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SYNTHESIS AND TRANSFORMATIONS OF NOVEL BENZO[*C*]FURANS

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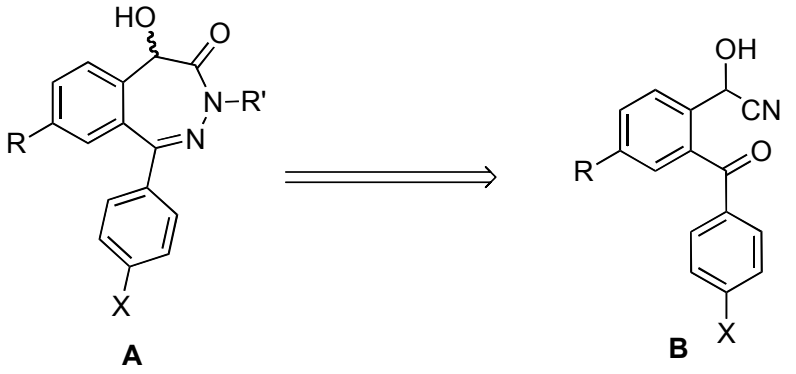
Abstract – Some novel 1-cyanoisobenzofurans have been synthesized by a convenient ring closure methodology. The new products easily reacted with electron-deficient olefins and acetylenes to yield Diels-Alder products. Theoretical calculations satisfactorily support the quinonoide character of the new isobenzofuran derivatives.

INTRODUCTION

In the course of earlier studies of one of the authors on 2,3-benzodiazepines with non-competitive AMPA antagonist activity, pharmacophore modelling studies[1] and considerations on possible metabolic transformations suggested that 5-hydroxylated 2,3-benzodiazepines of type **A** would be a promising candidate in this area. In order to justify this hypothesis, elaboration of a synthetic route to **A** seemed of interest. For this purpose, the retrosynthetic analysis **A** ⇒ **B** was considered (Scheme 1) and, thus, efforts have been made for the synthesis of the possible precursor **B**.



Scheme 1. Retrosynthetic analysis **A** ⇒ **B**

In contrast to these expectations, all efforts for preparation of cyanohydrins **B** as a candidate starting compound for the target ring system **A** failed and, instead, 1-cyanobenzo[*c*]furans as stable substances have been obtained as the result of accomplishment of the designed synthetic route. In this paper we report on this recently elaborated pathway to benzo[*c*]furans.

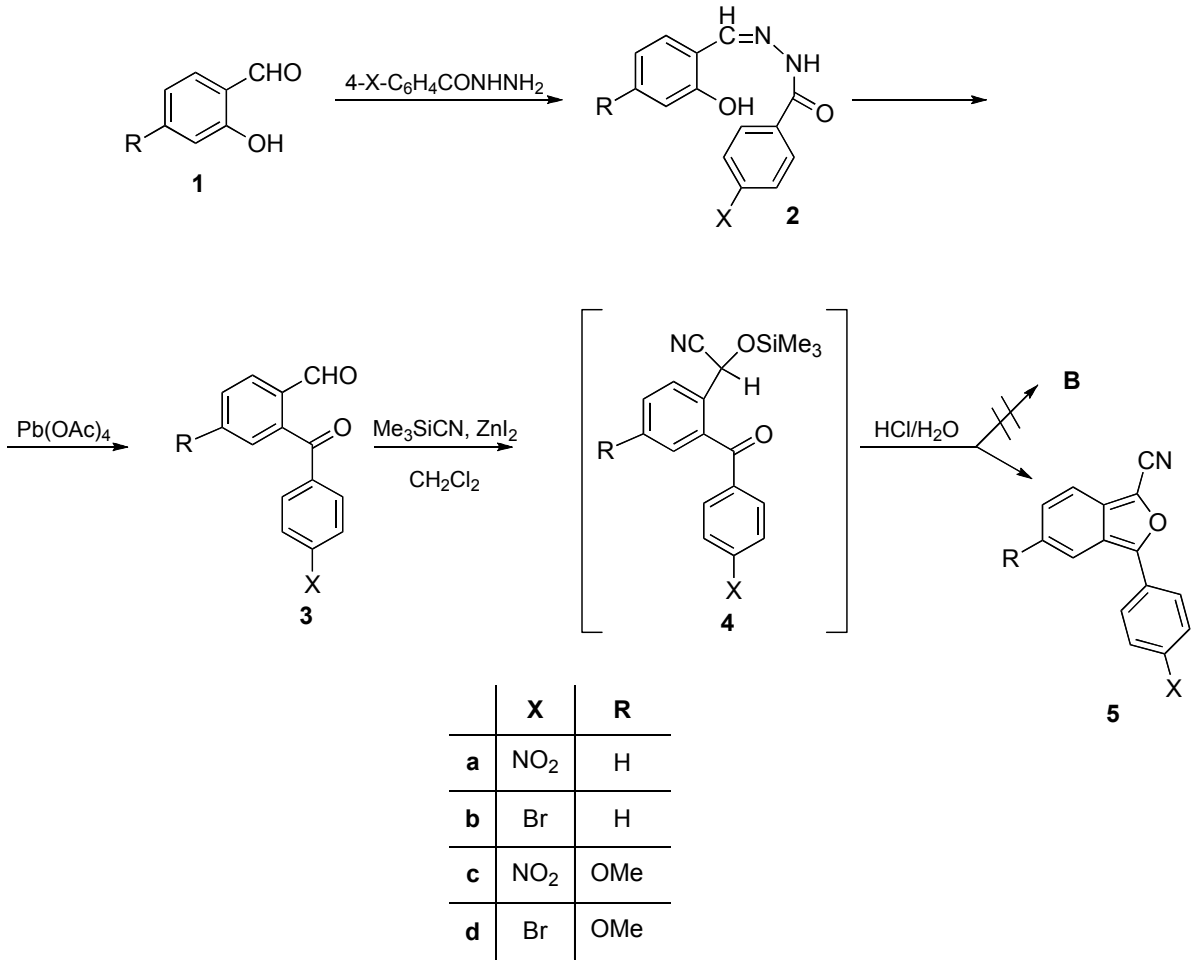
RESULTS AND DISCUSSION

Considerations of the possible access to the originally planned cyanohydrin **B** revealed that ketoaldehyde **3** could be an obvious source to this compound. Inspection of the pertinent literature, furthermore, revealed that a two-step protocol can conveniently be applied for the synthesis of **3** (Scheme 2). Accordingly, substituted salicylaldehydes (**1**) were first converted to *N*-benzoylhydrazones (**2**)[2] and, subsequently, this compound, when treated with lead tetraacetate, underwent rearrangement to give the ketoaldehyde (**3**).[3] Although several reaction conditions for this rearrangement have been published,[4] the lead tetraacetate method gave the best results in our hands.

Transformation of **3** to the original target (**B**) was tried by treatment with trimethylsilyl cyanide and subsequent acidic hydrolysis. When this reaction was carried out in dichloromethane, an oily colourless product was formed first, which, upon treatment with hydrochloric acid, was converted to a yellow product in a fast reaction. The appearance of an sp^2 quaternary carbon instead of the sp^3 CH carbon in the ^{13}C NMR spectrum, the yellow colour and the ^1H NMR assignment altogether supported the conclusion that **B** was not formed and, instead, a ring closure occurred to yield a benzo[*c*]furan derivative (**5**).

The first step in the course of this transformation is obviously formation of an *O*-trimethylsilylcyanohydrin (**4**) intermediate, which is followed by cyclization to the bicyclic product (**5**). This step is initiated by acidic desilylation and nucleophilic attack of the intermediate hydroxyl-oxygen atom on the carbonyl carbon atom activated by the strongly acidic medium. Finally, elimination of water can yield the product (**5**).

