Full Paper

CSIRO PUBLISHING

Aust. J. Chem. **2011**, *64*, 316–323

www.publish.csiro.au/journals/ajc

The Synthesis of Fluorescent DNA Intercalator Precursors through Efficient Multiple Heck Reactions

Nigel A. Lengkeek,[A] *Ramiz A. Boulos,*[A] *Allan J. McKinley,*[A] *Thomas V. Riley,*[C] *Boris Martinac,*[B] *and Scott G. Stewart*[A,D]

[A]M313, Chemistry, School of Biomedical, Biomolecular and Chemical Science, University of Western Australia, 35 Stirling Highway, Crawley, WA, 6009, Australia.

[B]Victor Chang Cardiac Research Institute, Lowy Packer Building, 405 Liverpool Street, Darlinghurst, Sydney, NSW 2010, Australia.

[C]M502, Microbiology and Immunology, School of Biomedical, Biomolecular and Chemical Sciences, The University of Western Australia, 35 Stirling Hwy, Nedlands, WA 6009, Australia.

[D]Corresponding author. Email: sgs@cyllene.uwa.edu.au

A highly efficient synthesis of *p*-carboethoxy-tristyryl and carboethoxy-terastyrenyl benzene derivatives through a multiple Heck cross coupling reaction is reported. This reaction provides an efficient route to DNA intercalator precursors containing a benzene core.

Manuscript received: 21 October 2010.
Manuscript accepted: 10 January 2011.

Introduction

Organic based DNA intercalators represent a variety of functionalized aromatic compounds from the straightforward acridine dye Proflavine (**1**, Fig. 1) to the more complex ligands such as the anthraquinone based natural product daunomycin (**2**). Most organic DNA intercalators have a variety of functional groups attached to the aromatic scaffold, many of which are normally vital to the activity and stability of the drug-DNA complex. For instance in the anthracyclines (i.e. daunomycin **2**) an electron deficient quinone system is needed to interact with the electron rich base pairs but the C9 hydroxyl moiety is considered the pharmocophore responsible for the drugs any anticancer activity.[1] Our interest in fluorescent DNA intercalators has initially been devised around medium-sized styryl compounds bearing a central benzene core (**3**–**7**). In designing the styryl ring system it was presumed these systems would be slightly less rigid than more traditional intercalators, but have similar π-stacking interactions. Many intercalators contain an amine at the periphery (as an ammonium cation at pH 7) which binds with the phosphate group of the DNA. In our system terminal and conjugated carboxylic acids were targeted, a functionality which was considered versatile enough to quickly access other functional groups such as amines, amides and phenols. An eventual objective was to provide derivatives that could dramatically alter their fluorescence profile on interaction with DNA.[2] Compounds of this type have also been examined for their use as optical brightening (OBAs) or optical bleaching agents.[3]

Reported literature preparation of such compounds normally involve a Wittig based approach in which the central fragment comes from either a di- or tri-benzaldehyde or the reverse where a central stabilized Horner-Wodsworth-Emmons phosphonate

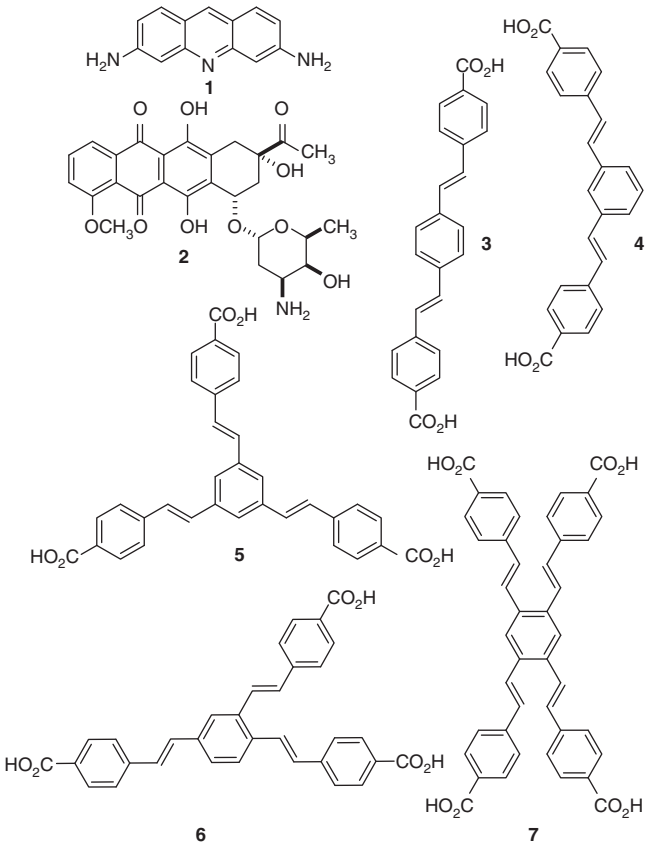
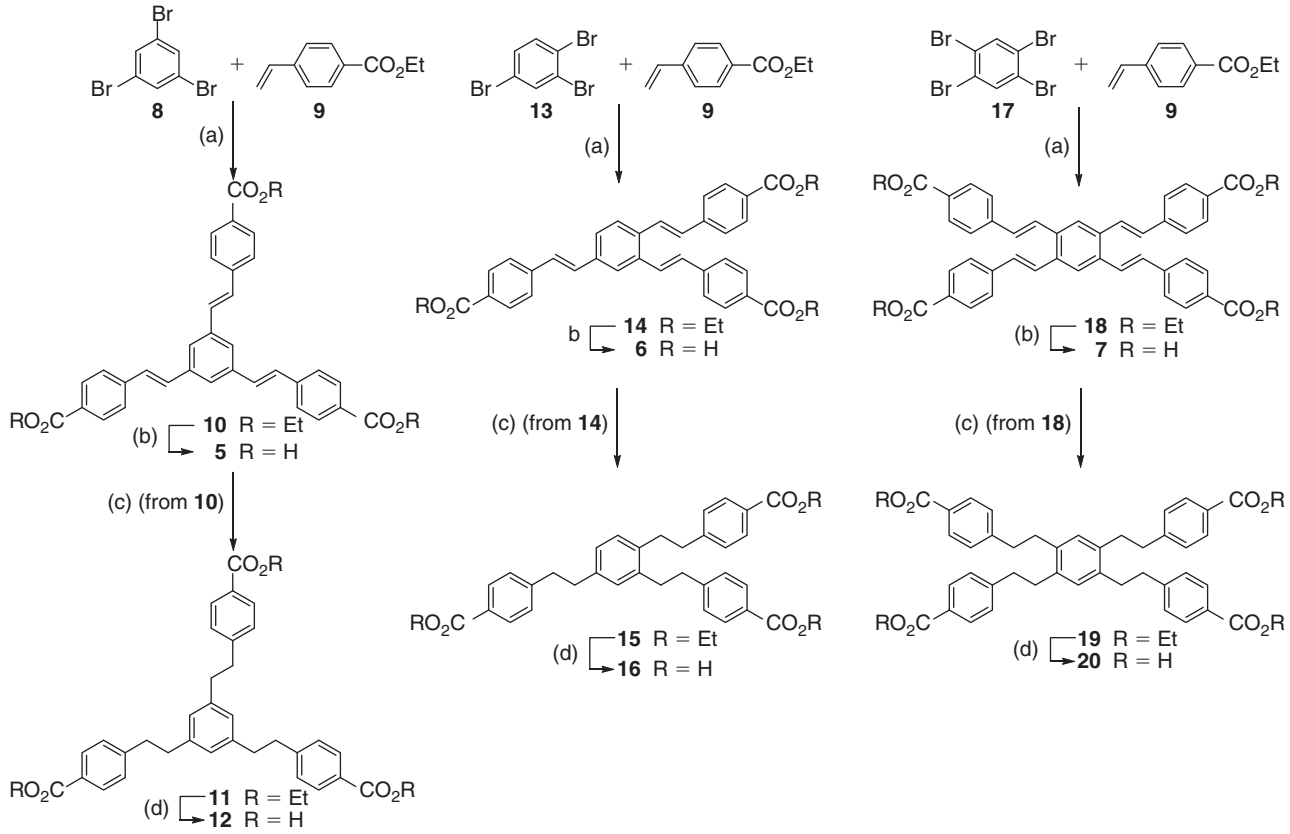


Fig. 1. Known DNA intercalators proflavine (**1**) and daunomycin (**2**) as well as proposed DNA intercalators precursors (**3**–**7**).

10.1071/CH10374 0004-9425/11/030316



Scheme 1. The synthesis of the target compounds through Heck cross coupling approach. *Reagents and conditions*: (a) $Pd_2(dba)_3$/[(*t*-Bu)$_3$PH]BF_4, THF, reflux, 17 h (82–97%). (b) LiOH, H_2O/EtOH, reflux, 3 h. (c) Pd/C-H_2, CH_2Cl_2/EtOH, 17 h. (d) LiOH, H_2O/EtOH, reflux, 3 h.

