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A versatile approach to chiral macrocycles

Susan E. Gibson,*[a] Nello Mainolfi,[a] S. Barret Kalindjian[b] and Paul T. Wright[b]
[a] *Department of Chemistry, King's College London, Strand, London, UK WC2R 2LS*
[b] *James Black Foundation, 68 Half Moon Lane, London, UK SE24 9JE*

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Head-to-tail Heck coupling of units derived from amino alcohols and iodoaryl aldehydes provides a short and versatile route to non-racemic chiral macrocycles.

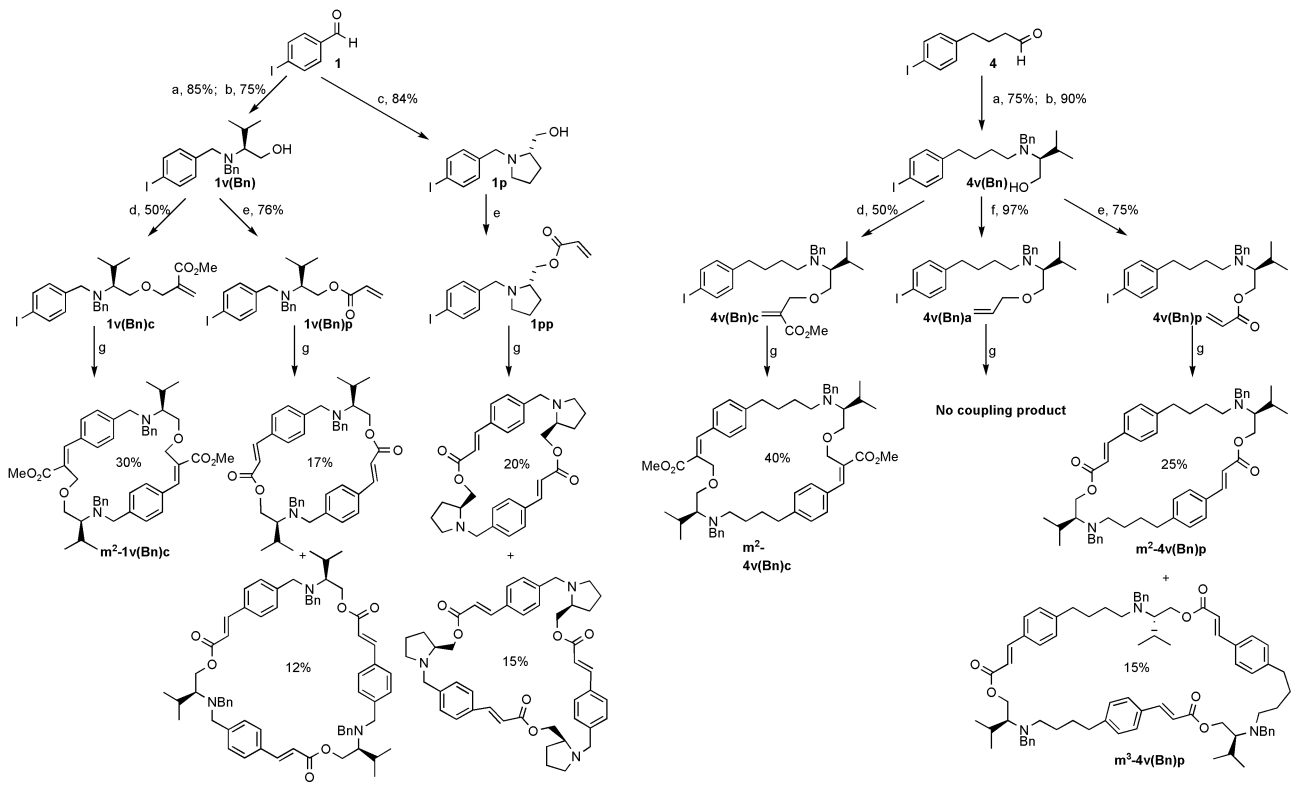
Macrocycles make excellent ligands for a wide range of metals. For example, the last decade has seen the synthesis and characterisation of many lanthanide complexes, several of which have found important applications—of particular note is their use as contrast-enhancing agents in diagnostic imaging procedures.[1] More recently interest has grown in the synthesis and characterisation of lanthanide complexes of chiral macrocycles,[2] and these are now beginning to be applied in the area of catalysis. For example, N,O-macrocycles form lanthanide complexes that catalyse asymmetric aldol reactions.[3] Macrocycles also play a key role in host–guest chemistry. They bind a wide range of entities, including anions, which are often bound to receptors containing protonated bases,[4] and small organic molecules, which often bind through hydrogen bonds, and/or lipophilic and aromatic stacking interactions.[5]

