Stereocontrolled Synthesis of *C*-Arylglycosides Applied to the South West Fragment of the Antibiotic Kendomycin

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Received 8 August 2002; revised 25 September 2002

Abstract: A nine step synthesis of the southwest fragment **3** of the antibiotic kendomycin (**1**) is reported. The tetrahydropyran ring is prepared in a highly stereocontrolled and efficient sequence. The key step concerns an *anti*-aldol reaction using chiral ketone **10**. *C*-Aryl glycoside **3** exhibits atropisomerism and the relative configuration around its tetrahydropyran ring was established by NOE experiments.

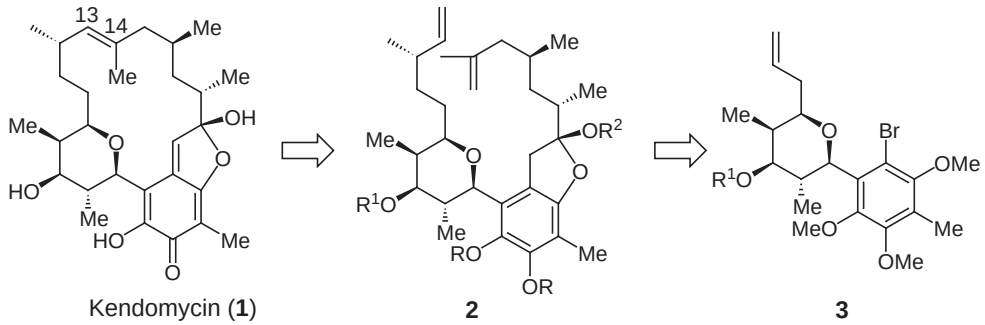
Key words: total synthesis, natural products, aldol reactions, glycosides, atropisomerism, antibiotics

Kendomycin [(–)-TAN 2162] (**1**), a polyketide produced from various *Streptomyces* species, was recently reported as a potent endothelin receptor antagonist and anti-osteoporotic compound.[1] Recently antibacterial activity and cytotoxic properties were also described.[2] This structurally unique polyketide features a quinone methide chromophore connected to a highly substituted tetrahydropyran ring with an aliphatic *ansa* chain. The remarkable pharmacological activity as well as the unique molecular architecture encouraged us to study the synthesis of **1**.

As presented in an earlier report,[3] our synthetic plan (Scheme 1) is centered around a ring closing metathesis for macrocyclization (C13/C14) of intermediate **2** as a late step in the sequence. Further disconnection of intermediate **2** gives **3** as a precursor of **1**. In this paper we describe a stereocontrolled synthesis of key fragment **3**, which structurally represents a *C*-aryl glycoside[4] with no less than five stereogenic centers along with a fully substituted highly oxygenated aryl ring.

The synthesis started from the known ester **4**,[3] which after bromination, subsequent hydrolysis, methylation and formylation led to aldehyde **7**[5] and dichloro compound **6** (which can be converted into **7** in an overall yield of 89%). In our first approach, aldehyde **7** was added to the known ketone **8**[6] using *anti*-aldol conditions [(*c*-$C_6H_{11})_2$BCl–Et_3N],[7] leading to the *anti*-aldol product **9** with 86% yield and a low diastereoselectivity (1.5:1) (Scheme 2). Since the diastereoselectivity of this aldol addition was even worse than the one in our first approach[3] it was necessary to develop a new, and hopefully more stereocontrolled route.

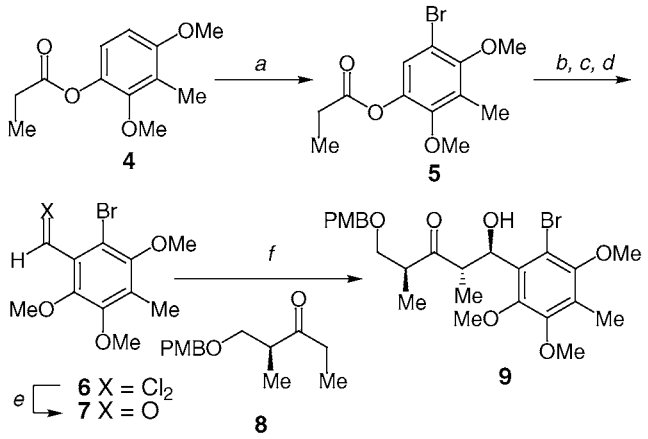
Thus, we used Evans aldol methodology with chiral β-keto imide **10**[8] as the aldol donor. Enolization of **10** and reaction with aldehyde **7** afforded the *anti*-aldol aduct **11** in 97% yield and high diastereoselectivity (ds > 98%) (Scheme 3). Subsequent *anti*-selective reduction with $Me_4NBH(OAc)_3$ gave diol **12** with ds 90:10. On treatment with a catalytic amount of DBU and in situ protection with TPSCl, lactone **13** was obtained. The introduction of the upper aliphatic chain was achieved via addition of allylmagnesium bromide to **13** to form the corresponding lactol, which was, without any further purification, reduced to tetrahydropyran **3** with Et_3SiH in the presence of $SnCl_4$. As a side product of the reduction desilylated product **14** (27% yield) was formed which was reprotected to give **3** in a combined yield of 90%.



