Isolation of Macrocyclic Metacyclophanes From the Attempted Synthesis of [7.0]Metacyclophanes of the Myricanone Series by Thorpe–Ziegler – Intramolecular Cyclization of Diaryls Substituted by ω-Cyanoalkyl Chains

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The syntheses of the diaryls **14** and **21**, substituted by two ω-cyanoalkyl chains (one on each ring), are described. Treatment of the unsymmetrical diaryl **14** with NaN(Me)Ph in a Thorpe–Ziegler reaction failed to give any definite product. Under the same conditions the symmetrical diaryl **21** led to an isomeric mixture of dimeric enaminonitriles **24**. Mild acidic hydrolysis of the latter yielded the isomeric β-ketonitriles **25**, whereas more drastic hydrolytic conditions led to the macrocyclic diketone **26**.

Introduction

Diarylheptanoids represent a distinct class of naturally occurring compounds which display the unique structural feature of two hydroxylated aromatic rings linked by a linear seven-carbon chain. Within this class are linear (**I**) and macrocyclic (**II**) diarylheptanoids. In the latter the aromatic rings are connected to form a diaryl ether or a diaryl moiety (Figure 1).[1] Most of the linear diarylheptanoids exhibit a broad range of potent biological activities including anti-inflammatory, antihepatotoxic, antifungal, antibacterial, and related properties.[1] Very recently, compounds possessing an inhibitory activity against nitric oxide production in activated murine macrophages have been isolated from the seeds of *A. blepharocalyx*.[2]

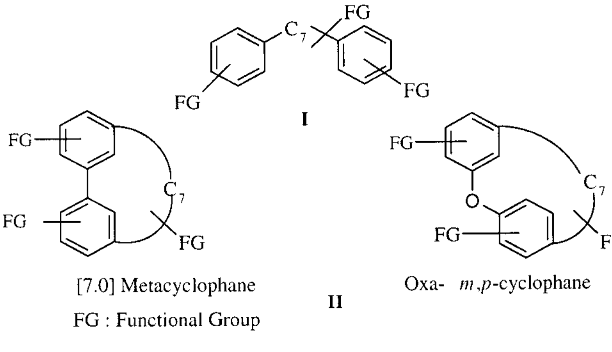

Figure 1. The various classes of natural diarylheptanoids

Most of the macrocyclic diarylheptanoids have been extracted from both plant families *Betulaceae* and *Myricacea*.[1b] Since the isolation of myricanone (**1**) and myricanol (**2**) (Figure 2) by Whiting and his co-workers[3] in 1970 from the stem bark of *Myrica nagi*, used in folk medicine, approximately 25 different diarylheptanoids of this type have been reported. Related natural products such as porson,[4] trideoxyasadaninene (**3**),[5] garugarin,[6] etc, have also been identified from other plant sources.

Evidence has been accumulated suggesting that the linear diarylheptanoids **I** are the biogenetic precursors of the macrocyclic congeners **II**.[7] Therefore synthetic routes to type **II** macrocycles, involving the cyclization of appropriate 1,7-diarylheptanoids, were investigated. To our knowledge the unique synthesis of myricanone (**1**) and myricanol (**2**) accomplished by Whiting et al. is based upon the Ni^0-catalyzed intramolecular diaryl coupling reaction of suitable linear diarylheptanoids.[8] This macrocyclization methodology was developed by Semmelhack et al. for the synthesis of alnusone.[9] Recently Zhu et al. described an intramolecular S_NAr reaction for the total synthesis of acerogenin-type macrocycles.[10]

A major drawback of Whiting's syntheses of **1** and **2**[8] is the poor yields (7–10%) of the formation of the aryl-aryl linkage in the *final step*. That is the reason why we considered using a synthetic scheme to [7.0]metacyclophanes which involved the early formation of the aryl-aryl bond followed by Thorpe–Ziegler cyclization (Scheme 1).

We report herein the synthesis of diaryls of type **5** and also the first attempts of macrocyclization *via* Thorpe–Ziegler condensation of *meta-meta* disubstituted (i) symmetrical diaryl bearing on each ring a cyanopropyl chain, and (ii) unsymmetrical diaryl bearing on one of the rings a cyanoethyl chain and on the second one a cyanobutyl chain.

Results and Discussion

Synthesis of the Unsymmetrical Diaryldinitrile 14

The diaryldinitrile **14** was assumed to be a precursor for *O*-methylmyricanone (**4**). Its synthesis was carried out as

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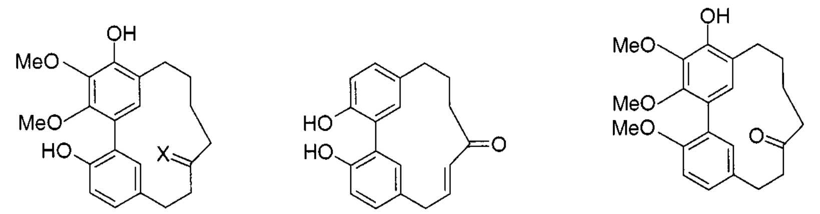
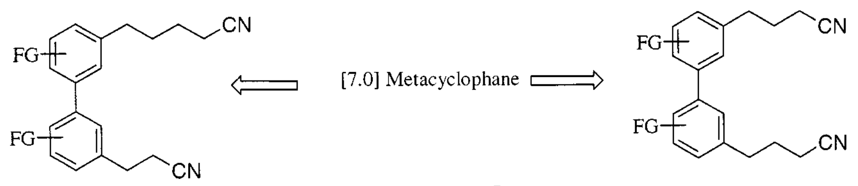


Natural diarylheptanoids isolated from *Myrica nagi*
X = O Myricanone **1**
X = H, OH (±) - Myricanol **2**

Natural diarylheptanoid isolated from *Ostrya japonica*
Trideoxyasadaninene **3**

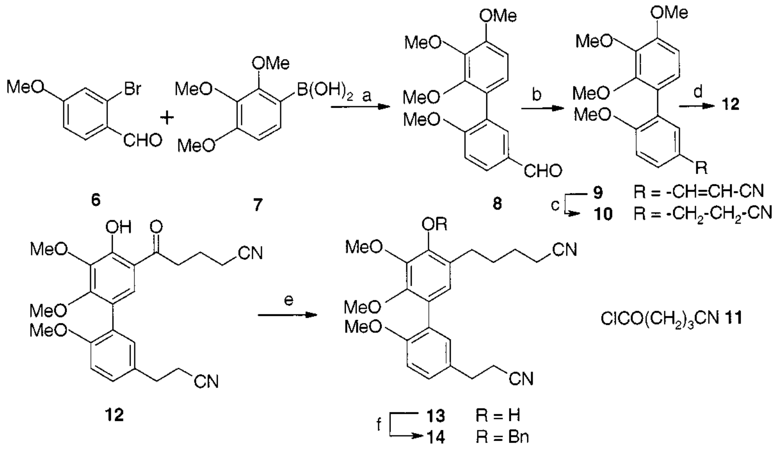
Non-natural diarylheptanoid
O-Methylmyricanone **4**

