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Application of ruthenium induced cyclization for construction of strained biaryl ether macrocyclic compounds

Srikanth Venkatraman,* F. George Njoroge and Viyyoor Girijavallabhan

A 301, MS-3545 Schering Plough Research Institute, K-15, 2015 Galloping Hill road, Kenilworth, NJ 07033, USA

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Abstract—Synthesis of strained macrocyclic biaryl ethers of type **1** and **2** were accomplished using η^6-ruthenium-induced macroetherification. This novel application demonstrates the versatility of this method in construction of constrained macrocyclic biaryl ether ring systems. © 2002 Elsevier Science Ltd. All rights reserved.

Isolation and characterization of a wide variety of macrocyclic biaryl ether containing glycopeptide antibiotics such as vancomycin, ristocetin, β-avoparcin, actaplanin, A33512B has spurred extensive investigation for the syntheses of these type of ring systems.[1] Chloropeptins, piperazinomycin, and protease inhibitors K-13, and OF49491-IV are other bioactive peptides containing macrocyclic biaryl ethers.[2] Vancomycin is currently the drug of choice for the treatment of methicillin resistant *staphylococcus* infections and is routinely used in bacterial infections for patients allergic to β-lactam antibiotics. Moreover, the formation of macrocyclic biaryl ether has been utilized for the synthesis of HIV, matrix metallo, and HCV protease inhibitors.[3] The incorporation of macrocyclic biaryl ether in the design of peptidic inhibitors render them resistant towards proteolytic enzymes and improve oral bioavailability and plasma pharmacokinetics.[4] Synthesis of these natural products from the corresponding amino acids require mild conditions in order to avoid potential epimerization and decomposition. Intensive research in the syntheses of natural products has resulted in the development of new mild methods for the formation of biaryl ethers. The use of arene ruthenium induced macroetherification, pioneered by the groups of Pearson and Rich has been showcased in the syntheses of vancomycin, ristocetin A, teicoplanin, OF4949III, and K-13.[3a,b,5] Yamamura, Evans and others have reported the oxidative methodology that utilizes thallium trinitrate for the syntheses of biaryl ethers in vancomycin and chloropeptin.[6] The classical method of Ullmann allowed the assembly of the diphenylether of the natural products K-13 and OF4949-III.[7] Alternate methods using triazines, *o*-nitrofluoro aromatics have also provided smooth access to the formation of these biaryl ring systems.[8]

In connection with our infectious diseases program we were challenged to synthesize macrocycles represented by structures **1** and **2** (Fig. 1).

The 16 and 18 member macrocycles **1** and **2** are derived from cyclization of nonproteinogenic amino acids (*S*)-7-hydroxy-1,2,3-tetrahydroisoquinoline-3-carboxylic acid ((*S*)-7-hydroxy-Tic), cyclohexylglycine, and phenylpropionic acid or phenylpentanoic acid. A comprehensive

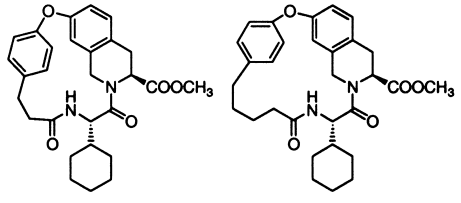

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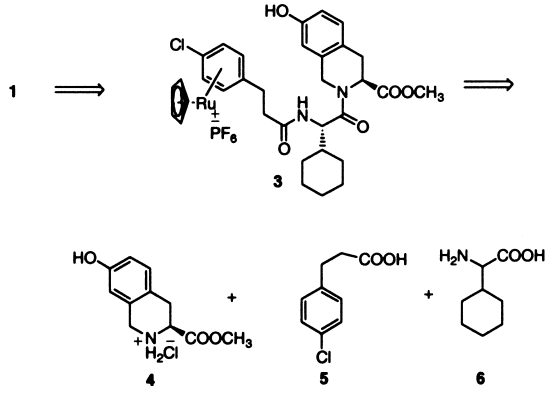
Figure 1.



