Ru(II)-Catalyzed Cascade Reactions in Stereocontrolled Construction of Rigid *as*-Indacene-Bridged Bis(α-amino acid) Derivatives

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The key construction in the preparation of *as*-indacene-bridged bis(α-amino acid) derivatives was effected by a Ru(II)-catalyzed RCM cascade reaction of appropriately substituted triynes. The latter were available after stepwise and stereocontrolled alkynylations of (2*R*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine as chiral auxiliary. The regio- and stereochemical transformations have been verified by a single-crystal X-ray analysis.

Introduction

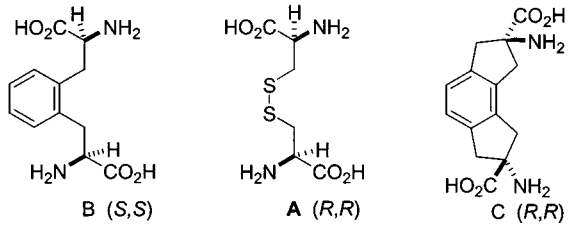
Cystine (**A**, Scheme 1) can be regarded as a four-atom bridged bis(α-amino acid). We have for some time been involved in the preparation of conformationally constrained C_4-bridged cystine analogues in which the disulfide moiety has been exchanged with a C_2-unit.[1,2] Conformational constraints were effected by insertion of a double or triple bond in the all-carbon C_4-bridge,[1] or by insertion of aryl or heteroaryl groups in the chain.[2] The conformational constraints in C_4-bridged molecules have been additionally increased by carbosubstitution at the α-carbon of the amino acid.[3]

In Scheme 1 the vicinal bis(alanine) structure **B** represents our first C_4-bridge with an inserted arene. The conformational freedom of this structure is largely lost when rotation around the single carbon−carbon bonds is prevented by ring annulations as in the tricyclic bis(α-amino acid) derivative **C**, a very rigid amino acid analogue.

In this report we describe methodology aimed at the construction of *as*-indacene-bridged bis(α-amino acid) derivatives by a Ru(II)-effected cascade reaction with an appropriate triyne as substrate. In a recent report we have described the preparation of tricyclic-bridged bis(α-amino acid) derivatives from ynedienes by a Diels−Alder reaction of the conjugated diene cascade products.[4]

The most significant step in the construction is a cascade reaction using Grubbs's versatile ring-closing metathesis (RCM) methodology with a precatalyst system consisting of bis(tricyclohexylphosphine)benzylidene ruthenium dichloride.[5] Recent modifications of the ligand systems in the precatalyst complex has further extended

Scheme 1



the scope of this methodology.[6] For the present work the original catalyst system was satisfactory, and the strategy used was adapted from a recent report on ruthenium-catalyzed conversion of triynes to benzene derivatives in a metathesis cascade reaction.[7]

Results and Discussion

Scheme 2 shows the preparation of intermediates to be used as substrates for the RCM reactions eventually affording tricyclic bridged bis(α-amino acid) structures. A C_4-alkyne bridge was initially constructed by alkylation of lithiated (2*R*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine (**1**) as the chiral auxiliary with 1,4-dibromo-2-butyne as previously described.[4] The reaction is stereoselective in that the electrophile becomes attached trans to the isopropyl group. The degree of stereoselectivity in this step is not important because the stereochemical information is lost when the bridged product **2** becomes the substrate for a second lithiation and alkynylation reaction. Only one stereoisomer was observed in the alkynylation reaction in accordance with previous experience in stepwise dialkylations of the bislactim ether substrate **1**.[8] The new electrophile enters trans to the isopropyl group thereby providing the stereoisomer **3**. Silyl-protected propargyl chloride was used for the alkylation of the dilithiated substrate **2** to provide the dialkylated product **3** in 60% yield. An initial attempt to

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(1) (a) Kremminger, P.; Undheim, K. *Tetrahedron* **1997**, *53*, 6925−6936. (b) Efskind, J.; Benneche, T.; Undheim, K. *Acta Chem. Scand.* **1997**, *51*, 942−952. (c) Möller, B. S.; Benneche, T.; Undheim, K. *Tetrahedron* **1996**, *52*, 8807−8812.

