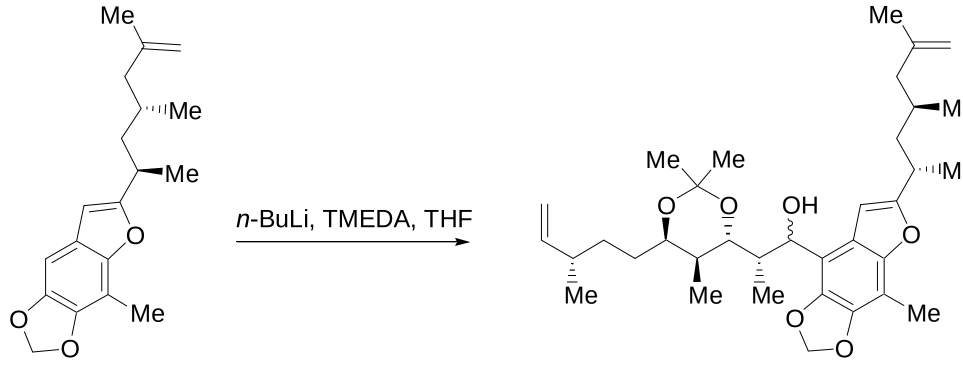
A Novel Approach Towards the Synthesis of Kendomycin: Selective Synthesis of a C-Aryl Glycoside as a Single Atropisomer by the Proper Choice of Protecting Group

Stefan Pichlmair, Maria M. B. Marques, Martin P. Green, Harry J. Martin and Johann Mulzer*

General Experimental

All moisture sensitive reactions were carried out under argon. Anhydrous THF was distilled from sodium/benzophenone ketyl. 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. Optical rotations were measured on a P 341 Perkin-Elmer polarimeter. NMR spectra were recorded on either a Brucker Avance DPX 250 MHz/400 MHz or 600 MHz spectrometer. Unless otherwise stated, all NMR spectra were measured in $CDCl_3$ solutions and referenced to the residual $CHCl_3$ signal (^1H, δ = 7.26; ^{13}C, δ = 77.0). All ^1H 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. High resolution mass spectra (HRMS) were performed with a Finnigan MAT 8230 with a resolution of 10000.

(*S*)-1-(6-((2*S*,4*S*)-4,6-dimethylhept-6-en-2-yl)-4-methylbenzofuro[6,5-d][1,3]dioxol-8-yl)-2-((4*R*,5*S*,6*R*)-2,2,5-trimethyl-6-((*S*)-3-methylpent-4-enyl)-1,3-dioxan-4-yl)propan-1-ol



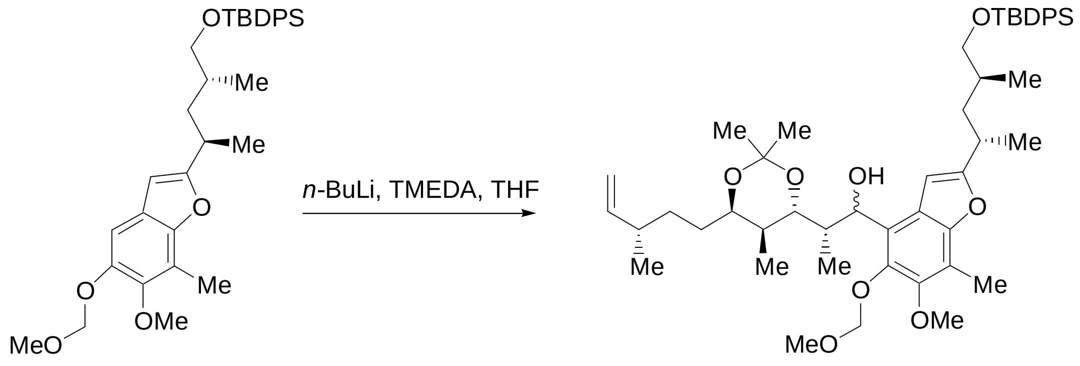
5a **25**

Benzofuran **5a** (547 mg, 1.822 mmol, 3 equ.) was dissolved in 2.5 mL of dry THF and freshly distilled TMEDA (271 µL, 1.822 mmol, 3 equ.) was added at ambient temperature. The solution was cooled to –40°C and *n*-Buli (1.14 mL, 1.82 mmol, 3 equ.) was added. In case of