Table 1. Trials of the Heck cross coupling reaction between 1,3,5-tribromobenzene (8) and ethyl 4-vinylbenzoate (9)

Entry	Catalyst	Mol-% cat[A]	Base/additive	Solvent	Temp [°C]	Time	Yield of **8** [%]
1	$Pd(OAc)_2$	5	K_2CO_3	DMF	100	2 d	0
2	$Pd(OAc)_2$	5	K_2CO_3	Toluene	111	2 d	0
3	$Pd(OAc)_2$[B]	2	K_2CO_3/NBu_4Br	DMF	100	6 d	3
4	$Pd(OAc)_2$/PPh_3	5	Et_3N	DMF	100	2 d	0
5	HB PC[C]	10	NBu_4OAc	Toluene	111	3 d	0
6	HB PC[C]	10	NBu_4OAc	DMF/MeCN/H_2O (5:5:1)	100	3 d	Trace[D]
7	$Pd(PPh_3)_4$	5	K_2CO_3	Toluene	111	2 d	0
8	$Pd(PPh_3)_4$	10	Cy_2MeN	THF	70	5 d	0
9	$Pd_2(dba)_3$/*t*-Bu_3P	15	Cy_2MeN	THF	70	14 h	97

[A]Mol-% catalyst per Heck reaction.
[B]Jeffery's conditions.[15]
[C]HB PC: Hermann-Beller Palladacycle.[11]
[D]Based on TLC analysis against isolated material.

ester is used. In many cases these processes are either low yielding or the procedure provides a mixture of *E* and *Z*-geometrical isomers at each tether.[4–7] Furthermore, for the purposes of producing reasonable quantities of a precursor olefin, the additional steps of providing a tri or tetra-phosphonate ester maybe time consuming and problematic. Recently, the group of Sinha has developed a domino based approach to these systems which results in good yields of the bis-arylated systems but this process may not be amenable to our benzyl esters/benzoic acids.[8] The Heck reaction provides a high yielding and *E*-selective approach to such unsaturated systems[9–11] Pioneering work by de-Meijere has provided a method for the construction of tri and tetra-styrene benzene derivatives through a tandem Heck approach using Jefferey's phosphine free conditions ($Pd(OAc)_2$, NBu_4Br, K_2CO_3, DMF)[12] while others have investigated dihalogenated systems in reasonable yields where the styrene coupling partner is substituted.[7,13,14] In this paper we plan to investigate the Heck cross coupling approach to various di-, tri- and tetra-styrenyl tethered benzene based compounds as precursors to our target compounds (**3**–**7**).

Results and Discussion

Initial strategies to follow the preparation of tristyrene **10** (Scheme 1) through a Wittig based approach, with 1,3,5-tribenzaldehyde were problematic.[4] Following these setbacks we investigated a Heck cross coupling based approach from the commercially available 1,3,5-tribomobenzene (**8**) and ethyl-4′-vinylbenzoate (**9**). It was assumed that following the first Heck

Table 2. Heck cross coupling between ethyl 4-vinylbenzoate 9 and various halobenzenes employing the $Pd_2(dba)_3$/*t*-Bu_3P catalytic system

Entry	Substrate	Mol-% catalyst[A]	Time [h]	Product	Yield [%]
1	**8**	15	14	**10**	97
2	**13**	2	15	**14**	88
3	**17**	5	15	**18**	82
4	**26**	5	18	**28**	84
5	**27**	5	72	**28**	29

[A]Mol-% catalyst per Heck reaction.

reaction the aromatic ring would be considered less electron rich improving the rate of oxidative addition for the second Heck reaction thus improving the chances of a multiple or tandem type process.[15] Initial attempts using $Pd(OAc)_2$ or Jeffery's phosphine free conditions (Table 1) unfortunately led to either none or only small amounts of the desired trisubstituted product **10** being isolated (Entries 1 to 3).[16] While some of the above mentioned conditions showed initial promise (Entries 3 and 6) small alterations to these conditions did not improve the overall yield.

Trials using the thermally stable palladacycle, popularized by Hermann and Beller, using toluene were not successful and trace amounts of the desired product were realized under specific solvent conditions (DMF/MeCN/H_2O, Entry 6).[13,17,18] Since similar synthetic transformations with matching catalytic conditions have been reported in a range of yields[13,19–21] it is assumed that the specific electronic nature of our coupling partner plays a large role in these observed low yields. Fortunately vast improvements in yield were finally realized with the use of the $Pd_2(dba)_3$ and P(*t*-Bu)$_3$ catalytic system.[22] Remarkably even at lower temperatures this successful catalytic system was highly effective for the multiple process.

As discussed earlier, despite the potential for numerous products as a result of incomplete alkenylation or dehalogenation,[10] we were still surprised to observe only the fully olefinated products. With these factors considered, in our hands this trihalogenalted system the Heck reaction provides a far more attractive route compared with the Wittig based approach from the unstable 1,3,5-tribenzaldehyde which is amenable to scale up.[4]

Having found an effective set of catalytic conditions for the multiple Heck reaction the $Pd_2(dba)_3$/P(*t*-Bu)$_3$ system (Table 2) was used as the key reaction to prepare the aforementioned target compounds **3**–**7** (Fig. 1). As this catalyst has also been shown to be effective with aryl chlorides,[22] trials with 1,4-dichlorobenzene were also attempted. Unfortunately, even at extended reaction times the yields (Entry 5) were considerably lower. While some reduction in catalyst loading was investigated, 2% per Heck reaction, further reductions may be possible, but remain to be investigated. As previously, the crude NMR spectra showed no signs of halogenated precursors or the *Z*-geometric isomer. As highlighted in Schemes 1 and 2, the approaches to the targets containing di-, tri- and tetra-tethers is identical. Since we sought to investigate the role of extended conjugation in DNA intercalation we also required the reduced derivatives. Hydrogentaion of the alkenes (Schemes 1 and 2) with 10% Pd/C in a hydrogen atmosphere proceeded well (79–98%), as did subsequent saponification (LiOH, 85–95% yield). In the unsaturated series of compounds (alkene tethered carboxylic acid derivatives **5**, **6**, **7**, **3**), the desired products were purified by recrystallisation thus alleviating the need for

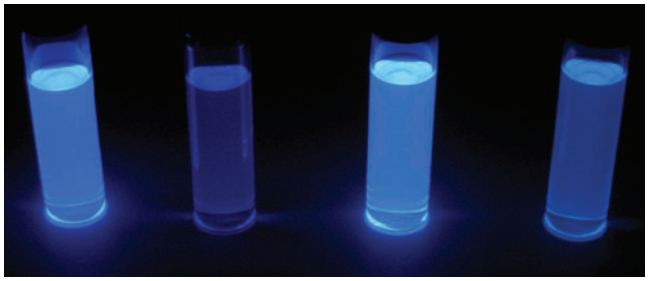


Fig. 2. Fluorescence of compounds **28**, **10**, **14** and **18** (left to right) in CH_2Cl_2 at 1×10^{-7} M irradiated at 364 nm.

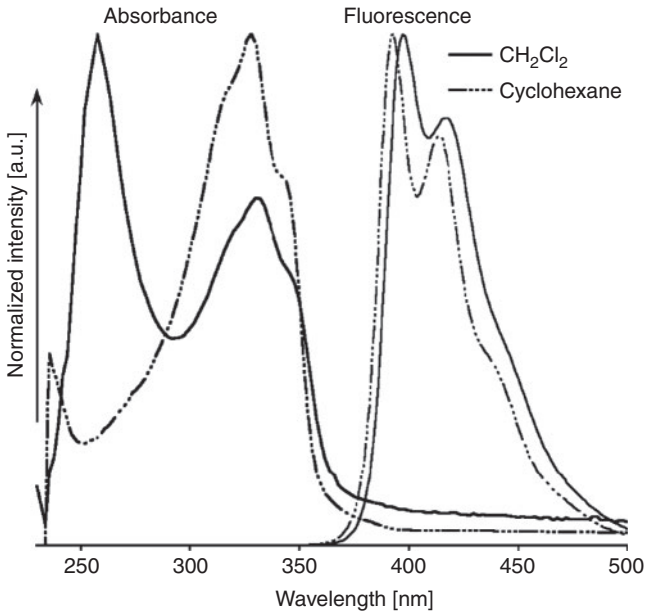


Fig. 3. Normalized UV-Vis and fluorescence spectra of **10** in CH_2Cl_2 (excitation at 330 nm) and cyclohexane (excitation at 328 nm).

