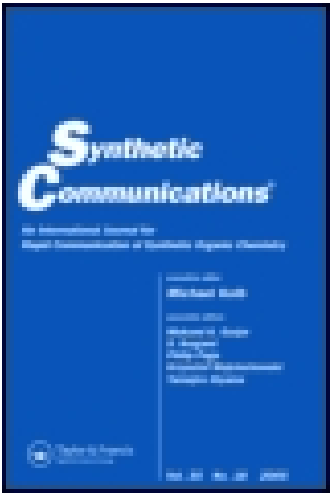

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Enantioselective Synthesis of A Wieland-Miescher Ketone Bearing an Angular Hydroxymethyl Group

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ENANTIOSELECTIVE SYNTHESIS OF A WIELAND-MIESCHER KETONE BEARING AN ANGULAR HYDROXYMETHYL GROUP

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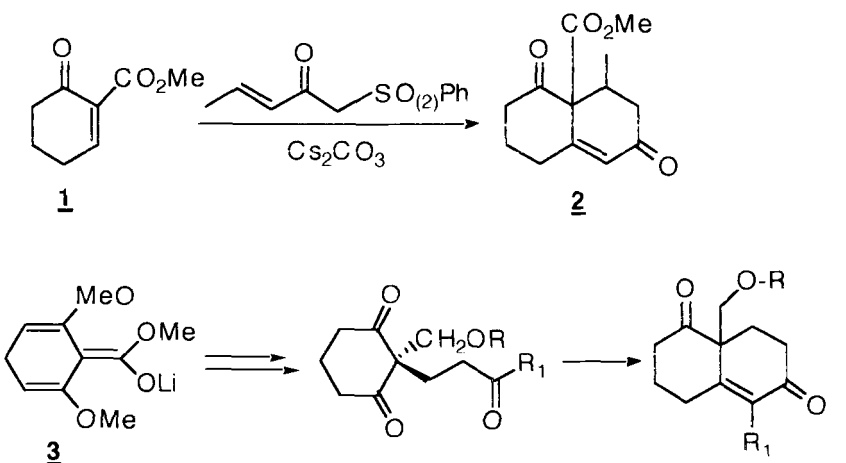
Abstract: The enatioselective synthesis of (R)-3,4,8,8a-tetrahydro-8a-allyl-1,6-(2H,7H)-naphthalenedione and the degradation of the angular allyl group to a hydroxymethyl group are reported.

Numerous terpenoidal natural products have been described in which a decalin ring system carries an oxygenated angular methyl group, of which several exhibit remarkable biological activities including insect antifeedant and anti HIV activity. Thus considerable effort has been spent to synthesize such natural products or simple analogs of them.[1] Biologically, the angular hydroxy methyl group is most likely formed via a late stage oxidation of a methyl group, however synthetically , it is more practical to introduce this functionality into an early intermediate.[2]

Wieland-Miescher ketone derivatives bearing an angular hydroxymethyl group (or a masked hydroxyl group) are particularly valuable inter-

mediates and considerable research has been carried out on the construction of such molecules. Thus, Deslongshamps et al.[3] synthesized racemic **2** and related molecules via cyclisation of 2-carbomethoxy -2-cyclohexenone **1** with substituted Nazarov reagents, while Uda et al.[4] synthesized **4** and **5** via alkylation of a dihydrodimethoxybenzene derivative **3** followed by an asymmetric Robinson annulation. This latter approach resembles that which Mander et al.[5] used to synthesize racemic **6** via intermediate **3** (Scheme 1).

Scheme 1:

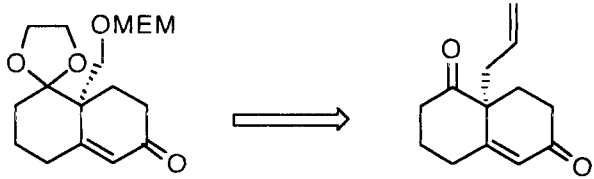


R_1=H; R=MEM **4**
R_1=Me; R=MOM **5**
R_1=H; R=MOM **6**

For an ongoing project, we needed multigram quantities of enantiomerically pure **7**. Although, the closely related compounds **4** and **6** had been synthesized by Uda et al[4] and Mander et al.,[5] the relatively low

