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Stereocontrolled construction of rigid tricyclic bis(α-amino acid) derivatives by Ru(II)-catalyzed cascade and Diels–Alder reactions

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In the preparation of rigid and annulated tricyclic bis(α-amino acid) derivatives the key construction was effected by a Ru(II)-catalyzed RCM cascade reaction of *gem*-dienynes. The substrates were available by stepwise and stereocontrolled alkynylations and alkenylations of (2*R*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine. The cascade products were bis-heterospiranes or symmetrical or unsymmetrical bis(α-amino acid) derivatives. Tricyclic Diels–Alder adducts were formed between diethyl acetylenedicarboxylate and the diene cascade products. Oxidative aromatization provided rigid tricyclic bis(α-amino acid) derivatives. X-Ray analysis was used to verify configurational assignments.

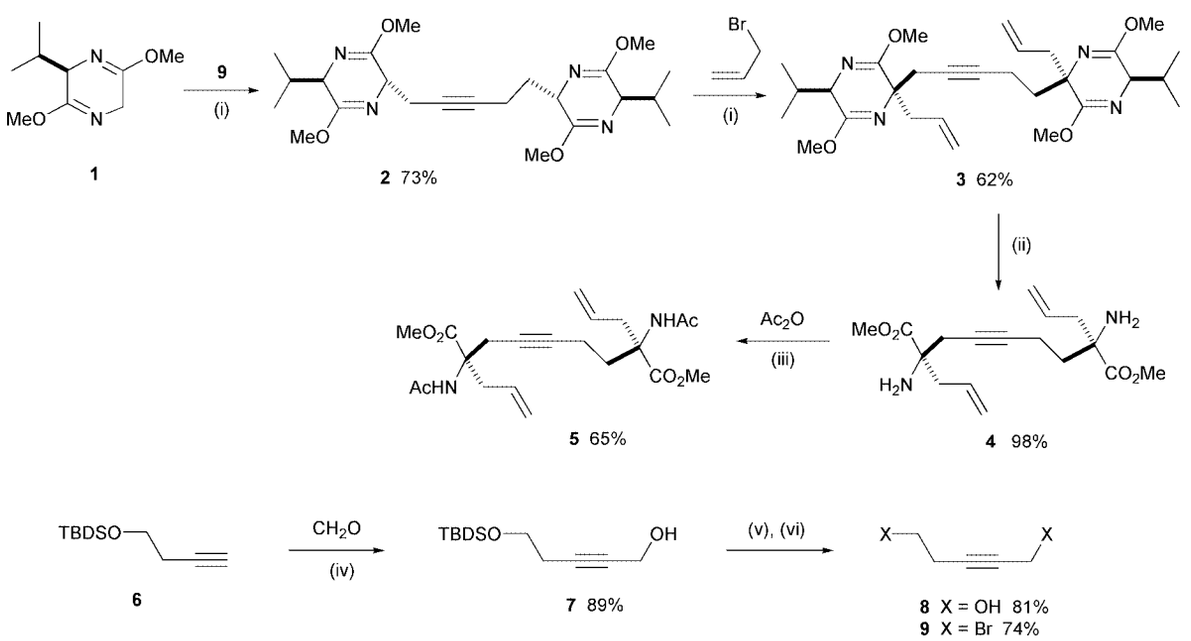
Introduction

Cystine is an important four-atom bridged bis(α-amino acid). We have for some time been involved in the construction of C_4-bridged analogues where the disulfide moiety has been replaced with a C_2-unit.[1,2] Conformational constraints may be introduced by a double or triple bond in the all-carbon bridge,[1,2] or by insertion of aryl or heteroaryl groups into the chain.[3] C_3-bridged bis(α-amino acids) have received wide attention because of antimicrobial activity associated with some members of this group.[4] Simple C_2-ethylene bridged as well as constrained C_2-bridged bis(α-amino acid) have been described.[5] Bis(α-amino acids) with longer bridges have been constrained by insertion of more than one triple bond,[6] by a heterocyclic ring,[3,7] or by ferrocene.[8] The conformational constraints in C_4-bridged molecules have been additionally increased by carbosubstitution at the α-carbon of the amino acid.[9]

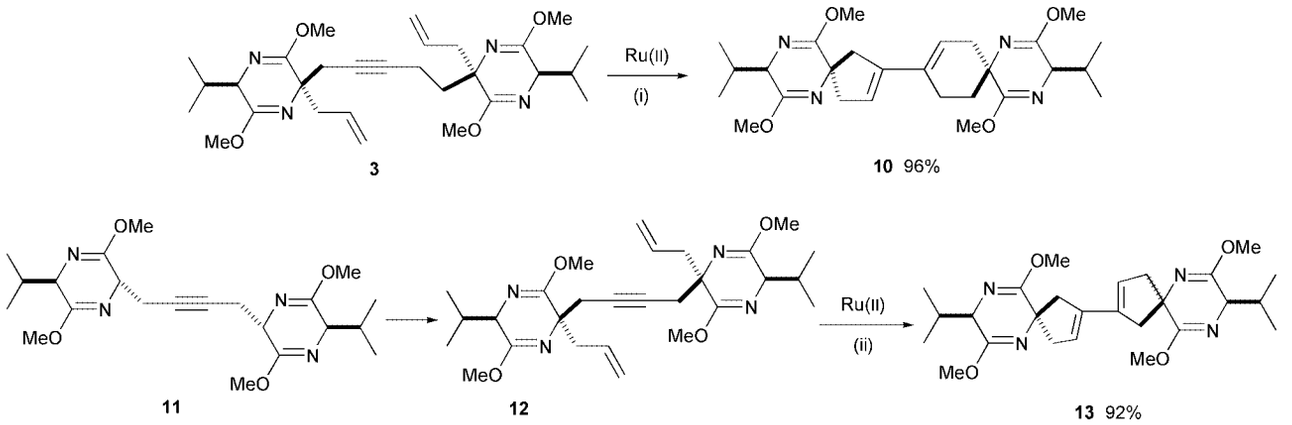
In this report we describe methodology which leads to highly rigid bis(α-amino acid) structures in the form of tricyclic bridges in which the distance between the α-amino acid centers can be varied by the ring sizes in the tricyclic bridge. Both symmetrical and unsymmetrical structures have been prepared. A key step in our constructions is effected by Ru(II)-catalyzed ring-closing metathesis (RCM) cascade reactions of dienyne substrates (see Scheme 2 and 3) using Grubbs bis(tricyclohexylphosphine)benzylidene ruthenium dichloride as a catalyst.[10,11] The scope of the original methodology has been further extended by recent modifications of the precatalyst ligand system.[12–15]

Results and discussion

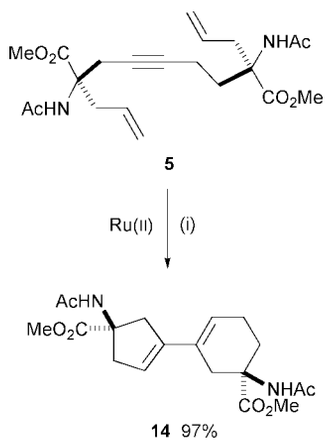
Preparation of intermediate substrates for the RCM reaction, *viz.* the C_5-alkyne bridged bis(α-amino acid) derivative **4** and its precursor **3** is shown in Scheme 1. The unsymmetrical alkylating reagent 1,5-dibromopent-2-yne **9** was prepared from but-3-yn-1-ol by TBDMS-*O*-protection followed by lithiation



Scheme 1 *Reagents and conditions*: (i) *n*BuLi, THF, −78 °C for 3 h and rt for 14 h; (ii) 0.1 M aq TFA–MeCN, rt, 4d; (iii) DMAP, CH_2Cl_2, rt, 5 h; (iv) *n*BuLi, THF, −45 °C, $(CH_2O)_n$, rt, 1 h; (v) TBAF, THF, rt, 3 h; (vi) Br_2, PPh_3, MeCN, 0 °C rt, 1 h.