Our interest in applications of the intramolecular Heck reaction[6] recently led to our serendipitous discovery of a head-to-tail coupling reaction that gave a range of cyclophanes containing dehydrophenylalanine units.[7] Seeing this as an opportunity to develop a new short route to macrocycles, we proposed several modifications to the synthesis, including the incorporation of non-racemic chiral centres. The resulting synthetic route, which offers access to a very wide range of chiral macrocycles in just a few steps, is reported herein.

The synthesis starts with substrates containing a substituted iodoarene and an aldehyde. In the two examples provided here (compounds **1** and **4**) these functionalities are linked in a *para* disposition by zero and three carbon atoms respectively. A large number of analogues of **1** and **4** containing other carbon chain lengths and *meta* or *ortho* substituted arenes are readily available from a palladium catalysed zipper reaction[8] between an appropriate di-iodoarene and an ω-hydroxyalkene.[7]

In step one, compounds **1** and **4** were subjected to reductive amination reactions with amino alcohols derived from proteinogenic amino acids (Scheme 1). This step introduces naturally available chirality and the opportunity to incorporate steric constraints or further functional groups depending on the choice of amino acid precursor. Illustrated here are the conversions of aldehyde **1** into (*S*)-valinol and (*S*)-prolinol derivatives **1v(Bn)** and **1p**, and aldehyde **4** into its valinol derivative **4v(Bn)** (secondary amines were protected as their benzyl derivatives).

Step two primed the system ready for the Heck reaction that it was anticipated would generate the target macrocycles. The alcohols of **1v(Bn)**, **1p** and **4v(Bn)** were reacted with appro-



Scheme 1 *Reagents and conditions*: a, (*S*)-valinol, $MgSO_4$, DCM, then $NaBH_4$, MeOH; b, K_2CO_3, BnBr, acetone; c, (*S*)- prolinol, $MgSO_4$, DCM, then $NaBH_4$, MeOH; d, NaH, THF, then Bu_4NI, methyl 2-(bromomethyl)acrylate; e, acryloylCl, Et_3N, DCM; f, NaH, THF, then Bu_4NI, allylBr; g, $Pd(OAc)_2$, Bu_4NCl, $NaHCO_3$, DMF (0.05 M), 110 °C, 16 h.

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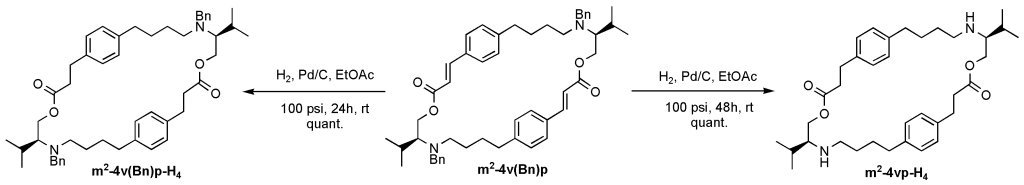

Scheme 2

priate halides to give 2-**c**arboxyprop-2-enyl, **p**rop-2-enoyl and **a**llyl derivatives **1v(Bn)c**, **1v(Bn)p**, **1pp**, **4v(Bn)c**, **4v(Bn)a** and **4v(Bn)p**.

Subjecting the six iodoarene-alkene substrates to Heck reaction conditions generated macrocycles in all cases except for the substrate bearing the relatively unactivated alkene **4v(Bn)a**.†‡ In the reactions where the 2-carboxyprop-2-enyl group was used as the Heck acceptor alkene, only the products of two head-to-tail couplings [**m²-1v(Bn)c** and **m²-4v(Bn)c**] were isolated.§ In contrast, it proved possible to isolate both the products of two head-to-tail couplings and the products of three head-to-tail couplings from all the reactions that used the prop-2-enoyl group as the Heck acceptor. It was assumed that the remaining material was polymeric in nature.