Scheme 1.

Keywords: macrocyclic biaryl ethers; ruthenium induced cyclization; macroetherification.

* Corresponding author; e-mail: srikanth.venkatraman@spcorp.com

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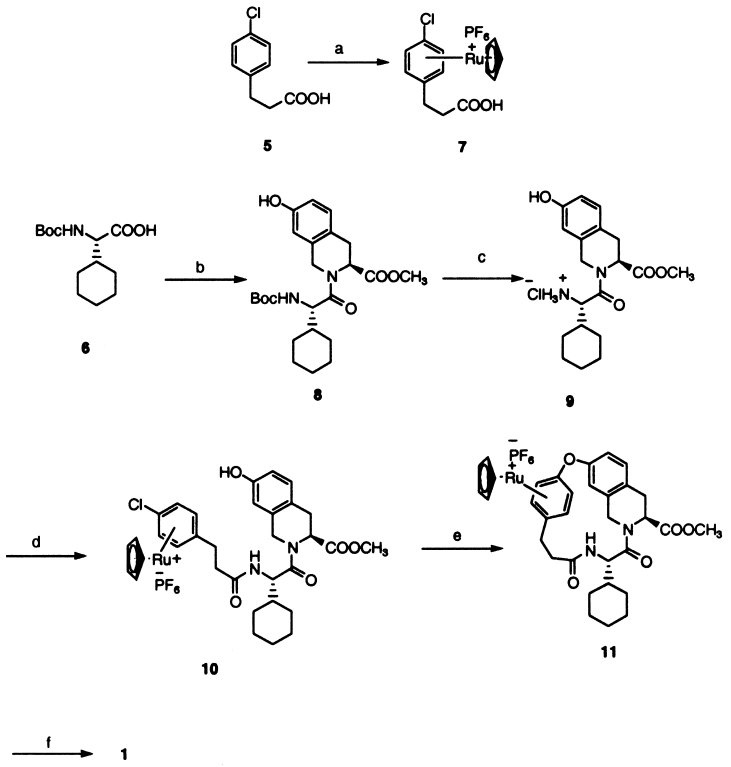


Scheme 2. *Reagents and conditions*: (a) $CpRu(CH_3CN)_3PF_6$, $ClCH_2CH_2Cl$, reflux, 2 h, 73% (b) 4, BOP reagent, Hünig's base, −20→25°C, 24 h, 63%; (c) 4 M HCl/ dioxane, (d) 7, EDCI, HOBt, DMF, rt, 24 h, 83%; (e) 5.0 equiv. Cs_2CO_3, DMF; (f) CH_3CN, $h\nu$, 350 nm, 48 h, 20%.

review of literature revealed a number of biaryl ether macrocycles synthesized mainly from phenylglycines and phenylalanines but none were prepared from (*S*)-7-hydroxy-Tic. In this communication we report the application of the arene ruthenium induced macrocylization method for the construction of the highly strained rings **1** and **2**.

As shown in the retrosynthesis of **1** (Scheme 1), our approach required ligating a cationic ruthenium reagent on the arene ring of 4-chlorophenylpropionic acid **5** and inducing a macroetherification using the hydroxyl of 7-hydroxy-Tic **4**.

