# Nonprostanoid Prostacyclin Mimetics. 4. Derivatives of 2-[3-[2-(4,5-Diphenyl-2-oxazolyl)ethyl]phenoxy]acetic Acid Substituted α to the Oxazole Ring[1]

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The 4,5-diphenyloxazole derivatives **2–4** were previously identified as nonprostanoid prostacyclin ($PGI_2$) mimetics. A series of derivatives of **2–4** bearing substitutents at the carbon atom α to the oxazole ring were synthesized and evaluated as inhibitors of ADP-induced aggregation of human platelets *in vitro*. In the unsaturated series, the α-carbethoxy derivative **10a**, evaluated as an equal mixture of geometrical isomers, inhibited platelet aggregation with an $IC_{50}$ of 0.36 μM. Evaluation of the individual methyl ester derivatives (*E*)-**9a** and (*Z*)-**9a** revealed that (*E*)-**9a** was 10-fold more potent than (*Z*)-**9a**. In the saturated series, the α-carbomethoxy-substituted compound **12a** inhibited platelet aggregation with an $IC_{50}$ of 0.08 μM, 15-fold more potent than the unsubstituted prototype **2**. The potency of **12a** was found to be sensitive to variation of the methoxy moiety. The ethyl (**12b**) and isopropyl (**12d**) esters were less effective as were the acid **12e** and a series of amides (**12f–h**). Other substituents introduced at this site of the pharmacophore included $P(O)(OEt)_2$ (**25**), $SCH_3$ (**31a**), $S(O)CH_3$ (**31b**), $SO_2CH_3$ (**31c**), isopropyl (**31d**), phenyl (**31f**), and $CH_2OH$ (**31i**). However, none were significantly more potent inhibitors of platelet function than the parent compound **2**. The results indicate the presence of a pocket in the $PGI_2$ receptor protein that preferentially recognizes small, polar but uncharged substituents. The structure–activity correlates are suggestive of a hydrogen-bond interaction between a donor moiety on the $PGI_2$ receptor and the methoxycarbonyl functionality of **12a** that is sensitive to both the size of the substituent and its stereochemical presentation in this structural class of $PGI_2$ mimetic. The ethyl ester **12b** dose-dependently displaced [$^3$H]iloprost from human platelet membranes and stimulated adenylate cyclase. However, the maximal stimulation was less than that recorded for iloprost, indicating that **12b** functions as a partial agonist at the $PGI_2$ receptor.

## Introduction

Clinical studies conducted with aspirin, dipyridamole, and ticlopidine have established the value of inhibitors of blood platelet aggregation in the prevention of arterial thrombosis and its sequelae.[2-7] However, these studies have also revealed deficiencies in these drugs[8,9] which provide an impetus to develop more effective platelet aggregation inhibitors with fewer side effects. As part of an effort to discover and develop broad spectrum inhibitors of blood platelet aggregation,[10-12] we have explored a series of nonprostanoid prostacyclin ($PGI_2$) mimetics.[1,13,14] These studies were initiated following the discovery that the triphenylated imidazole derivative octimibate (**1**) bound to the platelet prostacyclin receptor and stimulated adenylate cyclase.[15,16] A model of the $PGI_2$ mimetic pharmacophore intrinsic to octimibate was deduced from an analysis of the structure–activity relationships developed for a series of pyrazolo-alkanoic acids.[13] This model was further refined after synthesizing and evaluating a series of 4,5-diphenyloxazole derivatives[14] and related compounds.[1] BMY 42393 (**2**) was identified from these studies as a partial agonist at the human platelet $PGI_2$ receptor[14,17] that demonstrated effective and long-lasting antithrombotic activity in animal models of thrombosis.[17] An investigation of the structure–activity relationships associated with **2** revealed that biological activity was exquisitely sensitive to substitution or modification of the two phenyl rings bound to the oxazole heterocycle.[1] In contrast, the oxazole ring could be effectively replaced by a variety of 4,5-diphenylated heterocycle derivatives.[1] Modifications of the ethylene tether linking the oxazole heterocycle to the phenoxyacetic acid side chain moiety also had an impact on platelet inhibitory activity of **2**.[14] Although potency showed some dependence on the identity of the atoms comprising this tether, the most profound effect was a function of the topological relationship between the oxazole heterocycle and the side chain aromatic ring. The *trans* olefin **3** was found to be 1 order of magnitude weaker than **2** as an inhibitor of ADP-induced blood platelet aggregation while the *cis* isomer **4** was 6-fold more potent. In order to provide further insight into this nonprostanoid $PGI_2$ mimetic pharmacophore, we examined the effects of introducing substituents to the carbon atom α to the diphenylated oxazole ring of **2** and evaluated the capacity of these compounds to inhibit ADP-induced human platelet aggregation *in vitro*. The functional and steric demands of this region of the pharmacophore were probed by synthesizing and evaluating derivatives of **2** that incorporate hydrophobic substituents and hydrogen-bond-donating and -accepting functionality bound to this atom of the tether. As a result of this investigation, compounds that are intrinsically more potent inhibitors

