Pergamon

Tetrahedron 58 (2002) 10103–10112

TETRAHEDRON

Synthesis of B,B-dinor-B-*seco*steroids as potential cardenolide analogues

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Dedicated to the memory of Dr Benedicto del Rey

Received 11 June 2002; revised 30 September 2002; accepted 25 October 2002

Abstract—A novel chemical construction of B,B-dinor-B-*seco*steroids as simplified cardenolide analogs, starting from the Hajos–Parrish diketone was developed. The synthesis of the equivalent of the steroid A ring was carried out through a Diels–Alder reaction between an appropriate hydroindenyl acrylate derivative and Danishefsky's diene.

1. Introduction

Digitalis glycosides, used for the treatment of dropsy more than 200 years ago and for the treatment of congestive cardiac failure since the beginning of the past century,[1] have as major problem in their clinical use their narrow therapeutic index. The necessity of less toxic cardiotonic agents has prompted much research on natural cardiotonics and their synthetic analogues.[2]

As the genins of the CG are steroids that highly contribute to the interaction with the digitalis binding site,[3] previous work from our group has been undertaken to investigate the influence of the skeleton size on inotropic activity and toxicity. Thus, we studied diterpenic cardenolide analogues[4] and more simplified analogues, with only a cyclohexane[5] ring. Afterwards, we prepared hydroindenic derivatives (Fig. 1) which among other structural variations,[6] have a Δ^{3a} unsaturation and an amidino hydrazono moiety at C-5 (see compound **I**) showing a fairly positive inotropic effect without modifying the heart rate.[7]

After these results, we decided to broaden the study to B,B-dinor-B-*seco*steroids depicted in Fig. 2 as mimics of the genins of cardiac glycosides but lacking the whole steroid skeleton.[8] Starting from the Hajos–Parrish diketone **1** ((3a*S*,7a*S*)-3a-hydroxy-7a-methylperhydroindene-1,5-dione) the molecules already have the required absolute stereochemistry and the 3a-βOH (14β of the steroid) group, the major problem for the introduction of the A ring equivalent being the control of the configuration at the C-5 position, that also controls the preferred conformation of the hydroindenic derivatives. This question was solved by the group from Praxis[9] for compounds type **B**, in consequence other strategies are needed for type **A** derivatives and for type **C** derivatives.

In this paper we report the synthetic effort directed to the

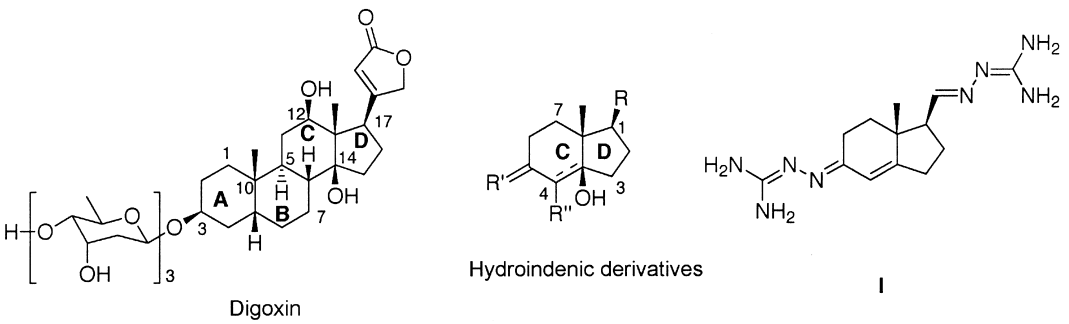

Figure 1. Structure of digoxin compared to hydroindenic derivatives.

Keywords: digitalis glycosides; hydroindenes; *seco*steroids.

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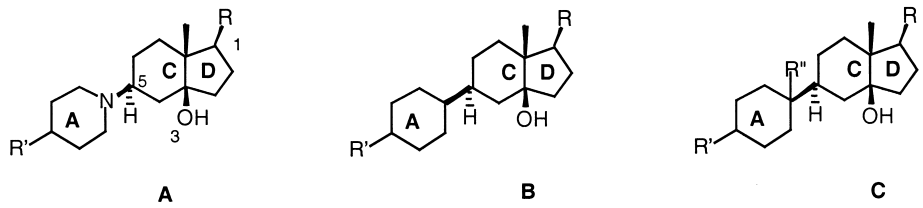


Figure 2. Structure of N-bonded piperidyl **A**, cyclohexyl **B** and **C** hydrindanic derivatives.

construction of the B,B-dinor-B-*seco*steroid skeleton from the hydroindenic Hajos–Parrish diketone.

2. Results and discussion

We started with the study of the transformation of **1** into *N*-substituted derivatives at C-5 and continued with the synthesis of the C-substituted derivatives at this position. Because of it is generally possible to chemoselectively transform the C-5 ketone, we centred our efforts on the construction of the A ring, independently of the substitution at C-1.

2.1. Hydroindenic derivatives *N*-substituted at C-5

A possibility for introducing a nitrogen atom with stereochemical control is the Mitsunobu reaction, because a nitrogen nucleophyle can replace the hydroxyl group with inversion of the configuration at the OH supporting carbon.[10] For our purpose an α-OH is required, thus the reduction of diketone **1** with lithium tri-*tert*-butoxyaluminiumhydride was carried out leading to a 2.6:1 mixture of the reduction products at C-5 **3a/3b** (39%) and to a small amount of the C-1 reduction product **2** (3%) (Scheme 1). When **3a** was treated under Mitsunobu conditions,[11] the undesired dehydration product **4** (75%) was obtained and this procedure was discarded for our purposes.

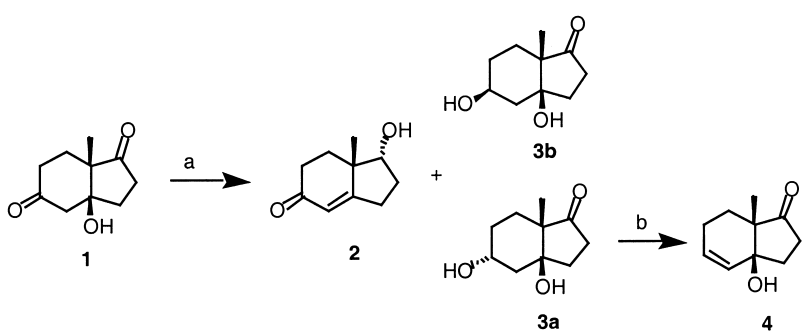
The introduction of the nitrogen substituent with the required β-stereochemistry was then tried by the reductive amination of the C-5 keto group. The tertiary hydroxyl group of **1** was protected (Scheme 2) as the trimethylsilyl-ether **5** (79%) in order to avoid secondary reactions. The reductive amination[12] of **5** led to a 7:1 mixture (65%) of **6a/6b**, respectively, showing a marked preference towards the 5α-amino-derivative. Diketone **5** was also treated with piperidine and sodium cyanoborohydride affording the nitrile **7** (23%), the keto-hydroxy derivative **8** (14%) and the ketopiperidine derivative **9** (33%) (Scheme 2). The stereochemical-conformational assignments have been based on the[13]C NMR shift of the methyl group at C-7a, because many hydroindenic derivatives show a clear difference in the chemical shift for equatorial C-7a methyl (>17 ppm) and axial C-7a methyl (<16 ppm) groups,[6b] as it can be appreciated for compounds **3a** and **3b**. These assignments are in agreement with other observations for compounds **6–9**, as it is the nOe on the β-axial-H7 upon irradiation of the equatorial C7a-methyl group and the appearance of the H-5 signal as a broad multiplet characteristic of an axial proton.

To know the influence of a different substitution at C-1 on the stereochemical course of the reductive amination at C-5, the methylene ketone **11** was obtained from the previously synthesized **10**.[13] Under standard conditions mixtures of piperidyl nitriles **12a/12b** and piperidines **13a/13b** (Scheme 2), with a 3:1 prevalence of the α-piperidyl derivatives, were produced. A subtle equilibrium between both conformations in the intermediate iminium ions during the reductive amination can be responsible for the mixtures obtained from ketones **5** and **11** and the prevalence of the unwanted α-substituted derivatives. Because of the difficulties observed to prepare derivatives type **A** with the requested stereochemistry, we decided to explore the other planned target molecules of type **C**.

