Hajos–Parrish ketone: approaches toward C-ring precursors of 7-deoxytaxol

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Two routes were evaluated for the preparation of multiply functionalized cyclohexane derivatives in a stereocontrolled fashion from readily available Hajos–Parrish ketone **1**. Reduction (catalytic or dissolving metal) led to the *cis*-isomer **8**, in stark contrast to previous literature. Finally, modification of earlier steroid chemistry allowed the synthesis of the *trans*-isomer **14**. The latter is a useful intermediate for the synthesis of 7-deoxytaxol derivatives.

Taxol® (Paclitaxel) is a diterpene alkaloid isolated from the bark extract of the Pacific Yew tree, *Taxus brevifolia*, and is used as a drug in the treatment of ovarian and breast cancers.[1] Several reviews on different aspects of the chemistry and pharmacology of Taxol® are available.[2] We chose 7-deoxytaxol as the target of our study because it is a simpler Taxol® analogue which still possesses high activity against experimental cancer cell lines.[3]

Our retrosynthetic reasoning for the synthesis of 7-deoxytaxol is shown in Scheme 1. Disconnection of the side chain leaves the ABCD taxane ring system, which is cleaved at the bonds between the C-9 and C-10 and C-1 and C-2 giving rise to two fragments of approximately equal size and complexity.[4] Our approach relies on inducing the desired chirality of the C-ring from the single stereogenic centre in the C-ring building block **1**, the Hajos–Parrish ketone. This in turn is derived, using well-established methodology, from 2-methylcyclopentane-1,3-dione and methyl vinyl ketone.[5] In this paper we report our approach for the preparation of the key C-ring building block for 7-deoxytaxol starting from **1**.

Results and discussion

The synthetic plan unfolded as follows (Scheme 2). Hajos–Parrish ketone **1** contains the desired source of chirality, as well as all the necessary functionalities for the installation of the C/D-ring components of 7-deoxytaxol. The starting material **1** was prepared according to literature methods, employing D-proline as the chiral catalyst.[6]

Bauduin and Pietrasanta have studied the reduction of the five-membered ring ketal isomer **2**.[7] They report that catalytic reduction leads to *cis*-fusion at the ring junction whereas dissolving metal reduction gives rise to *trans*-fused products. The regiospecifically generated enolate[8] (*e.g.* from the dissolving metal reduction[9]) can be trapped as the silyl enol ether (with TMSCl) which in turn reacts with the Eschenmoser salt[10a] [dimethyl(methylene)ammonium chloride] producing a Mannich base.[10b] We decided to make use of these observations, which combine the simultaneous preparation of the C- and D-ring fragments (shown in Scheme 1 in the retrosynthetic approach with the stereochemistry as predicted in the literature).

The five-membered ring ketal **2** was prepared with high selectivity using a slightly modified literature method under transketalization conditions.[7] The ketal **2** was reductively silylated. The intermediate silyl enol ether **3** was then aminomethylated to give the unstable amine **4**, which cleaved spontaneously to the methylene ketone **5**. In the ^{1}H NMR spectrum of **5**, only one methyl peak was observed at 0.99 ppm indicating the presence of a single diastereomer. However, spectral data alone could not satisfactorily convince us that the ring junction was the desired *trans*-form.

We therefore undertook a study of the stereochemistry of the ring junction by comparison of the spectral properties of two pairs of the saturated ketones prepared by catalytic reduction (leading to *cis*-fused **6**) and by dissolving metal reduction (leading to *trans*-fused **7**) starting from **1** and **2**, respectively (Scheme 3).

We were initially surprised to find that the GC retention times (chiral permethylated β-cyclodextrin column) of **6** and **9** were identical. Our worst fears were realized on careful examination of the 1D and 2D ^{1}H and ^{13}C NMR spectra of the protected ketones **7** and **8** as well as the diketones **6** and **9**. Based on these data the pairs were identical. These results also clearly demonstrate that the dissolving metal reduction directs the ring fusion to the *cis*-, not *trans*-conformation, in stark contrast to reports in the literature.[7] Independently, Joullie and coworkers[11] observed the same discrepancy. We were obviously forced to abandon this approach and find a new one.

