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Synthesis of the 5-hydroxymethyl-6-aryl-8-oxabicyclo[3.2.1]oct-3-en-2-one natural products descurainin and cartorimine

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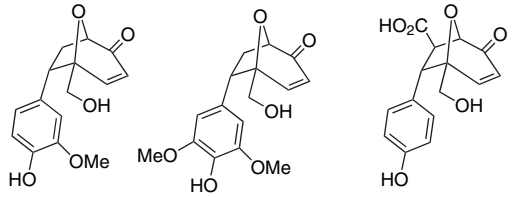
Abstract—Reaction of pyranulose **6** with styrenes **12c** or **13** and Et_3N in CH_2Cl_2 at 25 °C afforded the [5+2] cycloadducts **14c** and **15**, which were hydrolyzed to give the natural products **1** and descurainin (**2**) in 24 and 27% overall yield, respectively. Heating pyranulose **6** with cinnamate ester **21** in the presence of 2,6-di-*t*-butylpyridine in CH_3CN at 175 °C afforded the [5+2] cycloadduct, which was hydrolyzed to give cartorimine (**3**) in 13% yield.

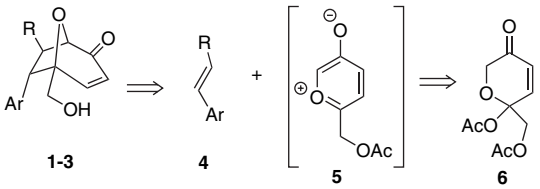
1. Introduction

Wen, He, Xue and Cao isolated the 8-oxabicyclo[3.2.1]oct-3-ene-2-one **1** in 1986 from *Ligusticum chuanxing*.[1] Li and co-workers isolated descurainin (**2**) with an additional methoxy group from the seeds of *Descurainia sophia* (L.) Webb ex Prantl which are used as a Chinese traditional medicine.[2] The structures of both the compounds were assigned by spectroscopic analysis.[3] Yin, He and Ye isolated the oxabicyclic acid cartorimine (**3**) from *Carthamus tinctorius* L., which is used as a traditional Chinese medicine to promote blood circulation. The structure was established from extensive NMR spectral data interpretation and single crystal X-ray analysis.[4,5]



1 **2** (descurainin) **3** (cartorimine)

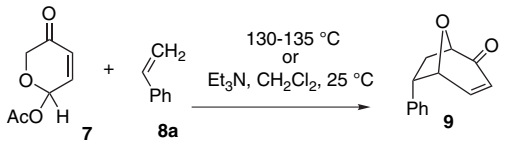
We thought that compounds **1**–**3** could be prepared by the [5+2] cycloaddition of the appropriate styrene derivative **4** with oxypyrylium zwitterion **5**, which could be generated in situ from pyranulose **6** (Scheme 1). This sequence is probably related to the biosynthesis of **1**–**3** because the required styrenes are natural products and **6** is generated by the dehydration and oxidation of fructose.[6]



1-3 **4** **5** **6**

Scheme 1. Retrosynthesis of **1**–**3**.

Hendrickson and Farina discovered that these [5+2] cycloadditions can be carried out by simply heating **7** and a dipolarophile at 130–135 °C to afford adducts analogous to **9** (Scheme 2).[7a] This reaction has been extensively developed by Sammes, who found that electron rich dipolarophiles were more reactive and that the reactions can also be carried out using Et_3N to generate the oxypyrylium zwitterion at room temperature.[8] Further examples of [5+2] cycloadditions have been reported by Heathcock and Ohmori.[9–11] Sammes reported that reaction of **7**, styrene (**8a**, 6 equiv) and Et_3N in CH_2Cl_2 at 25 °C afforded 65% of **9**, which lacks the hydroxymethyl and aryl substituents of **1** and descurainin (**2**).[8b] Oxypyrylium zwitterion **5** had not been previously prepared, but **6** should react similarly to **7** in these reactions. The para oxygen substituents on styrenes **12** and **13** should make them more electron rich and therefore more reactive than styrene (**8a**) itself.



7 **8a** **9**

Scheme 2.

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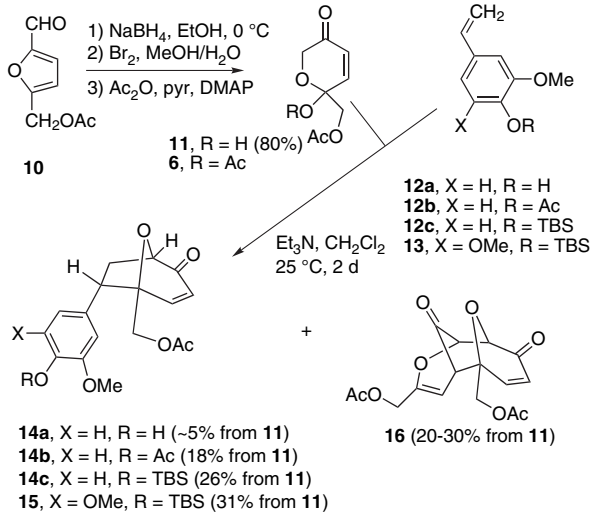
2. Results and discussion

5-(Acetoxymethyl)furfural (**10**) was reduced with $NaBH_4$ in EtOH for 10 min at 0 °C. The solution was quenched dropwise with HOAc and concentrated. The residue was taken up in water and treated with bromine in MeOH to give 80% of **11**.[6,12] Acetylation with Ac_2O, pyridine, and DMAP in CH_2Cl_2 afforded the unstable acetate **6**, which was used without purification (Scheme 3). 4-Hydroxy-3-methoxystyrene (**12a**) was prepared by decarboxylation of the corresponding cinnamic acid with Cu powder and quinoline at 210–240 °C.[13] Acetylation of **12a** with Ac_2O, DMAP, and pyridine gave **12b**[14] in 92% yield, and reaction of **12a** with TBSCl and imidazole afforded **12c**[14] in 91% yield. Styrene derivative **13**[15] was prepared in 99% yield by a Wittig reaction on the corresponding benzaldehyde.

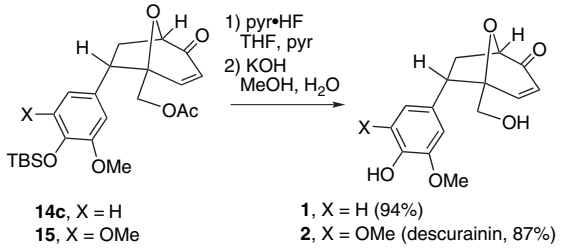


Scheme 3. Preparation of adducts **14** and **15**.