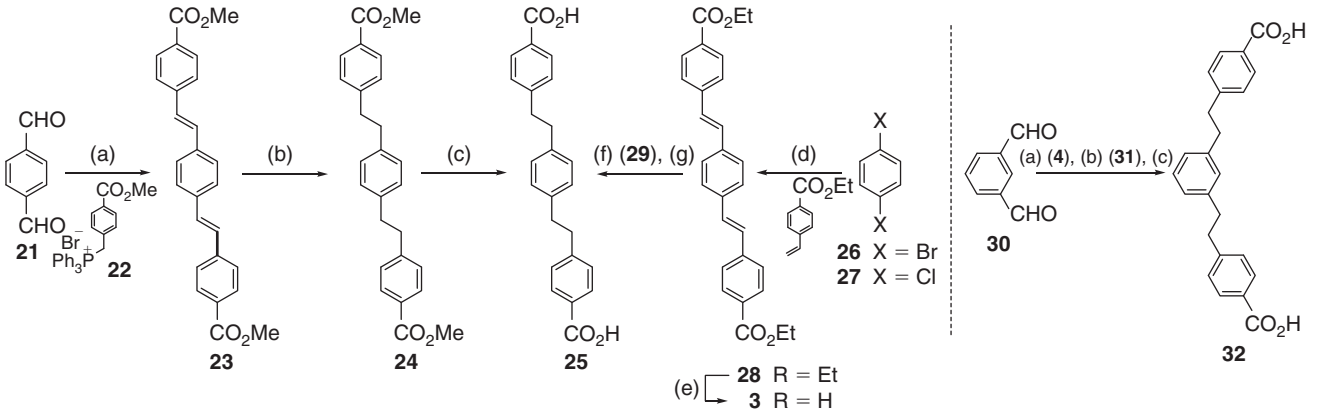
chromatography. In a further comparison of synthetic approaches, the synthesis of **25** was examined using both the Wittig and Heck procedures (Scheme 2).[23]

General Reaction Conditions: Halogenated benzene (1 equiv.), ethyl 4-vinylbenzoate **9** (1.1 equiv. per halogen), $Pd_2(dba)_3$/[(*t*-Bu)$_3$PH]BF_4, THF, reflux.

The Wittig approach gave the desired dialkene **23** as a mixture of *E*/*E* and *E*/*Z* isomers in a 40/60 ratio (44/56 ratio for 1,3 derivative **4**). The procedure adopted gave significantly higher yields than previously observed[6,24] while the Heck reaction equivalent gave solely an *E*/*E* isomeric mixture, **28**. As before reduction with Pd/C-H_2 and saponification with LiOH furnished the desired compound **25**. Although dibenzaldehydes are commercially available, preparation of the trialdehydes and tetraaldehydes can be problematic while a wide array of haloaromatics are commercially available.[25]

Electronic and Fluorescent Properties

Electronic and fluorescence data for specific compounds are indicated in Table 3 for both CH_2Cl_2 and cyclohexane (Image 2, Fig. 2). Comparable data for compounds from the literature, including stilbenes,[26] styrylstilbenes[6,27] and poly(styryl) benzenes are included (see Accessory Publication).[5,7,28] The structure of the spectra remains relatively unchanged, except for a small red-shift for all compounds consistent with the



Scheme 2. *Reagents and conditions*: (a) NaOMe, MeOH, **22**, rt, 17 h, 84%. (b) Pd/C (10% w/w), H_2, 1:1 CH_2Cl_2/MeOH, 17 h, rt, 93%. (c) LiOH, MeOH/H_2O, reflux, 17 h, 97%. (d) $Pd_2(dba)_3{\cdot}CHCl_3$, $[(t\text{-}Bu)_3PH]BF_4$, Cy_2NMe, THF, reflux, 17 h, 84% from **26**, 72 h, 29% from **27**. (e) LiOH, 9:1 EtOH/H_2O, reflux, 17 h, 66%. (f) Pd/C, H_2, 1:1 CH_2Cl_2/EtOH, 17 h, 96%. (g) LiOH, EtOH/H_2O, reflux, 17 h, 82%.

Table 3. Electronic and fluorescence data for 10, 14, 18 and 28

Compound	Solvent	UV/Vis-λ [log ε]	Fluorescence (l_{ex}[l_{emis}]) λ_{ex}	λ_{em}
10	CH_2Cl_2	258 [4.49], 330 [4.28]	258	414, 437
	Cyclohexane	328, 341	328	393, 413
14	CH_2Cl_2	258 [4.53], 338 [4.83]	258	436, 450
	Cyclohexane	334, 358 s	334	416, 440
18	CH_2Cl_2	258 [4.62], 312 [4.73], 346 [8.42]	258	455, 518
	Cyclohexane	241, 336	336	442
28	CH_2Cl_2	254 [3.85], 372 [4.74]	254	414, 437
	Cyclohexane	247, 369	369	404, 428

change to more polar CH_2Cl_2. All the compounds have shown an absorbance at *ca* 258 nm, which is consistent with a styryl *B*-band transition. Surprisingly, none of the compounds show an obvious absorbance at *ca* 300 nm that could correspond to a stilbene type absorbance.

The longer wavelength absorbances are consistent with a red-shift in the *K*-band absorbances due to the extended conjugation within the compounds. These are comparable to some analogues compiled in Table 3. While the red-shift increases from the tris- to tetra-compounds (**14** and **18**) the largest observed red-shift stilbene was in the bis-compound, suggesting the pattern of substitution may be as important as the degree of substitution. The fluorescence spectra of all compounds show a distinct redshift from cyclohexane to CH_2Cl_2, though the structure of the spectra remains relatively unaffected (for compound **10** see Fig. 3). The fluorescence spectra obtained were found to be largely independent of excitation at the *B*-band (~258 nm) or the longer wavelength bands, suggesting the excited states share a common intermediate state or the higher energy state decays through the lower. The anisotropy may be due to the complicated photochemistry of stilbenes[29] or the manifestation of 'dual fluorescence' commonly observed in *push-pull* stilbenes such as (*E*)-4-dimethylamino-4′-cyanostilbene (see Accessory Publication).[26c,29] The later is unlikely as the effect is generally eliminated in non-polar solvents, but persists in these compounds. Fluorescence spectra of the *tetra*-substituted compound, **18**, show several short wavelength emissions consistent with *trans-cis* isomerisation.[29a,30] The cursory examination of the photophysical properties of these compounds has revealed some interesting features and further investigations are underway to elucidate their photophysical properties.

In summary, we have described a simple synthesis of di-, tri- and tetra-phenylethyl benzene compounds containing carboxylic acid functional groups. This was achieved through the development of an efficient multiple Heck cross coupling reaction through the exploration of various palladium catalysts.

Experimental

Terephthaldehyde, tributylphosphonium tetrafluoroborate, 1,3,5-tribromobenzene and 1,2,4-tribromobenzene were purchased from the Sigma-Aldrich Chemical Co. Dry THF was distilled from sodium benzophenone ketyl radical and stored over a sodium mirror. *N*-Methyldicyclohexylamine was distilled under reduced pressure and stored under argon. Dess-Martin Periodinane,[31] Herrmann-Beller paladacycle,[17a] (methyl 4-carboxybenzyl)triphenylphosphonium bromide,[32] $Pd_2(dba)_3{\cdot}CHCl_3$,[33] and $Pd(PPh_3)_4$[34] were prepared as described previously. 1,3-Di(hydroxymethyl)benzene was prepared by the $LiAlH_4$ reduction of dimethyl 1,3-benzenedicarboxylate in a similar procedure to the 1,2-isomer.[35] Ethyl 4-vinylbenzoate was prepared by the Fischer esterification of 4-vinyl benzoic acid[36a] while *iso*-phthalaldehyde was prepared as via the literature.[36b]

NMR spectra were acquired on either a Bruker AV500 (^{1}H at 500.13 MHz, ^{13}C at 125.8 MHz) or a Bruker AV600 (^{1}H at 600.13 MHz, ^{13}C at 150.9 MHz) and all signals δ are reported in parts per million [ppm]. ^{1}H and ^{13}C assignments were made with the aid of DEPT, COSY, HSQC and HMBC sequences where appropriate. ^{1}H spectra were referenced to residual (partially) undeuterated solvents, $CDCl_3$ ($CHCl_3$ at 7.26 ppm) and d_6-DMSO (d_5-DMSO at 2.50 ppm (pentet)). ^{13}C spectra were referenced to the deuterated solvents, $CDCl_3$ at 77.16 ppm and d_6-DMSO at 39.52 ppm. Infrared spectra samples were prepared

using the KBr disc method and samples acquired on a Perkin–Elmer Spectrum One spectrometer at 2 cm^{-1} resolution. Electronic spectra were collected using a HP8452 spectrophotometer in 1 cm quartz cells at $\sim 1 \times 10^{-5}$ or $\sim 1 \times 10^{-6}$ mol L^{-1} in the solvents indicated. Fluorescence spectra were recorded on a Varian Fluorescence Spectrophotometer at 1×10^{-7} mol L^{-1}. Mass spectra were acquired on a VG Autospec employing the electron impact (EI) ionization mode.