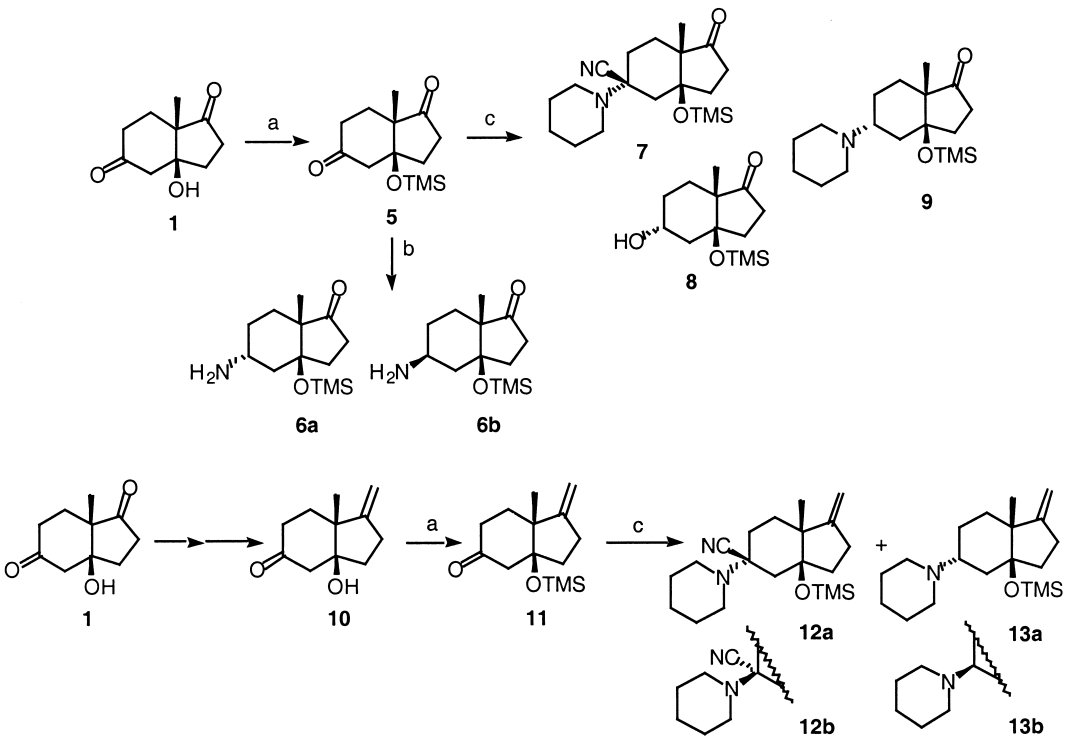
2.2. Hydroindenic derivatives *C*-substituted at C-5

Several methods were assayed to obtain these compounds, as it is shown in Scheme 3. Firstly, the malononitrile derivative **14** (80%) was synthesized from the diketone **1** by reaction with malononitrile[14] and β-alanine[15] as catalyst, followed by reduction of the tetrasubstituted double bond. The hydrogenation with H_2/Pd(C)[16] 10% afforded a complex mixture of products in which the C5α configuration always predominated. The reduction with DIBALH[17] yielded a 3:1 mixture of **15a/15b**, respectively, in low yield (27%).

The condensation of compound **1** with nitromethane was



Scheme 1. *Reagents and conditions*: (a) $LiAl(O^tBu)_3H$, THF, 0°C; (b) phthalimide, triphenylphosphine, DEAD, rt.



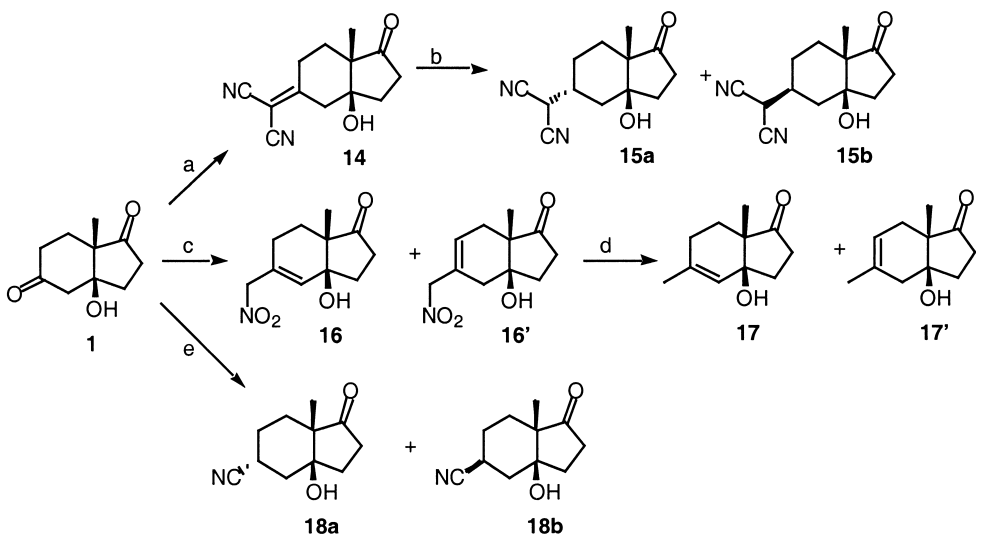
Scheme 2. *Reagents and conditions*: (a) TMSOTf, Et_3N, CH_2Cl_2, rt; (b) NH_4OAc, $NaBH_3CN$, MeOH, rt; (c) piperidine, HCl/MeOH, $NaBH_3CN$, rt.

carried out using ammonium acetate,[18] potassium fluoride[19] or ethylenediamine[20] as catalysts. The best result was obtained with the latter yielding the condensation product as a clean 4.5:1 mixture of **16/16′**, respectively (Scheme 3), whose reduction using H_2/Ni Raney,[21] H_2/PtO_2[22] and hydrazine hydrate[23] gave complex mixtures. Reaction with H_2/Pd(C) 10% yielded a 4:5 mixture of **17/17′**, produced by hydrogenolysis of the allylic nitro group. The disappearance of this group, required to further elaborate the A ring, made this procedure useless for the construction of B,B-dinor-B-*seco*steroids.

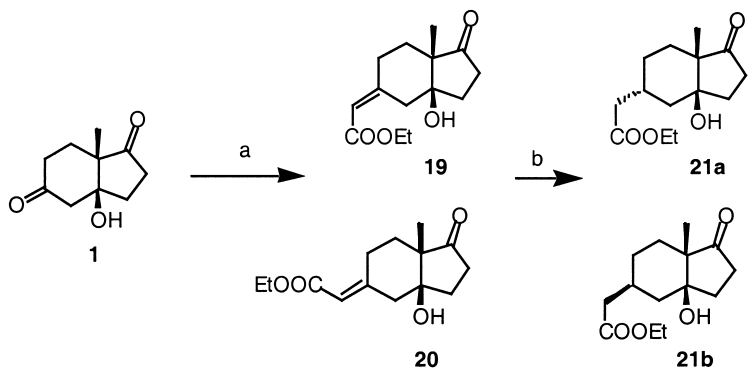
The direct transformation of diketone **1** into a 2:1 mixture of **18a/18b** (56%) was brought about by treatment with TosMIC and KO^{t}Bu[24] (Scheme 3). The crystal data of **18a** confirmed the stereochemical assignments of these hydrindanes (3a*R*,5*S*,7a*R* in this compound) and the preferred conformation in the crystalline state, which is the same observed in solution, with the C7a-methyl in an equatorial disposition (18.3 ppm). Its isomer **18b** shows the expected axial disposition for the methyl group (14.2 ppm).

2.3. Synthesis of the B,B-dinor-B-*seco*steroids

Another way to introduce a moiety for the construction of A ring and control the stereochemistry at C-5, is the hydrogenation of an alkenyl residue produced by means of the high yielding Wittig reaction. The treatment of diketone



Scheme 3. *Reagents and conditions*: (a) malononitrile, β-alanine, acetic acid, ethanol, rt; (b) DIBAL-H 1 M in hexane, THF, 0°C; (c) CH_3NO_2, ethylenediamine, Δ; (d) H_2, Pd(C) 10%, EtOH, rt; (e) TosMIC, K^{t}OBu, EtOH, 1,2-dimethoxyethane, rt.