enantiomeric excess (75%) for **6** and the difficulties in the final Robinson annulation encountered by Uda et al. and Mander et al., encouraged us to investigate alternative strategies. After initial attempts to synthesis **7** via cyclisation of 2-carbomethoxy-2-cyclohexenone **1** with suitable Nazarov reagent analogs failed,[6] we decided to explore the following approach. Good enantioselectivity has been reported in the preparation of the Wieland-Miescher ketone by the Robinson annulation of 2-methyl-1,3-cyclohexandione with methyl vinyl ketone.[7] Although functionalised methyl cyclohexandione derivatives are prone to eliminate or give complex mixtures on attempted Robinson annulation,[5] 2-allylcyclohexa-1,3-dione is known to react smoothly with methyl vinyl ketone, yielding the racemic Wieland-Miescher analog with an angular allyl moiety **8**.[8] We decided to try to prepare **8** enantioselectively, analogously to the racemic synthesis, but by means of an asymmetric Robinson annulation. Degradation of the allyl moiety in **8** to a hydroxy methyl group, and protection of the hydroxy- and ketone group should then yield our target molecule **7** (Scheme 2).

Scheme 2:

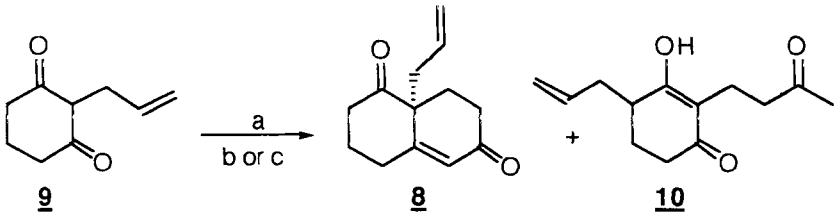


7 **8**

We started our approach from the readily available 2-allylcyclohexa-1,3-dione **9**.[9] Initial attempts to reproduce the racemic synthesis of **8** via the

intermediate Michael addition product and subsequent Robinson annulation with pyrrolidine as base, yielded a two component mixture, which was separated by column chromatography, yielding 4-allyl-2-(3-oxobutyl)-1,3-cyclohexadione **10** (52%), as well as the desired racemic **8** (18%) (Scheme 3). Further investigations revealed that the undesired byproduct **11** was mainly produced after all the methyl vinyl ketone had been consumed. Decreasing the amount of NaOH from 0.05 equivalents[10] to 0.02 equivalents, and immediately quenching the reaction when no 2-allylcyclohexa-1,3-dione was dedected by GC, gave a near quantitative yield of the intermediate Michael product, and after pyrrolidine induced Robinson annulation, **8** in 70% overall yield, together with minor amounts of **10** (10%).

Scheme 3:



9 **8** **10**

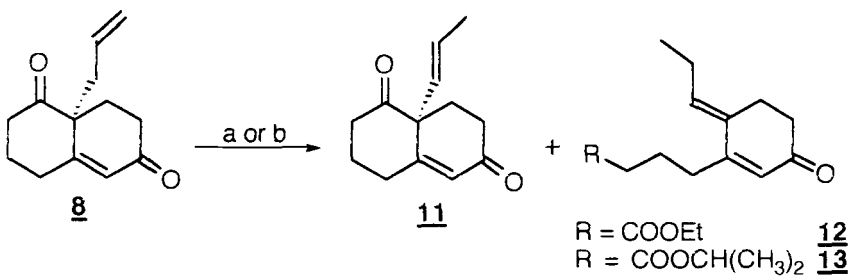
Reaction conditions: a) Methyl vinyl ketone, 80% aq. MeOH, NaOH (cat.), reflux; b) L-Proline, DMSO, rt; c) Pyrrolidine, benzene, reflux.

For the asymmetric synthesis of **8**, we treated the crude intermediate Michael adduct directly with L-proline in DMSO at room temperature, obtaining **8** as a yellow oil (ee=80%),[11] which was homogeneous by ^{1}H and ^{13}C-NMR. When it was stored at 0^{o} for several days, only a fraction of the oil crystallized, and this turned out to be the pure racemic form of **8**.