Figure 2. Some macrocyclic diarylheptanoids



Diaryls of type **5**

Scheme 1. Synthesis of [7.0] metacyclophanes



(a) $Pd(PPh_3)_4$, DME, Na_2CO_3 (2M), EtOH, **98%**; (b) KOH, MeCN, Dioxan, **91%**;
(c) Mg, MeOH, **80%**; (d) $AlCl_3$, $C_6H_5NO_2$,$ClCO(CH_2)_3CN$ **11**, **45%**;
(e) $NaCNBH_3$, BF_3-Et_2O, THF, **64%**; (f) KI, K_2CO_3, Acetone, BnCl, **100%**.

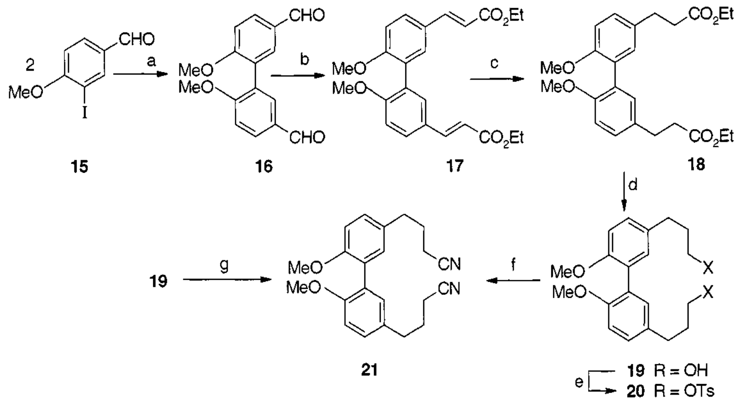
Scheme 2. Synthesis of the unsymmetrical diaryldinitrile **14**

described in Scheme 2. The known electron-rich areneboronic acid **7** was prepared from the corresponding aryl bromide according to literature procedures.[11] Suzuki cross-coupling reaction of bromo-*p*-anisaldehyde (**6**)[12] with the areneboronic acid **7** in the presence of palladium(0), EtOH, and Na_2CO_3 as base, afforded the required diaryl **8** in 98% yield.[13] Cyanomethylenation of **8** in dioxane using the direct KOH-catalyzed condensation of acetonitrile with aromatic aldehydes, [14] followed by reduction of the resulting intermediate **9**, gave the diaryl propanenitrile **10**. Another alkyl nitrile chain was introduced *via* Friedel–Crafts acylation of **10**, followed by reductive deoxygenation of the ketone function of the resulting intermediate **12**, thus affording the dinitrile **13**. Protection of the phenolic hydroxyl of the latter as benzyl ether afforded the diaryl **14** in 18% overall yield.

Synthesis of the Symmetrical Diaryldinitrile 21

We next chose to synthesize a rather simple diaryl bearing on each ring a cyanopropyl chain, as a potential precursor for trideoxyasadaninene (**3**). The diaryldicarbaldehyde **16** was generated from the aryl iodide **15** by an Ullmann reaction (Scheme 3).

Treatment of **16** with triethyl phosphonoacetate according to Wittig–Horner conditions smoothly afforded the diethylenic diester **17**. Catalytic hydrogenation of **17** over a Pd–C catalyst quantitatively gave the saturated diester **18**. The latter was converted into the corresponding diol **19** upon reduction with $LiAlH_4$ in ether. Reaction of **19** with tosyl chloride in the presence of pyridine yielded the ditosylate **20**, which was next converted into the desired dinitrile **21** by means of excess sodium cyanide in DMF. Alternat-



(a) Cu powder, 180°C, 5 h, **62%**; (b) $(EtO)_2P(O)$-CH_2CO_2Et, K_2CO_3, Dioxan, **86%**;
(c) 10% Pd-C, H_2, 4 bars, **100%**; (d) $LiAlH_4$, Et_2O, 35°C, 5 h, **100%**;
(e) TsCl, Pyr, $CHCl_3$, 0°C, 4 h, **91%**; (f) NaCN, DMF, 85 °C, 5 h, **96%**;
(g) Me_3SiCl, NaCN, KI, MeCN, DMF, 80 °C, 3 days, **76%**.

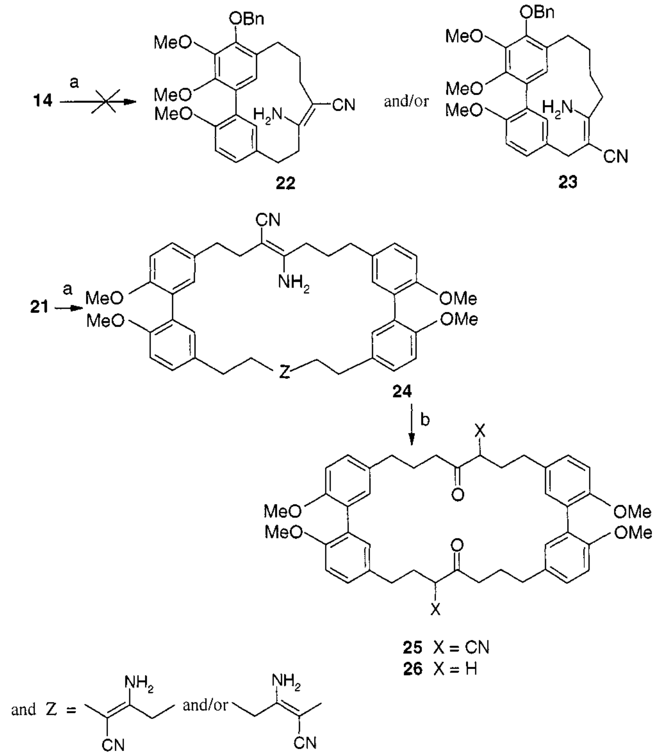
Scheme 3. Synthesis of the symmetrical diaryldinitrile **21**

ively, the dinitrile **21** was obtained in a one-pot reaction by treatment of the diol **19** with trimethylsilyl chloride and sodium cyanide in the presence of catalytic amounts of potassium iodide.

