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Two chemodivergent anionic domino processes from cyclic α-nitroketones and aromatic aldehydes

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ABSTRACT

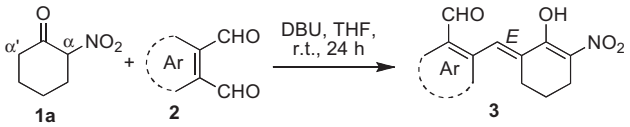
Treatment of cyclic α-nitroketones and aromatic 1,2-dialdehydes with DBU in tetrahydrofuran containing small amounts of water proceeded through two chemodivergent one-pot domino pathways, whose outcome depended on the ring size of the starting nitroketone. Thus, α-nitrocyclohexanone underwent diastereoselective α′-arylmethylenation reactions through a nitroaldol/aldol/reverse nitroaldol mechanism. On the other hand, α-nitrocycloheptanone and α-nitrocyclooctanone afforded 2-nitroindane-1,2-diols containing three contiguous stereocenters in a highly diastereoselective fashion through a nitroaldol/retro-Dieckmann/intramolecular nitroaldol process.

1. Introduction

The search for chemodivergent reactions is one of the keys for the success of the current bid for methods able to generate molecular diversity and complexity from simple and inexpensive starting materials, ideally in a single step. This type of chemistry is often considered as one of the most promising paradigms of drug discovery and has also become one of the main challenges for current organic synthesis.[1] Domino reactions, in which several transformations are combined in a one-pot procedure so that each individual step leads to a reactive species that undergoes further transformations under the same reaction conditions, are particularly promising as a pathway to molecular diversity and are finding increasing applications in organic synthesis,[2] including the total synthesis of natural products.[3] We describe here two chemodivergent, synthetically useful anionic domino processes based on the DBU-promoted reactions between cyclic α-nitroketones and aromatic aldehydes, with special emphasis on 1,2-dialdehydes, which were discovered in the course of our research into the synthetic applications of α-nitroketone anions.[4]

2. Results and discussion

As shown in Scheme 1, treatment of α-nitrocyclohexanone **1a** with several aromatic 1,2-dicarbaldehyde derivatives **2**[5] in THF containing DBU at room temperature for 24 h afforded compounds **3** as the only products, in good to excellent yields (see also Fig. 1).[6]



1a 2 3

Scheme 1.

These compounds have a particular value as synthetic building blocks in view of the synthetic relevance of α-nitroketones[7] and their high degree of functionalization, both at the carbocyclic and aromatic fragments. The reaction was found to be completely regioselective in favour of the α′ position of the starting nitroketone and gave exclusively compounds with an *E* geometry at the exocyclic double bond, as shown by NOE effects in compound **3a**, although in the case of compound **3c** some *E* to *Z* isomerization during column chromatography could not be avoided. The use of nonsymmetric starting aldehydes, namely 3-chlorophthalaldehyde and thiophene-1,2-dicarbaldehyde, led to the isolation of mixtures of regioisomers arising from reaction at either of the aldehyde groups (compounds **3d**, **e** and **3f**, **g**, respectively). This is an interesting transformation because it constitutes the first one-step α′-arylmethylenation of an α-nitroketone. The better-studied, related process consisting of the γ-alkenylidenation of β-dicarbonyl compounds is also a difficult synthetic problem, which has been solved only rather recently. Thus, Rodriguez has shown that the reaction between cyclic β-ketoesters and β-ketoamides and aldehydes in the presence of DBU in methanol affords γ-methylidene derivatives of the starting material,[8] which were subsequently employed as starting materials for the preparation of spiro compounds[9] and fused heterocycles.[10]

In order to provide some information on the mechanism of the above-mentioned transformation while increasing its synthetic

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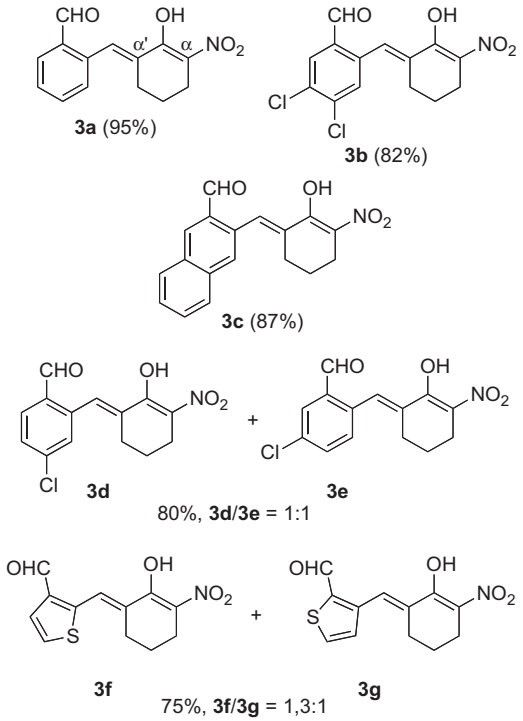
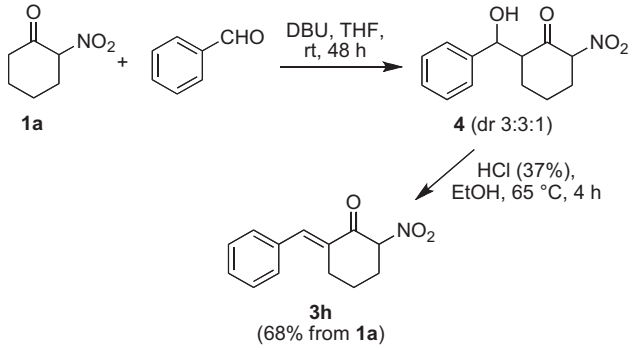


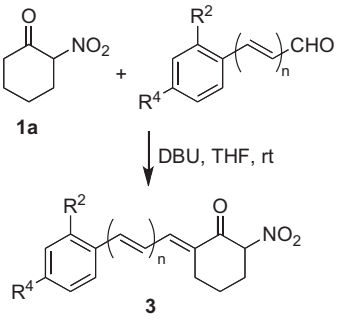
Fig. 1. Scope and yields of the arylmethylenation reactions with o-dialdehydes.

scope, we explored some related reactions involving the use of monofunctional aldehydes. Treatment of α-nitrocyclohexanone **1a** with benzaldehyde under the conditions used for the phthalaldehyde derivatives did not afford an arylmethylenation product, but instead gave the aldol adduct **4** as a 3:3:1 mixture of diastereomers (Scheme 2). In order for this reaction to go to completion, the use of 2 equiv of aldehyde was required, and an experiment starting from equimolecular amounts of **1a** and benzaldehyde proceeded only in 50% conversion. In an effort to adapt these conditions to the synthesis of α′-arylmethylene derivatives, we studied a number of acidic conditions for the elimination of water from compound **4**, and found that its treatment, in crude state, with HCl in EtOH–H_2O at 65 °C for 4 h gave compound **3h** in 68% overall yield from **1a** (Scheme 2).



Scheme 2.

Having in mind the objective of carrying out the arylmethylenation as a one-pot transformation, we did some experimentation with basic media for the elimination step, and discovered that the best results were obtained by simply increasing the reaction time between the starting α-nitroketones and aldehydes, which led to a mild and efficient, if quite slow, DBU-promoted elimination reaction, leading to compounds **3i**–**l** in 60–90% yields. Not unexpectedly, the addition steps of these reactions were sensitive to the nature of the substituents on the aromatic ring, and did not take place at a synthetically feasible rate when electron-releasing groups were present. Due to the scarcity of literature precedent for the generation of cyclic carbonyl compounds functionalized at α′ with chains showing extended conjugation,[8b] we also examined some reactions starting from cinnamaldehyde derivatives, which gave compounds **3j**–**l** (Scheme 3 and Table 1).