By diluting the scalemic mixture with hexanes/EtOH 3:1 and crystallising out the racemic form of **8**, a convenient method was found to obtain nearly enantiomerically pure **8** (ee>99%).[11]

Compound **8** was then treated with $RhCl_3$ in ethanol giving **11** and **12** as a 1:1 mixture. Surprisingly, in other solvent systems (benzene, butyl ether and isopropanol), we did not detect any product after several hours at reflux. The catalytic effect of an acid in rearrangements with $RhCl_3$ is known[12] and indeed adding conc.HCl as a cocatalyst to a solution of **8** in isopropanol gave **11** in 70% yield as well as 5% of **13** (scheme 4).

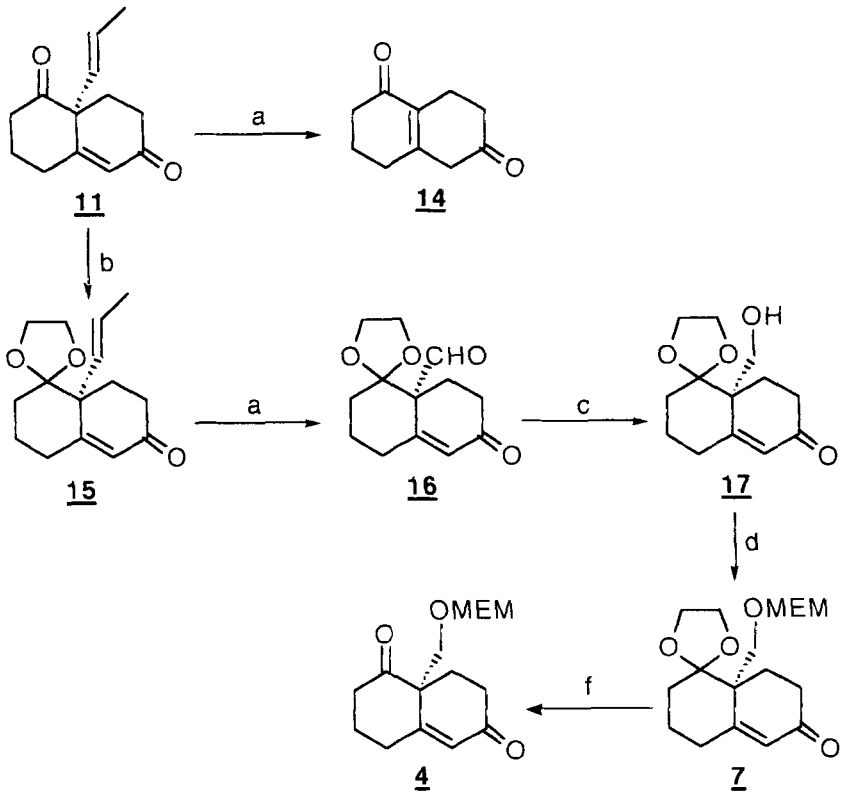
Scheme 4



Reaction conditions: a) $RhCl_3$, EtOH, reflux; b) $RhCl_3$, 2-propanol, conc.HCl, reflux

Compound **11** was then subject to ozonolysis in ethanol at -78°C. But to our surprise, after work up we isolated only the known product **14** [13]. We suspected that the strong electron withdrawing environment next to the quaternary center affected the mechanism of the methyl sulfide induced reduction of the intermediate ozonide, and that masking the ketone should change the outcome.

Scheme 5



Reaction conditions: a) O_3, EtOH, -78°C; b)2-Ethyl-2-methyl-1,3-dioxolane, TsOH, ethylene glycol, rt; c) $NaBH_4$, MeOH/CH_2Cl_2 (1:1), -78°C; d) MEMCl, diisopropylethyl amine, CH_2Cl_2, reflux; e) Champhorsulfonic acid, acetone, reflux.

Indeed, after protection of the ketone as a dioxolane **15** and ozonolysis, the aldehyde **16** was obtained quantitatively. Chemoselective reduction of **16** with $NaBH_4$[14] and protection of the hydroxy group in **17**, yielded the target molecule **7** (scheme 5).

The absolute configuration of **7** was established by converting **7** into the

known[4] compound **4** by hydrolysis of the dioxolane with camphorsulfonic acid in acetone, yielding **4** with the absolute stereochemistry as depicted in scheme 5.

Thus, a convenient synthetic route has been developed to synthesize an enantiomerically pure angular allyl Wieland-Miescher ketone in 53% yield,[15] and angular hydroxymethyl Wieland-Miescher ketone derivatives in an overall yield of 25% from 2-allylcyclohexa-1,3-dione **9**.