4a after 3.5 hours at –30° the solution was cooled to –78°C and aldehyde **4** (163 mg, 0.607 mmol) was addet by cannula as a solution in 1.8 mL of dry THF. The reaction mixture was warmed up to –25°C over two hours and finally quenched with saturated ammonium chloride solution. The reaction mixture was extracted with diethylether (3 x 20 mL), dried over $MgSO_4$, filtered and the solvent was evaporated at reduced pressure. The yellow oil collected was purified by column chromatography (silica gel, hexane/EtOAc 80:1 to 10:1) yielding 318 mg (92%) of a colourless oil as the coupled product **25**.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.19 (s, 1H), 5.68 (d, *J* = 1.2 Hz, 1H), 5.63 (d, *J* = 1.2 Hz, 1H), 5.50-5.39 (m, 1H), 4.74-4.62 (m, 3H), 4.5-4.45 (bs, 1H), 4.41-4.38 (bs, 1H), 3.54-3.48 (m, 2H), 2.93 (bs, 1H), 2.74 (q, *J* = 7.41, 1H), 2.09 (s, 3H), 1.86 (dd, *J* = 7.3 Hz, 11.6 Hz, 1H), 1.80-1.94 (m, 2H), 1.80-1.95 (m, 1H), 1.67-1.53 (m, 2H), 1.52-1.40 (m, 1H), 1.41 (s, 3H), 1.36-1.12 (m, 6H), 1.10 (s, 6H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.75 (d, *J* = 6.75 Hz, 3H), 0.60 (d, *J* = 6.6 Hz, 3H), 0.57 (d, *J* = 7.1 Hz, 3H), 0.56 (d, *J* = 6.57 Hz, 3H); **^{13}C-NMR ($CDCl_3$, 100.6 MHz):** δ [ppm] = 163.3, 149.5, 145.0, 140.6, 138.7, 120.2, 113.7, 113.0, 112.0, 103.3, 101.1, 101.0, 100.8, 75.3. 72.3, 70.2, 46.6, 41.3, 38.1, 36.2, 33.2, 31.6, 30.1, 28.7, 28.6, 25.7, 24.3, 22.6, 20.4, 19.8, 19.3, 12.7, 11.6, 9.1; **MS (ESI positiv)** *m/z* = 1159.2 (100%, $(2xM+Na)^+$), 591.3 (11%, $(M+Na)^+$); **HRMS (ESI positiv)** *m/z* = 828.4996 (M^+): found: *m/z* = 828.4996 ± 20 ppm (M^+); calc.: *m/z* = 568.3764 (M^+): found: *m/z* = 568.3764 ± 20 ppm (M^+).

(*S*)-1-(2-((2*S*,4*S*)-5-(tert-butyldiphenylsilyloxy)-4-methylpentan-2-yl)-6-methoxy-5-(methoxymethoxy)-7-methylbenzofuran-4-yl)-2-((4*R*,5*S*,6*R*)-2,2,5-trimethyl-6-((*S*)-3-methylpent-4-enyl)-1,3-dioxan-4-yl)propan-1-ol

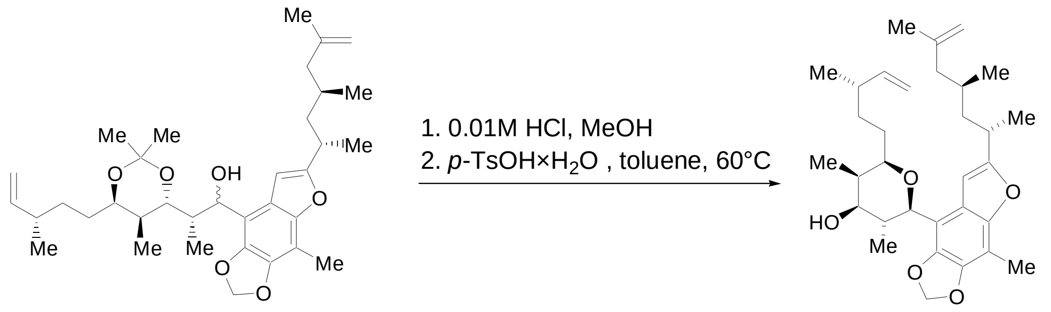


5b **26**

Benzofuran **5b** (11.2 g, 20.0 mmol, 1.09 equ.) was dissolved in 55 mL of dry THF and freshly distilled TMEDA (5.52 mL, 36.6 mmol, 2 equ.) was added at ambient temperature. The solution was cooled to –40°C and *n*-Buli (7.91 mL, 19.8 mmol, 1.08 equ.) was added. In case of **5b** after 1 hours at –30° the solution was cooled to –78°C and aldehyde **4** (4.91 g, 18.3 mmol) was added by cannula as a solution in 25 mL of dry THF. The reaction mixture was warmed up to –25°C within two hours and finally quenched with saturated ammonium chloride solution. The reaction mixture was extracted with diethylether (4 x 150 mL), dried over $MgSO_4$ filtered and the solvent was evaporated at reduced pressure. The yellow oil collected was purified by column chromatography (silica gel, hexane/EtOAc 80:1 to 10:1) yielding 13.8 g (88%) of the coupled product as a colourless oil **26**.

