# Homocoupling in the Preparation of Dimeric Cyclic Peptide Derivatives

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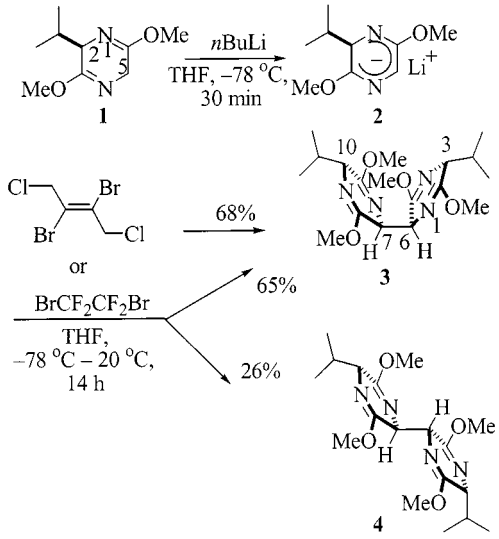
A method for the preparation of dimeric (2*R*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine and 5-alkenyl derivatives by homocoupling is described. Moderate stereoselectivity was observed. The major product has $C_2$-symmetry. The course of the stereochemical transformations has been ascertained by a single crystal X-ray analysis. A $C_2$-symmetrical bisallyl substrate in a $Ru^{II}$-catalyzed ring-closing metathesis reaction furnished the corresponding 1,2-bis(spiroannulated cyclic dipeptido)cyclohexane in >95% yield.

## Introduction

A variety of methods have been developed for the preparation of natural and non-proteinogenic α-amino acids either by stereocontrolled catalytic hydrogenations or by stoichiometric use of chiral auxiliaries. We have reported on the use of the Schöllkopf bislactim ether (2*R*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine for the preparation of conformationally constrained and bridged bis(α-amino acids).[1−4] $C_1-C_4$ bridges were introduced after two consecutive stereoselective alkylations of two bislactim ether units. Herein we describe a stereoselective dimerization process of two bislactim ether units whereby the two units become directly tethered to one another at the 5-positions. The synthetic concept for this work arose from observations made in some alkylation reactions where by-products due to homocoupling were formed. Thus in bridge alkylations with vicinal dibromoalkanes, significant amounts of homocoupled products may result. A simple case is the use of 1,2-dibromoethane for alkylation of the lithiated bislactim ether at −78 °C. When the vicinal halogens were a bromine and a chlorine, homocoupling is largely avoided because chlorine elimination as a chloride did not occur.[5]

## Results and Discussion

In this work we have shown that homocoupling can also occur using bis(allylic) halides. In reactions with (*E*)-2,3-dibromo-1,4-dichloro-2-butene, chloride elimination was a major reaction and the homocoupled product **3** was isolated in 68% yield (Scheme 1). In contrast, with (*E*)-1,4-dibromo- or 1,4-dichloro-2-butene high yields of $C_4$-bridged structures are formed.[1,2] Presumably the bulkiness of the olefinic bromines in the former reagent decreases the rate of nucleophilic substitution, to the extent that the rate for attack by the anionic carbon at the halogen becomes the faster process. The initial product may be the chlorinated bislactim ether, which reacts further in situ. 2,3-Dibromo-1,3-butadiene is presumably the second product in this reaction, but we made no attempt to isolate this diene.




