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Synthesis and Inotropic Activity of Hydroindene Derivatives†

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Abstract—A synthetic approach to hydroindenic inotropic agents has been developed, starting from enantiopure Hajos–Parrish (**1**), Hajos–Wiechert (**2**), and related diketones. Their transformation into C-1 formyl derivatives and other subsequent synthetic targets is described. The results of the thermodynamic equilibration between both epimers of each formyl derivative are analysed. The inotropic activities of selected compounds on right and left atrial preparations are also evaluated and discussed.

Introduction

Cardenolides constitute a very interesting and well known family of steroid glycosides, which have been used for a long time in the treatment of congestive heart failure. Among them, digoxin is the drug of election for this disease, although it has some toxic effects that limit its use. Therefore, a lot of effort has been done to design and synthesise other inotropic agents.[1] A great number of derivatives obtained by chemical transformations of natural steroids have been assayed, in order to find less toxic cardiotonic digitalis like compounds.[2–4] Non-steroidal synthetic analogues have also been obtained to this purpose,[5–8] but no definitive structure–activity relationship (SAR) has been deduced.

Some time ago we started out a research line directed at the synthesis of new 'nonsteroidal' cardenolide analogues. After the preparation of several diterpene[9–11] and cyclohexane[12,13] derivatives, lacking the cyclopentane D-ring, we moved to the synthesis of hydroindane derivatives (Fig. 1), as structural equivalents of the C-D rings of the steroid skeleton. By this approach it is possible to prepare a number of derivatives bearing substituents at positions C-4 and C-5, thus increasing the molecular size to mimic the A, B rings and the sugar moieties of cardenolides. In this way it is possible to study the structural requirements of the C, D-ring system and the minimum size of these molecules to display cardiotonic activity.

These ideas had been described in preliminary communications[14–16] and the previous results in the synthesis of the starting materials[17,18] and some derivatives[19] have already been published. To our knowledge, no previous approaches to cardenolide analogues by using hydroindane as the basic skeleton have been reported. Only recently, a similar approach to those shown in our previous communications has been applied in the synthesis of 9,10-*seco*steroids[20] and cyclohexylhydrindanes[21] as digitoxigenin analogues.

In this paper we describe the general methodology used at our laboratory for the synthesis of 3aβ-hydroxy and 3a-unsaturated derivatives of hydroindenes, carrying C-1, C-4, and/or C-5 substituents. The Y moiety at C-1 can be functional groups replacing the butenolide moiety and the Z one can contribute to increasing the size and/or the solubility of the final products. We have recently communicated the activity of some of these compounds,[22] which describe the positive inotropic effect displayed by the 3a-unsaturated bis(guanylhydrazone) derivative. In the present article we report the synthesis of some new derivatives, with different substituents at C-1 and the guanylhydrazone moiety at C-5, with the aim of assessing their inotropic activity.

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† Dedicated to the memory of Professor Joaquín de Pascual Teresa.

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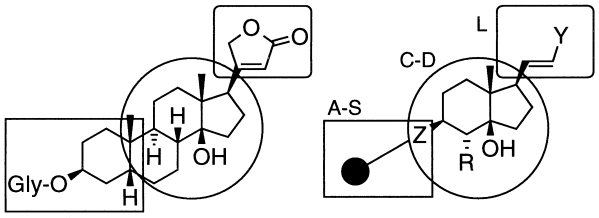


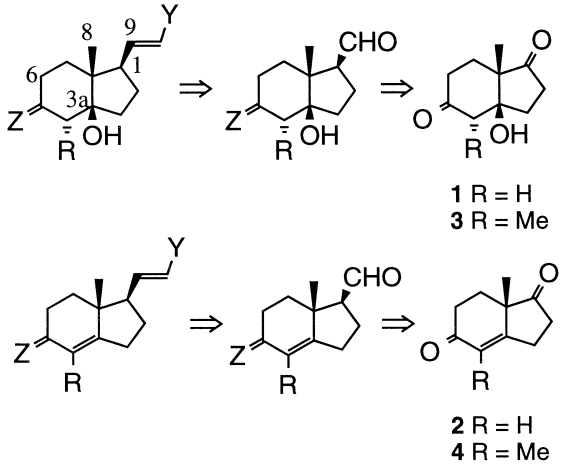
L = Lactone equivalent
Y = Michael acceptor
C-D = Steroid C-D rings
A-S = Equivalents of Steroid A ring and solubilizing groups

Figure 1. Structural comparison between cardenolides and projected hydroindenic inotropic agents.

Methods and Results

For the obtention of compounds with the hydroindane skeleton, we decided to start from available enantiopure materials with this skeleton and carry out their transformation into the target molecules. According to the retrosynthetic analysis depicted in Scheme 1, the C-1 formyl derivatives are intermediates of interest for our synthesis.

Starting from the easily available Hajos–Parrish ketone (**1**),[23,24] the dehydrated Hajos–Wiechert ketone (**2**),[25] or the 4-methyl derivative **3**,[26] and due to the higher reactivity of the C-5 keto group in these diketones, it was necessary for its protection to produce selective transformations of the C-1 keto group. Transformation of **1** or **3** into their dioxolane and dithiane derivatives by standard procedures[27,28] allowed us to obtain compounds **5**–**7** without any detectable amount of the C-1 protected products.[19] On the other hand, for unsaturated diketones **2** or **4** the selective protection of C-5 showed to be very variable depending on the structure and the reagent used. The selective protection of diketone **2** as the dithiane resulted favourable at position C-5, yielding **9**. The use of bis(trimethylsilyloxy)ethane[29,30] with diketone **2** for its protection as a dioxolane derivative, at −50°C, produced a mixture of **8′** and **8″**, protected at C-1 and C-5 positions, respectively, having observed transposition of the double bond from C-3a to C-2[31] in the case of **8″**. When lower temperatures were used (−78°C), the reaction proved to be chemoselective towards the C-5 derivative **8**. In the case of the methyl derivative **4**, the reaction only worked under conditions, which led to the C-1 protected product **10′**, without any detectable amount of **10**. In consequence, for unsaturated ketones **2** and **4**, it seemed that kinetic control produces C-5 protected derivatives, increasing C-1 protected products with temperature. As the reaction rate at C-5 decreases by the presence of the methyl at C-4 in **4**, a higher temperature is required for the process to work, thus yielding the thermodynamic product **10′**. In the case of **9**, the higher reactivity of 1,3-propanedithiol facilitates the formation of the C-5 protected 1,3-dithiane derivative **9** in good yield (Scheme 2).

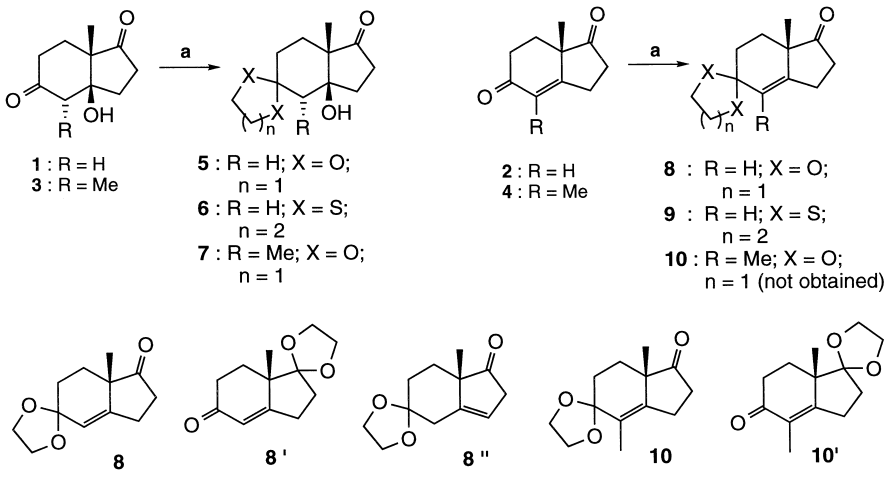


Scheme 1. Retrosynthetic analysis for planned hydroindenes.

