256 (19), 213 (12), 185 (10), 151 (28), 95 (20), 91 (100), 81 (18), 67 (22), 55 (26); HRMS (EI) m/e calcd for $C_{18}H_{24}O$ 256.1827, found 256.1827.

3-Methyl-3-(2-phenethyl)cyclohexan-1-one (14). Chromatography with hexanes/EtOAc (7/1) gave 48% recovered enone and 49 mg (0.23 mmol, 45%) of a yellow oil: IR (neat) 3026, 2938, 2890, 1709, 1655, 1647, 1496, 1454, 1228, 750, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25 (m, 2 H), 7.15 (m, 3 H), 2.54 (m, 2 H), 2.28 (m, 2 H), 2.22 (m, 2 H), 1.88 (m, 2 H), 1.65 (m, 2 H), 1.55 (m, 2 H), 1.00 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 211.9, 142.4, 128.4, 128.3, 125.8, 53.6, 43.9, 41.0, 38.7, 35.9, 30.0, 24.9, 22.1; MS (EI) m/e 216 (3), 131 (4), 111 (100), 97 (10), 91 (35), 55 (20); HRMS (EI) m/e calcd for $C_{15}H_{20}O$ 216.1574, found 216.1574.

3-Dodecylcyclohexan-1-one (16). Chromatography with hexanes/EtOAc (9/1) gave 33 mg (0.12 mmol, 82%) of a light yellow oil: IR (neat) 2922, 2851, 1716, 1464, 1458, 1313, 1225, 721 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.40-2.20 (m, 3 H), 2.00 (m, 2 H), 1.85 (m, 1 H), 1.70-1.55 (m, 3 H), 1.40-1.18 (broad s, 22 H), 0.85 (t, J = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 212.2, 53.4, 48.2, 41.5, 39.1, 36.6, 31.9, 31.3, 29.6, 29.4, 26.6, 25.3, 22.7, 14.1; MS (EI) m/e 266 (1.5), 223 (1.6), 97 (100), 69 (10), 57 (10), 55 (12); HRMS (EI) m/e calcd for $C_{18}H_{34}O$ 266.2610, found 266.2610.

1,3-Diphenylpentadecan-1-one (17). Chromatography with hexanes/EtOAc (24/1) gave 137 mg (0.36 mmol, 72%) of a pale yellow solid: mp 68-71 °C ($CHCl_3$); IR (neat film) 2914, 2847, 1674, 1440, 1425, 750, 700, 682 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.88 (m, 2 H), 7.51 (m, 1 H), 7.43 (m, 2 H), 7.10-7.30 (m, 5 H), 3.29 (m, 3 H), 1.66 (m, 2 H), 1.40-1.00 (broad, 20 H), 0.86 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 199.1, 145.1, 137.3, 132.8, 128.5, 128.4, 128.0, 127.5, 126.2, 46.0, 41.3, 36.4, 31.9, 29.6, 29.5, 29.4, 27.5, 22.7, 14.2; MS (EI) m/e 378 (1.5), 258 (78), 209 (87), 131 (10), 117 (30), 105 (100), 91 (47), 77 (39), 57 (21); HRMS (EI) m/e calcd for $C_{27}H_{38}O$ 378.2923, found 378.2923.

3-Cyclohexyl-1,3-diphenylpropan-1-one (19). Chromatography with hexanes/EtOAc (19/1) gave 40 mg (0.17 mmol, 33% from bromide **18a**; yield from iodide **18b**: 44% (ratio **18b**/SmI_2/chalcone = 4/4/1)) of a pale yellow solid: mp 120-122 °C; IR (neat film) 2930, 2900, 2850, 1690, 1630, 1540, 1490, 1425, 750, 700, 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.84 (m, 2 H), 7.49 (m, 1 H), 7.41 (m, 2 H), 7.10-7.30 (m, 5 H), 3.37 (m, 2 H), 3.17 (m, 1 H), 1.85 (m, 1 H), 1.70-1.45 (broad, 4 H), 1.40-1.00 (broad m, 4 H), 0.99 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 199.5, 143.8, 137.4, 132.8, 128.5, 128.4, 128.1, 126.1, 47.1, 43.2, 42.4, 31.4, 30.8, 26.6, 26.4; MS (EI) m/e 209 ($M^+ - cC_6H_{11}$, 19), 172 (75), 105 (100), 91 (22), 81 (12), 77 (40), 55 (20); HRMS (EI) m/e calcd for $C_{15}H_{13}O$ ($M^+ - cC_6H_{11}$) 209.0966, found 209.0966.

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Registry No. 1, 24892-63-5; (*R**,*S**)-4, 138695-36-0; (*R**,*R**)-4, 138695-37-1; 7, 138695-38-2; (*R**,*R**)-8, 138695-39-3; (*R**,*S**)-8, 138695-40-6; 9, 78739-83-0; 10, 17376-04-4; 11, 108011-20-7; 12, 123200-56-6; 13, 138695-45-1; 14, 138695-41-7; 15, 4292-19-7; 16, 138695-42-8; 17, 138695-43-9; 18a, 108-85-0; 18b, 626-62-0; 19, 138695-44-0; CuI, 7681-65-4; CuBr, 7787-70-4; CuSPh, 1192-40-1; CuCN, 544-92-3; PBu_3, 998-40-3; $P(OEt)_3$, 122-52-1; TMSCl, 75-77-4; DMS, 75-18-3; SmI_2, 32248-43-4; Sm, 7440-19-9; methyl vinyl ketone, 78-94-4; chalcone, 94-41-7; 2-cyclohexen-1-one, 930-68-7; (*R*)-(*N*)-carvone, 6485-40-1; 3-methyl-2-cyclohexen-1-one, 1193-18-6.

Supplementary Material Available: ^1H NMR and ^{13}C NMR spectra for compounds 4, 7, 8, 11, 12, 13, 14, 16, 17, and 19 (23 pages). Ordering information is given on any current masthead page.

Model Studies on the Synthesis of Carboxylate-Binding Pocket Analogues of Vancomycin Using Arene-Ruthenium Chemistry

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Preparation of several protected (D)-chlorophenylalanine derivatives in high optical purity and their complex formation with the $[RuCp]^+$ moiety are described. The complexation reaction, as well as subsequent photochemical decomplexations, proceeds with retention of optical purity. Reactions of these chloroarene complexes with 3-hydroxyphenylglycine derivatives proceed under mild conditions to give aryl ether-ruthenium complexes, which can be converted to diaryl ethers in which both aromatic rings have protected amino acid or peptide side chains. Efforts to effect cycloamidation to give vancomycin carboxylate-binding pocket analogues, using a number of known coupling reagents, were unsuccessful.

While it is well-established that nucleophilic displacement of halogen on halobenzene-$FeCp$[1] and -$Mn(CO)_3$[2] cationic complexes proceeds under very mild conditions, and that the corresponding tricarbonylchromium complexes require much more reactive nucleophiles,[3] the application of such methodology to the synthesis of highly functionalized aromatic compounds is still in its infancy.[4] The most serious limitations posed by the use of the iron or manganese complexes is the inability of sensitive functional groups to withstand the rather drastic conditions required for the attachment of the metal to the aromatic ring and/or the failure even to achieve such complexation in certain cases. For example, in our laboratory[5] conversion of protected 4-chlorophenylalanine

(1) Khand, I. U.; Pauson, P. L.; Watts, W. E. *J. Chem. Soc. C* **1968**, 2261. Abd-El-Aziz, A. S.; Lee, C. C.; Piorko, A.; Sutherland, R. G. *Synth. Commun.* **1988**, *18*, 291. Moriarty, R. M.; Gill, U. S. *Organometallics* **1986**, *5*, 253. Hamon, J.-R.; Astruc, D.; Michaud, P. *J. Am. Chem. Soc.* **1981**, *103*, 758. Nesmeyanov, A. N.; Vol'kenau, N. A.; Bolesova, I. N. *Dokl. Akad. Nauk SSSR* **1966**, *166*, 607. Lee, C. C.; Iqbal, M.; Gill, U. S.; Sutherland, R. G. *J. Organomet. Chem.* **1985**, *288*, 89.

(2) Pauson, P. L.; Segal, J. A. *J. Chem. Soc., Dalton Trans.* **1975**, 1677.

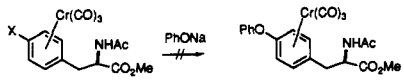
(3) Semmelhack, M. F.; Hall, H. T., Jr.; Yoshifuji, M.; Clark, G. *J. Am. Chem. Soc.* **1975**, *97*, 1247. Semmelhack, M. F.; Hall, H. T. *J. Am. Chem. Soc.* **1974**, *96*, 7091, 7092. See also: Jaouen, G. In *Transition Metal Organometallics in Organic Synthesis*; Alper, H., Ed.; Academic Press: New York, 1978; Vol. II, Chapter 2.

(4) Semmelhack, M. F.; Harrison, J. J.; Thebtaranonth, Y. *J. Org. Chem.* **1979**, *44*, 3275. Semmelhack, M. F. *Ann. N.Y. Acad. Sci.* **1977**, *295*, 3. Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987; Chapter 20.

(5) Bruhn, P. R. Ph.D. Dissertation, Case Western Reserve University, 1990.

0022-3263/92/1957-1744$03.00/0

derivatives to their $[Mn(CO)_3]^+$ complexes was found to be impossible using all the known methods. While the corresponding $Cr(CO)_3$ complexes can be prepared in good yield,[6] low reactivity of these to halide displacement limits their synthetic potential. In particular, attempted reactions of either 4-fluoro- or 4-chlorophenylalanine–$Cr(CO)_3$ derivatives **1** with phenoxide nucleophiles to give **2** were unsuccessful even at elevated temperatures and for prolonged times.[6]

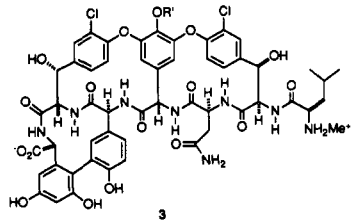


1 (a) X = Cl
(b) X = F

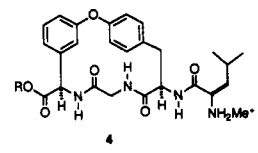
2

We considered that a process such as the conversion of **1** to **2** would provide a useful alternative to the standard Ullmann coupling procedure[7] (which has not yet been successfully applied to the *direct* coupling of *two* protected arylamino acids[8]) and to the more recently developed thallium(III)-promoted oxidative coupling,[9] an intramolecular version of which has found application in the vancomycin series.[10] A major objective of this effort was to identify arene–metal π-complexes that can be prepared from protected arylamino acids and that are sufficiently electrophilic to allow the construction of diaryl ethers under very mild conditions. Cationic arene–RuCp complexes appeared to be the most suitable candidates, since methods for their preparation using mild, essentially neutral reaction conditions have been described,[11] and their reactivity was expected to be quite similar to that of the arene–FeCp complexes mentioned earlier.[12]

The primary motivation for this work was to develop methodology for the construction of vancomycin carboxylate-binding pocket analogues.[13] Vancomycin (**3**) is a glycopeptide antibiotic that is known to act by binding peptides terminating in *N*-acyl-D-Ala-D-Ala.[14] Such binding inhibits bacterial cell wall construction, leading to ultimate destruction of the bacteria. A simple carboxylate-binding pocket analogue would be a molecule such as **4**, since this contains most of the functionality necessary for binding the mucopeptides. This paper outlines an approach to such molecules.