Scheme 2 *Reagents and conditions*: (i) Ph-CH=$RuCl_2(PCy_3)_2$ 2 × 5 mol%, toluene 85 °C, 2 × 5 h; (ii) PhCH=$RuCl_2$(IMes)(PCy_3) 3 × 10 mol%, toluene, 85 °C, 3 × 3 h.



Scheme 3 *Reagents and conditions*: (i) PhCH=$RuCl_2(PCy_3)_2$ 2 × 8 mol%, toluene, 90 °C, 2 × 5 h.

and hydroxymethylation to furnish the propargyl alcohol (prop-2-ynyl alcohol) **7**. Tetrabutylammonium fluoride (TBAF) was used to remove the silyl protecting group with formation of the diol **8**. The reactions proceeded well and this method competes favourably with alternative preparations of the diol.[16,17] Br_2·PPh_3 was used for the conversion of the diol to the dibromide **9** whereas previous workers have used PPh_3 and CBr_4.[16]

For the preparation of the C_5-alkyne bridged precursor for the tricyclic bis(amino acid) derivatives the Schöllkopf methodology was used.[18] The bislactim ether **1** was lithiated and alkynylated with 1,5-dibromopent-2-yne to yield the unsymmetrically bridged structure **2** in 73% yield. A minor product was due to monoalkylation and a subsequent HBr elimination in preference to a second alkylation. The product was identified by NMR and was not further characterized. Lithiation and alkylation with allyl bromide provided the dienyne **3** in 62% yield after two alkylation steps. The reaction is stereoselective in that the electrophile becomes attached *trans* to the isopropyl group. The degree of stereoselectivity in the first alkylation providing intermediate **2**, however, is not important because the stereochemical information is lost when this product becomes the substrate for a second lithiation and alkenylation reaction. Only one stereoisomer was observed in the second alkenylation reaction in accordance with previous experience in the stepwise dialkylation of the bislactim ether substrate **1**.[19] It is thus assumed that the new electrophile has entered *trans* to the isopropyl group in the metallated species of the bridged substrate **2** thereby providing the stereoisomer **3**. Mild acid hydrolysis with 0.1 M TFA, and protection of the amino group by acetylation, gave the products **4** and **5** in 98 and 65% yield, respectively.

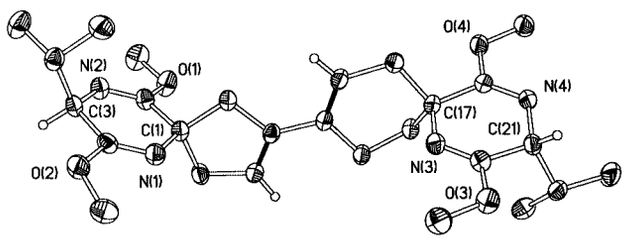
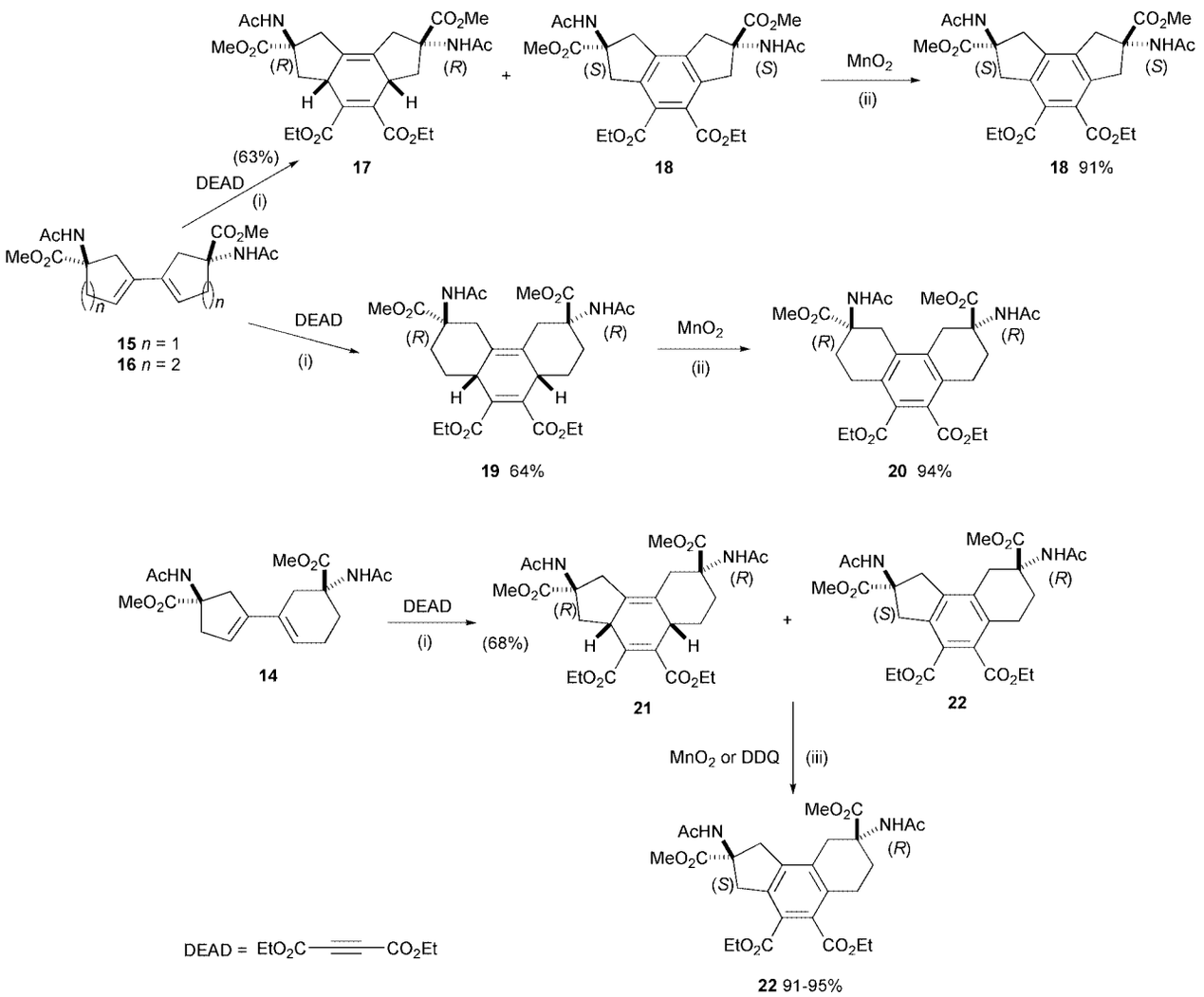


Fig. 1 The ORTEP plot of compound **10**. Ellipsoids are shown at 50% probability. For clarity only the hydrogens at stereogenic centers and at the diene are shown. The double bonds of the diene are drawn in black.

The cascade reaction of the pentyne-bridged substrate **3** proceeded almost quantitatively with the standard Grubbs Ru(II)-catalyst. After 5 hours at 85 °C about 60% conversion was observed with 5 mol% catalyst. The same amount of catalyst was added once more and the heating continued at this temperature for another 5 hours when close to quantitative yield of cascade product **10** was obtained (Scheme 2). Below 65 °C there was hardly any reaction. Low thermal stability of the catalyst becomes an important problem in slow reactions.[15,20] Therefore the catalyst was added in two portions.

The product was a crystalline material. To verify the regiochemistry as well as the stereochemistry in the transformations described, a single crystal X-ray analysis was carried out. The ORTEP plot of the X-ray structure in Fig. 1 shows the product to have the structure **10**. The compound crystallizes with *two* molecules in the asymmetric unit; the molecules are equal within the accuracy of the determination, all bond lengths and angles are as expected. The configuration of the molecule could not be determined by the Flack parameter (0.5(5)) but is settled by the known chirality at the positions of the isopropyl groups (C3 and C21).