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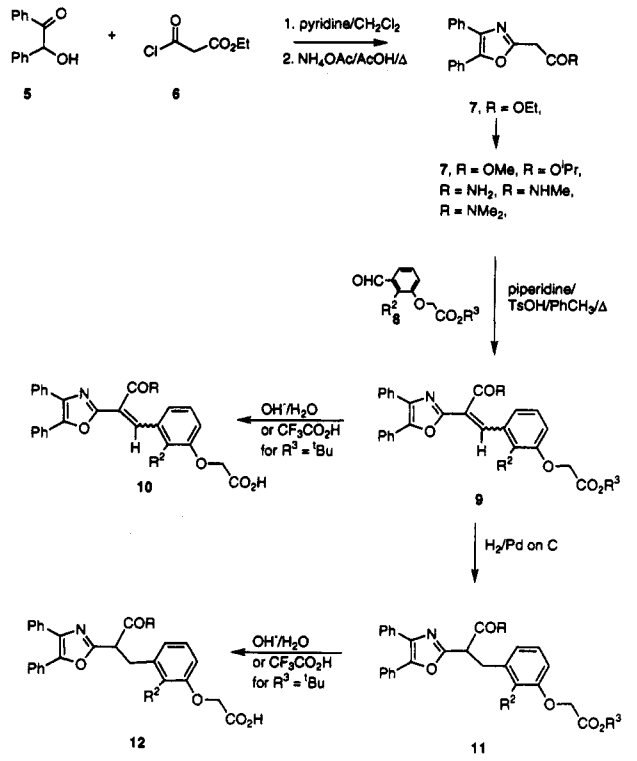
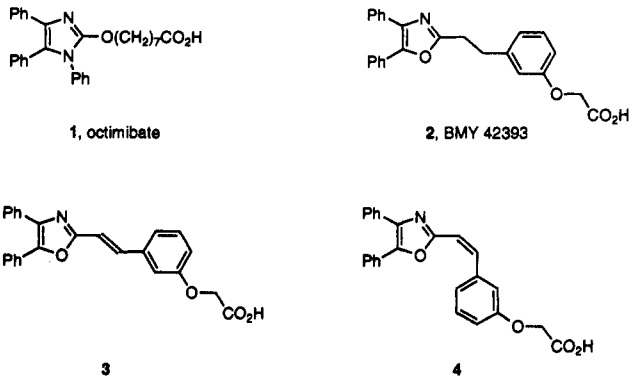
**Scheme I**



of platelet function *in vitro* than the prototype **2** have been identified.



## Chemistry

The ester[18] **7**, R = OEt, functioned as a versatile synthetic intermediate from which derivatives of **2** bearing $\alpha$-carboxy- and $\alpha$-carbamoyl substituents were prepared by the routes depicted in Scheme I. Acylation of benzoin (**5**) with ethyl malonyl chloride (**6**) followed by exposure of the crude product to an excess of $NH_4OAc$ in AcOH at reflux[19] provided ester **7**, R = OEt, which was purified by chromatography. Trans esterification of **7**, R = OEt, under basic or acidic conditions provided the corresponding methyl (**7**, R = OMe) and isopropyl esters (**7**, R = iPr) while being heated with $NH_3$, $MeNH_2$, or $Me_2NH$ at 150 °C in a sealed vessel afforded the respective amides (**7**, R = $NH_2$, R = NHMe, R = $NMe_2$). Condensation of **7** with an aromatic aldehyde **8**[14] under Knoenvenagel[20] conditions afforded the adducts **9** which, with the exception of **9f**, were isolated as mixtures of geometrical isomers. The ratio and identity of the (*E*) and (*Z*) isomers was determined by inspection of NMR spectral data. The olefinic proton resonating downfield was assigned to the (*E*) isomer in which this proton is *cis* to the carbonyl moiety. For **9f**, the geometry of the single product was determined to be of the (*Z*) configuration from the 8.2 Hz coupling constant measured between the olefinic proton and the oxazolyl C-2 carbon atom in the fully coupled $^{13}C$ spectrum, indicative of a *cis* relationship between these atoms.[21]

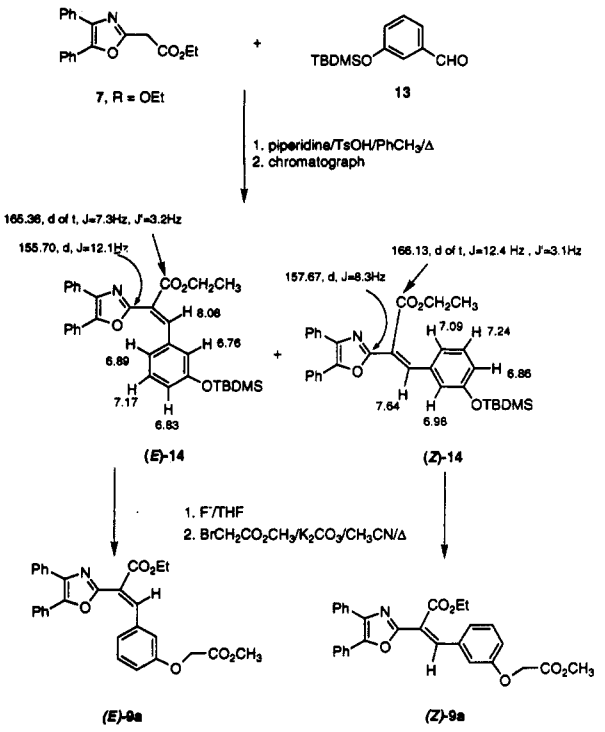
The choice of the oxyacetic ester moiety, $R^3$, of **8**, as either methyl or *tert*-butyl, was dictated by the nature of the subsequent synthetic transformations. An acid-sensitive *tert*-butyl ester was essential to facilitate selective unmasking of the phenoxyacetic acid functionality in the presence of other ester groups in **9** to afford the target acids **10**. Amide derivatives of **10** were prepared either by saponification of the methyl ester precursor or $CF_3CO_2H$-induced degradation of the *tert*-butyl ester. The diacid **10c** was obtained from **9**, R = OEt, $R^2$ = H, $R^3$ = Me, by saponification with NaOH in aqueous MeOH.