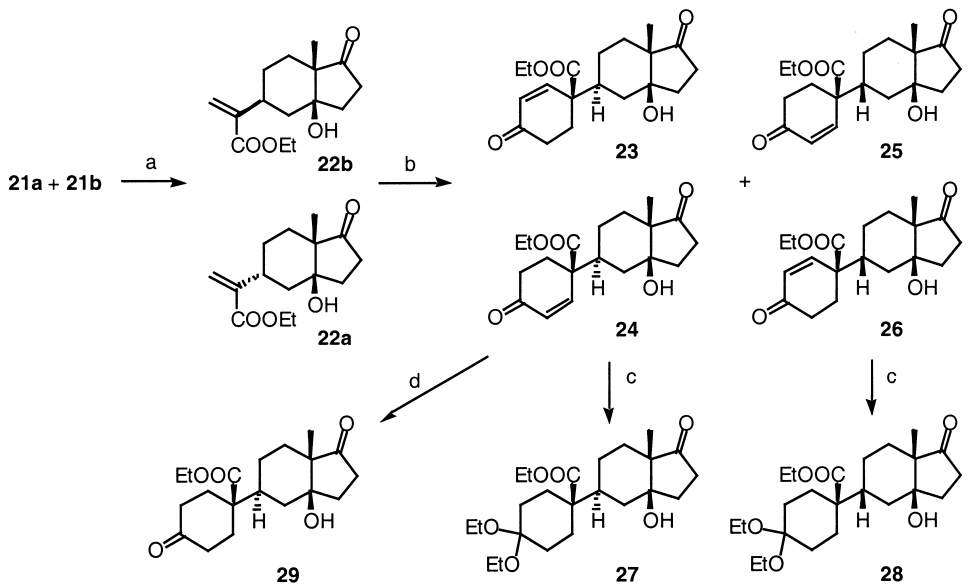
Scheme 4. *Reagents and conditions*: (a) $Ph_3P{=}CHCOOEt$, benzene, Δ; (b) H_2, Pd(C) 10%, EtOH, rt.

1 with ethoxycarbonylmethylenetriphenylphosphorane[25] gave a 3:2 mixture (97%) of **19**(*Z*)/**20**(*E*), respectively, that upon hydrogenation using Pd(C) 10% as catalyst quantitatively gave a 2:3 mixture of **21a/21b**, respectively. This two steps process leading to the ketoesters **21** (>95% yield from **1**) with predominance of the required C-5β stereochemistry (Scheme 4), is a good methodology for further elaborate the B,B-dinor-B-*seco*steroids.

Among other approaches for the synthesis of A ring, we choose the Diels–Alder methodology because it is straightforward, compatible with the hydroxy and keto functions at C-3a and C-1, and allows the control of the regiochemistry of final products. The designed strategy to complete this process was the introduction of a dienophyllic moiety in the α-position, followed by the Diels–Alder reaction with the Danishefsky's diene, which places a carbonyl group in the position where the R′ substituent (see Fig. 2) should be attached.

Due to the difficulties encountered for its resolution, the mixture of **21a/21b** was transformed into the corresponding dienophiles **22a/22b** via the Mannich[26] reaction with the Eschenmoser's salt,[27] alkylation with methyl iodide and Hofmann elimination with $NaHCO_3$. The acrylates **22a** and **22b** were difficult to separate and we used the mixture in the Diels–Alder reaction. Although four compounds can be produced (**23**–**26**, two stereoisomers at the α-position of the carboxylic esters for each, C5α and C5β derivatives), they will be reduced again to the mixture of only the 5α and 5β isomers (**27** and **28**) during the hydrogenation step, because the stereogenicity at the α-position is destroyed.

The 2:3 mixture of acrylates **22a/22b** was reacted with Danishefsky's diene,[28] affording the corresponding cycloaddition products. After hydrolysis, both 5β–5α diastereomeric mixtures were separated and the major components (**23** and **25**) isolated. Although not important for the whole process, the stereochemistry of these compounds could be established by means of key nOes observed between protons in A and C rings. The hydrogenations of the 5β (**23**+**24**) and 5α (**25**+**26**) diastereomeric mixtures, using Pd(C) 10% as catalyst and absolute ethanol as solvent, led to the hydrogenated and protected cyclohexanic ketones as diethyl ketals, **27** (89%) and **28** (82%), respectively (Scheme 5). When the hydrogenation was carried out in ethylenglycol, the mixture of **23**+**24** gave the diketo derivative **29** in 80% yield.



Scheme 5. *Reagents and conditions*: (a) (i) LDA, HMPTA, THF, −78°C, (ii) $H_2C{=}N(CH_3)_2I$, THF, −42°C to rt, (iii) CH_3I, *p*-dioxane, 90°C, (iv) $NaHCO_3$, H_2O/EtOAc, rt; (b) (i) Danishefsky's diene, benzene, 95°C, (ii) HCl c., $CHCl_3$, rt; (c) H_2, Pd(C) 10%, EtOH, rt; (d) H_2, Pd(C) 10%, $HOCH_2CH_2OH$, rt.

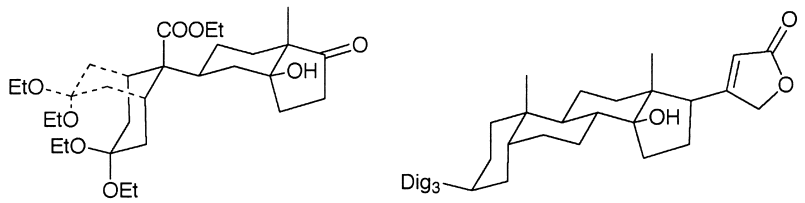


Figure 3. Comparison of compound **27** (two chairs conformations) with digitoxin.

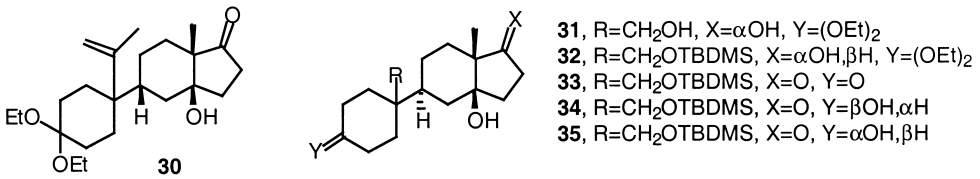


Figure 4. Structure of products obtained by further transformations of **27**.

By this procedure, the synthesis of the B,B-dinor-B-*seco*steroid **27** and **29** was completed. These compounds have the same stereochemistries at C-9, C-13 and C-14 as the natural cardenolides, the 14βOH and key functionalities at C-3 and C-17 to be converted into groupings conferring good affinities to the digitalis receptor (Fig. 3). Other structural characteristics of this compound are the symmetry of ring A, that facilitates its conversion into single isomers, and the presence of the carboxylate at C-19 that can be maintained, converted into other functions (as presented in several natural cardenolides) or removed to mimic the C-19 methyl of steroids.

Further transformations (Fig. 4) of **27** were carried out to check the possibilities of future transformations of these key compounds into cardenolide analogues. These reactions demonstrate the low reactivity of the ketone at C-1 of the hydrindane system, as for example in the Wittig reaction of **28**, taking place on the ester group rather than on the free keto group at C-1 (compound **30**). Only the reduction at the C-1 carbonyl (yielding α and β-OH derivatives) was readily produced with $LiAlH_4$ (compound **31**), although the $NaBH_4$ chemoselectively reduced the cyclohexanone (compound **33** to **34**, **35**). The selective protection of the hydroxymethyl group in the presence of α or βOH functions at C-1 was also achieved (**31** to **32**). Compound **33**, obtained by oxidation from **32**, is an interesting diketo derivative with two carbonyl groups of different reactivity.

3. Conclusion

In conclusion, a straightforward methodology for the preparation of B,B-dinor-B-*seco*steroids has been described (in five steps from Hajos–Parrish ketone in 41% overall yield: 25% overall of 9β 'steroid like' isomer **27** and 16% overall of 9α 'non-steroidal' isomer **28**). The synthesis of more elaborated products could be carried out by this procedure, although previous transformation of the C-1 keto group is desirable due to its low reactivity. New cardenolide analogues of this type will be synthesized by this procedure and submitted for biological assays.

4. Experimental

4.1. General

Solvents and reagents were used as purchased from Aldrich. Chromatographic separations were performed on silica gel columns by flash (Kieselgel 40, 0.040–0.063 mm; Merck) or gravity column (Kieselgel 60, 0.063–0.200 mm; Merck) chromatography. Reactions were monitored by thin-layer chromatography (TLC precoated silica gel polyester plates, 0.25 mm thickness, with fluorescent indicator UV 254, Polychrom SI F_{254}). Solutions were dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. Melting points were determined on a Buchi 510 apparatus and are uncorrected. IR spectra were obtained in CH_2Cl_2 film in a Nicolet (Impact 410) spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker WP 200-SY spectrometer at 200/50 MHz or on a Bruker DRX spectrometer at 400/100 MHz. Chemical shifts (δ) are given in ppm downfield from tetramethylsilane as an internal standard, and coupling constants (J values) are in hertz. GC-MS analyses were carried out with a Hewlett-Packard 5890 series II apparatus (70 eV). For HRMS analyses, a VG TS-250 apparatus (70 eV) was used.

