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Stereoselective synthesis of Sch 642305, an inhibitor of bacterial DNA primase

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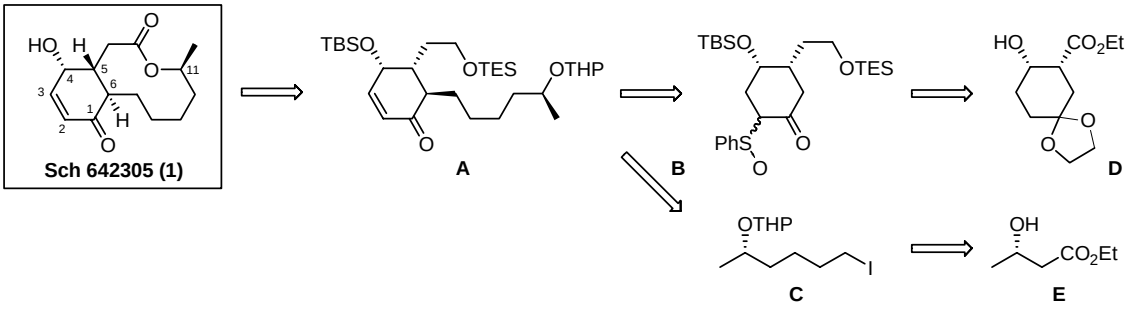
Abstract—Sch 642305 is a fungal nonanolide, which inhibits bacterial DNA primase and HIV-1 Tat transactivation. The enantioselective synthesis of Sch 642305 was succeeded starting from useful chiral building block via stereoselective dianion alkylation of β-ketosulfoxide and lactonization.

1. Introduction

Recently, mechanism-based drugs have been remarkably noticed, since they will potentially provide selective treatments for various diseases such as infections and cancers. In 2003, Chu et al. isolated Sch 642305 from *Penicillium verrucosum* as a potent inhibitor of bacterial DNA primase.[1] Because DNA primase is necessary for the replication of chromosomal DNA,[2,3] this compound is thought to provide an alternative treatment for infectious diseases. In addition, Jayasuriya and co-workers recently reported that Sch 642305 potently inhibits HIV-1 Tat transactivation.[4] A number of bioactive nonanolides have been isolated from a variety of fungal species.[5,6] Sch 642305 has a structure including 10-membered lactone fused with 4-hydroxycyclohexenone. Its unique structure as well as the significant biological activities prompted us to undertake the synthesis of this compound. During our work in progress, Mehta and Shinde also reported the total synthesis of Sch 642305, using ring closing metathesis as a key step.[7]

2. Results and discussion

Our retrosynthesis is shown in Scheme 1. We selected lactonization as a ring closing step. The precursor for the lactonization **A** would be prepared from dianion of β-ketosulfoxide **B** and iodide **C**. The ketosulfoxide **B** would be synthesized from a chiral building block **D**, which has been developed in our laboratory.[8,9] The iodide **C** would be obtained from chiral 3-hydroxybutylate **E**.[10,11]



Scheme 1. Synthetic plan.

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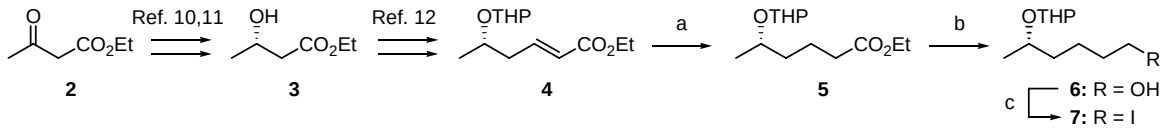
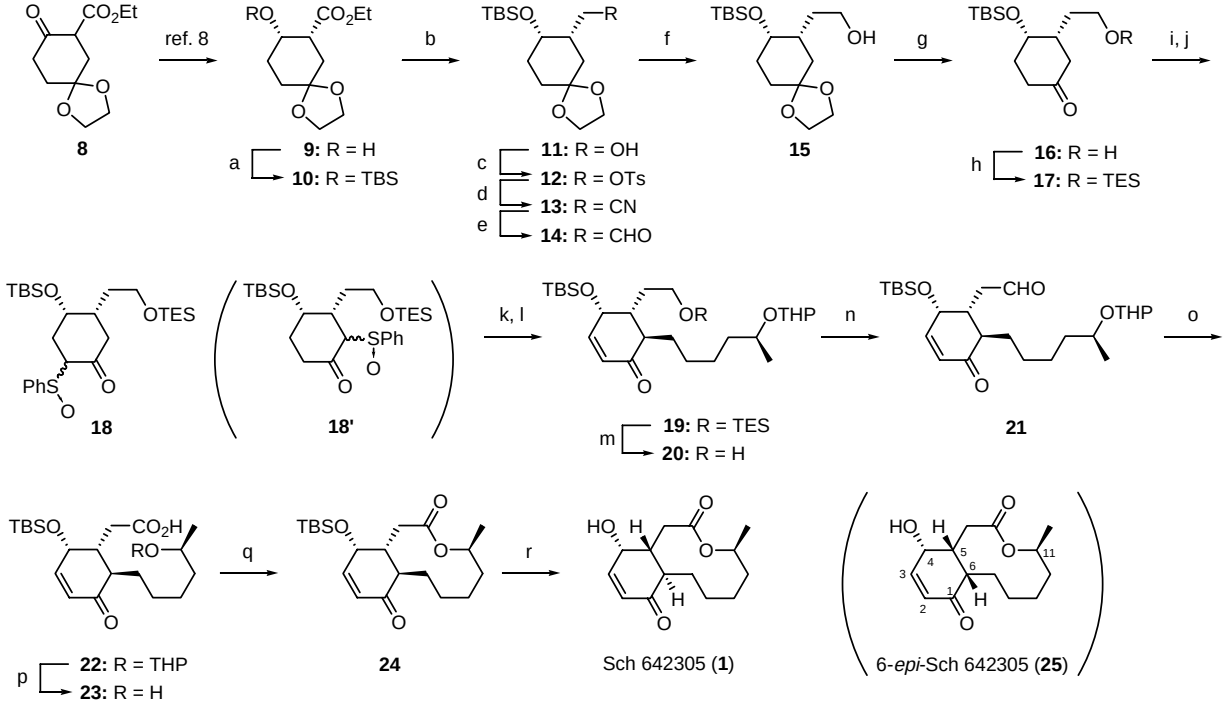


