Oxazolophanes as Masked Cyclopeptide Alkaloid Equivalents: Cyclic Peptide Chemistry without Peptide Couplings

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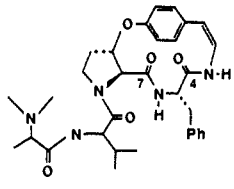
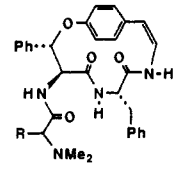
Abstract: Synthetic studies on the preparation of heteroatom-substituted, novel [3.3]oxazolophanes as precursors to the 14-membered ring system characteristic of the cyclopeptide alkaloids are reported. Simpler model systems are discussed, as is the successful formation of a fully functionalized, nonracemic cyclophane incorporating an oxazole nucleus. Unmasking of the requisite cyclic dipeptide is achieved in a single operation.

The synthetic challenges posed by the specific ion sequestering cyclopeptide alkaloids, a large group of natural products containing 13-, 14-, and 15-membered ring arrays,[2] have spawned numerous approaches aimed at addressing the critical issue of macrolactam construction. The concern is especially acute in the 14-membered ring system which contains two trans diamide linkages para fused across an aromatic ring, exemplified by mauritine A (**1**), crenatine (**2a**), and integeressine (**2b**). All published synthetic work to date



1, Mauritine A

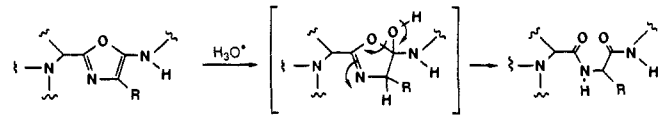


2a, Crenatine [R = $(CH_3)_2CHCH_2$]
b, Integeressine [R = $(CH_3)_2CH$]

in this field has concentrated on finding a suitable method for peptide bond formation across either the N-3, C-4 or N-6, C-7 positions (see **1**) from peptidic seco derivatives.[3-7] The innate strain associated with this system in particular has precluded realization of these targets in good yields.[8] Their reluctance toward efficient cyclization has been quite frustrating, since this step is usually reserved for the final stages of any synthetic scheme. As yet, however, there appears to be no general, efficient solution, despite extensive and otherwise impressive and clever contributions by the Joullie,[3] and Rapoport,[4] Schmidt,[5] and Pais[6] groups over the past several years. Success has been achieved, however, where 13-membered (e.g., dihydrozizyphine A and B)[5b] and 15-membered (e.g. mucronin B)[5d] ring systems are the targets.

In full appreciation of the problems faced by these workers, we embarked on a program designed to utilize heteroaromatic rings as dipeptide equivalents[9] based on the simple notion that, given the appropriate substitution patterns, the high energy content of selected systems could be used to advantage in an energetically downhill conversion to the dipeptide array. The oxazole nucleus was chosen initially, on the basis of the pioneering studies by Fleury et al.[10] who first demonstrated the facility with which secondary 5-aminooxazoles could be hydrolyzed to diamides due to the inherent ketene acetal-like moiety embedded in this unit. With this guiding feature and the security of previously successful openings to related dipeptides (Scheme I),[11] we began the process of constructing new heterocyclophanes which would house the key diamides/dipeptides in masked form. In this report, we present the details of our efforts to completely circumvent the problems encountered by others in macrocyclization.[3-7] Although success was ultimately achieved employing highly functionalized, nonracemic materials, there were some most unexpected surprises

Scheme I



encountered during the construction of model cyclophanes which still have not been fully rationalized (vide infra).

Studies on Model [3.3]Oxazolophanes. Construction of the C-8 desamino oxazolophane **13** commenced with two readily available educts, the isopropyl ester of *p*-hydroxyphenylacetic acid (**3a**) and

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(8) Where at least one proline is present in the acyclic precursor, yields on the order of 50% have been obtained;[3e,5f] in one case, with two prolines present, a yield of 67% has been reported.[5c]

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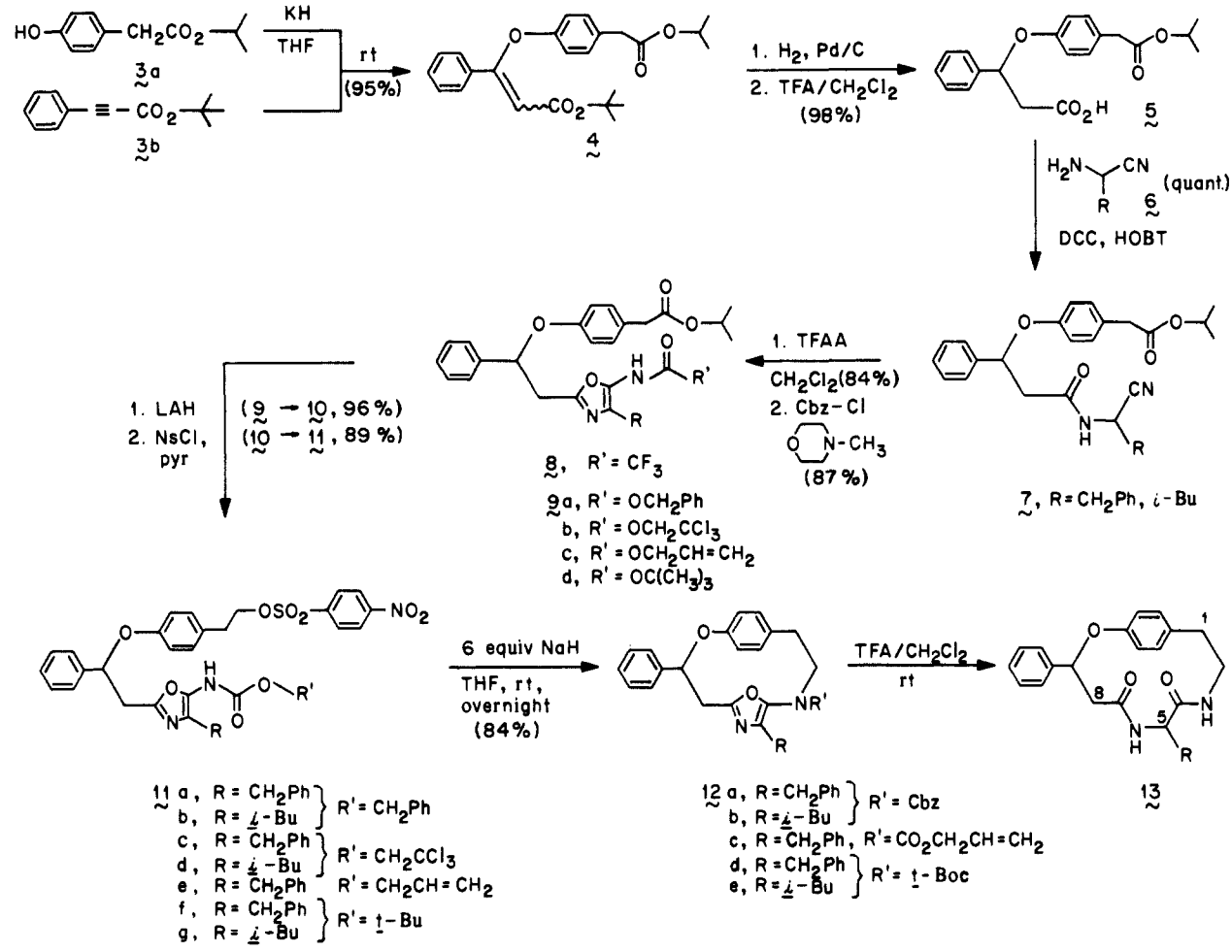
Scheme II



phenylpropiolic acid *tert*-butyl ester (**3b**) (Scheme II). Michael-like addition of the potassium salt of phenol **3a** to *tert*-butyl ester **3b** in THF containing catalytic quantities of 18-crown-6 ether afforded a mixture of enol ethers in 95% yield.[12] Crucial to the success of this step was the use of excess **3a** (2 equiv).[13] Hydrogenation of **4** proceeded without incident (98%), and subsequent removal of the *tert*-butyl group under standard conditions[14] led to acid **5** (100%, crude yield), which was entered directly into the DCC/HOBT coupling[15] with amine nitrile **6**.[16] Oxazole precursor **7** was thereby obtained in 93% overall yield for the four steps. Trifluoroacetic anhydride mediated ring closure[11] gave the protected 5-aminooxazole **8** (84%), which as observed previously is resistant to N-alkylation.[11] Exchange of the trifluoroacetyl moiety for the Cbz linkage[11] followed from treatment of **8** with CbzCl in CH_2Cl_2 containing *N*-methylmorpholine (1.5 equiv), the resulting imide suffering loss of the trifluoroacetyl group on workup. The newly formed Cbz derivative **9a** (76%, 87% based on recovered trifluoroacetamide) could be chemoselectively reduced at the isopropyl ester site by careful "titration" of **9a** at 0 °C with a clear solution of LAH in THF (96%). Conversion of the resulting primary alcohol (**10**) to the nosylate **11a** with recrystallized nosyl chloride in dry CH_2Cl_2 was straightforward (89%) as long as pyridine (2 equiv) was employed as base.[17] With the stage set for the macrocyclization invoking an N-alkylation rather than macrolactamization, **11a** was exposed to 1 equiv of NaH in THF (0.01 M) at 0 °C to room temperature. Unfortunately, a multitude of products was observed over time. Extensive efforts to effect ring closure, including variations in solvent, base, temperature, and concentration, were completely fruitless. Interestingly, among the array of undesired products formed there did not appear to be those resulting from elimination reactions, even in the presence of 2 equiv of e.g. NaH. On the basis of this observation, excess NaH (6 equiv) was slurried in THF at room temperature to which **11a** in THF was added via syringe pump (final concentration ca. 0.005 M). Stirring overnight followed by workup afforded what appeared to be the desired monomeric cyclophane **12** on the basis of spectroscopic (IR, NMR) and mass spectral data (EI, CI) obtained in 74% isolated yield. The identical series of steps applied to the leucine series (i.e., starting with **6**, R = *i*-Bu) led to seco nosylate **11b**, the cyclization of which likewise proceeded in 69% yield. The corresponding tosylates and brosylates did not cyclize at all, and the mesylates and triflates formed in unacceptably low yields.

Anticipating that the major hurdle had been overcome, unmasking of **11a** or **11b** to their respective diamides under conditions of catalytic hydrogenation (10% Pd/C, 3% HOAc/H_2O) developed previously[11] in the acyclic series (≥80% yields) was attempted. Unfortunately, none of the desired products (diastereomers) from either oxazolophane were formed according to TLC, NMR, and mass spectral analyses. Other hydrogenation catalysts ($Pd(OH)_2$, PtO_2), solvents (EtOH, EtOAc, PhH), and acids were equally ineffective, as were a number of other reagents (e.g., TMS-I, $AlCl_3$, LAH, and $LiAl(OMe)_3H$).[14] Extensive trials using HBr/HOAc[18] did indicate the removal of the Cbz group; however, the diastereomers isolated proved to be products of second-stage elimination across C-8, C-9, followed by HBr addition to the resulting olefin.

(12) For a related comparison reaction of this type, see refs 4a and 4c.
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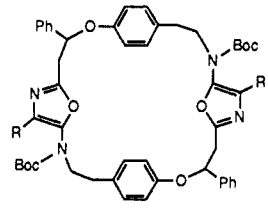
Reprocessing of trifluoroacetamide **8** with β,β,β-trichloroethoxycarbonyl chloride led to urethane **9b**, which was carried through the sequence to nosylate **11c**. Similar treatment of **11c** with base, as done successfully with Cbz derivative **11a**, afforded none of the anticipated cyclophane, presumably due to deactivation of the urethano anion by the electron-withdrawing trichloroethoxy unit. (Allyloxy)carbonyl derivative **9c** was subsequently prepared in the same manner, and this carbamate did cyclize to oxazolophane **12c** in ca. 65% yield. Numerous attempts to unravel **12c** using Pd(O)[19a] or cuprates[19b] led in all cases to rapid decomposition of the cyclophane which is attributed to the likely complexation between the basic heteroaromatic ring and the metal.

Success was supposedly in hand by virtue of the corresponding *t*-Boc analogue **11f**, which seemed in retrospect to be the ideal choice of amine derivative in that it introduced no stereoelectronic perturbation toward cyclization and should be removable under precisely the (acidic) conditions needed for unmasking of the intermediate aminooxazole. Insertion of the *t*-Boc group from urethane exchange with **8** proceeded efficiently (87%) to **9d**, as did the next two manipulations to arrive at nosylate **11f**. Cyclization as before (NaH, THF, room temperature) gave the macrocycle **12d** in 84% yield; the deprotection of which actually went uneventfully in 93% yield with the use of undistilled TFA in CH_2Cl_2 at room temperature to afford what was tentatively identified as diamide **13** (R = CH_2Ph). Thus, it seemed that in eight short steps, an extremely efficient (>20% overall) route to the target model system had been achieved.

Although the usual means of identification (including routine EI and CI MS) were in line with the assigned structures for both the cyclophanes and the derived diamides, both the FAB and LSIMS MS data claimed that *all* of our cyclized materials were predominantly, if not entirely, *dimeric*. This was shocking to say the least, since at no point in any of the ring closures were acyclic dimers observed by careful TLC or HPLC analyses. The implication then is that formation of a 26-membered dimeric species **14** is faster than intermolecular coupling to give linear dimers



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which were not observed. Moreover, the misleading information from the EI and CI mass spectral analyses must reflect the harsher nature of these techniques relative to the softer FAB mode of analysis, thereby severing the dimers symmetrically which then appear as monomeric masses.