Scheme 1

Subsequently we turned to more conventional methods for halogenation of the carbanionic carbon,[6] in particular to the use of 1,2-dibromo(tetrafluoro)ethane.[7] With this reagent the homocoupled product **3** was obtained in about the same yield (65%) as with the bis(allyl) reagent. Only two major products were seen. The second product was the diastereoisomer **4**, which is epimeric at C-5, and was isolated in 26% yield. The isomers **3** and **4** were separated by flash chromatography. Previously, under similar conditions, chlorination with hexachloroethane has provided the 5-

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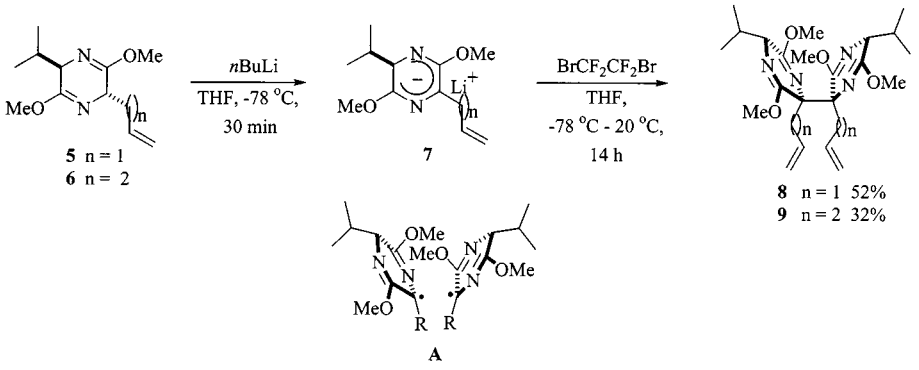



Scheme 2

chlorinated bislactim ether in 90% yield as a 94:6 isomer mixture in favour of the *cis*-5-chloro isomer.[8,9] The unusual *cis*-substitution with respect to the isopropyl group was attributed to a radical mechanism. Under our reaction conditions a 5-halo compound was not seen, but has been postulated as an intermediate in a reaction sequence leading to homocoupling (Scheme 2).

The homocoupling with formation of the $C_2$-symmetrical isomer **3** can be rationalized by a quasi-parallel approach of the heterocyclic planes ending with bond formation between the C-5 carbons in the two rings. Bond formation between oppositely charged species can be envisaged, but more likely the new bond formation is due to a dimerization process between the two radical species (**A**) in Scheme 2. The NMR spectra were consistent with $C_2$-symmetry in that the spectra contained one set of signals corresponding closely to the monomer **1**. The almost planar heterocyclic rings will preferentially have the isopropyl groups on the outside face, to minimize steric interactions as indicated for the arrangement **A** (Scheme 2).

The postulated mechanistic pathway for the homocoupling suggested that dimerization would also occur when the C-5 carbon of the bislactim ether was monoalkylated. The alkenyl derivatives **5** and **6** were used as substrates. The allyl derivative **5** gave the homocoupled product **8** in low yield (ca. 20%) when either 1,2,3,4-tetrabromo-2-butene or 2,3-dibromo-1,4-dichloro-2-butene was used as a reagent for the dimerization of the lithiated species **7**. With 1,2-dibromo-(tetrafluoro)ethane as the reagent, the dimeric product **8** was isolated in 52% yield. NMR analysis of the crude product before chromatographic purification showed about 11% yield of its diastereoisomer. This product was not isolated. The butenyl derivative **9** was obtained similarly in 32% yield. The simplicity of the NMR spectra for the products **8** and **9** was consistent with $C_2$-symmetry. In the case of compound **8** the structural assignment has been confirmed by a single crystal X-ray analysis of its (3*S*,6*R*,7*R*,10*S*)-enantiomer. The latter was prepared under the same reaction conditions as above from the (2*S*)-enantiomer of the chiral auxiliary **1**. A thermal ellipsoidal plot is shown in Figure 1. A noticeable feature is the central bond length 1.594(4) Å between the 6,7-postions indicating severe crowding. The