Thorpe–Ziegler Reaction

The Thorpe–Ziegler intramolecular cyclization of the dinitrile **14** was next attempted using a variety of bases and experimental conditions (Scheme 4). Thus, using sodium methylphenylamide as a base in high dilution conditions, led to a mixture of unidentified products which did not correspond to the structures **22** or **23** although the IR spectra indeed suggested that the nitrile groups (ν_{CN} = 2244 cm^{-1}) had been transformed into the requisite enaminonitrile function (ν_{CN} = 2179 cm^{-1}). No further information could be gained from the highly complex ^{1}H NMR spectra.

Under similar conditions as above, the symmetrical dinitrile **21** did not lead to the required cyclized monomeric enaminonitrile compound. The IR and HR mass spectra suggested that the reaction product had the dimeric structure **24**. Here again the ^{1}H NMR spectra were not exploitable. Hydrolysis of the compound(s) **24** under mild conditions (2M HCl, room temp., 2 h) gave the dimeric *bis*-β-ketonitrile **25** as evidenced from the IR and HR mass spectra. The macrocyclic diketone **26** was obtained upon hydrolysis of **22** under more drastic hydrolytic conditions, as evidenced from IR, ^{1}H and ^{13}C NMR spectra.



(a) $NaNC_6H_5Me$, THF; (b) 2 M HCl (rt, 2 h) or 12M HCl (reflux, 7 h)

Scheme 4. Thorpe–Ziegler reaction

Conclusion

We could not carry out the synthesis of [7.0] metacyclophanes by ring closure of chain substituted diaryl units (such as **14** and **21**), the formation of dimeric compounds being the only detectable event. Parallel to our efforts Nógrádi et al.[15] have very recently reported the unwanted synthesis of dimeric diarylheptanoids in their attempts at the synthesis of acerogenins based upon the early formation of aryl-aryl bond. All these failures might be due to the strain which prevents both CH_2CN subunits (of **14** or **21**) from coming close to one another.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using Bruker AC 400 (400 MHz), Bruker DPX 200 (200 MHz for ^{1}H) and (100 MHz for ^{13}C) spectrometers. Chemical shifts are given relative to TMS (δ = 0), coupling constants in Hz. – IR spectra were measured with Nicolet 5 DX and Genesis (Mattson) FFT spectrometers. – Melting points were measured with a Reichert microscope. – Elemental analyses were performed by the Service de Microanalyse du CNRS, Gif-sur-Yvette. – Mass spectra were run with a Varian Mat 311 spectrometer by Service de Spectrométrie de Masse Haute Résolution, University of Rennes. – All solvents and reagents were purified and dried according to standard procedures prior to use.

2,3,4-Trimethoxybenzeneboronic Acid (7):[16] 1-Bromo-2,3,4-trimethoxybenzene (7.35 g, 29.76 mmol) was added to a magnetically stirred suspension of oven-dried magnesium turnings (1.084 g, 44.64 mmol) in THF (39 mL) kept under a nitrogen atmosphere. The resulting mixture was heated at reflux for 90 min then cooled to room temperature.

THF (12 mL) was put in a three-necked, oven-dried flask equipped with a magnetic stirrer and a low-temperature thermometer, and kept under an atmosphere of dry nitrogen. The reaction vessel was cooled to –60 °C, then trimethyl borate (3.36 mL, 29.76 mmol) and the freshly prepared aryl Grignard reagent (29.76 mmol) in THF (39 mL) were added simultaneously (but independently), in a dropwise fashion to ensure that the reaction mixture was kept at –60 °C throughout the addition, and that equimolar quantities of each reagent were present in the reaction vessel at all times. After the addition, the reaction mixture was stirred at –60 °C for a further 30 min, then it was warmed to room temperature and stirred for 30 min more. It was acidified to pH 6–7 with 6 N HCl (30 mL) (while maintaining the temperature below 5 °C) and extracted with diethyl ether (4 × 50 mL). The combined ether layers were washed with brine (50 mL) and dried over $MgSO_4$. After removal of the solvent the areneboronic acid **7** (6.3 g, 90%) was obtained with 90% purity (ref.[11] 73%), m.p.70–72 °C (water). – IR (film): $\tilde{\nu}$ = 3350 cm^{-1}, 1596, 1469, 1344, 1290. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.86 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 4.08 (s, 3 H, OCH_3), 6.38 [s, 2 H, $B(OH)_2$], 6.74 (d, *J* = 9.0 Hz, 1 H), 7.53 (d, *J* = 9.0 Hz, 1 H).

2,2′,3′,4′-Tetramethoxydiphenyl-5-carbaldehyde (8):[16] To a suspension of tetrakis(triphenylphosphane)palladium (327 mg, 0.283 mmol) in anhydrous and degassed DME (50 mL) was added 3-bromo-*p*-anisaldehyde **6**[12] and the mixture was stirred for 10 min at room temperature. To this solution were sequentially added the areneboronic acid **7** (3.4 g, 14.14 mmol) in ethanol (8.5 mL) and 2 M aqueous Na_2CO_3 (9.43 mL, 18.86 mmol), and the mixture was refluxed for 18 h, cooled and filtered. The filtrate was evaporated to dryness and the residue was treated with brine (50 mL) and dichloromethane (50 mL), and then extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over $MgSO_4$. After removal of the solvent, the residue was triturated under toluene (30 mL) to induce crystallization of the diphenyl **8**. The supernatant solution was concentrated and chromatographed (toluene/methanol) thus affording a second crop of diphenyl **8**[13] (total yield: 2.80 g, 98%), m.p. 158–159 °C. – IR (nujol): $\tilde{\nu}$ = 2929 (OCH_3, Ar) cm^{-1}, 1687 (CHO), 1594 (C=C Ar), 1457 (CH_3), 1213 (C–O), 1101 (C–O), 1006 (C–O). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.73 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 3.91 (s, 6 H, 2 OCH_3), 3.91 (s, 6 H, 2 OCH_3), 6.73 (d, *J* = 8.5 Hz, 1 H), 6.93 (d, *J* = 8.5 Hz, 1 H), 7.07 (d, *J* = 8.5 Hz, 1 H), 7.75 (d, *J* = 2.0 Hz, 1 H), 7.88 (dd, *J* = 8.5 Hz, *J* = 2.0 Hz, 1 H), 9.91 (s, 1 H, CHO). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.9 (CH_3–O), 55.95 (CH_3–O), 60.7 (CH_3–O), 60.9 (CH_3–O), 106.9, 110.6, 125.1, 123.9, 125.1, 128.3, 129.5, 131.3, 133.1, 142.0, 151.7, 153.6, 162.1, 190.9. – $C_{17}H_{18}O_5$ (302.296): calcd. C 67.54, H 6.00, O, 26.46; found C 67.39, H 5.96, O 26.40.