Access to the saturated series **12** was readily accomplished by catalytic hydrogenation of **9** to provide the saturated esters **11**. These were converted to the acids **12** under basic ($R^3$ = Me) or acidic ($R^3$ = *t*Bu) conditions, depending on the identity of R. The diacid **12e**, isolated as its disodium salt due to the propensity for the free acid to suffer decarboxylation, was obtained by saponification of **11**, R = OEt, $R^2$ = H, $R^3$ = OMe, using 2 equiv of NaOH in $MeOH/H_2O$.

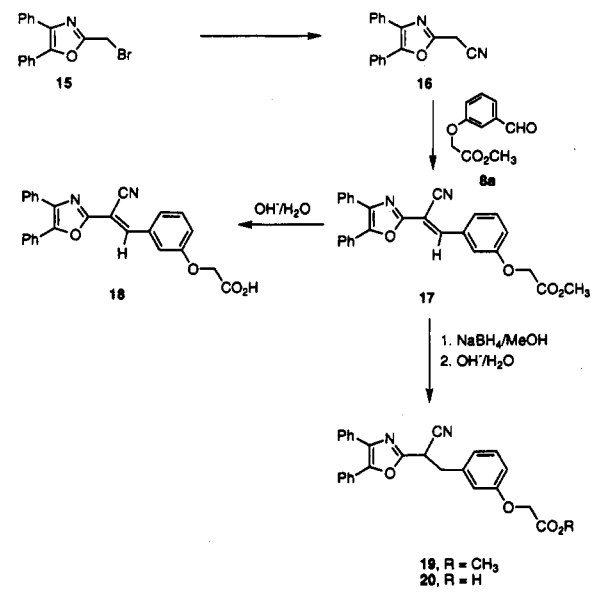
Attempts were made to separate the geometrical isomers of **10a** in order to determine the biological activity of the individual components, but these were not successful. Although (*E*)- and (*Z*)-**10a** were resolved by preparative HPLC (solvent, $CH_3CN/H_2O$/AcOH 55:44:1), concentration of apparently pure fractions led to the isolation of mixtures of geometrical isomers, presumably due to a facile acid-catalyzed equilibration. Since the methyl ester precursor to **2** is significantly unmasked in plasma during the 3-min incubation period,[14] an index of the relative platelet inhibitory activities of (*E*)- and (*Z*)-**10a** were inferred by evaluation of the methyl esters (*E*)- and (*Z*)-**9a**. These were isolated in homogenous form by the procedure outlined in Scheme II. Condensation of **7**, R = OEt, with aldehyde **13**[14] provided a mixture of the adducts **14** which were resolved by flash chromatography.[22] The less polar material was assigned the (*Z*) configuration on the basis of the measurement of long-range coupling constants between the olefinic proton and both the oxazole C-2 carbon and the ester carbonyl carbon observed in the fully coupled $^{13}C$ NMR spectrum. The magnitude of these coupling constants, which is summarized for (*E*)-**14** and (*Z*)-**14** in Scheme II, is dependent on geometry,[21] and complementary data recorded for the more polar material are consistent with designation as the (*E*) isomer. The individual isomers (*E*)-**14** and (*Z*)-**14** were desilylated by treatment with $nBu_4NF$ in anhydrous THF at −30 to −10 °C to provide the corresponding phenols with excellent retention of stereochemical integrity. Alkylation of the phenols with methyl bromoacetate in $CH_3CN$ at reflux, using $K_2CO_3$ as the base, provided (*E*)-**9a** and (*Z*)-**9a**.

The nitriles **18** and **20** were prepared by a similar strategy, which is summarized in Scheme III. Treatment of bromide **15**[23] with KCN provided the nitrile **16**,[18b] which was condensed with aldehyde **8a** to give a single adduct **17**. This material was identified as the (*E*) isomer on the basis of the observation that the C-2 carbon atom of the oxazole ring resonated as a doublet, $J$ = 7.8 Hz, at $\delta$ 155.7,

**Scheme II**




**Scheme III**

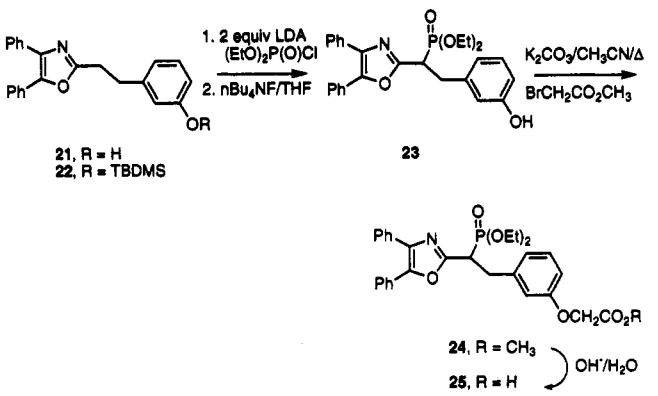



a coupling constant indicative of a *cis* relationship.[21] Saponification of **17** provided **18** while reduction with $NaBH_4$ in MeOH and subsequent saponification afforded acid **20**.