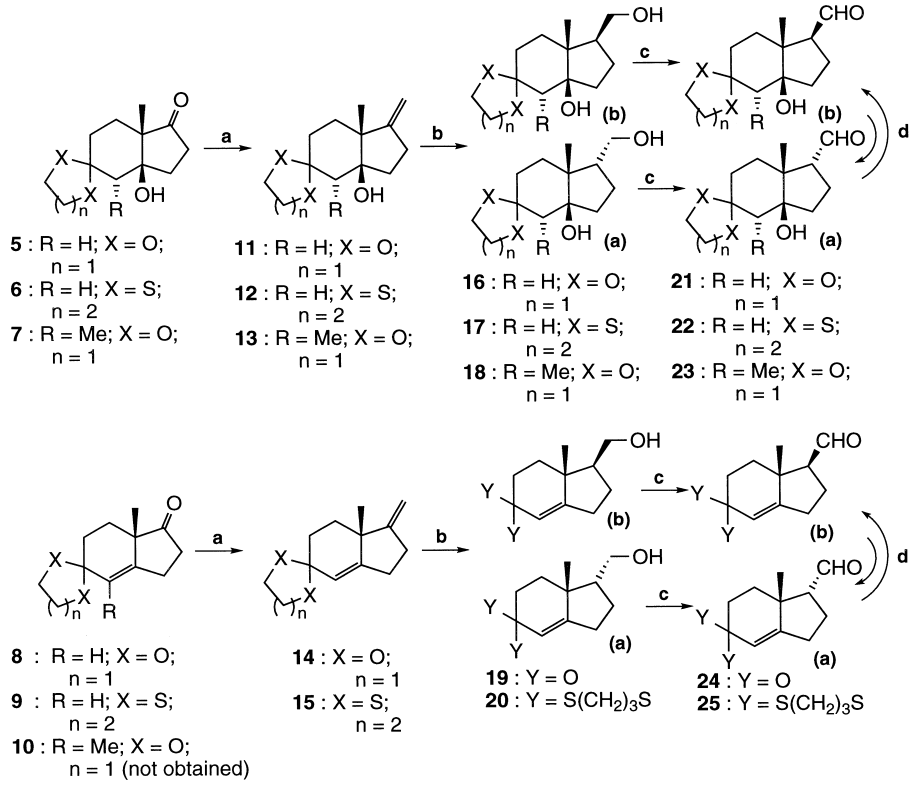
The transformation of protected ketones **5**–**9** into the formyl derivatives could be achieved by direct approaches, as methoxymethylenation-hydrolysis or by TOSMIC cyanation followed by DIBALH reduction, but those compounds showed a low reactivity, especially in the case of 3a-hydroxy derivatives **5**–**7**. Well known reactions for their utility with sterically hindered ketones, as the Peterson olefination and the reaction with 2-lithium-2-trimethylsilyl-1,3-dithiane, also failed to introduce one carbon fragment at the C-1 of those hydroxyketones. The one carbon elongation at C-1 was carried out[32] by following the Conia procedure[33,34] for the Wittig reaction and the methylenation of these hydroindane derivatives was then achieved in high yield (80%) to give **11**–**15**.[32]

The conversion into the formyl compounds at C-1 was brought about by hydroboration–oxydation of **11**–**15** to **16**–**20(a,b)**, followed by PCC oxidation to **21**–**25(a,b)**. The hydroboration–oxidation sequence produced the stereoisomeric alcohols β (**16b**–**20b**) and α (**16a**–**20a**) with very different ratios depending on the presence of a hydroxyl group or double bond at C-3a. Among the 3a-hydroxy derivatives the compound that displayed the most stereoselective outcome was **12**, resulting **17**, in a ratio α:β 3:7. The dioxolane derivatives **11** and **13**, produced equimolecular amounts of both stereoisomers **16a,b** and **18a,b**. In the case of unsaturated compounds **14** and **15**, the reaction with BBN-oxidation was almost stereospecific, being the β:α ratio in the crude reaction product 12:1 and 21:1, respectively. When the protected derivative **14** was used, the reaction took place with hydrolysis of the dioxolane group, thus yielding hydroxyketones **19a,b** (Scheme 3).

In order to know the preferred conformation for each starting olefin **11**–**15** and to correlate the accessibility of the double bond with the stereochemical outcome of the hydroboration–oxidation process, molecular mechanics calculations were carried out.[35] The hydroindenes show three preferred conformations A-B-C (Fig. 2) depending on the substituents at C-1, C-4, and C-5 for the 3a-hydroxy derivatives, while the 3a-unsaturated compounds have less conformational freedom, due to the presence of the double bond close to the ring junction, thus having D as the preferred spatial disposition. The calculated



Scheme 2. Reagents and conditions: (a) $HO(CH_2)_2OH$, $BF_3{\cdot}OEt_2$ or $TMSO(CH_2)_2OTMS$, TMSOTf, CH_2Cl_2, $-50°C$ or $HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2$, rt.



Scheme 3. Reagents and conditions: (a) $(C_6H_5)_3P+CH_3\ I^-$, NaOtAm, C_6H_6, reflux; (b) 1. BH_3/THF or 9-BBN, rt; 2. H_2O_2, NaOH, EtOH, 50°C; (c) CCP, CH_2Cl_2, rt; (d) KOH/ EtOH 5%, rt.

conformations are also in agreement with NMR experimental results and data, as they are: (a) the NOE observed at H4β upon irradiation of the C7a-methyl group for preferred A conformations and (b) the ^{13}C NMR shift of the C7a-methyl, signal which appears at <18 ppm when it is in axial disposition (A conformation) and >20 ppm when it is equatorially disposed (B conformation).

Compounds **11** and **12** show a preferred B conformation. Methyl derivative **13** has A as a preferred conformation due to the steric effect produced by the 4α-methyl on the rest of the skeleton in conformations B or C; finally, compounds **14** and **15** both display the D conformation (Fig. 3). The exocyclic double bond at C-1 shows no differences for accessibility of the hydroborating agent in the case of compounds with preferred A or B conformations, in agreement with the experimental data for hydroboration-oxidation of **11**–**13**. For the unsaturated derivatives **14** and **15**, the high α-stereoselective attack is justified by the accessibility of the reagent from this face of the double bond in conformation D.

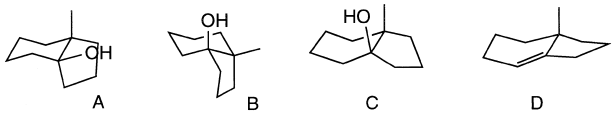


Figure 2. Preferred conformations for hydroindenes.

Since only the β-stereochemistry of the formyl group at C-1, obtained by this methodology, maintains the same relative stereochemistry at C-1 and C-7a as the natural cardenolides, compounds with type (**b**) structures are adequate to prepare hydroindene analogues of cardenolides. As a consequence, it would be desirable that α-formyl derivatives **21a**–**25a** could be transformed into the β-formyl derivatives **21b**–**25b**. In order to know the relative stability of both C-1 epimers in compounds **21**–**25**, theoretical calculations were carried out with these and other related structures.[36] The stability of the C-1-formyl β-isomers (**b**) is higher than that of C-1-formyl α-isomers (**a**) for the 3a-unsaturated derivatives **24** and **25** as well as for 3a-hydroxy derivatives **21**–**23**, although for other derivatives it depends on the substituents at position C-5. Calculations of heats of formation of compounds **23a** and **23b** gave $\Delta H(\beta)\text{-}\Delta H(\alpha) = -0.68$ kcal/mol, thus favouring the desired β-epimer. Similar calculations for **24a** and **24b** and for **25a** and **25b** also gave negative values for $\Delta H(\beta)\text{-}\Delta H(\alpha) = -0.8$ kcal/mol and higher differences were observed for **21** and **22**, as it was pointed out in our preliminary communication.[17] Thus, equilibration of compounds **21**–**25** in basic media produced the desired 1β-CHO epimers as major equilibration products. By this methodology, the required aldehydes **21b**–**25b** were prepared by oxidation of the corresponding beta alcohols or through oxidation–epimerisation processes starting from the epimeric alpha alcohols.

These formyl derivatives were used as synthetic intermediates for the preparation of some final products, carrying at C-1 unsaturated moieties, which usually confer inotropic activity when placed on a steroidal framework, as described in the literature.[1–4] By Wittig olefination of the aldehyde at C-9 with different ylides or by condensation with nitromethane, hydroxylamine, or aminoguanidine, followed by deprotection, reduction, or treatment of the C-5 keto group with aminoguanidine, different hydroindenic cardenolide analogues **26**–**41** have been obtained (Fig. 4). Other derivatives, carrying less elaborated chains at C-1, as the hydroxymethyl derivative **42**, have also been prepared, to be tested as inotropic agents.