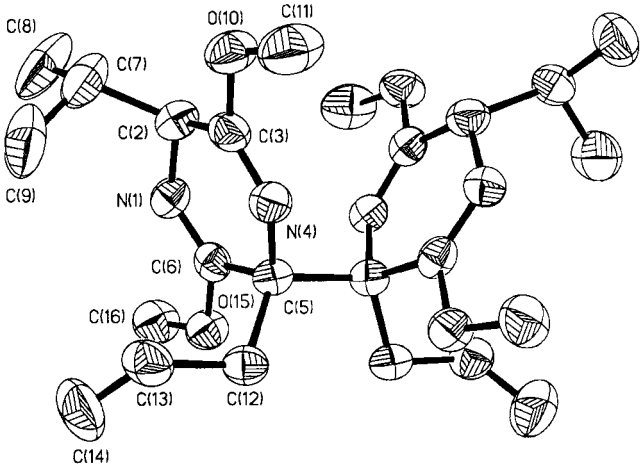
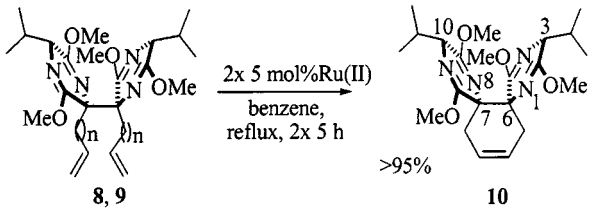



Figure 1. Thermal ellipsoid plot of (3*S*,6*R*,7*R*,10*S*)-6,7-diallyl-3,10-diisopropyl-2,5,9,12-tetramethoxy-1,4,8,11-tetraazadispiro-[5.0.5]dodeca-1,4,8,11-tetraene, the enantiomer of structure **8**; ellipsoids are drawn at the 70% probability level; for clarity hydrogens are left out; the absolute configurations at the new stereocenters are assigned relative to the known chirality (3*S*,10*S*)

plot of the crystal structure in Figure 1 shows a gauche conformation about this bond.

In the crystal structure of compound **8** in Figure 1 the two ene groups are close together and therefore accessible for cyclization reactions by $Ru^{II}$-catalyzed ring-closing metathesis (RCM).[10,11] In the RCM reaction the substrate **8** was heated with bis(tricyclohexylphosphane)benzylidene ruthenium dichloride in benzene (Scheme 3). Two portions




Scheme 3

of catalyst (each 5 mol %) were added to compensate for the thermal instability of the catalyst. An almost quantitative yield of the RCM product **10** was obtained at reflux temperature. No reaction was observed at ambient temperature. The new ring is six-membered. An RCM reaction of the butenyl derivative **9** would yield an unfavourable eight-membered ring structure. Despite expectations of a conformationally favoured state no RCM reaction was observed.

In summary, a method for homocoupling of the chiral auxiliary (2*R*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine and 5-alkyl derivatives has been found. Moderate stereoselectivity was observed. The diallyl derivative **8** was cyclized under $Ru^{II}$-catalyzed RCM conditions to yield a 1,2-bis(spiroannulated cyclic dipeptido)cyclohexane.

## 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 75 MHz or 50 MHz. Chemical shifts are reported in ppm with residual $CHCl_3$ ($\delta$ = 7.24) and $CDCl_3$ ($\delta$ = 77) 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(tricyclohexylphosphane)benzylidene ruthenium dichloride was purchased from Strem Chemicals Inc., 7 Mulliken Way, Newburyport, MA.

**X-ray Analysis:** A crystal of the enantiomer of structure **8**, suitable for X-ray analysis, was selected from a recrystallized sample from acetonitrile. X-ray measurements were carried out with a Siemens R3 diffractometer, using graphite-monochromatized Mo-$K_\alpha$ radiation ($\lambda$ = 0.71073 Å). The crystal was held at 130(2) K. Crystal data: triclinic, space group *P*1; *Z* = 2; *a* = 7.755(2), *b* = 8.489(2), *c* = 19.891(5) Å; $\alpha$ = 85.24(2), $\beta$ = 82.39(2), $\gamma$ = 89.09(2)°; max 2$\theta$ for intensity measurements: 50°. The structure was solved with SHELXS,[12] and refined by full-matrix least-squares methods with SHELXL-97.[13] Final $R_1$ = 0.037 for 3452 reflections with $F^2 > 2\sigma(F^2)$ (of 3810 measured). The central C−C distance is 1.597(4) Å. A thermal ellipsoid plot of one molecule is shown in Figure 1.

