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Stereoselective synthesis of the bacterial DNA primase inhibitor Sch 642305 and its C-4 epimer

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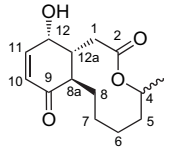
Abstract—A convergent stereoselective synthesis of the bacterial DNA primase inhibitor Sch 642305 and its non-natural epimer at C-4 is described. A key aspect was the construction of a *trans*-2,3-disubstituted cyclohexanone system by means of a stereoselective Michael addition/α-alkylation sequence. The macrolactone ring of either stereoisomer was created using the Mitsunobu and Yamaguchi procedures, respectively.

1. Introduction

Bacterial infections due to the rapid emergence of antibiotic-resistant strains have become a serious threat to public health worldwide.[1] Concerns of antibiotic resistance issues have brought an urgent sense to the discovery and development of new classes of antibacterial drugs. Mechanism-based drug discovery approaches are being explored to identify novel antimicrobial agents that may potentially provide alternative treatments for infectious diseases. Bacterial DNA primase (DnaG) is a DNA-dependent RNA polymerase that is required for the replication of chromosomal DNA.[2,3] Genetic validation of DnaG indicated that inhibition of bacterial primase causes a rapid cidal response of bacteria.[4,5] Interaction of primase, encoded by DnaG, with the single-stranded DNA template is mediated by contacts with the replicative DNA helicase encoded by DnaB.[6,7] In the cell, the helicase progresses along the duplex DNA and mediates unwinding to a single-stranded DNA template. The DNA primase associates with the helicase and intermittently initiates synthesis of ss RNA primers, required for de novo DNA synthesis. While replication of the leading-strand DNA requires only one RNA primer, replication of the lagging-strand DNA requires >2000 primer sites. Since interruption of this process would cause a catastrophic event in bacterial chromosome replication, the primase enzyme constitutes an attractive target for drug discovery.[8] Very recently, a natural compound of fungal origin has been shown to display a marked ability as a primase inhibitor (EC_{50}, 70 μM). The compound, named Sch 642305 (**1**), was isolated from the fermentation broth of the fungus *Penicillium verrucosum* (culture ILF-16214). Its structure, including the relative and absolute configuration (Fig. 1), was established on the basis of thorough NMR studies and an X-ray diffraction analysis of a crystalline derivative.[9] More recently, compound **1** has also been isolated from a microbial source and found to be a potent inhibitor of the HIV-1 Tat-dependent transactivation.[10]



1 4βMe
2 4αMe

Figure 1. Structures of Sch 642305 **1** and its C-4 epimer **2**.

Compound **1** contains a medium-sized (10-membered) lactone condensed with a cyclohexane ring. This bicyclic system has not been previously reported in any compound of natural origin.[11] Due to its interesting biological properties, lactone **1** has attracted the attention of the synthetic community. Four syntheses of **1** have been published in the last two years.[12] In two of these syntheses, the lactone ring was created with the aid of the Yamaguchi macrolactonization procedure[13] whereas in the others, macrocyclization was performed via olefinic ring-closing metathesis.[14] With the aim of performing structure–activity relationship studies, we have now performed syntheses of lactone **1** as well of **2**, its non-natural epimer at C-4.

Our retrosynthetic concept for the preparation of compound Sch 642305 **1** and its epimer **2** is shown in Scheme 1. Both

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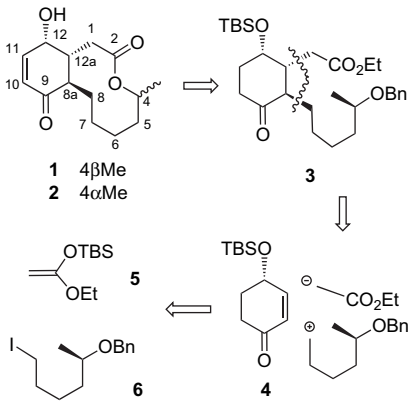


Scheme 1. Retrosynthetic analysis for lactones **1** and **2** (bicyclic system numbered according to the IUPAC).

