Organic & Biomolecular Chemistry

This article is part of the

OBC 10th anniversary

themed issue

All articles in this issue will be gathered together online at

www.rsc.org/OBC10

Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 5799

www.rsc.org/obc

COMMUNICATION

Sym-$(CH_2X)_5$-corannulenes: molecular pentapods displaying functional group and bioconjugate appendages†

Martin Mattarella and Jay S. Siegel*

Received 8th March 2012, Accepted 17th April 2012
DOI: 10.1039/c2ob25503k

Pentapodal ω-functional derivatives of corannulene have been synthesized from *sym*-pentachlorocorannulene by iron-catalyzed aryl–alkyl cross coupling reactions. Click chemistry gives access to pentapods with bioconjugate appendages.

With the advent of corannulene in kilogram scale,[1] and a robust procedure for converting corannulene into *sym*-pentachlorocorannulene,[2,3] comes the motivation to create an array of 5-fold symmetric pentasubstituted corannulenes that express a broad spectrum of functional groups suitable for incorporation into polymers,[4] materials,[5] bioconjugates[6] and supramolecular architectures.[7] For example, the synthesis of bioconjugated molecular pentapods based on corannulene would open the door to the study of high-order multivalent ligands,[8] templates for protein folding mimics or aromatic/nucleic acid conjugate assemblies. To achieve the general implementation of these molecular pentapods in molecular design strategies, access to derivatives bearing a broad spectrum functional groups is desired and therefore an efficient chemical synthesis is needed.

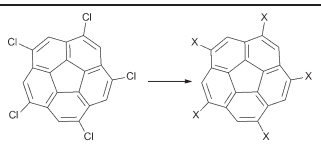
Synthesis

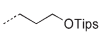
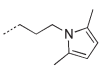
Sym-Pentachlorocorannulene[9] (**1**) provides a powerful platform from which to start building derivatives. The synthesis of several *sym*-pentaaryl, *sym*-pentaalkyl and *sym*-pentaalkynyl corannulenes have been already reported,[3] and functional groups have been introduced by palladium-catalyzed aryl–aryl coupling using functionalized aryl boronic acids.[10] For some applications, flexible alkyl chains bearing functional groups are desired. This need is addressed in the present report.

The iron-catalyzed alkyl–aryl cross coupling reaction[11] proved to be broadly applicable for the coupling of $MgBrCH_2R$ five times to **1**. It afforded the *sym*-pentakis(CH_2R) products in good yields and in short reaction times (Table 1).

Iron-catalyzed cross-couplings normally need an available β-hydrogen in the alkyl chain to undergo to β-hydride elimination and thereby activate the catalyst.[12] For this reason, MeMgBr normally reacts poorly (save for highly activated substrates such as acid chlorides, enol triflates and very electron-deficient heteroarenes). Despite these concerns, entry 1 shows that the coupling reaction between the *sym*-pentachlorocorannulene and MeMgBr works just as well as any other, implying a higher reactivity of **1** compared to normal arylchlorides.

Table 1 Cross-coupling of **1** with various alkylmagnesium bromides



Entry	X		Yield (%)
1	---Me	**2**	66
2	---Et	**3**	58
3		**4**	61
4		**5**	35
5		**6**	61
6		**7**	56
7		**8**	69
8		**9**	61
9		**10**	62

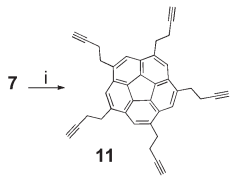
Reaction conditions: RMgBr (11 equiv.), $Fe(acac)_3$ (0.25 equiv.); THF–NMP 10 : 1; r.t.; 2.5 h (18 h for compound **5**).

The coupling reactions were performed using 11 mol. equiv. (*i.e.* 2.2 equiv. per coupling site) of the alkyl magnesium bromide, iron(III) acetyl acetonate (0.25 mol% *i.e.* 0.05 mol% per coupling site) in THF–NMP (10 to 1) at r.t. for 2.5 h, except for compound **5**, which was allowed to react for 18 h.

