ENANTIOSELECTIVE SYNTHESIS OF A TAXOL C RING

Cong MA[a1], Stéphanie SCHILTZ[a2] and Joëlle PRUNET[b,*]

[a] *Laboratoire de Synthèse Organique, CNRS UMR 7652, Ecole Polytechnique, DCSO, F91128 Palaiseau, France; e-mail: [1] ma@dcso.polytechnique.fr, [2] schiltz@dcso.polytechnique.fr*

[b] *WestCHEM, School of Chemistry, University of Glasgow, Joseph Black Building, University Avenue, Glasgow G12 8QQ, UK; e-mail: joelle.prunet@glasgow.ac.uk*

Received February 10, 2011
Accepted July 1, 2011
Published online December 23, 2011

Dedicated to Professor Pavel Kočovský on the occasion of his 60th birthday.

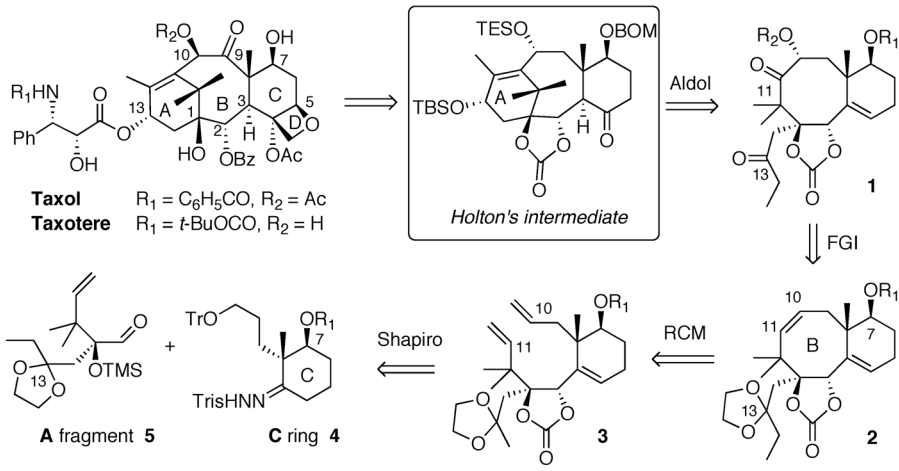
An enantioselective synthesis of a C ring of taxol has been accomplished. The key step is an oxidative cleavage of a derivative of the Wieland–Miescher ketone. A first attempt of a Shapiro reaction modelling the coupling of the C ring with the A fragment of taxol was also successful.

Keywords: Taxol; Wieland–Miescher ketone; Shapiro reaction; Synthesis design; Ozonolysis; Terpenoids.

Taxol® (paclitaxel) and taxotere® (docetaxel) (Scheme 1) are the highest-selling anticancer drugs of all time, with sales of over 3 billion USD/year for all the taxane market. They are used mainly against ovarian and breast cancers, and have also found use against non-small cell lung cancer[1]. In spite of numerous synthetic approaches, including six total syntheses[2] and a formal synthesis[3], they still constitute a remarkable challenge for organic chemists because of their densely functionalized structure, which encompasses an eight-membered ring.

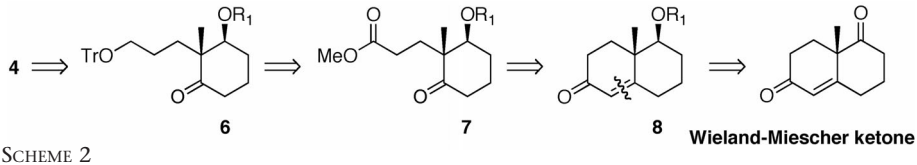
The retrosynthesis that we envisioned for taxol is delineated below (Scheme 1). The primary target is an intermediate in Holton's synthesis of taxol, which contains the ABC tricyclic scaffold with all the required functionalities. The A ring would be installed at a late stage by an intramolecular aldol reaction on diketone **1** at C11 and C13[4]. Bicycle **2**, available from compound **1** by a few functional group interconversions, would be formed by a ring-closing metathesis that would close the B ring between C10 and C11. The metathesis precursor **3** would be prepared by a Shapiro reaction between the vinyllithium derived from hydrazone **4** and aldehyde **5**.

doi:10.1135/cccc2011039



SCHEME 1

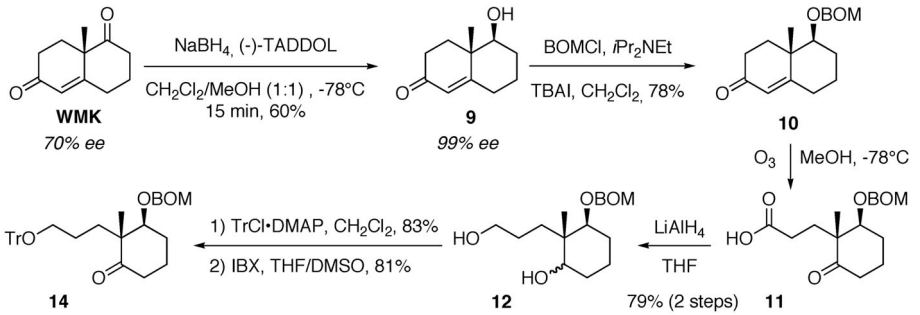
We have successfully synthesized model BC ring systems of taxol corresponding to compound **2** (with no protected hydroxy group at C7 and no ketal at C13)[5]. We planned an enantioselective synthetic route of the C ring inspired by the synthesis of the 7-deoxy C ring we previously reported[5k]. The target hydrazone **4** would be formed from the corresponding ketone **6**, which would be obtained from keto ester **7** (Scheme 2). This keto ester would be formed by oxidative cleavage of the derivative **8** of the Wieland–Miescher ketone[6].



SCHEME 2

Wieland–Miescher ketone (WMK) was synthesized under Hajos–Parrish conditions in the expected 70% ee [7]. Recrystallization was low yielding in our hands, so we adapted a procedure reported by Toda and co-workers for the chemoselective and enantioselective reduction of the saturated ketone function[8] in order to obtain the next intermediate in our synthesis in an efficient manner (Scheme 3). Reduction of WMK (70% ee) in 1:1 dichloromethane/MeOH at –78 °C in the presence of one equivalent of (–)-taddol led to enantiopure alcohol **9** (Scheme 3). In accord with literature precedent, **9** was formed in 99% ee (determined by comparing the optical rota-

tions). The undesired enantiomer decomposed during the reaction, and no reduction of the unsaturated ketone was observed. Since our target is the advanced intermediate in Holton's synthesis, protection of the hydroxy group as the BOM ether was chosen at first, and compound **10** was formed in 78% yield. When we used ruthenium trichloride and oxone, the oxidative cleavage of enone **10** led to the desired product in less than 10% conversion[9], but ozonolysis of **10** in methanol furnished acid **11**. In this reaction, some decomposition was always observed, probably due to partial oxidation of the BOM ether by ozone. These results are in stark contrast with the observations of Cravero et al.[10], who showed that oxidation of a compound similar to **10** could be performed with ruthenium dioxide and sodium periodate, but not with ozone. Reduction of keto acid **11** with $LiAlH_4$ gave diol **12** as a 1:1 mixture of diastereomers. Selective protection of the primary alcohol as the trityl ether **13** followed by oxidation of the secondary alcohol with iodoxybenzoic acid (IBX)[11] afforded ketone **14** in good overall yield.

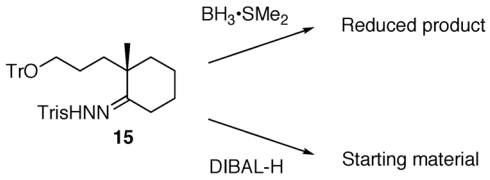


SCHEME 3

Unfortunately, transformation of the carbonyl group of **14** to the hydrazone performed with catalytic HCl led to removal of the trityl group, and the BOM ether was also not stable under these conditions. This side reaction was not observed in our previous studies on the 7-deoxy C ring[5k]. No reaction occurred under the conditions Smith and co-workers used in his approach to spongistatin 1, which transformed a ketone to the corresponding hydrazone without HCl in excellent yield[12].