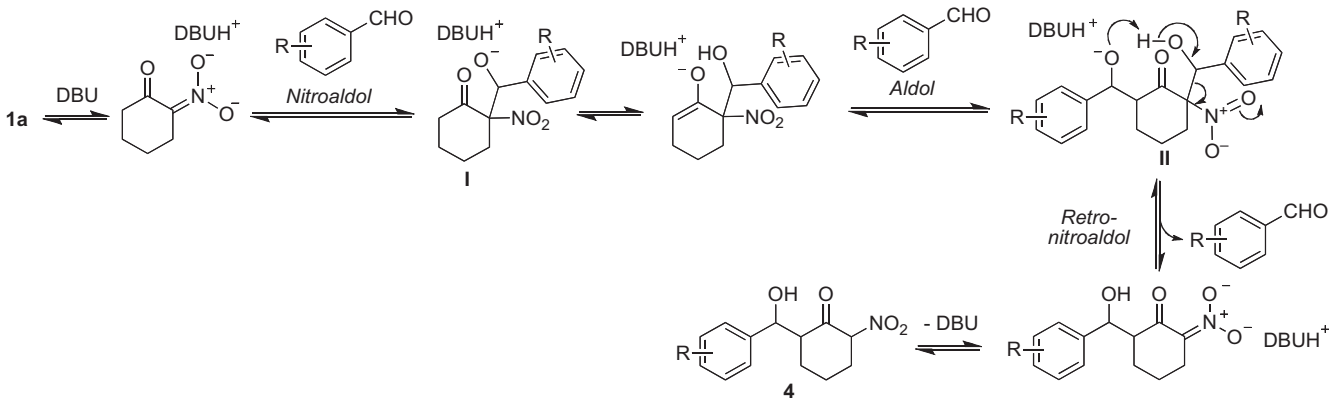


Scheme 3.

Table 1
One-pot synthesis of α′-arylmethylene derivatives of α-nitrocyclohexanone

Compd	*n*	R^2	R^4	Time	Yield, %
3i	0	H	NO_2	4d	88
3j	1	H	H	6d	60
3k	1	NO_2	H	5d	90
3l	1	H	NO_2	5d	85

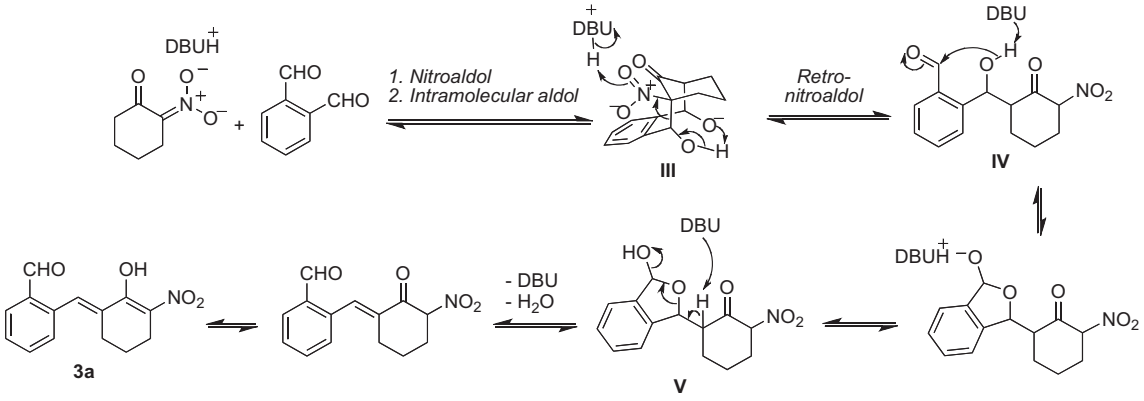
In order to rationalize our observations, the isolation of compound **4** must be explained in the first place. To this end, we propose the mechanism summarized in Scheme 4. The first reaction to take place would be a nitroaldol addition at the more reactive α position leading to **I**, which would be followed by intramolecular proton exchange, involving deprotonation of the α position, and an aldol reaction with a second molecule of aldehyde to give **II**. A final retro-nitroaldol reaction, with loss of one molecule of aldehyde, would explain the generation of **4**. This mechanism explains the need for at least 2 equiv of aldehyde for the reaction to go to completion and the isolation of equimolecular amounts of **4** and **1a** in the reaction using only 1 equiv of aldehyde. TLC monitoring of the reactions showed the formation of several intermediate spots, but the plates were too complex to allow any mechanistic conclusion other than the involvement of a multi-step mechanism. Furthermore, none of the proposed intermediates could be isolated. However, in an effort to further clarify the mechanism, we studied the reaction between 2-benzyl-2-nitrocyclohexanone (obtained by alkylation of 2-nitrocyclohexanone with benzyl bromide in the presence of DBU, see Supplementary data) and *o*-phthalaldehyde or *p*-nitrobenzaldehyde under our reaction conditions. While the expected α′-functionalization took place, in agreement with the proposed mechanism, these reactions afforded open-chain products generated via a retro-Dieckmann-type reaction prompted by the high stability of the nitronate anion, with a hydroxide anion (generated from DBU and traces of moisture in the reaction medium) acting as the nucleophile. This was proved by examination of the ^{13}C NMR spectra of the crude reaction products, which showed the absence of the ketone carbonyl, the presence of a carboxy carbonyl and a 10 ppm upfield displacement of the Cα-NO_2 signal, which is now a methine according to the DEPT experiment. The higher stability of intermediate **I** towards this ring opening must be attributed to its negative charge, which means that the retro-Dieckmann reaction would have a dianion as an intermediate.



Scheme 4.

In the original reactions starting from 1 equiv of phthalaldehyde derivatives (Scheme 5), the presence of two aldehyde groups in each molecule of the starting material would allow a mechanism similar to the one in operation in the presence of 2 equiv of benzaldehyde, although in this case a cyclic intermediate (**III**) would be generated and evolve to **IV** by a retro-nitroaldol mechanism. The facile isolation of elimination products **3** in these reactions rather than aldol adducts similar to **4**, even for short reaction times, must be due to the presence of the *ortho* aldehyde group, and can be explained by the likely tendency of the γ-hydroxycarbonyl moiety of **IV** to undergo an intramolecular cyclization leading to hemiacetal **V**, which would then be transformed into the **3a** by a DBU-induced elimination reaction.

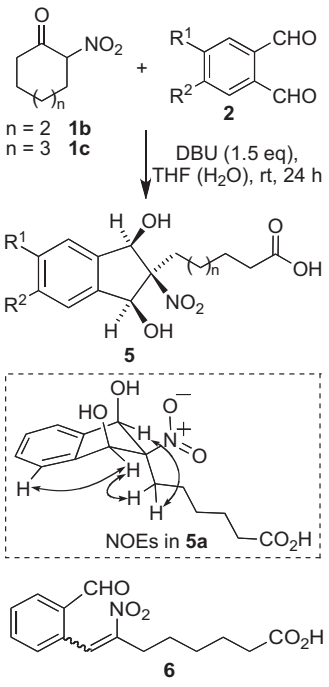
Indane derivatives have also served as rigid frameworks used as the basis for the design of chiral catalysts.[17] Furthermore, compounds **5** are interesting in that they contain three contiguous stereocenters, one of which is quaternary, and were isolated in good to complete diastereoselectivity. Although, to our knowledge, the domino process leading to compounds **5** is unprecedented, there is an early literature reference of the preparation of 1,3-indanediols from phthalaldehydes and nitromethane, nitroethane or ethyl nitroacetate in the presence of sodium carbonate.[18] The stereochemistry of compounds **5** was determined by NOESY experiments, which were interpreted in the light of symmetry considerations and are summarized for the case of compound **5a**. The internal symmetry of the major reaction products was proved by the equivalence of the



Scheme 5.

Attempts to carry out the reaction between higher cyclic α-nitroketones and monofunctional aldehydes led only to complex mixtures. However, when the DBU-promoted conditions were applied to the reactions between α-nitrocycloheptanone or α-nitrocyclooctanone and aromatic 1,2-dialdehydes, a remarkably abrupt change in the reactivity pattern was observed, and indane derivatives **5** were obtained (Scheme 6 and Table 2).[11] This experimentally simple and efficient access to highly functionalized indane derivatives is of interest in view of the importance of indane scaffolds in medicinal chemistry, which has made them attractive targets for diversity-oriented synthesis.[12] Thus, indane-based structural fragments are found in many aspartic protease inhibitors,[13] including the anti-retroviral agent indinavir, and are also present in compounds with other activities, such as inhibition of HIV integrase,[14] melatonin receptor agonism[15] and inhibition of the production of the inflammation factor TNF-α,[16] among others. $C_{1'}$–$C_{3'}$, $C_{4'}$–$C_{7'}$ and $C_{5'}$–$C_{6'}$ signals and those of the corresponding protons for all compounds except **4b** and **4d**, and this shows that the hydroxy groups must be cis. The NOE correlations between the H-1′ and H-3′ protons and the H-6 protons of the aliphatic chain at C-2 confirm the proposed structure.