Inotropic activity

Compounds **35**, **41** and **42** were selected for testing by virtue of their structural complementarity and differences with respect to those other indene derivatives previously evaluated[22] in order to perform a broader

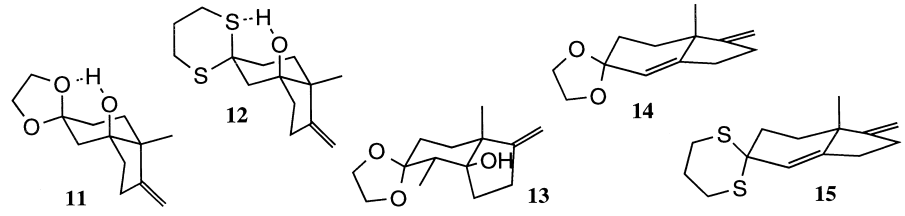


Figure 3. Preferred conformations of compounds **11**–**15**, from MM calculations and NMR data.

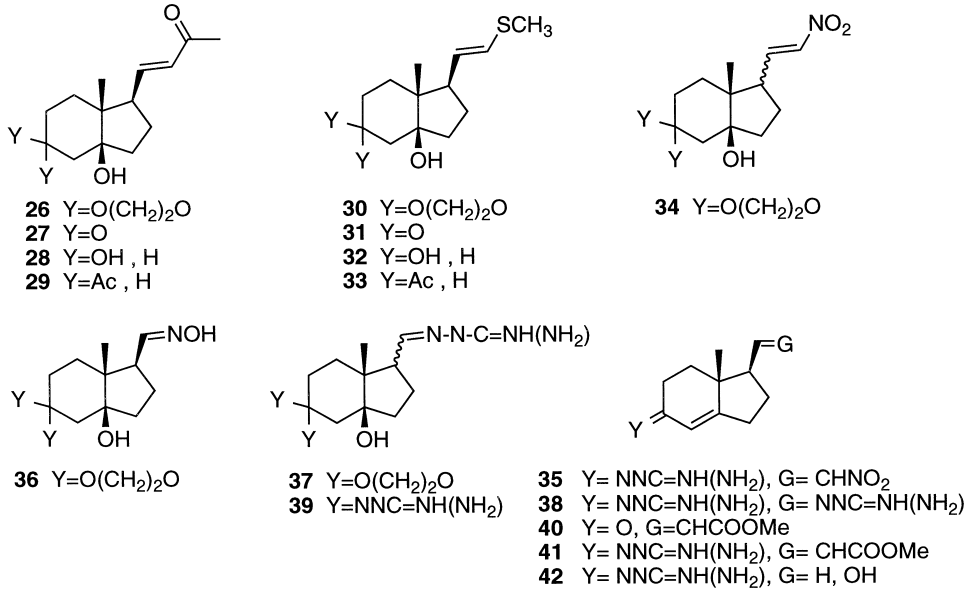


Figure 4. Synthesized molecules with hydroindene skeleton.

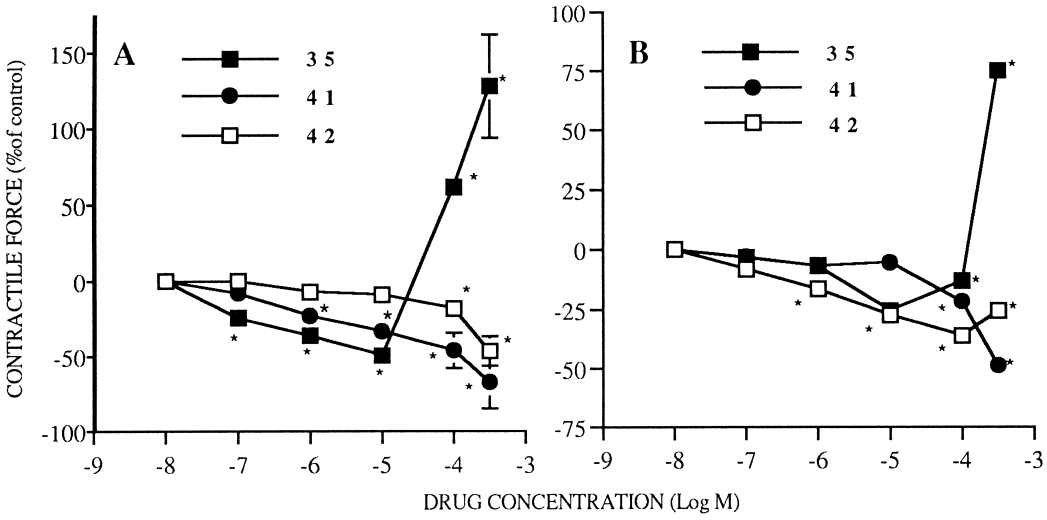


Figure 5. Cumulative concentration–response effect of compounds **35**, **41** and **42** on isolated guinea pig left (A) and right (B) atria contractile force. Each value represents the mean of at least five experiments. Vertical lines show ±SEM. * indicates $p < 0.05$ when compared with the corresponding control values.

analysis of the structure–activity relationships within this family of compounds. They have been evaluated on isolated guinea pig right and left atria. Right atria show spontaneous beating, and are used to evaluate the effect of the compounds tested on the contraction force and cardiac rhythm. Electrically stimulated left atria are used to evaluate the effect on the contractile force. Simultaneous studies are carried out with the solvent (DMSO) to confirm that the parameters checked are not influenced in none of the preparations.

The effect of these compounds on the left atria contractile force has been represented in Figure 5. Compound **41** shows a negative inotropic effect, concentration-dependent, on left atria, being significant at 10^{-7} M dose and showing a maximum of 68% at the highest concentration tested (3×10^{-4} M). Compound **42** also produces a negative inotropic effect, less potent than **41**, at doses higher than 10^{-5} M, reaching a maximum value of 46.6% at the same concentration. Similarly both compounds display light negative inotropic effect on right atria, which is more potent for **41**.

Compound **35** shows a different pattern of activity, with a biphasic effect. At low doses (10^{-7}–10^{-5} M) it displays a negative inotropic effect, similar (left atria) or slightly more pronounced (right atria) than those observed for compounds **41** and **42**, with a maximum of 50% at 10^{-5} M (Fig. 5). At concentrations higher than 10^{-5} M that effect begin to be reversed, turning towards a fair positive inotropic effect, which raises to maximum values of 128% on left atria and 75% on right atria, at the maximum assayed concentration (3×10^{-4} M). This fact implies the existence of two different mechanisms of interaction of the compound with the organ, one inducing relaxation and other, opposed and made evident at higher doses, that enhances the contractile force. None of the three compounds modifies significantly the cardiac beating rate.

Comparatively, the nitrovinyl derivative **35** displays inotropic profile and potency similar to those of its 1,5-bis(guanylhydrazone) analogue previously reported,[22] thus reinforcing the presence in this type of compounds of a Δ^{3a} double bond, rather than the 3a-OH group equivalent to that at C-14 in cardenolides, as an important structural factor for positive inotropic activity. On the other hand, the existence of that double bond together with the guanylhydrazone moiety at position C-5 does not constitute a structural guarantee for positive inotropic activity. The function at position C-1 is also very important, as it is proven with the carboxylate derivative **41**, the hydroxymethyl derivative **42** and other compounds previously reported.[22] Nevertheless, the number of compounds assayed and the results obtained are still low to permit SAR generalisations. To complement these studies, more specific evaluations on Na^+, K^+-ATPase inhibition by these and other compounds of the series are currently being studied.

In conclusion, we have established a synthetic methodology for the preparation of a variety of 1,5-disubstituted hydroindenes, and it can be stated that the dihydroindene structure constitutes, up to the date, the simplest homocyclic skeletal base for the construction of either cardiotonics or negative inotropic agents.

Experimental

General. Melting points were determined on a Buchi 510 instrument and are uncorrected. ^{1}H NMR and ^{13}C NMR were recorded on a 200 MHz (Bruker WP200SY) and 400 MHz (Bruker SY) spectrometer, using $CDCl_3$ as solvent with TMS as internal standard. IR spectra were obtained in CH_2Cl_2 film in a Nicolet (Impact 410) spectrophotometer. GC–MS analyses were carried out with a Hewlett–Packard 5890 Serie II apparatus (70 eV).

For FABHRMS analyses, a VG-TS250 apparatus (70 eV) was used. Optical rotations were measured at 20°C on a digital polarimeter. Column chromathography was performed over silica gel Merck (0.063–0.2 or 0.040–0.063 mm). TLC was performed on precoated silica gel polyester plates (0.25 mm thickness) with fluorescent indicator UV 254 (Polychrom SI F_{254}).