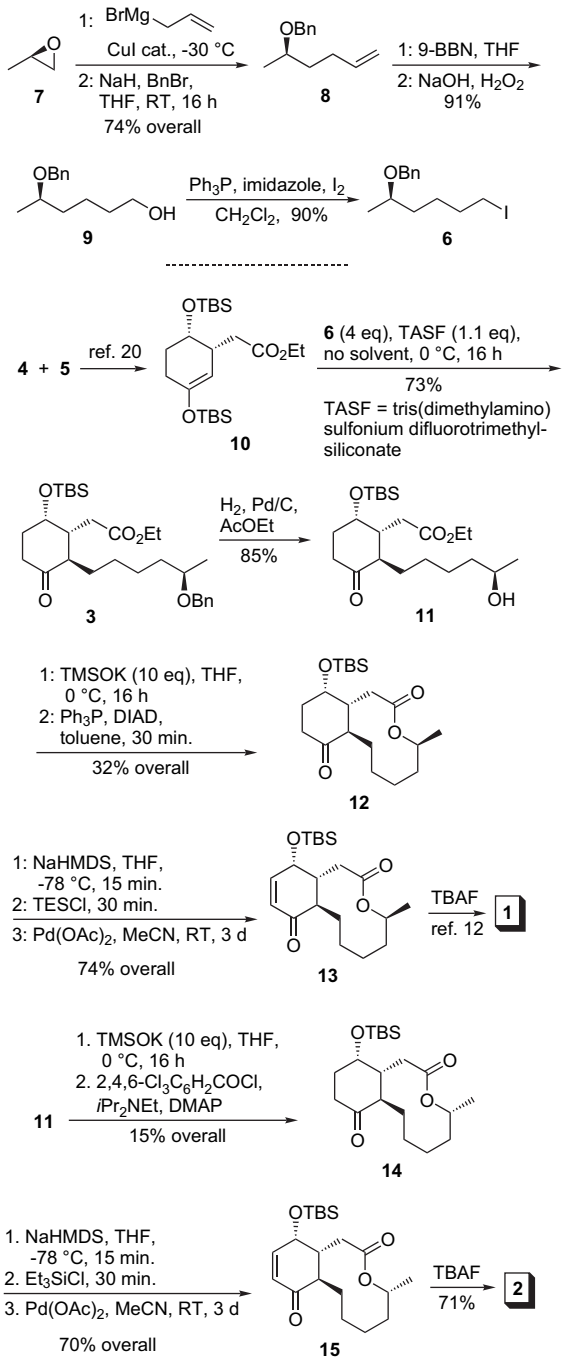
lactones can be referred to ester **3** via lactone opening (with inversion at C-4 in the case of **1**), hydroxyl protection, and reduction of the olefinic bond. Since **3** is a *trans*-2,3-dialkylated cyclohexanone, a disconnection to cyclohexenone **4** via a Michael addition/enolate alkylation sequence seemed a convenient route.[15,16] The necessary nucleophilic and electrophilic synthons materialize here into ketene silyl acetal **5**[17] and iodide **6**, respectively. Various methods for the preparation of enone **4** in enantioenriched form have been previously reported in the literature.[18]

2. Results and discussion

Scheme 2 depicts the details of the synthesis. Iodide **6**[19] was prepared from the commercially available propylene oxide (*R*)-**7** as the chiral starting material. Epoxide ring opening with an allyl cuprate reagent followed by *O*-benzylation gave ether **8**. Hydroboration–oxidation of the latter gave primary alcohol **9**, which was transformed into **6**.

The Lewis acid-catalyzed Michael reaction of enol silane **5** with enone **4** has been reported to yield silyl enol ether **10** as the only product.[20] Treatment of **10** with iodide **6** in the presence of TASF provided ester **3** as the sole stereoisomer detectable by NMR.[21,22] The reaction was best carried out with an excess of liquid iodide **6** in the absence of solvent. The TAS enolate,[21] formed as a reactive intermediate during the reaction, is highly prone to protonation with formation of the corresponding 3,4-disubstituted cyclohexanone (see Section 4). Even with the outmost care in drying the solvent, we were unable to prevent the formation of small amounts of this side product. When using **6** as the 'solvent', however, formation of the undesired ketone could be minimized.

Hydrogenolytic cleavage of the benzyl group in **3** gave hydroxy ester **11**. The hydrolysis of the ethyl ester group proved troublesome, due to the sensitivity of **11** to base-catalyzed epimerization, as well as to silyl cleavage. Ester cleavage took place finally in the presence of an excess of potassium trimethylsilanolate (TMSOK)[23] at 0 °C. The resulting crude hydroxy acid was then subjected to ring closure by means of the Mitsunobu procedure[24] to yield lactone **12**. Creation of the conjugated double bond was performed as reported[12d] by means of the Saegusa method[25] and gave enone **13**, which had already been obtained in one of the



Scheme 2. Stereoselective synthesis of **1** and **2**.

previous syntheses of **1** and was thus converted into the latter compound by means of desilylation.[12c]

In addition to **1**, lactone **2**, its epimer at C-4, was prepared for structure–activity relationship studies. As before, hydroxy ester **11** was the starting material. After ester cleavage with TMSOK, the crude hydroxy acid was subjected to various conditions for macrolactonization. Unfortunately, after many failed attempts,[26] only the Yamaguchi procedure[13] was able to provide lactone **14** in low yield. These disappointing results are in contrast with the fair yield (73%) obtained in the macrolactonization of the corresponding hydroxy acid epimeric at C-4.[12c] Indeed, it has often been shown that minor stereochemical changes exert a major

influence on the course of macrocyclization reactions, particularly in the case of medium-sized rings.[24] Finally, compound **14** was synthetically manipulated in the same way as above to yield **2**.[27,28]

3. Conclusions

The total synthesis of the bioactive metabolite Sch 642305 **1** has been performed in a completely stereoselective way and with an overall yield of 12.5% based on the known chiral enone **4** (longest linear sequence, 8 steps). This compares well with the most recent published synthesis[12d] (12% overall yield from **4** through a partly related reaction sequence) as well as with the three first syntheses,[12a–c] which are longer (>12 steps) and/or contain unselective steps. Furthermore, lactone **2**, an epimer of **1**, has been prepared for pharmacological studies.