4.2. Method A: general procedure for hydrogenation

To a solution 0.13 M of the starting material in EtOH, Pd(C) 10% was added and stirred under H_2 atmosphere (2 atm). After disappearance of the starting material, the reaction was filtered through a silica gel column and the solvent evaporated to obtain the hydrogenation products.

4.2.1. (1*R*,7a*S*)-1-Hydroxy-7a-methyl-2,3,5,6,7,7a-hexahydroinden-5-one (2), (3a*S*,5*S*,7a*S*)-3a,5-dihydroxy-7a-methylperhydroinden-1-one (3b) and (3a*S*,5*R*,7a*S*)-3a,5-dihydroxy-7a-methylperhydroinden-1-one (3a). A suspension of lithium tri-*tert*-butoxyaluminohydride (792 mg, 3.0 mmol) in 5.5 mL of dry THF was heated to reflux under Ar until it was completely dissolved. Next, it was cooled to 0°C and 500 mg (2.75 mmol) of diketone **1** were added. The mixture was stirred at 0°C for 1.5 h, then an aqueous solution of ammonium sulfate (1.5 g in 2.3 mL of H_2O) was added dropwise, with vigorous stirring and cooling. The

reaction was extracted with EtOAc and washed with brine. After column chromatography (hex/EtOAc 1:2) 60 mg (12%) of starting material, 14 mg (3%) of an uncoloured oil **2**, 52 mg (10%) of **3b** as a white crystalline product, 45 mg (9%) of a mixture of **3b/3a** and 101 mg (20%) of **3a** as a colourless oil were obtained.

Compound **2**: $[\alpha]_D$=+61.7° (*c* 0.41, $CHCl_3$); IR (NaCl) 3425, 1650, 1220, 1075 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (s, 3H, H8), 1.6–2.9 (m, 8H), 3.86 (dd, 1H, *J*=7.3, 10.6 Hz, H1), 5.79 (dd, 1H, *J*=1.8, 2.2 Hz, H4); ^{13}C NMR ($CDCl_3$) δ 15.1, 26.5, 29.2, 33.3, 34.1, 45.3, 80.7, 123.5, 175.3, 199.4; MS *m/z* 166 (M^+, 33), 148 (M^+-H_2O, 4).

3b: $[\alpha]_D$=+38.5° (*c* 0.65, $CHCl_3$); IR (NaCl) 3440, 1740, 1180, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) 400 MHz) δ 1.01 (s, 3H, H8), 1.4–2.1 (m, 8H), 2.21 (ddd, 1H, *J*=7.3, 9.4, 19.4 Hz, H2), 2.48 (ddd, 1H, *J*=4.5, 10.1, 19.4 Hz, H2), 4.05 (tt, 1H, *J*=2.9, 5.9 Hz, H5); ^{13}C NMR (CD_3OD) δ 12.1, 27.1, 27.9, 29.4, 31.6, 40.0, 51.1, 65.8, 77.5, 220.8; MS *m/z* 184 (M^+, 14), 166 (M^+-H_2O, 64).

3a: $[\alpha]_D$=+75.0° (*c* 0.26, $CHCl_3$); IR (NaCl) 3410, 1726, 1172, 1094 cm^{-1}; ^1H NMR ($CDCl_3$ 400 MHz) δ 0.96 (s, 3H, H8), 1.08–1.25 (m, 1H, H6), 1.30 (tt, 1H, *J*=3.9, 10.3, 19.6 Hz, H7), 1.39 (dd, 1H, *J*=9.4, 13.8 Hz, H4), 1.70–1.80 (m, 1H, H6), 1.87–2.20 (m, 4H), 2.26 (td, 1H, *J*=8.2, 19.6 Hz, H2), 2.48 (ddd, 1H, *J*=3.9, 10.3, 19.6 Hz, H2), 3.89 (tt, 1H, *J*=5.2, 9.2 Hz, H5); ^{13}C NMR ($CDCl_3$) δ 17.5, 27.3, 31.2, 33.0, 34.4, 44.0, 52.7, 66.1, 78.5, 220.2; MS *m/z* 184 (M^+, 8), 166 (M^+-H_2O, 34).

4.2.2. (3a*S*,7a*S*)-3a-Hydroxy-7a-methyl-2,3,3a,6,7,7a-hexahydro-1*H*-inden-1-one (4). To an ice-cooled solution of alcohol **3a** (52 mg, 0.28 mmol), phthalimide (63 mg, 0.42 mmol) and triphenylphosphine (110 mg, 0.42 mmol) in THF (3 mL); DEAD (0.07 mL, 0.42 mmol) was added dropwise under argon. The mixture was stirred at room temperature for 21 h. Then, THF was evaporated and the residue solved in ethyl acetate and washed with brine, dried (Na_2SO_4) and evaporated. The crude product was chromatographied (hex/EtOAc 7:1) to yield 35 mg (75%) of **4** as a colourless oil. $[\alpha]_D$=+183.1° (*c* 0.67, $CHCl_3$); IR (NaCl) 3438, 1732, 1171 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (s, 3H, H8), 1.3–2.6 (m, 8H), 5.70 (td, 1H, *J*=1.8, 10.0 Hz, H4), 5.87 (td, 1H, *J*=3.3, 10.0 Hz, H5); ^{13}C NMR ($CDCl_3$) δ 17.8, 22.0, 26.7, 33.3, 34.9, 51.9, 77.7, 131.2, 131.4, 220.5; MS *m/z* 166 (M^+, 26), 148 (M^+-H_2O, 9).

4.2.3. (3a*S*,7a*S*)-7a-Methyl-3a-trimethylsiloxyperhydroinden-1,5-dione (5). To a solution of diketone **1** (200 mg, 1.1 mmol) in 10 mL of dry CH_2Cl_2 under Ar atmosphere, dry Et_3N (0.18 mL, 1.32 mmol) and TMSOTf (0.25 mL, 1.32 mmol) were added. The mixture was stirred at room temperature for 1 h. The reaction was quenched with Et_3N (0.54 mL), extracted with CH_2Cl_2, washed with HCl 2N, $NaHCO_3$ and brine. The organic solvent was dried and evaporated to give 221 mg (79%) of **5**. IR (NaCl) 1750, 1730, 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.14 (s, 9H, –OTMS), 1.18 (s, 3H, H8); ^{13}C NMR ($CDCl_3$) δ 2.9, 15.1, 29.2, 32.7, 33.7, 36.6, 50.5, 53.7, 84.2, 207.8, 217.8; MS *m/z* 254 (M^+, 37).

4.2.4. (3a*S*,5*R*,7a*S*)-5-Amino-7a-methyl-3a-trimethylsiloxyperhydroinden-1-one (6a). To a solution of diketone **5** (245 mg, 0.96 mmol), ammonium acetate (746 mg, 9.7 mmol) and sodium cyanoborohydride (64 mg, 1.0 mmol) in 3 mL of anhydrous MeOH were added. After stirring for 48 h at room temperature, the mixture was extracted with EtOAc and washed with brine. The crude reaction was purified by column chromatography (hex/EtOAc 1:2+1% Et_3N) yielding 160 mg (65%) of a 7:1 **6a/6b** mixture. **6a**: IR (NaCl) 3370, 1742, 843 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.19 (s, 9H, –OTMS), 0.90 (s, 3H, H8), 0.9–2.7 (m, 10H), 3.0–3.3 (m, 1H, H5), 5.92 (bs, 2H, NH_2); ^{13}C NMR ($CDCl_3$) δ 2.3, 19.5, 27.2, 29.6, 32.4, 34.8, 42.5, 46.2, 53.6, 80.1, 217.7; MS *m/z* 255 (M^+, 2).

4.2.5. (3a*S*,5*R*,7a*S*)-7a-Methyl-1-oxo-5-piperidyl-3a-trimethylsiloxyperhydroinden-5-carbonitrile (7), (3a*S*,5*R*,7a*S*)-5-hydroxy-7a-methyl-3a-trimethylsiloxyperhydroinden-1-one (8) and (3a*S*,5*R*,7a*S*)-7a-methyl-5-piperidyl-3a-trimethylsiloxyperhydroinden-1-one (9). To a solution of piperidine (0.7 mL, 7.08 mmol) in MeOH (5.5 mL), a solution HCl/MeOH 5N (2 equiv.) was added. Then, 300 mg (1.18 mmol) of diketone **5** and $NaBH_3CN$ (1 equiv.) were added. The mixture was stirred at room temperature for 56 h. After usual work up and chromatography 95 mg (23%) of **7** (hex/EtOAc 5:1), 36 mg (14%) of **8** (hex/EtOAc 3:1) and 126 mg (33%) of **9** (hex/EtOAc 1:1) were isolated.