Synthesis of a Nonracemic, Fully Functionalized Ring. Although these coincidental events leave us little choice but to accept the mass spectral data, we were fortunate to be simultaneously pursuing the synthesis of a fully functionalized, nonracemic cyclophane and dipeptide (i.e., **27** and **28**, respectively). Although ultimately, target **28** corresponds to a product possessing the unnatural configurations at C-8 and C-9 (compare **28** with **1** or **2**), it was chosen simply on the basis of the availability of optically pure starting material **15**.[20] Following the general scheme established in the model studies, we hoped to arrive at a dihydro ring isomer of e.g. crenatine (**2a**) or integeressine (**2b**). We were especially intent on showing that the skeleton could be assembled without the assistance of cyclic amino acids (e.g., proline), which have been routinely used by others to minimize degrees of freedom during the cyclization step.[3-6]

The sequence began with (*S,S*)-amino diol **15**,[20] which was parlayed into **17** in 79% overall yield by initial acylation to the Cbz acetonide **16** and then to **17** by N-alkylation and hydrolysis (Scheme III). The primary hydroxyl was silylated with TBDMS-Cl to **18**, and the remaining benzylic alcohol was subjected to Mitsunobu coupling[21] using phenol **3a**. Best results were reproducibly obtained by syringe-pump addition of diethyl azodicarboxylate (DEAD) to a THF solution of the alcohol, phenol, and triphenylphosphine. The product, **19**, is drawn to reflect the recently established[22] inversion process that occurs with urethane derivatives of vicinally disposed amino alcohols. Cleavage of the silyl ether left a primary alcohol which was conveniently oxidized to acid **20** by using Sharpless conditions.[23] Activation of the acid with isobutylchloroformate in the presence of *N*-methylmorpholine followed by coupling with amine nitrile **21** gave amide nitrile **22**, suitably poised for cyclodehydration to protected 5-aminooxazole **23** under the influence of trifluoroacetic acid anhydride.[10,11] Following oxazole construction, urethane exchange of the *t*-Boc for trifluoroacetyl group proceeded uneventfully, and the resulting carbamate **24** could be chemoselectively reduced at the ester to **25** by using clear solutions of LAH at 0 °C. Nosylation of **25** to **26** was effected as before under controlled conditions,[17] with a slight modification. That is, use of catalytic DMAP was found to significantly enhance this sulfonylation, which now occurred at 0 °C. Exposure of precyclization intermediate **26** to excess NaH (25 equiv) in THF (ca. 0.01 M) at room temperature for about 24 h led to a new major product in 71% isolated yield. That *monomeric* cyclophane **27** had been formed was evident principally from the FAB and LSIMS mass spectral data, which showed a strong signal at *m/z* 660 ($M^+ + 1$) and barely a trace of what may be dimeric materials requiring greatly enhanced (×100) sensitivity settings for visualization. The 500-MHz NMR spectrum of **27** is interesting in that peaks tend to be quite broad with very little resolution, indicating a lack of free rotation expected for this densely packed oxazolophane. Final unraveling with TFA afforded a more polar product (by TLC) whose analysis by EI, CI, FAB, and LSIMS mass spectrometry showed only *monomeric* dipeptide **28**.

The stereochemistry at C-5 of the single product formed upon hydration of the oxazole nucleus has been tentatively assigned as that shown in **28**. The chemical shift for H-5 occurs at δ 4.5 ppm, which is precisely that found for the C-5 proton in crenatine A.[24] Although **28** is a dihydro analogue, Joullie has shown that chemical shifts in the natural enamides are relatively unperturbed upon saturation across C-1, C-2.[2a] The *R* configuration at C-5, and therefore the enantiomeric form (i.e., 5*R*, 8*R*, 9*R*) of the natural series, is also expected to be favored on thermodynamic grounds, as (1) the bulky residue at C-5, if in the unnatural configuration, would experience a serious steric interaction with the aromatic ring overhead; (2) ψ, φ rotations to avoid synperiplanar interactions between the amide carbonyls, borne out by X-ray determinations,[4b,25] would generate 1,3-diaxial-like relationships with the C-5 group facing upward. No such interactions are present in the natural orientation. Attempts at NOE experiments by irradiation at N-3, as used successfully by Rapoport in model systems,[4b] were inconclusive.

The realization of cyclic dipeptide **28** establishes the viability of this nonpeptidal approach to the cyclopeptide alkaloids. An

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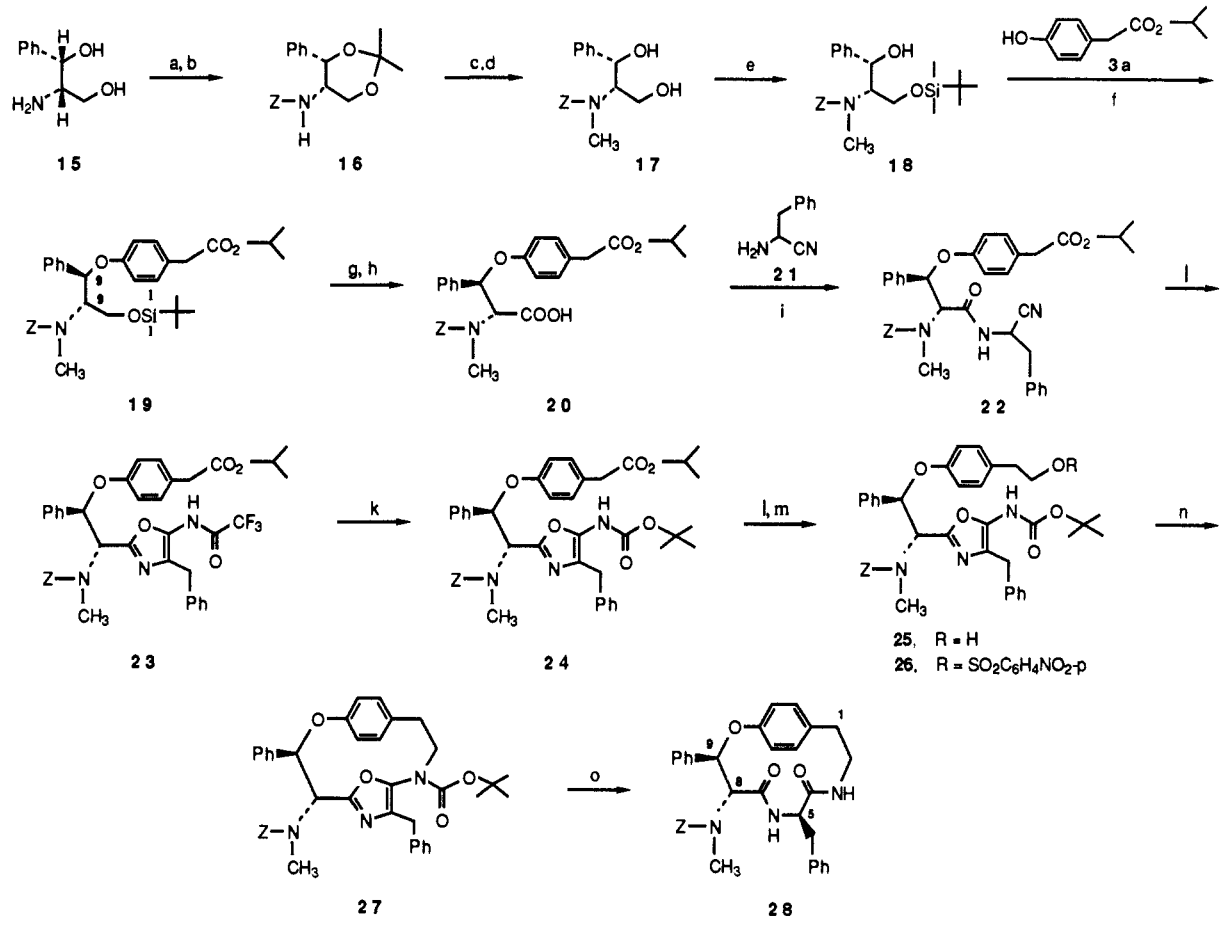
Scheme III[a]



[a] (a) Cbz-Cl, H_2O, $NaHCO_3$. (b) Dimethoxypropane, TsOH, room temperature. (c) NaH, DMF, MeI, 0 °C to room temperature. (d) TsOH, CH_3OH, 0 °C to room temperature, 4 h (79% overall). (e) TBDMS-Cl, CH_2Cl_2, DMAP, room temperature (90%). (f) DEAD, Ph_3P, THF, room temperature (90%). (g) TFA, CH_2Cl_2, room temperature (>95%). (h) Catalytic $RuCl_3$, $NaIO_4$, CH_3CN, CCl_4, H_2O, 0 °C, 2 h (55%). (i) *i*-BuO-COCl, *N*-methylmorpholine, then **21** (82%). (j) TFAA, catalytic TFA, 0 °C to room temperature (90%). (k) $(t\text{-BOC})_2$, *N*-methylmorpholine, THF, 0 °C to room temperature (88%). (l) LAH, THF, 0 °C; 30 min (88%). (m) NsCl(1.5 equiv), pyr(3 equiv), catalytic DMAP, CH_2Cl_2, 0 °C (90%). (n) NaH(25 equiv), THF, room temperature, ~1 day, 0.01 M (71%). (o) TFA (100 equiv), CH_2Cl_2, room temperature, 3–4 h (72%).

explanation behind the success (i.e., a monomeric product) in the "real" system, while model studies were of little predictive help, is not obvious. The only difference between the two (aside from the chirality issue) lies in the presence of the C-8 amino group, which is a good distance away from the site of cyclization. Although the mass spectral data on the simpler cyclophanes are at odds with the observed chemistry and our intuitive sense of this cyclization, it is at least comforting to know that no such ambiguities exist once full substitution is present on the ring. It is conceivable that the presence of the bulky tertiary urethane at C-8 imparts an element akin to a "*gem*-dimethyl effect"[26] which aids the cyclization.

Summary

Construction of model cyclic amides can be accomplished with the use of the N-alkylation of a protected 5-aminooxazole as the key ring forming step. Unmasking of the incorporated *t*-Boc group on nitrogen using TFA begins a cascade consisting of loss of isobutylene and CO_2, which then leads to oxazole hydration ultimately affording the diamide unit. Mass spectral data, however, suggests that the predominant, if not exclusive, cyclophanes and diamides derived therefrom are dimeric rather than monomeric. Effecting a modified sequence using nonracemic starting materials which lead to the fully functionalized skeleton ultimately affords a cyclophane and dipeptide which analyze for the desired, monomeric material. This route thus demonstrates that cyclic dipeptides characteristic of the naturally occurring cyclopeptide alkaloids can be prepared without resorting to traditional couplings of amino acids at any stage in the synthesis.

Experimental Section

General. Melting points were taken on a Fischer-Johns hot stage melting point apparatus. Both melting points and boiling points are uncorrected.

Proton nuclear magnetic resonance (^1H NMR) spectra were obtained on a General Electric GN-500 (500 MHz), Nicolet NT 300 (300 MHz), or Varian CFT 20/FT 80 (80 MHz) spectrometer in $CDCl_3$, CD_3OD, CD_3CN, or d_6-acetone containing ca. 0.05% tetramethylsilane (TMS) as internal reference. The spectral data are reported as follows: chemical shift in parts per million (ppm) downfield from TMS, relative number of protons by integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, m = multiplet, dd = doublet of doublets, dt = doublet or triplets), and coupling constants in hertz (Hz).

Infrared (IR) spectra were recorded by using a Perkin-Elmer 283 infrared spectrometer. Liquid samples were obtained as thin films on sodium chloride plates and solid samples were prepared as 1% in KBr pressed disks. Absorbing frequencies were reported in wavenumbers (cm^{-1}) and calibrated with use of the 1601.4 cm^{-1} absorbance of polystyrene.

Low- and high-resolution mass spectra or exact mass measurements were recorded on a VG 70-250HF or a ZAB 2-F mass spectrometer. Ionization was initiated by either electron impact (EI) with 70 eV of energy, positive chemical ionization (PCI) utilizing methane (CH_4) as carrier gas, ionized with 100–150 eV of energy, negative chemical ionization (NCI) utilizing methane, ionized with 100–150 eV of energy, fast atom bombardment (FAB) or LSIMS utilizing nitrobenzyl alcohol as the matrix. Data are reported as the mass to charge ratio (m/e) of the observed ion, where M^+ refers to the molecular ion followed by the intensity of the ion relative to the largest (base) peak assigned as 100%.

(26) See: Jung, M. E.; Gervay, J. *Tetrahedron Lett.* **1988**, *29*, 2429 and references therein.

The observed and calculated values for the ion of the given formula are reported.

High-performance liquid chromatography (HPLC) was carried out on a Perkin-Elmer Series 4 liquid chromatograph.

Thin-layer chromatography (TLC) determinations were accomplished on silica precoated glass plates (E. Merck silica gel 60, 230–400 mesh). TLC data is reported as R_f values (eluting solvent) and the TLC plates were developed in an iodine jar, or with phosphomolybdic acid (PMA), *p*-anisaldehyde (PAA), or ninhydrin solutions. Flash colum chromatography was performed with Merck silica gel 60 (230–400 mesh).

Reagent grade solvents for chromatography, including methylene chloride, ethyl acetate, ethanol, chloroform, 2-propanol, methanol, and acetone (all from Mallinckrodt), were used without further purification. Ether and petroleum ether (PE, bp 38–57 °C, Mallinckrodt or Fisher) were distilled prior to use. All solvent mixtures indicated were prepared by volume.

Solvents for chemical reactions were generally distilled prior to use: methylene chloride, from calcium hydride; benzene, toluene, and tetrahydrofuran (THF), from benzophenone ketyl; dimethylformamide (DMF), from P_2O_5; and triethylamine, from KOH.

Reagents were used as received except where stated otherwise. Allyl chloroformate, benzylamine, 4-(benzyloxy)phenol, benzyl chloroformate, *n*-butyllithium, diethyl azodicarboxylate, 4-(*N*,*N*-dimethylamino)-pyridine, lithium aluminum hydride (1 M in THF), *N*-methylmorpholine, 4-nitrobenzenesulfonyl chloride, 10% palladium on carbon, 20% palladium hydroxide on carbon, phenylacetaldehyde, phenoxypropiolic acid, potassium hydride, and β,β,β-trichloroethyl chloroformate were obtained from the Aldrich Chemical Co. Sodium hydride (50% in oil) was acquired from Alfa Products. 1,3-Dicyclohexylcarbodiimide and hydroxybenzotriazole hydrate were purchased from Fluka Chemical Corp. 4-Hydroxyphenylacetic acid, trifluoroacetic acid, and trifluoroacetic anhydride were acquired from Lancaster Synthesis, Ltd. Isobutylene was purchased from Matheson Gas Products. *tert*-Butyldimethylsilyl chloride was acquired from Petrarch Systems, Inc. 3-Hydroxyphenylacetic acid was obtained from the Sigma Chemical Co.

All nonaqueous reactions were carried out under argon, unless stated otherwise.

Isopropyl 4-Hydroxyphenylacetate (3a). A solution of 4-hydroxyphenylacetic acid (10.2 g, 67 mmol), sulfuric acid (2 mL, concentrated), and 2-propanol (100 mL) was refluxed overnight. The mixture was cooled to room temperature, poured into a separatory funnel containing water and EtOAc (150 mL each), extracted with EtOAc, washed with saturated sodium bicarbonate and brine (3 × 100 mL each), dried over sodium sulfate, and concentrated to a yellow oil. Chromatography on silica gel (30% EtOAc/PE) provided 12.6 g (97%) of a clear oil: R_f (30% EtOAc/PE) 0.42; IR (neat) 3321, 3203, 2984, 1726, 1717, 1696, 1599, 1490, 1457, 1360, 1278, 1155, 1104; ^{1}H NMR δ 7.11 (2 H, d, J = 8.4 Hz), 6.74 (2 H, d, J = 8.4 Hz), 5.00 (1 H, h, J = 6.3 Hz), 3.50 (2 H, s), 1.23 (6 H, d, J = 6.3 Hz); mass spectrum (EI), m/e (relative intensity) 194 (M^+, 15), 153 (3), 107 (100), 77 (8), 43 (57).