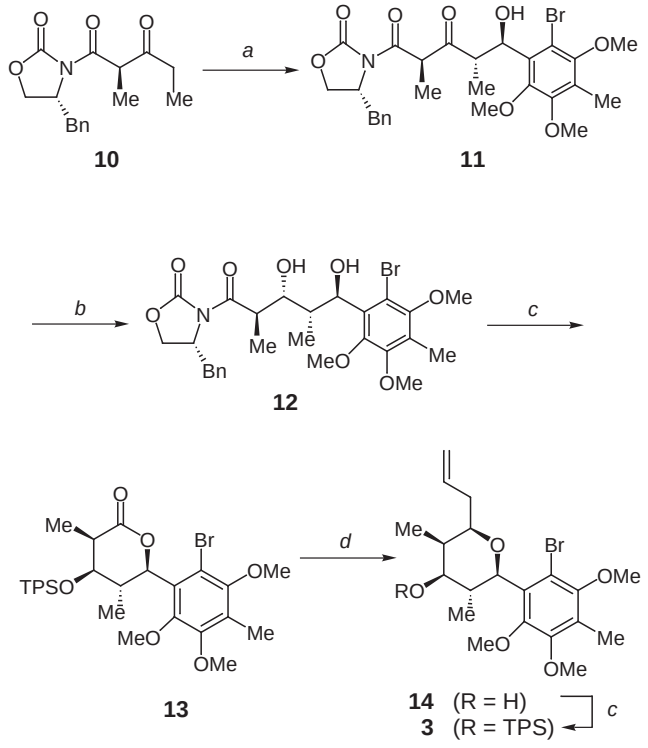
Scheme 1 Retrosynthetic plan of Kendomycin (**1**)

Synthesis 2002, No. 18, Print: 19 12 2002.
Art Id.1437-210X,E;2002,0,18,2766,2770,ftx,en;T09202SS.pdf.

ISSN 0039-7881



Scheme 2 *Reagents and conditions*: a) NBS (1.3 equiv), MeCN, r.t., 3 h, 97%; b) KOH (2 equiv), MeOH, H_2O, r.t., 1.5 h, 99%; c) Me_2SO_4 (2.4 equiv), K_2CO_3 (2.9 equiv), acetone, r.t., 17 h, 93%; d) $CHCl_2OMe$ (1.4 equiv), $SnCl_4$ (1.3 equiv), 0 °C, 7.5 h, 72%; e) DMF–NaOH (1 N) (1:1), 2 h, 100 °C, 72%; f) $(c\text{-}C_6H_{11})_2BCl$ (1.5 equiv), Et_3N (2 equiv), **8** (1.5 equiv), Et_2O, –78 °C, 86%, dr 1.5:1.



Scheme 3 *Reagents and Conditions*: a) $(c\text{-}C_6H_{11})_2BCl$ (1.6 equiv), NEt_2Me (1.8 equiv), Et_2O, 0 °C, 2 h, add **7**, –78 to 0 °C over 2 h, 97%, ds > 98%; b) $(Me)_4NBH(OAc)_3$ (3 equiv), MeCN–HOAc (1:1), –40 °C to r.t., 3.5 h, 63%, ds 90:10; c) DBU (0.05 equiv), CH_2Cl_2, r.t., 1.5 h; imidazole (1.2 equiv), TPSCl (1.1 equiv), r.t., overnight, 65% (over two steps); d) CH_2=$CHCH_2MgBr$ (3 equiv), THF, –78 °C, 2.5 h; Et_3SiH (10 equiv), $SnCl_4$ (1 equiv), –78 °C to –25 °C, 3 h, 60% (over 2 steps).

Lactone **13** and compounds **3** and **14** form mixtures of atropisomers, as a consequence of the hindered rotation around the arylic sp^2–sp^3 bond. This issue was observed in the tetrahydropyran ring system previously synthesized.[3]

In the case of the secondary alcohol **14**, separation of the atropisomers by means of chromatographic separation and crystallisation was not successful. Also ^{1}H NOE experiments were carried out to assign the configuration of the tetrahydropyran ring in **3** (Figure 1). The interaction of 1-H with 3-H and 5-H, and interaction of 4-Me with 2-H, as well as the coupling constant $J_{1,2}$ of 9.6 Hz corroborated the configuration attributed to **3**.

