Synthesis of the C1–C13 Fragment of Kendomycin: Atropisomerism around a C–Aryl Glycosidic Bond**

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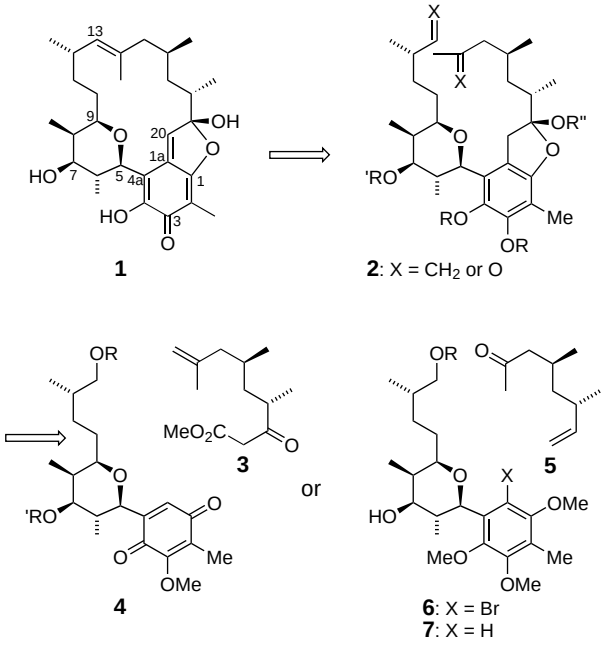
Kendomycin (**1**), a novel ansamycin compound produced from various Streptomyces species, was recently described as a potent endothelin receptor antagonist and anti-osteoporotic compound.[1] Recently, remarkable antibacterial activity and cytostatic effects were also reported.[2] The structure of **1** features an aliphatic carbon ansa chain with a highly substituted tetrahydropyran ring attached to a unique quinone methide chromophore. Its diverse pharmacological activity and the challenging molecular architecture have motivated us to embark on a laboratory synthesis of **1**.

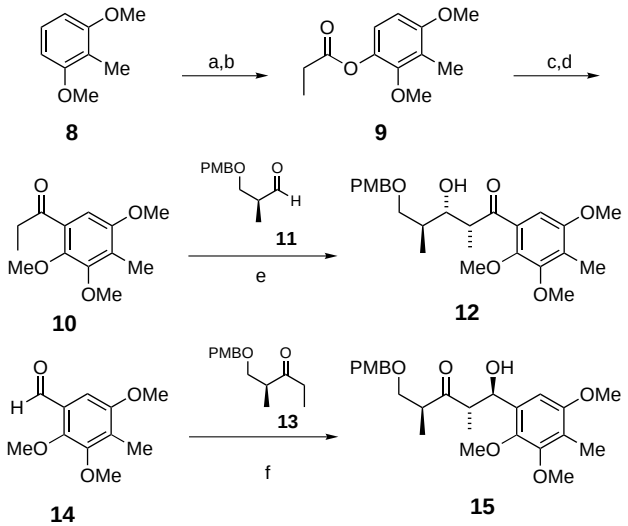
Our synthetic plan (Scheme 1) is centered around a ring-closing metathesis or McMurry reaction for macrocyclization of the seco intermediate **2**, which was either to be assembled



Scheme 1. Retrosynthesis of kendomycin (**1**).

by a Michael addition of keto ester **3** to quinone **4** or by a Heck coupling of alkene **5** and aryl bromide **6**. Herein we report the synthesis of the tetrahydropyran compounds **6** and **7** as well as the observation of a hindered rotation around the C–aryl glycosidic bond. As outlined in Schemes 2 and 3, the C5–C8 stereotetrad (C5–C8) of the tetrahydropyran ring was constructed by aldol addition[3] and diastereoselective reduction of β-hydroxyketones.

In the *syn*-selective aldol addition (Scheme 2) our synthesis started with a Friedel Crafts acylation of dimethoxytoluene (**8**) followed by a Baeyer–Villiger oxidation to deliver phenyl