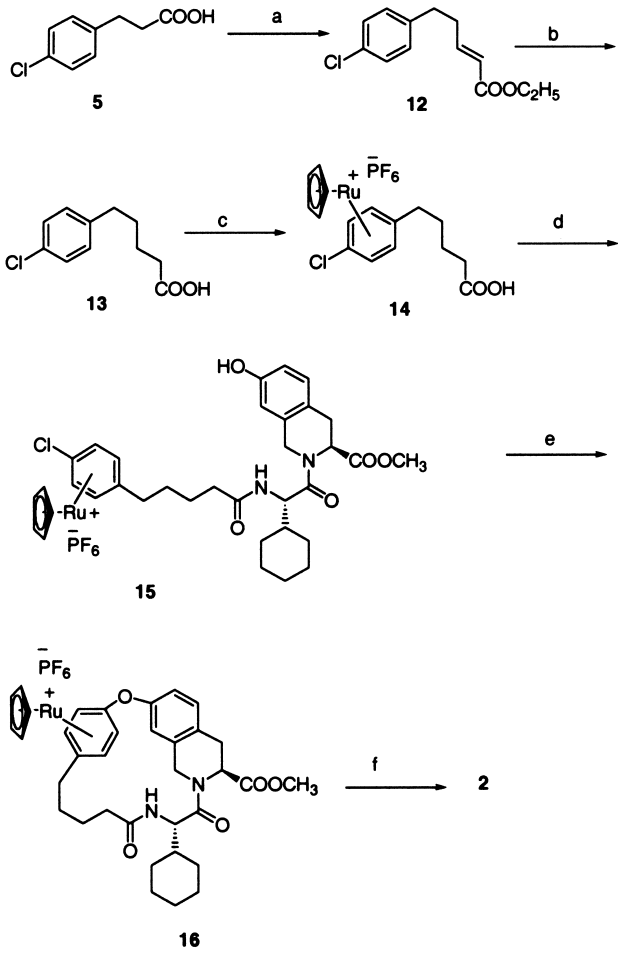
As outlined in Scheme 2, the synthesis of ruthenium complex **7** was initiated with 4-chlorophenylpropionic acid **5**. The reaction of 4-chlorophenylpropionic acid **5** with $CpRu(CH_3CN)_3PF_6$ in refluxing dichloroethane resulted in the smooth formation of the complex **7** in 73% yield, which crystallized out of the reaction mixture on cooling.[9] We were now ready to couple it to 7-hydroxy-Tic and cyclohexylglycine.

Dipeptide **8** was synthesized in 63% yield by the coupling of Boc protected (*S*)-cyclohexylglycine **6** with 7-OH-Tic methyl ester **4** using BOP reagent.[10] Deprotection of the Boc group followed by coupling with **7** using EDCI and HOBt resulted in the formation of macrocyclic precursor **10** in 83% yield. Initial attempts to cyclize **10** using 2,6 di-*tert*-butylphenoxide[11] failed and resulted only in the recovery of starting material. However treating tripeptide **10** with excess Cs_2CO_3 resulted in a smooth cyclization to form the macrocycle **11**. Synthesis of **1** in 20% yield from **10** was accomplished by the photolytic deprotection of ruthenium at 350 nm.

A similar route to that used in preparation of macrocycle **1** was also used for the synthesis of the 18 membered homologue **2** (Scheme 3).

As outlined in Scheme 3, synthesis of the 18 member biaryl ether macrocycle **2** began with 4-chlorophenyl propionic acid **5**. Reduction of acid **5** with BH_3·THF[12] followed by oxidation using Py·SO_3 and DMSO[13] gave 3-(4-chlorophenyl)propanal which was homologated using stabilized Wittig reagent[14] $(EtO)_2P(O)CH_2COOC_2H_5$ to yield **12** as a colorless oil. Reduction of the double bond by hydrogenation followed by hydrolysis of the ethyl ester gave 4-chlorophenylpentanoic acid **13**. As previously discussed, the ruthenium reagent was introduced by the reaction of **13** with $CpRu(CH_3CN)_3PF_6$ and subsequently coupling to the dipeptide **9** gave rise to the macrocyclic precursor **15**. Macrocyclization and photolytic deprotection of the arene ruthenium resulted in the formation of the strained macrocycle **2** in 15% yield.

In conclusion, we have completed the synthesis of the macrocycles **1** and **2** using the arene ruthenium chemistry. The composition of these macrocycles clearly extends the scope of the intramolecular ruthenium-activated cyclization methodology to generate novel strained macrocyclic biphenyl ethers derived from 7-hydroxy-Tic. We are currently exploring the ability to use these arene ruthenium reagents for the construction of ethers bridged by two heterocycles.