^{1}H-NMR (CDCl$_3$, 400 MHz): (major isomer) δ [ppm] = 7.64-7.53 (m, 4H), 7.23-7.3.8 (m, 6H), 6.50 (s, 1H), 5.62 (ddd, *J* = 17.1 Hz, 10.0 Hz, 7.1 Hz, 1H), 5.13-5.04 (m, 1H), 5.04-4.97 (m, 2H), 4.88 (s, 1H), 4.84 (s, 1H), 4.82 (d, *J* = 10.4 Hz, 1H), 3.68 (s, 3H), 3.56-3.66 (m, 1H), 3.488 (s, 3H), 3.46 (d, *J* = 7.8 Hz, 2H), 3.35 (d, *J* = 5.1 Hz, 1H), 3.17 (d, *J* = 10.4 Hz, 1H), 2.85 (tq, *J* = 7.0 Hz, 7.0 Hz, 1H), 2.30 (s, 3H), 2.26-2.15 (m, 1H), 2.10-1.99 (m, 1H), 1.91-1.25 (m, 8H), 1.20 (s, 6H), 1.17 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 1.00 (s, 9H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 3H), 0.63 (d, *J* = 6.7 Hz, 3H); **^{13}C-NMR (CDCl$_3$, 100.6 MHz):** δ [ppm] = 164.1, 150.6, 147.8, 144.9, 144.4, 136.0, 134.4, 129.9, 128.0, 125.6, 123.4, 114.5, 113.0, 101.9, 100.8, 100.3, 77.6, 74.6, 69.9, 69.1, 61.1, 58.1, 41.4, 39.3, 38.1, 37.0, 33.8, 33.2, 31.6, 27.3, 25.4, 24.0, 20.4, 19.7, 17.4, 12.0, 9.4, 9.2; **MS (EI, 70 eV)** *m/z* = 828.5 (5%, M$^+$), 709.9 (5%), 651.3 (7%), 557.2 (72%), 487.1 (19%), 301.0 (42%), 199.0 (65%), 94.9 (100%); **HRMS (EI, 70 eV)** calc.: *m/z* = 828.4996 (M$^+$): found: *m/z* = 828.4978 ± 0.0036 ppm (M$^+$).

(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(6-((2*S*,4*S*)-4,6-dimethylhept-6-en-2-yl)-4-methylbenzofuro[6,5-d][1,3]dioxol-8-yl)-3,5-dimethyl-6-((*S*)-3-methylpent-4-enyl)-tetrahydro-2H-pyran-4-ol



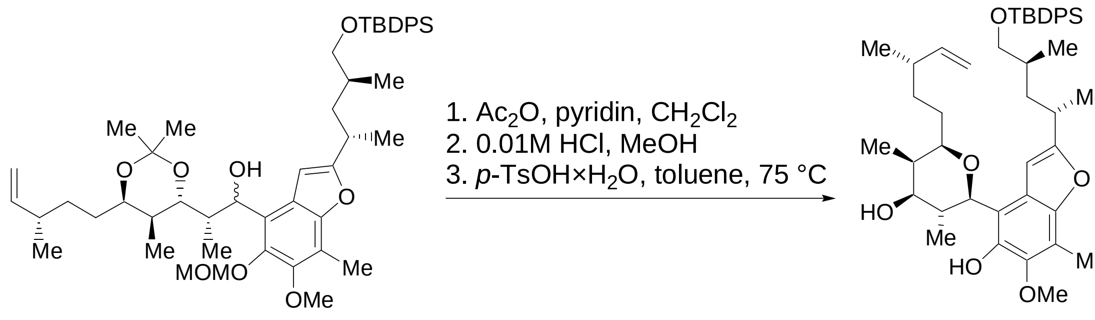
25

2a

Acetonide **25** (55mg, 0.097 mmol) was treated with 0.38 mL of 0.01M HCl in 9 mL of methanol at ambient temperature. After 15 h the reaction mixture was diluted with water and extracted with dichloromethane (4 x 15 mL). The organic layer was dried over MgSO$_4$, filtered and evaporated under reduced pressure. The crude product was dissolved in 3 mL of toluene and *p*-toluenesulfonic acid (1.8 mg, 0.01 mmol) was added at 60°C. After 30 minutes the reaction was stopped by adding sat. NaHCO$_3$ solution. The mixture was extracted with diethylether (3 x 15 mL), dried over MgSO$_4$, filtered and the solvent was evaporated at reduced pressure. The yellow oil collected was purified by column chromatography (silica gel, hexane/EtOAc 5:1) yielding 39 mg (78%) of product **2a** as a colourless oil.

