A Stereoselective Formal Synthesis of (−)-Fumagillol

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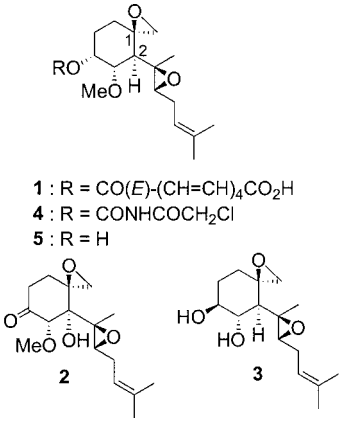
A novel formal synthesis of fumagillol, a direct precursor of the antiangiogenic sesquiterpene fumagillin, is described. The main features of the synthesis are a stereoselective Claisen–Ireland rearrangement, a ring-closing metathesis, a chemo- and stereoselective dihydroxylation, and a Julia–Kocienski olefination.

Fumagillin (**1**), isolated in 1951 by Elbe and Hanson[1] from the microbial organism *Aspergillus fumigatus*, is representative of a class of sesquiterpenes like ovalicin (**2**)[2] and FR 65814 (**3**),[3] which display various biological activities. Fumagillin (**1**) was originally described as an antimicrobial agent, but Folkman and co-workers[4] have more recently discovered that this compound is a potent and selective inhibitor of angiogenesis. The semisynthetic compound TNP-470 (**4**)[5,6] showed a better therapeutic index than fumagillin (**1**) and is one of the most promising drugs acting as an inhibitor of angiogenesis (Scheme 1).



Scheme 1

The recent discovery that methionine aminopeptidase II (MetAp-II) is selectively inhibited by fumagillin (**1**),[7] together with the X-ray structure of the covalent complex between fumagillin (**1**) and MetAp-II,[8] have increased interest in the synthesis of fumagillin (**1**) and of new fumagillin analogues.[9−11]

In 1972, Corey and Snider reported the first synthesis of (±)-fumagillin (**1**),[12] based on a Diels−Alder reaction to reach the cyclohexyl part of the molecule. This domain afterwards remained dormant for 25 years, but recently four syntheses of (−)-fumagillol (**5**), a close precursor of (−)-fumagillin (**1**), and of (−)-fumagillin (**1**) itself were successively published,[13−16] as well as two syntheses of the corresponding racemic material.[17,18]

Following the previous studies from our laboratory, we now report a novel and concise formal synthesis of (−)-fumagillol (**5**). Our initial strategy, by a Claisen−Ireland rearrangement/olefin ring-closing metathesis approach, allowed us to prepare several advanced intermediates in the synthesis of fumagillol (**5**).[19,20] However, several drawbacks such as the lack of selectivity of the side chain epoxidation or the number of steps prompted us as part of this strategy to reexamine a new strategy for the choice of the chiral pool starting material and for the introduction of the terminal side chain double bond.

Thus, diisopropylidenemannitol **6** was chosen as starting material and transformed into ketone **7** in nearly quantitative yield by a known sequence of reactions.[21,22] A selective Wittig olefination between ketone **7** and the phosphonium salt **8**[23] afforded the anticipated diene derivative **9** (Scheme 2). Selective removal of the acetonide unit in **9** gave rise to the diol derivative **10**, monoprotection of which afforded the diene alcohol **11** in good overall yield. On the other hand, the acid derivative **12** was obtained by oxidation ($NaClO_2$, NaH_2PO_4, methyl-2-butene, *t*BuOH/H_2O, yield > 95%) of the corresponding aldehyde as described previously by Evans' group.[24] Esterification between **11** and **12** afforded ester **13** in 52% overall yield from diisopropylidenemannitol **6** (Scheme 2).

With ester **13** we next examined the crucial Claisen−Ireland rearrangement. The same reaction conditions as previously described with other ester derivatives[19] afforded, after hydrolysis, the rearranged carboxylic acid derivative **14**, which was subjected directly to ring-clos-

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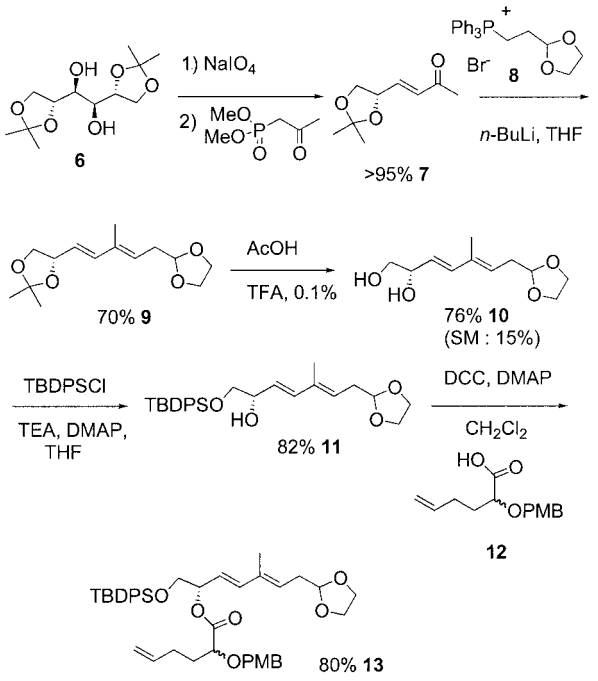
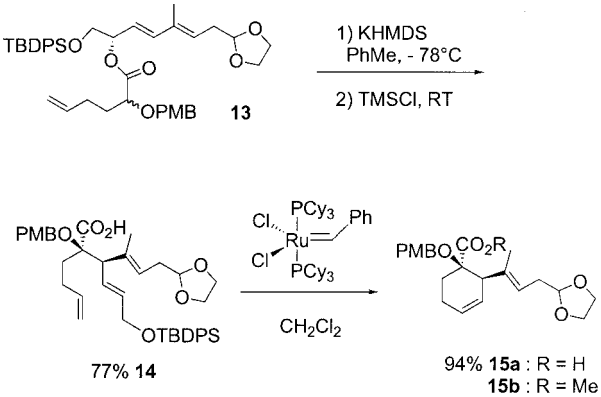


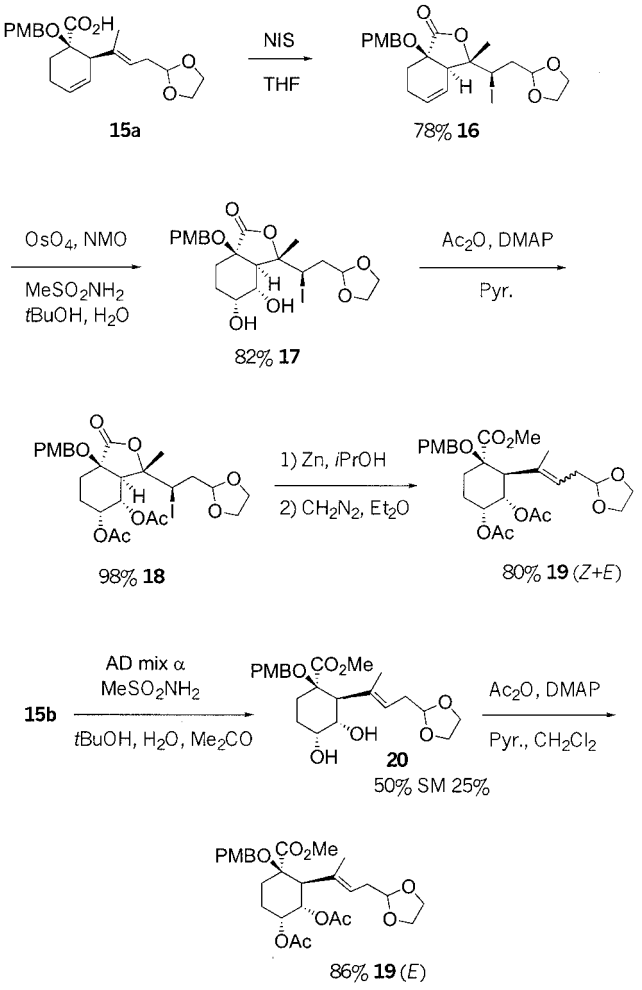
Scheme 2

ing metathesis. After treatment with the first generation Grubbs catalyst and then with diazomethane, the cyclohexene derivative **15b** was isolated in 72% overall yield for the three-step sequence (Scheme 3). A one-pot procedure, avoiding isolation of carboxylic acid **14** for this sequence, is also possible without any decrease in yield.