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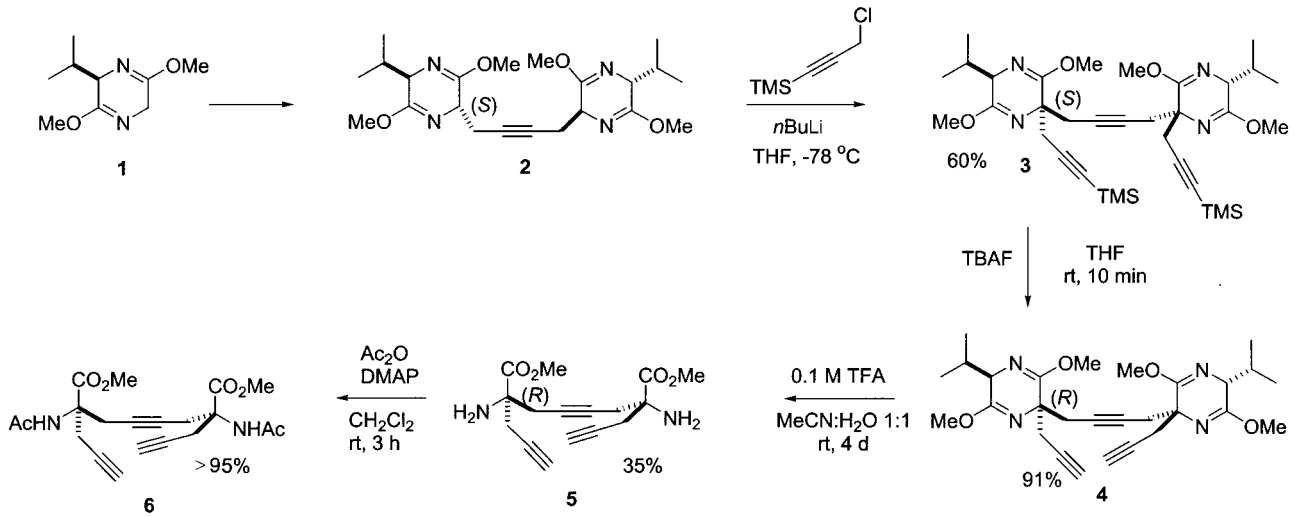
Scheme 2



use unprotected propargyl chloride for alkylation of the alkyne **2** in a direct preparation of the triyne **4** was unsatisfactory.

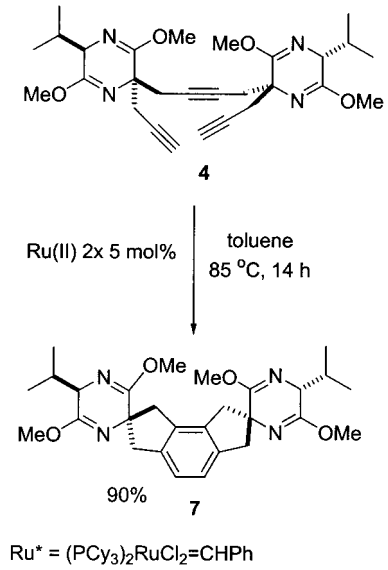
Removal of the TMS-protecting group in structure **3** proceeded readily with tetrabutylammonium fluoride (TBAF). The desilylated material **4** was subsequently subjected to hydrolysis under mild acid conditions, viz. 0.1 M TFA in aqueous acetonitrile at ambient temperature. In sterically crowed substrates such as the triyne **4** the hydrolysis is slow and is accompanied by partially hydrolyzed products. Hydrolysis under forcing conditions takes another course with formation of the corresponding diketopiperazines. The latter can be hydrolyzed further to amino acids when the substrate and the products are stable under the strongly acidic conditions necessary.[9]

The bridged amino ester **5** was *N*-protected before the RCM reaction to avoid interference with the catalyst system. For convenience, acetic anhydride was used to provide the diacetamide **6**.

All products **2**−**6** have C_2-symmetry as seen in the NMR spectra. Epimeric products at the new stereogenic centers would result in more complex NMR spectra. Since no NMR signals from the corresponding diastereoisomers of the dialkylated structures **3**−**6** were seen, stereochemically pure products were formed in these reactions.