Crystallographic data (excluding structure factors) for the structure included in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-155640. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

**(3*R*,6*S*,7*S*,10*R*)-3,10-Diisopropyl-2,5,9,12-tetramethoxy-1,4,8,11-tetraazadispiro[5.0.5]dodeca-1,4,8,11-tetraene (3) and (3*R*,6*R*,7*S*,10*R*)-3,10-Diisopropyl-2,5,9,12-tetramethoxy-1,4,8,11-tetraazadispiro[5.0.5]dodeca-1,4,8,11-tetraene (4). (i) Reaction with 1,2-Dibromo(tetrafluoro)ethane:** A solution of (2*R*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine (0.321 g, 1.74 mmol) in anhydrous THF (3.5 mL) at −78 °C was lithiated by the addition of a solution of *n*BuLi in hexane (1.11 mL, 1.57 M, 1.74 mmol). The solution was stirred at −78 °C for 30 min before a precooled solution of 1,2-dibromo(tetrafluoro)ethane (0.227 g, 0.104 mL, 0.87 mmol) in THF (1 mL) was added dropwise through a Teflon tube. The reaction mixture was allowed to reach ambient temperature overnight. The reaction was stopped by hydrolysis with phosphate buffer (pH 7). The mixture was extracted with diethyl ether, and the organic layer washed with water and dried ($MgSO_4$) before the solvent was distilled off. The residual material was subjected to flash chromatography using hexane/EtOAc 9:1. Isomer **3** was eluted first and was obtained in 65% yield (0.210 g) as a white solid. M.p. 67−68 °C. IR (ATR plate): $\tilde{\nu}$ = 3077 (w), 3011 (s), 2958 (s), 2871 (s), 2844 (s), 1694 (s), 1436 (s), 1232 (s), 1193 (s), 1099 (s), 1010 (s) cm$^{-1}$. $^1$H NMR ($CDCl_3$): $\delta$ = 0.64/1.03 (d, *J* = 6.8 Hz, 12 H, 2 × CH*Me*$_2$), 2.18−2.26 (dsept, *J* = 3.2, 6.9 Hz, 2 H, 2 × C*H*Me$_2$), 3.52/3.57 (s, 12 H, 4 × OMe), 3.87 (m, 2 H, H-6, H-7), 4.51 (dd, *J* = 2.4, 5.5 Hz, 2 H, H-3, H-10). $^{13}$C NMR ($CDCl_3$): $\delta$ = 17.2/19.8 (2 × CH*Me*$_2$), 32.1 (2 × *C*HMe$_2$), 52.6/52.8 (4 × OMe), 58.1 (C-6, C-7), 60.8 (C-3, C-10), 160.4/163.8 (C-2, C-5, C-9, C-12). MS (EI): *m*/*z* (%) = 366 (6) [M$^+$], 184 (15), 183 (38), 182 (6), 142 (7), 141 (100), 140 (10), 139 (5).126 (5), 111 (4). HRMS (electrospray) for $C_{18}H_{30}N_4O_4$: calcd. 367.2340; found 367.2322. $C_{18}H_{30}N_4O_4$: calcd. C 58.89, H 8.26; found C 59.21, H 8.23.