(7a*S*)-5,5-Ethylenedioxy-7a-methyl-2,3,5,6,7,7a-hexahydro-1*H*-inden-1-one (8). To a cooled solution (−78°C) of diketone **2** (100 mg, 0.61 mmol) in dry CH_2Cl_2 (0.4 mL), 1,2-bis(trimethylsilyloxy)ethane (0.17 mL, 0.67 mmol) and trimethylsilyl triflate (10 μL, 0.05 mmol) were added. The reaction was kept at −78°C for 24 h and then quenched with pyridine. The mixture was poured into a saturated sodium bicarbonate solution, diluted with CH_2Cl_2, washed with brine and dried to obtain **8** (120 mg, 95%) as a white solid.

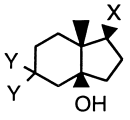
8. Mp: 87°C (CH_2Cl_2). $[\alpha]_D$ +148.9° (*c* 0.26, $CHCl_3$). IR: 1744, 1728, 1647, 866 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.17 (s, 3H, H_8), 1.55–2.80 (m, 8H), 3.81–4.10 (m, 4H, OCH_2), 5.49 (d, 1H, $J=1.1$, H_4). ^{13}C NMR (see Table 1). MS *m*/*z* (%): 164 ($M^+-C_2H_4O_2$, 89), 79 (100).

(7a*S*)-1,1-Ethylenedioxy-7a-methyl-2,3,5,6,7,7a-hexahydro-1*H*-inden-5-one (8′) and (7a*S*)-5,5-ethylenedioxy-7a-methyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-1-one (8″). To a cooled solution (−50°C) of diketone **2** (500 mg, 3.05 mmol) in dry CH_2Cl_2 (10 mL), 1,2-bis(trimethylsilyloxy)ethane (0.60 mL, 2.36 mmol) and trimethylsilyl triflate (60 μL, 0.3 mmol) were added. The reaction was maintained at −50°C for 24 h. After that time, it was worked up as usual. After chromatography (hexane: EtOAc, 3:1), **8′** (yellow oil, 203 mg, 32%), **8″** (white solid, 116 mg, 18%) and starting material (220 mg, 44%) were obtained.

8′. $[\alpha]_D$ −4.0° (*c* 0.73, $CHCl_3$). IR: 1692, 1651, 1087, 951 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.28 (s, 3H, H_8), 1.55–2.85 (m, 8H), 3.87–4.03 (m, 4H, OCH_2), 5.80 (dd, 1H, $J_1=J_2=1.8$, H_4). ^{13}C NMR (see Table 1). MS *m*/*z* (%): 208 (M^+, 81), 86 (100).

8″. $[\alpha]_D$ +106.3° (*c* 0.51, $CHCl_3$). IR: 1743, 1655, 1095, 859 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.19 (s, 3H, H_8), 1.4–3.2 (m, 8H), 3.9–4.0 (m, 4H, OCH_2), 5.71 (d, 1H, $J=1.8$, H_3). ^{13}C NMR (see Table 1). MS *m*/*z* (%): 208 (M^+, 6), 99 (100).

Table 1. ^{13}C NMR data for compounds **8–42**



	C-1	C-2	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	C-8	C-9	X	X	X	X	Y	Y	Y
8	218.6	36.5	26.3	149.1	120.9	106.4	30.2	28.3	48.1	20.3						64.5	64.9	
8′	117.3	31.5	26.6	174.2	123.0	198.7	32.9	26.4	47.6	19.8		64.7	65.6					
8″	220.6	41.5	118.0	145.5	37.5	108.8	30.7	29.5	49.9	19.0						65.5	64.5	
10′	117.7	31.5	25.6	166.9	128.5	198.3	32.9	26.4	47.3	10.4	20.1	64.7	65.6					
14	159.2	30.9	28.4	154.5	117.4	106.9	32.9	29.5	44.2	25.2		104.0				64.3	64.7	
19b	52.4	24.7	29.1	179.5	121.5	199.9	33.4	36.0	44.1	16.4		62.8						
20b	53.0	24.5	27.9	152.8	119.2	49.0	33.6	33.8	43.0	17.9		63.9				26.5	24.9	27.6
24b	61.8	21.1	28.5	175.7	122.0	198.3	33.0	35.7	45.4	18.1		202.2						
25b	62.5	20.6	27.6	150.7	120.1	48.7	33.3	33.3	44.8	19.6		203.6				26.4	24.8	27.6
26b	44.5	24.0	35.5	81.3	41.9	109.0	30.1	28.3	46.9	17.8		149.6	131.8	216.1	27.0	64.6	64.2	
27b	49.6	26.0	37.9	84.0	50.5	209.9	36.6	33.8	47.6	16.3		150.3	131.2	198.7	27.0			
28a	44.4	24.4	37.8	81.7	44.3	67.3	30.3	29.4	46.5	17.6		149.8	131.8	198.5	27.2			
28b	45.1	24.4	36.2	80.7	39.7	67.6	28.3	25.3	47.3	18.1		150.2	131.8	198.7	27.0			
29a	44.8	24.5	37.5	81.3	40.3	70.3	26.4	29.3	46.6	17.3		149.2	131.7	198.2	27.0	170.4	21.3	
29b	47.9	24.7	36.1	80.9	38.2	70.6	25.6	25.2	47.4	17.1		150.8	131.2	198.5	26.7	169.7	21.3	
30b	45.4	24.9	35.4	81.2	42.0	109.3	30.1	28.0	46.6	17.6		128.0	124.8	15.1		64.5	64.1	
31b	49.3	26.6	38.0	84.1	51.0	210.8	36.7	32.8	46.7	16.6		128.1	125.1	15.2				
33b	45.7	25.4	37.5	81.3	40.6	70.7	26.6	28.8	45.3	17.2		127.7	125.1	15.1		170.5	21.5	
34a	47.6	25.2	35.2	82.2	42.0	108.4	29.8	27.7	48.9	16.9		143.9	139.6			64.4	63.6	
34b	41.1	23.9	35.4	81.1	41.7	108.8	30.1	28.4	47.1	17.9		144.1	139.6			64.4	64.3	
35b[a]	51.2	22.5	27.7	157.3	119.5	163.7	29.6	34.4	41.1	18.0		142.6	141.7			155.3		
36′	41.5	22.6	35.3	81.2	41.7	109.2	29.9	28.6	46.0	17.8		153.6				64.2	64.2	
36″	36.7	22.1	35.6	81.2	41.7	109.2	30.3	29.2	46.8	17.8		154.3				64.5	64.5	
37a[a]	48.5	23.8	36.8	82.9	42.7	110.1	31.0	32.4	49.5	17.5		156.2	156.5			65.4	65.4	
37b[a]	47.7	25.7	38.3	83.9	40.9	110.1	31.6	35.8	48.1	16.1		157.8	158.6			64.6	64.6	
38b[b]	53.3	21.8	24.7	166.1	117.2	157.8	28.6	33.5	45.8	17.5		154.2	155.4[c]			155.8[c]		
39a[a]	49.8	24.8	38.0	83.2	44.0	160.4	31.2	34.4	54.4	17.1		156.8	156.5[c]			157.2		
39b[a]	50.6	25.2	37.1	83.7	37.5	160.4	30.6	36.1	54.3	18.3		157.5	156.5[c]			157.2[c]		
40a	48.1	28.0	29.5	177.4	121.7	199.2	33.3	34.8	47.0	16.9		148.3	122.0	166.5	51.3			
40b	53.4	26.4	29.1	176.8	122.2	198.9	33.2	34.8	46.1	17.3		147.0	122.9	166.6	51.7			
41b	53.4	22.5	26.7	163.2	118.2	156.2	28.6	33.4	45.6	17.5		147.7	122.5	166.6	51.6	154.1		
42b	54.0	23.0	26.0	166.5	118.5	157.2	29.4	35.7	44.4	16.9		63.4				156.1		

[a] Solvent: CD_3OD.
[b] Solvent: D_2O.
[c] Interchangeable signals.

(7a*S*)-1,1-Ethylenedioxy-4,7a-dimethyl-2,3,5,6,7,7a-hexahydro-1*H*-inden-5-one (10′). To a cooled solution (−50°C) of diketone **4** (1.07 g, 6.0 mmol) in dry CH_2Cl_2 (21 mL), 1,2-bis(trimethylsilyloxy)ethane (4.5 mL, 18 mmol) and trimethylsilyl triflate (0.4 mL, 1.8 mmol) were added. The reaction was kept at −20°C for 60 h under argon. After this period, it was worked up as usual, obtaining **10′** (1.2 g, 91%).