5′-(2-Cyanovinyl)-2,2′,3,4-tetramethoxydiphenyl (9):[16] In a 250 mL three-necked round-bottomed flask, equipped with a tap funnel, a reflux condenser, a nitrogen inlet, and a magnetic stirrer, were added 85% powdered KOH (109 mg, 1.65 mmol) and dry acetonitrile (1.4 mL). The mixture was heated to reflux and a solution of aldehyde **8** (500 mg, 1.65 mmol) in a 50:50 mixture of acetonitrile and dioxane (5.5 mL) was added *in one stream*. After the addition was complete, stirring was continued for 8 min and the hot solution was poured onto cracked ice (35 mL). This mixture was extracted with dichloromethane (4 × 25 mL), dried over $MgSO_4$ and evaporated in vacuo. Flash chromatography of the crude product gave the diphenylpropenenitrile **9** (486 mg, 91%), m.p. 98–101 °C (*E*/*Z*: 9:1). – IR (nujol): $\tilde{\nu}$ = 2923 (OCH_3 Ar) cm^{-1}, 2211(C≡N), 1596 (C=C Ar), 1213 (C–O), 1103 (C–O), 1010 (C–O). – ^{1}H NMR (400 MHz, $CDCl_3$): *E* Isomer (90%): δ = 3.73 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.90 (s, 6 H, 2 OCH_3), 5.75 (d, *J* = 16.6 Hz, 1 H), 6.73 (d, *J* = 8.5 Hz, 1 H), 6.91 (d, *J* = 8.5 Hz, 1 H), 6.97 (d, *J* = 8.6 Hz, 1 H), 7.35 (d, *J* = 16.6 Hz, 1 H), 7.44 (d, *J* = 2.3 Hz, 1 H), 7.48 (dd, *J* = 8.6, *J* = 2.3 Hz, 1 H). – *Z* Isomer (10%): δ = 3.73 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.90 (s, 6 H, 2 OCH_3), 5.30 (d, *J* = 12.1 Hz, 1 H), 6.73 (d, *J* = 8.5 Hz, 1 H), 6.91 (d, *J* = 8.5 Hz, 1 H), 6.97(d, *J* = 8.6 Hz, 1 H), 7.05 (d, *J* = 12.1 Hz, 1 H), 7.58 (d, *J* = 2.3 Hz, 1 H), 7.95 (dd, *J* = 8.6 Hz, *J* = 2.3 Hz, 1 H). – $C_{19}H_{19}NO_4$ (325.331): calcd. C 70.14, H 5.89, N 4.30, O 19.67; found C 69.94, H 6.06, N 4.11, O 19.89.

5′-(2-Cyanoethyl)-2,2′,3,4-tetramethoxydiphenyl (10):[16] To a solution of diphenylpropenenitrile **9** (440 mg, 1.35 mmol) in methanol (11 mL), magnesium turnings (658 mg, 27.66 mmol) were added cautiously in portions. An oversized flask and an efficient ice/water cooling bath were required to control the foaming from the vigorous exothermic reaction. The mixture was stirred for 5 h and then acidified with 6 M HCl and extracted with dichloromethane (4 × 25 mL). The combined organic layers were dried over $MgSO_4$. Removal of the solvent gave the crude compound **10** (335 mg, 80%), m.p. 102–103 °C. – IR (film $CDCl_3$): $\tilde{\nu}$ = 2938 (OCH_3 Ar) cm^{-1}, 2246 (C≡N), 1598 (C=C Ar), 1214 (C–O), 1103 (C–O), 1018 (C–O). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.62 (t, *J* = 7.3 Hz, CH_2, 2 H), 2.93 (t, *J* = 7.3 Hz, CH_2, 2 H), 3.72 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.90 (s, 6 H, 2 OCH_3), 6.72 (d, *J* = 8.6 Hz, 1 H), 6.93 (d, *J* = 8.6 Hz, 1 H) and (d, *J* = 8.6 Hz, 1 H), 7.08 (d, *J* = 2.3 Hz, 1 H), 7.20 (dd, *J* = 8.6 Hz, *J* = 2.3 Hz, 1 H). – HRMS ($C_{19}H_{21}NO_4$): calcd. 327.1470; found 327.1467. – $C_{19}H_{21}NO_4$ (327.345): calcd. C 69.71, H 6.47, N 4.28; found C 69.28, H 6.24, N 4.26.

4-Cyanobutanoyl Chloride (11):[16] To a stirred mixture of acrylonitrile (26.6 mL, 400 mmol) and isopropylidene malonate (28.8 g, 200 mmol) in dry dichloromethane (250 mL) was added dropwise triethylamine (29.5 mL, 220 mmol) for 15 min. The mixture was stirred for 92 h at 60 °C, cooled, then acidified with 10% HCl (200 mL), and extracted with dichloromethane (3 × 150 mL). The combined organic layers were washed with brine (150 mL) and dried over $MgSO_4$. After removal of the solvent crude 5-(2-cyanoethyl)-2,2-dimethyl-1,3-dioxan-4,6-dione (34 g, 86%), was obtained, m.p 115–116 °C (ref.[17] m.p. 123–124 °C). – IR (nujol): $\tilde{\nu}$ = 2250 (C≡N) cm^{-1}, 1784 (C=O, lactone), 1739 (CO–O–). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.77 (s, 3 H), 1.85 (s, 3 H), 2.45 (m, 2 H), 2.77 (t, *J* = 7.2 Hz, 2 H), 3.70 (t, *J* = 5.8 Hz, 1 H).

This unpurified compound was then dissolved in water/pyridine (17 mL:170 mL) containing Cu powder (1.7 g, 26.56 mmol) and heated under reflux for 3 h. The mixture was cooled and then the Cu was removed by filtration, and the filtrate acidified to pH 1–2 with 6 M HCl. The residue was saturated with ammonium sulfate then extracted with diethyl ether and dried over $MgSO_4$. Evaporation of the solvent gave crude 4-cyanobutanoic acid (9.24 g, 94%), m.p. 45–46 °C (ref.[18] m.p.45–50 °C). – IR (film): $\tilde{\nu}$ = 3482–2653 (O–H) cm^{-1}, 2250 (C≡N), 1712 (C=O). – ^{1}H NMR (400 MHz CDCl$_3$): δ = 2.00 (quint., *J* = 7.0 Hz, 2 H), 2.49 (t, *J* = 7.0 Hz, 2 H), 2.56 (t, *J* = 7.0 Hz, 2 H), 8.40 (s, 1 H, CO$_2$H).

