Ninhydrin as a building block in scaffold-linked chromophoric dyad construction

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Abstract

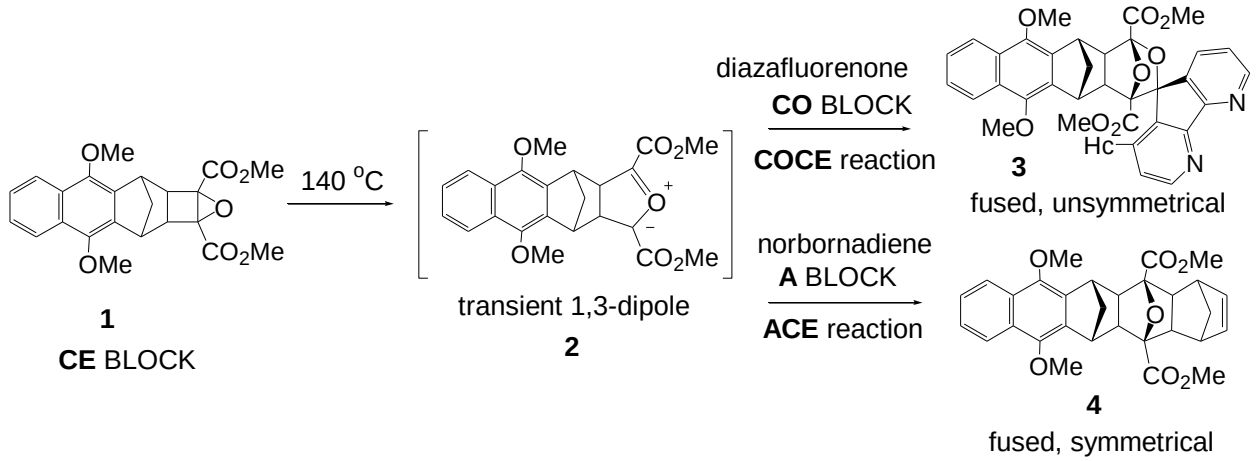
The reaction of ninhydrin with ester-activated cyclobutene epoxide (CE-**1**) containing the fused 1,4-dimethoxynaphthalene (**DMN**) chromophore, gave adducts formed by 1,3-dipolar cycloaddition at the central (C_2)-CO (major) and the outer ($C_{1,3}$)-CO (minor) positions. Conversion of the minor adduct to quinoxalines (**QIN**) by reaction with *o*-phenylenediamines at the α-dione moiety, albeit in poor yield, led to **spiro-DMN-1,4σ-QIN** dyad in which the plane of the chromophore was orthogonally orientated yet angled to the plane of the **DMN** chromophore. Reaction of ninhydrin with *o*-phenylenediamines yielded the corresponding 11-oxoindeno[1,2-b]quinoxalines which were coupled with CE-BLOCKs to form spiro adducts by reaction at the carbonyl site; the product from CE-**1** was identical with that formed above. Another class of spiro-fused dyads was produced by reaction of ninhydrin with a primary amine followed by cycloaddition of CE-BLOCKs at the carbonyl site, where the amine was available to deliver one chromophore and the CE-BLOCK another.

Keywords: Ninhydrin; quinoxalines; cycloaddition reactions; chromophores; polycycles

Introduction

We have reported that certain cyclic ketones can react with ester-activated cyclobutene epoxides (CEs) in a building BLOCK protocol to form rigid, spiro-fused molecular scaffolds.[1] The reaction proceeded via a transient 1,3-dipolar intermediate **2**[2] formed by thermal ring opening of the **C**yclobutane **E**poxide ring which was trapped by the **C**arb**O**nyl π-bond in a **COCE** [3π+2π] cycloaddition process, *e.g.* the reaction of 4,5-diazafluorenone produced the spiro-adduct **3** (Scheme 1). This finding added a new dimension to our building BLOCK technique for the construction of rigid scaffolds and complemented to more established ACE-reaction protocol (**A**cetylene

Cyclobutane **E**poxide) in which alkenes acted as the dipolarophile.[3,4] A major difference between the two reactions was that the COCE-reaction produced spiro-fused unsymmetrical scaffolds, whereas the ACE-protocol produced symmetrical or unsymmetrical scaffolds depending on the symmetry of the C=C dipolarophile.



Scheme 1. 1,3-dipolar cycloadditions of cyclobutene epoxide **1.**

In the preliminary study[5], we reported that cyclic α-diones were first-rate dipolarophiles[6], so we were curious to assess the potential of ninhydrin **5**, a tricyclic 1,2,3-trione, to participate in the COCE-reaction, in order to extend the scope of this synthetic methodology to various ketones. Questions which needed to be answered were a) What would be the site selectivity of the reaction? b) Would the reaction proceed past the 1:1 adduct stage? c) Could ninhydrin act as a linking agent to couple different chromophores? In this paper, we answer these questions and show how new synthetic protocols have been developed as a succinct route to rigid donor-spacer-acceptor dyads.[7]

Formation of dyads by the COCE-reaction

We devised a new synthetic strategy for dyad construction employing the COCE-reaction for attachment of one chromophore (the A-chromophore) by the cyclobutene epoxide reagent and the other (the B-chromophore) by carbonyl group. By linking these addends using the COCE reaction ensured that the two chromophores would be fused to a rigid carbocyclic frame which could act as a scaffold and hold the dyad chromophores in a fixed alignment (Diagram 1). By using ninhydrin **5** as the carbonyl reagent, the opportunity for reaction to occur at more than one site was available and the potential for sequential cycloadditions to arise was opened up. In practice, only single cycloadditions occurred to ninhydrin, however, the dyad strategy could still be taken forward productively by prior modification of the ninhydrin to form CO-containing derivatives that entered into the COCE reaction. In this way, the B-chromophore could be introduced using this derivative as the CO-BLOCK and stereoselectively linked to the CE-BLOCK thereby completing the rigid assembly of the two chromophores.

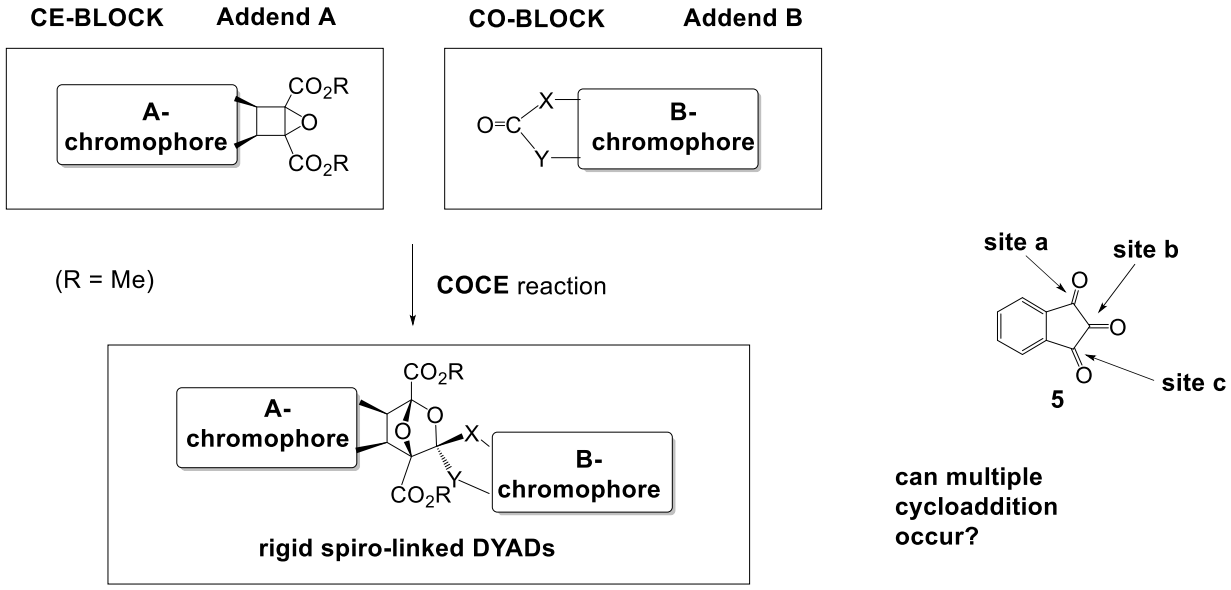


Diagram 1. Strategy of COCE dyad synthesis employing ninhydrin building BLOCK.