Experimental Part

Thin layer chromatography (TLC) was performed on Merck SilG 60 F_{254} with hexane/ethyl acetate 1:2 as eluent. Spots were made visible with UV light. Gas chromatography (GC) was performed on a Shimazu gas chomatograph GC 9A equipped with a flame ionization detector and a Megabore DB1 (15 m) column. The temperature program was 150°C for 5min., 10°C increase per min., 200°C for 20 min. Flash column chromatography was performed on Merck silica gel 60 (230-400 mesh) with distilled solvents.

Melting points were determined on a Leitz microscope hot-stage melting point apparatus and are uncorrected. Infrared spectra were recorded on a Mattson Instrument 4030 Galaxy FT-IR spectrometer. Optical rotations were recorded on a Rudolph AutoPol III polarimeter. Proton magnetic resonance spectra (^{1}H-NMR) and ^{13}C magnetic resonance spectra (^{13}C- NMR) were measured on a Bruker AM-400 NMR spectrometer.

(R)-3,4,8,8a-Tetrahydro-8a-allyl-1,6-(2H,7H)-naphthalenedione (**8**)

A solution of 2-allylcyclohexa-1,3-dione (10g, 65.7mmol), 10% aqueous

KOH (0.74 ml, 1.32mmol) and methyl vinyl ketone (6.91g, 98.6mmol) in 80% aqueous MeOH (400 ml) was refluxed for 75min. The solution was poured into ice/water, acidified with 10% aqueous HCl and extracted with $CHCl_3$ (3x75ml). The combined organic extracts were washed with brine (2x20ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residual oil was dissolved in DMSO (130ml) and L-proline (7.56g, 65.7mmol) was added. The mixture was stirred overnight at room temperature. The dark mixture was poured into ice/10% aqueous HCl and extracted with $CHCl_3$ (3x75ml). The combined organic extracts were washed with brine (2x10ml), dried with $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel (elution with hexane/ethyl acetate 2:1) and kugelrohr distillation (90-120°C/0.025Torr) yielding **8** as a yellow oil (8.8g, 66%, ee=80%).[11]

The scalemic mixture was dissolved in hexane/EtOH 3:1 (30ml) and stored at 0°C overnight. The crystals were filtered and dried under high vacuum, yielding racemic **8** (860mg, 6.4%) as white crystals. The supernatent was evaporated under reduced pressure and kugelrohr distilled (90-120°C/0.025Torr) yielding enantiomerically pure **8** as a yellow oil (7.1g, 53%). $[\alpha]^{25}_D$ +90° (c1.1, $CHCl_3$); ^{1}H-NMR (400MHz, $CDCl_3$):[16] δ 5.86 (1H, s, H-5), 5.61-5.50 (1H, m, $-CH_2-\underline{CH}=CH_2$), 5.12-5.08 (2H, m, $-CH_2-CH=\underline{CH_2}$), 2.77-2.05 (11H, m), 1.70-1.66 (1H, m, H'-3); ^{13}C- NMR (400 MHz, $CDCl_3$: DEPT): δ 209.0 (s, C-1), 197.9 (s, C-6), 164.6 (s, C-4a), 131.3 (d, $-CH_2-\underline{CH}=CH_2$), 126.2 (d, C-5), 119.1 (t, $-CH_2-CH=\underline{CH_2}$), 54.4 (s, C-8a), 39.5 (t, C-4), 38.1 (t, C-9), 33.1 (t, C-7), 31.6 (t, C-2), 25.9 (t, C-8), 23.0 (t, C-3); Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.35; H, 7.67; IR (5% in CCl_4, cm^{-1}): 1680, 1713.