When the length of the bridge was reduced to a C_4-chain as in the analogue structure **12**, the RCM reaction with the standard Grubbs catalyst failed.[21] With new variations of the catalyst system becoming available, this study was repeated in more detail in the present work. Substrate **12** was prepared by analogy to the above alkylations from the C_4-alkyne **11**.[21] With 5% Ru(II)-catalyst below 60 °C no conversion of substrate **12** was seen. At 85 °C some 15–20% yield of the cascade product **13** could be obtained. Besides thermolytic reactions, the catalytic activity may also reduce because the catalyst may be consumed in formation of complexes with components in the reaction medium.[22] To elucidate any such problem simple NMR studies were performed with the substrate **12** using 0.8 equivalents of the catalyst. There was no reaction at ambient temperature and hardly any at 50 °C. Slow transformations were seen at 85 °C but no complex formation between the catalyst and the substrate was detected and hence this cannot explain why the reaction did not proceed. We therefore applied



Scheme 4 *Reagents and conditions*: (i) anisole 145 °C, 14 h; (ii) dioxane, rt, 14 h; (ii) dioxane, rt, 14 h; (iii) dioxane, 100 °C, 5 h.

a slightly modified Grubbs catalyst with improved activity and thermal stability.[15] The catalyst was prepared from the Grubbs benzylidene complex by replacement of one of the phosphine ligands with the more nucleophilic 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes) ligand. The catalyst complex formed was $(PCy_3)(IMes)Cl_2Ru{=}CHPh$. With this new catalyst the cascade reaction could be effected at 85 °C in toluene. The reaction was incomplete after 3 h with 10 mol% catalyst. Addition of 10 mol% catalyst twice and heating for another two 3 hour periods furnished the cascade product **13** in very high yield (92%).

The steric interactions in the bislactim substrates **3** and **12** are significantly reduced in the corresponding *N*-protected bis(α-amino acid derivatives) such as the substrate **5** in Scheme 3. The cascade reaction in the latter case proceeded readily with almost quantitative formation (in >95%) of the bicyclic product **14**. Even with C_4-yne bridged analogues of substrate **5** the cascade reaction proceeded satisfactorily to furnish substrates **15** and **16** for the Diels–Alder in Scheme 4 in *ca.* 85% yield.[21]

The crude cascade products were slightly coloured due to ruthenium and phosphine impurities. Addition of lead tetraacetate for oxidation,[23] or tris(hydroxymethyl)phosphine for providing water soluble ruthenium complexes, has been recommended for removal of these impurities.[24] We have used the latter technique successfully.

With the cascade products in hand the conformational freedom due to the single carbon–carbon bond in the butadiene moiety was to be prevented by the introduction of a third ring. Thus the dienes were subjected to Diels–Alder reactions. For simplicity the symmetrical and highly reactive dienophile diethyl acetylenedicarboxylate was used in the Diels–Alder reactions. The reactions were run in anisole at 145 °C. From the RCM products **10** and **13** (Scheme 2) containing the bulky bislactim ether unit, no Diels–Alder adduct could be isolated. The failure is attributed to the crowding in these substrates. In the bis(amino acid) substrates **14**–**16**, however, Diels–Alder reactions proceeded satisfactorily (Scheme 4). In the bis(cyclopentenyl)diene substrate **15** a mixture of the cycohexadiene adduct **17** and its aromatized benzene analogue **18** was obtained in a total yield of 63%. The products were difficult to separate. The product mixture was therefore treated directly with manganese dioxide for the conversion to the benzo derivative **18**. The Diels–Alder product **19** from the bis(cyclohexene) substrate **16** was obtained in 64% yield. The adduct **19** was aromatized in almost quantitative yield to the benzo derivative **20** when reacted with manganese dioxide. The cyclopentenylcyclohexenyl diene **14** with acetylene dicarboxylate also gave a cyclohexadiene adduct **21** and its aromatized analogue **22** as a mixture, about 1 : 1 in 68% overall yield. The mixture was fully aromatized as above by the use of manganese dioxide. The aromatizations could also be effected with DDQ.

In conclusion, we have described a methodology for the preparation of rigid and enantiomerically pure tricyclic bis-(α-amino acid) derivatives. The reaction sequence was initiated by stereoselective alkynylations and alkenylations of (2*R*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine to provide dienyne substrates for Ru(II)-catalyzed cascade RCM reactions. The cascade products were substrates for Diels–Alder reactions in the preparation of the tricyclic α-amino acids. Novel acyclic and bicyclic α-amino acids were prepared which can be

regarded as target amino acid molecules, or versatile intermediates for the preparation of rigid tricyclic bis(α-amino acid) derivatives.

Experimental

^{1}H NMR spectra were recorded in $CDCl_3$ at 500, 300 or 200 MHz with Bruker DPX 500, DPX 300 or DPX 200 spectrometers. The ^{13}C spectra were recorded in $CDCl_3$ at 75 or 50 MHz. Chemical shifts are reported in ppm with residual $CHCl_3$ (7.24 ppm) and $CDCl_3$ (77 ppm) as references. *J* values are given in Hz. Mass spectra under electron-impact conditions (EI) were recorded at 70 eV ionizing potential. The spectra are presented as *m*/*z* (% rel. int.). IR spectra were measured on a Nicolet Magna 550 spectrometer using ATR (attenuated total reflectance). Optical rotations at 22 °C are given in 10^{-1} deg cm^2 g^{-1}. Dry THF was distilled from sodium and benzophenone under argon. Solvents were degassed by bubbling argon through. Bis(tricyclohexylphosphine)benzylidene ruthenium dichloride was purchased from Strem Chemicals Inc., 7 Mulliken Way, Newburyport, MA.

X-Ray crystallographic analysis data for compound 10 †

X-Ray data were collected on a Siemens SMART CCD diffractometer[25] using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Data collection method: ω-scan, range 0.6°, crystal to detector distance 5 cm. Data reduction and cell determination were carried out with the SAINT and XPREP programs.[25] Absorption corrections were applied by the use of the SADABS program.[26] The structure was determined and refined using the SHELXTL program package.[27] The non-hydrogen atoms were refined with anisotropic thermal parameters; hydrogen atoms were located from difference Fourier maps and refined with isotropic thermal parameters.

Crystal data for $C_{27}H_{40}N_4O_4$ (**10**), M = 484.63, monoclinic, $P2_1$, a = 15.094(1), b = 10.184(1), c = 17.828(1) Å, β = 96.19(1)°, V = 2724.4(3) Å^3, Z = 4, D_x = 1.182 Mg m^{-3}, μ = 0.080 mm^{-1}, T = 150(2) K, measured 51259 reflections in 2θ range 11.8–61.0°, R_{int} = 0.040. 951 parameters refined against 16207 F^2, R = 0.042 for $I_o > 2\sigma(I_o)$ and 0.065 for all data.

1,5-Bis[(2*R*,5*S*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazin-5-yl]pent-2-yne 2

A solution of (2*R*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine **1** (0.213 g, 1.06 mmol) in anhydrous THF (3 ml) at −78 °C was lithiated by the addition of a solution of *n*BuLi in hexane (0.69 ml, 1.53 M, 1.06 mmol). The solution was stirred at −78 °C for 0.5 h before a solution of 1,5-dibromopent-2-yne **9** (0.14 g, 0.51 mmol) in THF (10 ml) was added through a teflon tube. The reaction mixture was stirred at −78 °C for 3 h, allowed to reach ambient temperature overnight and the reaction was quenched by addition of phosphate buffer (pH 7) and water. The aqueous phase was extracted with dichloromethane, the combined organic extracts dried ($MgSO_4$), the solvent removed *in vacuo* and the product isolated after flash chromatography on silica gel using EtOAc–hexane 20 : 80. The product 0.168 g (73%) was an oil. HRMS: M 432.2744. $C_{23}H_{36}N_4O_4$ requires 432.2737; ν_{max}(film)/cm^{-1} 2959 (m), 2871 (w), 1697 (s), 1436 (m), 1238 (s), 1196 (m), 1017 (m); δ_H(300 MHz, $CDCl_3$) 0.60 (3 H, d, *J* 6.8, CH*Me*$_2$), 0.61 (3 H, d, *J* 6.8, CH*Me*$_2$), 0.96 (3 H, d, *J* 6.8, CH*Me*$_2$), 0.98 (3 H, d, *J* 6.8, CH*Me*$_2$), 1.56–1.68 (1 H, m, CHH), 1.88–2.28 (5 H, m, 3 × CHH and 2 × C*H*Me$_2$), 2.51–2.69 (2 H, m, 2 × C*H*H), 3.58–3.61 and 3.62–3.63 (12 H, s, 4 × OMe), 3.82–3.86 (1 H, m, H-2 or H-2′), 3.89–3.95 (2 H, m, H-5 and H-5′), 3.98–4.02 (1 H, m, H-2 or H-2′); δ_C(75 MHz, $CDCl_3$) 14.6 (*C*H$_2$-CH$_2$-CC), 16.5 (CH*Me*$_2$), 16.7 (CH*Me*$_2$), 19.05 (CH*Me*$_2$), 19.1 (CH*Me*$_2$), 25.5 (CH$_2$), 31.5–31.8 (2 × *C*HMe$_2$), 33.9 (2 × CH$_2$ *C*H$_2$-CC), 52.3 (OMe), 52.4 (2 × OMe), 52.5 (OMe), 54.2–54.8 (C-5 and C-5′), 60.8 (C-2 and C-2′), 76.1 (*C*C), 81.7 (*C*C), 162.1, 163.5, 164.6 (C-3, C-3′, C-6 and C-6′); *m*/*z* (EI): 432 (M$^+$, 6%), 417 (5), 390 (24), 389 (100), 388, (5), 250 (24), 249 (57), 207 (11), 183 (20), 141 (81), 140 (10).