Our new method was a modification of that used to prepare 19-norsteroids,[12] which utilizes the directing effect of a carboxy group in catalytic reduction.[13] We adopted this procedure for **2** (Scheme 4). Ketone **2** was transformed to the carboxylated enone **10**.[14] The organic phase contained two acids and some **2** as a consequence of facile decarboxylation. The main product was the desired acid **10** and the minor acidic component was **11**. In this context it is worth noting that under similar conditions the decalone derivative **12** afforded the acid shown as the major product (Scheme 4).[12,15]

The crude unsaturated acid **10** (or the acid mixture) was subjected to catalytic hydrogenation to give **13**, which was immediately used in the decarboxylative aldol reaction with formaldehyde to give the *exo*-methylene ketone **5**. Luche reduction ($NaBH_4$, $CeCl_3$)[16] gave rise to a mixture containing four components. The two main products (57 and 33%) were alcohols with *m*/*z* 224, and the two minor ones (7 and 3%) had *m*/*z* 224 and 212, respectively. The components were separated by

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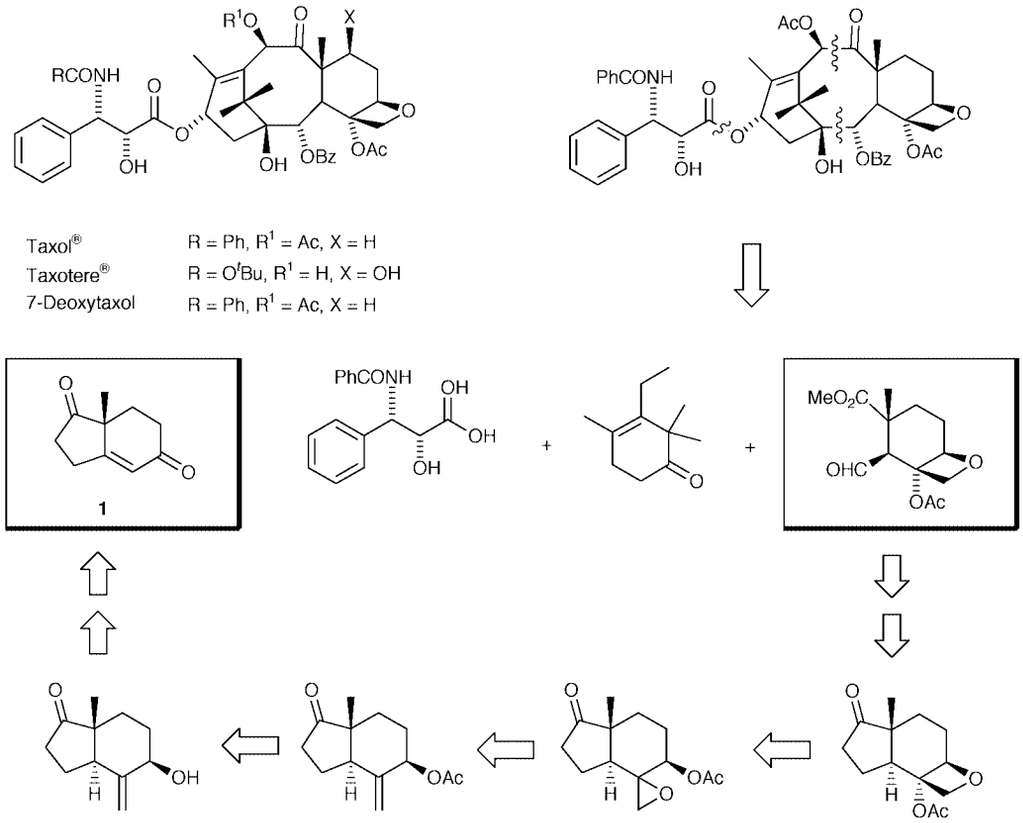
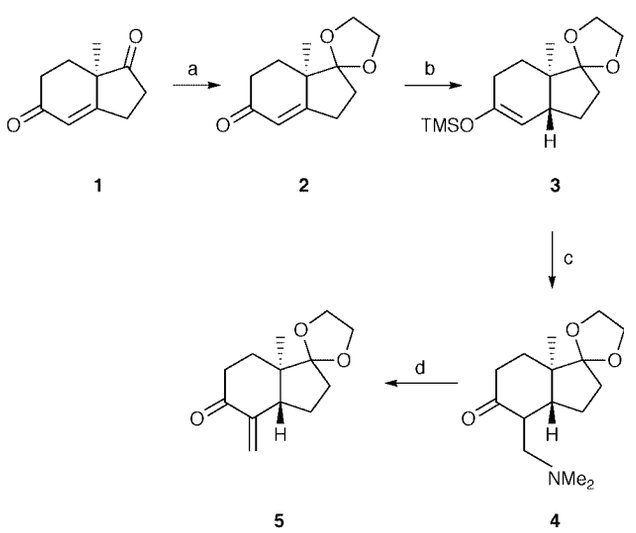
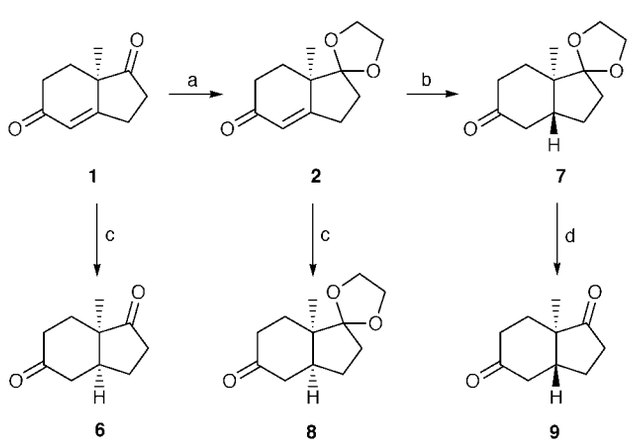