Some attempts were made to use bases different from DBU for the case of the reaction between α-nitrocycloheptanone and phthalaldehyde. These efforts were largely unsuccessful, with triethylamine and K_2CO_3 affording small amounts of the indane derivative **5a** but requiring very long reaction times, and hydroxide affording the nitroaldol condensation product **6** together with small amounts of the expected product **5a**. Organic bases different from DBU were not assayed. An attempt to use 2-acetylbenzaldehyde as the dicarbonyl component afforded only 3-hydroxy-1-indanone, from cyclization of the starting material by an intramolecular aldol reaction.



Scheme 6.

Table 2
Scope, yields and diastereomeric ratios obtained in the synthesis of indanes **5**

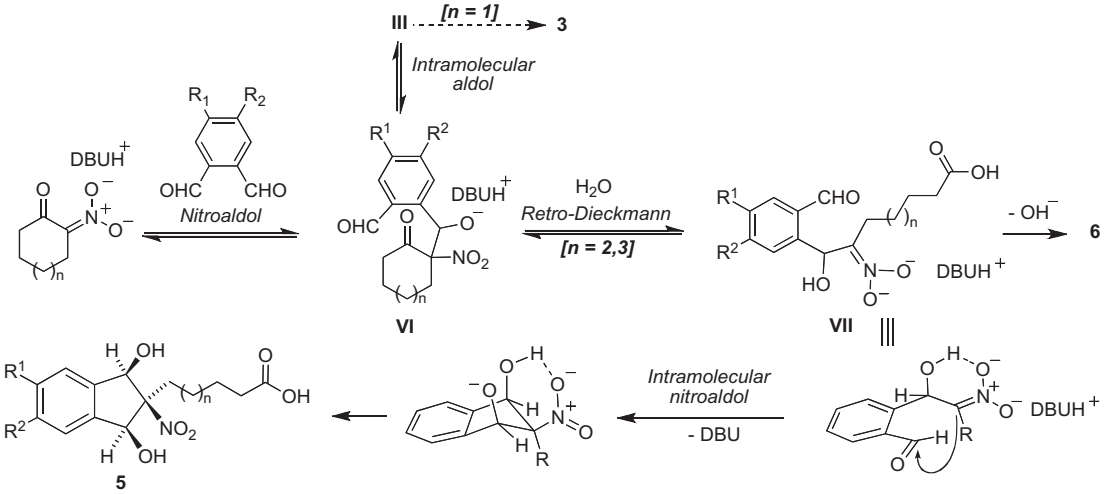
Compd	*n*	R^1	R^2	Yield, %	dr
5a	2	H	H	81	4:1[a]
5b	2	CH_3	H	96	1:0
5c	2	CH_3	CH_3	75[b]	1:0
5d	2	Cl	H	85	1:0
5e	2	Cl	Cl	78	1:0
5f	2	−CH=CH−CH=CH−		76	3.5:1[a]
5g	3	H	H	72[b,c]	3.5:1[a]
5h	3	CH_3	CH_3	70	1:0
5i	3	−CH=CH−CH=CH−		66[d]	3.5:1[a]

[a] The minor diastereomers could not be isolated.
[b] Based on unrecovered starting material.
[c] Together with 20% of the corresponding α′-arylmethylenation product (**3m**).
[d] Together with 22% of the corresponding α′-arylmethylenation product (**3n**).

The mechanism that we propose to explain the formation of compounds **5** from α-nitroketones and aromatic 1,2-dialdehydes is depicted in Scheme 7. An initial nitroaldol reaction affords intermediate **VI**, which in the cases where n>1 undergoes a retro-Dieckmann-type ring opening by a molecule of water from the reaction medium, which is probably previously deprotonated to a hydroxide anion by the alkoxide substituent in **VI**. The resulting nitronate anion **VII** finally cyclizes to compounds **5** through a second nitroaldol reaction, this time in intramolecular fashion. The observed diastereoselectivity in favour of a cis arrangement for the hydroxy and nitro groups can be explained by the initial formation of a hydrogen bond between the nitro group and one of the hydroxyls, which blocks one side of the molecule and forces the intramolecular attack of the nitronate anion to take place from the opposite one. When hydroxide is used as the base, it disrupts this intramolecular hydrogen bonding and allows the Henry reaction to follow the normal course, involving elimination of hydroxide to give compound **6**. For the reactions starting from α-nitrocyclohexanone (n=1), **VI** is sufficiently stable to allow a proton shift (or deprotonation by a second molecule of DBU) that generates an enolate anion, which is cyclized to the previously mentioned intermediate **III** via an intramolecular nitroaldol reaction.

3. Conclusion

In conclusion, the present study reports two unique, synthetically relevant one-pot sequences starting from aromatic 1,2-dialdehydes and cyclic α-nitroketones, which show completely divergent reactivities according to ring size. Thus, the first sequence leads to α′-arylmethylene derivatives of α-nitrocyclohexanone and is proposed to involve an anionic domino process comprising up to six individual steps that include inter- and intramolecular nitroaldol additions, ring opening through a retro-nitroaldol mechanism and an elimination. The second reaction, proceeding through an intermolecular nitroaldol/retro-Dieckmann/intramolecular nitroaldol sequence starting from α-nitrocycloheptanone or α-nitrocyclooctanone, affords indane derivatives and leads to the generation of two C−C and one C−O bonds in a single operation. The overall transformation can be considered as a three-component reaction, considering water as the third component. This reaction generates three contiguous stereocenters, one of which is quaternary, in high to complete diastereoselectivity. The reactions described in this paper give ready access to structures that are not easy to prepare by other synthetic methods and that should serve as useful building blocks in medicinal chemistry,



Scheme 7.

specially bearing in mind that their high degree of functionalization easily allows for subsequent elaboration. Finally, the synthetic processes described here are attractive from an environmental point of view, as they require only simple and readily available starting materials and reagents and have water as the only side product.

4. Experimental

4.1. General experimental information

All reagents (Aldrich, Fluka, SDS, Probus) and solvents (SDS, Scharlau) were of commercial quality and were used as received. Reactions were monitored by TLC on aluminium plates coated with silica gel with fluorescent indicator (SDS CCM221254). Separations by flash chromatography were performed on silica gel (SDS 60 ACC 40–63 mm). Melting points were measured on a Reichert 723 hot stage microscope and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer Paragon 1000 FT-IR spectrophotometer with all compounds examined as thin films on NaCl disks. NMR spectra were obtained on a Bruker Avance 250 spectrometer operating at 250 and 62.9 MHz for ^{1}H and ^{13}C NMR spectra, respectively (CAI de Resonancia Magnética Nuclear, Universidad Complutense) with the signal of the residual non-deuterated solvent as an internal standard. Combustion elemental analyses were determined by the CAI de Microanálisis Elemental, Universidad Complutense, using a Leco 932 CHNS microanalyzer.

4.2. General procedure for the synthesis of phthaldehydes via IBX oxidation

To a suspension of IBX (5.4 mmol) in ethyl acetate (75 ml) was added a solution of the suitable diol[19] (1.8 mmol) in acetone (5 ml). The reaction mixture was heated at 80 °C for 3.5 h, cooled and filtered, and the filtered solid was washed with acetone (2×5 ml). The combined filtrate and washings were evaporated under reduced pressure and purified by distillation, giving the desired dialdehydes in 66–80% yields.

4.3. General procedure for the anionic domino reactions

To a solution of the starting α-nitroketone (1 mmol) in tetrahydrofuran (5 ml) was added DBU (1.3 mmol). The resulting solution was stirred at room temperature for 5 min, under an argon atmosphere. A solution of the suitable dialdehyde (2 mmol) in tetrahydrofuran (5 ml) containing one drop of water was then added, and stirring at room temperature was maintained for 24 h, except where indicated otherwise. Then, CH_2Cl_2 (20 ml) and 2 M HCl (10 ml) were added, and the reaction mixture was separated and extracted with CH_2Cl_2 (3×10 ml). The combined organic layers were dried over anhydrous sodium sulfate and evaporated. The residue was chromatographed on silica gel, eluting with the mobile phase specified in each case.