Scheme 3. *Reagents and conditions*: (a) (i) BH_3·THF, THF, rt, 12 h, 98% (ii) Py·SO_3, DMSO, Et_3N, CH_2Cl_2, rt, 6 h, 77% (iii) NaH, $(C_2H_5O)_2P(O)CH_2COOC_2H_5$, THF, rt 12 h, 70% (b) (i) H_2/Pd/C, EtOAc, 93% (ii) LiOH·H_2O, CH_3OH/H_2O, 5 h, 96% (c) $CpRu(CH_3CN)_3PF6$, $ClCH_2CH_2Cl$, reflux, 2 h, 59% (d) **9**, EDCI, HOBt, DMF, rt, 24 h, 75%; (e) (i) 5.0 equiv. Cs_2CO_3, DMF; (f) CH_3CN, $h\nu$, λ=350 nm, 48 h.

1. Experimental

1.1. General methods

All glassware were dried in an oven at 150°C prior to use. Dry solvents were purchased from Aldrich or Acros and used without further purification. Other solvents or reagents were used as acquired except when otherwise noted. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel plates available from Analtech. Column chromatography was performed using Merck silica gel 60 (particle size 0.040–0.055 mm, 230–400 mesh). Visualization was accomplished with UV light or by staining with basic $KMnO_4$ solution, methanolic H_2SO_4 or Vaughn's reagent. NMR spectra were recorded in $CDCl_3$ unless otherwise noted in either 300 or 400 MHz (^{1}H NMR), or 75 or 100 MHz (^{13}C NMR).

1.1.1. η^6-3-(4-Chlorophenyl)-1-propionic acid](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (7). A solution of 4-chlorophenylpropionic acid (2.0 g, 10.8 mmol) **5** in dichloroethane (200 mL) was treated with $CpRu(CH_3CN)_3PF_6$ (4.7 g, 10.8 mmol, 1.0 equiv.)[9a] and heated at reflux for 2 h. The reaction mixture was cooled to rt, when colorless crystals of the ruthenium complex **7** precipitated out. The crystals were filtered and washed with a mixture of Et_2O/CH_2Cl_2 (1:1 v/v) and dried in vacuo. The colorless crystals (3.3 g, 73%) were analytically pure: ^{1}H NMR (d_6-DMSO, 400 MHz,) δ 6.64 (d, 2H, J=6.6 Hz), 6.22 (d, 2H, J=6.3 Hz), 5.35 (s, 5H), 2.49 (t, 2H, J=9.6 Hz), 2.74 (dd, 2H, J=4.3 Hz); ^{13}C NMR 139.6, 131.6, 129.7, 128.6, 128.5, 100.3, 35.5, 28.9; MS (ES) m/z, relative intensity: 350 [($C_{14}H_{14}ClRu^+$), M^+, 100]; Anal. calcd for $C_{14}H_{14}ClF_6O_2PRu$: C, 33.92; H, 2.85; Cl, 7.15, found: C, 34.04; H, 3.04; Cl, 7.09.