4-Allyl-2-(3-oxobutyl)-1,3-cyclohexadione **(10)**

mp. 81-82°C; ^{1}H-NMR (400MHz, $CDCl_3$): δ 5.83-5.72 (1H, m, CH_2=CH-CH_2-), 5.07-5.02 (2H, m, CH_2=CH-CH_2-), 2.65-2.57 (3H, m, CH_2=CH-CH_2-, -$CH_2CH_2COCH_3$), 2.42-2.34 (4H, m, H-6, -$CH_2CH_2COCH_3$), 2.31-2.23 (1H, m, H-4), 2.14-2.08 (1H, m, CH_2=CH-CH_2-), 2.13-1.99 (1H, m, H'-5), 1.96 (3H, s, -$CH_2CH_2COCH_3$), 1.70-1.60 (1H, m, H-5); ^{13}C-NMR (400MHz, $CDCl_3$: DEPT): δ 199.8 (s, -$CH_2CH_2COCH_3$), 178.8 (s, C-3), 155.9 (s, C-1), 136.4 (d, CH_2=CH-CH_2-), 133.2 (s, C-2), 116.6 (t, CH_2=CH-CH_2-), 45.4 (d, C-5), 34.1 (t, CH_2=CH-CH_2-), 33.1 (t, C-6 or -$CH_2CH_2COCH_3$), 31.9 (t, C-6 or -$CH_2CH_2COCH_3$), 26.7 (t, C-5), 21.1 (t, -$CH_2CH_2COCH_3$), 21.1 (q, -$CH_2CH_2COCH_3$); MS *m/z* : 222 (M^+, 44), 204 (35), 176 (33), 163 (45), 154 (57), 55 (100).

(R)-3,4,8,8a-Tetrahydro-8a-(1-propenyl)-1,6-(2H,7H)-naphthalenedione **(11)**

To a solution of **8** (4.0g, 19.6mmol) in isopropyl alcohol (140ml) was added $RhCl_3 \cdot 3\ H_2O$ (258mg, 0.98mmol) and 8 drops of conc.HCl from a Pasteur pipette. After refluxing the mixture for one hour the same amount of $RhCl_3 \cdot 3\ H_2O$ and conc.HCl as above were added and the mixture was refluxed for an other hour. Evaporation under reduced pressure of the red solution gave an oil, which was diluted with diethyl ether (200ml). The red suspension was stirred for 30min. at room temperature and then filtered. The supernatent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (elution with hexane/ethyl acetate 2:1), which gave **11** (2.9 g) and **13** (201mg, 3.9%) as slightly yellow oils. The main fraction was further purified by kugelrohr distillation (100-140°C/0.025Torr) yielding **11** as a slightly yellow oil

(2.8g, 70%). $[\alpha]^{25}_D$ -55.1° (c1.1, $CHCl_3$); ^{1}H-NMR (400MHz, $CDCl_3$): δ 5.95 (1H, s, H-5), 5.54 (1H, dq, J = 15.6, 6.5 Hz, -CH=CHCH$_3$), 5.23 (1H, dq, J = 15.6, 1.2 Hz, -CH=CHCH$_3$), 2.69-2.02 (9H, m), 1.69 (3H, dd, J = 6.5, 1.2 Hz, -CH=CHCH$_3$), 1.68-1.55 (1H, m, H'-3); ^{13}C- NMR (400 MHz, $CDCl_3$: DEPT): δ 208.5 (s, C-1), 198.6 (s, C-6), 163.1 (s, C-4a), 130.0 (d), 129.1 (d), 127.6 (d), 57.8 (s, C-8a), 38.6 (t, C-4), 33.3 (t, C-7), 32.3 (t, C-2), 29.5 (t, C-8), 22.6 (t, C-3), 17.9 (q, -CH=CHCH$_3$); MS *m/z* : 204 (M^+, 41), 176 (15), 147 (15), 119 (81), 106 (95), 91 (100); HRMS *m/z* (M^+) calc. 204. 1150, obsd. 204. 1157; IR (5% in CCl_4, cm^{-1}): 1679, 1717.

13: ^{1}H-NMR (400 MHz, $CDCl_3$).[17] δ 5.99 (1H, t, J = 7.3 Hz, -C=CHCH$_2$CH$_3$), 5.82 (1H, s, H-5), 5.00 (1H, hpt. J = 6.3 Hz, (CH$_3$)$_2$CHOOC-), 2.67 (2H, t, J = 7.1 Hz, H-8), 2.43-2.30 (8H, m), 1.85 (2H, m, H-3), 1.22 (6H, d, J = 6.3 Hz, (CH$_3$)$_2$CHOOC-), 1.06 (3H, t, J = 7.6 Hz, -C=CHCH$_2$CH$_3$); ^{13}C- NMR (400 MHz, $CDCl_3$: DEPT): δ 199.6 (s, C-6), 172.5 (s, (CH$_3$)$_2$CHOOC-), 158.8 (s, C-4a), 134.5 (d, -C=CHCH$_2$CH$_3$), 132.1 (s, C-8a), 125.4 (d, C-5), 67.7 (d, (CH$_3$)$_2$CHOOC-), 37.1 (t), 34.1 (t), 32.5 (t), 25.1 (t), 24.0 (t), 21.8 (t), 21.8 (q, (CH$_3$)$_2$CHOOC-), 13.8 (q, -C=CHCH$_2$CH$_3$); MS *m/z* : 264 (M^+,82), 222 (75), 163 (100), 91 (80); HRMS *m/z* (M^+) calc. 264.1725, obsd. 264. 1711; IR (5% in CCl_4, cm^{-1}): 1674, 1730.