*4.3.1. (E)-2-[(2-Hydroxy-3-nitrocyclohex-2-en-1-yliden)methyl] benzaldehyde (**3a**).* Isolated in 95% yield as a pale yellow oil after chromatography on silica gel, eluting with a gradient from petroleum ether to ethyl acetate. IR (NaCl) ν_{max}: 3472, 1695 (CO), 1574 and 1355 (NO_2), 1224 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ_H 14.07 (s, 1H, OH), 10.21 (s, 1H, CHO), 8.19 (s, 1H, H-1′), 7.97 (dd, 1H, *J*=7.5 and 1.3 Hz, H-6), 7.67 (td, 1H, *J*=7.5 and 1.4 Hz, H-4), 7.57 (td, 1H, *J*=7.5 and 1.2 Hz, H-5), 7.36 (d, 1H, *J*=7.5 Hz, H-3), 2.79 (t, 2H, *J*=6.3 Hz, H-4″), 2.54–2.49 (m, 2H, H-6″), 1.80 (q, 2H, *J*=6.3 Hz, H-5″) ppm. ^{13}C NMR (63 MHz, $CDCl_3$) δ_C 191.7 (CHO), 163.7 (C-2″), 137.7 (C-2), 134.0 (C-1), 133.5 (C-4), 133.5 (C-1′), 132.3 (C-1″), 131.3 (C-6), 130.1 (C-3), 128.8 (C-5), 126.0 (C-3″), 26.1 (C-6″), 24.5 (C-4″), 21.3 (C-5″) ppm. Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.02; N, 5.40. Found: C, 64.90; H, 4.72; N, 5.24.

*4.3.2. (E)-4,5-Dichloro-2-[(2-hydroxy-3-nitrocyclohex-2-en-1-yliden)methyl]benzaldehyde (**3b**).* Isolated in 82% yield as pale yellow oil after chromatography on silica gel, eluting with a gradient from petroleum ether to ethyl acetate. IR (NaCl) ν_{max}: 3344, 1767 (CO), 1557 and 1350 (NO_2), 1223 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ_H 13.84 (s, 1H, OH), 10.11 (s, 1H, CHO), 8.04 (s, 1H, H-1′), 7.66 (s, 1H, H-6), 7.46 (s, 1H, H-3), 2.81 (t, 2H, *J*=6.3 Hz, H-4″), 2.54–2.47 (m, 2H, H-6″), 1.83 (q, 2H, *J*=6.3 Hz, H-5″) ppm. ^{13}C NMR (63 MHz, $CDCl_3$) δ_C 188.4 (CHO), 161.5 (C-2″), 137.4 (C-2), 136.2 (C-1), 133.2 (C-4), 132.5 (C-5), 131.2 (C-1″), 130.7 (C-6), 130.5 (C-3), 128.9 (C-1′), 124.6 (C-3″), 25.2 (C-6″), 23.3 (C-4″), 20.2 (C-5″) ppm. Anal. Calcd for $C_{14}H_{11}NO_4Cl_2$: C, 51.21; H, 3.35; N, 4.27. Found: C, 51.32; H, 3.28; N, 4.24.

*4.3.3. (E)-3-[(2-Hydroxy-3-nitrocyclohex-2-en-1-yliden)methyl]-naphthalene-2-carbaldehyde (**3c**).* Obtained in 87% yield as a yellow oil after chromatography on silica gel, eluting with a gradient from petroleum ether to ethyl acetate. ^{1}H NMR (250 MHz, $CDCl_3$) δ_H 14.23 (s, 1H, OH), 10.27 (s, 1H, CHO), 8.42 (s, 1H, H-1′), 8.36 (s, 1H, H-1), 8.07 (d, 1H, *J*=8.4 Hz, H-8), 7.93 (d, 1H, *J*=8.4 Hz, H-5), 7.82–7.58 (m, 3H, H-4, 6, 7), 2.78 (t, 2H, *J*=6.3 Hz, H-4″), 2.64 (td, 2H, *J*=8.4 and 1.7 Hz, H-6″), 1.79 (q, 2H, *J*=6.2 Hz, H-5″) ppm. ^{13}C NMR (63 MHz, $CDCl_3$) δ_C 192.2 (CHO), 164.6 (C-2″), 136.4 (C-8a), 134.8 (C-1″), 134.6 (C-8), 132.3 (C-6), 132.1 (C-1), 131.9 (C-2), 130.9 (C-4a), 130.1 (C-3), 129.8 (C-5), 129.3 (C-7), 128.0 (C-4), 127.8 (C-1′), 125.7 (C-3″), 26.1 (C-6″), 24.5 (C-4″), 21.3 (C-5″) ppm. Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.63; H, 4.52; N, 4.41.

*4.3.4. (E)-4-Chloro-2-[(2-hydroxy-3-nitrocyclohex-2-en-1-yliden) methyl]benzaldehyde (**3d**) and (E)-5-chloro-2-[(2-hydroxy-3-nitrocyclohex-2-en-1-yliden)methyl]-benzaldehyde (**3e**).* Obtained as a 1:1 mixture of regioisomers in 80% yield as a viscous yellow oil after chromatography on silica gel, eluting with a gradient from petroleum ether to ethyl acetate. IR (NaCl) ν_{max}: 3367, 1765 (CO), 1563 and 1354 (NO_2), 1122 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ_H 13.95 (s, 1H, OH), 13.91 (s, 1H, OH), 10.18 (s, 1H, CHO), 10.14 (s, 1H, CHO), 8.08 (s, 1H, H-1′), 7.98–7.82 (m, H, 3H–Ar and H-1′), 7.73–7.46 (m, 4H, H–Ar), 7.34–7.30 (m, 2H, H–Ar), 2.83 (t, 4H, *J*=6.2 Hz, H-4″), 2.74–2.65 (m, 2H, H-6″), 2.57–2.45 (m, 2H, H-6″), 2.10–1.93 (m, 2H, H-5″), 1.89–1.73 (m, 2H, H-5″) ppm. ^{13}C NMR (63 MHz, $CDCl_3$) δ_C 191.2 (CHO), 191.0 (CHO), 163.7 (C-2″), 163.5 (C-2″), 140.6, 139.8, 136.6, 135.6, 135.5 (C-4), 134.0 (C-4), 132.8 (C-5), 132.2 (C-1″), 132.0 (C-6), 130.9 (C-3), 130.4 (C-1′), 129.4 (C-3″), 126.9 (C-3″), 126.7 (C-3″), 124.0 (C-3″), 123.2 (C-3″), 30.1 (C-6″), 26.5 (C-6″), 25.9 (C-4″), 24.8 (C-4″), 23.3 (C-5″), 21.6 (C-5″) ppm. Anal. Calcd for $C_{14}H_{12}NO_4Cl$: C, 57.25; H, 4.12; N, 4.77. Found: C, 57.00; H, 3.91; N, 4.73.