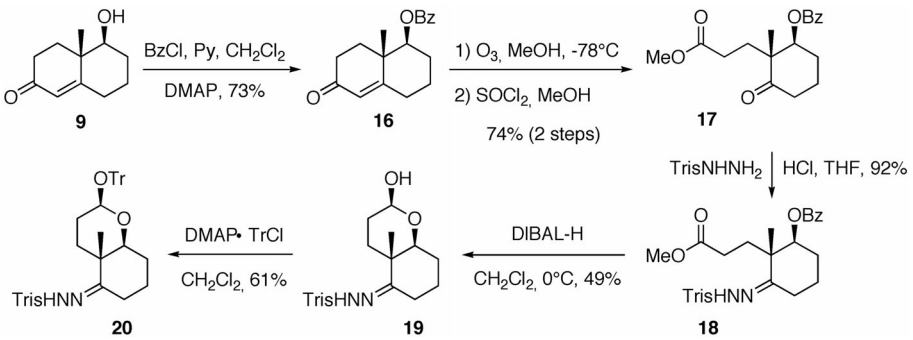
Since HCl was necessary for the formation of the hydrazone, we thought of realizing this step before protection of the diol group of the target molecule. In other words, the hydrazone moiety must tolerate reduction conditions under which the diol function would be obtained. Reduction assays of

model hydrazone **15** [5k] with dimethyl sulfide borane and DIBAL-H, that are normally unreactive towards imines, were performed. Only the latter did not reduce the hydrazone group (Scheme 4).



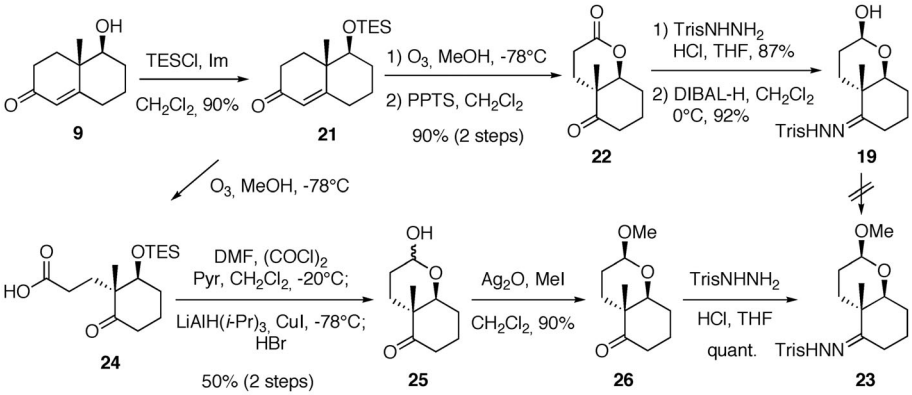
SCHEME 4

The synthesis plan for the C ring was thus slightly modified: hydrazone formation would be realized after the ozonolysis and esterification of the corresponding product, and formation and protection of the diol group would be carried out at a later stage. A benzoate was selected to protect temporarily the alcohol function of **9**, because this protecting group would be removed during the reduction of the ester. Benzoate **16** was produced in 73% yield from alcohol **9** (Scheme 5). Ozonolysis of **16** gave the corresponding carboxylic acid, which was directly submitted to $SOCl_2$ in MeOH to afford methyl ester **17**. Transformation of the carbonyl group of **17** to the hydrazone led to compound **18**. Unfortunately, reduction of **18** with four equivalents of DIBAL-H did not furnish the desired hydrazone but led to hemiacetal **19** in 49% yield. When only three equivalents of DIBAL-H were added to the reaction, the aldehyde peak was observed in ^{1}H NMR spectrum of the crude extract, but this compound could not be isolated. Subsequent treatment of hemiacetal **19** with 4-dimethylamino-*N*-triphenylmethylpyridinium chloride afforded the corresponding trityl acetal **20** in 61% yield[13].



SCHEME 5

At this point, we considered that the methyl acetal analogue of compound **20** could be an alternative precursor for the Shapiro reaction, and this compound became our targeted C ring. However, the reduction of diester **18** to hemiacetal **19** was not satisfying, so we devised a new synthesis for hemiacetal **19** via lactone **22** (Scheme 6). Direct ozonolysis of alcohol **9** only led to decomposition products. To avoid this decomposition, alcohol **9** was converted to the corresponding triethylsilyl ether **21**. Ozonolysis of **21** followed by acidic treatment of the resulting keto acid (**24**) furnished lactone **22** in excellent overall yield. Transformation of ketone **22** to the hydrazone and DIBAL-H reduction of the lactone moiety afforded lactol **19**, which was identical to the hemiacetal obtained by the previous route. Protection of the hemiacetal group as the methyl acetal was attempted using several methods. Not surprisingly, PPTS with methyl orthoformate hydrolyzed the hydrazone function, but MeI in the presence of NaH or Ag_2O [14] was also unsuccessful and only led to decomposition products[13].

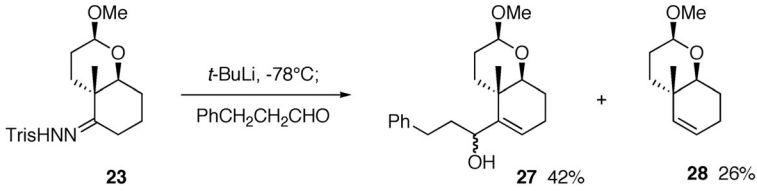


SCHEME 6

We then decided to install the hemiacetal protecting group before the formation of hydrazone. Chemoselective reduction of carboxylic acid **24** to the aldehyde using the Vilsmeier–Haack reagent was realized under Lebreton's conditions[15] (Scheme 6). Vilsmeier–Haack reagent was formed by mixing a large excess of DMF and oxalyl chloride at –20 °C, then crude carboxylic acid **24** was added followed by the reductive reagent; finally, acidic treatment *in situ* removed the TES group and furnished a 1:1 mixture of epimeric hemiacetals **25**. We then attempted to form the corresponding methyl acetal **26**. Curiously, no reaction occurred in the presence of PPTS and methyl orthoformate, but silver(I) oxide promoted methylation of **25**

to afford methyl acetal **26** in excellent yield[14]. Finally, transformation of **26** to hydrazone **23** proceeded in quantitative yield.

With hydrazone **23** in hand, we then tested the Shapiro reaction on a model aldehyde. Hydrocinnamaldehyde was added to the reaction mixture containing the vinyl anion that was formed by treatment of **23** with two equivalents of *t*-BuLi. Adduct **27** and alkene **28**, formed by protonation of the intermediate vinyl anion, were obtained in 42 and 26% respective unoptimized yields (Scheme 7).



23 **27** 42% **28** 26%

SCHEME 7

In conclusion, an enantiopure C ring of taxol was synthesized in six steps from the WMK in 24% overall yield. In addition, a first attempt of a Shapiro reaction modelling the coupling of the C ring with the A fragment was also successful.

EXPERIMENTAL

All air and/or water sensitive reactions were carried out under an argon atmosphere with dry, freshly distilled solvents using standard syringe-cannula/septa techniques. All corresponding glassware was carefully dried under vacuum with a flameless heat gun. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone. Flash chromatography was performed using silica gel 60, 230–400 mesh.