While synthesis of great number of symmetrically substituted benzo[*c*]furans has been published,[5,6] relatively few papers appeared on asymmetrically substituted derivatives.[7] In particular, only a few derivatives of 1-cyano-3-arylbenzo[*c*]furans have been described.[8,9] It is also important to note that in these syntheses potassium cyanide/acetic acid was used for the cyclization to derivatives of **5**, whereas in our procedure trimethylsilyl cyanide of markedly higher safety is applied for this purpose. In contrast to the relative instability of numerous benzo[*c*]furan derivatives, the obtained 1-cyano substituted compounds proved to be stable and can be stored without any precaution under normal conditions.



	X	R
a	NO_2	H
b	Br	H
c	NO_2	OMe
d	Br	OMe

Scheme 2. Four-step synthesis of 1-cyanoisobenzofurans

This experience prompted us to investigate the electronic distribution of these compounds in order to assess if the presence of the cyano group exerts any influence on the quinonoide character represented by the neutral chemical structure (Figure 1, structure **a**). In other words, consideration of contribution of the possible dipolar valence bond mesomeric structure (structure **b**) with a dipolar valence bond seemed of particular interest.

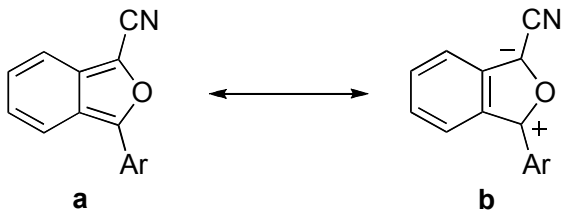


Figure 1. Some of the mesomeric structures of 1-cyano-3-arylbenzo[*c*]furan

A simple yet effective way to estimate relative weight of resonance forms is to examine computed bond lengths of the molecules of interest. Density functional calculations at the M06-2X/6-31G* level[10-13] were used to compare equilibrium geometries of benzo[*b*]furan (Figure 2, **d**), benzo[*c*]furan (**e**), and 1-cyano-3-(*p*-nitrophenyl)-benzo[*c*]furan (**f**), as well as the structurally related compounds butadiene (**a**), divinylether (**b**), and acrolein (**c**).

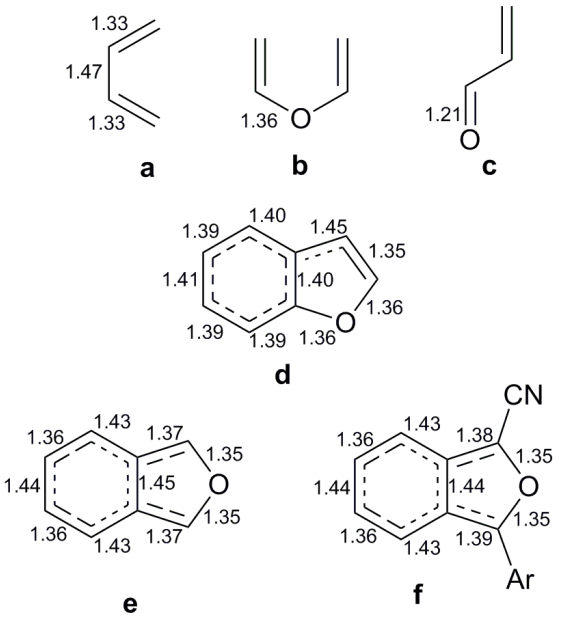


Figure 2. Calculated bond lengths (in angstroms) of benzofuran isomers and of some simple compounds treated as reference. Ar = *p*-nitrophenyl

It is apparent that benzo[*c*]furan (**e** and **f**), unlike benzo[*b*]furan (**d**), has markedly alternating C–C bond lengths in the aromatic ring, pointing to significant quinonoide character. Importantly, there are only very slight changes in the geometry upon the substitution of the electron withdrawing cyano group (*i.e*. **f** vs. **e**), which underlines the dominant role of the quinonoide structure also for the cyano substituted compounds discussed in the present work. This finding is also consistent with the properties of frontier molecular orbitals of the species of interest (Figure 3). The shape of the HOMO and the energy gap between the HOMO and the HOMO-1 are in agreement with a polyene character of **f** similar to **e**.

Upon the above theoretical conclusion the new compounds were considered as reactive candidates as dienes in Diels-Alder reactions. Such conversions with isobenzofurans of different substitution pattern have already been reported.[7b] These cycloadditions have been carried out with three different dienophiles: dimethyl acetylene dicarboxylate (DMAD), *N*-phenylmaleimide (Scheme 3), and ethyl acrylate (Scheme 4).

In all cases, these reactions took place in toluene under reflux conditions in medium to high yields. Thus, reaction with DMAD gave the diesters **6**, whereas cycloadditions with *N*-phenylmaleimide yielded the tetracyclic derivatives **7**.

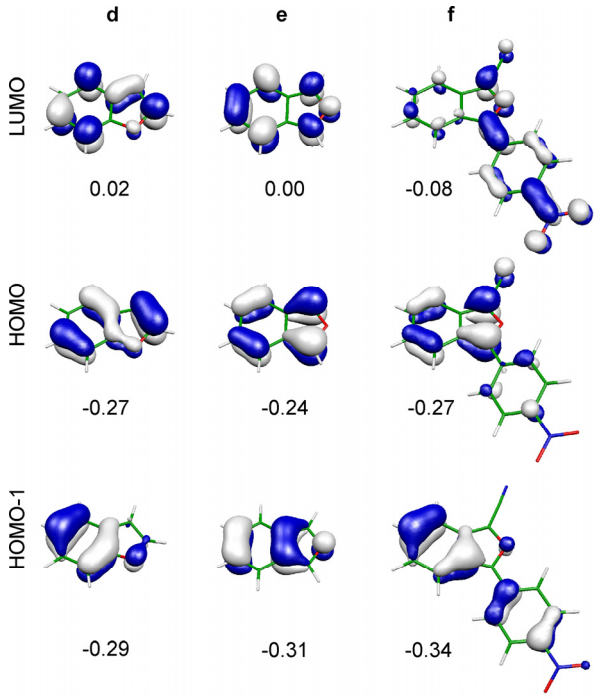
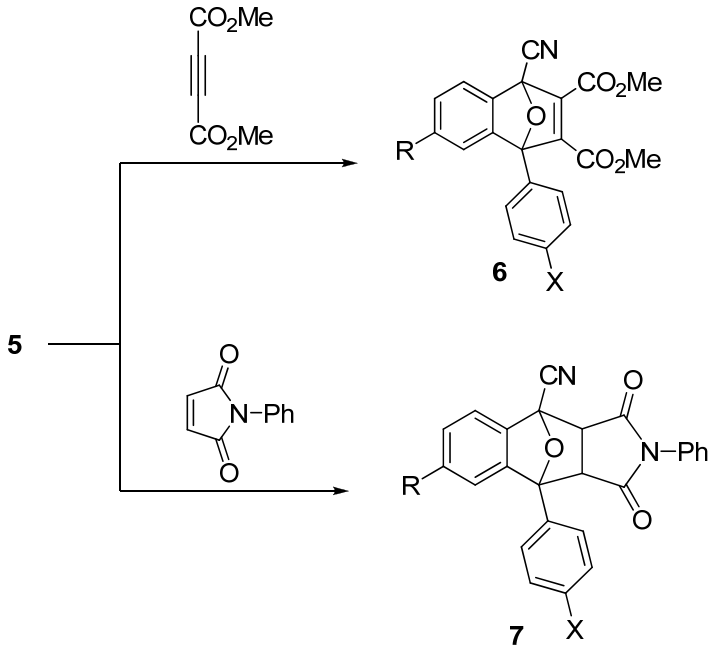


Figure 3. Frontier molecular orbitals of benzofuran isomers. Atom coloring: carbon-green, oxygen-red, nitrogen-blue, hydrogen-white. Surfaces were drawn with a cutoff of ±0.05 atomic units.[14] Orbital energies in hartrees are also shown.