^{1}H-NMR (CDCl$_3$, 600 MHz): δ [ppm] = 6.43-6.32 (m, 1H), 5.95 (s, 1H), 5.88 (d, *J* = 1.1 Hz, 1H), 5.67 (ddd, *J* = 17.3 Hz, 10.2 Hz, 7.4 Hz, 1H), 4.92 (d, *J* = 17.3 Hz, 1H), 4.88 (d, *J* = 10.2 Hz, 1H), 4.74 (s, 1H), 4.66 (s, 1H), 4.29 (d, *J* = 10.1 Hz, 1H), 3.60-3.54 (m, 1H), 3.53-3.48 (m, 1H), 2.99 (tq, *J* = 7.1 Hz, 7.1 Hz, 1H), 2.33 (s, 3H), 2.15-2.05 (m, 2H), 2.00 (t, *J* = 6.3, 1H), 1.87-1.81 (m, 1H), 1.67 (s, 3H), 1.74-1.32 (m, 6H), 1.28 (d, *J* = 6.87, 3H), 1.08 (d, *J* = 6.87, 3H), 0.98 (d, *J* = 6.71, 3H), 0.89-0.85 (m, 3H), 0.80 (2, *J* = 6.4 Hz, 3H); **^{13}C-NMR (CDCl$_3$, 150 MHz):** (because of rotameric effects and therefore broad signals not all signals are visible) δ [ppm] = 146.2, 145.9, 142.6, 114.0, 113.0, 81.09, 78.4, 47.5, 44.3, 39.4, 39.1, 33.8, 32.6, 31.9, 29.6, 23.6, 21.7, 21.6, 20.9, 20.2, 10.1, 7.3; **MS (EI, 70 eV)** *m/z* = 511.1 (20%), **HRMS (EI, 70 eV)** calc.: *m/z* = 510.3345 (M^+): found: *m/z* = 510.3364 ± 20 ppm (M^+).

2-((2*S*,4*S*)-5-(tert-butyldiphenylsilyloxy)-4-methylpentan-2-yl)-4-((2*R*,3*R*,4*S*,5*R*,6*R*)-4-hydroxy-3,5-dimethyl-6-((*S*)-3-methylpent-4-enyl)-tetrahydro-2H-pyran-2-yl)-6-methoxy-7-methylbenzofuran-5-ol



26 **27**

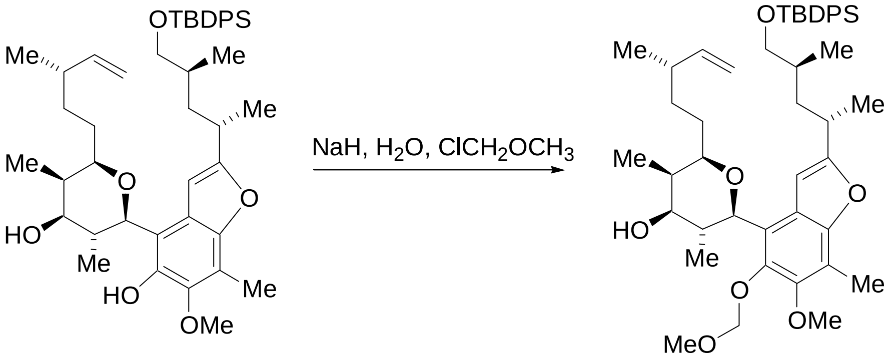
Acetonide **26** (167 mg, 0.20 mmol) was dissolved in 2 mL of dichloromethane and 0.5 mL of pyridine, N-dimethylaminopyridine (2.3 mg, 0.02 mmol, 0.1 equ.) and acetic anhydride (186 µL, 2.00 mmol, 10 equ.) were then added. The reaction mixture was stirred for 20 hours at ambient temperature and finally evaporated to dryness. The product was purified by column chromatography (silica gel, hexane/EtOAc 7:1).

The acetylated product (115 mg, 0.13 mmol) was dissolved in 12 mL MeOH and 0.5 mL of 0.01M HCl was added. After 15 hours solid NaOH (480 mg, 12 mmol, 92 equ.) was added at 0°C in order to give a 0.1M solution. The acetate was cleaved after 1.5 hours and the reaction mixture was neutralised with 0.65 mL conc. HCl solution and extracted with dichloromethane (4 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was dissolved in 4 mL toluene, *p*-toluenesulfonic acid was added and the mixture was heated to 75°C for one hour. The reaction was stopped by adding sat. $NaHCO_3$ solution and the mixture was extracted with dicholoromethane (4 x 30 mL), dried over $MgSO_4$, filtered and the solvent was evaporated at reduced pressure. The yellow oil collected was purified by column chromatography (silica gel, hexane/EtOAc 15:1 to 5:1) yielding 68 mg (71%, 2 steps) of the phenol **27**.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.75 (bs, 1H), 7.62-7.53 (m, 4H), 7.38-7.21 (m, 6H), 6.03 (bs, 1H), 5.63-5.51 (m, 1H), 4.91-4.75 (m, 2H), 4.30 (bs, 1H), 3.77 (bs, 3H), 3.37-3.58 (m, 4H), 2.87 (tq, *J* = 7.01 Hz, *J* = 7.2 Hz, 1H), 2.31 (s, 3H), 2.04 (tq, *J* = 6.8 Hz, *J* = 1.2 Hz, 1H), 1.98-1.91 (m, 1H), 1.77-1.45 (m, 6H), 1.44-1.28 (m, 1H), 1.18 (d, *J* = 4.0 Hz, 3H), 0.99 (s, 9H), 0.90 (d, *J*= 6.8 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.70 (d, *J* = 6.3 Hz, 3H); **^{13}C-NMR ($CDCl_3$, 100.6 MHz):** (because of rotameric effects and therefore broad signals not all signals are visible) δ [ppm] = 164.3, 136.0, 134.4, 129.9, 128.0, 113.2, 80.85, 69.2, 61.2, 39.8, 38.6, 38.0, 33.8, 32.3, 31.6, 30.0, 29.6, 27.3, 21.1, 20.4, 19.6, 20.4, 19.6, 17.3, 14.5, 9.5, 6.3; **MS**

