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# New dicyclopentadiene-based scaffolds

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**Abstract**—New tricyclic and tetracyclic derivatives have been obtained from dicyclopentadiene as scaffolds for the preparation of diterpene analogues. Key functionalities with well defined spatial dispositions were placed on three different skeletons. The inaccessibility of external (and also internal) reagents to the concave face of these compounds rendered them resistant to several transformations.


## 1. Introduction

Modern drug discovery takes advantage of the ideas and methodologies of combinatorial chemistry.[1] The search for new lead compounds and improvement of their pharmacological activities require accessible supporting structures to introduce high variability through the attachment of diverse substituents. To complete this goal, base structures, usually referred to as 'scaffolds', with geometrically defined attachment points are required.[2]

Dicyclopentadiene is a well known convex molecule that has found application in the search for new polymeric materials through different approaches,[3] some of them comprising the ring opening metathesis.[4] To our knowledge, it has received less attention in the field of medicinal chemistry in the search for new active compounds. Other applications of this starting material have been the synthesis of natural products: physostigmine alkaloids,[5] cyclitols,[6] kainic acid,[7] the carbocyclic nucleoside neplanocin,[8] terpenoids[9] and coronafacic acid[10] have been synthesised by dicyclopentadiene-based routes. Cage compounds[11] and C2 chiral building blocks[12] have also been prepared from this useful starting material. Flash vacuum pyrolysis has been used in many cases to produce monocyclic derivatives with a defined stereochemistry, previously produced on the dicyclopentadiene convex architecture.[13]

We have recently begun a research line directed at the preparation of simple analogues of active diterpenoids.[14] This requires the preparation of convex rigid core-substructures containing attachment points in order to introduce substituents with defined orientations. Dicyclopentadiene appears to fulfil these requirements in that it has two double bonds to introduce functionalities and a convex rigid structure to orient them. Following this reasoning, we attempted to prepare new scaffolds based on derivatives of dicyclopentadiene containing the X, Y and/or Z attachment positions (Fig. 1).

Owing to the vast array of possibilities available to accomplish this task, we selected three families of compounds to initiate our research: type **A**, carrying X and Y substituents; type **B**, with the X and Z substituents; and type **C**, containing the X, Y and Z substituents; X and Z being located on the convex side of the skeleton, whereas Y is located on the concave side in type **A** or on the convex side in type **C**.

The methodology chosen for the preparation of type **A** compounds was to introduce a functionalised carbon at position 3 of the tricyclic system by means of conjugate addition to dicyclopentadienone.[15] The well known cyclisation between nucleophilic substituents at position 1(3) of the dicyclopentane (octahydro-4,7-methane-1*H*-indene) and position 6(5), the latter acting as electrophilic position, is suitable for construction of the further cyclised type **B** compounds. The reaction is started at the double bond through different processes: epoxidation,[16] bromination with NBS[17] or acid treatment[3] and is completed by oxygen or nitrogen nucleophile at 1(3) (Fig. 2). The combination of addition and cyclisation can produce type **C** compounds.

In this paper, we report our results on the construction of scaffolds containing two or three attachment points as hydroxyl or amino functionality. The difficulties encountered in producing certain variations in the carbon framework of dicyclopentadiene, due to the spatial proximity between positions in the concave part of the skeleton, are also commented.

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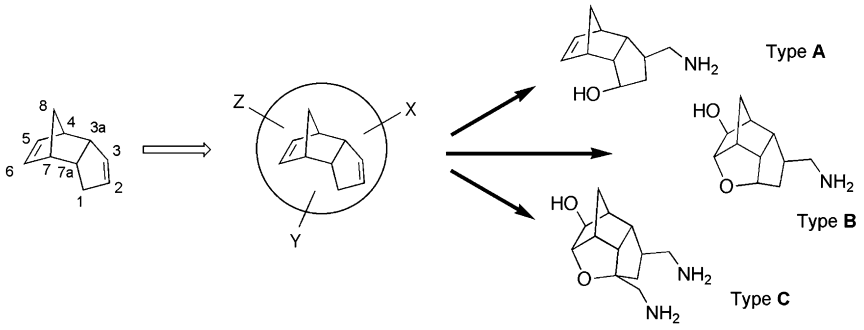



**Figure 1**.

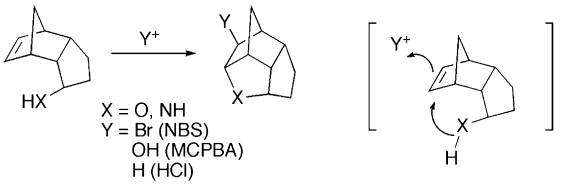



**Figure 2**.

## 2. Results and discussion

Following known methodologies, dicyclopentadiene was oxidised to dicyclopentadienone by means of selenium dioxide (either with $^t$BuOOH as cooxidant, 30% yield of hydroxy derivative; or with 1.5 mol of $SeO_2$/mol, 58%) followed by PCC,[18] other chromium(VI) oxidants ($CrO_3$/$^t$BuOOH as cooxidant, 37% yield; $Na_2Cr_2O_7$, mixtures) or oxygen (irradiation in presence of TPP porphine derivative, 100%).[19] In order to introduce one carbon substituent containing a nitrogen atom, cyanide and nitromethane can be used to, respectively, produce oxo-nitrile **1** or nitroketone **2** (Scheme 1). We began by checking the first possibility, employing diethylaluminium cyanide in toluene as an easy-to-handle cyanide reagent. With this procedure, the expected oxo-nitrile **1** was obtained, but in low yields.

Different reaction by-products can be invoked to account for the low yield of oxo-nitrile **1**. When the reaction was carried out by slow addition of the $Et_2AlCN$ reagent to a solution of dicyclopentadienone, the excess of the unsaturated ketone favoured polymerisation processes. A mixture of polymeric products with varying numbers of subunits and stereochemistries at the α,β-positions, which can be represented by structure **5** (Fig. 3), was separated as major reaction products. In order to avoid this undesired reactivity, we added dicyclopentadienone to the solution containing $Et_2AlCN$. In this case, no polymeric products were obtained, but in the presence of an excess of the reagent conjugate addition followed by direct addition to the cyanoketone formed, yielded hydroxydicyanide **6** as the major by-product of the reaction.

Although the yield was not sufficient to further proceed with this approach to our synthetic plan, compound **1** was of interest to prepare aminoalcohol **3** as a type **A** scaffold. Lithium aluminium hydride reduction of **1** followed by acetylation with $Ac_2O$ afforded the expected **4** in high yield. The whole process from **1** to **4** occurred with ≈50% yield, affording the diacetylated product, which was devoid of the high water solubility displayed by the aminoalcohol **3**.

An alternative route to aminoalcohol **3** based on the conjugate addition of nitromethane to dicyclopentadienone was also checked. The use of a large excess of nitromethane and a catalytic amount of tetrabutylammonium fluoride (0.1 mol/mol enone) in toluene at room temperature, yielded

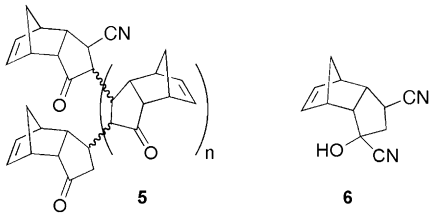
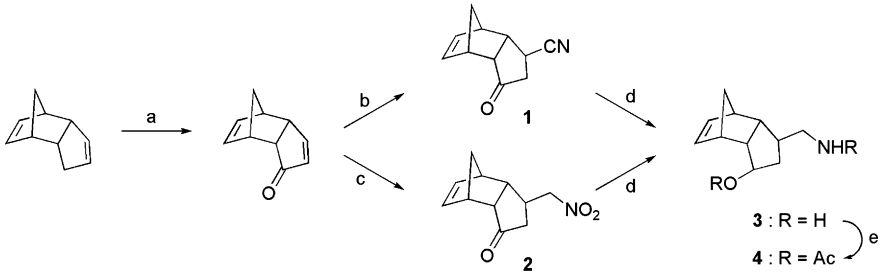
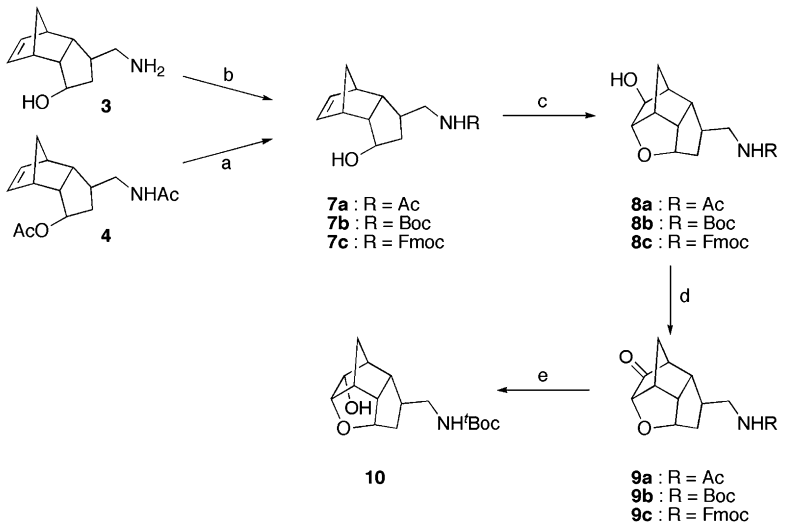



**Figure 3**.




**Scheme 1**. (a) (1) $SeO_2$, dioxane, 150 min, reflux; or (2) $SeO_2$ (20%), $^t$BuOOH, DCM at 0 °C, 72 h at rt, followed by PCC, DCM, 0 °C, 20 h at rt; or (3) $O_2$, TPP, $Ac_2O$, DMAP, Py, DCM, *hν* (400 W), 12 h, rt. (b) $Et_2AlCN$, toluene, 0 °C, 2 h at rt. (c) Nitromethane, TBAF, 12 h, rt. (d) $LiAlH_4$, THF, reflux, 1 h. (e) $Ac_2O$, Py, rt.




