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Synthesis and structural analysis of dehydrophenylalanine cyclophanes

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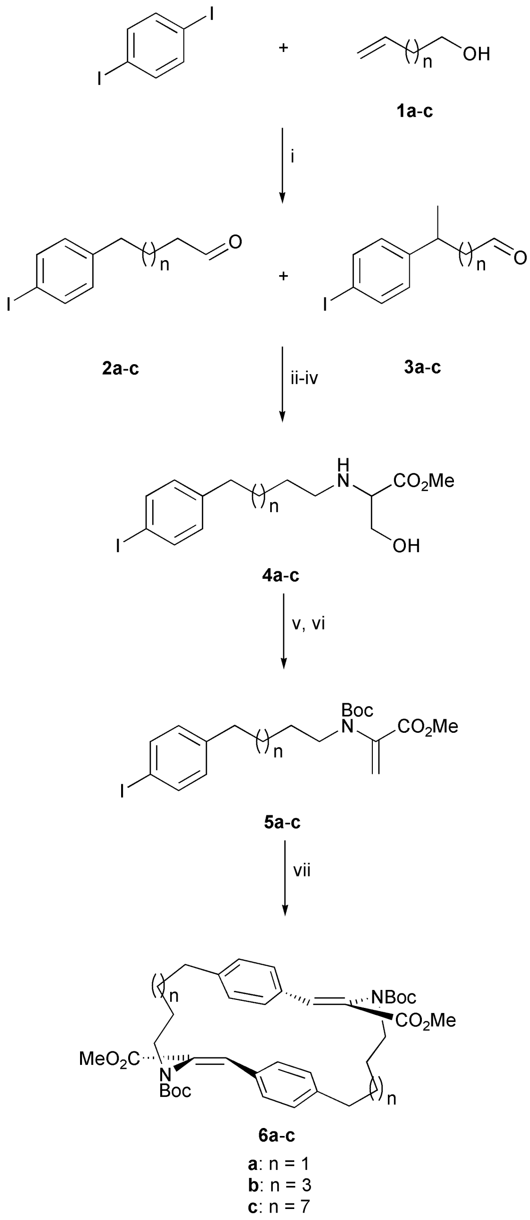
The syntheses and structures of three cyclophanes containing two (*Z*)-dehydrophenylalanine residues are reported; the length of the tethers between the two amino acid residues is easily altered and changing this parameter has a significant effect on the solid state structures of the cyclophanes.

The intermolecular Heck coupling of haloarenes and dehydroalanine derivatives, in which carbon–carbon bond formation occurs at the β-carbon of the dehydroalanine derivative to give (*Z*)-dehydrophenylalanine derivatives, is well established;[1] recent applications of this powerful reaction include its use in the synthesis of phenyltrisalanine, a new trifunctional amino acid,[2] and in the creation of a chiral dendrimer based on aromatic bis- and tris-amino acids.[3] A study of the Heck coupling of *o*-haloarenes tethered to dehydroalanine derivatives revealed that the intramolecular version of this reaction could be used to generate (*Z*)-dehydrophenylalanine residues embedded in seven-, eight- and nine-membered rings.[4] The products of the cyclisations were subsequently converted into the new conformationally constrained phenylalanine analogues, Sic, Hic and Nic[5] and these amino acids have been used in studies of CCK_2 receptor antagonists.[6]

There is currently considerable interest in the properties and applications of cyclophanes[7] and, more generally, in the control of molecular architecture and crystal engineering.[8] In view of this, we wish to report herein a synthesis of cyclophanes containing two (*Z*)-dehydrophenylalanine residues that is designed to allow the distance between the two amino acid residues to be easily varied; one of the key steps of the synthesis involves Heck coupling between *p*-iodoarenes tethered to dehydroalanine derivatives and the outcome of this reaction represents a new type of haloarene–dehydroalanine coupling reaction.