^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker AM 400 (400 MHz) or a Bruker Avance 400 (400 MHz) instrument. The chemical shifts are expressed in parts per million (δ, ppm) referenced to residual chloroform (7.27 ppm). Data are reported as follows: δ, chemical shift; multiplicity (recorded as br, broad; s, singlet; d, doublet; t, triplet; q, quartet; hex, hexuplet; hept, heptuplet; oct, octuplet and m, multiplet), integration and coupling constants (*J*, Hz). ^{13}C NMR spectra were recorded on the same instruments at 100.6 MHz. The chemical shifts are expressed in parts per million (δ, ppm), reported from the central peak of deuterochloroform (77.00 ppm). Assignments were obtained using J-mod or DEPT experiments, and when necessary, COSY, NOESY, HSQC and HMBC experiments. Taxol numbering is used for reporting assignments.

Infrared spectra (IR) were obtained on a Perkin–Elmer FT 1600 instrument and are reported in terms of frequency of absorption (ν, cm^{-1}).

Optical rotations were determined on a Perkin–Elmer 241-instrument operating at the D-line of Na and are reported as follows: $[\alpha]_D^{20}$ (g/100 ml, solvent).

Mass spectra (MS) were obtained on a Hewlett–Packard HP 5989B spectrometer via either direct injection or GC/MS coupling with a Hewlett–Packard HP 5890 chromatograph. Ioniza-

tion was obtained either by electron impact (EI) or chemical ionization with ammonia (CI, NH_3) or methane (CI, CH_4). Mass spectrum data are reported as *m/z*. High resolution mass spectra (HRMS) were performed with a Jeol GC Mate II apparatus, by direct introduction of the compound, in magnet mode.

(4a*S*,5*S*)-5-Hydroxy-4a-methyl-4,4a,5,6,7,8-hexahydro-3*H*-naphthalen-2-one (**9**)[8]

Acetic acid (50 µl), hydroquinone (1.8 mg, 0.16 mmol, 0.02 equiv.) and freshly distilled methyl vinyl ketone (2.2 g, 32 mmol, 2.0 equiv.) were added to a solution of 2-methyl-1,3-cyclohexanedione (2.0 g, 16 mmol) in distilled water (5 ml) at room temperature. The reaction mixture was stirred for 1 h at 80 °C, then cooled to room temperature, treated with NaCl (1.6 g) and diluted with AcOEt (6 ml). The layers were separated, and the aqueous phase was extracted with AcOEt. The combined organic layers were washed twice with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. The crude trione was dissolved in dried DMSO (20 ml) and recrystallized L-proline (92 mg, 0.8 mmol, 0.05 equiv.) was added. The mixture was stirred at room temperature for 6 days. The solvent was then evaporated and the residue was filtered through a pad of silica gel to give the crude WMK. To a solution of crude WMK and (–)-taddol (7.5 g, 16 mmol, 1.0 equiv.) in $MeOH/CH_2Cl_2$ (100 ml, 1:1) was added $NaBH_4$ (0.61 g, 32 mmol, 2.0 equiv.) at –78 °C. The reaction was stirred for 15 min at that temperature, then quenched with acetone, and the resulting mixture was allowed to warm up to room temperature. Water (10 ml) was added and the phases were separated, then the aqueous phase was extracted with dichloromethane. The combined organic fractions were washed with brine and dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (ethyl acetate/petroleum ether 80:20) afforded **9** (1.7 g, 60% yield over three steps, in 99% enantiomeric excess according to the literature) as a yellow oil; the (–)-taddol was also recovered in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$): 5.74 s, 1 H (H-2); 3.38 dd, 1 H, *J* = 11.5, 3.2 (H-7); 2.74–2.58 br s, 1 H (OH); 2.40–2.26 m, 2 H (H-4); 2.19–2.12 m, 2 H (H-10); 1.86–1.76 m, 3 H (CH_2); 1.73–1.65 m, 2 H (CH_2); 1.43–1.34 m, 1 H (CH_2); 1.16 s, 3 H (Me-8). $[\alpha]_D^{20}$ +122.0 (*c* 1.50, CH_2Cl_2).

(4a*S*,5*S*)-5-Benzyloxymethoxy-4a-methyl-4,4a,5,6,7,8-hexahydro-3*H*-naphthalen-2-one (**10**)

A solution of **9** (200 mg, 1.12 mmol) in dichloromethane was treated with BOMCl (1.55 ml, 11.2 mmol, 10.0 equiv.), TBAI (413 mg, 1.00 equiv.), *i*-Pr_2NEt (2.92 ml, 15.0 equiv.) at room temperature and the resulting mixture was stirred for 2 days, then diluted with water and extracted with dichloromethane. The combined organic fractions were washed with brine and dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (ethyl acetate/petroleum ether 50:50) afforded **10** (262 mg, 78% yield) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): 7.37–7.35 m, 5 H (H-Ar); 5.78 d, 1 H, *J* = 1.8 (H-2); 4.88 d, 1 H, *J* = 7.1 ($BnOCH_2$); 4.76 d, 1 H, *J* = 7.1 ($BnOCH_2$); 4.63 s, 2 H ($PhCH_2$); 3.38 dd, 1 H, *J* = 11.7, 4.3 (H-7); 2.45–2.30 m, 2 H (H-4); 2.25–2.20 m, 2 H (H-10); 2.05–2.01 m, 2 H (CH_2); 1.92–1.84 m, 2 H (CH_2); 1.73–1.63 m, 1 H (CH_2); 1.424–1.32 m, 1 H (CH_2); 1.24 s, 3 H (Me-8).

3-((1*R*,2*S*)-2-Benzyloxymethoxy-1-methyl-6-oxocyclohexyl)propionic Acid (**11**)

A stream of ozone was passed for 2 h through a solution of **10** (2.00 g, 6.06 mmol) in methanol/dichloromethane (20 ml, 4:1) at –78 °C. The reaction was monitored by TLC. Upon completion, the solvent was evaporated under reduced pressure to give crude **11** as a colorless oil. The crude product was used for the following step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): 7.38–7.29 m, 5 H (H-Ar); 4.84 d, 1 H, *J* = 7.2 ($BnOCH_2$); 4.72 d, 1 H, *J* = 7.2 ($BnOCH_2$); 4.62 d, 2 H, *J* = 2.6 ($PhCH_2$); 3.76 dd, 1 H, *J* = 6.9, 3.0 (H-7); 2.40 t, 2 H, *J* = 6.8 (H-4); 2.35 dd, 1 H, *J* = 11.0, 5.3 (H-10); 2.29 dd, 1 H, *J* = 11.0, 5.3 (H-10); 2.19–2.06 m, 2 H (CH_2); 2.05–2.00 m, 2 H (CH_2); 1.71–1.60 m, 2 H (CH_2); 1.15 s, 3 H (Me-8).

(2*S*,3*S*)-3-Benzyloxymethoxy-2-(3-hydroxypropyl)-2-methylcyclohexanol (**12**)

A solution of the ketocarboxylic acid **11** in THF (10 ml) was added dropwise at 0 °C to a suspension of $LiAlH_4$ (0.58 g, 15.2 mmol, 2.50 equiv.) in THF (50 ml). The resulting mixture was then allowed to warm slowly to room temperature, and stirred for 7 h. After cooling to 0 °C, water (2 ml), aqueous NaOH (6 M, 2 ml) and water (6 ml) were added, then the mixture was stirred for 45 min. The aluminum salts were filtered off under reduced pressure through a pad of celite, then the organic phase was dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography to afford **12** (1.62 g, 79% yield over two steps) as a colorless oil as a 1:1 mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$): 7.36–7.32 m, 5 H (H-Ar); 4.84 d, 1 H, *J* = 7.1 ($BnOCH_2$); 4.73 d, 1 H, *J* = 7.1 ($BnOCH_2$); 4.64 d, 2 H, *J* = 3.0 ($PhCH_2$); 3.61–3.57 m, 2 H (H-7, H-3); 3.51–3.47 m, 2 H (H-1); 1.84–1.68 m, 3 H (CH_2); 1.61–1.53 m, 5 H (CH_2); 1.30–1.24 m, 2 H (CH_2); 1.01 s, 3 H (Me-8).