The main CE-BLOCKs[8] and some new CO-BLOCKs derived from ninhydrin used in this paper are shown in Diagram 2. Not all combinations of COCE-BLOCK assemblies have been undertaken and not all those tried have been successful.

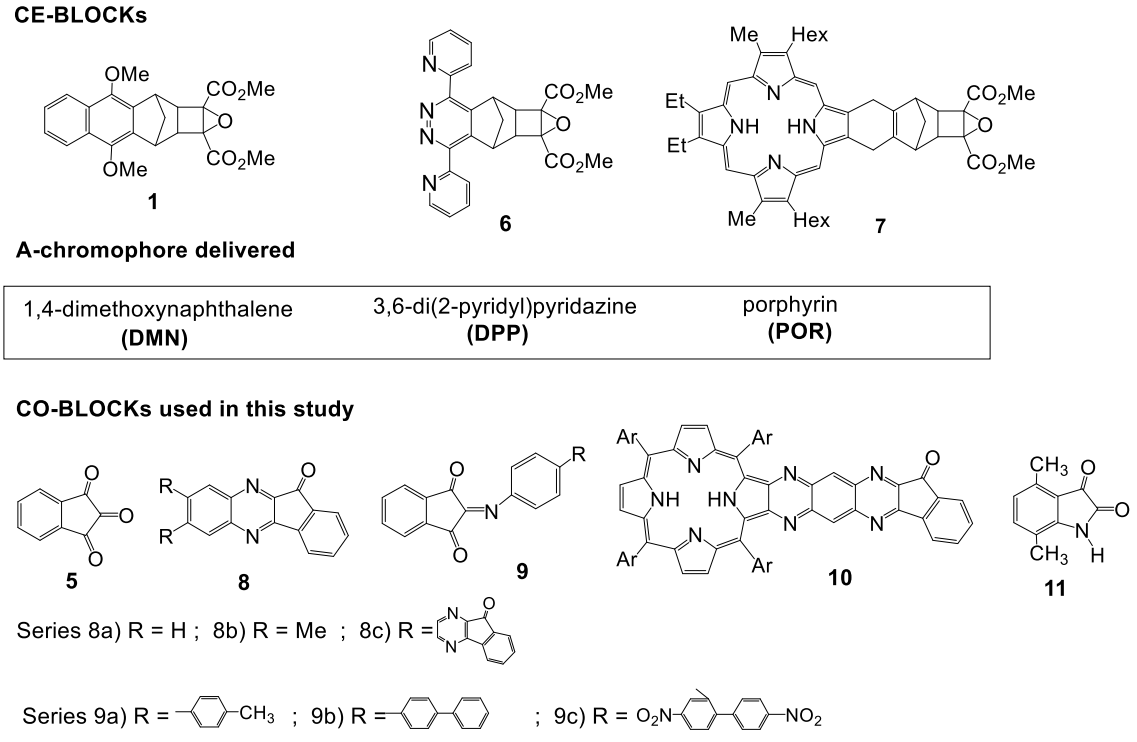


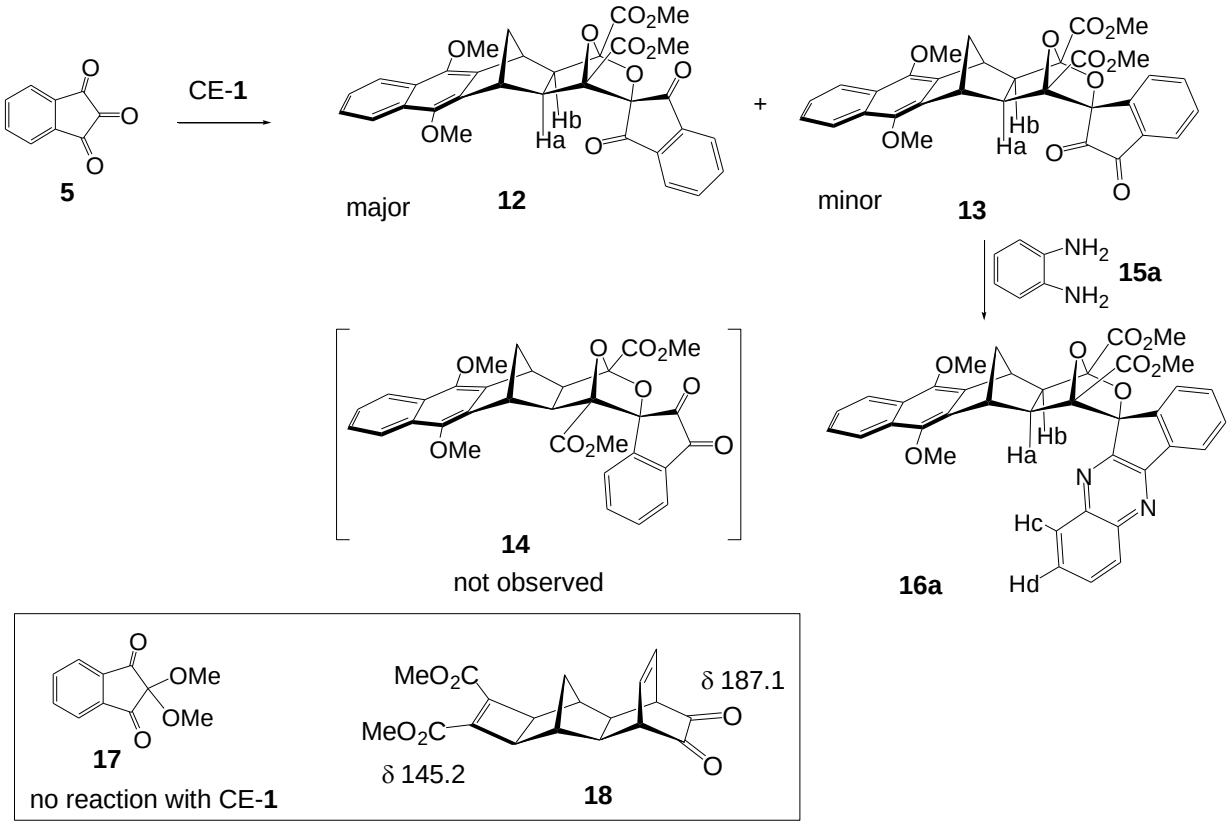
Diagram 2. Representative CO- and CE-BLOCK reagents.