To a stirred solution of 4-cyanobutanoic acid (3.63 g, 33.12 mmol) in dry dichloromethane (37 mL) was added dropwise oxalyl chloride (2.96 mL, 99.36 mmol) at room temperature. The mixture was then gently refluxed overnight. Removal of the solvent gave 4-cyanobutanoyl chloride **(11)** (4.05 g, 96%)[19] which was used without further purification. – IR (film): $\tilde{\nu}$ = 2254 (C≡N) cm^{-1}, 1791 (C=O). –^{1}H NMR (200 MHz, CDCl$_3$): δ = 2.08 (quint., *J* = 7.0 Hz, 2 H, CH$_2$), 2.56 (t, *J* = 7.0 Hz, 2 H, CH$_2$), 3.15 (t, *J* = 7.0 Hz, 2 H, CH$_2$).

5-(4-Cyanobutanoyl)-5′-(2-cyanoethyl)-4-hydroxy-2,2′,3-trimethoxydiphenyl (12):[16] In a 250 mL three-necked round-bottomed flask, equipped with a tap funnel, a nitrogen inlet, and a magnetic stirrer, was placed a solution of AlCl$_3$ (978 mg, 7.33 mmol) in nitrobenzene (7 mL). A mixture of biarylpropanenitrile **10** (400 mg, 1.22 mmol) and crude acyl chloride **11** (970 mg, 7.33 mmol) in nitrobenzene (6 mL) was added dropwise at 18 °C. The reaction mixture was stirred at room temperature for 4 h then acidified with 10% HCl (10 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine, dried over MgSO$_4$ and the solvents evaporated. Removal of the nitrobenzene by distillation (≈ 10^{-1}Torr at 40–45 °C) gave a mixture (687 mg) of starting material **10**, the dinitrile **12**, and aliphatic byproducts. Flash chromatography (toluene/ethyl acetate 90:10) gave a first fraction of **12** (137 mg). The chromatographic core was extracted with a 10% solution of NaOH. The aqueous layer was acidified with 10% HCl and then extracted with dichloromethane. The CH$_2$Cl$_2$ extracts were dried over MgSO$_4$ and evaporated, thus affording a second crop of dinitrile **12** (40 mg) (total: 177 mg, 45% yield with respect to the recovered unchanged starting material **10**). – IR (film CDCl$_3$): $\tilde{\nu}$ = 2921 (OH phenol) cm^{-1}, 2852 (OCH$_3$ Ar), 2246 (C≡N), 1637 (C=O ketone Ar). – ^{1}H NMR (200 MHz, CDCl$_3$): δ = 2.10 (m, 2 H), 2.52 (t, *J* = 7.1 Hz, 2 H), 2.65 (t, *J* = 6.9 Hz, 2 H), 2.95 (t, *J* = 7.1 Hz, 2 H), 3.15 (t, *J* = 6.9 Hz, 2 H), 3.79 (s, 3 H, OCH$_3$), 3.89 (s, 3 H, OCH$_3$), 3.93 (s, 3 H, OCH$_3$), 6.92 (d, *J* = 8.4 Hz, 1 H), 7.07 (d, *J* = 2.3 Hz, 1 H), 7.23 (dd, *J* = 8.4 Hz, *J* = 2.3 Hz, 1 H), 7.38 (s, 1 H), 12.45 (s, 1 H, OH). – HRMS (C$_{23}$H$_{24}$N$_2$O$_5$): calcd. 408.1685; found 408.1678.

5-(4-Cyanobutyl)-5′-(2-cyanoethyl)-4-hydroxy-2,2′,3-trimethoxydiphenyl (13):[16] To a magnetically stirred solution of ketone **12** (129 mg, 0.31 mmol) and boron trifluoride–diethyl ether (246 μL, 1.89 mmol) in dry THF (3 mL) was added sodium cyanoborohydride (84 mg, 1.26 mmol). The reaction mixture was stirred at room temperature for 48 h then at 50 °C for 8 h. After completion of the reaction (monitored by TLC), the mixture was diluted with ethyl ether (10 mL), washed with saturated aqueous Na$_2$CO$_3$ (3 × 10 mL) and dried over MgSO$_4$. After removal of the solvent, followed by chromatography of the residue (toluene/ethyl acetate 80:20 with methanol traces), the reduced compound **13** (78 mg, 64%) was obtained. – IR (film CDCl$_3$): $\tilde{\nu}$ = 3411 (OH) cm^{-1}, 2921 (OCH$_3$ Ar), 2246 (C≡N). – ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.75 (m, 4 H), 2.33 (t, *J* = 7.1 Hz, 2 H), 2.60 (m, 4 H), 2.90 (t, *J* = 7.3 Hz, 2 H), 3.61 (s, 3 H, OCH$_3$), 3.75 (s, 3 H, OCH$_3$), 3.91 (s, 3 H, OCH$_3$), 5.85 (s, 1 H, OH), 6.67 (s, 1 H, H-6), 6.90 (d, *J* = 8.4 Hz, 1 H, H-3′), 7.09 (d, *J* = 2.4 Hz, 1 H, H-6′), 7.20 (dd, *J* = 8.4 Hz, $J_{4'\text{-}6'}$ = 2.4 Hz, 1 H). – HRMS (C$_{23}$H$_{26}$N$_2$O$_4$): calcd. 394.1892; found 394.1890.

4-Benzyloxy-5-(4-cyanobutyl)-5′-(2-cyanoethyl)-2,2′,3-trimethoxydiphenyl (14):[16] To a mixture of phenol **13** (430 mg, 1.09 mmol), K$_2$CO$_3$ (225 mg, 1.64 mmol) and KI (7 mg, 0.043 mmol) in dry acetone (12 mL) was added benzyl chloride (189 μL, 1.64 mmol) dropwise. The mixture was heated at reflux for 18 h. The cooled solution was filtered and evaporated, thus affording crude compound **14** (527 mg, 100%). – IR (film CDCl$_3$): $\tilde{\nu}$ = 2921 (OCH$_3$ Ar) cm^{-1}, 2247 (C≡N), 1600 (C–O). –^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.65 (m, 4 H), 2.25 (t, *J* = 6.8 Hz, 2 H), 2.60 (t, *J* = 7.3 Hz, 4 H), 2.92 (t, *J* = 7.3 Hz, 2 H), 3.70 (s, 3 H, OCH$_3$), 3.78 (s, 3 H, OCH$_3$), 3.92 (s, 3 H, OCH$_3$), 5.08 (s, 2 H, OCH_2Ph), 6.75 (s, 1 H), 6.92 (d, *J* = 8.4 Hz, 1 H), 7.07 (d, *J* = 2.3 Hz, 1 H), 7.21 (dd, *J* = 8.4 Hz, *J* = 2.3 Hz, 1 H), 7.40 (m, 5 H, Ph). – ^{13}C NMR (100 MHz, CDCl$_3$): δ = 16.9 (CH$_2$), 19.6, 25.0, 29.0, 29.05, 30.7, 55.6 (OCH$_3$), 60.8 and 60.85 (OCH$_3$), 75.2, 111.1, 119.2, 119.8, 127.4, 127.7, 126.0, 127.9, 128.45, 128.5, 128.7, 129.7, 129.8, 131.3, 137.9, 146.1, 150.2, 150.25, 156.0. – HRMS (C$_{30}$H$_{32}$N$_2$O$_4$): calcd. 484.2362; found 484.2371.