Standard Conditions for Heck Cross Coupling Procedure

To a flame-dried schlenk flask was added the halobenzene (1 equiv.), $Pd_2(dba)_3{\cdot}CHCl_3$ (2–15 mol-%) and $[(t\text{-}Bu)_3PH]BF_4$ (10–60 mol-%) which were subsequently dried under vacuum for 15 min before being dissolved in dry THF. *N*-Methyldicyclohexylamine (4 equiv.) and ethyl 4-vinylbenzoate **7** (3.3 equiv.) were added via syringe and the reaction monitored by TLC (neat CH_2Cl_2). Upon completion of the reaction the residual THF was removed under vacuum, the crude material redissolved in CH_2Cl_2 and filtered to remove any insoluble material before being absorbed onto fine silica and eluting with 0:100 to 2:98 MeOH/CH_2Cl_2.

Standard Method for Reduction of Alkenes

The alkene was loaded into a glass autoclave tube and dissolved/suspended in 1:1 CH_2Cl_2/MeOH or 1:1 CH_2Cl_2/EtOH depending upon the ester present. Argon was bubbled through the mixture for 10 min before 10% Pd/C (~10 wt-% of alkene) was added, and the flask pressurized with H_2 (50 atm). The reaction was allowed to proceed for 17 h before being depressurized, purged with argon, filtered through a pad of celite and concentrated under reduced pressure. Further purification is described for each compound when necessary.

Standard Method for Saponification Reactions

The ester (1 equiv.) and LiOH (2 equiv. per ester) were dissolved in 9:1 H_2O/MeOH or H_2O/EtOH depending upon the ester and refluxed overnight. After cooling to room temperature the solvent was removed under reduced pressure, the remaining solution diluted with H_2O, cooled in an ice-bath and the pH adjusted to 3 by the addition of HCl (1 M). The precipitate was collected filtered and product dried under vacuum.

Preparation of Selected Compounds

*1,3,5-Tris[(1E)-2′-(ethyl 4″-benzoate)vinyl]benzene (**10**)*

Prepared as per the standard procedure using 1,3,5-tribromobenzene **8** (1010 mg, 3.21 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (882 mg, 0.85 mmol), $t\text{-}Bu_3PHBF_4$ (560 mg, 1.93 mmol), Cy_2NMe (3.0 mL), ethyl 4-vinylbenzoate **7** (1870 mg, 10.61 mmol) and THF (40 mL). The product was eluted with 2:98 MeOH/CH_2Cl_2 and recrystallized from CH_2Cl_2/EtOH to give **10** as an off white powder (1.86 g, 97%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.42 (t, *J* 7.1, 9H, CH_3), 4.40 (q, *J* 7.1, 6H, CH_2), 7.24 (AB quartet, 6H, vinyl), 7.60 (d, *J* 8.3, 6H, ArH), 7.61 (s, 3H, ArH), 8.06 (d, *J* 8.3, 6H, ArH).

^{13}C NMR (150 MHz, $CDCl_3$): δ 14.51 (CH_3), 61.13 (CH_2), 125.0 (CH), 126.5 (CH), 128.7 (CH), 129.7 (C), 130.2 (CH), 130.5 (CH), 137.9 (C), 141.5 (C), 166.5 (C=O). IR (KBr): ν [cm^{-1}] 2979, 2929, 1713, 1604, 1279, 1178, 1105, 762, 698; HR-EI$^+$-MS: $C_{39}H_{36}O_6$ requires 600.2512 amu, found 600.2513; EI$^+$-MS: MI = $C_{39}H_{36}O_6$; *m/z*: 600.3 (100%) = MI^+, 555.2 (7%) = $[MI - EtO]^+$; UV-Vis (CH_2Cl_2): λ [nm] ($\log \varepsilon$ [$M^{-1}\,cm^{-1}$]) 258 [4.49], 330 [4.28]; fluorescence (CH_2Cl_2): excitation [nm] (emission [nm]) 258 [397, 418, 518], 330 [397, 418]; (cyclohexane) 328 [393, 413].

*1,3,5-Tris[(1E)-2′-(4″-benzoic acid)vinyl]benzene (**5**)*

Using the standard saponification procedure, **10** (252.1 mg, 0.42 mmol), $LiOH{\cdot}H_2O$ (112.0 mg, 2.7 mmol) and 1:9 H_2O/EtOH (20 mL) gave an gelatinous precipitate that was collected and recrystallised from THF/H_2O and dried to give the triacid **5** as a pale brown powder (209 mg, 95%). ^{1}H NMR (500.1 MHz, d_6-DMSO): δ 7.49 (m, 6H, vinyl CH), 7.76 (d, *J* 8.5, 6H, ArH), 7.88 (s, 3H, core ArH), 7.98 (d, *J* 8.5, 6H, ArH); ^{13}C NMR (125.8 MHz, d_6-DMSO): δ [ppm] 125.0, 126.5, 128.4, 129.7, 129.9, 130.50, 137.6, 141.3, 167.1; IR (KBr): ν [cm^{-1}] 3067, 3026, 1684 ($\nu_{C=O}$), 1604, 1566, 1420, 1384, 1312, 1286, 1179; HR-EI$^+$-MS: $C_{33}H_{24}O_6$ requires 516.1573 amu, found 516.1564; EI$^+$-MS: MI = $C_{33}H_{24}O_6$; *m/z*: 516.1 (100%) = MI^+, 472.1 (11.3%) = $[MI - CO_2]^+$.

*1,3,5-Tris[(1E)-2′-(ethyl 4″-benzoate)ethyl]benzene (**11**)*

Conducted as per the standard reduction procedure with trimester **10** (251 mg, 0.42), Pd/C (20 mg) and 1:1 CH_2Cl_2/EtOH (15 mL). The crude product was recrystallized from CH_2Cl_2/EtOH to give the triester **11** (237 mg, 93%) of a white solid.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 1.38 (t, *J* 7.1, 9H, CH_3), 2.87 (m, 12H, bridge CH_2), 4.36 (q, *J* 7.1, 6H, CH_2), 6.76 (s, 3H), 7.20 (d, *J* 8.1, 6H, ArH), 7.97 (d, *J* 8.1, 6H, ArH); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.4, 37.5, 38.0, 60.8, 126.5, 128.3, 128.6, 129.7, 141.4, 147.2, 166.7; HR-EI-MS: $C_{39}H_{42}O_6$ requires 606.2981 amu, found 606.2994.

*1,3,5-Tris[2′-(4″-benzoic acid)ethyl]benzene (**12**)*

Using the standard procedure triester **11** (252.0 mg, 0.42 mmol), $LiOH{\cdot}H_2O$ (107.2 mg, 2.6 mmol) and 1:9 H_2O/EtOH (20 mL) gave triacid **3** (202 mg, 93%) as a white powder. ^{1}H-NMR (500 MHz, d_6-DMSO): δ 2.82 (cm, 12H, CH_2), 6.83 (s, 3H, ArH), 7.28 (d, *J* 8.2, 6H, ArH), 7.85 (d, *J* 8.2, 6H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 36.7, 37.1, 126.2, 128.4, 126.2, 129.3, 140.9, 146.9, 167.3; IR (KBr): ν [cm^{-1}] 3067, 2929, 1686, 1610, 1422, 1315, 1288, 1179; HR-FAB-MS: $C_{33}H_{31}O_6$ requires 523.2145 amu, found 523.2121; HR-FAB-MS: $C_{33}H_{29}O_5$ requires 505.2032 amu, found 523.2015; EI$^+$-MS: $MI^+ = C_{33}H_{30}O_6$; *m/z*: 504.2 (90%) = $[MI - H_2O]^+$, 387.1 (100%) = $[MI - CH_2(C_6H_4CO_2H)]^+$.