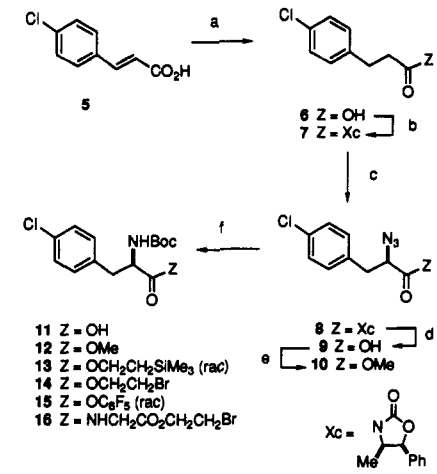


3



4

Scheme I[a]



[a] Reagents: (a) H_2/Pd–C; (b) pivaloyl chloride, Et_3N, 0 °C; LiXc; (c) KHMDS, −78 °C, trisyl azide; (d) LiOH, H_2O_2, 0 °C; (e) CH_2N_2, 0 °C; (f) see text and Experimental Section.

Preparation of Cyclopentadienylruthenium(II) Complexes of Protected 4-Chlorophenylalanines. The phenylalanine derivatives **11–16** required for complexation with ruthenium were prepared with high optical purity using the Evans asymmetric azidation method (Scheme I).[15] Thus, 4-chlorocinnamic acid (**5**) was hydrogenated and the hydrocinnamic acid **6** was converted to the acyloxazolidinone **7** using the mixed anhydride method. Deprotonation of **7** using KHMDS at low temperature, followed by reaction of the enolate with trisyl azide according to Evans' procedure,[15] afforded the azide derivative **8**. According to ^1H NMR spectroscopy, this compound was a single diastereomer, consistent with the reports that similar reactions proceed with >98% diastereoselectivity. Hydrolysis of **8** with LiOH afforded the azido acid **9**, which was converted to the methyl ester **10** by treatment with diazomethane. The acid **9** and the methyl ester **10** were each converted to the *N*-Boc derivatives **11** and **12** by a one-pot transformation. A sample of racemic **11** was also prepared by protection of commercially available (±)-4-chlorophenylalanine using standard methods. This material, or the (D)-compound, was converted to (trimethylsilyl)ethyl ester **13**, bromoethyl ester **14**, pentafluorophenyl ester **15**, and the bromoethyl ester-protected dipeptide **16**, using standard DCC-coupling techniques (see Experimental Section).

Complexation of all chlorophenylalanine derivatives **11–16** was studied using **17** under known reaction conditions (1,2-dichloroethane, reflux 1–5 h)[11] in an effort to prepare complexes **18–23**. The results of this study are summarized in the equation below, from which it can be

(6) Gouzoules, F. Unpublished work, Case Western Reserve University, 1987.

(7) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1989**, *54*, 2498; **1990**, *55*, 6000.

(8) Evans, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 1063. Schmidt, U.; Weller, D.; Holder, A.; Lieberknecht, A. *Tetrahedron Lett.* **1988**, *29*, 3227.

(9) Noda, H.; Niwa, M.; Yamamura, S. *Tetrahedron Lett.* **1981**, *22*, 3247. Nishiyama, S.; Nakamura, K.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1986**, *27*, 4481. Nishiyama, S.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1988**, *29*, 559. Nishiyama, S.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1989**, *30*, 379.

(10) Suzuki, Y.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1989**, *30*, 6043. Evans, D. A.; Ellman, J. A.; DeVries, K. M. *J. Am. Chem. Soc.* **1989**, *111*, 8912.

(11) Zelonka, R. A.; Baird, M. C. *J. Organomet. Chem.* **1971**, *35*, C43. Robertson, I. W.; Stephenson, T. A.; Tocher, D. A. *J. Organomet. Chem.* **1982**, *228*, 171. Gill, T. P.; Mann, K. R. *Organometallics* **1982**, *1*, 485.

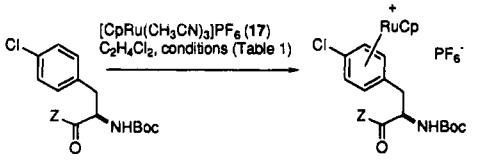
(12) For a preliminary communication of this work, see: Pearson, A. J.; Park, J. G.; Yang, S. H.; Chuang, Y.-H. *J. Chem. Soc., Chem. Commun.* **1989**, 1363. See also: Moriarty, R. M.; Ku, Y.-Y.; Gill, U. S. *J. Chem. Soc., Chem. Commun.* **1987**, 1837. Vol'kenau, N. A.; Belesova, I. N.; Shul'pina, L. S.; Kitaigorodskii, A. N. *J. Organomet. Chem.* **1984**, *267*, 313. Moriarty, R. M.; Ku, Y.-Y.; Guo, L. *J. Chem. Soc., Chem. Commun.* **1988**, 1627. Moriarty, R. M.; Guo, L.; Ku, Y.-Y.; Gilardi, R. *J. Chem. Soc., Chem. Commun.* **1990**, 1765. Moriarty, R. M.; Ku, Y.-Y.; Gill, U. S. *Organometallics* **1988**, *7*, 660.

(13) For a review on the isolation, structure, and biological properties of vancomycin, see: Barna, J. C. J.; Williams, D. H. *Ann. Rev. Microbiol.* **1984**, *38*, 339.

(14) Perkins, H. R. *Biochem. J.* **1969**, *111*, 195.

(15) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011. Evans, D. A.; Ellman, J. A.; Dorow, R. L. *Tetrahedron Lett.* **1987**, *28*, 1123. Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757.

seen that most compounds give good to excellent yields of complex.



11 - 16

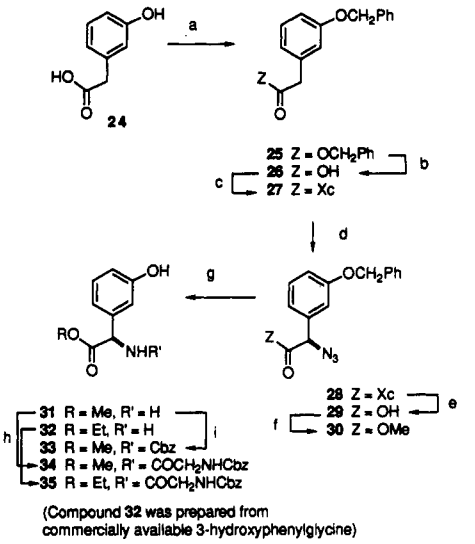
18 Z = OH (93%)
19 Z = OMe (87-89%)
20 Z = $OCH_2CH_2SiMe_3$ (rac) (0%; decomposition)
21 Z = OCH_2CH_2Br (75-99%)
22 Z = OC_6F_5 (rac) (0%; decomposition)
23 Z = $NHCH_2CO_2CH_2CH_2Br$ (99-100%)

Particularly noteworthy is the observation that the free carboxylic acid 11 can be complexed in good yield and that there is no loss of Boc protecting group. However, the (trimethylsilyl)ethyl ester 13 is problematic, possibly due to competing desilylation by the PF_6^- counterion, and the activated ester 15 does not appear to survive the complexation procedure. The formation of 18 is particularly encouraging because there is the possibility of conducting subsequent reactions without having to incorporate protection/deprotection steps, while the bromoethyl ester as in 21 acts as a blocking group that can be removed under essentially neutral conditions,[16] compatible with the projected incorporation of arylglycine moieties that are easily racemized under mildly basic conditions.[17]

Another important consideration is the demetalation of complexes 18–23, since conditions must be identified that do not lead to racemization of the amino acid or peptide side chain. We considered that pyrolysis in a donor solvent[18] would be unsuitable, and so we have examined photolytic decomplexation, following a modification of the method described by Gill and Mann.[19] Accordingly, complex 19 in acetonitrile solution was irradiated with a 275-W sunlamp to regenerate 12, which showed specific rotation identical to the untreated compound. Therefore, the process of complexation/decomplexation does not lead to significant racemization of the protected amino acid. Moreover, the $[CpRu(CH_3CN)_3]^+PF_6^-$ complex produced is easily recovered by ether precipitation and can be recycled, thereby offsetting the high cost of this reagent.

Preparation and Coupling Reactions of D-3-Hydroxyphenylglycine Derivatives. During the earlier stages of this work, commercially available D-3-hydroxyphenylglycine was used, but the supply was discontinued. Consequently, various protected derivatives were prepared using the Evans asymmetric azidation method as outlined in Scheme II. The azidation reaction itself (27 → 28) was rather low-yielding in this case (range 30–50%), which might be due to difficulties in decomposition of the sulfonyl triazene intermediate. Although addition of tetramethylammonium acetate accelerated the decomposition,[15] the overall yield remained unchanged. Hydrolysis of the acyloxazolidinone 28 requires basic conditions and in our hands gave some racemization, judged to be <10% from specific rotation measurements on the amino ester 31 and its hydrochloride salt (see Experimental Section). For our studies, this was considered acceptable. Using this approach, the protected amino methyl ester 33 and the protected dipeptide 34 were produced. The corresponding

Scheme II[a]



[a] Reagents: (a) 2.5 equiv of $BnBr/K_2CO_3$; (b) KOH; (c) pivaloyl chloride, Et_3N, 0 °C; LiXc; (d) KHMDS, −78 °C, trisyl azide; (e) LiOH; (f) *p*-toluenesulfonic acid/MeOH; (g) H_2/Pd–C; (h) $CbzNHCH_2CO_2H$/DCC/HOBT; (i) $ClCO_2Bn/NaHCO_3$.

Table I. Coupling of 3-Hydroxyphenylglycine Derivatives with Chloroarene–RuCp Hexafluorophosphate

entry	arylglycine	complex	product (yield, %)[a]	demetalation product (yield, %)
1	**34**	**18**	decomposition	
2	**34**	**21**	**36b** (95–97)	**37b** (65)
3	**33**	**23**	**36c** (80–87)	**37a** (57)
4	**33**	**21**	**36d** (84)	**37d** n.d.[b]
5	**35**	**19**	**36e** (99.8)	**37e** (97)
6	**35**	**23**	**36f** (64)	**37f** (73)

[a] Ranges are given for several experiments. [b] n.d. = not determined.

ethyl ester dipeptide 35 was prepared from commercially available (*R*)-3-hydroxyphenylglycine using standard methods.