3-Iodo-4-methoxybenzaldehyde (15): To a magnetically stirred solution of 4-methoxybenzaldehyde (8.91 g, 65 mmol) and dry silver trifluoroacetate (16.35 g, 74 mmol) in dichloromethane (250 mL), maintained under a nitrogen atmosphere was added iodine (13.33 g, 83.34 mmol) in small portions over 15 min. After stirring the resulting mixture for 24 h, the latter was filtered and the precipitated silver iodide was washed with dichloromethane. The combined filtrates were washed with a 10% solution of Na$_2$S$_2$O$_3$ and dried over MgSO$_4$. After removal of the solvent, the residue was triturated under diethyl ether to induce crystallization of the iodide **15** (15.80 g, 99%), m.p. 106–107 °C (ref.[20] 42%, m.p. 105–107 °C). – IR (nujol): $\tilde{\nu}$ = 1673 (CHO) cm^{-1}, 1590 (C=C, Ar), 1274, 1182, 1016 (CO). – ^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.98 (s, 3 H, OCH$_3$), 6.93 (d, *J* = 8.5 Hz, 1 H), 7.86 (dd, *J* = 8.5 Hz, *J* = 2 Hz, 1 H), 8.31 (d, *J* = 2 Hz, 1 H), 9.82 (s, 1 H, CHO).

2,2′-Dimethoxydiphenyl-5,5′-bicarbaldehyde (16): To the molten aryl iodide **15** (499 mg, 1.91 mmol) was added an excess of activated Cu powder.[21] The sealed tube was heated to 180 °C for 5 h. The cooled reaction mass was then triturated with dichloromethane and the Cu was removed by filtration. After removal of the solvent, the residue was triturated under diethyl ether to induce crystallization of the bicarbaldehyde **16** (244 mg, 62%), m.p. 134 °C (ref.[20a] 12%, m.p. 131–132 °C).

(*E*,*E*)-5,5′-Bis[2-(ethoxycarbonyl)vinyl]-2,2′-diphenyl (17): K$_2$CO$_3$ (1.84 g, 7 mmol), triethyl phosphonoacetate (3 g, 7 mmol), bicarbaldehyde **16** (1.51 g, 3.68 mmol), dioxane (7 mL) and water (120 μL) were stirred at 85 °C for 2 h. More K$_2$CO$_3$ (1.84 g, 7 mmol) and triethyl phosphonoacetate (3 g, 7 mmol) were then added at room temperature. The temperature was then increased to 85 °C for 3 additional hours. The mixture was then diluted with water, acidified to pH 5–6 with 10% HCl, and extracted with dichloromethane (5 × 20 mL). The combined organic layers were washed with a saturated solution of K$_2$CO$_3$ (3 × 20 mL) then with water (2 × 20 mL), and dried over MgSO$_4$. After removal of the solvent, the residue was triturated under diisopropyl ether to induce crystallization. Recrystallization from diethyl ether gave the diphenyl **17** (2.38 g, 86%), m.p. 146–147 °C (ref.[22] oily product). – IR (KBr): $\tilde{\nu}$ = 1703 (C=O) cm^{-1}, 1633 (C=C), 1252 (CO ether), 1165 (CO ester). – ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.32 (t, *J* = 7.1 Hz, 6 H, 3 CH$_2$), 3.80 (s, 6 H, 2 OCH$_3$), 4.24 (q, *J* = 7.1 Hz, 4 H, 2 CH$_2$), 6.33 (d, *J* = 16.0 Hz, 2 H), 6.98 (d, *J* = 8.5 Hz, 2 H), 7.43 (d, *J* = 2.3 Hz, 2 H), 7.52 (dd, *J* = 16.0 Hz, *J* = 2.3 Hz, 2 H), 7.67 (d, *J* = 16.0 Hz, 2 H).

5,5′-Bis[2-(ethoxycarbonyl)ethyl]-2,2′-dimethoxydiphenyl (18): A magnetically stirred solution of unsaturated diester **17** (730 mg, 1.78 mmol) in ethanol (25 mL) was hydrogenated at 4 bar with 10% Pd/C catalyst at 45 °C for 5 h. After filtering off the catalyst and evaporating the solvent, compound **18** was obtained as a yellow oil (734 mg, 100%) in agreement with ref.[22] – IR (KBr): $\tilde{\nu}$ = 1734 (C=O) cm^{-1}, 1608 (C=C), 1244 (CO, ether), 1182 (CO, ester). – ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.24 (t, J = 7.1 Hz, 6 H), 2.62 (t, J = 7.9 Hz, 4 H), 2.92 (t, J = 7.9 Hz, 4 H), 3.74 (s, 6 H, 2 OCH$_3$), 4.13 (q, J = 7.1 Hz, 4 H), 6.88 (d, J = 8.4 Hz, 2 H), 7.06 (d, J = 2.3 Hz, 2 H), 7.15 (dd, J = 8.4, J = 2.3 Hz, 2 H).

5,5′-Bis(3-hydroxypropyl)-2,2′-dimethoxydiphenyl (19): To a suspension of LiAlH$_4$ (0.73 g, 19.3 mmol) in dry diethyl ether (750 mL), maintained under a nitrogen atmosphere and kept in an ice/water cooling bath, was added dropwise a solution of diester **18** (1.6 g, 3.86 mmol) in diethyl ether (25 mL). After the reaction was complete, the reaction mixture was stirred at reflux for 5 h then it was cooled to 0 °C. Methanol (20 mL) and water (50 mL) were then added dropwise successively. The aqueous layer was acidified to pH 5–6 with 10% HCl and was extracted with dichloromethane (5 × 25 mL). The combined organic layers were washed with brine (2 × 20 mL) and dried over MgSO$_4$. Removal of the solvent gave compound **19** (1.26 g, 100%). – IR (film): $\tilde{\nu}$ = 3367 (OH) cm^{-1}, 1504 (C=C), 1261 (CO, alcohol), 1242 (CO, ether). – ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.59 (br s, 2 H), 1.90 (m, 4 H), 2.68 (t, J = 7.6 Hz, 4 H), 3.69 (t, J = 6.4 Hz, 4 H), 3.75 (s, 6 H, 2 OCH$_3$), 6.89 (d, J = 8.4 Hz, 2 H), 7.07 (d, J = 2.2 Hz, 2 H), 7.15 (dd, J = 8.4 Hz, J = 2.2 Hz, 2 H).