**Scheme 2**. (a) KOH/MeOH (10%) at 40 °C, 1 h. (b) FmocCl or $Boc_2O$, $Na_2CO_3$, dioxane/water 1:1, rt, 48 h, 40 °C, 1 h. (c) MCPBA, $CH_2Cl_2$, $Na_2CO_3$, rt, 24 h. (d) $(COCl)_2$, DMSO, $CH_2Cl_2$, −60 °C, then $Et_3N$, rt, 2 h. (e) Al, $HgCl_2$, dry $C_6H_6$/EtOH (abs) 1:1, reflux, 4 h.

≈95% of **2** after simple workup. Reduction with lithium aluminium hydride and acetylation also produced aminoalcohol **3** and diacetylated derivative **4** in good yield, in a very similar way to the process carried out through the cyanoketone. Taking into consideration the absence of by-products in the conjugate addition, which makes chromatographic separation of the reaction unnecessary, and the absence of cyanide reagents and the similar results obtained during the reduction, the conjugate addition of nitromethane was chosen for the preparation of the starting materials **3** and **4** at multigram scale.

Once the type **A** key structure had been obtained, we turned our attention to the transformation of these compounds, **3** and **4**, in more elaborated materials, namely the types **B** and **C** scaffolds (Scheme 2). For this the presence of the free hydroxyl group at position 1 is required, this can be achieved by starting from both the diacetylated material **4** or the water-soluble aminoalcohol **3**. From the former, selective acetate hydrolysis is quantitatively achieved by treatment with bases, yielding the acetamido derivative **7a**. In order to have materials that would be easier to handle, owing to their hydrophobic nature, on the way to the final amino products, we also prepared the amino-protected alcohols **7b** and **7c** by direct treatment of **3** with protecting reagents. Reduction of the nitroketone followed by reaction with $Boc_2O$ or with FmocCl allowed direct recovery of the protected material **7b** or **7c** from the organic phase in good yields (two-reaction process ≈70% in both cases) and no further purification was required. Any of the aminoalcohol derivatives **7a–c** proved to be very useful in the ensuing transformations, showing good solubility and an absence of reactivity of the protecting groups under the conditions used during the next steps.

The preparation of type **B** scaffold compounds was planned via epoxidation of the double bond of derivatives **7** (Fig. 4), whose transformation into the more cyclised products with structure **8** could either occur spontaneously or could require acid or basic treatment. The reactions of **7a**, **7b** and **7c** with *meta*-chloroperbenzoic acid readily produced the cyclised

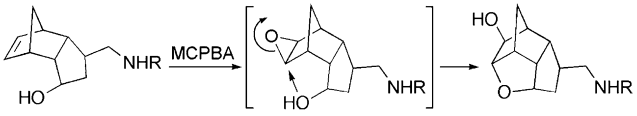



**Figure 4**.

derivatives **8a**, **8b** and **8c**, without isolation or detection of the intermediate epoxidic derivatives. The close proximity between the oxygen at position 1 and the backside of the epoxide at position 6, in an alignment favouring the interaction of the orbitals involved in the reaction, explains the effectiveness of this transformation.

With this procedure the preparation of type **B** scaffolds was accomplished in a straightforward way, requiring four steps from dicyclopentadienone. In order to increase the number of possibilities for the use of such types of compound we next decided to carry out transformations on compounds with structure **8**. In this respect, the oxidation of these epoxy-alcohols using Swern methodology yielded the corresponding ketones **9a–c**. Finally, we decided to reduce ketones **9** at the α-position (Fig. 5) as a means to recover the tricyclic structure of the starting dicyclopentadiene carrying the X, Y and Z substituents in order to produce type **C** scaffolds. The reduction at similar positions of related ketoethers has been described to produce the α-deoxyketones in good yields.[20]

Unfortunately, attempts to perform the reduction carried out under standard conditions failed to provide the desired transformation, converting the starting α-epoxyketone **9b** into the α-epoxyalcohol **10**, epimeric at position 5 of the already prepared α-epoxyalcohol **8b**.

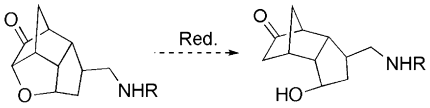
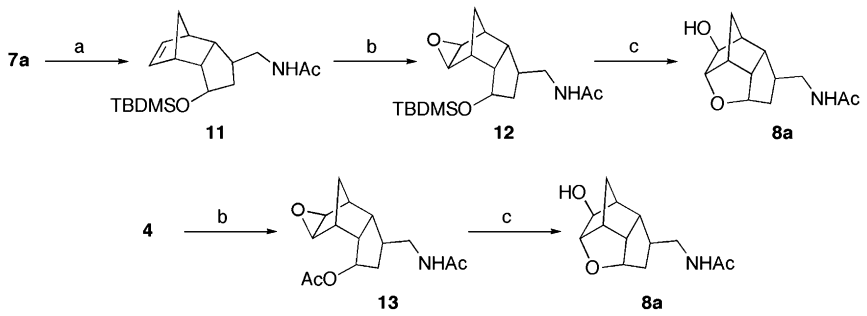



**Figure 5**.




**Scheme 3**. (a) TBDMSOTf, DMAP, $Et_3N$, DCM, 5 h, rt. (b) MCPBA, DCM, 24 h, rt. (c) KCN, MeOH, 24 h, rt.

After the synthesis of convex molecules **3**, **4** and **7–10**, we directed our attention to compounds carrying the oxirane ring at positions 5 and 6 and the oxygenated functionality at position 1 in order to check the possibilities of transforming these compounds without the simultaneous cyclisation depicted in Figure 4. To this end, we protected the 1-hydroxy group as an acetate or as a TBDMS derivative (Scheme 3).

The protection of hydroxy-acetamide **7a** as the TBDMS derivative **11** followed by treatment with MCPBA yielded the epoxyderivative **12**. Similarly, the epoxidation of **4** produced **13**, both compounds, **12** and **13**, being adequate to check the new possibilities for the transformation of these scaffolds (Scheme 3). One of our interests lays in the introduction of new carbonated moieties through the concave part of the skeleton. Among others, the most promising possibility, taking into consideration the requirement of a small nucleophile to elude the hindrance at this side of the skeleton, was the use of a cyanide to open the oxirane ring (Fig. 6).

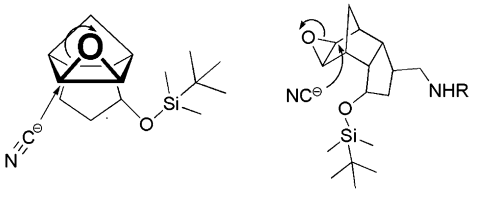



**Figure 6**.

This transformation failed and the expected cyano-derivative was not obtained. Instead, compound **8a** was produced as the only reaction product in high yields (Scheme 3). The strong concavity of the molecule, producing close proximity between the oxirane position 6 and the oxygen at position 1, is responsible for the lack of accessibility by external nucleophiles to position 5. In this particular case, the attack of the cyanide takes place on the silane moiety, facilitating the attack of the oxygen and internal opening of the oxirane. The same process occurred when the diacetylated derivative **13** was treated with the cyanide reagent, only **8a** being produced as a consequence of the attack on the acetyl group followed by oxirane opening instead of the direct attack on the oxirane. Accordingly, we attempted to introduce carbon residues at position 5 by means of an internal reaction with carbon substituents at position 1, a procedure that would permit the opening of the oxirane by the substituents that are responsible for the hindrance to external attack. Thus, the nucleophilic attack and the radical process depicted in Figure 7 were planned.

