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Studies related to furopyridinone antibiotics. Synthesis of 2-*epi*-CJ-16,170

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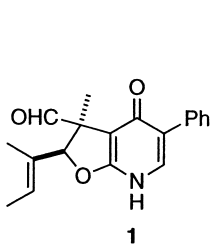
Abstract—Synthesis of a stereoisomer (**3**) of the natural furopyridinone antibiotic CJ-16,170 (**2**) is described. The relative stereochemistry of the substituents on the furan ring was established by a facially selective radical cyclization (**15→16**).

1. Introduction and discussion

The fungal metabolite cladobotryal, assigned the pyridinone structure **1**, was reported several years ago.[1] The compound, which appeared to represent a new heterocyclic class,[2] inhibits the growth of several phytopathogenic fungi[1] and, on this basis, is of interest as a lead in the design of antifungal agents. Very recently, cladobotryal, as well as a number of related fungal metabolites, have been described,[3] including CJ-16,170 (**2**), which is a reduced structural isomer of cladobotryal. This recent publication[3] assigns hydroxy-pyridine structures to **1** and **2** but, for simplicity, the pyridinone tautomers will be shown here. Cladobotryal has modest activity against some drug-resistant bacteria such as methicillin-resistant *Staphylococcus aureus*.[3] Furopyridinones with the types of ring fusion represented by **1** and **2** appear to represent compound classes worthy of evaluation for useful biological properties; here we report the synthesis of **3**, which is an epimer of **2**.



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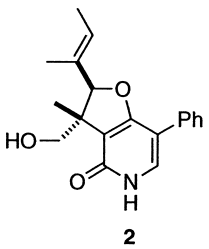

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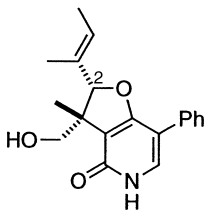

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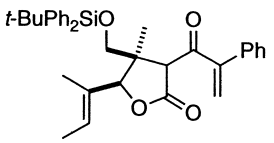

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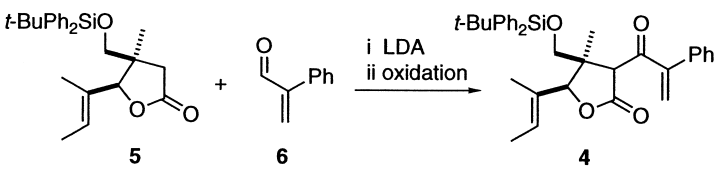
Compound **3**, which we call 2-*epi*-CJ-16,170, was obtained during attempts to form cladobotryal from the advanced intermediate **4**. In the event, our experiments with **4** led, not to the cladobotryal system, but to **3**—the same structural type that has now been reported[3] as a natural product (cf. **2** and **3**).

Keto lactone **4** was made from the two components **5** and **6**[4] (Scheme 1). Several routes were explored for the preparation of lactone **5**, and we eventually developed the approach summarized in Scheme 2.

Double deprotonation of the known dithioacetal **8**[5] (Scheme 2) and condensation with tiglic aldehyde (**7**) gave **9** (56 or 85% after correction for recovered **8** (34%)). Regeneration of the carbonyl ($PhI(OCOCF_3)$, aqueous MeOH, 78%)[6] then afforded the dihydroxy ketone **10**. Selective protection of the primary hydroxyl (**10→11**,



5 **6** **4**

Scheme 1.

Keywords: furopyridinone; quaternary carbon; radical cyclization.

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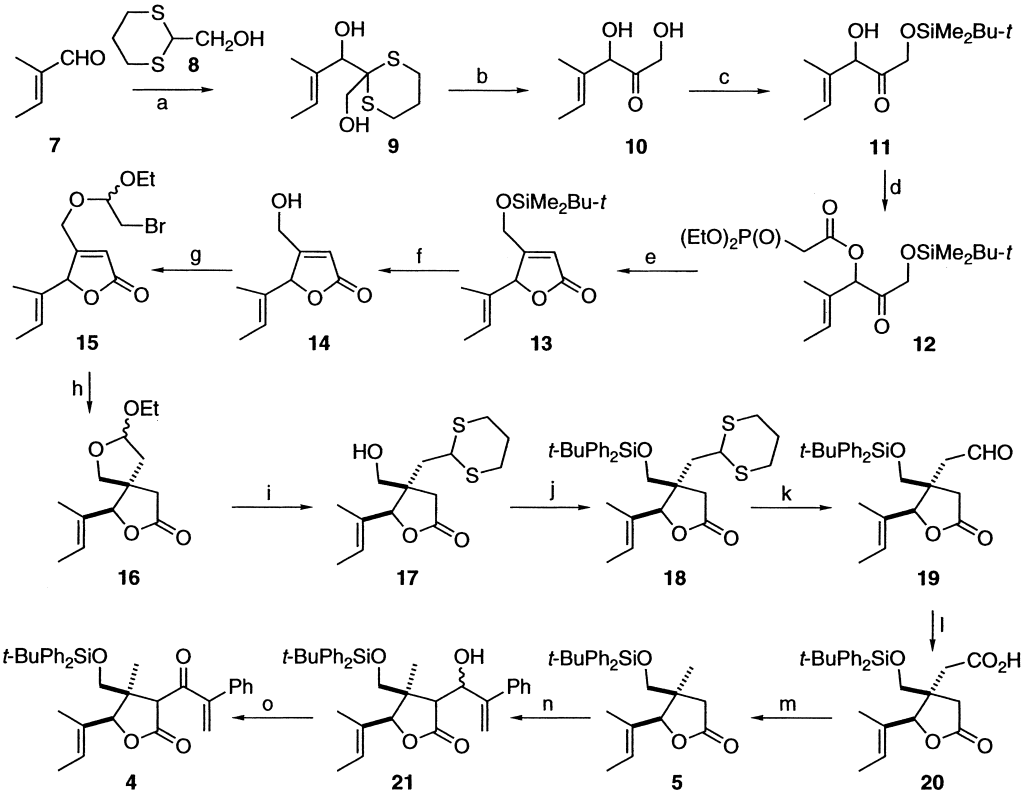