Scheme 1 The retrosynthetic analysis of 7-deoxytaxol.



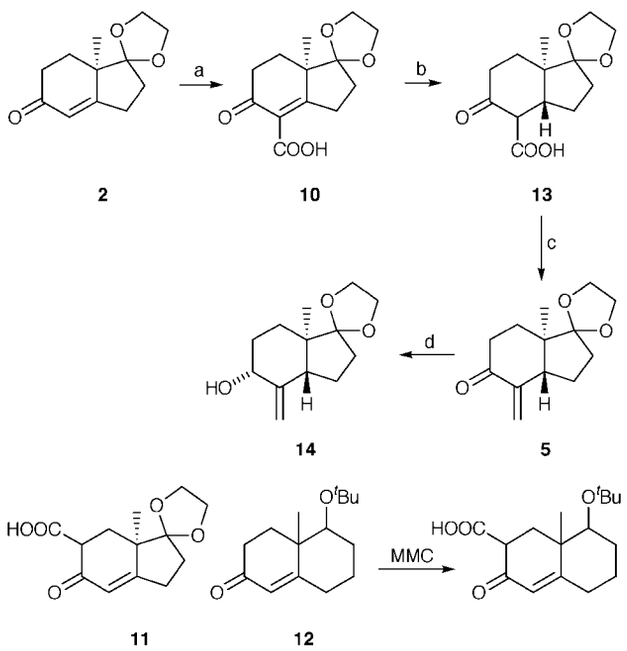
Scheme 2 *Reagents and conditions*: a) 2-Methyl-2-ethyl-1,3-dioxolane, ethylene glycol, *p*-TsOH, 15 °C, 65%; b) Li/NH_3, −65 °C, TMSCl, Et_3N, THF; c) $Me_2NCH_2^+Cl^-$, CH_2Cl_2; d) rt.



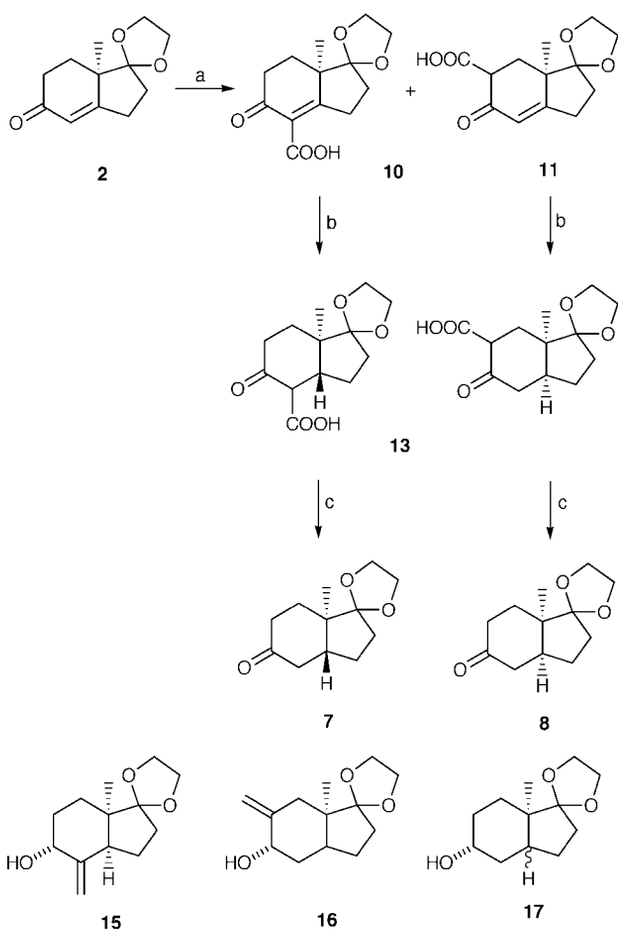
Scheme 3 *Reagents and conditions*: a) 2-Methyl-2-ethyl-1,3-dioxolane, ethylene glycol, *p*-TsOH, 15 °C, 65%; b) Li/NH_3, −65 °C, NH_4Cl, 97%; c) H_2, 10% Pd/C, MeOH, 84–87%; d) PyTsOH, Me_2CO, reflux, 75%.

flash chromatography and 1D and 2D ^1H and ^{13}C NMR spectra were recorded. The three components with *m*/*z* 224 all contained 12 carbon atoms and the *exo*-methylene group.