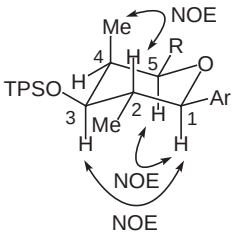


Figure 1 Assignment of the stereochemistry of **3** – NOE experiments

All moisture sensitive reactions were carried out under argon. Anhyd solvents were obtained as follows: THF distilled from sodium–benzophenone ketyl; Et_2O distilled from $LiAlH_4$; acetone, CH_2Cl_2 and DMF distilled from P_2O_5; Et_3N distilled from CaH_2. All other solvents were HPLC grade. Column chromatography was performed with Merck silica gel (0.04–0.63 μm, 240–400 mesh) under low pressure. TLC was carried out with E. Merck silica gel 60-F254 plates. Mps were determined on a Leica Galen III apparatus and are uncorrected. IR spectra were recorded using a Perkin–Elmer 1600 Series FTIR spectrometer and are reported in wave numbers (cm^{-1}). Optical rotations were measured on a P 341 Perkin–Elmer polarimeter. NMR spectra were recorded on either a Bruker Avance DPX 250 MHz, or a Bruker Avance DRX 600 MHz spectrometer. Unless otherwise stated, all NMR spectra were measured in $CDCl_3$ solutions and referenced to the residual $CHCl_3$ signal (^{1}H, δ = 7.26; ^{13}C, δ = 77.0). All ^{1}H and ^{13}C shifts are given in ppm (s = singlet; d = doublet; t = triplet; q = quadruplet; m = multiplet; br s = broad signal). Coupling constants *J* are given in Hz; assignments of proton resonances were confirmed, when possible, by selective homonuclear decoupling experiments or by correlated spectroscopy. Mass spectra were measured on a Micro mass, trio 200 Fisions Instruments. HRMS were performed with a Finnigan MAT 8230 with a resolution of 10000. Elemental analyses were recorded on a Perkin–Elmer-240-Elementaranalyser.

Propionic Acid 5-Bromo-2,4-dimethoxy-3-methylphenyl Ester (5)

NBS (1.07 g, 6.03 mmol) was added to a solution of **4** (1.00 g, 4.46 mmol) in absolute MeCN (20 mL) and stirred for 3 h. The solvent was removed by evaporation and the residue was treated with of CCl_4 (20 mL), whereby the precipitate was removed by filtration and the mother liquid was concentrated and dried in vacuum.

Yield: 1.32 g (97%) (without purification); slightly yellow oil; R_f 0.59 (SiO_2; hexane–EtOAc, 3:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.03 (s, 1 H, ArH), 3.72 (s, 3 H, OMe), 3.67 (s, 3 H, OMe), 2.53 (q, *J* = 7.6 Hz, 2 H, CH_2), 2.18 (s, 3 H, ArMe), 1.20 (t, *J* = 7.6 Hz, 3 H, *Me*CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 154.2, 150.6, 140.9, 128.1, 124.6, 111.5, 61.1, 60.8, 27.9, 10.7, 9.5.

MS (EI, 70 eV): *m/z* = 302 (11) $[M]^+$, 246 (100) $[M - CH_3CH_2CO]^+$, 231 (42) $[M - CH_3 - CH_3CH_2CO]^+$.

HRMS (60 °C, 70 eV): *m*/*z* calcd for $C_{12}H_{15}O_4Br$: 302.0154; found: 302.0163.

Anal. Calcd for $C_{12}H_{15}BrO_4$: C, 47.54; H, 4.99. Found: C, 47.70; H, 5.01.

The bromide **5** from the reaction above (486 mg, 1.60 mmol) was dissolved in MeOH (1 mL) under argon atmosphere, cooled to 0 °C and KOH (183 mg, 3.20 mmol) dissolved in MeOH (1 mL) was added. After 1.5 h, HCl (2 N, 8 mL) and Et_2O (6 mL) were added and the aq layer was extracted with Et_2O (4 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, evaporated and dried under high vacuum.

Yield: 393 mg (99%); slightly yellow oil.

Spectroscopic data are consistent with those in ref.[9]

The phenol from above (45.8 g, 0.19 mol) was dissolved in anhyd acetone and dimethyl sulfate (43.9 mL, 0.46 mol), and K_2CO_3 (76.8 g, 0.56 mol) was added. The reaction mixture was stirred for 17 h, then the K_2CO_3 was filtered off and the acetone was evaporated. The yellow oil was dissolved in Et_2O (500 mL), and ammonia (25%; 500 mL) was added. After 10 min stirring the aq layer was extracted with Et_2O (3 × 200 mL) and the combined organic layers were washed with H_2O (300 mL), HCl (1 N; 300 mL), sat. aq NaCl (300 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The methylated product was isolated without any further purification.