Results and Discussion

(a) Reaction of cyclobutene epoxides with ninhydrin

Several examples of ninhydrin being used as a C=O dienophile in hetero Diels-Alder cycloadditions have appeared in the literature,[9,10] but no record of its use as a dipolarophile has been reported. In those Diels-Alder reactions, exclusive site selectivity at the central CO bond was observed to occur. A single case of ninhydrin acting as a hetero-1,3-diene in which vicinal carbonyls act as the 4π-reagent with 2,3-dimethyl-2-butene by photochemical formal [4π+2π] addition takes place via 1,4-biradical.[11]

The reaction of CE-**1** with ninhydrin was conducted in dichloromethane at 140 °C in a sealed glass tube and produced two cycloadducts which were separated by radial chromatography. The major product was the 1:1-adduct **12** derived by attack at the central C=O dipolarophile (Scheme 2). The structure was assigned on the basis of mass spectrometry, NMR spectroscopy and chemical reactions. In particular, the ^{13}C-NMR showed two closely spaced CO-resonances at δ 193.7 and δ 193.9 typical of aryl ketones as well as two up-field CO-resonances for the ester groups (δ 163.6, 165.3). The lack of colour in this adduct supported the absence of α-dione chromophore which was consistent with the fact that no evidence for a quinoxaline derivative was observed on treating it with *o*-phenylenediamine **15a** (see later for contrasting behaviour of the minor 1:1-adduct **13**).



Scheme 2. COCE reaction of CE-**1** with ninhydrin.

The minor product **13** isolated from this reaction was yellow-coloured and shown to be a 1:1-adduct by mass spectroscopy. ^{13}C-NMR displayed four carbonyl resonances corresponding to the ester COs (δ 164.2, 165.1) and two well-separated resonances indicative of an aryl carbonyl (δ 194.1) and an aliphatic α-dione carbonyl (δ 184.6; note that those in the reference α-dione **18** resonated at δ 187.1). The presence of the α-dione functionality was confirmed by reaction of **13** with *o*-phenylenediamine **15a** to form the quinoxaline **16a**. Assignment of stereochemistry to adduct came down to a choice between stereoisomers **13** and **14**. Support for the former adduct structure was provided by a significant change in chemical shift for the *endo*- protons Ha, Hb that occurred on conversion of **13** (δ_H 3.04, 3.17) to the quinoxaline **16a** (δ_H 3.39, 4.18), indicative of their proximity to the quinoxaline ring and its attendant ring-current. This stereo-defining feature was only realisable in adduct in which the original α-dione had *endo*-stereochemistry, viz **13**. It is significant that no NOE correlation between the phenylene protons Hc, Hd and the norbornane scaffold *endo*-protons Ha, Hb was observed. The distances between the quinoxaline protons and the scaffold *endo*-protons were determined by molecular modelling (AM1 method) and the magnitude of nearest neighbour separations (Ha/Hc=4.07 Å and Hb/Hc=3.89 Å) helped to justify this lack of NOE enhancements (Figure 1). The separations between the aryl protons and the *endo*-protons of the norbornane scaffold in the fluorene-adduct **19**[Error! Bookmark not defined.], where there is no ambiguity about the *endo*-positioning of one phenylene ring and which does show NOE signals, are much smaller (Ha/Hc=2.19 Å and Hb/Hc=2.12 Å).

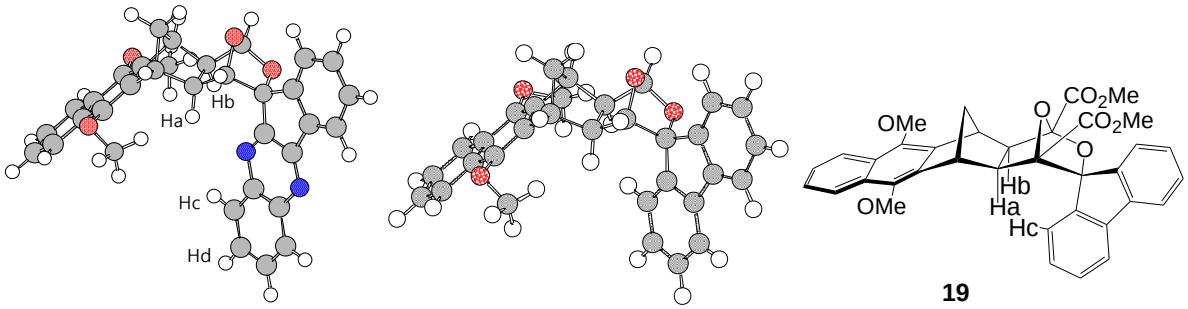


Figure 1. Optimised molecular structures (AM1) for quinoxaline **16a** and adduct **19** (esters are omitted for clarity).

No evidence for the production of 2:1-adducts from this reaction was evinced and this failure of either type of adduct to undergo further COCE-coupling was attributed to the steric congestion about the respective CO centres. In particular, the spiro-fused geometry ensured that both faces of the CO groups were sterically screened by the scaffold. Significantly, the ninhydrin ketal **17** failed to participate in the COCE reaction and steric screening of the carbonyl groups by the out of plane methoxy groups of the vicinally-related ketal would appear to be responsible. Semiempirical AM1 modelling supports this rationale.

(b) Couplings involving 11-oxoindeno[1,2-b]quinoxalines

Solid state reaction of ninhydrin **5** with *o*-phenylenediamines under high speed vibration milling (HSVM)[12] conditions (3600 rpm, 30 min) was used to produce a series of 11-oxoindeno[1,2-b]quinoxalines **8a-c**[13] (albeit in yields inferior to standard procedures, see Scheme 3, Table 1).[14] The parent product **8a** was reacted with the cyclobutene epoxide CE-**1** (sealed tube, DCM, 140 ºC, 12h) to afford a single 1:1 adduct **16a** (Scheme 3), identical with that produced above by the condensation route. Reference to Table 2 in which the chemical shifts of the *endo*-scaffold protons Ha/Hb for the various adducts are recorded, showed that derivation of α-dione **13** to the quinoxaline **16a** caused significant downfield shifts consistent with the stereochemical assignment.