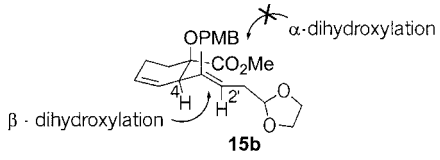
Scheme 3

At this stage we were faced with the problem of the selective dihydroxylation of the disubstituted cyclic double bond in the presence of the theoretically more reactive trisubstituted side chain double bond. Possible internal protection of the trisubstituted double bond was first examined. Accordingly, *N*-iodosuccinimide-promoted iodolactonisation of acid **15a** afforded the lactone **16** stereoselectively and in good yield.[25] Dihydroxylation under classical conditions gave rise to a single diol **17**, which after diacetylation furnished diacetate **18**. Retroiodolactonisation was performed in the presence of zinc in a 2-propanol/water mixture and afforded ester **19** after diazomethane treatment. However, careful examination of the NMR spectra of **19** and comparison with related compounds showed that **19** in fact consisted of a mixture of (*Z*) and (*E*) isomers. Moreover, the ratio of these isomeric compounds was not reproducible. (Scheme 4)



Scheme 4

As an alternative, examination of the most probable conformation[26] of this substituted cyclohexene derivative **15b** led us to speculate that the use of a dihydroquinine ligand known to induce α-face hydroxylation on a trisubstituted double bond (in our case the more hindered face) might allow us to overcome the undesired relative reactivity of our system. This hypothesis was confirmed by the experimental results.

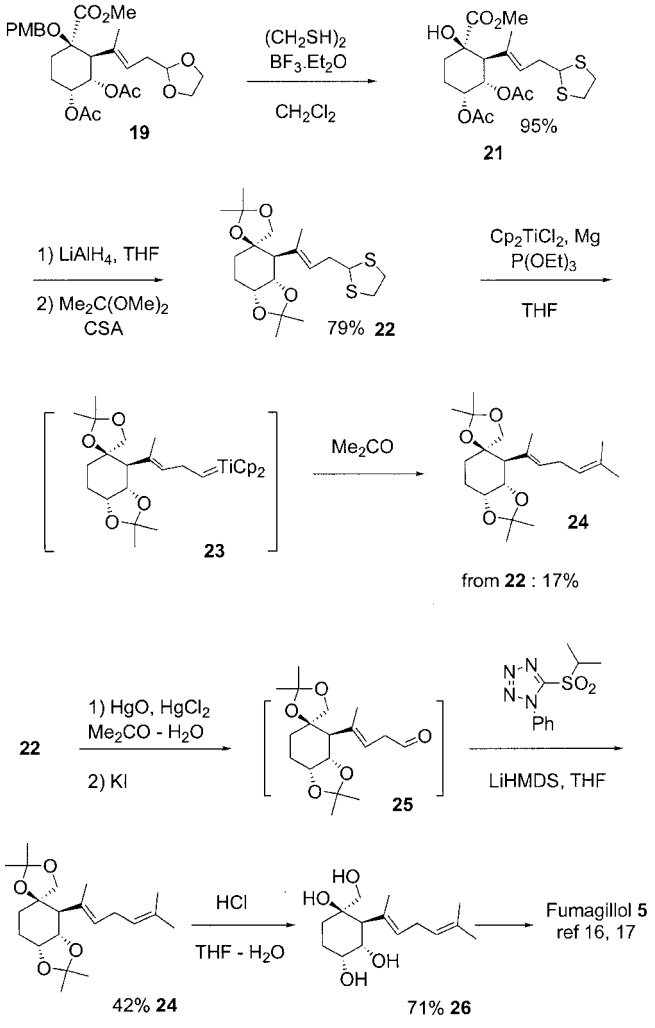


Thus, compound **15b** was treated with AD-mix-α[27] in the presence of methanesulfonamide in *t*BuOH/H_2O/

Me_2CO at room temperature for 48 h. Under these optimized reaction conditions, the expected diol **20** was isolated in 50% yield, with recovery of the starting material **15b** in 25% yield.[28] After this reaction, a classical acetylation afforded diacetate **19** (*E*) (Scheme 4).

The following step, unmasking of the dioxolane moiety in **19** in order to perform a subsequent Wittig olefination, proved to be more difficult than expected. In fact, under acidic hydrolysis reaction conditions, the expected aldehyde was always contaminated with its conjugated isomer.

To permit the use of other deprotection conditions, the dioxolane moiety in **19** was transformed into the corresponding dithioacetal **21**.[29] Gratifyingly, deprotection of the OPMB ether occurred in the same operation. Simultaneous reduction of the ester groups with $LiAlH_4$ was followed by protection of the alcohols, and the bis(acetonide) dithioacetal **22** was isolated in 79% yield (Scheme 5).



Scheme 5

At this stage, desulfurizative titanation of dithioacetals and subsequent treatment with carbonyl compounds as described by Takeda[30] seemed to be particularly attractive. Dithioacetal **22** was therefore treated with the low-valent titanium complex $[Cp_2Ti\{P(OEt)_3\}_2]$, prepared in situ, to give the (carbene)titanium intermediate **23**, which was quenched with an excess of acetone. Despite numerous investigations, however, the expected compound **24** was isolated only in low yield.[31] We assume that the presence of the β-γ double bond could give rise to by-products through a hydride β-elimination mechanism.

As an alternative, neutral conditions to generate the sensitive unconjugated aldehyde **25** were explored. Accordingly, cleavage of the dithioacetal group was performed under mild conditions with an $HgO/HgCl_2$ mixture in acetone/water, followed by treatment with an aqueous solution of KI.[32] The expected aldehyde **25** was thus isolated and applied in the subsequent step without any purification. Julia−Kocienski olefination[33] was used to generate the second side chain double bond. The expected diene derivative **24** was obtained in 42% yield from dithioacetal **22**. Final hydrolysis of the acetonides in **24** afforded tetrol **26**, identical in all respects with the compound described previously by Sorensen[16,17] (Scheme 5).

As tetrol **26** has been converted in three steps into fumagillol (**5**), this work constitutes a new formal synthesis of that compound.

In summary, we have developed a new strategy for the synthesis of a fumagillin precursor using a Claisen−Ireland rearrangement/olefin ring-closing metathesis sequence in the key steps. Selective dihydroxylation was achieved by taking advantage of mismatch selectivity with the more reactive double bond. In the final steps, a neutral cleavage of dithioacetal followed by a Julia−Kocienski olefination resulted in the construction of the 1,4-diene unit.

Experimental Section

General Remarks: ^1H and ^{13}C NMR spectra were recorded at 200, 250, 360 or 400 MHz and 50 or 62.5 MHz, respectively. IR spectra were recorded with a Perkin−Elmer Spectrum One FT-IR apparatus. Optical rotations were recorded at 20 °C. MS and HRMS analyses were performed with an MAT 95 (Finnigan) instrument with use of electrospray for ionisation. For compounds **9**, **10** and **11** only low-resolution results could be obtained by this method. Unless otherwise stated, chromatographic purifications were performed on 35−70 mesh silica gel (SDS, 60A) with the solvent system indicated. TLC analyses were performed on silica plates (Merck $60F_{254}$). Dichloromethane, acetonitrile, DMF and pyridine were distilled from calcium hydride. Toluene, diethyl ether and THF were distilled from sodium benzophenone ketyl. Chloroform used for optical measurements was filtered through basic alumina before use. All non-aqueous reactions were performed under argon in oven-dried glassware.