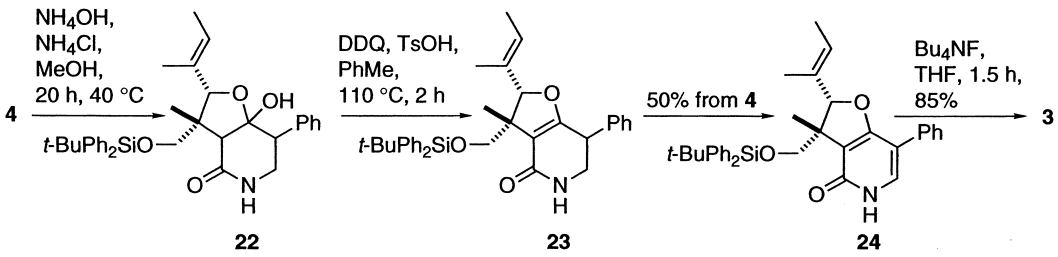
Scheme 2. (a) BuLi, **8**, THF, −78°C; then add **7**, −78°C for 1.5 h, 56% or 85% corrected for recovered **8** (34%). (b) $PhI(OCOCF_3)_2$, 9:1 MeOH–water, 0–25°C, 15 min, 78%. (c) *t*-$BuMe_2SiCl$, pyridine, DMF, 0°C, 45 min, 83%. (d) DCC, $(EtO)_2P(O)CH_2CO_2H$, CH_2Cl_2, 0°C, 1.5 h, 94%. (e) LiBr, Et_3N, THF, 0°C, 30 min, room temperature, 5 h, 72%. (f) $TsOH{\cdot}H_2O$, MeOH, 15 h, 98%. (g) Br_2, ethyl vinyl ether, CH_2Cl_2, −78–25°C; then −78°C, add **14** and 2,6-lutidine, 1 h, 25°C, ca. 2 h, 94%. (h) Bu_3SnH, addition over 3 h, AIBN, PhH, reflux, 48% of one isomer, 45% of second isomer. (i) $TiCl_4$, 1,3-propanedithiol, CH_2Cl_2, −78 to −20°C over 3 h, 82%. (j) *t*-$BuPh_2SiCl$, imidazole, CH_2Cl_2, 24 h, 89%. (k) HgO, $HgCl_2$, 10:1 acetone–water, 55°C, 40 h, 86 or 95% after correction for recovered **18** (9.7%). (l) $NaClO_2$, NaH_2PO_4 in water, added to **19** in 4:4:1 MeCN–*t*-BuOH–2-methyl-2-butene, 0°C, 25 min, ca. 100%. (m) Et_3N, DMAP, HOTT, THF, then *t*-dodecanethiol, reflux, 76% from **19**.(n) LDA, THF, −78°C, add **6**, 3.5 h, 51% of one isomer and 20% of second isomer. (o) For major isomer: Dess–Martin periodinane, CH_2Cl_2, 30 min, 83%; for minor isomer: PCC, 4 Å molecular sieves, CH_2Cl_2, 2.5 h, 65%.

t-$BuMe_2SiCl$, pyridine, DMF, 83%) and DCC-mediated acylation with diethylphosphonoacetic acid (**11**→**12**, 94%), set the stage for an intramolecular olefination. This was accomplished (72%) by treating **12** with LiBr and Et_3N.[7] The resulting lactone was deprotected under mildly acidic conditions ($TsOH{\cdot}H_2O$, MeOH, 98%) so as to afford the hydroxymethyl lactone **14**. Conversion to the derived Stork bromo acetals (**14**→**15**) required extensive optimization, but we eventually found conditions that are very effective. Treatment of ethyl vinyl ether with bromine, and addition of a solution of alcohol **14** and an excess of 2,6-lutidine served to give the desired acetals in high yield (94%). Slow addition of Bu_3SnH and AIBN to a refluxing solution of acetals **15** in PhH resulted in very efficient radical cyclization from the face opposite to the olefinic substituent on the lactone ring. The product (**16**) was isolated as two separable diastereoisomers (48 and 45%, respectively), differing in stereochemistry at the ethoxy-bearing carbon. This was established by X-ray analysis of the minor isomer and the fact that both isomers ultimately are converted into the same alcohol **17**. Treatment of **16** with 1,3-propanedithiol in the presence of $TiCl_4$ at −20°C gave dithioacetal **17** (82%). The primary hydroxyl was protected by silylation (**17**→**18**, *t*-$BuPh_2SiCl$, imidazole, 89%), and the latent aldehyde group was then released (**18**→**19**, HgO, $HgCl_2$, 95% after correction for recovered **11** (ca. 10%)).

In order to convert the CH_2CHO substituent of **19** into a methyl group (see **5**), the aldehyde was oxidized to the corresponding acid (**19**→**20**, $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene), and the acid was then converted into its Barton ester. Under standard conditions[8] the yield was low, but when HOTT[9] was used to form the Barton ester the efficiency was greatly improved, and heating in the presence of *t*-dodecanethiol (without protection from light) then gave **5** in 76% overall yield from aldehyde **19**.

Lactone **5** was converted into its enolate at 0°C (LDA, THF), and allowed to react at −78°C with the known aldehyde **6**.[4] The resulting alcohols (**21**) were obtained as two separable isomers (51 and 20%). The major one was oxidized with the Dess–Martin reagent (83%) to enone **4**. Oxidation of the minor isomer was best done with PCC, and gave **4** in 65% yield.

Exposure of **4** to aqueous ammonia (Scheme 3) in the presence of NH_4Cl in MeOH[10] at 40°C for 20 h gave **22** of undetermined ring junction stereochemistry. The crude material was heated with DDQ in the presence of TsOH, and under these conditions dehydration (**22**→**23**) and acid-facilitated[11] dehydrogenation (**23**→**24**) occurred, **24** being isolated in 50% overall yield from **4**. An attempt to dehydrogenate **23**, using DDQ alone was not successful;



Scheme 3.

the presence of TsOH is essential. In an exploratory experiment in which crude **22** was treated just with TsOH, compound **23** was obtained as a 3:2 mixture of separable isomers. The more polar was an oil, but the other isomer was obtained crystalline and the structure was determined by X-ray analysis. In that isomer the phenyl and quaternary methyl groups are *syn*. Finally, 2-*epi*-CJ-16,170 (**3**) was generated by desilylation of **24**.

2. Conclusion

The above experiments illustrate an effective method for generating a quaternary carbon[12] with stereochemical control by an adjacent stereogenic center, and offer a synthetic route to the unusual furopyridinone system represented by CJ-16,170.

3. Experimental

3.1. General

The same general procedures as used previously[13] were followed. The symbols s, d, t, and q used for ^{13}C NMR signals indicate zero, one, two, or three attached hydrogens, respectively. In cases where the number of ^{13}C signals is less than expected, we assume this is due to coincident chemical shifts.

3.1.1. (*E*)-1-[2-Hydroxymethyl-1,3-dithian-2-yl]-2-methylbut-2-en-1-ol (9). BuLi (2.5 M in hexane, 30 mL, 75 mmol) was added dropwise to a stirred and cooled (−78°C) solution of alcohol **8** (5.10 g, 0.339 mol) in THF (100 mL). Stirring was continued at −78°C for 1 h, and (*E*)-2-methyl-2-butenal (3.86 mL, 40 mmol) was then added dropwise. Stirring at −78°C was continued for 90 min and saturated aqueous NH_4Cl (50 mL) was added, followed by Et_2O (300 mL). The cooling bath was removed and, after 30 min, the mixture was washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4×3 cm), using 1:2 EtOAc–hexane, gave starting alcohol **8** (1.713 g, 34%), and **9** (4.441 g, 56%) as a solid: mp 75–77°C; FTIR (CH_2Cl_2, cast) 3406, 2915, 1663 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.63 (d of multiplets, J=6.7 Hz, 3H), 1.76 (t, J=1.2 Hz, 3H), 1.79–1.92 (m, 1H), 1.96–2.08 (m, 1H), 2.63 (dd, J=5.3, 3.8 Hz, 1H), 2.68 (dd, J=5.4, 3.7 Hz, 1H), 2.72 (br s, 2H), 2.76–2.90 (m, 2H), 3.87 (AB q, J=12.0 Hz, $\Delta\nu_{AB}$=46.0 Hz, 2H), 4.27 (s, 1H), 5.60 (q of multiplets, J=6.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.3 (q), 13.5 (q), 24.6 (t), 25.5 (t), 25.9 (t), 59.7 (s), 63.7 (t), 81.5 (d), 126.1 (d), 133.3 (s); exact mass m/z calcd for $C_{10}H_{18}O_2S_2$ 234.07483, found 234.07502.