Previous experience has shown that the Ru(II)-catalyzed RCM reaction is strongly affected by sterical factors. Thus, highly congested molecules may react with close to quantitative conversion while apparently subtle changes in such molecules may result in almost no conversion.[10] The cascade reaction of the congested triyne **4** in Scheme 3 gave the bis-spiro pentacyclic product **7** in high yield (90%). The reaction with the triyne **4** was effected in toluene at 85 °C over 14 h. At lower temperature there was no reaction, or the reaction was very slow. Catalyst (5 mol %) was added twice. A second addition of catalyst was necessary to compensate for the thermal instability of the catalyst at the temperature of

Scheme 3



the reaction. After 7 h, when the second portion of the catalyst was added, the RCM conversion was close to 60%. The high overall yield in this reaction seems remarkable in view of the number of steps involved. By analogy to suggestions made for the mechanism in triyne cascade reactions,[7] initial adduct formation between the catalyst complex and a terminal triple bond is envisaged. Subsequent eliminations to carbenoids and readditions eventually lead to the product **7**.

The structure assigned to the cascade product has been verified by a single-crystal X-ray analysis. An ORTEP plot of the X-ray structure of **7** is shown in Figure 1. The structure determination confirms both the regiochemistry in the cascade reaction and the relative stereochemistry in the earlier alkylation steps in the formation of structure **4**.

The cascade reaction with the *N*-protected alkyne-bridged bis(α-amino acid) derivative **6** also proceeded well (Scheme 4). The *as*-indacene-bridged bis(α-amido acid) derivative **8** was isolated in 58% yield under the same conditions as used above.

The product **9** with free amino groups was obtained by hydrolytic cleavage of the congested bis-spiro pentacyclic product **7** (Scheme 5). As in the hydrolytic reaction

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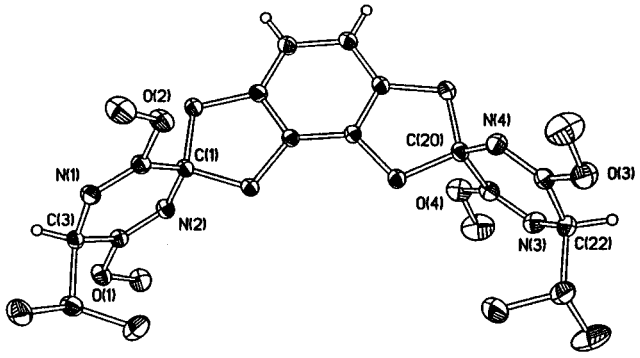
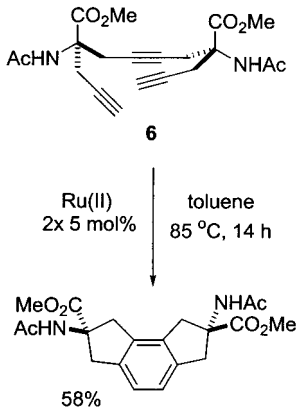
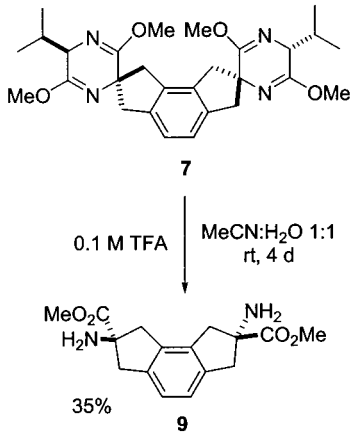


Figure 1. The ORTEP plot of compound **7**. The compound crystallized with one molecule acetonitrile per organic molecule. The acetonitrile molecule is omitted from the figure. Ellipsoids are shown at 50% probability. For clarity only the hydrogens at stereogenic centers and at the arene are shown.

Scheme 4



Scheme 5



of the triyne **4** (Scheme 2), the reaction under mild acidic conditions at ambient temperature was slow and partially completed when the reaction was stopped after 4 days, yield 35% of the target compound **9**.