Our initial attempt at cycloaddition by treating **6** and **12a** with 2 equiv of Et_3N in CH_2Cl_2 at 25 °C afforded only ~5% of the desired adduct **14a** (see Scheme 3). We suspected that the free phenol interfered with this reaction, so we examined the reaction of **6** with the acetate **12b**, which gave the desired adduct **14b** in 18% yield. Use of TBS ether **12c** gave adduct **14c** in better (26%) yield as expected from Sammes observations that more electron rich dipolarophiles are more reactive.[8] The yield of cycloadduct **15** from TBS ether **13** improved to 31%. These reactions were carried out using 1 equiv of both **6** and **12** or **13**. Using 6 equiv of styrene **12** or **13** as reported by Sammes for the reaction of **7** and styrene (**8a**) did not improve the yield significantly, complicated purification, and was wasteful of styrene **12** or **13**.

No isomeric adducts were detected, but we did obtain 20–30% of a non-polar dimer tentatively assigned structure **16** based on similar dimers obtained from **7** with Et_3N in CH_2Cl_2 at 25 °C by Hendrickson and Farina[7b,16] and 10–15% of a polar dimer that was not fully characterized. These dimers were most easily isolated by treatment of **6** with Et_3N in CH_2Cl_2 in the absence of dipolarophile, which gave dimer **16** in 25% yield and the uncharacterized dimer in 13% yield. The uncharacterized dimer has two CH_2OAc groups, but no alkene protons. Formation of dimer **16** was suppressed by slow addition of **6** over 1 d to a solution of **13** and Et_3N in CH_2Cl_2. However, the yield of **15** did not improve significantly. We obtained lower yields of **15** at 0 or 60 °C in a sealed tube. Yields also decreased using CH_3CN as the solvent or *i*-Pr(Et_2)N as the base.

Hydrolysis of the TBS ether of **14c** with pyridine·HF in THF and pyridine, followed by hydrolysis of the acetate ester with KOH in aqueous MeOH afforded natural product **1** in 94% yield (see Scheme 4). The ^{13}C NMR spectrum in pyridine-d_5 corresponds well to that reported,[1] except that all peaks absorb downfield by 0.4–0.6 ppm from the literature data. The ^1H NMR spectrum in $CDCl_3$ does not correspond well to that reported, but the spectrum in pyridine-d_5 does correspond well to literature data suggesting that it may have been recorded in pyridine-d_5, rather than $CDCl_3$ as indicated.[1]



Scheme 4. Preparation of **1** and descurainin (**2**).

Similar hydrolysis of **15** provided 87% of descurainin (**2**) with spectral data in DMSO-d_6 identical to those reported. The *endo* stereochemistry of the synthetic material was expected based upon earlier studies with **7**.[7–11] It was confirmed unambiguously by the NOEs between the aromatic hydrogens and H_2 and H_3 (see Fig. 1). The two H_7's can be assigned based on their coupling constants to H_1. H_{7exo} is coupled to H_1 with J=8.9 Hz (25°), while H_{7endo} is coupled to H_1 with J=<1 Hz (94°). The coupling constants between H_6 and H_{7endo} (J=7.3 Hz, 130°) and H_{7exo} (J=10.1 Hz, 8°) are consistent with those expected. An NOE between H_6 and H_{7exo} and a much larger NOE between H_1 and H_{7exo} than between H_1 and H_{7endo} confirm the stereochemical assignment. The assignment of the opposite stereochemistry in natural descurainin appears to result from switched assignments for the two H_7's.[2]

We examined the reaction of **6** with styrene (**8a**) to compare the reactivity of the oxypyrylium zwitterions formed from **6** and **7** because Sammes obtained **9** in 65% yield from **7** and styrene (6 equiv). Reaction of **6** and styrene (1 equiv) with Et_3N in CH_2Cl_2 gave only 14% of a 7:1 mixture of *endo*

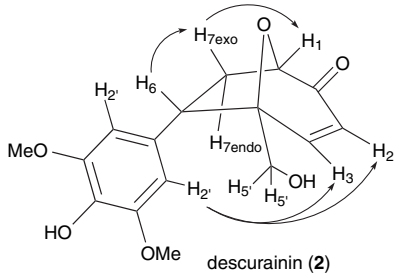
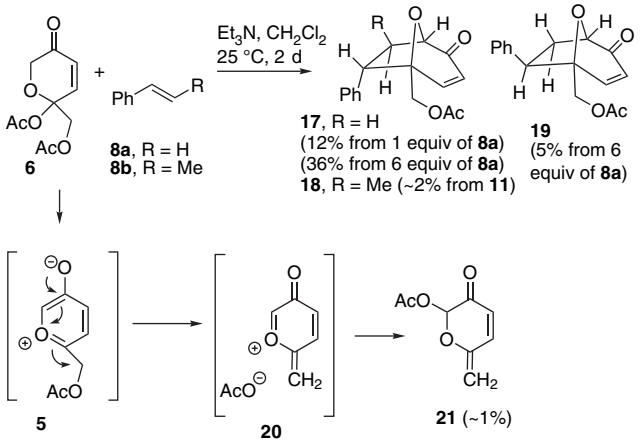


Figure 1. NOE's in synthetic descurainin (**2**).

adduct **17** and the unexpected *exo* adduct **19**. We isolated ~1% of acetoxy dienone **21** as a byproduct in these reactions. The ^{1}H NMR spectral data of **21** are similar to those of analogous compounds.[17–19] Oxypyrylium zwitterion **5** can eliminate acetate to give **20**. Attack of acetate on the cationic center will give acetoxy dienone **21**. Even though **21** is isolated in only 1% yield, this may be a major reaction pathway since **21** should polymerize readily under the basic reaction conditions. The competing formation of **21** may be responsible for the lower yields of [5+2] cycloadducts obtained from **6** than from **7**. Heathcock postulated that 2-methyl-6-methylene-2*H*-pyran-3(6*H*)-one, which differs from **21** only in the 2-substituent, was formed from 2,6-dimethyl-3-oxypyrylium zwitterion by internal proton transfer.[9] This compound was not isolated, but the dimer formed by the [5+2] cycloaddition of the *exo*-methylene group to the oxypyrylium zwitterion was formed in 52% yield.