(2*S*,3*S*)-3-Benzyloxymethoxy-2-methyl-2-(3-trityloxypropyl)cyclohexanol (**13**)

4-Dimethylamino-*N*-triphenylmethylpyridinium chloride (2.07 g, 3.90 mmol, 1.20 equiv.) was added at room temperature to a solution of diol **12** (1.00 g, 3.25 mmol) in dichloromethane (10 ml). The resulting mixture was refluxed overnight. After cooling, diethyl ether (20 ml) was added, and the white salts were filtered off. The solution was dried over magnesium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (diethyl ether/petroleum ether 30:70 then 40:60) to give **13** (1.48 g, 83% yield) as a colorless oil as a 1:1 mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$): 7.46–7.43 m, 6 H (H-Ar); 7.33–7.27 m, 11 H (H-Ar); 7.24–7.21 m, 3 H (H-Ar); 4.83 d, 1 H, *J* = 7.1 ($BnOCH_2$); 4.73 d, 1 H, *J* = 7.1 ($BnOCH_2$); 4.61 s, 2 H ($PhCH_2$); 3.55 d, 1 H, *J* = 4.9 (H-3); 3.48 dd, 1 H, *J* = 7.3, 3.1 (H-7); 3.06 t, 2 H, *J* = 6.4 (H-1); 1.78–1.72 m, 3 H (CH_2); 1.64–1.59 m, 3 H (CH_2); 1.47–1.42 m, 2 H (CH_2); 1.31–1.25 m, 2 H (CH_2); 1.04 s, 3 H (Me-8).

(2*R*,3*S*)-3-Benzyloxymethoxy-2-methyl-2-(3-trityloxypropyl)cyclohexanone (**14**)

A solution of IBX (154 mg, 0.55 mmol, 1.20 equiv.) in DMSO (15 ml) was added slowly at room temperature to a stirred solution of **13** (200 mg, 0.36 mmol) in THF (15 ml). The resulting mixture was stirred at room temperature overnight. When the reaction had gone to completion, water (20 ml) was added and the organic phase was diluted with diethyl ether (10 ml). The biphasic system was stirred for 3 h. The white salts were then filtered off on a

pad of celite. The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 10 ml). The combined organic fractions were washed with water (20 ml) and brine (20 ml), dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether 20:80) afforded the desired **14** (161 mg, 81% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): 7.47–7.45 m, 6 H (H-Ar); 7.37–7.30 m, 11 H (H-Ar); 7.27–7.24 m, 3 H (H-Ar); 4.85 d, 1 H, *J* = 7.2 ($BnOCH_2$); 4.74 d, 1 H, *J* = 7.2 ($BnOCH_2$); 4.64 d, 2 H, *J* = 2.2 ($PhCH_2$); 3.89 d, 1 H, *J* = 3.4 (H-7); 3.12–3.05 m, 2 H (H-1); 2.31–2.51 m, 2 H (H-4); 2.16–1.92 m, 3 H (CH_2); 1.81–1.75 m, 2 H (CH_2); 1.70–1.54 m, 2 H (CH_2); 1.46–1.38 m, 1 H (CH_2); 1.18 s, 3 H (Me-8).

(1*S*,8a*S*)-8a-Methyl-6-oxo-1,2,3,4,6,7,8,8a-octahydronaphthalen-1-yl Benzoate (**16**)

To a solution of **9** (2.52 g, 14.0 mmol) in dichloromethane (20 ml) was added pyridine (2.28 ml, 28.0 mmol, 2.00 equiv.) at 0 °C, then BzCl (1.95 ml, 16.8 mmol, 1.2 equiv.) and a catalytic quantity of DMAP were added. The resulting mixture was stirred for 12 h. The reaction was quenched by addition of aqueous sodium hydrogencarbonate (sat., 10 ml). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 10 ml). The combined organic fractions were washed with brine (20 ml), dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether 50:50) afforded **16** (2.88 g, 73% yield) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): 7.70–7.66 m, 1 H (H-Ar); 7.60–7.51 m, 2 H (H-Ar); 7.48–7.44 m, 2 H (H-Ar); 5.86 d, 1 H, *J* = 1.8 (H-2); 4.91 dd, 1 H, *J* = 11.7, 4.5 (H-7); 2.45–2.39 m, 3 H (H-10, H-4); 2.34–2.28 m, 1 H (H-10); 2.08–2.00 m, 2 H (CH_2); 1.94–1.80 m, 2 H (CH_2); 1.64–1.52 m, 2 H (CH_2); 1.43 s, 3 H (Me-8).

(1*S*,2*R*)-2-(2-Carboxyethyl)-2-methyl-3-oxocyclohexyl Benzoate (**16′**)

A stream of ozone was passed for 2 h through a solution of **16** (1.00 g, 3.52 mmol) in methanol (70 ml) at –78 °C. The reaction was monitored by TLC. Upon completion, the solvent was evaporated under reduced pressure to give crude **16′** as a colorless oil. The crude product was used for the following step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): 7.64–7.61 m, 1 H (H-Ar); 7.54–7.46 m, 2 H (H-Ar); 7.41–7.37 m, 2 H (H-Ar); 5.28–5.26 m, 1 H (H-7); 2.56–2.49 m, 1 H (H-4); 2.44–2.32 m, 3 H (H-10, H-4, H-10); 2.22–2.14 m, 2 H (CH_2); 2.10–1.80 m, 4 H (CH_2); 1.11 s, 3 H (Me-8).

(1*S*,2*R*)-2-(2-Methoxycarbonylethyl)-2-methyl-3-oxocyclohexyl Benzoate (**17**)

To a solution of **16′** and pyridine (0.83 g, 10.6 mmol, 3 equiv.) in MeOH was added dropwise $SOCl_2$ (0.30 ml, 4.22 mmol, 1.20 equiv.) at 0 °C. The mixture was stirred for 1.5 h and concentrated in vacuo with a trap of aqueous NaOH solution. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether 20:80) yielded **17** (0.83 g, 74% yield over two steps). ^{1}H NMR (400 MHz, $CDCl_3$): 7.99–7.97 m, 2 H (H-Ar); 7.58–7.55 m, 1 H (H-Ar); 7.45–7.42 m, 2 H (H-Ar); 5.30 dd, 1 H, *J* = 5.3, 2.8 (H-7); 3.65 s, 3 H (COOMe); 2.60–2.52 m, 1 H (H-4); 2.49–2.34 m, 2 H (H-10, H-4); 2.28–2.16 m, 2 H (H-10, H-9); 2.12–1.84 m, 5 H (H-9, H-6, H-5); 1.15 s, 3 H (Me-8). IR (film): 2954, 2874, 1715, 1600, 1449, 1270, 1173, 1107, 848, 795, 780, 661. $[\alpha]_D^{20}$ +36.6 (*c* 1.35, CH_2Cl_2). HRMS calculated for $C_{18}H_{22}O_5$ 318.1467; found 318.1477.