Scheme 3. Diels-Alder cyclizations with 1-cyanoisobenzofurans

The NMR spectra of this compound did not allow unambiguous determination of which of the possible diastereomer of **7** was formed in these cycloadditions concerning the position of the bridged oxygen containing ring and the pyrrole ring. However, DFT calculations[15] on **7a** carried out to identify the stereochemical preference revealed that the transition state leading to *endo*-**7a** is 2.2 kcal/mol lower in free energy than that leading to *exo*-**7a** (see structures on Figure 4). Relative stability of the products parallels that of the TSs, but the difference is smaller (0.7 kcal/mol).

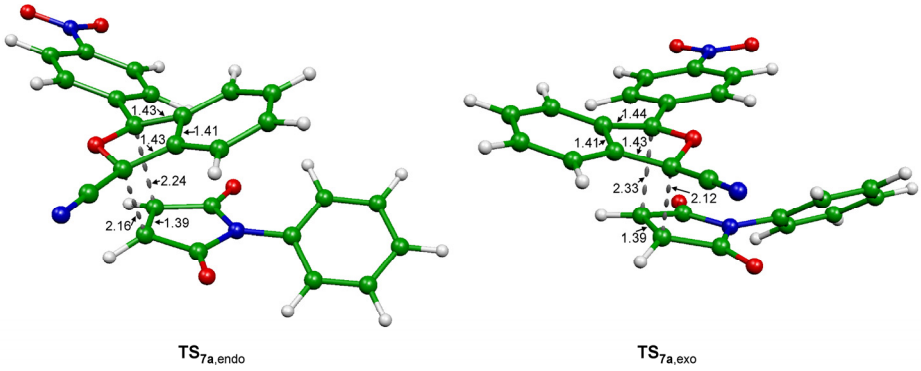
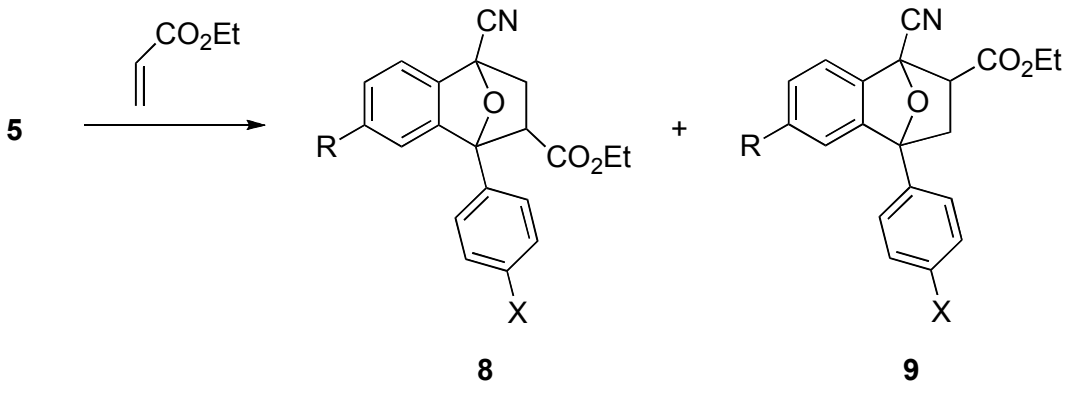


Figure 4. M06-2X/6-31G* optimized geometries of the transition states leading to *endo* and *exo* isomers of **7a**. Selected distances are given in angstroms.

Transformations with ethyl acrylate resulted in formation of mixtures of regioisomers **8** and **9** (Scheme 4). Thorough NMR analysis of the mixture **8b+9b** revealed that the two isomers are present in a ratio of roughly 3:1. The main product **8b** was separated by chromatography, and the pure compound was analyzed by spectroscopy. Predominance of **8** in the reaction mixtures seems to be in accordance with the expected polarization of the two reaction partners (Figure 1).



Scheme 4. Formation of regioisomeric cycloadducts in reaction of cyanoizobenzofurans with acryl ester

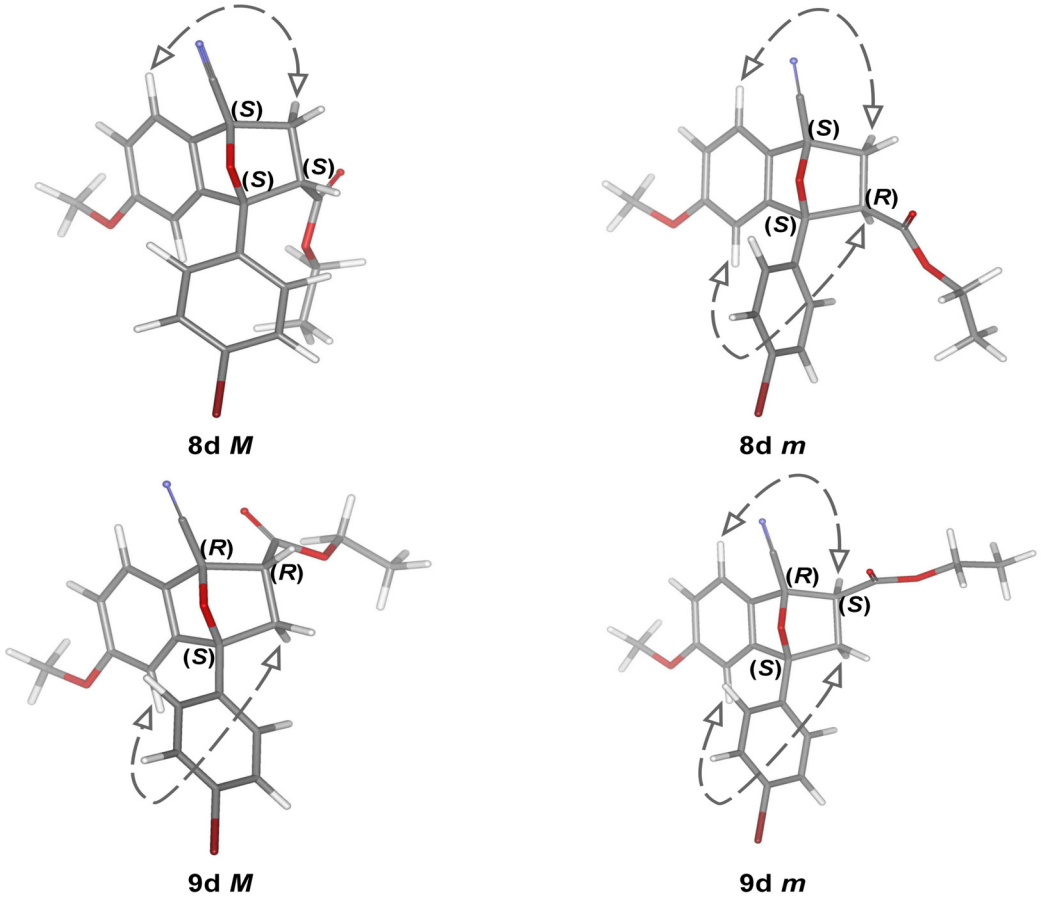


Figure 5. Comparison of structures of the diastereomeric isomer pairs (***M*** and ***m***) of regioisomers **8d** and **9d**. ***M*** stands for major diastereomer, ***m*** for minor diastereomer. The arrows indicate the relevant, rather weak NOE-s for distinguishing the diastereomers. The NOE enhancements (1% - 4%) were determined from selective 1D-NOESY experiments.

It is interesting to note that because of the resulting chiral centers in these products, pairs of diastereomers – major (***M***) and minor (***m***) ones - should be formed for both regioisomers **8** and **9** according to the relative positions of the ester and the cyano groups. Thus, four sets of signals were supposed to appear which were indeed observed in the ^{1}H-NMR spectrum of the **8c**+**9c** and **8d**+**9d** mixtures. Product ratios were as follows: **8c***M*/**8c***m*: 55 mol%/22 mol%; **9c***M*/**9c***m*: 16mol %/7 mol%; **8d***M*/**8d***m*: 50 mol%/25 mol%; **9d***M*/**9d***m*: 16 mol%/9 mol%. The regioisomeric ratios of **8c**:**9c** and **8d**:**9d** were 77:23 and 75:25, respectively. Comparison of the steric structures of isomers **8d *M***, **8d *m***, **9d *M***, and **9d *m*** are shown in Figure 5.