*4.3.5. (E)-2-[(2-Hydroxy-3-nitrocyclohex-2-en-1-yliden)methyl]-tiophene-3-carbaldehyde (**3f**) and (E)-3-[(2-hydroxy-3-nitrocyclohex-2-en-1-yliden)methyl]-tiophene-2-carbaldehyde (**3g**).* Obtained as a 1.3:1 mixture of regioisomers in 75% yield as a yellow oil after chromatography on silica gel, eluting with a gradient from petroleum ether to dichoromethane. Anal. Calcd for $C_{12}H_{11}NO_4S$: C, 54.33; H, 4.15; N, 5.28. Found: C, 54.51; H, 4.35; N, 5.37. Spectral data for **3f**: ^{1}H NMR (250 MHz, $CDCl_3$) δ_H 13.95 (s, 1H, OH), 10.08 (d, 1H, *J*=0.9 Hz, CHO), 8.59 (br s, 1H, H-1′g), 8.05 (br s, 1H, H-1), 7.79–7.66 (m, 2H, H-4b,5), 7.59 (d, 1H, *J*=5.3 Hz, H-4), 7.53 (d, 1H, *J*=5.3 Hz, H-5), 2.84–2.74 (m, 2H, H-4″), 2.69–2.63 (m, 2H, H-6), 1.97–1.79 (m, 2H, H-5) ppm. ^{13}C NMR (63 MHz, $CDCl_3$) δ_C 182.1 (CHO), 163.0 (C-2″), 147.1 (C-2), 143.5 (C-1″), 134.3 (C-3), 129.8 (C-5), 128.6 (C-4), 126.2 (C-1′), 124.4 (C-3″), 26.7 (C-6″), 24.2 (C-4″), 21.2 (C-5″) ppm. Spectral data for **3g**: ^{1}H NMR (250 MHz, $CDCl_3$) δ_H 14.08 (s, 1H, OH), 10.25 (s, 1H, CHO), 8.59 (br s, 1H, H-1′), 7.79–7.66

(m, 2H, H-4b,5), 2.84–2.74 (m, 2H, H-4″), 2.69–2.63 (m, 2H, H-6″), 1.97–1.79 (m, 2H, H-5″) ppm. ^{13}C NMR (63 MHz, $CDCl_3$) δ_C 184.2 (CHO), 163.4 (C-2″), 147.3 (C-3), 143.4 (C-1″), 133.5 (C-2), 131.8 (C-5), 128.8 (C-1′), 126.7 (C-4), 123.8 (C-3″), 27.0 (C-6″), 24.0 (C-4″), 20.9 (C-5″) ppm. Anal. Calcd for $C_{12}H_{11}NO_4S$: C, 54.33; H, 4.18; N, 5.28. Found: C, 54.10; H, 3.94; N, 5.03.

*4.3.6. (E)-6-(4-Nitrobenzylidene)-2-nitrocyclohex-1-enol (**3i**).* Isolated in 88% yield as a pale orange solid after 4 days of reaction followed by chromatography on silica gel, eluting with dichloromethane. Mp 117–118 °C. IR (NaCl) ν_{max}: 3380 (OH), 2932, 1558 and 1342 (NO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ_H 14.97 (s, 1H, OH), 8.30 (d, 2H, *J*=8.8 Hz, H-3″,5″), 7.77 (s, 1H, H-1′), 7.57 (d, 2H, *J*=8.8 Hz, H-2″,6″), 2.82 (t, 2H, *J*=6.2 Hz, H-3), 2.77–2.71 (m, 2H, H-5), 1.81 (quint, 2H, *J*=6.2 Hz, H-4) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ_C 162.9 (C-1), 147.1 (C-4″), 141.9 (C-1″), 133.2 (C-1′), 132.7 (C-6), 130.4 (C-2″,6″), 126.6 (C-2), 123.6 (C-3″,5″), 26.3 (C-5), 24.2 (C-3), 21.3 (C-4) ppm. Anal. Calcd for $C_{13}H_{12}N_2O_5$: C, 56.52; H, 4.34; N, 10.14. Found: C, 56.22; H, 4.54; N, 9.88.

*4.3.7. (E,E)-2-Nitro-6-(3-phenyl-2′-propenylidene)-cyclohex-1-enol (**3j**).* Isolated in 60% yield as a pale brown solid after 6 days of reaction followed by chromatography on silica gel, eluting with dichloromethane. Mp, 125–126 °C. IR (NaCl) ν_{max}: 3603 (OH), 2926, 1589 and 1398 (NO_2), 1210 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 14.38 (s, 1H, OH), 7.65–745 (m, 5H, H–Ar), 7.20–6.99 (m, 3H, CH=), 2.79 (t, 2H, *J*=6.2 Hz, H-6), 2.73–2.66 (m, 2H, H-5), 1.88 (quint, 2H, *J*=6.2 Hz, H-4) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 165.3 (C-1), 141.2 (C-1″), 136.3 (C-6), 129.2 (C-3′), 128.9 (C-3″,5″), 128.7 (C-4″), 127.6 (C-2′), 127.3 (C-2″,6″), 125.2 (C-1′), 123.4 (C-2), 25.0 (C-5), 24.5 (C-3), 21.0 (C-4) ppm. Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.03; H, 5.83; N, 5.44. Found: C, 69.90; H, 5.78; N, 5.46.

*4.3.8. (E,E)-2-Nitro-6-[3-(2-nitrophenyl)propenylidene]-cyclohex-1-enol (**3k**).* Isolated in 90% yield as a red solid after 5 days of reaction followed by chromatography on silica gel, eluting with dichloromethane. Mp 219–220 °C. IR (NaCl) ν_{max}: 3390 (OH), 2358, 1519 and 1342 (NO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 14.08 (s, 1H, OH), 8.03 (d, 1H, *J*=8.1 Hz, H-3″), 7.76 (d, 1H, *J*=7.8 Hz, H-6″), 7.65 (t, 1H, *J*=7.6 Hz, H-4″), 7.53–7.46 (m, 3H, H-3″ and H-2′,3′), 7.10 (dd, 1H, *J*=14.9 Hz, H-1′), 2.80 (t, 2H, *J*=6.1 Hz, H-6), 2.69 (m, 2H, *J*=5.9 Hz, H-5), 1.89 (quint, 2H, *J*=6.1 Hz, H-4) ppm. ^{13}C NMR (DMSO, 63 MHz) δ: 163.7 (C-1), 148.4 (C-2″), 134.6 (C-6), 134.4 (C-3′), 133.7 (C-5″), 132.5 (C-1″), 131.1 (C-6″), 130.0 (C-4″), 128.9 (C-2′), 126.4 (C-1′,3″), 124.9 (C-2), 24.8 (C-5), 24.6 (C-3), 20.9 (C-4) ppm. Anal. Calcd for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.63; N, 9.27. Found: C, 59.59; H, 4.64; N, 9.42.

*4.3.9. (E,E)-2-Nitro-6-[3-(4-nitrophenyl)-2′-propenylidene]cyclohex-1-enol (**3l**).* Isolated in 85% yield as a red solid after 5 days of reaction followed by chromatography on silica gel, eluting with dichloromethane. Mp 218–219 °C. IR (NaCl) ν_{max}: 3280 (OH), 2359, 1508, 1396 and 1336 (2 NO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 14.07 (s, 1H, OH), 8.26 (d, 2H, *J*=8.7 Hz, H-3″,5″), 7.66 (d, 1H, *J*=8.8 Hz, H-2″,6″), 7.55–7.43 (m, 1H, H-3′), 7.34–7.23 (m, 1H, H-2′), 7.04 (d, 1H, *J*=15.4 Hz, H-1′), 2.81 (t, 2H, *J*=6.1 Hz, H-3), 2.75–2.70 (m, 2H, H-5), 1.89 (quint, 2H, *J*=6.1 Hz, H-4) ppm. ^{13}C NMR (DMSO, 175 MHz) δ: 163.7 (C-1), 147.3 (C-4″), 143.4 (C-1″), 138.4 (C-3′), 134.8 (C-6), 132.8 (C-2″,6″), 128.9 (C-1′), 128.8 (C-2′), 126.6 (C-2), 124.4 (C-3″,5″), 24.9 (C-5), 24.7 (C-3), 21.0 (C-4) ppm. Anal. Calcd for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.63; N, 9.27. Found: C, 59.38; H, 4.70; N, 9.82.

*4.3.10. 6-(1-Hydroxy-1-phenylmethyl)-2-nitrocyclohexanone (**4**).* Obtained in 100% yield as a 3:3:1 mixture of diastereomers and the crude product as such for the synthesis of compound **3h** (see below). One of the diastereomers could be purified by chromatography on silica gel, eluting with a gradient from 1:1 petroleum ether–dichloromethane to neat dichloromethane. ^{1}H NMR ($CDCl_3$, 250 MHz) δ_H 8.12 (dd, 2H, *J*=8.2 and 1.2 Hz, H-2″,6″), 7.64 (tt, 1H, *J*=7.3 and 1.3 Hz, H-4″), 7.53–7.30 (m, 2H, H-3″,5″), 5.36 (m, 1H, H-1′), 4.94 (m, 1H, H-6), 2.81–2.60 (m, 3H, H-3), 2.53–2.41 (m, 2H, H-5), 1.97–1.82 (m, 2H, H-4) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ_C: 202.2 (C-1), 140.3 (C-1″), 129.6 (C-3″,5″), 128.8 (C-2″,6″), 127.2 (C-4″), 92.6 (C-2), 73.8 (C-1′), 57.9 (C-6), 32.6 (C-3), 30.8 (C-4), 24.2 (C-5) ppm. Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.45; H, 5.97; N, 5.43.