(1*S*,2*R*)-2-(2-Methoxycarbonylethyl)-2-methyl-3-benzoylcyclohexyl-*N'*-(2,4,6-triisopropylbenzenesulfono)hydrazone (**18**)

Two drops of concentrated hydrochloric acid were added to a solution of ketone **17** (158 mg, 0.50 mmol) and triisopropylbenzenesulfonyl hydrazine (149 mg, 0.50 mmol, 1.00 equiv.) in THF (5.0 ml). The resulting solution was stirred at room temperature for 2.5 h, and the reaction was quenched by addition of aqueous sodium hydrogencarbonate (sat., 5 ml). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 10 ml). The combined organic fractions were washed with brine (15 ml) and dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether 50:50) yielded **18** (274 g, 92% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): 7.97 s, 1 H (NH); 7.89–7.86 m, 2 H (H-Ar); 7.53–7.50 m, 1 H (H-Ar); 7.36–7.33 m, 2 H (H-Ar); 7.17 s, 2 H (H-Ar); 5.06 dd, 1 H, *J* = 4.8, 2.7 (H-7); 4.23 septet, 2 H, *J* = 6.7 (Ar-CH); 3.58 s, 3 H (COOMe); 2.89 septet, 1 H, *J* = 6.9 (Ar-CH); 2.53 dt, 1 H, *J* = 15.3, 5.0 (H-4); 2.21–2.01 m, 3 H (H-4, H-10); 1.89–1.82 m, 2 H (H-6); 1.80–1.66 m, 4 H (H-5, H-9); 1.26–1.21 m, 18 H (H-*i*Pr); 0.99 s, 3 H (Me-8). ^{13}C NMR (100.6 MHz, $CDCl_3$): 173.7 (C-1); 165.5 (C-3); 158.4 (C-BzC=O); 153.2 (C-Ar); 151.2 (C-Ar); 132.9 (C-Ar); 131.0 (C-Ar); 130.0 (C-Ar); 129.5 (C-Ar); 128.3 (C-Ar); 123.5 (C-Ar); 77.4 (C-7); 51.5 (COOMe); 45.8 (C-8); 34.1 (C-*i*Pr); 31.0 (C-10); 29.8 (C-*i*Pr); 28.1 (C-6); 25.2 (C-9); 24.8 ($CH(CH_3)_2$); 24.7 ($CH(CH_3)_2$); 23.5 ($CH(CH_3)_2$); 23.4 ($CH(CH_3)_2$); 22.2 (C-4); 19.9 (C-5); 19.3 (Me-8). IR (film): 3243, 2958, 2871, 1720, 1600, 1596, 1453, 1319, 1270, 1163, 1110, 1026, 871, 794, 748, 632, 525. $[\alpha]_D^{20}$ +71.0 (*c* 1.35, CH_2Cl_2). HRMS calculated for $C_{33}H_{46}N_2O_4S$ 598.3077; found 598.3081.

(2*S*,4a*R*,8a*S*)-2-Hydroxy-4a-methyloctahydrochromen-5-*N'*-(2,4,6-triisopropylbenzenesulfono)hydrazone (**19**)

To a solution of **18** (117 mg, 0.20 mmol) in dichloromethane (10 ml) was added dropwise DIBALH (0.80 ml, 1 M in hexanes, 0.80 mmol, 4.00 equiv.) at –78 °C, then the temperature was allowed to warm up to 0 °C. The reaction was stirred at that temperature for 1 h, and quenched with MeOH and a saturated aqueous $NaHCO_3$ solution. The two phases were separated and the aqueous phase was extracted with diethyl ether (3 × 10 ml). The combined organic fractions were washed with brine (20 ml), dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether 10:90) afforded **19** (45.0 mg, 49% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): 7.16 s, 2 H (H-Ar); 4.19 septet, 2 H, *J* = 6.8 (Ar-CH); 4.11 d, 1 H, *J* = 9.8 (H-7); 3.22 dd, 1 H, *J* = 10.3, 5.8 (H-1); 2.90 septet, 1 H, *J* = 6.9 (Ar-CH); 2.62 dt, 1 H, *J* = 14.3, 7.1 (H-4); 2.18 ddd, 1 H, *J* = 14.3, 5.3, 1.8 (H-4); 2.00–1.92 m, 1 H (H-10); 1.78–1.65 m, 5 H (H-10, H-6, H-9); 1.54–1.44 m, 2 H (H-5); 1.26–1.22 m, 18 H (H-*i*Pr); 1.14 s, 3 H (Me-8). ^{13}C NMR (100.6 MHz, $CDCl_3$): 213.3 (C-3); 153.2 (C-Ar); 151.5 (C-Ar); 131.1 (C-Ar); 123.7 (C-Ar); 89.1 (C-1); 80.0 (C-7); 77.2, 48.6 (C-8); 36.4 (C-4); 34.1 (C-*i*Pr); 29.8 (C-*i*Pr); 29.6 (C-6); 25.9 (C-10); 25.2 (C-9); 24.9 ($CH(CH_3)_2$); 24.8 ($CH(CH_3)_2$); 20.7 (C-5); 16.1 (Me-8).

(2*R*,4a*R*,8a*S*)-4a-Methyl-2-trityloxyoctahydrochromen-5-*N*′-(2,4,6-triisopropylbenzenesulfono)hydrazone (**20**)

4-Dimethylamino-*N*-triphenylmethylpyridinium chloride (51.0 mg, 0.13 mmol, 1.30 equiv.) was added at room temperature to a solution of **19** (450.0 mg, 0.10 mmol) in dichloromethane (10 ml). The resulting mixture was refluxed overnight. After cooling, diethyl ether (20 ml) was added, and the white salts were filtered off. The solution was dried over magnesium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (diethyl ether/petroleum ether 30:70 then 40:60) to give **20** (42 mg, 61% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): 7.98 s, 1 H (NH); 7.35–7.24 m, 15 H (H-Ar); 7.18 s, 2 H (H-Ar); 4.18 septet, 2 H, *J* = 6.7 (Ar-CH); 4.01 d, 1 H, *J* = 12.0, 4.2 (H-7); 3.22 dd, 1 H, *J* = 10.3, 5.8 (H-1); 2.93 septet, 1 H, *J* = 6.9 (Ar-CH); 2.62 m, 2 H (H-4); 2.05–1.91 m, 4 H (H-10, H-6); 1.82–1.68 m, 4 H (H-5, H-9); 1.28–1.24 m, 18 H (H-*i*Pr); 1.03 s, 3 H (Me-8).

(4a*S*,5*S*)-4a-Methyl-5-triethylsiloxy-4,4a,5,6,7,8-hexahydro-3*H*-naphthalen-2-one (**21**)

To a solution of **9** (4.30 g, 30.7 mmol) in dichloromethane (10 ml) was added imidazole (5.23 g, 76.8 mmol, 2.50 equiv.) and TESCl (6.90 g, 46.1 mmol, 1.50 equiv.). The mixture was stirred for 12 h at room temperature, then quenched with a saturated aqueous $NaHCO_3$ solution. The two phases were separated and the aqueous phase was extracted with diethyl ether (3 × 25 ml). The combined organic fractions were washed with brine (20 ml), dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether 10:90) afforded **21** (6.32 g, 90% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): 5.76 s, 1 H (H-1); 3.39 dd, 1 H, *J* = 10.6, 5.2 (H-7); 2.42–2.36 m, 2 H (H-4); 2.33–2.27 m, 1 H (H-10); 2.21–2.08 m, 2 H (H-10, CH_2); 1.86–1.80 m, 1 H (CH_2); 1.76–1.70 m, 2 H (CH_2); 1.42–1.30 m, 2 H (CH_2); 1.16 s, 3 H (Me-8); 0.95 t, 9 H, *J* = 7.9 (H-TES); 0.59 q, 6 H, *J* = 7.9 (H-TES).

3-((1*R*,6*S*)-1-Methyl-2-oxo-6-triethylsiloxycyclohexyl)propionic Acid (**24**)

A stream of ozone was passed for 2 h through a solution of **21** (2.0 g, 6.37 mmol) in methanol (70 ml) at –78 °C. The reaction was monitored by TLC. Upon completion, the solvent was evaporated under reduced pressure to give crude **24** as a colorless oil. The crude product was used for the following step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): 10.30–10.10 br s, 1 H (COOH); 3.82 dd, 1 H, *J* = 6.0, 2.0 (H-7); 2.41–2.25 m, 3 H (H-4, H-10); 2.16–2.07 m, 1 H (H-10); 2.06–1.94 m, 3 H (CH_2); 1.78–1.65 m, 3 H (CH_2); 1.03 s, 3 H (Me-8); 0.90 t, 9 H, *J* = 7.9 (H-TES); 0.54 q, 6 H, *J* = 7.9 (H-TES).