Scheme 2. a) EtCOCl, $TiCl_4$, benzene, 0 °C, 0.5 h, 96%; b) mCPBA, CH_2Cl_2, RT, 85%; c) BF_3OMe_2, 90 °C, 3 h, 76%; d) $(MeO)_2SO_2$, K_2CO_3, acetone, RT, 40 h, 99%; e) **10**, LiHMDS, −78 °C, THF, 0.75 h, $Ti(OiPr)_3Cl$, −78 → −40 °C, 1 h, −78 °C, addition of **11**, −78 → −40 °C, 3 h, then aq. NH_4F, 58%; f) **13**, NEt_3, $(c\text{-}C_6H_{11})_2BCl$, Et_2O, −78 → −40 °C, −40 °C, 1.5 h, −78 °C, addition of **14**, −78 → 15 °C, 16 h, then $NaBO_3$, 62%. mCPBA = *m*-chloroperbenzoic acid; LiHMDS = lithium hexamethyldisilazanide; PMB = *p*-methoxybenzyl.

propionate **9**. *ortho*-Fries rearrangement and O-methylation gave ketone **10**,[4] which after conversion into the titanium enolate was added to the known aldehyde **11**[5] to furnish *syn* aldol adduct **12** as the main isomer (58%). In the alternative *anti*-selective version, known ketone **13**[6] was converted into the enol borinate and then treated with the known aldehyde **14**[7] to give adduct **15** as the main isomer (62%). Either version affords the main diastereomer stereochemically pure in gram quantities.

Both aldol adducts **12** and **15** gave the same acetonide (**17**) in high yield and diastereoselectivity on diastereoselective reduction[8] with $Me_4NBH(OAc)_3$ (to give *anti*-diol **16**) and subsequent treatment with 2,2-dimethoxypropane (Scheme 3). For configurational assignments keto alcohol **12** was converted into benzylidene acetal **18** and acetonide **19**. The ^1H NMR coupling constants (**18:** $^3J_{7,8} = 10.0$, $^3J_{8,9ax} = 11.2$, $^3J_{8,9eq} = 4.5$ Hz; **19**: $^3J_{5,6} = 2.0$, $^3J_{6,7} = 1.8$ Hz) and NOESY experiments corroborated the relative configurations of C7/C8 in **18** and of C5/C6/C7 in **19**, and hence of the relative and absolute configurations of **12**, **15**, and **17**.

An intramolecular 1,4-addition of the C5-OH group to a C9–C11 enone was used for the construction of the tetrahydropyran ring (Scheme 4).[9] Thus, aldehyde **20**, prepared from **17** in two steps, was coupled with ketophosphonate **21**[10] in a Horner–Wadsworth–Emmons reaction to afford pure (*E*)-enone **22**. On removal of the acetonide with dilute HCl in methanol the free diol underwent the desired Michael-type

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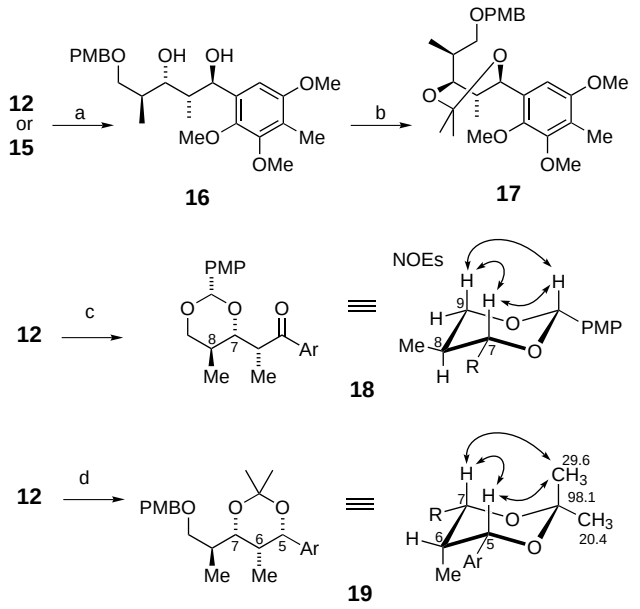
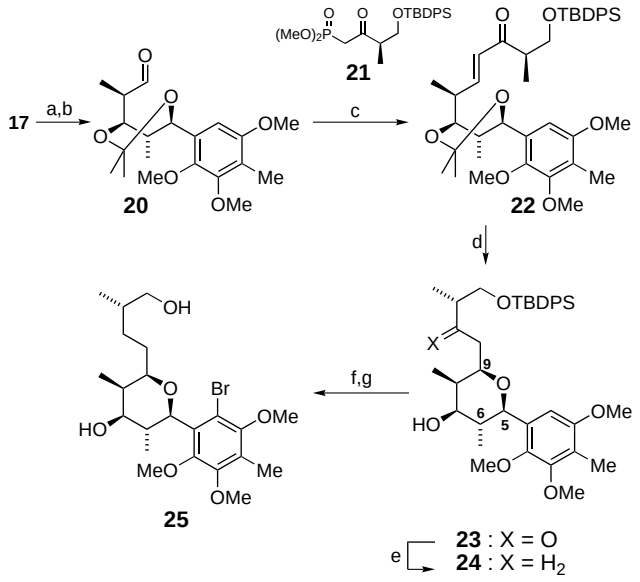