In conclusion, we have developed a synthesis of *as*-indacene-bridged bis(α-amino acid) derivatives where the key step involves a Ru(II)-catalyzed RCM cascade reaction of appropriately substituted triynes which had been prepared in a stereoselective manner.

Experimental Section

^{1}H NMR spectra were recorded in $CDCl_3$ at 500, 300, or 200 MHz with Bruker DPX 500, DPX 300, or DPX 200. The ^{13}C spectra were recorded in $CDCl_3$ at 125, 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 recorded on a Perkin-Elmer 1310 infrared spectrophotometer or a Nicolet Magna FT-IR 550 spectrophotometer with attenuated total reflectance (ATR spectra).

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 for Compund 7. X-ray data were collected on a Siemens SMART CCD diffractometer[11] using graphite monochromated MoKα 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.[11] Absorption corrections were applied by the use of the SADABS program.[12] The structure was determined and refined using the SHELXTL program package.[13] The non-hydrogen atoms were refined with anisotropic thermal parameters; hydrogen positions were found from difference Fourier maps and refined with isotropic thermal parameters.

The compound crystallizes with one molecule acetonitrile per organic molecule. Two of its hydrogen atoms were not observed in the difference Fourier map.

Crystal data for $C_{28}H_{38}N_4O_4.C_2H_3N$ (**7**), M = 535.66, monoclinic, $P2_1$, a = 7.772(1), b = 11.411(1), c = 16.813(1) Å, β = 95.79(1)°, V = 1483.5(2) Å^3, Z = 2, D_x = 1.195 mg m^{-3}, μ = 0.081 mm^{-1}, T = 150(2) K, 30949 measured reflections in 2θ range 11.7−72.6°, R_{int} = 0.022. 508 parameters refined against 13433 F^2, $R1$ = 0.045, $Rw2$ = 0.114 for $I_o > 2\sigma(I_o)$ and $R1$ = 0.057, $Rw2$ = 0.123 for all data.

The single-crystal X-ray analytical data for structure **7** have been deposited with the Cambridge Crystallographic Data Centre as deposition number CCDC 164970.

1,4-Bis[(2*R*,5*S*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazin-5-yl]-2-butyne 2. Compound **2** was prepared from lithiated (2*R*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine and 1,4-dichloro-2-butyne in 71% yield as described.[4]

1,4-Bis[(2*R*,5*S*)-2,5-dihydro-2-isopropyl-3,6-dimethoxy-5-(trimethylsilylpropargyl)pyrazin-5-yl]-2-butyne 3. *n*BuLi (1.51 M in hexane, 5.5 mL, 8.33 mmol) was added to a solution of 1,4-bis[(2*R*,5*S*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazin-5-yl]-2-butyne **2** (1.66 g, 3.97 mmol) in THF (10 mL) at −78 °C and the mixture stirred at this temperature for 1 h before a solution of trimethylsilylpropargyl bromide (1.59 g, 8.33 mmol) in THF (10 mL), precooled to −78 °C, was added dropwise. The reaction mixture was stirred at this temperature for 3 h and allowed to reach ambient temperature overnight. Phosphate buffer was added, the phases were separated, the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL), the combined organic phases were dried ($MgSO_4$) and evaporated, and the residual material was subjected to flash chromatography using 10% EtOAc in hexane. The product was a yellow crystalline solid with mp 101−103 °C (MeCN); yield 1.52 g, (60%). IR (film) 2958 (s), 2180 (m), 1698 (s) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.53 (s, 18 H, 2 × $SiMe_3$), 0.67 (d, 6 H, J = 6.8 Hz, 2 × CHC*H*$_3$Me), 1.06 (d, 6 H, J = 6.8 Hz, 2 × CHC*H*$_3$-Me), 2.29 (ds, 2 H, J = 6.8, 3.3 Hz, 2 × C*H*Me$_2$), 2.42−2.44 (m, 4 H, 2 × CH_2), 2.54 (s, 4 H, 2 × CH_2), 3.65 (s, 12 H, 4 × OMe), 3.91 (d, 2 H, J = 3.3 Hz, H-2 and H-2′). ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.0 (2 × $SiMe_3$), 17.1 (2 × *C*H$_3$MeCH), 19.7 (2 × *C*H$_3$-

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(12) Sheldrick, G. M., SADABS Version 2.01. Program for Empirical Correction of Area Detector Data, University of Göttingen, Germany, 2000.