Reaction of **6** with styrene (**8a**, 6 equiv) under Sammes conditions gave 41% of a 7:1 mixture of **17** and **19** indicating that lower yields of [5+2] cycloadducts are obtained from the oxypyrylium zwitterion **5** obtained from **6** (41% of **17** and **19**) than from the parent oxypyrylium zwitterion obtained from **7** (65% of **9**).[8b] Careful chromatography provided 36% of a ~10:1 mixture rich in the *endo* adduct **17** and 5% of a ~10:1 mixture rich in the *exo* adduct **19**, whose structure was established by COSY and 1D NOESY experiments. The spectra of **1**–**3**, **14**, **15**, and **17** are very similar indicating that they all have the same stereochemistry, whereas the chemical shifts and coupling constants of **19** are quite different (Scheme 5).

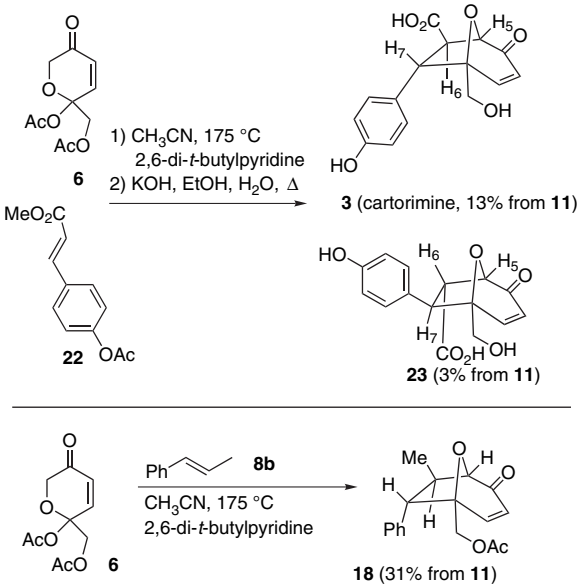


Scheme 5.

A competition experiment was carried out by reaction of **6** and Et_3N with 1 equiv of both **13** and styrene (**8a**). We obtained a 5:1 mixture of **15** and **17**, indicating that the sigma withdrawing, but pi donating, *para* oxygen substituent on the phenyl ring of **13** makes it five times as reactive as the parent styrene.

We now turned our attention to the preparation of cartorimine (**3**), which required the use of a less reactive cinnamate dipolarophile. Introduction of even a methyl substituent on the double bond of the styrene dipolarophile decreases its reactivity. Reaction of **6** with 6 equiv β-methylstyrene (**8b**) and Et_3N at 25 °C gave adduct **18** in only ~2% yield.

Acetoxy ester **22** was prepared in 94% yield from 4-hydroxycinnamic acid by esterification with methanolic HCl at reflux and acetylation with Ac_2O, pyridine, and DMAP in CH_2Cl_2. Reaction of **6** and **22** with Et_3N in CH_2Cl_2 at 25 °C or with $EtN(i\text{-}Pr)_2$ in CH_3CN at 80 °C did not afford the desired cycloadduct. Thermal reaction in CH_3CN at 150–175 °C was more successful, but not completely reproducible. Eventually, we concluded that residual pyridine from the preparation of **22** was important for the success of the reaction. Heating a 0.2 M solution of crude **6** in CH_3CN with 6 equiv of **22** and 1 equiv of 2,6-di-*t*-butylpyridine in a sealed tube in a 175 °C oil bath for 14 h afforded the crude bis acetoxymethyl ester of **3**. Hydrolysis with KOH in 4:1 EtOH/H_2O at reflux for 20 h and preparative TLC afforded 16% (from **11**) of a 4:1 mixture of cartorimine (**3**) and the stereoisomer **23**, which were separated by reverse phase HPLC. A similar reaction using pyridine, instead of 2,6-di-*t*-butylpyridine, afforded only 4% of a 3:1 mixture of **3** and **23**. The analogous cycloaddition of **6** with **8b** (6 equiv) provided 31% (from **11**) of **18** regio- and stereospecifically, confirming that the electron-withdrawing carbomethoxy group of **22** retards the reaction (Scheme 6).



Scheme 6. Preparation of cartorimine (**3**) and **18**.

The spectral data of **3** are identical to those previously reported.[4] Small NOEs from the aromatic hydrogens to the hydroxymethyl group of both **3** and **23** established that the minor product is a stereo- rather than a regioisomer. The vicinal coupling constants support this assignment. $J_{H5,H6}$= 1.5 Hz in **3** and 7.9 Hz in **23**, while $J_{H6,H7}$=7.5 Hz in **3** and 4.3 Hz in **23**. These coupling constants are consistent with those expected from MM2 calculations and analogous to those in the related stereoisomeric adducts formed from oxypyrylium zwitterions and dimethyl fumarate.[10]

Although natural products **1**–**3** are probably biosynthesized by similar [5+2] cycloadditions of achiral compounds, they were isolated with small $[\alpha]_D$ (+1.7° for **2**, −2.6° for **3**) or $\Delta\varepsilon$ (+0.01 for **1**) indicating that they are not completely racemic. However, a [5+2] cycloaddition in a chiral environment could lead to an optically enriched product as was observed.

In conclusion, we have completed the first syntheses of **1**, descurainin (**2**), and cartorimine (**3**) using a possibly biomimetic [5+2] cycloaddition to efficiently construct the fully functionalized 8-oxabicyclo[3.2.1]octenone skeleton. Reaction of **6** with styrenes **8a**, **12**, or **13** and Et_3N in CH_2Cl_2 proceeds at 25 °C, while reaction of **6** with cinnamate ester **21** is best carried out at 175 °C with 2,6-di-*t*-butylpyridine as a proton scavenger.

3. Experimental

3.1. General procedures

NMR spectra were recorded at 400 MHz in $CDCl_3$ unless otherwise indicated, chemical shifts are reported in δ, and coupling constants in Hertz. The silica gel used for chromatography was deactivated with methanol unless otherwise indicated. IR spectra are reported in cm^{-1}.