1-[(2*R*,5*R*)-5-Allyl-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazin-5-yl]-5-[(2*R*,5*S*)-5-allyl-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazin-5-yl]pent-2-yne 3

A solution of 1,5-bis[(2*R*,5*S*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazin-5-yl]pent-2-yne **2** (1.347 g, 3.12 mmol) in anhydrous THF (16 ml) at −78 °C was lithiated by addition of a solution of *n*BuLi in hexane (4.33 ml, 1.51 M, 6.55 mmol). The solution was stirred at −78 °C for 1 h before a precooled (−78 °C) solution of allyl bromide (0.792 g, 6.55 mmol) in THF (8 ml) was added through a teflon tube. The reaction mixture was stirred at −78 °C for 3 h, allowed to reach ambient temperature overnight and quenched by addition of phosphate buffer (pH 7) and water. The aqueous phase was extracted with Et_2O, the combined organic extracts dried ($MgSO_4$), the solvent removed *in vacuo* and the product isolated as a slightly yellow oil after flash chromatography on silica gel using EtOAc–hexane 7 : 93 with yield 0.989 g (62%); HRMS (electrospray): M 512.3349. $C_{29}H_{44}N_4O_4$ requires 512.3362; ν_{max}(film)/cm^{-1} 2959 (m), 2870 (w), 1693 (s), 1436 (m), 1307 (m), 1239 (s), 1197 (m), 1143 (m), 1002 (m); δ_H(300 MHz, $CDCl_3$) 0.58 (3 H, d, *J* 6.8, CH*Me*$_2$), 0.68 (3 H, d, *J* 6.8, CH*Me*$_2$), 1.04 (3 H, d, *J* 6.8, CH*Me*$_2$), 1.07 (3 H, d, *J* 6.8, CH*Me*$_2$), 1.69–2.05 (4 H, m, 4 × C*H*H), 2.14–2.47 (7 H, 5 × C*H*H, 2 × C*H*Me$_2$), 2.63 (1 H, m, C*H*H), 2.75 (1 H, m, C*H*H), 3.61 (3 H, s, OMe), 3.62 (3 H, s, OMe), 3.66 (3 H, s, OMe), 3.67 (3 H, s, OMe), 3.78 (1 H, d, *J* 3.2, H-2 or H-2′), 3.81 (1 H, d, *J* 3.2, H-2 or H-2′), 4.88–5.02 (4 H, m, 2 × CH=C*H*$_2$), 5.37–5.63 (2 H, m, 2 × C*H*=CH$_2$); δ_C(75 MHz, $CDCl_3$) 14.7 (*C*H$_2$CH$_2$-CC), 16.8, 17.0, 19.5, 19.6 (2 × CH*Me*$_2$), 30.4 (*C*HMe$_2$), 30.6 (*C*HMe$_2$), 30.9 (CH$_2$), 39.1 (CH$_2$), 44.6 (CH$_2$), 45.0 (CH$_2$), 52.1 (OMe), 52.3 (OMe), 52.3 (OMe), 52.4 (OMe), 60.6 (C-5 or C-5′), 60.8 (C-5 or C-5′), 61.5 (C-2 or C-2′), 61.8 (C-2 or C-2′), 76.5 (CC), 82.0 (C*C*), 118.3 (*C*H$_2$=CH), 118.5 (*C*H$_2$=CH), 133.1 (CH$_2$=*C*H), 133.2 (CH$_2$=*C*H), 162.7 (C-3 or C-3′ or C-6 or C-6′), 163.0 (C-3 or C-3′ or C-6 or C-6′), 163.1 (C-3 or C-3′ or C-6 or C-6′), 163.2 (C-3 or C-3′ or C-6 or C-6′); *m*/*z* (EI): 512 (M$^+$, 1%), 479 (15), 477 (11), 472 (30), 471 (100), 470 (17), 469 (54), 387 (12), 289 (29), 223 (29), 218 (14), 191 (17), 183 (13), 182 (11), 181 (84), 153 (14), 91 (15).

Dimethyl (2*R*,8*S*)-2,8-diallyl-2,8-diaminonon-4-yne-1,9-dioate 4

A solution of 1-[(2*R*,5*R*)-5-allyl-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazin-5-yl]-5-[(2*R*,5*S*)-5-allyl-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazin-5-yl]pent-2-yne **3** (0.989 g, 1.93 mmol) in MeCN (96 ml) and aqueous TFA (96 ml, 0.2 M) was stirred at ambient temperature for 4 d. The pH was adjusted to 10 by addition of aqueous conc. ammonia, the mixture extracted with dichloromethane, the combined organic extracts dried ($MgSO_4$), evaporated and the valine methyl ester removed by distillation under high vacuum at ambient temperature. The residual material was subjected to flash chromatography using MeOH–CH_2Cl_2 5 : 95. The product 0.387 g (98%) was an oil. HRMS: M 322.1894. $C_{17}H_{26}N_2O_4$ requires 322.1893; ν_{max}(film)/cm^{-1} 3378 (w), 3321 (w), 2953 (m), 2926 (m), 1735 (s), 1672 (m), 1640 (m), 1437 (m), 1217 (s); δ_H($CDCl_3$) 1.52–2.18 (4 H, m, 4 × C*H*H), 1.66 (4 H, s, 2 × NH$_2$), 1.82–2.59 (6 H, m, 6 × C*H*H), 3.63 (3 H, s, OMe), 3.65 (3 H, s, OMe), 5.01–5.08 (4 H, m, 2 × CH=C*H*$_2$), 5.47–5.71 (2 H, m, 2 × C*H*=CH$_2$); δ_C($CDCl_3$) 13.8 (CH$_2$), 29.9 (CH$_2$), 38.6 (CH$_2$), 43.4 (CH$_2$), 44.2 (CH$_2$), 52.1 (OMe), 52.2 (OMe), 60.3 (MeO-(CO)-*C*-NH$_2$), 60.5

† CCDC reference number(s) 162724. See http://www.rsc.org/suppdata/p1/b1/b103254m/ for crystallographic files in .cif or other electronic format.

(MeO-(CO)-*C*-NH_2), 75.3 (*C*C), 82.6 (*C*C), 119.4 (*C*H_2=CH), 119.6 (*C*H_2=CH), 132.2 (2 × CH_2=*C*H), 175.7 (*C*O-OMe), 176.4 (*C*O-OMe); *m*/*z* (EI): 322 (M^+, 0.6%), 282 (16), 281 (100), 264 (15), 249 (11), 221 (11), 195 (13), 194 (20), 189 (24), 138 (11), 134 (11), 128 (10), 120 (37).