4. Experimental

4.1. General

$^{1}H/^{13}C$ NMR spectra were measured at 500/125 MHz in $CDCl_3$ solution at 25 °C. The signals of the deuterated solvent ($CDCl_3$) were taken as the reference (the singlet at δ 7.25 for ^{1}H NMR and the triplet centered at 77.00 ppm for ^{13}C NMR data). Carbon atom types (C, CH, CH_2, CH_3) were determined with the DEPT pulse sequence. Mass spectra were run by the electron impact (EIMS, 70 eV) or the fast atom bombardment mode (FABMS, *m*-nitrobenzyl alcohol matrix) on a VG AutoSpec mass spectrometer. IR data are given only for compounds with relevant functions (OH, C=O) and were recorded as oily films on NaCl plates (oils) or as KBr pellets (solids). Optical rotations were measured at 25 °C. Reactions which required an inert atmosphere were carried out under N_2 with flame-dried glassware. Et_2O and THF were freshly distilled from sodium/benzophenone ketyl and transferred via syringe. Dichloromethane was freshly distilled from CaH_2. Tertiary amines were freshly distilled from KOH. Toluene was freshly distilled from sodium wire. Commercially available reagents were used as received. Unless detailed otherwise, 'work-up' means pouring the reaction mixture into brine, followed by extraction with the solvent indicated in parenthesis. If the reaction medium was acidic (basic), an additional washing with 5% aq $NaHCO_3$ (aq NH_4Cl) was performed. Drying over anhydrous Na_2SO_4 and elimination of the solvent under reduced pressure were followed by chromatography of the residue on a silica gel column (60–200 μm) with the indicated eluent. Where it was necessary to filter a solution through a Celite pad, the pad was additionally washed with the same solvent used, and the washings incorporated to the main organic layer.

4.1.1. (*R*)-5-Benzyloxyhex-1-ene (8). CuI (1.14 g, 6 mmol) was gently heated in vacuo under N_2 until the solid turned light yellow. The flask was then cooled to −30 °C, followed by addition of dry Et_2O (125 mL). A 1 M solution of allylmagnesium bromide in Et_2O (60 mL, 60 mmol) was then slowly added dropwise via syringe. The mixture was stirred for 5 min at −30 °C. Epoxide (*R*)-**7** (2.5 g, 43 mmol) was dissolved in dry Et_2O (15 mL) and added dropwise to the solution of the organocopper reagent. The reaction mixture was then stirred for 4 h at the same temperature. Work-up (Et_2O) afforded a yellowish oil, which was used in crude form in the next step.

A 60% commercial suspension of sodium hydride in mineral oil (2.82 g, equivalent to ca. 70 mmol of NaH) was stirred under N_2 with dry hexane. The suspension was decanted and the supernatant liquid was removed with a syringe. This operation was repeated once more with dry THF. After covering the solid NaH with dry THF (180 mL), a solution of the crude alcohol from above in dry THF (25 mL) was then added via syringe. The solution was stirred at room temperature for 30 min. Benzyl bromide (7.75 mL, 65 mmol) and tetra-*n*-butylammonium iodide (75 mg, ca. 0.2 mmol) were then added to the reaction mixture, which was stirred for 16 h at room temperature. Work-up (extraction with Et_2O) and column chromatography on silica gel (hexane–EtOAc, 98:2) afforded benzyl ether **8** (6.05 g, 74% overall for the two steps): oil; $[\alpha]_D$ −32.9 (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.30 (5H, m), 5.87 (1H, ddt, *J*=17, 10.5, 6.5 Hz), 5.07 (1H, dq, *J*=17, 2 Hz), 5.00 (1H, br d, *J*=10.5 Hz), 4.62 (1H, d, *J*=11.7 Hz), 4.50 (1H, d, *J*=11.7 Hz), 3.59 (1H, apparent sext, *J*~6 Hz), 2.30–2.15 (2H, m), 1.80–1.75 (1H, m), 1.65–1.55 (1H, m), 1.25 (3H, d, *J*=6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1 (C), 138.6, 128.3 (×2), 127.6 (×2), 127.3, 74.2 (CH), 114.4, 70.3, 35.9, 29.8 (CH_2), 19.6 (CH_3); HR EIMS *m*/*z* (% rel int.) 190.1359 (M^+, 1), 91 (100). Calcd for $C_{13}H_{18}O$, 190.1357.