By product **(12)**

Obtained as a pale yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$)[17]: δ 5.97 (1H, t, J=7.3Hz, C=CHCH$_2$CH$_3$), 5.81 (1H, d, J=3.9Hz, H-5), 4.11 (q, J=7.1Hz, -COOCH$_2$CH$_3$), 2.65 (2H, t, J=7.5Hz, H-8), 2.44-2.19 (8H, m), 1.89-1.79 (2H, m, H-3), 1.24 (3H, t, J=7.1Hz, -COOCH$_2$CH$_3$), 1.05 (3H, t, J=7.5Hz,

C=CHCH$_2$CH$_3$); ^{13}C- NMR (400 MHz, CDCl$_3$: DEPT): δ 199.6 (s, C-6), 173.0 (s, -COOCH$_2$CH$_3$), 158.7 (s, C-4a), 134.5 (d, -C=CHCH$_2$CH$_3$), 132.1 (s, C-8a), 125.4 (d, C-5), 60.3 (t, -COOCH$_2$CH$_3$), 37.1 (t), 33.6 (d), 32.4 (t), 25.0 (t), 23.9 (t), 21.8 (t), 14.2 (q), 13.8 (q); MS *m/z* : 250 (M$^+$,100), 221 (15), 205 (23), 163 (81), 91(95).

(R)-3,4,8,8a-Tetrahydro-8a-(1-propenyl)-1,6-(2H,7H)-naphthalenedione-1-ethylene acetal (**15**)

A mixture of **11** (2.75g, 13.5mmol), 2-ethyl-2-methyl-1,3-dioxolane (10.1ml, 80.8mmol), ethylene glycol (0.15ml, 2.7mmol) and p-toluene sulfonic acid monohydrate (0.192g, 1mmol) was stirred at room temperature for 24h. The solution was poured into ice/water, basified with 10% aqueous NH$_3$ and extracted with CHCl$_3$ (5x50ml). The combined organic extracts were washed with brine (2x10ml), dried with MgSO$_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with hexane/ethyl acetate 2:1) yielding **15** as a yellow oil (2.50 g, 75%). $[\alpha]^{25}_D$ +132° (c1.1, CHCl$_3$); ^{1}H-NMR (400MHz, CDCl$_3$): δ 5.98 (1H, d, J=2.1Hz, H-5), 5.61 (1H, dq, J=15.9, 1.6Hz, -CH=CHCH$_3$), 5.32 (1H, dq, J=6.4, 15.9Hz, -CH=CHCH$_3$), 4.00-3.95 (4H, m, -OCH$_2$CH$_2$O-), 2.40-2.22 (4H, m), 1.73 (3H, dd, J=6.4, 1.6Hz, -CH=CHCH$_3$), 1.79-1.65 (6H, m); ^{13}C-NMR (400MHz, CDCl$_3$: DEPT): δ 199.6 (s, C-6), 164.5 (s, C-4a), 130.2 (d), 128.2 (d), 127.9 (d), 111.7 (s, C-1), 65.3 (t, -OCH$_2$CH$_2$O-), 64.9 (t,-OCH$_2$CH$_2$O-), 52.9 (s, C-8a), 33.1 (t), 31.9 (t), 31.4 (t), 25.5 (t), 21.8 (t), 18.1 (q, -CH=CHCH$_3$); MS *m/z* : 248 (M$^+$,21), 119 (11), 105 (18), 99 (100), 91 (31), 55 (90); HRMS *m/z* (M$^+$) calc. 248.1412, obs. 248.1399; IR (5% in CCl$_4$, cm^{-1}): 1678.