Scheme 3. a) $Me_4NBH(OAc)_3$, MeCN:AcOH (1:1), $-30 \rightarrow 20\,^{\circ}C$, 16 h, 92–95%; b) $(MeO)_2CHMe_2$, RT, 18 h, 88–93%; c) DDQ, 4-Å molecular sieves, CH_2Cl_2, 3 h, 65%; d) 1. $NaBH_4$, EtOH, 0 °C, 0.5 h, 90%, separation of the ca. 1.5:1 mixture of *syn* and *anti* diols; 2. *syn* diol, $(MeO)_2CHMe_2$, CSA (0.1 equiv), 22 °C, 3 h, 92%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; CSA = (+)-camphorsulfonic acid; PMP = *p*-methoxyphenyl. The ^{13}C NMR chemical shifts of the diol protecting group are given for **19**.



Scheme 4. a) DDQ, 4-Å molecular sieves, CH_2Cl_2:pH 7 buffer (15:1), 0.5 h, 83%; b) DMSO, $(COCl)_2$, CH_2Cl_2, $-78\,^{\circ}C$, 1.5 h, then NEt_3, $-78 \rightarrow 0\,^{\circ}C$, 0.25 h; c) **21**, LiOH, Et_2O, 15 min, RT, then addition of **20**, RT, 4 h, 85%; d) MeOH:HCl_{aq}(0.2 M) (5:1), RT, 6 h, 92% (*ds* = 97:3); e) 1. *p*-$TsNHNH_2$, EtOH, 4-Å molecular sieves, reflux, 4 h; 2. $NaCNBH_3$, $ZnCl_2$, EtOH, reflux, 8 h, 65%; f) MeOH:HCl_{aq}(2 M) (5:1), RT, 4 h, 97%; g) NBS, CH_3CN, 40 °C, 12 h, 75%. DMSO = dimethylsulfoxide; *p*-Ts = *p*-toluenesulfonyl; NBS = *N*-bromosuccinimide; TBDPS = *tert*-butyldiphenylsilyl.

cyclization in situ to furnish tetrahydropyran **23**[11] in satisfactory yield (84%) and high diastereoselectivity (*ds* = 97:3). Reduction of the carbonyl group gave intermediate **24**, which was transformed into arene **25**[12] by O-deprotection and aromatic bromination.

The 5,9-*cis* configuration of the tetrahydropyran ring in **23** was assigned by 2D NMR experiments (COSY, HSQC, NOESY) (Figure 1, top). To our surprise, a very broad signal for the benzylic (5-H) and the neighboring proton (6-H), as