3.1.1. 6-[(Acetyloxy)methyl]-6-hydroxy-2*H*-pyran-3(6*H*)-one (11). A solution of 5-acetoxymethyl-2-furancarboxyaldehyde (**10**, 1.006 g, 5.98 mmol) in EtOH (17 mL) was added to a suspension of $NaBH_4$ (113 mg, 2.99 mmol) in EtOH (13 mL) at 0 °C and the resulting solution was stirred for 10 min at 0 °C. HOAc was added dropwise to quench the reaction and the EtOH was removed under reduced pressure. The brown residue was dissolved in H_2O (40 mL) and a solution of Br_2 (0.31 mL, 6.0 mmol) in MeOH (3 mL) was added dropwise. After 2 h, the solution was basified to pH 5 with saturated $NaHCO_3$ solution. The resulting aqueous solution was saturated with NaCl and extracted with EtOAc (4×40 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure (<30 °C) to give 894 mg (80%) of **11** with data identical to those previously reported.[6,12]

3.1.2. 6-Acetyloxy-6-[(acetyloxy)methyl]-2*H*-pyran-3(6*H*)-one (6). Ac_2O (20 mL), dry pyridine (10 mL), and DMAP (130 mg, 1.06 mmol) were added in succession to a solution of **11** (1.967 g, 10.6 mmol) in dry CH_2Cl_2 (120 mL) under N_2 and the resulting solution was stirred for 30 min at 0 °C. The solution was washed with 10% $CuSO_4$ solution (100 mL), H_2O (100 mL), saturated $NaHCO_3$ solution (100 mL), and brine (100 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give 1.541 g of crude brown **6** (~90% pure) that was used directly for the cycloadditions: ^1H NMR 7.24 (d, 1, *J*=10.4), 6.23 (d, 1, *J*=10.4), 4.61 (d, 1, *J*=17.4), 4.56 (d, 1, *J*=11.6), 4.44 (d, 1, *J*=11.6), 4.31 (d, 1, *J*=17.4), 2.11 (s, 3), 2.10 (s, 3); ^{13}C NMR 193.3, 170.2, 169.4, 143.4, 128.2, 97.4, 68.1, 65.1, 21.3, 20.8.

3.1.3. 2-Methoxy-4-vinylphenol acetate (12b).[14] Ac_2O (2.8 mL), dry pyridine (1.4 mL), and DMAP (17 mg, 0.140 mmol) were added in succession to a solution of 2-methoxy-4-vinylphenol (**12a**)[13] (210 mg, 1.40 mmol) in dry CH_2Cl_2 (14 mL) under N_2 and the resulting solution was stirred for 35 min at 0 °C. The solution was washed with 10% $CuSO_4$ solution (15 mL), saturated $NaHCO_3$ solution (15 mL), and brine (15 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give 248 mg (92%) of **12b** as a yellow oil: ^1H NMR 7.01 (d, 1, *J*=1.2), 6.99 (br s, 2), 6.68 (dd, 1, *J*=17.6, 10.8), 5.70 (d, 1, *J*=17.6), 5.25 (d, 1, *J*=10.8), 3.86 (s, 3), 2.32 (s, 3); ^{13}C NMR 169.1, 151.0, 139.3, 136.6, 136.2, 122.7, 118.9, 114.1, 109.8, 55.8, 20.6; IR (neat) 1764.

3.1.4. (1,1-Dimethylethyl)(4-ethenyl-2-methoxyphenoxy)dimethylsilane (12c).[14] TBSCl (524 mg, 3.48 mmol) and imidazole (494 mg, 7.26 mmol) were added in succession to a solution of 2-methoxy-4-vinylphenol (**12a**)[13] (435 mg, 2.90 mmol) in dry CH_2Cl_2 (15 mL) under N_2 and the resulting solution was stirred for 2 h at 25 °C. The solution was diluted with CH_2Cl_2 (20 mL), washed with brine (2×20 mL) and dried over $MgSO_4$. The solution was concentrated under reduced pressure to give 762 mg of a yellow liquid. Flash chromatography on silica gel (9:1 hexanes/EtOAc) yielded 698 mg (91%) of **12c** as a yellow oil: ^1H NMR 6.93 (d, 1, *J*=1.8), 6.87 (dd, 1, *J*=8.2, 1.8), 6.80 (d, 1, *J*=8.2), 6.64 (dd, 1, *J*=17.1, 10.4), 5.60 (d, 1, *J*=17.1), 5.14 (d, 1, *J*=10.4), 3.83 (s, 3), 0.99 (s, 9), 0.15 (s, 6); ^{13}C NMR 150.9, 145.1, 136.6, 131.5, 120.8, 119.3, 111.7, 109.5, 55.4, 25.7 (3C), 18.4, −4.7 (2C); IR (neat) 1414, 1278.

3.1.5. 4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3,5-dimethoxybenzaldehyde.[15] TBSCl (1.015 g, 6.73 mmol) and imidazole (952 mg, 14.0 mmol) were added in succession to a solution of 4-hydroxy-3,5-dimethoxybenzaldehyde (1.022 g, 5.61 mmol) in dry CH_2Cl_2 (40 mL) under N_2. The resulting solution was stirred for 30 min at 25 °C. The solution was diluted with CH_2Cl_2 (60 mL), washed with brine (2×100 mL) and dried over $MgSO_4$. The solution was concentrated under reduced pressure to give 1.980 g of a clear solid. Flash chromatography on silica gel (4:1 hexanes/EtOAc) yielded 1.261 g (76%) of the protected aldehyde as a white solid: mp 69–71 °C; ^1H NMR 9.83 (s, 1), 7.10 (s, 2), 3.87 (s, 6), 1.01 (s, 9), 0.16 (s, 6); ^{13}C NMR 191.0, 151.9 (2C), 140.6, 129.3, 106.6 (2C), 55.8 (2C), 25.6 (3C), 18.8, −4.6 (2C); IR (KBr) 1684.

3.1.6. (1,1-Dimethylethyl)(4-ethenyl-2,6-dimethoxyphenoxy)dimethylsilane (13).[15] LiHMDS (1.0 M) in THF (3.5 mL) was added dropwise to a suspension of $MeP(Ph)_3Br$ in dry THF (20 mL) at 0 °C under N_2 and the resulting solution was allowed to stir at 0 °C for 5 min. The above aldehyde (733 mg, 2.47 mmol) in dry THF (8 mL) was added dropwise to the cooled solution and the resulting solution was stirred for 4 h at 25 °C. Saturated NH_4Cl solution (40 mL) was added to the solution and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3×40 mL) and the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography on silica gel (9:1 hexanes/EtOAc) yielded 681 mg (99%) of **13** as a clear solid: mp 31–33 °C; ^1H NMR 6.62 (dd, 1, *J*=17.4, 11.0), 6.61 (s, 2), 5.61 (d, 1, *J*=17.4), 5.15 (d, 1, *J*=11.0), 3.81 (s, 6), 1.00 (s, 9), 0.13 (s, 6); ^{13}C NMR 151.6 (2C), 137.0, 134.5, 130.3, 111.9, 103.4 (2C), 55.7 (2C), 25.8 (3C), 18.7, −4.6 (2C); IR (KBr) 1409, 1253.