(4′*S*)-4-[5′-(1′′,3′′-Dioxolan-2′′-yl)-3′-methyl-1′,3′-pentadien-1′-yl]-2,2-dimethyl-1,3-dioxolane (9): [2-(1,3-Dioxolan-2-yl)ethyl]triphenylphosphonium bromide (35.5 g, 80 mmol, 1.75 equiv.) was dissolved in dry THF (400 mL) at −78 °C under argon, and *n*-butyllithium (1.6 M in hexane, 67 mL, 94 mmol, 2.3 equiv.) was added dropwise. After 45 min, a solution of the ketone **7** (7.77 g, 45 mmol) in THF (25 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirred overnight. The reaction was quenched with aqueous NH_4Cl (10%, 100 mL), and the mix-

ture was extracted with diethyl ether (3 × 150 mL). The combined organic layers were dried, filtered and concentrated. The residue was purified by silica gel column chromatography (heptane/EtOAc, 5:2) to afford the diene **9** as a pale yellow oil (8.4 g, yield 70%). R_f = 0.49 (heptane/EtOAc, 1:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.32 (d, *J* = 15.6 Hz, 1 H, 2′-H), 5.54 (t, *J* = 7.5 Hz, 1 H, 4′-H), 5.55−5.45 (m, 1 H, 1′-H), 4.89 (t, *J* = 4.7 Hz, 1 H, 2′′-H), 4.53 (q, *J* = 6.4 Hz, 1 H, 4-H), 4.06 (m, *J* = 6.4, 8 Hz, 1 H, 5-H), 3.98−3.81 [m, 4 H, $(OCH_2)_2$], 3.57 (dd, 1 H, 5-H), 2.52 (dd, 2 H, 5′-H), 1.76 (s, 3 H, 3′-Me), 1.42 [s, 3 H, $(O)_2CMe$], 1.37 [s, 3 H, $(O)_2CMe$] ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 138.6 (C-2′), 135.8 (C-3′), 126.9 (C-1′), 124.5 (C-4′), 109.5 [$(O)_2CMe_2$], 104.0 (C-2′′), 77.8 (C-4), 69.9 (C-5), 65.3 [$(OCH_2)_2$], 33.6 (C-5′), 27.1 (O_2CMe), 26.3 (O_2CMe), 13.0 (3′-Me) ppm. IR (film): ṽ = 2985, 2879, 1650, 1369, 1217, 1135, 1058 cm^{-1}. $[\alpha]_D^{20}$ = +18.1 (*c* = 1, $CHCl_3$). MS (electrospray): calcd. for [M + Na] 277.1; found 277.1.

(2*S*)-7-(1′,3′-Dioxolan-2′-yl)-5-methyl-3,5-heptadiene-1,2-diol (10): The diene **9** (8.3 g, 31 mmol) was dissolved at 0 °C in a solution of trifluoroacetic acid (0.1%) in acetic acid (160 mL). After 4 h, toluene (100 mL) was added, and the reaction mixture was concentrated under reduced pressure, this operation being repeated twice. Purification by silica gel column chromatography (EtOAc/heptane, 1:1 and then 3:1) gave the expected diol **10** (5.11 g, yield 76% and 15% of recovered starting material). R_f = 0.43 (EtOAc). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.37 (d, *J* = 15.8 Hz, 1 H, 4-H), 5.63−5.55 (m, 2 H, 6-H, 3-H), 4.92 (t, *J* = 4.7 Hz, 1 H, 2′-H), 4.29 (m, 1 H, 2-H), 4.00−3.80 [m, 4 H, $(OCH_2)_2$], 3.75−3.45 (m, 2 H, 1-H_a, 1-H_b), 2.54 (dd, *J* = 6.9 Hz, 2 H, 7-H), 2.25−2.00 (br. s, 2 H, OH), 1.77 (s, 3 H, 5-Me) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 136.7 (C-4), 135.6 (C-5), 126.2 (C-3), 125.5 (C-6), 103.7 (C-2′), 73.3 (C-2), 66.5 (C-1), 65.0 [$(OCH_2)_2$], 33.2 (C-7), 12.7 (5-Me) ppm. IR (film): ṽ = 3428, 2887, 1650, 1404, 1134, 1027 cm^{-1}. $[\alpha]_D^{20}$ = +7.1 (*c* = 0.95, $CHCl_3$). MS MS (electrospray): calcd. for [M + Na] 237.2; found 237.2.

(2*S*) 1-[(*tert*-Butyldiphenylsilyl)oxy]-7-(1′,3′-dioxolan-2′-yl)-5-methyl-3,5-heptadien-2-ol (11): DMAP (250 mg, 2 mmol, 10%) and triethylamine (3.72 mL, 26.8 mmol, 1.3 equiv.) were added to a solution of diol **10** (4.4 g, 20.6 mmol) in dry THF (200 mL). The mixture was cooled to 0 °C. A solution of *tert*-butyldiphenylsilyl chloride (6 mL, 22.9 mmol, 1.11 equiv.) in dry THF (50 mL) was added dropwise. After 3 h, the solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (EtOAc/heptane, 4:6). Allylic alcohol **11** was isolated (7.7 g, yield 82%). R_f = 0.63 (EtOAc/heptane, 1:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.69−7.64 (m, 4 H, ar-H), 7.42−7.35 (m, 6 H, ar-H), 6.31 (d, *J* = 15.4 Hz, 1 H, 4-H), 5.56−5.45 (m, 2 H, 3-H, 6-H), 4.90 (t, *J* = 4.8 Hz, 1 H, 2′-H), 4.4−4.25 (m, 1 H, 2-H), 3.99−3.80 [m, 4 H, $(OCH_2)_2$], 3.71−3.55 (m, 2 H, 1-H_a, 1-H_b), 2.52 (dd, 2 H, 7-H), 1.72 (s, 3 H, 5-Me), 0.93 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 136.7 (C-4), 135.7 (C-5), 135.6 (C^{Ar}), 133.2 (C_q^{Ar}), 129.9 (C^{Ar}), 127.8 (C^{Ar}), 125.9 (C-3), 125.2 (C-6), 103.8 (C-2′), 73.1 (C-2), 68.1 (C-1), 65.0 [$(OCH_2)_2$], 33.3 (C-7), 26.9 [Si−pC(Me)$_3$], 19.3 [Si−pC(Me)$_3$], 12.7 (5-Me) ppm. IR (film): ṽ = 3467, 2930, 2858, 1589, 1472, 1427, 1391, 1362, 1191, 1113, 1044 cm^{-1}. $[\alpha]_D^{20}$ = +4.2 (*c* = 0.5, $CHCl_3$). MS (electrospray): calcd. for [M + Na] 475.2; found 475.2.