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MeCH), 30.7 (2 × *C*HMe$_2$), 30.8 (2 × *C*H$_2$), 32.2 (2 × CH$_2$), 52.6 (2 × OMe), 52.6 (2 × OMe), 61.3 (C-2, C-2′), 61.3 (C-5, C-5′), 78.7 (2 × *C*C), 86.8 (2 × *C*CSi), 103.3 (2 × *C*CSi), 161.8 (C-3, C-3′ or C-6, C-6′), 164.1 (C-3, C-3′ or C-6, C-6′). MS(EI) (*m*/*z*): 638 (M$^+$, 10), 595 (11), 528 (37), 527 (100), 293 (51), 251 (39), 73 (38). HRMS: calcd for $C_{34}H_{54}N_4O_4Si_2$ 638.3671 (M$^+$); observed 638.3684. Anal. Calcd for $C_{34}H_{54}N_4Si_2$, C, 63.91; H, 8.52. Found: C, 64.33; H, 8.05.

1,4-Bis[(2*R*,5*R*)-2,5-dihydro-2-isopropyl-3,6-dimethoxy-5-propargylpyrazin-5-yl]-2-butyne 4. TBAF in THF (4.8 mL, 4.82 mmol) was added dropwise to a solution of 1,4-bis-[(2*R*,5*S*)-2,5-dihydro-2-isopropyl-3,6-dimethoxy-5-(trimethylsilylpropargyl)pyrazin-5-yl]-2-butyne **3** (0.77 g, 1.21 mmol) in THF (10 mL) at ambient temperature. TLC showed that the reaction had gone to completion after 10 min. Aqueous ammonium chloride was added, the phases were separated, the aqueous phase was extracted with diethyl ether (4 × 25 mL), the combined organic solutions were dried (MgSO$_4$) and evaporated, and the product was isolated from the residual material after flash chromatography using 15% EtOAc in hexane. The product was a yellow crystalline material with mp 95−97 °C (MeCN), yield 0.54 g (91%). IR (film) 3294 (m), 2946 (s), 1698 (s), 1236 (s) cm^{-1}. ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.68 (d, 6 H, J = 6.8 Hz, 2 × CHC*H*$_3$Me), 1.08 (d, 6 H, J = 6.8 Hz, 2 × CHC*H*$_3$Me), 1.83 (t, 2 H, J = 2.6 Hz, 2 × CC*H*), 2.30 (ds, 2 H, J = 6.8, 3.4 Hz, 2 × C*H*Me$_2$), 2.41−2.52 (m, 8 H, 4 × CH$_2$), 3.67 (s, 12 H, 4 × OMe), 3.99 (d, 2 H, J = 3.3 Hz, H-2 and H-2′). ^{13}C NMR (50 MHz, CDCl$_3$) δ 17.0 (2 × Me*C*H$_3$CH), 19.6 (2 × Me*C*H$_3$CH), 30.6 (2 × *C*HMe$_2$), 30.7 (2 × *C*H$_2$CCH), 30.8 (2 × *C*H$_2$), 52.5 (2 × OMe), 52.6 (2 × OMe), 61.0 (C-2, C-2′ and C-5, C-5′), 70.2 (2 × CH$_2$*C*CH), 78.5 (2 × *C*C), 80.2 (2 × CH$_2$*C*CH), 160.8 (C-3, C-3′ or C-6, C-6′), 163.0 (C-3, C-3′ or C-6, C-6′). MS(EI) (*m*/*z*): 479 (M$^+$, 14%), 455 (31), 222 (14), 221 (88), 180 (12), 179 (100.00), 164 (15). Anal. Calcd for $C_{28}H_{38}N_4O_4$: C, 67.99; H, 7.74. Found: C, 68.23; H,7.98.