1.1.2. (*S*,*S*)-(*N*-*tert*-Butoxycarbonyl)-cyclohexylglycine-7-hydroxy-1,2,3-tetrahydroisoquinoline-3-carboxylic acid methyl ester (8). A solution of Boc-Chg-OH **6** (3.84 g, 14.93 mmol) in CH_2Cl_2/DMF (1:1, 100 mL) at −20°C was treated with **4** (3.3 g, 13.57 mmol), Hünig's base (4.24 g, 32.84 mmol) and BOP reagent (6.60 g, 14.93 mmol). The reaction mixture was left in the freezer overnight and concentrated in vacuo. The residue was diluted with aq. HCl (1 M, 200 mL) and extracted with EtOAc (3× 100 mL). The combined organic layers were extracted with saturated $NaHCO_3$, brine, dried ($MgSO_4$), concentrated in vacuo and purified by chromatography (SiO_2, EtOAc/hex 2:3) to yield 3.8 g (63%) of **8** as a colorless fluffy solid: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 6.85 (d, 1H, J=8.1 Hz), 6.54 (d, 1H, J=2.4 Hz), 6.54 (dd, 1H, J=2.7, 5.7 Hz), 5.48 (d, 1H, J=9.3 Hz), 5.43 (dd, 1H, J=3.9, 2.1 Hz), 4.73 (d, 1H, J=15.3 Hz), 4.65 (dd, 1H, J=5.4, 9.3 Hz), 4.54 (d, 1H, J=19.2 Hz), 3.69 (s, 3H), 3.09 (dd, 1H, J=3.6, 12.3 Hz), 2.87 (dd, 1H, J=6.0, 9.9 Hz), 1.93–1.66 (m, 7H), 1.42 (s, 9H), 1.45–1.40 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.9, 171.1, 156.3, 155.4, 132.5, 128.9, 122.5, 113.9, 112.8, 80.4, 55.1, 52.3, 51.9, 45.3, 40.9, 29.6, 28.3, 27.2, 26.1, 25.9; MS (FAB) m/z, relative intensity: 469 ([M+Na]$^+$, 30), 447 ([M+1]$^+$, 45), 391 (58), 347 (100), 208 (85); HRMS m/z calcd for $C_{24}H_{35}N_2O_6$ $(M+1)^+$: 447.2491, found: 447.2505.

1.1.3. (*S*,*S*)-Cyclohexylglycine-7-hydroxy-1,2,3-tetrahydroisoquinoline-3-carboxylic acid methyl ester hydrochloride (9). A solution of **8** (3.8 g, 8.5 mmol) in HCl (60 mL, 4 M in dioxane) at rt was stirred for 3 h and concentrated in vacuo to yield **9** as a colorless solid. The residue was used as it is in further steps without further purification: ^{1}H NMR (CD_3OD, 300 MHz) δ 7.03 (d, 1H, J=7.8 Hz), 6.72–6.69 (d, 2H), 5.16 (t, 1H, J=6.3 Hz), 4.82, 4.61 (AB, 2H), 3.64 (s, 3H), 3.14–3.11 (m, 2H), 2.11–1.80 (m, 6H), 1.31–1.16 (m, 6H); ^{13}C NMR (CD_3OD, 75 MHz) δ 172.2, 169.5, 157.4, 134.3, 129.7, 124.2, 115.5, 113.5, 56.2, 54.7, 52.6, 46.6, 40.6, 30.4, 29.5, 28.1, 26.6; MS (FAB) HRMS m/z calcd for $C_{19}H_{27}N_2O_4$ $(M-Cl)^+$: 347.1971, found: 347.1964.

1.1.4. (*S*,*S*)-[η^6-3-(4-Chlorophenyl)-1-propionic acid-cyclohexylglycine-7-hydroxy-1,2,3-tetrahydroisoquinoline-3-carboxylic acid methyl ester](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (10). A solution of Cp$Ru(\eta^6$-4-chlorophenylpropionic acid **7**, (4.14 g, 8.36 mmol) in dry DMF (20 mL) was treated with HOBt (1.69 g 12.54 mmol) and Hünig's base (6.47 g, 9.20 mL, 50.16 mmol). The reaction mixture was cooled to 0°C and

treated with EDCI (2.39 g, 12.54 mmol). The reaction mixture was stirred at 0°C for 30 min and the ammonium salt **9** (2.90 g, 7.6 mmol) was added. The reaction mixture was stirred at rt for 12 h and the DMF was distilled out in vacuo. The residue was diluted with aq. HCl (1 M, 100 mL) and extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were extracted with aq. $NaHCO_3$ (1×100 mL), brine (100 mL), dried (Na_2SO_4), filtered, concentrated in vacuo to obtain 5.2 g (83%) of **10** as a brown solid which was used for cyclization without further purification. MS (ES) *m/z*, relative intensity: 647 [$(M-CH_3OH-PF_6)^+$, 100]; HRMS calcd for $C_{32}H_{34}ClN_2O_4Ru$ [$(M-CH_3OH-PF_6)]^+$: 647.1256, found: 647.1241.