3.1.2. (*E*)-1,3-Dihydroxy-4-methylhex-4-en-2-one (10). $PhI(OCOCF_3)_2$ (18.33 g, 42.62 mmol) was added in one portion to a stirred and cooled (0°C) solution of **9** (6.660 g, 28.42 mmol) in 9:1 MeOH–water (120 mL).[6] The ice bath was removed and stirring was continued for 15 min. Saturated aqueous $NaHCO_3$ (100 mL) was added, and the mixture was subjected to continuous extraction with Et_2O (300 mL) for 24 h. The organic extract was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3×30 cm), using 1:1 EtOAc–hexane, gave **10** (3.199 g, 78%) as an oil: FTIR (CH_2Cl_2, cast) 3387, 2918, 2862, 1727, 1669 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.46–1.50 (m, 3H), 1.66 (d of multiplets, J=6.7 Hz, 3H), 2.80 (br s, 1H), 3.43 (br s, 1H), 4.24–4.40 (m, 2H), 4.58 (s, 1H), 5.70 (q of multiplets, J=6.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 10.7 (q), 13.5 (q), 65.1 (t), 81.2 (d), 127.6 (d), 132.8 (s), 210.2 (s); exact mass m/z calcd for $C_7H_{12}O_3$ 144.07864, found 144.07872.

3.1.3. (*E*)-1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-hydroxy-4-methylhex-4-en-2-one (11). t-$BuMe_2SiCl$ (1.7714 g, 11.752 mmol) and pyridine (2.3 mL, 28 mmol) were added successively to a stirred and cooled (0°C) solution of **10** (1.540 g, 10.68 mmol) in DMF (28 mL). After 45 min at 0°C, the pyridine was removed by evaporation (rotary evaporator, water pump, room temperature). The residue was diluted with Et_2O (350 mL), washed with brine (three times), dried (Na_2SO_4) and evaporated. Flash chromatography the residue over silica gel (2×25 cm), using 1:10 EtOAc–hexane, gave **11** (2.282 g, 83%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3483, 2954, 2929, 2886, 2858, 1733 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 1.47 (t, J=1.1 Hz, 3H), 1.65 (d of multiplets, J=6.7 Hz, 3H), 3.61 (d, J=5.2 Hz, 1H), 4.32 (s, 2H), 4.69 (d, J=5.0 Hz, 1H), 5.68 (q of multiplets, J=6.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) (two signals overlap in this spectrum) δ −5.4 (q), 11.0 (q), 13.7 (q), 18.4 (s), 25.8 (q), 66.5 (t), 80.3 (d), 127.0 (d), 132.9 (s), 209.3 (s); exact mass (electrospray) m/z calcd for $C_{13}H_{26}NaO_3Si$ 281.15434, found 281.15391.

3.1.4. (Diethylphosphoryl)ethanoic acid (*E*)-1-[2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-oxoethyl]-2-methylbut-2-enyl ester (12). DCC (3.210 g, 0.0156 mol) was added in one portion to a stirred and cooled (0°C) solution of **11** (3.660 g, 0.0142 mol) in CH_2Cl_2 (64 mL). Diethylphosphonoacetic acid (2.5 mL, 0.016 mol) was then added dropwise. After 90 min at 0°C, the mixture was filtered and the solid was rinsed with CH_2Cl_2 (50 mL). The filtrate was

dried (Na_2SO_4) and evaporated. Flash chromatography the residue over silica gel (5×25 cm), using 1:1 EtOAc–hexane, gave **12** (5.810 g, 94%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2930, 2857, 1738, 1669 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.03 (s, 6H), 0.86 (s, 9H), 1.29 (dt, J=0.25, 7.1 Hz, 3H), 1.30 (dq, J=0.25, 7.1 Hz, 3H), 1.60 (t, J=1.2 Hz, 3H), 1.63 (d of multiplets, J=6.7 Hz, 3H), 3.00 (d of AB q, J=21.4, 14.5 Hz, $\Delta\nu_{AB}$=21.0 Hz, 2H), 4.09–4.18 (m, 4H), 4.32 (AB q, J=18.0 Hz, $\Delta\nu_{AB}$=14.1 Hz, 2H), 5.60 (s, 1H), 5.70 (q of multiplets, J=6.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ −5.5 (q), −5.4 (q), 12.3 (q), 13.7 (q), 16.36 [q(d, $^3J_{PC}$=6.1 Hz)], 16.38 [q(d, $^3J_{PC}$=6.1 Hz)], 18.5 (s), 25.8 (q), 34.0 [t(d, $^1J_{PC}$=133.5 Hz)], 62.7 [t(d, $^2J_{PC}$=6.5 Hz)], 62.8 [t(d, $^2J_{PC}$=6.5 Hz)], 67.3 (t), 82.0 (d), 128.6 (s), 128.9 (d), 164.9 [s(d, $^2J_{PC}$=6.1 Hz)], 202.9 (s); exact mass (electrospray) m/z calcd for $C_{19}H_{38}O_7PSi$ 437.21190, found 437.21174.

3.1.5. 4-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-5-[(*E*)-1-methylpropenyl]-5*H*-furan-2-one (13). LiBr (2.13 g, 24.5 mmol), followed by Et_3N (11.5 mL, 82.5 mmol), were added to a stirred and cooled (0°C) solution of **12** (3.565 g, 8.166 mmol) in dry THF (200 mL) (Ar atmosphere).[7] Stirring at 0°C was continued for 30 min. The cooling bath was removed and stirring was continued for 5 h. The mixture was filtered through a pad of silica gel (4×3 cm), using Et_2O (200 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (2×25 cm), using 1:10 EtOAc–hexane, gave **13** (1.650 g, 72%) as a solid: mp 46–47°C; FTIR (CH_2Cl_2, cast) 2955, 2929, 2858, 1790, 1759, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.05 (s, 6H), 0.89 (s, 9H), 1.39–1.41 (m, 3H), 1.67 (d of multiplets, J=6.7 Hz, 3H), 4.24 [(apparent AB q, J=17.3 Hz, $\Delta\nu_{AB}$=31.1 Hz (each component of the apparent AB q is split by long-range coupling), 2H], 5.19 (s, 1H), 5.68 (q of multiplets, J=6.7 Hz, 1H), 6.04–6.06 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) (two signals overlap in this spectrum) δ −5.4 (q), 9.4 (q), 13.6 (q), 18.3 (s), 25.8 (q), 59.4 (t), 87.6 (d), 116.2 (d), 128.1 (d), 130.0 (s), 170.8 (s), 172.5 (s); exact mass (electrospray) m/z calcd for $C_{15}H_{27}O_3Si$ 283.17240, found 283.17208.

