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3a-(*o*-Nitrophenyl)octahydroindol-4-ones: Synthesis and Spectroscopic Analysis

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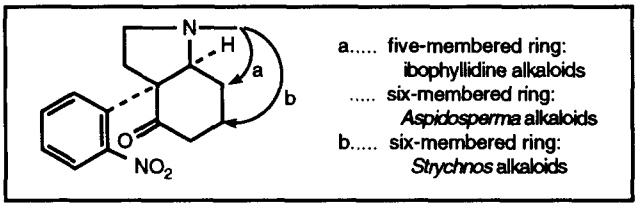
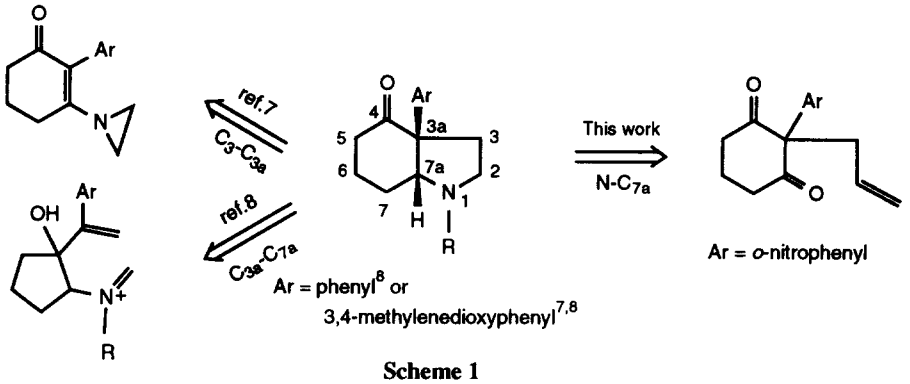
Abstract: A short entry to 3a-(*o*-nitrophenyl)octahydroindol-4-ones employing ozonolysis and double reductive amination of 2-allyl-2-(*o*-nitrophenyl)-1,3-cyclohexanedione (**9**) is described. The symmetric dione **9** is synthesized in a 50% overall yield from 1,3-cyclohexanedione by means of *o*-nitroarylation followed by *O*-allylation and subsequent Claisen rearrangement. Configurational and conformational aspects of azabicyclic derivatives **1** (**a-k**) are discussed.

In this paper we describe the new general entry to the valuable 3a-(*o*-nitrophenyl)octahydroindol-4-ones that we have developed recently[1] and we establish the spectroscopic features that allow the assignment of the stereochemical mode of fusion as well as the preferred conformation of the *cis* isomers.

3a-(*o*-Nitrophenyl)octahydroindol-4-ones are building blocks with a latent indole nucleus, which have considerable interest in the synthesis of alkaloids possessing the hexahydropyrrolo[2,3-*d*]carbazole unit such as *Strychnos*,[2] *Aspidosperma*,[3] and ibophyllidine[4] alkaloids.



In spite of the vast array of strategies developed to achieve 3a-aryloctahydroindolones to synthesize both natural products with this skeleton (i.e. mesembrine)[5] and intermediates in the synthesis of the more complex *Amaryllidaceae* alkaloids,[6] only two entries to these compounds when the ketone functionalization is located at C-4 have been described up to now.[7,8] In the first approach, by Whitlock and Smith,[7] the key step consists in the closure of the pyrrolidine ring by the formation of the C_3-C_{3a} bond from a 2-aryl-3-aziridinyl-2-cyclohexenone. In the second, Overman exploited the tandem cationic aza-Cope rearrangement/Mannich cyclization[8] for the preparation of this type of compound using 2-amino-1-(1-arylvinyl)cyclopentanols as intermediates (last bond formed C_{3a}-C_{7a}) (Scheme 1).



Scheme 1

The approach to 3a-(*o*-nitrophenyl)octahydroindol-4-ones that we describe in this work constitutes the first synthesis of these compounds and entails a concise sequence of only four steps. This strategy involves the formation of the crucial quaternary center at C-3a prior to the ring closure step. The need to develop a new synthetic entry to **1** was derived from the unsuccessful results obtained in the application of the strategy of Whitlock and Smith when the aryl group is an *o*-nitrophenyl.

Indeed, our initial attempts to synthesize octahydroindol-4-ones of type **1** via aziridine **5** resulted in failure. The aziridinyl group was successfully introduced throughout the cyclohexenone **4**,[9] but treatment of the aziridinyl derivative **5** with sodium iodide, in accordance with the protocol reported,[7] failed to provide the octahydroindolone nucleus, probably due to the electron-withdrawing character of the nitrophenyl group present in the substrate. In addition, a modification of this sequence was explored. Thus, reduction of enol ether **6** with DIBAH,[10] followed by treatment in an acidic medium furnished cyclohexenone **7**. This enone added aziridine but the resulting β-aziridinyl ketone underwent a retro-Michael process when treated with ethyl chloroformate, precluding its utilization in the octahydroindolone synthesis.[11] The failure could again be accounted for by the presence of the *o*-nitrophenyl substituent, which increases the acidity of the methine proton at C-2 in the β-aziridinyl adduct, thus making the retro-Michael process easier.

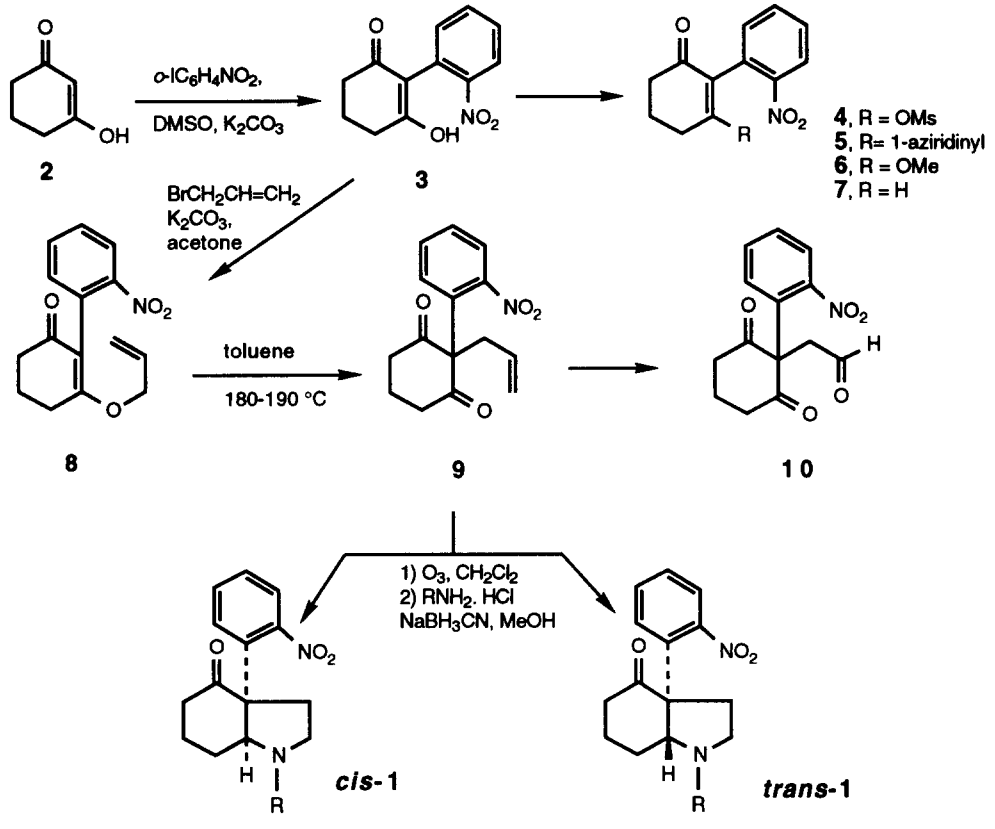
The starting material for these preliminary studies and for the successful synthesis is 2-(*o*-nitrophenyl)-1,3-cyclohexanedione (**3**). This compound was prepared by direct arylation of dione **2** by a nucleophilic aromatic substitution reaction[12] using potassium carbonate as a base and dimethyl sulfoxide as a solvent. Using *o*-fluoronitrobenzene as arylating agent[13] the yield was never better than 30%, the reaction could not be scaled-up to more than 10 g of dione **2** and the reaction mixture required tedious purification. Interestingly, when *o*-iodonitrobenzene was used as arylating agent in the same reaction conditions the process took place in better conditions.[14] The yield increased to 70%, the reaction could be carried out at multigram scale and the reaction mixture did not require purification from the synthetic standpoint.

