, 3H), 0.96 (d, J = 7 Hz, 3H), 1.30 (d, J = 7 Hz, 3H), 1.63 (m, 1H), 1.85 (m, 1H), 3.30 (s, 3H), 3.33 (s, 3H), 3.47 (m, 2H), 3.52 (m, 1H), 3.60 (m, 1H), 3.63 (dd, J = 2.5, 10 Hz, 1H), 4.00 (dd, J = 3 Hz, 1H), 4.43 (d, J = 2 Hz, 1H), 5.10 (d, J = 12 Hz, 1H), 5.18 (d, J = 12 Hz, 1H), 7.28–7.40 (m, 5H). MS (EI): 493 (76.3), 391 (23.7), 361 (100), 329 (25.4), 289 (23.8), 257 (83), 225 (18.6), 215 (20.3), 188 (28.8), 173 (22), 143 (33.9), 131 (64.4), 125 (44), 115 (72.9).

17. Mp = 96–97 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.10 (s, 6H), 0.82 (d, J = 7 Hz, 3H), 0.91 (s, 9H), 1.01 (d, J = 7 Hz, 3H), 1.24 (d, J = 7 Hz, 3H), 1.65 (m, 1H), 1.95 (m, 1H), 3.03 (t, J = 9 Hz, 1H), 3.09 (d, J = 3 Hz, 1H), 3.24 (s, 3H), 3.50 (s, 3H), 3.60 (dd, J = 3, 9 Hz, 1H), 3.71 (q, J = 7 Hz, 1H), 3.79 (dd, J = 2.5, 10 Hz, 1H), 4.00 (dd, J = 3 Hz, 1H), 4.72 (s, 1H), 5.10 (d, J = 12 Hz, 1H), 5.31 (d, J = 12 Hz, 1H), 7.30–7.38 (m, 5H).

18. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.10 (s, 6H), 0.89 (d, J = 7 Hz, 3H), 0.90 (s, 9H), 1.00 (d, J = 7 Hz, 3H), 1.30 (d, J = 7 Hz, 3H), 1.70 (m, 1H), 1.94 (m, 1H), 3.15 (m, 1H), 3.20 (s, 3H), 3.25 (m, 2H), 3.34 (s, 3H), 3.68 (dd, J = 3, 9 Hz, 1H), 3.88 (dd, J = 2.5, 10 Hz, 1H), 4.02 (dd, J = 3 Hz, 1H), 5.10 (d, J = 12 Hz, 1H), 5.19 (d, J = 12 Hz, 1H), 5.32 (d, J = 2 Hz, 1H), 7.28–7.40 (m, 5H). MS (EI): 493 (76.4), 361 (100), 257 (40), 183 (20), 170 (30.9), 153 (14.5), 143 (18.2), 125 (40), 115 (30.9).

19. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.12 (s, 3H), 014 (s, 3H), 0.87 (d, J = 7 Hz, 3H), 0.91 (s, 9H), 1.02 (d, J = 7 Hz, 3H), 1.19 (d, J = 7 Hz, 3H), 1.70 (m, 1H), 1.92 (m, 1H), 3.00 (m, 1H), 3.12 (m, 2H), 3.21 (s, 3H), 3.38 (s, 3H), 3.58 (dd, J = 3, 9 Hz, 1H), 3.95 (dd, J = 2.5, 10 Hz, 1H), 4.08 (dd, J = 3 Hz, 1H), 5.09 (d, J = 12 Hz, 1H), 5.20 (d, J = 2 Hz, 1H), 5.23 (d, J = 12 Hz, 1H), 7.28–7.40 (m, 5H).

(3′*R*,4′*S*,5′*R*,6′*S*)-2′-[2′,4′-Dihydroxy-3′-methoxy-6′-(1″-methoxy-2″ (*S*)-methylethyl)-5′-methyltetrahydropyran-2′-yl]propionic Acid Benzyl Ester (20 and 2). Treatment of **16** (100 mg, 196 μmol) with a solution of HF/pyr/THF[13] using the conditions described for **12**, followed by chromatography (EtOAc/hexane 1:4), afforded the two isomers **20** (25.5 mg, 33%) and **2** (40.4 mg, 52%). Similar treatment of **17** (19 mg, 37 μmol) gave **20** (4.9 mg, 33%) and **2** (7.5 mg, 51%). Similar treatment of **18** (42.5 mg, 83 μmol) gave **20** (9 mg, 28%) and **2** (16 mg, 49%).