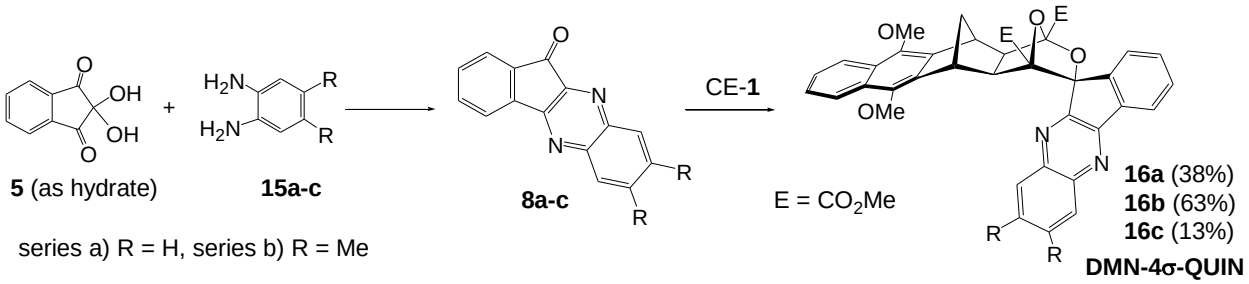
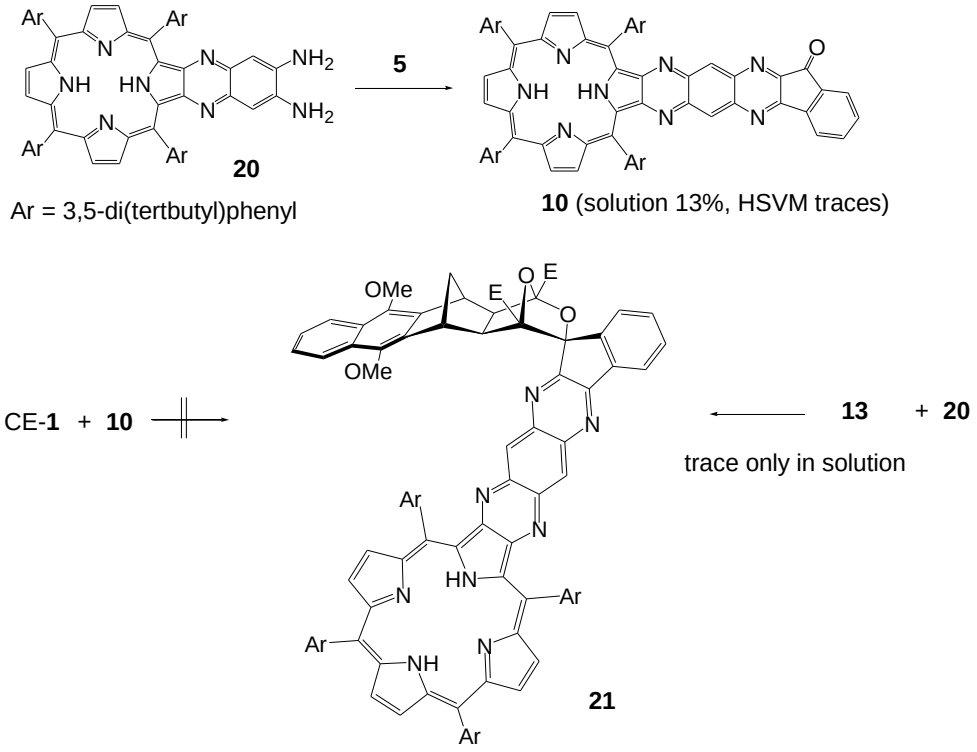


Table 1 Preparation of 11-oxoindeno[1,2-b]quinoxalines **8**

R	HSVM	Yield (%) standard
8a H	17	60
8b Me	22	72
8c 	13	43

Scheme 3. COCE couplings involving 11-oxoindeno[1,2-b]quinoxalines.

Introduction of a porphyrin chromophore into a dyad using the COCE method was approached using the porphyrin ketone **10** as a B-chromophore BLOCK. The required ketone was formed by reaction of the known porphyrin diamine **20**[15] with ninhydrin **5** (as the hydrate), a reaction which proceeded under thermal conditions in solution or solid state conditions (HSVM) at room temperature (Scheme 4). Reaction between ketone **10** and CE-**1** under the same thermal conditions as those used above with **8a**,**b** failed to produce the spiro-fused **TAAP-1,4σ-DMN** dyad **21** (**TAAP** = tetraazaanthraceno porphyrin). In an alternative approach, the condensation of α-dione adduct **13** with porphyrin diamine **20** produced only trace amounts of dyad **21** (Scheme 4). Identification of **21** rested on NMR and mass spectral data obtained from crude material (four non-equivalent methyl signals at characteristic positions δ 3.48, 3.71, 4.12, 4.23.



Scheme 4. COCE couplings of porphyrinic 11-oxoindeno[1,2-b]quinoxaline **10.**

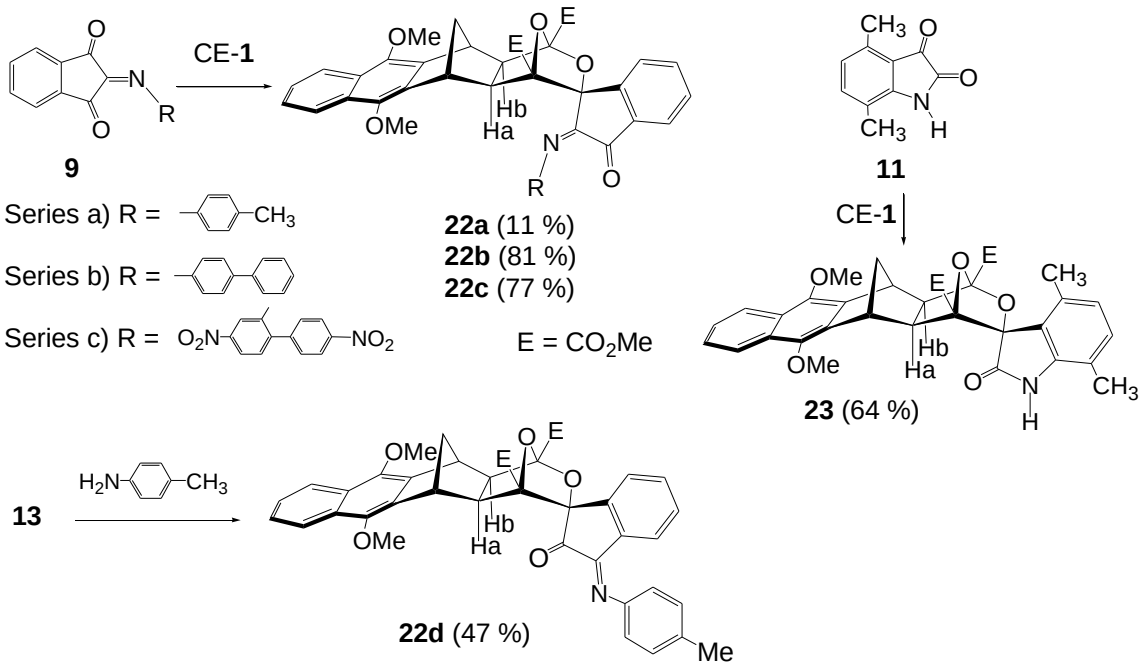
Table 2. Chemical ^{1}H and ^{13}C NMR shift data for selected compounds

Compound	Ha,Hb (δ_H)	Ester Me (δ_H)	NOE	^{13}C-NMR ester ketone
3	3.06; 3.17	3.41; 3.84	Yes	160.0; 164.6
12	3.11; 3.21	3.68; 3.88	No	163.6; 165.3
13	3.04; 3.17	3.54; 3.86	No	164.2; 165.1
16a	3.39; 4.18	3.42; 3.74	No	164.9; 165.9
16b	3.11; 3.34	3.40; 3.76	No	164.9; 165.9
16c	3.41; 3.44	3.47; 3.73	No	158.3, 166.2
range	3.04-4.18	3.40-3.88		