To shed more light on the assignment we carboxylated **2** in the usual way (Scheme 5). The product mixture (**10** and **11**) was then catalytically hydrogenated and finally decarboxylated by evaporation in a hot water bath. The separation was unsuccessful and the mixture (57:43) was studied by 500 MHz NMR analysis. The spectra were compared with those of **8**. The compound present in 57% yield showed identical spectral properties to the *cis-form* **8** but surprisingly the observed methyl signal was a weak doublet ($J = 0.61$ Hz). In both molecules the W-path from the methyl protons to a proton on an adjacent carbon atom was possible and in **7** two such paths are possible. The second compound has to be the *trans-form* **7** (due to the methyl peak at 0.97 ppm being a doublet, $J = 0.72$ Hz). The large amount of the *cis-form* **8** produced is possibly caused by the formation of acid **11** which after catalytic hydrogenation undergoes decarboxylation to **8**. In addition, the directing effect of the carboxy group in hydrogenation leads not only to the *trans*-hydrogenation product **13**, but also to the corresponding *cis*-product which is formed simultaneously, thus increasing the amount of **8** formed after decarboxylation of the *cis*-product. Hajos and co-workers[17] have shown that a bulky substituent at C-2 may assist catalytic hydrogenation to yield at least 50% of the *trans*-product. To compare the direction of catalytic hydrogenation in different solvents we took samples of the carboxylated product mixture (**10** and **11**) and hydrogenated them in isopropanol and in ethyl acetate. The difference in the ratio of



Scheme 4 *Reagents and conditions*: a) Magnesium methyl carbonate, DMF, 125 °C, 89%; b) H_2, 5% Pd/C, MeOH, 0 °C, 81%; c) 37% CH_2O, DMSO, piperidine; d) $NaBH_4$, $CeCl_3$, MeOH, 55%.



Scheme 5 *Reagents and conditions*: a) Magnesium methyl carbonate, DMF, 125 °C; b) H_2, 5% Pd/C, MeOH, 0 °C; c) Δ.

cis- and *trans*-forms was significant compared to the hydrogenation in methanol (1.3 : 1). In isopropanol the ratio of *cis*- and *trans*-forms was 3 : 1, and in ethyl acetate the ratio was 3.7 : 1. The results show that the directing effect of the carboxy group is not the only factor steering catalytic hydrogenation in this system. The conclusion that the smaller main component (33%) is the *trans*-form **14** is supported by the observations in the literature.[17b–19] The methyl signal of the *trans*-derivative appears at a higher field compared to the corresponding *cis*-form. Thus, the major alcohol components are **15** and **14**, and the two minor components are **16** (7%) and **17** (3%); the former from the acid **11** and the latter the alcohol from the cleavage of **10**.

These experiments show that introduction of a carboxy group in order to provide a directing effect in the hydrogenation of a five-membered ring protected ketal **2** does not lead diastereoselectively to the desired *trans*-substitution at the ring junction. Carboxylation occurs at both α-positions to the carbonyl group of **2** leading to a mixture of carboxylic acids. If it is supposed that carboxylic acid **11** is formed more slowly than **10** and that carboxylation is interrupted before all starting material has reacted and before the formation of **11**, the subsequent catalytic hydrogenation of the unreacted **2** will still produce the undesired *cis*-substituted **8**. The above reaction sequence shows that reactions of the chiral ketal **2** lead the methyl group and hydrogen atom at the Taxol® BC-ring junction to be *trans* with respect to each other, and that ketal **2** is sensitive to side reactions.

Experimental

General

Methanol was dried by distillation from magnesium methoxide. Methylene chloride was distilled prior to use from calcium hydride. Tetrahydrofuran was distilled from sodium metal–benzophenone ketyl. All other reagents and solvents were used as obtained from the supplier, without further purification. All air or moisture sensitive reactions were carried out under Ar with magnetic stirring. Reactions were monitored by TLC (on silica gel 60 F_{254} plates from Merck). The chromatograms were visualized by UV light and staining with ethanolic anisaldehyde–glacial acetic acid–H_2SO_4. Reaction temperatures refer to bath temperatures. NMR spectra were recorded on Bruker AM200, DPX400 or DRX500 FT spectrometers operating at 200, 400 and 500 MHz (for ^1H), respectively. Mass spectra were measured on a Kratos MS 80 mass spectrometer. $[\alpha]_D$ has units of 10^{-1} deg cm^2 g^{-1}.