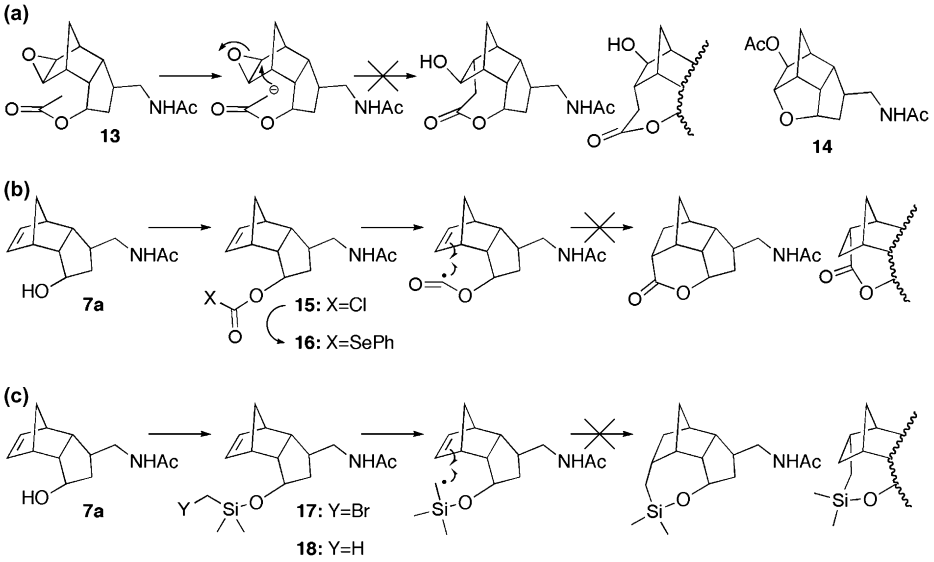



**Figure 7**. (a) (1) LiHMDS or (2) NaH, at 0 °C, 72 h at rt, followed by $Ac_2O$. (b) (1) Phosgene in $Et_2AlCN$, toluene, 0 °C, 2 h at rt; (2) PHSeH; (3) AIBN, $BU_3SnH$. (c) (1) $Me_2Si(CH_2Br)Cl$; (2) AIBN, $Bu_3SnH$.

When the nucleophilic attack by the enolate anion of acetate **13** was attempted (Fig. 7a) using an excess of LiHMDS or NaH, neither the expected 6-hydroxy-1,5-lactone nor the regioisomeric 5-hydroxy-1,6-lactone was produced. When the reaction product was recovered directly, epoxyalcohol **8a** was obtained, whereas following acetylation of the crude reaction product the diacetylated derivative **14** was produced. We conclude that the products derived from the internal attack of the enolate ion, although structurally stable, are not formed owing to the geometric restrictions arising during that process. Direct acetylation of hydroxyamide **8a** also yielded compound **14**, although during an experiment with this process the opening of the 1,6-epoxide took place, leading to transformation into the 5,6-oxirane **13**. The recovery of the products without the 1,6-epoxide substructure can be produced under basic or acidic conditions or by treatment of 5-bromo derivatives with metals.[21]

Attempts to carry out the cyclisation by means of a carbon radical according to Figure 7b also failed. In this case, treatment of hydroxyamide **7a** with phosgene followed by reaction of chloroformiate **15** with selenophenol produced selenocarbonate **16**, which was treated with TBTH/AIBN to initiate the cyclisation according to the literature.[22] Although many attempts were carried out under different experimental conditions the reaction produced complex mixtures in which no reaction product could be characterised. Again, the geometric restrictions for the cyclisation must be responsible for the absence of formation of the δ- or ε-lactone. The radical species, generated from the selenocarbonate, possibly evolve to produce a dicyclopentadiene radical, which may produce mixtures of rearranged products.[23] With this background, the cyclisations planned to introduce additional carbon atoms at position 5 or 6 seemed to be difficult owing to the geometry of the dicyclopentadiene system. Nevertheless, we attempted a final approach, as depicted in Figure 7c. Radical cyclisation of the bromomethyldimethylsiloxy derivative **17** to the seven- or eight-atom cyclosiloxane was carried out under standard conditions, but only reduction to the trimethylsilyl derivative **18** was observed, thus confirming the difficulty for the reactive intermediate to attack the double bond through the concave side of the molecule. This compound was also obtained by trimethylsilylation of **7a**.

In light of these results, we decided to assay the formation of type **C** compounds, taking into consideration the easy cyclisation of hydroxyl groups at position 1 to the activated position 6. To produce type **C** compounds, nucleophilic attack from the convex side to a 1-keto group would force the oxygen to the concave side. After the results discussed previously, a 6,7-oxirane was selected as the active group to facilitate the attack of the oxygen through the concave side. A comparison of both processes is depicted in Figure 8.

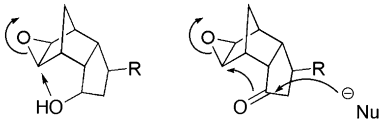
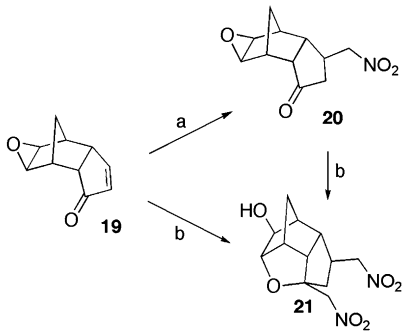



**Figure 8**.

Epoxyketone **19** was required to try the synthesis of type **C** compounds. Treatment of dicyclopentadienone with MCPBA is a chemospecific reaction yielding **19**, which is also obtained as a secondary oxidation product in the treatment of dicyclopentadiene with *tert*-butylhydroperoxide and chromium trioxide. Reaction of **19** with nitromethane-TBAF in aprotic solvents produced the conjugate addition in the same way as was observed for dicyclopentadienone, yielding nitroketone **20**.

Depending on the conditions (Scheme 4), the reaction can be stopped after the monomethylnitration or can be forced to go further to the double methylnitrated product **21**. Alternatively, the nitroketone **20**, once isolated, can be converted into **21**. This compound is a polycyclic material with a rigid geometry and having three attachment points with defined orientations.




**Scheme 4**. (a) $CH_3NO_2$, TBAF, toluene, 3 h, 0 °C. (b) $CH_3NO_2$, TBAF, toluene, 72 h, rt.

In conclusion, a group of interesting transformations has been carried out on the dicyclopentadiene system, allowing us to generate three new types of scaffolds for use in the search for active derivatives. The rigid geometry of this system, with convex and concave sides, is responsible for several particular transformations that were observed. The use of compounds **3**, **8** and **21** as starting materials to prepare derivatives of terpene-like core structures is now under way.

## 3. Experimental

### 3.1. Materials and methods

Reagents were used as purchased without further purification. Solvents (THF, DMF, $CH_2Cl_2$ and benzene) were dried and freshly distilled before use according to literature procedures. Chromatographic separations were performed on silica gel columns by flash (Kieselgel 40, 0.040–0.063; Merck) or gravity column (Kieselgel 60, 0.063–0.200 mm; Merck) chromatography. TLC was performed on precoated silica gel polyester plates (0.25 mm thickness) with fluorescent indicator UV 254 (Polychrom SI $F_{254}$). Melting points were determined on a Buchi 510 apparatus and are uncorrected. $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker WP 200-SY spectrometer at 200/50 MHz or on a Bruker SY spectrometer at 400/100 MHz. Chemical shifts ($\delta$) are given in parts per million downfield from tetramethylsilane as an internal standard and coupling constants ($J$ values) are in

hertz. GC–MS analyses were carried out in a Hewlett–Packard 5890 Series II apparatus (70 eV). For FABHRMS analyses, a VG-TS250 apparatus (70 eV) was used. A Helios-α UV-320 from Thermo-Spectronic was used for UV experiments and absorption spectra. HPLC analysis was carried out on HP-1100 from Agilent Technologies or Delta 600 from Waters instruments, using X-Terra® MS $C_{18}$ 5 μm (4.6×150 mm) and X-Terra® MS $C_8$ 5 μm (4.6×150 mm) columns with water/acetonitrile gradients.

Usual workup: reaction was quenched by the addition of(to) saturated $NaHCO_3$, water or other required agent and organic solvent (usually $CH_2Cl_2$ or EtOAc) followed by washing of the organic phase with saturated NaCl to neutrality. After drying with $Na_2SO_4$ and solvent evaporation crude reaction products were obtained.

**3.1.1. (±)-(1*S*,3a*R*,4*S*,7*R*,7a*R*)-3-Oxo-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-methanoindene-1-carbonitrile (1).** *Procedure A*: to 4.0 g (27.4 mmol) of dicyclopentadienone in 150 mL of dry toluene, 54 mL of 1 M $Et_2AlCN$ in toluene was added at 0 °C under argon and allowed to react for 2 h. Workup by the addition to saturated $NaHCO_3$ and washing with saturated NaCl to neutrality, followed by chromatography ($SiO_2$, hexane/EtOAc 8:2) yielded 284 mg (11%) of oxo-nitrile **1** and 617 mg of the polymeric material **5**.