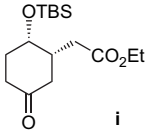
4.1.2. (*R*)-5-Benzyloxyhexan-1-ol (9). A solution of compound **8** (3.8 g, 20 mmol) in dry THF (120 mL) was treated at 0 °C under N_2 with 9-BBN (4.88 g, 40 mmol). The reaction mixture was then stirred for 16 h at room temperature and then quenched by addition of MeOH (40 mL), 6 M aq NaOH (15 mL), and 30% H_2O_2 (25 mL). The resulting mixture was then stirred at 50 °C for 1 h and worked up (extraction with Et_2O). Column chromatography on silica gel (hexanes–EtOAc, 7:3) afforded the desired alcohol **9** (3.79 g, 91%): oil; $[\alpha]_D$ −27.3 (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.25 (5H, m), 4.58 (1H, d, *J*=12 Hz), 4.46 (1H, d, *J*=12 Hz), 3.60 (2H, br t, *J*=6.5 Hz), 3.54 (1H, apparent sext, *J*~6 Hz), 2.00 (1H, br s, OH), 1.65–1.40 (6H, br m), 1.21 (3H, d, *J*=6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0 (C), 128.3 (×2), 127.6 (×2), 127.4, 74.8 (CH), 70.3, 62.6, 36.3, 32.7, 21.7 (CH_2), 19.5 (CH_3); IR ν_{max} 3380 (br, OH) cm^{-1}; HR EIMS *m*/*z* (% rel int.) 208.1462 (M^+, 1), 107 (20), 91 (100). Calcd for $C_{13}H_{20}O_2$, 208.1463.

4.1.3. (*R*)-2-Benzyloxy-6-iodohexane (6). Alcohol **9** (2.08 g, 10 mmol) was dissolved under N_2 in dry CH_2Cl_2 (40 mL), cooled to 0 °C and treated sequentially with imidazole (2.72 g, 40 mmol), triphenylphosphine (2.75 g, 10.5 mmol), and I_2 (3.04 g, 12 mmol). The mixture was stirred at 0 °C for 5 min and then at room temperature for 3 h. Work-up (extraction with CH_2Cl_2) and column chromatography on silica gel (hexanes–EtOAc, 9:1) afforded iodide **6** (2.86 g, 90%): oil; $[\alpha]_D$ −21.9 (*c* 0.85, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.25 (5H, m), 4.60 (1H, d, *J*=11.7 Hz), 4.48 (1H, d, *J*=11.7 Hz), 3.57 (1H, apparent sext, *J*~6 Hz), 3.20

(2H, t, J=7 Hz), 1.85 (2H, apparent quint, J~7 Hz), 1.65–1.45 (4H, br m), 1.23 (3H, d, J=6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0 (C), 128.3 (×2), 127.6 (×2), 127.4, 74.4 (CH), 70.3, 35.5, 33.5, 26.5, 6.9 (CH_2), 19.5 (CH_3); HR EIMS m/z (% rel int.) 318.0492 (M^+, 1), 135 (17), 91 (100). Calcd for $C_{13}H_{19}IO$, 318.0480.

4.1.4. Ethyl 2-[(1*R*,2*R*,6*S*)-2-{(*R*)-5-benzyloxyhexyl}-6-(*tert*-butyldimethylsilyloxy)-3-oxocyclohexyl]acetate (3). Silyl enol ether **10**[20] (857 mg, 2 mmol) was mixed under N_2 with iodide **6** (2.54 g, 8 mmol) and treated with TASF (606 mg, 2.2 mmol). The oily mixture was stirred at 0 °C for 16 h and then worked up. Column chromatography on silica gel (hexanes–EtOAc, 98:2 → 9:1) gave ketone **3** (737 mg, 73%) as a single stereoisomer: oil; $[\alpha]_D$ +14.1 (c 1.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.25 (5H, m), 4.56 (1H, d, J=11.7 Hz), 4.45 (1H, d, J=11.7 Hz), 4.16 (1H, m), 4.13 (2H, q, J=7 Hz), 3.50 (1H, apparent sext, J~6 Hz), 2.62 (1H, td, J=13, 6 Hz), 2.55 (1H, dd, J=16.5, 9 Hz), 2.45 (1H, m), 2.35–2.20 (3H, m), 2.00 (1H, m), 1.85 (1H, m), 1.65–1.50 (4H, m), 1.50–1.40 (2H, m), 1.35–1.25 (2H, m), 1.26 (3H, t, J=7 Hz), 1.17 (3H, d, J=6 Hz), 0.93 (9H, s), 0.09 (3H, s), 0.08 (3H, s); ^{13}C NMR (125 MHz) δ 211.6, 172.7, 139.2, 18.1 (C), 128.3 (×2), 127.6 (×2), 127.3, 74.9, 67.5, 49.5, 43.9 (CH), 70.3, 60.5, 36.5, 36.0, 34.4, 32.6, 27.0, 26.5 (one methylene signal is missing, most likely overlapped by the intense *tert*-butyl signal at 25.9 ppm) (CH_2), 25.9 (×3), 19.6, 14.2, −4.4, −5.3 (CH_3); IR ν_{max} 1733 (ester C=O), 1714 (ketone C=O) cm^{-1}; HR EIMS m/z (% rel int.) 504.3250 (M^+, 1), 447 ($M^+-{}^t$Bu, 18), 91 (100). Calcd for $C_{29}H_{48}O_5Si$, 504.3271.