Scheme 2. Reagents and conditions: (a) H_2, Pd–C, EtOAc, 95%; (b) $LiAlH_4$, ether, 98%; (c) I_2, PPh_3, imidazole, CH_2Cl_2 87%.

Preparation of iodide **7** (=**C**) is shown in Scheme 2. Optically active (*S*)-3-hydroxybutylate **3** (98% ee) could be easily prepared in a large amount from ethyl acetoacetate (**2**) via stereoselective reduction by baker's yeast and enzymatic improvement of the optical purity.[10,11] This compound was subjected to C2 elongation by the reported procedure[12] to afford α,β-unsaturated ester **4**. Hydrogenation of **4** was followed by LAH reduction to give alcohol **6**,[13–15] which was converted to the corresponding iodide **7** in a usual manner.

Hydroxyl group of another chiral building block **9** (99% ee),[8] which could be prepared in a large quantity via stereoselective reduction of **8** by baker's yeast, was protected as TBS ether (Scheme 3) to give **10**. After the reduction of ester group in **10**, resulting alcohol was converted to the corresponding tosylate **12**. Transformation to nitrile **13** and subsequent two-step reduction gave alcohol **15** in good yield. Ketone was liberated by transacetalization and hydroxyl group was then protected as TES ether to afford **17**. This ketone was treated with LDA and phenyl benzenethiosulfonate to give a sulfide, which was oxidized to corresponding sulfoxide **18** (60% as a diastereomeric mixture) together with its regioisomer **18′** (17%). After the easy removal of **18′** by silica gel chromatography, β-ketosulfoxide **18** was subjected to regio- and stereoselective alkylation with the iodide **7** by dianion procedure[16–18] and subsequent thermal elimination afforded tri-substituted cyclohexenone **19** as a single isomer in a moderate yield. As we expected, the alkylation occurred selectively from the less hindered β-face of the dianion. Selective removal of TES group of **19** and two-step oxidation were followed by removal of THP group to give hydroxy acid **23**, the lactonization precursor. It was subjected to Yamaguchi's method[19,20] to afford 10-membered lactone **24** (73%) successfully with a small amount of a dimeric lactone (13%). The final step, removal of TBS group, was found to be slightly difficult. Deprotection of **24** with TBAF or $HF\cdot NEt_3$ gave a decomposed product mainly and the desired compound was obtained only in low yield. Other conditions (*p*-TsOH in MeOH, Dowex®-50 in MeOH, KF-18-crown-6 in MeCN, or neutralized TBAF with HF in THF) resulted in a partial epimerization at C-6 position (β:α=3:1–1:1, see Section 3). During our efforts as above, Mehta and Shinde reported the successful removal of TBDPS group using TBAF–AcOH in their synthesis of Sch 642305.[7] According to their procedure, we also succeeded in the synthesis of Sch 642305 without epimerization. The NMR data of synthesized **1** were identical to those reported.[1,7] Its specific



Scheme 3. Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, quant.; (b) DIBAL, CH_2Cl_2, 94%; (c) TsCl, TEA, DMAP, CH_2Cl_2, 89%; (d) NaCN, DMSO, 93%; (e) DIBAL, CH_2Cl_2, 93%; (f) $NaBH_4$, EtOH, 99%; (g) *p*-TsOH, Me_2CO, quant.; (h) TESCl, TEA, CH_2Cl_2, quant.; (i) LDA, $PhSO_2SPh$, THF; (j) MCPBA, CH_2Cl_2, 60% in two steps; (k) LDA, **7**, THF; (l) $CaCO_3$, tol. 47% in two steps; (m) HF, CH_3CN, 98%; (n) Dess–Martin periodinane, CH_2Cl_2, 84%; (o) $NaClO_2$, 2-methyl-2-butene, $NaH_2PO_4\cdot 2H_2O$, *tert*-BuOH, water, 90%; (p) $MgBr_2\cdot Et_2O$, ether, quant.; (q) 2,4,6-trichlorobenzoylchloride, TEA, THF then DMAP, tol., 73%; (r) TBAF, AcOH, THF, 87%.

rotation {$[\alpha]_D^{29}$ +74 (*c* 0.50, MeOH)} and mp (151–153 °C) were slightly larger than those reported for natural Sch 642305 {$[\alpha]_D$ +67.44 (*c* 0.50, MeOH), mp 143–145 °C}.[1]

In conclusion, we have accomplished a stereoselective synthesis of Sch 642305 starting from two chiral sources, which were prepared by stereoselective reductions with baker's yeast. Alkylation of β-ketosulfoxide by dianion procedure selectively afforded the desired stereochemistry and Yamaguchi's lactonization was also successful in good yield. The overall yield was 10% in 18 steps started from chiral building block **9**. As fungal nonanolides have interesting biological activities, we wish our syntheses[21,22] of these compounds would offer any useful information for further investigation on the related fields.