(2*R*/*S*,1′*S*)-1′-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-6′-(1′′,3′′-dioxolan-2′′-yl)-4′-methyl-2′,4′-hexadien-1′-yl 2-[(4-Methoxybenzyl)oxy]-5-hexenoate (13): Allylic alcohol **11** (8.2 g, 18 mmol), acid **12** (7 g, 28 mmol, 1.4 equiv.) and DMAP (460 mg, 3.6 mmol) were dissolved in dichloromethane (220 mL) and the mixture was cooled to 0 °C. A solution of dicyclohexylcarbodiimide (5.8 g, 28 mmol, 1.4 equiv.) in dichloromethane (60 mL) was added dropwise. After 10 min, the reaction mixture was allowed to warm to room temperature and stirred for 2 h. The mixture was concentrated, and ether was added to the residue. The resulting suspension was filtered, and the filtrate was concentrated. Purification by silica gel column chromatography on silica gel (pentane/ether, 6:1, 4:1, 2:1 and 1:1) gave a 1:1 diastereoisomeric mixture of the ester **13** as an oil (10.8 g, yield 86%). R_f = 0.33 (pentane/ether, 4:1). Diastereoisomeric mixture. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.60−7.50 (m, 4 H, C^{Ar}-H), 7.35−7.20 (m, 6 H, C^{Ar}-H), 7.20−7.10 (m, 2 H, C^{PMBAr}-H), 6.75−6.68 (m, 2 H, C^{PMBAr}-H), 6.25−6.16 (dd, 1 H, 3′-H), 5.75−5.30 (m, 5 H, 5-H, 2 × 6-H, 2′-H, 5′-H), 4.90−4.75 (m, 3 H, 2′′-H, 1′-H, 2-H), 4.57−4.18 (AB system, 2 H, *p*-Me$OC_6H_4CH_2$), 3.89−3.61 [m, 9 H, 2 × SiOCH, $(OCH_2)_2$, OMe], 2.38 (m, 2 H, 2 × 6′-H), 2.15−2.0 (m, 2 H, 2 × 4-H), 1.75−1.65 (m, 2 H, 2 × 3-H), 1.58 (s, 3 H, 4′-Me), 0.95 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 172.3, 159.3, 138.8, 138.4, 137.5, 135.6, 135.4, 133.2, 133.1, 129.8, 127.7, 127.2, 127.1, 115.4, 113.8, 103.7, 77.0, 75.8, 71.8, 65.7, 65.0, 55.3, 33.3, 32.4, 32.2, 29.6, 29.5, 26.8, 19.3, 12.5 ppm. IR (film): ṽ= 3071, 2931, 1747, 1613, 1514, 1248, 1113 cm^{-1}. HRMS (electrospray): calcd. for [M + Na] 707.3455; found 707.3390.

Methyl (1*R*,2*R*)-2-[3′-(1′′,3′′-Dioxolan-2′′-yl)-1′-methyl-1′-propen-1′-yl]-1-[(4-methoxybenzyl)oxy]-3-cyclohexene-1-carboxylate (15b): The ester **13** (10.5 g, 15 mmol) was dissolved under argon in dry toluene (100 mL) and the mixture was then cooled to −78 °C. A solution of KHMDS in toluene (0.5 M) was added dropwise (40 mL, 20 mmol) over 15 min. After 45 min, freshly distilled TMSCl (3.8 mL, 30 mmol, 2 equiv.) was added and the resulting mixture was stirred for 5 min. The mixture was warmed to room temperature and stirred for an additional 3 h. The solution was then transferred by cannula to a flask containing Grubbs catalyst (1 g, 1.5 mmol, 0.1 equiv.) in CH_2Cl_2 (900 mL). This solution was heated at 40 °C for 2 h. After cooling, the reaction was quenched with 10% aqueous NH_4Cl solution and the layers were separated. The aqueous layer was extracted with dichloromethane, the combined organic layers were dried and filtered, and the solvent was removed under reduced pressure. The crude product was esterified with diazomethane, and the resulting methyl ester was purified by silica gel column chromatography (pentane/ether, 4:1) to give the ester **15b** as a colourless oil (4.22 g, yield 70%). R_f = 0.52 (ether/pentane, 1:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.20 (d, *J* = 8.3 Hz, 2 H, C^{Ar}-H), 6.77 (d, *J* = 8.3 Hz, 2 H, C^{Ar}-H), 5.90−5.77 (m, 1 H, 2′-H), 5.45−5.32 (m, 1 H, 3-H), 5.22−5.12 (m, 1 H, 4-H), 4.76 (t, *J* = 4.9 Hz, 1 H, 2′′-H), 4.49−4.31 (AB system, *J* = 10.7 Hz, 2 H, $ArCH_2$), 4.00−3.77 [m, 4 H, $(OCH_2)_2$], 3.75 (s, 3 H, OMe), 3.72 (s, 3 H, COOMe), 3.33 (m, 1 H, 2-H), 2.33 (t, *J* = 5.8 Hz, 2 H, 3′-H), 2.20−1.95 (m, 4 H, 5-H, 6-H), 1.6 (s, 3 H, 1′-Me) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 174.3 (*C*OOMe), 159.1 (C_q^{Ar}-OMe), 138.4 (C_q^{Ar}), 131.5 (C-1′), 128.9 (C^{Ar}), 127.7 (C-3), 126.8 (C-4), 122.6 (C-2′), 113.8 (C^{Ar}), 104.5 (C-2′′), 82.5 (C-1), 66.1 (ArCH_2O), 65.2 [$(OCH_2)_2$], 55.5 (C-2), 52.6 (ArOMe), 52.0 (COOMe), 33.4 (C-3′), 26.9 (C-5), 22.6 (C-6), 16.5 (1′-Me) ppm. IR (film): ṽ = 3024, 2951, 2838, 1744, 1613, 1514, 1249, 1131 cm^{-1}. $[\alpha]_D^{20}$ = +15.5 (*c* = 0.88, $CHCl_3$). HRMS (electrospray): calcd. for [M + Na] 425.1940; found 425.1930.

(1′*R*,3*S*,3a*S*,7a*R*)-3-[2′-(1′′,3′′-Dioxolan-2′′-yl)-1′-iodoethyl]-7a-[(4-methoxybenzyl)oxy]-3-methyl-3a,6,7,7a-tetrahydro-2-benzofuran-1(3*H*)-one (16): Acid **15a** (1.07 g, 2.75 mmol) was dissolved under argon in dry THF (10 mL). A solution of freshly prepared *N*-iodosuccinimide (0.8 g, 3.5 mol, 1.3 equiv.) in THF (5 mL) was added rapidly. After 2 h, the reaction was quenched with 5% aque-

ous $NaHCO_3$ solution and the layers were separated. The aqueous layer was extracted twice with ether, the combined organic layers were dried and filtered, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (pentane/ether, 2:3) to give iodolactone **A** as a colourless product (1.1 g, yield 78%). R_f = 0.45 (ether/pentane, 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.10 (d, *J* = 8.5 Hz, 2 H, C^{Ar}-H), 6.76 (d, *J* = 8.5 Hz, 2 H, C^{Ar}-H), 5.8−5.9 (m, 1 H, 4-H), 5.65−5.7 (m, 1 H, 5-H), 5.06 (dd, *J* = 3.7, *J* = 5.8 Hz, 1 H, 2′′-H), 4.42 (AB system, *J* = 3 Hz, 2 H, ArC*H*$_2$), 4.05 (dd, *J* = 4.2, *J* = 9.4 Hz, 1 H, 1′-H), 3.8−3.95 [m, 4 H, $(OCH_2)_2$], 3.71 (s, 3 H, OMe), 2.84 (br. s, 1 H, 3a-H), 2.4 (m, 2 H, 2′-H), 2.10−2.3 (m, 4 H, 6-H, 7-H), 1.61 (s, 3 H, 3-Me) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 172.3 (C-1), 159.5 (C_q^{Ar}-OMe), 130.3 (C_q^{Ar}), 129.8 (C-4), 129.4 (C-Ar), 121.5 (C-5), 114.1 (C-Ar), 104.4 (C-2′′), 88.1 (C-7a), 79.1 (C-3), 66.5 (Ar*C*H$_2$O), 65.4 [$(OCH_2)_2$], 65.2 [$(OCH_2)_2$], 55.6 (C-3a), 54.0 (ArO*Me*), 39.6 (C-6), 38.5 (C-1′), 24.5 (C-2′), 24.1 (C-7), 17.3 (3-Me) ppm. IR (film): ṽ = 3650, 3546, 2991, 2952, 2881, 2835, 1774, 1613, 1514, 1302, 1249 cm^{-1}. $[\alpha]_D^{20}$ = +15.7 (*c* = 1.4, $CHCl_3$). HRMS (electrospray): calcd. for [M + Na] 537.0750; found 537.0759.