The initial step in the synthesis is the one that provides flexibility with respect to the positioning of the two amino acid residues. It is based on a literature Heck reaction[9] between haloarenes and ω-hydroxyalkenes that forms ω-arylaldehydes by a mechanism that involves palladium hydride-catalysed migration of the expected Heck product alkene along the hydrocarbon chain to generate an enol that subsequently tautomerises to the product aldehyde. Although many ω-hydroxyalkenes are commercially available, for the purposes of this study we selected the 4-, 6- and 10-carbon units **1a–c** for reaction with 1,4-diiodobenzene, in the anticipation that these three chain lengths might provide significantly different final products. Reaction of **1a–c** with 1,4-di-iodobenzene (Scheme 1) provided the desired aldehydes **2a–c** albeit contaminated at levels of 13–23% with the branched isomers **3a–c**, produced by carbon-carbon formation at the internal carbon atom of the alkenes **1a–c**. Experience revealed that the branched isomers were most easily removed at the end of the next step, and so, the mixtures were carried forward into the next stage of the synthesis.

In order to introduce the desired dehydroalanine residue, the mixtures of **2** and **3** were subjected to a reductive amination protocol with serine methyl ester. Crystallisation of the reductive amination products from hexane–diethyl ether provided analytically pure samples of **4a–c** uncontaminated with any branched products.‡ Protection of the amine of **4** with Boc_2O followed by tosylation of the alcohol and a subsequent elimination reaction gave Heck substrates **5a–c** with the desired dehydroalanine residue connected to a remote *p*-iodoarene by hydrocarbon chains containing 4, 6 and 10 carbon atoms. Application of Heck reaction conditions to substrates **5a–c** gave



Scheme 1

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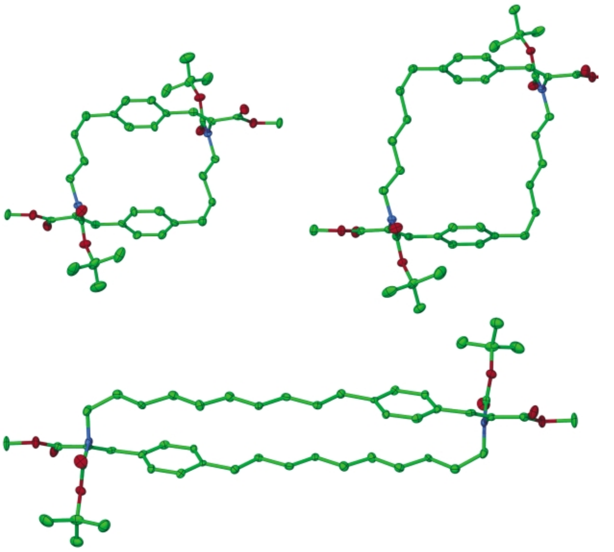

Fig. 1 ORTEP drawings for **6a**, **6b** and **6c**. Hydrogen atoms are omitted for clarity.

products that were tentatively identified as cyclophanes **6a–c** on the basis of their spectroscopic and analytical data.

Crystallisation of **6a–c** followed by X-ray crystallographic analysis§ of the colourless crystals obtained confirmed the structures of **6a–c** and revealed that in the solid state, these compounds adopt structures in which the (*Z*)-dehydrophenylalanine residues have quite different spatial relationships to each other (Fig. 1). Compounds **6a** and **6b** adopt an open ′barrel′ shaped structure that leaves a small cavity in the centre of the molecules. In contrast **6c** adopts a closed, linear structure in the solid state in which cavity volume is minimised. It is anticipated that the chemical and stereochemical properties of **6a–c** will prove to be significantly different.

Finally, structures **6a–c** contain two elements of chirality and the conformations identified in the solid state are *meso* structures. Experiments designed to access the dl pair of a smaller homologue in this series and separate the component enantiomers are underway.

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Notes and references

‡ The novel compounds **4a–c**, **5a–c** and **6a–c** all gave satisfactory spectroscopic (IR, ^{1}H NMR, ^{13}C NMR and low-resolution MS) and microanalytical data.