Yield: 45.0 g (93%); yellow oil.

Spectroscopic data are consistent with those in ref.[10]

2-Bromo-3,5,6-trimethoxy-4-methylbenzaldehyde (7) and 1-Bromo-2-dichloromethyl-3,4,6-trimethoxy-5-methylbenzene (6)

The methylated bromide from the previous reaction (3.00 g 11.5 mmol) and dichloromethyl methyl ether (1.43 mL, 15.8 mmol) was dissolved in anhyd CH_2Cl_2 at 0 °C. Tin tetrachloride (14.9 mmol, 14.9 mL of a 1 M solution in CH_2Cl_2) was added slowly within 20 min. The reaction mixture was stirred for 7.5 h, then CH_2Cl_2 (60 mL) and ice (30 g) were added, and the mixture was stirred for 1.5 h while it was allowed to warm up to r.t. The mixture was extracted with Et_2O (3 × 50 mL), washed with sat. aq NaCl, dried ($MgSO_4$), filtered and evaporated to give a black oil which was purified by column chromatography (silica gel; hexane–EtOAc, 15:1) to give the aldehyde **7** (2.02 g, 61%) and 1-bromo-2-dichloromethyl-3,4,6-trimethoxy-5-methylbenzene (**6**) (1.19 g, 30%) as a byproduct. Compound **6** (1.19 g, 3.46 mmol) was hydrolysed to the desired aldehyde in DMF–aq NaOH (1 N) (1:1; 15 mL) for 2 h at 100 °C. After cooling down to r.t., the mixture was diluted with H_2O (50 mL) and extracted with Et_2O (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated. After column chromatography more aldehyde **5** [725 mg (72%)] could be obtained.

Aldehyde 7

R_f 0.33 (SiO_2; hexane–EtOAc, 6:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.35 (s, 1 H, CHO), 6.82 (s, 1 H, ArH), 2.89 (s, 3 H, OMe), 2.86 (s, 3 H, OMe), 2.84 (s, 3 H, OMe), 2.20 (s, 3 H, ArMe).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.73, 152.90, 152.39, 133.75, 129.25, 127.37, 113.83, 62.61, 60.90, 60.86, 11.18.

MS (EI, 70 eV): *m*/*z* = 290 (100) $[M]^+$, 275 (66) $[M - CH_3]^+$, 260 (14), $[M - 2 \times CH_3]$ 247 (25) $[M - CH_3 - CHO]^+$.

HRMS (20 °C, 70 eV): *m*/*z* calcd for $C_{11}H_{13}O_4{}^{79}Br$: 288.9997; found: 288.0005.

Anal. Calcd for $C_{11}H_{13}BrO_4$: C, 45.70; H, 4.53. Found: C, 45.62; H, 4.52.

Compound 6

R_f 0.40 (SiO_2; hexane–EtOAc, 6:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.3 (br s, 1 H $CHCl_2Ar$), 3.87 (s, 6 H, OMe), 3.78 (s, 3 H, OMe), 2.30 (s, 3 H, ArMe).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.73, 149.20, 139.53, 125.20, 118.64, 115.78, 61.45, 61.02, 60.94, 60.72, 10.61.

MS (EI, 70 eV): *m*/*z* = 343 (65) $[M]^+$, 325 (60) $[M - CH_3]^+$, 309 (56) $[M - Cl]^+$, 394 (31) $[M - Cl - CH_3]$.

Anal. Calcd for $C_{11}H_{13}BrCl_2O_3$: C, 38.40; H, 3.81. Found: C, 38.34; H, 3.79.

5-Benzyloxy-1-(2-bromo-3,5,6-trimethoxy-4-methylphenyl)-1-hydroxy-2,4-dimethylpentan-3-one (9)

$BCl(C_6H_{11})_2$ (1.27 mmol; 1.28 mL, 1.0 M in hexane) and Et_3N (0.24 mL, 1.70 mmol) was stirred in anhyd Et_2O (3 mL) at –78 °C for 15 min. Afterwards ketone **8** (200 mg, 0.85 mmol) was added in 0.5 mL of Et_2O within 5 minutes and the temperature was allowed to warm up to –35 °C within 1.5 h. The temperature was kept at –35 °C for another 1.5 h until aldehyde **7** (367 mg, 1.27 mmol) was added in Et_2O (0.8 mL) at –81 °C within 30 min. After 18 h stirring at –78 °C the reaction was quenched with KH_2PO_4 buffer (20 mL, 1 M, pH 7.0) and extracted with Et_2O (3 × 20 mL). The organic phase was dried (Na_2SO_4), filtered and the solvent was evaporated. The crude product was stirred with $NaBO_3$ (391 mg, 2.54 mmol) in H_2O–THF (1:1; 3.6 mL) for 15 h to cleave the boron complex. The mixture was diluted with H_2O (5 mL) and extracted with Et_2O (3 × 15 mL). The organic layer was dried (Na_2SO_4), filtered and the solvent was evaporated. The residue was purified by column chromatography (silica gel; hexane–EtOAc, 5:1) to give **9** as a mixture of diastereomers (60:40).