(EI, 70 eV) *m/z* = 726.5 (14%, M^+), 556.3 (7%), 443.1 (4%), 368.3 (9%), 310.1 (13%), 256.2 (16%), 199.0 (51%), 82.9 (46%), 69.0 (66%), 57.0 (96%), 54.9 (100%); **HRMS (EI, 70 eV)** calc.: *m/z* = 726.4316 (M^+): found: *m/z* = 726.4290 ± 0.0036 (M^+); α_D^{20} = 50.7 (c = 0.48, $CHCl_3$).

(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(2-((2S,4S)-5-(tert-butyldiphenylsilyloxy)-4-methylpentan-2-yl)-6-methoxy-5-(methoxymethoxy)-7-methylbenzofuran-4-yl)-3,5-dimethyl-6-((*S*)-3-methylpent-4-enyl)-tetrahydro-2H-pyran-4-ol

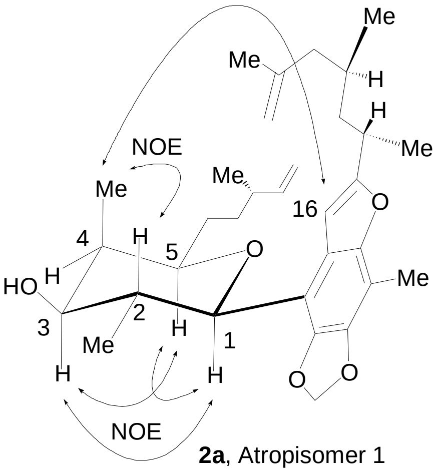


27 **2b**

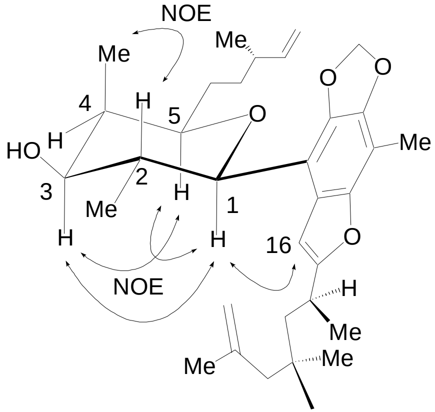
Phenol **27** (60 mg, 0.083 mmol) was dissolved in 200 µL of DMF and a suspension of NaOH (0.33 mL, 0.41 mmol, 5 equ., prepared from 12.5 mmol NaH and 12.5 mmol of H_2O in DMF) was added to the solution at 0°C. The yellow suspension was treated with methoxymethyl chloride (31 µL, 0.41 mmol, 5 equ.) for another hour. The reaction mixture was quenched with saturated ammoniumchloride solution and extracted with diethylether (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Column chromatography was carried out (silica gel, hexane/EtOAc 10:1 to 6:1) yielding 61mg (95%) of **2b** as a colourless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.62-7.50 (m, 4H), 7.89-7.21 (m, 6H), 6.45 (s, 1H), 5.63-5.50 (m, 1H), 5.03 (d, *J* = 5.6 Hz, 1H), 4.97 (d, *J* = 5.6 Hz, 1H), 4.88-4.75 (m, 2H), 4.63 (d, *J* = 10.1 Hz, 1H), 3.71 (s, 3H), 3.59-3.52 (m, 1H), 3.50 (s, 3H), 3.48-3.41 (m, 3H), 2.89 (*J* = 7.2 Hz, 7.11 Hz, 1H), 2.30 (s, 3H), 2.08-1.06 (m, 4H), 1.80-1.32 (m, 6H), 1.46 (s, 3H), 1.20 (d, *J* = 6.6 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.99 (s, 9H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 5.8 Hz, 3H), 0.67 (d, *J* = 6.6 Hz, 3H); **^{13}C-NMR ($CDCl_3$, 100.6 MHz):** δ [ppm] = 164.42, 147.72, 144.84, 136.01, 134.40, 129.90, 127.97, 122.90, 122.16, 115.15, 113.02, 101.12, 100.36, 80.20, 78.64, 78.01, 69.24, 61.15, 58.17, 38.54, 38.00, 37.68, 33.69, 32.86, 31.51, 30.50, 30.08, 27.29, 20.32, 19.73, 19.46, 17.26, 13.49, 9.46, 6.56; **MS (EI 70 eV)** *m/z* = 770.9 (6%, M^+), 556.2 (5%), 528.3 (3%), 285.1 (12%), 284.2 (12%), 256.1 (11%), 239.1 (11%), 199.0 (14%), 97.0 (37%), 82.9 (47%), 69.0 (65%), 57.0 (100%); **HRMS (EI 70 eV)** calc.: *m/z* = 770.4578 (M^+): found: *m/z* = 770,4546 ± 0.0036 (M^+); α_D^{20} = 10.2 (c = 00.62, $CHCl_3$).