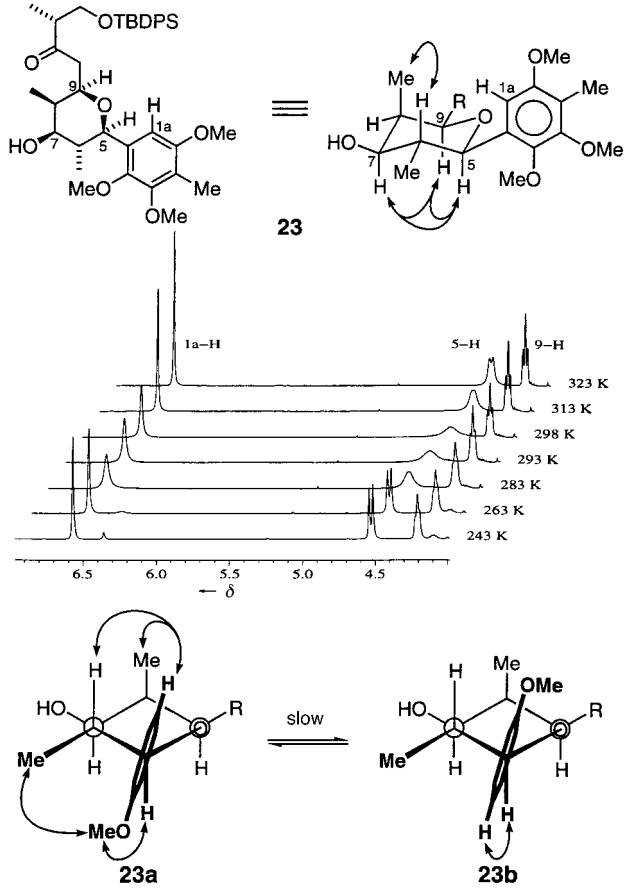


Figure 1. Hindered rotation in compound **23**. Top: structural formulas and indication of the NOEs in the THP unit; middle: NMR spectra of **23** at various temperatures showing the region containing the signals for 1a-, 5-, and 9-H; bottom: NOE interactions of the aromatic *ortho* substituents at $-40\,^{\circ}C$ in the main isomer **23a** and the minor isomer **23b**.

well as a slightly less-broad signal for the aromatic proton (1a-H) was found in both compounds **23** and **24**. In addition, the corresponding signals (C1a, C5, and C6) were missing in the ^{13}C NMR spectra of **23** and **24**. These phenomena were attributed to dynamic effects, and indeed, a temperature-dependent ^1H NMR study of compound **23** (Figure 1, middle) revealed that at lower temperature a second set of signals appeared at lower field, while the benzylic proton (5-H) sharpened to the expected doublet with a *trans*-diaxial coupling constant ($J_{5,6} = 10.7$ Hz). The NOE effects of **23** indicate there is a relatively rigid chairlike conformation, and hence these dynamic effects were assigned to a restricted sp^2–sp^3 rotation,[13] with a coalescence temperature between 15 and 25 °C. The individual rotamers **23a** and **23b**, in which the middle planes of the THP rings and arene planes are almost perpendicular to one another, could be identified from the NOE experiments. Thus, it was concluded that compound **23** exists as a 93:7 equilibrium mixture of the rotamers **23a** and **23b** at $-40\,^{\circ}C$ (Figure 1, bottom). Remarkably, the phenom-

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enon is connected with the configuration at C9; the ^{1}H NMR spectrum of 9-*epi*-**23** showed sharp signals over the entire temperature range. The C9 side chain has to adopt an axial position in 9-*epi*-**23** which could lead to a twist conformation of the dihydopyran ring and hence to a larger degree of rotational freedom for the aryl residue.

The rotational barrier in aryl bromide **25** is considerably increased. Analysis of 2D NMR experiments indicated that **25** exists as a 1:5 mixture of the rotamers **25a** and **25b** (assignment from NOEs, Figure 2, top). In contrast to **23**, the

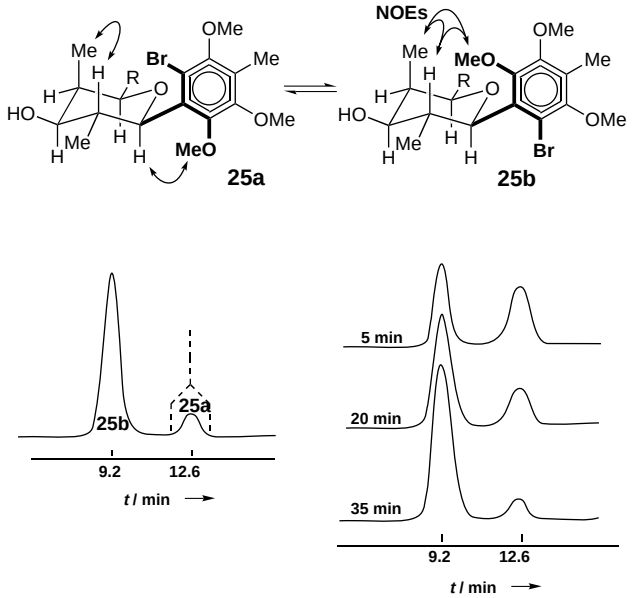

Figure 2. Atropisomerism of compound **25**. Top: NOE interactions in the THP unit of **25a** and **25b**; bottom left: HPLC separation of the rotamers **25a** and **25b**; bottom right: HPLC chromatograms of an pure solution of **15a**, analyzed after the given time intervals.