The second product eluted from the chromatography column was isomer **4** (yield: 0.083 g, 26%) as an oily material. IR (film): $\tilde{\nu}$ = 2940 (s), 2850 (m), 1680 (s), 1460 (m), 1430 (m), 1375 (m), 1360 (m), 1305 (m), 1280 (m), 1230 (s), 1195 (m), 1140 (m), 1015 (s) cm$^{-1}$. $^1$H NMR ($CDCl_3$): $\delta$ =·0.70 (d, *J* = 6.8 Hz, 3 H, CH*Me*$_2$), 0.72 (d, *J* = 6.8 Hz, 3 H, CH*Me*$_2$), 1.07 (d, *J* = 6.8 Hz, 3 H, CH*Me*$_2$), 1.11 (d, *J* = 6.8 Hz, 3 H, CH*Me*$_2$), 2.04−2.42 (m, 2 H,2 × C*H*Me$_2$), 3.63 (s, 3 H, OMe), 3.65 (s, 3 H, OMe), 3.66 (s, 3 H, OMe), 3.68 (s, 3 H, OMe), 3.86 (dd, *J* = 3.5, 6.7 Hz, 1 H, H-3 or H-10), 3.96 (dd, *J* = 3.5, 3.8 Hz, 1 H, H-3 or H-10), 4.46 (dd, *J* = 2.3, 6.7 Hz, 1 H, H-6 or H-7), 4.59 (dd, *J* = 2.3, 3.8 Hz, 1 H, H-6 or H-7). $^{13}$C ($CDCl_3$): $\delta$ = 15.7 (CH*Me*$_2$), 16.3 (CH*Me*$_2$), 18.3 (CH*Me*$_2$), 18.8 (CH*Me*$_2$), 29.6 (*C*HMe$_2$), 30.6 (*C*HMe$_2$), 51.3 (OMe), 51.5 (OMe), 51.6 (OMe), 51.6 (OMe), 58.1 (C-6 or C-7), 58.3 (C-6 or C-7), 59.5 (C-3 or C-10), 59.9 (C-3 or C-10), 159.8 (C-2 or C-5 or C-9 or C-12), 160.3 (C-2 or C-5 or C-9 or C-12), 162.8 (C-2 or C-5 or C-9 or C-12), 164.0 (C-2 or C-5 or C-9 or C-12). MS (CI): *m*/*z* (%) = 366 (15) [M$^+$], 184 (17), 183 (46), 141 (100). HRMS (electrospray) for $C_{18}H_{31}N_4O_4$: calcd. 367.2339; found 367.2347.

**(ii) Reaction with (*E*)-2,3-dibromo-1,4-dichloro-2-butene:** A solution of (2*R*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine (1.56 g, 8.45 mmol) in anhydrous THF (17.0 mL) at −78 °C was lithiated by the addition of a solution of *n*BuLi in hexane (7.57 mL, 1.17 M, 8.86 mmol). The solution was stirred at −78 °C for 30 min before a solution of precooled (−78 °C) (*E*)-2,3-dibromo-1,4-dichloro-2-butene (1.16 g, 4.11 mmol) in THF (4 mL) was added dropwise through a Teflon tube. The reaction mixture was allowed to reach ambient temperature overnight. The reaction was stopped by hydrolysis with phosphate buffer (pH 7). The mixture was extracted with diethyl ether, and the organic layer washed with water and dried ($MgSO_4$) before the solvent was distilled off. The crude product was subjected to flash chromatography using $Et_2O/CH_2Cl_2$ 1:9; yield 1.10 g (68%) of the homocoupled product **3**. The physical data are given above.

**(3*R*,6*S*,7*S*,10*R*)-6,7-Diallyl-3,10-diisopropyl-2,5,9,12-tetramethoxy-1,4,8,11-tetraazadispiro[5.0.5]dodeca-1,4,8,11-tetraene (8):** A solution of (2*R*)-5-allyl-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine

(**5**)[14] (0.168 g, 0.83 mmol) in anhydrous THF (3 mL) at −78 °C was lithiated by the addition of a solution of *n*BuLi in hexane (1.32 mL, 1.44 M, 0.92 mmol). The solution was stirred at −78 °C for 30 min before a solution of 1,2-dibromo(tetrafluoro)ethane (0.108 g, 50 mL, 0.42 mmol) in THF (2 mL) was added dropwise. The reaction mixture was allowed to reach ambient temperature overnight. The reaction was stopped by hydrolysis with phosphate buffer (pH 7). The mixture was extracted with diethyl ether, and the organic layer washed with water and dried ($MgSO_4$) before the solvent was distilled off. The residual material was subjected to flash chromatography using hexane/EtOAc 19:1; yield 0.135 g (52%) of a white solid with m.p. 104−106 °C (MeCN). $^1$H NMR spectroscopy of the crude product before chromatography showed about 11% of the diastereoisomer had been formed together with the title compound. The diastereoisomer was not isolated and was removed by the chromatographic operation. IR (ATR plate): $\tilde{\nu}$ = 3090 (w), 3014 (m), 2971 (s), 2956 (s), 2860 (m), 1725 (s), 1686 (s), 1660 (s), 1435 (s), 1307 (s), 1235 (s), 1144 (s) cm$^{-1}$. $^1$H ($CDCl_3$): δ = 0.56/1.02 (d, *J* = 6.8 Hz, 12 H, 4 × CH*Me*$_2$), 2.18−2.26 (dsept, *J* = 3.1, 6.8 Hz, 2 H, 2 × C*H*Me), 2.73−2.95 (m, 4 H, 2 × $CH_2$), 3.47 (d, *J* = 3.1 Hz, 2 H, H-3, H-10), 3.53 (s, 6 H, 2 × OMe), 3.62 (s, 6 H, 2 × OMe), 4.83−5.01 (m, 2 H, 2 × $CH_2$), 5.28−5.41 (m, 2 H, 2 × CH=$CH_2$). $^{13}$C ($CDCl_3$): δ = 17.0/19.5 (2 × $CHMe_2$), 30.6 (2 × $CHMe_2$), 38.2 (2 × $CH_2$−CH=$CH_2$), 51.9/52.1 (2 × OMe), 59.4 (C-3, C-10), 68.7 (C-6, C-7), 117.1 ($CH_2$=CH), 135.3 ($CH_2$=CH), 161.7/163.0 (C-2, C-5, C-9, C-12). MS (EI): *m*/*z* (%) = 224 (40) [M − 222], 223 (59), 182 (11), 181 (100), 179 (5), 166 (5), 166 (5), 165 (5). MS (electrospray) for $C_{24}H_{38}N_4O_4$ [M + H$^+$]: calcd. 447.2966; found 447.2963.

**(3*R*,6*S*,7*S*,10*R*)-6,7-di(3-butenyl)-3,10-diisopropyl-2,5,9,12-tetramethoxy-1,4,8,11-tetraazadispiro[5.0.5]dodeca-1,4,8,11-tetraene (9):** A solution of (2*R*)-5-(3-butenyl)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine (**6**)[15] (0.476 g, 1.98 mmol) in anhydrous THF (5 mL) at −78 °C was lithiated by the addition of a solution of *n*BuLi in hexane (1.4 mL, 1.44 M, 2.2 mmol). The solution was stirred at −78 °C for 30 min before a solution of 1,2-dibromo-(tetrafluoro)ethane (0.260 g, 0.12 mL, 1.00 mmol) in THF (2 mL) was added dropwise. The reaction mixture was allowed to reach ambient temperature overnight. The reaction was stopped by hydrolysis with phosphate buffer (pH 7). The mixture was extracted with diethyl ether, and the organic layer washed with water and dried ($MgSO_4$) before the solvent was distilled off. Flash chromatography of the residual material using hexane/EtOAc 19:1 gave the product as a white solid with m.p. 71−73 °C; yield 0.151 g (32%). IR (ATR plate): $\tilde{\nu}$ = 3347 (w), 3077 (m), 2947 (s), 2870 (s), 1678 (s), 1641 (s), 1462 (s), 1435 (s), 1016 (s) cm$^{-1}$. $^1$H NMR ($CDCl_3$): δ = 0.58/1.03 (d, *J* = 6.8 Hz, 12 H, 4 × CH(Me)$_2$], 1.41−1.91 (m, 4 H, 2 × $CH_2$), 2.06−2.26 (m, 6 H, 2 × $CHMe_2$, 2 × $CH_2$), 3.56 (d, *J* = 3.1 Hz, 2 H, H-3, H-10), 3.59 (s, 6 H, 2 × OMe), 3.71 (s, 6 H, 2 × OMe), 4.93−5.08 (m, 4 H, 2 × CH=C*H*$_2$), 5.78−5.98 (m, 2 H, 2 × C*H*=$CH_2$). $^{13}$C NMR ($CDCl_3$): δ = 16.8/19.5 (2 × CH*Me*$_2$), 29.8 (2 × $CH_2$), 30.2 (2 × *C*H$Me_2$), 32.9 (2 × *C*H$_2$−CH=$CH_2$), 51.8/52.2 (4 × OMe), 59.4 (C-3, C-10), 69.1 (C-6, C-7), 113.9 (*C*H$_2$=CH), 132.3 ($CH_2$=*C*H), 162.0/163.1 (C-2, C-5, C-9, C-12). MS (EI): *m*/*z* = 238 (33) [M − 236], 237 (81), 197 (12), 196 (12), 195 (100), 194 (5), 153 (20). HRMS (electrospray) for $C_{26}H_{42}N_4O_4$ [M + H$^+$]; calcd. 475.3279; found 475.3276.