These experimental findings reveal that the elaborated synthetic route provides a relatively easy access to stable isobenzofurans. These compounds – in accordance with the theoretical considerations – possess quinonoide character, which enables their easy conversion with dienophiles to give cycloadducts in good yield.

EXPERIMENTAL

General: Melting points were determined on a Kofler apparatus and are uncorrected. The IR spectra were recorded on a Thermo Nicolet Avatar 320 FT-IR spectrometer. NMR experiments were performed on Varian INOVA-200 or Varian INOVA-400 spectrometer equipped with a 5 mm inverse detection z-gradient probe. ^{1}H and ^{13}C NMR spectra were measured at room temperature (25 ^{o}C) in an appropriate solvent. ^{1}H and ^{13}C chemical shifts are expressed in ppm (δ) referenced to residual solvent signals. The elemental analysis has been carried out with an Elementar Vario EL III apparatus. Chromatographic separations were carried out on Merck Kieselgel 60 (230-400 mesh). Reactions were monitored with Merck Kieselgel 60 F_{254}-precoated TLC plates (0.25 mm thickness). All chemicals and solvents were used as supplied.

Compounds **2a-d** were synthesized analogously to the literature procedure published for related compounds.[4a]

(*Z*)-*N*'-(2-Hydroxybenzylidene)-4-nitrobenzohydrazide (2a): This compound has been reported in the literature.[2a, 3b, 18] Colourless crystals, mp 288-293 °C. (lit., mp 280-283 °C[2a]; 277-279 °C[3b]; 291-292 °C[14]).

(*Z*)-4-Bromo-*N*'-(2-hydroxybenzylidene)benzohydrazide (2b): Colourless crystals 4.29 g (90%), mp 225-230 °C. IR (KBr, cm^{-1}): 3221, 3064, 1645, 1483, 1297, 1152, 1010, 748; ^{1}H NMR δ (DMSO-d_6): 6.92 (t, 2H), 7.31 (t, 1H), 7.56 (d, 1H), 7.76 (d, 2H), 7.89 (d, 2H), 8.64 (s, 1H), 11.2 (s, 1H), 12.1 (s, 1H). ^{13}C NMR δ (DMSO-d_6): 116.4, 118.7, 119.4, 125.8, 129.5, 129.7, 131.6, 131.9, 148.6, 157.5, 161.9. Anal. Calcd for $C_{14}H_{11}BrN_3O_4$ (318.00): C, 52.69; H, 3.47; N, 8.78. Found: C, 53.08; H, 3.41; N, 8.73.

(*Z*)-*N*'-(2-Hydroxy-4-methoxybenzylidene)-4-nitrobenzohydrazide (2c): Although synthesis of this compound has been reported[2b] no characterization has yet been described. Yellow crystals 4.5 g (98%), mp 218-220 °C. IR (KBr, cm^{-1}): 3550, 3203, 3024, 1656, 1516, 1351, 1282, 831, 709; ^{1}H NMR δ (DMSO-d_6): 3.78 (s, 1H), 6.53 (d, 2H), 7.47 (d, 2H), 8.15 (d, 2H), 8.37 (d, 2H), 8.58 (s, 1H), 11.44 (s, 1H), 12.26 (s, 2H). ^{13}C NMR δ (DMSO-d_6): 55.2, 101.1, 106.5, 111.6, 123.5, 129.0, 130.9, 138.5, 149.2, 149.5, 159.4, 160.8, 162.2. Anal. Calcd for $C_{15}H_{13}N_3O_5$ (315.09): C, 57.14; H, 4.16; N, 13.33. Found: C, 57.35; H, 4.31; N, 13.56.

(*Z*)-4-Bromo-*N*'-(2-hydroxy-4-methoxybenzylidene)benzohydrazide (2d): Colourless crystals 4.78 g (91%), mp 196-199 °C. IR (KBr, cm^{-1}): 3424, 3252, 3063, 1627, 1507, 1352, 1278, 835, 806; ^{1}H NMR δ (DMSO-d_6): 3.77 (s, 3H), 6.51 (m, 2H), 7.44 (d, 1H), 7.75 (d, 2H), 7.87 (d, 2H), 8.54 (s, 1H), 11.55 (s,

1H), 12.04 (s, 1H). ^{13}C NMR δ (DMSO-d_6): 55.3, 101.1, 106.5, 111.7, 125.6, 129.6, 131.1, 131.5, 132.0, 149.0, 159.4, 161.6, 162.1. Anal. Calcd for $C_{15}H_{13}BrN_2O_3$ (348.01): C, 51.60; H, 3.75; N, 8.02. Found: C, 51.42; H, 3.47; N, 7.89.

Compounds **3a-d** were synthesized according to the published procedure[3a] using lead tetraacetate.

2-(4-Nitrobenzoyl)benzaldehyde (3a): This compound has been reported in the literature.[2a, 3b] Yellow crystals, mp 152-156 °C. (lit., mp 151-152 °C[2a]; 153-155 °C[3b]).

2-(4-Bromobenzoyl)benzaldehyde (3b): This compound has been described in the literature.[9] Colourless crystals, mp 112-115 °C. (lit., mp 110-113 °C[9]).

2-(4-Nitrobenzoyl)-4-methoxybenzaldehyde (3c): This compound has been described in the literature.[19] Starting from **2c** (1 g) yellow crystals were obtained, 0.35 g (39%), mp 135-140 °C. IR (KBr, cm^{-1}): 3206, 2919, 2850, 1602, 1519, 1347, 1283, 1219, 1109, 965, 850, 832; ^{1}H NMR δ ($CDCl_3$): 3.93 (s, 3H), 6.95 (s, 1H), 7.19 (d, 1H), 7.92 (t, 3H), 8.26 (d, 2H), 9.80 (s, 1H). ^{13}C NMR δ ($CDCl_3$): 55.9, 114.4, 115.3, 123.7,128.0, 130.0, 134.8, 141.3, 141.8, 150.3, 164.1, 189.0, 194.9. Anal. Calcd for $C_{15}H_{11}NO_5$ (285.06): C, 63.16; H, 3.89; N, 4.91. Found: C, 63.03; H, 3.86; N, 5.24.

2-(4-Bromobenzoyl)-4-methoxybenzaldehyde (3d): Starting from **2d** (1 g) brown crystals were obtained, 0.41 g (47%), mp 97-100 °C. IR (KBr, cm^{-1}): 3090, 2945, 2857, 1665, 1562, 1396, 1294, 1218, 1106, 962, 847; ^{1}H NMR δ ($CDCl_3$): 3.90 (s, 3H), 6.91 (s, 1H), 7.12 (d, 1H), 7.61 (q, 4H), 7.94 (d, 1H), 9.82 (s, 1H). ^{13}C NMR δ ($CDCl_3$): 56.1, 114.2, 115.5, 128.3, 129.1, 131.2, 132.2, 133.8, 135.8, 143.1, 164.0, 189.1, 195.6. Anal. Calcd for $C_{15}H_{11}BrO_3$ (317.99): C, 56.45; H, 3.47. Found: C, 56.15; H, 3.27.

General Procedure for preparation of isobenzofurans 5a-d: To a stirred solution of the appropriate aldehyde (2 mmol, **3a-d**) in CH_2Cl_2 (6 mL) trimethylsilyl cyanide (338 mg, 3.4 mmol) and few crystals of ZnI_2 were added. The reaction mixture was stirred at rt for 24 h and evaporated to dryness *in vacuum*. The residue was mixed with water (4 mL) and conc. hydrochloric acid (4 mL) and stirred at 40 °C for 1 h. The resulting solution was cooled down to rt, and was extracted with Et_2O (3x30 mL) and chloroform (5x20 mL). The combined organic solution was dried over Na_2SO_4 and evaporated to dryness to give solid product, which was treated with ethanol and filtered off to give **5a-d**.