3.1.6. 4-(Hydroxymethyl)-5-[(*E*)-1-methylpropenyl]-5*H*-furan-2-one (14). $TsOH{\cdot}H_2O$ (72.0 mg, 0.418 mmol) was added to a stirred solution of **13** (0.5330 g, 1.887 mmol) in MeOH (88 mL). Stirring was continued for 15 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5×30 cm), using 1:1 EtOAc–hexane, gave **14** (0.310 g, 98%) as an oil: FTIR (CH_2Cl_2, cast) 3426, 2919, 2862, 1791, 1747, 1673, 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.36 (s, 3H), 1.64 (dd, J=6.7, 0.9 Hz, 3H), 2.78 (br s, 1H), 4.26 [apparent AB q, J=17.5 Hz, $\Delta\nu_{AB}$=23.5 Hz (each component of the apparent AB q is split by long-range coupling), 2H], 5.19 (s, 1H), 5.68 (q of multiplets, J=6.7 Hz, 1H), 6.06 (q, J=1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 9.2 (q), 13.5 (q), 58.7 (t), 88.0 (d), 115.9 (d), 128.5 (d), 129.7 (s), 171.5 (s), 173.2 (s); exact mass m/z calcd for $C_9H_{12}O_3$ 168.07864, found 168.07854.

3.1.7. 4-[(2-Bromo-1-ethoxyethoxy)methyl]-5-[(*E*)-1-methylpropenyl]-5*H*-furan-2-one (15). Br_2 (0.83 mL, 16 mmol) was added dropwise to a stirred and cooled (−78°C) solution of ethyl vinyl ether (1.9 mL, 20 mmol) in CH_2Cl_2. After 15 min at −78°C, the cooling bath was removed and stirring was continued for 15 min. The mixture was recooled to −78°C and a solution of **14** (1.09 g, 6.48 mmol) and 2,6-lutidine (2.3 mL, 20 mmol) in CH_2Cl_2 was added dropwise. Stirring was continued for 1 h at −78°C after the addition, the cooling bath was removed, and stirring was continued for 2 h. Water (20 mL) was added to the mixture, which was then diluted with Et_2O (400 mL), washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3×8 cm), using 1:7 EtOAc–hexane, gave **15** (1.95 g, 94%) as an oil, which was a mixture of two isomers: FTIR (CH_2Cl_2, cast) 2977, 2919, 1790, 1757, 1652 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 0.90 (t, J=7.1 Hz, 3H), 1.12–1.16 (m, 3H), 1.24–1.30 (m, 3H), 2.94 (d, J=5.6 Hz, 1H), 2.95 (d, J=5.5 Hz, 1H), 3.00–3.22 (m, 2H), 3.59–3.78 (m, 2H), 4.31 (t, J=5.6 Hz, 0.5H), 4.32 (t, J=5.5 Hz, 0.5H), 4.74–4.79 (m, 1H), 5.19–5.28 (m, 1H), 5.96–5.99 (m, 1H); ^{13}C NMR (C_6D_6, 100.6 MHz) (some of the signals overlap; the spectrum is too complicated to identify the signals of the individual isomers) δ 9.09 (q), 9.11 (q), 13.2 (q), 15.1 (q), 30.88 (t), 30.93 (t), 60.5 (t), 61.2 (t), 62.35 (t), 62.41 (t), 87.2 (d), 87.3 (d), 101.1 (d), 101.6 (d), 117.7 (d), 117.9 (d), 127.6 (d), 130.6 (s), 130.7 (s), 166.2 (s), 166.4 (s), 171.6 (s); exact mass (electrospray) m/z calcd for $C_{13}H_{20}^{79}BrO_4$ 319.054495, found 319.054112.

3.1.8. (1*R,5*S**)-8-Ethoxy-1-[(*E*)-1-methylpropenyl]-2,7-dioxaspiro[4.4]nonan-3-one (16).** A solution of Bu_3SnH (4.4 mL, 16 mmol) and AIBN (170.0 mg, 1.035 mmol) in PhH (50 mL) was added over 3 h to a stirred and heated (oil bath at 80°C) solution of **15** (1.950 g, 6.109 mmol) and AIBN (30.0 mg, 0.183 mmol) in PhH (80 mL). The mixture was refluxed for 2 h after the addition, cooled to room temperature, and evaporated. Et_2O (100 mL), followed by aqueous KF (10%, 80 mL) was added and the mixture was stirred overnight (ca. 15 h). The mixture was filtered through a pad of Celite (4×3 cm), using Et_2O (200 mL). The filtrate was washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2×30 cm), using 1:5–1:4 EtOAc–hexane, gave **16**-isomer A (less polar) (0.688 g, 48%) as a colorless oil and **16**-isomer B (more polar) (0.656 g, 45%) as a solid.

Isomer A: FTIR (CH_2Cl_2 cast) 2976, 2929, 1781 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.15 (t, J=7.1 Hz, 3H), 1.56–1.59 (m, 3H), 1.65 (d of multiplets, J=6.7 Hz, 3H), 2.00 (dd, J=13.3, 1.5 Hz, 1H), 2.21 (dd, J=13.3, 5.4 Hz, 1H), 2.75 (AB q, J=18.0 Hz, $\Delta\nu_{AB}$=39.6 Hz, 2H), 3.39 (dq, J=9.6, 7.1 Hz, 1H), 3.68 (dq, J=9.6, 7.1 Hz, 1H), 3.74 (AB q, J=9.1 Hz, $\Delta\nu_{AB}$=26.8 Hz, 2H), 4.67 (s, 1H), 5.11 (dd, J=5.4, 1.5 Hz, 1H), 5.57 (q of quintets, J=6.7, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 12.6 (q), 13.1 (q), 15.2 (q), 41.0 (t), 45.5 (t), 49.5 (s), 63.0 (t), 72.1 (t), 91.6 (d), 103.3 (d), 125.6 (d), 130.6 (s), 175.4 (s); exact mass m/z calcd for $C_{13}H_{20}O_4$ 240.13615, found 240.13594.

Isomer B: mp 75–77°C; FTIR (CH_2Cl_2, cast) 2975, 2927, 1781 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.16 (t, J=7.1 Hz, 3H), 1.57 (t, J=1.1 Hz, 3H), 1.65 (d of multiplets, J=6.8 Hz, 3H), 2.05 (dd, J=13.3, 5.2 Hz, 1H), 2.14

(dd, J=13.3, 2.8 Hz, 1H), 2.56 (AB q, J=7.7 Hz, $\Delta\nu_{AB}$=98.9 Hz, 2H), 3.40 (dq, J=9.5, 7.1 Hz, 1H), 3.68 (AB q, J=8.9 Hz, $\Delta\nu_{AB}$=46.6 Hz, 2H), 3.69 (dq, J=9.5, 7.1 Hz, 1H), 4.98 (s 1H), 5.14 (dd, J=5.2, 2.8 Hz, 1H), 5.58 (q of multiplets, J=6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 12.5 (q), 13.3 (q), 15.2 (q), 41.1 (t), 46.3 (t), 49.7 (s), 63.3 (t), 71.3 (t), 90.9 (d), 103.4 (d), 126.0 (d), 130.5 (s), 175.1 (s); exact mass m/z calcd for $C_{13}H_{20}O_4$ 240.13615, found 240.13586. A sample was recrystallized from EtOAc–hexane for X-ray analysis.