(7a*R*)-1,1-Ethylenedioxy-7a-methyl-5,6,7,7a-tetrahydroindan-5-one (2)

(*R*)-(−)-Hajos–Parrish ketone (**1**) [7.1 g, 43.3 mmol, $[\alpha]_D$ = −350 (*c* 1.0, toluene)], 2-methyl-2-ethyl-1,3-dioxolane (40 ml), ethylene glycol (0.4 ml) and *p*-TsOH (130 mg) were stirred at 15 °C for seven days. The reaction was quenched by adding benzene (150 ml) and neutralizing with a few drops of triethylamine. The mixture was then washed with water and saturated aqueous NaCl. After drying ($MgSO_4$) and evaporation crude **2** was obtained (7.8 g). It contained 65% of **2**, 6% of six-membered ring ketal, 3% of isomerized six-membered ring ketal, 2% of diketalized product and 24% of starting compound **1**. Monoketal **2** was purified by silica gel flash chromatography (hexane–acetone 10 : 1); ^1H NMR (200 MHz, $CDCl_3$) δ 5.71 (s, 1H), 3.86 (m, 4H), 2.72–2.50 (m, 1H, H-3), 2.52–2.22 (m, 2H, H-6), 2.43–2.13 (m, 2H, H-7), 2.25–2.03 (m, 1H, H-4), 2.25–1.98 (m, 1H, H-3), 1.90–1.75 (m, 1H, H-4), 1.58–1.45 (m, 1H, H-6), 1.17 (s, 3H, H-8); ^{13}C NMR (50 MHz, $CDCl_3$) δ 198.5, 174.0, 122.9, 117.2, 65.5, 64.7, 47.5, 32.3, 31.4, 26.6, 26.3, 19.8; MS *m*/*z* 208 (80%, M^+), 193 (4), 165 (12), 153 (11), 151 (12), 138 (22), 121 (9), 107 (14), 99 (22), 93 (20), 86 (100), 79 (26), 77 (15), 55 (7) (Lit.[17,18] HRMS: Found: 208.1088. Calcd for $C_{12}H_{16}O_3$, 208.1099).

(3a*S*,7a*R*)-1,1-Ethylenedioxy-7a-methyl-4-methylene-3a,4,5,6,7,7a-hexahydroindan-5-one (5)

Lithium (0.34 g, 48.9 mmol) was dissolved in dry freshly distilled ammonia (75 ml) at −65 °C. Monoketal **2** (3.40 g, 16.3

mmol) and dry *tert*-butyl alcohol (0.97 g, 13.0 mmol) in dry THF (65 ml) were then added to the blue ammonia solution by syringe. The mixture was stirred for 5 min at −65 °C. Excess Li was destroyed by addition of distilled isoprene (5 ml). The clear solution was allowed to warm to rt while ammonia was distilled off. The solution was then evaporated and the residue was dissolved in dry THF (40 ml) and cooled to −30 °C. 2 ml of Et_3N–TMSCl (1 : 1) was added to the reaction mixture. The mixture was stirred and allowed to warm to rt, 50 ml of petrol ether (bp 40–60 °C) was added, the solution was cooled in an ice bath and washed first with ice-cold saturated aq. $NaHCO_3$ (3 × 25 ml) and then with ice-cold brine. After drying ($NaSO_4$) and evaporation of solvents the crude product was purified by silica gel flash chromatography (hexane–ether 10 : 1) to give silyl enol ether **3** (1.50 g, 33%); MS *m*/*z* 282 (9%, M^+), 237 (6), 221 (7), 196 (12), 183 (41), 181 (7), 167 (2), 140 (5), 109 (8), 100 (29), 99 (100), 86 (17), 75 (46), 73 (54), 55 (25). Eschenmoser salt[10a] (0.64 g, 6.9 mmol) was suspended in a solution of the silyl enol ether (1.50 g, 5.3 mmol) in dry CH_2Cl_2 (50 ml). The mixture was stirred at rt until TLC showed all silyl enol ether had reacted (2 h). After filtration and evaporation, a crude mass of 2.1 g was obtained. The basic components were extracted into 2 M HCl, released from the salt with K_2CO_3 and then extracted into petrol ether. The amine **4** was unstable and cleaved spontaneously to the corresponding *exo*-methylene ketone **5** whose structure was confirmed by NMR and MS analysis; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (d, 1H), 5.08 (d, 1H), 3.87 (m, 4H), 2.78 (m, 1H), 2.45–2.33 (m, 1H), 2.05–1.45 (m, 6H), 0.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 146.1, 121.5, 65.3, 64.2, 50.3, 45.9, 36.3, 33.2, 27.4, 17.5; MS *m*/*z* 222 (2%, M^+), 207 (3), 122 (2), 101 (42), 99 (100), 93 (6), 91 (7), 86 (81), 79 (20), 77 (13), 65 (10), 55 (32), 41 (16).