*Procedure B*: to 74 mL of 1 M $Et_2AlCN$ in toluene under argon at 0 °C, a solution of 5.45 g (37.3 mmol) of dicyclopentadiene ketone in 220 mL of dry toluene was added dropwise (one drop/1 s) and finally allowed to react for 1 h at room temperature. Usual workup and chromatography yielded 1.94 g (30%) of **1**, 545 mg of **5** and 1.49 g (20%) of **6**.

Oxo-nitrile **1**. IR: 3060, 2239, 1732 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): 1.46 (1H, dt, *J*=8.7, 0.9), 1.59 (1H, dt, *J*=8.7, 1.3), 2.36 (1H, dd, *J*=18.4, 10.6), 2.49 (1H, ddd, *J*=18.4, 6.9, 1.5), 2.62 (1H, ddd, *J*=10.6, 6.9, 4.3), 3.05 (1H, ddd, *J*=9.7, 4.6, 0.7), 3.17 (1H, m), 3.19 (1H, m), 3.28 (1H, t, *J*=9.7, 4.3), 6.12 (1H, dd, *J*=5.9, 2.9), 6.16 (1H, dd, *J*=5.9, 2.9). $^{13}C$ NMR (100.5 MHz, $CDCl_3$): 25.7 (d), 44.7 (t), 46.3 (d), 46.5 (d), 46.8 (d), 52.3 (t), 53.8 (d) 122.1 (s), 133.8 (d), 137.9 (d), 214.2 (s). MS *m*/*z* (%): 173 ($M^+$), 66 (100).

Hydroxydicyanide **6**. IR: 3355, 3060, 2254, 1090 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): 1.45 (1H, d, *J*=8.5), 1.62 (1H, d, *J*=8.5), 2.30 (2H, br d), 2.64 (1H, ddd, *J*=6.4, 4.4, 2.0), 3.10 (1H, m), 3.15 (1H, dd, *J*=8.4, 4.0), 3.24 (1H, m), 3.30 (1H, ddd, *J*=8.4, 4.4, 2.0), 6.25 (1H, dd, *J*=5.8, 3.0), 6.35 (1H, dd, *J*=5.8, 3.0). $^{13}C$ NMR (100.5 MHz, $CDCl_3$): 29.4 (d), 46.1 (d), 46.2 (t), 47.1 (d), 51.1 (d), 52.3 (t), 61.0 (d), 74.5 (s), 119.4 (s), 122.3 (s), 135.3 (d), 136.7 (d). MS *m*/*z* (%): 173 (1), 146 (2), 128 (2), 66 (100).

**3.1.2. (±)-(3*R*,3a*R*,4*R*,7*S*,7a*R*)-3-(Nitromethyl)-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-methanoinden-1-one (2).** To 5.0 g (34.1 mmol) of dicyclopentadiene ketone, in 120 mL of dry toluene, 889 mg (3.4 mmol) of TBAF and 160 mL of nitromethane were added. The reaction was maintained at room temperature under argon for 12 h. The crude reaction product was washed with saturated $NaHCO_3$ and brine to neutrality. After evaporation to dryness 6.6 g (93.4%) of pure nitroketone **2** was obtained.

IR: 3059, 1737, 1548 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): 1.29 (1H, d, *J*=8.8), 1.42 (1H, d, *J*=8.8), 1.93 (1H, dd, *J*=18.8, 6.4), 2.13 (1H, dd, *J*=18.8, 9.6), 2.37 (1H, m), 2.63 (1H, dt, *J*=9.6, 4.0), 2.87 (1H, dd, *J*=4.4, 4.0), 2.94 (1H, br s), 3.03 (1H, br s), 4.33 (2H, m), 6.01 (1H, br s), 6.08 (1H, br s). $^{13}C$ NMR (100.5 MHz, $CDCl_3$): 35.0 (d), 44.6 (t), 45.8 (d), 46.3 (d), 46.8 (d), 52.1 (t), 54.7 (d), 79.7 (t), 134.8 (d), 136.6 (d), 217.4 (s). MS *m*/*z* (%): 207 ($M^+$), 66 (100). EA ($C_{11}H_{13}NO_3$) found: 64.06% C, 6.67% H, 6.76% N. Calculated: 63.76% C, 6.32% H, 6.96% N.

**3.1.3. (±)-(1*S*,3*S*,3a*R*,4*R*,7*S*,7a*R*)-3-(Aminomethyl)-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-methanoinden-1-ol (3).** A stirred solution of 10 g (48.3 mmol) of nitroketone **2** in THF (400 mL) was maintained for 1 h under argon, while 9.2 g (241 mmol) of $LiAlH_4$ was slowly added along this time. Once the addition was finished, the reaction mixture was refluxed for additional 1 h. The excess of $LiAlH_4$ was destroyed with AcOEt and then with water, the reaction mixture was washed and evaporated to quantitatively yield compound **3**.

$^1H$ NMR (400 MHz, $CDCl_3$): 1.42 (1H, br d, *J*=8.1), 1.54 (1H, d, *J*=8.1), 1.6–1.9 (3H, m), 2.39 (1H, ddd, *J*=8.4, 4.4, 4.0), 2.57 (1H, dd, *J*=8.4, 3.6), 2.8–2.9 (4H, m), 4.28 (1H, ddd, *J*=7.5, 7.0, 6.2), 6.13 (1H, br s), 6.34 (1H, br s).

**3.1.4. (±)-(1*S*,3*S*,3a*R*,4*R*,7*S*,7a*R*)-3-[(Acetylamino)-methyl]-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-methanoinden-1-yl acetate (4).** The reduced product **3** was acetylated in an acetic anhydride (15 mL) and pyridine (15 mL) mixture. After usual workup the crude product was chromatographed on silica gel column (hexane/EtOAc 1:9), yielding 6.8 g (53.5%) of pure **4**.

IR: 3446, 3059, 1739 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): 1.30 (1H, br d, *J*=8.0), 1.38 (1H, dt, *J*=8.0, 1.8), 1.59 (1H, m), 1.60 (1H, m), 1.66 (1H, m), 1.94 (3H, s), 2.00 (3H, s), 2.34 (1H, ddd, *J*=8.8, 4.0, 3.3), 2.72 (1H, br s), 2.80 (1H, br s), 2.98 (1H, m), 3.01 (1H, m), 3.09 (1H, m), 5.03 (1H, ddd, *J*=8.2, 8.0, 8.0), 6.02 (1H, dd, *J*=5.5, 2.9), 6.10 (1H, dd, *J*=5.5, 2.9). $^{13}C$ NMR (100.5 MHz, $CDCl_3$): 21.2 (c), 23.3 (c), 37.4 (t), 39.0 (d), 45.2 (t), 46.4 (d), 47.2 (d), 49.9 (d), 50.0 (d), 52.5 (t), 75.7 (d), 133.9 (d), 137.5 (d), 170.4 (s), 170.9 (s). MS *m*/*z* (%): 263 ($M^+$), 66 (100). HRMS *m*/*z* ($C_{15}H_{21}NO_3$): 263.1555 (found); 263.1521 (calculated). HPLC Column $C_8$ $t_R$: 5.95 min. Column phenylic $t_R$: 5.34 min.

**3.1.5. (±)-(1*S*,3*S*,3a*R*,4*R*,7*S*,7a*R*)-*N*-[(3-Oxo-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-methanoinden-1-yl)methyl]acetamide (7a).** Compound **4** (500 mg, 1.9 mmol) was dissolved in 10 mL of 10% KOH/MeOH. After 1 h at 40 °C, 439 mg (100%) of **7a** was obtained by the usual workup.

IR: 3307, 1735, 1656 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): 1.40 (1H, d, *J*=8.0), 1.52 (1H, dd, *J*=8.0, 2.0), 1.60 (3H, m), 1.97 (3H, s), 2.37 (1H, dt, *J*=9.6, 4.8), 2.81 (1H, br s), 2.83 (1H, m), 2.90 (1H, br s), 3.09 (1H, ddd, *J*=13.2, 6.0, 5.2), 3.20 (1H, ddd, *J*=13.2, 6.8, 6.4), 4.32 (1H, ddd, *J*=7.2, 7.0, 6.8), 6.10 (1H, dd, *J*=3.2, 1.8), 6.34 (1H, dd, *J*=3.2, 1.8). $^{13}C$ NMR (100.5 MHz, $CDCl_3$): 23.3 (c), 39.4 (d), 41.9 (t), 44.4 (t), 45.0 (d), 45.8 (d), 51.0 (d), 52.5 (d),

53.6 (t), 73.0 (d), 134.3 (d), 137.6 (d), 170.0 (s). MS *m*/*z* (%): 221 ($M^+$), 66(100).

