A Formal Total Synthesis of the ACE Inhibitor K-13. An Application of Arene-Ruthenium Chemistry to Complex Chemical Synthesis

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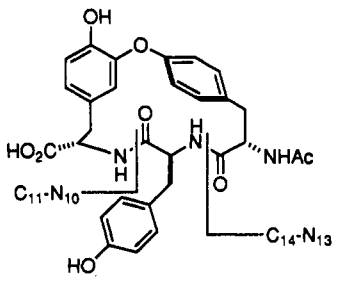
Stoichiometric ruthenium activation of 4-chlorophenylalanine derivatives toward nucleophilic substitution, using phenoxide nucleophiles that are derived from protected dipeptides, allowed the formation of isodityrosine derivatives that are synthetic precursors to the ACE inhibitor K-13. An evaluation of carboxyl blocking groups revealed that a 2-bromoethyl ester is the most useful in terms of its compatibility with ruthenium complexation and subsequent nucleophile addition but that its removal is problematic. Conversion to iodoethyl ester using Finkelstein reaction conditions, in the presence of the peptide and amino acid functionality, provided a solution to this problem, since the iodoethyl group was easily removed on treatment with samarium diiodide.

K-13 (1) is an L,L-isodityrosine-derived cyclic tripeptide, isolated from the culture broth of *Micromonospora halophytica* subsp. *exilisia* K-13,[1] that has been shown to be a novel, noncompetitive inhibitor of angiotensin I converting enzyme (I_{50} = 0.17 μg/mL, K_i = 0.35 μM) and a weak inhibitor of aminopeptidase B. Its structure was elucidated by spectroscopic and chemical degradation studies.[2] The key structural features of K-13 are the isodityrosine subunit which is connected by a diaryl ether linkage of the amino acid residues



K-13 (1)

and cyclic peptide bond linkages that can be set in place during synthesis via cycloamidation at either the C_{11}–N_{10} bond[3] or the C_{14}–N_{13} bond.[4] The synthesis of isodityrosine subunits is a challenging problem because the amino acid functionality is heat- and base-sensitive and therefore is not compatible with the harsh reaction conditions usually required for construction of the diaryl ether linkage. The classical Ullmann reaction[5] has been applied in the direct synthesis of an isodityrosine derivative, but the yield (1.5%) was disappointingly low.[2] More recently, Schmidt's group[6] has reported a modified Ullmann reaction for the preparation of an isodityrosine precursor, and this has been applied in the synthesis of K-13 and the related compound OF 4949-III by Evans.[4] Other variations of the Ullmann reaction using different Cu reagents such as CuBr,[3] CuBr · SMe_2[7] and CuCl[8] have also been reported.

An alternative method for the synthesis of isodityrosine-derived cyclic peptides is the biomimetic, oxidative thallium trinitrate (TTN)-promoted two-step phenolic coupling method introduced by Yamamura, which was illustrated in total syntheses of K-13,[9] OF 4949-III,[10] and piperazinomycin.[11] This method was modified later by Evans, using $CrCl_3$ instead of (Zn/AcOH) for reduction of the products from the TTN coupling reaction, and was used in an approach to the vancomycin family.[12] In other approaches to vancomycin models, Hamilton adopted a method involving S_NAr displacement, by phenolate (or phenoxide), of a tosylate from an activated dinitrotyrosine derivative,[13] while Brown and Crimmin used the reactivity of aryliodonium salts toward the phenoxide of tyrosine to give aryl ether derivatives without racemization.[14] Still has prepared similar thioethers by a photochemical $S_{RN}1$ reaction in ammonia.[15] Most recently, Rao's group[16] reported new routes to isodityrosines by using the reactivity of 2-bromobenzoquinone and 2,6-dibromobenzoquinone toward phenoxide nucleophilic addition to give bis-(aryloxy)benzoquinone, followed by conversion of the benzoquinone skeleton to the corresponding arylamino acid. Another interesting approach to these kinds of compounds is the reaction of dienone monoepoxides with potassium phenoxides, followed by CH_2N_2, Zn/AcOH to give diphenyl ethers having the tyrosine moiety in good yield (33–72%).[17]

We have previously used transition-metal moieties derived from Mn,[18] Fe,[19] and Ru[20] to activate chloroarenes toward nucleophilic substitution, allowing the use of very mild conditions to effect the construction of diaryl ethers

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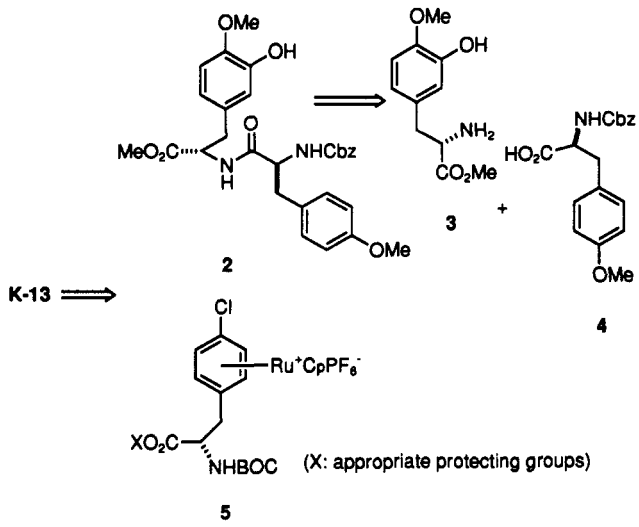
Scheme 1



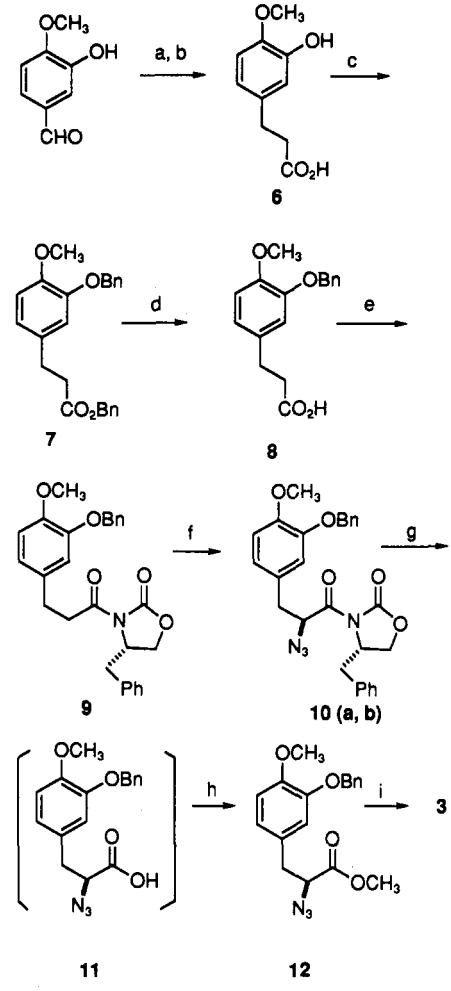
from amino acid derivatives, with little or no racemization. Among these transition-metal-mediated couplings, the Ru method is the only one suitable for the *direct* coupling of two amino acid-containing aromatic molecules, because the attachment of (cyclopentadienyl)ruthenium to the chloroarene derivative and its subsequent S_NAr reaction can be conducted under very mild conditions that are compatible with even the most sensitive amino acid functionality. This paper describes the use of arene–ruthenium chemistry in a convergent formal synthesis of K-13 that illustrates these features. An evaluation of carboxylate blocking groups on the chlorophenylalanine–Ru complex is also reported, which should prove useful for future studies in this area.

Results and Discussion

We have previously shown that arene–metal complexes (especially Ru) can be coupled with phenolic derivatives under very mild conditions (e.g., 2,6-di-*tert*-butylphenol + NaH, THF, −78 °C, or −20 °C).[20] On the basis of the analysis shown in Scheme 1, three intermediates (**3**, **4**, and **5**) were prepared.

Intermediate **3** was prepared by using Evans' asymmetric azidation method (Scheme 2). Benzylation of the phenolic and carboxylic groups of the known[21,22] compound **6**, followed by saponification, afforded **8** in quantitative yield. The purified monoacid **8** was then treated with pivaloyl chloride and triethylamine to obtain the mixed anhydride, which upon treatment with 1.0 equiv of lithiated (4*S*)-4-(phenylmethyl)-2-oxazolidinone[23] at −78 °C, afforded the carboximide **9** as a white crystalline solid in good yield. Complete enolization of the carboximide **9** by the rapid addition of 1.3 equiv of KHMDS at −78 °C, and then reaction of the resulting enolate with trisyl azide,[24] followed by the usual acetic acid quench according to the established procedure,[25] gave the crude α-azido carboximide **10**. The diastereomer ratio was 97:3 by HPLC, and the crude

Scheme 2



[a] Reaction conditions, reagents, and yields; (a) malonic acid, piperidine, pyridine, 3 h (105 °C), 1 h (145 °C), 86%; (B) Pd–C (10%), MeOH, 12 h rt, 88%; (c) BnBr (2.1 equiv), K_2CO_3 (3.0 equiv), 20 h, rt, 89%; (d) KOH (2.1 equiv) 20 h, rt, 96%; (e) Et_3N, pivaloyl chloride, then (4*S*)-4-(phenylmethyl)-2-oxazolidinone/*n*-BuLi, 83%; (f) KHMDS, trisyl azide, 71%; (g) LiOOH (2.0 equiv), 0 °C, 1 h, 98%; (h) *p*-TSA/MeOH, reflux, 8 h, 84%; (i) Pd–C (10%), THF, 8 h, rt, 85%.

product was purified by flash chromatography followed by recrystallization (hexane/EtOAc, 9/1; 71% yield). Removal of the chiral auxiliary from **10** with LiOOH at 0 °C,[26] followed by protection of the carboxyl group as its methyl ester, and subsequent simultaneous catalytic reduction of the azide group and deprotection of benzyl group of the phenolic moiety in **12** afforded the desired intermediate **3** in good yield.

The intermediate **4** was prepared from L-tyrosine ethyl ester hydrochloride (**13**, Sigma chemicals) as shown in Scheme 3. Cbz protection of **13** under mildly basic conditions (Na_2CO_3),[27] followed by saponification of the ester and simultaneous *in situ* protection of the phenolic group as its methyl ether (dimethyl sulfate/excess of NaOH), afforded the desired intermediate **4** with an $[\alpha]_D$ value consistent with the literature (see Experimental Section).[28a] To synthesize the requisite dipeptide **2**, which

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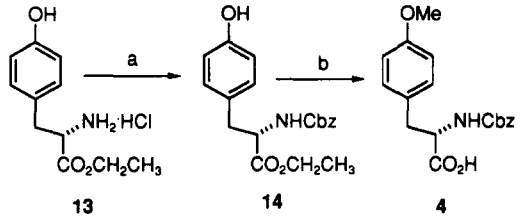
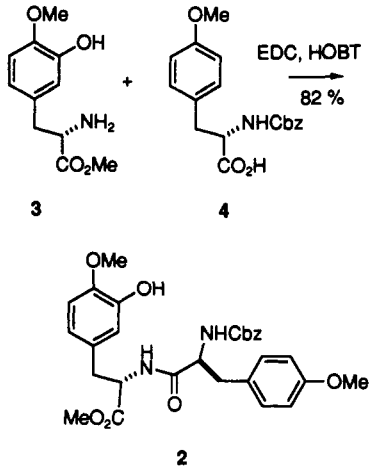
Scheme 3



[a] Reaction conditions, reagents, and yields: (a) Cbz-Cl, Na_2CO_3, 0 °C, then rt, 91%; (b) Me_2SO_4, NaOH, rt, 92%.