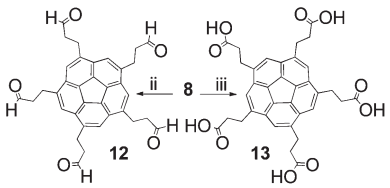
The reported conditions allow the coupling of several alkyl and functionalized alkyl chains on **1**:† simple alkyl chains[13] (entries 1 and 2) chiral alkyl chains (entry 3), bulky moieties (entry 4), terminal alkenes (entry 5), protected terminal alkynes

Organic Chemistry Institute, University of Zurich, Winterthurerstrasse 190, 8057 Zurich, Switzerland. E-mail: jss@oci.uzh.ch; Fax: +41 44 635 6888; Tel: +41 44 635 4281

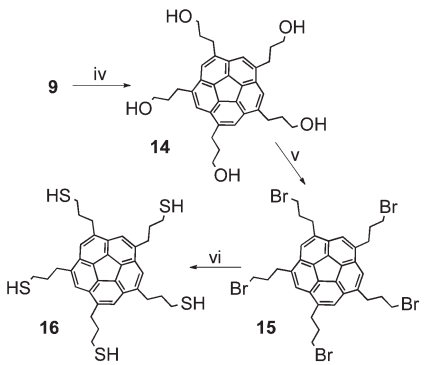
†Electronic supplementary information (ESI) available. See DOI: 10.1039/c2ob25503k



Scheme 1 Reaction conditions: (i) NaOH, MeOH–THF–H_2O, r.t., 24 h, (84%).



Scheme 2 Reaction conditions: (ii) AcOH–HCl 1 M, THF, reflux, 2.5 h, (99%); (iii) Oxone®, THF–H_2O, r.t., 2 d, (89%).



Scheme 3 Reaction conditions: (iv) TFA, acetone–H_2O–THF, reflux, 2 d, (91%); (v) NBS, PPh_3, DMF, r.t., 1 h (77%); (vi) (a) thiourea, EtOH–THF, reflux, 2 h; (b) NaOH, H_2O, reflux, 2 h (96%).

(entry 6), alkyl acetal (entry 7), protected alcohol (entry 8) and heteroaryl moieties (entry 9). The cross-coupling reaction was scaled-up to 1 g of **1** without change in yield.

Additional chemical functionality can be introduced by further elaboration of the initial coupling products. Specifically the chemistry of **7**, **8** and **9** are exemplified here.

Treating compound **7** with a solution of NaOH 10% in water in a solvent mixture methanol and THF in a 1 : 1 : 1 ratio produces the deprotected terminal alkyne **11** in good yield (Scheme 1).

Starting from compound **8** the carbonyl **12** and carboxyl **13** derivatives were obtained by hydrolysis and oxidative deprotection,[14] respectively (Scheme 2). Both reactions deliver clean products in high yields.

The deprotection of compound **9** (Scheme 3) was performed using TFA in mixture of acetone, water and THF; these conditions are necessary because common procedures did not afford the fully deprotected product **14** in our hands[15]. Bromination of **14** with NBS and PPh_3 in DMF yielded **15**. By treating compound **15** with thiourea and sequential basic hydrolysis, it is possible to obtain the corresponding thiol (**16**).

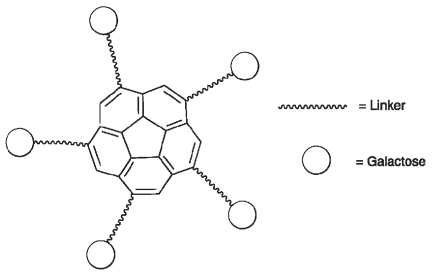
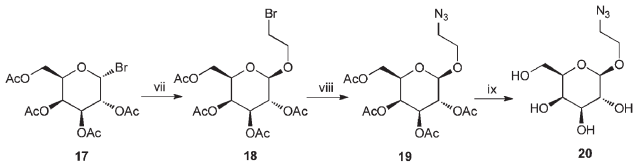


Fig. 1 Target pentakis-bioconjugate of galactose.