(3a*S*,7a*R*)-7a-Methyl-3a,4,5,6,7,7a-hexahydroindane-1,5-dione (6)

(*R*)-(−)-Hajos–Parrish ketone (**1**) (108.0 mg, 0.52 mmol) and 10% Pd/C (10.0 mg) were added to MeOH (10 ml). Oxygen was evacuated and replaced with argon. The mixture was stirred under a balloon of hydrogen at rt for 2 h. The catalyst was filtered off (Celite) and the solvent was evaporated to give **6** (92 mg, 84%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.54 (dd, J = 15.1, 6.4 Hz, 1H, H-2), 2.36 (m, 1H, H-2a), 2.39–2.25 (m, 2H, H-4), 2.38–2.28 (m, 1H, H-7), 2.26–2.17 (m, 1H, H-2), 2.20–2.12 (m, 1H, H-7), 2.11–2.02 (m, 1H, H-3), 2.00–1.91 (m, 1H, H-6), 1.62–1.52 (m, 1H, H-6), 1.61–1.50 (m, 1H, H-3), 1.19 (s, 3H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.1, 210.6, 47.6, 44.9, 42.2, 37.4, 35.6, 30.2, 25.5, 20.9; MS *m*/*z* 166 (100%, M^+), 151 (4), 138 (15), 122 (38), 109 (48), 96 (37), 82 (51), 81 (48), 68 (96), 67 (55), 55 (98), 53 (32), 41 (52), 39 (42) (HRMS: Found: 166.1000. Calcd for $C_{10}H_{14}O_2$, 166.0994).

(3a*S*,7a*R*)-1,1-Ethylenedioxy-7a-methyl-3a,4,5,6,7,7a-hexahydroindan-5-one (8)

(a) By catalytic hydrogenation of 2. Ketal **2** (172.0 mg, 0.83 mmol) was hydrogenated with 10% Pd/C (31.0 mg) in MeOH for 2 h, after which the mixture was filtered and evaporated to give **8** (152 mg, 87%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (m, 4H), 2.46–2.35 (m, 1H, H-2), 2.35–2.20 (m, 2H, H-7), 2.23–2.15 (m, 1H, H-2), 2.20 (m, 1H, H-2a), 1.95–1.82 (m, 1H, H-6), 1.90–1.73 (m, 2H, H-4, H-3), 1.68–1.60 (m, 1H, H-6), 1.39–1.25 (m, 1H, H-3), 1.10 (s, 3H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.4, 119.8, 65.6, 64.8, 44.7, 44.5, 42.6, 37.5, 33.3, 29.8, 26.1, 18.8; MS *m*/*z* 210 (2%, M^+), 139 (1), 126 (1), 122 (2), 113 (2), 108 (3), 100 (24), 99 (100), 86 (12), 81 (6), 79 (5), 77 (4), 67 (8), 55 (20), 53 (8), 41 (9) (HRMS: Found: 210.1256. Calcd for $C_{12}H_{18}O_3$, 210.1256).

(b) By dissolving metal reduction of 2. Ketal **2** (268.0 mg, 1.29 mmol) was reduced as before and then quenched by adding NH_4Cl in small portions. Ammonia was evaporated in a stream of Ar. The residue was dissolved in water (20 ml) and extracted with CH_2Cl_2 (4 × 10 ml), then dried with $MgSO_4$; yield 262 mg (97%). A sample of the product was purified by silica gel flash chromatography (hexane–ether 10 : 1) for analysis. ^{1}H NMR and ^{13}C NMR spectra of the sample were identical with the spectral data of **8**.

(c) A sample (200 mg, 0.95 mmol) of the product from the above dissolving metal reduction was dissolved in acetone (10 ml) and refluxed with pyridinium tosylate (75 mg) for 3 h. After cooling, ether was added and then the mixture was filtered. The filtrate was washed twice with saturated aqueous $NaHCO_3$ and NaCl. After drying and evaporation the crude product was purified by silica gel flash chromatography (hexane–ether 10 : 1) to give 119 mg (75%) of the product, whose recorded ^{1}H NMR and ^{13}C NMR spectra were identical with the spectral data of **6**.