***tert*-Butyl Phenylpropiolate (3b).** Isobutylene (ca. 100 mL) was condensed into a cooled (−78 °C) pressure flask. Phenylpropiolic acid (10 g, 68.4 mmol) in 15 mL of Et_2O, followed by 25 mL of Et_2O was added. Sulfuric acid (1 mL, concentrated) was added dropwise, the flask was sealed, allowed to come to room temperature, and the mixture was stirred for 24 h. The pressure bottle was then cooled to −78 °C, EtOAc (40 mL) was added, and the mixture was allowed to come to room temperature. After evolution of the residual gas, the mixture was poured into a separatory funnel, washed with saturated sodium bicarbonate, water, and brine (3 × 100 mL each), dried over sodium sulfate, concentrated to a light oil, and passed through a short column of silica gel, eluting with 5% Et_2O/PE extra to yield 12.94 g (94%) of a clear oil: R_f (5% Et_2O/PE) 0.28; IR (neat) 2982, 1706, 1491, 1445, 1370, 1299, 1268, 1207, 1161, 844; ^{1}H NMR δ 7.57 (2 H, m), 7.39 (3 H, m), 1.55 (9 H, s); mass spectrum (EI), m/e (relative intensity) 202 (M^+, 9), 157 (8), 146 (76), 129 (100), 118 (18), 102 (29), 75 (13).

(*Z*,*E*)-*tert*-Butyl 3-Phenyl-3-[4-[(isopropoxycarbonyl)methyl]phenoxy]-2-propenoate (4). Phenol **3a** (16.11 g, 83 mmol) in 50 mL THF was added via cannula to a 0 °C suspension of oil free KH (1.52 g, 38 mmol) in 60 mL THF. After the initial H_2 evolution, the reaction was warmed to room temperature for 20 min. The acetylene **3b** (7.89 g, 39 mmol) and 18-crown-6 (0.62 g, 2 mmol) in 75 mL of THF were added via cannula. The mixture was allowed to warm to room temperature overnight. The reaction was quenched by cannula addition into 200 mL of 0 °C saturated NH_4Cl. The solution was extracted with EtOAc, washed with water and brine, dried over sodium sulfate, and concentrated in vacuo. Chromatography on silica gel (15% EtOAc/PE) afforded 14.69 g (95%) of a clear oil as an ca. 2:1 mixture of the E/Z isomers: R_f (10% EtOAc/PE) 0.19; IR (neat) 2990, 2940, 1880, 1730, 1695; ^{1}H NMR δ 7.25 (9 H. m), 5.15 and 6.06 (1 H, s, vinyl), 5.00 (1 H, h, J = 6.3 Hz), 3.46 and 3.60 (2 H, s, $PhCH_2$), 1.28 and 1.36 (9 H, s), 1.18 and 1.26 (6 H, d, J = 6.3 Hz); mass spectrum (PCI), m/e (relative intensity) 397 (M^+ + 1, 41), 326 (15), 311 (100), 193 (49).

***tert*-Butyl 3-Phenyl-3-[4-[(isopropoxycarbonyl)methyl]phenoxy]-propanoate.** Diester **4** (14.7 g, 37.1 mmol) in 75 mL of EtOAc was added to 0.9 g of 10% Pd/C suspended in 50 mL of EtOAc under a balloon of H_2. The mixture was stirred for 3 h, filtered through Celite, concentrated, and passed through a short column of silica gel (15% EtOAc/PE) to give 14.43 g (98%) of a water white syrup: R_f (20% EtOAc/PE) 0.37; IR (neat) 2790, 2940, 1730, 1615; ^{1}H NMR δ 7.1 (9 H, m), 5.59 (1 H, m), 5.00 (1 H, m), 3.41 (2 H, s), 2.75 (2 H, m), 1.40 (9 H, s), 1.19 (6 H, d, J = 5.8 Hz); mass spectrum (PCI), m/e (relative intensity) 398 (M^+ + 1,18), 343 (87), 195 (100), 149 (71), 107 (99).

3-Phenyl-3-[4-[(isopropoxycarbonyl)methyl]phenoxy]propanoic Acid (5). A 0 °C solution of the dihydro derivative of diester **4** (14.8 g, 37.1 mmol) in 50 mL of CH_2Cl_2 was treated with trifluoroacetic acid (14.3 mL, 186 mmol). The mixture was stirred for 3 h, slowly transferred via cannula into 100 mL of rapidly stirred 0 °C saturated $NaHCO_3$. After 20 min the pH was adjusted to 3 with 1 M HCl, extracted with EtOAc, washed with water and brine, dried over sodium sulfate, and concentrated to yield 12.7 g (99.8%) of a clear oil of sufficient purity to be used as is: R_f (20% EtOAc/PE) 0.19; ^{1}H NMR δ 7.07 (10 H, m), 5.60 (1 H, m), 4.95 (1 H, m), 3.44 (2 H, s), 2.95 (2 H, m), 1.20 (6 H, d, J = 6.3 Hz); mass spectrum (PCI), m/e (relative intensity) 342 (M^+ + 1, 21), 325 (53), 283 (64), 237 (55), 107 (100).

***N*-(1-Cyano-2-phenylethyl)-3-phenyl-3-[4-[(isopropoxycarbonyl)-methyl]phenoxy]propanamide (7).** The acid **5** (6.3 g, 18.5 mmol) in 60 mL of $CHCl_3$ was cooled to 0 °C and treated with 1,3-dicyclohexylcarbodiimide (5 g, 24 mmol) and 1-hydroxybenzotriazole hydrate (2.8 g, 20.7 mmol). After 15 min, 1-cyano-3-phenethylamine (**6**), R = CH_2Ph (6.0 g, 40.7 mmol), in 40 mL of $CHCl_3$ was added, and the mixture was allowed to warm to room temperature overnight. The solution was filtered, and the filtrate was washed with 1 M HCl, saturated $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, and concentrated. Chromatography on silica gel (30% EtOAc/PE) afforded 8.9 g (100%) of a light yellow oil: R_f (30% EtOAc/PE) 0.26; IR (neat) 3316, 3034, 2982, 2935, 2208, 1728, 1667, 1510, 1455, 1374, 1233, 1175, 1106, 1023; ^{1}H NMR δ 7.45 (13 H, m), 6.8 (2 H, m), 6.3 (1 H, dd, J = 18.9, 8.4 Hz), 5.52 (1 H, m), 5.19 (1 H, m), 4.91 (1 H, m), 3.45 (2 H, d, J = 3.9 Hz), 2.84 (2 H, m), 1.19 (6 H, d, J = 6.3 Hz); mass spectrum (EI), m/e (relative intensity) 470 (M^+, 2), 443 (4), 383 (2), 277 (78), 250 (18), 235 (48), 194 (31), 173 (15), 146 (29), 131 (53), 107 (100); mol wt calcd for $C_{29}H_{30}N_2O_4$ 470.2205, found 470.2190.

2-[2-Phenyl-2-[4-[(isopropoxycarbonyl)methyl]phenoxy]ethyl]-4-benzyl-5-(trifluoroacetamido)oxazole (8, R = CH_2Ph). The amide nitrile **7**, R = CH_2Ph (8.7 g, 18.5 mmol) was dissolved in 90 mL of CH_2Cl_2, cooled to 0 °C, and treated with trifluoroacetic anhydride (7.8 mL, 55.5 mmol) and trifluoroacetic acid (3.0 mL, 37 mmol). The mixture was stirred for 5 h, and then slowly transferred via cannula into 100 mL of rapidly stirred, 0 °C, saturated $NaHCO_3$ solution. After 30 min the mixture was extracted with EtOAc, washed with water and brine, dried over Na_2SO_4, and concentrated. Chromatography on silica gel (20% EtOAc/PE) gave 8.8 g (84%) of a thick clear oil; R_f (30% EtOAc/PE) 0.38; IR (neat) 3236, 3064, 3033, 2982, 2936, 1753, 1733, 1665, 1612, 1570, 1511, 1454, 1427, 1233, 1167, 1106, 1026; ^{1}H NMR δ 8.34 (1 H, s), 7.31 (10 H, m), 6.73 (2 H, d, J = 8.4 Hz), 5.65 (1 H, dd, J = 9.6, 3.6 Hz), 4.99 (1 H, h, J = 6.3 Hz), 3.43 (1 H, s), 3.33 (1 H, dd, J = 15, 9 Hz), 3.15 (1 H, dd, J = 15, 3.9 Hz), 1.24 (6 H, d, J = 6.3 Hz); mass spectrum (EI), m/e (relative intensity) 566 (M^+, 6), 479 (2), 372 (44), 283 (100), 232 (32), 107 (33), 91 (40); mol wt calcd for $C_{31}H_{29}N_2O_5F_3$ 566.2027, found 566.2007.

2-[2-Phenyl-2-[4-[(isopropoxycarbonyl)methyl]phenoxy]ethyl]-4-benzyl-5-[(carbobenzyloxy)amino]oxazole (9a, R = CH_2Ph). Benzyl chloroformate (1.45 mL, 10.2 mmol) and *N*-methylmorpholine (1.12 mL, 10.2 mmol) were added to a 0 °C solution of oxazole **8**, R = CH_2Ph (1.92 g, 3.4 mmol) in 15 mL of CH_2Cl_2. After stirring for 4 h, the mixture was quenched with 5 mL of saturated NH_4Cl, extracted with EtOAc, washed with water and brine, dried over Na_2SO_4, and concentrated. Chromatography on silica gel (20% EtOAc/PE) gave 1.76 g (86%) of a clear oil: R_f (20% EtOAc/PE) 0.34; IR (neat) 3281, 3064, 3033, 2980, 2933, 1733, 1670, 1611, 1569, 1510, 1454, 1302, 1233, 1176, 1105, 1045; ^{1}H NMR δ 7.41 (15 H, m), 7.00 (2 H, d, 8.4 Hz), 6.75 (2 H, d, J = 8.4 Hz), 6.25 (1 H, br s), 5.59 (1 H, dd, J = 8.7, 4.8 Hz), 5.15 (2 H, s), 4.98 (1 H, h, J = 6.3 Hz), 3.76 (2 H, s), 3.44 (2 H, s), 3.38 (1 H, dd, J = 15, 9 Hz), 3.16 (1 H, dd, J = 15, 4.8 Hz), 1.21 (6 H, d, J = 6.3 Hz); mass spectrum (PCI), m/e (relative intensity) 605 (M^+ + 1, 0.2), 497 (3), 303 (13), 283 (8), 277 (4), 250 (4), 195 (14), 153 (34), 135 (10), 121 (10), 107 (63), 91 (100), 79 (56); mol wt calcd for $C_{37}H_{37}N_2O_6$ (M^+ + 1) 605.2652, found 605.2686.

2-[2-Phenyl-2-[4-[(isopropoxycarbonyl)methyl]phenoxy]ethyl]-4-benzyl-5-[[(β,β,β-trichloroethoxy)carbonyl]amino]oxazole (9b, R = CH_2Ph). 65%, clear oil: R_f (50% EtOAc/PE) 0.33; IR (neat) 3295, 3064, 3029, 3011, 2950, 1757, 1672, 1603, 1582, 1495, 1454, 1383, 1307, 1250, 1219, 1155, 1107, 1048, 820, 759; ^1H NMR δ 7.23 (10 H, m), 6.70 (4 H, m), 5.59 (1 H, dd, J = 15, 4.8 Hz), 4.75 (2 H, s), 3.79 (2 H, s), 3.39 (1 H, dd, J = 15, 9 Hz), 3.18 (1 H, dd, J = 15, 4.8 Hz), 2.74 (2 H, t, J = 6.3 Hz); mass spectrum (EI), m/e (relative intensity) 440 (M^+ − 148, loss of CCl_3CH_2OH, 100), 302 (15), 276 (14), 231 (26), 227 (38), 158 (7), 131 (70), 121 (76); mol wt calcd for $C_{27}H_{24}N_2O_4$ (M^+ − 148, loss of CCl_3CH_2OH) 440.1736, found 440.1753.

2-[2-Phenyl-2-[4-[(isopropoxycarbonyl)methyl]phenoxy]ethyl]-4-benzyl-5-[(carboallyloxy)amino]oxazole (9c, R = CH_2Ph). 98%, white foam: R_f (20% EtOAc/PE) 0.24; IR (neat) 3307, 3278, 3257, 3226, 3089, 3057, 3034, 2982, 2931, 1736, 1672, 1611, 1567, 1509, 1454, 1425, 1379, 1313, 1236, 1176, 1050, 826, 733, 703; ^1H NMR δ 7.27 (10 H, m), 6.96 (2 H, d, J = 8.4 Hz), 6.73 (2 H, d, J = 8.4 Hz), 6.24 (2 H, s), 5.88 (1 H, br s), 5.55 (1 H, dd, J = 8.7, 5.1 Hz), 5.24 (2 H, m), 4.57 (2 H, d, J = 4.2 Hz), 3.75 (2 H, s), 3.36 (1 H, dd, J = 15, 9 Hz), 3.13 (1 H, dd, J = 14.7, 4.8 Hz), 2.71 (2 H, t, J = 6.3 Hz); mass spectrum (EI), m/e (relative intensity) 498 (M^+, 11), 361 (8), 303 (6), 275 (6), 232 (10), 227 (100), 131 (22), 107 (25), 104 (24), 91 (28), 77 (12); mol wt calcd for $C_{30}H_{30}N_2O_5$ 498.2154, found 498.2177.

2-[2-Phenyl-2-[4-(β-hydroxyethyl)phenoxy]ethyl]-4-benzyl-5-[(carbobenzyloxy)amino]oxazole (10, R = CH_2Ph, R′ = Cbz). Oxazole **9a**, R = CH_2Ph (1.3 g, 2.1 mmol) was azeotropically dried with toluene (3 × 1 mL), dissolved in 10 mL of THF and cooled to 0 °C. LAH (3.2 mL, 3.2 mmol of a 1 M solution in THF) was added dropwise. After 15 min, the mixture was transferred via cannula onto 50 mL of rapidly stirred 0 °C saturated NH_4Cl, and then enough 1 M HCl was added to dissolve salts. The resulting solution was extracted with EtOAc, washed with 1 M HCl, H_2O, and brine, dried over Na_2SO_4, and concentrated. Chromatography on silica gel (50% EtOAc/PE) provided 1.1 g (96%) of a clear viscous oil: R_f (50% EtOAc/PE) 0.32; IR (neat) 3335, 3230, 3064, 3030, 2948, 1733, 1671, 1610, 1567, 1509, 1454, 1305, 1236, 1177, 1046, 825; ^1H NMR δ 7.24 (15 H, m), 6.95 (2 H, d, J = 8.7 Hz), 6.72 (2 H, d, J = 8.4 Hz), 6.30 (1 H, s), 5.53 (1 H, dd, J = 8.7, 4.8 Hz), 5.11 (2 H, s), 3.73 (4 H, app t), 3.35 (1 H, dd, J = 15, 9 Hz), 3.12 (1 H, dd, J = 14.7, 4.8 Hz), 2.69 (2 H, t, J = 6.3 Hz); mass spectrum (EI), m/e (relative intensity) 548 (M^+ + 1), 440 (20), 302 (8), 276 (11), 227 (33), 131 (30), 121 (41), 107 (100), 91 (97), 79 (79); mol wt calcd for $C_{34}H_{33}N_2O_5$ (M^+ + 1) 549.2389, found 549.2441.