3. Experimental

3.1. General

Optical rotations were recorded with a JASCO DIP-1000 polarimeter. IR spectra were measured with a JASCO FT/IR-230 spectrophotometer. ^1H and ^{13}C NMR were recorded on JEOL JNM AL300 or JEOL JNM GSX500. Chemical shifts (δ) were referenced to the residual solvent peak as the internal standard ($CDCl_3$: $\delta_H=7.26$, $\delta_C=77.0$; CD_3OD: $\delta_H=3.30$, $\delta_C=49.0$). Mass spectra were recorded on JEOL JMS-700T. Column chromatography was performed using Merck silica gel 60 (0.060–0.200 mm). TLC was carried out on Merck glass plates precoated with silica gel 60 F_{254} (0.25 mm). Melting points are uncorrected values.

3.2. Synthetic studies

3.2.1. Ethyl (*S*)-5-tetrahydropyranyloxyhexanoate (5). To a solution of unsaturated ester **4** (4.97 g, 21.8 mmol) in ethyl acetate (40 ml) was added 5% Pd/C (1.3 g) and the mixture was stirred at room temperature for 5 h under H_2. The mixture was filtered through Celite® and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (1/1) gave **5** (4.75 g, 95%) as a colorless oil.

Spectroscopic data were identical to those reported.[14]

3.2.2. (*S*)-5-Tetrahydropyranyloxyhexan-1-ol (6). To a solution of ester **5** (4.89 g, 21.2 mmol) in ether (60 ml) was added $LiAlH_4$ (0.53 g, 14 mmol) at 0 °C and the mixture was stirred at 0 °C for 1 h under argon. The reaction mixture was quenched with MeOH, poured into saturated NH_4Cl solution and extracted with ether. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (1/1) gave **6** (4.19 g, 98%) as a colorless oil.

Spectroscopic data were identical to those reported.[14]

3.2.3. (*S*)-1-Iodo-5-tetrahydropyranyloxyhexane (7). To a solution of alcohol **6** (2.19 g, 10.8 mmol), imidazole (2.94 g, 43.2 mmol) and PPh_3 (2.94 g, 11.2 mmol) in CH_2Cl_2 (30 ml) was added iodine (3.3 g, 13 mmol) at 0 °C and the mixture was stirred at room temperature for 3 h. This mixture was poured into saturated NH_4Cl solution and extracted with ether. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with toluene–ethyl acetate (20/1) gave **7** (2.94 g, 87%) as a slightly yellow oil.

$n_D^{27}=1.5019$. $[\alpha]_D^{26}$ +1.6 (*c* 1.0, $CHCl_3$). IR (film): $\nu=1454$, 1372, 1282, 1258, 1131, 1022, 870, 813 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): $\delta=1.12$ (1.5H, d, $J=6.3$ Hz), 1.23 (1.5H, d, $J=6.3$ Hz), 1.35–1.9 (12H, m), 3.19 (1H, t, $J=6.9$ Hz), 3.21 (1H, t, $J=6.9$ Hz), 3.45–3.55 (1H, m), 3.65–3.95 (2H, m), 4.6–4.75 (1H, m). FAB-HRMS *m/z* calcd for $C_{11}H_{22}IO_2$ $[M+H]^+$ 313.0664, found 313.0658.

3.2.4. Ethyl (1*R*,2*S*)-5,5-ethylenedioxy-2-(*tert*-butyldimethylsilyloxy)cyclohexanecarboxylate (10). A solution of alcohol **9** (6.00 g, 26.1 mmol), TBSOTf (6.2 ml, 27 mmol) and 2,6-lutidine (6.1 ml, 52 mmol) in CH_2Cl_2 (100 ml) was stirred at room temperature for 2 h. The reaction mixture was poured into saturated NH_4Cl solution and extracted with ether. The organic layer was washed with 1 N HCl, saturated $NaHCO_3$ solution and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (4/1) gave **10** (9.03 g, quant.) as a slightly yellow oil.

$n_D^{27}=1.4600$. $[\alpha]_D^{26}$ +24 (*c* 1.0, $CHCl_3$). IR (film): $\nu=1739$, 1254, 1182, 1086, 1065, 1041, 833 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): $\delta=-0.01$ (3H, s), 0.04 (3H, s), 0.85 (9H, s), 1.25 (3H, t, $J=7.2$ Hz), 1.51 (1H, m), 1.7–1.85 (3H, m), 1.95 (1H, dt, $J=6.0$, 12.6 Hz), 2.16 (1H, t, $J=13.2$ Hz), 2.66 (1H, ddd, $J=13.2$, 3.6, 2.4 Hz), 3.85–4.25 (6H, m), 4.42 (1H, m). FAB-HRMS *m/z* calcd for $C_{17}H_{33}O_5Si$ $[M+H]^+$ 345.2097, found 345.2059.