10′. $[\alpha]_D$ −18.6° (*c* 1.45, $CHCl_3$). IR: 1662, 1156, 1073 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.25 (s, 3H, H_8), 1.5–2.7 (m, 8H), 1.69 (s, 3H, H_9), 3.85–4.03 (m, 4H, OCH_2). ^{13}C NMR (see Table 1). MS *m*/*z* (%): 222 (M^+, 37), 86 (100).

(7a*R*)-7a-Methyl-1-methylene-2,3,5,6,7,7a-hexahydro-1*H*-inden-5-one ethylenic acetal (14). To a suspension of methyltriphenylphosphonium iodide (509 mg, 1.26 mmol) in dry benzene (4 mL), a solution of ^{t}AmONa 4.5N (1.3 mmol) in benzene, diluted with dry benzene (4 mL) was added at room temperature, being immediately formed the bright-yellow phosphorane. The mixture was heated to reflux and a solution of **8** (210 mg, 1.01 mmol) in dry benzene (1.5 mL) was added. After 1 h at reflux, it was cooled and filtered; the solution was extracted with EtOAc and washed with brine. The product was purified by flash chromatography (hexane:EtOAc, 9:1 + 1% of Et_3N) to yield **14** as a colourless oil (120 mg, 58%).

14. $[\alpha]_D$ + 175.2° (c 0.82, $CHCl_3$). IR: 1669, 1075, 885 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.12 (s, 3H, H_8), 1.60–2.80 (m, 8H), 3.81–4.10 (m, 4H, OCH_2), 4.74 (t, 1H, J = 1.8, H_9), 4.79 (t, 1H, J = 1.8, H_9), 5.27 (s, 1H, H_4). ^{13}C NMR (see Table 1).

(7a*R*)-1-Hydroxymethyl-7a-methyl-2,3,5,6,7,7a-hexahydro-1*H*-inden-5-one (19). To a solution of 9-BBN (170 mg, 1.40 mmol) in dry THF (2.2 mL), a solution of **14** (106 mg, 0.51 mmol) in dry THF (1.6 mL) was added at room temperature under argon. The resulting solution was stirred for 1 h and 10 min. After that time, it was cooled to 0°C; ethanol (2 mL), NaOH 6 N (0.65 mL, 3.9 mmol) and 30% H_2O_2 (0.35 mL, 3.1 mmol) were sequentially added. The mixture was heated to 50°C for 1 h, and then was allowed to reach room temperature, diluted with EtOAc, washed with brine and dried to obtain 260 mg of an oil that was chromatographed on silica gel column (hexane:EtOAc, 1:1) yielding **19b** as a yellow oil (53 mg, 58%) and **19a** (5 mg) along with some impurities.

19b. $[\alpha]_D$ + 67.1° (*c* 0.55, $CHCl_3$). IR: 3416, 1649, 1078 cm^{-1}. ^1H NMR (400 MHz) ($CDCl_3$) δ 1.05 (s, 3H, H_8), 1.47–1.63 (m, 1H, H_2), 1.82 (dt, 1H, J_1 = 13.8 and J_2 = 5.0, H_7), 1.85–1.95 (m, 1H, H_1), 1.90–2.00 (m, 1H, H_2), 2.17 (ddd, 1H, J_1 = 13.8, J_2 = 5.3 and J_3 = 2.0, H_7), 2.30 (dddd, 1H, J_1 = 18.7, J_2 = 5.0, J_3 = 1.3 and J_4 = 0.7, H_6), 2.35–2.55 (m, 2H, H_3 and H_6), 2.66 (ddt, 1H, J_1 = 20.0, J_2 = 10.9, and J_3 = 2.8, H_3), 3.67 (dd, 1H, J_1 = 10.7 and J_2 = 7.0, H_9), 3.74 (dd, 1H, J_1 = 10.7 and J_2 = 7.0, H_9), 5.72 (s, 1H, H_4). ^{13}C NMR (see Table 1). MS *m*/*z* (%): 180 (M^+, 17), 121 (100).

(7a*R*)-1-Hydroxymethyl-7a-methyl-2,3,5,6,7,7a-hexahydro-1*H*-inden-5-one propylenic thioacetal (20). The reaction was carried out under the same conditions as for the compound **19**. From **15** (917 mg, 3.64 mmol), after chromatography (hexane:EtOAc, 3:1), a mixture 21:1 of **20b** and **20a** (820 mg, 84%) was obtained as a white solid.

20b. $[\alpha]_D$ + 65.8° (*c* 0.33, $CHCl_3$). IR: 3417, 1665, 1033 cm^{-1}. ^1H NMR (400 MHz) ($CDCl_3$) δ 0.92 (s, 3H, H_8), 1.3–1.5 (m, 2H, H_2 and OH), 1.67 (dt, 1H, J_1 = 13.5 and J_2 = 3.0, H_7), 1.71–1.99 (m, 4H, H_1, H_2, H_7 and $H_{dithiane}$), 1.99–2.08 (m, 1H, $H_{dithiane}$), 2.15 (dt, 1H, J_1 = 14.0, J_2 = 3.0, H_6), 2.26 (dddd, 1H, J_1 = 17.0, J_2 = 9.4, J_3 = 6.7 and J_4 = 1.8, H_3), 2.43–2.55 (m, 2H, H_3 and H_6), 2.72 (ddd, 1H, J_1 = 14.0, J_2 = 6.2 and J_3 = 3.0, $H_{dithiane}$), 2.82 (ddd, 1H, J_1 = 14.0, J_2 = 6.2 and J_3 = 3.0, $H_{dithiane}$), 2.93 (ddd, 1H, J_1 = 14.0, J_2 = 10.5 and J_3 = 3.0, $H_{dithiane}$), 3.00 (ddd, 1H, J_1 = 14.0, J_2 = 10.5 and J_3 = 3.0, $H_{dithiane}$), 3.63 (dd, 1H, J_1 = 10.7 and J_2 = 7.1, H_9), 3.73 (dd, 1H, J_1 = 10.7 and J_2 = 7.1, H_9), 5.45 (d, 1H, J = 1.9, H_4). ^{13}C NMR (see Table 1). MS *m*/*z* (%): 270 (M^+, 94), 196 (100).

(1*S*,7a*R*)-7a-Methyl-5-oxo-2,3,5,6,7,7a-hexahydro-1*H*-inden-1-carbaldehyde (24b). To a suspension of pyridinium chlorochromate (199 mg, 0.93 mmol) and 4 Å molecular sieves (110 mg) in dry CH_2Cl_2 (31 mL), a solution of **19b** (111 mg, 0.62 mmol) in CH_2Cl_2 (13 mL) was added under argon. It was stirred at room temperature for 2 h. Later, the mixture was passed through a silica gel column (hexane:EtOAc, 1:2) obtaining **24b** (86 mg, 78%) as a white solid.

24b. $[\alpha]_D$ + 158.9° (*c* 0.64, $CHCl_3$). IR: 2740, 1727, 1647, 1634 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.19 (s, 3H, H_8), 1.90–3.00 (m, 8H), 5.79 (d, 1H, J = 1.5, H_4), 9.87 (d, 1H, J = 1.8, H_9). ^{13}C NMR (see Table 1). MS *m*/*z* (%): 178 (M^+, 7), 121 (100).

(1*S*,7a*R*)-7a-Methyl-5,5-propylenedithio-2,3,5,6,7,7a-hexahydro-1*H*-indene-1-carbaldehyde (25b). Using the same procedure as for compound **24b**, from **20b** (520 mg, 1.93 mmol), after the chromatographic column (hexane:EtOAc, 3:1), **25b** (white solid, 250 mg, 48%), **20b** (30 mg, 6%) and sulfoxide-aldehyde (80 mg, 15%) were obtained.

25b. Mp: 119°C ($CHCl_3$). $[\alpha]_D$ + 184.8° (*c* 1.04, $CHCl_3$). IR: 2753, 1716 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.02 (s, 3H, H_8), 1.70–3.20 (m, 14H), 5.50 (dd, 1H, J_1 = 3.7 and J_2 = 1.5, H_4), 9.83 (d, 1H, J = 1.8, H_9). ^{13}C NMR (see Table 1). MS *m*/*z* (%): 268 (M^+, 100).