The coupling between the chlorophenylalanine–RuCp complexes and the above 3-hydroxyphenylglycines was studied next. Previous work in our laboratory[20] has shown that deprotonation of the phenolic OH of these arylglycines using NaH in THF at 0 °C leads to slow racemization (ca. 10% after 30 min). This problem is solved by using the weak, sterically hindered base, sodium 2,6-di-*tert*-butylphenoxide,[20b] in the presence of which no racemization of 33 and related compounds occurs in THF at 0 °C even after several hours (mild acid quench, followed by measurement of specific rotation). This provides suitable conditions for the coupling: reaction of 33 with 21 and 23, reaction 34 with 18 and 21, and reaction of 35 with 19 and 21 were each studied, and the results are given in Table I. Disappointingly, we were unable to effect coupling with the unprotected carboxylic acid derivative 18, even in the presence of 2 equiv of base. Considerable decomposition of the complex occurred during the attempted coupling, and demetalation of the crude material so produced did not yield any of the expected diaryl ether. However, all other complexes behaved well and gave coupled products in good to excellent yield. Demetalation using the pho-

(16) Anderson, L. C.; Pinnick, H. W. *J. Org. Chem.* **1978**, *43*, 3417. Kunz, H.; Buchholq, M. *Chem. Ber.* **1979**, *112*, 2145. Eckert, H.; Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 681. See also: Ho, T. L. *Synthesis* **1975**, 510. Ho, T. L. *Synthesis* **1974**, 715.

(17) Bodanszky, M. *Principles of Peptide Synthesis*; Springer-Verlag: New York, 1985.

(18) Segal, J. A. *J. Chem. Soc., Chem. Commun.* **1985**, 1338.

(19) Gill, T. P.; Mann, K. R. *Organometallics* **1982**, *1*, 485.

(20) (a) Lee, S. H.; Russell, A.; Shin, H. Unpublished results, Case Western Reserve University. (b) The use of sodium 2,6-di-*tert*-butylphenoxide as a mild nonnucleophilic base for these reactions was developed by A. Russell in these laboratories.

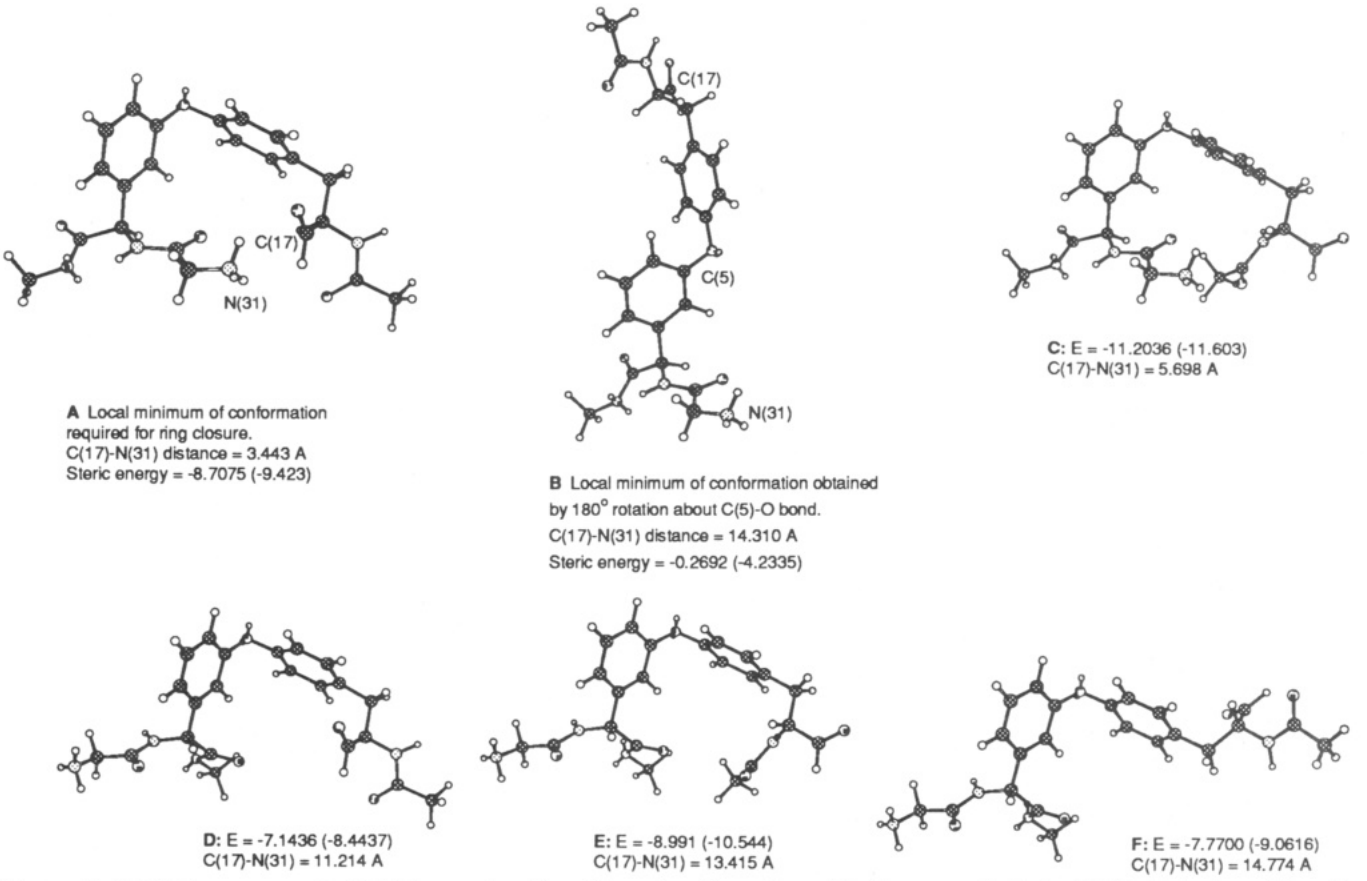
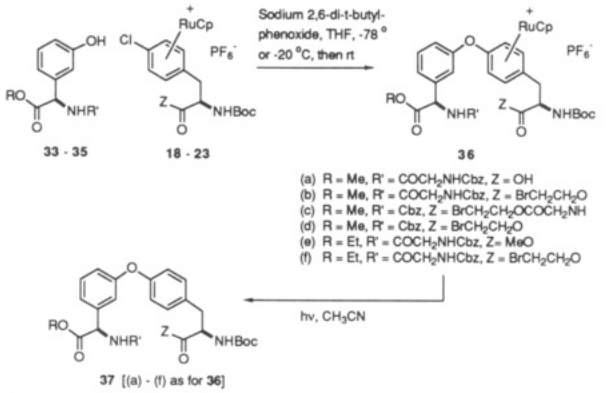


Figure 1. Model for vancomycin B/C ring construction: Pre-set conformations. Steric energy (kcal) for C(17) aldehyde model and, in parentheses, for C(17) carboxylic acid.

tochemical procedure described earlier gave the diaryl ethers **37b–f**, each produced in good yield and in high diastereomeric purity as judged by HPLC (^{1}H NMR was not informative in this regard).



Deprotection and Cyclopeptidation Studies on Compound 37f. Removal of the bromoethyl ester blocking group from **37f** was effected using standard conditions,[16] to give **38** in 75% yield, which was converted via hydrogenolysis of the benzyloxycarbonyl group to the amino acid **39**. It should be noted that the removal of the bromoethyl group was rather capricious. We were unable to reproduce this deprotection for compounds **37b** or **37c**, despite their very close similarity to **37f**; several attempts gave the corresponding hydroxyethyl ester, presumably via a neighboring group participation from the ester carbonyl, although as far as we are aware this problem has not been reported elsewhere.

A number of attempts to effect intramolecular amide formation using **39**, in conjunction with reagents that have been previously used for related cyclizations,[21] uniformly failed (reagents are summarized in Scheme III). No molecular ion was found in the FAB MS of the products corresponding to the desired product **40** or to dimer or cyclic dimer. Williams' group have reported similar difficulties and have attributed the failure of amino acid **41** to give **42**, under conditions analogous to ours, to "the difficulty of macrocyclic lactamization of conformationally restricted systems".[22] In order to determine whether the conformation of these molecules that is required for cyclization is significantly higher in energy than other available conformations, we have carried out MM2 calculations.[23] Given the potential errors of applying this approach to these molecules, because of uncertainty in MM2 parameters and the fact that they apply to gas-phase systems, our conclusions are only tentative.

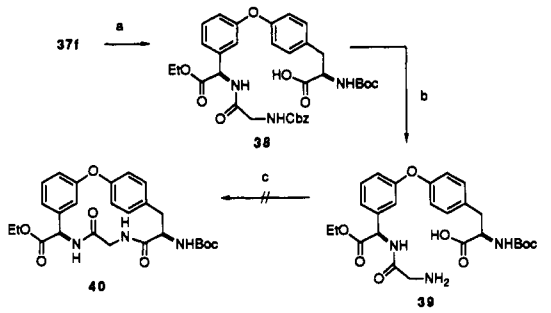
Figure 1 shows six conformations for two series of compounds, the structures of which are self-explanatory, corresponding to aldehyde and carboxylic acid at C-17

(21) Mann, M. J.; Pant, N.; Hamilton, A. D. *J. Chem. Soc., Chem. Commun.* **1986**, 158. Pant, N.; Hamilton, A. D. *J. Am. Chem. Soc.* **1988**, *110*, 2002. Crimmin, M. J.; Brown, A. G. *Tetrahedron Lett.* **1990**, *31*, 2017 and 2021. For basic methodology, applied to other coupling reactions, see the following. DPPA: Brady, S. F.; Varga, S. L.; Freidinger, R. M.; Schwenk, D. A.; Mendlowski, M.; Holly, F. W.; Veber, D. F. *J. Org. Chem.* **1979**, *44*, 3101. Brady, S. F.; Freidinger, R. M.; Paleveda, W. J.; Colton, C. D.; Hommick, C. F.; Whitter, W. L.; Curley, P.; Nutt, R. F.; Veber, D. F. *J. Org. Chem.* **1987**, *52*, 764. DCC: Miyazawa, T.; Otomatsu, T.; Yamada, T.; Kuwata, S. *Tetrahedron Lett.* **1989**, *25*, 771. Morpho CDI: Sheehan, J. C.; Hlavaka, J. J. *J. Org. Chem.* **1956**, *21*, 439. BOP: Castro, B.; Dormoy, J.-R.; Dourtoglu, B.; Evin, G.; Selve, C.; Ziegler, J.-C. *Synthesis* **1976**, 751. Castro, B.; Dormoy, J.-R.; Evin, G.; Selve, C. *Tetrahedron Lett.* **1975**, 1219. Knorr, R.; Trzeciak, A.; Bannworth, W.; Gillessen, D. *Tetrahedron Lett.* **1989**, *30*, 1927.

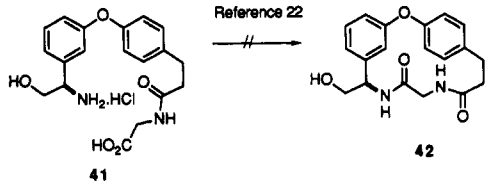
(22) Stone, M. J.; van Dyke, M. S.; Booth, P. M.; Williams, D. H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1629.

(23) MM2 calculations were performed using Chem 3D Plus software, which includes a new implementation of N. L. Allinger's MM2 force field (QCPE 395), based on the work of J. W. Ponder of Yale university.