3.2.5. [(1*S*,2*S*)-5,5-Ethylenedioxy-2-(*tert*-butyldimethylsilyloxy)cyclohexyl]methanol (11). To a solution of ester **10** (10.6 g, 30.9 mmol) in dry CH_2Cl_2 (150 ml) was added 1.01 M solution of DIBAL in toluene (67.3 ml, 68.0 mmol) dropwise at −78 °C and the mixture was stirred at −78 °C for 2 h under argon. The reaction mixture was quenched with MeOH, poured into saturated Rochelle's salt solution and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (2/1–1/1) gave **11** (9.08 g, 97%) as an amorphous solid.

$[\alpha]_D^{26}$ +34 (*c* 1.0, $CHCl_3$). IR (Nujol): $\nu=3479$, 1253, 1108, 1076, 1032, 832 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): $\delta=$ 0.08 (6H, s), 0.90 (9H, s), 1.45–2.0 (7H, m), 3.55–3.7 (2H, m), 3.9–4.0 (4H, m), 4.08 (1H, m). FAB-HRMS *m/z* calcd for $C_{15}H_{31}O_4Si$ $[M+H]^+$ 303.1992, found 303.1969.

3.2.6. [(1*S*,2*S*)-5,5-Ethylenedioxy-2-(*tert*-butyldimethylsilyloxy)cyclohexyl]methyl *p*-toluenesulfonate (12). To a solution of alcohol **11** (9.08 g, 30.0 mmol), triethylamine (12.5 ml, 90.0 mmol) and DMAP (367 mg, 3.00 mmol) in CH_2Cl_2 (150 ml) was added TsCl (6.86 g, 36.0 mmol) at

0 °C and the mixture was stirred at room temperature for 16 h. The reaction mixture was poured into saturated NH_4Cl solution and extracted with ether. The organic layer was washed with 1 N HCl, saturated $NaHCO_3$ solution and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (3/1) gave **12** (12.2 g, 89%) as colorless crystals.

Mp 65–67 °C. $[\alpha]_D^{24}$ +32 (*c* 1.0, $CHCl_3$). IR (Nujol): ν= 1595, 1254, 1188, 1176, 1102, 1072, 957, 835, 665 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): δ= −0.03 (3H, s), 0.02 (3H, s), 0.81 (9H, s), 1.35–1.8 (5H, m), 1.87 (1H, dt, *J*=4.2, 12.9 Hz), 2.0–2.15 (1H, m), 2.45 (3H, s), 3.76 (1H, dd, *J*= 9.0, 6.6 Hz), 3.85–4.05 (6H, m), 7.34 (2H, d, *J*=8.1 Hz), 7.77 (2H, d, *J*=8.1 Hz). FAB-HRMS *m/z* calcd for $C_{22}H_{37}O_6SSi$ $[M+H]^+$ 457.2080, found 457.2079.

3.2.7. [(1*R*,2*S*)-5,5-Ethylenedioxy-2-(*tert*-butyldimethylsilyloxy)cyclohexyl]acetonitrile (13). A mixture of tosylate **12** (19.2 g, 42.0 mmol), NaCN (3.1 g, 63 mmol) and DMSO (150 ml) was heated to 100 °C and stirred for 4 h. After cooling, the reaction mixture was diluted with 150 ml of ether and washed with water and brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was recrystallized from hexane to give **13** (12.2 g, 93%) as colorless needles.

Mp 49–51 °C. $[\alpha]_D^{24}$ +31 (*c* 1.0, $CHCl_3$). IR (Nujol): ν= 2246, 1253, 1144, 1103, 1065, 994, 838 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): δ=0.09 (3H, s), 0.10 (3H, s), 0.90 (9H, s), 1.45–1.95 (6H, m), 2.12 (1H, br m), 2.25 (1H, dd, *J*=16.5, 6.9 Hz), 2.38 (1H, dd, *J*=16.5, 8.4 Hz), 3.9–4.05 (5H, m). FAB-HRMS *m/z* calcd for $C_{16}H_{30}NO_3Si$ $[M+H]^+$ 312.1995, found 312.1969.

3.2.8. 2-[(1*R*,2*S*)-5,5-Ethylenedioxy-2-(*tert*-butyldimethylsilyloxy)cyclohexyl]acetaldehyde (14). To a solution of nitrile **13** (1.00 g, 3.21 mmol) in dry CH_2Cl_2 (20 ml) was added 1.01 M solution of DIBAL in toluene (3.4 ml, 3.4 mmol) dropwise at −78 °C and the mixture was stirred at −78 °C for 2.5 h under argon. The reaction mixture was quenched with MeOH, poured into saturated Rochelle's salt solution and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (4/1–2/1) gave **14** (0.93 g, 94%) as an amorphous solid.

$[\alpha]_D^{24}$ +29 (*c* 1.0, $CHCl_3$). IR (film): ν=1726, 1103, 1067, 999, 832, 773 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): δ= 0.02 (3H, s), 0.05 (3H, s), 0.88 (9H, s), 1.45–1.6 (2H, m), 1.7–1.8 (3H, m), 1.89 (1H, dt, *J*=5.7, 12.0 Hz), 2.2–2.5 (2H, m), 2.56 (1H, m), 3.85 (1H, m), 3.9–3.95 (4H, m), 9.77 (1H, t, *J*=1.8 Hz). FAB-HRMS *m/z* calcd for $C_{16}H_{31}O_4Si$ $[M+H]^+$ 315.1992, found 315.1965.