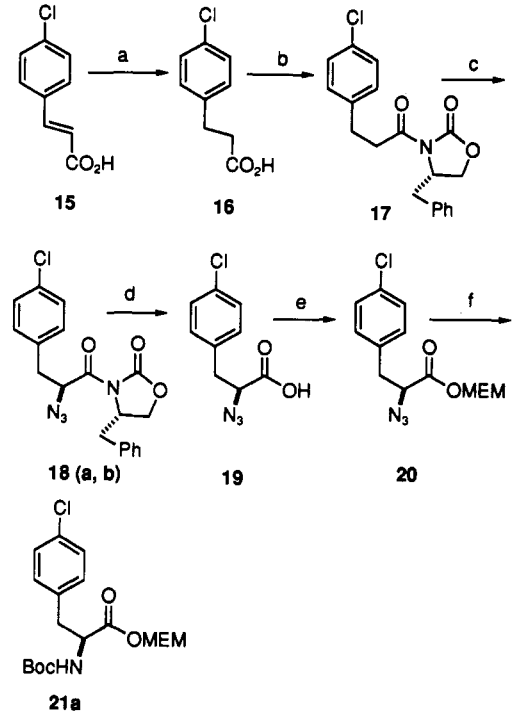
Scheme 4



has a free phenolic group, **3** and **4** were reacted in the presence of EDC and HOBT at 0 °C and stirred overnight. After purification by flash chromatography, the dipeptide was obtained in 82% yield (Scheme 4).

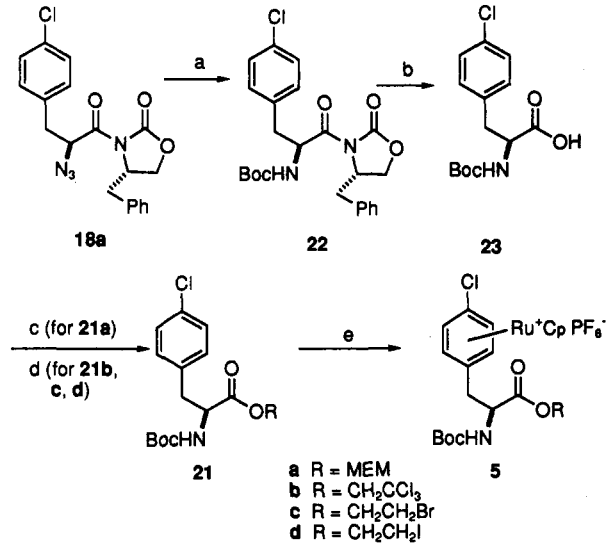
The chiral ruthenium complexes **5a-d**, having various carboxyl protecting groups, were prepared from *N*-Boc-(*S*)-4-chlorophenylalanine, which was in turn prepared by the Evans asymmetric azidation methodology (Scheme 5). Catalytic hydrogenation of commercially available *p*-chlorocinnamic acid (**15**) with Pd–C (10 %)/H_2 (1 atm) gave the known compound **16**[28b] which was converted to the azido derivative **18** in the usual way (diastereomer ratio 95:5 by HPLC). The crude product was purified by flash chromatography, followed by recrystallization (hexane/EtOAc, 9/1). Removal of the chiral auxiliary was effected by treatment with LiOH (2.0 equiv) in THF at 0 °C to give the α-azido acid **19** in 92% yield. At this point, ester-protecting groups were evaluated for their potential compatibility with the Ru metalation, nucleophile addition, and demetalation reactions and their suitability for selective removal at the later stage. The MEM (methoxyethoxymethyl) ester protecting group was the first choice for our trial, because this group was reported to be deprotected easily with neutral $MgBr_2/Et_2O$.[29] The intermediate **19** was treated with MEM-Cl/Hünig base[30] at 0 °C, and the resulting compound **20** was treated with $(Boc)_2O$/Ra–Ni, H_2 (1 atm) to effect reduction of the azide and *in situ* protection of the amino group. The yield of the latter step was poor, so we turned our attention to another route (Scheme 6). From previous unpublished work in our laboratory, (4*S*)-4-(phenylmethyl)-2-oxazolidinone was known to be stable toward the hydrogenation conditions, so **18a** was treated with Pd–C (10%)/H_2 (1 atm), HCl (2.0 equiv) to give the amine hydrochloride, which was reacted with $(Boc)_2O/K_2CO_3$, affording the *N*-Boc protected compound **22** in 85% yield. After removal of the chiral auxiliary with LiOH (2.0 equiv), the resulting crude acid **23** was used without purification for the next reaction, leading to the fully protected amino acid derivative **21a** in 96% yield. Conversion of **21a** to its RuCp

Scheme 5



[a] Reaction conditions, reagents, and yields: (a) Pd–C (10%), THF, 4 h, rt, 88%; (b) Et_3N, pivaloyl chloride, (4*S*)-4-(phenylmethyl)-2-oxazolidinone/*n*-BuLi, 86%; (c) KHMDS, trisyl azide, 76%; (d) LiOH (2.0 equiv), 0 °C, 1 h, 92%; (e) MEMCl, *i*-Pr_2NEt, 0 °C, 2 h, 75%; (f) Raney Ni/H_2 (1 atm), $(Boc)_2O$ (1.2 equiv), 44%.

Scheme 6



[a] Reaction conditions, reagents, and yields: (a) Pd–C (10%), HCl (2.0 equiv), H_2 (1 atm), then K_2CO_3 (2.5 equiv), $(Boc)_2O$, 85%; (b) LiOH (2.0 equiv), 0 °C, 1 h, 77%; (c) MEMCl (1.2 equiv), *i*-Pr_2NEt (1.1 equiv), 0 °C, 2 h, 96%; (d) 2-haloethanol (1.2 equiv), DCC (1.1 equiv), pyridine (2.0 equiv), 0 °C, overnight, 76–92%; (e) $[(CH_3CN)_3RuCp]^+[PF_6^-]$ (1.5 equiv), 1,2-dichloroethane, reflux, 5 h, 93–98%.

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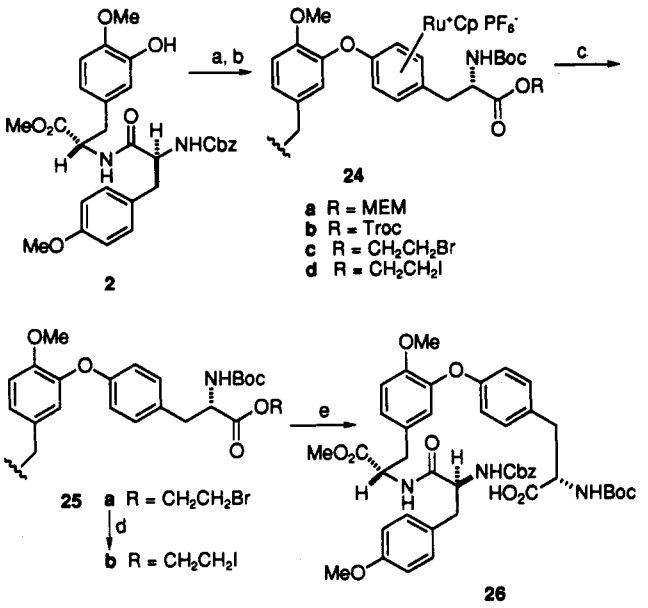
Scheme 7

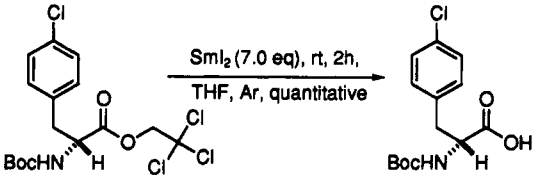


[a] Reaction conditions, reagents, and yields: (a) sodium 2,6-di-*tert*-butylphenoxide (1.1 equiv), 0 °C, N_2, 20–30 min; (b) **5** (1.0 equiv), 1 h (−78 °C), then 3.5 h (rt), 29–81%; (c) sunlamp (275 W), CH_3CN, N_2, 20–24 h, 48–65%; (d) NaI (5.0 equiv), reflux, 7 h, N_2, 95%; (e) SmI_2 (7.0 equiv), THF, 35 °C, 10 h, Ar, 70%.

complex **5a** was accomplished by refluxing it with $[(CH_3CN)_3RuCp]^+[PF_6^-]$[31] in 1,2-dichloroethane for 5 h under N_2,[20] and the resulting crude complex was purified by filtering the reaction solution through a Celite pad and then through a neutral alumina column to provide complex that was sufficiently pure for the next step. Due to the intrinsic difficulty of purification of these kinds of cationic metal complexes, we did not attempt further purification of Ru complex **5a**.

For the coupling reaction, 2,6-di-*tert*-butylphenol, sodium salt was used as a sterically hindered weak base. The dipeptide **2** was reacted with 1.1 equiv of the base at 0 °C for 30 min, then it was transferred into a precooled (−78 °C) solution of **5a** via a cannula, and the resulting solution was stirred for 1–2 h at −78 °C and then for 3–4 h at rt. The diaryl ether complex **24a** was isolated in only 29% yield (Scheme 7). The condensation reaction was easily confirmed by ^1H NMR which showed that, after condensation, complexed, aromatic H peaks were shifted upfield to *ca.* 6.05 ppm and the Cp peak was also shifted upfield slightly to *ca.* 5.35 ppm, owing to the electron-donating diaryl ether oxygen. We were unable to improve the yield of this reaction, presumably due to the instability of MEM ester protecting group and/or Ru complexed compound itself toward these reaction conditions, and the use of MEM protection was abandoned.

The next candidate for implementation of this strategy was the 2,2,2-trichloroethyl ester (Troc) protecting group, which has been widely used in peptide synthesis[32,33] and is easily removed by nonbasic deprotecting reagents such as Zn/HOAc/H_2O[32] and Zn-dust/buffer.[34] But more importantly, in our preliminary experiments using a model compound, this protecting group was removed quantitatively under very mild conditions (SmI_2 (7.0 equiv), rt., 2 h, Ar) (eq 1). The synthesis of **21b** and its Ru complexation were accomplished by using the standard reaction conditions. However, the attempted condensation of **5b** with the phenoxide from **2** gave very disappointing yields (<5%), possibly due to the reactivity of Troc-ethyl ester functionality toward arylation reaction conditions.



(1)

In contrast to the above disappointing results, the bromoethyl ester **5c** was found to be exceptionally well-behaved during both the complexation and aryl ether-forming reactions. We approached the use of this blocking group with some trepidation, however, since previous studies in our laboratory[35,36] had revealed that various deprotection methods, such as Zn with or without NaI[37,38] in boiling aqueous THF (or MeOH), $Zn/ZnCl_2$,[37] ethanedithiol/NaH/CH_3CN,[39] Na_2CS_3/ CH_3CN,[40] vitamin B_{12}b/aqueous EtOH (or DMF),[41] Na/liquid NH_3,[36] Ca/liquid NH_3,[36] $Pd(PPh_3)_4$/ CH_3CN,[36] led to exclusive formation of 2-hydroxyethyl esters and/or complete destruction of the starting material. A similar problem was reported by Magnus[42] for deprotection of 2-chloroethyl carbamates.

The Ru complex **5c** was subjected to condensation reaction conditions similar to those used for **5a** to give virtually pure product **24c** in *ca.* 80% yield. For the demetalation reaction, **24c** was irradiated with UV light (sunlamp, 275 W) in a quartz tube (typical size 1.5 × 20 cm, CH_3CN, N_2) for *ca.* 20 h at rt, and after the reaction was complete, the organic product was separated from $[(CH_3CN)_3RuCp]^+[PF_6^-]$ (ether-insoluble) by adding the concentrated CH_3CN solution to diethyl ether. The average recovery of $[(CH_3CN)_3RuCp]^+[PF_6^-]$ was *ca.* 85%, indicating that the stoichiometric use of ruthenium for these reactions is not greatly disadvantageous. After purification by flash chromatography, **25a** was obtained in 65% yield, and the structure was confirmed by ^1H NMR.