(1′*R*,3*S*,4*S*,5*R*,3a*S*,7a*R*) 3-[2′-(1′′,3′′-Dioxolan-2′′-yl)-1′-iodoethyl]-4,5-dihydroxy-7a-[(4-methoxybenzyl)oxy]-3-methylhexahydro-2-benzofuran-1(3*H*)-one (17): Iodolactone **16** (1 g, 1.9 mmol), NMO (0.9 g, 6.6 mmol, 3.3 equiv.) and $MeSO_2NH_2$ (225 mg, 2.35 mmol, 1.2 equiv.) were dissolved in a *tert*-butyl alcohol/water mixture (1:1, 20 mL), and the mixture was cooled to 0 °C. Osmium tetroxide (60 mg, 0.2 mmol, 0.1 equiv.) was added in one portion, and the resulting mixture was vigorously stirred for 4 h. The reaction was stopped by addition of solid Na_2SO_3 (7 g) and water (10 mL). The aqueous layer was extracted with diethyl ether (3 × 20 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (Et_2O, followed by Et_2O/2% MeOH) to give the iodolactone diol **17** (0.9 g, yield 82%). R_f = 0.1 (ether). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 8.5 Hz, 2 H, C^{Ar}-H), 6.76 (d, *J* = 8.5 Hz, 2 H, C^{Ar}-H), 5.12 (dd, *J* = 2.8, *J* = 6.7 Hz, 1 H, 2′′-H), 4.46−4.51 (dd, *J* = 2.45, *J* = 10.9 Hz, 1 H, 4-H), 4.37 (AB system, *J* = 10.6, *J* = 12.5 Hz, 2 H, ArC*H*$_2$), 4.2−4.24 (m, 1 H, 5-H) 4.05 (dd, 1 H, 1′-H), 3.8−3.95 [m, 4 H, $(OCH_2)_2$], 3.79 (s, 3 H, OMe), 3.04 (d, *J* = 11 Hz, 1 H, 3a-H), 2.67 (br. s, 2 H, OH), 2.4−2.56 (m, 2 H, 2 × 2′-H), 2.17−2.31 (m, 1 H, 6-H$_a$), 1.77−2.06 (m, 3 H, 2 × 7-H, 6-H$_b$), 1.76 (s, 3 H, 3-Me) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 171.8 (C-1), 159.7 (C_q^{Ar}-OMe), 129.9 (C^{Ar}), 129.8 (C_q^{Ar}), 114.2 (C^{Ar}), 104.9 (C-2′′), 88.1 (C-7a), 81.2 (C-3), 69.7 (C-4), 68.6 (C-5), 66.0 (Ar*C*H$_2$O), 65.4 [$(OCH_2)_2$], 65.1 [$(OCH_2)_2$], 55.6 (C-3a), 47.9 (ArO*Me*), 41.0 (C-1′), 40.0 (C-6), 27.1 (C-7), 23.0 (3-Me), 21.7 (C-2′) ppm. IR (film): ṽ = 3487, 2997, 2957, 2884, 2838, 1768, 1613, 1515, 1464, 1251, 1129, 1062, 1033 cm^{-1}. $[\alpha]_D^{20}$ = −18.4 (*c* = 1.1, $CHCl_3$). HRMS (electrospray): calcd. for [M + Na] 571.0850; found 571.0861.

(1′*R*,3*S*,4*S*,5*R*,3a*S*,7a*R*)-3-[2′-(1′′,3′′-Dioxolan-2′′-yl)-1′-iodoethyl]-7a-[(4-methoxybenzyl)oxy]-3-methyl-1-oxooctahydro-2-benzofuran-4,5-diyl Diacetate (18): Iodolactone diol **17** (0.5 g, 0.91 mmol) was dissolved in pyridine (5 mL) with a catalytic amount of DMAP (25 mg, 0.1 equiv.). Acetic anhydride (1.5 mL, 14.5 mmol, 16 equiv.) was added, and the mixture was stirred for 2 h. The reaction was quenched with saturated aqueous $CuSO_4$ (200 mL), and the mixture was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (pentane/ether, 1:1) to afford the expected iodolactone diacetate **18** (563 mg, yield 98%). R_f = 0.23 (ether/pentane, 1:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 8.3 Hz, 2 H, C^{Ar}-H), 6.87 (d, *J* = 8.3 Hz, 2 H, C^{Ar}-H), 5.5 (m, 1 H, 5-H), 5.4 (dd, *J* = 2.9, *J* = 11.7 Hz, 1 H, 4-H), 5.12 (dd, *J* = 2.8, *J* = 6.7 Hz, 1 H, 2′′-H), 4.43 (AB system, 3 H, ArC*H*$_2$, 1′-H), 3.9−3.95 [m, 4 H, $(OCH_2)_2$], 3.81 (s, 3 H, OMe), 3.32 (d, *J* = 11.7 Hz, 1 H, 3a-H), 2.3−2.5 (m, 2 H, 2 × 2′-H), 2.11 [s, 3 H, C(O)CH_3], 1.98 [s, 3 H, C(O)CH_3], 1.7−1.95 (m, 4 H, 2 × 6-H, 2 × 7-H), 1.62 (s, 3 H, 3-Me) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 170.3 (C-1), 169.8 [*C*(O)CH_3), 169.4 [*C*(O)CH_3), 159.3 (C_q^{Ar}-OMe), 129.5 (C^{Ar}), 128.5 (C_q^{Ar}), 113.8 (C^{Ar}), 104.2 (C-2′′), 86.7 (C-7a), 80.5 (C-3), 68.9 (C-4), 68.0 (C-5), 66.5 (Ar*C*H$_2$O), 65.9 [$(OCH_2)_2$], 65.7 [$(OCH_2)_2$], 55.1 (C-3a), 47.2 (ArO*Me*), 41.2 (C-1′), 40.0 (C-6), 24.9 (C-7), 21.9 (C-2′), 21.0 (3-Me), 20.8−20.7 [2 × C(O)*C*H$_3$] ppm. IR (film): ṽ = 3657, 2938, 1776, 1744, 1614, 1515, 1458, 1372, 1251, 1129, 1056 cm^{-1}. $[\alpha]_D^{20}$ = +1.95 (*c* = 1.22, $CHCl_3$). HRMS (electrospray): calcd. for [M + Na] 655.1016; found 655.1020.

Methyl (1*R*,2*S*,3*S*,4*R*)-2-[3′-(1′′,3′′-Dioxolan-2′′-yl)-1′-methyl-1′-propen-1′-yl]-3,4-dihydroxy-1-[(4-methoxybenzyl)oxy]cyclohexanecarboxylate (20): AD-mix-α (7 g) and $MeSO_2NH_2$ (600 mg, 6.3 mmol, 1.28 equiv.) were dissolved in a *tert*-butyl alcohol/water mixture (1:1, 50 mL), and the mixture was stirred for 5 min. A solution of ester **15b** (2 g, 4.9 mmol) in acetone (10 mL) was added, and the resulting mixture was vigorously stirred for 48 h. The reaction was stopped by addition of solid Na_2SO_3 (10 g) and water (70 mL). The aqueous layer was extracted with diethyl ether (3 × 100 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (Et_2O, followed by Et_2O/2% MeOH) to give the diol **20** (1.05 g, 50% yield and 25% of recovered starting material). R_f = 0.1 (ether). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.5 Hz, 2 H, C^{Ar}-H), 6.81 (d, *J* = 8.5 Hz, 2 H, C^{Ar}-H), 5.14 (t, *J* = 6.2 Hz, 1 H, 2′-H), 4.76 (t, 1 H, 2′′-H), 4.49−4.31 (AB system, *J* = 10.7 Hz, 2 H, Ar*C*H$_2$), 4.05−3.93 (m, 2 H, 3-H, 4-H), 3.92−3.77 [m, 4 H, $(OCH_2)_2$], 3.71 (s, 3 H, OMe), 3.62 (s, 3 H, COOMe), 2.70 (d, *J* = 10.5 Hz, 1 H, 2-H), 2.40−2.20 (m, 3 H, 2 × 3′-H, 5-H$_a$), 2.00−1.70 (m, 3 H, 2 × 6-H, 5-H$_b$), 1.62 (s, 3 H, 1′-Me) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 175.8 (*C*OOMe), 161.9 (C_q^{Ar}-OMe), 139.3 (C_q^{Ar}), 133.7 (C-1′), 131.7 (C^{Ar}), 126.0 (C-2′), 116.0 (C^{Ar}), 106.6 (C-2′′), 88.5 (C-1), 71.5 (C-3), 71.0 (C-5), 68.5 (Ar*C*H$_2$O), 67.2 [$(OCH_2)_2$], 57.1 (ArO*Me*), 56.7 (COO*Me*), 53.6 (C-2), 35.2 (C-3′), 29.0 (C-5), 25.8 (C-6), 16.0 (1′-Me) ppm. IR (film): ṽ = 3474, 3337, 2950, 1741, 1612, 1514, 1249 cm^{-1}. $[\alpha]_D^{20}$ = −88.4 (*c* = 0.605, $CHCl_3$). HRMS (electrospray): calcd. for [M + Na] 459.1995; found 459.1997.