**3.1.6. *tert*-Butyl (±)-(1*S*,3*S*,3a*R*,4*R*,7*S*,7a*R*)-[(3-hydroxy-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-methanoinden-1-yl)-methyl]carbamate (7b).** Over a solution of **3** (2.0 g, 11.2 mmol) in 30 mL of 1:1 dioxane/water (15 mL:15 mL), 2.4 g of di-*tert*-butyl carbonate (11.2 mmol) and 2.0 g of $Na_2CO_3$ were added. The reaction mixture was stirred for 48 h at room temperature. By extraction with $CH_2Cl_2$/water and usual workup 1.9 g (60%) of **7b** was isolated.

$^1$H NMR (400 MHz, $CDCl_3$): 1.41 (1H, d, *J*=8.1), 1.44 (9H, s), 1.53 (1H, d, *J*=8.1), 1.62 (2H, m), 1.68 (1H, m), 2.38 (1H, dt, *J*=9.5, 4.8), 2.81 (1H, m), 2.83 (1H, br s), 2.90 (1H, br s), 2.99 (1H, m), 3.03 (1H, m), 4.30 (1H, ddd, *J*=8.4, 8.0, 8.0), 6.11 (1H, br s), 6.34 (1H, br s). $^{13}$C NMR (100.5 MHz, $CDCl_3$): 28.4 (c), 39.7 (d), 42.0 (t), 45.0 (d), 45.5 (t), 45.8 (d), 51.1 (d), 52.6 (d), 53.7 (t), 73.1 (d), 79.1 (s), 134.6 (d), 137.4 (d), 156.0 (s). MS *m*/*z* (%): 279 ($M^+$), 140 (100). HRMS *m*/*z* ($C_{16}H_{25}NO_{63}$): 279.1839 (found); 279.1834 (calculated). EA ($C_{11}H_{13}NO_3$) found: 68.43% C, 10.28% H, 5.18% N. Calculated: 68.79% C, 9.02% H, 5.01% N. HPLC Column $C_8$ $t_R$: 8.72 min. Column phenylic $t_R$: 9.95 min.

**3.1.7. 9*H*-Fluoren-9-ylmethyl (±)-(1*S*,3*S*,3a*R*,4*R*,7-*S*,7a*R*)-*N*-[(3-hydroxy-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-methanoinden-1-yl)methyl]carbamate (7c).** Over a solution of **3** (2.0 g, 11.17 mmol) in 30 mL of 1:1 dioxane/water, 2.9 g of 9-fluorenylmethyl chloroformiate (11.17 mmol) and 2.0 g of $Na_2CO_3$ were added. The reaction mixture was stirred for 48 h at room temperature. By extraction with $CH_2Cl_2$/water and usual workup 3 g (67%) of **7c** was isolated.

$^1$H NMR (400 MHz, $CDCl_3$): 1.41 (1H, d, *J*=8.1), 1.53 (1H, d, *J*=8.1), 1.60 (3H, m), 2.38 (1H, dt, *J*=9.2, 4.4), 2.81 (2H, br s), 2.91 (1H, br s), 3.08 (1H, m), 3.13 (1H, m), 4.22 (1H, t, *J*=6.7), 4.30 (1H, ddd, *J*=8.4, 8.0, 8.0), 4.43 (2H, d, *J*=6.7), 6.12 (1H, br s), 6.35 (1H, br s), 7.31 (2H, t, *J*=7.5), 7.40 (2H, t, *J*=7.5), 7.59 (2H, d, *J*=7.5), 7.76 (2H, d, *J*=7.5). $^{13}$C NMR (100.5 MHz, $CDCl_3$): 39.7 (d), 41.9 (t), 45.0 (d), 45.8 (d), 45.9 (t), 47.3 (d), 51.0 (d), 52.6 (d), 53.7 (t), 66.5 (t), 73.1 (d), 119.9 (d)×2, 124.9 (d)×2, 126.9 (d)×2, 126.9 (d)×2, 134.5 (d), 137.5 (d), 141.3 (s)×2, 143.9 (s)×2, 156.4 (s). MS *m*/*z* (%): 401 ($M^+$), 66 (100). HRMS *m*/*z* ($C_{26}H_{27}NO_3$): 401.1964 (found); 401.1990 (calculated). HPLC Column $C_8$ $t_R$: 8.72 min. Column phenylic $t_R$: 7.95 min.

**3.1.8. (±)-(1*S*,3*S*,3a*S*,4*S*,5*S*,6*S*,7*R*,7a*S*)-*N*-[(5-Hydroxyperhydro-1,6-epoxy-4,7-methanoinden-3-yl)methyl]acetamide (8a).** *Procedure A*: to 170 mg (0.77 mmol) of **7a** in 5 mL of $CH_2Cl_2$, 192 mg (1.08 mmol) of *meta*-chloroperbenzoic acid and 1.0 g of $Na_2CO_3$ were added. The reaction mixture was stirred at room temperature for 24 h, then washed with saturated sodium thiosulfate and worked up to yield the crude product. Purification by chromatography over silica gel column (hexane/EtOAc 6:4) yielded 108 mg (45%) of **8a**.

*Procedure B*: to an ice-bath cooled solution of 1.3 mL (11.3 mmol) of hexamethyldisilazane (HMDS) in 10 mL of dry THF under argon, 3.5 mL (5.6 mmol) of 1.6 M *n*-BuLi was added. After 10 min, 733 mg (2.8 mmol) of **13** in 10 mL of dry THF was added and maintained for 6 h at room temperature. After addition of water (three drops) and evaporation, 700 mg (100%) of pure **8a** was obtained.

IR: 3306, 1652, 1056 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): 1.50 (1H, ddd, *J*=17.6, 7.2, 4.4), 1.59 (1H, d, *J*=10.4), 1.97 (3H, s), 2.10 (2H, m), 2.20 (3H, m), 2.70 (2H, br s), 3.13 (1H, ddd, *J*=12.8, 6.8, 6.0), 3.20 (1H, ddd, *J*=12.8, 6.8, 6.0), 3.74 (1H, s), 3.97 (1H, d, *J*=4.0), 4.38 (1H, dd, *J*=4.0, 4.0). $^{13}$C NMR (100.5 MHz, $CDCl_3$): 23.2 (c), 36.7 (t), 36.8 (d), 41.9 (t), 44.8 (d), 45.3 (t), 46.7 (d), 49.0 (d), 50.8 (d), 77.3 (d), 84.9 (d), 87.9 (d), 170.4 (s). HPLC Column $C_8$ $t_R$: 2.07 min. Column phenylic $t_R$: 2.43 min.

**3.1.9. *tert*-Butyl (±)-(1*S*,3*S*,3a*S*,4*S*,5*S*,6*S*,7*R*,7a*S*)-*N*-[(5-hydroxyperhydro-1,6-epoxy-4,7-methanoinden-3-yl)methyl]carbamate (8b).** To 1.9 g (6.77 mmol) of **7b** in 50 mL of $CH_2Cl_2$, 1.8 g (10.1 mmol) of *meta*-chloroperbenzoic acid and 1.8 g of $Na_2CO_3$ were added. The reaction mixture was stirred at room temperature for 24 h, then washed with saturated sodium thiosulfate and worked up to yield the crude product. By purification via chromatography over silica gel column (hexane/EtOAc 5:5) 880 mg (44%) of **8b** was isolated.

$^1$H NMR (400 MHz, $CDCl_3$): 1.43 (9H, s), 1.49 (1H, ddd, *J*=17.5, 7.6, 4.5), 1.59 (1H, d, *J*=10.2), 2.10 (2H, m), 2.20 (3H, m), 2.70 (2H, br s), 3.00 (2H, m), 3.75 (1H, s), 3.97 (1H, d, *J*=4.1), 4.38 (1H, dd, *J*=1.6, 1.2). $^{13}$C NMR (100.5 MHz, $CDCl_3$): 28.3 (c), 36.6 (t), 37.2 (d), 41.8 (t), 44.8 (d), 46.3 (t), 46.7 (d), 48.9 (d), 50.7 (d), 77.6 (d), 79.2 (s), 84.9 (d), 87.9 (d), 156.1 (s). MS *m*/*z* (%): 295 ($M^+$), 84 (100). EA ($C_{16}H_{25}NO_4$) found: 61.11% C, 10.8% H, 4.05% N. Calculated: 65.06% C, 8.53% H, 4.74% N. HPLC Column $C_8$ $t_R$: 5.01 min. Column phenylic $t_R$: 4.46 min.