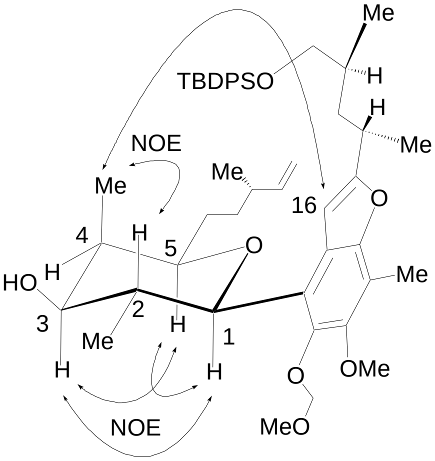
Structural Comparison of Kendomycin with the Observed Atropisomers



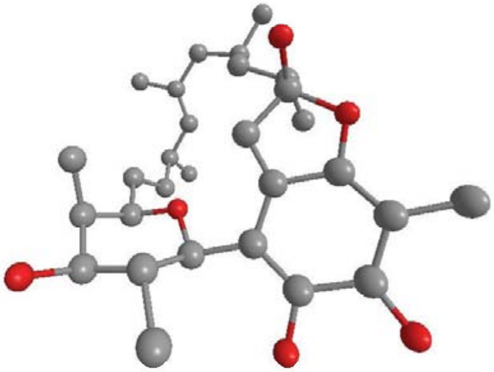
2a, Atropisomer 1



2a, Atropisomer 2



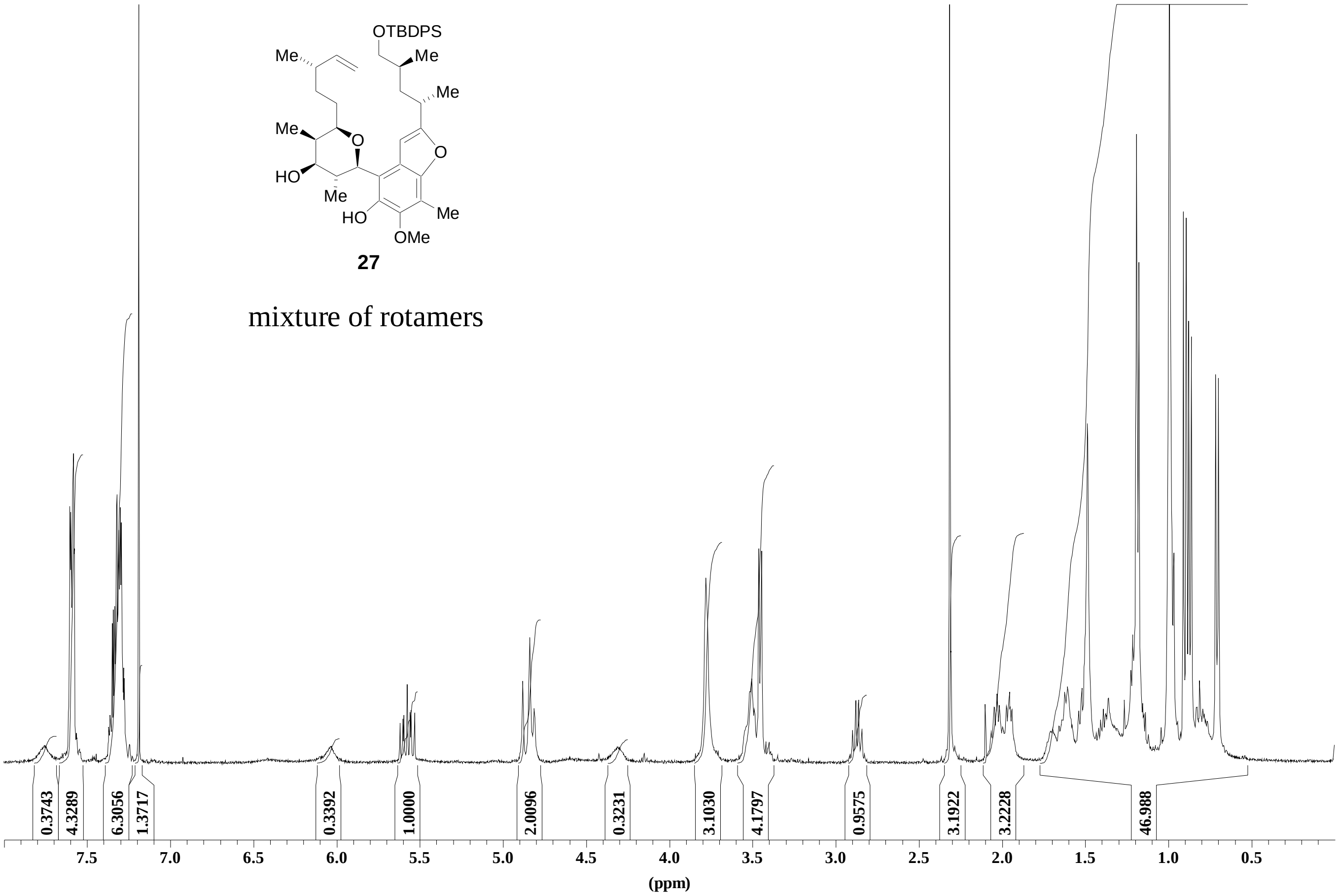
2b



Kendomycin (Crystal Structure)