2-[2-Phenyl-2-[4-[2-[[(p-nitrophenyl)sulfonyl]oxy]ethyl]phenoxy]ethyl]-4-benzyl-5-[(carbobenzyloxy)amino]oxazole (11a). *p*-Nitrobenzenesulfonyl chloride (0.8 g, 3.6 mmol) was added in roughly four equal portions over 1 h to a 0 °C solution of pyridine (0.36 mL, 4.5 mmol) and oxazole **10**, R = CH_2Ph, R′ = Cbz (0.82 g, 1.5 mmol), in 3 mL of CH_2Cl_2. After 4 h the reaction was quenched by the addition of 1 M HCl (1 mL). The resulting mixture was extracted with EtOAc, washed with 1 M HCl, 10% $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, and concentrated. Chromatography on silica gel (40% EtOAc/PE) gave 0.98 g (89%) of a slightly yellow oil: R_f (40% EtOAc/PE) 0.36; IR (neat) 3354, 3106, 3064, 3032, 2959, 1739, 1670, 1609, 1566, 1532, 1510, 1454, 1350, 1312, 1236, 1183, 1082, 1029, 909; ^1H NMR δ 8.18 (2 H, d, J = 9 Hz), 7.80 (2 H, d, J = 8.7 Hz), 7.25 (15 H, m), 6.83 (2 H, d, J = 8.4 Hz), 6.66 (2 H, d, J = 8.4 Hz), 6.09 (1 H, bs), 5.54 (1 H, dd, J = 8.7, 5.1 Hz), 4.20 (2 H, m), 5.13 (2 H, s), 3.76 (1 H, s), 3.38 (1 H, dd, J = 15.3, 8.7 Hz), 3.15 (1 H, dd, J = 15.3, 5.1 Hz), 2.83 (2 H, t, J = 6.6 Hz).

2-[2-Phenyl-2-[4-[2-[[(p-nitrophenyl)sulfonyl]oxy]ethyl]phenoxy]ethyl]-4-benzyl-5-[(carboallyloxy)amino]oxazole (11e). 70%, white foam: R_f (40% EtOAc/PE) 0.37; IR (neat) 3103, 3063, 3031, 2986, 2960, 2930, 1739, 1671, 1609, 1569, 1532, 1510, 1454, 1426, 1367, 1352, 1314, 1236, 1183, 1095, 1053, 988, 955, 908, 855, 827, 766, 701; ^1H NMR δ 8.19 (2 H, d, J = 8.7 Hz), 7.80 (2 H, d, J = 8.7 Hz), 7.26 (10 H, m), 6.84 (2 H, d, J = 6.9 Hz), 6.77 (2 H, d, J = 6.9 Hz), 6.1 (2 H, s), 5.86 (1 H, br s), 5.55 (1 H, dd, J = 8.7, 5.1 Hz), 5.27 (2 H, m), 4.59 (2 H, m), 4.2 (2 H, oct, J = 3.9 Hz), 3.77 (2 H, s), 3.39 (1 H, dd, J = 15.3, 8.7 Hz), 3.15 (1 H, dd, J = 15, 5.1 Hz), 2.84 (2 H, t, J = 6.6 Hz); mass spectrum (FAB), m/e (relative intensity) 684 (M^+, 20), 412 (18), 361 (32), 232 (7), 154 (100), 136 (82), 120 (19), 107 (33), 91 (70), 77 (45).

Oxazolophane 12a. Oxazole **11a** (1.28 g, 1.74 mmol) was azeotropically dried with toluene (3 × 3 mL), purged with argon, dissolved in 25 mL of THF, taken up in a 30-mL syringe, and added via syringe pump (Sage Instruments Model 302) at a rate of 3.3 mL/h to a stirred suspension of oil free NaH (0.26 g, 11 mmol) in 320 mL of THF at room temperature. After a total of 28 h, the reaction was quenched with 5 mL of saturated NH_4Cl, and then 1 M HCl was added to dissolve the salts. The solvent was removed in vacuo. The residue was taken up in CH_2Cl_2 and washed with 1 M HCl, H_2O, and brine, dried over Na_2SO_4, and concentrated to yield 0.84 g (91% crude) of an amber oil. The oil was dissolved in a minimum of CH_2Cl_2 and diluted with 5 mL of EtOAc with stirring. The stir bar was removed, and the solution was allowed to stand at room temperature. After ca. 1 h a white precipitate formed and was collected via filtration to yield 0.65 g (71%) of a fine white powder: mp 210–211 °C; R_f (5% EtOAc/CH_2Cl_2) 0.42; IR (neat) 3411, 3063, 3033, 2951, 2920, 1723, 1654, 1601, 1589, 1569, 1495, 1454, 1394, 1350, 1322, 1213, 1192, 1157, 1117, 1087, 1046, 1028, 919; ^1H NMR δ 7.3 (15 H, m), 6.52 (4 H, dd, J = 18.9, 9 Hz), 5.47 (1 H, dd, J = 25, 9.9 Hz), 5.10 (2 H, s), 3.71 (2 H, br s), 3.25 (4 H, m), 2.30 (2 H, m); mass spectrum (EI), m/e (relative intensity) 530 (M^+, 8), 396 (6), 131 (84), 121 (12), 116 (11), 103 (20), 91 (100); mol wt calcd for $C_{34}H_{30}N_2O_4$ 530.2205, found 530.2199; mass spectrum (FAB), m/e (relative intensity) 1061 (2 M^+, 22), 746 (11), 307 (25), 154 (100), 136 (75).

Oxazolophane 12c: 94% crude, 65% precipitated from EtOAc; white powder; mp 228–230 °C; R_f (20% acetone/benzene) 0.63; IR (KBr) 3064, 3030, 2941, 1723, 1664, 1610, 1579, 1507, 1453, 1383, 1332, 1277, 1235, 1195, 1176, 1124, 1060, 1047, 991, 931, 826, 763, 701; ^1H NMR δ 7.34 (10 H, m), 6.53 (4 H, m), 5.82 (1 H, br s), 5.49 (1 H, dd, J = 25.8, 9 Hz), 5.21 (2 H, m), 4.56 (2 H, d, J = 3.9 Hz), 3.77 (2 H, s), 3.23 (4 H, m), 2.32 (2 H, m); mass spectrum (EI), m/e (relative intensity) 960 (52, 2 M^+), 876 (11), 569 (22), 480 (35), 396 (6), 360 (6), 329 (6), 300 (7), 289 (7), 260 (8), 232 (18), 167 (6), 143 (10), 131 (100), 121 (46), 115 (22), 107 (27), 103 (32), 91 (89).

***N*-(1-Cyano-3-methylbutyl)-3-phenyl-3-[4-[(isopropoxycarbonyl)methyl]phenoxy]propanamide (7, R = *i*-Bu).** The carboxylic acid **5** (1.79 g, 5.79 mmol) was dissolved in 14 mL of $CHCl_3$ and cooled to 0 °C. DCC (1.3 equiv, 1.55 g, 7.53 mmol) and HOBT (1.1 equiv, 0.861 g, 6.37 mmol) were added, and the heterogeneous reaction mixture was stirred for about 15 min. The amine was free-based by extraction from saturated Na_2CO_3 with $CHCl_3$, dried over Na_2SO_4, evaporated, and dried well. The resulting oil was resuspended in $CHCl_3$ and added via cannula to the reaction mixture which was stirred at room temperature for 12 h. The dicyclohexylcarbourea was removed by filtration through paper and washed with $CHCl_3$. The filtrate was evaporated and resuspended in 50 mL of EtOAc and washed with H_2O and brine (1 × 25 mL each). The organic layer was dried over Na_2SO_4 and evaporated to a yellow oil. Flash chromatography (60/40 EtOAc/PE) gave 2.22 g (88%) of a light yellow oil: R_f (50/50 EtOAc/PE) 0.29; IR ($CHCl_3$) 3320, 3045, 3040, 2980, 1735, 1660, 1515, 1240, 1110; ^1H NMR (500 MHz) 7.34 (5 H, m), 7.09 (2 H, m), 6.79 (2 H, dd, J = 17.0, 8.5 Hz), 6.34 (1 H, br t, J = 8.0 Hz), 5.55 (1 H, m), 4.93 (2 H, m), 3.45 (2 H, d, J = 2.5 Hz), 2.83 (1 H, m), 2.69 (1 H, m), 1.62 (3 H, 7), 1.20 (6 H, d, J = 6.5 Hz), 0.90 (6 H, m); mass spectrum (CI), m/e (relative intensity) 437 (M^+ + 1, 22.0), 395 (5.3), 368 (8.8), 283 (7.1), 243 (100.0), 216 (26.3), 201 (100.0), 131 (18.4), 105 (53.0); (HRCI) mol wt calcd for $C_{26}H_{33}N_2O_4$ (M^+ + 1) 437.2440, found 437.2446.

2-[2-Phenyl-2-[4-[(isopropoxycarbonyl)methyl]phenoxy]ethyl]-4-isobutyl-5-(trifluoroacetamido)oxazole (8, R = *i*-Bu). The amide nitrile **7**, R = *i*-Bu (5.77 g, 13.21 mmol) was dissolved in 26 mL of $CHCl_3$. The TFA (3 equiv, 39.64 mmol, 3.1 mL) and TFAA (5 equiv, 66.07 mmol, 9.4 mL) were added, and the reaction was stirred at room temperature for 4 h. The reaction was poured into rapidly stirring saturated $NaHCO_3$/EtOAc solution and then extracted 3 × 25 mL with EtOAc. The organic extracts were dried over Na_2SO_4 and evaporated to a yellow oil. Flash chromatography with 30/70 EtOAc/PE gave 6.14 g (87%) of a yellow oil: R_f (50/50 EtOAc/PE) 0.35; t_R 3.82 min (89/10/1 Hex/EtOAc/MeCN, 2 mL/min, Perkin/Elmer 83 mm 3 Å silica, 254 nm detection); IR ($CHCl_3$) 2975, 1730, 1670, 1510, 1470, 1455, 1240, 1170, 910; ^1H NMR δ (500 MHz) 8.51 (1 H, s), 7.43 (5 H, m), 7.00 (2 H, d, J = 8.5 Hz) 6.80 (2 H, d, J = 9.0 Hz), 5.66 (1 H, dd, J = 9.5, 4.0 Hz), 4.99 (1 H, m), 3.46 (2 H, s), 3.34 (1 H, dd, J = 15.0, 9.5 Hz), 3.18 (1 H, m, J = 4.0 Hz), 2.20 (2 H, d, J = 7.0 Hz), 1.93 (1 H, h, J = 6.5 Hz), 1.24 (6 H, d, J = 6.0 Hz), 0.88, (6 H, d, J = 6.5 Hz); mass spectrum (CI), m/e (relative intensity) 533.1 (M^+ + 1, 44.0), 339.1 (100.0), 283.1 (63.6), 243.1 (14.1), 201.1 (14.1); (HRCI) mol wt calcd for $C_{28}H_{32}N_2O_5F_3$ (M^+ + 1) 533.2262, found 533.2242.

2-[2-Phenyl-2-[4-[(isopropoxycarbonyl)methyl]phenoxy]ethyl]-4-isobutyl-5-[(carbobenzyloxy)amino]oxazole (9a, R = *i*-Bu). Trifluoroacetamide **8**, R = *i*-Bu (0.785 g, 1.47 mmol), was dissolved in 4.0 mL of CH_2Cl_2 and cooled to 0 °C. Cbz-Cl (1.5 equiv, 2.21 mmol, 0.32 mL) was added followed by *N*-methylmorpholine (1.5 equiv, 2.21 mmol, 0.24 mL). The reaction mixture was warmed to room temperature and stirred for 3.5 h. The reaction was quenched by adding it to a stirring 0 °C solution of saturated aqueous NH_4Cl/EtOAc. The quench solution was added to a separatory funnel and extracted with 3 × 25 mL of EtOAc. The combined extracts were dried over Na_2SO_4 and evaporated to a yellow oil. Flash chromatography with 20/80 EtOAc/PE gave 0.597 g (71%, 92% based on recovered starting material) of a white foam: R_f (30/70 EtOAc/PE) 0.41; t_R 6.64 min (89/10/1 Hex/EtOAc/MeCN,

2 mL/min, Perkin-Elmer 83 mm 3 Å silica, 254-nm detection); IR ($CHCl_3$) 3300, 2965, 1732, 1615, 1525, 1460, 1240, 1112; ^1H NMR δ (300 MHz) 7.34 (10 H, m), 7.04 (2 H, d, J = 8.7 Hz), 6.77 (2 H, d, J = 8.4 Hz), 6.42 (1 H, br s), 5.57 (1 H, dd, J = 8.4, 5.4 Hz), 5.16 (2 H, s), 4.95 (1 H, pent, J = 6.3 Hz), 3.42 (2 H, s), 3.40 (1 H, dd, J = 15.0, 8.7 Hz), 3.15 (1 H, dd, J = 14.7, 4.8 Hz), 2.22 (2 H, d, J = 9.9 Hz), 1.91 (1 H, dd, J = 14.7, 4.8 Hz), 1.18 (6 H, d, J = 3.3 Hz), 0.85 (6 H, d, J = 6.6 Hz); mass spectrum (CI), m/e (relative intensity) 571 (M^+ + 1, 10.9), 463 (19.7), 283 (100.0), 269 (41.0), 241 (33.2); (HRCI) mol wt calcd for $C_{34}H_{39}N_2O_6$ (M^+ + 1) 571.2808, found 571.2792.