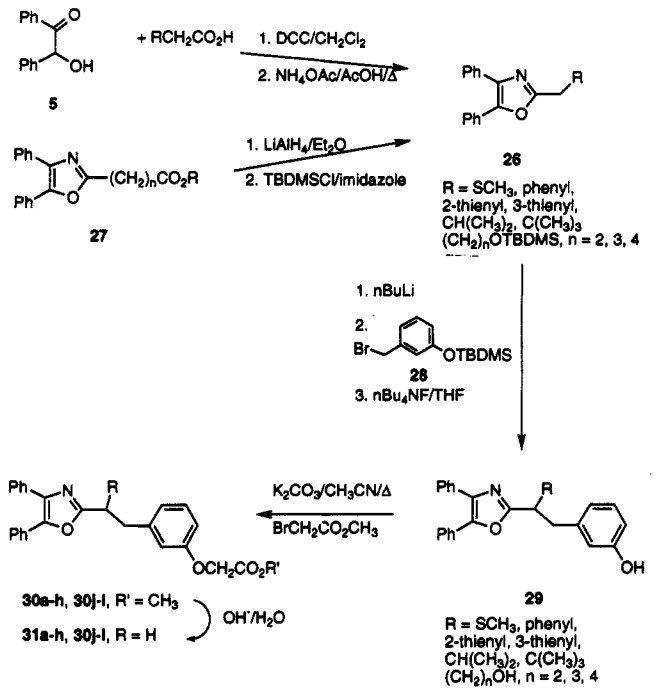
Scheme IV outlines the synthetic approach adopted to prepare the phosphonate **25**. Phenol **21**[14] was protected as its TBDMS[24] ether, **22**, and deprotonated[25] by treatment with 2 equiv of LDA in THF at −78°C. Addition of a slight excess of diethyl chlorophosphate provided a second anion which was quenched by adding $NH_4Cl$ solution, and the TBDMS protecting group was removed by exposing the crude reaction product to $nBu_4NF$ in THF. The phenol **23** was purified by chromatography and alkylated with methyl bromoacetate to afford **24**. Hydrolysis of **24** with LiOH in $MeOH/H_2O$ furnished the target acid **25**.

The complementary general synthetic strategy delineated in Scheme V provided access to the series of

**Scheme IV**

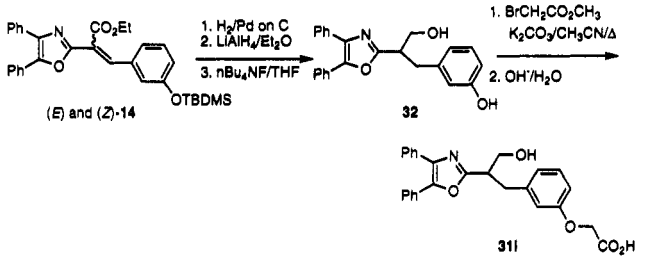



**Scheme V**

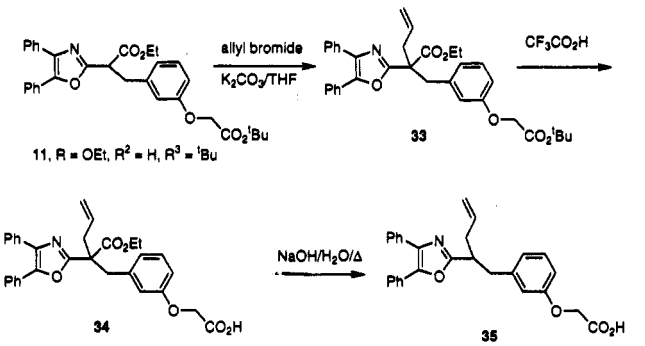



α-substituted compounds **31a–h** and **31j–l**. The requisite oxazole precursors were obtained by condensing benzoin (**5**) with a substituted acetic acid derivative and exposing the crude product to an excess of $NH_4OAc$ in AcOH at reflux to effect cyclization of the intermediate esters to the heterocycles **26**, R = $SCH_3$, phenyl, 2-thienyl, 3-thienyl, $CH(CH_3)_2$, and $C(CH_3)_3$. The TBDMS-protected alkyl alcohols **26**, R = $(CH_2)_nOTBDMS$, $n$ = 2, 3, and 4, were obtained from the appropriate oxazolo alkanoate ester[14] **27** by reduction with $LiAlH_4$ in $Et_2O$ and subsequent exposure to TBDMS-Cl and imidazole in DMF.[24] Deprotonation[25] of **26** with nBuLi in THF followed by the addition of the bromide **28**[1] afforded phenols **29**, after desilylation by exposing the crude reaction product to $nBu_4NF$ in THF. A 2-fold excess of $nBu_4NF$ was used to effect concomitant unmasking of the alkyl alcohol moiety in those substrates containing an additonal TBDMS protecting group. The phenols **29** were alkylated with methyl bromoacetate in $CH_3CN$ at reflux to furnish the phenoxyacetic esters **30a–h** and **30j–l** in good yield. The methyl sulfide **30a**, (**30**, R = $SCH_3$) was oxidized to the corresponding sulfoxide **30b**, R = $SOCH_3$, and sulfone **30c**, R = $SO_2CH_3$, using Oxone,[26] the former being selectively produced with limited reagent at −10 °C. Saponification of **30a–h** and **30j–l** provided the acids **31a–h** and **31j–l**.