Yield: 391 mg (88%).

Separation by HPLC of the desired major product delivered an analytically pure sample.

R_f 0.13 (SiO_2, hexane–EtOAc, 5:1); $[\alpha]_D^{20}$ + 0.2 (*c* 1.53 $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (d, *J* = 8.2 Hz, 2 H, ArH), 6.78 (d, *J* = 8.2 Hz, 2 H, ArH), 5.43 (t, *J* = 9.3 Hz, 1 H, ArC*H*OH), 4.39 (d, *J* = 11.5 Hz, 1 H, ArCH*H*O), 4.34 (d, *J* = 11.5 Hz, 1 H, ArC*H*HO), 3.84 (s, 3 H, OMe), 3.72 (s, 3 H, OMe), 3.71 (s, 3 H, OMe), 3.68 (s, 3 H, OMe), 3.61 (t, *J* = 8.3, 1 H, OH), 3.30–3.50 m, 3 H, OCH_2CHMe and C*H*Me), 3.02 (q, *J* = 6.8, 1 H, C*H*Me), 2.17 (s, 3 H, $ArCH_3$), 1.07 (d, *J* = 7.1, 1 H, CH*Me*), 0.82 (d, *J* = 6.8, 1 H, CH*Me*).

^{13}C (100 MHz, $CDCl_3$): δ = 216.42, 159.58, 151.84, 149.34, 130.55, 129.64, 127.21, 114.14, 73.42, 72.43, 61.47, 60.67, 60.36, 55.64, 47.22, 15.66, 14.10, 13.85, 10.53.

MS (EI, 70 eV): *m*/*z* = 525 (0.2) $[M]^+$, 508 (15) $[M - OH]^+$, 427 (4), 372 (55), 288 (84), 236 (33), 121 (100) $[MeOPhCH_2]^+$.

HRMS (60 °C, 70 eV): *m*/*z* calcd for $C_{25}H_{31}O_6{}^{79}Br$: 506.1304; found: 506.1321.

Anal. Calcd for $C_{24}H_{31}BrO_6$: C, 58.19; H, 6.31. Found: C, 58.35; H, 6.30.

(2*R*,4*S*,5*R*)-1-[(4*R*)-Benzyl-2-oxo-oxazolidin-3-yl]-5-(2-bromo-3,5,6-trimethoxy-4-methylphenyl)-5-hydroxy-2,4-dimethylpentane-1,3-dione (11)

$B(C_6H_{11})_2Cl$ (4.44 mL, 4.44 mmol, 1 M in hexane) was added to a solution of ketone **10** (1.00 g, 3.46 mmol) in anhyd Et_2O (24 mL) under argon at 0 °C. Then $NEtMe_2$ (0.48 mL, 5.00 mmol) was added slowly and the mixture was stirred for 2 h at 0 °C. The slightly yellow suspension thus formed was cooled to –78 °C and a solution of 2-bromo-3,5,6-trimethoxy-4-methylbenzaldehyde (**7**) (0.80 g, 2.77 mmol) in anhyd Et_2O (2.4 mL) was added via canula. The resulting mixture was allowed to warm up to 0 °C over 2 h and was

quenched by the addition of aq $NaHCO_3$ (5%; 50 mL). The mixture was stirred for 10 min and then diluted with CH_2Cl_2 (50 mL). The layers were separated and the aq layer washed with CH_2Cl_2 (2 × 50 mL). The organic layers were collected, dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel; hexane–EtOAc, gradient 9:1→2:1). Aldol adduct **11** was obtained as a white foam.