The next step in our approach to perhydroindol-4-ones of type **1** involved the construction of the quaternary carbon center. Treatment of β-diketone **3** with allyl bromide provided exclusively the *O*-allylated product **8**,[15] but heating of this allyl vinyl ether gave the α,α-disubstituted cyclohexanedione **9** through a Claisen rearrangement.[16] Attempts to obtain compound **9** by a reverse sequence, first allylation[17] and then arylation, from 1,3-cyclohexanedione, failed in the second step.

With the prochiral dione **9** in hand, we undertook the elaboration of the pyrrolidine ring. The amine moiety was introduced by a double reductive amination process;[18] the first, in an intermolecular way, upon the

aldehyde group of the tricarbonyl derivative resulting from the ozonolysis of 2-allyl-2-(*o*-nitrophenyl)-1,3-cyclohexanedione (**9**), and the second, in an intramolecular manner,[19] upon one of the two enantiotopic ketone carbonyl groups.

Attempts to carry out the transformation in two steps, through aldehyde **10**, failed,[20] whereas the one-pot procedure[21] was satisfactory. Thus, conversion of dione **9** to the target compound **1a** was effected through a one-pot procedure that involves six successive chemical transformations: ozonolysis of the allyl group, ozonide



Series	R	1 (Overall yield)	*cis*/*trans* ratio
a	CH_3	62 %	1.5 : 1
b	CH_2CO_2Et	51 %	1 : 1
c	$CH_2C_6H_5$	56 %	2.1 : 1
d	$CH_2CH_2SeC_6H_5$	41 %	2.5 : 1
e	$CH(C_6H_5)_2$	22 %	4.5 : 1
f	$CH_2CH(OCH_3)_2$	33 %	1 : 3
g	(*R*)-$CH(CH_3)C_6H_5$	35 %	4 : 1 (78:<2/15:5)
h	(*S*)-$CH(CH_3)COOCH_3$	53 %	2 : 1 (54:12/20:13)
i	(*S*)-$CH(CH_3)CH_2OH$	20 %	0 : 1
j	(*S*)-$CH(C_6H_5)CH_2OH$	46 %	2.3 : 1
k	(*S*)-$CH(CH_3)CH(OCH_3)_2$	18 %	0 : 1

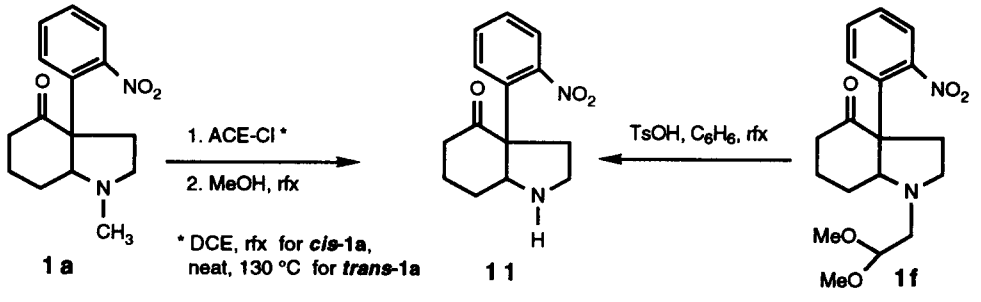
Scheme 2

cleavage with sodium cyanoborohydride, aldimine formation, aldimine reduction, cyclization, and further reduction of the resulting N-C_{7a} iminium salt. The process was carried out with several substituted primary amines. In this way, octahydroindolones of series **a-k** were prepared; yields and stereochemical data are summarized in Scheme 2. As reflected, both the *cis/trans* ratio and the overall yield of this multistep sequence depend on the bulkiness of the substituent in the amine; while the chemical yield diminishes, the stereoselectivity increases when the volume of the substituent grows. In all cases both epimers were easily separated by flash chromatography; in each series the *trans* isomer eluted first and the *cis* isomer was the more polar epimer.

The preparation of 3a-(*o*-nitrophenyl)octahydroindol-4-ones in an enantiomeric pure form[22,23] was the second goal pursued in this work. The use of a chiral amine (series g-k) would allow for both discrimination of the diastereotopic ketone groups and face differentiation in the symmetrical dione **9**, once the first intermolecular reductive amination has taken place.

The results obtained using enantiomerically pure amines as condensating agents in the process of cyclizative double reductive amination are depicted in Scheme 2. From these results we cannot establish any conclusive relationship between the type of chiral amine and the stereoselectivity. Neverthless, some noteworthy features are: i) the complete diastereo- and enantioselectivity obtained when (*S*)-alaninol and (*S*)-2,2-dimethoxy-1-methylethylamine (entries i and k) were used as condensating agents. In each case only one *trans* diastereomer (***trans*-1i** or ***trans*-1k**) was isolated; the same diastereoselectivity was also obtained with 2,2-dimethoxyethylamine (entry f). This suggests that amines having a β-oxygen are of choice in order to obtain *trans* octahydroindoles. ii) In contrast, chiral benzyl amines (entries g and j) must be used when *cis* octahydroindoles are desired. The isolation of ***cis*-1g** in an enatiomerically pure form in a 28% yield could allow in the future the obtention of enantiomerically pure ***cis*-11** and its subsequent utilization in the synthesis of *Strychnos* indole alkaloids.[2]

The valuable secondary amine **11** (R=H) could not be obtained by the new procedure described in this paper, operating with ammonium sources (ammonium bromide or ammonium nitrate) as condensating agents. However, the compound ***cis*-11** was prepared from octahydroindolone ***cis*-1a** ($R=CH_3$) by treatment with α-(chloroethyl)chloroformate[24] and warming of the resulting carbamate in a methanol solution. The compound ***trans*-1a** was more resistant to dealkylation than the *cis* isomer when subjected to the above conditions, presumably because of the steric hindrance at the nitrogen atom. The corresponding carbamate was obtained, in good yield, when the *N*-methyl derivative ***trans*-1a** was warmed in neat α-chloroethylchloroformate.[25] Boiling of this carbamate in methanol afforded the secondary amine ***trans*-11**.



Scheme 3

In addition, the secondary amines ***cis*-11** and ***trans*-11** were prepared by an alternative procedure. Thus, treatment of the octahydroindoles ***cis*-1f** and ***trans*-1f** with *p*-toluenesulfonic acid in benzene at reflux[26] furnished the secondary amines ***cis*-11** and ***trans*-11** in 48% and 43% yield, respectively.

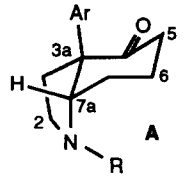
Spectroscopic Analysis of octahydroindol-4-ones 1.

Two spectroscopic features clearly differentiate the two series, *cis* and *trans*, of 3a-(*o*-nitrophenyl) octahydroindol-4-ones: (i) the carbonyl IR absorption, which appears around 1718 cm^{-1} in the *trans* epimers but is never higher than 1700 cm^{-1} in the *cis* isomers; (ii) the ^{1}H-NMR chemical shift of the most deshielded aromatic proton, which appears as a doublet at δ 8.83 (± 0.3 ppm) in the *trans*-derivatives, but at δ 7.91 (±0.15 ppm) in the *cis* series.