**Scheme VI**




**Scheme VII**




The hydroxymethyl substituted analogue of **2**, alcohol **31i**, was obtained from a mixture of (*E*)-**14** and (*Z*)-**14** by the sequence of reactions shown in Scheme VI. Sequential reduction of the olefin ($H_2$/Pd on C) and ester ($LiAlH_4$/$Et_2O$) followed by deprotection ($nBu_4NF$/THF) gave phenol **32**, which was selectively alkylated with methyl bromoacetate, and the product was saponified to provide the target acid **31i**.

The allyl-substituted ester **34** was prepared from **11**, R = OEt, $R^2$ = H, $R^3$ = *t*Bu by alkylation with allyl bromide, using $K_2CO_3$ as the base in THF at room temperature, to afford **33**. (Scheme VII). Dissolution of **33** in trifluoroacetic acid provided ester acid **34**, which was saponified and decarboxylated in a single operation by heating with methanolic hydroxide to provide target compound **35**.

The compounds comprising this study of 4,5-diphenyloxazole-derived prostacyclin mimetics are compiled in Table I along with characteristic physicochemical properties.

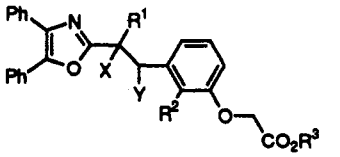
## Results and Discussion

The synthetic compounds were evaluated as inhibitors of human platelet aggregation *in vitro* in platelet-rich plasma (PRP) using 5.86 $\mu$M ADP as the inducing agent according to the previously described experimental protocol.[13,15] Under the standard conditions, the drug was incubated with PRP for 3 min prior to the addition of the agonist. The extent of aggregation in the presence of the test compound was compared with that in vehicle-treated controls, dose–response curves were obtained, and $IC_{50}$ values were determined. The results are presented in Table I, in which data for the oxazoles **2–4** are included for purposes of comparison. In this assay, $PGI_2$, iloprost, and octimibate exhibit $IC_{50}$'s of 8 nM, 2 nM and 1.02 $\mu$M, respectively.

The results summarized in Table I demonstrate that the presence of a substituent $\alpha$ to the oxazole ring of both **2** and the unsaturated derivatives **3** and **4** exerts a significant influence on the platelet inhibitory properties of this structural class of prostacyclin mimetic. Potency is sensitive to both the size and nature of the substituent and the structure–activity correlates provide further information about the structural and functional demands of the nonprostanoid $PGI_2$ mimetic pharmacophore.

Within the series of unsaturated derivatives (**10**) that were examined, the ethoxycarbonyl derivative **10a**, evaluated as a 1:1 mixture of geometrical isomers, is significantly more potent than the unsubstituted prototype **3** and only 2-fold weaker than the *cis* olefin isomer **4**. Although we were unable to isolate the individual isomers of **10a** in geometrically homogenous form and determine their platelet aggregation inhibititory activity, an index of the contribution of the individual components was derived by evaluating the methyl ester derivatives (*Z*)-**9a** and (*E*)-**9a**. The validity of this approach is based on the observation that in plasma the methyl ester of **2** is rapidly converted to the carboxylic acid with a half-life of approximately 1 min.[14,27] Indeed, as a reflection of the facility with which this occurs, the methyl ester of **2** is equipotent with **2** as an inhibitor of ADP-induced platelet aggregation *in vitro* under the standard conditions, which involve a 3 min incubation of drug in PRP prior to the addition of the agonist. This phenomenon was observed with the methyl esters of a number of the phenoxyacetic acid-containing nonprostanoid prostacyclin mimetics although the efficiency with which esterase-mediated cleavage occurred showed some variation and was dependent on structural identity.[28] Evaluation of the esters **9a** revealed that (*E*)-configured methyl ester (*E*)-**9a** is 10-fold more potent than its geometrical isomer (*Z*)-**9a**. However, these esters are approximately 1 order of magnitude weaker than would be anticipated on the basis of the activity recorded for the mixture of parent acids **10a**, which presumably reflects incomplete cleavage of the side chain methyl ester during the 3-min incubation period in plasma. The potency advantage enjoyed by (*E*)-**9a** over its isomer (*Z*)-**9a** parallels the structure–activity correlate recorded for the simpler olefins **3** and **4**[14] and reinforces the superiority of the *cis* relationship between the oxazole heterocycle and the side chain aromatic ring in this class of $PGI_2$ mimetic. However, the 10-fold difference in potency between the individual isomers of **9a** is somewhat less than that observed for **3** and **4** and is conceivably an underestimate of the differences should significant equilibration of the geometric isomers occur under the conditions of the platelet aggregation assay. Nevertheless, extrapolating this index of relative potency to the acids **10a** suggests that (*E*)-**10a** would exhibit an $IC_{50}$ of approximately 0.18 $\mu$M while (*Z*)-**10a** would be 1 order of magnitude weaker with an $IC_{50}$ of approximately 1.8 $\mu$M. Comparison of these estimates with the data recorded for **3** and **4** suggests that, for the *cis*-configured compound **4**, introduction of the ethoxycarbonyl moiety does not have a marked impact on biological activity. In contrast, the addition of the ethoxycarbonyl functionality to the *trans* isomer **3** appears to enhance potency by approximately 7-fold, an observation that suggests a specific interaction between the ester moiety of (*Z*)-**10a** and the receptor protein. However, the same functionality in (*E*)-**10a** would appear to be unable to take full advantage of this interaction, observations that suggest subtle differences in the manner in which (*E*)-**10a** and (*Z*)-**10a** bind to the $PGI_2$ receptor. In the earlier study,a topological model of the mode of binding of **3** and **4** was presented that suggested a high degree of overlap between the 4,5-diphenyloxazole and olefinic moieties of **3** and **4**, a projection that placed