(7a*R*)-1,1-Ethylenedioxy-7a-methyl-5-oxo-5,6,7,7a-tetrahydroindane-4-carboxylic acid (10)

Compound **2** (3.06 g, 14.7 mmol) in dry DMF (30 ml) was heated with 2 M magnesium methyl carbonate (25 ml) under argon in an oil bath (125 °C). Heating was continued until all **2** had been consumed (6 h, TLC analysis). After cooling, DMF was evaporated, finally in a high vacuum. The brownish-red Mg chelate was extracted with CH_2Cl_2 to remove any residual starting material. All following treatments were performed at 0 °C. Mg chelate was suspended in ice water (20 ml) and CH_2Cl_2 (20 ml) and carefully acidified with 1 M H_3PO_4. At pH 6 a light precipitate formed. After filtration, the water phase was extracted with CH_2Cl_2. More acid was added to the water phase (until pH 3), and extractions with CH_2Cl_2 were repeated. TLC showed that at lower pH a second compound started to form. The combined extracts were dried ($MgSO_4$) and the solvent evaporated to yield crude **10** (3.28 g, 89%). An analytical sample was separated and purified by silica gel flash chromatography (hexane–EtOAc 4 : 1 + 1% AcOH). Acid **10**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 12.2 (s, 1H, H-9), 3.95 (m, 4H), 3.36–3.27 (m, 1H), 2.95–2.68 (m, 2H), 2.45–1.91 (m, 4H), 1.71–1.61 (ddd, 1H, J = 13, 5, 3 Hz) 1.33 (s, 3H, H-8); ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.4, 194.6, 164.0, 120.6, 116.9, 65.8, 64.9, 50.8, 33.2, 31.6, 31.1, 24.7. The minor acidic component was the acid **11**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.81 (br s, 1H, H-9), 5.94 (s, 1H, H-2), 3.96 (m, 4H), 3.44 (dd, 1H, J = 14, 5 Hz, H-7), 2.85–2.40 (m, 2H), 2.30–1.85 (m, 2H), 1.30 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 199.2, 196.3, 174.6, 121.8, 117.2, 65.8, 65.0, 48.1, 32.9, 31.6, 30.0, 27.0, 26.6, 20.0.

(3a*S*,5*R*,7a*R*)1,1-Ethylenedioxy-7a-methyl-4-methylene-3a,4,5,6,7,7a-hexahydroindan-5-ol (14) and (3a*R*,5*R*,7a*R*)1,1-Ethylenedioxy-7a-methyl-4-methylene-3a,4,5,6,7,7a-hexahydroindan-5-ol (15)

The residue from the previous reaction containing crude **10** (3.28 g) was dissolved in dry MeOH. Oxygen was evacuated and replaced with argon. 5% Pd/C (295 mg) was added, and the mixture was stirred under a balloon of hydrogen at 0 °C until TLC showed that all acid **10** had reacted (4 h). The catalyst was filtered off using Kieselruhr. After evaporation the yield of the yellow-brownish oily acid **13** was 3.02 g (81%). The crude acid **13** (3.02 g, 11.9 mmol), DMSO (25 ml), 37% formaldehyde (4.2 ml) and piperidine (98 µl) were stirred at rt. According to TLC decarboxylation was over in 1 h. A 1 : 1 mixture of water and saturated aqueous NaCl (50 ml) was added and stirring was continued for 5 min. The mixture was then extracted with CH_2Cl_2 (4 × 25 ml), the combined extracts were washed twice with brine, and dried with $MgSO_4$. The solvent was changed to MeOH (*ca*. 50 ml), and the reaction mixture was cooled in an ice bath. Solid $CeCl_3 \cdot 7H_2O$ (5.80 g, 15.6 mmol) was added. When dissolution was complete, $NaBH_4$ (2.00 g, 52.0 mmol) was added in small portions. Stirring was continued for 1 h.