Epimerization of aldehyde 25. To a 5% KOH/EtOH solution (2 mL), a mixture 18:1 of aldehydes **25b/25a** (50 mg, 0.19 mmol) was added. The resultant solution was stirred at room temperature for 1.5 h and then extracted with CH_2Cl_2, washed with brine, dried and evaporated to obtain a mixture 7.7:1 of aldehydes **25b:25a** (48 mg, 96%).

4-[(1*R*,3a*S*,7a*R*)-5,5-Ethylenedioxy-3a-hydroxy-7a-methylperhydroinden-1-yl]-3*E*-buten-2-one (26b). A solution

of aldehyde **21b** (270 mg, 1.12 mmol) and acetonylidentriphenylphosphorane (752 mg, 2.36 mmol) in dry benzene (4.8 mL) was stirred at reflux under argon for 4.5 h. The crude product was chromatographed on a silica gel column (hexane:EtOAc 8:2) to obtain **26b** (275 mg, 93%).

26b. Mp: 75°C (hexane). $[\alpha]_D$ +0.27° (*c* 1.00, $CHCl_3$). IR: 3450, 1680, 1625, 1180 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.86 (s, 3H, H_8), 2.27 (s, 3H, CH_3CO), 2.76 (q, 1H, $J=8.0$, H_1), 3.98 (s, 4H, OCH_2), 5.99 (d, 1H, $J=16.0$, H_{10}), 6.71 (dd, 1H, $J_1=16.0$ and $J_2=8.0$, H_9). ^{13}C NMR (see Table 1). MS *m*/*z* (%): 280 (M^+, 1), 262 (M^+-H_2O), 99 (100).

(1*R*,3a*S*,7a*R*)-3a-Hydroxy-7a-methyl-1-(3-oxo-1*E*-butenyl)perhydroinden-5-one (27b). A solution of **26b** (170 mg, 0.64 mmol) in AcOH:H_2O, 4:1, (10 mL) was stirred at room temperature for 9 h. The crude product was neutralised with $NaHCO_3$, extracted with CH_2Cl_2 and washed with brine. The extract was dried and evaporated to obtain compound **27b** (135 mg, 95%).

27b. IR: 3400, 1710, 1665, 1620, 1150 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.04 (s, 3H, H_8), 2.29 (s, 3H, CH_3CO), 2.49 (d, 1H, $J=16.6$, H_4), 2.63 (d, 1H, $J=16.6$, H_4), 6.03 (d, 1H, $J=15.8$, H_{10}) 6.92 (dd, 1H, $J_1=15.8$ and $J_2=9.0$, H_9). ^{13}C NMR (see Table 1). MS *m*/*z* (%): 236 (M^+, 3), 218 (M^+-H_2O, 3), 43 (100).

4-[(1*R*,3a*S*,5*R*,7a*R*)-3a,5-Dihydroxy-7a-methylperhydroinden-1-yl]-3*E*-buten-2-one (28a) and 4-[(1*R*,3a*S*,5*S*,7a*R*)-3a,5-dihydroxy-7a-methylperhydroinden-1-yl]-3*E*-buten-2-one (28b). To an ice-cold solution (−5°C) of **27b** (117 mg, 0.53 mmol) in dry MeOH, $NaBH_4$ (7 mg, 0.18 mmol) was added. The mixture was stirred at −5°C under argon for 1 h and 15 min. Then, it was extracted with EtOAc, washed with brine, dried and evaporated. The crude reaction product was purified by chromatography (hexane:EtOAc, 9:1) to obtain **28a** (30 mg, 25%) and **28b** (35 mg, 29%).

28a. $[\alpha]_D$ −4.1° (*c* 0.90, $CHCl_3$). IR: 3400, 1670, 1620, 1170, 1060 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.83 (s, 3H, H_8), 2.27 (s, 3H, CH_3-CO), 2.87 (q, 1H, $J=8.5$, H_1), 3.86 (m, 1H, H_5), 6.01 (d, 1H, $J=15.8$, H_{10}), 6.71 (dd, 1H, $J_1=15.8$ and $J_2=8.4$, H_9). ^{13}C NMR (see Table 1).

28b. $[\alpha]_D$ +7.9° (*c* 0.80, $CHCl_3$). IR: 3380, 1660, 1620, 1160, 1100 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.88 (s, 3H, H_8), 2.27 (s, 3H, CH_3-CO), 2.70 (q, 1H, $J=8.4$, H_1), 4.16 (m, 1H, H_5), 5.99 (d, 1H, $J=15.8$, H_{10}), 6.75 (dd, 1H, $J_1=15.8$ and $J_2=8.4$, H_9). ^{13}C NMR (see Table 1).

(1*R*,3a*S*,5*R*,7a*R*)-3a-Hydroxy-7a-methyl-1-(3-oxo-1*E*-butenyl)perhydroinden-5-yl acetate (29a). To a solution of **28a** (28 mg, 0.12 mmol) in CH_2Cl_2 (1 mL), pyridine (0.30 mL) and acetic anhydride (0.30 mL) were added. After stirring for 12 h, it was worked up as usually yielding **29a** (30 mg, 92%).

29a. $[\alpha]_D$ +3.40° (c 0.95, $CHCl_3$). IR: 3420, 1720, 1670, 1625, 1170 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.85 (s, 3H, H_8), 1.72 (dd, 1H, $J_1=13.6$ and $J_2=11.0$, H_4), 1.90 (ddd, 1H, $J_1=13.6$, $J_2=4.0$ and $J_3=2.2$, H_4), 2.04 (s, 3H, CH_3COO), 2.25 (s, 3H, CH_3CO), 2.83 (q, 1H, J = 8.4, H_1), 4.95 (tt, 1H, $J_1=10.5$ and $J_2=4.4$, H_5), 6.02 (d, 1H, $J=15.8$, H_{10}), 6.74 (dd, 1H, $J_1=15.8$ and $J_2=8.2$, H_9). ^{13}C NMR (see Table 1).

(1*R*,3a*S*,5*S*,7a*R*)-3a-Hydroxy-7a-methyl-1-(3-oxo-1*E*-butenyl)perhydroinden-5-yl acetate (29b). The reaction was carried out under the previously described conditions. From **28b** (25 mg, 0.11 mmol), **29b** (28 mg, 95%) was obtained.

29b. $[\alpha]_D$ −111° (*c* 0.70, $CHCl_3$). IR: 3450, 1725, 1680, 1625, 1165 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.91 (s, 3H, H_8), 1.36 (ddd, 1H, $J_1=14.4$, $J_2=6.8$ and $J_3=4.8$), 1.50 (ddd, 1H, $J_1=14.8$, $J_2=14.4$ and $J_3=9.6$), 1.76 (dd, 1H, $J_1=14.4$ and $J_2=6.0$, H_4), 1.96 (dd, 1H, $J_1=14.4$, $J_2=4.2$, H_4) 2.08 (s, 3H, CH_3COO), 2.26 (s, 3H, CH_3CO), 2.59 (q, 1H, $J=7.2$, H_1), 5.04 (tt, 2H, $J_1=6.2$ and $J_2=4.2$, H_5), 5.96 (d, 1H, $J=15.8$, H_{10}), 6.82 (dd, 1H, $J_1=15.8$ and $J_2=9.0$, H_9). ^{13}C NMR (see Table 1).

(1*R*,3a*S*,7a*R*)-3a-Hydroxy-7a-methyl-1-[(*E*)-methylthiovinyl]perhydroinden-5-one ethylenic acetal (30b). To $CH_3SCH_2PO(OEt)_2$ (0.29 mL, 328 mg, 1.6 mmol), 80% NaH (in paraffin oil, 50 mg, 1.1 mmol) was added while the reaction flask was cooled down to −5°C. After evolution of H_2, a solution of **21b** (199 mg, 0.83 mmol) in dry benzene (3 mL) was added, followed by refluxing under argon for 4.5 h. The crude product was chromatographed on silica gel column (hexane:EtOAc, 8:2) to give **30b** (150 mg, 63%).

30b. $[\alpha]_D$ +10.2° (c 1.00, $CHCl_3$). IR: 3460, 1620, 1175 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.81 (s, 3H, H_8), 2.25 (s, 3H, CH_3S), 2.67 (q, 1H, $J=8.0$, H_1), 3.97 (br s, 4H, OCH_2), 5.31 (dd, 1H, $J_1=15.0$ and $J_2=8.0$, H_9), 5.93 (d, 1H, $J=15.0$, H_{10}). ^{13}C NMR (see Table 1). MS *m*/*z* (%): 284 (M^+, 3), 266 (M^+-H_2O, 49), 169 (100).