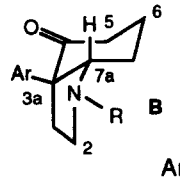
The *cis* stereochemistry of compound ***cis*-1a** and its preferred conformation are apparent from the NMR data. Thus, the 7a-methine proton appears as a doublet of doublets with J = 6.6 and 3.7 Hz, which is consistent only with an equatorial disposition of H-7a respect to the cyclohexane ring. The ^{13}C-NMR chemical shifts of the cyclohexanone methylenes reveal the *cis* relationship of the two rings. All of these are shielded strongly when compared with sterically unencumbered cyclohexanones.[27] This implies a γ-effect over C-5, C-6, and C-7 only appreciated with a *cis* fusion and when the alkylamino is axially oriented in the ketone ring, and limits the compound to conformation of type **A**. This feature is in agreement with the known thermodynamic preference of *cis*-3a-arylhydroindoles for a conformation that places the C-3a aryl substituent in axial orientation.[28] The chemical shift of C-3, C-6, C-7a, and C_{ipso}[29] are of diagnostic value for the assignment of *cis-trans* configuration in compounds **1a**, as well as in all compounds of this type synthesized.

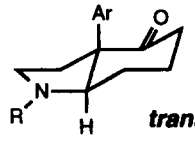
The small variance of the chemical shifts for compounds of the *cis* series **1b**, **1c**, **1d**, **1f**, and **1h'** shows the conformational identity of these compounds with respect to ***cis*-1a**. However, compounds **1e**, **1g** and **1h** show a different pattern of NMR data, which suggests a conformation of type **B**.[30] Thus, the H-7a proton shows a coupling splitting (J = 11 and 5 Hz) that implies a trans-diaxial relationship only feasible in this conformation. Moreover, the chemical shifts of C-2 and C-7a are more deshielded than those expected for a conformation of type **A**.[31]Additionally, the chemical shifts of C-5 and C-7 are slightly shielded by the change of the 1,3-diaxial relationship between the C_3-Ar to C_3-C_{3a} bond.The similarities in the values of C-6 could be derived from a shielding effect of the β-alkylamino moiety[32] in the **B** conformation. Finally, the chemical shift of C-*ipso* of the aryl group is also significant and consistent with a conformational change. In compounds with conformation of type **B**, C_{ipso} is more deshielded (δ 139) than in the aforementioned compounds (δ 136-138).[29,33]

The 3a-(*o*-nitrophenyl) substituted octahydroindoles **1e**, **1g**, **1h**, and **1j** constitute a rare example, in which the preferred conformation locates the 3a-aryl group equatorial respect to the cyclohexane ring. Interestingly, the secondary amine ***cis*-11** also shows this preferred conformation, suggesting that the steric



***cis*-1**





***trans*-1**

Ar = *o*-nitrophenyl

factor is not the only one responsible for this conformational change. Thus, the presence of the *o*-nitro substituent could explain this behaviour, not observed in octahydroindolones substituted in C-3a with phenyl or 3,4-methylenedioxyphenyl groups, which have been studied profusely.

Table 1. ^{13}C NMR Chemical Shifts of 3a-(*o*-Nitrophenyl)-octahydroindol-4-ones

Compound	C-2	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'
***cis*-1a**	51.8	33.2	62.4	208.5	37.8	20.5	22.4	70.2	135.9	149.5	125.0	128.0	132.5	130.2
***cis*-1b**	48.7	33.6	61.7	208.6	37.2	19.8	23.0	68.3	136.9	148.6	125.0	127.9	132.7	130.5
***cis*-1c**	48.5	33.5	62.1	209.0	37.2	19.8	22.1	68.6	137.8	148.3	125.0	127.8	132.5	131.0
***cis*-1d**	50.3	33.3	61.9	208.8	37.1	19.7	22.2	68.7	137.6	148.2	125.0	127.8	132.7	131.1
***cis*-1e**	47.1	33.2	61.9	209.2	36.6	19.6	20.5	66.1	139.5	147.7	125.4	127.9	132.7	131.4
***cis*-1f**	52.7	33.8	61.9	208.7	37.3	19.9	22.6	69.8	137.6	148.1	124.9	127.6	132.4	130.7
***cis*-1g**	47.4	33.5	62.0	209.4	36.8	19.5	20.7	66.1	139.3	148.0	125.0	127.4	132.5	131.6
***cis*-1h**	44.7	33.5	61.4	209.0	36.8	19.3	24.2	67.5	138.4	148.0	125.2	127.8	132.8	130.9
***cis*-1h'**	44.1	33.0	61.4	208.4	37.8	20.1	25.0	66.5	135.6	149.4	125.1	128.0	132.5	129.9
***cis*-1j**	46.1	32.7	62.1	208.7	36.6	19.5	22.3	67.1	138.8	147.3	125.3	127.7	132.6	130.7
***cis*-1l**	44.2	34.9	64.4	209.5	36.2	20.1	27.9	67.3	137.9	148.0	126.1	128.2	133.5	129.3
***trans*-1a**	53.3	30.1	63.3	207.4	38.6	22.7	25.7	78.4	133.5	150.6	124.0	127.7	131.4	132.7
***trans*-1b**	50.9	30.3	62.7	207.2	38.5	23.1	25.6	75.4	133.2	150.8	124.1	128.0	131.6	132.7
***trans*-1c**	51.0	30.0	63.2	207.4	38.8	23.3	25.7	76.9	133.2	151.0	124.2	127.2	131.4	132.6
***trans*-1d**	53.7	30.0	63.1	207.4	38.7	23.1	25.6	76.3	132.8	150.8	124.1	127.9	131.6	133.0
***trans*-1e**	49.5	30.1	63.7	207.5	38.8	24.8	25.7	75.8	133.0	150.9	124.3	127.7	131.4	132.7
***trans*-1f**	51.4	30.3	62.6	207.0	38.8	23.3	25.7	76.4	132.8	150.5	123.9	127.7	131.2	132.4
***trans*-1g**	45.1	30.0	63.0	207.7	38.7	23.7	25.8	74.5	133.2	150.7	124.1	127.7	131.3	132.6
***trans*-1i**	40.4	30.8	62.7	207.0	39.0	22.9	25.7	72.1	131.9	150.7	124.3	128.0	131.2	131.7
***trans*-1j**	42.1	30.3	62.2	206.6	38.9	23.0	25.4	71.8	133.6	150.8	124.2	128.0	131.2	131.7
***trans*-1k**	41.5	30.9	62.2	207.6	39.0	22.9	25.8	72.2	132.5	150.8	123.9	127.7	131.2	132.7
***trans*-1l**	42.3	32.4	62.3	207.4	39.0	25.5	26.0	71.3	132.1	150.6	124.0	127.8	131.3	132.4

***cis*-1a**: 38.1 (NCH_3); ***cis*-1b**: 170.8 (COO), 60.2 (OCH_2), 51.6 (NCH_2), 13.8 (CH_3); ***cis*-1c**: 139.3 (*ipso*-C), 128.3 and 128.0 (*o*- and *m*-C), 126.9 (*p*-C), 54.8 (NCH_2); ***cis*-1d**: 132.4 (*m*-C), 131.0 (*ipso*-C), 129.0 (*o*-C), 125.7 (*p*-C), 48.1 (NCH_2), 27.0 ($SeCH_2$); ***cis*-1e**: 143.8 (*ipso*-C), 142.8 (*ipso*-C), 128.7 (*m*-C), 127.2 (*p*-C), 126.9 (*o*-C), 69.5 (ArCHAr); ***cis*-1f**: 103.2 ($CH(OCH_3)_2$), 53.7 (OCH_3), 53.2 (OCH_3), 49.5 (NCH_2); ***cis*-1g**: 145.9 (*ipso*-C), 128.4 (*m*-C), 127.0 (*p*-C), 126.8 (*o*-C), 59.0 (NCHAr), 22.2 (CH_3); ***cis*-1h**: 174.8 (COO), 56.7 (CHCOO), 51.4 (OCH_3), 16.0 (CH_3); ***cis*-1h'**: 173.7 (COO), 55.1 (CHCOO), 51.0 (OCH_3), 16.5 (CH_3); ***cis*-1j**: 139.8 (*ipso*-C), 128.4 and 128.2 (*o*- and *m*-C), 127.5 (*p*-C), 64.7 (NCHAr), 64.0 (CH_2OH); ***trans*-1a**: 40.8 (NCH_3); ***trans*-1b**: 171.2 (COO), 60.6 (OCH_2), 54.3 (NCH_2CO), 14.0 (CH_3); ***trans*-1c**: 139.2 (*ipso*-C), 128.5 and 128.4 (*o*- and *m*-C), 127.9 (*p*-C), 59.0 (NCH_2); ***trans*-1d**: 132.6 (*m*-C), 130.5 (*ipso*-C), 129.2 (*o*-C), 127.0 (*p*-C), 50.1 (NCH_2), 27.2 ($SeCH_2$); ***trans*-1e**: 143.4 (*ipso*-C), 141.8 (*ipso*-C), 127.3-128.6 (several CH), 73.6 (ArCHAr); ***trans*-1f**: 103.1 ($CH(OCH_3)_2$), 55.4 (NCH_2), 53.9 (OCH_3), 52.8 (OCH_3); ***trans*-1g**: 144.9 (*ipso*-C), 128.4 (*m*-C), 127.3 (*o*-C), 126.9 (*p*-C), 58.9 (NCHAr), 14.6 (CH_3); ***trans*-1l**: 64.9 (CH_2OH), 53.8 (NCH), 6.5 (CH_3); ***trans*-1j**: 141.9 (*ipso*-C), 128.9 and 128.7 (*o*- and *m*-C), 128.3 (*p*-C), 63.0 (NCHAr), 62.4 (CH_2OH); ***trans*-1k**: 106.7 ($CH(OMe)_2$); 55.1 and 52.9 (OCH_3); 52.5 (NCH); 5.7 (CH_3).