7: $[\alpha]_D$=+50.3° (*c* 0.65, $CHCl_3$); IR (NaCl) 2230, 1742, 1251, 842 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.22 (s, 9H, –OTMS), 0.99 (s, 3H, H8), 1.1–2.7 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 2.4, 18.4, 24.1, 25.7, 26.1, 30.8, 32.5, 34.6, 42.6, 47.5, 53.2, 58.9, 79.7, 118.4, 218.2; MS *m/z* 321 (M^+-CN, 13).

8: $[\alpha]_D$=+23.8° (*c* 0.18, $CHCl_3$); IR (NaCl) 3417, 1740, 1252, 842 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.17 (s, 9H, –OTMS), 0.91 (s, 3H, H8), 1.0–2.5 (m, 10H), 3.86 (tt, 1H, *J*=4.0, 9.5 Hz, H5); ^{13}C NMR ($CDCl_3$) δ 2.3, 18.4, 27.3, 32.1, 32.9, 34.7, 44.8, 53.6, 66.7, 81.3, 219.0; MS *m/z* 256 (M^+, 1)

9: $[\alpha]_D$=+55.8° (*c* 0.43, $CHCl_3$); IR (NaCl) 1742, 1251, 841 cm^{-1}; ^1H NMR ($CDCl_3$ 400 MHz) δ 0.14 (s, 9H, –OTMS), 0.85 (s, 3H, H8), 1.04 (ddd, 1H, *J*=5.6, 11.3, 18.7 Hz, H2), 1.10–1.25 (m, 1H, H4), 1.31 (dt, 1H, *J*=4.0, 13.6 Hz, H7), 1.32–2.59 (m, 5H), 1.6–1.7 (m, 1H, H6), 1.70–3.35 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 2.3, 19.6, 24.6, 25.9, 26.3, 28.6, 33.0, 34.9, 38.5, 50.1, 53.9, 58.6, 81.0, 219.0; MS *m/z* 323 (M^+, 6).

4.2.6. (3a*S*,7a*R*)-7a-Methyl-1-methylen-3a-trimethylsiloxyperhydroinden-5-one (11). By the same procedure previously described for **5**, from 150 mg (0.83 mmol) of **10**, 187 mg (90%) of **11** were obtained. $[\alpha]_D$=+1.4° (*c* 0.29, $CHCl_3$); IR (NaCl) 1723, 841 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 9H, –OTMS), 0.95 (s, 3H, H8), 1.5–2.7 (m, 10H), 4.82 (t, 1H, *J*=2.5 Hz, H9), 4.85 (t, 1H, *J*=2.2 Hz, H9); ^{13}C NMR ($CDCl_3$) δ 2.0, 22.1, 27.5, 31.8, 34.8, 37.3, 48.8, 50.4, 86.4, 105.4, 154.5, 209.9; MS *m/z* 252 (M^+, 23).

4.2.7. (3a*S*,5*R*,7a*R*)-7a-Methyl-1-methylen-5-piperidyl-3a-trimethylsiloxyperhydroinden-5-carbonitrile (12a) and *N*-[(3a*S*,5*R*,7a*R*)-7a-methyl-1-methylen-3a-trimethylsiloxyperhydroinden-5-yl] piperidine (13a). By

the same procedure as previously described for **9**, from 132 mg (0.52 mmol) of ketone **11**, after column chromatography (hex/EtOAc 5:1), 60 mg (33%) of a 2:1 (**12a/12b**) mixture, 9 mg (5.3%) of **13a** and 29 mg (17%) of a 2:1 (**13a/13b**) mixture were obtained.

12a: IR (NaCl) 2217, 1250, 1100, 841 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.19 (s, 9H, –OTMS), 0.94 (s, 3H, H8), 1.2–2.7 (m, 20H), 4.77 (t, 1H, J=2.5 Hz, H9), 4.84 (t, 1H, J=2.2 Hz, H9); ^{13}C NMR ($CDCl_3$) δ 2.3, 24.3, 24.8, 26.2, 27.4, 28.0, 30.4, 34.6, 42.7, 47.4, 48.0, 59.4, 81.8, 106.0, 119.1, 153.3; MS m/z 320 (M^+–CN, 2).

13a: $[\alpha]_D$=+32.4° (c 0.29, $CHCl_3$); IR (NaCl) 1250, 1091, 841 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.12 (s, 9H, –OTMS), 0.84 (s, 3H, H8), 4.74 (t, 1H, J=2.5 Hz, H9), 4.79 (t, 1H, J=2.2 Hz, H9); ^{13}C NMR ($CDCl_3$) δ 2.4, 24.7, 24.8, 25.2, 26.3, 27.5, 30.4, 35.0, 37.2, 48.8, 50.3, 59.8, 83.1, 104.8, 154.2; MS m/z 321 (M^+, 13).

4.2.8. (3a*S*,7a*S*)-3a-Hydroxy-7a-methyl-1-oxoperhydroinden-5-yliden]malononitrile (14). To a solution 0.4 M of diketone **1** (50 mg, 0.27 mmol) in EtOH (0.7 mL) at room temperature, 19.6 mg (0.30 mmol) of malononitrile, 0.2 mg (0.0027 mmol) of β-alanine and 0.3 mL of acetic acid were sequentially added. After stirring for 2 h at room temperature, the mixture was extracted with EtOAc and washed with brine. The residue was chromatographed (hex/EtOAc 3:1) yielding 50 mg (80%) of **14** as a white solid. $[\alpha]_D$=+27.0° (c 0.73, $CHCl_3$); IR (NaCl) 3486, 2235, 1741 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (s, 3H, H8), 1.1–2.9 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 15.4, 30.6, 30.7, 32.3, 33.7, 43.6, 52.9, 81.6, 85.1, 111.2, 111.5, 179.9, 216.8; MS m/z 166 (M^+–$C(CN)_2$, 26). HRMS (EI) calcd for $C_{13}H_{14}N_2O_2$ 230.1055; found 230.1057.

4.2.9. (3a*S*,5*R*,7a*S*)-3a-Hydroxy-7a-methyl-1-oxoperhydroinden-5-yl]malononitrile (15a). To a cooled solution (0°C) of nitrile **14** (95 mg, 0.41 mmol) in 1.5 mL of dry THF, 1.03 mL (1.03 mmol) of DIBAL-H 1 M in hexane were dropwise added. After, stirring for 30 min, 0.3 mL of NH_4Cl sat and 0.37 mL of 10% H_2SO_4 were added and stirred for 10 min. After usual work up and column chromatography (hex/EtOAc 1:1) 26 mg (27%) of a 3:1 (**15a/15b**) mixture and 9 mg of more polar products. **15a/15b**: IR (NaCl) 3468, 2257, 2226, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (s, 3H, H8, minor isomer), 1.02 (s, 3H, H8, major isomer), 1.0–2.7 (m, 12H), 3.62 (dd, 1H, J=4.4, 6.2 Hz, H5β, major), 3.9–4.1 (m, 1H, H5α, minor); ^{13}C NMR ($CDCl_3$) (data for major isomer **15a**) δ 19.3, 27.0, 27.9, 28.8, 33.2, 34.6, 34.8, 40.0, 52.4, 81.3, 111.5, 111.6, 217.2; MS m/z 232 (M^+, 3).

4.2.10. (3a*S*,7a*S*)-3a-Hydroxy-7a-methyl-5-nitromethyl-2,3,3a,6,7,7a-hexahydro-1*H*-inden-1-one (16). To a solution of diketone **1** (100 mg, 0.55 mmol) in 5.4 mL of freshly distilled nitromethane under Ar atmosphere, 8 μL of ethylenediamine were added. The mixture was heated to reflux for 13 h. After that time, the solvent was evaporated and the crude of reaction purified by column chromatography (hex/EtOAc 1:4) yielding 89 mg (77%) of a 4.5:1 (**16/16′**) mixture. **16**: IR (NaCl) 3445, 1731, 1556 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (s, 3H, H8), 1.2–2.7 (m, 9H), 4.85 (s, 2H, CH_2NO_2), 5.92 (s, 1H, H4); ^{13}C NMR ($CDCl_3$) δ 17.0, 23.8, 26.9, 33.3, 34.7, 51.4, 76.4, 81.1, 131.5, 136.3, 219.7; MS m/z 179 (M^+–NO_2, 53).