Methyl (1*R*,2*S*,3*S*,4*R*)-3,4-Bis(acetyloxy)-2-[3′-(1′′,3′′-dioxolan-2′′-yl)-1′-methyl-1′-propen-1′-yl]-1-[(4-methoxybenzyl)oxy]cyclohexanecarboxylate (19): Diol **20** (1.3 g, 2.9 mmol) was dissolved in pyridine (15 mL) with a catalytic amount of DMAP (100 mg, 0.1 equiv.). Acetic anhydride (3 mL, 31.8 mmol, 12 equiv.) was added, and the mixture was stirred for 2 h. The reaction was quenched with saturated aqueous $CuSO_4$ (150 mL), and the mixture was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (pentane/ether, 1:1) to afford the expected diacetate **19** (1.34 g, yield 86%). R_f = 0.61 (ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 8.6 Hz, 2 H, C^{Ar}-H), 6.88 (d, *J* = 8.6 Hz, 2 H, C^{Ar}-H), 5.43−5.36 (m, 2 H, 3-H, 4-H), 5.25 (t, *J* = 6.2 Hz, 1 H, 2′-H), 4.80 (t, 1 H, 2′′-H), 4.52−4.24 (AB system, *J* = 10.1 Hz, 2 H, ArC*H*$_2$), 3.99−3.84 [m, 4 H, $(OCH_2)_2$], 3.82 (s, 3 H, OMe), 3.73

(s, 3 H, COOMe), 2.95 (d, J = 11.8 Hz, 1 H, 2-H), 2.36 (dd, 2 H, 2 × 3′-H), 2.34−2.20 (m, 1 H, 5-H_a), 2.14 [s, 3 H, C(O)CH_3), 2.06 (m, 1 H, 6-H_a), 1.91 [s, 3 H, C(O)CH_3), 1.85 (m, 2 H, 5-H_b 6-H_b), 1.58 (s, 3 H, 1′-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7 (*C*OOMe), 170.9 [*C*(O)CH_3), 170.6 [*C*(O)CH_3), 159.5 (C_q^{Ar}-OMe), 135.5 (C_q^{Ar}), 130.7 (C-1′), 129.5 (C^{Ar}), 124.2 (C-2′), 114.1 (C^{Ar}), 104.5 (C-2′′), 85.8 (C-1), 69.6 (C-3), 69.1 (C-4), 66.8 (Ar*C*H_2O), 65.2 [$(OCH_2)_2$], 55.7 (ArO*Me*), 53.1 (COO*Me*), 52.2 (C-2), 33.3 (C-3′), 24.8 (C-5), 24.5 (C-6), 21.7 [C(O)CH_3), 21.2 [C(O)CH_3), 14.4 (1′-Me) ppm. IR (film): ν̃ = 3440, 3054, 2987, 1740, 1421, 1265, 738 cm^{-1}. $[\alpha]_D^{20}$ = −67.7 (c = 0.46, $CHCl_3$). HRMS (electrospray): calcd. for [M + Na] 543.2206; found 543.2212.

Methyl (1*R*,2*S*,3*S*,4*R*)-3,4-Bis(acetyloxy)-2-[3′-(1′′,3′′-dithiolan-2′′-yl)-1′-methyl-1′-propen-1′-yl]-1-hydroxycyclohexanecarboxylate (21): Diacetate **19** (670 mg, 1.28 mmol) and ethanedithiol (602 mg, 6.4 mmol, 6 equiv.) were dissolved under argon in distilled dichloromethane (20 mL). BF_3·Et_2O (273 mg, 1.92 mmol, 1.5 equiv.) was then added, and the resulting mixture was stirred at room temperature for 30 min. The reaction was quenched with aqueous 10% sodium hydrogencarbonate solution and the layers were separated. The aqueous layer was extracted twice with dichloromethane (20 mL), and the combined organic layers were dried, filtered and concentrated. Chromatography on silica gel (ether/pentane, 1:1) of the residue afforded the tertiary alcohol **21** in high yield (555 mg, 99%). R_f = 0.32 (ether/pentane, 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.38−5.26 (m, 2 H, 3-H 4-H), 5.28 (t, 1 H, 2′-H), 4.41 (t, J = 6.25 Hz, 1 H, 2′′-H), 3.79 (s, 3 H, COOMe), 3.22−3.18 [m, 4 H, $(SCH_2)_2$], 2.92 (d, J = 11.75 Hz, 1 H, 2-H), 2.48 (t, 2 H, 2 × 3′-H), 2.15−2.05 (m, 2 H, 5-H), 2.11 [s, 3 H, C(O)CH_3], 1.93−1.75 (m, 2 H, 6-H), 1.92 [s, 3 H, C(O)CH_3), 1.56 (s, 3 H, 1′-Me) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 175.2 (*C*OOMe), 170.2 [*C*(O)CH_3), 170.1 [*C*(O)CH_3), 133.7 (C-1′), 127.1 (C-2′), 78.2 (C-1), 69.7 (C-3), 68.8 (C-4), 53.4 (COO*Me*), 52.8 (C-2), 49.9 (C-2′′), 38.4 [$(SCH_2)_2$], 37.3 (C-3′), 30.0 (C-5), 24.2 (C-6), 21.1 [C(O)*C*H_3), 20.8 [C(O)*C*H_3), 15.6 (1′-Me) ppm. IR (film): nu(tilde = 3501, 2930, 1739, 1437, 1373, 1246, 1051, 1027, 736 cm^{-1}. $[\alpha]_D^{20}$ = −13.0 (c = 0.964, $CHCl_3$). HRMS (electrospray): calcd. for [M + Na] 455.1174; found 455.1172.