3.1.7. *endo*-5-[(Acetyloxy)methyl]-6-(4-acetyloxy-3-methoxyphenyl)-8-oxabicyclo[3.2.1]oct-3-en-2-one (14b). Et_3N (0.16 mL, 1.1 mmol) was added dropwise to a solution of crude **6** (128 mg, 0.561 mmol) and **12b** (108 mg, 0.561 mmol) in dry CH_2Cl_2 (2 mL) under N_2 at 0 °C. The resulting solution was stirred at 25 °C for 2 d and was

concentrated under reduced pressure. Flash chromatography on silica gel (4:1–1:1 hexanes/EtOAc) yielded 36 mg (18% from **11**) of **14b** as a yellow wax: ^{1}H NMR 6.96 (d, 1 J=8.0), 6.74 (d, 1, J=9.8), 6.73–6.72 (m, 2), 6.29 (d, 1, J=9.8), 4.69 (br d, 1, J=8.9), 4.49 (d, 1, J=12.2), 4.31 (d, 1, J=12.2), 3.80 (s, 3), 3.52 (dd, 1, J=9.8, 7.0), 3.00 (ddd, 1, J=13.7, 9.8, 8.9), 2.31 (s, 3), 2.10 (s, 3), 2.04 (br dd, 1, J=13.7, 7.0); ^{13}C NMR 196.1, 170.6, 168.9, 151.1, 151.0, 139.3, 135.0, 128.6, 122.9, 120.8, 112.8, 83.5, 80.8, 64.8, 55.9, 49.7, 34.1, 20.7, 20.6; IR (neat) 1765, 1745, 1703.

3.1.8. *endo*-5-[(Acetyloxy)methyl]-6-[3-methoxy-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-phenyl]-8-oxabicyclo[3.2.1]oct-3-en-2-one (14c). Et_3N (0.25 mL, 1.8 mmol) was added dropwise to a solution of crude **6** (204 mg, 0.894 mmol) and **12c** (237 mg, 0.896 mmol) in dry CH_2Cl_2 (4 mL) under N_2. The resulting solution was stirred for 2 d at 25 °C and was concentrated under reduced pressure. Flash chromatography on silica gel (9:1 hexanes/EtOAc) gave 26 mg of an impure 5:2:1 mixture of **14c**, **12c**, and **21**, respectively, followed by 129 mg (26% from **11**) of **14c** as a clear wax. Elution with EtOAc gave 19 mg of impure **16**.

Data for **14c**: ^{1}H NMR 6.75 (d, 1, J=8.6), 6.68 (d, 1, J=10.4), 6.60 (m, 2), 6.27 (d, 1, J=10.4), 4.67 (br d, 1, J=8.9), 4.49 (d, 1, J=12.2), 4.28 (d, 1, J=12.2), 3.77 (s, 3), 3.47 (dd, 1, J=9.8, 6.7), 2.97 (ddd, 1, J=13.4, 9.8, 8.9), 2.10 (s, 3), 2.02 (br dd, 1, J=13.4, 6.7), 0.99 (s, 9), 0.14 (s, 6); ^{13}C NMR 196.3, 170.6, 151.4, 150.8, 144.7, 129.2, 128.4, 121.0, 120.8, 112.5, 83.5, 80.8, 65.0, 55.6, 49.4, 33.9, 25.6 (3C), 20.7, 18.4, −4.6 (2C); IR (KBr) 1743, 1704, 1605, 1043; HRMS (DCI/NH_3) calcd for $C_{23}H_{36}NO_6Si$ (MNH_4^+) 450.2312, found 450.2302.

3.1.9. *endo*-5-[(Acetyloxy)methyl]-6-[3,5-dimethoxy-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-phenyl]-8-oxabicyclo[3.2.1]oct-3-en-2-one (15). Et_3N (0.36 mL, 2.6 mmol) was added dropwise to a solution of crude **6** (292 mg, 1.28 mmol) and **13** (357 mg, 1.28 mmol) in dry CH_2Cl_2 (6 mL) under N_2. The resulting solution was stirred for 2 d at 25 °C and was concentrated under reduced pressure. Flash chromatography on silica gel (4:1 hexanes/EtOAc) gave 18 mg of an impure 2:1 mixture of **15** and **21**, followed by 237 mg (31% from **11**) of **15** as a clear wax. Elution with EtOAc gave 78 mg of an impure 2:1 mixture of **16** and **15**.

Data for **15**: ^{1}H NMR 6.70 (d, 1, J=10.4), 6.29 (s, 2), 4.67 (br d, 1, J=8.9), 4.49 (d, 1, J=11.9), 4.31 (d, 1, J=11.9), 3.75 (s, 6), 3.44 (dd, 1, J=10.1, 7.3), 2.98 (ddd, 1, J=14.0, 10.1, 8.9), 2.10 (s, 3), 2.01 (ddd, 1, J=14.0, 7.3, 1.7), 1.00 (s, 9), 0.12 (s, 6); ^{13}C NMR 196.3, 170.6, 151.54 (2C), 151.46, 134.0, 128.27, 128.25, 105.8 (2C), 83.6, 80.8, 65.0, 55.8 (2C), 49.9, 33.9, 25.7 (3C), 20.7, 18.7, −4.6 (2C); IR (KBr) 1745, 1703, 1588, 1031; HRMS (DCI/NH_3) calcd for $C_{24}H_{38}NO_7Si$ (MNH_4^+) 480.2418, found 480.2398.

3.1.10. (1α,2α,6α,7α)-4,7-Di(acetyloxy)methyl-3,11-dioxa-tricyclo[5.3.1.1.^{2,6}]dodeca-4,8-diene-10,12-dione (16) Et_3N (0.20 mL, 1.4 mmol) was added dropwise to a solution of crude **6** (163 mg, 0.714 mmol) in dry CH_2Cl_2 (3 mL) under N_2 and the resulting solution was stirred for 2 d at 25 °C and was concentrated under reduced pressure. Flash chromatography on silica gel (22:3 hexanes/EtOAc) yielded 39 mg (25% from **11**) of **16** as a clear oil, followed (EtOAc as eluent) by 20 mg (13% from **11**) of a dimer of unknown structure.