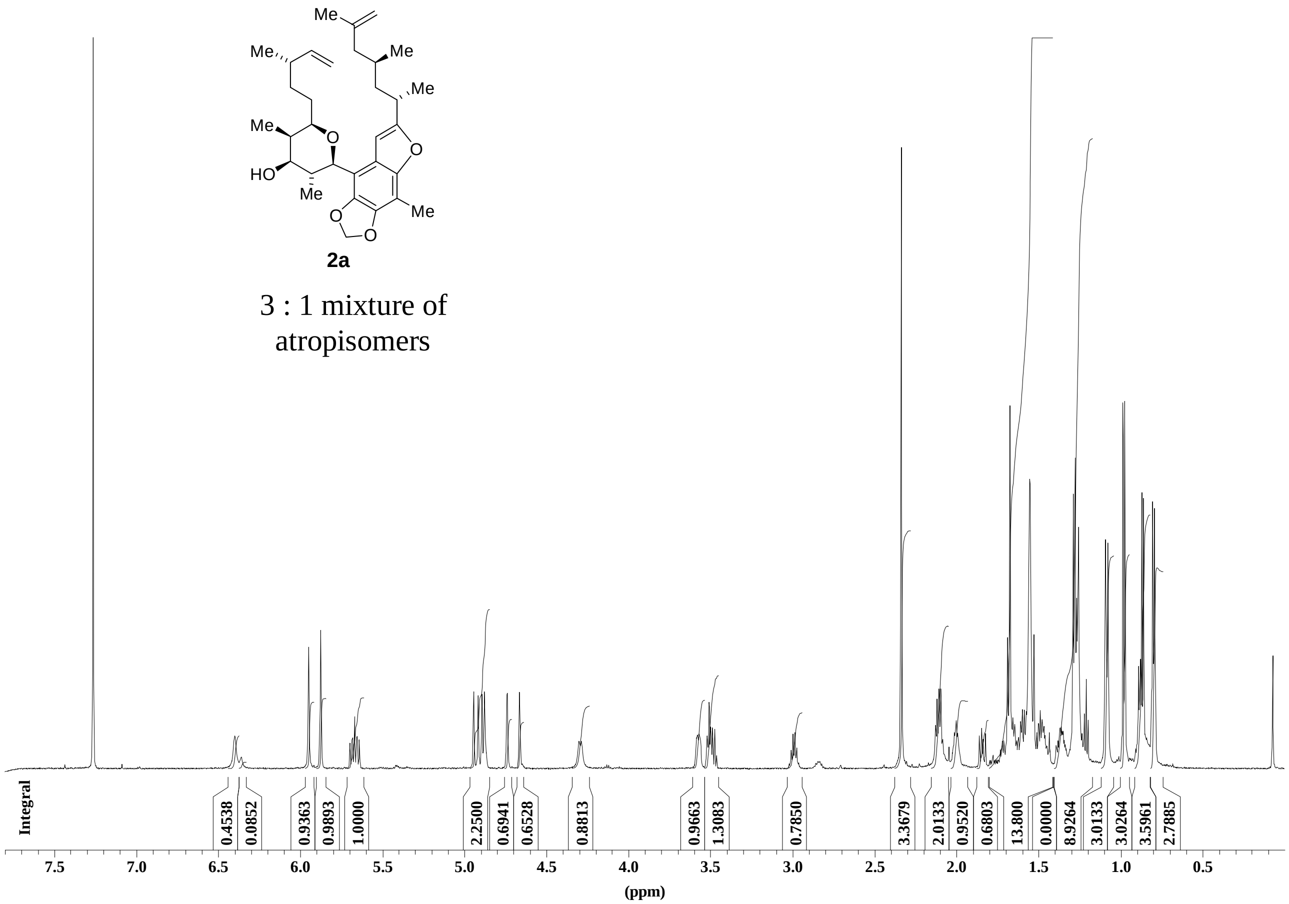
Stereochemical assignment of the two atropisomers and the carbon skeleton of advanced intermediate **2a** and **2b** was performed by HH-COSY, CH-COSY, NOESY and HMBC NMR experiments. Characteristic key correlations observed were depicted for each atropisomer.