3.1.9. (4*R* *,5*S* *)-4-[(1,3-Dithian-2-yl)methyl]-4-(hydroxymethyl)-5-[(*E*)-1-methylpropenyl]dihydrofuran-2-one (17). $TiCl_4$ (1.2 mL, 11 mmol) was added dropwise to a stirred and cooled (−78°C) solution of **16** (a mixture isomers, 1.312 g, 5.460 mmol) and 1,3-propanedithiol (1.65 mL, 16.4 mmol) in CH_2Cl_2 (120 mL). The cold bath was left in place but was not recharged, and stirring was continued for 3 h, by which time the temperature had risen to −20°C. Saturated aqueous $NaHCO_3$ (100 mL) was added, the cold bath was removed, and stirring was continued for 30 min. The mixture was diluted with EtOAc (100 mL) and filtered through a pad of Celite (4×3 cm), using EtOAc (400 mL). The filtrate was washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2×30 cm), using 1:2 EtOAc–hexane, gave **17** (1.360 g, 82%) as a colorless, thick oil: FTIR (CH_2Cl_2, cast) 3465, 2904, 1774 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.67 (d of multiplets, J=6.7 Hz, 3H), 1.68–1.70 (m, 3H), 1.78–2.15 (m, 5H), 2.64 (AB q, J=17.6 Hz, $\Delta\nu_{AB}$=17.8 Hz, 2H), 2.82 (ddd, J=14.3, 4.6, 3.3 Hz, 2H), 2.88–2.98 (m, 2H), 3.56 (AB q, J=11.8 Hz, $\Delta\nu_{AB}$=30.8 Hz, 2H), 4.07 (t, J=5.8 Hz, 1H), 4.62 (s, 1H), 5.69 (q of multiplets, J=6.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) (two signals overlap in this spectrum) δ 13.2 (q), 13.8 (q), 25.0 (t), 31.0 (t), 38.0 (t), 41.5 (t), 43.0 (d), 48.5 (s), 63.8 (t), 89.5 (d), 124.2 (d), 130.3 (s), 175.2 (s); exact mass m/z calcd for $C_{14}H_{22}O_3S_2$ 302.10104, found 302.10112.

3.1.10. (4*R* *,5*R* *)-4-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-4-[(1,3-dithian-2-yl)methyl]-5-[(*E*)-1-methylpropenyl]dihydrofuran-2-one (18). Imidazole (1.530 g, 22.47 mmol) was added in one portion to a stirred solution of **17** (1.360 g, 4.497 mmol) in CH_2Cl_2 (100 mL), and *t*-$BuPh_2SiCl$ (5.8 mL, 22 mmol) was then added dropwise. The mixture was stirred for 24 h, saturated aqueous NH_4Cl solution (120 mL) was added, and the mixture was extracted with Et_2O (200 mL). The organic extract was washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography the residue over silica gel (3×25 cm), using 1:8 EtOAc–hexane, gave **18** (2.160 g, 89%) as a colorless, thick oil: FTIR (CH_2Cl_2, cast) 3070, 2930, 2857, 1779, 1589 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.06 (s, 9H), 1.49 (t, J=1.0 Hz, 3H), 1.55 (d of multiplets, J=6.7 Hz, 3H), 1.71–1.83 (m, 1H), 1.80 (dd, J=15.1, 6.9 Hz, 1H), 1.99–2.08 (m, 1H), 2.04 (dd, J=15.1, 5.2 Hz, 1H), 2.66 (AB q, J=17.6 Hz, $\Delta\nu_{AB}$=25.5 Hz, 2H), 2.67–2.84 (m, 4H), 3.46 (AB q, J=10.6 Hz, $\Delta\nu_{AB}$=26.9 Hz, 2H), 3.93 (dd, J=6.9, 5.2 Hz, 1H), 4.67 (s, 1H), 5.56 (q of multiplets, J=6.7 Hz, 1H), 7.34–7.46 (m, 6H), 7.57–7.62 (m, 4H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) (three signals overlap in this spectrum) δ 13.1 (q), 13.4 (q), 19.2 (s), 25.1 (t), 26.9 (q), 30.9 (t), 31.0 (t), 38.0 (t), 41.0 (t), 43.1 (d), 48.5 (s), 65.2 (t), 89.7 (d), 124.5 (d), 127.77 (d), 127.83 (d), 129.6 (s), 129.9 (d), 130.0 (d), 132.6 (s), 132.8 (s), 135.79 (d), 135.82 (d), 175.5 (s); exact mass (electrospray) m/z calcd for $C_{30}H_{41}O_3S_2Si$ 541.22609, found 541.22624.

3.1.11. (2*R* *,3*S* *)-[3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-2-[(*E*)-1-methylpropenyl]-5-oxotetrahydrofuran-3-yl]ethanal (19). HgO (2.17 g, 10.0 mmol) and $HgCl_2$ (2.72 g, 10.0 mmol) were added successively to a stirred solution of **18** (2.16 g, 3.99 mmol) in 10:1 acetone–water (66 mL). The mixture was stirred at 55°C (oil bath) for 40 h, cooled to room temperature and filtered through a pad of Celite (4×3 cm), using Et_2O (250 mL). The filtrate was washed with aqueous KI (10%) and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2×15 cm), using 1:6 EtOAc–hexane, gave starting **18** (210 mg, 9.7%) and **19** (1.550 g, 86 or 95% after correction for recovered **18**) as a colorless oil: FTIR (CH_2Cl_2, cast) 3071, 2930, 2857, 2029, 1958, 1782, 1722, 1588 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (s, 9H), 1.43 (s, 3H), 1.53 (d, J=6.8 Hz, 3H), 2.62 (dd, J=16.9, 1.4 Hz, 1H), 2.65 (AB q, J=17.6 Hz, $\Delta\nu_{AB}$=40.6 Hz, 2H), 2.79 (dd, J=16.9, 2.1 Hz, 1H), 3.50 (AB q, J=10.4 Hz, $\Delta\nu_{AB}$=44.6 Hz, 2H), 4.70 (s, 1H), 5.50 (q of multiplets, J=6.8 Hz, 1H), 7.35–7.48 (m, 6H), 7.53–7.59 (m, 4H), 9.73 (dd, J=2.1, 1.4 Hz, 1H); ^{13}C ($CDCl_3$, 100.6 MHz) δ 13.0 (q), 13.1 (q), 19.2 (s), 26.9 (q), 37.8 (t), 47.3 (s), 48.6 (t), 65.3 (t), 89.4 (d), 125.0 (d), 127.8 (d), 127.9 (d), 129.3 (s), 130.0 (d), 130.1 (d), 132.3 (s), 132.5 (s), 135.57 (d), 135.62 (d), 175.0 (s), 199.4 (d); exact mass (electrospray) m/z calcd for $C_{27}H_{34}NaO_4Si$ 473.21186, found 473.21207.