Saturated NaCl was added to the cold slurry followed by 1 M HCl until the solution cleared (pH 5). The mixture was extracted with CH_2Cl_2 (4 × 50 ml), the combined extracts were washed first with saturated aq. $NaHCO_3$, then with water and finally brine. Drying ($MgSO_4$), filtration and evaporation gave the crude product (1.80 g, 55% from **2**). The crude product contained three alcohols (with *m*/*z* 224) of 57, 33 and 7% yield and a component of 3% (*m*/*z* 212) yield. The components were separated by silica gel flash chromatography (isooctane–ether 9:1). Data for **15** (57%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99 (t, 1H, J = 2 Hz, H-8a), 4.81 (t, 1H, J = 2 Hz, H-8b), 4.28–4.25 (ddt, J = 12, 5, 2 Hz, 1H, H-1), 3.87 (m, 4H, ketal group), 2.62 (t, 1H, J = 10 Hz, H-2a), 2.22 (br s, 1H, OH), 2.10–1.30 (m, 8H, H-3, H-4, H-6, H-7), 0.86 (s, 3H, H-9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 120.2, 107.3, 69.3, 65.8, 64.7, 53.0, 48.0, 35.0, 33.3, 29.4, 25.4, 16.8; MS *m*/*z* 224 (2%, M^+), 181 (1), 162 (1), 136 (6), 118 (6), 100 (32), 99 (100), 86 (45), 73 (2), 55 (10); MS *m*/*z* (CI, NH_3) 225 (100%, M + 1^+), 207 (45), 196 (1), 180 (1), 165 (1), 145 (5), 121 (1), 99 (30), 94 (1), 86 (21) (HRMS: Found: 224.1378. Calcd for $C_{13}H_{20}O_3$, 224.1412). Data for **14** (33%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 (td, 1H, J = 3, 2 Hz, H-8a), 4.65 (td, 1H, J = 3, 2 Hz, H-8b), 3.98 (ddt, 1H, J = 11, 6, 2 Hz, H-1), 3.87 (m, 4H), 2.32 (ddt, 1H, J = 12, 7, 2 Hz, H-2a), 2.10–1.30 (m, 8H, H-3, H-4, H-6, H-7), 0.74 (s, 3H, H-9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 119.4, 103.1, 73.2, 65.6, 65.0, 48.9, 48.4, 35.0, 33.0, 29.2, 20.5, 14.8; MS *m*/*z* (CI) 224 (M^+), 206 (1%), 181 (1), 134 (1), 113 (2), 100 (35), 99 (100), 86 (32), 79 (2), 55 (6), 41 (3); MS *m*/*z* (CI, NH_3) 225 (100%, M + 1^+), 207 (59), 163 (17), 99 (66), 86 (10) (HRMS: Found: 224.1407. Calcd for $C_{13}H_{20}O_3$, 224.1412). Data for **16** (7%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.96 (s, 1H, H-8a), 4.81 (s, 1H, H-8b), 4.22 (t, 1H, J = 4 Hz, H-1), 3.90 (m, 4H), 2.56 (d, 1H, J = 14 Hz, H-7), 2.1–1.74 (m, 8H, H-3, H-5, H-6, H-6a, H-7), 0.86 (s, 3H, H-9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 120.0, 110.7, 72.0, 65.1, 64.4, 52.4, 41.1, 34.6, 34.1, 33.3, 25.6, 19.3. MS *m*/*z* (CI) 224 (M^+), 182 (<1%), 162 (1), 136 (2), 118 (6), 100 (15), 99 (100), 86 (10), 73 (2), 55 (6); MS *m*/*z* (CI, NH_3) 225 (M + 1^+). Data for **17** (3%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.90 (m, 4H), 3.65 (m, 1H, H-1), 2.20–1.08 (m, 11H), 0.94 (s, 3H); MS *m*/*z* 212 (1%, M^+), 150 (2), 124 (2), 100 (15), 99 (100), 86 (7), 55 (5); MS *m*/*z* (CI, NH_3) 213 (M + 1^+).

(3a*R*,7a*R*)-1,1-Ethylenedioxy-7a-methyl-3a,4,5,6,7,7a-hexahydroindan-5-one (7)

A mixture of **10** and **11** (2.41 g, 9.6 mmol) from carboxylation of **2** was hydrogenated using 5% Pt/C (286 mg) as catalyst in MeOH at 0 °C. After the usual work up the crude product mixture was decarboxylated by evaporation in a hot water bath and purified by silica gel flash chromatography (isooctane–acetone 95:5). The two components (57:43) were not separable by chromatographic methods (TLC or flash) and the ^{1}H NMR spectrum was recorded from the mixture (57:43). The NMR spectrum of the major component was identical to the spectrum of *cis*-form **8**. Data for **7**: ^{1}H NMR (benzene-d_6, 500 MHz) δ 3.55 (m, 4 H), 2.10–2.00 (m, 1H, H-4), 1.88 (m, 1H, H-6), 1.85 (m, 1H, H-4), 1.53–1.45 (m, 1H, H-3), 1.40–1.34 (m, 1H, H-6), 1.24–1.14 (m, 1H, H-3), 0.98 (d, 3H, J = 0.72 Hz, H-8), H-2, H-2a and H-7 were covered by the peaks of *cis*-form **8**; MS *m*/*z* 210 (1%, M^+), 139 (1), 126 (3), 113 (3), 108 (2), 100 (26), 99 (100), 86 (12), 81 (4), 79 (4), 77 (3), 67 (6), 55 (16), 53 (7), 41 (8).

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