(3a*S*,4*S*,5*R*,7a*R*)-4-[3′-(1′′′,3′′′-Dithiolan-2′′′-yl)-1′-methyl-1′-propen-1′-yl]-2,2,2′′,2′′-tetramethyltetrahydro-4*H*-spiro[1,3-benzodioxole-5,4′′-[1′′,3′′]dioxolane] (22): The tertiary alcohol **21** (556 mg, 1.28 mmol) was dissolved under argon in dry THF (10 mL). Lithium aluminium hydride (122 mg, 3.2 mmol, 2.5 equiv.) was added in two portions at 0 °C. After 1 h, additional lithium aluminium hydride (122 mg, 3.2 mmol, 2.5 equiv.) was added in order to complete the reaction. The reaction was quenched slowly with saturated aqueous Na_2SO_4 (1 mL), and the mixture was vigorously stirred for 2 h. After filtration and removal of the solvent, the residue was dissolved in 2,2-dimethoxypropane (50 mL) with a catalytic amount of camphorsulfonic acid (40 mg, 0.17 mmol, 0.13 equiv.). After 2 h, solid potassium carbonate was added and the solution was filtered. The filtrate was concentrated, and the residue was purified by silica gel column chromatography (pentane/ether, 2:1) to afford dithioacetal **22** (404 mg, yield 79%). R_f = 0.57 (ether/pentane, 1:2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.22 (t, J = 6.1 Hz, 1 H, 2′-H), 4.43 (t, J = 6.25 Hz, 1 H, 2′′′-H), 4.28−4.19 (m, 2 H, 3a-H, 7a-H), 3.83−3.51 (AB system, J = 7.75 Hz, 2 H, 2 × 4′′-H), 3.19−3.07 [m, 4 H, $(SCH_2)_2$], 2.53 (dd, 2 H, 2 × 3′-H), 2.10 (d, J = 9.25 Hz, 1 H, 4-H), 2.05−1.40 (m, 4 H, 2 × 7-H, 2 × 6-H), 1.70 (s, 3 H, 1′-Me), 1.36 [s, 3 H, $(O)_2$CMe], 1.29 [s, 3 H, $(O)_2$CMe], 1.24 [s, 3 H, $(O)_2$CMe], 1.21 [s, 3 H, $(O)_2$CMe] ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 135.4 (C-1′), 128.4 (C-2′), 109.7 [$C(O)_2$], 108.2 [$C(O)_2$], 83.3 (C-5), 76.6 (C-3a), 73.4 (C-7a), 71.8 (C-4′′), 54.1 (C-4), 53.7 (C-2′′′), 38.9 [$(SCH_2)_2$], 37.8 (C-3′), 31.4 (C-7), 28.9 [$(O)_2$C*Me*], 28.4 [$(O)_2$C*Me*], 27.1 [$(O)_2$C*Me*], 26.7 [$(O)_2$C*Me*], 22.5 (C-6), 16.6 (1′-Me) ppm. IR (film): ν̃ = 3051, 2986, 2931, 2882, 1430, 1380, 1368, 1266, 1055, 738 cm^{-1}. $[\alpha]_D^{20}$ = −93.0 (c = 1.58, $CHCl_3$). HRMS (electrospray): calcd. for [M + Na] 423.1640; found 423.1637.

(3a*S*,4*S*,5*R*,7a*R*)-4-(1′,5′-Dimethyl-1′,4′-hexadien-1′-yl)-2,2,2′′,2′′-tetramethyltetrahydro-4*H*-spiro[1,3-benzodioxole-5,4′′-[1′′,3′′]-dioxolane] (24). Takeda's Procedure: Cp_2TiCl_2 (200 mg, 0.81 mmol, 4.3 equiv.), molecular sieves (4 Å, 100 mg) and magnesium turnings (40 mg, 1.65 mmol, 8.7 equiv.) was heated at 100 °C under vacuum (10 Torr) in a Schlenk flask overnight. After cooling, dry THF (3 mL) and $P(OEt)_3$ (260 μL, 1.52 mmol, 8 equiv.) were added, then the mixture was gently heated at 35 °C for 3 h. A solution of dithioacetal **22** (76 mg, 0.19 mmol) in THF (1 mL) was added. After 30 min, acetone (60 μL, 0.76 mmol, 4 equiv.) was added. The reaction mixture was warmed at 60 °C for 1 h. After cooling, the reaction was quenched by an NaOH aqueous solution (2 N, 5 mL), and extracted with ether (3 × 5 mL). The combined organic layers were dried, filtered and concentrated. The residue was purified by silica gel column chromatography (pentane/ether, 4:1) to afford 10 mg of expected diene **24** (yield: 15 %).

Hydrolysis/Julia−Kocienski's Procedure: Dithioacetal **22** (40 mg, 0.1 mmol) was dissolved in an acetone/water (8:2) mixture (1 mL), and HgO (60 mg, 0.27 mmol, 2.7 equiv.) and $HgCl_2$ (100 mg, 0.37 mmol, 3.7 equiv.) were added. The progress of the reaction was monitored by TLC; if the reaction was not completed overnight, an additional portion of $HgCl_2$ was added. The suspension was filtered, and the mercury salts were washed with diethyl ether (15 mL). The organic layer was washed with aqueous KI (10%, 15 mL), the layers were separated, and the aqueous one was extracted with ether (2 × 10 mL). The combined organic layers were dried, filtered and concentrated. The crude aldehyde **25** was not purified by silica gel column chromatography to avoid any conjugated isomer formation. LiHMDS (1 M in hexane, 220 μL, 2.2 equiv.) was added dropwise at −78 °C to a solution of 5-(isopropylsulfonyl)-1-phenyl-1*H*-tetrazole (63 mg, 0.25 mmol, 2.5 equiv.) in THF (1.5 mL). The yellow solution was stirred at −78 °C for 30 min. This solution was added in one portion at −78 °C, by precooled syringe, to a solution of aldehyde **25** (32 mg, 0.1 mmol) in THF (1 mL). The reaction mixture was stirred at −78 °C for 2 h, and the mixture was then allowed to warm slowly to room temperature and stirred for 3 h. The reaction mixture was diluted with diethyl ether and washed with aqueous NH_4Cl solution (10%). The organic layer was dried, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (pentane/ether, 4:1) to afford the diene **24** as a colourless oil (11 mg, yield 42%). R_f = 0.42 (ether/pentane, 1:4).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.30 (t, J = 7.25 Hz, 1 H, 2′-H), 5.12 (t, J = 7.3 Hz, 1 H, 4′-H), 4.40−4.25 (m, 2 H, 3a-H, 7a-H), 3.83−3.60 (AB system, J = 8 Hz, 2 H, 2 × 4′′-H), 2.53 (dd, 2 H, 2 × 3′-H), 2.14 (d, J = 9.25 Hz, 1 H, 4-H), 2.12−1.40 (m, 4 H, 2 × 7-H, 2 × 6-H), 1.77 (s, 3 H, 3 × 6′-H), 1.67 (s, 3 H, 1′-Me), 1.61 (s, 3 H, 5′-Me), 1.47 [s, 3 H, $(O)_2$CMe], 1.39 [s, 3 H, $(O)_2$CMe], 1.35 [s, 3 H, $(O)_2$CMe], 1.26 [s, 3 H, $(O)_2$CMe] ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 131.5 (C-1′, C-5′), 129.9 (C-4′), 122.9 (C-2′), 109.4 [$C(O)_2$], 107.9 [$C(O)_2$], 83.1 (C-5), 77.0 (C-3a), 73.2 (C-7a), 71.4 (C-4′′), 52.7 (C-4), 31.1 (C-3′), 28.6 [$(O)_2$C*Me*], 28.1 [$(O)_2$C*Me*], 27.2 (C-7), 26.5 [$(O)_2$C*Me*], 26.4 [$(O)_2$C*Me*], 25.5 (C-6′), 22.2 (C-6), 17.7 (1′-Me), 16.9 (5′-Me) ppm. IR (film): ν̃ =

2985, 2930, 2878, 1651, 1454, 1367, 1214, 1160, 1057 cm^{-1}. $[\alpha]_D^{20}$ = −109.1 (*c* = 1.32, $CHCl_3$). HRMS (electrospray): calcd. for [M + Na] 373.2355; found 373.2350.