3.2.9. 2-[(1*R*,2*S*)-5,5-Ethylenedioxy-2-(*tert*-butyldimethylsilyloxy)cyclohexyl]ethanol (15). To a solution of sodium borohydride (1.9 g, 50 mmol) in EtOH (120 ml) was slowly added a solution of aldehyde **14** (8.00 g, 25.4 mmol) in EtOH (30 ml) at −20 °C. The reaction mixture was stirred at 0 °C for 3 h, poured into saturated NH_4Cl solution and extracted with ether. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (5/1–1/1) gave **15** (7.96 g, 99%) as colorless needles.

Mp 51–52 °C. $[\alpha]_D^{26}$ +19 (*c* 1.0, $CHCl_3$). IR (Nujol): ν= 3340, 1251, 1142, 1076, 1037, 996, 834 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): δ=0.05 (3H, s), 0.06 (3H, s), 0.90 (9H, s), 1.4–1.95 (9H, m), 3.67 (2H, t, *J*=6.3 Hz), 3.8–3.85 (1H, m), 3.85–4.0 (4H, m). FAB-HRMS *m/z* calcd for $C_{16}H_{33}O_4Si$ $[M+H]^+$ 317.2148, found 317.2153.

3.2.10. (3*R*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-3-(2-hydroxyethyl)cyclohexanone (16). A solution of acetal **15** (1.00 g, 3.16 mmol) and *p*-toluenesulfonic acid monohydrate (59 mg, 0.31 mmol) in acetone (100 ml) was stirred at room temperature for 2 days. The reaction mixture was poured into saturated ammonium sulfate solution. The organic layer was concentrated in vacuo and the residue was dissolved in EtOAc. The aqueous layer was extracted with EtOAc. Combined organic layers were washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (1/1) gave **16** (0.86 g, quant.) as a colorless oil.

n_D^{27}=1.4701. $[\alpha]_D^{26}$ +18 (*c* 1.0, $CHCl_3$). IR (film): ν=3417, 1713, 1254, 1059, 837, 775 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): δ=0.11 (6H, s), 0.93 (9H, s), 1.54 (1H, m), 1.7–1.9 (2H, m), 2.0–2.15 (2H, m), 2.15–2.3 (2H, m), 2.48 (1H, t, *J*=13.2 Hz), 2.66 (1H, dt, *J*=6.3, 13.5 Hz), 3.6–3.75 (2H, m), 4.03 (1H, br m). FAB-HRMS *m/z* calcd for $C_{14}H_{29}O_3Si$ $[M+H]^+$ 273.1886, found 273.1852.

3.2.11. (3*R*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-3-(2-triethylsilyloxyethyl)cyclohexanone (17). Triethylamine (2.20 ml, 15.8 mmol) and TESCl (690 μl, 4.11 mmol) were added to a solution of alcohol **16** (860 mg, 3.16 mmol) in CH_2Cl_2 (30 ml). The reaction mixture was stirred at room temperature for 45 min, poured into saturated NH_4Cl solution and extracted with ether. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (20/1) gave **17** (1.23 g, quant.) as a colorless oil.

n_D^{27}=1.4614. $[\alpha]_D^{27}$ +1.9 (*c* 1.0, $CHCl_3$). IR (film): ν=1721, 1254, 1080, 835, 742 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): δ=0.11 (6H, s), 0.58 (6H, q, *J*=7.8 Hz), 0.92 (9H, s), 0.94 (9H, t, *J*=7.8 Hz), 1.48 (1H, m), 1.71 (1H, m), 1.81 (1H, m), 2.0–2.15 (2H, m), 2.15–2.25 (2H, m), 2.47 (1H, t, *J*= 13.5 Hz), 2.67 (1H, dt, *J*=6.0, 13.5 Hz), 3.61 (1H, dt, *J*= 10.5, 6.3 Hz), 3.66 (1H, dt, *J*=10.5, 6.3 Hz), 4.01 (1H, br m). FAB-HRMS *m/z* calcd for $C_{20}H_{43}O_3Si_2$ $[M+H]^+$ 387.2751, found 387.2753.

3.2.12. (2*RS*,4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-2-phenylsulfinyl-5-(2-triethylsilyloxyethyl)cyclohexanone (18). To a solution of diisopropylamine (701 μl, 5.00 mmol) in THF (20 ml) was added 1.56 M solution of *n*-BuLi

(3.3 ml, 5.0 mmol) dropwise at −20 °C and stirred for 45 min under argon. This solution was cooled down to −78 °C and a solution of ketone **17** (1.93 g, 5.00 mmol) in THF (5 ml) was slowly added to it. Stirring for 3 min was followed by dropwise addition of a solution of phenyl benzenethiosulfonate (1.25 g, 5.0 mmol) in THF (5 ml). The reaction mixture was stirred at −78 °C for 1 h, poured into saturated NH_4Cl solution and extracted with ether. The organic layer was washed with 1 N HCl, saturated $NaHCO_3$ solution and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (20/1) gave a diastereomeric mixture of sulfides (2.68 g) as slightly yellow solids. This mixture was used for next reaction without further purification.