Scheme III[a]



[a] Reagents: (a) Zn, NaI, THF, H_2O, reflux; (b) 1,3-cyclohexadiene, Pd–C, EtOH, reflux; (c) (the following coupling methods were examined) (i) DPPA, $NaHCO_3$, DMF, 0 °C, 3 days; (ii) DCC, $CuCl_2$, CH_3CN, DMF; (iii) DCC, HOBT, DMF, 0 °C; (iv) Morpho–CDI, DMF, rt, 2 days; (v) BOP, DMF i-Pr_2NEt, 0 °C. DPPA = diphenyl phosphorazidate; DCC = dicyclohexylcarbodiimide; Morpho–CDI = 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate; BOP = benzotriazolyl-*N*-oxytris(dimethylamino)phosphonium hexafluorophosphate.



(arbitrary numbering). While these do not accurately represent the intermediates for each cyclization attempt, the fact that the trends in steric energy are the same for each series suggests that this is not critical. Each conformation was pre-set and then minimized; steric energies are given on the diagrams. Interestingly, conformation **B** is higher in energy than all conformations (**A** and **C–F**) that place the arylamino acid residues relatively close. This appears to be due mainly to higher torsional energy (−15.6651 for carboxylic acid **B** vs −18.2029 for **A**) and non-1,4-van der Waals interaction (−5.6390 vs −8.0906). Conformation **A**, in which the amino (N-31) and carbonyl (C-17) groups are placed sufficiently close for cyclization (3.443 Å) is not significantly higher in energy than conformation **E**, where they are much further apart. The lowest energy conformation, **C**, is expected to account for ca. 98% of the whole, but still places amine and carbonyl groups fairly close, and is converted to **A** by rotation about the C(15)–C(16) bond. Consequently, we do not believe that conformational effects adequately explain the difficulties encountered in this reaction. The success of cycloamidation with aryl ether derivatives is quite variable. While this strategy has worked well for the synthesis of K-13 and OF4949,[7-9] it has been found problematic in synthetic approaches to related molecules such as deoxybouvardin[24] and combretastatin D-2.[25] In these cases the problem was solved by using an intramolecular aryl ether formation to effect cyclization. This is similar to the approach used by the Evans and Yamamura groups in the vancomycin series,[10] which suggests that an intramolecular variant of the ruthenium-promoted etherification would provide a solution to the problem encountered in the present work. This will form the basis of future investigations in our laboratory.

Conclusions

This work has shown that chloroarene–RuCp complexes can be prepared from chlorophenylalanine derivatives in the presence of standard amino acid and peptide blocking groups. The processes of complexation and decomplexation do not cause racemization or loss of protecting group, and these complexes can be used to prepare diaryl ether derivatives by *direct* coupling with hydroxyphenylglycine derivatives. These are the first examples of coupling of two protected arylamino acids. The major obstacle to using this strategy for the construction of vancomycin carboxylate-binding pocket analogues is the difficulty in effecting cycloamidation of the so-formed diaryl ether peptide derivatives.

Experimental Section

General procedures and methods for characterization are described elsewhere.[26] Melting points are uncorrected.

(4*R*,5*S*)-4-Chloro-1-[3-oxo-3-(2-oxo-4-methyl-5-phenyl-3-oxazolidinyl)propyl]benzene (7). To a stirred solution of 4-chlorohydrocinnamic acid (312.0 mg, 1.69 mmol) and 282.7 μL (1.2 equiv) of triethylamine in 20 mL of THF was added 218.6 μL (1.05 equiv) of pivaloyl chloride at −78 °C, and the mixture was stirred for 10 min at −78 °C and 30 min at 0 °C. The resulting white slurry was cooled to −78 °C and then a solution of lithiated oxazolidinone [from 300.0 mg (1.69 mmol) of oxazolidinone in 20 mL of THF and 735 μL (1.69 mmol) of 2.3 M n-BuLi in hexane at −78 °C] was added via a Teflon cannula. The mixture was stirred for 15 min at −78 °C and then the reaction was warmed to rt (45 min). The reaction was quenched with 10 mL of a 1 N $NaHSO_4$ aqueous solution. THF was evaporated on a rotatory evaporator and the product was extracted with CH_2Cl_2, washed with dilute $NaHCO_3$ and with brine, and then dried over $MgSO_4$. Flash chromatography on silica gel (30% EtOAc–Hexs) afforded 528.0 mg (90.9%) of a white crystalline solid. The product **7** was further purified by crystallization from EtOAc–hexanes, mp 94.5–95 °C; R_f 0.28 (30% EtOAc–Hexs); IR ($CHCl_3$) 3540, 3020, 2920, 1780, 1700, 1350 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.43 (9 H, m, aromatic), 5.65 (1 H, d, J = 7.3 Hz, C_6H_5CH), 4.75 (1 H, quintet, J = 7.0 Hz, CH_3CH), 3.28 (2 H, m, CH_2CO), 2.98 (2 H, t, J = 7.3 Hz, $ArCH_2$), 0.88 (3 H, d, J = 6.5 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.81, 152.97, 138.89, 133.13, 131.95, 129.92, 128.69, 128.51, 125.58, 79.03, 54.73, 37.07, 29.55, 14.51; $[\alpha]_D$ +32.9° (*c* 0.51, $CHCl_3$); MS *m/z* 343.0954 ($[M^+]$, $C_{19}H_{18}ClNO_3$ requires 343.0975).

(4*R*,5*S*,2*R*)-4-Chloro-1-[2-azido-3-oxo-3-(2-oxo-4-methyl-5-phenyl-3-oxazolidinyl)propyl]benzene (8). To a stirred solution of 5.0 g (14.54 mmol) of **7** in 50 mL THF at −78 °C was added via a cannula 13.57 mL (1.05 equiv) of 1.125 M KHMDS in THF (purchased from Alfa Products). The mixture was stirred for 30 min at −78 °C. To this solution was added a precooled (−78 °C) solution of 5.40 g (17.45 mmol, 1.2 equiv) of trisyl azide in 50 mL of THF with a cannula. The solution was stirred for 2 min at −78 °C and then quenched by rapid addition of 4.16 mL (72.7 mmol, 5 equiv) of glacial acetic acid with immediate warming to 30 °C with a water bath. After stirring the yellow to white slurry at room temperature for 1.5 h, it was diluted with CH_2Cl_2, washed with brine and with dilute $NaHCO_3$, and then dried over $MgSO_4$. Flash chromatography on silica gel (10% EtOAc–petroleum ether then EtOAc) afforded 3.82 g (68%) of **8** as a yellow oil: R_f 0.41 (30% EtOAc–Hexs); IR (neat) 3100, 2920, 2110, 1780, 1700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.42–7.22 (9 H, m, aromatic Hs), 5.56 (1 H, d, J = 7.2 Hz, $PhCH$), 5.22 (1 H, dd, J = 9.2 and 5.3 Hz, CHN_3), 4.67 (1 H, quintet, J = 7 Hz, CH_3CH), 3.18 (1 H, dd, J = 13.7 and 5.3 Hz, $ArCHH$), 2.97 (1 H, dd, J = 13.7 and 9.2 Hz, $ArCHH$), 0.92 (3 H, d, J = 4.8 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.16, 152.85, 134.68, 133.64, 132.92, 131.06, 129.43, 129.21, 125.98, 79.84, 61.99, 55.63, 37.35, 14.80; $[\alpha]_D$ −12.97° (*c* 0.37, $CHCl_3$); MS *m/z* $[M]^+$ not found, 356.0914 ($[M - N_2]^+$, $C_{19}H_{17}ClN_2O_3$ (M − N_2) requires 356.0928).

D-(−)-*N*-Diaza-4-chlorophenylalanine Methyl Ester (10) and Its Deprotection To Give 12. To a precooled (0 °C) solution of 941.8 mg (2.45 mmol) of **8** in 50 mL of THF was added dropwise an aqueous LiOOH solution (prepared from 107.9 mg, 1.05 equiv

(24) Boger, D. L.; Yohannes, D. *J. Am. Chem. Soc.* **1991**, *113*, 1427. Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1991**, *56*, 1763.
(25) Boger, D. L.; Sakya, S. M.; Yohannes, D. *J. Org. Chem.* **1991**, *56*, 4204.
(26) Pearson, A. J.; Lee, S.-H.; Gouzoules, F. *J. Chem. Soc., Perkin Trans. 1* **1990**, 723.

of LiOH, and 1.25 mL of 30% H_2O_2 in 17 mL of H_2O). The mixture was stirred for 1 h at 0 °C, the reaction was quenched by dropwise addition of a solution of 2.55 g $NaHSO_3$ in 30 mL of H_2O, and the mixture was stirred for an additional 15 min at 0 °C. The organic solvent was removed in vacuo. The aqueous residue was diluted with 1 N $NaHSO_4$ and then extracted with CH_2Cl_2. The combined organic phase was dried over $MgSO_4$ and then concentrated. The unpurified acid (**9**) was diluted with 50 mL of ethyl ether and treated with an excess (3 equiv) of CH_2N_2 in ether (the reaction was monitored by TLC). The excess CH_2N_2 was removed by bubbling N_2 through the solution. Flash chromatography on silica gel gave 527.2 mg (crude yield, 89.8%) of a pale yellow oil: R_f 0.38 (30% EtOAc–Hexs). This ester (**10**) was always contaminated with inseparable impurities. Consequently, the crude ester was converted to compound **12**: A suspension of 40 mg of 10% Pd–C in 5 mL of ethyl acetate was vigorously stirred under H_2 (1 atm) until the uptake of H_2 ceased. To this was added a mixture of 401.9 mg (1.68 mmol) of azido ester **10** and 439.2 mg (2.02 mmol, 1.2 equiv) of $(Boc)_2O$ in 2 mL of ethyl acetate. The resulting solution was stirred under H_2 at room temperature for 3 h. Flash chromatography on silica gel (10% EtOAc/benzene) afforded 354.6 mg (67% yield) of white solid **12**, which was further purified by recrystallization from hexanes (white needles): mp 78–80 °C; R_f 0.39 (10% EtOAc/benzene); IR ($CHCl_3$) 3430, 3000, 2980, 1740, 1705, 1490 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.23 (2 H, d, J = 8.4 Hz, aromatic Hs, ortho to Cl), 7.02 (2 H, d, J = 8.4 Hz, aromatic Hs, meta to Cl), 4.92 (1 H, br d, N-*H*, J = ~7 Hz), 4.53 (1 H, br q, J = ~5 Hz, NHC*H*CO_2), 3.68 (3 H, s, CO_2CH_3), 3.07 (1 H, dd, J = 14 and 5.5 Hz, ArC*H*H), 2.96 (1 H, dd, J = 14 and 8 Hz, ArCH*H*), 1.38 (9 H, s, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.01, 154.93, 134.52, 132.86, 130.58, 128.59, 79.98, 54.22, 52.24, 37.68, 28.21; $[\alpha]_D$ = −44.8° (c 0.5, CH_2Cl_2); MS m/z 313.1840 ($[M]^+$, $C_{15}H_{20}ClNO_4$ requires 313.1081).