(1*R*,2*S*,3*S*,4*R*)-3-(1′,5′-Dimethyl-1′,4′-hexadien-1′-yl)-4-(hydroxymethyl)-1,2,4-cyclohexanetriol (26): The diene **24** (11 mg, 0.031 mmol) was dissolved in tetrahydrofuran (1 mL), and an HCl aqueous solution was added (2 N, 1 mL). After 2 h, the reaction was quenched with aqueous sodium hydrogencarbonate (10%) and the mixture was extracted with ethyl acetate (3 × 5 mL). The organic layers were dried (Na_2SO_4) and filtered. The filtrate was concentrated and the residue was purified by preparative TLC (EtOAc) to give tetrol **26** (6 mg, yield 71%). R_f = 0.29 (EtOAc). ^1H NMR (250 MHz, $CDCl_3$): δ = 5.41 (m, 1 H, 2′-H), 5.07 (m, 1 H, 4′-H), 4.12 (m, 1 H, 1-H), 4.03−3.99 (m, 1 H, 2-H), 3.55−3.50 (m, 1 H, 4-CH_a), 3.31 (d, *J* = 11.25 Hz, 1 H, 4-CH_b), 2.77 (m, 2 H, 2 × 3′-H), 2.32 (d, *J* = 10.5 Hz, 1 H, 3-H), 2.25−1.40 (m, 8 H, 2 × 6-H, 2 × 5-H, 4 × OH), 1.80 (s, 3 H, 3 × 6′-H), 1.68 (s, 3 H, 1′-Me), 1.62 (s, 3 H, 5′-Me) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 133.2 (C-1′), 132.7 (C-5′), 121.7 (C-4′, C-2′), 74.5 (C-4), 69.7, 68.1, 28.8, 26.9, 25.6, 24.9, 17.7 ppm. IR (film): $\tilde{\nu}$ = 3400 (OH) cm^{-1}. $[\alpha]_D^{20}$ = −61.1 (*c* = 0.195, $CHCl_3$). HRMS (electrospray): calcd. for [M + Na] 293.1729; found 293.1728.

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[1] T. E. Elbe, F. R. Hanson, *Antibiot. Chemother.* **1951**, *1*, 54.
[2] H. P. Sigg, H. P. Weber, *Helv. Chim. Acta* **1968**, *51*, 1395.
[3] H. Hatanaka, T. Kino, M. Hashimoto, Y. Tsurumi, A. Kuroda, H. Tanaka, T. Goto, M. Okuhara, *J. Antibiot.* **1988**, *41*, 999.
[4] D. Ingber, T. Fujita, S. Kishimoto, K. Sudo, T. Kanamaru, H. Brem, J. Folkman, *Nature* **1990**, *348*, 555.
[5] B. J. Dezube, J. H. Von Roenn, J. Holden-Wiltse, T. W. Cheung, S. C. Remick, T. P. Cooley, J. Moore, J. P. Sommadosi, S. L. Shriver, C. W. Suckow, P. S. Gill, *J. Clin. Oncol.* **1998**, *16*, 1444.
[6] [6a] For other TNP-470 derivatives see: S. Marui, T. Yamamoto, K. Sudo, H. Akimoto, S. Kishimoto, *Chem. Pharm. Bull.* **1995**, *43*, 588. [6b] N. Sin, L. Meng, M. Q. Wang, J. J. Wen, W. G. Bornmann, C. M. Crews, *Proc. Natl. Acad. Sci. U. S. A.* **1997**, *94*, 6099. [6c] E. C. Griffith, Z. Su, S. Niwayama, C. A. Ramsey, Y. H. Chang, J. O. Liu, *Proc. Natl. Acad. Sci. U. S. A.* **1998**, *95*, 15183. [6d] C. K. Han, S. K. Ahn, N. S. Choi, R. K. Hong, S. K. Moon, H. S. Chun, S. J. Lee, J. W. Kim, C. I. Hong, D. Kim, J. H. Yoon, K. T. No, *Bioorg. Med. Chem.* **2000**, *10*, 39.
[7] W. T. Lowther, D. A. McMillen, A. M. Orville, B. W. Matthews, *Proc. Natl. Acad. U. S. A.* **1998**, *95*, 12153.
[8] S. Liu, J. Widom, C. W. Kemp, C. M. Crews, J. Clardy, *Science* **1998**, *282*, 1324.
[9] For a review concerning low molecular weight compound inhibitors of angiogenesis, see: A. Giannis, F. Rubsam, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 588.
[10] For a recent synthesis of an oxafumagillin analogue, see: J. E. Baldwin, P. G. Bulger, R. Marquez, *Tetrahedron* **2002**, *58*, 5441.
[11] V. Rodeschini, J. G. Boiteau, P. Van de Weghe, C. Tarnus, J. Eustache, *J. Org. Chem.* **2004**, *69*, 357.
[12] E. J. Corey, B. B. Snider, *J. Am. Chem. Soc.* **1972**, *94*, 2549.
[13] D. Kim, S. K. Ahn, H. Bae, W. J. Choi, H. S. Kim, *Tetrahedron Lett.* **1997**, *38*, 4437.
[14] D. F. Taber, T. E. Christos, A. L. Rheingold, I. A. Guzei, *J. Am. Chem. Soc.* **1999**, *121*, 5589.
[15] J. G. Boiteau, P. Van de Weghe, J. Eustache, *J. Org. Lett.* **2001**, *3*, 2737.
[16] D. A. Vosburg, S. Weiler, E. J. Sorensen, *Chirality* **2003**, *15*, 156.
[17] D. A. Vosburg, S. Weiler, E. J. Sorensen, *Angew. Chem. Int. Ed.* **1999**, *38*, 971.
[18] M. Hutchings, D. Moffat, N. S. Simpkins, *Synlett* **2001**, 661.
[19] W. Picoul, R. Urchegui, A. Haudrechy, Y. Langlois, *Tetrahedron Lett.* **1999**, *40*, 4797.
[20] W. Picoul, O. Bedel, A. Haudrechy, Y. Langlois, *Pure Appl. Chem.* **2003**, *75*, 235.
[21] S. Takano, K. Ogasawara, *J. Synth. Org. Chem. Jpn.* **1987**, *45*, 1157.
[22] S. Ohira, T. Ida, M. Moritani, T. Hasegawa, *J. Chem. Soc., Perkin Trans. 1* **1998**, 293.
[23] Y. Sakata, Y. Hirano, H. Tatemitsu, S. Misumi, H. Ochiai, H. Shibata, *Tetrahedron* **1989**, *45*, 4717.
[24] D. A. Evans, D. H. B. Ripin, D. P. Halstead, K. R. Campos, *J. Am. Chem. Soc.* **1999**, *121*, 6816.
[25] P. D. Bartlett, J. Myerson, *J. Am. Chem. Soc.* **1978**, *100*, 3950.
[26] NOE experiments showed a spatial interaction between 4-H and 3′-H.
[27] For a comprehensive review, see: H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483.
[28] Dihydroxylation of **15** without chiral ligand (OsO_4 cat., NMO, $MeSO_2NH_2$, *t*BuOH/H_2O) afforded a mixture of three compounds: the two regioisomeric diols and a small amount of tetrol.
[29] M. Ihara, I. Sudow, K. Fukumpto, T. Kametani, *J. Chem. Soc., Perkin Trans. 1* **1986**, 117.
[30] [30a] Y. Horikawa, M. Watanabe, T. Fujiwara, T. Takeda, *J. Am. Chem. Soc.* **1997**, *119*, 1127. [30b] For a recent review, see: R. C. Hartley, G. J. Mc Kiernan, *J. Chem. Soc., Perkin Trans. 1* **2002**, 2763.
[31] Takeda's reaction with the corresponding diphenyl dithioacetal derivative was also studied. However, compound **24** was isolated almost in the same yield.
[32] [32a] A. Hoppmann, P. Weyerstahl, *Tetrahedron* **1978**, *34*, 1723. [32b] For a recent use of this method, see: D. L. J. Clive, X. Huang, *Tetrahedron* **2002**, *58*, 10243.
[33] [33a] P. J. Kocienski, A. Bell, P. R. Blakemore, *Synlett* **2000**, 365. [33b] For a recent example of this olefination, see: C. Meyers, E. M. Carreira, *Angew. Chem. Int. Ed.* **2003**, *42*, 694.

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