1.1.5. Cyclic-(*S*,*S*)-[η^6-3-phenyl-1-propionic acid-cyclohexylglycine-7-hydroxy-1,2,3-tetrahydroisoquinoline-3-carboxylic acid methyl ester](η^5-cyclopentadienyl)-ruthenium hexafluorophosphate (1). A solution of the ruthenium complex **10** (5.0 g, 6.01 mmol) in dry DMF (300 mL) was degassed with dry N_2 and treated with Cs_2CO_3 (10.0 g, 30 mmol). The reaction mixture was stirred at rt for 24 h. and concentrated in vacuo. The residue was diluted with water (100 mL) and extracted with CH_2Cl_2 (3×100 mL) and propionitrile (3×100 mL). The combined organic layers were extracted with brine (100 mL), dried (Na_2SO_4) filtered, concentrated in vacuo, and dried in vacuum overnight to yield 5.1 g of **11** as a brown solid. It was used for photolytic removal of Ru without any further purification. MS (ES) *m/z*, relative intensity: 643 [$(M-PF_6)^+$, 100], HRMS calcd for $C_{33}H_{37}N_2O_5{}^{102}Ru$ $(M-PF_6)^+$: 643.1755, found: 643.1746.

Crude **11** was dissolved in CH_3CN (50 mL) and filtered into a quartz tube. The solution was degassed and photolysed in a Rayonet (λ=350 nm) for 48 h. The reaction mixture was concentrated in vacuo and the residue was purified by chromatography (SiO_2, EtOAc/hexanes 3:2) to yield a tan colored solid **1** (289 mg, 20%); R_f: 0.73 (acetone/hexanes 3:7); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.19 (d, 2H, *J*=6.1 Hz), 7.20–7.11 (m, 2H), 6.92 (d, 2H, *J*=8.1 Hz), 6.85 (dd, 1H, *J*=2.1, 7.2 Hz), 6.76 (s, 1H), 5.41 (d, 1H, *J*=17.7 Hz), 4.24–4.18 (m, 2H), 4.00 (bs, 1H), 3.68 (s, 3H), 3.42 (dd, 1H, *J*=12.0, 3.3 Hz), 3.01–2.86 (m, 1H) 2.94 (t, 2H, *J*=7.8 Hz), 2.63 (t, 2H, *J*=8.1 Hz), 2.18–2.10 (m, 1H), 1.84–1.62 (m, 5H), 1.34–1.03 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.2, 167.0, 163.8, 156.5, 155.1, 135.7, 132.7, 130.2, 129.6, 126.2, 119.1, 117.5, 115.7, 60.2, 55.5, 51.6, 44.2, 41.9, 35.7, 33.6, 30.1, 29.3, 26.4, 26.2, 25.7, 25.6; MS (ES) *m/z*, relative intensity: 477 [$(M+1)^+$, 100], 315 (20); HRMS calcd for $C_{28}H_{33}N_2O_5$ $(M+1)^+$: 477.2389, found: 477.2375; Anal. calcd for $C_{28}H_{32}N_2O_5{\cdot}0.5H_2O$: C, 69.26; H, 6.85; N, 5.77, found: C, 69.62; H, 6.59; N, 5.77.