Dimethyl (2*R*,7*R*)-2,7-Diamino-2,7-dipropargyl-4-octanynedioate 5. TFA (0.2 M,7.5 mmol, 35.5 mL) was added to a solution of 1,4-bis[(2*R*,5*R*)-2,5-dihydro-2-isopropyl-3,6-dimethoxy-5-propargylpyrazin-5-yl]-2-butyne **4** (0.37 g, 0.75 mmol) in MeCN (35.5 mL) and the mixture stirred at ambient temperature for 4 d. The pH was adjusted to 10 by addition of aq ammonia, the mixture was extracted with CH_2Cl_2 (3 × 40 mL), the extracts were dried (MgSO$_4$) and evaporated, and the product was isolated from the residual material after flash chromatography using 8% MeOH in CH_2Cl_2. The product was a yellow oil, yield 80 mg (35%). IR (film) 3375 (m), 3290 (s), 2954 (m), 1737 (s), 1597 (m), 1438 (s), 1211 (s) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.96 (s, 4 H, 2 × NH$_2$), 2.04 (t, 2 H, J = 2.6 Hz, 2 × CH), 2.45−2.65 (m, 8 H, 4 × CH$_2$), 3.73 (s, 6 H, 2 × OMe). ^{13}C NMR (75 MHz, CDCl$_3$) δ 29.4 (2 × CH$_2$), 29.6 (2 × CH$_2$), 52.7 (2 × OMe), 60.4 (2 × *C*NH$_2$), 71.8 (2 × *C*CH), 78.4 (2 × *C*CH or 2 × *C*C), 78.9 (2 × *C*CH or 2 × *C*C), 174.5 (*C*O$_2$Me). MS(EI) (*m*/*z*): 304.1 (M$^+$, 2%), 266 (15), 265 (100), 246 (15), 245 (93), 179 (76), 126 (92), 120 (70), 66 (65). HRMS: calcd for $C_{16}H_{20}N_2O_4$ (M$^+$), 304.1423; observed 304.1413. Anal. Calcd for $C_{16}H_{20}N_2O_4$: C, 62.14; H, 6.62. Found: C, 62.24; H, 6.67.

Dimethyl (2*R*,7*R*)-2,7-Diacetamido-2,7-dipropargyl-4-octanynedioate 6. A solution of acetic anhydride (0.10 g, 0.98 mmol) in CH_2Cl_2 (4 mL) was added slowly to a solution of dimethyl (2*R*,7*R*)-2,7-diamino-2,7-dipropargyl-4-octanynedioate **5** (0.12 g, 0.40 mmol) and DMAP (0.13 g, 1.06 mmol) in CH_2Cl_2 (4 mL) at ambient temperature. The mixture was stirred at ambient temperature for 3 h. The reaction was quenched by addition of saturated ammonium chloride. The phases were separated, and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried (MgSO$_4$) before removal of the solvent at reduced pressure. The product was isolated from the residual material after flash chromatography using 8% MeOH in CH_2Cl_2. The product was a yellow oily material, yield 0.15 g (>95%). IR (film) 3289 (s), 3061 (m), 2960 (m), 2268 (w), 2129 (w), 1744 (s), 1656 (s), 1549 (s) cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.96−1.97 (m, 2 H, 2 × CH), 1.97 (s, 6 H, 2 × NCOC*H*$_3$), 2.68 (d, 2 H, J = 14.4 Hz, 2 × CCC*H*H), 2.82 (dd, 2 H, J = 16.8, 2.4 Hz, 2 × CHCC*H*H), 2.95−3.04 (m, 4 H, 2 × CCCH*H* and 2 × CHCCH*H*), 3.68 (s, 6 H, 2 × CO$_2$Me), 7.06 (br s, 2 H, 2 × NH). ^{13}C NMR (125 MHz, CDCl$_3$) δ 23.0 (2 × *C*CH), 25.1 (2 × CC*C*H$_2$), 52.9 (2 × CO$_2$*C*H$_3$), 61.2 (2 × CHH*C*CHH), 71.4 (2 × *C*H), 77.5 (2 × C*C*), 78.4 (2 × HC*C*CH$_2$), 170.1 (2 × N*C*OMe), 171.27 (2 × *C*O$_2$Me). MS(EI) (*m*/*z*): 388 (M$^+$, 1%), 350 (17), 349 (89), 290 (83), 287 (50), 270 (42), 265 (78), 220 (46), 162 (51), 126 (83), 43 (100). HRMS: calcd for $C_{20}H_{24}N_2O_6$: 388.1634 (M$^+$); observed 388.1659.