(c) Cycloadditions at the carbonyl π-centre on ninhydrin imines

Cycloaddition at the C_1,C_3-carbonyls of ninhydrin was unprecedented until the present studies.[16] As mentioned above, attempts to direct cycloaddition onto the C_1,C_3 positions of ninhydrin by converting the C_2-carbonyl to its ketal were unsuccessful. In order to better assess the potential for attack at the C_1,C_3-carbonyl positions, we studied the reactions of ninhydrin Schiff's bases **9** formed by treatment of ninhydrin with primary amines.[17] We reasoned that steric hindrance would no longer be a problem as a Schiff's base **9a**[18] was a planar system. Indeed, reaction with CE-**1** proceeded smoothly to produce a single, red-coloured 1:1-adduct **22a** (Scheme 5). That reaction had

occurred at the CO-group rather that at the imine was supported by the presence of a single ^{13}C ketone resonance at δ 182.8 and an imine ^{13}C resonance at δ 163.1. In all cases to date (ninhydrin, indenopyridazines), the phenylene component had been preferentially positioned in the *exo*- site and this stereo-preference was retained in this reaction as no NOE correlation was observed between the either phenylene protons and the aryl protons of the *N*-substituents and the *endo*- protons Ha, Hb. Again, interatomic distance considerations backed up by molecular modelling (AM1) supported the lack of NOE correlations. Interestingly, different product **22d** was obtained by condensation of minor adduct **13** with *p*-toluidine. Here condensation with dione occurred at the C_1-carbonyl position, as suggested by NMR spectroscopy. Notably, the *endo*- protons Ha, Hb are less shielded by tolyl group and appear at higher magnetic field. In addition, imine phenyl group is less affected by naphthalene ring magnetic shielding



Scheme 5. COCE reactions of ninhydrin Schiff's bases **9a-c** and 4,7-dimethylisatin.

Similar regiodirection with an exclusive addition at the C_1-carbonyl position[19] was obtained in reaction of CE-**1** with 4,7-dimethylisatin **11** (Scheme 5). Stereochemistry of spiro cycloadduct **23** was established by the chemical shift of the *endo*-protons Ha, Hb (δ 3.11, 3.34) and the lack of NOE enhancements between the methyl group and the *endo*-protons.

Conclusions

Ninhydrin was used for synthesis of diversity of chromophoric molecular dyads employing 1,3-dipolar cycloaddition to carbonyl bonds. This synthetic protocol delivers an orthogonal orientation

of chromophores separated by the rigid polycyclic scaffold and extends reaction scope to 1,2,3-triketones and various aromatic ketones. Molecular modelling indicates that formation of 2:1 cycloadducts of ninhydrin with CE-**1** should take place only in the case of minor 1:1 adduct **13** at the 1,3-carbonyls, however, approach of the 1,3-dipole is obstructed by steric reasons.

Experimental Section

General. Reagents were supplied by Aldrich and solvents were used without further purification. For chromatography petroleum ether fraction bp 40-60 °C was used. Thin layer chromatography (TLC) was performed on alumina sheets coated with Merck Kieselgel 60 F_{254}. Column chromatography on silica was carried out using Merck Silica Gel 60 (230-400 mesh). Preparative plates for radial chromatography on chromatotron (Harrison Research) were produced with Merck Silica Gel 60 PF_{254} containing gypsum. Melting points were determined on a Gallenkamp melting point apparatus and were uncorrected. The ^{1}H and ^{13}C NMR spectra were acquired using Bruker AMX300 (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) or Bruker Avance DPX400 (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) spectrometers at 303 K. Chemical shifts (δ) are reported in parts per million relative to tetramethylsilane (TMS) as internal standard. COSY and NOESY two dimensional correlation NMR experiments employed the standard Bruker parameters. The high resolution mass spectra were obtained by ESMS (electrospray mass spectrometry) on a Micromass Platform II single quadrupole mass spectrometer by Mr. Thomas Frey. Mechanochemical syntheses were carried out in the custom-made high speed vibrational mill (HSVM, 3600 rpm, 60 Hz).[20]

Spiro[dimethyl-3,10-dimethoxy-1α,12α,13β,14α,17α,18β-16,19-dioxahexacyclo[10,6,1.1^{14,17} 0^{2,11}0^{4,9}0^{13,18}]-dodeca-2,4,6,8,10-pentaene-14,17-dicarboxylate-15,1'-indan-[2,3]-dione] (13) and spiro[dimethyl-3,10-dimethoxy-1α,12α,13β,14α,17α,18β-16,19-dioxahexacyclo[10,6,1. 1^{14,17}0^{2,11}0^{4,9}0^{13,18}]-dodeca-2,4,6,8,10-pentaene-14,17-dicarboxylate-15,1'-indan-[1,3]-dione] (12). A solution of epoxide (60 mg, 0.146 mmol) and ninhydrin (26 mg, 0.144 mmol) in dichloromethane (5 mL) was heated at 140 °C overnight. Solvent was removed *in vacuo* to afford a colourless solid. Radial chromatography (starting with petroleum ether - ethyl acetate 10:1, then solvent polarity was gradually increased to ethyl acetate) afforded two adducts in order of elution:
13. Colourless solid. 12 mg, yield 14 %, mp 214-216 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.55 (1H, d, *J* 10.1 Hz), 2.73 (1H, d, *J* 10.1 Hz), 3.04 (1H, d, *J* 6.5 Hz), 3.17 (1H, d, *J* 6.5 Hz), 3.53 (1H, s), 3.54 (3H, s), 3.86 (3H, s), 3.89 (1H, s), 4.11 (6H, s), 7.49-7.52 (2H, m), 7.64 (1H, t, *J* 7.8 Hz), 7.87-7.93 (2H, m), 8.02-8.08 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 42.2, 42.3, 42.8, 46.4, 47.6, 53.2, 53.9, 55.6, 62.1, 81.4, 94.0, 105.5, 122.7, 124.0, 126.2, 126.5, 128.5, 128.6, 133.1, 133.2, 133.4, 133.8, 138.0, 138.8, 144.2, 145.3, 146.3, 155.9, 164.2, 165.1, 184.6, 196.9; HRMS (ESI) calculated for $C_{32}H_{26}O_{10}$: 570.1526 found 570.1516.
12. Colourless solid. 38 mg, yield 44 %, mp 260-262 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.54 (1H, d, *J* 10.0 Hz), 3.11 (1H, d, *J* 6.5 Hz), 3.14 (1H, d, *J* 10.0 Hz), 3.21 (1H, d, *J* 6.5 Hz), 3.56 (1H, s), 3.68 (3H, s), 3.82 (1H, s), 3.88 (3H, s), 4.03 (3H, s), 4.04 (3H, s), 7.47-7.50 (2H, m), 7.86-7.88 (2H,

m), 7.94-7.96 (2H, m, 8.11-8.12 (1H, m), 8.15-8.16 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 42.2, 42.3, 42.6, 42.9, 47.9, 53.5, 53.9, 55.9, 62.3, 89.3, 96.7, 102.2, 122.5, 122.7, 124.0, 124.2, 126.1 (2C), 128.6, 128.7, 133.6, 134.1, 136.9, 137.2, 140.8, 142.2, 144.8, 145.3, 163.6, 165.3, 194.1, 194.2; HRMS (ESI) calculated for $C_{32}H_{26}O_{10}$: 570.1526 found 570.1521.