(4a*R*,8a*S*)-4a-Methylhexahydrochromene-2,5-dione (**22**)

To a solution of crude **21′** in dichloromethane (10 ml) was added a catalytic quantity of PPTS. The mixture was stirred for 1 h at room temperature and then quenched with a saturated $NaHCO_3$ aqueous solution. The two phases were separated and the aqueous phase was extracted with diethyl ether (3 × 25 ml). The combined organic fractions were washed with brine (20 ml), dried over magnesium sulfate, filtered and the solvent was removed under

reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether 10:90) afforded the desired **22** (1.04 g, 90% yield over two steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): 4.11 dd, 1 H, *J* = 11.6, 4.5 (H-7); 2.61–2.45 m, 3 H (H-4, H-10); 2.20–2.10 m, 2 H (H-10, H-6); 2.00–1.85 m, 3 H (H-5, H-6); 1.68–1.63 m, 1 H (H-9); 1.54–1.40 m, 1 H (H-9); 1.11 s, 3 H (Me-8). ^{13}C NMR (100.6 MHz, $CDCl_3$): 210.1 (C-3); 170.5 (C-1); 81.0 (C-7); 47.9 (C-8); 36.1 (C-9); 26.6 (C-5); 26.2 (C-6); 25.5 (C-10); 19.7 (C-4); 16.3 (Me-8). IR (film): 4197, 3465, 3059, 2963, 2883, 2306, 1743, 1454, 1425, 1380, 1216, 1184, 1053, 1015, 892, 821, 711, 659, 607. $[\alpha]_D^{20}$ –41.3 (*c* 1.50, CH_2Cl_2). HRMS calculated for $C_{10}H_{14}O_3$ 182.0943; found 182.0945.

(4a*R*,8a*S*)-4a-Methylhexahydrochromene-2-one-5-*N*′-(2,4,6-triisopropylbenzenesulfono)hydrazone (**22′**)

Two drops of concentrated hydrochloric acid were added to a solution of ketone **22** (60 mg, 0.33 mmol) and triisopropylbenzenesulfonyl hydrazine (100 mg, 0.33 mmol, 1.00 equiv.) in THF (5.0 ml). The resulting solution was stirred at room temperature for 1 h, and the reaction was quenched by addition of aqueous sodium hydrogencarbonate (sat., 5 ml). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 10 ml). The combined organic fractions were washed with brine (15 ml) and dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether 20:80) yielded **22′** (132 mg, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 8.33 s, 1 H (NH); 7.15 s, 2 H (H-Ar); 4.17 septet, 2 H, *J* = 6.7 (Ar-CH); 3.99 dd, 1 H, *J* = 12.0, 4.2 (H-7); 2.89 septet, 1 H, *J* = 6.9 (Ar-CH); 2.68 dt, 1 H, *J* = 14.6, 5.0 (H-4); 2.56–2.51 m, 2 H (H-10); 2.00–1.88 m, 4 H (H-4, H-9, H-6, H-7); 1.76–1.65 m, 2 H (H-6, H-7); 1.34–1.28 m, 1 H (H-9); 1.24–1.22 m, 18 H (H-*i*Pr); 1.01 s, 3 H (Me-8). ^{13}C NMR (100.6 MHz, $CDCl_3$): 171.1 (C-1); 158.4 (C-Ar); 153.2 (C-Ar); 151.0 (C-3); 130.8 (C-Ar); 123.4 (C-Ar); 82.3 (C-7); 41.4 (C-8); 33.9 (C-*i*Pr); 29.5 (C-*i*Pr); 28.6 (C-6); 26.9 (C-10); 26.0 (C-5); 24.7 (C-$CH(CH_3)_2$); 24.5 (C-$CH(CH_3)_2$); 23.4 (C-$CH(CH_3)_2$); 23.4 (C-$CH(CH_3)_2$); 21.7 (C-4); 20.7 (C-9); 16.8 (Me-8).

(4a*R*,8a*S*)-2-Hydroxy-4a-methyloctahydrochromen-5-one (**25**)

To a solution of DMF (5.88 ml, 76.5 mmol, 10.0 equiv.) in anhydrous CH_2Cl_2 (20 ml) was added oxalyl chloride (2.00 ml, 23.0 mmol, 3.00 equiv.) at –20 °C. After 90 min, the mixture was concentrated under reduced pressure. Dry acetonitrile (10 ml) and THF (25 ml) were added at –30 °C and a solution of **24** (2.43 g, 7.65 mmol) in THF (10 ml) and pyridine (2 ml) was added dropwise. The resulting mixture was stirred for 90 min at –30 °C, cooled to –78 °C and a solution of copper iodide (10 mole %) and tri-*tert*-butoxyaluminum hydride (3.89 g, 15.3 mmol, 2.00 equiv.) in THF (15 ml) was added. After stirring for 15 min, the reaction was quenched with 7% aqueous HBr solution (15 ml). The resulting mixture was allowed to warm up to room temperature and basified with 30% aqueous NaOH solution (5 ml). The aqueous layer was extracted with diethyl ether. The combined extracts were washed with saturated aqueous sodium hydrogencarbonate solution, brine, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography (diethyl ether/petroleum ether 20:80) to give **25** (704 mg, 50% yield) as a 1:1 mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$): 5.24 s, 0.5 H (H-1); 4.72 d, 0.5 H, *J* = 10.3 (H-1); 4.01 dd, 0.5 H, *J* = 12.0, 4.2 (H-7); 3.58–3.54 br s, 0.5 H (OH); 3.37 dd, 0.5 H, *J* = 11.6, 4.2 (H-7); 2.87–2.84 br s, 0.5 H (H-OH); 2.62 dt, 1 H, *J* = 14.4, 7.0 (H-4); 2.23–2.16 m, 1 H (H-4);

2.02–1.92 m, 1.5 H (CH_2); 1.91–1.77 m, 3 H (CH_2); 1.74–1.68 m, 1.5 H (CH_2); 1.63–1.52 m, 2 H (CH_2); 1.25 s, 1.5 H (Me-8); 1.21 s, 1.5 H (Me-8).

(2*S*,4a*R*,8a*S*)-2-Methoxy-4a-methyloctahydrochromen-5-one (**26**)

A solution of **25** (515 mg, 2.8 mmol) in dichloromethane (10 ml) was treated with silver(I) oxide (650 mg, 2.8 mmol, 1.00 equiv.) and excess methyl iodide (0.55 ml). The black suspension was stirred overnight at room temperature, then filtered through a cotton plug and concentrated in vacuo. The residue was purified by flash chromatography (diethyl ether/petroleum ether 10:90) to give **26** (499 mg, 90% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): 4.16 dd, 1 H, *J* = 9.6, 2.3 (H-1); 3.36 s, 3 H (H-OMe); 3.20 dd, 1 H, *J* = 11.5, 4.3 (H-7); 2.54 dt, 1 H, *J* = 14.5, 7.1 (H-4); 2.23–2.16 ddd, 1 H, *J* = 14.7, 4.9, 1.5 (H-4); 1.91–1.84 m, 1 H (C-10); 1.82–1.72 m, 2 H (C-6); 1.64–1.58 m, 3 H (C-9, C-5); 1.53–1.35 m, 2 H (C-5, C-10); 1.11 s, 3 H (Me-8). ^{13}C NMR (100.6 MHz, $CDCl_3$): 213.1 (C-3); 103.6 (C-1); 79.0 (C-7); 56.1 (C-OMe); 48.4 (C-8); 36.2 (C-4); 29.0 (C-9); 27.0 (C-5); 25.7 (C-6); 20.6 (C-10); 16.0 (Me-8). IR (film): 3682, 3510, 3403, 2854, 2747, 2641, 2251, 2140, 1915, 1736, 1431, 1337, 1264, 1247, 1080, 984, 953, 914, 856, 778, 730, 565. HRMS calculated for $C_{11}H_{18}O_3$ 198.1256; found 198.1255.