**3.1.10. 9*H*-Fluoren-9-ylmethyl (±)-(1*S*,3*S*,3a*S*,4*S*,5*S*,6*S*,7*R*,7a*S*)-*N*-[(5-hydroxyperhydro-1,6-epoxy-4,7-methanoinden-3-yl)methyl]carbamate (8c).** To 278 mg (0.69 mmol) of **7c** in 25 mL of $CH_2Cl_2$, 179 mg (1.01 mmol) of MCPBA and 300 mg of $Na_2CO_3$ were added. The reaction mixture was stirred for 24 h, then extracted with saturated sodium thiosulfate and worked up, yielding after flash chromatography (EtOAc) 104 mg (36%) of **8c**.

$^1$H NMR (400 MHz, $CDCl_3$): 1.49 (1H, m), 1.61 (1H, d, *J*=9.2), 2.10 (2H, m), 2.2 (3H, m), 2.70 (2H, br s), 3.13 (2H, br s), 3.76 (1H, s), 3.98 (1H, d, *J*=4.8), 4.21 (1H, t, *J*=6.4), 4.39 (1H, br s), 4.43 (2H, d, *J*=6.4), 7.29 (2H, t, *J*=7.2), 7.40 (2H, t, *J*=7.2), 7.59 (2H, d, *J*=7.2), 7.76 (2H, d, *J*=7.2). $^{13}$C NMR (100.5 MHz, $CDCl_3$): 36.6 (t), 37.2 (d), 41.7 (t), 44.8 (d), 46.7 (t), 46.8 (d), 47.3 (d), 48.9 (d), 50.7 (d), 66.5 (t), 77.6 (d), 84.9 (d), 87.9 (d), 119.9 (d)×2, 124.9 (d)×2, 127.0 (d)×2, 127.6 (d)×2, 141.3 (s)×2, 143.9 (s)×2, 156.5 (s). EA ($C_{26}H_{27}NO_4$) found: 73.92% C, 6.24% H, 3.23% N. Calculated: 74.8% C, 6.52% H, 3.35% N. HPLC Column $C_8$ $t_R$: 9.58 min. Column phenylic $t_R$: 9.47 min.

**3.1.11. (±)-(1*S*,3*S*,3a*R*,4*S*,6*S*,7*R*,7a*S*)-*N*-[(5-Oxo-perhydro-1,6-epoxy-4,7-methanoinden-3-yl)methyl]acetamide (9a).** To cooled (−60 °C) $CH_2Cl_2$ (15 mL) under argon, a

2 M solution of oxalyl chloride (2.64 mL, 5.27 mmol) in $CH_2Cl_2$ and DMSO (0.75 mL, 10.54 mmol) in 5 mL of $CH_2Cl_2$ was successively added. After 10 min, 500 mg (2.11 mmol) of **8a** in 10 mL of $CH_2Cl_2$ and 1 mL of DMSO (freshly distilled) was slowly added. The mixture was allowed to react for 20 min and, after the addition of 1.76 mL (12.6 mmol) of $Et_3N$, for 2 h at room temperature. The reaction mixture was washed with 2 M HCl and saturated $NaHCO_3$, yielding 297 mg (60%) of pure **9a** after flash chromatography on silica gel column ($CH_2Cl_2$/MeOH 95:5).

$^1$H NMR (400 MHz, $CDCl_3$): 1.54 (1H, ddd, $J$=14.0, 9.2, 3.6), 1.79 (1H, d, $J$=11.2), 1.84 (1H, m), 1.90 (1H, d, $J$=11.2), 1.94 (3H, s), 2.13 (1H, dd, $J$=14.0, 7.6), 2.41 (1H, br d, $J$=3.6), 2.45 (1H, m), 3.00 (1H, m), 3.01 (1H, ddd, $J$=13.3, 6.8, 6.4), 3.02 (1H, d, $J$=4.4), 3.32 (1H, ddd, $J$=13.3, 6.8, 6.4), 3.84 (1H, d, $J$=4.4), 4.54 (1H, br s). $^{13}$C NMR (100.5 MHz, $CDCl_3$): 23.1 (c), 32.6 (t), 39.8 (d), 41.2 (t), 44.0 (t), 44.8 (d), 47.5 (d), 50.6 (d), 50.9 (d), 81.7 (d), 85.8 (d), 170.4 (s), 212.7 (s). MS *m*/*z* (%): 235 ($M^+$), 126 (100). HPLC Column $C_8$ $t_R$: 7.25 min. Column phenylic $t_R$: 7.14 min.

**3.1.12. *tert*-Butyl (±)-(1*S*,3*S*,3a*R*,4*S*,6*S*,7*R*,7a*S*)-*N*-[(5-oxoperhydro-1,6-epoxy-4,7-methanoinden-3-yl)methyl]carbamate (9b).** To cooled (−60 °C) $CH_2Cl_2$ (15 mL) under argon, a 2 M solution of oxalyl chloride (3.05 mL, 6.1 mmol) in $CH_2Cl_2$ and DMSO (0.87 mL, 12.20 mmol) in 5 mL of $CH_2Cl_2$ was successively added. After 10 min, 600 mg (2.03 mmol) of **8b** in 10 mL of $CH_2Cl_2$ was slowly added. The mixture was allowed to react for 20 min and, after the addition of 3.30 mL (24.0 mmol) of $Et_3N$, for 2 h at room temperature. The reaction mixture was washed with 2 M HCl and saturated $NaHCO_3$, yielding 277 mg (47%) of pure **9b** after flash chromatography on silica gel column (hexane/EtOAc 5:5).

$^1$H NMR (400 MHz, $CDCl_3$): 1.40 (9H, s), 1.56 (1H, ddd, $J$=14.2, 9.2, 3.7), 1.80 (1H, d, $J$=11.4), 1.86 (1H, m), 1.90 (1H, d, $J$=11.4), 2.16 (1H, dd, $J$=14.2, 7.6), 2.43 (1H, d, $J$=4.6), 2.47 (1H, m), 3.00 (1H, d, $J$=5.0), 3.02 (1H, m), 3.07 (1H, m), 3.11 (1H, m), 3.86 (1H, d, $J$=5.0), 4.56 (1H, dd, $J$=4.0, 4.0). $^{13}$C NMR (100.5 MHz, $CDCl_3$): 28.3 (c), 32.6 (t), 40.1 (d), 40.9 (t), 44.8 (d), 45.2 (t), 47.4 (d), 50.6 (d), 50.8 (d), 79.3 (s), 81.6 (d), 85.8 (d), 156.2 (s), 212.5 (s). MS *m*/*z* (%): 293 ($M^+$), 84 (100). EA ($C_{16}H_{25}NO_4$) found: 65.39% C, 8.11% H, 4.62% N. Calculated: 65.5% C, 7.9% H, 4.77% N. HPLC: Column $C_8$ $t_R$: 6.97 min. Column phenylic $t_R$: 6.35 min.

**3.1.13. 9*H*-Fluoren-9-ylmethyl (±)-(1*S*,3*S*,3a*R*,4*S*,6*S*,7*R*,7a*S*)-*N*-[(5-oxoperhydro-1,6-epoxy-4,7-methanoinden-3-yl)methyl]carbamate (9c).** To cooled (−60 °C) $CH_2Cl_2$ (15 mL) under argon, a 2 M solution of oxalyl chloride (3.24 mL, 6.47 mmol) in $CH_2Cl_2$ and DMSO (0.92 mL, 13 mmol) in 5 mL of $CH_2Cl_2$ was successively added. After 10 min, 900 mg (2.16 mmol) of **8c** in 10 mL of $CH_2Cl_2$ was slowly added. The mixture was allowed to react for 20 min and, after the addition of 3.60 mL (26.0 mmol) of $Et_3N$, for 2 h at room temperature. The reaction mixture was washed with 2 M HCl and saturated $NaHCO_3$, yielding 625 mg (70%) of pure **9c** after flash chromatography on silica gel column (hexane/EtOAc 5:5).

$^1$H NMR (400 MHz, $CDCl_3$): 1.54 (1H, ddd, $J$=10.4, 9.2, 3.6), 1.83 (1H, d, $J$=11.2), 1.90 (1H, m), 1.92 (1H, d, $J$=11.2), 2.19 (1H, dd, $J$=10.4, 7.6), 2.42 (1H, s), 2.46 (1H, m), 3.03 (1H, m), 3.06 (1H, d, $J$=5.2), 3.15 (1H, ddd, $J$=13.3, 7.4, 6.8), 3.22 (1H, ddd, $J$=13.3, 7.4, 6.8), 3.90 (1H, d, $J$=5.2), 4.20 (1H, t, $J$=6.8), 4.42 (2H, d, $J$=6.8), 4.83 (1H, br s), 7.31 (2H, t, $J$=7.4), 7.40 (2H, t, $J$=7.4), 7.58 (2H, d, $J$=7.4), 7.76 (2H, d, $J$=7.4). $^{13}$C NMR (100.5 MHz, $CDCl_3$): 32.7 (t), 40.0 (d), 41.0 (t), 44.8 (d), 45.6 (t), 47.2 (d), 47.3 (d), 50.7 (d), 50.8 (d), 66.5 (t), 81.7 (d), 85.8 (d), 119.9 (d)×2, 124.9 (d)×2, 127.0 (d)×2, 127.6 (d)×2, 141.3 (s)×2, 143.8 (s)×2, 156.6 (s), 212.5 (s). EA ($C_{26}H_{25}NO_4$) found: 74.88% C, 5.95% H, 3.27% N. Calculated: 75.16% C, 6.06% H, 3.37% N. HPLC Column $C_8$ $t_R$: 10.61 min. Column phenylic $t_R$: 10.46 min.