2,7-Bis[(2*R*,5*R*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine-5-spiro)-1,2,3,6,7,8-hexahydro-*as*-indacene 7. A solution of 1,4-bis[(2*R*,5*R*)-2,5-dihydro-2-isopropyl-3,6-dimethoxy-5-propargylpyrazin-5-yl]-2-butyne **4** (0.564 g, 1.14 mmol) in degassed toluene (3 mL) and bis(tricyclohexylphosphine)-benzylidene ruthenium dichloride (5 mg, 5 mol %) was heated at 85 °C for 3 h, another 5 mol % of the Ru(II)-catalyst added, and the heating continued overnight.

The solvent was distilled off at reduced pressure and the residual material subjected to flash chromatography using 20% EtOAc in hexane. The product was a pale yellow solid with mp 168−171 °C (MeCN), yield 0.51 g (90%). [α]$^{20}_D$: −120.5 (c 0.09, CH_2Cl_2). IR (film) 2945 (m), 1689 (s) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.72 (d, 6 H, J = 6.8 Hz, 2 × CHC*H*$_3$Me),1.08 (d, 6 H, J = 6.8 Hz, 2 × CHC*H*$_3$Me), 2.25 (ds, 2 H, J = 6.9, 3.4 Hz, 2 × C*H*Me$_2$), 2.74 (d, 2 H, J = 15.7 Hz, 2 × C*H*H), 2.93 (d, 2 H, J = 15.1 Hz, 2 × C*H*H), 3.38 (d, 2 H, 2 × C*H*H, J = 15.7 Hz), 3.58 (d, 2 H, J = 15.1 Hz, 2 × C*H*H), 3.57 (s, 6 H, 2 × OMe), 3.67 (s, 6 H, 2 × OMe), 4.02 (d, 2 H, J = 3.4 Hz, H-2 and H-2′), 7.02 (s, 2 H, 2 × Ar-*H*). ^{13}C NMR (75 MHz, CDCl$_3$) δ 16.9 (2 × Me*C*H$_3$CH), 19.3 (2 × Me*C*H$_3$CH), 31.2 (2 × *C*HMe$_2$), 47.2 (2 × *C*H$_2$), 48.5 (2 × *C*H$_2$), 52.4 (2 × OMe), 52.4 (2 × OMe), 61.1 (C-2, C-2′), 63.9 (C-5, C-5′), 122.5 (2 × Ar−H), 136.9 (2 × Ar), 139.7 (2 × Ar), 161.3 (C-3, C-3′ or C-6, C-6′), 165.6 (C-3, C-3′ or C-6, C-6′). MS(EI) (*m*/): 495 (M$^+$, 6%), 494 (14), 453 (7), 452 (33), 451 (100). HRMS: calcd for $C_{28}H_{38}N_4O_4$, M 494.2890 (M$^+$); observed. 494.2893. Anal. Calcd for $C_{28}H_{38}N_4O_4$: C, 67.99; H, 7.74. Found C, 66.23; H, 7.46.