Data for **16**: ^{1}H NMR 6.85 (d, 1, J=10.4), 6.33 (d, 1, J=10.4), 5.01 (d, 1, J=9.2), 4.81 (d, 1, J=7.3), 4.80 (dd, 1, J=9.2, 2.9), 4.45 (d, 1, J=13.4), 4.384 (d, 1, J=13.4), 4.38 (d, 1, J=12.2), 4.29 (d, 1, J=12.2), 3.29 (dd, 1, J=7.3, 2.9); ^{13}C NMR 198.3, 189.0, 170.4, 170.2, 150.8, 147.9, 129.6, 100.9, 81.5, 81.4, 75.9, 66.7, 61.7, 48.5, 20.7, 20.6; IR (neat) br 1745, br 1698, 1043.

Data for the dimer of unknown structure: ^{1}H NMR 4.88 (d, 1, J=6.1), 4.74 (d, 1, J=4.3), 4.61 (d, 1, J=13.4), 4.56 (d, 1, J=13.4), 4.46 (br s, 1), 4.27 (d, 1, J=12.2), 4.23 (d, 1, J=12.2), 4.02 (br s, 1), 2.80 (d, 1, J=16.5), 2.72 (dd, 1, J=16.5, 4.3), 2.68 (br d, 1, J=6.1), 2.12 (s, 3), 2.11 (s, 3).

3.1.11. *endo*-6-(4-Hydroxy-3-methoxyphenyl)-5-(hydroxymethyl)-8-oxabicyclo[3.2.1]oct-3-ene-2-one (1). Pyridine·$(HF)_x$ (1.4 M, 3.5 mL) (5 mL of pyridine·$(HF)_x$ in 20 mL of pyridine and 20 mL of THF) was added to a solution of **14c** in THF (5 mL) and the resulting solution was stirred at 25 °C for 12 h. The solution was neutralized with saturated $NaHCO_3$ solution and the resulting aqueous solution was extracted with EtOAc (3×100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to give a brown residue. The residue was dissolved in 4:1 MeOH/H_2O (5 mL), KOH (18 mg, 0.321 mmol) was added, and the resulting solution was stirred at 25 °C for 1 h. The solution was acidified to pH 5 using saturated NaH_2PO_4 solution and the MeOH was removed under reduced pressure. The residue was diluted with H_2O (2 mL), saturated with NaCl, and extracted with EtOAc (3×15 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to yield 69 mg (94% from **14c**) of **1** as a tan powder: mp 168–170 °C; ^{1}H NMR (C_5D_5N) 7.19 (d, 1, J=7.9), 7.06 (d, 1, J=9.5), 7.05 (br s, 1), 6.92 (dd, 1, J=7.9, 1.8), 6.46 (dd, 1, J=9.5, 1.2), 5.02 (br, 1, OH), 4.89 (br d, 1, J=8.9), 4.30 (d, 1, J=12.5), 4.13 (d, 1, J=12.5), 3.98 (dd, 1, J=10.1, 7.3), 3.73 (s, 3), 2.90 (ddd, 1, J=12.8, 10.1, 8.9), 2.19 (br d, 1, J=12.8, 7.3); ^{13}C NMR (C_5D_5N) 197.8, 155.0, 148.9, 147.9, 129.2, 128.5, 122.3, 116.9, 113.9, 87.5, 81.5, 63.6, 56.3, 48.1, 34.5; IR (KBr) 3482, 1679, 1608, 1037; UV (EtOH) λ_{max} (log ε) 210 (3.58), 230 (sh 3.53), 282 nm (sh 2.85); HRMS (DCI/NH_3) calcd for $C_{15}H_{20}NO_5$ (MNH_4^+) 294.1341, found 294.1335. The spectral data match well with those reported for the natural product, which was isolated as white needles: mp 184–185 °C; CD $\Delta\varepsilon$ +0.01 (355 nm, MeOH).[1]

3.1.12. *endo*-6-(4-Hydroxy-3,5-dimethoxyphenyl)-5-(hydroxymethyl)-8-oxabicyclo[3.2.1]oct-3-ene-2-one (Descurainin, 2). Pyridine·$(HF)_x$ (1.4 M, 7.0 mL) (5 mL of pyridine·$(HF)_x$ in 20 mL of pyridine and 20 mL of THF) was added to a solution of **15** in THF (10 mL) and the resulting solution was stirred at 25 °C for 12 h. The solution was neutralized with saturated $NaHCO_3$ solution and the resulting aqueous solution was extracted with EtOAc (3× 200 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to a brown residue. The residue was dissolved in 4:1 MeOH/H_2O (10 mL), KOH (18 mg, 0.321 mmol) was added, and the resulting solution was stirred at 25 °C for 1 h. The solution was

acidified to pH 5 using saturated NaH_2PO_4 solution and the MeOH was removed under reduced pressure. The residue was diluted with H_2O (2 mL), saturated with NaCl, and extracted with EtOAc (3×30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to yield 137 mg (87% from **15**) of **2** as a tan powder: mp 183–185 °C; ^{1}H NMR (DMSO-d_6) 8.29 (s, 1, OH), 6.82 (d, 1, J=10.1), 6.41 (s, 2), 6.19 (br d, 1, J=10.1), 5.13 (t, 1, J=6.1, OH), 4.50 (br d, 1, J=8.9), 3.76–3.67 (m, 1), 3.71 (s, 6), 3.60 (dd, 1, J=12.8, 6.1), 3.46 (dd, 1, J=10.1, 7.3), 2.82 (ddd, 1, J=13.1, 10.1, 8.9), 1.92 (br dd, 1, J=13.1, 7.3); ^{13}C NMR (DMSO-d_6) 196.9, 154.5, 147.6 (2C), 134.7, 127.2, 127.1, 106.3 (2C), 85.8, 79.7, 62.3, 56.0 (2C), 47.2, 32.9; HRMS (DCI/NH_3) calcd for $C_{16}H_{22}NO_6$ (MNH_4^+) 324.1447, found 324.1451. The spectral data match those reported for the natural product which was isolated as colorless needles: mp 193–195 °C; $[\alpha]_D^{20}$ +1.7° (*c* 0.23, MeOH).[2] The 1D NOESY experiments showed: (a) NOEs from H_3 at δ 6.82 to the phenyl protons at δ 6.41, H_2 at δ 6.19, and the CH_2OH group at δ 5.13, 3.76–3.67 and 3.60. (b) NOEs from the phenyl protons at δ 6.41 to H_3 at δ 6.82, H_2 at 6.19, H_6 at δ 3.46, and H_{7endo} at δ 1.92. (c) NOEs from H_2 at δ 6.19 to H_3 at δ 6.82 and the phenyl protons at δ 6.41. (d) NOEs from H_1 at δ 4.50 to H_{7exo} at δ 2.82 (larger) and H_{7endo} at δ 1.92 (smaller). (e) NOEs from H_6 at δ 3.46 to the phenyl protons at δ 6.41, the CH_2OH group at δ 5.13, 3.76–3.67, and H_{7exo} at δ 2.82. (f) NOEs from H_{7exo} at δ 2.82 to H_1 at δ 4.50, H_6 at δ 3.46, and H_{7endo} at δ 1.92. (g) NOEs from H_{7endo} at δ 1.92 to the phenyl protons at δ 6.41, H_1 at δ 4.50, and H_{7exo} at δ 2.82.