*1,2,4-Tris[(1E)-2′-(ethyl 4″-benzoate)vinyl]benzene (**14**)*

Using the standard Heck cross-coupling procedure, 1,2,4-tribromobenzene **13** (1.018 g, 3.2 mmol), ethyl 4-vinylbenzoate **9** (1.843 g, 10.5 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (87.6 mg, 0.08 mmol), $[(t\text{-}Bu)_3PH]BF_4$ (122.6 mg, 0.42 mmol), Cy_2NMe (3 mL) in THF (40 mL) were heated for 17 h. The crude mixture was subjected to flash chromatography eluting with neat CH_2Cl_2. The crude product was recrystallised from CH_2Cl_2/EtOH to give (1.681 g, 88%) of a pale yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.409, 1.413, 1.416 (3 × t, *J* 7.1, 9H, CH_3), 4.392, 4.394, 4.400 (3 × q, *J* 7.1, 6H, CH_2), 7.06–7.11 (m, 2H, vinyl CH), 7.17–7.28 (m, 2H, vinyl CH), 7.51–7.67 (cm, 9H), 7.73 (m, 1H, core ArH), 8.04–8.09 (cm, 6H, ArH); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.5 (CH_3), 61.1, 61.13, 61.1 (CH_2), 125.8 (CH), 126.5 (CH), 126.5 (CH), 126.6 (CH), 126.4 (CH), 127.3 (CH), 128.3 (CH), 128.4 (CH), 128.7 (CH), 129.6 (C), 129.8 (C), 129.8 (C), 130.2 (CH), 130.2 (CH), 130.3 (CH), 130.5 (C), 130.7 (C), 131.3 (C), 135.6 (C), 136.4 (C), 136.9 (C), 141.62 (C=O),

141.66 (C=O), 141.7 (C=O); IR (KBr): ν [cm^{-1}] 2981, 1713 ($\nu_{C=O}$), 1604, 1278, 1178, 1107; HR-EI$^+$-MS: $C_{39}H_{36}O_6$ requires 600.2512 amu, found 600.2504; EI$^+$-MS: MI = $C_{39}H_{36}O_6$; *m/z*: 600.2 (100%) = MI$^+$, 555.2 (13.3%) = [MI − EtO]$^+$, 437.1 (70.1%) = [MI − 2 × OEt − EtO_2CH]$^+$.

UV-Vis (Solv): λ [nm] (ε [$M^{-1}cm^{-1}$]) 258 [4.53], 338 [4.83], 362 [4.76, shoulder]; fluorescence (CH_2Cl_2): excitation [nm] (emission [nm]) 258 [436 (shoulder), 450], 338 [436 (shoulder), 450]; (cyclohexane) 334 [416, 440].

*1,2,4-Tris[(1E)-2′-(4″-benzoic acid)vinyl]benzene (**6**)*

Triester **14** (250 mg, 0.42 mmol) and LiOH·H_2O (70.2 mg, 1.67 mmol) in 9:1 EtOH/H_2O were treated as described in the general saponifiaction procedure giving the triacid **6** (186.6 mg, 86%) as a yellow/brown solid; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.06–7.61 (m, 17H, ArH, CH), 7.66 (d, *J* 8.3, 1H, CH=CH), 7.48 (s, 2HHHH, CH=CH), 7.32 (m, 2H, ArH); ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.6 (3 × C=O), 141.76 (C), 141.71 (C), 141.6 (C), 137.0 (C), 136.3 (C), 135.4 (C), 131.2 (CH), 130.7 (CH), 130.5 (CH), 130.44 (C), 130.38 (C), 130.2 (CH), 130.16 (CH), 130.18 (CH), 128.4 (C), 128.3 (C), 127.9 (C), 127.4 (CH), 127.35 (CH), 127.15 (C), 126.9 (CH), 125.5 (C); IR (KBr): ν [cm^{-1}] 2929, 1684 ($\nu_{C=O}$), 1603, 1419, 1315, 1287, 1178, 1125, 763; HR-EI$^+$-MS: $C_{33}H_{24}O_6$ requires 516.1572 amu, found 516.1571.

*1,2,4-Tris[2′-(ethyl 4″-benzoate)ethyl]benzene (**15**)*

Triester **14** (306 mg, 0.51 mmol) and Pd/C (10% w/w, *ca* 40 mg) in 1:1 EtOH/CH_2Cl_2 (20 mL) was treated as described. The crude product was recrystallised from THF and hexane to give ester **15** 305 mg (98%). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 1.376, 1.381, 1.393 (3 × t, 3 × CH_3, 9H), 2.79–2.95 (m, 12H), 4.33–4.40 (m, 6H), 6.86 (s, 1H), 6.95 (d, *J* 7.8, 1H), 7.04 (d, *J* 7.8, 1H), 7.17 (AB d, *J* 8.0, 2H), 7.19 (AB d, *J* 8.0, 2H), 7.21 (AB d, *J* 8.1, 2H), 7.95 (cm, *J* 7.7, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.48, 14.50, 34.0, 34.4, 37.2, 37.7, 38.1, 61.0, 61.0, 126.6, 128.43, 128.54, 128.56, 128.7, 129.5, 129.7, 129.8, 129.9, 136.7, 139.0, 139.3, 147.2, 147. 2, 147.3, 166.7, 166.8, 166.8; IR (KBr): ν [cm^{-1}] 2981, 2942, 1713, 1610, 1283, 1177, 1123, 1108; HR-EI$^+$-MS: $C_{39}H_{42}O_6$ requires 606.2981 amu, found 606.2975.

EI$^+$-MS: MI = $C_{39}H_{42}O_6$; *m/z*: 606.2 (6%) = MI$^+$, 560.14 (36%) = [MI − HOEt]$^+$, 397 (100%).

*1,2,4-Tris[2′-(4″-benzoic acid)ethyl]benzene (**16**)*

Triester **15** (200 mg, 0.33 mmol) and LiOH·H_2O (92.2 mg, 2.15 mmol) in 9:1 EtOH/H_2O (25 mL) was treated as described in the general saponification procedure, giving triacid **16** (161 mg, 94%). ^{1}H NMR (500.1 MHz, d_6-DMSO): δ 2.77–2.91 (m, 12H, methylene), 6.960 (AB, *J* 8.5, 1H), 6.967 (s, 1H), 7.07 (AB, *J* 8.5, 1H), 7.271 (AB, *J* 8.4, 2H), 7.296 (AB, *J* 8.4, 2H), 7.299 (AB, *J* 8.4, 2H), 7.82–7.87 (m, 6H), 12.83 (br s, CO_2H); ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 33.1, 33.5, 36.3, 36.7, 37.0, 126.2, 128.5, 128.6, 128.6, 128.6, 129.0, 129.3, 129.4, 136.4, 138.6, 138.7, 146.9, 146.9, 167.3, 167.3; IR (KBr): ν [cm^{-1}] 1688, 1610, 1422, 1315, 1289, 1178; HR-EI$^+$-MS: $C_{33}H_{30}O_6$ requires 522.2042 amu, found 522.2045; EI$^+$-MS: MI = $C_{33}H_{30}O_6$; *m/z*: 522.2 (9%) = MI$^+$, 504.2 (86%) = [MI − H_2O]$^+$, 387.1 (100%) = [MI − $CH_2(C_6H_4CO_2H)$]$^+$.

*1,2,4,5-Tetrakis[(1E)-2′-(ethyl 4″-benzoate)vinyl] benzene (**18**)*

1,2,4,5-Tetrabromobenzene **17** (255.8 mg, 0.66 mmol), ethyl-4-vinylbenzoate **9** (498.6 mg, 2.83 mmol), $Pd_2(dba)_3$·$CHCl_3$ (69.2 mg, 0.07 mmol), [(*t*-Bu)$_3$PH]BF_4 (75.4 mg, 0.26 mmol), Cy_2NMe (0.8 mL) in THF (8 mL) were treated under the aforementioned cross-coupling procedure. The product was purified by flash chromatography with CH_2Cl_2/MeOH (100:0–99:1) an the eluent. The crude material was recrystallized from CH_2Cl_2/EtOH to give triester **18** (541.2 mg, 82%) as a bright yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.41 (t, *J* 7.1, 12H, CH_3), 4.40 (q, *J* 7.1, 8H, CH_2), 7.13 (d, *J* 16, 4H, vinyl CH), 7.56 (d, *J* 16.1, 4H, vinyl CH), 7.60 (d, *J* 8.3, 8H, ArH), 7.83 (s, 2H, core ArH), 8.06 (d, *J* 8.3, 4H, ArH); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.3 (CH_3), 61.0 (CH_2), 125.2 (ArCH, core), 126.5 (ArCH), 128.1 (CH, vinyl), 129.7 (C_q), 130.1 (ArCH), 131.0 (CH, vinyl), 135.6 (C), 141.4 (C), 166.3 (C=O); IR (KBr): ν [cm^{-1}] 2981, 1710, 1637, 1617, 1604, 1282, 1180, 1107; HR-EI$^+$-MS: $C_{50}H_{46}O_8$ required 774.3193 amu, found 774.3506; EI$^+$-MS: MI = $C_{50}H_{46}O_8$; *m/z*: 774.4 (100%) = MI$^+$, 729.1 (16%) = [MI − OEt]$^+$, 611.1 (45%) = [MI − $CH_2(C_6H_4CO_2Et)$]$^+$.

UV-Vis (Solv): λ [nm] (log ε [$M^{-1}cm^{-1}$]) 258 [4.62], 312 [4.73], 346 [4.82]; fluorescence (CH_2Cl_2): excitation [nm] (emission [nm]) 258 [455, 518], 312 [362, 381, 452], 346 [381, 454]; (cyclohexane) 336 [442].