Yield: 1.54 g (97%); ds = 98%; R_f 0.10 (SiO_2; hexane–EtOAc, 5:1); $[\alpha]_D^{20}$ –107.0 (*c* 1.73 CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.20 (m, 5 H, ArH), 5.49 (t, 1 H, *J* = 9.3 Hz, C*H*OH), 5.11 (q, 1 H, *J* = 7.0 Hz, COCCH$_3$*H*CO), 4.78–4.71 (m, 1 H, NCH), 4.28 (t, 1 H, *J* = 9.0 Hz, OC*H*$_2$CHN), 4.21 (dd, 1 H, *J* = 2.5, 8.8 Hz, OC*H*$_2$CHN), 3.96 (s, 3 H, ArOMe), 3.79 (s, 3 H, ArOMe), 3.74 (s, 3 H, ArOMe), 3.64–3.62 (m, 1 H, COC*H*CH$_3$CHOH), 3.32 (dd, 1 H, *J* = 3.2, 13.3 Hz, C*H*$_2$Ph), 2.81 (dd, 1 H, *J* = 9.5, 13.3 Hz, C*H*$_2$Ph), 2.23 (s, 3 H, ArMe), 1.54 (d, 3 H, *J* = 7.0 Hz, COC*H*$_3$CO), 0.93 (d, 3 H, *J* = 7.0 Hz, COC*H*$_3$CHOH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.0, 170.6, 154.2, 151.8, 149.3, 135.4, 129.8, 129.4, 129.3, 127.8, 127.6, 127.3, 66.7, 61.5, 60.6, 60.4, 53.1, 52.8, 38.3, 15.0, 13.8, 10.5.

MS (EI, 70 eV): *m*/*z* = 579 (3) $[M]^+$, 400 (67) [M – BnCHNHCOOCH$_2$ + H]$^+$, 290 (100) [ArCHOH + H]$^+$, 92 (93) $[Bn]^+$.

HRMS (170 °C, 70 eV): *m*/*z* calcd for $C_{27}H_{32}O_8N^{79}Br$: 579.1345; found: 579.1332.

Anal. Calcd for $C_{27}H_{32}BrNO_8$: C, 56.06; H, 5.58; N, 2.42. Found: C, 56.22; H, 5.60; N, 2.42.

(2*R*,3*R*,4*R*,5*R*)-{(4*R*)-Benzyl-3-[5-(2-bromo-3,5,6-trimethoxy-4-methylphenyl)-3,5-dihydroxy-2,4-dimethylpentanoyl]oxazolidin-2-one} (12)

A solution of $(CH_3)_4NBH(OCOCH_3)_3$ (1.60 g, 6.08 mmol) in MeCN–HOAc (1:1; 1.5 mL) was slowly added via canula to a solution of **11** (1.20 g, 2.07 mmol) in MeCN–HOAc (1:1; 7 mL) at –40 °C. After the addition, the temperature was allowed to warm up to –20 °C within 2 h. Then the bath was replaced by an ice bath and the temperature was slowly warmed up to r.t. within 1.5 h. Then the reaction was diluted with CH_2Cl_2 (50 mL) and quenched by addition of sat. aq Na/K-tartrate (50 mL), while stirring vigorously. Then solid $NaHCO_3$ was added until the gas evolution was over. The resulting mixture was stirred overnight at r.t., then the layers were separated and the aq layer was washed with CH_2Cl_2 (3 × 50 mL). The organic layers were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure to give a colourless oil that was purified by column chromatography (silica gel; hexane–EtOAc, 1:1) to give compound **12**.

Yield: 754 mg (63%); white foam; ds 88%; R_f 0.43 (SiO_2; hexane–EtOAc, 1:1); $[\alpha]_D^{20}$ –36.1 (*c* 1.73 CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (m, 5 H, Ph*H*), 5.11 [t, 1 H, *J* = 10.4 Hz, ArC*H*(OH)], 4.59–4.54 (m, 1 H, PhCH$_2$C*H*), 4.43–4.39 [m, 1 H, CH(Me)C(OH)*H*CH(Me)], 4.11–4.10 (m, 2 H, CH$_2$C*H*CH$_2$Ph), 4.00 [t, 1 H, *J* = 7.2 Hz, COC(Me)*H*], 3.86 (s, 3 H, ArO*Me*), 3.70 (s, 3 H, ArO*Me*), 3.66 (s, 3 H, ArO*Me*), 3.58 (br s, 1 H, OH), 3.18 (dd, 1 H, *J* = 3.28, 13.3 Hz, CHC*H*$_2$Ph), 2.48 (dd, 1 H, *J* = 9.5, 13.3 Hz, CHC*H*$_2$Ph), 2.58 (d, 1 H, *J* = 5.3 Hz, OH), 2.16 (s, 3 H, Ar*Me*), 1.35 (d, 3 H, *J* = 6.8 Hz, CO*Me*CO), 0.70 (d, 3 H, *J* = 7.0 Hz, CO*Me*CHOH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.4, 151.8, 150.7, 150.2, 147.5, 134.0, 132.3, 128.5, 128.0, 126.4, 125.3, 101.7, 71.1, 68.6, 59.9, 59.2, 58.9, 53.9, 43.5, 40.4, 36.6, 13.6, 9.7, 9.0.

MS (EI, 70 eV): 402 (52) [M – BnCHNHCOOCH$_2$ + H]$^+$, 289 (52) [ArCHOH]$^+$, 92 (100) $[Bn]^+$.