(2*S*,4a*R*,8a*S*)-2-Methoxy-4a-methyloctahydrochromen-5-*N*′-(2,4,6-triisopropylbenzenesulfono)hydrazone (**23**)

Two drops of concentrated hydrochloric acid were added to a solution of ketone **26** (499 mg, 2.55 mmol) and triisopropylbenzenesulfonyl hydrazine (912 mg, 3.06 mmol, 1.20 equiv.) in THF (5.0 ml). The resulting solution was stirred at room temperature for 1 h, and the reaction was quenched by addition of aqueous sodium hydrogencarbonate (sat., 5 ml). The phases were separated, then the aqueous phase was extracted with diethyl ether (3 × 10 ml). The combined organic fractions were washed with brine (15 ml) and dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether 20:80) yielded **23** (1.22 g, quantitative yield). ^{1}H NMR (400 MHz, $CDCl_3$): 7.67 s, 1 H (NH); 7.15 s, 2 H (H-Ar); 4.22–4.14 m, 3 H (Ar-CH, H-7); 3.45 s, 3 H (H-OMe); 3.11 dd, 1 H, *J* = 10.3, 5.6 (H-1); 2.91 septet, 1 H, *J* = 6.9 (Ar-CH); 2.56–2.50 m, 1 H (H-4); 2.01–1.96 m, 1 H (H-4); 1.92–1.87 m, 2 H (H-10); 1.72–1.66 m, 2 H (H-6); 1.64–1.51 m, 4 H (H-5, H-9); 1.26–1.22 m, 18 H (H-*i*Pr); 1.01 s, 3 H (Me-8). ^{13}C NMR (100.6 MHz, $CDCl_3$): 161.6 (C-Ar); 153.2 (C-Ar); 151.1 (C-3); 131.2 (C-Ar); 123.5 (C-Ar); 104.0 (C-1); 79.4 (C-7); 56.3 (C-OMe); 42.0 (C-8); 34.1 (C-*i*Pr); 31.3 (C-9); 29.8 (C-*i*Pr); 27.5 (C-5); 26.1 (C-6); 24.8 (C-$CH(CH_3)_2$); 24.7 (C-$CH(CH_3)_2$); 23.6 (C-$CH(CH_3)_2$); 23.5 (C-$CH(CH_3)_2$); 21.6 (C-10); 21.5 (C-4); 17.3 (Me-8). IR (film): 3240, 2954, 2872, 2836, 2752, 2635, 1712, 1629, 1596, 1550, 1453, 1384, 1326, 1252, 1203, 1160, 1067, 912, 730, 653, 584. HRMS calculated for $C_{26}H_{42}N_2O_4$ 478.2865; found 478.2855.

1-((2*S*,4a*S*,8a*S*)-2-Methoxy-4a-methyl-3,4,4a,7,8,8a-hexahydro-2*H*-chromen-5-yl)-3-phenylpropan-1-ol (**27**) and (2*S*,4a*S*,8a*S*)-2-Methoxy-4a-methyl-3,4,4a,7,8,8a-hexahydro-2*H*-chromene (**28**)

tert-Butyllithium (0.33 ml, 0.46 mmol, 2.20 equiv., titrated at 1.40 M) was added dropwise to a solution of hydrazone **23** (100 mg, 0.21 mmol) in THF (10 ml) at –78 °C. The solution

turned red and was stirred at –78 °C for 30 min until the color turned dark red, then the temperature was allowed to warm to 0 °C. When nitrogen evolution was finished and the color had turned to red, the solution was cooled again to –78 °C. A cooled solution of hydrocinnamaldehyde (30.5 µl, 0.23 mmol, 1.10 equiv.) in THF (5.0 ml) was added dropwise via cannula. The resulting mixture was stirred at –78 °C for 30 min. The reaction was quenched by addition of aqueous sodium hydrogencarbonate (sat., 10 ml). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 15 ml). The combined organic fractions were washed with brine (20 ml) and dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether 5:100) yielded **27** (27 mg, 42% yield) and **28** (9.8 mg, 26% yield) as pale yellow oils.

Compound **27**. ^{1}H NMR (400 MHz, $CDCl_3$): 7.30–7.26 m, 2 H (H-Ar); 7.21–7.18 m, 3 H (H-Ar); 5.70–5.68 m, 1 H (H-4); 4.37–4.32 m, 1 H (H-1′); 4.17–4.10 m, 1 H (H-1); 3.52 s, 1.5 H (OMe); 3.51 s, 1.5 H (OMe); 3.35–3.27 m, 1 H (H-7); 2.88–2.72 m, 1 H (H-3′); 2.68–2.58 m, 1 H (H-3′); 2.25–2.18 m, 2 H (H-5); 1.95–1.82 m, 3 H (H-6, H-2′); 1.78–1.65 m, 3 H (H-10, H-2′); 1.62–1.52 m, 1 H (H-9); 1.40–1.30 m, 1 H (H-9); 1.19 s, 1.5 H (Me-8); 1.10 s, 1.5 H Me-8). ^{13}C NMR (100.6 MHz, $CDCl_3$): 148.2 (C-Ar); 146.8 (C-Ar); 142.0 (C-3); 141.9 (C-3); 128.4 (C-Ar); 128.4 (C-Ar); 125.8 (C-Ar); 121.4 (C-4); 121.2 (C-4); 103.9 (C-1′); 103.9 (C-1′); 78.9 (C-7); 78.7 (C-7); 69.4 (C-1); 69.0 (C-1); 56.3 (C-OMe); 56.3 (C-OMe); 39.6 (C-6); 39.3 (C-6); 36.5 (C-8); 36.2 (C-8); 32.7 (C-3); 32.5 (C-3); 32.4 (C-2′); 27.7 (C-9); 27.7 (C-9); 24.5 (C-5); 24.4 (C-5); 23.5 (C-10); 19.7 (Me-8); 19.6 (Me-8). IR (film): 3041, 2957, 2863, 1451, 1434, 1281, 1266, 1250, 1065, 936, 787, 686, 664. HRMS calculated for $C_{20}H_{28}O_3$ 316.2039; found 316.2027.

Compound **28**. ^{1}H NMR (400 MHz, $CDCl_3$): 5.46–5.40 m, 2 H (H-3, H-4); 4.38 dd, 1 H, J = 8.4, 4.2 (H-1); 3.52 s, 3 H (OMe); 3.28 dd, 1 H, J = 11.7, 4.4 (H-7); 2.20–2.16 m, 2 H (H-5); 1.80–1.67 m, 4 H (H-6, H-10); 1.60–1.55 m, 1 H (H-9); 1.46–1.38 m, 1 H (H-9); 1.05 s, 3 H (Me-8). ^{13}C NMR (100.6 MHz, $CDCl_3$): 135.5 (C-4); 124.5 (C-3); 104.4 (C-1); 78.5 (C-7); 56.4 (C-OMe); 35.0 (C-9); 34.2 (C-8); 27.9 (C-10); 25.4 (C-5); 23.7 (C-6); 19.6 (Me-8). IR (film): 3041, 2985, 2956, 2844, 1449, 1388, 1250, 1159, 1109, 1062, 1010, 949, 686, 665. HRMS calculated for $C_{11}H_{18}O_2$ 182.1307; found 182.1316.

Financial support was provided by the CNRS, the Ecole Polytechnique and the University of Glasgow.