3-(4-Nitrophenyl)isobenzofuran-1-carbonitrile (5a): Brown crystals, 0.211 g (40%), mp 227-231 °C. IR (KBr, cm^{-1}): 3081, 2920, 2850, 2206, 1592, 1509, 1341, 1107, 854, 743; ^{1}H NMR δ (DMSO-d_6): 7.37 (1H, dd, J = 8.0, 7.7 Hz, H5), 7.45 (1H, dd, J = 7.9, 7.7 Hz, H6), 7.74 (1H, d, J = 7.9 Hz, H7), 8.22 (1H, d, J = 8.0 Hz, H4), 8.29 (2H, m, H3' + H5'), 8.36 (2H, m, H2' + H6'). ^{13}C NMR δ (DMSO-d_6): 112.6 (CN), 117.9 (C1), 121.0 (C4), 122.0 (C3a), 125.1 (C2' + C6'), 127.2 (C3' + C5'), 128.6 (C5), 130.5 (C6), 133.4 (C7a), 134.7 (C1'), 147.5 (C4'), 148.5 (C3). Anal. Calcd for $C_{15}H_8N_2O_3$ (264.24): C, 68.18; H, 3.05; N, 10.60. Found: C, 68.11; H, 3.02; N, 10.56.

3-(4-Bromophenyl)isobenzofuran-1-carbonitrile (5b): Yellow crystals, 0.326 g (55%), mp 125-130 °C. IR (KBr, cm^{-1}): 3082, 2923, 2205, 1454, 1435, 1404, 1070, 1005, 829, 740; ^{1}H NMR δ ($CDCl_3$): 7.22 (m, 2H), 7.60 (m, 3H), 7.82 (m, 3H). ^{13}C NMR δ ($CDCl_3$): 112.5, 117.6, 120.3, 126.5, 127.3, 128.0, 128.6, 129.0, 131.7, 132.4, 133.6, 149.6. Anal. Calcd for $C_{15}H_8BrNO$ (296.98): C, 60.43; H, 2.70; N, 4.70. Found: C, 60.06; H, 2.56; N, 4.53.

3-(4-Nitrophenyl)-5-methoxyisobenzofuran-1-carbonitrile (5c): Orange crystals, 0.153 g (26%), mp 223-228 °C. IR (KBr, cm^{-1}): 2924, 2853, 2209, 1594, 1519, 1346, 1265, 1231, 1103, 1014, 845, 814; ^{1}H NMR δ ($CDCl_3$): 3.87 (s, 3H), 6.95 (t, 2H), 7.45 (d, 1H), 7.95 (d, 2H), 8.30 (d, 2H). ^{13}C NMR δ ($CDCl_3$): 55.9, 94.4, 97.4, 111.8, 119.2, 124.6, 125.5, 126.1, 130.7, 135.6, 159.4. Anal. Calcd for $C_{16}H_{10}N_2O_4$ (294.06): C, 65.31; H, 3.43; N, 9.52. Found: C, 65.56; H, 3.45; N, 9.54.

3-(4-Bromophenyl)-5-methoxyisobenzofuran-1-carbonitrile (5d): Brown crystals, 0.566 g (89%), mp 169-174 °C. IR (KBr, cm^{-1}): 3083, 2942, 2201, 1642, 1558, 1476, 1434, 1260, 1227, 1178, 1073, 1008, 823; ^{1}H NMR δ ($CDCl_3$): 3.89 (s, 3H), 6.95 (t, 2H), 7.46 (d, 1H), 7.65 (m, 4H). ^{13}C NMR δ ($CDCl_3$): 55.4, 94.7, 112.5, 118.8, 120.9, 122.8, 125,7, 126.9, 129.0, 122.8, 125,7, 126.9, 129.0, 130.9, 131.8, 132.4, 147.6, 158.2. Anal. Calcd for $C_{16}H_{10}BrNO_2$ (328.16): C, 58.56; H, 3.07; N, 4.27. Found: C, 58.16; H, 3.39; N, 4.08.

General procedure for preparation of cycloadducts 6a-d: To a solution of the appropriate isobenzofuran derivative (**5a-d**, 1 mmol) in toluene (20 mL) DMAD (2 mmol) was added, and this mixture was refluxed for 24 h. After evaporation of the reaction mixture the residue was treated with cold EtOH to give colourless crystals, which were filtered off and recrystallized from EtOH.

Dimethyl 1-cyano-4-(4-nitrophenyl)-1,4-dihydro-1,4-epoxynaphthalene-2,3-dicarboxylate (6a): Colourless crystals, 0.284 g (70%), mp 159-163 °C. IR (KBr, cm^{-1}): 2962, 2919, 2850, 1729, 1715, 1515, 1353, 1293, 1133, 1020, 1003, 853; ^{1}H NMR δ ($CDCl_3$): 3.76 (s, 3H), 3.87 (s,3H), 7.42 (m, 2H), 7.68 (m, 2H), 7.85 (d, 2H), 8. 37 (d, 2H). ^{13}C NMR δ ($CDCl_3$): 53.0, 53.1, 94.5, 112.6, 121.0, 121.8, 124.0, 127.4, 127.6, 127.7, 137.9, 144.6, 145.6, 148.6, 155.2, 160.0, 163.1. Anal. Calcd for $C_{21}H_{14}N_2O_7$ (406.08): C, 62.07; H, 3.47; N, 6.89. Found: C, 62.24; H, 3.47; N, 6.50.

Dimethyl 1-cyano-4-(4-bromophenyl)-1,4-dihydro-1,4-epoxynaphthalene-2,3-dicarboxylate (6b): Colourless crystals, 0.263 g (60%), mp 112-114 °C. IR (KBr, cm^{-1}): 2954, 1737, 1728, 1638, 1439, 1312, 1242, 1126, 1012, 973, 827; ^{1}H NMR δ ($CDCl_3$): 3.73 (3H, s, $COOC\underline{H}_3$"'), 3.84 (3H, s, $COOC\underline{H}_3$"), 7.22 (2H, m, H7 + H8), 7.41 (1H, m, H6), 7.48 (2H, m, H2' + H6'), 7.62 (2H, m, H3' + H5'), 7.63 (1H, m, H5). ^{13}C NMR δ ($CDCl_3$): 52.9 ($COO\underline{C}H_3$"'), 53.0 ($COO\underline{C}H_3$"), 79.7 (C4), 95.3 (C1), 112.9 (<u>C</u>N), 120.8 (C5), 122.4 (C6), 124.3 (C4'), 127.1 (C7), 127.6 (C8), 128.5 (C2' + C6'), 130.2 (C1'), 132.2 (C3' + C5'), 145.0 + 145.1 (C4a + C8a), 145.6 (C2), 155.9 (C3), 160.2 ($\underline{C}OOCH_3$"), 163.5 ($\underline{C}OOCH_3$"'). Anal. Calcd for $C_{21}H_{14}BrNO_5$ (439.01): C, 57.29; H, 3.21; N, 3.18. Found: C, 57.43; H, 3.07; N, 3.07.

Dimethyl 1-cyano-4-(4-nitrophenyl)-6-methoxy-1,4-dihydro-1,4-epoxynaphthalene-2,3-dicarboxylate (6c): Yellow crystals, 0.235 g (54%), mp 152-155 °C. IR (KBr, cm^{-1}): 3006, 2964, 1727, 1525, 1350, 1259, 1220, 1128, 1006, 856; ^{1}H NMR δ ($CDCl_3$): 3.75 (s, 3H), 3.80 (s, 3H), 3.86 (s, 3H), 6.67 (d, 1H), 6.98 (s, 1H), 7.55 (d, 1H), 7.82 (d, 2H), 8.37 (d, 2H). ^{13}C NMR δ ($CDCl_3$): 53.0, 53.1, 55.9, 94,3, 109.4, 111.5, 112.7, 121.7, 124.0, 127.5, 135.8, 137.9, 146.2, 146.5, 148.5, 154.5, 159,3, 160.1, 163.2. Anal. Calcd for $C_{22}H_{16}N_2O_8$ (436.09): C, 60.55; H, 3.70; N, 6.42. Found: C, 60.38; H, 3.54; N, 6.11.