4.2.11. (3a*S*,7a*S*)-3a-Hydroxy-5,7a-dimethyl-2,3,3a,6,7,7a-hexahydro-1*H*-inden-1-one (17). Following method A, from 46 mg (0.2 mmol) of a 4.5:1 (**16/16′**) mixture, 36 mg (100%) of a 4.5:1 (**17/17′**) mixture were obtained. **17**: IR (NaCl) 3451, 1733, 1145, 858 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (s, 3H, H8), 1.68 (s, 3H, Me–C5), 0.8–2.6 (m, 9H), 5.42 (c, 1H, J=1.5 Hz, H4); ^{13}C NMR ($CDCl_3$) δ 17.7, 23.6, 27.0 (×2), 33.5, 34.7, 51.4, 76.4, 126.2, 139.6, 220.7; MS m/z 180 (M^+, 58).

4.2.12. (3a*S*,5*R*,7a*S*)-3a-Hydroxy-7a-methyl-1-oxoperhydroinden-5-carbonitrile (18a) and (3a*S*,5*S*,7a*S*)-3a-hydroxy-7a-methyl-1-oxoperhydroinden-5-carbonitrile (18b). To a cooled solution (0°C) (500 mg, 2.75 mmol) of diketone **1** and TosMIC (719 mg, 3.6 mmol) in 9.5 mL of dry 1,2-dimethoxyethane and 0.25 mL of absolute EtOH, 312 mg (2.6 mmol) of KO^{t}Bu in small portions were added. The solution got darker and after stirring for 6 h under Ar at room temperature, the precipitate was removed by filtration. The filtrate was extracted with ether, washed with brine and dried (Na_2SO_4) yielding a yellow oil (5α/5β 1.7:1). The crude was purified by column chromatography (hex/EtOAc 2:1) to give 90 mg (17%) of **18a** as a white crystalline solid, 197 mg (37%) of a mixture of both epimers and 7 mg (1%) of **18b**.

18a: mp 159–160°C (CH_2Cl_2). $[\alpha]_D$=+81.7° (c 0.29, $CHCl_3$); IR (NaCl) 3458, 2249, 1731, 1194 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (s, 3H, H8), 1.1–2.9 (m, 11H); ^{13}C NMR ($CDCl_3$) δ 18.3, 23.9, 26.1, 27.6, 32.5, 34.3, 38.7, 52.1, 76.2, 122.2, 217.6, MS m/z 193 (M^+, 3). Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25; Found: C, 68.72; H, 8.09; N, 7.01.

18b: $[\alpha]_D$=+31.8° (c 0.27, $CHCl_3$); IR (NaCl) 3436, 2252, 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (s, 3H, H8), 1.3–2.8 (m, 11H); ^{13}C NMR ($CDCl_3$) δ 14.2, 24.5, 25.9, 29.6, 30.9, 33.5, 36.6, 52.2, 77.7, 121.4, 218.7; MS m/z 193 (M^+, 15).

4.2.13. Ethyl (*Z*)-[(3a*S*,7a*S*)-(3a-hydroxy-7a-methyl-1-oxoperhydroinden-5-yliden)]acetate (19) and ethyl (*E*)-[(3a*S*,7a*S*)-(3a-hydroxy-7a-methyl-1-oxoperhydroinden-5-yliden)]acetate (20). A solution of diketone **1** (1.93 g, 10.6 mmol) and ethoxycarbonylmethylen-triphenylphosphorane (6.3 g, 18.02 mmol) in 42.4 mL of dry benzene was heated to reflux for 3.5 h. After evaporating the solvent, the residue was chromatographed (hex/EtOAc 1:1) yielding 2.6 g (97%) of a 3:2 (**19/20**) mixture. Both stereoisomers were separated by new column chromatographies.

19: $[\alpha]_D$=+58.2° (c 1.00, $CHCl_3$); IR (NaCl) 3479, 1739, 1714, 1152 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11 (s, 3H, H8), 1.29 (t, 3H, J=6.9 Hz, –COO–CH_2–CH_3), 1.4–2.7 (m, 9H), 2.83 (d, 1H, J=13.0 Hz, H4), 3.19 (d, 1H, J=13.0 Hz, H4), 4.16 (c, 2H, J=6.9 Hz, COO–CH_2–CH_3), 5.80 (s, 1H, =CH–COOEt); ^{13}C NMR ($CDCl_3$) δ 14.1, 14.8, 31.6, 32.0, 32.9, 33.6, 38.2, 53.1, 60.0, 80.8, 116.1, 158.1, 166.8, 219.7; MS m/z 252 (M^+, 16). Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99; Found: C, 66.87; H, 8.12.

20: mp 92–94°C (CH_2Cl_2). $[\alpha]_D$=+22.7° (*c* 1.06, $CHCl_3$); IR (NaCl) 3472, 1736, 1714, 1147 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (s, 3H, H8), 1.31 (t, 3H, *J*=7.3 Hz, –COO–CH_2–*CH_3*), 1.4–2.7 (m, 10H), 3.34 (td, 1H, *J*=5.7 Hz, 14.3, H6), 4.17 (c, 2H, *J*=7.3 Hz, COO–*CH_2*–CH_3), 5.74 (s, 1H, =*CH*–COOEt); ^{13}C NMR ($CDCl_3$) δ 14.1, 14.2, 24.6, 31.0, 31.5, 33.6, 45.9, 53.2, 60.0, 80.7, 116.5, 157.3, 166.2, 219.5; MS *m*/*z* 252 (M^+, 8). Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99; Found: C, 66.79; H, 8.10.

4.2.14. Ethyl [(3a*S*,5*R*,7a*S*)-2-(3a-hydroxy-7a-methyl-1-oxoperhydroinden-5-yl)]acetate (21a). Following method A, from 6 g (23.8 mmol) of a 3:1 (**19/20**) mixture, after column chromatography (hex/EtOAc 2:1) a quantitative mixture 1:1.4 (**21a/21b**) was obtained. Only compound **21a** was isolated from the mixture. $[\alpha]_D$=+74.0° (*c* 0.20, $CHCl_3$); IR (NaCl) 3469, 1738, 1732, 1201 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (s, 3H, H8), 1.25 (t, 3H, *J*=6.9 Hz, –COO–CH_2–*CH_3*), 0.7–2.7 (m, 14H), 4.12 (c, 2H, *J*=6.9 Hz, COO–*CH_2*–CH_3); ^{13}C NMR ($CDCl_3$) δ 14.3, 19.6, 28.7, 29.4, 29.6, 32.9, 34.7, 41.2, 43.1, 52.8, 60.5, 79.6, 172.9, 219.1; MS *m*/*z* 254 (M^+, 5). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72; Found: C, 66.72; H, 8.53.

4.2.15. Ethyl 2-[(3a*S*,5*R*,7a*S*)-(3a-hydroxy-7a-methyl-1-oxoperhydroinden-5-yl)]acrylate (22a) and ethyl 2-[(3a*S*,5*S*,7a*S*)-(3a-hydroxy-7a-methyl-1-oxoperhydroinden-5-yl)]acrylate (22b). To a solution of LDA (4 equiv., 62.8 mmol) in 200 mL of dry THF at −78°C, 4 g (15.7 mmol) of 3:2 (**21b/21a**) mixture in 360 mL of dry THF and 15.6 mL (86.3 mmol) of HMPTA were slowly added. After the addition, the solution was stirred at −78°C for 15 min, the temperature was raised to −42°C and then kept for 15 min. In another reaction flask, 30 g (162 mmol) of the Eschenmoser's salt (previously dried at 80°C and high vacuum) were suspended in THF (300 mL). The enolate solution was passed via canule to the Eschenmoser's salt flask at −42°C. The mixture was stirred at −42°C for 45 min, and then allowed to reach the room temperature for 14 h. HCl 2N until acid pH and solid Na_2CO_3 until basic pH were added. The organic layer was extracted five times with EtOAc, dried and evaporated to give an oil.

Methyl iodide (200 mL) and 100 mL of dioxane were added to the crude product. The mixture was vigorously stirred and heated at 90°C under Ar atmosphere for 19 h. After evaporating the solvent, the solid was dissolved in 50 mL of water. $NaHCO_3$ in excess and 200 mL of ethyl acetate were added and the reaction mixture was vigorously stirred for 30 min. The organic layer was dried and evaporated yielding a 6 g residue that was chromatographed (hex/EtOAc 3:1) to give 3.42 g (77%) of a 2:3 (**22a/22b**) mixture. Both stereoisomers were separated for characterization by new column chromatographies.