1.1.6. Ethyl-5-(4-chlorophenyl)-2-pentenoate (12). A solution of 3-[4-chlorophenyl]propan-1-ol (9.2 g, 54.1 mmol) in dry CH_2Cl_2 (200 mL) was treated with DMSO (35 mL) and Et_3N (16.4 g, 16.3 mmol, 23.4 mL). It was cooled to 0°C and treated with $Py{\cdot}SO_3$ (12.9 g, 81.2 mmol, 1.50 equiv.) dissolved in DMSO (30 mL). The reaction mixture was stirred at 0°C for 0.5 h and rt for 6 h. It was concentrated in vacuo and diluted with Et_2O (100 mL) and H_2O (200 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3×100 mL). The combined organic layers were extracted with HCl (2 M, 3×100 mL), brine (1×100 mL) concentrated in vacuo and purified by chromatography (SiO_2, EtOAc/hex 1:7) to yield 3-(4-chlorophenyl)-1-propanal[14] which solidified to a waxy solid on standing (7.1 g, 77%). Anal. calcd for C_9H_9ClO: C, 64.11; H, 5.38, found: C, 64.08; H, 5.30.

A solution of triethylphosphonoacetate (6.72 g, 30 mmol) in dry THF (100 mL) was treated with NaH (60% 1.5 g, 35 mmol) at 0°C. The reaction mixture was stirred at 25°C for 1 h until the H_2 evolution ceases. A solution of 3-(4-chlorophenyl)-propanal (4.2 g, 25.0 mmol) in dry THF (5.0 mL) was added and the reaction mixture was stirred for 36 h. The reaction mixture was diluted with H_2O (100 mL) and extracted with Et_2O (3×70 mL). The combined organic layer was dried ($MgSO_4$), filtered concentrated in vacuo and chromatographed to yield alkene **12** (4.2 g, 70%) which was used for reduction without further purification.

1.1.7. 5-(4-Chlorophenyl)pentanoic acid (13). A solution of α,β-unsaturated ester **12** (4.2 g, 8.0 mmol) in EtOAc (50 mL) was treated with Pd/C (10% w/w, 500 mg) and hydrogenated at 50 psi. The reaction mixture was filtered through a plug of celite and concentrated in vacuo to yield the reduced ester (3.9 g, 93%) used for hydrolysis.

A solution of the reduced ester (3.9 g, 16.2 mmol) in $CH_3OH/THF/H_2O$ (1:1:0.1, 110 mL) was treated with $LiOH{\cdot}H_2O$ (1.2 g, 30 mmol) and stirred at rt for 5 h. The reaction mixture was concentrated in vacuo and the residue was diluted with H_2O (100 mL) and extracted into Et_2O (3×50 mL). The aqueous layer was acidified to pH ∽1 with concentrated HCl and the turbid aqueous layer was extracted with Et_2O (3×100 mL). The combined organic layers were dried ($MgSO_4$) filtered concentrated in vacuo to yield acid **13** (3.1 g, 96%) as a colorless solid. Anal. calcd for $C_{11}H_{13}ClO_2$: C, 62.12, H, 6.16, found: C, 62.27, H, 6.23.

1.1.8. η^6-[5-(4-Chlorophenyl)pentanoic acid]-η^5-(cyclopentadienyl)ruthenium hexafluoro phosphate (14). A solution of 5-(4-chlorophenyl) pentanoic acid **13** (3.0 g, 14.15 mmol) in dry dichloroethane (150 mL) was treated with $CpRu(CH_3CN)_3PF_6$ (6.75 g, 15.10 mmol) and heated at reflux for 2.5 h. The reaction mixture was cooled to 0°C and filtered. The filtrate was concentrated in vacuo and dissolved in CH_3CN (20 mL) and treated with a large excess of Et_2O. Ether and acetonitrile were decanted and the residual gum was dissolved in CH_2Cl_2/CH_3OH (1:1, 100 mL) and concentrated in vacuo to obtain **14** as brown gum which solidifies on standing (4.36 g, 59%). MS (ES) *m/z*, relative intensity: 379 [$(M-PF_6)^+$, 100] HRMS calcd for $C_{16}H_{18}O_2Cl{}^{102}Ru$ $(M-PF_6)^+$: 379.0039, found: 379.0035.