**Table I.** Physical Properties and Biological Activity of 4,5-Diphenyloxazole Derivatives



| compd | $R^1$ | X, Y | $R^2$ | $R^3$ | mp, °C | anal.[a] | inhibition of ADP-induced aggregation of human platelets, $IC_{50}$, μM[b] |
|---|---|---|---|---|---|---|---|
| iloprost | | | | | | | 0.002 |
| **2** | H | H | H | H | 153–154.5 | $C_{25}H_{21}NO_4$ | 1.2 |
| **3** | H | bond (*E*) | H | H | 213–215 | $C_{25}H_{19}NO_4$ | 13 |
| **4** | H | bond (*Z*) | H | H | indistinct | $C_{25}H_{18}NO_4Na·1.45H_2O$ | 0.18 |
| **10a** | $CO_2Et$ | bond (1:1) | H | H | 54–56 | $C_{28}H_{23}NO_6·0.15H_2O$ | 0.36 |
| **(*Z*)-9a** | $CO_2Et$ | bond (*Z*) | H | Me | oil | $C_{29}H_{25}NO_6·0.3H_2O·0.15CHCl_3$ | 19.7 |
| **(*E*)-9a** | $CO_2Et$ | bond (*E*) | H | Me | oil | $C_{29}H_{25}NO_6·0.1H_2O·0.2CH_2Cl_2$ | 2.0 |
| **9ab** | $CO_2Et$ | bond (1:1) | H | tBu | oil | $C_{32}H_{31}NO_6$ | >60 |
| **10b** | $CO_2Et$ | bond (1:1) | OMe | H | 50–60 | $C_{29}H_{25}NO_7·0.4H_2O$ | 0.13 |
| **10c** | $CO_2H$ | bond (3:2) | H | H | 178–182 | $C_{26}H_{19}NO_6·0.15H_2O$ | 20.3 |
| **10d** | $CONHMe$ | bond (1:1) | H | H | 166–171 | $C_{27}H_{22}N_2O_5·0.7H_2O$[c] | 15.0 |
| **10e** | $CONMe_2$ | bond (*Z*) | H | H | 223–226 | $C_{28}H_{24}N_2O_5·0.4H_2O$ | 12.2 |
| **12a** | $CO_2Me$ | H | H | H | 122–127 | $C_{27}H_{23}NO_6$ | 0.08 |
| **12b** | $CO_2Et$ | H | H | H | 140–145 | $C_{28}H_{25}NO_6·1.2H_2O$ | 0.12 |
| **12c** | $CO_2Et$ | H | OMe | H | 47–53 | $C_{29}H_{27}NO_7·0.5H_2O$ | 1.18 |
| **12d** | $CO_2{}^iPr$ | H | H | H | 88–93 | $C_{29}H_{27}NO_6·0.3H_2O$ | 1.22 |
| **12e** | $CO_2Na$ | H | H | Na | indistinct | $C_{26}H_{19}NO_6·Na_2·0.65H_2O$ | 14.0 |
| **12f** | $CONH_2$ | H | H | H | 80–84 | $C_{26}H_{22}N_2O_5·0.7H_2O$ | 3.75 |
| **12g** | $CONHMe$ | H | H | H | 85–89 | $C_{27}H_{24}N_2O_5·0.4H_2O$ | 0.69 |
| **12h** | $CONMe_2$ | H | H | H | 76–80 | $C_{28}H_{26}N_2O_5·0.4H_2O$ | 3.56 |
| **18** | CN | bond (*E*) | H | H | 154–159 | $C_{26}H_{18}N_2O_4·0.6H_2O$ | 0.25 |
| **20** | CN | H | H | H | 166–171 | $C_{26}H_{20}N_2O_4·1.5H_2O$[d] | 0.44 |
| **25** | $P(O)(OEt)_2$ | H | H | H | glass | $C_{29}H_{30}NO_7P·0.3H_2O$ | 0.90 |
| **31a** | SMe | H | H | H | 127–129 | $C_{26}H_{23}NO_4S·0.1H_2O$ | 1.30 |
| **31b** | $S(O)Me$[e] | H | H | H | indistinct | $C_{26}H_{23}NO_5S·0.2H_2O·0.2C_4H_{10}O$ | 7.08 |
| **31c** | $SO_2Me$ | H | H | H | 105 (dec) | $C_{26}H_{23}NO_6·0.2H_2O·0.2CH_2Cl_2$ | 7.96 |
| **31d** | $CMe_2$ | H | H | H | 50–55 | $C_{28}H_{27}NO_4·0.6H_2O$ | 0.97 |
| **31e** | $CMe_3$ | H | H | H | 60–65 | $C_{29}H_{29}NO_4·0.5H_2O$ | 3.66 |
| **31f** | Ph | H | H | H | 108–110 | $C_{31}H_{25}NO_4·0.5CH_2Cl_2$ | 23.2 |
| **31g** | 2-thienyl | H | H | H | 149–151 | $C_{29}H_{23}NO_4S·0.1H_2O$ | 33.2 |
| **31h** | 3-thienyl | H | H | H | 139–140 | $C_{29}H_{23}NO_4S·0.1H_2O$ | 20.7 |
| **31i** | $CH_2OH$ | H | H | H | 78–84 | $C_{26}H_{23}NO_5$ | 9.31 |
| **31j** | $(CH_2)_2OH$ | H | H | H | 55–60 | $C_{27}H_{25}NO_5·0.7H_2O$ | 2.92 |
| **31k** | $(CH_2)_3OH$ | H | H | H | 53–58 | $C_{28}H_{27}NO_5·0.7H_2O$ | 1.70 |
| **31l** | $(CH_2)_4OH$ | H | H | H | 55–57 | $C_{29}H_{29}NO_5·0.5H_2O$ | 4.68 |
| **34** | $CO_2Et$ | X = $CH_2CH{=}CH_2$, Y = H | H | H | | $C_{31}H_{29}NO_6·0.5H_2O$ | 7.68 |
| **35** | $CH_2CH{=}CH_2$ | H | H | H | glass | $C_{28}H_{25}NO_4·0.15H_2O$ | 0.57 |