**3.1.14. *tert*-Butyl (±)-(1*S*,3*S*,3a*S*,4*S*,5*R*,6*S*,7*R*,7a*S*)-*N*-[(5-hydroxyperhydro-1,6-epoxy-4,7-methanoinden-3-yl)methyl]carbamate (10).** To 90 mg (0.31 mmol) of **9b** and 90 mg (3.3 mmol) of Al in dry benzene/abs EtOH (3 mL:3 mL), a small amount of $HgCl_2$ was added. The reaction mixture was refluxed under argon for 4 h, then diluted with EtOAc and treated with $Na_2SO_4$/$Na_2CO_3$ (3 g:3 g). Once filtered and evaporated 60 mg (62%) of **10** was obtained.

$^1$H NMR (400 MHz, $CDCl_3$): 1.34 (1H, d, $J$=10.8), 1.43 (9H, s), 1.47 (1H, d, $J$=10.8), 1.58 (1H, ddd, $J$=11.1, 6.8, 6.0), 2.16 (1H, br s), 2.29 (1H, m), 2.30 (1H, dd, $J$=11.1, 8.1), 2.88 (3H, m), 2.97 (2H, m), 3.74 (1H, br d, $J$=6.0), 4.12 (1H, dd, $J$=6.0, 5.0), 4.47 (1H, dd, $J$=4.1, 4.1). $^{13}$C NMR (100.5 MHz, $CDCl_3$): 28.3 (c), 34.9 (t), 36.6 (d), 40.7 (d), 41.4 (t), 46.9 (t), 47.4 (d), 51.1 (d), 51.2 (d), 75.0 (d), 78.5 (d), 79.1 (s), 85.3 (d), 156.1 (s). MS *m*/*z* (%): 295 ($M^+$), 178 (100).

**3.1.15. (±)-(1*S*,3*S*,3a*R*,4*S*,7*R*,7a*R*)-*N*-{[3-(*tert*-Butyl(dimethyl)siloxy)-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-methanoinden-1-yl]methyl}acetamide (11).** To 300 mg (1.36 mmol) of **7a** in 20 mL of dry $CH_2Cl_2$, 0.63 mL (2.72 mmol) of TBDMSOTf, 250 mg (2.05 mmol) of DMAP and 0.29 mL (2.05 mmol) of $Et_3N$ were added. The reaction mixture was stirred at room temperature under argon for 5 h, then washed with saturated $NaHCO_3$, 2 N HCl and water. Compound **11** (349 mg, 77%) was purified by flash chromatography.

IR: 3287, 1651, 837 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): −0.01 (3H, s), 0.04 (3H, s), 0.88 (9H, s), 1.26 (1H, d, $J$=7.6), 1.35 (1H, d, $J$=7.6), 1.45 (1H, ddd, $J$=12.8, 10.0, 2.4), 1.5–1.7 (2H, m), 1.97 (3H, s), 2.28 (1H, ddd, $J$=8.8, 4.4, 2.4), 2.76 (1H, ddd, $J$=8.8, 8.4, 2.4), 2.78 (1H, br s), 2.82 (1H, br s), 2.97 (1H, m), 3.11 (1H, m), 4.28 (1H, ddd, $J$=8.4, 8.0, 7.6), 5.96 (1H, dd, $J$=5.6, 3.2), 6.21 (1H, dd, $J$=5.6, 2.8). $^{13}$C NMR (100.5 MHz, $CDCl_3$): −4.8 (c), −4.9 (c), 18.0 (s), 23.3 (c), 25.8 (c), 39.0 (d), 40.7 (t), 45.2 (t), 45.9 (d), 46.7 (d), 49.7 (d), 51.7 (t), 52.1 (d), 73.2 (d), 132.4 (d), 138.8 (d), 170.1 (s). MS *m*/*z* (%): 335 ($M^+$), 278 (100). HPLC Column $C_8$ $t_R$: 13.93 min. Column phenylic $t_R$: 12.11 min.

**3.1.16. (±)-(1*S*,3*S*,3a*S*,4*R*,5*R*,6*S*,7*S*,7a*S*)-*N*-[(3-(*tert*-Butyldimethylsiloxy)-perhydro-5,6-epoxy-4,7-methanoinden-1-yl)methyl]acetamide (12).** To a solution of 900 mg (2.68 mmol) of **11** in 25 mL of $CH_2Cl_2$, 600 mg (3.48 mmol)

of MCPBA and 600 mg of $Na_2CO_3$ were added. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was thoroughly washed with sodium thiosulfate and worked up to yield 528 mg (75%) of **12**.

$^1$H NMR (400 MHz, $CDCl_3$): −0.03 (3H, s), −0.01 (3H, s), 0.76 (1H, d, *J*=9.8), 0.85 (9H, s), 1.40 (1H, d, *J*=9.8), 1.8–2.2 (4H, m), 1.90 (3H, s), 2.04 (1H, s), 2.44 (1H, br s), 2.52 (1H, br s), 2.74 (1H, ddd, *J*=9.6, 4.6, 4.4), 2.94 (1H, m), 3.08 (1H, m), 3.22 (1H, br d, *J*=3.3), 3.41 (1H, br d, *J*=3.3), 5.09 (1H, ddd, *J*=8.8, 8.4, 8.2).

**3.1.17. (±)-(1*S*,3*S*,3a*S*,4*S*,5*S*,6*R*,7*R*,7a*S*)-3-Acetamidomethylperhydro-5,6-epoxy-4,7-methanoinden-1-yl acetate (13).** To a solution of 500 mg (1.90 mmol) of **4** in 20 mL of $CH_2Cl_2$, 656 mg (3.80 mmol) of MCPBA and 600 mg of $Na_2CO_3$ were added. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was thoroughly washed with sodium thiosulfate and worked up to yield 491 mg (98%) of **13**.

$^1$H NMR (400 MHz, $CDCl_3$): 0.76 (1H, d, *J*=9.8), 1.40 (1H, d, *J*=9.8), 1.8–2.2 (4H, m), 1.93 (3H, s), 2.05 (3H, s), 2.44 (1H, br s), 2.52 (1H, br s), 2.74 (1H, ddd, *J*=9.6, 4.6, 4.4), 2.94 (1H, m), 3.08 (1H, m), 3.22 (1H, br d, *J*=3.3), 3.41 (1H, br d, *J*=3.3), 5.09 (1H, ddd, *J*=8.8, 8.4, 8.2). $^{13}$C NMR (100.5 MHz, $CDCl_3$): 21.1 (c), 23.1 (c), 29.1 (t), 36.1 (d), 37.7 (t), 40.5 (d), 40.7 (d), 44.6 (t), 47.4 (d), 48.2 (d), 49.9 (d), 50.2 (d), 75.1 (d), 170.7 (s)×2.

**3.1.18. (±)-(1*S*,3*S*,3a*S*,4*S*,5*S*,6*S*,7*R*,7a*S*)-3-Acetamidomethylperhydro-1,6-epoxy-4,7-methanoinden-5-yl acetate (14).** To 79 mg (3 mmol) of NaH under argon, 12 mL of dry THF followed by 79 mg (0.3 mmol) of **13** in 8 mL of dry THF and 0.13 mL (0.45 mmol) of TBAF were added. After stirring for 15 h at room temperature the excess of NaH was destroyed with water and the reaction mixture was diluted with water and $CH_2Cl_2$, the aqueous layer was acetylated with $Ac_2O$ and pyridine, yielding 9.2 mg (11%) of **14**.

IR: 3306, 1731, 1625, 1030 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): 1.64 (1H, d, *J*=10.6), 1.94 (1H, d, *J*=10.6), 1.98 (3H, s), 2.04 (3H, s), 2.1–2.3 (5H, m), 2.77 (2H, br s), 3.14 (1H, m), 3.32 (1H, m), 4.11 (1H, s), 4.42 (1H, d, *J*=3.7), 4.61 (1H, s). $^{13}$C NMR (100.5 MHz, $CDCl_3$): 21.2 (c), 23.3 (c), 36.9 (t), 37.2 (d), 41.8 (t), 42.7 (d), 45.0 (t), 46.9 (d), 49.0 (d), 50.7 (d), 80.2 (d), 85.1 (d), 85.4 (d), 170.3 (s), 170.4 (s). MS *m*/*z* (%): 279 ($M^+$), 66 (100). HPLC Column $C_8$ $t_R$: 2.72 min. Column phenylic $t_R$: 2.85 min.