D,L-*N*-[(1,1-Dimethylethoxy)carbonyl]-4-chlorophenylalanine 2-(Trimethylsilyl)ethyl Ester (13). (±)-*N*-Boc-4-chlorophenylalanine (129.2 mg, 0.43 mmol, prepared from (±)-4-chlorophenylalanine purchased from Aldrich) was covered with 0.4 mL of acetonitrile. To this stirred slurry were added 0.1 mL of DMF (or sufficient to produce a homogeneous solution), 69.7 μL (2 equiv) of pyridine, and 74.0 μL (1.2 equiv) of 2-(trimethylsilyl)ethanol. The mixture was cooled to 0 °C, and then 97.5 mg (1.1 equiv) of DCC was added. After stirring overnight at 0 °C, 12.9 mL of 5 M oxalic acid in DMF was added, and the reaction was allowed to come to room temperature. The white precipitate (DCU) was filtered off and discarded. Flash chromatography on silica gel (30% EtOAc/Hexs) afforded 192.7 mg of a clear oil. The product was further purified by flash chromatography on silica gel (20% EtOAc/petroleum ether) and preparative TLC (30% EtOAc/Hexs) to give 149.9 mg (86.9% yield) of white solid **13**: mp 91–92.5 °C; R_f 0.46 (30% EtOAc/Hexs), 0.49 (20% EtOAc/petroleum ether); IR ($CHCl_3$) 3440, 3020, 2940, 1730, 1710, 1495 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.24 (2 H, d, J = 8.4 Hz, aromatic Hs, ortho to Cl), 7.05 (2 H, d, J = 8.4 Hz, aromatic Hs, meta to Cl), 4.96 (1 H, br d, N-*H*), 4.50 (1 H, br m, ArCH_2C*H*), 4.16 (2 H, m, $CO_2CH_2CH_2$), 3.08 (1 H, dd, J = 14 and 5.9 Hz ArC*H*H), 2.98 (1 H, dd, J = 14 and 6.5 Hz, ArCH*H*), 1.40 (9 H, s, OC(CH_3)$_3$), 0.93 (2 H, dd, J = 10 and 7 Hz, CH_2SiMe_3), 0.02 (9 H, s, Si(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.65, 154.93, 134.65, 132.79, 130.67, 128.53, 79.88, 63.82, 54.34, 37.75, 28.23, 17.30, −1.60.

D-(−)-*N*-[(1,1-Dimethylethoxy)carbonyl]-4-chlorophenylalanine 2-Bromoethyl Ester (14). To a stirred suspension of 244 mg (0.82 mmol) of D-(−)-*N*-Boc-4-chlorophenylalanine in 0.8 mL of acetonitrile was added the minimum amount of DMF need to make a clear solution, followed by 69 μL (1.2 equiv) of 2-bromoethanol and 131.8 μL (2 equiv) of pyridine. This solution was cooled to 0 °C and 185.0 mg (0.90 mmol, 1.1 equiv) of DCC was added. The mixture was stirred for 16 h at 0 °C. The reaction was quenched with 24.5 μL of 5 M oxalic acid in DMF and then allowed to come to room temperature. The mixture was filtered and the solvent was evaporated. The residue was dissolved in CH_2Cl_2, washed with water, and dried over $MgSO_4$. Flash chromatography on silica gel (30% EtOAc/Hexs) afforded a white solid, which was further purified by recrystallization from hexanes to give **14** as white needles (220.8 mg, 66.6% yield after recrystallization); mp 70–71 °C; R_f 0.46 (30% EtOAc/Hexs); IR ($CHCl_3$) 3460, 2960, 2920, 1740, 1710, 1490, 1110 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.25 (2 H, d, J = 7 Hz, aromatic Hs, ortho to Cl), 7.07 (2 H, d, J = 7 Hz, aromatic Hs, meta to Cl), 4.93 (1 H, br, N-*H*), 4.55 (1 H, br, C*H*NH), 4.39 (2 H, t, J = 6 Hz, OCH_2CH_2), 3.45 (2 H, t, J = 6 Hz, CH_2Br), 3.11 (1 H, dd, J = 14 and 6 Hz, ArC*H*H), 3.00 (1 H, dd, J = 14 and 7 Hz, ArCH*H*), 1.3 (9 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.21, 154.93, 134.32, 132.96, 130.63, 128.66, 80.11, 64.57, 54.19, 37.56, 28.21, 28.11; $[\alpha]_D$ −20.5° (c 0.60, CH_2Cl_2). The racemic compound was also prepared, following the same procedure as above in 92% yield: mp 64–65 °C.

D,L-*N*-[(1,1-Dimethylethoxy)carbonyl]-4-chlorophenylalanine Pentafluorophenyl Ester (15). To a stirred solution of 106.4 mg (0.36 mmol) of (±)-*N*-Boc-4-chlorophenylalanine in 2 mL of THF was added 196 mg (116 mL, 3 equiv) of pentafluorophenol. The mixture was cooled to 0 °C, DCC (109.9 mg, 1.5 equiv) was added, and the mixture was stirred for 2 h at 0 °C. The reaction was allowed to reach to room temperature and then stirred overnight. The resulting reaction mixture was filtered and concentrated in vacuo, and the residue was diluted with CH_2Cl_2, washed with 1 N K_2CO_3 (twice) and with brine, and then dried over $MgSO_4$. Purification by flash chromatography on silica gel (50% EtOAc/Hexs) afforded **15** (152.8 mg, 92.4% yield) as a white solid: mp 118.5–119 °C; R_f 0.57 (50% EtOAc/Hexs); IR ($CHCl_3$) 3430, 2980, 1770, 1710, 1520 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.30 (2 H, d, J = 8.5 Hz, aromatic Hs, ortho to Cl), 7.15 (2 H, d, J = 8.5 Hz, aromatic Hs, meta to Cl), 4.89 (1 H, br s, CH_2CH), 3.24 (2 H, br m, ArCH_2), 1.41 (9 H, s, OC(CH_3)$_3$).

D-(+)-*N*-[(1,1-Dimethylethoxy)carbonyl]-4-chlorophenylalanylglycine 2-Bromoethyl Ester (16). To a stirred solution of 1.27 g (4.83 mmol) of glycine 2-bromoethyl ester HBr salt in 5 mL DMF were added 674 μL (4.83 mmol) of Et_3N and a solution of 1.09 g (4.83 mmol) of the crude 2-azido acid **9** in 5 mL of DMF, followed by addition of 0.81 g (1.1 equiv) of HOBT. The mixture was cooled to 0 °C, 1.20 g (1.2 equiv) of DCC was added, and the mixture was stirred for 2 h at 0 °C and for 17 h at room temperature. DMF was removed in vacuo (0.05 mmHg, 25 °C), the residue was taken up into 15 mL of ethyl acetate, and the resulting solution was filtered. The filtrate was washed with water and an $NaHCO_3$ solution and dried over $MgSO_4$. Flash chromatography on silica gel (50% EtOAc–Hexs) afforded 2.00 g of oil. This crude product was added to a H_2-saturated suspension of 200 mg of 10% Pd–C in 20 mL of ethyl acetate, followed by addition of 1.27 g (1.2 equiv) of $(Boc)_2O$. H_2 was bubbled through the suspension for 1.5 h at room temperature. The catalyst was filtered off, and solvent was removed in vacuo to give a solid residue. The crude product was purified by recrystallization from EtOAc–Hexs to furnish **16** (1.76 g, 78.5% over two steps) as white needles: mp 121–2 °C; R_f 0.37 (50% EtOAc–Hexs); IR ($CHCl_3$) 3430, 2985, 1754, 1680, 1492 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.25 (2 H, d, J = 8.5 Hz, aromatic ring, ortho to Cl), 7.13 (2 H, d, J = 8.5 Hz, aromatic ring, meta to Cl), 6.44 (1 H, br, CON*H*CH_2), 4.92 (1 H, br, N*H*Boc), 4.43 (2 H, t, J = 6 Hz, $CO_2CH_2CH_2$Br), 4.37 (1 H, m, chiral center), 4.02 (2 H, m, NHCH_2CO_2), 3.48 (2 H, t, J = 6 Hz, CH_2Br), 3.09 (1 H, dd, J = 14.5 and 7 Hz, ArC*H*H), 2.99 (1 H, dd, J = 14.5 and 8 Hz, ArCH*H*), 1.38 (9 H, s, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.44, 168.93, 155.38, 134.98, 132.68, 130.60, 128.59, 80.32, 64.45, 55.23, 41.00, 37.54, 28.11; $[\alpha]_D$ +3.01° (c 1.03, CH_2Cl_2). Anal. Calcd for $C_{18}H_{24}BrClN_2O_5$: C, 46.62; H, 5.22; N, 6.04. Found: C, 46.33; H, 5.24; N, 5.92.

[η^6-D-4-Chloro-1-[2-[*N*-[(1,1-dimethylethoxy)carbonyl]-amino]-3-hydroxy-3-oxopropyl]benzene](η^5-cyclopentadienyl)ruthenium Hexafluorophosphate (18). To a heated (60 °C) and stirred solution of 100.0 mg (0.33 mmol) of *N*-Boc-4-chlorophenylalanine (**11**), prepared as above, in 1,2-dichloroethane was added 144.9 mg (0.33 mmol) of $[(CH_3CN)_3Ru^+Cp]PF_6^-$ in one portion. The mixture was refluxed for 45 min, during which time the color changed from dark brown to brown-yellow. The reaction mixture was cooled to room temperature and solvent was removed in vacuo. The residue was dissolved in 0.5 mL of CH_2Cl_2 and then added to 30 mL of ether to precipitate 180.3 mg (88.4%) of product **18**, obtained as brown powder: IR (CH_2Cl_2) 3599, 3420, 3084, 2933, 1709, 843 cm^{-1}; ^1H NMR (200 MHz, CD_3CN) δ 6.53 (2 H, d, J = 6 Hz, aromatic ring, ortho to Cl), 6.26 (1 H, d, J = 6 Hz, aromatic ring, meta to Cl),

6.15 (1 H, d, J = 6 Hz, aromatic ring, meta to Cl), 5.70 (1 H, br, N-*H*), 5.43 (5 H, s, *Cp*), 4.30 (1 H, br, chiral center), 3.05 (1 H, dd, J = 14 and 4.6 Hz, ArC*H*H), 2.74 (1 H, dd, J = 14 and 9.7 Hz, ArCH*H*), 1.37 (9 H, s, $C(CH_3)_3$). Due to the inherent instability and difficulties in purification of this compound, other analyses were not satisfactory.

[η^6-D-4-Chloro-1-[2-[*N*-[(1,1-dimethylethoxy)carbonyl]amino]-3-oxo-3-methoxypropyl]benzene](η^5-cyclopentadienyl)ruthenium Hexafluorophosphate (19). The amino ester **12** (144.5 mg, 0.461 mmol), prepared as above, was dissolved in 10 mL of N_2-purged 1,2-dichloroethane, followed by addition of 200 mg (0.461 mmol) of $(CH_3CN)_3RuCpPF_6$ at room temperature. The color immediately changed from yellow to dark brown. The mixture was heated to reflux for 5 h under N_2 (monitored by NMR). The reaction mixture was filtered through Celite (CH_2Cl_2) and concentrated to ~2 mL, and the solution was added to 100 mL of ether to remove unreacted ester. The ether-insoluble dark brown residue was dissolved in CH_3CN and filtered through a neutral alumina column (CH_3CN) to afford **19** (192.8 mg, 88.8% yield, 99.9% based on the recovered pure starting material) as a brown foam. From the ether layer, 35.5 mg of unreacted ester was recovered. **19**: IR ($CHCl_3$) 3420, 3100, 3040, 2980, 1740, 1705, 845 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.46–6.1 (4 H, m, aromatic Hs), 5.45 (5 H, s, *Cp*), 4.42 (1 H, m, CH_2CHNH), 3.80 (3 H, s, CO_2CH_3), 3.07 (1 H, dd, J = 14 and 5 Hz, ArC*H*H), 2.82 (1 H, dd, J = 14 and 7.7 Hz, ArC*H*H), 1.37 (9 H, s, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.71, 155.14, 104.97, 100.91, 86.94, 86.74, 82.89, 80.35, 54.13, 52.81, 36.64, 28.02; MS m/z 625.0133 ($[M]^+$, $C_{20}H_{25}ClF_6NO_4PRu$ requires 625.0151).