Dimethyl (2*R*,8*S*)-2,8-diallyl-2,8-diacetamidonon-4-yne-1,9-dioate 5

A solution of acetic acid anhydride (0.164 g, 1.61 mmol) in dichloromethane (6 ml) was added dropwise to a solution of dimethyl (2*R*,8*S*)-2,8-diallyl-2,8-diaminonon-4-yne-1,9-dioate **4** (0.140 g, 0.669 mmol) and DMAP (0.204 g, 1.67 mmol) in dichloromethane (12 ml) at 0 °C and the solution stirred at ambient temperature for 5 h. The reaction was stopped by addition of saturated aqueous ammonium chloride, the mixture extracted with dichloromethane and the combined organic extracts dried ($MgSO_4$), the solvent removed *in vacuo* and the product purified by flash chromatography using MeOH–CH_2Cl_2 5 : 95 to furnish a viscous oil, 176 mg (65%): HRMS: *M* 406.2105. $C_{21}H_{30}N_2O_6$ requires 406.2104; ν_{max}(film)/cm^{-1} 3281 (m), 3075 (m), 2952 (m), 2926 (m), 1740 (s), 1653 (s), 1540 (m), 1436 (m), 1221 (m); δ_H($CDCl_3$) 1.83–2.11 (3 H, m, 3 × C*H*H), 1.96 (3 H, s, COMe), 1.98 (3 H, s, COMe), 2.42 (2 H, dt, *J* 7.3, 14.6, CH_2), 2.51–2.61 (1 H, m, C*H*H), 2.67 (1 H, d, *J* 16.7, C*H*H), 2.95 (1 H, dd, *J* 7.3, 16.7, C*H*H), 3.05–3.17 (2 H, m, 2 × C*H*H), 3.71 (6 H, s, 2 × OMe), 4.97–5.06 (4 H, m, 2 × CH=CH_2), 5.43–5.61 (2 H, m, 2 × C*H*=CH_2), 6.32 (1 H, s, NH), 6.37 (1 H, s, NH); δ_C($CDCl_3$) 13.9 (*C*H_2CH_2-CH=CH_2), 23.6 (*Me*CO-), 23.9 (*Me*CO-), 25.3 (CH_2*C*H_2-CH=CH_2), 33.6 (CH_2), 38.9 (CH_2), 39.2 (CH_2), 52.7 (OMe), 52.7 (OMe), 62.8 (MeO-(CO)-*C*-NH), 63.8 (MeO-(CO)-*C*-NH), 75.4 (*C*C), 81.3 (*C*C), 119.0 (*C*H_2=CH), 119.3 (*C*H_2=CH), 131.6, (CH_2=*C*H), 131.9 (CH_2=*C*H), 169.2 (*C*ONHR), 169.5 (-*C*ONHR), 172.4 (CO_2Me), 173.5 (CO_2Me); *m*/*z* (CI): 406 (M^+, 6%), 366 (21), 365 (100), 361 (28), 347 (27), 323 (41), 305 (24), 283 (45), 281 (35), 263 (21), 237 (38), 236 (21), 221 (21), 204 (24), 194 (23), 171 (24), 128 (57), 91 (47).

1-(*tert*-Butyldimethylsilyloxy)but-3-yne 6

TBDSM-Cl (1.40 g, 9.32 mmol) was added to a solution of triethylamine (1.03 g, 1.40 ml, 10.17 mmol), DMAP (0.103 g, 0.849 mmol) and but-3-yn-1-ol (0.594 g, 8.49 mmol) in dichloromethane (27 ml). The mixture was stirred under argon at ambient temperature for 3 h, diluted by addition of diethyl ether, extracted with aq NH_4Cl, and the organic solution was dried ($MgSO_4$), the solvent distilled off and the product isolated after flash chromatography using EtOAc–hexane 1 : 10. The product 1.470 g (93%) was a liquid. δ_H($CDCl_3$) 0.05 (6 H, s, 2 × $SiCH_3$), 0.87 (9 H, s, 3 × CCH_3), 1.93 (1 H, t, *J* 2.7, CCH), 2.38 (2 H, dt, *J* 2.7, 7.1, CH_2CH_2O-), 3.72 (2 H, t, *J* 7.1, CH_2CH_2O-); δ_C($CDCl_3$) −5.3 (2 × $SiCH_3$), 18.3 (*C*Me_3), 22.8 (*C*H_2CCH), 25.9 (C*Me*$_3$), 61.7 (CH_2O), 69.3 (C*C*H), 81.5 (*C*CH).

5-(*tert*-Butyldimethylsilyloxy)pent-2-yn-1-ol 7

*n*BuLi in a hexane (20.30 ml, 1.50 M, 30.46 mmol) was added dropwise to a solution of 1-(*tert*-butyldimethylsilyloxy)but-3-yne **6** (5.63 g, 30.46 mmol) in THF (60 ml) at −40 °C and the mixture stirred at this temperature for 15 min before the solution was transferred through a teflon tube to a suspension of paraformaldehyde (2.92 g, 91.38 mmol) in THF (30 ml) at −45 °C. The reaction mixture was stirred at ambient temperature for 1 h, diethyl ether added, the organic phase washed with brine, dried ($MgSO_4$) and the solvent distilled off. The product was isolated after flash chromatography using EtOAc–hexane; 20 : 80 as an oil, yield 5.82 g (89%). δ_H($CDCl_3$) 0.05 (6 H, s, 2 × $SiCH_3$), 0.88 (9 H, s, 3 × CCH_3), 1.99 (1 H, t, *J* 3.8, CH_2O*H*), 2.44 (2 H, tt, *J* 1.4, 4.8, *H*$_2CH_2O$-), 3.73 (2 H, t, *J* 4.8, CH_2CH_2O-Si), 4.21–4.24 (2 H, m, CCCH_2O-H); δ_C($CDCl_3$) −5.3 (2 × $SiCH_3$), 18.3 (*C*Me_3), 23.1 (*C*H_2CCH), 25.8 (C*Me*$_3$), 51.2 (CH_2OH), 61.8 (*C*H_2OSi), 79.5 (C*C*CH_2OH), 83.2 (*C*CCH_2OH).

Pent-2-yne-1,5-diol 8

TBAF in THF (1.7 ml, 1.0 M, 1.70 mmol) was added to a solution of the 5-(*tert*-butyldimethylsilyloxy)pent-2-yn-1-ol **7** (0.282 g, 1.31 mmol) in THF (8.5 ml) at 0 °C. The mixture was stirred at 0 °C for 30 min, at ambient temperature for 3 h, and the solvent was removed by distillation and the product isolated after flash-chromatography using MeOH–CH_2Cl_2 1 : 10. The product 0.106 g (81%) was a liquid. ν_{max}(film)/cm^{-1} 3332 (s), 2884 (m), 1423 (m), 1135 (m), 1034 (s), 1012 (s); δ_H($CDCl_3$) 1.65 (1 H, s, CH_2O*H*), 2.16 (1 H, s CH_2O*H*), 2.47 (2 H, tt, *J* 2.2, 6.1, HOCH_2CH_2), 3.71 (1 H, t, *J* 6.1, HOC*H*$_2CH_2$), 4.24 (1 H, s, CCH_2OH); δ_C($CDCl_3$) 23.0 (HOCH_2*C*H_2), 50.9 (HO*C*H_2CH_2), 60.8 (HO*C*H_2C), 80.2 (C*C*), 83.1 (*C*C); *m*/*z* (EI): 82 (M^+ − 18, 30), 70 (10), 69 (9), 53 (20), 52 (100), 51 (13)(lit.[16,17]).