EXPERIMENTAL

General. Unless otherwise noted, ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 200 and 50.3 MHz respectively, using Me_4Si as internal standard. Chemical shifts are reported in ppm downfield (δ) from Me_4Si. IR spectra were recorded on a Nicolet 205 FT infrared spectrophotometer and only noteworthy absorptions are listed. Melting points were determined in a capillary tube and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. TLC was carried out on SiO_2 (silica gel 60 F_{254}, Merck), and the spots were located with iodoplatinate reagent. Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230-400 mesh ASTM). Drying of organic extracts during workup of reactions was performed over anhydrous Na_2SO_4. Evaporation of solvents was accomplished with a rotatory evaporator. Microanalyses were performed by Centro de Investigación y Desarrollo (CSIC), Barcelona.

2-(*o*-Nitrophenyl)-1,3-cyclohexanedione (3). A mixture of 1,3-cyclohexanedione (18 g, 160.6 mmol), anhydrous potassium carbonate (33.3 g, 241 mmol), and *o*-iodonitrobenzene (20 g, 80.3 mmol) in dimethyl sulfoxide (250 ml) was heated to 85-90 °C for 4 h. After cooling, the mixture was poured into water. The resulting solution was acidified with concentrated hydrochloric acid and extracted with methylene chloride. The combined organic extracts were washed with brine, dried, and evaporated to give a brown foam (18.5 g), which was used in the next reaction without purification. An analytical sample was obtained by crystallization from CH_2Cl_2: mp 208-209 °C (white powder). An aliquot of the crude dione **3** was chromatographed (CH_2Cl_2, 2% MeOH) to give pure dione in 72% yield. IR (KBr) 3250-2950, 1605, 1590, 1505, 1370 cm^{-1}. ^1H NMR δ 1.9-2.1 (br, 2H, H-5), 2.35-2.5 (br, 4H, H-4 and H-6), 7.18 (d, J = 7 Hz, H-6'), 7.33 (t, J = 8 Hz, H-4'), 7.49 (dd, J = 8 and 7 Hz, H-5'), 7.87 (d, J = 8 Hz, H-3'), 8.96 (br, OH). Anal. Calcd for $C_{12}H_{11}NO_4$ (233.23): C, 61.80; H, 4.75; N, 6.00. Found: C, 61.88; H, 4.75; N, 5.97.

When the reaction was carried out with 1,3-cyclohexanedione (10 g, 89 mmol), anhydrous potassium carbonate (30.8 g, 223 mmol), and *o*-fluoronitrobenzene (9.4 ml, 89 mmol) in dimethyl sulfoxide (200 ml) two chromatohraphic purifications were needed to obtain arylated dione **3** (6.24 g) in 30 % yield.

3-(Methylsulfonyloxy)-2-(*o*-nitrophenyl)-2-cyclohexenone (4). To a stirred solution of dione **3** (1 g, 4.25 mmol) in methylene chloride (20 ml) were added at room temperature methanesulfonyl chloride (0.33 ml, 4.25 mmol) and anhydrous potassium carbonate (1.77 g, 12.8 mmol). After stirring for 2 h, the reaction mixture was diluted with methylene chloride and washed with water and brine. The organic solution was dried and evaporated to give a crude oil, which was chromatographed (1:1 hexane-EtOAc) affording 925 mg (70%) of mesylate **4**. ^1H NMR δ 2.12-2.34 (m, 2H, H-5), 2.56-2.68 (m, 2H, H-4), 2.78 (s, CH_3), 2.90-3.10 (m, 2H, H-6), 7.38 (dd, J = 7.5 and 1.5 Hz, H-6'), 7.55 (td, J = 7.5 and 1.5 Hz, H-4'), 7.68 (td, J = 7.5 and 1.5 Hz, H-5'), 8.13 (dd, J = 8 and 1.5 Hz, H-3').

3-Aziridinyl-2-(*o*-nitrophenyl)-2-cyclohexenone (5). To a stirred solution of mesylate **4** (1.18 g, 3.8 mmol) in methylene chloride (25 ml), aziridine (0.5 ml) and anhydrous potassium carbonate (2 g, 14.5 mmol) were added at room temperature. After being stirred for 12 h, the reaction mixture was diluted with methylene chloride and washed with brine. The organic phase was dried and evaporated to give an oil, which

was chromatographed (CH_2Cl_2) affording 424 mg (43%) of aziridine **5**. From the aqueous layer, after acidification and extraction with methynene chloride, 300 mg of dione **3** were recovered.

Compound **5**: ^1H NMR δ 1.90-2.01 (m, 4H, aziridine), 2.08-2.21 (m, 2H, H-5), 2.42-2.55 (m, 2H, H-4), 2.59-2.72 (m, 2H, H-6), 7.42-7.54 (m, H-4' and H-6'), 7.63 (t, J = 7.5 Hz, H-5'), 8.03 (d, J = 7.5 Hz, H-3').

3-Methoxy-2-(*o*-nitrophenyl)-2-cyclohexenone (6). To a solution of dione **3** (1 g, 4.27 mmol) and dimethyl sulfate (0.4 ml, 4.27 mmol) in anhydrous acetone (15 ml) was added potassium carbonate (650 mg, 4.7 mmol). The mixture was refluxed for 2 h and then stirred at room temperature for 1 h. After filtering through celite and concentrating, the residue was dissolved in methylene chloride and washed with aqueous sodium bicarbonate solution. The organic extract dried and evaporated yielded quantitatively the enol ether **6** (1.05 g). An analytical sample was obtained by crystallization (EtOAc): mp 121-123 °C. IR ($CHCl_3$) 1647, 1617, 1599, 1523, 1358 cm^{-1}. ^1H NMR δ 2.16 (m, 2H, H-5), 2.51 (t, J = 6 Hz, 2H, H-4), 2.71 (t , J = 6 Hz, 2H, 6-H), 3.72 (s, OCH_3), 7.25 (dd, J = 8 and 1.5 Hz, H-6'), 7.41 (td, J = 8 and 1.2 Hz, H-4'), 7.57 (td, J = 8 and 1.5 Hz, H-5'), 7.96 (dd, J = 8 and 1.5 Hz, H-3'). Anal. Calcd for $C_{13}H_{13}NO_4$ (247.25): C, 63.15; H, 5.30; N, 5.57. Found: C, 63.16; H, 5.33; N, 5.57.