Removal of the 2-bromoethyl protecting group from **25a** proved to be impossible, no free carboxyl being obtained from using any of the standard procedures[35] or from treatment with excess samarium diiodide. On the basis of the known reactivities of β-haloethyl ester protecting groups, we turned our attention to the use of 2-iodoethyl. A model compound (eq 2) was reacted with SmI_2 (7.0 equiv)

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(35) The deprotection trials of amino acid based N-Boc, 2-bromoethyl ester compounds by various reported methods always gave 2-hydroxyethyl esters as the major compound, and the results were confirmed by ^1H NMR and by conversion of 2-hydroxyethyl esters into their corresponding 2-acetoxyethyl esters. For more information, see refs 20 and 36.
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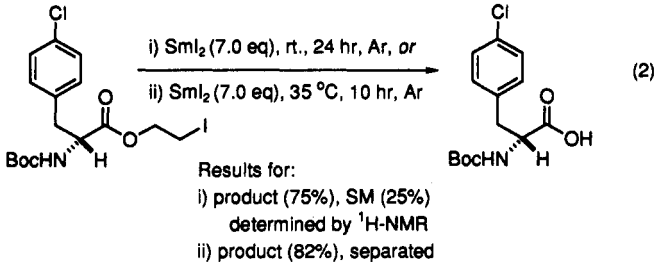

(2)

at rt under deoxygenated Ar for 1 day to give 75% of free acid and 25% of unreacted ester. Prolonged stirring (2 days) and/or use of an excessive amount of SmI_2 (10.0 equiv) did not lead to further deprotection. At a slightly elevated temperature (35 °C) with use of 7.0 equiv of SmI_2, the reaction was determined complete after *ca.* 10 h from the ^1H NMR of crude product. Conversion of the 2-bromoethyl ester **25a** into the 2-iodoethyl ester **25b** was achieved in excellent yield (~95%) by refluxing with NaI in anhydrous acetone for 7 h (Finkelstein reaction).[43] The final transformation of the key intermediate **25b** into its corresponding acid **26** was accomplished by using the same reaction conditions (SmI_2 7.0 equiv, 35 °C, 10 h, THF, deoxygenated Ar) as in the model study. The specific rotation ($[\alpha]_{Hg,365}$ = +30.4°, *c* 0.38, MeOH) of the pure product was somewhat higher than the value ($[\alpha]_{Hg,365}$ = +27.6°, *c* 0.54, MeOH) reported by Evans and co-workers.[4] The ^1H NMR spectrum of **26** in methanol-d_4 matched that reported by Evans, but the broad residual OH peak that appears at *ca.* 5 ppm masked some characteristic peaks, such as the methylene of the Cbz group, and proton–deuterium exchange leads to gradual loss of the amide absorptions. To circumvent this problem, CD_3CN–$CDCl_3$ (*ca.* 7:3 mixture) was used as solvent, and the ^1H NMR spectrum clearly exhibited amide proton peaks and Cbz methylene peaks. Intermediate **26** has been converted to K-13 by Evans,[4] and therefore the present work constitutes a formal total synthesis of this compound.

We next turned our attention to a more direct way to prepare the 2-iodoethyl ester-protected condensation product **24d**. Conversion of **23** to **21d** by treatment with 2-iodoethanol/DCC in methylene chloride at 0 °C, followed by Ru complexation and condensation, afforded the diaryl ether Ru complex **24d** in 59% yield. This Ru complex was less stable than its bromoethyl counterpart **24c**; after filtering it through a Celite pad and then through a short neutral alumina column (1 × 5 cm), the yield decreased considerably even though the purity was only marginally improved. Demetalation of **24d** proceeded satisfactorily under the standard photochemical conditions to give **25b** in 48% yield. The $[\alpha]_D$ value (+34.8°, *c* 0.69, $CHCl_3$) of **25b** from the direct process was almost identical to that (+34.3°, *c* 0.58, $CHCl_3$) acquired from the two-step sequence, also suggesting that there is no racemization during either sequence. Even though one more step (Finkelstein reaction) is required, the two-step sequence was found to be better than the more direct sequence in terms of overall yield.

Conclusions

A formal asymmetric total synthesis of K-13 has been developed which uses arene–ruthenium chemistry for the key aryl ether bond formation. The ruthenium methodology allows direct coupling of phenolic and haloarene components that have protected amino acids and/or peptide side chains and allows a useful approach to isodityrosine-derived compounds. While the cost of ruthenium may detract from its use as a stoichiometric activating group, it can be recovered in good yield and recycled. The operational simplicity of this chemistry should allow its widespread application to this type of synthesis problem and is expected to pave the way for the ultimate development of a procedure that is catalytic in ruthenium or related metals. Among the various acid protecting groups that were examined, the 2-bromoethyl ester was found to be the best during complexation, condensation, and demetalation reactions. Difficulties during the removal of this protecting group were overcome by its conversion to 2-iodoethyl, followed by deprotection using SmI_2, providing a versatile, reproducible way for protection/deprotection of the carboxyl group.

Experimental Section

General. All reactions were conducted under dry N_2 except SmI_2-mediated deprotection reactions (under deoxygenated, dry Ar). ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded in $CDCl_3$ or CD_3CN-$CDCl_3$ on a Varian Gemini-300 spectrometer. ^1H NMR was referenced to TMS and ^{13}C NMR was referenced to $CHCl_3$ (77.0 ppm). IR spectra were recorded on a Perkin-Elmer Series 1600 FT-IR using solutions in $CHCl_3$ or CH_2Cl_2. Melting points were obtained on a Thomas-Hoover apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 141 polarimeter. Mass spectra were recorded in-house on a Kratos MS 25A instrument and CHN analyses were performed by Galbraith Laboratories, Knoxville, TN. Thin-layer chromatography was performed using E. Merck silica gel 60 F-254 0.25-mm plates. Visualization was accomplished with UV, phosphomolybdic acid, or ninhydrin solution. Flash chromatography was carried out on E. Merck 320–400-mesh silica gel and solvents are reported as v/v percent mixture. Analytic HPLC was performed on a Rainin HPLC using a Dynamax-60A normal phase analytical column. THF was distilled from the sodium ketyl of benzophenone. CH_2Cl_2, Et_3N, and CH_3CN were distilled from calcium hydride. All solvents were distilled under dry nitrogen. *n*-Butyllithium in hexane was obtained from Aldrich Co. and standardized according to the method of Kofron and Baclawski.[44] SmI_2 (0.1 M in THF) was purchased from Aldrich Co. and used directly without titration. All other commercial reagents were purchased from Aldrich Co. and used without purification.

[3-(Benzyloxy)-4-methoxyphenyl]propionic Acid, Benzyl Ester (7). To a stirred suspension of crude **6** (4.12 g, 20.98 mmol) and 8.70 g (3.0 equiv) of K_2CO_3 in 60 mL of dry acetone was added 5.35 mL (2.1 equiv) of benzyl bromide in one portion. The reaction mixture was refluxed for 20 h under N_2, cooled to rt, and then filtered through Celite. The filter cake was washed well with acetone, and the combined organic layers were evaporated to give the crude product. Purification by flash chromatography on silica gel (hexanes/EtOAc, 85/15) provided 8.29 g (89%) of **7** as a white solid: mp 60.0–61.5 °C; R_f 0.32 (hexanes/EtOAc, 80/20); IR ($CHCl_3$) 3020, 2954, 1734, 1591, 1515, 1214 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45–7.26 (m, 10 H, aromatic), 6.83–6.75 (m, 3 H, aromatic), 5.09 (s, 4 H, $ArOCH_2Ph$ overlapping with $-CO_2CH_2Ph$), 3.86 (s, 3 H, $-OCH_3$), 2.87 (t, 2H, J = 7.5 Hz), 2.61 (t, 2H, J = 2.5 Hz); ^{13}C NMR ($CDCl_3$) δ 172.7, 148.2, 148.1, 137.1, 135.9, 132.9, 128.5, 128.2, 127.8, 127.3, 120.8, 114.4, 111.9, 71.0, 66.2, 56.0, 36.1, 30.4; HRMS calcd for $C_{24}H_{24}O_4$ 376.1674, found 376.1666.

[3-(Benzyloxy)-4-methoxyphenyl]propionic Acid (8). To a stirred solution of **7** (5.38 g, 14.3 mmol) in 30 mL of THF, 20 mL of MeOH, and 20 mL of water was added a solution of 1.68 g (2.1 equiv) of KOH in 10 mL of water. The mixture was stirred for 2 h at rt, and then all of the organic solvent was removed *in*

(43) (a) Larock, R. C. *Comprehensive Organic Transformations*; VCH Publishers: New York, 1989; p 339. (b) Abraham, E. P.; Smith, J. C. *J. Chem. Soc.* **1936**, 1605.

(44) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

vacuo. The aqueous layer was acidified to *ca.* pH 2 with 5 N HCl and extracted with EtOAc (30 mL × 3). The combined organic extracts were washed with brine and dried over $MgSO_4$, and the solvent was removed *in vacuo* to give the crude product which was purified by recrystallization (EtOAc/hexanes, 60/40) to afford 3.59 g of pure product **8**. The residue was flash-chromatographed on silica gel (hexanes/EtOAc, 20/80) to give a second crop (320 mg) of **8**: total yield 3.91 g (96%); mp 122.5–124.5 °C; R_f 0.41 (hexanes/EtOAc, 20/80); IR ($CHCl_3$) 3522, 3017, 2935, 1710, 1591, 1515, 1211 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45–7.26 (m, 5 H, aromatic), 6.84–6.74 (m, 3 H, aromatic), 5.13 (s, 2 H, -OCH_2Ph), 3.86 (s, 3 H, -OCH_3), 2.85 (t, 2 H, J = 7.7 Hz, -CH_2-C$H_2$$CO_2$H), 2.60 (t, 2 H, J = 7.7 Hz, -CH_2C$H_2$$CO_2$H); ^{13}C NMR ($CDCl_3$) δ 179.0, 148.2, 148.0, 137.1, 132.6, 128.5, 127.8, 127.3, 120.7, 114.5, 111.9, 71.0, 56.0, 35.7, 30.0; HRMS calcd for $C_{17}H_{18}O_4$ 286.1205, found 286.1210.

(4*S*)-3-(Benzyloxy)-4-methoxy-[3-oxo-3-[2-oxo-4-(phenylmethyl)-3-oxazolidinyl]propyl]benzene (9). To a stirred solution of **8** (1.57 g, 5.47 mmol) in 50 mL of dry THF at −78 °C was added freshly distilled Et_3N (0.99 mL, 1.3 equiv) followed by distilled pivaloyl chloride (0.74 mL, 1.1 equiv). The mixture was stirred for 15 min at −78 °C and 50 min at rt to form the mixed anhydride and then cooled again to −78 °C under N_2. In a separate flask, 0.90 g (1.0 equiv) of (4*S*)-4-(phenylmethyl)-2-oxazolidinone in 30 mL of THF at −78 °C was added 2.3 mL (2.35 M in hexane, 1.0 equiv) of *n*-BuLi by syringe, then the solution was stirred for 20 min at −78 °C under N_2. The mixture was transferred to the above mixed anhydride solution via cannula, and the resulting mixture was stirred for 15 min at −78 °C and 4 h at rt. After the reaction was quenched with 30 mL of 1 N $NaHSO_4$ and removal of THF *in vacuo*, the product was extracted into CH_2Cl_2 (30 mL × 3). The combined extracts were washed with dilute $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford the crude product as a yellow solid. The first crop (1.89 g) of pure product was obtained by recrystallization (hexanes/EtOAc, 60/40), and the residue was flash-chromatographed on silica gel (hexanes/EtOAc, 70/30) to give a second crop (0.14 g) of pure product: total yield 2.03 g (83%); mp 122.0–123.5 °C; $[\alpha]^{22}_D$ +41.9° (*c* 0.49, $CHCl_3$); R_f 0.23 (hexanes/EtOAc, 70/30); IR ($CHCl_3$) 3019, 2924, 1781, 1700, 1515, 1255, 1214 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.47–7.16 (m, 10 H, aromatic), 6.84 (m, 3 H, aromatic), 5.14 (s, 2 H, -OCH_2Ph), 4.68–4.60 (m, 1 H, -NCH-CH_2^{ox}), 4.17–4.13 (m, 2 H, -NCHCH_2^{ox}-), 3.86 (s, 3 H, -OCH_3), 3.31–3.12 (m, 3 H, ArC$H_2$$CH_2$CO- overlapping with -NCHCH-HPh^{ox}), 2.92 (t, 2 H, J = 7.0 Hz, ArCH_2CH_2CO-), 2.74 (dd, 1 H, J = 13.4, 9.5 Hz, -NCHCHHPh^{ox}); ^{13}C NMR ($CDCl_3$) δ 172.4, 153.4, 148.1, 148.0, 137.1, 135.1, 132.9, 129.4, 128.9, 128.5, 127.7, 127.4, 121.1, 114.6, 111.9, 71.0, 66.1, 56.1, 55.1, 37.8, 37.2, 29.8; HRMS calcd for $C_{27}H_{27}NO_5$ 445.1889, found 445.1890.