3.1.12. (2*R* *,3*S* *)-[3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-2-[(*E*)-1-methylpropenyl]-5-oxotetrahydrofuran-3-yl]ethanoic acid (20). A solution of $NaClO_2$ (3.05 g, 33.7 mmol) and NaH_2PO_4 (3.86 g, 28.0 mmol) in water (20 mL) was added over 5 min to a stirred and cooled (0°C) solution of **19** (1.500 g, 3.329 mmol) in 4:4:1 MeCN–*t*-BuOH-2-methyl-2-butene (75 mL). The mixture was stirred for an additional 20 min at 0°C, and then extracted with EtOAc (3×100 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. The residue was kept under oil pump vacuum (0.025 mmHg) for 5 h, and then diluted with EtOAc (ca. 20 mL). The solvent was evaporated and the residue was kept under oil pump vacuum for 2 h, to afford the crude acid **20** (1.770 g, ca. 100%). An analytical sample was recrystallized from EtOAc–hexane: mp 153–154°C; FTIR (CH_2Cl_2, cast) 3071, 2931, 2858, 1781, 1752, 1709, 1589 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (s, 9H), 1.43 (s, 3H), 1.52 (d, J=6.8 Hz, 3H), 2.64 (AB q, J=15.9 Hz, $\Delta\nu_{AB}$=74.7 Hz, 2H), 2.70 (AB q, J=17.8 Hz, $\Delta\nu_{AB}$=33.1 Hz, 2H), 3.48 (AB q, J=10.4 Hz, $\Delta\nu_{AB}$=32.7, 2H), 4.80 (s, 1H), 5.52 (q of multiplets, J=6.8 Hz, 1H), 7.33–7.45 (m, 6H), 7.54–7.59 (m, 4H), [the CO_2H signal was not detected (0–17 ppm)]; ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.06 (q), 13.13 (q), 19.2 (s), 26.9 (q), 37.6 (t), 38.1 (t), 47.1 (s), 65.4 (t), 88.5 (d), 124.8 (d), 127.79 (d), 127.84 (d), 129.3 (s), 129.97 (d), 130.04 (d), 132.4 (s), 132.6 (s), 135.6 (d), 135.7 (d), 175.26 (s), 175.33 (s); exact mass (electrospray) m/z calcd for $C_{27}H_{34}NaO_5Si$ 489.20677,

found 489.20673. Anal. Calcd for $C_{27}H_{34}O_5Si$: C 69.49; H 7.34. Found: C 69.19; H 7.48.

3.1.13. (4*R* *,5*S* *)-4-[[[(1,1-Dimethylethyl)diphenylsilyl]-oxy]methyl]-4-methyl-5-[(*E*)-1-methylpropenyl]dihydrofuran-2-one (5). A solution of crude acid **20** (1.770 g, crude, ca. 3.319 mmol), Et_3N (1.90 mL, 13.6 mmol) and DMAP (41.0 mg, 0.336 mmol) in THF (32 mL) was added dropwise with stirring to an aluminum foil-wrapped flask containing HOTT[9] (2.00 g, 5.38 mmol). The mixture was stirred in the dark for 2 h. *t*-Dodecanethiol (1.60 mL, 6.79 mmol) was then added to the resulting bright yellow solution of the Barton ester and the aluminum foil was removed. The mixture was refluxed (oil bath 75°C) for 1 h, cooled and diluted with Et_2O (200 mL). The mixture was washed with saturated aqueous NH_4Cl and brine, dried (Na_2SO_4) and evaporated. Flash chromatography the residue over silica gel (2×30 cm), using 1:8 EtOAc–hexane, gave **5** (1.074 g, 76% over two steps) as a solid: mp 83–85°C; FTIR ($CDCl_3$, cast) 2963, 2858, 1783 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.05 (s, 9H), 1.21 (s, 3H), 1.50–1.53 (m, 3H), 1.56 (d of multiplets, J=6.8 Hz, 3H), 2.47 (AB q, J=17.3 Hz, $\Delta\nu_{AB}$=152.3 Hz, 2H), 3.38 (AB q, J=10.3 Hz, $\Delta\nu_{AB}$=45.4 Hz, 2H), 4.53 (s, 1H), 5.56 (q of multiplets, J=6.8 Hz, 1H), 7.35–7.47 (m, 6H), 7.57–7.64 (m, 4H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) (two signals overlap in this spectrum) δ 13.0 (q), 13.3 (q), 19.2 (s), 22.9 (q), 26.8 (q), 40.0 (t), 45.4 (s), 66.7 (t), 91.5 (d), 123.6 (d), 127.71 (d), 127.73 (d), 129.6 (s), 129.81 (d), 129.83 (d), 132.9 (s), 133.0 (s), 135.6 (d), 175.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{26}H_{34}NaO_3Si$ 445.21695, found 445.21626.

3.1.14. (4*R* *,5*S* *)-4-[[[(1,1-Dimethylethyl)diphenylsilyl]-oxy]methyl]-3-(1-hydroxy-2-phenyl-2-propenyl)-4-methyl-5-[(*E*)-1-methylpropenyl]dihydrofuran-2-one (21). A solution of **5** (550 mg, 1.30 mmol) in THF (12 mL) was added dropwise to a stirred and cooled (−78°C) solution of LDA (2.60 mmol) in THF (10 mL). The mixture was stirred at −78°C for 30 min, the cold bath was replaced by an ice bath, and stirring was continued for 45 min. The mixture was recooled to −78°C and freshly-made aldehyde **6**[4] (305 mg, 2.31 mmol) in THF (10 mL) was added dropwise. The mixture was stirred at −78°C for 3.5 h, and saturated aqueous NH_4Cl (10 mL) was added, followed by Et_2O (150 mL). The cooling bath was removed, and stirring was continued for 30 min. The mixture was washed with saturated aqueous NH_4Cl and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5×40 cm), using 1:6 EtOAc–hexane, gave **21** as two isomers: isomer A (less polar, 0.370 g, 51%) as a solid and isomer B (more polar, 270 mg) as a thick oil, which was not pure. Isomer B was crystallized from Et_2O–hexane to afford the pure compound (144 mg, 20%) as a white solid.