2-(*o*-Nitrophenyl)-2-cyclohexenone (7). DIBAL-H (1 M in toluene, 8.25 ml) was added dropwise to a stirred solution of enol ether **6** (1.36 g, 5.5 mmol) in toluene (75 ml), keeping the temperature below -50 °C. After 3 h at -50 °C, the reaction mixture was poured into dilute hydrochloric acid and stirred at room temperature for 15 min. The organic layer was separated, washed with aqueous sodium bicarbonate solution, dried, and evaporated. The residue chromatographed (7:3 hexane-EtOAc) afforded 870 mg (73%) of enone **7**. An analytical sample was obtained by crystallization (hexane-EtOAc): mp 96-98 °C. IR ($CHCl_3$) 1660, 1510, 1345 cm^{-1}. ^1H NMR δ 2.15 (m, 2H, H-5), 2.53-2.64 (m, 4H, H-4 and H-6), 7.01 (t, J = 8.5 and 4.5 Hz, H-3), 7.26 (dd, J = 8 and 1.5 Hz, H-6'), 7.47 (td, J = 8 and 1.5 Hz, H-4'), 7.61 (td, J = 8 and 1.5 Hz, H-5'), 8.03 (dd, J = 8 and 1.5 Hz, H-3'). Anal. Calcd for $C_{12}H_{11}NO_3$ (217.23): C, 66.35; H, 5.10; N, 6.45. Found: C, 66.37; H, 5.12; N, 6.45.

3-Allyloxy-2-(*o*-nitrophenyl)-2-cyclohexenone (8). A mixture of purified dione **3** (21 g, 89.7 mmol), anhydrous potassium carbonate (24.8 g, 0.18 mol), and allyl bromide (8.34 ml, 98.7 mmol) in dry acetone (500 ml) was stirred at reflux temperature for 3 h. The solvent was removed and the residue was partitioned between water and methylene chloride. The aqueous layer was extracted with methylene chloride. The combined organic extracts were washed with water, dried and concentrated to give an oil, which was chromatographed (CH_2Cl_2) affording 20.8 g (85%) of enol ether **8** as an oil. IR ($CHCl_3$) 1653, 1610, 1600, 1523, 1352 cm^{-1}. ^1H NMR δ 2.15 (m, 2H, H-5), 2.52 (t, J = 6 Hz, 2H, H-4), 2.71 (*t*, J = 6 Hz, 2H, H-6), 4.49 (d, J = 5.4 Hz, OCH_2), 5.16 (dd, J = 16 and 1.3 Hz, H-*trans*), 5.17 (dd, J = 11 and 1.3 Hz, H-*cis*), 5.80 (ddd, J = 16, 11 and 5.4 Hz, H-*gem*), 7.27 (dd, J = 7.5 and 1.4 Hz, H-6'), 7.41 (td, J = 8, 7.5 and 1.4 Hz, H-4'), 7.57 (td, J = 7.5 and 1.3 Hz, H-5'), 7.99 (dd, J = 8 and 1.3 Hz, H-3'). Anal. Calcd for $C_{15}H_{15}NO_4$ (273.29): C, 65.92; H, 5.53; N, 5.12. Found: C, 65.90; H, 5.53, N, 5.10.

When crude arylated dione (18.5 g) was used in the same reaction conditions, compound **8** (14.45 g) was isolated after chromatography in a 66 % yield from *o*-iodonitobenzene.

2-Allyl-2-(*o*-nitrophenyl)-1,3-cyclohexanedione (9). A solution of enol ether **4** (4.45 g, 16.3 mmol) in anhydrous toluene (45 ml) was stirred at 180-190 °C in a sealed tube for 12 h. After evaporating the solvent, the residue was chromatographed (CH_2Cl_2) affording 3.56 g (80%) of dione **3**. An analytical sample was obtained by crystallization from EtOAc-hexane: mp 160-161 °C (yellow needles). IR (KBr) 1700, 1675, 1505, 1340 cm^{-1}. ^1H NMR δ 2.06 and 2.48 (2m, 1H each, H-5), 2.66-2.96 (m, 4H, H-4 and H-6), 3.06 (d, J = 6.5 Hz, CH_2), 5.14 (dd, J = 10 and 1.2 Hz, H-*cis*), 5.24 (dd, J = 17 and 1.4 Hz, H-*trans*), 5.58 (m, J = 17, 10 and 6.5 Hz, H-*gem*), 7.40-7.74 (m, 3H, ArH), 8.11 (dd, J = 8 and 1.3 Hz, H-3'). Anal. Calcd for $C_{15}H_{15}NO_4$ (273.29): C, 65.92; H, 5.53; N, 5.12. Found: C, 65.85; H, 5.22; N, 5.47.

2-(Formylmethyl)-2-(*o*-nitrophenyl)-1,3-cyclohexanedione (10). Sodium metaperiodate (780 mg, 3.64 mmol) was added portionwise during 45 min to a mixture of dione **9** (250 mg, 0.91 mmol) and osmium tetroxide (61 mg, 0.24 mmol) in water-diethyl ether 1:1 (15 ml). After stirring at room temperature for 24 h, the mixture was diluted with water and extracted with diethyl ether. The organic layer was washed with water, dried and evaporated to give the aldehyde **10** (200 mg, 80%). ^1H NMR δ 2.1-2.5 (m, H-5), 2.7-3.0 (m, H-4 and H-6), 3.22 (d, J = 2 Hz, CH_2CO), 7.39 (dd, J = 8 and 1.5 Hz, H-6'), 7.55 (td, J = 8 and 1.5 Hz, H-4'), 7.71 (td, J = 8 and 1.5 Hz, H-5'), 8.10 (dd, J = 8 and 1.5 Hz, H-3'), 9.51 (t, J = 2 Hz, CHO).

Table 2. ^{13}C NMR Chemical Shifts[a] of 2-(*o*-Nitrophenyl)cyclohexanone Derivatives 3-10

C-Atom	3	4[b]	5[b]	6[b]	7	8[b]	9[b]	10[b]
C(1)	187.9	196,5	194.6	196.2	196.7	196.4	205.5	204.5
C(2)	114.4	126.6	120.4	117.1	139.2	*c*	72.6	70.5
C(3)	187.9	162.2	166.6	172.8	147.0	171.9	205.5	204.5
C(4)	32.4	29.2	28.8	25.0	25.9	25.4	36.5	36.8
C(5)	20.0	20.1	20.4	20.0	22.2	20.2	16.6	16.9
C(6)	32.4	36.6	36.1	36.1	38.0	36.2	36.5	36.8
C(1')	128.1	128.6	129.0	128.7	132.0	128.8	132.1	133.8
C(2')	149.5	148.6	148.9	149.4	148.5	149.4	147.8	147.8
C(3')	124.2	124.6	123.1	123.9	124.0	124.0	126.0	126.2
C(4')	128.2	129.6	127.3	127.8	128.7	127.9	128.7	129.4
C(5')	133.7	133.3	132.7	133.4	133.4	133.4	133.8	134.0
C(6')	132.7	132.7	131.7	132.3	131.7	132.4	131.3	130.8

[a] In ppm relative to TMS. Recorded at 50.3 MHz. [b] Substituent signals: **4**, 39.0 (OMs); **5**, 27.2 (aziridine); **6**, 55.6 (OMe); **8**, 68.6, 117.6, 132.1 ($OCH_2CH{=}CH_2$); **9**, 37.6, 119.9, 130.8 ($CH_2CH{=}CH_2$); **10**, 45.1, 197.9 (CH_2CHO). [c] Not observed

General Procedure for Ozonolysis-Double Reductive Amination of Dione 9.

1-Methyl-3a-(*o*-nitrophenyl)octahydroindol-4-one (1a). A stirred solution of dione **9** (8 g, 29.3 mmol, 1 equiv) in methylene chloride (500 ml) at -78 °C was charged with a constant stream of ozone. After 5 h, the solution turned characteristic pale blue and was purged with oxygen. The solvent was removed

with a rotatory evaporator without warming, and the residue was dissolved in methanol (100 ml). To this solution were added first a solution of methylamine hydrochloride (8 g, 119 mmol, 4 equiv) in methanol (100 ml) and then sodium cyanoborohydride (0.93 g, 14.8 mmol, 0.5 equiv). After being stirred for 30 min, an additional portion of sodium cyanoborohydride (0.93 g, 14.8 mmol, 0.5 equiv) was added and stirring was continued for 1 h. At this time, an additional portion of sodium cyanoborohydride (2.79 g, 44.5 mmol, 1.5 equiv) was added and stirring was continued for 2.5 h. The reaction was quenched with 1N hydrochloric acid (50 ml) and the stirring was continued for 30 min. After removal of the methanol under reduced pressure, the aqueous mixture was extracted with ether, and the organic layers were discarded. The aqueous layer was made alkaline with solid potassium carbonate, and extracted with methylene chloride. The combined organic extracts were dried and evaporated to give an oil, which was chromatographed. On elution with methylene chloride, 1.86 g (23%) of octahydroindole ***trans*-1a** were obtained and on elution with methylene chloride with 2% MeOH 2.93 g (36%) of octahydroindole ***cis*-1a** were obtained.