HRMS (200 °C, 70 eV): *m*/*z* calcd for $C_{27}H_{34}O_8N^{79}Br$: 581.1453; found: 581.1465.

Anal. Calcd for $C_{27}H_{34}BrNO_8$: C, 55.87; H, 5.90; N, 2.42. Found: C, 55.99; H, 5.88; N, 2.41.

(5*S*,3*R*,4*R*,6*R*)-6-(2-Bromo-3,5,6-trimethoxy-4-methylphenyl)-3,5-dimethyl-4-triphenylsilanyloxytetrahydropyran-2-one (13)

DBU (8.46 μL, 0.06 mmol) was added to a solution of the diol (**12**) (0.71 mg, 1.22 mmol) in CH_2Cl_2 (16 mL) under argon. The resulting mixture was stirred at r.t. for 1.5 h until the starting material was consumed. Imidazole (100 mg, 1.47 mmol) and chlorotriphenylsilane (406 mg, 1.37 mmol) were added and the reaction mixture was stirred at r.t. overnight. The reaction was quenched by addition of sat. aq NH_4Cl (30 mL) and the aq layer was washed with CH_2Cl_2 (3 × 30 mL). The organic layers were collected, dried ($MgSO_4$), filtered and the solvent was evaporated at reduced pressure. The remaining crude oil was purified by column chromatography (silica gel; hexane–EtOAc, 5:1) to give lactone **13** after crystallisation from hexane–Et_2O as a mixture of atropisomers (1: 0.66). Only the major atropisomer was assigned.

Yield: 522 mg (65%); colourless crystals; mp 69–70 °C; R_f 0.31 (SiO_2; hexane–EtOAc, 5:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.64 (m, 6 H, ArH), 7.46–7.35 (m, 9 H, ArH), 5.39 (d, 1 H, *J* = 11.1 Hz, CHAr), 3.84 (s, 3 H, ArOMe), 3.83 (s, 3 H, ArOMe), 3.72 (s, 3 H, ArOMe), 3.60–3.55 (m, 1 H, CHOTPS), 3.00–2.94 (m, 1 H, C*H*CH$_3$CHAr), 2.83–2.75 (m, 1 H, COC*H*Me), 2.23 (s, 3 H, ArMe), 1.25 (d, 3 H, *J* = 7.3 Hz, CH*Me*CO), 0.70 (d, 3 H, *J* = 7.0 Hz, CH*Me*CHAr).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.0, 135.9, 135.3, 134.4, 134.3, 130.6, 130.5, 128.3, 128.2, 82.8, 78.2, 61.5, 60.6, 60.3, 45.5, 40.6, 15.4, 15.0, 10.6.

MS (EI, 70 eV): *m*/*z* = 660 (11) $[M]^+$, 259 (32) $[TPS]^+$, 199 (92), 96 (100).

HRMS (240 °C, 70 eV): *m*/*z* calcd for $C_{35}H_{37}O_6Si^{79}Br$: 660.1543; found: 660.1427.

Anal. Calcd for $C_{35}H_{37}BrO_6Si$: C, 63.53; H, 5.64. Found: C, 63.64; H, 5.65.

(5*S*,3*S*,4*S*,6*R*,2*R*)-[2-Allyl-6-(2-bromo-3,5,6-trimethoxy-4-methylphenyl)-3,5-dimethyltetrahydropyran-4-yloxy]triphenylsilane (3) and (5*S*,3*S*,4*S*,6*R*,2*R*)-2-Allyl-6-(2-bromo-3,5,6-trimethoxy-4-methylphenyl)-3,5-dimethyltetrahydropyran-4-ol (14)

Allylmagnesium bromide (0.9 mL; 0.9 mmol, 1 M in Et_2O) was added to a solution of lactone **13** (200 mg, 0.30 mmol) in anhyd THF (1.8 mL) at –78 °C. After stirring for 2.5 h, the reaction was quenched by addition of sat. aq NH_4Cl (1 mL) and allowed to warm up to r.t. After extraction with Et_2O (3 × 20 mL) the organic layers were collected, dried ($MgSO_4$), filtered and the solvent was evaporated at reduced pressure. A crude brown oil (214 mg) was obtained, which was dissolved in CH_2Cl_2 (2 mL) under argon atmosphere, and Et_3SiH (0.48 mL, 3.00 mmol) was added. The mixture was cooled to –78 °C and $SnCl_4$ (40.0 μl, 0.34 mmol) was added, whereby the colour of the mixture changed from colourless to yellow. The temperature was slowly allowed to warm up to –60 °C within 1 h and then to –25 °C within 2 h. The reaction was quenched by addition of H_2O (2 mL) and HCl (1 M; 1 mL). The layers were separated and the aq layer was washed with CH_2Cl_2 (3 × 20 mL) and Et_2O (3 × 20 mL). The organic layers were collected and dried ($MgSO_4$), filtered and the solvent was evaporated at reduced pressure. The brown oil collected was purified by column chromatography (silica gel; hexane–EtOAc, 7:1). Compound **3** was crystallized from hexane–Et_2O to give a mixture of atropisomers (1:0.33) along with the deprotected product **14** which was isolated as a mixture of atropisomers (1:0.35). In both cases only the major atropisomers were assigned.