(1*R*,3a*S*,7a*R*)-3a-Hydroxy-7a-methyl-1-[(*E*)-2-methylthiovinyl]perhydroinden-5-one (31b). The reaction was carried out under the conditions described above for compound **27b**, yielding **31b** (99%).

31b. IR: 3410, 1710, 1150 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.96 (s, 3H, H_8), 2.27 (s, 3H, CH_3S), 2.41 (d, 1H, $J=14.8$, H_4), 2.53 (d, 1H, $J=14.8$, H_4), 2.70 (q, 1H, $J=8.8$, H_1), 5.45 (dd, 1H, $J_1=14.8$ and $J_2=8.8$, H_9), 6.02 (d, 1H, $J=14.8$, H_{10}). ^{13}C NMR (see Table 1). MS *m*/*z* (%): 240 (M^+, 32), 222 (M^+-H_2O, 12), 85 (100).

(1*R*,3a*S*,5*S*,7a*R*)-7a-Methyl-1-[(*E*)-2-methylthiovinylperhydroindene-3a,5-diol (32b). The reaction was carried out under the conditions previously described for **28b**, obtaining **32b** (75%).

32b. Mp: 168°C (AcOEt/diethyl ether). IR: 3320, 1610, 1170, 1060 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.77 (s, 3H, H_8), 2.25 (s, 3H, CH_3S), 2.78 (q, 1H, $J=8.6$, H_1), 3.85 (tt, 1H, $J_1=10.4$ and $J_2=5.8$, H_5), 5.28 (dd, 1H, $J_1=14.8$ and $J_2=8.8$, H_9), 5.94 (d, 1H, $J=14.8$, H_{10}). ^{13}C NMR

(see Table 1). MS *m/z* (%): 242 (M^+, 38), 224 ($M^+ - H_2O$, 18), 85 (100).

(1*R*,3a*S*,5*S*,7a*R*)-3a-Hydroxy-7a-methyl-1-[(*E*)-2-methylthiovinyl]perhydroinden-5-yl acetate (33b). Compound **33b** was obtained in the same way as that of **29b**, in 70% yield.

33b. ^{1}H NMR ($CDCl_3$) δ 0.80 (s, 3H, H_8), 2.03 (s, 3H, CH_3COO), 2.25 (s, 3H, CH_3S), 2.77 (q, 1H, $J=8.8$, H_1), 4.94 (tt, 1H, $J_1=11.0$ and $J_2=6.0$, H_5), 5.28 (dd, 1H, $J_1=15.0$ and $J_2=8.6$, H_9), 5.94 (d, 1H, $J=15.0$, H_{10}). ^{13}C NMR (see Table 1).

(1*S*,3a*S*,7a*R*)-3a-Hydroxy-7a-methyl-1-[(*E*)-2-nitrovinyl]-perhydroinden-5-one ethylenic acetal (34a) and (1*R*,3a*S*,7a*R*)-3a-hydroxy-7a-methyl-1-[(*E*)-2-nitrovinyl]-perhydroinden-5-one ethylenic acetal (34b). A solution of aldehyde **21b** (134 mg, 0.47 mmol) and NH_4AcO (48 mg, 0.6 mmol) in CH_3NO_2 (3 mL) was refluxed for 1 h. After that period of time, it was extracted with CH_2Cl_2, washed with brine and dried to obtain 180 mg of a mixture of two isomers, which was resolved through a column chromatography (CH_2Cl_2:EtOAc, 8:2) yielding **34b** (60 mg, 37%) and **34a** (40 mg, 26%).

34a. ^{1}H NMR ($CDCl_3$) δ 0.95 (s, 3H, H_8), 2.87 (q, 1H, $J=8.3$, H_1), 6.99 (d, 1H, $J=13.5$, H_{10}), 7.27 (dd, 1H, $J_1=13.5$ and $J_2=8.8$, H_9). ^{13}C NMR (see Table 1).

34b. ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 3H, H_8), 2.82 (q, 1H, $J=8.4$, H_1), 6.92 (d, 1H, $J=13.6$, H_{10}), 7.23 (dd, 1H, $J_1=13.6$ and $J_2=8.8$, H_9). ^{13}C NMR (see Table 1).

(1*R*,7a*R*)-7a-Methyl-1-[(*E*)-2-nitrovinyl]-2,3,5,6,7,7a-hexahydro-1*H*-indene-5-one guanylhydrazone (35b). To a solution of the nitroderivative **34b** (45 mg. 0.16 mmol) in dry methanol (4 mL), aminoguanidine hydrochloride (1 mmol, prepared by adding HCl 2 N to aminoguanidine bicarbonate until pH 5) was added. The reaction mixture was heated to reflux for 30 min. The solvent was removed under vacuum and the resultant solid was recrystallised from MeOH/ether to obtain **35b** (26 mg, 62%) as a white solid.

35b. $[\alpha]_D$ +34.6° (c 0.45). IR: 3310, 1672, 1626, 1520, 1350 cm^{-1}. ^{1}H NMR (CD_3OD) δ 0.91 (s, 3H, H_8), 5.91 (s, 1H, H_4), 7.11 (d, 1H, $J=13.2$, H_{10}), 7.23 (dd, 1H, $J_1=13.2$ and $J_2=7.3$, H_9). ^{13}C NMR (see Table 1). FABHRMS *m/z*: calcd: 277.3261; found: 277.6628.

(1*S*,3a*S*,7a*R*)-3a-Hydroxy-1-hydroxyiminomethyl-7a-methylperhydroinden-5-one ethylenic acetal (36). To a solution of aldehyde **21b** (110 mg, 0.46 mmol) in EtOH (15 mL), pyridine (1.5 mL), $HONH_2.HCl$ (73.5 mg, 1.37 mmol) and $NaOAc.3H_2O$ (93.5 mg, 0.29 mmol) were sequentially added. The mixture was refluxed for 2 h, then extracted with CH_2Cl_2, washed and dried. After evaporating the solvent, a mixture of isomers Z/E **36′** and **36″** (110 mg, 94%) was obtained.

36′. ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 3H, H_8), 2.82 (q, 1H, $J=8$, H_1), 7.36 (d, 1H, $J=8$, H_9), 8.61 (br s, 1H, =N–OH). ^{13}C NMR (see Table 1).

36″. ^{1}H NMR ($CDCl_3$) δ 0.95 (s, 3H, H_8), 3.70 (q, 1H, $J=8$, H_1), 6.65 (d, 1H, $J=8$, H_9), 7.32 (1H, =N–OH). ^{13}C NMR (see Table 1).MS *m/z* (%): 238 (M^+, 21), 222 ($M^+ - H_2O$, 2), 99 (100).

(1*S*,7a*R*)-7a-Methyl-5-oxo-2,3,5,6,7,7a-hexahydro-1*H*-indene-1-carbaldehyde bis(guanylhydrazone) (38b). Aldehyde **21b** (100 mg, 0.41 mmol) was dissolved in EtOH (7 mL). The resultant solution was treated with aminoguanidine hydrochloride (2 equiv, prepared by adding HCl 2 N to aminoguanidine bicarbonate until pH 5). The mixture was refluxed for 30 min. Then the solvent was evaporated and the solid recrystallised to obtain **38b** (70 mg, 58%) as a white solid.

38b. Mp: 248°C (MeOH). $[\alpha]_D$ +4.1° (**c** 0.75%, MeOH). IR: 3200, 1670, 1625, 1115, 990, 865 cm^{-1}. ^{1}H NMR (D_2O) δ 0.93 (s, 3H, H_8), 5.94 (s, 1H, H_4), 7.50 (d, 1H, $J=6.4$, H_9). ^{13}C NMR (see Table 1). MS *m/z* (%): 291 ($M^+ + 1$, 43), 185 (100).

(3a*S*,7a*R*)-5,5-Ethylenedioxy-3a-hydroxyperhydroinden-1-carbaldehyde guanylhydrazone (37). To a solution of **21b** (30 mg, 0.13 mmol) in EtOH (7 mL), aminoguanidine hydrochloride (1 equiv) was added. The reaction mixture was refluxed for 30 min. The solvent was evaporated and the solid crystallised from MeOH to obtain **37** (36 mg, 97%) as a mixture, in a 2:1 ratio, of the two isomers (**37a/37b**). IR: 3350, 1672, 1626, 1121, 873 cm^{-1}.

37a. ^{1}H NMR (CD_3OD) δ 0.75 (s, 3H, H_8), 2.61 (q, 1H, $J=7.2$, H_1) 3.76 (m, 4H, OCH_2), 7.32 (d, 1H, $J=7.2$, H_9). ^{13}C NMR (see Table 1).