Dimethyl 1-cyano-4-(4-bromophenyl)-6-methoxy-1,4-dihydro-1,4-epoxynaphthalene-2,3-dicarboxylate (6d): Colourless crystals, 0.257 g (55%), mp 136-138 °C. IR (KBr, cm^{-1}): 3000, 2948, 2836, 1707, 1630, 1473, 1439, 1292, 1217, 1012, 823; ^{1}H NMR δ ($CDCl_3$): 3.74 (s, 3H), 3.80 (s, 3H), 3.84 (s, 3H), 6.64 (d, 1H), 7.00 (s, 1H), 7.50 (t, 3H), 7.62 (d, 2H). ^{13}C NMR δ ($CDCl_3$): 53.1, 53.2, 56.1, 95.3, 109.5, 112.1, 113.2, 121.6, 124.4, 128.7, 130.4, 136.7, 146.4, 147.2, 155.4, 159.5, 160.5, 163.7. Anal. Calcd for $C_{22}H_{16}BrNO_6$ (469.02): C, 56.19; H, 3.43; N, 2.98. Found: C, 56.23; H, 3.21; N, 2.98.

General procedure for preparation of 7a-d: A solution of the appropriate isobenzofuran derivative (**5a-d**, 1 mmol) in toluene (20 mL) *N*-phenylmaleimide (2 mmol) was added and this mixture was refluxed for 8 h. After evaporation of the reaction mixture the residue was treated with cold ethanol to

give white crystals, which was filtered off and recrystallized from EtOH.

9-(4-Nitrophenyl)-1,3-dioxo-2-phenyl-1,2,3,3a,9,9a-hexahydro-4*H*-4,9-epoxybenzo[*f*]isoindole-4-carbonitrile (7a): Colourless crystals, 0.357 g (86%), mp 245-249 °C. IR (KBr, cm^{-1}): 3119, 3092, 1783, 1715, 1527, 1353, 1291, 1183, 1016, 789; ^{1}H NMR δ ($CDCl_3$+DMSO-d_6): 4.22 (d, 1H), 4.52 (d, 1H), 6.46 (dd, 2H), 7.02 (d, 1H), 7.31 (d, 3H), 4.74 (tt, 2H), 7.61 (d, 1H), 8.16 (d, 2H), 8.37 (d, 2H). ^{13}C NMR δ ($CDCl_3$+DMSOd_6): 52.1, 54,1, 91.5, 113.6, 120.5, 120.7, 125.7, 127.6, 128.7, 129.1, 129.8, 130.0, 137.6, 140.7, 141.0, 148.0, 169.6, 171.4. Anal. Calcd for $C_{25}H_{15}N_3O_5$ (437.10): C, 68.65; H, 3.46; N, 9.61. Found: C, 68.34; H, 3.27; N, 9.43.

9-(4-Bromophenyl)-1,3-dioxo-2-phenyl-1,2,3,3a,9,9a-hexahydro-4*H*-4,9-epoxybenzo[*f*]isoindole-4-carbonitrile (7b): Colourless crystals, 0.434 g (92%), mp 245-250 °C. IR (KBr, cm^{-1}): 3086, 2919, 1781, 1712, 1496, 1383, 1181, 1007, 787; ^{1}H NMR δ ($CDCl_3$): 4.11 (1H, d, J = 8.7 Hz, H3a), 4.35 (1H, d, J = 8.7 Hz, H9a), 6.44 (2H, m, H2" + H6"), 7.00 (1H, ddd, J = 7.3, 1.0, 0.9 Hz, H5), 7.27 (3H, m, H3" + H4" + H5"), 7.38 (1H, ddd, J = 7.4, 7.3, 1.2 Hz, H6), 7.45 (1H, ddd, J = 7.6, 7.4, 1.0 Hz, H7), 7.59 (1H, ddd, J = 7.6, 1.2, 0.9 Hz, H8), 7.64 (2H, m, H3' + H5'), 7.78 (2H, m, H2' + H6'). ^{13}C NMR δ ($CDCl_3$): 52.3 (C3a), 54.6 (C9a), 77.2 (C9), 92.5 (C4), 114.1 (CN), 120.8 (C8), 121.3 (C5), 123.8 (C4'), 126.0 (C2" + C6"), 128.6 (C2' + C6'), 129.1 (C3" + C4" + C5"), 129.3 (C7), 130.1 (C6), 130.4 (C1"), 132.1 (C3' + C5'), 133.3 (C1'), 138.0 (C8a), 141.9 (C4a), 169.9 (C1); 171.7 (C3). Anal. Calcd for $C_{25}H_{15}BrN_2O_3$ (470.03): C, 63.71; H, 3.21; N, 5.94. Found: C, 63.71; H, 3.25; N, 5.61.

9-(4-Nitrophenyl)-7-methoxy-1,3-dioxo-2-phenyl-1,2,3,3a,9,9a-hexahydro-4*H*-4,9-epoxybenzo[*f*]isoindole-4-carbonitrile (7c): Light brown crystals, 0.294 g (63%), mp 206-210 °C. IR (KBr, cm^{-1}): 3086, 2986, 1782, 1713, 1522, 1347, 1195, 1012, 731; ^{1}H NMR δ ($CDCl_3$): 3.73 (s, 3H), 4.11 (d, 1H), 4.37 (d, 1H), 6.52 (d, 3H), 6.94 (d, 1H), 7.32 (s, 3H), 7.50 (d, 1H), 8.14 (d, 2H), 8.38 (d, 2H). ^{13}C NMR δ ($CDCl_3$): 52.5, 54.8, 55.9, 92.0, 107.6, 109.7, 113.9, 114.3, 122.0, 124.1, 125.9, 127.9, 129.1, 129.2, 129.7, 130.3, 140.9, 143.1, 148.5, 161.5, 169.8, 171.6. Anal. Calcd for $C_{26}H_{17}N_3O_6$ (467.11): C, 66.81; H, 3.67; N, 8.99. Found: C, 66.45; H, 3.60; N, 8.78.

9-(4-Bromophenyl)-7-methoxy-1,3-dioxo-2-phenyl-1,2,3,3a,9,9a-hexahydro-4*H*-4,9-epoxybenzo[*f*]-isoindole-4-carbonitrile (7d): Colourless crystals 0.445 g (89%), mp 245-248 °C. IR (KBr, cm^{-1}): 3092, 2983, 2936, 1785, 1722, 1593, 1496, 1371, 1282, 1182, 1005, 830; ^{1}H NMR δ ($CDCl_3$): 3.72 (s, 3H), 4.09 (d, 1H), 4.33 (d, 1H), 6.52 (m, 3H), 6.91 (d, 1H), 7.30 (s, 3H), 7.46 (d, 1H), 7.65 (d, 2H), 7.78 (d, 2H).

^{13}C NMR δ ($CDCl_3$): 52.3, 54.9, 55.9, 92.5, 107.7, 114.2, 121.8, 123.8, 126.0, 127.9, 128.6, 129.0, 129.9, 130.5, 132.0, 133.2, 134.1, 143.7, 161.4, 170.0, 171.6. Anal. Calcd for $C_{26}H_{17}BrN_2O_4$ (500.04): C, 62.29; H, 3.42; N, 5.59. Found: C, 62.02; H, 3.39; N, 5.65.

General procedure for cycloadditions of isobenzofurans 5a-d with ethyl acrylate to yield cycloadducts 8 and 9: A solution of the appropriate isobenzofuran derivative (**5a-d**, 1 mmol) in toluene (20 mL) ethyl acrylate (2 mmol) was added and the mixture was refluxed for 24 h. After evaporation of the reaction mixture, the oil was purified by column chromatography (silica, eluent: hexane: EtOAc= 2:1).