2-[2-Phenyl-2-[4-(β-hydroxyethyl)phenoxy]ethyl]-4-isobutyl-5-[(carbobenzyloxy)amino]oxazole (10, R = *i*-Bu, R′ = Cbz). Isopropyl ester **9a**, R = *i*-Bu (2.073 g, 3.63 mmol) was dissolved in 18 mL of THF and cooled to 0 °C. $LiAlH_4$ (1 M in THF, 1.5 equiv, 5.45 mL, 5.45 mmol) was added, and the reaction was stirred for 1.5 h. The reaction was quenched with cold NH_4Cl/EtOAc solution and extracted with 3 × 25 mL of EtOAc. The extracts were dried over Na_2SO_4 and evaporated to a yellow foam. Flash chromatography gave 1.82 g (96%) of a white foam: R_f (30/70 EtOAc/PE, twice eluted) 0.16; IR ($CHCl_3$) 3300, 2942, 1730, 1515, 1240, 1050; ^1H NMR δ (300 MHz) 7.34 (10 H, m), 6.99 (2 H, d, J = 8.7 Hz), 6.76 (2 H, d, J = 8.7 Hz), 6.33 (1 H, br s), 5.55 (1 H, dd, J = 8.4, 5.1 Hz), 5.15 (2 H, s), 3.74 (2 H, t, J = 6.6 Hz), 3.37 (1 H, dd, J = 14.7, 8.7 Hz), 3.15 (1 H, dd, J = 18.0, 8.4 Hz), 2.70 (2 H, t, J = 6.6 Hz), 2.22 (2 H, d, J = 9.9 Hz), 1.91 (1 H, pent, J = 6.3 Hz), 1.69 (1 H, br s), 0.85 (6 H, br d, J = 6.6 Hz); mass spectrum (CI), m/e (relative intensity) 515 (M^+ + 1, 10.1), 407 (11.8), 377 (19.1), 333 (16.2), 285 (8.4), 269 (41.7), 232 (55.9); (HRCI) mol wt calcd for $C_{31}H_{35}N_2O_5$ (M^+ + 1) 515.2546, found 515.2533.

2-[2-Phenyl-2-[4-[2-[[(*p*-nitrophenyl)sulfonyl]oxy]ethyl]phenoxy]ethyl]-4-isobutyl-5-[(carbobenzyloxy)amino]oxazole (11b, R = *i*-Bu). The alcohol **10**, R = *i*-Bu, R′ = Cbz (3.35 g, 6.50 mmol) was azeotropically dried with toluene, dissolved in CH_2Cl_2, and cooled to 0 °C. Pyridine (3 equiv, 1.58 mL, 19.53 mmol) was added followed by portionwise addition of NsCl (about 2 equiv, 2.89 g, 13.02 mmol) over 6 h. When the starting material had been consumed (as judged by TLC) the reaction mixture was added to a separatory funnel and extracted with 3 × 50 mL of EtOAc from saturated NH_4Cl solution. The combined extracts were dried over Na_2SO_4 and evaporated to a yellow oil. Flash chromatography with 60/30/10 PE/CH_2Cl_2/EtOAc gave the nosylate as a light yellow foam (3.70 g, 81%): R_f (60/40 PE/EtOAc) 0.47; IR ($CHCl_3$) 3115, 3040, 2985, 2880, 1740, 1535, 1515, 1350, 1180; ^1H NMR δ (300 MHz) 8.23 (2 H, d, J = 12.0 Hz), 7.85 (2 H, d, J = 8.7 Hz), 7.33 (10 H, m), 6.86 (2 H, d, J = 8.7 Hz), 6.70 (2 H, d, J = 8.4 Hz), 6.25 (1 H, br s), 5.56 (1 H, dd, J = 8.4, 5.4 Hz), 5.16 (2 H, br s), 4.19 (2 H, m, J = 3.3 Hz), 3.38 (1 H, dd, J = 15.0, 8.4 Hz), 3.17 (1 H, dd, J = 15.3, 5.7 Hz), 2.83 (2 H, t, J = 7.2 Hz), 2.21 (2 H, br d, J = 7.2 Hz), 1.92 (1 H, pent, J = 6.6 Hz), 0.85 (6 H, d, J = 6.4 Hz); mass spectrum (FAB), m/e (relative intensity) 700 (M^+ + 1, 5.3), 460 (3.2), 377 (4.5), 289 (13.1).

2-(Carbobenzyloxy)-1⁴-isobutyl-7-phenyl-2-aza-5(1,4)-benzena-6-oxa-1(2,5)-oxazolacyclooctaphane (12b). The nosylate **11b** (1.954 g, 2.64 mmol) was dissolved in 20 mL of THF and added via syringe pump (over 10 h) to a stirring suspension of washed and dried (2 × 2 mL of hexane) NaH (3.7 equiv, 0.32 g, 9.67 mmol). The reaction mixture was stirred overnight and then quenched by adding to a cold aqueous NH_4Cl/EtOAc solution followed by extraction with EtOAc (3 × 100 mL). The combined extracts were dried over Na_2SO_4 and evaporated to a yellow oil. Flash chromatography with 30/70 EtOAc/PE gave 0.892 g (68%, with some starting material remaining) of a light yellow foam: R_f (30/70 EtOAc/PE) 0.38; IR ($CHCl_3$) 3065, 3040, 1760, 1675, 1615, 1575, 1520, 1458, 1410, 1280, 1180; ^1H NMR δ (300 MHz) 7.38 (10 H, m), 6.57 (4 H, d, J = 7.8 Hz), 5.45 (1 H, d, J = 10.8 Hz), 5.42 (1 H, d, J = 10.5 Hz), 5.12 (2 H, s), 3.35 (2 H, m), 3.15 (1 H, m), 2.45 (2 H, m), 2.17 (2 H, br m), 2.04 (2 H, m), 0.87 (6 H, d, J = 5.4 Hz); mass spectrum (EI, in beam), m/e (relative intensity) 992 ($2M^+$), 949, 858, 654, 585, 497, 453, 363, 236, 131; (FAB) 993, 497; (CI) 993 ($2M^+$ + 1, 1.0), 949 (0.8), 859 (0.9), 725 (0.4), 587 (0.3), 527 (0.3), 499 (2.4), 496 (1.3), 455 (1.2).

2-[2-Phenyl-2-[4-[(isopropoxycarbonyl)methyl]phenoxy]ethyl]-4-isobutyl-5-[(*tert*-butyloxycarbonyl)amino]oxazole (9d, R = *i*-Bu). The trifluoroacetamide **8**, R = *i*-Bu (0.050 g, 0.094 mmol) was dissolved in 1 mL of CH_2Cl_2 and cooled to 0 °C. DMAP (catalytic amount) and *tert*-butyl dicarbonate (3.0 equiv, 0.61 g, 0.282 mmol) were added followed by *N*-methylmorpholine (1.5 equiv, 0.015 mL, 0.141 mL). The reaction was warmed to room temperature and stirred for 20 min. The reaction mixture was then added to a separatory funnel and extracted from saturated NH_4Cl solution with 3 × 15 mL of EtOAc. The combined extracts were dried over Na_2SO_4 and evaporated to a light yellow oil. Flash chromatography with 30/70 EtOAc/Hex gave 0.437 g (87%) of a yellow foam: R_f (10/90 EtOAc/CH_2Cl_2) 0.47; IR (neat) 2985, 1733, 1670, 1515, 1455, 1372, 1240, 1168, 1110, 1030; ^1H NMR δ (500 MHz) 7.31 (6 H, m), 7.04 (2 H, d, J = 8.7 Hz), 6.76 (2 H, d, J = 8.7 Hz), 5.95 (1 H, br s), 5.58 (1 H, dd, J = 8.7, 5.1 Hz), 4.96 (1 H, pent, J = 6.3 Hz), 3.43 (2 H, s), 3.36 (1 H, dd, J = 14.7, 8.7 Hz), 3.12 (1 H, dd, J = 14.7, 5.4 Hz), 2.25 (2 H, d, J = 7.2 Hz), 1.95 (1 H, pent, J = 6.9 Hz), 1.45 (9 H, br s), 1.21 (6 H, d, J = 6.3 Hz), 0.87 (6 H, d, J = 6.6 Hz); mass spectrum (CI), m/e (relative intensity) 537 (M^+ + 1, 54.1), 481 (40.9), 463 (5.3), 436 (39.4), 343 (13.0), 283 (48.7), 269 (16.1), 241 (77.3); (HRCI) mol wt calcd (M^+ + 1) 537.2964, found 537.2933.

2-[2-Phenyl-2-[4-(β-hydroxyethyl)phenoxy]ethyl]-4-isobutyl-5-[(*tert*-butyloxycarbonyl)amino]oxazole (10, R = *i*-Bu, R′ = *O*-*t*-Bu). Isopropyl ester **9d**, R = *i*-Bu (3.54 g, 6.61 mmol), was azeotropically dried with 2 × 1 mL of toluene and then dissolved in THF and cooled to 0 °C. $LiAlH_4$ (1 M) in THF (1.5 equiv, 9.9 mL, 9.92 mmol) was added dropwise and the resulting foamy solution stirred for 15 min. The reaction was quenched by adding aqueous NH_4Cl/EtOAc and extracting with 3 × 20 mL of EtOAc. The combined extracts were dried over Na_2SO_4 and evaporated to a white foam. MPLC with EtOAc/CH_2Cl_2 gave 2.68 g (85%) of a white foam: R_f (10/90 EtOAc/CH_2Cl_2) 0.12; IR (neat) 3300, 2963, 2940, 1718, 1670, 1610, 1560, 1505, 1455, 1370, 1238, 1160, 1048, 1040; ^1H NMR δ (500 MHz) 7.36 (1 H, d, J = 7.5 Hz), 7.32 (2 H, t, J = 8.0 Hz), 7.26 (1 H, m), 6.99 (2 H, d, J = 8.5 Hz), 6.76 (2 H, d, J = 8.5 Hz), 5.96 (1 H, br s), 5.56 (1 H, dd, J = 9.0, 5.5 Hz), 3.75 (2 H, t, J = 6.5 Hz), 3.37 (2 H, t, J = 6.5 Hz), 3.15 (1 H, dd, J = 15.0, 8.5 Hz), 2.72 (2 H, t, J = 6.5 Hz), 2.24 (2 H, d, J = 7.0 Hz), 1.95 (1 H, pent, J = 7.0 Hz), 1.45 (9 H, br s), 0.88 (6 H, d, J = 6.5 Hz); mass spectrum (FAB), m/e (relative intensity) 481 (M^+ + 1, 83.0), 425 (18.6), 380 (11.6), 343 (15.7), 287 (82.2), 243 (93.5), 227 (65.7), 198 (39.9); (HRCI) mol wt calcd (M^+ + 1) 481.2702, found 481.2733.

2-[2-Phenyl-2-[4-[2-[[(*p*-nitrophenyl)sulfonyl]oxy]ethyl]phenoxy]ethyl]-4-isobutyl-5-[(*tert*-butylcarboxy)amino]oxazole (11g). The alcohol **10**, R = *i*-Bu, R′ = *t*-Bu (0.300 g, 0.624 mmol), was dissolved in 3 mL of CH_2Cl_2 and cooled to 0 °C. Pyridine (5.0 equiv, 0.252 mL, 3.121 mmol) was added followed by portionwise addition of NsCl (about 2.0 equiv, 0.277 g, 1.248 mL) over about 2 h. The reaction progress was followed closely by TLC; when complete, the reaction mixture was extracted with 3 × 25 mL of EtOAc from saturated NH_4Cl. The combined extracts were dried over Na_2SO_4 and evaporated to a yellow oil. MPLC with 25/75 EtOAc/CH_2Cl_2 gave 0.298 g (72%) of a light yellow foam: R_f (EtOAc/Hex) 0.15; HPLC t_R 3.69 min (20/80 EtOAc/Hex, 2 mL/min, Perkin-Elmer 83 mm 3 Å silica, 254-nm detection); IR ($CHCl_3$) 3250, 3105, 2980, 2868, 1720, 1670, 1610, 1560, 1530, 1510, 1468, 1458, 1360, 1240, 1170, 1090, 1050, 1025; ^1H NMR δ (500 MHz) 8.22 (2 H, d, J = 8.5 Hz), 7.85 (2 H, d, J = 8.5 Hz), 7.35 (5 H, m), 7.26 (1 H, m), 6.85 (2 H, d, J = 8.5 Hz), 6.70 (2 H, d, J = 8.5 Hz), 6.03 (1 H, br s), 5.56 (1 H, dd, J = 8.5, 5.5 Hz), 4.20 (2 H, m), 3.39 (1 H, dd, J = 15.0, 8.5 Hz), 3.16 (1 H, dd, J = 15.0, 8.5 Hz), 2.83 (2 H, t, J = 7.0 Hz), 2.24 (2 H, d, J = 7.0 Hz), 1.95 (1 H, pent, J = 7.0 Hz), 1.45 (9 H, br s), 0.87 (6 H, d, J = 6.5 Hz); mass spectrum (FAB), m/e (relative intensity) 666 (M^+ + 1, 15.7), 411 (6.5), 287 (25.3), 243 (26.1), 198 (18.2); (HRCI) mol wt calcd (M^+ + 1) 666.2485; found 666.2371.

2-(*tert*-Butyloxy)-1⁴-isobutyl-7-phenyl-2-aza-5(1,4)-benzena-6-oxa-1-(2,5)-oxazolacyclooctaphane (12e). The nosylate **11g** (0.955 g, 1.434 mmol) was dissolved in 20 mL of THF and added slowly via syringe pump (over 20 h) to a suspension of washed and dried NaH (2 × 1 mL of hexane, 15 equiv, 0.516 g, 21.51 mmol) in 285 mL of THF (0.005 M) at 40 °C. The light yellow reaction was stirred overnight and then cooled to room temperature. The reaction mixture was then added slowly to a stirring solution of saturated NH_4Cl/EtOAc. The aqueous layer was saturated with NaCl and then extracted with 3 × 50 mL of EtOAc. The combined extracts were dried over Na_2SO_4 and evaporated to a yellow waxy solid. The residue was taken up in EtOAc and the solids filtered. The white solid filter cake was washed well with EtOAc and dried in vacuo to give 0.554 g (84%): R_f (30/70 EtOAc/Hex) 0.55; t_R 1.95 min (20/80 EtOAc/Hex, 2 mL/min, Perkin-Elmer 83 mm 3 Å silica, 254 nm detection); ^1H NMR δ (500 MHz) 7.45 (2 H, t, J = 7.5 Hz), 7.37 (2 H, m), 7.30 (1 H, m), 6.61 (4 H, m), 5.52 (1 H, br d, J = 9.0 Hz), 5.43 (1 H, br d, J = 9.5 Hz), 3.32 (3 H, m), 3.17 (1 H, dd, J = 5.5, 2.5 Hz), 3.14 (1 H, dd, J = 6.0, 2.5 Hz), 2.46 (2 H, br m), 2.22 (2 H, m), 2.08 (1 H, sext, J = 7.0 Hz), 1.40 (9 H, s), 0.93 (6 H, d, J = 6.5 Hz), 0.91 (6 H, d, J = 7.0 Hz); ^{13}C NMR δ 158.18, 156.75, 153.87, 153.77, 142.81, 140.75, 140.69, 131.88, 130.95, 130.89, 129.46, 128.88, 128.11, 125.65, 115.60, 81.38, 79.30, 78.60, 51.01, 50.92, 50.72, 38.68, 34.50, 34.07, 28.17, 27.40, 22.61, 22.48; mass spectrum (FAB), m/e (relative intensity) 926 ($2M^+$ + 1, 21.6), 825 (12.4), 363 (13.4), 273 (15.6), 198 (19.4), 154 (24.3); (LSIMS) 925, 824.