[η^6-4-Chloro-1-[D-2-[*N*-[(1,1-dimethylethoxy)carbonyl]amino]-3-oxo-3-(2-bromoethoxy)propyl]benzene](η^5-cyclopentadienyl)ruthenium Hexafluorophosphate (21). To a stirred, heated (75 °C) solution of 100 mg (0.246 mmol) of *N*-Boc-4-chlorophenylalanine 2-bromoethyl ester (**14**) in 8 mL of N_2-purged 1,2-dichloroethane was added 160.2 mg (1.5 equiv, 3.69×10^{-4} mol) of $(CH_3CN)_3CpRuPF_6$ complex as a solid in one portion. The mixture was refluxed for 5 h under N_2 cooled to room temperature and insolubles were filtered off on a Celite pad. The filtrate was evaporated in vacuo, and the black residue dissolved in CH_3CN was eluted through a neutral alumina column (CH_3CN). The acetonitrile solution was concentrated to ~2 mL and then added to 50 mL of ether to remove the organic starting material. The ether-insoluble precipitate was further washed with ether. The residue was dissolved in 3 mL of chloroform, and the precipitate was removed by filtration through a Celite column (0.5 × 2 cm). The chloroform solution was evaporated in vacuo to afford **21** as a dark brown solid (167.0 mg, 94.6%): IR ($CHCl_3$) 3427, 3088, 2933, 1746, 1707, 1454, 1214, 846 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.44–6.26 (4 H, m, aromatic Hs), 5.45 (5 H, s, *Cp*), 4.49 (2 H, t, J = 6 Hz, OCH_2CH_2Br overlapping with 1 H, br, *CH*NH), 3.58 (2 H, t, J = 6 Hz, CH_2Br), 3.11 (1 H, dd, J = 14.2 and 5 Hz, ArC*H*H), 2.85 (1 H, 14.2 and 8 Hz, ArCH*H*), 1.38 (9 H, s, $OC(CH_3)_3$).

D-3-Hydroxyphenylglycine Ethyl Ester (32). To a stirred solution of D-3-hydroxyphenylglycine (1.33 g, 7.97 mmol) in 50 mL of absolute ethanol was added 3.03 g (2 equiv) of *p*-toluenesulfonic acid hydrate, and the mixture was refluxed for 16 h. The reaction mixture was cooled to room temperature, and the solvent was removed in vacuo. The white residue was triturated with 500 mL of ether, filtered, and dried. The powder was dissolved in 60 mL of cold water and treated with 669.6 mg (1 equiv) of $NaHCO_3$ at 0 °C, and the product was extracted with ethyl acetate (3 × 100 mL). Recrystallization from ethanol gave **32** (919.0 mg, 59.1%) as pale yellow needles: mp 147–8 °C; IR (KBr) 3470, 3400, 3350, 3120, 3100, 2940, 1740 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.18 (1 H, t, J = 8 Hz, aromatic ring 5-H), 6.89 (1 H, d, J = 8 Hz, aromatic ring 6-H), 6.82 (1 H, t, J = 2 Hz, aromatic ring 2-H), 6.72 (1 H, dd, J = 8 and 2 Hz, aromatic ring 4-H), 4.50 (1 H, s, ArC*H*NH), 4.13 (2 H, m, OCH_2CH_3), 1.18 (3 H, t, J = 7 Hz, CH_3); MS m/z 195.0901 ($[M]^+$, $C_{10}H_{13}NO_3$ requires 195.0895).

D-(−)-*N*-[[*N*′-(Benzyloxycarbonyl)amino]acetyl]-3-hydroxyphenylglycine Methyl Ester (34). Hydrogen gas was bubbled through a solution of the azido ester **30** (1.49 g, 5.03 mmol) and 100 mg of 10% Pd–C in 20 mL of MeOH at room temperature overnight. The catalyst was separated by centrifuging the mixture. MeOH was removed in vacuo to give 587 mg (crude, 64%) of grey powder **31**. To a stirred solution of 122.3 mg (0.68 mmol) of crude **31** in 4 mL of DMF were added 136.8 mg (1.5 equiv) of HOBT and 169.4 mg (1.2 equiv) of *N*-Cbz-glycine. The solution was cooled to 0 °C, followed by addition of 155.3 mg (1.2 equiv) of EDC. The mixture was stirred for 2 h at 0 °C, the reaction was allowed to warm to room temperature, and stirring was continued for 16 h. DMF was distilled off in vacuo (0.1 mmHg, 25 °C), and the residue (oil) was dissolved in 50 mL of CH_2Cl_2, washed with 1 N $NaHSO_4$, $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. Flash chromatography on silica gel (60% EtOAc–Hexs) afforded **34** (226 mg, 92%) as a clear oil: R_f 0.23 (60% EtOAc–Hexs); IR ($CHCl_3$) 3415, 3030, 3013, 2956, 1740, 1681, 1511 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.54 (1 H, br d, J = ~6 Hz, ArCHN*H*), 7.28 (5 H, br s, CH_2Ph), 7.15 (1 H, t, J = 8 Hz, aromatic 5-H), 6.79 (3 H, m, aromatic Hs), 5.64 (1 H, br t, J = 5.8 Hz, $COCH_2NH$), 5.43 (1 H, d, J = 6.8 Hz, chiral center H), 5.00 (2 H, s, CH_2Ph), 3.93 (2 H, m, $COCH_2NH$), 3.67 (3 H, s, CO_2Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.31, 169.58, 157.08, 156.99, 136.64, 135.87, 130.18, 128.46, 128.16, 128.01, 119.10, 116.18, 113.95, 67.29, 56.56, 52.88, 43.98; $[\alpha]_D$ −91.3° (*c* 0.52, $CHCl_3$); MS m/z 372.1319 ($[M]^+$, $C_{19}H_{20}NO_6$ requires 372.1321).

D-(−)-2-[*N*-[[*N*′-(Benzyloxycarbonyl)amino]acetyl]-amino]-2-(3-hydroxyphenyl)acetic Acid Ethyl Ester (35). To a stirred solution of the amino ester **32** (900 mg, 4.61 mmol) in 20 mL of CH_2Cl_2 were added 964.0 mg (4.61 mmol) of *N*-Cbz-glycine and 998.7 mg (4.84 mmol, 1.05 equiv) of DCC. The mixture was stirred for 16 h at room temperature, the white precipitate was filtered off, and the filter cake was washed with CH_2Cl_2. The filtrate was evaporated in vacuo. Flash chromatography of the residue on silica gel (80% EtOAc/Hex), followed by removal of solvent in vacuo, afforded **35** (1.60 g, 89.8%) as a white foam which melted at 42–44 °C: R_f 0.35 (80% EtOAc/Hexs); IR ($CHCl_3$) 3580, 3400, 3330, 3000, 1750, 1670 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.53 (1 H, br d, J = ~7 Hz, ArCHN*H*), 7.38 (1 H, br s, O-*H*), 7.25 (5 H, s, OCH_2Ph), 7.11 (1 H, t, J = 8.5 Hz, aromatic ring 5-H), 6.75 (3 H, m, aromatic Hs), 5.65 (1 H, t, J = 5.8 Hz, N*H*Cbz), 5.39 (1 H, d, J = 7.1 Hz, ArC*H*NH), 4.97 (2 H, s, CH_2Ph), 4.11 (2 H, m, OCH_2CH_3), 3.90 (2 H, m, $COCH_2NHCbz$), 1.14 (3 H, t, J = 7 Hz, OCH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.28, 170.09, 157.49, 137.26, 136.35, 130.48, 128.85, 128.52, 128.37, 119.35, 116.44, 114.45, 67.63, 62.52, 57.07, 44.40, 14.23; $[\alpha]_D$ −75.8° (*c* 0.79, CH_2Cl_2); MS m/z 386.1484 ($[M]^+$, $C_{20}H_{22}N_2O_6$ requires 386.1478).

[η^6-1-D-[2-[*N*-[(1,1-Dimethylethoxy)carbonyl]amino]-3-(2-bromoethoxy)-3-oxopropyl]-4-D-[3-[1-[*N*-[[*N*′-(benzyloxycarbonyl)amino]acetyl]amino]-2-methoxy-2-oxoethyl]phenoxy]benzene](η^5-cyclopentadienyl)ruthenium Hexafluorophosphate (36b). Sodium hydride (48.0 mg, 50% in oil) was stirred with 206.3 mg (1.0 mmol, 1 equiv) of 2,6-di-*tert*-butylphenol in 20 mL of dry THF. After H_2 evolution ceased (30 min), the resulting yellow solution was cooled to 0 °C, and 372.4 mg (1.0 mmol) of **34** was added. The resulting solution was stirred for 5 min at 0 °C and transferred via cannula to a precooled (−78 °C) solution of 719.7 mg (1.0 mmol) of **21** in 25 mL of dry THF. The mixture was stirred for 15 min at −78 °C and 1 h at room temperature. The reaction mixture was filtered through a Celite pad (CH_2Cl_2), concentrated to ~5 mL, and added to 150 mL of ether. The precipitate was filtered, washed well with ether, and dried to give **36b** (1.00 g, 95%) as a brown powder: R_f 0.58 (5% MeOH–1,2-dichloroethane, aluminum oxide plate); IR ($CHCl_3$) 3436, 3030, 2950, 1741, 1506, 850 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.47 (1 H, t, J = 8 Hz, uncomplexed aromatic ring 5-H), 7.34 (5 H, br s, CH_2Ph), 7.12 and 7.01 (3 H, m, uncomplexed aromatic 2-, 4-, and 6-H), 6.06 (4 H, m, complexed aromatic Hs), 5.35 (5 H, s, *Cp*), 5.12 (2 H, s, CH_2Ph), 4.49 (2 H, t, J = 6 Hz, $CO_2CH_2CH_2Br$), 4.48 (1 H, m, phenylalanine chiral center), 3.95 (2 H, m, $NHCOCH_2NH$), 3.77 (3 H, s, CO_2Me), 3.58 (2 H, t, J = 6 Hz, CH_2Br), 2.94 (2 H, m, $ArCH_2CHNHBoc$), 1.41 (9 H, s, $C(CH_3)_3$).