Scheme 4 Reaction conditions: (vii) bromo-ethanol, Ag_2CO_3, DCM, r.t., 2d (36%) (viii) NaN_3, DMF, 60 °C, 3h (97%) (ix) MeONa, MeOH, r.t., 19 h (99%).

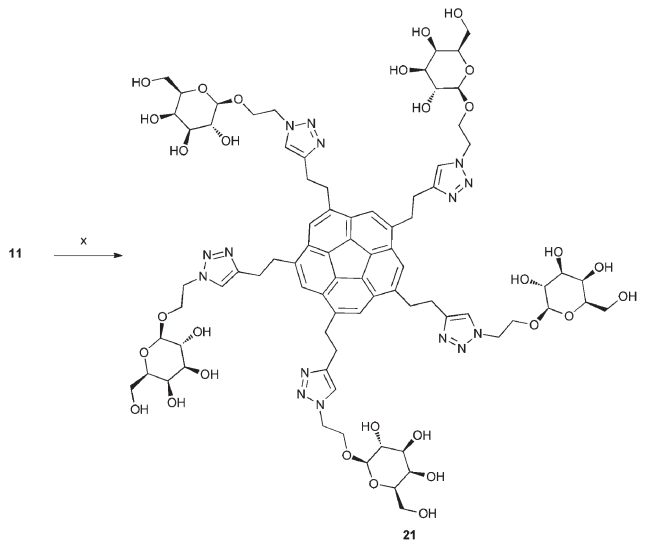
Having access to such a broad array of terminal functional groups, makes these corannulene derivatives especially suitable for developing tectons for supramolecular chemistry, building blocks for dendrimer chemistry, cores for multivalent bioconjugate chemistry or active elements for liquid crystal and optoelectronic materials. Virtually any variant of modern day "click" chemistry can be used to couple molecular modules to these pentapods.[16]

To illustrate this point, the copper catalyzed azide–alkyne cycloaddition reaction (CuAAC) was chosen to prepare a target pentakis-bioconjugate of galactose (Fig. 1), which represents a leit-motif for potential multivalent binders to biological complexes like Cholera Toxins.[17] CuAAC is widely used for the synthesis of bioconjugated system because of the high yields and product purities that this class of reaction shows. Furthermore, due to the large number azides known or commercial available, this procedure should be representative for the preparation of a wide window of corannulene architectures.

In the present case, the synthesis of the azidoalkyl galactoside **20** was a prerequisite to trying the coupling. The preparation of **20** starts from 2,3,4,6-tetra-*O*-acetyl-*a*-D-galactopyranosyl bromide (**17**), which undergoes a Koenings–Knorr displacement with 2-bromoethanol affording compound **18**.[18] Azide **19** can be prepared in excellent yield by treatment of **18** with sodium azide in DMF, followed by removal of the acetyl groups with sodium methoxide to afford the sugar azide **20** (Scheme 4).[19]

Several reaction conditions for the CuAAC on **11** were tried: copper source, temperature, solvent and heating system were varied. Performing the reaction using copper nanoparticles[20] in DMF at 60 °C by microwave irradiation reasonable yield, purity and time of reaction were obtained.

Pentapod **21** was synthesized using 7.5 mol. equiv. (*i.e.* 1.5 equiv. per reacting site) of the azide **20**, copper nanoparticles (7.5 mol. equiv.) in DMF at 60 °C for 2 h (Scheme 5) in good yield (59%) and purity.



Scheme 5 Reaction conditions: (x) **20**, Cu nonoparticles, DMF, 60 °C (μ wave), 2 h (59%).