22a: $[\alpha]_D$=+37.5° (*c* 0.87, $CHCl_3$); IR (NaCl) 3469, 1731, 1182, 858 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (s, 3H, H8), 1.24 (t, 3H, *J*=7.3 Hz, –COO–CH_2–*CH_3*), 1.0–2.6 (m, 10H), 2.80 (dt, 1H, *J*=3.3, 16.1 Hz, H4), 4.11 (c, 2H, *J*=7.3 Hz, COO–*CH_2*–CH_3), 5.39 (dd, 1H, *J*=1.5, 2.9 Hz, =CH_2), 6.13 (dd, 1H, *J*=1.8, 3.3 Hz, =CH_2); ^{13}C NMR ($CDCl_3$) δ 14.3, 19.8, 28.8, 29.5, 41.1, 41.1, 41.4, 43.8, 52.8, 60.4, 75.2, 119.7, 142.8, 172.7, 206.6; MS *m*/*z* 266 (M^+, 5), 248 (M^+-H_2O, 11). Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33; Found: C, 67.87; H, 8.55.

22b: $[\alpha]_D$=+6.4° (*c* 0.86, $CHCl_3$); IR (NaCl) 3469, 1729, 864 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (s, 3H, H8), 1.27 (t, 3H, *J*=7.3 Hz, –COO–CH_2–*CH_3*), 1.1–2.6 (m, 10H), 3.05 (dt, 1H, *J*=3.3, 17.2 Hz, H4), 4.15 (c, 2H, *J*=7.3 Hz, COO–*CH_2*–CH_3), 5.46 (dd, 1H, *J*=1.1, 2.6 Hz, =CH_2), 6.20 (dd, 1H, *J*=1.5 Hz, 3.3, =CH_2); ^{13}C NMR ($CDCl_3$) δ 12.9, 14.3, 26.9, 32.2, 32.6, 38.8, 39.5, 41.2, 53.1, 60.5, 77.7, 120.3, 141.9, 172.4, 208.2; MS *m*/*z* 266 (M^+, 2), 248 (M^+-H_2O, 7). Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33; Found: C, 67.96; H, 8.80.

4.2.16. Ethyl (1*S*)-1-[(3a*S*,5*S*,7a*S*)-(3a-hydroxy-7a-methyl-1-oxoperhydroinden-5-yl)]-4-oxocyclohex-2-ene carboxylate (23) and ethyl (1*R*)-1-[(3a*S*,5*R*,7a*S*)-(3a-hydroxy-7a-methyl-1-oxoperhydroinden-5-yl)]-4-oxocyclohex-2-enecarboxylate (25). To a solution of 2:3 (**22a/22b**) mixture (829 mg, 3.11 mmol) in 4 mL of dry benzene, 4.9 mL (21.8 mmol) of Danishefsky's diene were added and heated to 95°C under Ar for 26 h. After that time, the solvent was evaporated and the residue was solved in 40 mL of $CHCl_3$, adding 28 drops of concentrated HCl. The mixture was stirred for 1 h at room temperature. It was extracted with CH_2Cl_2, and washed with brine, to give an oil crude that was purified by column chromatography (hex/EtOAc 2:1) yielding 334 mg (37%) of a 3.5:1 (**23/24**) mixture and 263 mg (25%) of 2:1 (**25/26**) mixture. These fractions were again chromatographed allowing the separation of the major products of these mixtures.

23: IR (NaCl) 3469, 1732, 1667, 1182 cm^{-1}; ^1H NMR ($CDCl_3$ 400 MHz) δ 1.09 (s, 3H, H8), 1.24 (t, 3H, *J*=7.2 Hz, –COO–CH_2–*CH_3*), 1.1–2.5 (m, 15H), 2.83 (ddd, 1H, *J*=4.8, 10.5, 16.9 Hz, H5′), 4.12 (c, 2H, *J*=7.2 Hz, COO–*CH_2*–CH_3), 5.93 (d, 1H, *J*=10.1 Hz, H3′), 6.91 (d, 1H, *J*=10.1 Hz, H2′); ^{13}C NMR ($CDCl_3$) δ 13.5, 14.2, 26.8, 32.5, 32.7, 34.2, 35.1, 40.1, 41.0, 44.6, 50.0, 53.9, 60.4, 78.5, 128.3, 152.9, 172.0, 198.5, 219.9; MS *m*/*z* 334 (M^+, 12).

25: IR (NaCl) 3469, 1732, 1674, 1186 cm^{-1}; ^1H NMR ($CDCl_3$ 400 MHz) δ 1.11 (s, 3H, H8), 1.24 (t, 3H, *J*=7.2 Hz, –COO–CH_2–*CH_3*), 0.7–2.9 (m, 16H), 4.11 (c, 2H, *J*=7.2 Hz, COO–*CH_2*–CH_3), 5.97 (d, 1H, *J*=10.0 Hz, H3′), 6.61 (d, 1H, *J*=10.0 Hz, H2′); ^{13}C NMR ($CDCl_3$) δ 14.2, 20.1, 29.2, 29.5, 29.6, 33.7, 34.0, 40.8, 45.1, 47.1, 50.4, 54.4, 60.4, 75.6, 129.1, 151.9, 172.3, 198.1, 217.2; MS *m*/*z* 334 (M^+, 11).

4.2.17. Ethyl 4,4-diethoxy-1-[(3a*S*,5*S*,7a*S*)-3a-hydroxy-7a-methyl-1-oxoperhydroinden-5-yl)] cyclohexanecarboxylate (27). Following method A, from 240 mg (0.72 mmol) of a 3.5:1 (**23/24**) mixture, 242 mg (82%) of **27** as a colourless oil were obtained. IR (NaCl) 3500, 1738, 1732, 1152 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (s, 3H, H8), 1.1–1.3 (m, 9H, –COO–CH_2–*CH_3* and 2·OCH_2*CH_3*), 1.0–2.5 (m, 20H), 3.3–3.5 (m, 4H, *J*=6.9 Hz, 2·O*CH_2*CH_3), 4.17 (c, 2H, *J*=7.3 Hz, COO–*CH_2*–CH_3); ^{13}C NMR ($CDCl_3$) δ 13.3, 14.3, 15.3, 15.5, 26.8, 29.7, 30.1, 30.9, 32.5, 32.5, 34.7, 40.6, 41.1, 41.5, 48.0, 53.9, 54.8, 55.0, 60.3, 78.0, 98.8, 172.4, 224.7; MS *m*/*z* 364 (M^+−EtO, 12).

4.2.18. Ethyl 4,4-diethoxy-1-[(3a*S*,5*R*,7a*S*)-3a-hydroxy-7a-methyl-1-oxoperhydroinden-5-yl)] cyclohexanecarboxylate (28). Following method A, from 70 mg (0.21 mmol) of a 2:1 (**25**/**26**) mixture, 77 mg (89%) of **28** as a colourless oil were obtained. $[\alpha]_D$=+40.6° (*c* 1.34, $CHCl_3$); IR (NaCl) 3469, 1732, 1163 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (s, 3H, H8), 1.1–1.3 (m, 9H, –COO–CH_2–CH_3 and 2·OCH_2CH_3), 0.7–2.4 (m, 20H), 3.41 (c, 2H, *J*=6.9 Hz, OCH_2CH_3), 4.12 (c, 2H, *J*=6.9 Hz, COO–CH_2–CH_3); ^{13}C NMR ($CDCl_3$) δ 14.3, 15.4, 15.6, 21.6, 29.7, 29.7, 30.0, 30.0, 31.2, 35.6, 41.1, 41.1, 44.8, 45.6, 49.0, 53.8, 55.1, 55.3, 60.4, 77.8, 98.7, 172.7, 222.7; MS *m*/*z* 364 (M^+−EtO, 39). Anal. Calcd for $C_{23}H_{38}O_6$: C, 67.29; H, 9.33; Found: C, 67.61; H, 9.62.

4.2.19. Ethyl 1-[(3a*S*,5*S*,7a*S*)-3a-hydroxy-7a-methyl-1-oxoperhydroinden-5-yl)]-4-oxocyclohexane carboxylate (29). To a solution of 49 mg (0.15 mmol) of a 3.5:1 (**23**/**24**) mixture, in $HOCH_2CH_2OH$, 10 mg Pd(C) 10% were added and stirred under H_2 atmosphere (2 atm). After disappearance of the starting material (36 h), the reaction was filtered through a silica gel column and the solvent evaporated to obtain 40 mg (80%) of **29**. $[\alpha]_D$=+13.4° (*c* 0.51, $CHCl_3$); IR (NaCl) 3500, 1732, 1716, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (s, 3H, H8), 1.28 (t, 3H, *J*=7.3 Hz, –COO–CH_2–CH_3), 4.16 (c, 2H, *J*=7.3 Hz, COO–CH_2–CH_3); ^{13}C NMR ($CDCl_3$) δ 13.5, 14.3, 27.0, 32.7, 33.0, 34.9, 37.9 (×2), 38.2, 40.9, 41.2, 42.0, 47.1, 54.4, 60.6, 78.5, 172.4, 210.7, 223.3; MS *m*/*z* 336 (M^+, 4). HRMS (EI) calcd for $C_{19}H_{28}O_5$ 336.1937; found 336.1940.