Isomer A: mp 140–141°C; FTIR (CH_2Cl_2, cast) 3451, 3051, 2931, 2858, 1749 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.98 (s, 9H), 1.33 (s, 3H), 1.35 (t, J=1.1 Hz, 3H), 1.45 (d of multiplets, J=6.8 Hz, 3H), 2.77 (d, J=4.3 Hz, 1H), 2.84 (d, J=4.3 Hz, 1H), 3.19 (AB q, J=10.2 Hz, $\Delta\nu_{AB}$=123.7 Hz, 2H), 4.66 (s, 1H), 5.25 (tt, J=4.3, 1.5 Hz, 1H), 5.31 (t, J=1.2 Hz, 1H), 5.46 (q of multiplets, J=6.8 Hz, 1H), 5.48 (t, J=1.5 Hz, 1H), 7.21–7.57 (m, 15H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.0 (q), 13.1 (q), 18.6 (q), 19.1 (s), 26.8 (q), 48.4 (s), 49.7 (d), 67.9 (t), 72.6 (d), 91.8 (d), 115.3 (t), 124.8 (d), 127.0 (d), 127.6 (d), 127.7 (d), 127.8 (d), 128.5 (d), 129.7 (d), 129.8 (d), 130.0 (s), 132.6 (s), 132.8 (s), 135.66 (d), 135.72 (d), 139.0 (s), 148.4 (s), 177.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{35}H_{42}NaO_4Si$ 577.27446, found 577.27477.

Isomer B: mp 147–148°C; FTIR (CH_2Cl_2, cast) 3452, 3051, 2930, 2858, 1752, 1589 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.92 (s, 9H), 1.28 (s, 3H), 1.41 (s, 3H), 1.49 (d, J=6.8 Hz, 3H), 2.79 (d, J=3.8 Hz, 1H), 3.10 (d, J=3.4 Hz, 1H), 3.16 (AB q, J=10.2 Hz, $\Delta\nu_{AB}$=109.4 Hz, 2H), 4.76 (s, 1H), 4.92 (t, J=3.6 Hz, 1H), 5.34–5.38 (m, 2H), 5.52 (q of multiplets, J=6.8 Hz, 1H), 7.18–7.49 (m, 15H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) (two signals overlap in this spectrum) δ 12.9 (q), 13.3 (q), 17.4 (q), 19.0 (s), 26.7 (q), 47.5 (s), 49.3 (d), 67.1 (t), 72.4 (d), 90.8 (d), 115.2 (t), 124.1 (d), 127.2 (d), 127.56 (d), 127.62 (d), 127.7 (d), 128.5 (d), 129.4 (s), 129.65 (d), 129.71 (d), 132.8 (s), 132.9 (s), 135.6 (d), 139.2 (s), 148.5 (s), 175.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_{35}H_{42}NaO_4Si$ 577.27446, found 577.27400.

3.1.15. (4*R* *,5*S* *)-4-[[[(1,1-Dimethylethyl)diphenylsilyl]-oxy]methyl]-4-methyl-5-[(*E*)-1-methylpropenyl]-3-(1-oxo-2-phenyl-2-propenyl)dihydrofuran-2-one (4). Dess–Martin reagent (558.0 mg, 1.316 mmol) was added in one portion to a stirred solution of **21** (major isomer, 365 mg, 0.658 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred for 30 min, diluted with Et_2O (100 mL), washed with 2:1 saturated aqueous $NaHCO_3$–10% aqueous $Na_2S_2O_3$, and brine, dried (Na_2SO_4) and evaporated. Flash chromatography the residue over silica gel (1.5×30 cm), using 1:9 EtOAc–hexane, gave **4** (301 mg, 83%) as an oil: FTIR (CH_2Cl_2, cast) 3070, 2931, 2858, 1776, 1683, 1589 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) (signals for major component; minor signals were present, and we attribute these to the enolized form) δ 1.07 (two overlapping singlets, 12H), 1.51 (s, 3H), 1.56 (d of multiplets, J=6.8 Hz, 3H), 3.40 (AB q, J=10.3 Hz, $\Delta\nu_{AB}$=106.2, 2H), 4.61 (s, 1H), 4.89 (s 1H), 5.56 (q of multiplets, J=6.8 Hz, 1H), 6.07 (s, 1H), 6.11 (s, 1H), 7.14–7.64 (m, 15H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) (signals for major component; minor signals were present, and we attribute these to the enolized form) δ 13.0 (q), 13.5 (q), 17.3 (q), 19.2 (s), 26.8 (q), 49.8 (s), 56.6 (d), 67.5 (t), 89.8 (d), 124.0 (d), 127.82 (d), 127.84 (d), 128.0 (s), 128.3 (d), 128.46 (s), 128.52 (d), 128.55 (d), 129.96 (d), 130.01 (d), 135.6 (d), 135.7 (d), 135.8 (s), 149.9 (t), 172.8 (s), 197.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_{35}H_{40}NaO_4Si$ 575.25881, found 575.25851.

Oxidation of the minor isomer was more efficient with PCC than with the Dess–Martin reagent: powdered 4 Å molecular sieves (50 mg) was added to a stirred solution of alcohol **21** (minor isomer) (11.0 mg, 0.020 mmol) in dry CH_2Cl_2 (1 mL). PCC (8.5 mg, 0.04 mmol) was added and stirring was continued. After 1 h, another portion of PCC (4.5 mg, 0.02 mmol) was added and stirring was continued for 1.5 h. The mixture was diluted with Et_2O (5 mL) and the mixture was filtered through a pad (2×1.5 cm) of flash chromatography silica gel, using Et_2O (30 mL) as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (0.6×15 cm), using 1:9

EtOAc–hexane, gave ketone **4** (7.1 mg, 65%) as an oil, spectroscopically identical to material obtained from the major isomer.

3.1.16. (2*R,3*S**)-3-[[[(1,1-Dimethylethyl)diphenylsilyl]-oxy]methyl]-3-methyl-2-[(*E*)-1-methylpropenyl]-7-phenyl-3,5,6,7-tetrahydro-2*H*-furo[3,2-*c*]pyridin-4-one (23).** $TsOH{\cdot}H_2O$ (20.0 mg, 0.116 mmol) and powdered 4 Å molecular sieves (800 mg) were added successively to a stirred solution of crude **22** (prepared, as described below, from **4** (110 mg, 0.199 mmol)) in PhMe (20 mL), and the mixture was stirred at 110°C (oil bath) for 15 h. The mixture was cooled and filtered through a pad (3×2 cm) of Grade III neutral alumina, using EtOAc (80 mL). Evaporation of the solvent and flash chromatography of the residue over silica gel (1×40 cm), using 2:3 EtOAc–hexane, gave **23** as two individual isomers, each of which contained small impurities: isomer A (less polar, 29.0 mg, 26%) as a solid and isomer B (more polar, 20.5 mg, 19%) as a thick oil.