Formation of the mixture of ethyl 1-(4-nitrophenyl)-4-cyano-1,2,3,4-tetrahydro-1,4-epoxynaphthalene-2-carboxylate (8a) and ethyl 4-(4-nitrophenyl)-1-cyano-1,2,3,4-tetrahydro-1,4-epoxynaphthalene-2-carboxylate (9a): Colourless crystals, 0.229 g (63%), mp 130-132 °C. IR (KBr, cm^{-1}): 3112, 3080, 2983, 1740, 1712, 1521, 1350, 1279, 1052, 1041, 977. ^{1}H NMR δ ($CDCl_3$): 1.03 (3H, t, *J* = 7.0 Hz, C<u>H</u>$_3$ {**8a**}), 1.28 (3H, t, *J* = 7.0 Hz, C<u>H</u>$_3$ {**9a**}), 2.49 (1H, dd, *J* = 11.5, 3.8 Hz, H3b{**8a**}), 2.57 (1H, dd, *J* = 12.0, 10.5 Hz H3a{**9a**}), 2.62 (1H, dd, *J* =12.0, 4.4 Hz, H3b{**9a**}), 2.95 (1H, dd, *J* = 11.5, 10.7 Hz, H3a{**8a**}); 3.77 (1H, m,H2{**9a**}), 3.78 (1H, dd, *J* = 10.7, 3.8 Hz, H2{**8a**}), 3.71-3.77 (2*3H, OC<u>H</u>$_3$ {**8a**, **9a**}), 3.9-4.1 (2*2H, C<u>H</u>$_2$ {**8a**, **9a**}), 6.92(1H, d, *J* = 8.0 Hz, H5{**9a**}), 7.00 (1H, d, *J* = 8.1 Hz, H8{**8a**}), 7.33 (2*1H, t, *J* = 8.0 Hz, H7{**9a**}+ H6{**8a**}), 7.36 (1H, t, *J* = 8.0 Hz, H6{**9a**}), 7.42 (1H, t, *J* = 8.1 Hz,H7{**8a**}), 7.48 (1H, d, *J* = 8.0 Hz, H8{**9a**}); 7.57 (1H, d, *J* = 8.1 Hz, H5{**8a**}), 7.70 (2H, m, H2'+H6'{**9a**}), 7.96 (2H, m, H2'+H6'{**8a**}), 8.34 (2*2H, m, H3'+H5'{**8a**, **9a**}).

^{13}C NMR δ ($CDCl_3$) of **8a**: 13.9 (<u>C</u>H_3), 39.7(C3), 48.5 (C2), 61.6 (<u>C</u>H_2CH$_3$), 75.9 (C4), 91.2 (C1), 115.5 (<u>C</u>N), 118.7 (C5), 121.4 (C8), 123.5 (C3'+C5'), 128.6 (C6), 128.8 (C7), 129.0 (C2'+C6'), 130.3 (C1'), 141.8 (C4a), 142.3 (C8a), 148.3 (C4'), 169.4 (C=O). ^{13}C NMR δ ($CDCl_3$) of **9a**: 14.1 (<u>C</u>H_3), 35.8 (C3), 51.7 (C2), 61.9 (<u>C</u>H_2CH$_3$), 77.0 (C1), 90.3 (C4); 115.5 (<u>C</u>N), 119.0 (C8), 120.3 (C5), 124.0 (C2'+C6'), 126.9 (C3'+C5'), 128.0 (C7), 129.4 (C6), 130.2 (C1'), 141.8 (C8a), 142.3 (C4a), 148.2 (C4'), 169.2 (C=O). Anal. Calcd for $C_{20}H_{16}N_2O_5$ (364.11): C, 65.93; H, 4.43; N, 7.69. Found: C, 65.83; H, 4.18; N, 7.42.

Ethyl 1-(4-bromophenyl)-4-cyano-1,2,3,4-tetrahydro-1,4-epoxynaphthalene-2-carboxylate (8b): Colourless crystals, 0.175 g (44%), mp 100-102 °C. IR (KBr, cm^{-1}): 2983, 2903, 1730, 1460, 1263, 1041, 1010, 827; ^{1}H NMR δ ($CDCl_3$): 1.02 (3H, t, *J* = 6.8Hz, COOCH$_2$-C<u>H</u>$_3$), 2.44 (1H, dd, *J* = 11.7, 3.6 Hz,

H3a), 2.91 (1H, dd, *J* = 11.7, 10.8 Hz, H3b), 3.77 (1H, dd, *J* = 10.8, 3.6 Hz, H2), 3.89 (2H, q, *J* = 6.8 Hz, $COOC\underline{H}_2$-CH_3), 6.98 (1H, d, *J* = 7.4 Hz, H8), 7.27 (1H, dd, *J* = 7.7, 7.4 Hz, H7), 7.36 (1H, dd, *J* = 7.7, 7.5 Hz, H6), 7.52 (1H, d, *J* = 7.5 Hz, H5), 7.58 (4H, m, H2' + H3' + H5' + H6'). ^{13}C NMR δ ($CDCl_3$): 13.9 ($COOCH_2$-$\underline{C}H_3$), 39.7 (C3), 47.8 (C2), 61.3 ($COO\underline{C}H_2$-CH_3), 75.6 (C4); 91.8 (C1), 115.8 ($\underline{C}N$), 118.4 (C5), 121.6 (C8), 123.6 (C4'), 128.4 (C6); 128.5 (C7), 129.8 + 131.6 (C2' + C3' + C5' + C6'), 133.7 (C1'), 142.3 (C8a), 142.6 (C4a), 169.7 (CO). Anal. Calcd for $C_{20}H_{16}BrNO_3$ (397.03): C, 60.32; H, 4.05; N, 3.52. Found: C, 60.33; H, 3.86; N, 3.36.

Formation of the mixture of ethyl 1-(4-nitrophenyl)-4-cyano-7-methoxy-1,2,3,4-tetrahydro-1,4-epoxy-naphthalene-2-carboxylate (8c) and ethyl 4-(4-nitrophenyl)-1-cyano-6-methoxy- 1,2,3,4-tetra-hydro-1,4-epoxynaphthalene-2-carboxylate (9c): Orange oil, 0.240 g (61%).

M stands for the major diastereomer, whereas m for the minor diastereomer. Thus, the four sets of signals can be assigned to the two pairs of diastereomers **8c***M*, **8c***m*, **9c***M*, **9c***m*.

^{1}H NMR δ ($CDCl_3$): 0.9 (3H, t, *J* = 7.0 Hz, $C\underline{H}_3$ {**8c***m*}), 1.05 (3H, t, *J* = 7.0 Hz, $C\underline{H}_3$ {**8c***M*}), 1.25 (3H, t, *J* = 7.0 Hz, $C\underline{H}_3$ {**9c***M*}); 1.28 (3H, t, *J* = 7.0 Hz, $C\underline{H}_3$ {**9c***m*}), 2.35 (1H, dd, *J* = 11.7, 8.7 Hz, H3a {**8c***m*}), 2.38 (1H, dd, *J* = 11.6, 8.6 Hz, H3a {**9c***m*}), 2.49 (1H, dd, *J* = 11.6, 3.9 Hz, H3b {**8c***M*}), 2.54 (1H, dd, *J* =12.0, 4.4 Hz, H3b {**9c***M*}), 2.57 (1H, dd, *J* = 12.0, 10.5 Hz H3a {**9c***M*}), 2.70 (1H, dd, *J* = 11.6, 4.7 Hz, H3b {**9c***m*}), 2.93 (1H, dd, *J* = 11.6, 10.7 Hz, H3a {**8c***M*}), 2.98 (1H, dd, *J* = 11.7, 4.9 Hz, H3b {**8c***m*}), 3.07 (1H, dd, *J* = 8.6, 4.7 Hz, H2 {**9c***m*}), 3.13 (1H, dd, *J* = 8.7, 4.9Hz, H2 {**8c***m*}), 3.75 (1H, dd, *J* = 10.7, 3.9 Hz, H2 {**8c***M*}), 3.85 (1H, dd, *J* = 10.5, 4.4 Hz, H2 {**9c***M*}), 3.71-3.77 (4*3H, $OC\underline{H}_3$ {**8c***M*, **8c***m*, **9c***M*, **9c***m*}), 3.9-4.1 (4*2H, $C\underline{H}_2$ {**8c***M*, **8c***m*, **9c***M*, **9c***m*}), 6.38 (1H, d, *J* = 2.0 Hz, H5 {**9c***M*}), 6.42 (1H, d, *J* = 2.0 Hz, H5 {**9c***m*}), 6.48 (1H, d, *J* = 2.0 Hz, H8 {**8c***M*}), 6.62 (1H, d, *J* = 2.0 Hz, H8 {**8c***m*}), 6.77 (1H, dd, *J* = 8.1, 2.0Hz, H7 {**9c***M*}); 6.82 (2*1H, m, H6 {**8c***m*}+ H7 {**9c***m*}), 6.86 (1H, dd, *J* = 8.1, 2.0Hz, H6 {**8c***M*}), 7.34 (1H, d, *J* =8.1 Hz, H8 {**9c***M*}), 7.40-7.43 (3*1H, m, H5 {**8c***M*, **8c***m*}+H8{**9c***m*}), 7.62-7.78 (3*2H, m, H2'+H6' {**8c***M*}), 7.94 (3*2H, m, H2'+H6' {**8c***m*, **9c***M*, **9c***m*}), 8.26-8.38 (4*2H, m, H3'+H5' {**8c***M*, **8c***m*, **9c***M*, **9c***m*}).