3.1.13. *endo*-5-[(Acetyloxy)methyl]-6-phenyl-8-oxabicyclo[3.2.1]oct-3-en-2-one (17) and *exo*-5-[(acetyloxy)-methyl]-6-phenyl-8-oxabicyclo[3.2.1]oct-3-en-2-one (19). Et_3N (0.24 mL, 1.7 mmol) was added dropwise to a solution of crude **6** (196 mg, 0.859 mmol) and styrene (0.10 mL, 0.859 mmol, 1 equiv) in dry CH_2Cl_2 (4 mL) under N_2. The resulting solution was stirred for 2 d at 25 °C and was concentrated under reduced pressure. Flash chromatography on silica gel (22:3 hexanes/EtOAc) yielded 37 mg (12% from **11**) of a 7:1 mixture of **17** and **19** as a clear oil.

Purification of an identical reaction on a larger amount of silica gel (9:1 hexanes/EtOAc) gave **17** in lower yield preceded by 2 mg (1% from **11**) of ~90% pure 2-acetoxy-6-methylene-2*H*-pyran-3(6*H*)-one (**21**): ^{1}H NMR 7.15 (d, 1, J=10.4), 6.28 (s, 1), 6.21 (br d, 1, J=10.4), 5.17 (dd, 1, J=1.5, 1.5), 4.91 (br s, 1), 2.12 (s, 3). A 1D NOESY experiment showed NOE's between the *exo*-methylene hydrogen at δ 4.91 and H_3 at δ 7.15 and the other *exo*-methylene hydrogen at δ 5.17.

Et_3N (0.27 mL, 1.97 mmol) was added dropwise to a solution of crude **6** (298 mg, 1.31 mmol) and **8a** (0.90 mL, 7.9 mmol, 6 equiv) in dry CH_2Cl_2 (0.65 mL) under N_2 at 0 °C. The resulting solution was stirred at 25 °C for 16 h and was concentrated under reduced pressure. Flash chromatography on silica gel (22:3 hexanes/EtOAc) gave 162 mg (36% from **11**) of a 10:1 mixture of **17** and **19** as a clear oil, followed by 23 mg (5% from **11**) of a 10:1 mixture of **19** and **17** as a yellow oil.

Data for **17** were determined from the 10:1 mixture: ^{1}H NMR 7.34–7.25 (m, 3), 7.15 (br d, 2, J=7), 6.65 (d, 1, J=10.1), 6.29 (d, 1, J=10.1), 4.70 (br d, 1, J=9.2), 4.51 (d, 1, J=11.9), 4.25 (dd, 1, J=11.9), 3.55 (dd, 1, J=9.8, 6.7), 3.00 (ddd, 1, J=14.0, 9.8, 9.2), 2.10 (s, 3), 2.10–2.05 (m, 1); ^{13}C NMR 196.1, 170.6, 150.9, 136.1, 128.74, 128.66 (4C), 127.8, 83.6, 80.9, 64.9, 49.7, 33.7, 20.7; IR (neat) 1744, 1704, 1602, 1030.

Data for **19** were determined from the 10:1 mixture: ^{1}H NMR 7.35–7.21 (m, 6), 6.11 (d, 1, J=9.8), 4.83 (br d, 1, J=8.5), 4.07 (d, 1, J=11.9), 3.65 (d, 1, J=11.9), 3.42 (dd, 1, J=8.9, 3.4), 2.59 (ddd, 1, J=14.0, 8.5, 3.4), 2.49 (ddd, 1, J=14.0, 8.9, 1.9), 2.02 (s, 3); ^{13}C NMR 196.2, 170.3, 152.9, 139.5, 128.7 (2C), 128.3 (2C), 127.6, 126.2, 84.2, 81.5, 65.3, 49.2, 36.4, 20.6. The 1D NOESY experiments showed: (a) NOEs from H_1 at δ 4.83 to H_{7exo} at δ 2.59 (larger) and H_{7endo} at δ 2.49 (smaller). (b) NOEs from H_6 at δ 3.42 to the phenyl protons at 7.35–7.21, the CH_2OH group at 4.07, H_{7exo} at δ 2.59 (smaller) and H_{7endo} at δ 2.49 (larger). (c) NOEs from H_{7exo} at δ 2.59 to the phenyl protons at δ 7.35–7.21, H_1 at δ 4.83, H_6 at δ 3.42, and H_{7endo} at δ 2.49. (d) NOEs from H_{7endo} at δ 2.49 to H_1 at δ 4.83, H_6 at δ 3.42, and H_{7exo} at δ 2.59.

3.1.14. Methyl (2*E*)-3-[4-(acetyloxy)phenyl]-2-propenate (22). AcCl (13 mL, 0.18 mol) was added dropwise to MeOH (36 mL) at 0 °C and the resulting solution was stirred at room temperature for 30 min. 4-Hydroxycinnamic acid (6.014 g, 36.6 mmol) was added and the solution was heated to reflux for 2 h. The reaction was cooled and concentrated under reduced pressure. The residue was dissolved in dry CH_2Cl_2 (360 mL) and cooled to 0 °C under N_2. Ac_2O (74 mL), dry pyridine (36 mL) and DMAP (448 mg, 3.37 mmol) were added in succession and the resulting solution was stirred for 35 min at 0 °C. The solution was washed with 10% $CuSO_4$ solution (400 mL), water (400 mL), saturated $NaHCO_3$ solution (400 mL), and brine (400 mL). The organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to give 7.610 g (94%) of **22**: ^{1}H NMR 7.67 (d, 1, J=16.2), 7.54 (d, 2, J=8.5), 7.12 (d, 2, J=8.5), 6.40 (d, 1, J=16.2), 3.81 (s, 3), 2.32 (s, 3); ^{13}C NMR 169.3, 167.4, 152.2, 143.9, 132.3, 129.3 (2C), 122.3 (2C), 118.1, 51.9, 21.3.