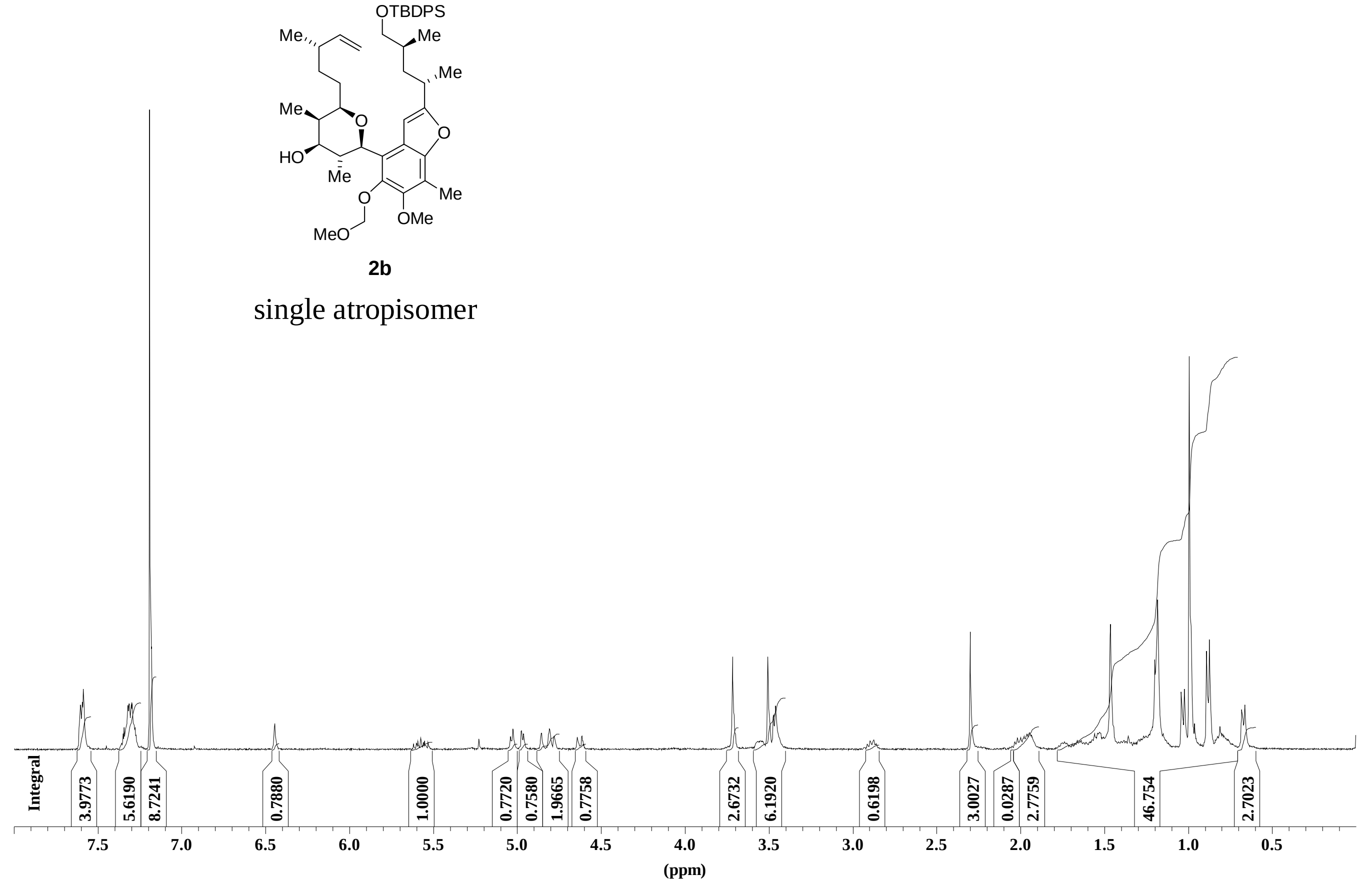
Selected Spectras



2a

3 : 1 mixture of atropisomers





2b

single atropisomer