(4*S*,2*S*)-3-(Benzyloxy)-4-methoxy-[2-azido-3-oxo-3-[2-oxo-4-(phenylmethyl)-3-oxazolidinyl]propyl]benzene (10a). To a precooled (−78 °C), stirred solution of 17.2 mL (1.3 equiv) of KHMDS (0.5 M in toluene) in 30 mL of dry THF was added 2.95 g (1.0 equiv) of **9** in 40 mL of dry THF via cannula, and the resulting mixture was stirred for 30 min at −78 °C under N_2. To this mixture was transferred a precooled (−78 °C) solution of trisyl azide (2.25 g, 1.1 equiv) in 40 mL of dry THF, via cannula, and the resulting mixture was stirred for 2 min at −78 °C, then rapidly quenched by the addition of 1.1 mL of glacial acetic acid, followed by immediate warming to 30 °C with a water bath. The white slurry was stirred further for 3 h at rt and then partitioned between 130 mL of CH_2Cl_2 and brine (50 mL), and the aqueous layer was washed with CH_2Cl_2 (30 mL × 2). The combined organic extracts were washed with dilute $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated to afford a pale yellow residue which was purified by flash chromatography on silica gel (hexanes/EtOAc, 80/20). Further purification by recrystallization (hexanes/EtOAc, 90/10) gave 2.28 g (71%) of **10a** as a diastereomerically pure product. The diastereomeric minor product **10b** was separated by succesive elutions (>20 times) of the crude product loaded on a prep-TLC plate (silica gel, hexanes/EtOAc, 85/15), and the diastereoselectivity was determined to be 97:3 by HPLC (RAININ HPXL, 284 nm, Dynamax-60A normal phase analytical column, hexanes/EtOAc, 80/20, 2 mL/min; t_R **10a** = 13.3 min, **10b** = 9.7 min). **10a**: mp 93.5–94.5 °C; $[\alpha]^{22}_D$ +75.5° (*c* 0.50, $CHCl_3$); R_f 0.22 (hexanes/EtOAc, 70/30); IR ($CHCl_3$) 3023, 2936, 2110, 1782, 1707, 1515, 1258, 1219 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.47–7.20 (m, 10 H, aromatic), 6.85 (m, 3 H, aromatic), 5.19 (dd, 1 H, J = 9.1, 5.5 Hz, ArCH_2C$H$$N_3$-), 5.15 (s, 2 H, -OC$H_2$Ph), 4.54 (m, 1 H, -NC$H$ CH_2OCO^{ox}-), 4.20–4.05 (m, 2 H, -CHC$H_2$$OCO^{ox}$-), 3.87 (s, 3 H, -OC$H_3$), 3.30 (dd, 1 H, J = 13.4, 3.2 Hz, -NCHCH-HPh^{ox}), 3.11 (dd, 1 H, J = 13.6, 5.5 Hz, ArCH$H$$CHN_3$-), 2.93 (dd, 1 H, J = 13.6, 9.1 Hz, ArC$H$$HCHN_3$-), 2.82 (dd, 1 H, J = 13.4, 9.4 Hz, -NCHCHHPh^{ox}); ^{13}C NMR ($CDCl_3$) δ 170.5, 152.8, 148.9, 148.1, 136.9, 134.7, 129.4, 129.0, 128.5, 127.9, 127.8, 127.5, 122.0, 114.9, 111.8, 70.9, 66.5, 61.4, 56.0, 55.4, 37.6, 37.2; HRMS calcd for $C_{27}H_{26}N_4O_5$ 486.1903, found 486.1900.

10b: $[\alpha]^{21}_D$ +30.0° (*c* 0.34, $CHCl_3$); R_f 0.26 (hexanes/EtOAc, 70/30); IR ($CHCl_3$) 3027, 2935, 2110, 1782, 1708, 1516, 1257, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45–7.13 (m, 10 H, aromatic), 6.96–6.84 (m, 3 H, aromatic), 5.15 (s, 2 H, -OCH_2Ph), 5.12 (dd, 1 H, J = 9.4, 4.9 Hz, ArCH_2C$H$$N_3$-), 4.77–4.69 (m, 1 H, -NC$H$$CH_2$-$OCO^{ox}$-), 4.32–4.11 (m, 2 H, -NCHC$H_2$$OCO^{ox}$-), 3.87 (s, 3 H, -OC$H_3$), 3.20 (m, 2 H, ArC$H$$HCHN_3$- overlapping with -NCH-CHHPh^{ox}), 2.91 (dd, 1 H, J = 13.7, 9.4 Hz, ArCH$H$$CHN_3$-), 2.70 (dd, 1 H, J = 13.4, 9.4 Hz, -NCHCHHPh^{ox}).

(*S*)-2-Azido-3-[3-(benzyloxy)-4-methoxyphenyl]propionic Acid, Methyl Ester (12). To a precooled (0 °C) solution of 1.12 g (2.42 mmol) of **10a** in 40 mL of THF and 10 mL of water was added 1.48 mL (6.0 equiv) of H_2O_2 (30%) followed by 9.7 mL of a 0.5 M LiOH solution. The mixture was stirred for 1.5 h at 0 °C, the reaction was quenched by the addition of 10.6 mL of a Na_2SO_3 (1.5 N, 6.6 equiv) solution, and the resulting solution was stirred for 15 min at 0 °C. After the solution was buffered to basic with saturated $NaHCO_3$, THF was removed under reduced pressure, and neutrals were extracted with CH_2Cl_2 (10 mL × 3). The aqueous layer was acidified with 5 N HCl to *ca.* pH 2, then extracted with EtOAc (30 mL × 3), dried over $MgSO_4$, and concentrated *in vacuo* to afford the product **11** (775 mg, 98%). The crude acid (719 mg, 2.2 mmol) was disolved in 30 mL of anhydrous MeOH containing 418 mg (1.0 equiv) of *p*-toluenesulfonic acid, and the reaction mixture was heated at reflux for 8 h under N_2. After being cooled to rt. the mixture was treated with saturated $NaHCO_3$ to basify, extracted with EtOAc (30 mL × 2), washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography on silica gel (hexanes/EtOAc, 80/20) gave 633 mg (84%) of the methyl ester **12** as a colorless oily product which solidified in the refrigerator: mp 38.0–39.5 °C; $[\alpha]^{23}_D$ −31.6° (*c* 0.52, $CHCl_3$); R_f 0.32 (hexanes/EtOAc, 80/20); IR ($CHCl_3$) 3024, 2956, 2109, 1744, 1592, 1516, 1260, 1214 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46–7.26 (m, 5 H), 6.77 (m, 3 H), 5.15 (s, 2 H, -OCH_2Ph), 3.97 (dd, 1 H, J = 8.6, 5.3 Hz, ArCH_2C$H$$N_3$-), 3.88 (s, 3 H, -OC$H_3$), 3.74 (s, 3 H, -OC$H_3$), 3.06 (dd, 1 H, J = 14.1, 5.3 Hz, ArC$H$$HCHN_3$-), 2.89 (dd, 1 H, J = 14.1, 8.6 Hz, ArCH$H$$CHN_3$-); ^{13}C NMR ($CDCl_3$) δ 170.4, 148.9, 148.1, 137.0, 128.5, 128.2, 127.8, 127.3, 121.9, 115.2, 111.8, 71.0, 63.4, 56.0, 52.6, 37.2; HRMS calcd for $C_{18}H_{19}N_3O_4$ 341.1375, found 341.1380.

3-Hydroxy-4-methoxy-L-phenylalanine, Methyl Ester (3). A solution of **12** (3.3 g, 9.7 mmol) in 20 mL of THF was added to a stirred, presaturated (by H_2) slurry of Pd–C (10%) (400 mg) in 30 mL of THF, and the resulting mixture was stirred for 8 h at rt under H_2 (1 atm). After filtration through Celite, the solution was concentrated under reduced pressure to afford the solid residue which was chromatographed on silica gel (EtOAc/MeOH, 95/5). Further purification by recrystallization from diethyl ether gave 1.86 g (85%) of **3** as a white solid: mp 82.5–84.5 °C; $[\alpha]^{22}_D$ +9.5° (*c* 0.60, $CHCl_3$); R_f 0.17 (EtOAc/MeOH, 95/5); IR ($CHCl_3$) 3542, 3384, 3026, 2955, 1736, 1593, 1513, 1273, 1226 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.78–6.64 (m, 3 H,), 3.87 (s, 3 H, -OCH_3), 3.73 (s, 3 H, -OCH_3), 3.70 (dd, 1 H, J = 7.8, 5.1 Hz, ArCH_2CH-), 3.01 (dd, 1 H, J = 13.5, 5.1 Hz, ArC$H$$HCHCO_2$-), 2.77 (dd, 1 H, J = 13.5, 7.8 Hz, ArCH$H$$CHCO_2$-); ^{13}C NMR ($CDCl_3$) δ 175.4, 145.63, 145.57, 130.2, 120.7, 115.4, 110.7, 55.9, 55.8, 52.0, 40.3; HRMS calcd for $C_{11}H_{15}NO_4$ 225.1001, found 225.0980.

***N*-[*N*-[(phenylmethoxy)carbonyl]-*O*-methyl-L-tyrosyl]-3-hydroxy-4-methoxy-L-phenylalanine, Methyl Ester (2).** To a stirred, precooled (0 °C) solution of free amine **3** (1.7 g, 7.6 mmol) and free acid **4** (3.0 g, 1.2 equiv) in 20 mL of THF and 20 mL of DMF were added 1.54 g (1.5 equiv) of HOBT and 1.75 g (1.2 equiv) of EDC. The reaction mixture was stirred for 20 h at 0 °C under N_2, poured into 30 mL of water, and then extracted

with EtOAc (50 mL × 3). The combined organic extracts were washed with 10% $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give a solid residue. Purification by flash chromatography on silica gel (EtOAc/CH_2Cl_2, 20/80) and further purification by recrystallization (hexanes/EtOAc, 80/20) afforded 3.33 g (82%) of pure product **2** as a white solid: mp 131.5–133.5 °C; $[\alpha]^{23}_D$ +45.2° (*c* 1.1, $CHCl_3$); R_f 0.27 (CH_2Cl_2/EtOAc, 80/20); IR ($CHCl_3$) 3542, 3418, 3015, 2956, 1740, 1718, 1680, 1513 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43–7.13 (m, 5 H, Cbz), 7.10–6.78 (m, 4 H, Ar^{OMe}), 6.69–6.42 (m, 3 H, $Ar^{OMe,OH}$), 6.12 (bd, 1 H, *J* = 7.6 Hz, $Ar^{OMe,OH}CH_2CHNH$-), 5.65 (s, 1 H, phenolic H of $Ar^{OMe,OH}$), 5.29 (bd, 1 H, *J* = 8.4 Hz, $PhCH_2CO_2NH$-), 5.10 (s, 2 H, $PhCH_2OCONH$-), 4.74–4.68 (m, 1 H, $Ar^{OMe,OH}CH_2CHNH$-), 4.37–4.30 (m, 1 H, $Ar^{OMe}CH_2CHC$-), 3.83 (s, 3 H, $-OCH_3$), 3.77 (s, 3 H, $-OCH_3$), 3.70 (s, 3 H, $-OCH_3$), 3.00–2.90 (m, 4 H, $Ar^{OMe,OH}CH_2CHNH$- overlapping with $Ar^{OMe}CH_2CHC$-); ^{13}C NMR ($CDCl_3$) δ 171.3, 170.4, 158.6, 155.9, 145.8, 145.5, 136.1, 130.3, 128.5, 128.4, 128.2, 128.0, 120.6, 115.5, 114.1, 110.7, 67.1, 56.2, 55.8, 55.2, 53.3, 52.3, 37.5, 37.1; HRMS calcd for $C_{29}H_{32}N_2O_8$ 536.2159, found 536.2198.