***cyclo*-[*N*-[3-[[4-(β-Aminoethyl)phenyl]oxy]-9-phenylpropanoyl]leucyl] (13, R = *i*-Bu).** The cyclophane **12e** (0.100 g, 0.216 mmol) was dissolved in CH_2Cl_2 (0.5 M, 4.3 mL) in the presence of 30 equiv of H_2O (0.12 mL,

6.49 mL). TFA (120 equiv, 2.02 mL, 25.94 mmol) was added and the light yellow reaction mixture stirred for 1 h. About 20 mL of CH_2Cl_2 was added followed by an equal volume of brine. Saturated Na_2CO_3 solution was added slowly dropwise until the aqueous layer was neutralized. The quench solution was added to a separatory funnel and extracted with 3 × 15 mL of CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and evaporated to a white solid. The solid was purified through a small plug of silica gel with 5/95 MeOH/CH_2Cl_2 to give 0.75 g (93%): R_f (5/95 MeOH/CH_2Cl_2) 0.20; ^{1}H NMR δ (500 MHz, $CDCl_3$/TFA) 6.95 (3 H, m), 6.80 (2 H, m), 6.75 (2 H, m), 6.66 (2 H, m), 5.55 (1 H, m), 4.46 (1 H, m), 2.76 (4 H, m), 2.20 (2 H, m), 1.61 (2 H, m), 1.25 (1 H, m), 0.92 (6 H, m); (500 MHz ($CDCl_3$/DMSO-d_6), 7.39 (2 H, d, J = 7.0 Hz), 7.33 (3 H, t, J = 8.0 Hz), 7.26 (2 H, m), 6.88 (2 H, m), 6.77 (3 H, m), 5.64 (1 H, d, J = 10.0 Hz), 4.33 (1 H, m), 2.92 (2 H, m), 2.72 (1 H, m), 2.53 (1 H, d, J = 2.0 Hz), 2.50 (3 H, d, J = 2.0 Hz), 2.25 (1 H, m), 1.68 (1 H, m), 1.57 (2 H, m), 0.93 (6 H, d, J = 6.0 Hz), 0.89 (6 H, d, J = 6.0 Hz); mass spectrum (FAB), m/e (relative intensity) 762 ($2M^+$ + 1, 100.0), 642 (21.3), 600 (11.0), 518 (22.0), 460 (22.4), 381 (36.2), 365 (25.2), 307 (17.3); (LSMS) 841 (unidentified), 761, 459 (unidentified), 391, 381.

(1*S*,2*S*)-2-[*N*-(Carbobenzyloxy)amino]-1-phenyl-1,3-propanediol. (1*S*,2*S*)-(+)-Aminophenylpropanediol **15** (10.0 g, 0.0598 mol) was dissolved in 75 mL (0.8 M) of distilled H_2O and cooled to 0 °C. $NaHCO_3$ (2.0 equiv, 10.17 g, 0.120 mol) was added to the diol followed by Cbz-Cl (1.01 equiv, 8.66 mL, 0.060 mol). The heterogeneous suspension was corked, warmed to room temperature, and stirred overnight. The white solid (mp 102–103 °C) was filtered (Buchner funnel) and washed very well with hexane. The filter cake was dried in vacuo to give 17.99 g (99%): R_f (5/95 MeOH/CH_2Cl_2) 0.18; IR ($CHCl_3$) 3430, 3020, 1700, 1510, 1455, 1330, 1218, 1050; $[\alpha]'_D$ (MeOH) +47.2°, t 20.9 °C, c 1.0; ^{1}H NMR δ (500 MHz) 7.32 (10 H, m), 5.50 (1 H, d, J = 3.5 Hz), 5.00 (2 H, s), 3.88 (1 H, m), 3.78 (2 H, m), 3.20 (1 H, br s), 2.57 (1 H, br s); mass spectrum (CI), m/e (relative intensity) 302 (M^+ + 1, 3.0), 284 (7.7), 240 (6.9), 194 (7.6), 150 (11.7); (HRCI) mol wt calcd for $C_{17}H_{20}NO_4$ (M^+ + 1) 302.1392, found 302.1374.

(4*S*,5*S*)-5-[*N*-(Carbobenzyloxy)amino]-2,2-dimethyl-4-phenyl-1,3-dioxolane (16). The diol (10.0 g, 33.18 mmol) was dissolved in 82 mL (0.4 M) of dry acetone with about 25 g of 4-Å sieves. Dimethoxypropane (5.0 equiv, 20 mL, 165.92 mmol) and TsOH (about 0.10 g) were added, and the reaction was stirred overnight at room temperature. The reaction was vacuum filtered through sintered glass, and the filtrate was concentrated. The resulting oil was resuspended in EtOAc and washed 1 × 50 mL each of saturated $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and evaporated to a yellow oil. The product may be used crude for the next step or purified by flash chromatography with 20/80 EtOAc/Hex: R_f (30/70 EtOAc/Hex) 0.31; IR (neat) 3450, 3350, 3170, 3040, 2950, 2980, 1950, 1700, 1590, 1500, 1040, 980; $[\alpha]'_D$ (EtOH) +45.68°, t 23.4 °C, c 0.701; ^{1}H NMR δ (500 MHz) 7.31 (6 H, m), 7.16 (4 H, d, J = 10.0 Hz), 5.46 (1 H, d, J = 9.5 Hz), 5.16 (1 H, d, J = 2.0 Hz), 4.90 (1 H, d, J = 12.5 Hz), 4.87 (1 H, d, J = 12.5 Hz), 4.23 (1 H, dd, J = 12.0, 2.0 Hz), 3.91 (2 H, ABX, J = 12.0, 9.5, 2.0 Hz), 1.55 (3 H, s), 1.52 (3 H, s); ^{13}C NMR δ 155.76, 155.09, 138.17, 136.35, 128.58, 128.35, 128.09, 127.87, 127.75, 127.44, 125.49, 99.45, 72.23, 66.59, 66.41, 64.79, 48.85, 29.59, 18.46; mass spectrum (CI), m/e (relative intensity) 342 (M^+ + 1, 1.5), 248 (21.1), 240 (8.4), 177 (15.8), 132 (8.1); (HRCI) mol wt calcd for $C_{20}H_{24}NO_4$ (M^+ + 1) 342.1705, found 342.1702.

(4*S*,5*S*)-5-(*N*-Carbobenzyloxy-*N*-methylamino)-2,2-dimethyl-4-phenyl-1,3-dioxolane. The urethane (10.8 g, 31.63 mmol) was dried well and dissolved in 80 mL of DMF (0.4 mL) and cooled to 0 °C. NaH (1.2 equiv, 0.91 g, 37.96 mmol) was added, and the anion was allowed to form over 20 min. The MeI (1.1 equiv, 2.2 mL, 34.08 mmol) was added slowly and the reaction warmed to room temperature. After stirring overnight the reaction was added to a quench solution of saturated aqueous NH_4Cl/EtOAc and extracted with 4 × 50 mL of EtOAc. The combined extracts were dried over Na_2SO_4 and evaporated to a brown oil. Flash chromatography with 20/80 EtOAc/Hex gave 7.3 g (65%) of a light yellow oil: R_f (EtOAc/PE) 0.46; IR (neat) 3040, 3022, 3005, 2880, 1743, 1700, 1500, 1450, 1410, 1388, 1320, 1160, 1023; $[\alpha]'_D$ (EtOH) −8.31°, t 23.6 °C, c 1.497; ^{1}H NMR δ (500 MHz, 1.6:1 E/Z Cbz rotamers) *major isomer* 7.37 (2 H, d, J = 7.5 Hz), 7.25 (6 H, m), 7.05 (2 H, d, J = 7.5 Hz), 5.27 (1 H, d, J = 3.5 Hz), 4.97 (1 H, d, J = 13.0 Hz), 4.85 (1 H, d, J = 12.5 Hz), 4.57 (1 H, m), 4.36 (1 H, dd, J = 13.0, 4.0 Hz), 3.98 (1 H, ABX, J = 12.5, 6.5, 1.5 Hz), 3.05 (3 H, s), 1.52 (6 H, m); *minor isomer* 5.15 (1 H, d, J = 3.5 Hz), 4.85 (1 H, d, J = 12.0 Hz), 4.62 (1 H, d, J = 12.0 Hz), 4.30 (2 H, dd, J = 12.5, 4.0 Hz), 4.26 (2 H, m), 3.15 (3 H, s); ^{13}C NMR δ *major isomer* 156.58, 138.18, 138.02, 136.77, 136.37, 128.10, 128.09, 127.79, 127.69, 127.38, 126.92, 125.50, 125.14, 99.13, 99.09, 72.21, 66.43, 63.82, 50.19, 32.26, 28.95, 18.75; *minor isomer* 155.64, 72.88, 66.86, 63.48, 50.48, 32.7, 18.82; mass spectrum (CI), m/e (relative intensity) 356 (M^+ + 1, 3.0), 344 (8.2), 298 (100.0), 254 (8.6), 191 (19.7), 146 (34.5), 132 (6.6); (HRCI) mol wt calcd (M^+ + 1) 356.1862, found 356.1857.

(1*S*,2*S*)-2-(*N*-Carbobenzyloxy-*N*-methylamino)-1-phenylpropane-1,3-diol (17). The acetonide (7.43 g, 20.54 mmol) was dissolved in about 50 mL of MeOH and cooled to 0 °C. About 0.1 g of TsOH was added and the reaction stirred for 1 h at 0 °C. The reaction was then warmed to room temperature and stirred for about 3 h. The reaction mixture was then added to a separatory funnel and extracted with 3 × 50 mL of EtOAc from brine containing a small amount of $NaHCO_3$ to neutralize the TsOH. The combined extracts were dried over Na_2SO_4 and evaporated to a yellow oil which was used crude for the next step: R_f (30/70 EtOAc/Hex) 0.09; IR (neat) 3400, 3070, 3040, 2950, 2900, 1678, 1480, 1452, 1408, 1345, 1220, 1155, 1050; $[\alpha]'_D$ (EtOH) +38.85°, t 23.6 °C, c 0.590; ^{1}H NMR δ (500 MHz), 7.29 (10 H, m), 5.10 (1 H, d, J = 12.5 Hz), 5.03 (1 H, d, J = 12.5 Hz), 4.92 (2 H, br m), 4.37 (2 H, br m), 3.92 (1 H, br m), 3.75 (1 H, m), 2.80 (3 H, s); mass spectrum (CI), m/e (relative intensity) 316 (M^+ + 1, 2.6), 298 (12.3), 209 (12.3), 208 (100.0), 194 (11.8), 176 (22.7), 164 (23.0), 132 (28.0), 117 (7.6); (HRCI) mol wt calcd for $C_{18}H_{22}NO_4$ (M^+ + 1) 316.1549, found 316.1568.

(1*S*,2*S*)-2-(*N*-Carbobenzyloxy-*N*-methylamino)-3-phenyl-3-hydroxy-1-(*tert*-butyldimethylsilyl)propanol (18). The alcohol **17** (5.79 g, 18.37 mmol) was azeotropically dried with 2 × 2 mL of toluene and then suspended in 45 mL (0.4 M) of CH_2Cl_2 at 0 °C. TBDMS-Cl (1.01 equiv, 2.79 g, 18.54 mmol) and DMAP (catalytic amount) was added. Et_3N (2.2 equiv, 4.44 mL, 40.39 mmol) was added and the reaction stirred at 0 °C for 2 h and then at room temperature for 1 h. At this time the reaction was added to a separatory funnel and extracted with 3 × 50 mL of EtOAc from NH_4Cl solution. The combined extracts were dried over Na_2SO_4 and evaporated to a yellow oil. Flash chromatography with 20/80 EtOAc/Hex gave 6.22 g (79% after four steps starting from the Cbz derivative of **15**) of a water-white oil which solidifies on standing (mp 76–78 °C): R_f (30/70 EtOAc/Hex) 0.30; IR ($CHCl_3$) 3400, 3020, 2948, 2930, 2860, 1675, 1450, 1405, 1343, 1255, 1215, 1151, 1118; $[\alpha]'_D$ (EtOH) +28.37°, t 22.6 °C, c 0.822; ^{1}H NMR δ (500 MHz) 7.31 (10 H, m), 5.06 (1 H, d, J = 12.0 Hz), 4.97 (1 H, m), 4.30 (1 H, br s), 3.95 (1 H, m), 3.89 (1 H, br s), 3.83 (1 H, m), 3.61 (1 H, d, J = 4.5 Hz), 2.80 (3 H, s), 0.87 (9 H, s), 0.01 (3 H, s), −0.01 (3 H, s); mass spectrum (CI), m/e (relative intensity) 430 (M^+ + 1, 3.6), 412 (30.4), 368 (6.3), 350 (7.1), 322 (100.0), 292 (8.8), 278 (73.4), 262 (11.7), 244 (8.7), 220 (62.0), 190 (13.4); (HRCI) mol wt calcd for $C_{24}H_{34}NO_3Si$ (M^+ + 1 − OH) 412.2308, found 412.2331.