[η^6-1-D-[2-[*N*-[(1,1-Dimethylethoxy)carbonyl]amino]-3-[[2-(2-bromoethoxy)-2-oxoethyl]amino]-3-oxopropyl]-4-D-[3-[1-[*N*-(benzyloxycarbonyl)amino]-2-methoxy-2-oxoethyl]phenoxy]benzene](η^5-cyclopentadienyl)ruthenium Hexafluorophosphate (36c). The title complex was prepared following the same procedure as **36b**: yield = 80–87%; IR ($CHCl_3$) 3425, 3034, 2984, 1749, 1718, 1685, 1497, 847 cm^{-1}; ^1H NMR (200

MHz, $CDCl_3$) δ 7.48 (1 H, t, J = 8 Hz, uncomplexed aromatic 5-H), 7.31 (5 H, s, CH_2Ph), 7.06–6.99 (4 H, m, uncomplexed aromatic Hs), 6.19 (1 H, d, J = 5.2 Hz, phenylglycine chiral center), 6.01–5.88 (4 H, m, complexed aromatic Hs), 5.58 (1 H, br, N*H*), 5.32 (5 H, s, Cp), 5.08 (2 H, m, CH_2Ph), 4.50 (1 H, br, phenylalanine chiral center), 4.41 (2 H, t, J = 6.2 Hz, $CO_2CH_2CH_2Br$), 4.05 (2 H, m, $CONHCH_2CO$), 3.76 (3 H, s, CO_2Me), 3.49 (2 H, t, J = 6.2 Hz, CH_2Br), 2.95 (2 H, m, $ArCH_2CHNHBoc$), 1.38 (9 H, s, $C(CH_3)_3$).

[η⁶-1-D-[2-[*N*-[(1,1-Dimethylethoxy)carbonyl]amino]-3-(2-bromoethoxy)-3-oxopropyl]-4-[3-[1-[*N*-(benzyloxycarbonyl)amino]-2-methoxy-2-oxoethyl]phenoxy]benzene](η⁵-cyclopentadienyl)ruthenium Hexafluorophosphate (36d). The title complex was prepared following the general procedure. **36d**: yield = 84%; IR ($CHCl_3$) 3425, 3034, 2956, 1717, 1642, 1528, 847 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.85 (1 H, t, J = 8 Hz, uncomplexed aromatic 5-H), 7.32 (5 H, br s, CH_2Ph), 7.06~6.99 (3 H, m, uncomplexed aromatic Hs), 6.12 (1 H, br, N*H*), 6.03–5.94 (4 H, m, complexed aromatic Hs), 5.34 (5 H, s, *Cp*), 5.08 (2 H, m, CH_2Ph), 4.49 (2 H, t, J = 6 Hz, $CO_2CH_2CH_2Br$), 4.42 (1 H, m, phenylalanine chiral center), 3.77 (3 H, s, CO_2Me), 3.58 (2 H, t, J = 6 Hz, CH_2Br), 3.08 (1 H, dd, J = 14 and 5 Hz, ArC*H*H), 2.88 (1 H, dd, J = 14 and 8 Hz, ArCH*H*), 1.40 (9 H, s, $C(CH_3)_3$).

[η⁶-1-(*R*)-[3-[1-[*N*-[[*N'*-(Benzyloxycarbonyl)amino]-acetyl]amino]-2-oxo-2-ethoxyethyl]phenoxy]-4-[(*R*)-2-[[*N*-(1,1-dimethylethoxy)carbonyl]amino]-3-oxo-3-methoxypropyl]benzene](η⁵-cyclopentadienyl)ruthenium Hexafluorophosphate (36e). The 3-hydroxyphenylglycine derivative **35** (32.5 mg, 1.05 equiv) was reacted with complex **19** (50 mg, 0.08 mmol) using the general procedure to give **36e** (77.8 mg, 99.8%) as a brown foam: IR ($CHCl_3$) 3400, 3100, 2950, 1730, 1700, 1500, 850 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.4 (1 H, t, J = 8 Hz, uncomplexed aromatic ring, 5-H), 7.31 (5 H, br s, CH_2Ph), 7.10 (1 H, br m, uncomplexed aromatic ring, 6-H), 6.94 (2 H, m, uncomplexed aromatic ring, 2- and 4-H), 6.15–5.89 (4 H, m, complexed aromatic Hs), 5.54 (1 H, br, $CHNHCOCH_2$), 5.39 (1 H, overlaps with Cp, ArC*H*NH), 5.33 (5 H, s, *Cp*), 5.10 (2 H, s, CH_2Ph), 4.37 (1 H, br m, $MeCO_2CHNH$), 4.22 (2 H, m, $CO_2CH_2CH_3$), 3.91 (2 H, br m, $COCH_2NH$), 3.79 (3 H, s, CO_2CH_3), 2.97 (1 H, dd, J = 14 and 4 Hz, ArC*H*H), 2.75 (1 H, dd, J = 14 and 7 Hz, ArCH*H*), 1.39 (9 H, s, $OC(CH_3)_3$), 1.23 (3 H, t, J = 7 Hz, $CO_2CH_2CH_3$).

[η⁶-1-(*R*)-[3-[1-[*N*-[[*N'*-(Benzyloxycarbonyl)amino]-acetyl]amino]-2-oxo-2-ethoxyethyl]phenoxy]-4-(*R*)-[2-[[*N*-(1,1-dimethylethoxy)carbonyl]amino]-3-oxo-3-(2-bromoethoxy)propyl]benzene](η⁵-cyclopentadienyl)ruthenium Hexafluorophosphate (36f). Reaction of **35** (426.5 mg, 1.10 mmol, 1.05 equiv) with complex **21** (754.6 mg) using the general procedure gave **36f** (717 mg, 64%): IR ($CHCl_3$) 3412, 3019, 2893, 1737, 1710, 1502, 1210, 847 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.38 (1 H, t, J = 8 Hz, uncomplexed aromatic 5-H), 7.29 (5 H, br s, CH_2Ph), 7.01–6.90 (3 H, m, uncomplexed aromatic Hs), 6.08–5.91 (4 H, m, complexed aromatic Hs), 5.55–5.42 (3 H, m, difficult to assign due to overlapping), 5.31 (5 H, s, *Cp*), 5.09 (2 H, s, CH_2Ph), 4.45 (overlap of OCH_2CH_2Br) (2 H, t, J = 6 Hz) and tyrosine chiral center), 4.28 (2 H, m, OCH_2CH_3), 3.91 (2 H, d, J = 5.7 Hz, $COCH_2NHCbz$), 3.54 (2 H, t, J = 6 Hz, CH_2Br), 3.05–2.74 (2 H, two dd, difficult to assign J due to broad lines), 1.38 (9 H, s, $OC(CH_3)_3$), 1.21 (3 H, t, J = 7 Hz, $CO_2CH_2CH_3$).

***O*-[(*R*)-3-[1-[*N*-[[*N'*-(Benzyloxycarbonyl)amino]acetyl]-amino]-2-oxo-2-methoxyethyl]phenyl]-(*R*)-*N*-[(1,1-dimethylethoxy)carbonyl]tyrosine 2-Bromoethyl Ester (37b).** The complex **36b** (161.4 mg, 0.153 mmol) was dissolved in 16 mL of N_2-purged CH_3CN in a quartz tube, and the solution was irradiated with UV light (sunlamp, 275 W) for 16 h at room temperature. The resulting mixture was concentrated to ~5 mL and then added dropwise to 50 mL of ether. The ether-insoluble precipitate was collected and washed well with ether. The filtrate and washings were combined and concentrated in vacuo, and the yellow residue was purified by flash chromatography on silica gel (50% EtOAc–Hexs) to give **37b** (74 mg, 65%) as a pale yellow oil: R_f 0.21 (50% EtOAc–Hexs); IR ($CHCl_3$) 3436, 3030, 2955, 1741, 1711, 1506 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.34 (5 H, br s, CH_2Ph), 7.0 (8 H, m, aromatic Hs), 5.38 (1 H, d, J = 7.3 Hz, phenylglycine chiral center), 5.5 (1 H, br, CH_2NHCO_2), 5.13 (2 H, s, CH_2Ph), 5.03 (1 H, br, N*H*Boc), 4.59 (1 H, br m, phenylalanine chiral center), 4.42 (2 H, t, J = 6 Hz, $CO_2CH_2CH_2Br$), 3.93 (2 H, d, J = 5.5 Hz, $NHCOCH_2NH$), 3.74 (3 H, s, CO_2Me), 3.48 (2 H, t, J = 6 Hz, CH_2Br), 3.12 (1 H, dd, J = 14 and 5.5 Hz, ArC*H*H), 3.08 (1 H, dd, J = 14 and 6 Hz, ArCH*H*), 1.42 (9 H, s, $C(CH_3)_3$). The optical rotation was not measured because of minor impurities found in both ^1H and ^{13}C NMR spectra, which were not removed by usual purification methods. Also attempted MS analysis did not give the molecular ion peak.

***O*-D-3-[1-[*N*-(Benzyloxycarbonyl)amino]-2-oxo-2-methoxyethyl]phenyl]-D-*N*-[(1,1-dimethylethoxy)carbonyl]tyrosylglycine 2-Bromoethyl Ester (37c).** The Ru complex **36c** (400 mg, 0.38 mmol) was irradiated with a sunlamp (275 W) in 35 mL of CH_3CN for 24 h at room temperature. The reaction was monitored by NMR. The reaction mixture was concentrated to ~1 mL and the resulting residue was introduced into ~75 mL of ether. The ether-insoluble precipitate was filtered off. The filtrate and washings were combined, solvent was removed, and product was purified by flash chromatography on silica gel (EtOAc/Hexs = 8:2) to give **37c** (36.6 mg, 57%) as a white foam: R_f 0.42 (EtOAc/Hexs = 8:2); IR ($CHCl_3$) 3430, 3028, 2956, 1746, 1718, 1684, 1505, 1247 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.32 (5 H, s, CO_2CH_2Ph), 7.3~6.9 (8 H, m, Ar-*H*), 6.38 (1 H, m, N*H*Cbz), 5.83 (1 H, m, $CONHCH_2CO_2$), 5.32 (1 H, d, J = 7.7 Hz, $CHNHCbz$), 5.08 (2 H, dd, J = 12 and 14 Hz, $NHCO_2CH_2Ph$), 4.98 (1 H, br, N*H*Boc), 4.42 (2 H, t, J = 6 Hz, CH_2CH_2Br), 4.38 (1 H, m, $(Ar)CH_2CH(NHBoc)$), 4.02 (2 H, m, $CONHCH_2CO_2$), 3.71 (3 H, s, CO_2Me), 3.47 (2 H, t, J = 6 Hz, CH_2Br), 3.05 (2 H, d, J = 6.8 Hz, $(Ar)CH_2CH(NH\text{-}Boc)$), 1.40 (9 H, s, NH*Boc*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.88, 170.98, 169.13, 157.66, 155.33, 138.31, 135.96, 131.96, 130.66, 130.07, 128.41, 128.03, 127.58, 121.62, 119.11, 118.92, 118.14, 117.32, 80.05, 67.03, 64.42, 57.55, 55.44, 52.81, 40.99, 37.68, 28.16; $[\alpha]_D$ 4.6° (*c* = 0.8, EtOAc).