3.1.15. Cartorimine (3). 2,6-Di-*t*-butylpyridine (0.45 mL, 2.0 mmol) was added to a solution of crude **6** (459 mg, 2.01 mmol) and **22** (2.664 g, 12.1 mmol, 6 equiv) in dry CH_3CN (10 mL). The resulting solution was degassed using the freeze-thaw method[20] and heated to 175 °C for 14 h in a sealed tube. The reaction was cooled and concentrated under reduced pressure to give 3.119 g of a black solid. Most of the unreacted **22** was removed by filtering the black solid through 50 g of silica gel (3:2 hexanes/EtOAc) to afford 239 mg of crude bis acetoxy ester, which was dissolved in 4:1 EtOH/H_2O (50 mL). KOH (178 mg, 3.18 mmol) was added, and the resulting red solution was heated at reflux for 20 h and cooled. The solution was acidified to pH 3 using a saturated NaH_2PO_4 solution and the EtOH was then removed under reduced pressure. The resulting aqueous solution was extracted with CH_2Cl_2 (3×50 mL) to remove less polar impurities. The resulting aqueous solution was saturated with NaCl and extracted with EtOAc (4×50 mL). The EtOAC solution was dried over $MgSO_4$ and concentrated

under reduced pressure to give 159 mg of crude **3**. Preparative TLC (7:3 $CHCl_3$/acetone) yielded 110 mg (16% from **11**) of a 4:1 mixture of (1*R**,5*R*,6*R*,7*S*)-1-(hydroxymethyl)-7-(4-hydroxyphenyl)-4-oxo-8-oxabicyclo[3.2.1]oct-2-ene-6-carboxylic acid (cartorimine, **3**) and its stereoisomer (1*R**,5*R*,6*S*,7*R*)-1-(hydroxymethyl)-7-(4-hydroxyphenyl)-4-oxo-8-oxabicyclo[3.2.1]oct-2-ene-6-carboxylic acid (**23**). Separation of **3** and **23** was achieved by HPLC on a Zorbex Eclipse XDB-C18 4.6×250 mm column (9:1 H_2O/MeOH) flow rate=1 mL min^{-1} with sample loadings of 0.5 mg: t_R=12.3 (**23**), t_R=18.3 (**3**).

Data for **3**: ^1H NMR (CD_3OD) 7.07 (d, 2, *J*=8.5), 6.80 (d, 1, *J*=10.4), 6.71 (d, 2, *J*=8.5), 6.18 (br d, 1, *J*=10.4), 4.70 (br s, 1), 3.84 (d, 1, *J*=6.7), 3.82 (d, 1, *J*=12.5), 3.73 (d, 1, *J*=12.5), 3.13 (br d, 1, *J*=6.7); ^{13}C NMR (CD_3OD) 197.9, 158.2, 155.6, 131.1 (2C), 128.9, 128.4, 116.4 (2C), 88.4, 86.1, 64.2, 54.2 (2C) (one quaternary carbon was not observed). The spectral data matches those reported for the natural product: mp 206–207 °C; $[\alpha]_D^{25}$ −2.6° (*c* 0.005, MeOH)[4]

Data for **23**: ^1H NMR (CD_3OD) 7.47 (d, 1, *J*=9.5), 7.09 (d, 2, *J*=7.6), 6.73 (d, 2, *J*=7.6), 6.05 (d, 1, *J*=9.5), 3.83–3.64 (m, 2), 3.19 (d, 1, *J*=12.2) (one proton is under the OH peak at δ 4.8 and one is proton under the MeOH peak at δ 3.31); ^1H NMR ($(CD_3)_2CO$) 7.57 (d, 1, *J*=10.1), 7.15 (d, 2, *J*=8.5), 6.81 (d, 2, *J*=8.5), 6.01 (br d, 1, *J*=10.1), 4.89 (br d, 1, *J*=7.9), 3.83–3.79 (m, 1), 3.77 (d, 1, *J*=4.3), 3.37 (d, 1, *J*=11.6), 3.26 (d, 1, *J*=11.6); ^{13}C NMR (CD_3OD) 157.8, 156.8, 132.1, 131.2 (2C), 127.8, 116.3 (2C), 88.7, 85.2, 65.5 (four carbons were not observed).

3.1.16. (1*R,5*R*,6*S*,7*R*)-5-[(Acetyloxy)methyl]-7-methyl-6-phenyl-8-oxabicyclo[3.2.1]oct-3-en-2-one (18).** 2,6-Di-*t*-butylpyridine (0.19 mL, 0.86 mmol) was added to a solution of crude **6** (196 mg, 0.86 mmol) and *trans*-β-methylstyrene (0.69 mL, 5.2 mmol, 6 equiv) in dry CH_3CN (5 mL). The resulting solution was degassed using the freeze-thaw method[20] and heated to 175 °C for 14 h in a sealed tube. The reaction was cooled and concentrated under reduced pressure to give 738 mg of a black liquid. Flash chromatography on silica gel (22:3 hexanes/EtOAc) yielded 76 mg (31%) of **18**: ^1H NMR 7.32–7.26 (m, 3), 7.14 (dd, 2, *J*=7.0, 1.8), 6.70 (d, 1, *J*=9.8), 6.26 (d, 1, *J*=9.8), 4.46 (d, 1, *J*=11.9), 4.27 (br s, 1), 4.21 (d, 1, *J*=11.9), 3.00 (d, 1, *J*=6.7), 2.54 (br dq, 1, *J*=6.7, 6.7), 1.36 (d, 3, *J*=6.7); ^{13}C NMR 195.8, 170.6, 151.1, 135.6, 128.9 (2C), 128.7 (2C), 128.3, 127.9, 88.0, 84.7, 65.3, 59.4, 43.0, 20.7, 19.6.

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20. A resealable tube with a threaded Teflon seal containing a solution of dipolarophile and pyranone in CH_3CN was frozen in a dry ice/acetone bath. The sample was placed under vacuum at 0.2 torr for 5 min. The tube was sealed and warmed to room temperature. This process was repeated twice.