**3.1.19. (±)-(1*S*,3*S*,3a*R*,4*R*,7*S*,7a*R*)-3-Acetamidomethyl-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-methanoinden-1-yl phenylselenocarbonate (16).** To 200 mg of **7a** (0.90 mmol) in 10 mL of dry THF, 3 mL (5.43 mmol) of $COCl_2$ was slowly added, followed by 0.5 mL (2.7 mmol) of $Et_3N$. After 2 h at room temperature the solvent was evaporated and the residue was dissolved in benzene/pyridine (3 mL:3 mL). After the addition of 200 μL (1.89 mmol) of phenylselenol the reaction was maintained for 20 h at room temperature and then worked up to yield 179 mg of crude reaction product **16**.

$^1$H NMR (400 MHz, $CDCl_3$): 1.32 (1H, d, *J*=8.8), 1.42 (1H, d, *J*=8.8), 1.6–1.8 (3H, m), 1.96 (3H, s), 2.36 (1H, dt, *J*=8.8, 4.0), 2.75 (1H, br s), 2.82 (1H, br s), 2.97 (1H, m), 3.05 (1H, m), 3.20 (1H, m), 5.26 (1H, ddd, *J*=8.0, 7.6, 6.2), 6.05 (1H, br s), 6.05 (1H, br s), 7.36 (3H, m), 7.61 (2H, m). $^{13}$C NMR (100.5 MHz, $CDCl_3$): 23.3 (c), 37.3 (t), 39.0 (d), 44.5 (t), 45.8 (d), 46.6 (d), 49.9 (d), 49.9 (d), 52.6 (t), 80.4 (d), 129.3 (d)×3, 133.9 (d), 134.2 (s), 135.9 (d)×2, 137.6 (d), 166.4 (s), 170.4 (s).

To 75 mg (0.18 mmol) of crude product **16** in 7 mL of dry benzene, 7 mg (0.04 mmol) of AIBN and 61.5 μL (0.2 mmol) of tris(trimethylsilyl)silane in 3 mL of dry benzene were added. Once degasified the reaction mixture was refluxed for 30 h. After usual workup, no reaction products could be detected in the crude product or after chromatography.

**3.1.20. (±)-(1*S*,3*S*,3a*R*,4*R*,7*S*,7a*R*)-*N*-{[3-(Bromomethyl-(dimethyl)siloxy)-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-methanoinden-1-yl]methyl}acetamide (17).** To 500 mg (2.27 mmol) of **3** in 25 mL of dry $CH_2Cl_2$ under argon were successively added 415 mg of DMAP (3.4 mmol), 47.4 μL (3.4 mmol) of $Et_3N$ and 465 μL (3.4 mmol) of BMDMSCl, and allowed to react for 5 h. The reaction mixture was washed with water and worked up to yield 742 mg (88%) of **17**.

$^1$H NMR (400 MHz, $CDCl_3$): 0.25 (3H, s), 0.25 (3H, s), 1.34 (1H, br d, *J*=8.1), 1.44 (1H, d, *J*=8.1), 1.6–1.8 (3H, m), 2.06 (3H, s), 2.30 (1H, m), 2.44 (2H, s), 2.8–2.9 (5H, m), 4.33 (1H, m), 6.00 (1H, br s), 6.21 (1H, br s).

To 100 mg (0.27 mmol) of bromosilylated product **17** in dry benzene (10 mL), 27.6 mg (0.16 mmol) of AIBN and 122.8 (0.35 mmol) of triphenyltin hydride in 5 mL of dry benzene were added. The mixture was degassed and refluxed for 20 h, then passed through silica gel and evaporated. The reduced trimethylsilyl derivative **18** was the only product detected (not isolated) in the crude of the reaction.

**3.1.21. (±)-(3a*S*,4*S*,5*S*,6*R*,7*R*,7a*S*)-3a,4,5,6,7,7a-Hexahydro-1*H*-5,6-epoxy-4,7-methanoinden-1-one (19).** Obtained by direct epoxidation of dicyclopentadienone or as a by-product of the allylic oxidation of dicyclopentadiene.

IR: 3040, 1700 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): 1.15 (1H, d, *J*=9.2), 1.64 (1H, d, *J*=9.2), 2.76 (2H, br s), 2.90 (2H, br s), 3.15 (1H, br s), 3.41 (1H, m), 6.15 (1H, d, *J*=5.6), 7.57 (1H, dd, *J*=5.6, 2.6). $^{13}$C NMR (100.5 MHz, $CDCl_3$): 29.7 (t), 36.8 (d), 38.1 (d), 47.6 (d), 48.2 (d), 49.3 (d), 50.5 (d), 135.8 (d), 163.1 (d), 208.3 (s). HPLC Column $C_8$ $t_R$: 2.60 min. Column phenylic $t_R$: 2.68 min.

**3.1.22. (±)-(3*S*,3a*S*,4*S*,5*S*,6*R*,7*R*,7a*S*)-3-Nitromethylperhydro-5,6-epoxy-4,7-methanoinden-1-one (20).** To 500 mg (3.08 mmol) of epoxyketone **19** in 20 mL of dry toluene, 78 mg (0.3 mmol) of tetrabutylammonium fluoride and 15 mL of nitromethane were added. The reaction was maintained at 0 °C, under argon for 3 h. After usual workup 545 mg (79%) of nitrated product **20** was isolated.

IR: 2973, 1732, 1549 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): 0.88 (1H, d, *J*=10.0), 1.49 (1H, d, *J*=10.0), 2.28 (1H, dd, *J*=18.7, 7.3), 2.53 (1H, dd, *J*=18.7, 13.3), 2.59 (1H, d,

$J$=10.2), 2.68 (1H, d, $J$=2.8), 2.83 (1H, br s), 2.85 (1H, br s), 2.97 (1H, m), 3.13 (1H, d, $J$=2.6), 3.28 (1H, d, $J$=2.6), 4.41 (2H, d, $J$=7.2). $^{13}$C NMR (100.5 MHz, $CDCl_3$): 29.4 (t), 32.0 (d), 40.2 (d), 40.4 (d), 45.4 (d), 46.9 (d), 48.4 (d), 48.8 (d), 53.1 (d), 79.8 (t), 215.3 (s). MS *m/z* (%): 223 ($M^+$), 82 (100). EA ($C_{11}H_{13}NO_4$) found: 59.43% C, 5.87% H, 5.82% N. Calculated: 59.19% C, 5.87% H, 6.27% N. HPLC Column $C_8$ $t_R$: 4.08 min. Column phenylic $t_R$: 4.15 min.

**3.1.23. (±)-(1*S*,3*S*,3a*S*,4*S*,5*S*,6*S*,7*R*,7a*S*)-1,3-Bis(nitromethyl)-perhydro-1,6-epoxy-4,7-methanoinden-5-ol (21).** To 500 mg (3.08 mmol) of epoxyketone **19** in 20 mL of dry toluene, 78 mg (0.3 mmol) of tetrabutylammonium fluoride and 15 mL of nitromethane were added. The reaction was maintained at room temperature, under argon for 72 h. After usual workup 598 mg (68%) of dinitrated product **21** was isolated.

IR: 3407, 1548, 1022 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): 1.63 (1H, d, $J$=10.9), 1.79 (1H, dd, $J$=14.3, 9.2), 2.16 (1H, d, $J$=10.9), 2.25 (1H, br s), 2.27 (1H, m), 2.49 (1H, m), 2.81 (1H, dd, $J$=5.1, 5.0), 2.87 (1H, m), 2.90 (1H, m), 3.92 (1H, br s), 4.13 (1H, d, $J$=5.1), 4.34 (1H, dd, $J$=12.8, 8.3), 4.40 (1H, dd, $J$=12.8, 6.4), 4.45 (1H, d, $J$=11.4), 4.49 (1H, d, $J$=11.4). $^{13}$C NMR (100.5 MHz, $CDCl_3$): 34.5 (d), 36.5 (t), 43.2 (t), 44.4 (d), 45.7 (d), 49.1 (d), 53.4 (d), 76.9 (d), 79.5 (t), 80.8 (t), 88.6 (d), 90.5 (s). MS *m/z* (%): 284 ($M^+$), 84 (100). EA ($C_{12}H_{16}N_2O_6$) found: 50.51% C, 6.60% H, 8.87% N. Calculated: 50.70% C, 5.67% H, 9.85% N. HPLC Column $C_8$ $t_R$: 3.88 min. Column phenylic $t_R$: 4.04 min.

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