**(3*R*,6*S*,7*S*,10*R*)-3,10-Diisopropyl-2,5,9,12-tetramethoxy-1,4,8,11-tetraazadispiro[5.0.5.4]hexadeca-1,4,8,11,14-pentaene (10):** Bis-(tricyclohexylphosphane)benzylidene ruthenium dichloride (3 mg, 0.0061 mmol) was added to compound **8** (0.137 g, 0.31 mmol) dissolved in dry benzene (1 mL). The reaction mixture was stirred at ambient temperature for 5 min, then heated under reflux with stirring for 5 h. At this time the catalyst had been deactivated. Another portion of the ruthenium catalyst (3 mg, 0.0061 mmol) was therefore added to the cooled reaction mixture which was reheated under reflux and stirring for another 5 h. The solvent was distilled off and the crude product was isolated after flash chromatography using EtOAc/$CH_2Cl_2$ 1:19; yield 0.150 g (100%) of a colourless oil. IR (film): $\tilde{\nu}$ = 2969 (m), 2943 (m), 2904 (m), 2870 (m), 1693 (s), 1462 (m), 1435 (m), 1238 (s), 1197 (m), 1023 (m) cm$^{-1}$. $^1$H NMR ($CDCl_3$): δ = 0.60/1.00 (d, *J* = 6.8 Hz, 12 H, 2 × C*H*Me$_2$), 2.11−2.23 (dsept, *J* = 3.2, 6.8 Hz, 2 H, 2 × C*H*Me$_2$), 2.35−2.42 (m, 4 H, 2 × $CH_2$), 3.53/3.59 (s, 12 H, 4 × OMe), 3.71 (d, *J* = 3.2 Hz, 2 H, H-3, H-10), 5.68−5.71 (m, 2 H, 2 × C*H*=CH). $^{13}$C ($CDCl_3$): δ = 16.6/19.2 (2 × $CHMe_2$), 30.7 (2 × *C*H$Me_2$), 37.2 (2 × *C*H$_2$), 52.0/52.2 (4 × OMe), 59.9 (C-3, C-10), 61.7 (C-6, C-7), 124.1 (2 × *C*H=CH), 162.8/163.9 (C-2, C-5, C-9, C-12). MS (EI): *m*/*z* (%) = 418 (11) [M$^+$], 376 (23), 375 (100), 333 (6), 235 (18), 193 (12), 179 (13). HRMS (electrospray) for $C_{22}H_{35}N_4O_4$ [M + H$^+$]: calcd. 418.2664; found 419.2653.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