Further eluted from the column were 145 mg (18%) of ketone **i**, formed through proton transfer to the intermediate TAS enolate.



i

4.1.4.1. Ethyl 2-[(1*S*,2*S*)-2-(*tert*-butyldimethylsilyloxy)-5-oxo-cyclohexyl]acetate (i). Formed as a side product during the alkylation of **10** with **6** (see main text): oil; $[\alpha]_D$ +24.5 (c 1.06, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.00 (3H, m), 2.50 (1H, td, J=14.2, 6.3 Hz), 2.40–2.30 (2H, m), 2.25 (1H, m), 2.10–2.00 (3H, br m), 1.95 (1H, m), 1.70 (1H, br t, J~13 Hz), 1.13 (3H, t, J=7 Hz), 0.82 (9H, s), 0.00 (3H, s), −0.02 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.7, 171.6, 17.8 (C), 67.1, 39.7 (CH), 60.1, 41.9, 36.9, 35.2, 32.4 (CH_2), 25.6 (×3), 14.0, −4.8, −5.5 (CH_3); IR ν_{max} 1733 (ester C=O), 1717 (ketone C=O) cm^{-1}; HR EIMS m/z (% rel int.) 299.1667 (M^+−Me, 1), 257 ($M^+-{}^t$Bu, 65), 75 (100). Calcd for $C_{16}H_{30}O_4Si$−Me, 299.1678.

4.1.5. Ethyl 2-[(1*R*,2*R*,6*S*)-6-(*tert*-butyldimethylsilyloxy)-2-{(*R*)-5-hydroxyhexyl}-3-oxocyclohexyl]acetate (11). Pd/C (10%, 900 mg) was suspended in dry EtOAc (25 mL) under an H_2 atmosphere and stirred for 15 min. Benzyl ether **3** (707 mg, 1.4 mmol) dissolved in EtOAc (5 mL) was then added via syringe. The mixture was stirred at room temperature and ambient pressure for 3 h (*TLC monitoring!*), and then filtered through Celite. Solvent removal in vacuo and column chromatography on silica gel (hexanes–EtOAc, 7:3) gave alcohol **11** (493 mg, 85%): oil; $[\alpha]_D$ +19.3 (c 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.13 (1H, m), 4.10 (2H, q, J=7 Hz), 3.74 (1H, apparent sext, J~6 Hz), 2.59 (1H, td, J=13, 6 Hz), 2.52 (1H, dd, J=16.5, 9 Hz), 2.42 (1H, m), 2.30–2.15 (3H, m), 1.97 (1H, m), 1.80 (1H, m), 1.70 (1H, br s, OH), 1.55–1.50 (2H, m), 1.45–1.35 (3H, m), 1.30–1.20 (3H, m), 1.23 (3H, t, J=7 Hz), 1.13 (3H, d, J=6 Hz), 0.90 (9H, s), 0.06 (3H, s), 0.04 (3H, s); ^{13}C NMR (125 MHz) δ 211.6, 172.7, 18.1 (C), 67.8, 67.5, 49.4, 43.7 (CH), 60.4, 39.0, 35.9, 34.4, 32.5, 26.7, 26.3, 25.9 (CH_2), 25.8 (×3), 23.4, 14.2, −4.5, −5.3 (CH_3); IR ν_{max} 3450 (br, OH), 1733 (ester C=O), 1713 (ketone C=O) cm^{-1}; HR EIMS m/z (% rel int.) 399.2568 (M^+−Me, 3), 357 ($M^+-{}^t$Bu, 98), 339 (100). Calcd for $C_{22}H_{42}O_5Si$−Me, 399.2566.

4.1.6. (4*S*,8a*R*,12*S*,12a*R*)-12-(*tert*-Butyldimethylsilyloxy)-4-methyloctahydro-1*H*-benzo[*d*]oxecine-2,9(10*H*,11*H*)-dione (12). A solution of alcohol **11** (415 mg, 1 mmol) was dissolved under N_2 in dry THF (30 mL), cooled to 0 °C, and treated with TMSOK (1.28 g, 10 mmol). The mixture was stirred for 16 h at room temperature. After this time, a 0.5 M aq solution of citric acid (30 mL) was added, and the stirring was continued for 20 min. Work-up (extraction with EtOAc) provided a hydroxy acid, which was used in crude form in the next step.