A solution of MCPBA (ca. 80%, 1.1 g, 5.1 mmol) in CH_2Cl_2 (10 ml) was added to a mixture of crude sulfides (2.68 g) in CH_2Cl_2 (20 ml) at −78 °C and stirred for 1 h. The reaction mixture was poured into 10% $Na_2S_2O_3$ solution and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (6/1) gave **18** (1.53 g, 60% in two steps) and its regioisomer **18′** (0.43 g, 17% in two steps).

$n_D^{27}=1.5069$. $[\alpha]_D^{27}$ −2.6 (*c* 1.0, $CHCl_3$). IR (film): $\nu=1714$, 1087, 1047, 1006, 836, 776, 747 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): $\delta=-0.36$, −0.11, −0.02, 0.02, 0.11, 0.22 (total 6H, 6 singlets), 0.53 (3H, q, $J=4.1$ Hz), 0.58 (3H, q, $J=4.1$ Hz), 0.75–1.0 (18H, m), 1.35–1.7 (2H, m), 1.8–2.8 (5H, m), 3.5–3.7 (2H, m), 4.0–4.15 (2H, m), 7.45–7.55 (4H, m), 7.65–7.7 (1H, m). FAB-HRMS *m/z* calcd for $C_{26}H_{47}O_4SSi_2$ $[M+H]^+$ 511.2734, found 511.2758.

3.2.13. (4*S*,5*R*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-6-[(*S*)-5-tetrahydropyranyloxyhexyl]-5-(2-triethylsilyloxyethyl)cyclohex-2-en-1-one (19). To a solution of diisopropylamine (463 μl, 3.30 mmol) in THF (25 ml) was added 1.56 M solution of *n*-BuLi (2.1 ml, 3.3 mmol) in hexane dropwise at −20 °C and stirred for 45 min under argon. This mixture was cooled down to −60 °C, a solution of ketosulfoxide **18** (675 mg, 1.32 mmol) in THF (4 ml) was slowly added to this mixture (the color of reaction mixture was immediately changed to orange). After stirring for 5 min, iodide **7** (478 mg, 1.53 mmol) was added to the mixture at −60 °C and stirring was kept for 30 min until the orange color was changed to pale yellow. The reaction mixture was poured into saturated NH_4Cl solution and extracted with ether. The organic layer was washed with 1 N HCl, saturated $NaHCO_3$ solution and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (6/1–4/1) gave a crude oil (590 mg). This crude product was used for the next reaction without further purification.

A mixture of crude product (590 mg), $CaCO_3$ (0.5 g, 5 mmol) and toluene (20 ml) was stirred at 100 °C for 2 h. The reaction mixture was filtered through Celite® and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (15/1) gave **19** (354 mg, 47% in two steps) as a slightly yellow oil. $n_D^{27}=1.4773$. $[\alpha]_D^{24}$ +147 (*c* 1.0, $CHCl_3$). IR (film): $\nu=$ 1680, 1254, 1108, 1022, 837, 773 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): $\delta=0.11$ (6H, s), 0.57 (6H, q, $J=$ 7.8 Hz), 0.90 (9H, s), 0.94 (9H, t, $J=7.8$ Hz), 1.10 (1.5H, d, $J=6.0$ Hz), 1.21 (1.5H, d, $J=6.0$ Hz), 1.2–1.7 (15H, m), 1.75–1.8 (1H, m), 1.95–2.1 (1H, m), 2.25–2.4 (1H, m), 2,45–2.6 (1H, m), 3.45–3.55 (1H, m), 3.64 (2H, t, $J=$ 9.9 Hz), 3.65–3.95 (1H, m), 4.65–4.8 (2H, m), 5.82 (1H, d, $J=9.9$ Hz), 6.63 (1H, d, $J=9.9$ Hz). FAB-HRMS *m/z* calcd for $C_{31}H_{61}O_5Si_2$ $[M+H]^+$ 569.4058, found 569.4055.

3.2.14. (4*S*,5*R*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-(2-hydroxyethyl)-6-[(*S*)-5-tetrahydropyranyloxyhexyl]-cyclohex-2-en-1-one (20). To a solution of TES ether **19** (685 mg, 1.20 mmol) in acetonitrile (40 ml) was added 0.23 N HF (1 ml) at room temperature and stirred for 15 min. The reaction mixture was diluted with ether, washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (2/1) gave **20** (538 mg, 98%) as a colorless oil.

$n_D^{27}=1.4842$. $[\alpha]_D^{24}$ +99 (*c* 1.0, $CHCl_3$). IR (film): $\nu=3486$, 1680, 1112, 1022, 837, 774, 668 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): $\delta=0.15$ (6H, s), 0.93 (9H, s), 1.10 (1.5H, d, $J=$ 6.0 Hz), 1.21 (1.5H, d, $J=6.0$ Hz), 1.3–1.95 (15H, m), 2.02 (1H, m), 2.25–2.35 (1H, m), 2.45–2.5 (1H, m), 3.45–3.55 (1H, m), 3.6–3.8 (3H, m), 3.8–3.95 (1H, m), 4.6–4.7 (1H, m), 4.75–4.8 (1H, m), 5.85 (1H, d, $J=9.0$ Hz), 6.64 (1H, d, $J=9.0$ Hz). FAB-HRMS *m/z* calcd for $C_{25}H_{47}O_5Si$ $[M+H]^+$ 455.3193, found 455.3193.