^{13}C NMR data of **8c***M*, δ ($CDCl_3$): 13.9 ($\underline{C}H_3$), 40.0 (C3), 48.5 (C2), 55.7 ($O\underline{C}H_3$), 61.5 ($\underline{C}H_2CH_3$), 75.6 (C4), 91.3 (C1), 108.4 (C8), 113.0 (C6), 115.6 ($\underline{C}N$), 120.0 (C5), 123.6 (C3'+C5'), 129.1 (C2'+C6'), 131.5 (C1'), 134.5 (C4a), 141.7 (C4'), 143.7 (C8a), 160.2 (C7), 169.4 (C=O).

^{13}C NMR data of **9c***M,* δ ($CDCl_3$): 14.1 ($\underline{C}H_3$), 35.8 (C3), 52.0 (C2), 55.8 (O$\underline{C}H_3$), 61.8 ($\underline{C}H_2CH_3$), 77.3 (C1), 90.3 (C4), 105.9 (C5), 112.5 (C7), 115.4 ($\underline{C}N$), 121.2 (C8), 123.6 (C3'+C5'), 127.2 (C2'+C6'), 131.0 (C1'), 131.1 (C8a), 143.2 (C4'), 146.9 (C4a), 160.8 (C6), 168.2 (C=O).
Diastereomeric ratios: **8c***M* 55 mol%, **8c***m* 22 mol%; **9c***M* 16mol%, **9c***m* 7 mol%. Regioisomeric ratio **8c**:**9c** = 77:23.

Formation of the mixture of ethyl 1-(4-bromophenyl)-4-cyano-7-methoxy-1,2,3,4-tetrahydro-1,4-epoxynaphthalene-2-carboxylate (8d) and ethyl 4-(4-bromophenyl)-1-cyano-6-methoxy-1,2,3,4-tetrahydro-1,4-epoxynaphthalene-2-carboxylate (9d): Yellow oil 0.205 g (48%).

M stands for the major diastereomer, whereas m for the minor diastereomer. Thus, the four sets of signals can be assigned to the two pairs of diastereomers **8d***M*, **8d***m*, **9d***M*, **9d***m*.

^{1}H NMR δ ($CDCl_3$): 0.9 (3H, t, *J* = 7.0 Hz, C$\underline{H}_3$ {**8d***m*}), 1.03 (3H, t, *J* = 7.0 Hz, C$\underline{H}_3$ {**8d***M*}), 1.28 (3H, t, *J* = 7.0 Hz, C$\underline{H}_3$ {**9d***M*}), 1.35(3H, t, *J* = 7.0 Hz, C$\underline{H}_3$ {**9d***m*}), 2.27 (1H, dd, *J* = 11.3, 8.0 Hz, H3a {**9d***m*}), 2.30 (1H, dd, *J* = 11.3, 8.1 Hz, H3a {**8d***m*}), 2.43 (1H, dd, *J* =11.3, 3.6 Hz, H3b {**9d***M*}), 2.45 (1H, dd, *J* = 11.3, 3.6 Hz, H3b {**8d***M*}), 2.57 (1H, dd, *J* = 11.3, 10.1 Hz H3a {**9d***M*}), 2.70 (1H, dd, *J* = 11.3, 4.0 Hz, H3b {**9d***m*}), 2.87 (1H, dd, *J* = 11.3, 10.1 Hz, H3a {**8d***M*}), 2.95 (1H, dd, *J* = 11.5, 4.4 Hz, H3b {**8d***m*}), 3.04 (1H, dd, *J* = 8.0, 4.0 Hz, H2 {**9d***m*}), 3.05 (1H, dd, *J* = 8.1, 4.4Hz, H2 {**8d***m*}), 3.77 (1H, dd, *J* = 10.1, 3.6 Hz, H2 {**8d***M*}), 3.82 (1H, dd, *J* = 10.1, 3.6 Hz, H2 {**9d***M*}), 3.71-3.77 (4*3H, O$\underline{C}H_3$ {**8d***M*, **8d***m*, **9d***M*, **9d***m*}), 3.9-4.1 (4*2H, C$\underline{H}_2$ {**8d***M*, **8d***m*, **9d***M*, **9d***m*}), 6.40(1H, d, *J* = 2.0 Hz, H5 {**9d***M*}), 6.42 (1H, d, *J* = 2.0 Hz, H5 {**9d***m*}), 6.48 (1H, d, *J* = 2.0 Hz, H8 {**8d***M*}), 6.64 (1H, d, *J* = 2.0 Hz, H8 {**8d***m*}), 6.75 (1H, dd, *J* = 8.1, 2.0 Hz, H6 {**8d***m*}), 6.79 (2*1H, dd, *J* = 8.1, 2.0 Hz, H7 {**9d***M*}+ H7{**9d***m*}), 6.84 (1H, dd, *J* = 8.1, 2.0 Hz, H6 {**8d***M*}), 7.36 (1H, d, *J* =8.1 Hz, H8 {**9d***M*}), 7.42 (1H, d, *J* =8.1 Hz, H8 {**9d***m*}), 7.40 (2*1H, m, H5 {**8d***M*, **8d***m*}); 7.56-760 (4*4H, m, H2'+H3'+H5'+H6' ({**8d***M*, **8d***m*, **9d***M*, **9d***m*}).

^{13}C NMR data of **8d***M* δ ($CDCl_3$): 13.9 ($\underline{C}H_3$), 40.0 (C3), 47.9 (C2), 55.7 (O$\underline{C}H_3$), 61.3 ($\underline{C}H_2CH_3$), 75.3 (C4), 91.9 (C1), 108.5 (C8), 112.9 (C6), 115.8 ($\underline{C}N$), 119.6 (C5), 123.6 (C4'), 129.9 (C2'+C6'), 131.5 (C3'+C5'), 132.0 (C1'), 134.2 (C4a), 144.2 (C8a), 160.1 (C7), 169.6 (C=O).

^{13}C NMR data of **9d***M* δ ($CDCl_3$): 13.7 ($\underline{C}H_3$), 35.4 (C3), 52.1 (C2), 55.8 (O$\underline{C}H_3$),61.2 ($\underline{C}H_2CH_3$), 77.3 (C1), 90.7 (C4), 106.2 (C5), 112.4 (C7), 115.8 ($\underline{C}N$), 123.0 (C4'), 127.4 (C8), 129.9 (C2'+C6'), 131.6

(C3'+C5'), 131.7 (C8a), 131.9 (C1'), 146.0 (C4a), 160.3 (C6), 170.8 (C=O).

Diastereomeric ratios: **8d***M* 50 mol%, **8d***m* 25 mol%; **9d***M* 16mol%, **9d***m* 9 mol%. Regioisomeric ratio **8d**:**9d** = 75:25.

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