37b. ^{1}H NMR (CD_3OD) δ 0.92 (s, 3H, H_8), 2.37 (dd, 1H, $J_1=9.0$ and $J_2=4.6$, H_1), 6.77 (d, 1H, $J=8.6$, H_9). ^{13}C NMR (see Table 1).

(3a*S*,7a*R*)-3a-Hydroxy-7a-methyl-5-oxoperhydroindene-1-carbaldehyde bis(guanylhydrazone) (39). To a suspension of HgO (red) (255 mg, 1.2 mmol) in THF:H_2O, 85:15 (6.15 mL), $BF_3{\cdot}Et_2O$ (0.29 mL, 2.30 mmol) was added. A solution of **22b** (150 mg, 0.52 mmol) in THF (27.3 mL) was added next. The mixture was stirred for 20 h at room temperature and then quenched by addition of CH_2Cl_2, filtrated and washed with Na_2CO_3 and brine. After evaporation, the corresponding keto-aldehyde (80 mg, 76%) was obtained. This keto-aldehyde (80 mg, 0.33 mmol) was dissolved in dry EtOH (7.3 mL), and treated with aminoguanidine hydrochloride (2 equiv, prepared by adding HCl 6 N to a solution of aminoguanidine bicarbonate until pH 5). The reaction mixture was refluxed for 30 min under argon. The solvent was evaporated and the residue crystallised from MeOH:benzene to obtain a mixture of two isomers in a 1:1 ratio (**39a:39b**) (solid, 15 mg, 14%). IR: 3457, 1675, 1631, 1142, 1003, 880, 855 cm^{-1}.

39a. ^{1}H NMR (CD_3OD) δ 0.90 (s, 3H, H_8), 7.48 (d, 1H, $J=3.0$, H_9). ^{13}C NMR (see Table 1).

39b. ^{1}H NMR (CD_3OD) δ 0.88 (s, 3H, H_8), 7.51 (d, 1H, $J=3.0$, H_9). ^{13}C NMR (see Table 1).

Methyl [(1*R*,7a*R*)-7a-methyl-5-oxo-2,3,5,6,7,7a-hexahydro-1*H*-inden-1-yl]acrylate (40b) and methyl [(1*S*, 7a*R*)-7a-methyl-5-oxo-2,3,5,6,7,7a-hexahydro-1*H*-indene-1-yl]acrylate (40a). A solution of aldehyde **24b** (44 mg, 0.25 mmol) and methoxycarbonylmethylentriphenylphosphorane (100 mg, 0.30 mmol) in dry benzene (1 mL) was stirred at reflux under argon for 1 h 30 min. The crude product was chromatographed on a silica gel column (hexane:EtOAc, 6:1) to yield **40b** (34 mg, 58%) and **40a** (6 mg, 9%), both as colourless oils.

40a. $[\alpha]_D$ −94° (*c* 0.15, $CHCl_3$). IR: 1715, 1667, 1649, 1201, 829 cm^{-1}. ^1H NMR (CD_3OD) δ 1.12 (s, 3H, H_8), 3.60–3.80 (m, 1H, H_1), 3.71 (s, 3H, OMe), 5.79 (dd, 1H, $J_1 = 2.2$ and $J_2 = 1.8$, H_4), 5.93 (d, 1H, $J = 11.5$, H_{10}), 6.19 (dd, 1H, $J_1 = 11.5$ and $J_2 = 10.4$, H_9). ^{13}C NMR (see Table 1). MS *m*/*z* (%) 234 (M^+, 9), 202 (52), 174 (100).

40b. $[\alpha]_D$ +81° (*c* 0.38, $CHCl_3$). IR: 1727, 1667, 1649, 1201, 829 cm^{-1}. ^1H NMR (CD_3OD) δ 1.08 (s, 3H, H_8), 3.76 (s, 3H, OMe), 5.80 (dd, 1H, $J_1 = 1.8$ and $J_2 = 1.8$, H_4), 5.90 (dd, 1H, $J_1 = 15.7$ and $J_2 = 1.5$, H_{10}), 6.97 (dd, 1H, $J_1 = 15.7$ and $J_2 = 7.7$, H_9). ^{13}C NMR (see Table 1). MS *m*/*z* (%) 234 (M^+, 1), 202 (69), 174 (100).

Methyl [(1*R*,7a*R*)-5-guanylhydrazono-7a-methyl-2,3,5,6,7,7a-hexahydro-1*H*-indene-1-yl]acrylate (41). To a solution of **40b** (37 mg, 0.16 mmol) in ethanol (3.4 mL), aminoguanidine hydrochloride (19 mg, 0.17 mmol) and HCl 2 N (74 μL) were added. The reaction mixture was refluxed for 45 min, the solvent evaporated and the residue crystallised from CH_2Cl_2:diethyl ether to obtain **41** (mixture 6:1 of *E*/*Z* isomers, 45 mg, 97%) as a white solid.

41. $[\alpha]_D$ +37.1° (*c* 0.35, MeOH). IR: 3352, 1719, 1671, 1624, 1277, 999 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.91 (s, 3H, H_8 (*E*)), 0.98 (s, 3H, H_8 (*Z*)), 3.75 (s, 3H, OMe), 5.84 (s, 1H, H_4), 5.92 (s, 1H, H_{10}), 6.95 (dd, 1H, $J_1 = 15.0$, $J_2 = 6.9$, H_9). ^{13}C NMR (see Table 1). FABHRMS *m*/*z*: calcd: 290.3648; found: 290.5718.

[(1*S*,7a*R*)-1-Hydroxymethyl-7a-methyl-2,3,5,6,7,7a-hexahydro-1*H*-indene-5-one]guanylhydrazone (42). The reaction was carried out in the way previously described. From 1-hydroxymethyl-5-ketone **19b** (75 mg, 0.42 mmol), after crystallisation from MeOH:diethyl ether, **42** was obtained (mixture 3:1 of *E*/*Z* isomers, 97 mg, 99%), as a yellow solid.

42. $[\alpha]_D$ +40.5° (*c* 0.61, MeOH). IR: 3309, 1630, 1618, 885 cm^{-1}. ^1H NMR (CD_3OD) δ 0.75 (s, 3H, H_8 (*E*)), 0.84 (s, 3H, H_8 (*Z*)), 3.36–3.55 (m, 2H, H_9), 5.76 (s, 1H, H_4 (*E*)), 6.70 (s, 1H, H_4 (*Z*)). ^{13}C NMR (see Table 1).

Inotropic activity assays

Guinea pigs of both sexes weighing 300–500 g were killed by cervical dislocation and their hearts were excited quickly. Right and left atria were dissected and mounted vertically in 5 mL organ baths containing Tyrode solution of the following composition (mM): NaCl, 125; KCl, 5.4; $CaCl_2$, 1.8; $MgCl_2$, 1.05; $NaHCO_3$, 24; NaH_2PO_4, 0.42; glucose, 11. The solution was bubbled with 95% O_2–5% CO_2 and maintained at 34°C. Under these conditions, right atria beat spontaneously, while left atria were electrically driven at a basal rate of 2 Hz through bipolar platinum electrodes, with rectangular pulses (1 ms duration, twice threshold strength) delivered from a multipurpose programmable stimulator (Cibertec CS.220, Cibertec SA, Madrid, Spain). Rate and amplitude of contractions were measured isometrically by a force-displacement transducer and recorded on a Grass Moder 7B polygraph (Grass Instrument Co., Quincy, MA, USA). Resting tension was adjusted to 1 g and a 60 min equilibration period was allowed to elapse before control measurements were taken.

The parameters of isometric contractions and cardiac rate were determined as previously described.[37] Following a 60 min equilibration period, cumulative dose–response curves to digoxin and compounds **35**, **41** and **42** were constructed, increasing concentration at 20 min intervals. Compound concentrations were used in the range 10^{-7}–10^{-6} M for digoxin (Boehringer digoxin®) and 10^{-7}–3×10^{-4} M for **35**, **41** and **42**. Dose–response curves with the vehicle employed for dissolving the compounds (0.1–3% DMSO) were used as controls. The values for different parameters obtained in the absence of drug were used as control and compared with those obtained after each increment in drug concentration.

The results obtained from a minimum of five experiments were expressed as means ± SEM Statistical analysis of results were performed by unpaired Student's *t* test. Probability levels of < 0.05 were taken as indicating statistical significance.

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