1.1.9. (*S*,*S*)-[η^6-3-(4-Chlorophenyl)-1-pentanoic acid-cyclohexylglycine-7-hydroxy-1,2,3-tetrahydroisoquinoline-3-carboxylic acid methyl ester](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (15). A solution of [CpRu(η^6-4-chlorophenylpentanoic acid)]PF_6 **14** (2.2 g, 4.0 mmol) in dry DMF (10 mL) was treated with HOBt (810 mg 5.99 mmol) and Hünig's base (2.58 g, 3.6 mL, 19.9 mmol) The reaction mixture was cooled to 0°C and

treated with EDCI (1.14 g, 6.0 mmol) The reaction mixture was stirred at 0°C for 30 min. and the ammonium salt **9** (1.60 g, 4.0 mmol) was added. The reaction mixture was stirred at rt for 12 h and concentrated in vacuo. The residue was diluted with aq. HCl (1 M, 100 mL) and extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were extracted with aq. $NaHCO_3$ (40 mL), brine (100 mL), dried (Na_2SO_4), filtered, concentrated in vacuo to yield **15** as a brown solid (2.41 g, 75%) which was used for cyclization as it is. HRMS calcd for $C_{35}H_{42}N_2O_5Cl^{102}Ru$ $(M-PF_6)^+$: 707.1826, found: 707.1825.

1.1.10. Cyclic-(*S*,*S*)-[η⁶-3-phenyl-1-pentanoic acid-cyclohexylglycine-7-hydroxy-1,2,3-tetrahydroisoquinoline-3-carboxylic acid methyl ester](η⁵-cyclopentadienyl)-ruthenium hexafluorophosphate (2). A solution of complex **15** (2.40 g, 2.8 mmol) in dry DMF (250 mL) was degassed and treated with Cs_2CO_3 (4.6 g, 14.0 mmol). The reaction was stirred at rt for 24 h and concentrated in vacuo. The residue was diluted with water (100 mL) and extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were extracted, with aq. HCl (1 M, 100 mL), $NaHCO_3$ (100 mL), brine (100 mL), dried (Na_2SO_4), filtered, concentrated in vacuo, and dried in vacuum to yield **16** as a brown solid (1.9 g, 79%). It was used for photolytic removal of Ru without further purification; MS (ES) *m/z*, relative intensity: 671 $[(M-PF_6)^+$, 40]; HRMS calcd for $C_{35}H_{41}N_2O_5Ru$ $(M-PF_6)^+$: 671.2059, found: 671.2045.

The cyclized compound **16** was dissolved in CH_3CN (60 mL) and filtered into a quartz tube. The solution was degassed and photolysed in a Rayonet (λ=350 nm) for 48 h. The reaction mixture was concentrated in vacuo and the residue was purified by chromatography (SiO_2, acetone/hex 3:7) to yield **2** as a tan colored solid (140 mg, 13%). R_f: 0.73 (acetone/hexanes 3:7); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30–7.12 (m, 5H), 6.92–8.83 (m, 2H), 6.74 (d, 1H, J=2.4 Hz), 5.43 (dd, 1H, J=13.7, 3.3 Hz), 4.22–4.11 (m, 2H), 4.00 (bs, 1H), 3.66 (s, 3H), 3.44–3.39 (m, 1H), 3.02–2.91 (m, 1H), 2.66–2.57 (m, 3H), 2.36–2.13 (bt, 1H), 2.10–2.06 (bt, 1H), 1.83–1.64 (m, 8H), 1.36–1.23 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.2, 167.1, 163.9, 156.7, 154.6, 149.4, 140.3, 132.6, 130.1, 129.9, 129.6, 129.3, 128.4, 120.4, 119.3, 119.1, 117.3, 115.6, 60.2, 60.1, 55.4, 55.2, 51.5, 44.1, 42.0, 34.8, 34.0, 33.8, 33.7, 33.6, 30.9, 30.6, 29.9, 26.5; MS (FAB) *m/z*, relative intensity 505 $[(M+1)^+$, 80], 232 (40), HRMS calcd for $C_{30}H_{37}N_2O_5$ $(M+1)^+$: 505.2702, found: 505.2698.

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