A solution of Ph_3P (1.31 g, 5 mmol) in dry toluene (175 mL) was treated dropwise under N_2 with DIAD (990 μL, 5.02 mmol). After stirring at room temperature for 20 min, the crude hydroxy acid from above was dissolved in dry toluene (15 mL) and added to the mixture, which was subsequently stirred for 30 min. Work-up (extraction with EtOAc) and column chromatography on silica gel (hexanes–EtOAc, 8:2) furnished lactone **12** (118 mg, 32% overall for the two steps) as an amorphous solid: $[\alpha]_D$ −21.2 (c 1, $CHCl_3$), lit.[12d] $[\alpha]_D$ −22.2 (c 0.37, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.05 (1H, m), 4.02 (1H, m), 2.66 (1H, td, J=14.5, 6.5 Hz), 2.60–2.45 (4H, br m), 2.20 (1H, m), 2.15–1.95 (3H, m), 1.85–1.75 (3H, m), 1.35–1.20 (4H, br m), 1.25 (3H, d, J=6 Hz), 0.91 (9H, s), 0.10 (3H, s), 0.08 (3H, s); ^{13}C NMR (125 MHz) δ 211.7, 171.6, 18.3 (C), 73.0, 71.0, 50.1, 40.3 (CH), 40.9, 35.1, 32.0, 29.7, 23.2, 21.6, 18.1 (CH_2), 25.9 (×3), 23.0, −4.4, −4.9 (CH_3); IR ν_{max} 1723 (br, ketone and lactone C=O) cm^{-1}; HR EIMS m/z (% rel int.) 353.2137 (M^+−Me, 3), 311 ($M^+-{}^t$Bu, 100), 219 (30). Calcd for $C_{20}H_{36}O_4Si$−Me, 353.2148.

4.1.7. (4*S*,8a*R*,12*S*,12a*R*)-12-(*tert*-Butyldimethylsilyloxy)-4-methyl-4,5,6,7,8,8a-hexahydro-1*H*-benzo[*d*]-oxecine-2,9(12*H*,12a*H*)-dione (13). A solution of lactone **12** (92 mg, 0.25 mmol) was dissolved under N_2 in dry THF (1.5 mL), cooled to −78 °C, and treated at this temperature with NaHMDS (300 μL of a 1 M solution in THF, 0.3 mmol). The mixture was further stirred for 15 min. Triethylsilyl chloride (50 mg, 0.33 mmol) dissolved in dry THF (500 μL) was then added, and the stirring was continued at the same temperature for 30 min. The reaction mixture was then filtered through a pad of silica gel and the pad was eluted with hexanes–EtOAc (8:2). After removal of all volatiles under reduced pressure, a silyl enol ether was obtained and used in crude form in the next step.

The crude compound from above was dissolved under N_2 in dry, degassed MeCN (10 mL). After addition of $Pd(OAc)_2$ (280 mg, 1.25 mmol), the mixture was stirred at room temperature until consumption of the starting material (about 3 d, TLC monitoring). The reaction mixture was then filtered through Celite, and the filter was further washed with EtOAc. Removal of all volatiles under reduced pressure and column chromatography on silica gel (hexanes–EtOAc, 9:1) afforded lactone **13** (68 mg, 74% overall for the two steps) as a white solid: 103–105 °C, lit.[12c] mp 104–106 °C; $[\alpha]_D$ +53.2 (*c* 1.1, $CHCl_3$), lit.[12c] $[\alpha]_D$ +56 (*c* 1, $CHCl_3$), lit.[12d] $[\alpha]_D$ +52.1 (*c* 0.48, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.85 (1H, dd, *J*=9.9, 5.5 Hz), 5.95 (1H, d, *J*=9.9 Hz), 5.08 (1H, m), 4.22 (1H, dd, *J*=5.2, 3.2 Hz), 2.81 (1H, tt, *J*=11, 2.5 Hz), 2.72 (1H, dt, *J*=11, 3.5 Hz), 2.57 (1H, dd, *J*=17, 11 Hz), 2.48 (1H, dd, *J*=17, 2 Hz), 2.25–2.05 (2H, m), 1.80 (1H, m), 1.60 (1H, m), 1.40–1.20 (3H, br m), 1.26 (3H, d, *J*=6.5 Hz), 1.10 (1H, ddd, *J*=14.5, 10.5, 3 Hz), 0.88 (9H, s), 0.10 (3H, s), 0.08 (3H, s); ^{13}C NMR (125 MHz) δ 200.4, 171.5, 18.3 (C), 146.7, 130.1, 73.1, 67.6, 46.6, 37.3 (CH), 39.3, 29.7, 23.1, 22.9, 21.6 (CH_2), 25.8 (×3), 18.1, −3.9, −4.8 (CH_3); IR ν_{max} 1726 (lactone C=O), 1680 (ketone C=O) cm^{-1}; HR EIMS *m/z* (% rel int.) 351.2005 (M^+−Me, 1), 309 (M^+−^{t}Bu, 20), 117 (100), 75 (46). Calcd for $C_{20}H_{34}O_4Si$−Me, 351.1991.