[a] Elemental analyses for C, H, and N are within ±0.4 of the theoretical values. [b] Blood platelet aggregometry was performed as previously described and the results presented are the result of a single experiment or the average of duplicates. Maximum variance (geometrical mean) was 70%. Octimibate displayed an $IC_{50}$ of 1.02 μM under these conditions. [c] N: calcd, 6.00; found, 5.26. [d] H: calcd, 5.14; found 4.38. N: calcd, 6.21; found, 5.36. [e] Isolated and evaluated as a 1.2:1 mixture of diastereoisomers.

the side chain aromatic rings in distinct regions of the receptor.[14] However, an alternative arrangement in which the side phenoxy rings of (*E*)-**10a** and (*Z*)-**10a** occupy a similar region of the receptor may account for the deduced potency differences between these compounds. Binding in this fashion would necessitate some differences in the way that the diphenylated oxazole moieties of the two isomers are accommodated by the receptor and, as a conequence, the carbethoxy groups of (*E*)-**10a** and (*Z*)-**10a** would be presented to the receptor protein in distinct orientations. Under these circumstances, the carbethoxy moiety of (*Z*)-**10a** may be in a position to align quite effectively with complementary functionality on the receptor protein, presumably a hydrogen-bond donor. However, the influence of the receptor protein on the orientation of (*E*)-**10a** may be such that the carbethoxy functionality of this isomer is distorted, relative to (*Z*)-**10a**, to the point that it is incapable of participating in the same hydrogen-bond donor–acceptor interaction.

Support for the contention that the activity of the individual isomers of **9a** is due to plasma esterase cleavage to the parent acid was obtained by evaluation of the *tert*-butyl ester **9ab**. This compound is inactive, presumably because the bulky *tert*-butyl moiety enhances stabilty towards plasma esterases thereby impeding rapid hydrolysis to the phenoxyacetic acid during the 3-min incubation period prior to the addition of ADP. The introduction of a methoxy substituent to the phenoxy ring of **10a** provided an equal mixture of isomers **10b** almost 3 times more potent than the prototype. This trend is qualitatively similar to that recorded for the same structural modification in the simpler olefin **3**, but the magnitude is diminished. However, interpretation of this result is difficult since the activity of the individual isomers of **10b** was not determined and cannot readily be estimated.

The structural variants of the ethyl ester moiety of **10a** that were evaluated did not provide compounds more active than the prototype. The mixtures of isomeric carboxylic acids **10c** and monomethyl amides **10d** are

considerably less potent than the mixture of ethyl esters **10a**. The dimethylamide **10e**, evaluated as the pure (*Z*) isomer, is 5-fold less than that estimated above for the corresponding ethyl ester, a structure–activity trend that suggests that smaller substituents are more readily tolerated at this site of the pharmacophore. Indeed, a sterically undemanding nitrile substituent provided compound **18**, isolated and evaluated as the pure (*E*) isomer, similar in efficacy to the mixture of esters **10a**. Remarkably, the nitrile **18** is over 50-fold more potent than the unsubstituted *trans* olefin **3** and only slightly less active than the *cis* isomer **4**. The significant benefit accorded by the linear nitrile moiety in **18**, particularly with respect to the angular ester (*Z*)-**10a**, may derive from an enhanced ability to participate in a hydrogen-bond donor–acceptor interaction with the receptor.[29] This geometrical arrangement suggests that the hydrogen-bond-donor moiety present in the $PGI_2$ receptor protein lies close to the junction of the olefin and oxazole heterocyle and in a similar plane.