REFERENCES AND NOTES

1. Oberlies N. H., Kroll D. J.: *J. Nat. Prod.* **2004**, *67*, 129.
2. For reviews on the chemistry of taxol, see: a) Nicolaou K. C., Dai W.-M., Guy R. K.: *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15; b) Kingston D. G. I.: *Chem. Commun.* **2001**, 867; For the total syntheses, see: c) Nicolaou K. C., Yang Z., Liu J. J., Ueno H., Nantermet P. G., Guy R. K., Claiborne C. F., Renaud J., Couladouros E. A., Paulvannan, K., Sorensen E. J.: *Nature* **1994**, *367*, 630; d) Nicolaou K. C., Nantermet P. G., Ueno H., Guy R. K., Couladouros E. A., Sorensen E. J.: *J. Am. Chem. Soc.* **1995**, *117*, 624; e) Nicolaou K. C., Liu J. J., Yang Z., Ueno H., Sorensen E. J., Claiborne C. F., Guy R. K., Hwang C. K., Nakada M., Nantermet P. G.: *J. Am. Chem. Soc.* **1995**, *117*, 634; f) Nicolaou K. C., Yang Z., Liu J. J., Nantermet P. G., Claiborne C. F., Renaud, J., Guy R. K., Shibayama K.: *J. Am. Chem. Soc.* **1995**, *117*, 645; g) Nicolaou K. C., Ueno H., Liu J. J., Nantermet P. G.,

Yang Z., Renaud J., Paulvannan K., Chadha R.: *J. Am. Chem. Soc.* **1995**, *117*, 653; h) Holton R. A., Somoza C., Kim H. B., Liang F., Biediger R. J., Boatman P. D., Shindo M., Smith C. C., Kim S., Nadizadeh H., Suzuki Y., Tao C., Vu P., Tang S., Zhang P., Murthi K. K., Gentile L. N., Liu J. H.: *J. Am. Chem. Soc.* **1994**, *116*, 1597; i) Holton R. A., Kim H. B., Somoza C., Liang F., Biediger R. J., Boatman P. D., Shindo M., Smith C. C., Kim S., Nadizadeh H., Suzuki Y., Tao C., Vu P., Tang S., Zhang P., Murthi K. K., Gentile L. N., Liu J. H.: *J. Am. Chem. Soc.* **1994**, *116*, 1599; j) Masters J. J., Link J. T., Snyder L. B., Young W. B., Danishefsky S.: *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1723; k) Wender P. A., Badham N. F., Conway S. P., Floreancig P. E., Glass T. E., Gränicher C., Houze J. B., Jänichen J., Lee D., Marquess D. G., McGrane P. L., Meng W., Mucciaro T. P., Mühlebach M., Natchus M. G., Paulsen H., Rawlins D. B., Satkofsky J., Shuker A. J., Sutton J. C., Taylor R. E., Tomooka K.: *J. Am. Chem. Soc.* **1997**, *119*, 2755; l) Wender P. A., Badham N. F., Conway S. P., Floreancig P. E., Glass T. E., Houze J. B., Krauss N. E., Lee D., Marquess D. G., McGrane P. L., Meng W., Natchus M. G., Shuker A. J., Sutton J. C., Taylor R. E.: *J. Am. Chem. Soc.* **1997**, *119*, 2757; m) Mukaiyama T., Shiina I., Iwadare H., Saitoh M., Nishimura T., Ohkawa N., Sakoh H., Nishimura H., Tani Y.-I., Hasegawa M., Yamada K., Saito K.: *Chem. Eur. J.* **1999**, *5*, 121; n) Morihara, K., Hara R., Kawahara S., Nishimori T., Nakamura N., Kusama H., Kuwajima I.: *J. Am. Chem. Soc.* **1998**, *120*, 12980.

3. Doi T., Fuse S., Miyamoto S., Nakai K., Sasuga D., Takahashi T.: *Chem. Asian J.* **2006**, *1*, 370.
4. Swindell C. S., Patel B. P.: *J. Org. Chem.* **1990**, *55*, 3.
5. For previous work on approaches towards taxol from our group, see: a) Muller B., Delaloge F., den Hartog M., Férézou J.-P., Pancrazi A., Prunet J., Lallemand J. Y., Neuman A., Prangé T.: *Tetrahedron Lett.* **1996**, *37*, 3313; b) Delaloge F., Pancrazi A., Prunet J., Lallemand J.-Y.: *Tetrahedron Lett.* **1997**, *38*, 237; c) Grimaud L., Férézou J.-P., Prunet J., Lallemand J.-Y.: *Tetrahedron* **1997**, *53*, 9253; d) Muller B., Férézou J.-P., Lallemand J.-Y., Pancrazi A., Prunet J., Prangé T.: *Tetrahedron Lett.* **1998**, *39*, 279; e) Bourgeois D., Lallemand J. Y., Pancrazi A., Prunet J.: *Synlett* **1999**, 1555; f) Bourgeois D., Pancrazi A., Ricard L., Prunet J.: *Angew. Chem. Int. Ed.* **2000**, *39*, 725; g) Bourgeois D., Mahuteau J., Pancrazi A., Nolan S. P., Prunet J.: *Synthesis* **2000**, 869; h) Bourgeois D., Prunet J., Pancrazi A., Prangé T., Lallemand J.-Y.: *Eur. J. Org. Chem.* **2000**, 4029; i) Bourgeois D., Pancrazi A., Nolan S. P., Prunet J.: *J. Organomet. Chem.* **2002**, *643–644*, 247; j) Schiltz S., Ma C., Ricard L., Prunet J.: *J. Organomet. Chem.* **2006**, *691*, 5438; k) Ma C., Schiltz S., Le Goff X. F., Prunet J.: *Chem. Eur. J.* **2008**, *14*, 7314.
6. For previous syntheses of taxane derivatives using the Wieland–Miescher ketone, see ref. 2j and: a) Brown P. A., Jenkins P. R., Fawcett J., Russell D. R.: *J. Chem. Soc., Chem. Commun.* **1984**, 253; b) Bonnert R. V., Jenkins P. R.: *J. Chem. Soc., Chem. Commun.* **1987**, 1540; c) Brown P. A., Jenkins P. R.: *J. Chem. Soc., Perkin Trans. 1* **1986**, 1303; d) Bonnert R. V., Jenkins P. R.: *J. Chem. Soc., Perkin Trans. 1* **1989**, 413; e) Rubenstein S. M., Williams R. M.: *J. Org. Chem.* **1995**, *60*, 6215.
7. a) Wieland P., Miescher K.: *Helv. Chim. Acta* **1950**, *33*, 2215; b) Gutzwiller J., Buchschacher P., Fürst A.: *Synthesis* **1977**, 167; c) Buchschacher P., Fürst A., Gutzwiller J.: *Org. Synth.* **1985**, *63*, 37.
8. Toda F., Kiyoshige K., Yagi M.: *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 320.
9. Yang D., Zhang C.: *J. Org. Chem.* **2001**, *66*, 4814.

10. Labadie G. R., Luna L. E., Gonzalez-Sierra M., Cravero R. M.: *Eur. J. Org. Chem.* **2003**, 3429.
11. Frigerio M., Santagostino M., Sputore S.: *J. Org. Chem.* **1999**, *64*, 4537.
12. Smith III A. B., Doughty V. A., Sfouggatakis C., Bennett C. S., Koyanagi J., Takeuchi M.: *Org. Lett.* **2002**, *4*, 783.
13. We chose to protect the hemiacetal as a trityl acetal because of the mild conditions required for this transformation.
14. Paquette L. A., Sturino C. F., Wang X., Prodger J. C., Koh D.: *J. Am. Chem. Soc.* **1996**, *118*, 5620.
15. Felpin F.-X., Bertrand M.-J., Lebreton J.: *Tetrahedron* **2002**, *58*, 7381.