5,5′-Bis[3-*p*-toluenesulfonyloxy(propyl)-2,2′-dimethoxydiphenyl (20): To a mixture of compound **19** (120 mg, 0.36 mmol), pyridine (97 µL, 1.16 mmol) and chloroform (1.3 mL) maintained at 0 °C, was added tosyl chloride (165 mg, 0.86 mmol) in small portions over 15 min. The resulting mixture was stirred for 4 h at 0 °C, diluted with dichloromethane (10 mL), and washed with 10% HCl (10 mL) then with a saturated solution of K$_2$CO$_3$ (10 mL). The organic layer was dried over MgSO$_4$. Removal of the solvents gave the crude compound **20** which was recrystallized from diisopropyl ether (120 mg, 91%), m.p. 121–123 °C. – IR (nujol): $\tilde{\nu}$ = 1598 (C=C) cm^{-1}, 1356 (SO$_3$), 1244 (CO, ether). – ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.95 (m, 4 H), 2.41 (s, 6 H), 2.62 (t, J = 6.4 Hz, 4 H), 3.72 (s, 6 H), 4.07 (t, J = 6.2 Hz, 4 H), 6.85 (d, J = 8.4 Hz, 2 H), 6.97 (d, J = 2.3 Hz, 2 H), 7.03 (dd, J = 2.2 Hz, J = 8.4 Hz, 2 H), 7.31 (d, J = 8.3 Hz, 4 H), 7.78 (d, J = 8.3 Hz, 4 H). – ^{13}C NMR (100 MHz, CDCl$_3$): δ = 21.7 (2 CH$_3$), 30.6, 55.8 (2 OCH$_3$), 69.9 (CH$_2$OSO$_2$), 111.2, 127.7, 127.9, 128.4, 129.9, 131.4, 132.0, 133.1, 144.8, 155.5.

5,5′-Bis*(*3-cyanopropyl)-2,2′-dimethoxydiphenyl (21): To a solution of the ditosylate **20** (136 mg, 0.22 mmol) in DMF (2 mL) at room temperature was added sodium cyanide (52 mg, 0.88 mmol). The mixture was heated at 85 °C for 5 h, cooled to room temperature, then diluted with dichloromethane (20 mL). The excess cyanide was removed by filtration. The filtrate was washed with a 10% solution of K$_2$CO$_3$ then with water (10 mL), and dried over MgSO$_4$. Removal of the solvents gave the crude compound **21** which was recrystallized from diethyl ether (74 mg, 96%), m.p. 94–95 °C. – IR (nujol): $\tilde{\nu}$ = 2245 (CN) cm^{-1}, 1608 (C=C), 1356 (SO$_3$), 1240 (CO, ether). – ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.98 (m, 4 H), 2.35 (t, J = 7.1 Hz, 4 H), 2.76 (t, J = 7.4 Hz, 4 H), 3.75 (s, 6 H, 2 OCH$_3$), 6.91 (d, J = 8.4 Hz, 2 H), 7.05 (d, J = 2.3 Hz, J = 8.4 Hz, 2 H), 7.13 (dd, J = 8.4 Hz, J = 2.3 Hz, 2 H). – ^{13}C NMR (200 MHz, CDCl$_3$): δ = 16.0 (*C*H$_2$CN), 26.8 (CH$_2$), 33.2 (CH$_2$), 55.5 (OCH$_3$), 111.1, 119.5 (CN), 127.3, 128.3, 131.1, 131.2, 155.3. – $C_{22}H_{24}N_2O_2$ (348.404): calcd. C 75.83, H 6.94, N, 8.04; found C 75.25, H 6.91, N 7.96.

Isomeric Mixture of Enaminonitriles (24):[16] The procedure of Marshall[23] was modified. To a stirred mixture of sodium hydride (73 mg, 1.82 mmol), (oil removed by washing with pentane) in THF (10 mL) was added *N*-methylaniline (227 µL, 2.1 mmol). The mixture was warmed to reflux for 2–3 h whereupon the dinitrile **21** (50 mg, 0.14 mmol) in THF (2 mL) was added to the refluxing solution in a regular and dropwise fashion. The solution was cooled to room temperature, hydrolyzed with 1 M HCl (2 mL), diluted with water (15 mL), and was then extracted with diethyl ether. The combined organic layers were washed with brine and then dried over MgSO$_4$. Removal of the solvent, followed by chromatography of the residue (toluene/ethyl acetate) gave a mixture of enaminonitriles **24** as a yellow powder (14 mg, 28%), m.p. 80–85 °C. – IR (film CDCl$_3$): $\tilde{\nu}$ = 3471, 3363, 3255 (NH$_2$) cm^{-1}, 2179 (C≡N), 1641 (C=C), 1602 (δNH$_2$). – ^{1}H NMR (400 MHz, CDCl$_3$): Complicated spectrum not possible to interpret. – HRMS ($C_{44}H_{48}N_4O_4$): calcd. 697.3754; found 697.3727.

Isomeric Mixture of β-Ketonitriles (25):[16] The crude mixture of enaminonitriles **24** (14 mg) was treated with 6 M HCl (1 mL), diluted with water, and extracted with diethyl ether. The combined organic layers were washed with 10% Na$_2$CO$_3$ solution and then dried over MgSO$_4$. Removal of the solvent, followed by chromatography of the residue (toluene/ethyl acetate) gave the β-ketonitrile **25** as a yellow powder (10 mg, 20% with respect to the dinitrile **21**), m.p. 200–210 °C. – IR (film CDCl$_3$): $\tilde{\nu}$ = 2247 (C≡N) cm^{-1}, 1726 (C=O). – ^{1}H NMR (400 MHz, CDCl$_3$): Complicated spectrum not possible to interpret. – HRMS ($C_{44}H_{46}N_2O_6$): calcd. 698.3349; found 698.3356.