20. Mp = 110–111 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.90 (d, J = 7 Hz, 3H), 0.98 (d, J = 7 Hz, 3H), 1.27 (d, J = 7 Hz, 3H), 1.88 (m, 2H), 3.12 (dd, J = 1, 3 Hz, 1H), 3.15 (s, 3H), 3.20 (q, J = 7 Hz, 1H), 3.35 (s, 3H), 3.38 (m, 1H), 3.43 (d, J = 10 Hz, 1H), 3.56 (dd, J = 3, 9 Hz, 1H), 3.91 (ddd, J = 3, 10 Hz, 1H), 4.01 (dd, J = 2.5, 10 Hz, 1H), 4.50 (s, 1H), 5.10 (d, J = 12 Hz, 1H), 5.22 (d, J = 12 Hz, 1H), 7.30–7.40 (m, 5H). IR ($CHCl_3$): 3460, 1700 cm^{-1}. MS (FD): 397 (M + H)$^+$, 379 (M − HO)$^+$. Anal. Calcd for $C_{21}H_{32}O_7$: C, 63.62; H, 8.14. Found: C, 63.80; H, 8.40.

2. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.90 (d, J = 7 Hz, 3H), 1.00 (d, J = 7 Hz, 3H), 1.20 (d, J = 7 Hz, 3H), 1.85 (m, 2H), 3.15 (q, J = 7 Hz, 1H), 3.18 (m, 2H), 3.27 (s, 3H), 3.33 (dd, J = 3, 9 Hz, 1H), 3.39 (s, 3H), 3.80 (d, J = 10 Hz, 1H), 3.97 (ddd, J = 3, 10 Hz, 1H), 4.08 (dd, J = 2.5, 10 Hz, 1H), 5.15 (d, J = 12 Hz, 1H), 5.20 (d, J = 12 Hz, 1H), 5.22 (s, 1H), 7.30–7.40 (m, 5H). IR ($CHCl_3$): 3420, 1695 cm^{-1}. MS (FD): 397 (M + H)$^+$, 379 (M − HO)$^+$. Anal. Calcd for $C_{21}H_{32}O_7$: C, 63.62; H, 8.14. Found: C, 64.0; H, 8.20.

(3′*R*,4′*S*,5′*R*,6′*S*)-2′-[4′-[(*tert*-Butyldimethylsilyl)oxy]-2′-hydroxy-3′-methoxy-6′-(1″-methoxy-2″(*S*)-methylethyl)-5′-methyltetrahydropyran-2′-yl]propionic Acid *tert*-Butyl Ester (21–23). The reaction was performed with *tert*-butyl propionate (188 mg, 1.44 mmol) and the lactone **3** (500 mg, 1.44 mmol) using the procedure described for **10** and **11**, and the mixture was stirred for 2 h at −78 °C, for 10 min at 0 °C, and again for 2 h at −78 °C. Chromatography (EtOAc/hexane 1:5) yielded **21** (43 mg, 6%), **22** (238.7 mg, 35%), and **23** (21 mg, 3%).

21. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.14 (s, 3H), 0.15 (s, 3H), 0.85 (d, J = 7 Hz, 3H), 0.90 (s, 9H), 1.02 (d, J = 7 Hz, 3H), 1.21 (d, J = 7 Hz, 3H), 1.50 (s, 9H), 1.70 (m, 1H), 1.95 (m, 1H), 3.00 (q, J = 7 Hz, 1H), 3.25 (m, 1H), 3.35 (s, 3H), 3.37 (m, 1H), 3.40 (s, 3H), 3.69 (dd, J = 3, 9 Hz, 1H), 3.87 (dd, J = 2.5, 10 Hz, 1H), 4.10 (dd, J = 3 Hz, 1H), 5.35 (d, J = 2 Hz, 1H). MS (CI): 494 (10.2, M$^+$ + 18), 476 (83, M$^+$), 314 (15.2), 327 (62.7), 317 (69.5), 279 (15.2), 278 (100), 261 (25.4), 222 (66.1).

22. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.10 (s, 6H), 0.87 (d, J = 7 Hz, 3H), 0.94 (s, 9H), 1.00 (d, J = 7 Hz, 3H), 1.21 (d, J = 7 Hz, 3H), 1.5 (s, 9H), 1.65 (m, 1H), 1.85 (m, 1H), 3.32 (m, 4H), 3.49 (m, 5H), 3.68 (m, 2H), 4.00 (m, 1H), 4.52 (s, 1H). MS (CI): 494 (15.2, M$^+$ + 18), 462 (13.6), 476 (100, M$^+$), 344 (18.6), 327 (61). Anal. Calcd for $C_{24}H_{48}O_7$ Si: C, 60.47; H, 10.15. Found: C, 60.80; H, 10.20.

23. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.00 (s, 6H), 0.75 (d, J = 7 Hz, 3H), 0.80 (s, 9H), 0.95 (d, J = 7 Hz, 3H), 1.10 (d, J = 7 Hz, 3H), 1.40 (s, 9H), 1.51 (m, 1H), 1.90 (m, 1H), 3.0 (m, 1H), 3.20 (s, 3H), 3.27 (m, 2H), 3.40 (s, 3H), 3.58 (m, 2H), 3.89 (m, 1H), 4.95 (s, 1H).

(3′*R*,4′*S*,5′*R*,6′*S*)-2′-[2′,4′-Dihydroxy-3′-methoxy-6′-(1″-methoxy-2″(*S*)-methylethyl)-5′-methyltetrahydropyran-2′-yl]propionic Acid *tert*-Butyl Ester (24 and 25). Treatment of **21** (33 mg, 69 μmol) with a solution of HF/pyr/THF[13] using the conditions described for **12**, followed by chromatography (EtOAc/hexane 1:4), afforded the isomer **25** (16.5 mg, 66%). Similar treatment of **22** (99 mg, 208 μmol) gave a 3:2 mixture of **24** and **25** (6.6 mg, 9%) and pure **25** (44 mg, 59%). As **24** slowly converted to **25**, we were unable to prepare a pure sample of **24**.

24. ^{1}H NMR (360 MHz, CDCl3) δ: 0.90 (d, J = 7 Hz, 3H), 1.00 (d, J = 7 Hz, 3H), 1.21 (d, J = 7 Hz, 3H), 1.50 (s, 9H), 1.89 (m, 2H), 3.05 (q, J = 7 Hz, 1H), 3.15 (m, 1H), 3.35 (s, 3H), 3.36 (m, 1H), 3.40 (s, 3H), 3.60 (dd, J = 3, 9 Hz, 1H), 3.69 (d, J = 10 Hz, 1H), 3.92 (m, 1H), 4.05 (dd, J = 2.5, 10 Hz, 1H), 4.88 (s, 1H). MS (EI): 345 (32.2), 327 (44), 289 (50.8), 271 (100), 243 (50.8), 199 (47.5), 170 (54.2), 149 (81.4), 129 (27.1), 125 (61).

25. Mp = 86–87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (d, J = 7 Hz, 3H), 1.00 (d, J = 7 Hz, 3H), 1.19 (d, J = 7 Hz, 3H), 1.50 (s, 9H), 1.88 (m, 2H), 2.89 (q, J = 7 Hz, 1H), 3.15 (m, 1H), 3.21 (dd, J = 7, 9 Hz, 1H), 3.30 (s, 3H), 3.38 (s, 3H), 3.50 (dd, J = 3, 9 Hz, 1H), 3.89 (d, J = 10 Hz, 1H), 3.95 (ddd, J = 3, 10 Hz, 1H), 4.08 (dd, J = 2.5, 10 Hz, 1H), 5.77 (s, 1H). MS (EI): 345 (100), 327 (30.5), 289 (59.3), 271 (35.6), 243 (28.8), 189 (40.7), 166 (52.5), 143 (45.8), 125 (23.7), 111 (27.1). Anal. Calcd for $C_{18}H_{34}O_7$: C, 59.65; H, 9.45. Found: C, 59.70; H, 9.60.

Supplementary Material Available: NMR data with peak assignments and copies of ^{1}H NMR spectra of **3**, **6–10**, **16–19**, **21**, **23**, and **24** (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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