Spiro[dimethyl-3,10-dimethoxy-1α,12α,13β,14α,17α,18β-16,19-dioxahexacyclo[10,6,1.1^{14,17} 0^{2,11}0^{4,9}0^{13,18}]-dodeca-2,4,6,8,10-pentaene-14,17-dicarboxylate-15,11'-11H-indeno[1,2-b]quinoxalin] (**16a**)

Method A. A solution of dione **13** (9 mg, 0.015 mmol) and *o*-phenylene diamine (3.5 mg, 0.030 mmol) in chloroform (2 mL) was heated at 60ºC for 3 h. The ^{1}H NMR analysis revealed full conversion to **16a**. Solvent was removed *in vacuo* and product purified by radial chromatography (petroleum ether - ethyl acetate 10:1, then solvent polarity was gradually increased to ethyl acetate) (8 mg, 89%).

Method B. A solution of epoxide **1** (100 mg, 0.243 mmol) and ketone **8a** (50 mg, 0.200 mmol) was heated in *o*-dichlorobenzene (5 mL) at 140 ºC for 2 hours. Solvent was removed *in vacuo* to afford a yellow oily residue. Product was purified by radial chromatography (starting with petroleum ether - ethyl acetate 10:1, then solvent polarity was gradually increased to ethyl acetate).

16a. Colourless solid, 48 mg, yield 38 %, mp 168-170 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.60 (1H, td, *J* 9.9 Hz, *J* 1.3 Hz), 2.91 (1H, td, *J* 9.9 Hz, *J* 1.1 Hz), 3.39 (1H, d, *J* 6.7 Hz), 3.42 (3H, s), 3.54 (1H, s), 3.74 (3H, s) 3.96 (1H, s), 4.06 (3H, s), 4.13 (3H, s), 4.19 (1H, d, *J* 6.7 Hz), 7.52-7.56 (5H, m), 7.70 (1H, tdd, *J* 6.5 Hz, *J* 1.5 Hz, *J* 1.3 Hz), 7.81 (1H, dd, *J* 8.5 Hz, *J* 1.1 Hz), 8.06-8.08 (4H, m), 8.11-8.13 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 42.4, 42.5, 43.2, 47.7, 52.9, 53.8, 55.9, 61.9, 86.3, 91.1, 107.7, 122.1, 122.7, 122.8, 125.9, 126.0, 127.3, 128.6, 128.7, 129.4, 129.6, 130.4, 130.9, 131.5, 132.7, 134.1, 134.8, 136.9, 141.3, 143.1, 144.9, 145.0, 145.1, 155.1, 156.4, 164.9, 165.9; HRMS (ESI) calculated for $C_{38}H_{30}N_2O_8$: 642.2002 found 642.1993.

Spiro[dimethyl-3,10-dimethoxy-1α,12α,13β,14α,17α,18β-16,19-dioxahexacyclo [10,6,1.1^{14,17}0^{2,11}0^{4,9}0^{13,18}]-dodeca-2,4,6,8,10-pentaene-14,17-dicarboxylate-15,11'-3,4-dimethyl-11H-indeno[1,2-b]quinoxalin] (**16b**). A solution of epoxide **1** (60 mg, 0.143 mmol) and ketone **8b** (50 mg, 0.192 mmol) in *o*-dichlorobenzene (10 mL) was heated at 140 ºC for 2 hours. Solvent was removed *in vacuo* to afford yellow coloured oily residue. Product was purified by radial chromatography (starting with petroleum ether - ethyl acetate 10:1, then solvent polarity was gradually increased to ethyl acetate).

16b. Yellow coloured solid, 67 mg, yield 69%, mp 270-273 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.55 (1H, d, *J* 10.2 Hz), 2.36 (3H, s), 2.46 (3H, s), 2.93 (1H, td, *J* 10.2 Hz, *J* 1.6 Hz), 3.39 (1H, d, *J* 6.6 Hz), 3.40 (3H, s), 3.54 (1H, s), 3.76 (3H, s), 3.96 (1H, s), 4.06 (3H, s), 4.13 (3H, s), 4.19 (1H, d, *J* 6.6 Hz), 7.51-7.56 (4H, m), 7.62 (1H, s), 7.83 (1H, s), 8.03-8.08 (2H, m), 8.10-8.11 (1H, m), 8.19-8.23 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 20.3, 20.7, 42.5, 42.6, 43.2, 47.4, 52.8, 53.6, 53.7, 55.9, 61.9, 86.5, 94.2, 197.6, 121.8, 122.7, 122.8, 125.8, 125.9, 127.3, 128.5, 128.7, 129.5, 131.3,

132.1, 137.3, 134.3, 134.8, 134.7, 137.3, 140.1, 140.3, 141.4, 141.9, 144.8, 144.9, 145.0, 154.3, 155.2, 164.9, 165.9; HRMS (ESI) calculated for $C_{40}H_{34}N_2O_8$: 670.2315 found 670.2321.

Spiro[dimethyl-3,10-dimethoxy-1α,12α,13β,14α,17α,18β-16,19-dioxahexacyclo [10,6,1.1^{14,17}0^{2,11}0^{4,9}0^{13,18}]-dodeca-2,4,6,8,10-pentaene-14,17-dicarboxylate-15,11'-]9'*H*-indeno-9'-one-[1',2'-*b*]:1',4'-diaza-11'*H*-fluoreno[2',3'-*g*]quinoxalin) (16c). A solution of epoxide **1** (60 mg, 0.143 mmol) and dione **8c** (53 mg, 0.143 mmol) in *o*-dichlorobenzene (3 mL) was heated at 140 ºC for 2 hours. Solvent was removed *in vacuo* to afford yellow coloured oily residue. Product was purified by radial chromatography (starting with petroleum ether - ethyl acetate 10:1, then solvent polarity was gradually increased to ethyl acetate).

16c. Yellow coloured solid, 18 mg, yield 16%, mp 221-223 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.63 (1H, d, *J* 10.7 Hz), 2.97 (1H, d, *J* 10.7 Hz), 3.41 (1H, d, *J* 3.6 Hz), 3.44 (1H, d, *J* 3.6 Hz), 3.47 (3H, s), 3.56 (1H, s), 3.73 (3H, s), 3.97 (1H, s), 4.08 (3H, s), 4.13 (3H, s), 7.51-7.52 (7H, m), 7.84 (1H, t, *J* 7.1 Hz), 7.97 (1H, d, *J* 7.6 Hz), 8.09 (1H, td, *J* 8.2 Hz, *J* 2.4 Hz), 8.15-8.21 (1H, m), 8.24 (1H, d, *J* 7.6 Hz), 8.65 (1H, s), 8.81 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 30.1, 42.7, 42.8, 42.9, 48.1, 53.0, 53.2, 56.1, 60.2, 80.2, 87.1, 109.2, 122.5, 122.7, 122.8, 123.1, 125.3, 126.3, 126.4, 127.4, 128.2, 129.1, 131.8, 133.2, 133.3, 133.6, 133.7, 134.1, 134.5, 134.8, 135.2, 137.5, 137.9, 140.1, 143.1, 144.2, 144.3, 145.2, 147.2, 147.3, 149.2, 149.3, 151.3, 156.1, 158.3, 166.2; HRMS (ESI) calculated for $C_7H_{32}N_4O_9$: 796.2169 found 796.2153.