4.3.11. (±)-(1′S,2′S*,3′R*)-6-(1′,3′-dihydroxy-2′-nitroindan-2′-yl) hexanoic acid (**5a**).* Isolated in 81% yield, initially as a 4:1 mixture of diastereoisomers. Chromatography on silica gel, eluting with a gradient from petroleum ether to dichloromethane, followed by ethyl acetate, afforded the pure compound **5a**, as a white solid. *Data for the major diastereomer of* **5a**: Mp 102–103 °C; IR (NaCl) ν_{max}: 3397 (OH); 1702 (CO), 1534, 1353 (NO_2) cm^{-1}. ^{1}H NMR (250 MHz, acetone-d_6) δ_H: 7.44–7.34 (m, 4H, H–Ar), 5.69 (s, 2H, H-1′,3′), 5.50 (br s, 2H, OH), 2.17–2.25 (m, 4H, H-2, 6), 1.44–1.56 (m, 2H, H-3), 1.14–1.33 (m, 4H, H-4, 5) ppm. ^{13}C NMR (63 MHz, acetone-d_6) δ_C: 174.2 (C-1), 140.9 (C-3′a,7′a), 129.0 (C-5′,6′), 123.8 (C-4′,7′), 105.8 (C-2′), 77.1 (C-1′,3′), 33.5 (C-6), 29.8 (C-2), 29.4 (C-5), 24.7 (C-3), 24.3 (C-4) ppm. Anal. Calcd for $C_{15}H_{19}NO_6$: C, 58.25; H, 6.19; N, 4.53. Found: C, 58.03; H, 6.08; N, 6.02. *Data for the minor diastereomer of* **5a** (*obtained from the initial mixture*): ^{1}H NMR (250 MHz, acetone-d_6): δ=7.50–7.20 (m, 4H, H–Ar), 5.94 and 5.00 (2s, 2H, H-1′,3′), 5.27 (s, 2H, 2OH), 2.30–1.80 (m, 4H, H-2,6), 1.60–1.30 (m, 6H, H-3,4,5) ppm. ^{13}C NMR (63 MHz, acetone-d_6): δ=178.8 (C-1), 140.8 (C-3a′), 137.4 (C-7a′), 130.2 (C-5′), 129.4 (C-6′), 125.2 (C-4′), 124.3 (C-7′), 35.4 (C-2), 32.3 (C-6), 29.6 (C-5), 24.1 and 23.9 (C-3,4) ppm.

4.3.12. (±)-(1′S,2′S*,3′R*)-6-(1′,3′-dihydroxy-5′-methyl-2′-nitroindan-2′-yl)hexanoic acid (**5b**).* Isolated in 96% yield as a colourless viscous oil after chromatography on silica gel, eluting with a gradient from petroleum ether to dichloromethane, followed by ethyl acetate. ^{1}H NMR (250 MHz, $CDCl_3$) δ_H: 7.40 (d, 1H, *J*=7.9 Hz, H-7), 7.31–7.29 (m, 1H, H-4), 7.22 (d, 1H, *J*=7.9 Hz, H-4), 5.51–5.48 (2s, 2H, 2OH), 5.26 and 5.23 (2s, 2H, H-1′, H-3′), 2.40 (s, 3H, CH_3), 2.42–2.28 (m, 4H, H-2, 6), 2.20–1.95 (m, 2H, H-3), 1.27–1.30 (m, 2H, H-4, 5) ppm. ^{13}C NMR (63 MHz, $CDCl_3$) δ_C 141.6 (C-3′a), 141.2 (C-7′a), 132.0 (C-5′), 126.5 (C-6′), 138.6 (C-4′), 137.7 (C-7′), 105.8 (C-2′), 77.3 (C-1′), 81.5 (C-3′), 33.3 (C-6), 27.9 (C-2), 26.2 (C-5), 22.2 (C-3), 21.8 (C-4), 21.8 (CH_3) ppm. Anal. Calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.38; H, 6.71; N, 4.19.

4.3.13. (±)-(1′S,2′S*,3′R*)-6-(1′,3′-Dihydroxy-5′,6′-dimethyl-2′-nitroindan-2′-yl)hexanoic acid (**5c**).* Obtained in 75% yield (based on unrecovered starting material) as a white solid after chromatography on silica gel, eluting with a gradient from petroleum ether to dichloromethane, followed by ethyl acetate. Mp 105–107 °C; IR (NaCl) ν_{max}: 3390 (OH), 1702 (CO), 1534 and 1353 (NO_2) cm^{-1}. ^{1}H NMR (250 MHz, acetone-d_6) δ_H 7.17 (d, 2H, *J*=7.9 Hz, H-7, 4), 5.59 (s, 2H, H-1′,3′), 2.29 (s, 6H, 2 CH_3), 2.15–2.27 (m, 4H, H-2, 6), 1.50–1.56 (m, 2H, H-3), 1.27–1.30 (m, 4H, H-4, 5) ppm. ^{13}C NMR (63 MHz, acetone-d_6) δ_C 174.1 (C-1), 138.6 (C-3′a, C-7′a), 137.5 (C-5′, C-6′), 124.8 (C-4′, C-7′), 105.8 (C-2′), 77.2 (C-1′, C-3′), 33.4 (C-6), 29.7 (C-2), 29.5 (C-5), 24.6 (C-3), 24.2 (C-4), 19.5 ($2CH_3$) ppm. Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.38; H, 6.72; N, 3.99.

4.3.14. (±)-(1′S,2′S*,3′R*)-6-(5′-Chloro-1′,3′-dihydroxy-2′-nitroindan-2′-yl)hexanoic acid (**5d**).* Obtained in 85% yield as a pale brown oil after chromatography on silica gel, eluting with a gradient from petroleum ether to dichloromethane, followed by ethyl acetate. IR (NaCl) ν_{max}: 3360 (OH), 1711 (CO), 1597 and 1424 (NO_2) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ_H 7.80–7.08 (m, 3H, H–Ar), 5.55

(s, 1H, H-1′,3′), 5.33 (s, 1H, H-1′,3′), 2.85–2.02 (m, 4H, H-2, 6), 1.98–0.66 (m, 6H, H-3, 4, 5) ppm. ^{13}C NMR (63 MHz, $CDCl_3$) δ_C 179.4 (C-1), 140.7 (C-3′a), 137.2 (C-7′a), 135.1 (C-5′), 129.6 (C-7′), 125.2 (C-4′), 124.9 (C-6′), 104.8 (C-2′), 75.8 (C-1′,3′), 33.5 (C-6), 29.5 (C-2), 28.9 (C-5), 24.6 (C-3), 24.2 (C-4) ppm. Anal. Calcd for $C_{15}H_{18}NO_6Cl$: C, 52.41; H, 5.28; N, 4.07. Found: C, 52.23; H, 5.28; N, 4.00.

4.3.15. (±)-(1′S,2′S*,3′R*)-6-(5′,6′-Dichloro-1′,3′-dihydroxy-2′-nitroindan-2′-yl)hexanoic acid (**5e**).* Obtained in 78% yield as a pale brown oil after chromatography on silica gel, eluting with a gradient from petroleum ether to dichloromethane, followed by ethyl acetate. ^{1}H NMR (250 MHz, acetone-d_6) δ_H 7.57 (s, 2H, H–Ar); 5.72 (s, 2H, H-1′,3′), 2.27–2.11 (m, 4H, H-2, 6), 1.56–1.49 (m, 2H, H-3), 1.31–1.21 (m, 4H, H-4, 5) ppm. ^{13}C NMR (63 MHz, acetone-d_6) δ_C 175.0 (C-1), 142.5 (C-3′a,7′a); 133.2 (C-5′,6′), 126.8 (C-4′,7′), 106.6 (C-2′), 77.0 (C-1′,3′), 34.3 (C-6), 30.6 (C-2), 30.3 (C-5), 25.5 (C-3), 25.3 (C-4) ppm. Anal. Calcd for $C_{15}H_{17}Cl_2NO_6$: C, 47.64; H, 4.53; N, 3.70; Found: C, 47.48; H, 4.32; N, 3.55.