1,5-Dibromopent-2-yne 9

The reagent Br_2PPh_3 was prepared by the addition of Br_2 (3.98 g, 1.28 ml, 24.90 mmol) to a solution of PPh_3 (6.52 g, 24.90 mmol) in MeCN (53 ml) at 0 °C. Subsequently a solution of pent-2-yne-1,5-diol **8** (1.132 g, 11.32 mmol) in MeCN (10 ml) was added. The mixture was stirred at 0 °C for 15 min, at ambient temperature for 1 h, and the solvent was distilled off and the residual material triturated with diethyl ether. The undissolved and precipitated phosphine oxide was removed by filtration, the filtrate evaporated and the residual material subjected to flash chromatography using EtOAc–hexane; 1 : 10. The product was isolated as an oil, yield 1.892 g (74%). HRMS: *M* 225.8826. $C_5H_{10}Br_2$ requires 225.8816; ν_{max}(film)/cm^{-1} 3002 (w), 2969 (w), 2237 (w), 1417 (w), 1271 (m), 1211 (m); δ_H($CDCl_3$) 2.80 (2 H, tt, *J* 2.2, 7.2, CH_2CH_2Br), 3.40 (2 H, t, *J* 7.2, BrCH_2CH_2), 3.89 (2 H, t, *J* 2.2, BrCH_2CC); δ_C($CDCl_3$) 14.8 (BrCH_2*C*H_2), 23.3 (Br*C*H_2CH_2), 29.0 (Br*C*H_2C), 77.3 (C*C*), 84.2 (*C*C); *m*/*z* (EI): 228 (M^+, 10%), 226 (M^+, 17), 224 (M^+, 9), 147 (58), 145 (56), 81 (10), 79 (12), 66 (53), 65 (100), 63 (23), 62 (15) (lit.[16]).

(2*S*,5*R*)-2,5-Dihydro-5-isopropyl-3,6-dimethoxy-4′-[(2*R*,5*R*)-2,5-dihydro-5-isopropyl-3,6-dimethoxypyrazine-2-spiro-(cyclopent-3′-en-3′-yl)]pyrazine-2-spiro(cyclohex-3′-ene) 10

Bis(tricyclohexylphosphine)benzylidene ruthenium dichloride (50 mg, 0.0608 mmol) was added to a solution of 1-[(2*R*,5*R*)-5-allyl-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazin-5-yl]-5-[(2*R*,5*S*)-5-allyl-2,5-dihydro-2-isopropyl-3,6-dimethoxy-pyrazin-5-yl]pent-2-yne **3** (0.623 g, 1.22 mmol) in dry degassed toluene (50 ml) under argon. The reaction mixture was kept at 85 °C for 5 h when another portion of the catalyst (50 mg, 0.0603 mmol) was added and the heating continued for 5 h. The cold mixture was filtered, the filtrate evaporated and dry dichloromethane added. Any remaining catalyst was complexed by addition of tri(hydroxymethyl)phosphine (50 mg, 0.304 mmol) and triethylamine (84 μl) and the product isolated after flash chromatography using EtOAc–hexane 10 : 90. The product 0.567 g (96%) was a white solid with mp 138 °C (MeCN). HRMS: *M* 484.3033. $C_{27}H_{40}N_4O_4$ requires 484.3050 (Found: C, 66.92; H, 8.78. $C_{27}H_{40}N_4O_4$ requires: C, 66.91; H, 8.32%); ν_{max}(ATR plate)/cm^{-1} 2957 (m), 2944 (m), 2871 (w), 1690 (s), 1462 (m), 1436 (m), 1300 (m), 1232 (s), 1032 (m); δ_H(300 MHz, $CDCl_3$) 0.67 (3 H, d, *J* 6.9, CH*Me*$_2$), 0.69 (3 H, d, *J* 6.9, CH*Me*$_2$), 1.05 (3 H, d, *J* 6.9, CH*Me*$_2$), 1.07 (3 H, d, *J* 6.9, CH*Me*$_2$), 1.49–1.55 (1 H, m, C*H*H-CH_2), 1.88 (1 H, dd, *J* 4.1, 18.3, C*H*H-CH=C), 2.07 (1 H, dt, *J* 5.4, 12.4, C*H*H), 2.17–2.30 (3 H, m, CH*H* and 2 × $CHMe_2$), 2.46–2.56 (3 H, m, 3 × CH*H*-CH=C), 2.72–2.79 (1 H, m, CH*H*-CH=C), 2.94–3.13 (2 H, m, 2 × CH*H*-CH=C), 3.58 (3 H, s, OMe), 3.62 (3 H, s,

OMe), 3.64 (3 H, s, OMe), 3.68 (3 H, s, OMe), 3.93 (1 H, d, *J* 3.4, H-2 or H-2′), 3.98 (1 H, d, *J* 3.4, H-2 or H-2′), 5.43–5.51 (1 H, m, C*H*=C cyclopent.), 5.57–5.64 (1 H, m, C*H*=C cyclohex); δ_C(75 MHz, $CDCl_3$) 16.9 (CH*Me*$_2$), 16.95 (CH*Me*$_2$), 19.3 (CH*Me*$_2$), 19.4 (CH*Me*$_2$), 22.1 (CH_2), 30.9 (*C*HMe$_2$), 31.3 (*C*HMe$_2$), 33.1 (CH_2), 37.3 (CH_2), 48.8 (CH_2), 49.4 (CH_2), 52.2 (OMe), 52.3 (OMe), 52.4 (OMe), 52.5 (OMe), 55.8 (C-2 or C-2′), 60.6 (C-2 or C-2′), 61.1 (C-5 or C-5′), 62.2 (C-5 or C-5′), 120.9 (C=*C*H), 121.4 (C=*C*H), 132.5 (*C*=CH), 141.2 (*C*=CH), 161.0 (C-3 or C-3′ or C-6 or C-6′), 161.4, (C-3 or C-3′ or C-6 or C-6′), 166.2 (C-3 or C-3′ or C-6 or C-6′); *m*/*z* (EI): 484 (M^+, 100), 457 (21), 451 (13), 442 (20), 441 (73), 409 (14), 289 (11), 245 (39), 197 (12), 195 (11), 154 (13), 153 (28).

The structure has been verified by a single crystal X-ray analysis (Fig. 1).

3′,3″-Bi[(2*R*,5*R*)-2,5-dihydro-5-isopropyl-3,6-dimethoxypyrazine-2-spiro(cyclopent-3′-en-3′-yl)] 13

(IMes)(PCy_3)$RuCl_2$(=CHPh) (12 mg, 0.0144 mmol) was added to a solution of 1,4-bis[(2*R*,5*R*)-5-allyl-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazin-5-yl]but-3-yne[21] **12** (0.072 g, 0.144 mmol) in dry degassed toluene (6 ml) under argon and the reaction heated at 85 °C for 3 h when more catalyst (12 mg, 0.0144 mmol) was added and the heating continued for 3 h. Another portion (12 mg, 0.0144 mmol) of the catalyst was added and the mixture heated for another 3 h. The solvent was then distilled off and the product isolated after flash chromatography using EtOAc–hexane 10 : 90. The product was a white solid mp 141 °C, 0.062 g (92%). HRMS: *M* 471.2968. $C_{26}H_{39}N_4O_4$ requires 471.2966; ν_{max}(KBr)/cm^{-1} 2940 (m), 1675 (s), 1455 (w), 1430 (w), 1295 (m), 1230 (s), 1215 (s), 1190 (m), 1132 (m), 1025 (m), 995 (m); δ_H($CDCl_3$) 0.69 (6 H, d, *J* 6.8, CH*Me*$_2$), 1.05 (6 H, d, *J* 6.8, CH*Me*$_2$), 2.21 (2 H, dsept, *J* 3.4, 6.8, 2 × CHMe$_2$), 2.41–2.54 (4 H, m, 4 × C*H*H), 3.02–3.12 (4 H, m, 4 × C*H*H), 3.61 (6 H, s, 2 × OMe), 3.68 (6 H, s, 2 × OMe), 3.97 (2 H, d, *J* 3.4, H-2 and H-2′), 5.47 (2 H, br s, 2 × C*H*=C); δ_C($CDCl_3$) 16.9 (2 × CH*Me*$_2$), 19.3 (2 × CH*Me*$_2$), 31.3 (2 × CHMe$_2$), 49.1 (2 × CH_2), 49.4 (2 × CH_2), 51.3 (2 × OMe), 52.5 (2 × OMe), 61.1 (C-5 and C-5′), 62.7 (C-2 and C-2′), 124.2 (2 × C=CH), 136.9 (2 × C=CH), 161.3 (C-3, C-3′ or C-6, C-6′), 165.8 (C-3, C-3′ or C-6, C-6′); *m*/*z* (CI) 471 (M^+ + 1, 100%), 470 (M^+, 52%), 440 (11), 439 (37), 427 (37), 295 (50), 294 (19), 293 (16), 279 (18), 263 (21), 251 (22), 225 (12), 123 (31).