Tetra-(3,5-di-*t*-butyl)porphyrino[*b*]-1,4-diaza-11*H*-fluoreno[2,3-*g*]quinoxalin-11-one (10). Solution of porphyrin dione[Error! Bookmark not defined.] (100 mg, 0.092 mmol) in dry pyridine (5 mL) was treated with phenylene tetramine tetrahydrochloride **15c** (26 mg, 0.092 mmol) and reaction mixture refluxed for 1 hour under an nitrogen atmosphere to afford diamine **20**. Ninhydrin (16 mg, 0.092 mmol) was added and refluxed for additional two hours. Reaction mixture was diluted with diethyl ether and washed with water (3 times), dried ($MgSO_4$) and solvent removed *in vacuo*. Product was purified by flash column chromatography on silicagel (starting with petroleum ether - DCM 5:1, then solvent polarity was gradually increased to DCM and 20% ethyl acetate).

10. Brown coloured solid, 38 mg, yield 31%, mp >350 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H -2.37 (2H, s), 1.38-1.62 (56H, m), 7.69 (1H, t, *J* 7.3 Hz), 7.82 (2H, *J* 1.7 Hz), 7.88 (1H, t, *J* 7.6 Hz), 7.98 (1H, t, *J* 1.7 Hz), 8.02-8.07 (8H, m), 8.11 (2H, s), 8.12 (2H, s), 8.36 (1H, d, *J* 7.1 Hz), 8.67 (1H, s), 8.79 (2H, s), 8.88 (1H, s), 8.99 (2H, m), 8.91 (2H, t, *J* 7.7 Hz), HRMS (ESI) calculated for $C_{91}H_{98}N_8O_1+H^+$: 1319.7942 found: 1319.7911.

Spiro[dimethyl-3,10-dimethoxy-1α,12α,13β,14α,17α,18β-16,19-dioxahexacyclo[10,6,1.1^{14,17} 0^{2,11}0^{4,9}0^{13,18}]-dodeca-2,4,6,8,10-pentaene-14,17-dicarboxylate-15,11'-(tetra-(3,5-di-*t*-butyl) porphyrino[*b*]-1',4'-diaza-11'*H*-fluoreno[2',3'-*g*]quinoxalin) (21). A solution of epoxide **1** (4 mg, 0.010 mmol) and porphyrin ketone **10** (10 mg, 0.008 mmol) in dichloromethane (1 mL) was heated in a sealed glass tube at 140 ºC for 2 hours. Product was purified by flash column chromatography (starting with petroleum ether - DCM 5:1, then solvent polarity was gradually increased to DCM and 5% ethyl acetate) to afford impure product.

21. Spectral data obtained from crude mixture: ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.57 (54H, s, tBu), 3.48 (3H, s), 3.71 (3H, s), 4.12 (3H, s), 4.23 (3H, s); HRMS (ESI) calculated $C_{114}H_{120}N_8O_8+H^+$: 1729.9307 found: 1729.9275.

Spiro[dimethyl-3,10-dimethoxy-1α,12α,13β,14α,17α,18β-16,19-dioxahexacyclo [10,6,1.1^{14,17}0^{2,11}0^{4,9}0^{13,18}]-dodeca-2,4,6,8,10-pentaene-14,17-dicarboxylate-15,1'-[2'-(*p*-tolylimino)-2'*H*-indene-3'-one] (22a). A solution of epoxide **1** (100 mg, 0.244 mmol) and imine **9a** (60 mg, 0.245 mmol) in dichloromethane (1 mL) was heated in a sealed glass tube at 140 ºC for 2 hours. Solvent was removed in vacuo to obtain red oily residue. Product was purified by radial chromatography (starting with petroleum ether - ethyl acetate 10:1, then solvent polarity was gradually increased to ethyl acetate).

22a. Red oil which solidifies on standing, 18 mg, yield 11%, mp 162-165 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.56 (1H, d, *J* 10.2 Hz), 2.27 (3H, s), 2.84 (1H, d, *J* 10.2 Hz), 3.13 (1H, d, *J* 6.7 Hz), 3.51 (1H, d, *J* 6.7 Hz), 3.53 (3H, s), 3.57 (1H, s), 3.90 (3H, s), 3.95 (1H, s), 4.04 (3H, s), 4.09 (3H, s), 6.62 (2H, d, *J* 8.2 Hz); 7.01 (2H, d, *J* 8.2 Hz), 7.45-7.48 (2H, m), 7.48 (1H, t, *J* 7.1 Hz), 7.68 (1H, d, *J* 7.6 Hz), 7.74 (1H, t, *J* 7.6 Hz), 8.06-8.09 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 42.3, 42.4, 42.6, 43.2, 47.9, 53.0, 53.8, 55.6, 61.9, 94.1, 107.9, 118.8, 119.1, 122.5, 122.7, 123.7, 125.9, 127.9, 128.5, 128.7, 129.2, 129.3, 133.7, 134.6, 135.5, 137.1, 137.6, 144.8, 145.2, 146.1, 147.4, 160.5, 164.8, 165.8, 182.9; HRMS (ESI) calculated $C_{39}H_{33}N_1O_9$: 659.2155 found: 659.2154.

Spiro[dimethyl-3,10-dimethoxy-1α,12α,13β,14α,17α,18β-16,19-dioxahexacyclo [10,6,1.1^{14,17}0^{2,11}0^{4,9}0^{13,18}]-dodeca-2,4,6,8,10-pentaene-14,17-dicarboxylate-15,1'-[3'-(*p*-tolylimino)-2'*H*-indene-2'-one] (22d). A solution of adduct **12** (100 mg, 0.17 mmol) and *p*-anisidine (100 mg, 0.81 mmol) in chloroform (1 mL) was heated in a sealed glass tube at 60 ºC for 2 hours, and additionally at 120 ºC for 2 hours. Solvent was removed in vacuo to obtain brown oily residue. Product was purified by radial chromatography (starting with petroleum ether - ethyl acetate 10:1, then solvent polarity was gradually increased to ethyl acetate).

22d. Brown oil, 53 mg, yield 47 %; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.51 (1H, d, *J* 9.8 Hz), 2.32 (3H, s), 2.80 (1H, d, *J* 9.8 Hz), 3.06 (1H, d, *J* 6.2 Hz), 3.18 (1H, d, *J* 6.2 Hz), 3.49 (1H, s), 3.54 (3H, s), 3.87 (3H, s), 3.91 (1H, s), 4.07 (3H, s), 4.08 (3H, s), 6.97 (2H, d, *J* 8.4 Hz); 7.10 (2H, d, *J* 8.4 Hz), 7.41 (1H, d, *J* 7.9 Hz), 7.49-7.51 (2H, m), 7.59 (1H, t, *J* 7.1 Hz), 7.90-8.05 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 39.9, 42.4, 42.6, 43.2, 42.8, 53.0, 55.6, 56.1, 62.1, 93.1, 111.6, 118.8, 119.1, 122.5, 122.6, 124.0, 126.1, 126.2, 128.5, 130.4, 131.6, 133.7, 134.6, 135.5, 138.4, 138.8, 140.7, 145.2, 146.1, 147.4, 158.1, 159.0, 166.1, 179.9; HRMS (ESI) calculated for $C_{39}H_{33}N_1O_9$: 659.2155 found: 659.2159.

Spiro[dimethyl-3,10-dimethoxy-1α,12α,13β,14α,17α,18β-16,19-dioxahexacyclo [10,6,1.1^{14,17}0^{2,11}0^{4,9}0^{13,18}]-dodeca-2,4,6,8,10-pentaene-14,17-dicarboxylate-15,1'-[2'-(*p*-biphenylimino)-2'*H*-indene-3'-one] (22b). A solution of epoxide **1** (60 mg, 0.146 mmol) and imine **9b** (45 mg, 0.141 mmol) in o-dichlorobenzene (2 mL) was heated at 140 ºC for 2 hours. Solvent was removed in vacuo to afford a red coloured oily residue. Product was purified by radial chromatography (starting with petroleum ether - ethyl acetate 10:1, then solvent polarity was gradually increased to ethyl acetate).