4.1.8. (4*S*,8a*R*,12*S*,12a*R*)-12-Hydroxy-4-methyl-4,5,6,7,-8,8a-hexahydro-1*H*-benzo[*d*]oxecine-2,9(12*H*,12a*H*)-dione (Sch 642305, 1). Desilylation of lactone **13** was performed as reported.[12] This gave lactone **1**: white solid, mp 149–151 °C (lit.[9] for natural Sch 642305, mp 143–145 °C, lit.[12b] for synthetic Sch 642305, mp 142–144 °C, lit.[12c] for synthetic Sch 642305, mp 151–153 °C); $[\alpha]_D$ +59 (*c* 0.3, $CHCl_3$), $[\alpha]_D$ +75.3 (*c* 0.11, MeOH) {lit.[9] for natural Sch 642305, $[\alpha]_D$ +67.44 (*c* 0.5, MeOH), lit.[12a] for synthetic Sch 642305, $[\alpha]_D$ +71 (*c* 0.31, MeOH), lit.[12b] for synthetic Sch 642305, $[\alpha]_D$ +62.4 (*c* 0.87, MeOH), lit.[12c] for synthetic Sch 642305, $[\alpha]_D$ +74 (*c* 0.50, MeOH), lit.[12d] for synthetic Sch 642305, $[\alpha]_D$ +76.1 (*c* 0.92, MeOH)}. ^1H NMR (500 MHz, CD_3OD) δ 7.05 (1H, dd, *J*=9.8, 5.5 Hz), 5.98 (1H, d, *J*=9.8 Hz), 5.07 (1H, m), 4.23 (1H, dd, *J*=5.5, 3.8 Hz), 2.84 (1H, tt, *J*=11.5, 3 Hz), 2.70 (1H, dd, *J*=17, 2.5 Hz), 2.68 (1H, dt, *J*=11, 4 Hz), 2.56 (1H, dd, *J*=17, 11.5 Hz), 2.25–2.10 (2H, m), 1.87 (1H, m), 1.60 (1H, m), 1.45–1.20 (3H, br m), 1.29 (3H, d, *J*=6.5 Hz), 1.12 (1H, ddd, *J*=14.5, 10.5, 3 Hz); ^1H NMR (500 MHz, $CDCl_3$) δ 6.96 (1H, dd, *J*=9.9, 5.7 Hz), 6.03 (1H, d, *J*=9.9 Hz), 5.10 (1H, m), 4.30 (1H, dd, *J*=5.5, 3.6 Hz), 2.82 (1H, m), 2.70–2.65 (3H, m), 2.20–2.05 (3H, m), 1.80 (1H, m), 1.64 (1H, m), 1.40–1.15 (4H, br m), 1.27 (3H, d, *J*=6.5 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 202.3, 173.7 (C), 149.5, 130.6, 74.7, 67.1, 47.8, 37.8 (CH), 39.8, 30.9, 24.2, 24.1, 22.6 (CH_2), 18.6 (CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.9, 171.7 (C), 145.9, 130.7, 73.4, 67.0, 45.8, 36.8 (CH), 38.7, 30.2, 22.9, 22.7, 22.2 (CH_2), 18.5 (CH_3). IR ν_{max} 3450 (br, OH), 1723 (lactone C=O), 1677 (ketone C=O) cm^{-1}; HR EIMS *m/z* (% rel int.) 252.1360 (M^+, 1), 152 (65), 107 (40), 84 (82), 82 (100), 55 (91). Calcd for $C_{14}H_{20}O_4$, 252.1361.

4.1.9. (4*R*,8a*R*,12*S*,12a*R*)-12-(*tert*-Butyldimethylsilyloxy)-4-methyloctahydro-1*H*-benzo[*d*]oxecine-2,9(10*H*,11*H*)-dione (14). A solution of alcohol **11** (104 mg, 0.25 mmol) was treated with TMSOK as described above for the synthesis of **12**. This gave a crude hydroxy acid, used in the next step.