3.2.15. {(1*R*,2*S*,6*R*)-2-(*tert*-Butyldimethylsilyloxy)-6-[(*S*)-5-tetrahydropyranyloxyhexyl]-5-oxocyclohex-3-en-1-yl}acetaldehyde (21). To a solution of alcohol **20** (770 mg, 1.69 mmol) in CH_2Cl_2 (20 ml) was added Dess–Martin periodinane (1.08 g, 2.54 mmol) at 0 °C and stirred for 1 h under argon. The reaction mixture was poured into 10% $Na_2S_2O_3$ solution and extracted with ether. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (10/1–2/1) gave **21** (641 mg, 84%) as a colorless oil.

$n_D^{27}=1.4837$. $[\alpha]_D^{28}$ +118 (*c* 1.0, $CHCl_3$). IR (film): $\nu=$ 1726, 1680, 1109, 1023, 773 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): $\delta=0.10$ (3H, s), 0.13 (3H, s), 0.90 (9H, s), 1.11 (1.5H, d, $J=6.0$ Hz), 1.22 (1.5H, d, $J=6.0$ Hz), 1.25–1.85 (14H, m), 2.2–2.45 (2H, m), 2.8–2.95 (2H, m), 3.45–3.55 (1H, m), 3.65–3.8 (1H, m), 3.8–4.95 (1H, m), 4.6–4.65 (0.5H, m), 4.65–4.7 (0.5H, m), 4.75–4.8 (1H, m), 5.87 (1H, d, $J=7.8$ Hz), 6.61 (1H, d, $J=7.8$ Hz), 9.77 (1H, t, $J=$ 1.2 Hz). FAB-HRMS *m/z* calcd for $C_{25}H_{45}O_5Si$ $[M+H]^+$ 453.3036, found 453.3065.

3.2.16. {(1*R*,2*S*,6*R*)-2-(*tert*-Butyldimethylsilyloxy)-6-[(*S*)-5-tetrahydropyranyloxyhexyl]-5-oxocyclohex-3-en-1-yl}acetic acid (22). To a solution of aldehyde **21** (600 mg, 1.33 mmol) and 2-methyl-2-butene (2 ml) in *tert*-BuOH (15 ml) was added a solution of $NaH_2PO_4\cdot 2H_2O$ (1.04 g, 6.65 mmol) and $NaClO_2$ (0.24 g, 2.66 mmol) in water

(15 ml) at 0 °C and stirred for 1 h. The reaction mixture was poured into 10% $Na_2S_2O_3$ solution and extracted with ethyl acetate. The organic layer was washed with 0.1 N HCl and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (2/1) gave **22** (557 mg, 90%) as a colorless oil.

$n_D^{27}=1.4856$. $[\alpha]_D^{28}$ +131 (*c* 1.0, $CHCl_3$). IR (film): $\nu=$ 1711, 1679, 1466, 1385, 1255, 1109, 1024 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): $\delta=0.12$ (3H, s), 0.13 (3H, s), 0.91 (9H, s), 1.10 (1.5H, d, $J=6.0$ Hz), 1.21 (1.5H, d, $J=$ 6.0 Hz), 1.25–1.85 (14H, m), 2.15–2.3 (1H, m), 2.49 (1H, m), 2.7–2.85 (2H, m), 3.45–3.55 (1H, m), 3.65–3.8 (1H, m), 3.85–4.0 (1H, m), 4.6–4.7 (1H, m), 4.74 (1H, m), 5.88 (1H, d, $J=9.0$ Hz), 6.63 (1H, d, $J=9.0$ Hz). FAB-HRMS *m/z* calcd for $C_{25}H_{45}O_6Si$ $[M+H]^+$ 469.2985, found 469.2990.

3.2.17. {(1*R*,2*S*,6*R*)-2-(*tert*-Butyldimethylsilyloxy)-6-[(*S*)-5-hydroxyhexyl]-5-oxocyclohex-3-en-1-yl}acetic acid (23). To a solution of THP ether **22** (150 mg, 0.32 mmol) in ether (6 ml) was added $MgBr_2\cdot Et_2O$ (248 mg, 0.96 mmol) at 0 °C under argon. The reaction mixture was stirred at room temperature for 2 h and poured into saturated NH_4Cl solution. Water was added to the mixture until dark red precipitate was completely dissolved and the resulting solution was extracted with EtOAc. The organic layer was washed with 0.1 N HCl and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with chloroform–methanol (50/1) gave **23** (128 mg, quant.) as a slightly yellow oil.

$n_D^{27}=1.4883$. $[\alpha]_D^{26}$ +88 (*c* 1.0, $CHCl_3$). IR (film): $\nu=3454$, 1713, 1681, 1253, 1101, 837, 779 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): $\delta=0.12$ (3H, s), 0.13 (3H, s), 0.91 (9H, s), 1.18 (3H, d, $J=6.0$ Hz), 1.25–1.75 (8H, m), 2.22 (1H, dd, $J=16.5$, 7.8 Hz), 2.51 (1H, m), 2.7–2.85 (2H, m), 3.81 (1H, m), 4.75 (1H, m), 5.88 (1H, d, $J=9.9$ Hz), 6.63 (1H, d, $J=9.9$ Hz). FAB-HRMS *m/z* calcd for $C_{20}H_{37}O_5Si$ $[M+H]^+$ 385.2410, found 385.2421.