4.3.16. (±)-(1′S,2′S*,3′R*)-6-(1′,3′-Dihydroxy-2′-nitro-2′,3′-dihydro-1H-ciclopenta[b]naphtalen-2′-yl)hexanoic acid (**5f**).* Obtained in 76% yield, initially as a 3.5:1 mixture of diastereoisomers. Chromatography on silica gel, eluting with a gradient from petroleum ether to dichloromethane, followed by ethyl acetate, afforded the pure compound **5f**, as a colourless oil. *Data for the major diastereomer of* **5f**: IR (NaCl) ν_{max} 3360 (OH); 1711 (CO), 1597 and 1424 (NO_2) cm^{-1}. ^{1}H NMR (500 MHz, acetone-d_6) δ_H 7.91 (dd, 2H, *J*=6.0 and 3.2 Hz, H-5′,8′), 7.85 (s, 2H, H-4′,9′), 7.49 (dd, 2H, *J*=6.3 and 3.2 Hz, H-6′,7′), 5.78 (s, 2H, H-1′,3′), 5.59–5.56 (br s, 2H, 2OH), 2.20–2.14 (m, 4H, H-2, 6), 1.48–1.42 (m, 2H, H-3), 1.32–1.20 (m, 4H, H-4, 5) ppm. ^{13}C NMR (125 MHz, acetone-d_6) δ_C 179.1 (C-1), 138.8 (C-3′a,9′a), 134.4 (C-4′a,8′a), 128.1, 126.0 and 122.2 (C-4′,5′,6′,7′,8′,9′); 105.1 (C-2′), 76.7 (C-1′,3′), 33.7 (C-6), 29.7 (C-2), 28.8 (C-5), 24.5 (C-3), 24.0 (C-4) ppm. Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.22; H, 5.90; N, 3.83. *Data for the minor diastereomer of* **5f** (*obtained from the initial mixture*): ^{1}H NMR (250 MHz, $CDCl_3$) δ_H 8.04–7.70 (m, 4H, H-4′,5′,8′,9′), 7.60–7.43 (m, 2H, H-6′,7′), 6.18 and 5.41 (2s, 2H, H-1′,3′), 5.31 (s, 2H, 2OH), 2.50–2.00 (m, 4H, H-2,6), 2.80–0.79 (m, 6H, H-3,4,5) ppm. ^{13}C NMR (63 MHz, $CDCl_3$) δ_C 179.0 (C-1), 138.1 and 136.7 (C-3′a,9′a), 133.9 and 133.8 (C-4′a,8′a), 133.6 128.6, 126.6, 126.4, 124.7 and 123.5 (C-4′,9′), 101.1 (C-2′), 77.4 and 76.9 (C-1′,3′), 31.8 (C-6), 30.1 (C-2), 29.2 (C-5), 28.7 (C-3), 23.8 (C-4) ppm.

4.3.17. (±)-(1′S,2′S*,3′R*)-7-(1′,3′-Dihydroxy-2′-nitroindan-2′-yl) heptanoic acid (**5g**) and (E)-2-[(3-nitro-2-oxocyclooctyliden)methyl] benzaldehyde (**3m**).* Compound **5g** was obtained in 72% yield, initially as a 3:1 mixture of diastereoisomers. Chromatography on silica gel, eluting with a gradient from petroleum ether to ethyl acetate, afforded the pure compound **5g**, as a yellow oil. Compound **3m** (20%) was obtained from the same column as a yellow solid. *Data for the major diastereomer of* **5g**: IR (NaCl) ν_{max} 3415 (OH), 1722, 1711 (CO), 1536 and 1357 (NO_2) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ_H 7.59–7.32 (m, 4H, H–Ar), 5.59 (s, 2H, H-1′,3′), 5.00–3.41 (br s, 2H, 2 OH), 2.31 (t, 2H, *J*=7.3 Hz, H-2), 2.19–2.10 (m, 2H, H-7), 1.59–1.54 (m, 2H, H-3), 1.37–1.12 (m, 6H, H-4, 5, 6) ppm. ^{13}C NMR (63 MHz, $CDCl_3$) δ_C 179.2 (C-1), 138.6 (C-3′a,7′a), 129.4 (C-5′,6′), 123.7 (C-4′,7′), 104.1 (C-2′), 76.3 (C-1′,3′), 33.6 (C-2), 29.8 (C-7), 29.2 (C-5), 28.2 (C-4), 24.2 (C-3), 24.0 (C-6) ppm. Anal. Calcd for $C_{16}H_{21}NO_6$: 59.43; H, 6.55; N, 4.33. Found: C, 59.28; H, 6.39; N, 4.20. *Data for the minor diastereomer of* **5g** (*obtained from the initial mixture*): ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.75–7.20 (m, 4H, H–Ar), 5.98 (s, 2H, 2OH), 5.31 and 5.21 (2s, 2H, H-1′,3′), 2.36–2.00 (m, 4H, H-2,7), 1.85–1.40 (m, 2H, H-3), 1.39–1.00 (m, 6H, H-4, 5, 6) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ=179.9 (C-1), 141.3, 137.7, 130.6, 129.7, 125.7, 124.8, 101.7 (C-2′), 77.4, 76.6, 34.2 (2C); 29.5, 28.9, 24.7 (2C), 24.3 ppm. *Data for* **3m**: IR (NaCl) ν_{max} 2936 (OH), 1694 (CO), 1594, 1556 and 1357 (NO_2) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ_H 10.16 (s, 1H, CHO), 8.01 (s, 1H, H-1′), 7.96 (dd, 1H, *J*=7.5 and 1.4 Hz, H-6), 7.68 (td, 1H, *J*=7.4 and 1.5 Hz, H-4), 7.59 (td, 1H, *J*=7.5 and 1.0 Hz, H-5), 7.31 (d, 1H, *J*=7.4 Hz, H-3), 5.91 (dd, 1H, *J*=10.3 and 5.7 Hz, H-3″), 2.75 (dt, 1H, *J*=14.9 and 4.0 Hz, H-8″), 2.53–2.30 (m, 3H, H-4″,8″), 1.93–1.59 (m, 4H, H-5″,6″,7″), 1.53–1.25 (m, 2H, H-6″,7″) ppm. ^{13}C NMR (63 MHz, $CDCl_3$) δ_C 195.2 (C-2″), 191.9 (CHO), 139.8 (C-1″), 139.4 (C-1′), 137.7 (C-2), 134.5 (C-1), 134.3 (C-4), 132.1 (C-6), 129.7 (C-3), 129.4 (C-5), 90.2 (C-3″), 32.7 (C-4″), 29.5 (C-7″), 25.8 (C-6″), 25.6 (C-8″), 22.8 (C-5″) ppm. Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.61; H, 6.08; N, 4.66.

4.3.18. (±)-(1′S,2′S*,3′R*)-7-(1′,3′-Dihydroxy-5′,6′-dimethyl-2′-nitroindan-2′-yl)heptanoic acid (**5h**).* Obtained in 70% yield as a yellow oil after chromatography on silica gel, eluting with a gradient from petroleum ether to ethyl acetate. ^{1}H NMR (250 MHz, $CDCl_3$) δ_H 7.52 (s, 2H, H-4′,7′); 5.54 (s, 2H, H-1′,3′); 2.42–2.05 (m, 10H, H-2, 7, 2× CH_3); 1.59–1.54 (m, 2H, H-3); 1.37–1.12 (m, 6H, H-4, 5, 6) ppm. ^{13}C NMR (63 MHz, $CDCl_3$) δ_C 179.2 (C-1), 137.0 (C-3′a,7′a), 135.4 (C-5′,6′), 125.2 (C-4′,7′), 104.5 (C-2′), 76.9 (C-1′,3′), 34.1 (C-2), 30.3 (C-7), 29.5 (C-5), 28.8 (C-4), 25.9 (C-3), 24.7 (C-6), 20.4 (CH_3) ppm. Anal. Calcd for $C_{18}H_{25}NO_6$: C, 61.52; H, 7.17; N, 3.99. Found: C, 61.30; H, 6.89; N, 3.70.