Finally, one of the Heck products obtained, **m²-4v(Bn)p**, was hydrogenated. Gratifyingly, it proved possible to identify conditions that led to the reduction of the two alkenes to give **m²-4v(Bn)p-H$_4$** and conditions that led to both alkene reduction and amine deprotection to give **m²-4vp-H$_4$** (Scheme 2).

In summary, we have designed a new approach to non-racemic chiral macrocycles that is short and flexible. Our initial studies readily generated 0.25–1.00 g quantities of the macrocycles and we are now in a position to start to investigate the catalytic and host–guest properties of our macrocycles.

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Notes and references

† All compounds reported gave satisfactory spectroscopic (IR, ^{1}H NMR, ^{13}C NMR, and low resolution MS) and microanalytical data.

‡ The head-to-tail Heck reaction of **4v(Bn)p** is typical: A 250 cm^3 flask containing a stirrer bar and fitted with a condenser was placed under an inert atmosphere of nitrogen and charged with **4v(Bn)p** (2.53 g, 5 mmol, 1 eq.), palladium(II) acetate (0.11 g, 0.5 mmol, 0.1 eq.), sodium hydrogencarbonate (1.05 g, 12.5 mmol, 2.5 eq.) and tetra-*n*-butylammonium chloride (1.39 g, 5 mmol, 1 eq.). Dry dimethylformamide (100 cm^3, 0.05 M) was added and the mixture was saturated with nitrogen. The flask was lowered into a preheated oil bath held at 110 °C and stirred for 16 h. After cooling, the product mixture was diluted with diethyl ether (200 cm^3) and the precipitate filtered. The filtrate was concentrated *in vacuo* and subjected to flash column chromatography (SiO_2; hexane–diethyl ether 3 : 1) to afford **m²-4v(Bn)p** as a white solid (0.47 g, 0.62 mmol, 25%) and **m³-4v(Bn)p** as a bright yellow solid (0.28 g, 0.25 mmol, 15%). Data for **m²-4v(Bn)p**: (Found: C, 79.4; H, 8.0; N, 3.6. $C_{50}H_{62}N_2O_4$ requires C, 79.54; H, 8.28; N, 3.71%); $[\alpha]_D^{20}$ = −43.5 (*c* 0.08, CH_2Cl_2); ν_{max}(neat)/cm^{-1} 1709s (C=O), 1635m (C=C); δ_H(360 MHz, $CDCl_3$) 0.87 (3H, d, *J* 6.5, CHC*H*$_3$), 0.97 (3H, d, *J* 6.5, CHC*H*$_3$), 1.28–1.38 (1H, m, NCH$_2$C*H*H), 1.39–1.52 (3H, m, ArCH$_2$C*H*$_2$ and NCH$_2$C*H*H), 1.89–1.95 (1H, m, CH$_3$C*H*CH$_3$), 2.38–2.45 (2H, m, NC*H*$_2$CH$_2$), 2.49–2.59 (2H, m, ArC*H*$_2$CH$_2$), 2.6–2.75 (1H, m, NC*H*CH), 3.58 (1H, d, *J* 14, NC*H*Ar), 3.73 (1H, d, *J* 14, NC*H*Ar), 4.19 (1H, dd, *J* 12 and 7, C*H*HOC=O), 4.40 (1H, dd, *J* 12 and 2, CH*H*OC=O), 