A solution of the crude hydroxy acid in dry CH_2Cl_2 (25 mL) was treated dropwise under N_2 at room temperature with *N*,*N*-diisopropyl ethylamine (130 μL, 0.75 mmol) and then with 2,4,6-trichlorobenzoyl chloride (78 μL, 0.5 mmol). After stirring at room temperature for 1 h, DMAP (30 mg, 0.25 mmol) was added to the mixture, which was subsequently stirred for 2 h. Work-up (extraction with CH_2Cl_2) and column chromatography on silica gel (hexanes–EtOAc, 9:1) provided lactone **14** (14 mg, 15% overall) as an oil: $[\alpha]_D$ +16.1 (*c* 0.35, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 4.96 (1H, m), 4.06 (1H, m), 2.74 (1H, br d, *J*=11 Hz), 2.64 (1H, td, *J*=14, 6.5 Hz), 2.60 (1H, m), 2.45 (1H, dd, *J*=12, 10.5 Hz), 2.30–2.20 (2H, br m), 2.10–1.80 (3H, br m), 1.75–1.45 (6H, br m), 1.28 (3H, d, *J*=6 Hz), 1.11 (1H, m), 0.93 (9H, s), 0.10 (6H, s); ^{13}C NMR (125 MHz) δ 211.3, 174.5, 18.1 (C), 72.7, 72.5, 49.9, 40.9 (CH), 45.9, 35.2, 32.5, 31.5, 31.0, 24.0, 20.9 (CH_2), 25.9 (×3), 22.6, −4.3, −4.8 (CH_3); IR ν_{max} 1727 (ketone and lactone C=O) cm^{-1}; HR EIMS *m/z* (% rel int.) 353.2145 (M^+−Me, 2), 311 (M^+−^{t}Bu, 100), 219 (30), 159 (100), 125 (30), 75 (62). Calcd for $C_{20}H_{36}O_4Si$−Me, 353.1248.

4.1.10. (4*R*,8a*R*,12*S*,12a*R*)-12-(*tert*-Butyldimethylsilyloxy)-4-methyl-4,5,6,7,8,8a-hexahydro-1*H*-benzo[*d*]-oxecine-2,9(12*H*,12a*H*)-dione (15). A solution of lactone **14** (11 mg, 0.03 mmol) was subjected to the same reaction sequence and conditions as those used in the conversion of **12** into **13**. This furnished lactone **15** (8 mg, 70% overall) as an oil: $[\alpha]_D$ +100.9 (*c* 0.22, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.78 (1H, dd, *J*=9.9, 5.6 Hz), 5.95 (1H, d, *J*=9.9 Hz), 5.00 (1H, apparent quint, *J*~7 Hz), 4.26 (1H, dd, *J*=5.5, 1.8 Hz), 2.92 (1H, m), 2.55–2.45 (2H, m), 2.27 (1H, m), 2.05–1.80 (4H, br m), 1.65–1.45 (3H, br m), 1.27 (3H, d, *J*=6.5 Hz), 1.00 (1H, m), 0.89 (9H, s), 0.12 (3H, s), 0.09 (3H, s); ^{13}C NMR (125 MHz) δ 200.7, 174.6, 18.1 (C), 145.8, 129.8, 72.9, 69.3, 46.7, 41.6 (CH), 39.7, 31.3, 30.3, 30.2, 24.8, 21.6 (CH_2), 25.8 (×3), 21.4, −3.8, −4.8 (CH_3); IR ν_{max} 1725 (lactone C=O), 1685 (ketone C=O) cm^{-1}; HR EIMS *m/z* (% rel int.) 351.1968 (M^+−Me, 2), 309 (M^+−^{t}Bu, 100), 189 (60), 117 (46). Calcd for $C_{20}H_{34}O_4Si$−Me, 351.1991.

4.1.11. (4*R*,8a*R*,12*S*,12a*R*)-12-Hydroxy-4-methyl-4,5,6,7,8,8a-hexahydro-1*H*-benzo[*d*]oxecine-2,9(12*H*,12a*H*)-dione (2). Lactone **15** (7 mg, 0.02 mmol) was desilylated under the same conditions reported for the conversion of **13** into **1**. This gave **2** (3.5 mg, 71%): white solid, mp 125–127 °C; $[\alpha]_D$ +67.1 (*c* 0.3, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.89 (1H, dd, *J*=9.9, 5.7 Hz), 6.02 (1H, d, *J*=9.9 Hz), 5.00 (1H, m), 4.32 (1H, m), 2.81 (1H, dt, *J*=11.5, 3.7 Hz), 2.65–2.55 (2H, m), 2.40 (1H, d, *J*=12 Hz), 2.05 (1H, m), 1.90–1.80 (2H, m), 1.70–1.50 (5H, br m), 1.26 (3H, d, *J*=6.5 Hz), 1.05 (1H, m); ^{13}C NMR (125 MHz) δ 200.0, 174.3 (C), 145.0, 130.7, 73.0, 68.6, 46.5, 39.1 (CH), 40.9, 31.2, 29.7, 24.6, 21.7 (CH_2), 21.2 (CH_3); IR ν_{max} 3420 (br, OH), 1724 (lactone C=O), 1680 (ketone C=O) cm^{-1}; HR EIMS *m/z* (% rel int.) 252.1358 (M^+, 1), 234 (M^+−H_2O, 3), 152 (100). Calcd for

$C_{14}H_{20}O_4$, 252.1361. Anal. Calcd: C, 66.65; H, 7.99. Found: C, 66.80; H, 8.10.

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