4.3.19. (±)-(1′S,2′S*,3′R*)-7-(1′,3′-Dihydroxy-2′-nitro-2′,3′-dihydro-1H-ciclopenta[b]naphtalen-2′-yl)heptanoic acid (**5i**) and (E)-3-[(3′-nitro-2′-oxocyclooctyliden)methyl]naphtalene-2-carbaldehyde (**3n**).* Compound **5i** was isolated in 66% yield, initially as a 3:1 mixture of diastereoisomers. Chromatography on silica gel, eluting with a gradient from petroleum ether to ethyl acetate, afforded the pure compound **5i**, as a yellow oil. Compound **3n** (22%) was isolated as a yellow solid. *Data for the major diastereomer of* **5i**: IR (NaCl) ν_{max} 3415 (OH), 1722, 1711 (CO), 1536 and 1357 (NO_2) cm^{-1}. ^{1}H NMR (250 MHz, MeOD) δ_H 7.92 (dd, 2H, *J*=6.6 and 3.3 Hz, H-5′,8′), 7.85 (s, 2H, H-4′,9′), 7.49 (dd, 2H, *J*=6.2 and 3.2 Hz, H-6′,7′), 5.78 (s, 2H, H-1′,3′), 2.25–2.12 (m, 4H, H-2, 7), 1.54–1.48 (m, 2H, H-3), 1.31–1.23 (m, 8H, H-4, 5, 6, 2OH) ppm. ^{13}C NMR (63 MHz, MeOD) δ_C 179.2 (C-1), 138.6 (C-3′a,9′a), 131.9 (C-4′a,8′a), 129.4, 124.9, 123.7 (C-4′,5′,6′,7′,8′,9′), 104.1 (C-2′), 76.3 (C-1′,3′), 33.6 (C-2), 29.8 (C-7), 29.2 (C-5), 28.2 (C-3), 24.2 (C-4), 24.0 (C-6) ppm. Anal. Calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.30; H, 6.20; N, 3.62. *Data for the minor diastereomer of* 5i (*obtained from the initial mixture*): ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 8.10–7.80 (m, 4H, H-4′,5′,8′,9′), 7.75–7.60 (m, 2H, H-6′,7′), 6.20 (s, 2H, H-1′,3′), 5.60 (s, 2H, OH), 2.40–2.30 (m, 4H, H-2,7), 2.30–2.10 (m, 2H, H-3), 1.80–1.50 and 1.40–1.20 (2 m, 6H, H-4, 5, 6) ppm. ^{13}C NMR (63 MHz, $CDCl_3$) δ_C 168.3 (C-1), 137.7 and 137.1 (C-3′a,9′a), 135.6 and 134.4 (C-4′a,8′a), 132.7, 131.3, 129.2, 128.6, 126.7 and 123.5 (C-4′,5′,6′,7′,8′,9′), 102.1 (C-2′), 77.5 and 76.1 (C-1′,3′), 34.1 (C-2), 29.5 (C-7), 28.7 (C-5), 24.8 (C-3), 24.5 (C-4), 23.1 (C-6) ppm. *Data for* **3n**: ^{1}H NMR (250 MHz, $CDCl_3$) δ_H 10.18 (s, 1H, CHO), 8.51 (s, 1H, H-1′), 8.12 (s, 1H, H-1), 8.07 (d, 1H, *J*=8.0 Hz, H-8), 7.93 (d, 1H, *J*=7.9 Hz, H-5), 7.81–7.64 (m, 3H, H-4, 6, 7), 5.97 (m, 1H, H-3″), 2.91 (dt, 1H, *J*=14.8 and 4.0 Hz, H-8″), 2.53–2.20 (m, 3H, H-4″,8″), 1.94–1.12 (m, 4H, H-5″,6″,7″), 0.98–0.75 (m, 2H, H-6″,7″) ppm. Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.16; H, 5.91; N, 4.33.

4.4. (*E*)-6-Benzylidene-2-nitrocyclohex-1-enol (3h)

A solution of crude 4 (700 mg, 2.8 mmol) in ethanol (2 ml) was added 35% aqueous hydrochloric acid (0.12 ml). The reaction mixture was stirred at room temperature for 48 h and was then heated at 60 °C for 4 h. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel eluting with dichloromethane, to give compound **3h** (439 mg, 68%) as a pale

brown oil. IR (NaCl) ν_{max}: 2934, 1558 and 1342 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ: 14.39 (s, 1H, OH), 7.80 (s, 1H, H-1′), 7.45–7.29 (m, 5H, H–Ar), 2.81–2.75 (m, 4H, H-4″, H-6″), 1.80 (quint, 2H, J=6.3 Hz, H-5″) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 165.7 (C-1), 136.7 (C-1″), 136.0 (C-6), 130.4 (C-1′), 130.3 (C-4″), 129.3 (C-3″,5″), 128.9 (C-2″,6″), 126.0 (C-2), 26.8 (C-5), 24.8 (C-3), 21.9 (C-4) ppm. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.37; H, 5.94; N, 5.80.

4.5. Reaction between 2-nitrocyclohexanone and phthalaldehyde in the presence of potassium hydroxide

To a solution of 2-nitrocycloheptanone (500 mg, 3.18 mmol) in methanol containing 5% KOH (195 ml) was added phthalaldehyde (640 mg, 4.77 mmol) and the reaction mixture was stirred at room temperature for 29 h, poured on water (200 ml) and washed with dichloromethane (3×30 ml). The aqueous layer was acidified with 2 M aqueous HCl and extracted with dichloromethane (3×200 ml). The combined organic layers were dried over anhydrous sodium sulfate and evaporated, and the residue was purified by chromatography on silica gel, eluting with a gradient from 9:1 petroleum ether–ethyl acetate to neat ethyl acetate, to obtain 160 mg (16%) of compound **5a**, 300 mg (32%) of compound **6**, as a yellow viscous oil containing a 5:1 mixture of diastereomers **a** and **b** and 93 mg (22%) of isobenzofuran-1(3*H*)-one as a white solid. *Data for* **6**: IR (NaCl) ν_{max}: 1693, 1524, 1335 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ_H: 10.13 (s, 1H, CHO**a**), 10.10 (s, 1H, CHO**b**), 8.43 (s, 1H, H-8**a**), 7.95 (dd, 1H, J=7.4, 1.4 Hz, H-3′**a**), 7.88–7.85 (m, 1H, H-3′**b**), 7.73–7.61 (m, 2H, H-4′**a**, H-5′**a**), 7.58–7.50 (m, 2H, H-4′**b**,5′**b**), 7.33 (d, 1H, J=7.3 Hz, H-6′**a**), 7.24–7.21 (m, 1H, H-6′**b**), 7.09 (s, 1H, H-8**b**), 2.74 (t, 2H, J=7.0 Hz, H-6**b**), 2.61 (t, 2H, J=7.6 Hz, H-6**a**), 2.40 (t, 2H, J=7.2 Hz, H-2**b**), 2.27 (t, 2H, J=7.4 Hz, H-2**a**), 1.73–1.62 (m, 4H, H-4**b**,5**b**), 1.61–1.48 (m, 4H, H-4**a**,5**a**), 1.33–1.23 (m, 4H, H-3**ab**) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ_C: 192.6 (CHO**b**), 192.1 (CHO**a**), 180.1 (C-1**b**), 180.0 (C-1**a**), 153.1 (C-7**a**), 152.6 (C-7**b**), 134.7 (C-2′**a**), 134.5 (C-5′**a**), 134.4 (C-5′**b**), 134.3 (C-1′**a**), 133.7 (C-3′**ab**), 133.2 (C-8**a**), 130.2 (C-4′**a**,1′**b**,2′**b**), 129.8 (C-6′**a**), 129.4 (C-4′**b**), 129.2 (C-6′**b**), 126.1 (C-8**b**), 33.6 (C-2**b**), 33.6 (C-2**a**), 32.5 (C-6**b**), 28.2 (C-3**a**), 27.8 (C-3**b**), 27.3 (C-5**a**), 26.5 (C-6**a**), 26.3 (C-5**b**), 24.0 (C-4**b**), 23.9 (C-4**a**) ppm. Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.84; H, 6.05; N, 4.30.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.05.115.

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