Methyl (1*R*,3*R*′)-1-acetamido-3-(4-acetamido-4-methoxycarbonylcyclopent-1-en-1-yl)cyclohex-3-enecarboxylate 14

Compound **14** was prepared as above from (tricyclohexylphosphine)benzylidene ruthenium dichloride (2 × 54 mg, 0.132 mmol) and dimethyl (2*R*,8*S*)-2,8-diacetamido-2,8-diallylnon-4-yne-1,9-dioate **5** (0.321 g, 0.792 mmol). After removal of the solvent, the residue was redissolved in dichloromethane and tri(hydroxymethyl)phosphine (210 mg, 1.32 mmol) and triethylamine (0.36 ml) added. Evaporation and flash chromatography using MeOH–CH_2Cl_2 7 : 93 gave the product as a white solid 0.290 g (97%) with mp 270 °C. HRMS (electrospray): *M* 379.1871. $C_{19}H_{26}N_2O_6$ requires 379.1864; ν_{max}(KBr)/cm^{-1} 3260 (m), 3020 (w), 1725 (s), 1645 (s), 1525 (s), 1425 (m), 1360 (m), 1290 (m), 1215 (m), 1075 (w); δ_H($CDCl_3$) 1.87–1.97 (1 H, m, CH_2), 1.90 (3 H, s, COMe), 1.91 (3 H, s, COMe), 2.11–2.22 (1 H, m, CH_2CH$_2$-C=CH), 2.28–2.39 (3 H, m, 3 × C*H*H), 2.59–2.81 (3 H, m, 3 × CH*H*), 3.03–3.16 (2 H, m, 2 × CH*H*), 3.66 (3 H, s, OMe), 3.68 (3 H, s, OMe), 5.25 (1 H, m, CH=C), 5.45 (1 H, m, CH=C), 5.66–5.74 (2 H, s, 2 × NH-Ac); δ_C($CDCl_3$) 22.2 (*C*H$_2$CH$_2$-C=CH), 22.8 (*Me*CO-), 23.0 (*Me*CO-), 27.1 (CH$_2$*C*H$_2$-C=CH), 34.2 (*C*H$_2$-C=CH), 43.5 (CH$_2$CH=C), 44.5 (CH$_2$CH=C), 52.4 (OMe), 52.7 (OMe), 120.4 (*C*H=C), 121.2 (*C*H=C), 132.4 (CH=*C*), 140.4 (CH=*C*), 170.1 (*C*O), 170.2 (*C*O), 174.1 (*C*O), 174.2 (*C*O); *m*/*z* (EI): 378 (M^+, 0%), 333 (3), 319 (13), 261 (15), 260 (100), 245 (7), 213 (7), 201 (11), 200 (15), 169 (9), 141 (8).

Dimethyl (2*R*,7*R*)-2,7-diacetamido-4,5-bis(ethoxycarbonyl)-1,2,3,3a,5a,6,7,8-octahydro-*as*-indacene-2,7-dicarboxylate 17 and dimethyl (2*S*,7*S*)-2,7-diacetamido-4,5-bis(ethoxycarbonyl)-1,2,3,6,7,8-hexahydro-*as*-indacene-2,7-dicarboxylate 18

Dimethyl (1*R*,1′*R*)-1,1′-diacetamido-3,3′-bicyclopenta-3,3′-diene-1,1′-dicarboxylate **15** (0.172 g, 0.469 mmol) and diethyl acetylenedicarboxylate (0.119 g, 0.705 mmol) were heated together in anisole (6 ml) at 145 °C overnight. The solvent was distilled off at reduced pressure and the products were isolated by flash chromatography using MeOH–CH_2Cl_2 7 : 93. Separation of the aromatized product **18** and the dihydro product **17** was not effected under these conditions. The ratio between the compounds was determined by ^{1}H NMR and found to be **17**–**18** 66 : 33; total yield 0.160 g (63%). This mixture was used directly. Thus MnO_2 (0.520 g, 6.0 mmol) was added to a solution of the mixture (0.160 g, 0.300 mmol) in dioxane (15 ml), and the reaction stirred at ambient temperature for 4 h. Filtration through silica gel using CH_2Cl_2–MeOH 80 : 20 and evaporation of the filtrate left a white solid, mp 248 °C (decomp.), yield 0.146 g (91%) (Found: C, 58.64; H, 6.06. $C_{26}H_{32}N_2O_{10}$ requires: C, 58.77; H, 6.16%); MS (electrospray): *M* 533.2132. $C_{26}H_{33}N_2O_{10}$ requires: 533.2130; $[\alpha]_D$ +30.96 (*c* = 0.062, DMSO); ν_{max}(film)/cm^{-1} 3271 (m), 3053 (m), 2983 (m), 2955 (m 2930 (m), 2849 (m), 2253 (w), 1716 (s), 1652 (s), 1538 (s), 1432 (m), 1372 (m), 1411 (s), 1198 (s), 1067 (m), 1040 (m); δ_H($CDCl_3$) 1.29 (6 H, t, *J* 7.1, 2 × Me), 1.92 (6 H, s, 2 × MeCO), 3.21 (2 H, d, *J* 16.8, 2 × C*H*H), 3.37 (2 H, d, *J* 17.0, 2 × C*H*H), 3.57 (2 H, d, *J* 16.8, 2 × C*H*H), 3.61 (2 H, d, *J* 17.0, 2 × C*H*H), 3.67 (6 H, s, 2 × OMe), 4.29 (4 H, q, *J* 7.1, 2 × CH_2-Me), 6.25 (2 H, s, 2 × NH); δ_C($CDCl_3$) 14.1 (2 × Me), 23.1 (2 × *Me*CO-N), 41.5 (2 × CH_2), 43.7 (2 × CH_2), 61.6 (2 × O*C*H$_2$Me), 61.6 (2 × MeO-(CO)-*C*-NH), 67.1 (2 × OMe), 127.5 (2 × Ar), 139.5 (2 × Ar), 140.1 (2 × Ar), 167.3 (2 × CO), 170.2 (2 × CO), 173.1 (2 × CO); *m*/*z* (EI): 550 (M^+ + 18, 18%), 521 (4), 519 (3), 518 (10), 493 (3), 487 (4), 486 (3).

Dimethyl (3*R*,6*R*)-3,6-diacetamido-9,10-bis(ethoxycarbonyl)-1,2,3,4,5,6,7,8,8a,10a-decahydrophenanthrene-3,6-dicarboxylate 19

Dimethyl (1*R*,1′*R*)-1,1′-diacetamido-3,3′-bicyclohexa-3,3′-diene-1,1′-dicarboxylate[21] **16** (0.235 g, 0.645 mmol) and diethyl acetylenedicarboxylate (0.204 g, 1.20 mmol) were heated together in anisole (10 ml) at 145 °C overnight. The solvent was distilled off at reduced pressure. The residual material was subjected to flash chromatography using MeOH–CH_2Cl_2 4 : 96. The product was a white solid, 0.220 g (64%); δ_H($CDCl_3$) 1.23 (3 H, t, *J* 7.1, OCH$_2$C*H*$_3$), 1.24 (3 H, t, *J* 7.1, OCH$_2$C*H*$_3$), 1.65 (1 H, d, *J* 14.3, C*H*H), 1.78 (1 H, dt, *J* 3.3, 13.3, C*H*H), 1.15–1.37 (2 H, m, 2 × C*H*H), 1.88–2.24 (6 H, m, 6 × C*H*H), 1.92 (3 H, s, CO*Me*), 2.01 (3 H, s, CO*Me*), 2.51 (1 H, dd, *J* 1.5, 13.9, C*H*H), 2.87–2.93 (2 H, m, C=C-C*H*), 3.01 (1 H, d, *J* 14.3, C*H*H), 3.63 (3 H, s, O*Me*), 3.64 (3 H, s, OMe), 4.11–4.24 (4 H, m, OCH_2CH$_3$), 6.68 (1 H, s, NH-Ac), 8.16 (1 H, s, NH-Ac); δ_C($CDCl_3$) 13.9 (2 × OCH$_2$*C*H$_3$), 22.3 (CO*Me*), 22.7 (CO*Me*), 28.1 (CH_2), 28.4 (CH_2), 29.6 (CH_2), 34.9 (CH_2), 36.0 (CH_2), 36.5 (CH_2), 40.6 (2 × *C*H-C=C), 52.2 (OCH$_3$), 52.6 (OCH$_3$), 59.1 (MeO-(CO)-*C*-NH), 59.4 (MeO-(CO)-*C*-NH), 61.1 (2 × O*C*H$_2$CH$_3$), 123.8 (*C*=C), 127.1 (*C*=C), 133.1 (*C*=C), 135.89 (*C*=C), 167.3 (*C*O), 169.9 (*C*O), 170.2 (2 × *C*O), 173.8 (*C*O), 174.3 (*C*O).