§ *Crystal data*: for **6a** : $C_{19}H_{25}NO_4$, M = 331.40, 0.20 × 0.10 × 0.10 mm, triclinic, space group $P1$ (no. 2), a = 9.068(2), b = 10.189(3), c = 11.317(3) Å, α = 68.324(15), β = 75.548(16), γ = 77.333(15)°, V = 931.5(4) Å^3, Z = 2, D_c = 1.182 g cm^{-3}, F_{000} = 356, KappaCCD, Mo-Kα radiation, λ = 0.71073 Å, T = 100(2)K, 2θ_{max} = 50.0°, 4700 reflections collected, 3015 unique (R_{int} = 0.1335). The structure was solved and refined using the programs SHELXS-90[10] and SHELXL-97,[11] respectively. The program X-Seed[12] was used as an interface to the SHELX programs, and to prepare the figures. Final GOF = 1.278, $R1$ = 0.1500, $wR2$ = 0.2157, R indices based on 1970 reflections with $I > 2\sigma(I)$ (refinement on F^2), 222 parameters, 0 restraints. L_p and absorption corrections applied, μ = 0.082 mm^{-1}. For **6b**: $C_{42}H_{58}N_2O_8$, M = 718.90, colourless block, 0.25 × 0.25 × 0.10 mm, triclinic, space group $P1$ (no. 2), a = 9.1007(7), b = 9.9502(7), c = 11.8468(8) Å, α = 74.339(5), β = 80.254(4), γ = 81.103(4)°, V = 1011.31(13) Å^3, Z = 1, D_c = 1.180 g cm^{-3}, F_{000} = 388, KappaCCD, Mo-Kα radiation, λ = 0.71073 Å, T = 120(2) K, 2θ_{max} = 49.6°, 5761 reflections collected, 3435 unique (R_{int} = 0.0439). The structure was solved and refined using the programs SHELXS-90[10] and SHELXL-97,[11] respectively. The program X-Seed[12] was used as an interface to the SHELX programs, and to prepare the figures. Final GOF = 1.025, $R1$ = 0.0421, $wR2$ = 0.0968, R indices based on 2577 reflections with $I > 2\sigma(I)$ (refinement on F^2), 240 parameters, 0 restraints. L_p and absorption corrections applied, μ = 0.081 mm^{-1}. For **6c**: $C_{52}H_{78.10}Cl_{3.90}N_2O_{8.70}$, M = 1008.72, colourless plate, 0.20 × 0.15 × 0.10 mm, triclinic, space group $P1$ (no. 2), a = 8.1987(4), b = 8.8260(6), c = 20.8707(13) Å, α = 101.52(4), β = 91.999(4), γ = 113.079(3)°, V = 1350.58(14) Å^3, Z = 1, D_c = 1.240 g cm^{-3}, F_{000} = 540, KappaCCD, Mo-Kα radiation, λ = 0.71073 Å, T = 100(2) K, 2θ_{max} = 50.0°, 7441 reflections collected, 4708 unique (R_{int} = 0.0937). The structure was solved and refined using the programs SHELXS-90[10] and SHELXL-97,[11] respectively. The program X-Seed[12] was used as an interface to the SHELX programs, and to prepare the figures. Final GOF = 1.106, $R1$ = 0.1299, $wR2$ = 0.2724, R indices based on 3141 reflections with $I > 2\sigma(I)$ (refinement on F^2), 302 parameters, 180 restraints. L_p and absorption corrections applied, μ = 0.268 mm^{-1}.

General comment: Overall precision for compounds **6a** and **6c** is relatively poor as a result of sample quality. The samples took the form of small needles with a tendency towards twinning. Compound **6c** included disorder solvent of crystallisation modelled satisfactorily as a mixed site containing 65% $CHCl_3$ and 35% MeOH. Solvent atoms were treated isotropically.

CCDC 188015, 188016 and 189757. See http://www.rsc.org/suppdata/cc/b2/b205752m/ for crystallographic data in CIF or other electronic format.

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