Compund ***cis*-1a**: mp 95-96 °C (ether-acetone). IR ($CHCl_3$) 1699, 1528, 1356 cm^{-1}. ^1H NMR (500 MHz) δ 1.68-1.76 (m, H-7ax), 1.95-2.09 (m, H-6ax, H-6eq, and H-7eq), 2.19 (ddd, J = 14, 9 and 4 Hz, H-3α), 2.29 (s, NCH_3), 2.35-2.42 (m, H-5eq), 2.47 (ddd, J = 16, 7 and 5.5 Hz, H-5ax), 2.61 (ddd, J = 14, 9 and 6.5 Hz, H-3β), 2.80 (dt, J = 9 and 6.5 Hz, H-2α), 2.98 (td, J = 9 and 4 Hz, H-2β), 3.24 (dd, J = 6.5 and 3.5 Hz, H-7a), 7.40 (td, J = 8 and 1.5 Hz, H-4'), 7.48 (dd, J = 8 and 1.5 Hz, H-6'), 7.57 (td, J = 8 and 1.5 Hz, H-4'), 7.74 (dd, J = 8 and 1.5 Hz, H-3'). Anal. Calcd for $C_{15}H_{18}N_2O_3$ (274.32): C, 65.68; H, 6.61; N, 10.21. Found: C, 65.55; H, 6.57; N, 10.12.

Compound ***trans*-1a**: IR ($CHCl_3$) 1719, 1532, 1362 cm^{-1}. ^1H NMR (500 MHz) δ 1.47-1.68 (m, 7-Hax), 1.82-1.92 (m, H-6eq, H-7eq, and H-3α), 1.97 (qd, J = 13 and 6 Hz, H-6ax), 2.22 (td, J = 13 and 6.5 Hz, H-5ax), 2.25 (m, H-7a), 2.30 (m, H-2β and H-5eq), 2.34 (s, NCH_3), 2.83 (ddd, J = 13.5, 11 and 7 Hz, H-3β), 3.21 (ddd, J = 10, 8.5 and 7 Hz, H-2α), 7.35 (t, J = 7.5 Hz, H-4'), 7.48 (d, J = 7.5 Hz, H-3'), 7.53 (t, J =7.5 Hz, H-5'), 8.79 (dd, J = 7.5 and 1.5 Hz, H-6'). Anal. Calcd for $C_{15}H_{18}N_2O_3$ (274.32): C, 65.68; H, 6.61; N, 10.21. Found: C, 65.82; H, 6.75; N, 10.20.

Ethyl 3a-(*o*-Nitrophenyl)-4-oxooctahydroindoleacetate (1b). The sequence of ozonolysis (bubbling ozone for 5 min) of dione **9** (200 mg, 0.73 mmol) and reductive amination with glycine ethyl ester hydrochloride (4 equiv) was carried out according to the above procedure. Chromatography (hexane to 7:3 EtOAc-hexane) afforded 66 mg (26%) of octahydroindole ***trans*-1b** and 63 mg (25 %) of octahydroindole ***cis*-1b**.

Compound ***cis*-1b**: mp 140-141 °C (ether). IR ($CHCl_3$) 1731, 1700, 1528, 1356 cm^{-1}. ^1H NMR δ 1.20 (t, J = 7 Hz, CH_3), 1.68 (m, H-7ax), 1.95-2.55 (m), 3.03 (td, J = 10 and 4.4 Hz, H-2α), 3.32 (dt, J = 9 and 6.5 Hz, H-2β), 3.38-3.40 (2s, 1H each, CH_2COO), 3.67 (dd, J = 8 and 4.5 Hz, H-7a), 4.09 (q, J = 7 Hz, $COOCH_2$), 7.42 (ddd, J = 8, 6.5 and 2 Hz, H-4'), 7.50-7.67 (m, H-5' and H-6'); 7.83 (dd, J = 8 and 1 Hz, H-3'). Anal. Calcd for $C_{18}H_{22}N_2O_5$ (346.39): C, 62.42; H, 6.40; N, 8.09. Found: C, 62.43; H, 6.42; N, 7.97.

Compound ***trans*-1b**: IR ($CHCl_3$) 1719, 1531, 1361 cm^{-1}. ^1H NMR δ 1.32 (t, J = 7 Hz, CH_3), 1.4-2.75 (m, H), 2.84 (ddd, J = 13, 10 and 7.5 Hz, H-3β), 3.33 (m, H-2α), 3.33 and 3.52 (2d, 1H each, J = 17 Hz, CH_2COO), 4.22 (q, J = 7 Hz, $COOCH_2$), 7.40 (td, J = 8 and 1.5 Hz, H-4'), 7.52 (dd, J = 8 and 1.5 Hz,

H-3'), 7.60 (td, J = 8 and 1.5 Hz, H-5'), 8.93 (dd, J = 8 and 1.5, H-6'). Anal. Calcd for $C_{18}H_{22}N_2O_5$ (346.39): C, 62.42; H, 6.40; N, 8.09. Found: C, 62.39; H, 6.46; N, 7.86.

1-Benzyl-3a-(*o*-nitrophenyl)octahydroindol-4-one (1c). Operating as above, starting from 300 mg (1.1 mmol) of dione **9** and benzylamine hydrochloride, and after chromatography (hexane to 7:3 hexane-EtOAc) octahydroindole ***trans*-1c** (70 mg, 18%) and octahydroindole ***cis*-1c** (146 mg, 38%) were isolated.

Compound ***cis*-1c**: mp 123-124 °C (EtOAc-ether); IR ($CHCl_3$) 1696, 1525, 1355 cm^{-1}. ^1H NMR δ 1.74 (m, H-7ax), 1.95-2.60 (m, 7H), 2.80-3.04 (m, 2H, H-2), 3.49 (dd, J = 9 and 4.5 Hz, H-7a), 3.65 and 3.76 (2d, 1H each, J = 13.5 Hz, CH_2Ar), 7.05-7.30 (m, ArH), 7.44 (ddd, J = 8.5, 7 and 1.5 Hz, H-4'), 7.47 (dd, J = 8.5 and 1.5 Hz, H-6'), 7.63 (ddd, J = 8.5, 7 and 1.5 Hz, H-5'), 7.88 (dd, J = 8 and 1.5 Hz, H-3'). Anal. Calcd for $C_{21}H_{22}N_2O_3$ (350.42): C, 71.98; H, 6.33; N, 7.99. Found: C, 71.99; H, 6.39; N, 8.05.

Compound ***trans*-1c**: IR ($CHCl_3$) 1719, 1531, 1367 cm^{-1}. ^1H NMR δ 1.60-2.53 (m, H), 2.80 (ddd, J = 13, 10.5 and 7.5 Hz, H-3β), 3.04 (m, H-2α), 4.15 and 4.26 (2d, 1H each, J = 13 Hz, CH_2Ar), 7.26-7.47 (m, 5H, ArH), 7.53 (dd, J = 8 and 1.5 Hz, H-3'), 7.63 (td, J = 8 and 1.5 Hz, H-5'), 8.97 (dd, J = 8 and 1.5 Hz, H-6'). Anal. Calcd for $C_{21}H_{22}N_2O_3$ (350.42): C, 71.98; H, 6.33; N, 7.99. Found: C, 71.77; H, 6.34; N, 8.04.