Compound 3

Yield: 125 mg (60%); colourless crystals; mp 124–125 °C; R_f 0.43 (SiO_2; hexane–EtOAc, 7:1).

IR (neat): 2962, 2933, 2850, 1456, 1429, 1400, 1375 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.66 (m, 6 H, ArH), 7.44–7.35 (m, 9 H, ArH), 5.97–5.87 (m, 1 H, C*H*=CH_2), 5.07–4.98 (m, 2 H, CH=CH_2), 4.57 (d, 1 H, *J* = 9.5 Hz, OCHAr), 3.88 (s, 3 H, ArOMe), 3.86 (s, 3 H, ArOMe), 3.70 (s, 3 H, ArOMe), 3.22–3.07 [m, 2 H, *H*C(CH_2CHCH_2) and HCOTPS], 2.71–2.62 (m, 1 H, C*H*MeCHAr), 2.47–2.42 (m, 1 H, CH_2CH=CH_2), 2.31–2.25 (m, 1 H, CH_2CH=CH_2), 2.22 (s, 3 H, ArMe), 1.87–1.86 [m, 1 H, C*H*MeCH(OTPS)], 0.80 [d, 3 H, *J* = 6.3 Hz, CH*Me*C(CH_2CH=CH_2)], 0.60 (d, 3 H, *J* = 6.3 Hz, CH*Me*CHAr).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.0, 151.7, 150.3, 136.0, 135.2, 130.9, 130.1, 128.2, 128.1, 126.8, 126.6, 116.6, 115.8, 112.6, 83.2, 79.9, 77.1, 43.1, 41.7,38.0,15.1,14.7,10.5.

MS (EI, 70 eV): *m*/*z* = 686 (17) $[M]^+$, 345 (38) $[MeCHCHOTP\text{-}SCHMe]^+$, 259 (100) $[TPS]^+$, 199 (29).

HRMS (120 °C, 70 eV): *m*/*z* calcd for $C_{38}H_{43}O_5SiBr$: 686.2063; found: 686.2084.

Anal. Calcd for $C_{39}H_{43}BrO_5$: C, 69.74; H, 6.45. Found: C, 69.77; H, 6.45.

Compound 14

Yield: 35.5 mg (27% yield); mp 79–80 °C; R_f 0.19 (SiO_2; hexane–EtOAc, 7:1).

^1H NMR (400 MHz, $CDCl_3$): δ = 6.02–5.99 (m, 1 H, C*H*=CH_2), 5.08–4.99 (m, 2 H, CH=CH_2), 4.74 (d, 1 H, *J* = 10.3 Hz, OCHAr), 3.83 (s, 3 H, ArOMe), 3.81 (s, 3 H, ArMe), 3.75 (s, 3 H, ArOMe), 3.33–3.26 [m, 1 H, C*H*(CH_2CH=CH_2)], 3.04–2.97 [m, 1 H, C*H*(OH)], 2.64–2.26 (m, 3 H, C*H*MeCHAr and CH_2CH=CH_2), 2.23 (s, 3 H, ArMe), 1.06–1.50 [m, 1 H, C*H*MeCH(OH)], 1.03 [d, 3 H, *J* = 6.5 Hz, CH*Me*C(CH_2CH = CH_2)], 0.80 (d, 3 H, *J* = 6.8 Hz, CH*Me*CHAr).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.4, 150.4, 148.9, 133.9, 130.3, 125.6, 115.4, 114.5, 81.9, 80.1, 78.8, 60.4, 60.0, 59.0, 41.7, 40.4, 36.4, 12.3, 12.1, 9.1.

MS (EI, 70 eV): *m*/*z* = 429 (100) $[M + 1]^+$, 428 (21) $[M]^+$, 273 (67), 250 (25), 222 (26).

HRMS (110 °C, 70 eV): *m*/*z* calcd for $C_{20}H_{28}O_5{}^{79}Br$: 428.1188; found: 428.1202.

Anal. Calcd for $C_{20}H_{29}BrNO_5$: C, 56.95; H, 6.81. Found: C, 56.04; H, 6.82.

Acknowledgment

Financial support (project P14729-CHE) by the Austrian Science Fund (FWF) and by Fundação para a Ciência e Tecnologia (SFRH/PBD/3561/2000) (Lisbon, Portugal) is gratefully acknowledged.

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