(4*S*)-4-Chloro-[3-oxo-3-[2-oxo-4-(phenylmethyl)-3-oxazolidinyl]propyl]benzene (17). To a stirred solution of 4-chlorohydrocinnamic acid (**16**, 1.44 g, 7.82 mmol) in 40 mL of THF at −78 °C were added 1.4 mL (1.3 equiv) of Et_3N and 1.1 mL (1.1 equiv) of pivaloyl chloride, and the resulting mixture was stirred for 15 min at −78 °C and for 45 min at 0 °C and then cooled again to −78 °C. In a separate flask, to 1.26 g (1.05 equiv) of (4*S*)-4-(phenylmethyl)-2-oxazolidinone in 30 mL of THF at −78 °C was added 5.2 mL (1.05 equiv) of *n*-BuLi (1.57 M in hexane) by syringe, and then the solution was stirred for 20 min at −78 °C. The metalated oxazolidinone was transferred to the above white slurry via cannula, and the resulting slurry was stirred for 15 min at −78 °C, then warmed to rt, and stirred for 10 h. The reaction was quenched with 60 mL of 1 N $NaHSO_4$ solution, and THF was removed under reduced pressure. The product was extracted into CH_2Cl_2 (30 mL × 3), and the combined organic layers were washed with dilute $NaHCO_3$ and brine and then dried over $MgSO_4$. The solvent was removed *in vacuo* to provide a pale yellow residue. The first crop (2.14 g) of pure product was obtained by recrystallization (hexanes/EtOAc, 90/10) and a second crop (0.18 g) of product was obtained by flash chromatography of the liquors on silica gel (hexanes/EtOAc, 70/30). The total yield of pure product **17** was 2.32 g (86%): mp 116.5–118.0 °C; $[\alpha]^{26}_D$ +64.2° (*c* 0.55, $CHCl_3$); R_f 0.35 (hexanes/EtOAc, 70/30); IR ($CHCl_3$) 3018, 2982, 1781, 1700, 1494, 1385 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.14, (m, 9 H), 4.70–4.62 (m, 1 H, $-NCHCH_2OCO^{ox}$-), 4.23–4.14 (m, 2 H, $-NCHCH_2OCO^{ox}$-), 3.36–3.16 (m, 3 H, $ArCH_2CH_2CON$- overlapping with $-CHCHHPh^{ox}$), 3.00 (t, 2H, *J* = 7.1 Hz, $ArCH_2CH_2CON$-), 2.75 (dd, 1 H, *J* = 13.3, 9.5 Hz, $-CHCHHPh^{ox}$); ^{13}CNMR ($CDCl_3$) δ 172.0, 153.4, 138.9, 135.1, 132.0, 130.0, 129.4, 128.9, 128.5, 127.4, 66.2, 55.1, 37.8, 37.0, 30.0; HRMS calcd for $C_{19}H_{18}NO_3Cl$ 343.0975, found 343.0999.

(4*S*,2*S*)-4-Chloro-[2-azido-3-oxo-3-[2-oxo-4-(phenylmethyl)-3-oxazolidinyl]propyl]benzene (18a). A precooled (−78 °C) solution of 1.61 g (4.67 mmol) of **17** in 40 mL of dry THF was added to a precooled (−78 °C) solution of 12.1 mL of KHMDS (0.5M in toluene, 1.2 equiv) in 30 mL of THF via cannula, and the resulting solution was stirred for 30 min at −78 °C under N_2. To this solution was added a precooled (−78 °C) solution of 1.59 g (1.1 equiv) of trisyl azide in 40 mL of THF via cannula, and the resulting solution was stirred for 2 min at −78 °C under N_2 and then quenched by the rapid addition of 0.8 mL (3.0 equiv) of glacial acetic acid, followed by immediate warming to 30 °C with a water bath. The white slurry was stirred for 3 h at rt and then partitioned between 150 mL of CH_2Cl_2 and brine, and the aqueous layer was washed again with CH_2Cl_2 (30 mL × 2). The combined organic extracts were washed with dilute $NaHCO_3$ and brine and dried over $MgSO_4$. The solvent was removed *in vacuo* to afford a yellow oily product which was purified by flash chromatography on silica gel (hexanes/EtOAc, 80/20). Recrystallization from (hexanes/EtOAc, 90/10) gave 1.36 g (76%) of diastereomerically pure product **18a** as a white solid. The diastereomeric minor product **18b** was separated by multiple elution (>20 times) of crude product loaded on a prep-TLC plate (silica, hexanes/EtOAc, 85/15), and the diastereoselectivity was determined to be 95:5 by HPLC (RAININ HPXL, 254-nm UV detector, Dynamax-60A normal phase analytical column, hexanes/EtOAc = 80/20, 2 mL/min; t_R **18a** = 8.7 min, **18b** = 6.5 min): **18a**: mp 115.0–117.0 °C; $[\alpha]^{22}_D$ +84.7° (*c* 0.55, $CHCl_3$); R_f 0.33 (hexanes/EtOAc, 70/30); IR ($CHCl_3$) 3019, 2926, 2112, 1781, 1707, 1494, 1387 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35–7.20, (m, 9 H), 5.22 (dd, I H, *J* = 9.3, 5.2 Hz, $ArCH_2CHN_3$-), 4.66–4.60 (m, 1 H, $-NCHCH_2Ph^{ox}$), 4.24–4.14 (m, 2 H, $-NCHCH_2OCO^{ox}$-), 3.30 (dd, 1 H, *J* = 13.5, 3.2 Hz, $-NCHCHHPh^{ox}$), 3.18 (dd, 1 H, *J* = 13.7, 5.2 Hz, $ArCHHCHN_3$-), 2.99 (dd, 1 H, *J* = 13.7, 9.3 Hz, $ArCHHCHN_3$-), 2.84 (dd, 1 H, *J* = 13.5, 9.5 Hz, $-NCHCHHPh^{ox}$); ^{13}C NMR ($CDCl_3$) δ 170.1, 152.8, 134.5, 134.2, 133.2, 130.6, 129.4, 129.1, 128.8, 127.6, 66.6, 61.4, 55.4, 37.5, 36.8; HRMS calcd for $C_{19}H_{17}N_2O_3Cl$ (M^+ − 2N) 359.0928, found 359.0949.

18b (diastereomeric minor product): mp 86–88 °C; $[\alpha]^{22}_D$ +55.1° (*c* 0.21, $CHCl_3$); R_f 0.38 (hexanes/EtOAc, 70/30); IR ($CHCl_3$) 3026, 2926, 2115, 1782, 1708, 1494, 1387 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37–7.15 (m, 9 H), 5.14 (dd, 1 H, *J* = 9.6, 4.6 Hz, $ArCH_2CHN_3$-), 4.79–4.71 (m, 1 H, $-NCHCH_2OCO^{ox}$-), 4.34–4.23 (m, 2 H, $-NCHCH_2OCO^{ox}$-), 3.29–3.20 (m, 2 H, $ArCHHCHN_3$- overlapping with $-NCHCHHPh^{ox}$), 2.98 (dd, 1 H, *J* = 13.7, 9.6 Hz, $ArCHHCHN_3$-), 2.74 (dd, 1 H, *J* = 13.4, 9.4 Hz, $-NCHCHHPh^{ox}$).

(*S*)-2-Azido-3-(4-chlorophenyl)propionic Acid (19). To a precooled (0 °C) solution of 628 mg (1.63 mmol) of **18** in 24 mL of THF and 8 mL of water was added 1.0 mL (6.0 equiv) of 30% H_2O_2, followed by 6.5 mL of 0.5 M aqueous LiOH solution. The resulting mixture was stirred at 0 °C for 1 h, and the excess peroxide was destroyed at 0 °C by adding 7.2 mL of a 1.5 N Na_2SO_3 solution. The solution was made basic with saturated aqueous $NaHCO_3$ and after the removal of THF *in vacuo*, the neutrals were removed by CH_2Cl_2 extraction (15 mL × 3). The aqueous layer was acidified to *ca.* pH 2 with 5 N HCl and the product was extracted into EtOAc (25 mL × 3). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford a solid residue. Purification by flash chromatography (EtOAc/MeOH, 85/15) gave 338 mg (92%) of pure product **19** as a white solid: $[\alpha]^{21}_D$ −55.7° (*c* 0.52, $CHCl_3$); R_f 0.16 (EtOAc/MeOH, 85/15); IR ($CHCl_3$) 3026, 2112, 1722, 1494 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.38 (bs, 1 H, $ArCH_2CHCO_2H$), 7.32 (d, 2 H, *J* = 8.4 Hz), 7.20 (s, 2 H, *J* = 8.4 Hz), 4.15 (dd, I H, *J* = 8.7, 5.0 Hz, $ArCH_2CHCO_2$-), 3.19 (dd, 1 H, *J* = 14.2, 5.0 Hz, $ArCHHCHCO_2$-), 3.00 (dd, 1 H, *J* = 14.2, 8.7 Hz, $ArCHHCHCO_2$-); ^{13}C NMR ($CDCl_3$) δ 175.5, 134.0, 133.4, 130.6, 128.9, 62.8, 36.7; HRMS calcd for $C_9H_8N_3O_2Cl$ 225.0305, found 225.0291.

(*S*)-2-Azido-3-(4-chlorophenyl)propionic Acid, (Methoxyethoxy)methyl Ester (20). To a stirred, precooled (0 °C) solution of 0.66 g (2.92 mmol) of **19** in 20 mL of CH_2Cl_2 under N_2 were added 0.56 mL (1.1 equiv) of *i*-Pr_2NEt and 0.4 mL (1.2 equiv) of MEMCl, and the resulting solution was stirred at 0 °C for 2 h under N_2. The reaction was quenched by adding 3.0 mL (0.1 equiv) of 0.1 N HCl. The product was extracted into CH_2Cl_2 (20 mL × 3), and the combined extracts were washed with brine and dried over $MgSO_4$. After evaporation of solvent *in vacuo*, the crude product was flash-chromatographed on silica gel (hexanes/EtOAc, 70/30), affording 691 mg (75%) of pure **20** as a colorless oil: R_f 0.31 (hexanes/EtOAc, 70/30). $[\alpha]^{21}_D$ −43.6° (*c* 0.69, $CHCl_3$); IR ($CHCl_3$) 3016, 2932, 2111, 1747 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (d, 2 H, *J* = 8.4 Hz, aromatic Hs *ortho* to -Cl), 7.18 (d, 2 H, *J* = 8.4 Hz, aromatic Hs *meta* to -Cl), 5.43 (d, 1H, *J* = 5.9 Hz, $-CO_2CHHOCH_2$-), 5.40 (d, 1H, *J* = 5.9 Hz, $-CO_2CHHOCH_2$-), 4.09 (dd, 1 H, *J* = 8.4, 5.5 Hz, $ArCH_2CHCO_2$-), 3.74–3.71 (m, 2 H, $-CO_2CH_2CH_2O$-), 3.55–3.52 (m, 2 H, $-CO_2CH_2CH_2O$-), 3.16 (dd, I H, *J* = 8.4, 5.5 Hz, $ArCHHCHCO_2$-), 3.00 (dd, 1 H, *J* = 14.1, 8.4 Hz, $ArCHHCHCO_2$-); ^{13}C NMR ($CDCl_3$) δ 169.2, 134.3, 133.2, 130.6, 128.8, 90.7, 71.3, 69.9, 63.0, 59.1, 36.7; HRMS calcd for $C_{13}H_{16}NO_4Cl$ (M^+ − 2N) 285.0768, found 285.0766.