2(*S*)-(*N*-Carbobenzyloxy-*N*-methylamino)-3(*R*)-phenyl-3-[4-[(isopropoxycarbonyl)methyl]phenoxy]-1-(*tert*-butyldimethylsilyl)propanol (19). The alcohol **18** (7.0 g, 16.293 mmol), the phenol **3a** (1.0 equiv, 3.16 g, 16.293 mmol), and PPh_3 (1.1 equiv, 4.70 g, 17.92 mmol) were mixed and azeotropically dried with toluene. These components were then resuspended in dry THF (41 mL, 0.4 M). DEAD (1.1 equiv, 2.8 mL, 17.92 mmol) in enough THF to bring the volume to 5 mL and was added via syringe pump at 2 mL/h. The orange solution was stirred overnight and then placed directly on a silica gel column and eluted with a EtOAc/Hex gradient starting with 10/90 and ending with 20/80 to give a clear oil (8.91 g, 90%): R_f (30/70 EtOAc/Hex) 0.62; IR (neat) 3039, 2940, 2860, 1700, 1610, 1585, 1450, 1400, 1320, 1240, 1150, 1105, 1005; $[\alpha]'_D$ (EtOH) −16.28°, t 22.6 °C, c 1.300; ^{1}H NMR δ (500 MHz, 1.3:1 E/Z Cbz rotamers) *major isomer* 7.39 (5 H, m), 7.30 (5 H, m), 7.12 (2 H, dd, J = 8.5 Hz), 6.81 (2 H, d, J = 8.5 Hz), 5.52 (1 H, d, J = 7.0 Hz), 5.15 (1 H, d, J = 12.5 Hz), 5.07 (1 H, d, J = 12.5 Hz), 5.02 (1 H, pent, J = 6.0 Hz), 4.32 (1 H, br t, J = 10.0 Hz), 4.27 (1 H, br m), 3.98 (1 H, br m), 3.48 (2 H, s), 2.88 (3 H, br s), 1.24 (6 H, d, J = 6.54 Hz), 0.89 (9 H, s), 0.31 (3 H, s), 0.01 (3 H, s); *minor isomer* 6.75 (2 H, d, J = 8.5 Hz), 5.26 (1 H, d, J = 8.0 Hz), 4.96 (1 H, d, J = 12.5 Hz), 4.45 (1 H, br m), 4.14 (1 H, dd, J = 10.5, 8.5 Hz), 2.89 (3 H, br s), 0.87 (9 H, s); ^{13}C NMR δ 156.93, 138.67, 130.21, 130.17, 128.17, 128.48, 127.19, 127.86, 127.65, 126.70, 126.60, 115.98, 115.87, 79.06, 68.18, 67.30, 66.78, 60.26, 40.83, 25.89, 25.84, 21.88; mass spectrum (CI), m/e (relative intensity) 548 (M^+ + 1 − (*tert*-butyl), 5.2), 412 (100.0), 368 (5.8), 322 (20.3), 278 (31.9), 220 (6.4); (RHCI) mol wt calcd for $C_{34}H_{44}NO_6Si$ (M^+ + 1 − CH_3) 590.2938, found 590.2963.

2-(*S*)-(*N*-Carbobenzyloxy-*N*-methylamino)-3(*R*)-phenyl-3-[4-[(isopropoxycarbonyl)methyl]phenoxy]-1-propanol. The TBS ether **19** (7.961 g, 13.14 mmol) was dissolved in CH_2Cl_2 (65 mL, 0.2 M) and cooled to 0 °C. TFA (3.0 equiv, 3.0 mL, 39.42 mmol) was added slowly, and the reaction was stirred overnight at room temperature. The reaction was added to a stirring quench solution of 100 mL each of CH_2Cl_2/$NaHCO_3$ solution (saturated). The quench solution was added to a separatory funnel, and the organic layer was removed. The aqueous layer was saturated with NaCl and extracted with 3 × 50 mL of EtOAc. The combined extracts were dried over Na_2SO_4 and evaporated. The re-

sulting thick oil was pushed through a short plug of silica gel with 50/50 EtOAc/CH_2Cl_2 to give 6.382 g (99%) of a clear oil: R_f (30/70 EtOAc/Hex) 0.12; IR (neat) 3450, 3039, 2983, 2940, 1680, 1610, 1505, 1450, 1400, 1350, 1235, 1150, 1104, 1045; $[\alpha]'_D$ (Et_2O) −10.68°, *t* 23.1 °C, *c* 0.805 g/mL; ^1H NMR δ (500 MHz, 1.9:1 *E*/*Z* Cbz rotamers) *major isomer* 7.33 (4 H, m), 7.24 (5 H, m), 7.17 (1 H, m), 7.05 (2 H, d, *J* = 8.5 Hz), 6.75 (2 H, d, *J* = 8.5 Hz), 5.52 (1 H, d, *J* = 7.0 Hz), 5.13 (1 H, d, *J* = 12.5 Hz), 5.03 (1 H, d, *J* = 12.5 Hz), 4.95 (1 H, pent, *J* = 6.0 Hz), 4.18 (1 H, dd, *J* = 11.0, 7.0 Hz), 4.03 (2 H, m), 3.43 (2 H, s), 2.72 (3 H, s), 2.59 (1 H, br s), 1.18 (6 H, d, *J* = 6.5 Hz); *minor isomer* 6.67 (2 H, d, *J* = 8.5 Hz), 5.20 (1 H, d, *J* = 7.0 Hz), 4.33 (1 H, br s), 2.90 (3 H, s); mass spectrum (CI), *m/e* (relative intensity) 492 (M^+ + 1, 1.9), 474 (11.9), 388 (7.7), 384 (10.8), 298 (100.0), 283 (10.1); (HRCI) mol wt calcd for $C_{29}H_{32}NO_5$ (M^+ + 1 − OH) 475.2280, found 475.2301.

2(*R*)-(*N*-Carbobenzyloxy-*N*-methylamino)-3(*R*)-phenyl-3-[4-[(isopropoxycarbonyl)methyl]phenoxy]-1-propanecarboxylic Acid (20). The alcohol prepared above (6.453 g, 13.09 mmol) was suspended in CH_3CN (0.4 M, 33 mL), CCl_4 (0.6 M, 22 mL), and H_2O (0.6 M, 22 mL) and cooled to 0 °C. The $NaIO_4$ (8.0 equiv, 22.0 g, 104.72 mmol) was added followed by a catalytic amount of $RuCl_3$ dihydrate (0.01 equiv, 0.034 g, 0.13 mmol). The reaction was stirred very vigorously for 2 h and followed closely by TLC. About 50 mL of Et_2O was then added, and the chunky reaction mixture was filtered through a plug of Celite. The filtrate was added to a separatory funnel, and the organic layer was washed with 1 × 100 mL each of brine and $Na_2S_2O_3$ solution. The organic layer was dried over Na_2SO_4 and filtered through a plug of silica to remove some of the dark color. The filtrate was evaporated and purified by flash chromatography with an EtOAc/Hex gradient starting with 30/70 EtOAc and ending with about 50/50 EtOAc/Hex to give a water-white oil (3.63 g, 55%, two steps starting with **19**). The resulting oil was typically stored in benzene in the freezer: R_f (30/70 EtOAc/CH_2Cl_2) 0.11; IR (neat) 3400, 3063, 3038, 2980, 2590, 1700, 1610, 1578, 1470, 1450, 1400, 1250, 1105, 1030, 970; $[\alpha]'_D$ (EtOH) +33.67°, *t* 23.4 °C, *c* 2.047; ^1H NMR δ (500 MHz, 1.3:1 *E*/*Z* Cbz rotamers) *major isomer* 7.32 (5 H, m), 7.23 (5 H, m), 7.05 (2 H, dd, *J* = 8.5, 2.5 Hz), 6.80 (2 H, d, *J* = 8.5 Hz), 5.71 (1 H, d, *J* = 8.5 Hz), 5.09 (1 H, d, *J* = 12.5 Hz), 4.98 (3 H, m), 4.72 (1 H, br d, *J* = 7.5 Hz), 3.43 (2 H, s), 2.70 (3 H, s), 1.17 (6 H, d, *J* = 6.5 Hz); *minor isomer* 6.73 (2 H, d, *J* = 8.5 Hz), 5.52 (1 H, d, *J* = 9.0 Hz), 2.82 (3 H, s); mass spectrum (CI), *m/e* (relative intensity) 402 (10.2), 312 (100.0), 298 (9.8), 283 (53.4), 268 (17.7), 222 (31.3), 195 (16.2).

***N*-(1-Cyano-3-methylphenyl)-2(*R*)-(*N*-carbobenzyloxy-*N*-methylamino)-3(*R*)-phenyl-3-[4-[(isopropoxycarbonyl)methyl]phenoxy]propanamide (22).** The carboxylic acid **20** (2.083 g, 4.11 mmol) was dissolved in 10 mL (0.4 M) of THF and cooled to 0 °C. Isobutyl chloroformate (1.01 equiv, 0.55 mL, 4.162 mmol) was added followed by *N*-methylmorpholine (1.01 equiv, 0.46 mL, 4.162 mmol). A white precipitate forms almost immediately. The free-based amine (formed by extraction with $CHCl_3$ from Na_2CO_3) dissolved in a little THF was added via cannula to the reaction and then stirred at 0 °C for 4 h. The reaction was added to a separatory funnel and extracted with 3 × 25 mL of EtOAc from brine. The combined extracts were dried over Na_2SO_4 and evaporated to a yellow oil. Flash chromatography in 30/70 EtOAc/Hex gave a white foam (2.089 g, 80%): R_f (30/70 EtOAc/Hex) 0.30; IR (neat) 3320, 3062, 3040, 2988, 2940, 1720, 1680, 1625, 1510, 1455, 1400, 1305, 1270, 1230, 1153, 1109; $[\alpha]'_D$ (CH_2Cl_2) +20.51°; *t* 22.0 °C, *c* 1.929; ^1H NMR δ (500 MHz, 1.1:1 *E*/*Z* Cbz rotamers) *major isomer* 7.32 (4 H, m), 7.24 (11 H, m), 7.05 (2 H, t, *J* = 8.0 Hz), 6.75 (2 H, t, *J* = 7.0 Hz), 5.70 (1 H, d, *J* = 9.5 Hz), 5.50 (1 H, t, *J* = 6.0 Hz), 5.13 (1 H, m), 5.00 (3 H, m), 4.95 (1 H, pent, *J* = 6.5 Hz), 4.74 (1 H, d, *J* = 9.5 Hz), 3.42 (2 H, s), 3.00 (2 H, d, *J* = 6.5 Hz), 2.74 (3 H, s), 1.19 (6 H, t, *J* = 6.0 Hz); *minor isomer* 5.64 (1 H, d, *J* = 9.5 Hz), 4.7m (1 H, d, *J* = 9.5 Hz), 3.44 (2 H, s), 2.63 (3 H, s); mass spectrum (CI), *m/e* (relative intensity) 440 (100.0), 413 (12.1), 396 (11.1), 350 (6.5), 333 (17.7), 323 (55.0), 305 (24.3), 283 (98.8), 279 (32.2); (HRCI) mol wt calcd (M^+ + 1) 634.2917, found 634.2916.

2-[1-(*R*)-(*N*-Carbobenzyloxy-*N*-methylamino)-2(*R*)-phenyl-2-[4-[(isopropoxycarbonyl)methyl]phenoxy]ethyl]-4-benzyl-5-(trifluoroacetamido)oxazole (23). The amide nitrile **22** (0.234 g, 0.370 mmol) was dissolved in CH_2Cl_2 (2.0 mL, 0.2 M) and cooled to 0 °C. TFAA (15.0 equiv, 0.78 mL, 5.54 mmol) and TFA (3.0 equiv, 0.085 mL, 1.11 mmol) were added, and the flask was corked and warmed to room temperature where stirring was continued overnight. The reaction mixture was added to a solution of EtOAc/$NaHCO_3$, and this was added to a separatory funnel and extracted with 3 × 25 mL of EtOAc. The combined extracts were dried over Na_2SO_4 and evaporated to a yellow oil. Flash chromatography 20/80 EtOAc/PE gave 0.252 g (93%) of a light yellow foam: R_f (30/70 EtOAc/Hex) 0.25; IR ($CHCl_3$) 3220, 3030, 2985, 1900, 1880, 1690, 1605, 1500, 1450, 1400, 1200, 1103, 1001, 965, 900; $[\alpha]'_D$ (CH_2Cl_2) +35.47°, *t* 23.3 °C, *c* 0.148; ^1H NMR δ (500 MHz, 1.1:1 *E*/*Z* Cbz rotamers) *major isomer* 7.98 (1 H, br s), 7.46 (2 H, m), 7.28 (6 H, m), 7.10 (6 H, m), 6.92 (2 H, d, *J* = 8.0 Hz), 6.71 (2 H, d, *J* = 8.5 Hz), 5.75 (1 H, s), 5.67 (1 H, d, *J* = 9.5 Hz), 4.99 (2 H, 7), 4.91 (1 H, d, *J* = 11.5 Hz), 4.83 (1 H, d, *J* = 12.0 Hz), 3.81 (2 H, s), 3.43 (2 H, s), 2.83 (3 H, s), 1.22 (6 H, d, *J* = 5.5 Hz); *minor isomer* 8.14 (1 H, br s), 6.65 (2 H, d, *J* = 8.0 Hz), 5.56 (1 H, d, *J* = 9.5 Hz), 3.78 (2 H, d, *J* = 3.0 Hz), 2.87 (3 H, s); mass spectrum (CI), *m/e* (relative intensity) 730 (M^+ + 1, 15.3), 536 (51.3), 446 (28.5), 402 (32.5), 373 (13.8), 312 (13.4), 283 (41.5); (HRCI) mol wt calcd for $C_{40}H_{39}N_3O_7F_3$ (M^+ + 1) 730.2740, found 730.2724.

2-[1(*R*)-(*N*-Carbobenzyloxy-*N*-methylamino)-2(*R*)-phenyl-2-[4-[(isopropoxycarbonyl)methyl]phenoxy]ethyl]-4-benzyl-5-[(*tert*-butoxycarbonyl)amino]oxazole (24). The trifluoroacetamide **23** (1.125 g, 1.172 mmol) was dissolved in 9 mL of THF (0.2 M) and cooled to 0 °C. The DMAP (catalytic amount) and *t*-Boc dicarbonate (1.5 equiv, 0.56 g, 2.56 mmol) were added, and the reaction was stirred overnight at room temperature. *N*-Methylmorpholine (1.0 equiv, 0.19 mL, 1.172 mmol) was added followed by more *t*-Boc dicarbonate (about 3 equiv additional) until the reaction was complete. About 7–8 equiv of *t*-Boc dicarbonate total was added. The reaction was added to a separatory funnel and extracted with EtOAc (3 × 25 mL) from saturated aqueous NH_4Cl. The combined extracts were dried over Na_2SO_4 and evaporated. Flash chromatography in 10/90 EtOAc/CH_2Cl_2 gave 1.0225 g (81%) of a white foam: R_f (30/70 EtOAc/Hex) 0.26, (5/95 *i*-PrOH/toluene) 0.42; IR (neat) 3030, 2972, 2865, 1795, 1760, 1720, 1608, 1550, 1450, 1250, 1125, 1025, 965; $[\alpha]'_D$ (Et_2O) +27.28°, *t* 24.1 °C, *c* 0.533; ^1H NMR δ (500 MHz, 1.1:1 *E*/*Z* Cbz rotamers) *major isomer* 7.45 (1 H, d, *J* = 5.5 Hz), 7.33 (2 H, d, *J* = 7.0 Hz), 7.28 (2 H, d, *J* = 6.0 Hz), 7.24 (2 H, m), 7.18 (7 H, m), 7.09 (1 H, m), 7.02 (2 H, m), 6.68 (2 H, d, *J* = 8.5 Hz), 5.89 (1 H, d, *J* = 9.0 Hz), 5.75 (2 H, m), 4.95 (2 H, m), 4.77 (1 H, d, *J* = 12.5 Hz), 3.74 (2 H, d, *J* = 4.5 Hz), 3.41 (2 H, d, *J* = 4.5 Hz), 2.86 (3 H, s), 1.29 (9 H, s), 1.18 (6 H, d, *J* = 6.5 Hz); *minor isomer* 6.73 (2 H, d, *J* = 8.5 Hz), 2.81 (3 H, s); mass spectrum (CI), *m/e* (relative intensity) 734 (M^+ + 1, 4.9), 678 (3.6), 634 (3.5), 484 (5.6), 450 (10.9), 440 (13.1), 350 (16.0), 332 (9.9), 305 (11.8), 283 (12.9); (HRCI) mol wt calcd for (M^+ + 1) 734.3441, found 734.3405.