*1,2,4,5-Tetrakis[(2′-(ethyl 4″-benzoate)ethyl)benzene (**19**)*

Triester **18** (200.4 mg, 0.24 mmol) and Pd/C (10% w/w, *ca* 30 mg) in 1:1 EtOH/CH_2Cl_2 (40 mL) was treated as described. The crude product was recrystallized from CH_2Cl_2 and EtOH to give compound **19** (147.1 mg, 79%) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.38 (t, *J* 7.2, 12H), 2.82 (m, 16H), 4.36 (q, *J* 7.2, 8H), 6.81 (s, 2H), 7.18 (d, *J* 8.0 Hz, 8H, ArH), 8.00 (d, *J* 8.0 Hz, 8H, ArH); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.8, 34.0, 37.8, 61.0, 128.5, 128.6, 129.8, 130.6, 136.9, 147.2, 166.7; IR (KBr): ν [cm^{-1}] 2980, 2935, 1716, 1611, 1285, 1176, 1107, 1022; HR-EI$^+$-MS: $C_{50}H_{54}O_8$ requires 782.3819 amu, found 782.3809 EI$^+$-MS: MI = $C_{50}H_{54}O_8$; *m/z*: 782.1 (4%) = MI$^+$, 736.1 (27%) = [MI − HOEt]$^+$, 573 (100%).

*1,2,4,5-Tetrakis[2′-(4″-benzoic acid)ethyl]benzene (**20**)*

Triester **19** (101.4 mg, 0.13 mmol), LiOH·H_2O (51 mg, 1.22 mmol) in 9:1 EtOH/H_2O (25 mL) were treated as described in the general saponification procedure, to give tetraacid **20** (87.3 mg, 97%) as a white solid; ^{1}H NMR (500.1 MHz, d_6-DMSO): δ 2.77 (s, 16H, CH_2CH_2), 6.86 (s, 2H, H2), 7.26 (AB, *J* 8.3, 8H, H2′), 7.84 (AB, *J* 8.3, 8H, H3′); ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 33.1, 36.8, 128.5, 128.6, 129.4, 136.3, 147.0, 167.3; IR (KBr): ν [cm^{-1}] 2945, 2863, 1688, 1610, 1422, 1315, 1288, 1178; HR-EI$^+$-MS: $C_{42}H_{38}O_8$ requires 670.2567 amu, found 670.2562; EI$^+$-MS: MI = $C_{42}H_{38}O_8$; *m/z*: 517.0 (100%) = [MI − H_2O − $CH_2(C_6H_4CO_2H)$]$^+$, 499.0 (12%) = [MI − 2(H_2O) − $CH_2(C_6H_4CO_2H)$]$^+$, 381.0 (19.5%) = [MI − H_2O − $2CH_2(C_6H_4CO_2H)$]$^+$, 135.0 = [$CH_2(C_6H_4CO_2H)$]$^+$.

*1,4-Bis[(1E)-2′-(ethyl 4″-benzoate)vinyl]benzene (**28**)*

Method A: 1,4-Dibromobenzene **26** (101.5 mg, 0.43 mmol), ethyl 4-vinyl benzoate **7** (166 mg, 0.94 mmol), $Pd_2(dba)_3$·$CHCl_3$ (45.1 mg, 0.04 mmol), [(*t*-Bu)$_3$PH]BF_4 (52.2 mg, 0.18 mmol), Cy_2NMe (300 µL) in THF (5 mL) were heated at reflux overnight. The THF was removed under reduced pressure, the crude product purified using flash chromatography with CH_2Cl_2 as the eluent. Additional recrystallisation from CH_2Cl_2 and EtOH, gave **28** (152.2 mg, 84%).

Method B: 1,4-dichlorobenzene **27** (59.9 mg, 0.41 mmol), ethyl 4-vinyl benzoate **7** (160 mg, 0.91 mmol), $Pd_2(dba)_3$·$CHCl_3$ (42.1 mg, 0.04 mmol), [(*t*-Bu)$_3$PH]BF_4 (47.7 mg, 0.16 mmol),

Cy_2NMe (300 µL) in THF (5 mL) were heated at reflux for 3 days. The reaction mixture was concentated under reduced pressure, the crude product was purified by chromatography with CH_2Cl_2 as the eluent. Additional recrystallisation from CH_2Cl_2 and EtOH, gave **28** 49.8 mg (29%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.41 (t, *J* 7.1, 6H), 4.39 (q, *J* 7.1, 4H), 7.14 (AB, *J* 16.3, 2H, vinyl CH), 7.24 (AB, *J* 16.3, 2H, vinyl CH), 7.55 (s, 4H), 7.57 (d, *J* 8.1, 4H), 8.04 (d, *J* 8.1, 4H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.5 (CH_3), 61.1 (CH_2), 126.5 (CH), 127.4 (CH), 128.0 (CH), 129.5 (C), 130.2 (CH), 130.7 (CH), 136.9 (C), 141.8 (C), 166.5 (C=O); IR (KBr): ν [cm^{-1}] 2984, 2925, 1716 (C=O), 1708 (C=O), 1279, 1179, 1107; HR-EI$^+$-MS: $C_{28}H_{26}O_4$ requires 426.1831 amu, found 426.1824 UV-Vis (Solv): λ [nm] ($\log \varepsilon$ [$M^{-1}\,cm^{-1}$]) 254 [3.85], 372 [4.74]; fluorescence (CH_2Cl_2): excitation [nm] (emission [nm]) 254 [414, 437], 372 [414, 437]; (cyclohexane) 328 [393, 413].

*1,4-Bis[2′-(methyl 4″-benzoate)vinyl]benzene (**23**)*

(Methyl 4-carboxybenzyl)triphenylphosphonium bromide (**22**) (4.43 g, 9.02 mmol) was dissolved in MeOH (100 mL) and treated with NaOMe (45 mL 0.222 M in MeOH). The ensuing yellow solution was treated with terephthalaldehyde (512 mg, 3.82 mmol) in one portion and the resultant mixture was heated at reflux for 17 h. The resulting yellow precipitate formed was collected and washed with MeOH to give **23** (1.27 g, 84%). 40:60 mixture of the *E*/*E* and *E*/*Z* products. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 3.834 (s, CH_3, *EE*), 3.837 (s, CH_3, *EZ*), 3.85 (s, CH_3, *EZ*), 6.691 (AB, *J* 12.3, vinyl CH, *EE*), 6.726 (AB, *J* 12.3, vinyl CH, *EZ*), 6.735 (AB, *J* 12.3, vinyl CH, *EE*), 6.774 (AB, *J* 12.3, vinyl CH, *EZ*), 7.10 (s, core ArH, *EE*), 7.23 (AB, *J* 8.3, ArH, *EZ*), 7.326 (AB, *J* 16.4, vinyl CH, *EZ*), 7.345 (AB, *J* 8.4, ArH, *EE*), 7.389 (AB, *J* 16.4, vinyl CH, *EZ*), 7.393 (AB, *J* 8.4, ArH, *EZ*), 7.54 (AB, *J* 8.3, ArH, *EZ*), 7.72 (AB, *J* 8.5, ArH, *EZ*), 7.84 (AB, *J* 8.4, ArH, *EE*), 7.87 (AB, *J* 8.4, ArH, *EZ*), 7.85 (AB, *J* 8.5, ArH, *EZ*); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 52.1 (CH_3), 52.1 (CH_3), 126.6 (CH), 126.9 (CH), 127.6 (CH), 128.2 (C), 128.2 (C), 128.3 (C), 128.7 (CH), 128.8 (CH), 129.1 (CH), 129.2 (CH), 129.3 (CH), 129.4 (CH), 129.6 (CH), 130.7 (CH), 131.6 (CH), 135.6 (C), 136.0 (C), 136.1 (C), 141.8 (C), 141.8 (C), 142.0 (C); IR (KBr): ν [cm^{-1}] 3011, 2959, 1716, 1606, 1436, 1276, 1182, 1109; HR-EI-MS: $C_{26}H_{22}O_4$ requires 398.1518 amu, found 398.1515.

*1,4-Bis[2′-(methyl 4″-benzoate)ethyl]benzene (**24**)*

Diester **23** (1.27 g, 3.19 mmol) and Pd/C (10% w/w *ca* 100 mg) in 1:1 MeOH/CH_2Cl_2 (30 mL) was treated as described in the general procedure section. The crude product was recrystallized from CH_2Cl_2 and MeOH to give (1.20 g, 93%) as a white solid; ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.93 (AA′BB′, 8H, CH_2CH_2), 3.91 (s, 6H, OCH_3), 7.05 (s, 4H, H2/H3), 7.21 (d, *J* 7.6, 4H, H2′), 7.95 (d, *J* 7.6, 4H, H3′); ^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] 37.2, 38.0, 52.1, 128.1, 128.6, 128.7, 129.8, 139.0, 147.3, 167.3; IR (KBr): ν [cm^{-1}] 2944, 2923, 1726, 1609, 1431, 1280, 1176, 1105. HR-EI$^+$-MS: $C_{26}H_{26}O_4$ requires 402.1831 amu, found 402.1834; EI$^+$-MS: MI = $C_{26}H_{26}O_4$; *m*/*z*: 402.2 (8%) = MI$^+$, 370.1 (33.2%) = [MI − MeOH]$^+$, 253.1 (100%) = [MI − $CH_2C_6H_4CO_2Me$]$^+$, 149.1 = $[CH_2C_6H_4CO_2Me]^+$.