***N*-[(1,1-Dimethylethoxy)carbonyl]-4-chloro-L-phenylalanine, (Methoxyethoxy)methyl Ester (21a). (i) With Pd–C (10%) Catalyst.** A suspension of 6.3 mg of Pd–C (10%) in 5 mL of THF was vigorously stirred under H_2 (1 atm) for 1 h. To this was added a mixture of 28 mg of **20** and 23 mg (1.2 equiv) of $(Boc)_2O$ in 5 mL of THF, and the resulting slurry was stirred for 4 h at rt, filtered through Celite, and concentrated *in vacuo* to give an oily product. Purification by flash chromatography on silica gel (hexanes/EtOAc, 70/30) gave 11 mg (33%) of pure **21a** which solidified in the refrigerator: mp 39.0–40.5 °C; $[\alpha]^{21}_D$ +21.7°

(*c* 0.71, $CHCl_3$); R_f 0.24 (hexanes/EtOAC, 70/30); IR ($CHCl_3$) 3016, 2982, 1746, 1710, 1493 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27 (d, 2 H, J = 8.5 Hz), 7.10 (d, 2 H, J = 8.5 Hz), 5.40 (d, 1 H, J = 6.1 Hz, -CO_2CHHOCH_2-), 5.32 (d, 1 H, J = 6.1 Hz, -CO_2CHHOCH_2-), 4.99 (bd, 1 H, J = 7.9 Hz, ArCH_2CHN*H*-), 4.62–4.55 (m, 1 H, ArCH_2C*H*NH-), 3.73–3.69 (m, 2 H -$CO_2CH_2CH_2$O-), 3.55–3.52 (m, 2 H, -$CO_2CH_2CH_2$O-), 3.39 (s, 3 H, -$OCH_2CH_2OCH_3$), 3.17–3.01 (m, 2 H, ArCH_2CHNH-), 1.42 (s, 9 H, -$CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 171.2, 155.0, 134.4, 132.9, 130.7, 128.7, 90.3, 80.1, 71.4, 69.8, 59.0, 54.3, 37.5, 28.2; HRMS calcd for $C_{18}H_{26}NO_6C$: 387.1449, found mp387.1464.

(ii) With Raney Ni Catalyst. To a stirred solution of 264 mg (0.84 mmol) of **20** in 20 mL of CH_2Cl_2 were added 20 mg of Raney nickel (washed successively with water (×3), methanol (×3), and CH_2Cl_2 (×3) previously) and Boc_2O (229 mg, 1.2 equiv). The reaction slurry was stirred overnight under an H_2 atmosphere, filtered through Celite, and concentrated under reduced pressure to provide an oily residue. Purification by flash chloromatography on silica gel (hexanes/EtOAc, 70/30) gave 144 mg (44%) of pure product **21a** as a white solid, identical to that obtained from (i).

(iii) From Compound 22 (see following preparation). To a precooled (0 °C), stirred solution of 2.28 g (5.38 mmol) of **22** in 60 mL of THF and 20 mL of methanol was added 21.5 mL (2.0 equiv) of aqueous LiOH (0.5 M), and the resulting mixture was stirred at 0 °C for 1 h. The mixture was then treated with saturated $NaHCO_3$, and the organic solvent was removed under reduced pressure at rt. The neutrals were extracted into CH_2Cl_2 (30 mL × 3) and the aqueous layer was acidified with 1N HCl to pH 5; then the product was extracted into EtOAc (30 mL × 3). The combined EtOAc layers were washed with brine and dried over $MgSO_4$, and the solvent was evaporated to give 1.25 g (77%) of crude acid **23** which was used for next reaction without purification. To a precooled (0 °C), stirred solution of 218 mg (0.73 mmol) of crude acid **23** in 20 mL of CH_2Cl_2 were added 140 μL (1.1 equiv) of *i*-Pr_2NEt and 119 μL (1.2 equiv) of MEMCl, and the resulting mixture was stirred for 2 h at 0 °C under N_2. The reaction was quenched with 0.7 mL of 0.1 N HCl and then diluted with 30 mL of CH_2Cl_2. The organic layer was washed with brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure to give the crude product as a oily residue. Flash chromatography on silica gel (hexanes/EtOAc, 7/3) afforded 271 mg (96%) of **21a** as an oily product which solidified in the refrigerator: mp 39.0–40.5 °C; $[\alpha]^{22}_D$ +21.8° (*c* 0.83, $CHCl_3$); all other data were the same as before.

(4*S*,2*S*)-4-Chloro-[2-[[(1,1-dimethylethoxy)carbonyl]amino]-3-oxo-3-[2-oxo-4-(phenylmethyl)-3-oxazolidinyl]propyl]benzene (22). (i) One-Step (*in-situ*) Protection with Pd–C (10%) Catalyst. To a stirred, presaturated (by H_2) slurry of 10% Pd–C (30 mg) in 20 mL of CH_2Cl_2 were added 291 mg of **18a** (0.76 mmol) and 330 mg (2.0 equiv) of $(Boc)_2O$. The resulting mixture was stirred for 30 h at rt under an H_2 atmosphere and then filtered through Celite. The filter cake was washed with CH_2Cl_2 (10 mL × 2), and the combined organic layers were concentrated *in vacuo* to give a solid residue which was purified by flash chromatography on silica gel with (hexanes/EtOAc, 80/20), affording 159 mg (46%) of pure **22**.

(ii) Two-Step Protection with Pd–C (10%) Catalyst. To a stirred, presaturated (by H_2) slurry of 10% Pd–C (265 mg) in 40 mL of THF and 10 mL of MeOH were added 2.65 g (6.9 mmol) of **18a** and 2.8 mL (2.0 equiv) of 5 N HCl. The resulting suspension was stirred for 8 h at rt under an atmospheric pressure of H_2. The reaction mixture was filtered through Celite, and the filter cake was washed well with THF/MeOH (1:1, 10 mL × 3). The combined organic layers were evaporated to give amine·HCl salt as a white solid. The crude amine·HCl salt was dissolved in 40 mL of THF and 10 mL of water; then to this solution were added 2.03 g (1.5 equiv) of $(Boc)_2O$ and 2.14 g (2.5 equiv) of K_2CO_3. The resulting suspension was stirred overnight at rt and then poured into 30 mL of water and extracted with EtOAc (20 mL × 5). The combined organic extracts were washed with saturated brine, dried over $MgSO_4$, and evaporated to give the crude product. Flash chromatography of the crude product on silica gel (hexanes/EtOAc, 80/20) afforded 2.69 g (85%) of pure **22** as a white solid (all the data were the same for both methods): mp 150–152 °C; $[\alpha]^{22}_D$ +80.1° (*c* 0.49, $CHCl_3$); R_f 0.25 (hexanes/EtOAc, 70/30); IR ($CHCl_3$) 3440, 3027–2930, 1784, 1703, 1492, 1385, 1368 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37–7.18 (m, 9 H), 5.72–5.65 (m, 1 H, ArCH_2C*H*NH-), 5.15 (bd, 1 H, J = 7.0 Hz, ArCH_2CHN*H*-), 4.62–4.57 (m, 1 H, -NC*H*CH_2Ph^{ox}), 4.22–4.11 (m, 2 H, -NCHCH_2-OCO^{ox}-), 3.33 (dd, 1 H, J = 13.6, 1.3 Hz, -NCHC*H*HPh^{ox}), 3.14 (dd, 1 H, J = 12.2, 2.0 Hz, ArC*H*HCHNH-), 2.81–2.74 (m, 2 H, ArCH*H*CHNH- overlapping with -NCHCH*H*Ph^{ox}), 1.38 (s, 9 H, -$CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 172.6, 155.1, 152.7, 135.0, 134.6, 132.9, 130.8, 129.4, 129.0, 128.6, 127.4, 80.1, 66.5, 55.50, 54.1, 38.0, 37.5, 28.2; HRMS calcd for $C_{20}H_{18}N_2O_4Cl$ (M^+ – $O(CH_3)_3$) 385.0955, found 385.0953.

***N*-[(1,1-Dimethylethoxy)carbonyl]-4-chloro-L-phenylalanine, 2,2,2-Trichloroethyl Ester (21b).** To a precooled (0 °C), stirred solution of 501 mg (1.68 mmol) of crude acid **23** (see preparation of **21a** method iii) in 20 mL of CH_2Cl_2 were added 271 μL (2.0 equiv) of pyridine and 193 μL of 2,2,2-trichloroethanol (1.2 equiv), and the mixture was stirred for 10 min at 0 °C under N_2. To this solution was added 381 mg (1.1 equiv) of DCC in one portion, and the mixture was stirred overnight at 0 °C under N_2. The reaction was quenched with 22.7 mg (0.15 equiv) of oxalic acid in 0.5 mL of THF, and the resulting mixture was allowed to come to rt and stirred for 30 min. The mixture was filtered and the filter cake was washed well with CH_2Cl_2 (10 mL × 3). The combined organic extracts were washed with brine and dried over $MgSO_4$, and the solvent was evaporated to give the crude product. Flash chromatography on silica gel (hexanes/EtOAc, 80/20) and further recrystallization from hexane afforded 659 mg (92%) of **21b** as a white solid: mp 131–133 °C; $[\alpha]^{21}_D$ +8.0° (*c* 0.54, $CHCl_3$); R_f 0.20 (CH_2Cl_2/hexanes, 70/30); IR ($CHCl_3$) 3441, 3020, 1759, 1712, 1494 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28 (d, 2 H, J = 8.2 Hz), 7.13 (d, 2 H, J = 8.2 Hz), 4.92 (bd, 1 H, J = 8.2 Hz, ArCH_2CHN*H*-), 4.81 (d, 1 H, J = 12.0 Hz, -CO_2CH*H*CCl_3), 4.72–4.68 (m, 2 H, -CO_2CH*H*CCl_3 overlapping with ArCH_2CH*H*CO_2-), 3.21 (dd, 1 H, J = 13.9, 5.6 Hz, ArC*H*HCHCO_2-), 3.06 (dd, 1 H, J = 13.9, 6.9 Hz, ArCH*H*CHCO_2-), 1.41 (s, 9 H, -$CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 170.3, 155.0, 134.0, 133.2, 130.6, 128.8, 94.3, 80.4, 74.6, 54.2, 37.4, 28.2; HRMS calcd for $C_{11}H_8O_2Cl_4$ (M^+ – $H_2NCO_2C(CH_3)_3$) 311.9278, found 311.9287.

***N*-[(1,1-Dimethylethoxy)carbonyl]-4-chloro-L-phenylalanine, 2-Bromoethyl Ester (21c).** Reaction procedures were the same as for **21b** except for the use of 2-bromoethanol instead of 2,2,2-trichloroethanol: yield 76%; mp 77.5–79.0 °C; $[\alpha]^{22}_D$ +22.5° (*c* 0.63, CH_2Cl_2); R_f 0.45 (hexanes/EtOAc, 70/30); IR ($CHCl_3$) 3020, 1745, 1709, 1493 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28 (d, 2 H, J = 8.4 Hz), 7.11 (d, 2 H, J = 8.4 Hz), 4.94 (bd, 1 H, J = 8.2 Hz, ArCH_2CHN*H*-), 4.61–4.59 (m, 1 H, ArCH_2C*H*NH-), 4.44–4.40 (m, 2 H, -$CO_2CH_2CH_2$Br), 3.48 (m, 2 H, -$CO_2CH_2CH_2$Br), 3.14 (dd, 1 H, J = 13.8, 5.7 Hz, ArC*H*HCHNH-), 3.04 (dd, 1 H, J = 13.8, 6.4 Hz, ArCH*H*CHNH-), 1.42 (s, 9 H, -$CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 171.2, 155.0, 134.3, 133.0, 130.7, 128.7, 80.2, 64.6, 54.2, 37.6, 28.3, 28.1; HRMS calcd for $C_{12}H_{12}N_{10}O_3BrCl$ (M^+ – $OC(CH_3)_3$) 331.9690, found 331.9683.