(S)-3,4,8,8a-Tetrahydro-8a-(formyl)-1,6-(2H,7H)-naphthalenedione-1-ethylene acetal (**16**)

A solution of **15** (1.7g, 6.9mmol) in ethanol (200ml) was ozonised for 2.5h at -78°C until no starting material was dedected by TLC. The solution was degassed by passing a stream of N_2 through the solution for 10min and then excess methyl sulfide (10ml) was added at -78°C. The solution was stirred in a defreezing acetone/CO_2 bath for 4h. After removal of the solvent under reduced pressure, **16** was obtained as white crystals (1.62g, 100%). Mp. 121-122°C; $[\alpha]^{25}_D$+203° (c1.1, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.76 (1H, s, -CHO), 6.01 (1H, d, J=0.7 Hz, C-5), 4.10-3.98 (4H, m, -OCH_2CH_2O-), 2.41-1.50 (10H, m); ^{13}C-NMR (400MHz, $CDCl_3$: DEPT): δ 200.5 (s, -CHO), 197.7 (s, C-6), 159.4 (s, C-4a), 128.5 (d, C-5), 109.6 (s, C-1), 65.5 (t, -OCH_2CH_2O-), 65.0 (t, -OCH_2CH_2O-), 61.9 (s, C-8a), 33.8 (t), 33.3 (t), 32.7 (t), 21.6 (t), 21.3 (t); MS *m/z* : 236 (M^+,22), 207 (12), 148 (12), 99 (100); Anal. Calcd. for C_{13} H_{16} O_4: C, 66.09; H, 6.83. Found: C, 66.11; H, 6.89; IR (KBr, cm^{-1}): 1655, 1711.

(S)-3,4,8,8a-Tetrahydro-8a-(hydroxymethyl)-1,6-(2H,7H)-naphthalenedione-1-ethylene acetal (**17**)

To a solution of **16** (1.25g, 5.3mmol) in CH_2Cl_2/MeOH 1:1 (30ml) was added $NaBH_4$ (1.0g, 26.45mmol) at -78°C. The suspension was stirred for 45min. and then quenched with acetone (5ml) and stirred for 30min. The suspension was poured into ice/water, basified with 10% aqueous NaOH and extracted with $CHCl_3$ (3x30ml). The combined organic extracts were washed with brine (2x10ml), dried with $MgSO_4$ and evaporated under reduced pressure, yielding **17** as white crystals (1.21g, 96%). Mp. 105-108°C; $[\alpha]^{25}_D$ +117° (c1.1, $CHCl_3$); ^{1}H-NMR (400MHz,

$CDCl_3$): δ 5.88 (1H,s, H-5), 4.13 (1H, d, J=11.9Hz, -$\underline{CH_2}$OH), 4.04-3.93 (4H, m, -O$\underline{CH_2CH_2}$O-), 3.67 (1H, dd, J=10.2Hz, 11.9Hz, -$\underline{CH_2}$OH), 3.09 (1H, d, J=10.2Hz, -$CH_2\underline{OH}$), 2.49-1.62 (10H, m); ^{13}C-NMR (400MHz, $CDCl_3$: DEPT): δ 198.9 (s, C-6), 163.5 (s, C-4a), 127.3 (d, C-5), 112.9 (s, C-1), 65.4 (t, -O$\underline{CH_2}CH_2$O-), 64.6 (t, -OCH$_2\underline{CH_2}$O-), 64.5 (t, -$\underline{CH_2}$OH), 49.6 (s, C-8a), 33.8 (t), 32.2 (t), 30.7 (t), 21.7 (t), 21.5 (t); MS *m/z* : 238 (M^+,8), 208 (32), 164 (45), 99 (100); Anal. Calcd. for C_{13} H_{18} O_4: C, 65.53; H, 7.62. Found: C, 65.24; H, 7.67; IR (KBr, cm^{-1}): 1653.

(S)-3,4,8,8a-Tetrahydro-8a-(((2-methoxyethoxy)methoxy)methyl)-1,6-(2H, 7H) naphthalenedione-1-ethylene acetal (**7**)