*1,4-Bis[2′-(4″-benzoic acid)ethyl]benzene (**25**)*

Method 1: Diester **24** (308.6 mg, 0.77 mmol), LiOH·H_2O (125 mg, 3.0 mmol) in MeOH/H_2O (9:1, 20 mL) were treated as described in the general saponification procedure, to provide diacid **25** 280 mg (97%).

Method 2: Diacid **3** (107.2 mg, 0.25 mmol) and Pd/C (10% w/w *ca* 10 mg) in 1:1 EtOH/CH_2Cl_2 (10 mL) was treated as described. The crude mixture containing **29** (103 mg, 96%) was suspended in 9:1 EtOH/H_2O (10 mL) and LiOH·H_2O (26.3 mg, 0.63 mmol) added and treated under the general saponification procedure described earlier to afford diacid **3** (73.2 mg, 82%). ^{1}H NMR (500.1 MHz, d_6-DMSO): δ 2.88 (AA′BB′, 8H, CH_2CH_2), 7.11 (s, 4H, H2/H3), 7.32 (d, *J* 8.2, 6H, ArH), 7.85 (d, *J* 8.2, 6H, ArH); ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 36.2, 37.0, 128.3, 128.6, 129.3, 138.7, 146.8, 167.3; IR (KBr): ν [cm^{-1}] 2944, 2923, 1685 (C=O), 1610, 1425, 1318, 1292, 1180, 537.

*1,3-Bis[2′-(methyl 4″-benzoate)vinyl]benzene (**4**)*

Isophthaldehyde **30** (460 mg, 3.43 mmol), **22** (4.4 g, 8.95 mmol), NaOMe (20 mL, 1.0 M) in MeOH (100 mL) were treated under analogous conditions to those described for the preparation of alkene **23**. The white precipitate was filtered, washed with MeOH, and dried to give **4** (0.85 g, 62%). The product was a 44:56 mixture of the *E*/*E* and *E*/*Z* products. ^{1}H NMR (600.1 MHz, $CDCl_3$): δ 3.82 (s, CH_3, ct), 3.83 (s, CH_3, *E*/*E*), 3.85 (s, CH_3, *E*/*Z*), 6.64 (AB, *J* 12.4, *trans* vinyl CH, *E*/*E*), 6.67 (AB, *J* 12.4, *trans* vinyl CH, *E*/*E*), 6.76 (AB, *J* 12.3, *trans* vinyl CH, *E*/*Z*), 6.81 (AB, *J* 12.3, *trans* vinyl CH, *E*/*Z*), 7.05 (dd, J_1 7.6, J_2 1.4, H4, ee), 7.08 (s, H2, ee), 7.10 (d, *J* 7.7, H4/H6, *E*/*Z*), 7.13 (AB, *J* 16.5, *cis* vinyl CH, *E*/*Z*), 7.17 (t, *J* 7.6, H5, *E*/*E*), 7.25 (AB, *J* 8.2, H2′, *E*/*Z*), 7.27 (t, *J* 7.7, H5, *E*/*Z*), 7.33 (AB, *J* 16.5, *cis* vinyl CH, *E*/*Z*), 7.36 (AB, *J* 8.2, ArH, *E*/*Z*), 7.46 (s, H2, *E*/*Z*), 7.50 (d, *J* 7.7, H4/H6, *E*/*Z*), 7.66 (AB, *J* 8.3, ArH, *E*/*Z*), 7.76 (AB, *J* 8.4, H3′, *E*/*E*), 7.84 (AB, *J* 8.3, ArH, *E*/*Z*), 7.92 (AB, *J* 8.4, ArH, *E*/*Z*); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 52.1 (CH_3), 52.1 (CH_3), 126.2 (CH), 126.6 (CH), 127.0 (CH), 127.6 (CH), 127.9 (CH), 128.1 (C), 128.2 (C), 128.3 (C), 128.3 (CH), 128.3 (CH), 128.7 (CH), 128.9 (CH), 128.9 (CH), 129.2 (CH), 129.3 (CH), 129.3 (CH), 129.5 (CH), 129.6 (CH), 130.9 (CH), 131.7 (CH), 131.8 (CH), 136.6 (C), 136.8 (C), 136.8 (C), 141.6 (C), 141.9 (C), 165.9 (C), 165.9 (C), 166.0 (C); IR (KBr): ν [cm^{-1}] 1720, 1606, 1435, 1280, 1179, 1109; HR-EI$^+$-MS: $C_{26}H_{22}O_4$ requires 398.1518 amu, found 398.1518.

*1,3-Bis[2′-(methyl 4″-benzoate)ethyl]benzene (**31**)*

The *E*/*Z* isomeric mixture **4** (499.3 mg, 1.25 mmol) and Pd/C (10% w/w, *ca* ~50 mg) in MeOH/CH_2Cl_2 (40 mL, 1:1) was treated as described previously. The crude product was recrystallized from CH_2Cl_2/MeOH to give ester **31** (489.7 mg, 98%) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.8–2.96 (AA′BB′, 8H, CH_2CH_2), 3.90 (s, 6H, Me), 6.91 (s, 1H, H2), 6.99 (dd, 2H, *J* 7.6 and 1.4, 2H, H4/H6), 7.16–7.25 (cm, 5H, ArH), 7.96 (d, *J* 8.2, 4H, H3′); ^{13}C NMR (150 MHz, $CDCl_3$): δ 37.5, 38.0, 52.1, 126.3, 128.0, 128.5, 128.7, 128.8, 129.8, 141.3, 147.3, 167.2; IR (KBr): ν [cm^{-1}] 1715, 1607 (m), 1438, 1279, 1109; HR-EI$^+$-MS: $C_{26}H_{26}O_4$ requires 402.1831 amu, found 402.1840.

*1,3-Bis[2′-(4″-benzoic acid)vinyl]benzene (**32**)*

Ester **25** (202.6 mg, 0.50 mmol), LiOH·H_2O (92.2 mg, 2.20 mmol) and 9:1 MeOH/H_2O (30 mL) were treated as described in the general saponfication procedure, giving (175.8 mg, 94%) as a white solid. ^{1}H NMR (500.1 MHz, d_6-DMSO): δ 2.87 (AA′BB′, 8H, CH_2CH_2), 6.99–7.05 (m, 3H, ArH), 7.15 (t, *J* 7.4, 1H, H5), 7.31 (AB, *J* 8.4, 4H, H2′), 7.84 (AB, *J* 8.4, 4H, H3′), 12.8 (br s, 2H, CO_2H); ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 36.5, 37.0, 126.0, 128.1, 128.4, 128.6, 128.6,

129.3, 141.0, 146.9, 167.3; HR-EI$^+$-MS: $C_{24}H_{22}O_4$ requires 374.1518 amu, found 374.1523; EI$^+$-MS: MI = $C_{24}H_{22}O_4$; *m*/*z*: [%] = MI$^+$, 239.0 (100%) = [MI − $CH_2(C_6H_4CO_2H)$]$^+$, 193.0 (34%) = [MI − $CH_2(C_6H_4CO_2H)$ − CO_2H − H^+]$^+$.

Acknowledgements

The authors would like to thank the National Health and Medical Research Council. R.A.B. is the recipient of a UWA postgraduate award. Dr Ben Corry, Dr Lindsay Byrne and Dr Anthony Reeder are gratefully acknowledged for their assistance with fluorescence spectroscopy, NMR spectrometry and mass spectrometry respectively.

References

[1] (a) A. Rescifina, M. A. Chiacchio, A. Corsaro, E. De Clercq, D. Iannazzo, A. Mastino, A. Piperno, G. Romeo, R. Romeo, V. Valveri, *J. Med. Chem.* **2006**, *49*, 709. doi:10.1021/JM050772B
(b) N. J. Wheate, C. R. Brodie, J. G. Collins, S. Kemp, J. R. Aldrich-Wright, *Mini Rev. Med. Chem.* **2007**, *7*, 627. doi:10.2174/138955707780859413
(c) Y. Pommier, *Chem. Rev.* **2009**, *109*, 2894. doi:10.1021/CR900097C
(d) E. White, *Curr. Pharm. Des.* **2006**, *12*, 3645. doi:10.2174/138161206778522083

[2] (a) W. Shi, R. S. Coleman, T. L. Lowary, *Org. Biomol. Chem.* **2009**, *7*, 3709. doi:10.1039/B909153J
(b) A. K. Ray, U. Diederichsen, *Eur. J. Org. Chem.* **2009**, 4801.