D-(−)-*N*-[(1,1-Dimethylethoxy)carbonyl]-4-[3-[1-[*N*-[[*N'*-(benzyloxycarbonyl)amino]acetyl]amino]-2-oxo-2-ethoxyethyl]phenoxy]phenylalanine Methyl Ester (37e). Complex **36e** (189 mg, 0.19 mmol) was treated as above to give **37e** (125.7 mg, 97%) as a pale yellow oil. From the ether insoluble residue, 89.3 mg (85%) of crude $(CH_3CN)_3CpRuPF_6$ was isolated. **36e**: R_f 0.55 (5% MeOH/1,2-dichloroethane, alumina); IR ($CHCl_3$) 3430, 3000, 1730, 1710, 1500 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.30 (5 H, br s, CH_2Ph), 7.06–6.85 (8 H, m, aromatic Hs), 5.48 (1 H, d, J = 7 Hz, phenylglycine chiral center), 5.40 (1 H, br, $COCH_2NH$), 5.09 (2 H, s, CH_2Ph), 5.00 (1 H, br d, N*H*Boc), 4.86 (1 H, br, tyrosine chiral center H), 4.15 (2 H, m, $CO_2CH_2CH_3$), 3.89 (2 H, d, J = 5.8 Hz, $COCH_2NH$), 3.69 (3 H, s, CO_2CH_3), 3.03 (2 H, m, $ArCH_2CH$), 1.38 (9 H, s, $OC(CH_3)_3$), 1.18 (3 H, t, J = 7.2 Hz); $[\alpha]_D$ −16° (*c* 0.47, CH_2Cl_2).

D-*N*-[(1,1-Dimethylethoxy)carbonyl]-4-D-[3-[1-[*N*-[[*N'*-(benzyloxycarbonyl)amino]acetyl]amino]-2-oxo-2-ethoxyethyl]phenoxy]phenylalanine 2-Bromoethyl Ester (37f). Complex **36f** (717.5 mg, 0.672 mmol) was treated as above to give **37f** (369.2 mg, 72.6%) as a clear oil: R_f 0.61 (80% EtOAc/Hexs); 0.13 (50% EtOAc/Hexs); IR ($CHCl_3$) 3435, 3032, 2984, 1736, 1711, 1505 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.30 (5 H, br s, CH_2Ph), 7.11–6.86 (8 H, m, aromatic Hs), 5.84 (1 H, d, J = 7.2 Hz, phenylglycine chiral center), 5.40 (1 H, br, N*H*), 5.09 (2 H, s, CH_2Ph), 5.00 (1 H, br, N*H*Boc), 4.60 (1 H, br m, phenylalanine chiral center), 4.35 (2 H, t, J = 6 Hz, $CO_2CH_2CH_2Br$), 4.15 (2 H, m, $CO_2CH_2CH_3$), 3.89 (2 H, d, J = $NHCOCH_2CO_2$), 3.44 (2 H, t, J = 6 Hz, CH_2Br), 3.10 (1 H, dd, J = 14 and 5.5 Hz, ArC*H*H), 2.97 (1 H, dd, J = 14 and 7 Hz, ARCH*H*), 1.39 (9 H s, $C(CH_3)_3$), 1.18 (2 H, t, J = 7 Hz, $CO_2CH_2CH_3$). The optical rotation was not taken because of minor impurities found in both ^1H and ^{13}C NMR spectra, where were not removed by usual purification methods. Also attempted FAB MS analysis did not give the molecular ion peak.

D-*N*-[(1,1-Dimethylethoxy)carbonyl]-*O*-[D-3-[1-[*N*-[[*N'*-(benzyloxycarbonyl)amino]acetyl]amino]-2-oxo-2-ethoxyethyl]phenyl]tyrosine (38). To a stirred solution of 97.8 mg (0.13 mmol) of the ester **37f** in 8 mL of THF and 7 mL of water were added 84.5 mg (1.29 mmol, 10 equiv) of zinc dust and 96.9 mg (0.65 mmol, 5 equiv) of NaI. The mixture was refluxed overnight, the white precipitate was filtered, and the filter cake was washed well with THF. The filtrate was concentrated in vacuo, and the residue was taken up into CH_2Cl_2 and then dried

over $MgSO_4$. The solution was filtered and evaporated, and the residue was purified by flash chromatography on silica gel (10% MeOH–$CHCl_3$) to give **38** (63.3 mg, 75.4%) as an oil: R_f 0.23 (10% MeOH–$CHCl_3$); IR ($CHCl_3$) 3425, 3343, 2912, 1737, 1727, 1710, 1691, 1502 cm^{-1}; ^1H NMR (200 MHz, CD_3CN) δ 7.36 (5 H, s, CH_2Ph), 7.3–6.9 (8 H, m, aromatic Hs), 6.02 (1 H, br, $NHCOCH_2NH$), 5.50 (1 H, br, $NHCOCH_2NH$), 5.44 (1 H, d, J = 7.2 Hz, phenylglycine chiral center), 5.09 (2 H, s, CH_2Ph), 5.09 (1 H, br, NHBoc, overlapping with CH_2Ph), 4.35 (1 H, br, phenylalanine chiral center), 4.16 (2 H, m, $CO_2CH_2CH_3$), 3.79 (2 H, d, J = 6 Hz, $NHCOCH_2NH$), 3.16 (1 H, dd, J = 14 and 4 Hz, ArCHH), 2.94 (1 H, dd, J = 14 and 6 Hz, ArCHH), 1.37 (9 H, s, $C(CH_3)_3$), 1.17 (3 H, t, J = 7 Hz, $CO_2CH_2CH_3$). The optical rotation was not taken because of minor impurities found in both ^1H and ^{13}C NMR spectra, which were not removed by usual purification methods. FAB MS analysis did not give a molecular ion peak.

D-*N*-[(1,1-Dimethylethoxy)carbonyl]-*O*-[D-3-[1-[*N*-(2-aminoacetyl)amino]-2-oxo-2-ethoxyethyl]phenyl]tyrosine (39). To a stirred solution of 116.8 mg (0.18 mmol) of **38** in 2 mL of absolute ethanol were added 170.1 μL (1.8 mmol, 10 equiv) of 1,3-cyclohexadiene and 100 mg of 10% Pd–C. The mixture was refluxed overnight. The removal of the catalyst and solvent gave 68.5 mg of yellow powder. Attempted purification of a 10-mg sample by ether trituration resulted in deterioration of the compound. An ^1H NMR spectrum of the crude sample showed clear disappearance of the Cbz peak. **39**: R_f 0.09 (10% MeOH–$CHCl_3$); ^1H NMR (DMSO-d_6) δ 8.63 (1 H, br, NH), 8.17 (1 H, br, NH), 7.4–6.7 (8 H, m, aromatic Hs), 5.46 (1 H, br s, phenylglycine chiral center), 4.95 (1 H, br s, phenylalanine chiral center), 4.1–3.8 (4 H, m, $NHCOCH_2NH_2$ and $CO_2CH_2CH_3$), 1.3 (9 H, s, $C(CH_3)_3$), 1.2 (3 H, overlapping with impurities, $CO_2CH_2CH_3$).

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Supplementary Material Available: Experimental details for the preparation of compounds **25, 26, 28,** and **30,** together with physical and spectroscopic data, details of attempted macrolactamization of **39,** and proton NMR spectra of selected compounds (32 pages). Ordering information is given on any current masthead page.

A Common Intermediate Providing Syntheses of Ψ-Tabersonine, Coronaridine, Iboxyphylline, Ibophyllidine, Vinamidine, and Vinblastine

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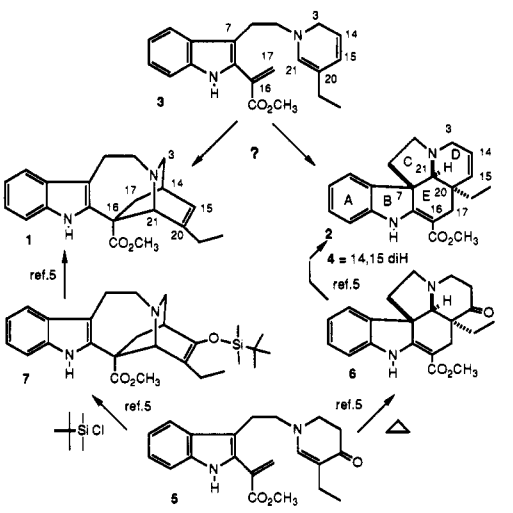
Generation of the key tetracyclic intermediates **14a,b** in six steps (42% overall) and subsequent short reduction, oxidation, and arylation sequences results in total syntheses of the title compounds **8, 9, 10, 11, 12,** and **13.**

The biogenetic postulate of derivation of catharanthine (**1**) and tabersonine (**2**) from the common precursor dehydrosecodine (**3**, Scheme I)[1,2] had provided the stimulus for our synthetic studies on intramolecular enamine–acrylate reactions, which led, with great efficacy, to pentacyclic aspidosperma alkaloids such as vincadifformine (**4**).[3] While the actual generation of catharanthine (**1**) and tabersonine (**2**) from dehydrosecodine (**3**) was never realized, in spite of widespread efforts,[4] we could nevertheless exploit the underlying concept of two alternative modes of (formal) intramolecular Diels–Alder reactions by use of a common oxosecodine intermediate (**5**), which provided, selectively, 15-oxovincadifformine (**6**) on heating or 15-(silyloxy)catharanthine **7** on O-silylation. Subsequent deoxygenation steps then gave the racemic alkaloids tabersonine (**2**) and catharanthine (**1**).[5] Intrigued by the possibility of other common precursors for a diversity of alkaloid structures, we developed a generalized synthetic strategy for members of the aspidosperma and iboga manifold and thus obtained as well Ψ-tabersonine (**8**, formerly Ψ-catharanthine), coronaridine (**9**), iboxyphylline (**10**), ibophyllidine (**11**), and the binary alkaloids vinamidine (**12**, formerly catharinine) and vinblastine (**13**) from a common tetracyclic intermediate "versatiline" (**14a,b**), generated as a mixture of C-20 epimers (Scheme II).

Scheme I



Our key intermediates **14a,b** were generated from methyl acrylate and the pyrrolidine enamine derivative of butyraldehyde (Scheme III). The initial monoalkylation product **15** was derivatized to an acetal (**16**) with ethylene glycol and that ester was then converted to the corre-

(1) Wenkert, E. *J. Am. Chem. Soc.* **1962**, *84*, 98.
(2) Scott, A. I. *Acc. Chem. Res.* **1970**, *3*, 151.
(3) (a) Kuehne, M. E.; Roland, D. M.; Hafter, R. *J. Org. Chem.* **1978**, *43*, 3705. (b) Kuehne, M. E.; Huebner, J. A.; Matsko, T. H. *J. Org. Chem.* **1979**, *44*, 2477.
(4) For a review, see footnote 5. For a summary of alternative syntheses of alkaloids described here, see footnote 16 and Overman, L. E.; Sworin, M. *Alkaloids: Chemical and Biological Perspectives*; New York, 1985; Vol. 3, p 275.
(5) Kuehne, M. E.; Bornmann, W. G.; Early, W. G.; Markó, I. *J. Org. Chem.* **1986**, *51*, 2913.

0022-3263/92/1957-1752$03.00/0