Dimethyl (3*R*,6*R*)-3,6-diacetamido-9,10-bis(ethoxycarbonyl)-1,2,3,4,5,6,7,8-octahydrophenanthrene-3,6-dicarboxylate 20

MnO_2 (0.231 g, 2.66 mmol) was added to a solution of dimethyl (3*R*,6*R*)-3,6-diacetamido-9,10-bis(ethoxycarbonyl)-1,2,3,4,5,6,

7,8,8a,10a-decahydrophenanthrene-3,6-dicarboxylate **19** (0.071 g, 0.126 mmol) in dioxane (5 ml) and the reaction mixture stirred at ambient temperature for 4 h. The reaction mixture was filtered through silica gel using CH_2Cl_2–MeOH 80 : 20, and the filtrate evaporated. The remaining product was a white solid mp 127–129 °C; yield 0.066 g (94%). HRMS (electrospray): *M* 561.2418. $C_{28}H_{37}N_2O_{10}$ requires 561.2443; $[\alpha]_D$ −46.81 (*c* = 0.045, DMSO); ν_{max}(ATR plate)/cm^{-1} 3357 (m), 3296 (m), 3060 (m), 2982 (m), 2953 (m), 1728 (s), 1655 (s), 1535 (s), 1435 (s), 1370 (s), 1271 (s), 1186 (s), 1043 (m), 1025 (m); δ_H($CDCl_3$) 1.30 (6 H, t, *J* 7.1, 2 × -CH_2CH_3), 1.89 (6 H, s, 2 × MeCO), 1.93–2.00 (2 H, m, 2 × C*H*H), 2.39–2.49 (2 H, m, 2 × C*H*H), 2.71–2.95 (4 H, m, 4 × C*H*H), 2.87 (2H, d, *J* 17.3, 2 × CH*H*-Ar), 3.08 (2H, d, *J* 17.3, 2 × CH*H*-Ar), 3.70 (6 H, s, 2 × OMe), 4.21–4.31 (4 H, t, 2 × -CH_2CH_3), 6.03 (2 H, s, 2 × NH-Ac); δ_C($CDCl_3$) 14.0 (2 × CH_3CH_2O), 22.9 (2 × *Me*CO-N), 23.3 (2 × CH_2CH_2Ar), 27.5 (2 × CH_2CH_2Ar), 35.1 (2 × CH_2Ar), 52.7 (2 × OMe), 58.2 (2 × MeO-(CO)-*C*-NH), 61.6 (2 × OCH_2CH_3), 130.1 (2 × Ar), 131.1 (2 × Ar), 134.7 (2 × Ar), 167.9 (2 × *C*O), 170.4 (2 × *C*O), 173.7 (2 × *C*O); *m*/*z* (EI): 560 (M^+, 0%), 514 (24), 396 (29), 395 (100), 366 (53), 349 (32), 323 (27), 308 (41), 290 (32), 191 (31), 178 (48), 177 (39), 176 (51), 165 (44), 152 (29).

Dimethyl (2*R*,8*R*)-2,8-diacetamido-4,5-bis(ethoxycarbonyl)-2,3,3a,5a,6,7,8,9-octahydro-1*H*-cyclopenta[*a*]naphthalene-2,8-dicarboxylate 21 and dimethyl (2*R*,8*S*)-2,8-diacetamido-4,5-bis(ethoxycarbonyl)-2,3,6,7,8,9-hexahydro-1*H*-cyclopenta[*a*]-naphthalene-2,8-dicarboxylate 22

Methyl (1*R*,3*R*′)-1-acetamido-3-(4-acetamido-4-methoxycarbonylcyclopent-1-en-1-yl)cyclohex-3-enecarboxylate **14** (0.290 g, 0.767 mmol) was heated together with diethyl acetylenedicarboxylate (0.26 g, 0.153 mmol) in anisole (7 ml) at 145 °C overnight. The solvent was removed *in vacuo* and the products were isolated by flash chromatography using MeOH–CH_2Cl_2 6 : 94. The adduct **21** and its aromatized product **22** were not separated under these conditions and were isolated in the ratio 1 : 1, in all 0.287 g (68%). Part of the mixture was aromatized either by treatment with DDQ or with MnO_2.

DDQ: The 1 : 1 product mixture (33 mg, 0.060 mmol) was dissolved in dioxane (5 ml) and stirred with DDQ (20 mg, 0.090 mmol) at 100 °C for 5 h. The product was isolated as a white solid after flash chromatography using MeOH–CH_2Cl_2 5 : 95. Yield: 0.30 g (91%), mp 270 °C (CH_2Cl_2).

MnO_2: The product mixture (22 mg, 0.040 mmol) was dissolved in dioxane (3 ml) and the solution stirred with MnO_2 (70 mg, 0.80 mmol) at 100 °C for 5 h. The product was isolated as a white solid after flash chromatography using MeOH–CH_2Cl_2 5 : 95. Yield: 0.21 g (>95%) mp 270 °C (CH_2Cl_2). HRMS: *M* 547.2304. $C_{27}H_{34}N_2O_{10}$ requires 547.2286; $[\alpha]_D$ +19.91 (*c* = 0.024, DMSO); ν_{max}(ATR plate)/cm^{-1} 3350 (m), 3294 (m), 3065 (w), 2960 (m), 2927 (m), 1724 (s), 1656 (s), 1537 (m), 1434 (m), 1370 (m), 1298 (s), 1259 (s), 1201 (s), 1085 (m), 1020 (m); δ_H($CDCl_3$) 1.23 (3 H, t, *J* 7.1, OCH_2CH_3), 1.24 (3 H, t, *J* 7.1, OCH_2CH_3), 1.75 (3 H, s, COMe), 1.77 (3 H, s, COMe), 1.86–1.99 (1 H, m, C*H*H), 2.21–2.25 (1 H, m, C*H*H), 2.58–2.76 (2 H, m, 2 × C*H*H), 2.90 (1 H, d, *J* 17.1, C*H*H), 3.11 (1 H, d, *J* 17.2, C*H*H), 3.15 (1 H, d, *J* 17.1, C*H*H), 3.39–3.47 (2 H, m, C*H*H), 3.53–3.61 (1 H, m, C*H*H), 3.58 (3 H, s, OMe), 3.61 (3 H, s, 2 × OMe), 4.17–4.26 (4 H, m, OCH_2CH_3), 8.20 (1 H, s, 2 × NH-Ac), 8.57 (1 H, s, NH-Ac); δ_C($CDCl_3$) 13.8 (OCH_2CH_3), 13.9 (OCH_2CH_3), 22.2 (CO*Me*), 22.2 (CO*Me*), 23.0 (CH_2), 27.6 (CH_2), 33.8 (CH_2), 41.3 (CH_2), 43.7 (CH_2), 52.1 (OCH_3), 52.3 (OCH_3), 56.3 (MeO_2C-*C*-NH), 60.9 (OCH_2CH_3), 61.0 (OCH_2CH_3), 64.0 (MeO_2C-*C*-NH), 123.5 (Ar), 130.4 (Ar), 132.9 (Ar), 135.7 (Ar), 137.8 (Ar), 141.2 (Ar), 166.0 (EtO_2C), 167.7 (EtO_2C), 169.6 (*C*ONHAc), 169.7 (*C*ONHAc), 173.3 (CO_2Me), 173.6 (CO_2Me).

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