Dimethyl (2*R*,7*R*)-2,7-Diacetamido-1,2,3,6,7,8-hexahydro-*as*-indacene-2,7-dicarboxylate 8. A solution of bis-(tricyclohexylphosphine)benzylidene ruthenium dichloride (0.01 g, 0.012 mmol) in toluene (1.5 mL) was added slowly to a solution of dimethyl (2*R*,7*R*)-2,7-diacetamido-2,7-dipropargyl-4-octanynedioate **6** (0.07 g, 0.18 mmol) in degassed toluene (1 mL). The mixture was heated with stirring at 85 °C for 2 h when another portion of 5 mol % Ru(II)-catalyst was added and the stirred mixture heated at 85 °C overnight. The mixture was evaporated to dryness at reduced pressure and the product isolated from the residual material after flash chromatography using 8% MeOH in CH_2Cl_2. The product was a white solid, mp >300 °C (MeCN), yield 40 mg (58%). [α]$^{20}_D$: −31.0 (*c* 0.30, MeCN). IR (ATR) 3373 (s), 3350 (s), 3295 (m), 3044 (m), 2951 (m), 2927 (m), 2849 (m) 1740 (s), 1719 (s), 1666 (s) cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.94 (s, 6 H, 2 × NCOMe), 3.11 (d, 2 H, *J* 16.5 Hz, αH-1 and βH-8), 3.20 (d, 2 H, J = 16.1 Hz, αH-3 and βH-6), 3.55 (d, 2 H, J = 16.5 Hz, βH-1 and αH-8), 3.59 (d, 2 H, J = 16.1 Hz, βH-3 and αH-6), 3.74 (s, 6 H, 2 × CO$_2$Me), 5.99 (s, 2 H, 2 × N*H*Ac), 7.04 (s, 2 H, H-4 and H-5). ^{13}C NMR (125 MHz, CDCl$_3$) δ 23.1 (2 × NCO*C*H$_3$), 42.0 (C-1 and C-8), 43.6 (C-3 and C-6), 52.9 (2 × CO$_2$*C*H$_3$), 65.9 (C-2 and C-7), 123.3 (C-4 and C-5), 136.0 (*C*C-1 and *C*C-8 or *C*C-3 and *C*C-6), 138.8 (*C*C-1 and *C*C-8 or *C*C-3 and *C*C-6), 170.3 (2 × N*C*OMe), 173.5 (2 × *C*O$_2$Me). HRMS (electrospray): calcd for $C_{20}H_{25}N_2O_6$, 389.1713 (M + H)$^+$; observed, 389.1707. Anal. Calcd for $C_{20}H_{24}N_2O_6$: C, 61.21; H, 6.58. Found: C, 61.80; H, 6.23.

Dimethyl (2*R*,7*R*)-2,7-Diamino-1,2,3,6,7,8-hexahydro-*as*-indacene-2,7-dicarboxylate 9. TFA (0.2 M, 0.67 g, 5.87 mmol, 30 mL) was added to a solution of 2,7-bis[(2*R*,5*S*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine-5-spiro)-1,2,3,6,7,8-hexahydro-*as*-indacene **7** (0.29 g, 0.59 mmol) in MeCN (30 mL) and the resultant solution stirred at ambient temperature for 5 d. Aqueous ammonia was added until pH 10, the mixture was extracted with CH_2Cl_2, the organic extracts were dried (MgSO$_4$) and evaporated at reduced pressure, and the residual material was subjected to flash chromatography using 8%

MeOH in CH_2Cl_2. The product was a noncrystalline material, yield 0.06 g (35%).; $[\alpha]^{20}_D$: +13.6 (*c* 0.102, CH_2Cl_2). IR (film) 3371 (w), 2951 (w), 1729 (s), 1596 (w), 1433 (m), 1220 (s) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.77 (s, 4 H, br 2 × NH_2), 2.73 (d, 2 H, J = 15.7 Hz, αH-1 and βH-8), 2.83 (d, 2 H, J = 15.3 Hz, αH-3 and βH-6), 3.45 (d, 2 H, J = 15.7 Hz, βH-1 and αH-8), 3.48 (d, 2 H, J = 15.3 Hz, βH-3 and αH-6), 3.74 (s, 6 H, 2 × OMe), 7.02 (s, 2 H, 2 × CH). ^{13}C NMR_(125 MHz, $CDCl_3$) δ 44.6 (C-1 and C-8), 46.1 (C-3 and C-6), 52.4 (2 × OCH_3), 65.1 (C-2 and C-7), 123.3 (C-4 and C-5), 136.5 (C-3a, C-5a or C-8a, C-8b), 139.1 (C-3a, C-5a or C-8a, C-8b), 177.1 (2 × CO). MS(EI) (*m*/*z*): 305 (M^+, 3%), 304 (14), 246 (17), 245 (10), 228 (31), 185 (26), 169 (23), 168 (32), 93 (16). HRMS: calcd for $C_{16}H_{20}N_2O_4$, 304.1422 (M^+); observed, 304.1423. Anal. Calcd for $C_{16}H_{20}N_2O_4$: C 63.16; H, 6.72. Found: C, 63.14; H, 6.62.

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