1-(2-Phenylselenenylethyl)-3a-(*o*-nitrophenyl)octahydroindol-4-one (1d). Operating as above, starting from 685 mg (2.5 mmol) of dione **9** and 2-phenylselenenylethylamine hydrochloride,[34] and after chromatography (hexane to 4:1 hexane-EtOAc) octahydroindole ***trans*-1d** (133 mg, 12%) and octahydroindole ***cis*-1d** (333 mg, 30%) were isolated.

Compound ***cis*-1d**: mp 123-124 °C (ether). IR ($CHCl_3$) 1698, 1527, 1356 cm^{-1}. ^1H NMR δ 1.52-3.25 (m), 3.45 (dd, J = 9 and 4.5 Hz, H-7a), 7.16-7.46 (m, ArH), 7.49 (dd, J = 8 and 1.5 Hz, H-6'), 7.61 (td, J = 8 and 1.5 Hz, H-5'), 7.88 (dd, J = 8 and 1.5 Hz, H-3'). Anal. Calcd for $C_{22}H_{24}N_2O_3Se$ (443.41): C, 59.59; H, 5.46; N, 6.32. Found: C, 59.63; H, 5.57; N, 6.31.

Compound ***trans*-1d**: mp 113-114 °C (acetone-ether). IR ($CHCl_3$) 1718, 1531, 1363 cm^{-1}. ^1H NMR δ 1.36-2.66 (m), 2.78 (ddd, J = 14, 12 and 8 Hz, H-3b), 3.04-3.35 (m), 7.22-7.68 (m, ArH), 8.86 (dd, J = 8 and 1 Hz, H-6'). Anal. Calcd for $C_{22}H_{24}N_2O_3Se$ (443.41): C, 59.59; H, 5.46; N, 6.32. Found: C, 59.37; H, 5.45; N, 6.33.

1-Benzhydryl-3a-(*o*-nitrophenyl)octahydroindol-4-one (1e). Operating as above, starting from 300 mg (1.1 mmol) of dione **9** and benzhydrylamine hydrochloride, and after chromatography (hexane to 4:1 hexane-EtOAc) octahydroindole ***trans*-1e** (19 mg, 4%) and octahydroindole ***cis*-1e** (84.5 mg, 18%) were isolated.

Compound ***cis*-1e**: IR (KBr) 1699, 1521, 1347 cm^{-1}. ^1H NMR δ 1.5-3.6 (m, H), 2.75 (td, J = 10 and 4 Hz, H-2a), 3.08 (td, J = 10 and 6 Hz, H-2b), 3.51 (dd, J = 11 and 5 Hz, H-7a), 4.66 (s, ArCHAr), 6.9-7.5 (m, ArH), 7.52 (t, J = 8 Hz, H-4'), 7.68 (d, J = 8 Hz, H-6'), 7.77 (t, J = 8 Hz, H-5'), 8.05 (d, J = 8 Hz, H-3'). Anal. Calcd for $C_{27}H_{26}N_2O_3$ (426.52): C, 76.04; H, 6.14; N, 6.57. Found: C, 76.25; H, 6.15; N, 6.56.

Compound ***trans*-1e**: IR (film) 1719, 1529, 1361 cm^{-1}. ^1H NMR δ 1.4-2.6 (m, H), 2.72 (m, H-3β), 3.07 (m, H-2α), 4.78 (s, ArCHAr), 7.1-7.8 (m, ArH), 9.07 (dd, J = 8, 1 Hz, H-6').

1-(2,2-Dimethoxyethyl)-3a-(*o*-nitrophenyl)octahydroindol-4-one (1f). Operating as above, starting from 300 mg (1.1 mmol) of dione **9** and 2,2-dimethoxyethylamine hydrochloride, and after chromatography (hexane to 6:4 hexane-EtOAc) octahydroindole ***trans*-1f** (95 mg, 25%) and octahydroindole ***cis*-1f** (30 mg, 8%) were isolated.

Compound ***cis*-1f**: IR (KBr) 1699, 1527, 1356 cm^{-1}. ^1H NMR δ 1.50-1.75 (m), 1.95-2.20 (m), 2.30-2.55 (m), 2.71 (d, J = 5.5 Hz, NCH_2), 2.95-3.10 (m), 3.10-3.30 (m), 3.20 (s, OCH_3), 3.30 (s, OCH_3), 3.40-3.55 (m), 4.33 (t, J = 5.5 Hz, $CH(OMe)_2$), 7.35-7.65 (m, ArH), 7.89 (dd, J = 8, 1 Hz, H-3'). Anal. Calcd for $C_{18}H_{24}N_2O_5$ (348.40): C, 62.05; H, 6.94; N, 8.04. Found: C, 61.99; H, 6.86; N, 8.04.

Compound ***trans*-1f**: IR (KBr) 1720, 1530, 1363 cm^{-1}. ^1H NMR δ 1.45-1.70 (m), 1.85-2.15 (m), 2.20-2.65 (m), 2.75-2.92 (m), 3.03 (dd, J = 13, 6 Hz), 3.29 (q, J = 9 Hz), 3.43 (s, OCH_3), 3.46 (s, OCH_3), 4.58 (t, J = 5 Hz, $CH(OMe)_2$), 7.35-7.64 (m, ArH), 8.88 (d, J = 8 Hz, H-6'). Anal. Calcd for $C_{18}H_{24}N_2O_5$ (348.40): C, 62.05; H, 6.94; N, 8.04. Found: C, 62.06; H, 6.93; N, 8.01.

(3a*R,7a*S**)-1-[α(*R*)-Methylbenzyl)-3a-(*o*-nitrophenyl)octahydroindol-4-one (1g).** Operating as above, starting from 400 mg (1.46 mmol) of dione **9** and α-(*R*)-Methylbenzylamine hydrochloride, and after chromatography (hexane to 7:3 hexane-EtOAc) octahydroindole ***cis*-1g** (149 mg, 28%) as a sole epimer and an 1:3 unseparated mixture of the two octahydroindoles ***trans*-1g** (37 mg,7%) were isolated.

Compound ***cis*-1g** : $[\alpha]_D$ = +22.8 (*c* 2.0, CH_3OH). IR ($CHCl_3$): 1697, 1527, 1356 cm^{-1}. ^1H NMR δ 1.20 (d, J = 6.4 Hz, CH_3); 1.52-2.95 (m); 3.69 (q, J = 6.4 Hz, NCH); 3.77 (dd, J = 11 and 5 Hz, H-7a); 7.0-7.5 (m, ArH); 7.65 (td, J = 8 and 1.5 Hz, H-5'); 7.99 (dd, J = 8 and 1 Hz, H-3'). Anal. Calcd for $C_{22}H_{24}N_2O_3$ (364.45): C, 72.17; H, 6.65; N, 7.68. Found: C, 72.01; H, 6.58; N, 7.63.

Methyl (2*S*)-2-[(3a*R, 7a*S**)-3a-(*o*-Nitrophenyl)-4-oxooctahydroindol-1-yl]propionate (1h).** Operating as above, starting from 250 mg (0.91 mmol) of dione **9** and *L*-alanine methyl ester hydrochloride, and after chromatography (hexane to 1:1 hexane-EtOAc) ***cis*-1h** (20 mg, 6%), ***cis*-1h'** (92 mg, 28%), and an 1:1 unseparated mixture of the two trans octahydroindoles (56 mg, 17%) were obtained.

Compound ***cis*-1h**: IR ($CHCl_3$): 1732, 1704, 1530, 1357 cm^{-1}. ^1H NMR δ 1.30 (d, J = 7.2 Hz, CH_3), 1.7-2.7 (m); 3.0-3.2 (m, H-2α and H-2β); 3.51 (s, OCH_3); 3.54 (q, J = 7.2 Hz, NCH); 3.68 (t, J = 4.5 Hz, H-7a); 7.42 (ddd, J = 8, 7 and 1.5 Hz, H-4'); 7.50 (dd, J = 8 and 1.5 Hz, H-6'); 7.59 (ddd, J = 8, 7 and 1.5 Hz, H-5'); 7.76 (dd, J = 8 and 1.5 Hz, H-3').