Table 2 UV-vis absorption and emission data for **2–16**[a]

Compound	Adsorbtion λ_{max}	Emission λ_{max}
Corannulene[b]	251, 286	421
2[b]	260, 295	431
3[c]	263, 297	431
4	261, 299	438
5	263, 301	438
6	261, 298	436
7	262, 299	438
8	263, 298	433
9	263, 298	439
10	262, 299	519
11	262, 299	435
12	261, 298	438
13	263, 298	433
14	261, 298	435
15	261, 299	438
16	263, 301	438
21	264, 300	435

[a] Absorption–emission measurements in THF (DMSO for **16** and **21**), wavelengths in nm. [b] See ref. 9. [c] See ref. 3.

Properties

All the derivatives, **2–16**, and **21** show a small red shift of the π–π* absorption band in the UV-vis spectra comparing to the corannulene (Table 2). The red shift follows that expected by Woodward–Fieser rules for UV absorption in substituted aromatic systems.[21] Otherwise their absorption profile is relatively constant within the error of band shape and position.

The data collected show that the derivatives bearing functionalized alkyl chains (**6–16**) have similar absorption behaviour to those with unfunctionalized alkyl chains (**2–5**). Also the emission spectra show no serious differences in the properties of functionalized and unfunctionalized alkyl-chain derivatives; one exception is compound **10**, which shows an higher Stokes' shift, probably due to the presence of the electron rich pyrrole ring.

Sym-Pentasubstituted corannulenes like **2** undergo rapid a bowl-flip mechanism that interconverts equal proportions of enantiomeric conformations. When the arms bear chiral substituents, as in the case of **4** and **21**, the interconversion is between diasteromers and the symmetry required equality of proportions is broken. One might expect to detect this in a deviation from van't Hoff's additivity rule for optical rotation;[22] *i.e.* the specific rotation for **4** or **21** should deviate from 5 times the specific rotation for a reference "arm".

As such the specific rotation of compound **4** and **21** were measured: **4** has a $[\alpha]_D^{25}$ value of +68.9° which is 6.5 times the specific rotation value of (*S*)-2-methyl-butylpheny ($[\alpha]_D^{25}$ = +10.5°);[23] **21** has a $[\alpha]_D^{25}$ value of +349.3° which is 4.5 times the specific rotation value of β-D-galactose ($[\alpha]_D^{25}$ = +78.0°).[24] These results indicate that the contribution to the optical activity from the bias is small. This result could come about because the rotary power of an enantiomer of a compound like **2** is small or because the energetic bias for one diasteromeric conformation of **4** or **21** is small. Circular dichroism spectra of **4** and **21** were also measured (see ESI†).

In conclusion, a powerful and robust procedure for the synthesis of *sym*-pentaalkyl corannulenes has been described. Performing coupling reactions with **1** and functionalized alkyl chains resulted in the synthesis of various functionalized corannulene derivatives in hundreds of milligrams scale. Compounds **2–15** show solubility in common organic solvents (THF, DCM, MeOH); as hypothesized, the introduction of an alkyl chain between the functional group and the corannulene solves the solubility issues. The only exception is compound **16** which displays appreciable solubility only in DMSO.

The possibility to synthesize hundreds of milligrams of a broad class of soluble corannulene derivatives with a broad spectrum of functional groups facilitates the synthesis of *sym*-pentapodal corannulenes conjugated to active molecular modules. This core–module approach should further stimulate create molecular design and engineering of materials based on these components.[25]

Representative experimental procedures†

sym-Penta-(1-(trimethylsilyl)-1-butyn-4-yl)-corannulene (7)

1-Bromo-4-trimethylsilyl-3-butyne (2.4 g, 11.7 mmol) was added to a suspension of Mg (575 mg, 19.7 mmol) and a crystal of iodine in THF (40 mL) at 0 °C; the mixture was stirred at room temperature for 3.5 h. The Grignard solution was added to a suspension of *sym*-pentachlorocorannulene (465 mg, 1.1 mmol) and $Fe(acac)_3$ (97 mg, 0.27 mmol) in THF (10 mL) and NMP (1.0 mL) at 0 °C. The reaction was stirred at room temperature for 2.5 hours. The solution was then cooled to 0 °C and quenched by slowly addition of diethyl ether followed by a 1 M solution of HCl in water. The organic layer was separated and the aqueous phase was extracted with ethyl acetate. The collected organic phases were dried over Na_sSO_4 and evaporated to yield the crude product. The product was purified by column chromatography on silica gel eluted with a mixture hexane–diethyl ether 98 : 2. The solvent was evaporated to yield a yellow solid (537 mg, 61%). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.64 (s, 5H), 3.33 (t, ^3J = 7.5 Hz, 10H), 2.75 (t, ^3J = 7.5 Hz, 10H),