Diketone (26):[16] A stirred crude mixture of enaminonitriles **24** (50 mg) in 12 M HCl (2 mL) was heated at reflux for 24 h, cooled, diluted with water, and extracted with diethyl ether. The combined organic layers were washed with 10% Na$_2$CO$_3$ solution and then dried over MgSO$_4$. Removal of the solvent, followed by chromatography of the residue (toluene/ethyl acetate) gave the diketone **26** as a yellow oily product (6 mg, 15% with respect to the dinitrile **21**). – IR (film CDCl$_3$): $\tilde{\nu}$ = 1710 (C=O) cm^{-1}. – ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.03 (dd, J = 8.3 Hz, J = 2.3 Hz, 4 H), 6.91 (d, J = 2.3 Hz, 4 H), 6.80 (d, J = 8.3 Hz, 4 H), 3.67 (s, 12 H, 4 OCH$_3$), 2.53 (m, 8 H, 4 CH$_2$CO), 2.33 (m, 8 H, 4 CH$_2$Ar), 1.85 (m, 8 H, 4 CH$_2$). – ^{13}C NMR (100 MHz, CDCl$_3$): δ = 215.0 (CO), 155.40, 133.25, 131.49, 128.31, 127.83, 111.05, 55.81 (CH$_3$–O), 41.94 (CH$_2$–CO), 34.17 (CH$_2$–Ar), 25.42 (CH$_2$).

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[1] [1a] G. M. Keserü, M. Nógrádi, *The Chemistry of Natural Diarlheptanoids*, in *Studies in Natural Products Chemistry* (Ed.: Atta-Ur-Rahman), Elsevier Science B. V., New-York, **1995**, *17*, 357. – [1b] P. Cleason, P. Tuchinda, V. Reutrakul, *J. Indian Chem. Soc.* **1994**, *71*, 509.

[2] P. J. Kumar, T. Yasuhiro, H. Koji, B. Purusotam, D. Hui, N. Tsuneo, K. Shigetoshi, *Biol. Pharm. Bull.* **1998**, *21*, 371.

[3] P. J. Begley, R. V. M. Campbell, L. Crombie, B. Tuck, D. A. Whiting, *J. Chem. Soc. (C)* **1971**, 3634.

[4] T. Anthonsen, G. B. Lorentzen, K. E. Malterud, *Acta Chem. Scand., Ser. B* **1975**, *29*, 529.

[5] M. Yasue, *Ringyo Shinkenjo Kenkyu Hokoku* **1968**, *209*, 77; *Chem. Abstr.* **1969**, *70*, 48743s.

[6] [6a] A. K. Mishra, M. M. Haribal, B. K. Sabata, *Phytochemistry* **1985**, *24*, 2463. – [6b] M. M. Haribal, A. K. Mishra, B. K. Sabata, *Phytochemistry* **1985**, *24*, 4949. – [6c] G. Venkatraman, A. K. Mishra, P. S. Thombare, B. K. Sabata, *Phytochemistry* **1993**, *33*, 1221.

[7] [7a] P. J. Roughley, D. A. Whiting, *Tetrahedron Lett*. **1971**, 3741. – [7b] P. J. Roughley, D. A. Whiting, *J. Chem. Soc., Perkin Trans.1* **1973**, 2379. – [7c] T. Inoue, N. Kenmochi, N. Furukawa, M. Fujita, *Phytochemistry* **1987**, *26*, 1409.

[8] [8a] A. D. Whiting, A. F. Wood, *Tetrahedron Lett.* **1978**, *26*, 2335. – [8b] A. D. Whiting, A. F. Wood, *J. Chem. Soc., Perkin Trans. 1* **1980**, 623.

[9] [9a] M. F. Semmelhack, L. S. Ryono, *J. Am. Chem. Soc.***1975**, *97*, 3873. – [9b] M. F. Semmelhack, P. Helquist, L. D. Jones, L. Keller, L. Mendelson, L. S. Ryono, J. Gorzynski, R. D. Stauffer, *J. Am. Chem. Soc*. **1981**, *103*, 6460.

[10] G. I. Gonzalez, J. Zhu, *J. Org. Chem*. **1999**, *64*, 914.

[11] [11a] M. G. Banwell, J. M. Cameron, M. P. Callis, G. T. Crisp, R. W. Gable, E. Hamel, J. N. Lambert, M. F. Mackay, M. E. Reum, J. A. Scoble, *Aust. J. Chem*. **1991**, *44*, 705. – [11b] V. Nair, D. W. Powell, S. C. Suri, *Synth. Commun*. **1987**, *17*, 1897. – [11c] S. C. Suri, V. Nair, *Synthesis* **1990**, 695.

[12] S. Torii, H. Tanaka, T. Sirui, M. Akada, *J. Org. Chem*. **1979**, *44*, 3305.

[13] In this laboratory, P. Gizecki prepared the diaryl **8** in 32% yield by a mixed Ullmann reaction (activated Cu powder/220° C/2 h) between 1-iodo-2,3,4-trimethoxybenzene and 3-iodo-4-methoxy-benzaldehyde.

[14] S. A. DiBiase, B. A. Lipisko, A. Haag, R. A. Wolak, G. W. Gokel, *J. Org. Chem*. **1979**, *44*, 4640.

[15] M. Nógrádi, G. M. Keserü, M. Kajtár-Peredy, B. Vermes, N. Thi Thu Ha, Z. Dinya, *ACH-Models Chem.* **1998**, *135*, 57.

[16] This procedure is part of B. Dansou's Ph. D. thesis.

[17] C. Chan, X. Huang, *Synthesis* **1984**, 224.

[18] [18a] F. Foubelo, F. Uoret, M. Yus, *Tetrahedron Lett*. **1993**, *49*, 8465. – [18b] *Dictionary of Organic Compounds*, 5th ed., Chapman and Hall (New York), **1982**, Vol. 2, 1326.

[19] W. S. Marshall, S. K. Sigmund, C. A. Whitesitt, S. L. Lifer, C. R. Roman, L. E. Rinkema, R. A. Hahn, J. H. Fleisch, *Agents and Actions* **1989,** *27*, 3; *Chem. Abstr.* **1989**, *111*, 33125 h.

[20] [20a] E. Fujita, K. Fuji, K. Tanaka, *J. Chem. Soc.(C)* **1971**, 205. – [20b] D. J. Hart, W. P. Hong, *J. Org. Chem*. **1985**, *50*, 3670.

[21] E. C. Kleider, R. Adams, *J. Am. Chem. Soc.* **1933**, *55*, 4219.

[22] V. Karpunin, *Zh. Prikl. Khim. (Leningrad)* **1978**, *51*, 2387; *Chem. Abst.* **1979**, *90*, 138346 g.

[23] [23a] J. A. Marshall, J. C. Peterson, L. Lebioda, *J. Am. Chem. Soc.***1984**, *106*, 6006. – [23b] N. L. Allinger, M. Nakazaki, V. Zalkow, *J. Am. Chem. Soc.***1959**, *81*, 4074.

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