To a solution of **17** (200mg, 0.84mmol) and N, N-diisopropylethylamine (0.716 g, 5.5mmol) in CH_2Cl_2 (10ml) was added 2-methoxyethoxymethyl chloride (0.627g, 5.1mmol) at 0°C. The solution was stirred at 0°C for 10min. and then slowly warmed up and refluxed for 3h. The mixture was poured into ice/10% aqueous HCl and extracted with $CHCl_3$ (3x5ml). The combined organic extracts were washed with brine (2x5ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with hexane/ethyl acetate 1:1), yielding **7** as a clear oil (240 mg, 88 %). ^{1}H-NMR (400MHz, $CDCl_3$): δ 5.93 (1H, s, H-5), 4.65 (1H, d, J=6.8Hz, -O$\underline{CH_2}$OCH$_2$CH$_2$OCH$_3$), 4.63 (1H,d, J=6.8Hz, -O$\underline{CH_2}$O CH$_2$CH$_2$OCH$_3$), 4.02 (1H, d, J=9.6Hz, -CH$_2$O-), 3.96-3.91 (4H, m, -O$\underline{CH_2CH_2}$O-), 3.74 (1H, d, J=9.6Hz, -CH$_2$O-), 3.62-3.49 (4H, m, -OCH$_2$O$\underline{CH_2CH_2}$OCH$_3$), 3.35 (3H, s, -OCH$_2$O-CH$_2$CH$_2$O$\underline{CH_3}$), 2.61-2.24 (5H, m), 1.94-1.67 (5H, m); ^{13}C-NMR (400MHz, $CDCl_3$: DEPT): δ 199.9 (s, C-6), 163.4 (s, C-4a), 127.6 (d, C-5), 111.8 (s, C-1), 95.6 (t, -O$\underline{CH_2}$OCH$_2$CH$_2$OCH$_3$), 72.2 (t,

-$OCH_2OCH_2CH_2OCH_3$), 71.6 (t, -OCH_2O-$CH_2CH_2OCH_3$), 67.0 (t, -CH_2O-), 65.3 (t, -OCH_2CH_2O-), 64.7 (t, -OCH_2CH_2O-), 58.9 (q, -$OCH_2OCH_2CH_2OCH_3$), 49.2 (s, C-8a), 34.9 (t), 32.1 (t), 30.9 (t), 24.8 (t), 22.2 (t); MS *m/z* : 326 (M^+, 12), 251 (15), 221 (45), 99 (100); HRMS *m/z* (M^+) calc. 326.1729, obs. 326.1707; IR (5% in CCl_4, cm^{-1}): 1674.

(S)-3,4,8,8a-Tetrahydro-8a-(((2-methoxyethoxy)methoxy)methyl)-1,6-(2H,7H)-naphthalenedione **(4)**

A mixture of **7** (35mg, 0.11mmol) and (±)-camphorsulfonic acid (30mg, 0.13mmol) in acetone (4ml) was refluxed for 15h. The solution was poured into 10% aqueous Na_2CO_3/ice and extracted with $CHCl_3$ (3x2ml). The combined organic extracts were washed with brine (2x2ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with hexane/ethyl acetate 1:2), yielding the known compound **4** as a clear oil (24mg, 80%). $[\alpha]^{25}_D$ +102.8° (c0.14, $CHCl_3$), [lit.[4] $[\alpha]_D$ +76.6° (c0.14, $CHCl_3$); **4** had identical spectroscopic properties with those published.[4]

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References and Footnotes

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10. Reusch et al.,[8] only published a vague description of the amount of NaOH they used (one pellet of NaOH), which was approximated to be roughly 0.05 equivalents.

11. The enantiomeric excess of **8** was determined by means of a 1:1 molar mixture of the chiral shift reagent europium tris(d,d-dicampholymethanate) and **8** in $CDCl_3$, which induced a Δ of 0.15ppm to the H-5's of the two antipodes in the ^{1}H-NMR.

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15. During the preparation of this manuscript, Ziegler et al. published a paper in which they used racemic **8** for the total synthesis of (±)-Scopadulcic acid A and B and (±)-Scopadulciol as well as reporting preliminary studies about the synthesis of chiral **8** (Ziegler, E. F.; Wallace, O. B. *J. Org. Chem.* **1995**, *60*, 3626).

16. ^{1}H-NMR (100 MHz, $CDCl_3$) according Reusch et. al:[8] d 5.8 (m, 1H), 5.2 (m, 3H), 2.0-2.9 (m, 12H). Those data are somewhat

erroneous in that H'-3 at 1.70-1.66 ppm was not reported and instead was assumed to be underneath the unresolved multiples between 2.0-2.9 ppm. However, COSY and HSC spectra clearly revealed that this multiplet at 1.70-1.66 ppm has to be assigned to H'-3.

17. Wieland-Miescher ketone numbering

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