1.53 (s, 45H). ^{13}C-NMR (125 MHz, $CDCl_3$): d 139.65, 135.22, 129.64, 123.26, 106.53, 86.02, 32.86, 23.10, 0.35. UV (THF) λ_{max}, nm: 262, 299. HRMS (APCI) *m*/*z*: found 871.4396 (M + H); calc ($C_{55}H_{71}Si_5$) 871.4397.

sym-Penta-(1-butyn-4-yl)-corannulene (11)

Aqueous 10% NaOH was added to a solution of **7** (156 mg, 0.18 mmol) in MeOH (1.5 ml); THF was added to clarify the solution. The reaction was stirred at room temperature for 24 h. The solution was then cooled to 0 °C, acidified with a 1 M solution of HCl in water and extracted with diethyl ether. The collected organic phases were dried over Na_2SO_4 and evaporated to yield the crude product, which was purified by column chromatography on silica gel eluted with a 6 : 4 mixture of hexane–dichloromethane. The solvent was evaporated to yield a pale yellow solid (77 mg, 84%). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.68 (s, 5H), 3.37 (t, ^3J = 7.5 Hz, 10H), 2.73 (dt, ^3J = 7.5 Hz, ^4J = 2.5 Hz, 10H), 2.05 (t, ^4J = 2.5 Hz, 5H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 139.35, 135.26, 129.66, 123.32, 83.88, 69.80, 32.54, 21.48. UV (THF) λ_{max}, nm: 262, 299. HRMS (ESI) *m*/*z*: found 511.2420 (M + 23); calcd ($C_{40}H_{31}$) 511.2420.

sym-Penta-(2-(1,2,3-triazole-4-ethyl)-ethyl-β-D-galactopyranoside)-corannulene (21)

A mixture of **20** (42.0 mg, 0.17 mmol), **11** (11.6 mg, 23 μmol) and copper nanoparticles (10.8 mg, 0.17 mmol) in DMF (1 mL) in a microwave vessel was heated at 60 °C in a microwave reactor (200 W) for 2 h. The mixture was then filtered over Celite, the solvent was evaporated and MeOH was added to the crude product. The solid was then filtrated and washed with cold MeOH to yield a white solid (24 mg, 59%) ^{1}H-NMR (500 MHz, d^6-DMSO): δ 8.19 (s, 5H), 7.81 (s, 5H), 5.01 (d, ^3J = 4.5 Hz, 5H), 4.77 (d, ^3J = 5.5 Hz, 5H), 4.62–4.51 (m, 15H), 4.17 (d, ^3J = 7.5 Hz, 5H), 4.08 (m, 5H), 3.86 (m, 5H), 3.62 (t, ^3J = 4.0 Hz, 5H), 3.51 (m, 20H), 3.16 (t br, ^3J = 7.0 Hz, 10H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 146.14, 140.6, 134.02, 129.48, 123.08, 103.45, 75.36, 73.30, 70.41, 68.16, 67.26, 60.48, 49.50, 32.43, 27.99. UV (DMSO) λ_{max}, nm: 264, 300. $[\alpha]_D^{25}$ = +349.3 (*c* = 0.15 in H_2O). HRMS (ESI) *m*/*z*: found 878.8647 (M + 2H); calc ($C_{80}H_{107}N_{15}O_{30}$) 878.8649.