Compound ***cis*-1h'**: IR ($CHCl_3$): 1735, 1701, 1526, 1355 cm^{-1}. ^1H NMR δ 1.18 (d, J = 7 Hz, CH_3), 1.5-2.6 (m); 3.1-3.3 (m, H-2α and H-2β); 3.44 (q, J = 7 Hz, NCH); 3.58 (dd, J = 10 and 4.5 Hz, H-7a); 3.65 (s, OCH_3); 7.41 (ddd, J = 8, 7 and 1.5 Hz, H-4'); 7.49 (dd, J = 8 and 1.5 Hz, H-6'); 7.61 (ddd, J = 8, 7 and 1.5 Hz, H-5'); 7.93 (dd, J = 8 and 1.5 Hz, H-3').

(3a*R,7a*R**)-1-[(1*S*)-2-Hydroxy-1-methylethyl]-3a-(*o*-nitrophenyl)octahydroindol-4-one (*trans*-1i).** Operating as above, starting from 500 mg (1.82 mmol) of dione **9** and and (*S*)-alaninol hydrochloride, and after chromatography (hexane to 2:3 hexane-EtOAc) 120 mg (20%) of octahydroindole ***trans*-1i** were obtained. $[\alpha]_D$ = -32.7 (*c* 1.6, CH_3OH). IR (film) 3422, 1716, 1531, 1367 cm^{-1}. ^1H NMR δ 0.83 (d, J = 6.5 Hz, CH_3), 1.36-2.90 (m), 3.1-3.3 (m, H-2α), 3.34-3.56 (m, CH_2OH), 7.3-7.6 (m, 3H,

ArH), 8.48 (d, J = 8 Hz, H-6'). Anal. Calcd for $C_{17}H_{22}N_2O_4.1/4\ H_2O$ (322.88): C, 63.24; H, 7.02; N, 8.68. Found: C, 63.58; H, 7.06; N, 8.31.

1-[(*S*)-2-Hydroxy-1-phenylethyl]-3a-(*o*-nitrophenyl)octahydroindol-4-one (1j). Operating as above, starting from 300 mg (1.1 mmol) of dione **9** and (*S*)-phenylglycinol hydrochloride, and after chromatography (CH_2Cl_2 to CH_2Cl_2, 1% MeOH) 58.5 mg (14%) of octahydroindole ***trans*-1j** and 134 mg (32%) of octahydroindole ***cis*-1j** were obtained.

Compound ***cis*-1j**: $[\alpha]_D$ = -14.3 (*c* 1.0, CH_3OH). IR ($CHCl_3$) 3027, 1698, 1529, 1355 cm^{-1}. ^1H NMR δ 1.35-1.80 (m), 1.85-2.51 (m), 2.70-3.15 (m), 3.40-3.80 (m), 7.00-7.75 (m, ArH), 8.01 (d, J = 8 Hz, H-3'). Anal. Calcd for $C_{22}H_{24}N_2O_4$ (380.45): C, 69.46; H, 6.36; N, 7.36. Found: C, 69.49; H, 6.56; N, 7.04.

Compound ***trans*-1j**: IR ($CHCl_3$) 3020, 1719, 1533, 1362 cm^{-1}. ^1H NMR δ 1.38-1.66 (m), 1.84-2.04 (m), 2.10-2.44 (m), 2.65 (dd, J = 11, 4 Hz), 2.80-3.04 (m), 3.86 (dd, J = 7.5, 3 Hz), 4.02-4.22 (m), 7.06-7.66 (m, ArH), 8.63 (dd, J = 8, 1 Hz, H-6'). Anal. Calcd for $C_{22}H_{24}N_2O_4$ (380.45): C, 69.46; H, 6.36; N, 7.36. Found: C, 69.22; H, 6.50; N, 7.14.

(3a*R,7a*R**)-1-[(*S*)-2,2-Dimethoxy-1-methylethyl]-3a-(*o*-nitrophenyl)octahydroindol-4-one (*trans*-1k).** Operating as above, starting from 500 mg (1.84 mmol) of dione **9** and (*S*)-2,2-Dimethoxy-1-methylethylamine hydrochloride,[35] and after chromatography (CH_2Cl_2) 120 mg (18%) of octahydroindole ***trans*-1k** were obtained. IR (film) 1718, 1530, 1364 cm^{-1}. ^1H NMR δ 0.95 (d, J = 6.5 Hz, CH_3), 1.50-1.70 (m), 1.80-2.10 (m), 2.20-2.50 (m), 2.50-2.70 (m), 2.75-3.00 (m), 3.21 (t, J = 7 Hz), 3.39-3.50 (m), 3.44 (s, OCH_3), 3.47 (s, OCH_3), 4.27 (d, J = 13 Hz, $CH(OCH_3)_2$), 7.36-7.62 (m, ArH), 8.96 (dd, J = 8.1 Hz, H-6').

***cis*-3a-(*o*-nitrophenyl)octahydroindol-4-one (*cis*-11).**

Method A: To a solution of the *N*-methyl derivative ***cis*-1a** (100 mg, 0.36 mmol) in 1,2-dichloroethane (5 ml) containing 1,8-bisdimethylaminonaphthalene (proton sponge) (77 mg, 0.36 mmol) was added at 0 °C α-chloroethyl chloroformate (0.16 ml, 1.44 mmol). The resulting solution was refluxed for 3 h. The solvent was evaporated, the residue was redissolved in methanol and heated at reflux for 3 h. After evaporating the methanol, the residue was purified by chromatography (CH_2Cl_2, 6% MeOH) to give ***cis*-11** (73 mg, 78%).

Method B: A solution of acetal ***cis*-1f** (43 mg, 0.12 mmol) and *p*-toluenesulfonic acid monohydrate (31 mg, 0.16 mmol) in benzene (15 ml) was refluxed in a flask with a Dean-Stark condenser for 6 h. The resulting mixture was poured into saturated aqueous Na_2CO_3. The organic layer was washed with brine, dried and evaporated to give a residue, which after chromatography afforded the amine ***cis*-11** (15 mg, 48%); IR (film) 3635, 1699, 1532, 1362 cm^{-1}.^1H NMR δ 1.50-2.70 (m, H), 3.2-3.5 (m, H-2α and H-2β), 3.65 (dd, J = 11 and 5.5 Hz, H-7a), 7.34 (d, J = 8 Hz, H-6'), 7.45 (t, J = 8 Hz, H-4'), 7.62 (t, J = 8 Hz, H-5'), 8.05 (d, J = 8 Hz, H-3').

***trans*-3a-(*o*-nitrophenyl)octahydroindol-4-one (*trans*-11).**

Method A: The *N*-methyl derivative ***trans*-1a** (100 mg, 0.36 mmol) in α-chloroethyl chloroformate (0.8 ml, 3.64 mmol) was heated at 130 °C for 24 h. The residue was taken up in methylene chloride and washed with diluted hydrochloric acid and aqueous sodium bicarbonate solution. The organic extract was dried

and evaporated. The residue was dissolved in methanol and heated at reflux for 3 h. After evaporating the methanol, the residue was purified by chromatography (CH_2Cl_2, 4% MeOH), to give 40 mg (43%) of octahydroindole ***trans*-11**.

Method B: A solution of acetal ***trans*-1f** (90 mg, 0.26 mmol) and *p*-toluenesulfonic acid monohydrate (64 mg, 0.34 mmol) in benzene (30 ml) was refluxed in a flask with a Dean-Stark condenser for 6 h. The resulting mixture was poured into saturated aqueous Na_2CO_3. The organic layer was washed with brine, dried and evaporated to give a residue, which after chromatography afforded the amine ***trans*-11** (28 mg, 43%). IR (film) 3600, 1718, 1532, 1363 cm^{-1}. ^1H NMR δ 1.43-1.70 (m), 1.81-1.98 (m), 2.00- 2.43 (m), 2.73 (dt, J = 13, 9.8 Hz), 2.98 (td, J = 10.1, 7.1 Hz), 3.20-3.33 (m), 7.40 (ddd, J = 8.3, 7 and 1.4 Hz), 7.53 (dd, J = 7.9 and 1.7 Hz, (H-3'), 7.58 (ddd, J = 8.9, 7.1 and 1.7 Hz), 8.70 (dd, J = 8 and 1.4 Hz, H-6').

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