^{1}H NMR spectrum of **25** did not change with the temperature (up to 100 °C), which suggests that the rotation is too slow to show dynamic NMR effects. Hence, compound **25** should exist as a mixture of two relatively long-lived atropisomers which might be separable by high-pressure liquid chromatography (HPLC). In fact, a base-line separation of **25a** and **25b** was achieved by maintaining the temperature of the HPLC column at 5 °C. The minor isomer **25a** was collected, stored at 0 °C, and reinjected after intervals of 5, 20, and 35 minutes (Figure 2, bottom) to show that the equilibration of the atropisomers **25a** and **25b** was complete at 0 °C within 30 minutes. In view of the abundance of C–aryl glycosides in the realm of natural products[14] this phenomenon is certainly of interest.[15, 16]

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[11] Analytical data of **23**: ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.61$ (dt, $J =$ 1.3, 7.7 Hz, 4H), 7.43–7.38 (m, 2H), 7.37–7.32 (m, 4H), 6.55 (br s, 1H), 4.56–4.25 (br s, 1H), 4.15 (t, $J = 5.9$ Hz, 1H), 3.83–3.77 (m, 1H), 3.80, 3.77, 3.76 (3s, 3 × 3H), 3.69–3.63 (br s, 1H), 3.61 (dd, $J = 5.4$, 10.1 Hz, 1H), 2.88 (dd, $J = 6.5$, 17.4 Hz, 1H), 2.77 (sext., $J = 6.3$ Hz, 1H), 2.65 (dd, $J = 6.3$, 17.4 Hz, 1H), 2.11 (s, 3H), 2.09–2.03 (m, 1H), 1.95–1.75 (br s, 1H), 1.06 (d, $J = 7.1$ Hz, 3H), 0.99 (d, $J = 6.8$ Hz, 3H), 0.98 (s, 9H), 0.78 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (62 MHz, $CDCl_3$): $\delta = 211.2$, 154.8, 145.9, 135.9, 133.7, 131.2, 130.1, 128.1, 121.0, 66.2, 61.7, 60.7, 56.1, 49.4, 45.4, 38.4, 37.8, 27.2, 19.6, 13.7, 13.4, 9.3, 6.5; IR (film) $\tilde{\nu} = 2960$, 2930, 2856, 1714, 1486, 1463, 1428, 1404, 1387, 1361, 1260, 1237, 1189, 1129, 1112, 1086, 1034 cm^{-1}; MS (EI, 70 eV, 190 °C): *m*/*z*: 648, 351, 223, 195; HR-MS (EI, 70 eV, 190 °C): calcd for $C_{38}H_{52}O_7Si$: 648.3482, found: 648.3469; $[\alpha]_D^{20} = +11.5$ ($c = 0.78$, $CHCl_3$).

[12] Analytical data of **25** [minor atropisomer if assignable in brackets]: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.70$ (d, $J = 10.3$ Hz, 1H, 5-H) [4.65, (d, $J = 10.7$ Hz)], 3.86, 3.82, 3.75 (3s, 9H, 3 × OCH_3) [3.79, 3.78, 3.76 (3s)], 3.54–3.59 (m, 4H), 2.58–2.46 (m, 1H, 6-H) [2.74–2.62], 2.23 (s, 3H, $ArCH_3$), 2.02–1.92 (m, 1H, 8-H), 1.68–1.42 (m, 6H), 1.06 (d, $J =$ 6.8 Hz, 3H, 8-CH_3) [1.13 (d, $J = 6.8$ Hz)], 0.92 (d, $J = 6.7$ Hz, 3H, 12-CH_3) [0.91 (d, $J = 6.8$ Hz)], 0.79 (d, $J = 6,5$ Hz, 3H, 6-CH_3) [0.72 (d, $J = 6.5$ Hz)]; ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 152.80$ (C_{ar}), 151.81(C_{ar}), 150.23 (C_{ar}), 131.87 (C_{ar}), 127.08 [126.88] (C_{ar}), 115.85 (C_{ar}), 84.10 [78.71] (C5), 80.42 [80.87] (C9), 78.14 [78.27] (C7), 68.53 (C13), 61.63 (OCH_3), 60.57 (OCH_3), 60.48 (OCH_3), 38.86 (C8), 36.29 [34.46] (C6), 36.20 (C12), 30.34, 29.45 (C10/C11), 16.9 (12-CH_3), 13.59 [13.70] (6-CH_3), 10.59 ($ArCH_3$), 6.00 [6.92] (8-CH_3); IR (film) $\tilde{\nu} = 3340$ (br), 2938, 1712, 1458, 1400, 1384, 1100, 1029 cm^{-1}; MS (EI, 120 °C): *m*/*z*: 476 (20.0), 474 (19.4), 302 (25.0), 300 (24.1), 289 (56), 206 (17), 183 (16), 149 (50), 121 (30), 57 (100); HR-MS (EI, 100 °C): calcd for $C_{22}H_{35}O_6Br$: 474.1617, found 474.1623.

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