4.2.20. (3a*S*,5*R*,7a*S*)-5-(4,4-Diethoxy-1-isopropenylcyclohexyl)-3a-hydroxy-7a-methylperhydroinden-1-one (30). To a suspension of 0.2 g (0.42 mmol) of methyltriphenylphosphonium iodide in 3.3 mL of dry benzene under Ar, a solution of NaO^{t}Am 4.5N (87.4 mg, 0.42 mmol) in benzene was added at room temperature and the bright-yellow phosphorane was immediately formed. The mixture was heated to reflux and a solution of **28** (58 mg, 0.14 mmol) in 0.4 mL of benzene was added and the mixture was gently refluxed for 1 h 30 min. After cooling and filtration, the solution was diluted with EtOAc and washed with brine. After purification by column chromatography (hex/EtOAc 5:1) 11 mg (21%) of **30** and 2 mg of deprotected starting material were obtained. $[\alpha]_D$=+55.9° (*c* 0.32, $CHCl_3$); IR (NaCl) 3500, 1731, 1162, 887 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (s, 3H, H8), 1.10–1.25 (m, 6H, 2·OCH_2CH_3), 1.60 (s, 3H, $CH_3C{=}CH_2$), 0.5–2.2 (m, 20H), 3.41 (c, 2H, *J*=6.9 Hz, OCH_2CH_3), 3.50 (c, 2H, *J*=6.9 Hz, OCH_2CH_3), 4.62 (s, 1H, $=CH_2$), 4.73 (d, 1H, *J*=1.5 Hz, $=CH_2$); ^{13}C NMR ($CDCl_3$) δ 15.5, 15.7, 21.6, 22.5, 29.8, 30.1 (×2), 30.3, 30.4, 31.3, 35.6, 45.1, 45.2, 46.0, 49.1, 54.1, 55.1, 55.3, 76.5, 98.8, 111.9, 143.6, 222.8; MS *m*/*z* 378 (M^+, 2). HRMS (EI) calcd for $C_{23}H_{38}O_4$ 378.2770; found 378.2771.

4.2.21. (1*R*,3a*S*,5*S*,7a*R*)-5-(4,4-Diethoxy-1-hydroxymethylcyclohexyl)-7a-methylperhydroinden-1,3a-diol (31). To a solution of **27** (235 mg, 0.57 mmol) in 3 mL of dry ether, 2 equiv. of $LiAlH_4$ were added at room temperature. After stitting under Ar atmosphere for 45 min, ether saturated of water was added. The mixture was filtrated under vacuum and the precipitate washed with hot THF several times. The organic layer was dried and evaporated yielding 109 mg (52%) of a mixture of the α and β triols. The major product **31** was isolated by chromatography (hex/EtOAc 1:2+1% Et_3N) as a white foaming solid. IR (NaCl) 3419, 1177 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (s, 3H, H8), 1.1–1.3 (m, 6H, 2·OCH_2CH_3), 0.8–2.1 (m, 21H), 3.3–3.5 (m, 4H, OCH_2CH_3), 3.6–3.7 (m, 2H, CH_2OH), 3.80 (bs, 1H, H1); ^{13}C NMR ($CDCl_3$) δ 15.5, 15.7, 17.4, 27.8, 29.8, 30.2, 31.3, 31.6, 32.0, 36.3, 39.8, 41.3, 44.9, 48.0, 55.1, 55.1, 60.3, 80.2, 89.4, 99.5, C7a not obs; MS *m*/*z* 324 (M^+−EtO, 34).

4.2.22. (1*R*,3a*S*,5*S*,7a*R*)-5-[(1-*tert*-Butyldimethylsiloxymethyl-4,4-diethoxy)cyclohexyl]-7a-methyl perhydroinden-1,3a-diol (32). To a solution of **31** (105 mg 0.28 mmol) in 10 mL of dry CH_2Cl_2, 0.21 mL of Et_3N and 0.14 mL (0.6 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate were added. The mixture was stirred under Ar for 3 h, after that time it was diluted with CH_2Cl_2, washed with $NaHCO_3$ and brine. After habitual process, the residue was chromatographed (hex/EtOAc 1:1+1% Et_3N) and **32** was quantitatively isolated as a white solid. IR (NaCl) 3466, 1256, 1095, 837 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 6H, $OSiMe_2$), 0.84 (s, 9H, OSi^{t}Bu), 0.98 (s, 3H, H8), 1.0–1.2 (m, 6H, 2·OCH_2CH_3), 0.8–2.0 (m, 21H), 3.3–3.5 (m, 4H, OCH_2CH_3), 3.55–3.65 (m, 2H, CH_2O–), 3.75 (bs, 1H, H1); ^{13}C NMR ($CDCl_3$) δ −5.3, 15.5, 15.6, 17.4, 18.3, 25.9, 27.8, 30.1, 31.2, 31.6, 32.1, 36.3, 39.8, 41.2, 44.9, 45.9, 48.0, 55.0, 55.0, 60.8, 80.2, 89.4, 99.4, C7a not obs; MS *m*/*z* 438 (M^+−OEt, 1).

4.2.23. (3a*S*,5*S*,7a*S*)-5-[(1-*tert*-Butyldimethylsiloxymethyl-4-oxo)cyclohexyl]-3a-hydroxy-7a-methyl perhydroinden-1-one (33). To a suspension of 350 mg (1.6 mmol) of CCP, 200 mg of 4 Å molecular sieves and 0.26 mL (3.2 mmol) of dry pyridine in 48 mL of dry CH_2Cl_2, a solution of **32** (130 mg, 0.27 mmol) in 15 mL of dry CH_2Cl_2 was added. The reaction mixture was stirred at room temperature for 45 min and the mixture was passed through a column (hex/EtOAc 2:1+1% Et_3N) and the diketone **33** was obtained quantitatively. $[\alpha]_D$=−1.93° (*c* 1.09, $CHCl_3$); IR (NaCl) 3480, 1731, 1716, 1255, 1166, 838 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.07 (s, 6H, $OSiMe_2$), 0.90 (s, 9H, OSi^{t}Bu), 1.11 (s, 3H, H8), 1.0–2.7 (m, 20H), 3.6–3.7 (m, 2H, CH_2OTBDMS); ^{13}C NMR ($CDCl_3$) δ −5.2, 13.6, 18.4, 26.0, 27.3, 33.3, 33.3, 34.8, 37.7, 37.9, 38.2, 39.5, 41.3, 42.1, 47.0, 54.8, 60.6, 78.6, 211.0, 223.8; MS *m*/*z* 393 (M^+−15, 1). Anal. Calcd for $C_{23}H_{40}O_4Si$: C, 67.60; H, 9.87; Found: C, 68.01; H, 10.12.

4.2.24. (3a*S*,5*S*,7a*S*)-5-[(1-*tert*-Butyldimethylsiloxymethyl-4-hydroxy)cyclohexyl]-3a-hydroxy-7a-methyl perhydroinden-1-one (34). To a solution of 64 mg (0.16 mmol) of diketone **33** in 4 mL of dry MeOH at −15°C, 2 mg (0.043 mmol) of $NaBH_4$ were added. After stirring at −15°C for 15 min, the reaction mixture was quenched with water, extracted with EtOAc, washed with brine, to yield 64 mg (98%) of a 2:1 (**34**/**35**) mixture. **34**: IR (NaCl) 3445, 1724, 1098 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 6H, $OSiMe_2$), 0.88 (s, 9H, OSi^{t}Bu), 1.03 (s, 3H, H8), 3.6–3.7 (m, 2H, CH_2OTBDMS); ^{13}C NMR ($CDCl_3$) δ −5.3, 13.5, 18.3, 25.9, 27.3, 31.6, 31.9, 32.3, 32.4, 33.0, 36.6, 39.5, 41.4, 41.8, 48.0, 54.3, 60.6, 69.8, 78.6, 225.4; MS *m*/*z* 353 (M^+−57, 61).

Acknowledgements

Financial support came from Junta de Castilla y León (SA-02/99, the Consejeria de Educación y Cultura and the European Social Fund). L. G. S. thanks the Spanish Ministry of Education for a predoctoral grant.

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