***N*-(1,1-Dimethylethoxy)carbonyl]-4-chloro-L-phenylalanine, 2-Iodoethyl Ester (21d).** The reaction procedure was the same as for **21b** except for the use of 2-iodoethanol instead of 2,2,2-trichloroethanol: yield: 81%; mp 78.5–80.0 °C; $[\alpha]^{26}_D$ +15.3° (*c* 0.77, $CHCl_3$); R_f 0.37 (hexanes/EtOAc, 70/30); IR ($CHCl_3$) 3437, 3019, 2981, 1745, 1711, 1601, 1493 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28 (d, 2 H, J = 8.3 Hz), 7.11 (d, 2 H, J = 8.3 Hz), 4.95 (d, 1 H, J = 7.2 Hz, ArCH_2CHN*H*-), 4.59–4.57 (m, 1 H, ArCH_2C*H*NH-), 4.39–4.34 (m, 2 H, -$CO_2CH_2CH_2$I), 3.28–3.00 (m, 4 H, -$CO_2CH_2CH_2$I overlapping with ArCH_2CHNH-), 1.42 (s, 9 H, -$CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 171.1, 155.0, 134.4, 133.0, 130.7, 128.7, 80.2, 65.4, 54.2, 37.7, 28.3, –0.6; HRMS calcd for $C_{16}H_{21}NO_4ClI$ 453.0206, found 453.0213.

[η^6-(*S*)-4-Chloro-1-[2-[*N*-[(1,1-dimethylethoxy)carbonyl]-amino]-3-oxo-3-(methoxyethoxymethoxy)propyl]benzene]-(η^5-cyclopentadienyl)ruthenium Hexafluorophosphate (5a). To a stirred suspension of 183 mg (0.47 mmol) of the amino ester **21a** in 15 mL of 1,2-dichloroethane was added 308 mg (1.5 equiv) of $[(CH_3CN)_3RuCp]^+[PF_6^-]$ in one portion, and the resulting mixture was bubbled with N_2 for 20 min and then heated at reflux for 5 h under N_2. The reaction mixture was cooled to rt, filtered through a Celite pad (1 × 2 cm), and concentrated *in vacuo* to give a dark brown residue. The crude product was dissolved in 20 mL of CH_3CN and filtered through a neutral alumina column (1 × 5 cm) to afford a dark brown solution. After

evaporation of solvent *in vacuo*, the dark brown residue was dissolved in $CHCl_3$ and then passed through a Celite pad (1 × 2 cm), and the solvent was evaporated to provide 308 mg (95%) of **5a** as a yellowish brown foam. This product was sufficiently pure (^1H NMR) for the next reaction: IR ($CHCl_3$) 3024, 2932, 1747, 1706, 1602, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.49–6.30 (m, 4 H, aromatic), 5.51–5.38 (m, 7 H, Cp overlapping with $-CO_2CH_2O-$), 4.47–4.46 (m, 1 H, $ArCH_2CHCO_2-$), 3.87–3.84 (m, 2 H, $-CH_2OCH_2CH_2O-$), 3.59–3.56 (m, 2 H, $-CH_2OCH_2CH_2O-$), 3.38, (s, 3 H, $-OCH_3$), 3.13 (dd, 1 H, J = 14.0, 4.7 Hz, $ArCHHCHCO_2-$), 2.86 (dd, 1 H, J = 14.0, 8.5 Hz, $ArCHHCHCO_2-$), 1.39 (s, 9 H, $-CO_2C(CH_3)_3$).

[η⁶-(*S*)-4-Chloro-1-[2-[*N*-[(1,1-dimethylethoxy)carbonyl]amino]-3-oxo-3-(2,2,2-trichloroethoxy)propyl]benzene](η⁵-cyclopentadienyl)ruthenium hexafluorophosphate (5b). The reaction procedure was the same as for **5a** except for the use of **21b** instead of **21a**. **5b:** yield 93%; IR ($CHCl_3$) 3426, 3019, 2984, 1761, 1706, 1502, 1223 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.48–6.32 (m, 4 H), 5.48 (s, 5 H, Cp), 4.88 (d, 1 H, J = 11.9 Hz, $-CO_2CHHCCl_3$), 4.82 (d, 1 H, J = 11.9 Hz, $-CO_2CHHCCl_3$), 4.56–4.52 (m, 1 H, $ArCH_2CHCO_2-$), 3.16 (dd, 1 H, J = 14.2, 4.9 Hz, $ArCHHCHCO_2-$), 2.94 (dd, 1 H, J = 14.2, 8.7 Hz, $ArCHHCHCO_2-$), 1.38 (s, 9 H, $-CO_2C(CH_3)_3$).

[η⁶-(*S*)-4-Chloro-1-[2-[*N*-[(1,1-dimethylethoxy)carbonyl]amino]-3-oxo-3-(2-bromoethoxy)propyl]benzene](η⁵-cyclopentadienyl)ruthenium Hexafluorophosphate (5c). The reaction procedure was the same as **5a** except for the use of **21c** instead of **21a**. **5c:** yield 95%; IR ($CHCl_3$) 3426, 3020, 2982, 1747, 1707, 1501, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.47–6.28 (m, 4 H), 5.48 (s, 5 H, Cp), 4.53–4.44 (m, 3 H, $-CO_2CH_2CH_2Br$ overlapping with $ArCH_2CHCO_2-$), 3.64–3.58 (m, 2 H, $-CO_2CH_2CH_2Br$), 3.13 (dd, 1 H, J = 14.1, 4.9 Hz, $ArCHHCHCO_2-$), 2.87 (dd, 1 H, J = 14.1, 8.0 Hz, $ArCHHCHCO_2-$), 1.40(s, 9 H, $-CO_2C(CH_3)_3$).

[η⁶-(*S*)-4-Chloro-1-[2-[*N*-[(1,1-dimethylethoxy)carbonyl]amino]-3-oxo-3-(2-iodoethoxy)propyl]benzene](η⁵-cyclopentadienyl)ruthenium Hexafluorophosphate (5d). The reaction procedure was the same as for **5a** except for the use of **21d** instead of **21a**. **5d:** yield 98%; IR ($CHCl_3$) 3427, 3019, 2981, 1745, 1707, 1602, 1499, 1456 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.47–6.28 (m, 4 H), 5.48 (s, 5 H, Cp), 4.48–4.43 (m, 3 H, $ArCH_2CHCO_2-$ overlapping with $-CO_2CH_2CH_2I$), 3.40–3.36 (m, 2 H, $-CO_2CH_2CH_2I$), 3.14 (dd, 1 H, J = 14.1, 4.9 Hz, $ArCHHCHCO_2-$), 2.87 (dd, 1 H, J = 14.1, 8.2 Hz, $ArCHHCHCO_2-$), 1.40 (s, 9 H, $-CO_2C(CH_3)_3$).

[η⁶-(*S*,*S*)-4-[2-Methoxy-5-[*N*-[*O*-methyl-*N*-[(phenylmethoxy)carbonyl]-L-tyrosinyl]-2-amino-3-oxo-3-methoxypropyl]phenoxy]-1-[2-[*N*-[(1,1-dimethyethoxy)carbonyl]amino]-3-oxo-3-(methoxyethoxymethoxy)propyl]benzene](η⁵-cyclopentadienyl)ruthenium Hexafluorophosphate (24a). **(i)** A stock solution of sodium 2,6-di-*tert*-butylphenoxide was made as follows: Into a 50-mL round bottom flask containing 276 mg (1.34 mmol) of 2,6-di-*tert*-butylphenol and NaH (54 mg, 1.0 equiv, 60% in mineral oil) was added 20 mL of freshly distilled THF by syringe, and the resulting slurry was stirred for 30 min at rt under N_2 and then cooled to 0 °C. **(ii)** To a stirred, precooled (0 °C) solution of 361.9 mg (0.67 mmol) of **2** was added 9.6 mL (1.1 equiv) of the above stock solution by syringe, and the mixture was stirred for 15 min at 0 °C under N_2 and then transferred via cannula into a precooled (−78 °C) solution of **5a** (472 mg, 1.0 equiv) in 15 mL of THF. The resulting mixture was stirred for 1 h at −78 °C and then 3.5 h at rt under N_2, filtered through Celite, and concentrated *in vacuo* to give a dark brown residue which was dissolved in 15 mL of acetonitrile. The resulting solution was filtered through a neutral alumina column (1 × 5 cm), concentrated to *ca.* 1 mL under reduced pressure, and then diluted with 40 mL of diethyl ether. The etheral solution was cooled in a refrigerator and decanted, and the brown residue was further washed with cold diethyl ether (10 mL × 3). The residue was dried *in vacuo* to afford 231 mg (29%) of **24a** as a pale brown solid foam which was pure enough for the next reaction (confirmed by ^1H NMR): IR ($CHCl_3$) 3422, 3016, 2981, 1740, 1711, 1513, 1478 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–6.78 (m, 12 H), 6.44 (d, 1 H, J = 6.3 Hz, $Ar^{OMe,O}CH_2CHNH-$), 6.15–5.95 (m, 4 H, arene-Ru), 5.52–5.31 (m, 9 H, $PhCH_2OCONH-$ overlapping with $Ar^{Ru+}CH_2CHNH-$, and 5 H of Cp, $-CO_2CH_2OCH_2CH_2O-$), 5.07 (s, 2 H, $PhCH_2OCONH-$), 4.79–4.75 (m, 1 H, $Ar^{OMe,O}CH_2CHNH-$), 4.42–4.31 (m, 2 H, $Ar^{O}CH_2CHNH-$ overlapping with $Ar^{OMe}CH_2CHCO-$), 3.87–3.84 (m, 2 H, $-OCH_2CH_2OCH_3$), 3.79 (s, 3 H, $-OCH_3$), 3.77 (s, 3 H, $-OCH_3$), 3.70 (s, 3 H, $-OCH_3$), 3.58–3.55 (m, 2 H, $-OCH_2CH_2OCH_3$), 3.37 (s, 3 H, $-OCH_2CH_2OCH_3$), 3.08–2.82 (m, 6 H, benzyl Hs of $Ar^{OMe,O}$, Ar^{Ru+}, Ar^{OMe} except for Cbz), 1.41 (s, 9 H, $-CO_2C(CH_3)_3$).

[η⁶-(*S*,*S*)-4-[2-Methoxy-5-[*N*-[*O*-methyl-*N*-[(phenylmethoxy)carbonyl]-L-tyrosinyl]-2-amino-3-oxo-3-methoxypropyl]phenoxy]-1-[2-[*N*-[(1,1-dimethylethoxy)carbonyl]amino]-3-oxo-3-(2-bromoethoxy)propyl]benzene](η⁵-cyclopentadienyl)ruthenium Hexafluorophosphate (24c). To a stirred, precooled (0 °C) solution of 169 mg (0.32 mmol) of **2** in 15 mL of THF was added 5.2 mL (1.1 equiv) of sodium 2,6-di-*tert*-butylphenoxide stock solution by syringe, and the mixture was stirred for 15 min at 0 °C under N_2. The resulting solution was transferred via cannula into a precooled (−78 °C) solution of **5c** (226 mg, 1.0 equiv) in 10 mL of dry THF. The resulting mixture was stirred for 1 h at −78 °C and 3.5 h at rt under N_2 and then filtered through a Celite pad (1 × 2 cm), and the solvent was evaporated to provide a dark brown residue. The residue was worked up as above to afford 311 mg (81%) of **24c** as a pale brown solid foam which was pure enough for the next reaction. **24c:** R_f 0.71 (Al_2O_3 IB-F, CH_3CN); IR ($CHCl_3$) 3418, 3014, 2981, 1741, 1712, 1681, 1613, 1513, 1478 cm^{-1}; ^1NMR ($CDCl_3$) δ 7.39–6.79 (m, 12 H), 6.45 (d, 1 H, J = 9.1 Hz), 6.13–5.94 (m, 4 H), 5.49–5.30 (m, 7 H, $PhCH_2OCONH-$ overlapping with $Ar^{Ru+}CH_2CHNH-$, 5 H of Cp), 5.06 (s, 2 H), 4.77–4.75 (m, 1 H), 4.51–4.31 (m, 4 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.69 (s, 3 H), 3.59–3.55 (m, 2 H, $-CO_2CH_2CH_2Br$), 3.13–2.80 (m, 6 H), 1.42 (s, 9 H).