3.2.18. *O*-(*tert*-Butyldimethylsilyl)Sch 642305 (24). Triethylamine (15 mg, 0.15 mmol) and 2,4,6-trichlorobenzoyl chloride (19 µl, 0.13 mmol) were added to a solution of the hydroxy acid **23** (40 mg, 0.10 mmol) in THF (1 ml). The reaction mixture was stirred at room temperature for 3 h and then filtered through Celite® under argon. The resultant solution was added slowly using syringe pump to a refluxing solution of DMAP (244 mg, 2.00 mmol) in dry toluene (100 ml) over 14 h. After the addition was complete, the reaction mixture was stirred for additional 1 h and concentrated in vacuo. The residue was dissolved in ether and washed with 1 N HCl, saturated $NaHCO_3$ solution and brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (20/1) gave **24** (28 mg, 73%) as colorless crystals and a small amount of dimeric lactone (5 mg).

Mp 104–106 °C. $[\alpha]_D^{27}$ +56 (*c* 1.0, $CHCl_3$). IR (Nujol): $\nu=1722$, 1671, 1255, 1163, 1088, 1036 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): $\delta=0.08$ (3H, s), 0.11 (3H, s), 0.88 (9H, s), 1.09 (1H, m), 1.26 (3H, d, $J=6.6$ Hz), 1.34 (1H, m), 1.5–1.7 (4H, m), 2.0–2.3 (2H, m), 2.4–2.9 (4H, m), 4.23 (1H, m), 5.09 (1H, m), 5.97 (1H, d, $J=9.9$ Hz), 6.85 (1H, dd, $J=9.9$, 5.7 Hz). FAB-HRMS *m/z* calcd for $C_{20}H_{35}O_4Si$ $[M+H]^+$ 367.2305, found 367.2297.

3.2.19. Sch 642305 (1). A mixture of 1.01 M solution of TBAF in THF (600 µl, 0.6 mmol) and acetic acid (36 mg, 0.6 mmol) was added to a solution of TBS ether **24** (20 mg, 0.05 mmol) in THF (1.5 ml) and stirred at room temperature for 3 h under argon. The reaction mixture was poured into saturated NH_4Cl solution and extracted with ether. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by preparative TLC [hexane–ether (3/1)] and recrystallization from acetone–hexane to give **1** (12 mg, 87%) as colorless needles.

Mp 151–153 °C. $[\alpha]_D^{29}$ +74 (*c* 0.50, CH_3OH). IR (KBr): $\nu=$ 3472, 2933, 1703, 1659, 1255, 1201, 1083, 874 cm^{-1}. ^1H NMR (500 MHz in CD_3OD): $\delta=1.08$ (1H, ddd, $J=14.0$, 10.5, 3.8 Hz), 1.2–1.4 (3H, m), 1.27 (3H, d, $J=6.7$ Hz), 1.54 (1H, m), 1.83 (1H, m), 2.05–2.2 (2H, m), 2.53 (1H, dd, $J=16.8$, 11.5 Hz), 2.64 (1H, dt, $J=11.5$, 3.8 Hz), 2.67 (1H, dd, $J=16.8$, 2.4 Hz), 2.81 (1H, ddt, $J=3.5$, 2.4, 11.5 Hz), 4.21 (1H, dd, $J=5.6$, 3.5 Hz), 5.05 (1H, m), 5.96 (1H, d, $J=$ 9.9 Hz), 7.02 (1H, dd, $J=9.9$, 5.6 Hz). ^{13}C NMR (125 MHz in CD_3OD): $\delta=18.6$, 22.6, 24.2, 30.8, 37.9, 39.9, 47.8, 67.2, 74.7, 130.7, 149.5, 173.8, 202.4. FAB-HRMS *m/z* calcd for $C_{14}H_{21}O_4$ $[M+H]^+$ 253.1440, found 253.1444.

3.2.20. 6-*epi*-Sch 642305 (25). Partial epimerization at C-6 position was observed under the several conditions for the deprotection of TBS ether **24**. Treatment of **24** with *p*-toluenesulfonic acid in MeOH or KF and 18-crown-6 in acetonitrile gave about 1:1 mixture of **1** and **25**. Treatment of **24** with Dowex®-50 in MeOH gave approximately 3:1 mixture of **1** and **25**. These isomers were easily separated by preparative TLC [hexane–ether (3/1)]. The structure of **25** was confirmed by NOE experiments. NOEs were observed between 4-H, 5-H and 6-H.

^1H NMR (500 MHz in CD_3OD): $\delta=0.8$–1.15 (2H, m), 1.25–1.65 (3H, m), 1.28 (3H, d, $J=6.6$ Hz), 1.87 (1H, m), 2.0–2.25 (2H, m), 2.09 (1H, dd, $J=17.1$, 12.3 Hz), 2.36 (1H, dt, $J=12.3$, 3.3 Hz), 2.84 (1H, dd, $J=17.1$, 2.4 Hz), 3.32 (1H, m), 4.90 (1H, m), 5.04 (1H, m), 5.99 (1H, dd, $J=$ 10.2, 2.7 Hz), 6.67 (1H, dt, $J=10.2$, 1.8 Hz). FAB-HRMS *m/z* calcd for $C_{14}H_{21}O_4$ $[M+H]^+$ 253.1440, found 253.1444.

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