6.25 (1H, d, *J* 16, C*H*C=O), 6.92 (2H, m, *H*-2,6), 7.08–7.21 (5H, m, *H*-8–12), 7.26 (2H, m, *H*-3,5), 7.50 (1H, d, *J* 16, ArC*H*=C); δ_C\{^{1}H\}(90.4 MHz, $CDCl_3$) 20.9 (*C*H$_3$), 22.2 (*C*H$_3$), 27.9 (CH$_3$*C*HCH$_3$), 28.8 (NCH$_2$*C*H$_2$) 29.8 (ArCH$_2$*C*H$_2$), 36.1 (Ar*C*H$_2$), 51.3 (N*C*H$_2$CH$_2$), 55.6 (N*C*H$_2$Ar), 62.4 (CH*C*H$_2$O), 64.1 (N*C*H), 117.7 (CH=*C*HC=O), 127.1 (*C*-3,5), 128.53, 128.55, 129.0, 129.2 (*C*-2,6,8–12), 132.1 (*C*-4), 141.3 (*C*-7), 145.1 (Ar*C*H=CH), 146.2 (*C*-1), 167.4 (*C*=O); *m*/*z* (ESI) 755.5 (M$^+$, 98%), 452.4 (M − (CH$_2$)$_4$(NBn)CH(CH$_3$)$_2$CHCH$_2$OC=OCH=CH − 2H, 50), 410.4 (M − (CH$_2$)$_4$(NBn)CH(CH$_3$)$_2$CHCH$_2$OC=OCH=CH − (CH$_3$)$_2$CH − H, 35), 242.4 (CH$_2$CH(CH$_3$)$_2$CHN(CH$_2$)$_4$C$_6$H$_4$CH=CH, 69), 119.1 (CH$_2$NBn, 100). Data for **m³–4v(Bn)p**: (Found: C, 79.3; H, 8.1; N, 3.5. $C_{75}H_{93}N_3O_6$ requires C, 79.54; H, 8.28; N, 3.71%); $[\alpha]_D^{20}$ = −59.4 (*c* 0.05, CH_2Cl_2); ν_{max}(neat)/cm^{-1} 1711s (C=O), 1634m (C=C); δ_H(360 MHz, $CDCl_3$) 0.84 (3H, d, *J* 6.5, CHC*H*$_3$), 0.95 (3H, d, *J* 6.5, CHC*H*$_3$), 1.32–1.50 (4H, m, NCH$_2$C*H*$_2$ and ArCH$_2$C*H*$_2$), 1.77–1.80 (1H, m, CH$_3$C*H*CH$_3$), 2.43–2.59 (5H, m, NC*H*$_2$CH$_2$, ArC*H*$_2$CH$_2$ and NC*H*CH), 3.50 (1H, d, *J* 14, NC*H*Ar), 3.77 (1H, d, *J* 14, NC*H*Ar), 4.22 (1H, dd, *J* 12 and 7, C*H*HOC=O), 4.34 (1H, dd, *J* 12 and 2, CH*H*OC=O), 6.25 (1H, d, *J* 16, C*H*C=O), 6.95 (2H, m, *H*-2,6), 7.08–7.21 (5H, m, *H*-8–12), 7.31 (2H, m, *H*-3,5), 7.57 (1H, d, *J* 16, ArC*H*=C); δ_C\{^{1}H\}(90.4 MHz, $CDCl_3$) 19.3 (*C*H$_3$), 20.4 (*C*H$_3$), 27.3 (NCH$_2$*C*H$_2$), 27.6 (CH$_3$*C*HCH$_3$), 27.7 (ArCH$_2$*C*H$_2$), 34.6 (Ar*C*H$_2$), 49.9 (N*C*H$_2$CH$_2$), 54.2 (N*C*H$_2$Ar), 62.1 (CH*C*H$_2$O), 62.8 (N*C*H), 116.1 (CH=*C*HC=O), 125.6 (*C*-3,5), 127.1, 127.6 × 2, 128.2 (*C*-2,6,8–12), 130.8 (*C*-4), 139.9 (*C*-7), 143.8 (Ar*C*H=CH), 144.5 (*C*-1), 166.1 (*C*=O); *m*/*z* (ESI) 1132.9 (M$^+$, 12.5%), 510.3 (C$_6$H$_4$(CH$_2$)$_4$(NBn)CH(CH$_3$)$_2$CHCH$_2$OC-=OCH=CHC$_6$H$_4$(CH$_2$)$_4$ + H, 27), 326.4 (CH$_2$OC-=OCH=CHC$_6$H$_4$(CH$_2$)$_4$NCHCH$_2$OC=OCH=CH − H, 25), 119.2 (CH$_2$NBn, 100).

§ The stereochemistry of the trisubstituted double bonds was assigned using NOESY experiments which revealed a throughspace interaction between the protons of the CH$_2$O and the aryl substituents.

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