2-[1(*R*)-(*N*-Carbobenzyloxy-*N*-methylamino)-2(*R*)-phenyl-2-[4'-(β-hydroxyethyl)phenoxy]ethyl]-4-benzyl-5-[(*tert*-butyloxycarbonyl)-amino]oxazole (25). The ester **24** (0.052 g, 0.068 mmol) was dried azeotropically (2 × 1 mL with toluene) and dissolved in 0.68 mL of THF (0.1 M) and cooled to 0 °C. LAH/THF solution (1 M) was added slowly dropwise (1.5 equiv, 0.13 mL, 0.13 mmol), and the reaction was stirred for 15 min. It was then added to a stirring quench solution of EtOAc/saturated aqueous NH_4Cl, then added to a separatory funnel, and extracted with 3 × 15 mL EtOAc (sometimes a little 1 M HCl was added to dissolve any aluminum salts). The combined extracts were dried over Na_2SO_4 and evaporated to a light oil. Flash chromatography in 10/90 to 30/70 EtOAc/CH_2Cl_2 gave 0.0414 g (89%) of a white foam: R_f (5/95 EtOAc/CH_2Cl_2) 0.07, (30/70 EtOAc/Hex) 0.05; IR (neat) 3300, 2920, 2860, 1690, 1600, 1450, 1360, 1150, 1020; $[\alpha]'_D$ (Et_2O) +32.20°, *t* 24.1 °C, *c* 0.217; ^1H NMR δ (500 MHz, 1.1:1 *E*/*Z* Cbz rotamers) *major isomer* 7.44 (1 H, m), 7.33 (1 H, m), 7.23 (14 H, m), 7.09 (1 H, m), 6.93 (2 H, m), 5.87 (1 H, br s), 5.70 (1 H, d, *J* = 9.0 Hz), 5.63 (1 H, s), 4.92 (1 H, t, *J* = 12.5 Hz), 4.78 (1 H, d, *J* = 12.5 Hz), 3.81 (2 H, d, *J* = 7.5 Hz), 3.765 (2 H, q, *J* = 6.0 Hz), 2.81 (3 H, s), 2.71 (2 H, t, *J* = 6.5 Hz), 1.42 (9 H, br s), 0.92 (6 H, m); *minor isomer* 6.65 (2 H, d, *J* = 8.5 Hz), 5.92 (1 H, br s), 5.80 (1 H, d, *J* = 9.5 Hz), 4.98 (1 H, d, *J* = 12.5 Hz), 2.86 (3 H, s); mass spectrum (CI), *m/e* (relative intensity) 678 (M^+ + 1, 1.8), 440 (23.5), 396 (5.2), 350 (21.8), 332 (17.6), 305 (34.3), 279 (9.7), 227 (20.8), 202 (9.8); (HRCI) mol wt calcd for $C_{40}H_{44}N_3O_7$ (M^+ + 1) 678.3179, found 678.3159.

2-[1(*R*)-(*N*-Carbobenzyloxy-*N*-methylamino)-2(*R*)-phenyl-2-[4-[2-[[(*p*-nitrophenyl)sulfonyl]oxy]ethyl]phenoxy]ethyl]-4-benzyl-5-[(*tert*-butylcarboxy)amino]oxazole (26). The alcohol **25** (0.092 g, 0.136 mmol) was dried well in vacuo and dissolved in CH_2Cl_2 (1.4 mL, 0.1 M) and cooled to 0 °C. DMAP (catalytic amount), and pyridine (3.0 equiv, 0.033 mL, 0.407 mmol) was added followed by portionwise addition of NsCl (about 1.5 equiv, 0.45 g, 0.204 mmol, over 2 h). The reaction was followed closely by TLC, and when complete, it was quenched by adding to a separatory funnel and extracted with 3 × 15 mL of $CHCl_3$ from aqueous saturated NH_4Cl. The combined extracts were dried over Na_2SO_4 and evaporated to a light yellow waxy oil. Flash chromatography with 30/70 EtOAc/Hex gave 0.095 g (82%) of a light yellow foam: R_f (30/70 EtOAc/Hex) 0.28; IR ($CHCl_3$) 3300, 3063, 3038, 2980, 2870, 1700, 1608, 1500, 1350, 1240, 1150, 950; $[\alpha]'_D$ (CH_2Cl_2) +53.84°, *t* 24.2 °C, *c* 0.086; ^1H NMR δ (500 MHz, 1.1:1 *E*/*Z* Cbz rotamers) *major isomer* 8.19 (2 H, dd, *J* = 9.0, 2.0 Hz), 7.70 (2 H, d, *J* = 8.5 Hz), 7.45 (2 H, m), 7.28 (8 H, m), 7.14 (5 H, m), 6.78 (2 H, dd, *J* = 8.0, 2.5 Hz), 6.62 (2 H, d, *J* = 8.5 Hz), 5.73 (1 H, d, *J* = 9.5 Hz), 5.66 (1 H, s), 4.96

(1 H, d, J = 12.5 Hz), 4.79 (1 H, d, J = 12.0 Hz), 4.23 (1 H, m), 4.12 (1 H, m), 3.80 (2 H, d, J = 6.5 Hz), 2.83 (5 H, s), 1.43 (9 H, br s); *minor isomer* 6.56 (2 H, d, J = 8.5 Hz), 5.84 (1 H, d, J = 9.5 Hz), 5.01 (1 H, d, J = 12.5 Hz), 4.91 (1 H, d, J = 2.5 Hz), 2.87 (3 H, s); mass spectrum (FAB), m/e (relative intensity) 863 (M^+ + 1, 10.4), 450 (12.6), 350 (6.8), 307 (16.8), 289 (9.3).

1⁴-Benzyl-2-(*tert*-butyloxycarbonyl)-8(*R*)-[*N*-(carbobenzyloxy)-*N*-methylamino]-7(*R*)-phenyl-2-aza-5(1,4)-benzena-6-oxa-1(2,5)-oxazolacyclooctaphane (27). Nosylate **26** (0.0262 g, 0.0304 mmol) was dissolved in THF (3.0 mL, 0.01 M) and cooled to 0 °C. NaH (washed 2 × 1 mL of Hex and dried in vacuo, 10.0 equiv, 0.007 g, 0.304 mmol) was added, and the reaction was warmed to room temperature where it was stirred for 2 days. The light yellow reaction mixture was added to a stirring solution of saturated NH_4Cl/EtOAc (about 50 mL each). The quench solution was added to a separatory funnel and extracted with 3 × 50 mL of EtOAc. The combined extracts were dried over Na_2SO_4 and evaporated to a light yellow oil. Flash chromatography in 10/90 EtOAc/CH_2Cl_2 gave 0.0151 g (76%) of a light yellow foam: R_f (5/95 *i*-PrOH/toluene) 0.33, (10/90 EtOAc/CH_2Cl_2) 0.37-very light blue UV active spot; t_R 6.76 min (25/75 EtOAc/Hexane, 2 mL/min, Zorbax silica, 270 nm detection); IR ($CHCl_3$) 3370, 3065, 3060, 2978, 2930, 1710, 1682, 1650, 1610, 1500, 1450, 1395, 1370, 1335, 1250, 910; $[\alpha]'_D$ ($CHCl_3$) +21.37°, t 22.0 °C, c 0.292; ^{1}H NMR δ (500 MHz) 7.47 (2 H, J = 7.0 Hz), 7.34 (4 H, m), 7.25 (4 H, m), 7.15 (3 H, m), 7.02 (2 H, d, J = 6.5 Hz), 6.90 (2 H, d, J = 8.0 Hz), 6.68 (2 H, d, J = 8.5 Hz), 5.22 (1 H, s), 5.06 (1 H, br m), 4.98 (2 H, br m), 3.76 (2 H, br s), 3.52 (2 H, br s), 3.14 (3 H, s), 2.68 (2 H, br s), 1.34 (9 H, br s); mass spectrum (CI), m/e (relative intensity) 660 (M^+ + 1, 70.2), 604 (34.5), 540 (22.6), 512 (22.0), 484 (23.8), 450 (39.0), 305 (26.8).

5-Benzyl-8(*R*)-[*N*-(carbobenzyloxy)-*N*-methylamino]-9(*R*)-phenyl-4,7-dioxo-3,6-diaza-11-benzena-10-oxacycloundecaphane (28). The cyclophane **27** (29 mg, 0.044 mmol) was dissolved in CH_2Cl_2 (0.5 mL). TFA (50 equiv, 0.15 mL) was added and the reaction stirred at room temperature for 4 h. The reaction was then concentrated in vacuo. Flash chromatography with 30/70 EtOAc/CH_2Cl_2 gave 18 mg (72%) of a white solid: R_f (5/95 *i*-PrOH/toluene) 0.23; IR ($CHCl_3$) 3310, 3020, 2930, 2862, 1720, 1700, 1640, 1510, 1450, 1345, 1340, 1210; $[\alpha]'_D$ ($CHCl_3$) +15.2°, t 23.1 °C, c 1.11; ^{1}H NMR δ (500 MHz, 2:1 E/Z Cbz rotamers) *major isomer* 7.31 (5 H, m), 7.19 (6 H, m), 7.14 (2 H, d, J = 7.0 Hz), 7.09 (2 H, br s), 6.84 (2 H, d, J = 8.0 Hz), 6.70 (2 H, d, J = 8.5 Hz), 6.58 (1 H, d, J = 7.5 Hz), 6.49 (1 H, t, J = 5.0 Hz), 4.98 (2 H, s), 4.55 (1 H, q, J = 7.0 Hz), 3.39 (2 H, m), 3.29 (1 H, m), 3.15 (1 H, m), 2.99 (1 H, m), 2.87 (3 H, s), 2.67 (1 H, m), 2.60 (1 H, pent, J = 7.0 Hz), 2.50 (1 H, pent, J = 7.0 Hz); *minor isomer* 6.96 (2 H, d, J = 8.5 Hz), 6.72 (2 H, d, J = 8.5 Hz), 6.30 (1 H, d, J = 8.0 Hz), 5.15 (1 H, d, J = 2.0 Hz), 5.10 (2 H, d, J = 12.0 Hz), 4.70 (1 H, q, J = 7.5 Hz); (500 MHz, $C_2D_2Cl_4$ at 125 °C), 7.15 (17 H, m), 6.86 (2 H, d, J = 8.5 Hz), 6.62 (2 H, d, J = 8.5 Hz), 6.29 (1 H, d, J = 6.0 Hz), 4.97 (2 H, s), 4.50 (1 H, dd, J = 12.5, 9.0 Hz), 3.30 (2 H, dd, J = 9.0, 6.0 Hz), 3.00 (2 H, m), 2.81 (3 H, s), 2.54 (2 H, sext, J = 9.0 Hz); (500 MHz, benzene-d_6) 7.20 (13 H, m), 6.77 (2 H, d, J = 8.5 Hz), 6.74 (2 H, d, J = 8.5 Hz), 6.69 (2 H, d, J = 8.5 Hz), 6.50 (1 H, m), 5.45 (2 H, br m), 5.00 (2 H, s), 4.73 (1 H, q, J = 7.5 Hz), 3.56 (1 H, t, J = 6.5 Hz), 3.41 (1 H, q, J = 6.5 Hz), 3.26 (1 H, pent, J = 7.0 Hz), 3.14 (1 H, m), 3.00 (1 H, m), 2.85 (3 H, br s), 2.40 (1 H, pent, J = 6.5 Hz), 2.35 (1 H, pent, J = 6.5 Hz); mass spectrum (LSIMS), m/e (relative intensity) 578 (M^+ + 1), 470, 441, 391, 374; (CI) 578 (M^+ + 1, 5.2), 560 (4.9), 498 (15.5), 470 (100.0), 441 (13.4), 352 (28.2), 333 (7.1), 305 (38.7); (HRLSIMS), mol wt calcd (M^+ + 1) 578.2655, found 578.2659; (CI) mol wt calcd (M^+ + 1) 578.2655, found 578.2648.

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Registry No. 3a, 41997-33-5; **3b**, 93139-50-5; (*Z*)-4, 127086-73-1; (*E*)-**4**, 127086-74-2; dihydro-**4**, 127086-76-4; **5**, 127086-75-3; **6** (R = CH_2Ph), 50288-70-5; **6** (R = *i*-Bu), 65451-12-9; **7** (R = CH_2Ph), 127086-77-5; **7** (R = *i*-Bu), 127086-78-6; **8** (R = CH_2Ph), 127086-79-7; **8** (R = *i*-Bu), 127086-80-0; **9a** (R = CH_2Ph), 127086-93-5; **9a** (R = *i*-Bu), 127086-97-9; **9b** (R = CH_2Ph), 127086-94-6; **9b** (R = *i*-Bu), 127086-98-0; **9c** (R = CH_2Ph), 127086-95-7; **9d** (R = CH_2Ph), 127086-96-8; **9d** (R = *i*-Bu), 127086-99-1; **10** (R = CH_2Ph, R^1 = CH_2Ph), 127087-00-7; **10** (R = *i*-Bu; R^1 = CH_2Ph), 127087-01-8; **10** (R = *i*-Bu; R^1 = *t*-Bu), 127087-02-9; **11a**, 127087-03-0; **11b**, 127102-46-9; **11c**, 127087-12-1; **11d**, 127087-13-2; **11e**, 127087-04-1; **11f**, 127087-05-2; **11g**, 127087-06-3; **12a** (dimer), 127087-07-4; **12b** (dimer), 127087-08-5; **12c** (dimer), 127087-09-6; **12d** (dimer), 127087-10-9; **12e** (dimer), 127102-47-0; **13** (dimer), 127087-11-0; **15**, 28143-91-1; **15** (*N*-Cbz derivative), 127102-27-6; **16**, 127086-81-1; **16** (*N*-methyl derivative), 127086-92-4; **17**, 127086-82-2; **18**, 127086-83-3; **19**, 127086-84-4; **19** (desilylated), 127086-85-5; **20**, 127102-44-7; **22**, 127086-86-6; **23**, 127086-87-7; **24**, 127086-88-8; **25**, 127086-89-9; **26**, 127086-90-2; **27**, 127102-45-8; **28**, 127086-91-3; 4-$HOC_6H_4CH_2COOH$, 156-38-7; PhC≡CCOOH, 637-44-5.