Isomer A: mp 175–178°C; FTIR (CH_2Cl_2 cast) 3203, 3069, 1780, 1738 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.03 (s, 9H), 1.50 (s, 3H), 1.54 (d of multiplets, J=6.8 Hz, 3H), 1.62 (t, J=0.9 Hz, 3H), 3.36 (ddd, J=12.1, 5.8, 2.9 Hz, 1H), 3.70 (ddd, J=12.1, 6.3, 1.7 Hz, 1H), 3.74 (AB q, J=10.3 Hz, $\Delta\nu_{AB}$=3.4 Hz, 2H), 3.77 (t, J=6.1 Hz, 1H), 4.65 (s, 1H), 5.01 (s, 1H), 5.59 (q of multiplets, J=6.8 Hz, 1H), 7.24–7.65 (m, 15H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 13.1 (q), 14.0 (q), 19.4 (s), 23.1 (q), 27.1 (q), 40.4 (d), 47.5 (t), 51.2 (s), 64.7 (t), 98.2 (d), 110.3 (s), 122.6 (d), 127.38 (d), 127.4 (d), 127.6 (d), 127.7 (d), 128.7 (d), 129.37 (d), 129.43 (d), 130.7 (s), 133.4 (s), 133.6 (s), 135.7 (d, two overlapping signals), 137.7 (s), 167.0 (s), 168.6 (s); exact mass (electrospray) m/z calcd for $C_{35}H_{42}NO_3Si$ 552.29340, found 552.29336.

A sample was recrystallized from EtOAc–hexane for X-ray analysis.

Isomer B: FTIR (CH_2Cl_2 cast) 3228, 3070, 1664 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.04 (s, 9H), 1.52 (s, 3H), 1.53 (d, J=6.8 Hz, 3H), 1.58 (br s, 3H), 3.38 (ddd, J=12.1, 7.2, 2.3 Hz, 1H), 3.67 (ddd, J=12.1, 6.4, 2.1 Hz, 1H), 3.79 (t, J=6.8 Hz, 1H), 3.81 (AB q, J=10.3 Hz, $\Delta\nu_{AB}$=66.1 Hz, 2H), 4.69 (s, 1H), 4.98 (br s, 1H), 5.45 (q of multiplets, J=6.8 Hz, 1H), 7.21–7.67 (m, 15H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.1 (q), 14.0 (q), 19.3 (s), 23.4 (q), 27.0 (q), 40.8 (d), 47.5 (t), 51.2 (s), 64.6 (t), 98.2 (d), 111.2 (s), 122.5 (d), 127.4 (d), 127.5 (d), 127.7 (d), 128.0 (d), 128.7 (d), 129.4 (d), 129.5 (d), 131.4 (s), 133.4 (s), 133.8 (s), 135.8 (d), 135.9 (d), 137.3 (s), 167.1 (s), 168.5 (s); exact mass (electrospray) m/z calcd for $C_{35}H_{42}NO_3Si$ 552.29340, found 552.29245.

3.1.17. (2*R,3*S**)-3-[[[(1,1-Dimethylethyl)diphenylsilyl]-oxy]methyl]-3-methyl-2-[(*E*)-1-methylpropenyl]-7-phenyl-3,5-dihydro-2*H*-furo[3,2-*c*]pyridin-4-one (24).** NH_4Cl (115 mg, 2.15 mmol) and concentrated (28–30% w/w) ammonia solution (1.9 mL)[10] were added successively to a stirred solution of **4** (120 mg, 0.217 mmol) in MeOH (10 mL), and the mixture was stirred for 2 h. The mixture was then placed in an oil bath set at 40°C, and stirring was continued for 20 h. The mixture was cooled to room temperature and evaporated. The residue was diluted with 1:2 CH_2Cl_2–EtOAc (30 mL). The solution was dried ($MgSO_4$), and filtered through a pad of silica gel (2×3 cm), using EtOAc (3×30 mL). Evaporation of the filtrate gave the crude product (**22**) (123 mg).

$TsOH{\cdot}H_2O$ (22.0 mg, 0.128 mmol) and DDQ (102 mg, 0.449 mmol) were added to a stirred solution of the above crude product (123 mg) in PhMe (20 mL) and the mixture was stirred at 110°C (oil bath) for 2 h. The mixture was cooled and evaporated. The residue was diluted with EtOAc (50 mL) and washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (30 mL), and all the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography the residue over silica gel (1×40 cm), using 3:2 EtOAc–hexane, gave **24** (60.0 mg, 50%) as a yellow solid: mp 205–207°C; FTIR (CH_2Cl_2, cast) 3047, 2930, 2857, 1654, 1622, 1600, 1578, 1561 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.95 (s, 9H), 1.58 (s, 3H), 1.66 (d, J=6.7 Hz, 3H), 1.76 (s, 3H), 3.82 (AB q, J=10.3 Hz, $\Delta\nu_{AB}$=6.9 Hz, 2H), 4.87 (s, 1H), 5.77 (q of multiplets, J=6.7 Hz, 1H), 7.22–7.64 (m, 16H; it was not clear if the NH signal is in this multiplet); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.2 (q), 14.2 (q), 19.2 (s), 21.3 (q), 26.8 (q), 50.6 (s), 64.4 (t), 97.7 (d), 111.0 (s), 113.6 (s), 122.4 (d), 127.3 (d), 127.45 (d), 127.46 (d), 127.6 (d), 128.6 (d), 129.40 (d), 129.43 (d), 130.5 (s), 133.27 (s), 133.32 (s), 133.6 (s), 134.6 (d), 135.7 (d), 135.8 (d), 162.4 (s), 166.6 (s); exact mass (electrospray) m/z calcd for $C_{35}H_{40}NO_3Si$ 550.27720, found 550.27627.

In an earlier experiment, omission of DDQ gave **23** as a mixture of two isomers, as described above.

3.1.18. (2*R,3*S**)-3-(Hydroxymethyl)-3-methyl-2-[(*E*)-1-methylpropenyl]-7-phenyl-3,5-dihydro-2*H*-furo[3,2-*c*]pyridin-4-one (3).** Bu_4NF (1 M in THF, 0.45 mL, 0.45 mmol) was added dropwise to a stirred solution of **24** (50.0 mg, 0.091 mmol) in THF (10 mL). Stirring was continued for 90 min, and then saturated aqueous NH_4Cl solution (5 mL) was added. The mixture was extracted with EtOAc (3×6 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography the residue over silica gel (0.8×25 cm), using 1:40 MeOH–CH_2Cl_2 (containing ca. six drops of Et_3N), gave (±)-**3** (24.0 mg, 85%) as a pale yellow solid: mp 194–195°C; FTIR (CD_2Cl_2, cast) 2925, 2862, 1648, 1614, 1598, 1559, 1500 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.54 (s, 3H), 1.57 (s, 3H), 1.63 (d, J=6.8 Hz, 3H), 3.64 (AB q, J=10.9 Hz, $\Delta\nu_{AB}$=167.1 Hz, 2H), 4.0–4.8 (br signal, not integrated), 4.93 (s, 1H), 5.55 (q, J=6.8 Hz, 1H), 7.29–7.34 (m, 1H), 7.36–7.42 (m, 2H), 7.49 (s, 1H), 7.50–7.54 (m, 2H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) (two signals overlap in this spectrum) δ 13.2 (two overlapping quartets), 24.6 (q), 49.4 (s), 66.5 (t), 99.5 (d), 111.9 (s), 116.8 (s), 124.9 (d), 127.5 (d), 127.7 (d), 128.7 (d), 131.2 (s), 132.4 (s), 134.5 (d), 162.9 (s), 166.8 (s); exact mass m/z calcd for $C_{19}H_{21}NO_3$ 311.15213, found 311.15252.

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