[η⁶-(*S*,*S*)-[4-[2-Methoxy-5-[*N*-[*O*-methyl-*N*-[(phenylmethoxy)carbonyl]-L-tyrosinyl]-2-amino-3-oxo-3-methoxypropyl]phenoxy]-1-[2-[*N*-[(1,1-dimethylethoxy)carbonyl]amino]-3-oxo-3-(2-iodoethoxy)propyl]benzene](η⁵-cyclopentadienyl)ruthenium Hexafluorophosphate (24d). To a stirred, precooled (−78 °C) solution of 67 mg (0.13 mmol) of **2** in 10 mL of THF was added 2.1 mL (1.1 equiv) of sodium 2,6-di-*tert*-butylphenoxide stock solution by syringe, and the mixture was stirred for 15 min at 0 °C under N_2. Then the resulting solution was transferred via cannula into a precooled (−78 °C) solution of **5d** (97 mg, 1.0 equiv) in 5 mL of THF. The resulting mixture was stirred for 1 h at −78 °C and then for 3.5 h at rt under N_2 and then worked up as above to give 95 mg (59%) of **24d** as a pale brown solid foam which was sufficiently pure for the next reaction. **24d:** IR ($CHCl_3$) 3417, 3020, 2956, 1741, 1713, 1681, 1602, 1513, 1443 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–6.78 (m, 12 H), 6.43 (d, 1 H, J = 8.9 Hz), 6.14–5.97 (m, 4 H), 5.50–5.28 (m, 7 H), 5.07 (s, 2 H), 4.78–4.76 (m, 1 H), 4.49–4.30 (m, 4 H), 3.79 (s, 3 H), 3.77 (s, 3 H), 3.70 (s, 3 H), 3.40–3.33 (m, 2 H, $-CO_2CH_2CH_2I$), 3.12–2.84 (m, 6 H), 1.42 (s, 9 H).

(*S*)-3-[4-[2-[[(1,1-Dimethylethoxy)carbonyl]amino]-3-oxo-3-(2-bromoethoxy)propyl]phenoxy]-*O*-methyl-*N*-[*O*-methyl-*N*-[(phenylmethoxy)carbonyl]-L-tyrosinyl]-L-tyrosine, α-Methyl Ester (25a). The arene–Ru complex **24c** (298 mg, 0.24 mmol) was dissolved in 20 mL of dry CH_3CN in a quartz cell (1.5 × 20 cm), and the resulting solution was bubbled with N_2 for 20 min. The solution was irradiated with a sunlamp (275 W) for 24 h under N_2, concentrated *in vacuo* to *ca.* 2 mL, and diluted with 50 mL of Et_2O. The ether-insoluble precipitate of $[(CH_3CN)_3Ru]^+[CpPF_6^-]$ was filtered off and washed well with Et_2O (20 mL × 3). The combined ethereal extracts were evaporated to give a pale brown residue which was purified by flash chromatography on silica gel (CH_2Cl_2/EtOAc, 85/15), providing 144 mg (65%) of **25a** as a white solid. From the ether-insoluble residue was recovered 90 mg (85%) of $[(CH_3CN)_3Ru]^+[CpPF_6^-]$. **25a:** mp 52.0–53.5 °C; $[\alpha]^{26}_D$ +31.6° (*c* 0.57, $CHCl_3$); R_f 0.26 (hexanes/EtOAc, 60/40); ^1H NMR ($CDCl_3$) δ 7.37–6.58 (m, 16 H), 6.25 (bd, 1 H, J = 7.3 Hz, $Ar^{OMe,O}CH_2CHNH-$), 5.31 (bs, 1 H, $PhCH_2OCONH-$), 5.13–5.04 (m, 3 H, $PhCH_2OCO-$ overlapping with $Ar^{O}CH_2CHNH-$), 4.72–4.66 (m, 1 H, $Ar^{OMe,O}CH_2CHNH-$), 4.59–4.53 (m, 1 H, $Ar^{O}CH_2CHNH-$), 4.44–4.35 (m, 3 H, $-CO_2CH_2CH_2Br$ overlapping with $Ar^{OMe}CH_2CHCO-$), 3.77 (s, 3 H, $-OCH_3$), 3.76 (s, 3 H, $-OCH_3$), 3.60 (s, 3 H, $-OCH_3$), 3.47–3.43 (m, 2 H, $-CO_2CH_2CH_2Br$), 3.11–2.85 (m, 6 H, benzylic Hs except Cbz), 1.41 (s, 9 H, $-CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 171.5, 171.1, 170.4, 158.6, 157.1, 155.8, 155.1, 150.6, 144.4, 136.1, 130.4, 130.3, 129.7, 128.5, 128.4, 128.1, 127.9, 125.7, 122.1, 116.9, 114.0, 112.7, 80.0, 67.0, 64.4, 56.1, 55.9, 55.1, 54.4, 53.3, 52.3, 37.5,

37.3, 37.0, 28.2, 28.1. Anal. Calcd for $C_{45}H_{52}N_3O_{12}Br$: C, 59.65; H, 5.79, found C, 59.59; H, 5.77.

(*S*)-3-[4-[2-[[(1,1-Dimethylethoxy)carbonyl]amino]-3-oxo-3-(2-iodoethoxy)propyl]phenoxy]-*O*-methyl-*N*-[*O*-methyl-*N*-[(phenylmethoxy)carbonyl]-L-tyrosinyl]-L-tyrosine, α-Methyl Ester (25b). (i) Synthesis from 25a. To a stirred solution of **25a** (115 mg, 0.127 mmol) in 15 mL of dry acetone was added 95 mg (5.0 equiv) of NaI (anhydrous, 99+%), and the resulting slurry was heated at reflux for 7 h under N_2. The reaction mixture was cooled to rt and filtered, and the filter cake was washed well with acetone (10 mL × 3). The combined organic extracts were evaporated to provide a solid residue which was dissolved in 50 mL of CH_2Cl_2, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was flash-chromatographed on silica gel (hexanes/EtOAc, 65/35) to give 115 mg (95%) of **25b** as a white solid: mp 63.5–65.5 °C; $[\alpha]^{26}_D$ +34.3° (*c* 0.58, $CHCl_3$); R_f 0.19 (hexanes/EtOAc, 60/40); IR ($CHCl_3$) 3427, 3028, 2983, 1742, 1713, 1683, 1612, 1505, 1228 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34–6.59 (m, 16 H), 6.27 (d, 1 H, *J* = 7.1 Hz, $Ar^{OMe,O}$-CH_2CHNH-), 5.33 (bs, 1 H $PhCH_2OCONH$-), 5.12–5.04 (m, 3 H, $PhCH_2OCONH$- overlapping with Ar^OCH_2CHNH-), 4.72–4.68 (m, 1 H, $Ar^{OMe,O}CH_2CHNH$-), 4.56–4.54 (m, 1 H, Ar^OCH_2CHNH-), 4.36–4.32 (m, 3 H, $-CO_2CH_2CH_2I$ overlapping with Ar^{OMe}-CH_2CHCO-), 3.77 (s, 3 H, $-OCH_3$), 3.76 (s, 3 H, $-OCH_3$), 3.60 (s, 3 H, $-OCH_3$), 3.25–3.20 (m, 2 H, $-CO_2CH_2CH_2I$), 3.11-2.85 (m, 6 H, benzylic Hs except Cbz), 1.41 (s, 9 H, $-CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 171.3, 171.1, 170.4, 158.6, 157.1, 155.8, 155.1, 150.6, 144.4, 136.1, 130.4, 130.3, 129.7, 128.5, 128.4, 128.1, 127.9, 125.7, 122.1, 116.9, 114.0, 112.8, 80.0, 67.0, 65.2, 56.1, 55.9, 55.1, 54.4, 53.3, 52.3, 37.5, 37.3, 37.0, 28.2, −0.4. Anal. Calcd for $C_{45}H_{52}N_3O_{12}I$: C, 56.65; H, 5.50, found C, 56.56; H, 5.43.

(ii) Synthesis from 24d. Arene–Ru complex **24d** (85 mg, 0.067 mmol) was dissolved in 10 mL of CH_3CN in a quartz cell (1.5 × 20 cm) and degassed with N_2 bubbling for 10 min. The resulting solution was irradiated with a sunlamp (275 W) for 20 h under N_2 and concentrated *in vacuo* to *ca.* 1 mL. The residual solution was diluted with 30 mL of Et_2O and filtered. The ether-insoluble precipitate was washed well with Et_2O (20 mL × 3) and the combined filtrate and washings were evaporated to give a brown residue. The product was purified by flash chromatography on silica gel (hexanes/EtOAc, 60/40), affording 30 mg (48%) of **25b** as a white solid: $[\alpha]^{22}_D$ +34.8° (*c* 0.69, $CHCl_3$), spectroscopically identical to that prepared in (i).

(*S*)-3-[4-[2-Carboxy-2-[[(1,1-dimethylethoxy)carbonyl]-amino]ethyl]phenoxy]-*O*-methyl-*N*-[*O*-methyl-*N*-[(phenylmethoxy)carbonyl]-L-tyrosinyl]-L-tyrosine, α-Methyl Ester (26). To a stirred, precooled (0 °C) solution of **25b** (76 mg, 0.08 mmol) in 10 mL of freshly distilled THF was added 5.6 mL (7.0 equiv) of SmI_2 (0.1M in THF, Aldrich Chemical Co.) by syringe, and the resulting mixture was warmed to 35 °C for 10 h under deoxygenated Ar. The reaction mixture was cooled to rt and diluted with 20 mL of EtOAc, and the reaction was quenched by the addition of 10 mL of 0.1 N HCl. The organic layer was separated and the aqueous layer was washed well with EtOAc (10 mL × 2). The combined organic extracts were washed with 10 mL of 0.2 M $Na_2S_2O_3$ (sodium thiosulfate) solution, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a solid residue. Purification by short column chromatography on silica gel (1 × 15 cm, CH_2Cl_2/MeOH, 95/5, then EtOAc/MeOH, 95/5) gave 45 mg (70%) of pure acid **26**: $[\alpha]^{23}_{Hg,365}$ +30.4° (*c* 0.38, MeOH), lit.[4] $[\alpha]_{Hg,365}$ +27.6° (*c* 0.54, MeOH); R_f 0.17 (EtOAc/MeOH, 90/10); IR (CH_2Cl_2) 3412, 3054, 2985, 2939, 2865, 1741, 1715, 1684, 1612, 1513, 1262 cm^{-1}; ^1H NMR ($CD_3CN/CDCl_3$, 70/30) δ 7.34–6.72 (m, 17 H,), 5.70 (bd, 1 H, *J* = 6.3 Hz, $PhCH_2$-$OCONH$-), 5.33 (bd, 1 H, *J* = 7.0 Hz, Ar^OCH_2CHNH-), 5.05 (d, 1 H, *J* = 12.6 Hz, $PhCHHOCO$-), 4.98 (d, 1 H, *J* = 12.6 Hz, $PhCHHOCO$-), 4.65–4.58 (m, 1 H, $Ar^{OMe,O}CH_2CHNH$-), 4.40–4.24 (m, 2 H, Ar^OCH_2CHNH- overlapping with $Ar^{OMe}CH_2CHCO$-), 3.75 (s, 3 H), 3.74 (s, 3 H), 3.62 (s, 3 H), 3.08–2.73 (m, 6 H, benzylic Hs except Cbz), 1.38 (s, 9 H).

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Supplementary Material Available: ^1H and ^{13}C NMR spectra of all compounds and experimental description for the preparation of compounds **4**, **6**, **14**, and **16** (55 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.