[3] I. Puskas, M. Schmitt, *US patent 4,537,985*.

[4] J. Gross, G. Harder, A. Siepen, J. Harren, F. Vögtle, H. Stephan, K. Gloe, B. Ahlers, K. Cammann, K. Rissanen, *Chemistry* **1996**, *2*, 1585. doi:10.1002/CHEM.19960021218

[5] M. Uda, A. Momotake, T. Arai, *Org. Biomol. Chem.* **2003**, *1*, 1635. doi:10.1039/B303412G

[6] S. Nakatsuji, K. Matsuda, Y. Uesugi, K. Makashima, S. Akiyama, G. Katzer, W. Fabian, *J. Chem. Soc., Perkin Trans. 2* **1991**, 861. doi:10.1039/P29910000861

[7] Z. I. Niazimbetova, A. Menon, M. E. Galvin, D. Evans, *J. Electroanal. Chem.* **2002**, *529*, 43. doi:10.1016/S0022-0728(02)00940-3

[8] A. Sharma, N. Sharma, R. Kumar, A. Shard, A. K. Sinha, *Chem. Commun.* **2010**, *46*, 3283. doi:10.1039/C001980A

[9] I. P. Beletskaya, A. V. Cherpakov, *Chem. Rev.* **2000**, *100*, 3009. doi:10.1021/CR9903048

[10] W. Tao, S. Nesbitt, R. F. Heck, *J. Org. Chem.* **1990**, *55*, 63. doi:10.1021/JO00288A013

[11] (a) D. A. Alonso, C. Nájera, C. M. Pacheco, *Adv. Synth. Catal.* **2002**, *344*, 172. doi:10.1002/1615-4169(200202)344:2<172::AID-ADSC172>3.0.CO;2-9
(b) S. D. Bull, S. G. Davies, A. D. Smith, *J. Chem. Soc., Perkin Trans. 1* **2001**, 2931. doi:10.1039/B107440G
(c) F. Berthiol, I. Kondolff, H. Doucet, M. Santelli, *J. Organomet. Chem.* **2004**, *689*, 2786. doi:10.1016/J.JORGANCHEM.2004.06.007

[12] (a) A. Lansky, O. Reiser, A. De Meijere, *Synlett* **1990**, 405. doi:10.1055/S-1990-21107
(b) B. Stulgies, P. Prinz, J. Magull, K. Rauch, K. Meindl, S. Rühl, A. de Meijere, *Chemistry* **2005**, *11*, 308. doi:10.1002/CHEM.200400723

[13] J. N. G. Pillow, P. L. Burn, I. D. W. Samual, M. Halim, *Synth. Met.* **1999**, *102*, 1468. doi:10.1016/S0379-6779(98)00541-4

[14] A. J. Amoroso, J. P. Maher, J. A. McCleverty, M. D. Ward, *J. Chem. Soc. Chem. Commun.* **1994**, 1273. doi:10.1039/C39940001273

[15] In the reported transformation the individual Heck cross coupling reactions are assumed to either occur simultaneously or one after each other. This reaction cannot be classified as a domino reaction defined as 'a transformation of two or more bond forming reactions under identical reaction conditions, in which the latter transformations take place at the functionalities obtained in the former bond forming reactions.' L. F. Tietze, G. Brasche, K. M. Gericke, *Domino Reactions in Organic Synthesis* **2006** (Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim). The transformation in this case could be classified as a tandem reaction because the reaction sites are different from one another and it could be assumed that the products following the first Heck cross coupling reaction are more activated that the first. The reaction could also be classified as a multiple Heck reaction as in the previously reported cases. By Braese, Stefan; De Meijere, Armin, *Handbook of Organopalladium Chemistry for Organic Synthesis* **2002**, 1, 1179–1208 (John Wiley & Sons, Inc).

[16] T. Jeffery, *Tetrahedron Lett.* **1985**, *26*, 2667. doi:10.1016/S0040-4039(00)98131-0

[17] (a) W. A. Herrmann, C. B. Broßmer, K. Öfele, C.-P. Reisinger, T. Priermeier, M. Beller, H. Fisher, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1844. doi:10.1002/ANIE.199518441
(b) L. F. Tietze, S. G. Stewart, M. E. Polomska, A. Modi, A. Zeeck, *Chemistry* **2004**, *10*, 5233. doi:10.1002/CHEM.200400342

[18] M. Castella, F. Calahorra, D. Sainz, D. Velasco, *Org. Lett.* **2001**, *3*, 541. doi:10.1021/OL000370S

[19] E. Díez-Barra, J. C. García-Martínez, S. Merino, R. del Rey, J. Rodríguez-López, P. Sánchez-Verdú, J. Tejeda, *J. Org. Chem.* **2001**, *66*, 5664. doi:10.1021/JO015764R

[20] J. Nierle, D. Kuck, *Synlett* **2006**, *18*, 2914.

[21] A. Peruga, J. A. Matta, D. Sainz, E. Peris, *J. Organomet. Chem.* **2001**, *637–639*, 191. doi:10.1016/S0022-328X(01)00903-2

[22] (a) A. F. Littke, G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 6989. doi:10.1021/JA010988C
(b) M. R. Netherton, G. C. Fu, *Org. Lett.* **2001**, *3*, 4295. doi:10.1021/OL016971G
(c) S. G. Stewart, D. Spagnolo, M. E. Polomska, M. Sin, M. Karimi, L. J. Abraham, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5819. doi:10.1016/J.BMCL.2007.08.042

[23] T. W. Campbell, R. N. McDonald, *J. Org. Chem.* **1959**, *24*, 1246. doi:10.1021/JO01091A022

[24] A. Mylona, J. Nikokavouras, I. M. Takakis, *J. Org. Chem.* **1988**, *53*, 3838. doi:10.1021/JO00251A032

[25] T. Schrievers, U. H. Brinker, *Synthesis* **1988**, 330. doi:10.1055/S-1988-27561

[26] (a) R. N. Beale, E. M. F. Roe, *J. Chem. Soc.* **1952**, 2755.
(b) J. C. Roberts, J. A. Pincock, *J. Org. Chem.* **2006**, *71*, 1480. doi:10.1021/JO052123D
(c) Y. V. Il'ichev, W. Kühnle, K. A. Zachariasse, *Chem. Phys.* **1996**, *211*, 441. doi:10.1016/0301-0104(96)00200-5

[27] R. Benshafrut, M. Rabinovitz, Z. Dee-Noor-Barzily, A. J. de Meijere, *Phys. Org. Chem* **1999**, *12*, 333. doi:10.1002/(SICI)1099-1395(199904)12:4<333::AID-POC118>3.0.CO;2-J

[28] (a) H. Meier, R. Zertani, K. Noller, D. Oelkrug, G. Krabichler, *Chem. Ber.* **1986**, *119*, 1716. doi:10.1002/CBER.19861190523
(b) A. E. Siegrist, P. Liechti, H. R. Meyer, K. Weber, *Helv. Chim. Acta* **1969**, *52*, 2521. doi:10.1002/HLCA.19690520836
(c) J. L. Segura, R. Gmez, N. Martn, D. M. Guldi, *Org. Lett.* **2001**, *3*, 2645. doi:10.1021/OL016083L

[29] (a) D. H. Waldeck, *Chem. Rev.* **1991**, *91*, 415. doi:10.1021/CR00003A007
(b) E. Gilabert, R. Lapouyade, C. Rullière, *Chem. Phys. Lett.* **1988**, *145*, 262. doi:10.1016/0009-2614(88)80004-6

[30] A. A. Kubicki, *Chem. Phys. Lett.* **2003**, *373*, 471.

[31] M. Frigerio, M. Santagostino, S. Sputore, *J. Org. Chem.* **1999**, *64*, 4537. doi:10.1021/JO9824596

[32] J. Gross, G. Harder, A. Siepen, J. Harren, F. Vögtle, H. Stephan, K. Gloe, B. Ahlers, K. Cammann, K. Rissanen, *Chemistry* **1996**, *2*, 1585. doi:10.1002/CHEM.19960021218

[33] T. Ukai, H. Kawazazura, Y. Ishui, J. J. Bonnet, J. A. Ibers, *J. Organomet. Chem.* **1974**, *65*, 253. doi:10.1016/S0022-328X(00)91277-4

[34] D. R. Coulson, *Inorg. Synth.* **1972**, *13*, 121. doi:10.1002/9780470132449.CH23

[35] K. B. Sharpless, R. Oi, *Org. Synth.* **1996**, *73*, 1.

[36] (a) R. Broos, D. Tavernier, M. J. Antunis, *Chem. Ed.* **1978**, *55*, 813. doi:10.1021/ED055P813
(b) D. L. Tullen, B. A. J. Hess, *J. Chem. Ed.* **1971**, *48*, 476. doi:10.1021/ED048P476
(c) J. H. Ackerman, A. R. Surrey, *Org. Synth.* **1967**, *47*, 76.