Notes and references

1 A. M. Butterfield, B. Gilomen and J. S. Siegel, *Org. Process Res. Dev.*, 2012, **16**, DOI: 10.1021/op200387s.
2 *Sym*- here means 1,3,5,7,9-pentasubstitution.
3 G. H. Grube, E. J. Elliott, R. J. Steffens, C. S. Jones, K. K. Baldridge and J. S. Siegel, *Org. Lett.*, 2003, **5**, 713–716.
4 M. Stuparu, *Chimia*, 2011, **65**, 799–801.
5 D. Miyajima, K. Tashiro, F. Araoka, H. Takezoe, J. Kim, K. Kato, M. Takata and T. Aida, *J. Am. Chem. Soc.*, 2009, **131**, 44–45.
6 L. Baldini, A. Casnati, F. Sansone and R. Ungaro, *Chem. Soc. Rev.*, 2007, **36**, 254–266.
7 (*a*) Y. T. Wu and J. S. Siegel, *Chem. Rev.*, 2006, **106**, 4843–4867; (*b*) A. J. Olson, Y. H. E. Hu and E. Keinan, *Proc. Nat. Acad. Sci.*, 2007, **104**, 20731.
8 T. Hayama, PhD dissertation, University of Zurich, (CH), 2008.
9 T. J. Seiders, E. J. Elliott, G. H. Grube and J. S. Siegel, *J. Am. Chem. Soc.*, 1999, **121**, 7804–7813.
10 D. Pappo, T. Mujuch, O. Reany, E. Solel, E. Keinan and M. Gurram, *Org. Lett.*, 2009, **11**, 1063–1066.
11 A. Fürstner, A. Leiter, M. Mendez and H. Krause, *J. Am. Chem. Soc.*, 2002, **124**, 13856–13863.
12 B. Bogdanovic and M. Schwickad, *Angew. Chem., Int. Ed.*, 2000, **39**, 4610–4612.
13 T. J. Seiders, K. K. Baldridge, E. L. Elliott, G. H. Grube and J. S. Siegel, *J. Am. Chem. Soc.*, 1999, **32**, 7439–7440.
14 A. Orita, J. Yaruva and J. Otera, *Angew. Chem., Int. Ed.*, 1999, **38**, 2267.
15 T. W. Green, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Wiley-Interscience, New York, 1999.
16 (*a*) H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004–2012; (*b*) J. E. Moses and A. D. Moorhouse, *Chem. Soc. Rev.*, 2007, **36**, 1249–1262.
17 E. Fan, Z. Zhang, W. E. Minke, Z. Hou, C. L. M. J. Verlinde and W. G. J. Hol, *J. Am. Chem. Soc.*, 2000, **122**, 2663.
18 M. E. Jung, E. C. Yang, B. T. Vu, M. Kiankarimi, E. Spyrou and J. Kaunitz, *J. Med. Chem.*, 1992, **42**, 3899.
19 F. Fazio, M. C. Bryan, O. Blixt, J. C. Paulson and C.-H. Wong, *J. Am. Chem. Soc.*, 2002, **124**, 14397.
20 F. Alonso, Y. Moglie, G. Radivoy and M. Yus, *Tetrahedron Lett.*, 2009, **50**, 2358.
21 Woodward–Fieser rules would predict a red shift for substituents in the order of π-conjugation; see: J. B. Lambert, H. F. Shurvell, D. A. Lightner, R. G. Cooks, *Organic Strucutral Spectroscopy*, Prentice Hall, Upper Saddle River, New Jersey, 1998, ch. 11.
22 J. H. van't Hoff, *Arrangement of Atoms in Space*, English, Longmans, London, 2nd edn, 1898, ch. 7, pp. 160–169.
23 R. L. Letsinger, *J. Am. Chem. Soc.*, 1948, **70**, 406.
24 U. Avico, R. Guaitolini and P. Zuccaro, *Boll. Chim. Farm*, 1977, **116**, 341.
25 This concept has also been developed for decasubstituted corannulenes starting from **1** by first replacing chlorine by phenoxide and then further halogenation, see: A. Pogoreltsev, E. Solel, D. Pappo and E. Keinan, *Chem. Commun.*, 2012, DOI: 10.1039/C2CC31801F.