22b. Red oil, 84 mg, yield 81%; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.55 (1H, d, *J* 10.2 Hz), 3.14 (1H, d, *J* 10.2 Hz), 3.15 (1H, d, *J* 6.7 Hz), 3.54 (1H, d, *J* 6.7 Hz), 3.59 (1H, s), 3.92 (4H, s), 4.05 (3H, s), 4.11 (3H, s), 6.79 (2H, d, *J* 9.4 Hz), 7.28 (1H, d, *J* 7.1 Hz), 7.38 (2H, t, *J* 7.8 Hz), 7.44-7.46 (8H, m), 7.75 (1H, d, *J* 5.5 Hz), 7.57 (1H, d, *J* 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 42.3, 43.1, 47.6, 48.0, 53.0, 53.9, 55.6, 62.0, 53.2, 94.0, 107.9, 108.3, 119.5, 122.5, 122.7, 123.8, 124.0, 126.0, 126.2, 127.3, 127.5, 128.6, 129.0, 131.3, 131.6, 133.7, 134.5, 137.4, 137.6, 138.7, 138.8, 141.0, 144.,8, 145.2, 147.5, 147.9, 160.4, 165.8, 182.8, 184.6, 196.9; HRMS (ESI) calculated for $C_{44}H_{35}N_1O_9$: 721.2468 found 721.2300.

Spiro[dimethyl-3,10-dimethoxy-1α,12α,13β,14α,17α,18β-16,19-dioxahexacyclo [10,6,1.1^{14,17}0^{2,11}0^{4,9}0^{13,18}]-dodeca-2,4,6,8,10-pentaene-14,17-dicarboxylate-15,1'-[2'-(4',4''-dinitro-2''-biphenylimino)-2'*H*-indene-3'-one] (**22c**): A solution of epoxide **1** (60 mg, 0.146 mmol) and imine **9c** (58 mg, 0.146 mmol) was heated in o-dichlorobenzene (1 mL) at 140 ^{o}C for 2 hours. Solvent was removed *in vacuo* to afford a red oily residue. Product was purified by radial chromatography (starting with petroleum ether - ethyl acetate 10:1, then solvent polarity was gradually increased to ethyl acetate).

22c. Red solid, 92 mg, yield 78%, mp 208-210 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.56 (1H, d, *J* 10.0 Hz), 2.82 (1H, td, *J* 10.0 Hz, *J* 1.1 Hz), 2.94 (1H, d, *J* 6.4 Hz), 3.14 (1H, d, *J* 6.4 Hz), 3.43 (3H, s), 3.46 (1H, s), 3.92 (1H, s), 3.98 (3H, s), 4.04 (3H, s), 4.13 (3H, s), 7.32 (2H, d, *J* 8.4 Hz), 7.36 (1H, d, *J* 8.6 Hz), 7.43-7.58 (2H, m), 7.65-7.67 (1H, m), 7.79 (1H, td, *J* 7.1 Hz, *J* 1.1 Hz), 7.98-8.11 (2H, m), 8.29 (2H, d, *J* 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 42.4, 42.5 (d, *J* 11.2 Hz), 43.3, 47.8, 53.1, 53.9 (q, *J* 12.5 Hz), 55.4, 61.9 (q, *J* 11.6 Hz), 62.8 (q, *J* 11.0 Hz), 83.4, 89.0, 107.8, 113.6, 120.8, 122.6, 122.7, 123.8, 124.0, 126.1, 126.7, 128.1, 128.6, 128.7, 130.8, 131.0, 131.4, 133.1, 135.1, 135.4, 138.2, 143.8, 144.6, 145.3, 148.1, 148.2, 148.3, 148.6, 164.4, 164.5, 165.6, 188.6; HRMS (ESI) calculated for $C_{44}H_{33}N_3O_{13}$: 811.2013 found: 811.2003.

Spiro[dimethyl-3,10-dimethoxy-1α,12α,13β,14α,17α,18β-16,19-dioxahexacyclo [10,6,1.1^{14,17}0^{2,11}0^{4,9}0^{13,18}]-dodeca-2,4,6,8,10-pentaene-14,17-dicarboxylate-15,1'-3',5',8'-trimethyl-3'-aza-indan-2'-one] (23). A solution of epoxide **1** (50 mg, 0.122 mmol) and 4,7-dimethyl isatin **11** (30 mg, 0.171 mmol) in dichloromethane (1 mL) was heated in a sealed glass tube at 140 ^{o}C overnight. Solvent was removed *in vacuo* to yield yellow oily residue. Product was purified by radial chromatography (starting with petroleum ether - ethyl acetate 5:1, then solvent polarity was gradually increased to ethyl acetate).

23. Yellow solid, 46 mg, yield 64%, mp 178-180 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$ at 60 ^{o}C): δ_H 1.51 (1H, d, *J* 9.9 Hz), 1.96 (3H, s), 2.45 (3H, s), 2.86 (1H, td, *J* 9.9 Hz, *J* 1.6 Hz), 3.11 (1H, d, *J* 6.2 Hz), 3.34 (1H, d, *J* 6.2 Hz), 3.54 (3H, s), 3.55 (1H, s), 3.75 (1H, s), 3.89 (3H, s), 4.01 (3H, s), 4.03 (3H, s), 6.67 (1H, d, *J* 7.9 Hz), 6.84 (1H, d, *J* 7.9 Hz), 7.44-7.47 (2H, m), 7.63 (1H, br s), 8.03-8.13 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 14.9, 19.9, 42.2, 42.7, 43.2, 46.7, 52.8, 53.5, 55.7, 61.8, 62.2, 86.6, 96.5, 118.6, 122.6, 122.9, 125.9 (2C), 126.6, 128.6, 128.7, 132.0, 133.8, 134.8, 136.1, 139.6, 144.5, 145.3, 164.6, 165.8, 174.6; HRMS (ESI) calculated for $C_{33}H_{31}N_1O_9$: 585.1999 found: 585.1984.

9*H*-indeno-9-one-[1,2-*b*]:1,4-diaza-11*H*-fluoreno[2,3-*g*]quinoxalin-11-one (8c). Ninhydrin **5** (18 mg, 0.10 mmol) and 1,2,4,5-benzenetetramine tetrahydrochloride **15c** (15 mg, 0.05 mmol) were ball-milled for 30 min at RT at 3600 rpm. Product was purified by radial chomatography (petrol/ethyl acetate) followed by recystallization from toluene.
8c. Yellow solid, 3 mg, yield 13%, mp > 350°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.71 (1H, t, *J* 7.6 Hz), 7.87 (1H, t, *J* 7.6 Hz), 8.02 (1H, d, *J* 7.9 Hz), 8.26 (1H, d, *J* 7.9 Hz), 8.83 (1H, s), 9.19 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 120.1, 122.3, 124.5, 127.9, 129.2, 130.2, 132.4, 133.7, 137.1, 138.2, 144.6, 151.1, 183.3; HRMS (m/z): calcd. for $C_{24}H_{10}N_4O_2$: 386.0804 found: 386.0811.

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