Relief of the stereoelectronic constraints imposed by the unsaturation in **10a** removed the ambiguities associated with working with mixtures of geometrical isomers (but replaced it with enantiomeric mixtures) and provided compounds with enhanced platelet inhibitory activity. The saturated ethyl ester **12b** is 3-fold more potent than the mixture of esters **10a**, and the $IC_{50}$ is comparable to that estimated above for the more active component of **10a**. Moreover, the ester **12b** is over 1 order of magnitude more effective than the unsubstituted prototype **2**, clearly demonstrating the value of the ethoxycarbonyl substituent in this setting. An explanation for this obervation depends upon the hydrogen-bond donor–acceptor interaction postulated above. Thus, an increase in the conformational mobility of the ester moiety coupled with its altered geometrical disposition in these saturated compounds presumably allows the oxygen atoms to align more effectively with the putative hydrogen bond donating amino acid of the receptor.

The potency of **12b** is sensitive to the identity of the ester moiety, with the smaller methyl homologue **12a** more potent and the bulkier isopropyl ester **12d** considerably weaker, a finding suggestive of limited steric tolerance at this site of the pharmacophore. However, this structure–activity trend also correlates with the susceptibility of the ester moiety to plasma esterase-mediated hydrolysis, a premise dependent upon the relative potency of the parent carboxylic acid as an inhibitor of blood platelet aggregation. This would appear to be an unlikely explanation since carboxylic acid **12e** is a considerably weaker inhibitor of ADP-induced platelet aggregation than the esters **12a**, **12b**, and **12d**. The introduction of a methoxy substituent at a site on the side chain aryl ring known to be tolerant from the earlier study[14] is detrimental in this series and **12c** is 1 order of magnitude weaker than **12b**. This may be the result of unfavorable steric interactions between the ester and methoxy moieties that conspire to adversely influence conformational mobility. These interactions presumably interfere with the ability of **12c** to adopt a conformation able to effectively bind to the $PGI_2$ receptor and stimulate adenylate cyclase.

Since the acid **12e** is a weak inhbitor of platelet function, a series of amides were prepared and evaluated with the anticipation that they would offer enhanced metabolic stability *in vivo* compared to the ester moities of **12a–d**. However, none of amide derivatives **12f–h** provided a significant advantage over the esters **12a–d** or indeed the prototypical compound **2**. The monomethylamide **12g** is the most potent inhibitor of platelet function *in vitro* identified from this short series of compounds, but the unsubstituted primary amide **12f** and homologous dimethyl derivative **12h** are significantly less effective. The nitrile derivative **20** demonstrates enhanced potency compared to **2** and the isopropyl ester **12d** but is inferior to the smaller esters **12a** and **12b**. That the nitrile substituent is a less effective substituent than an ester in this setting, compared to the unsaturated series, is consistent with the arguments developed above for a hydrogen-bonding interaction that is highly sensitive to the stereochemical presentation of the acceptor functionality to the receptor donor.

Other polar substituents $\alpha$ to the oxazole ring were also explored in an effort to identify efficient platelet aggregation inhibitors and to further define this region of the nonprostanoid $PGI_2$ mimetic pharmacophore The diethyl phosphonate ester **25** is over 7-fold weaker than than ethyl ester **12b** but comparable with the isopropyl ester **12d** and parent structure **2**. The structure–activity trends elaborated for the carboxy esters and amides suggest that this is probably a consequence of the increased bulk associated with the diethyl phosphonate ester moiety. A methylthio substituent provided compound **31a** with no advantage over the prototype **2**, a result consistent with the role of the ester carbonyl of **12a–d** being that of a hydrogen-bond acceptor. Oxidation to the sulfoxide **31b** would provide a more effective hydrogen-bond-accepting functionality,[29] but surprisingly, this modification, evaluated as an inseparable mixture of diastereomers, led to a marked reduction in potency. The fully oxidized sulfone **31c** is of similar efficacy to sulfoxide **31b** as an inhibitor of ADP-induced platelet aggregation.

A series of compounds presenting lipophilic substituents $\alpha$ to the oxazole heterocycle were also prepared and evaluated. An isopropyl substituent provided compound **31d** with only a marginal advantage over the parent compound **2** while the *tert*-butyl homologue **31e** is considerably weaker. Increasing both the size and planarity of the substituent to that of a phenyl ring (**31f**) significantly diminished potency. A similar circumstance prevailed with the thiophene derivatives **31g** and **31h**, examined in both of the possible configurations, demonstrating an effective isosteric relationship[30] with a phenyl ring in this setting.

Hydroxyalkyl substituents offer the potential for participation in both hydrogen-bond-donating and -accepting interactions with the $PGI_2$ receptor in a fashion that can be modulated by varying the length of the alkylene chain. However, substituting **2** with a hydroxymethyl moiety provided compound **31i**, 7-fold weaker than the progenitor as a platelet aggregation inhibitor. Homologation of **31i** led to a progressive enhancement in potency that was optimal with the propyl alcohol **31k** but diminished as the chain was further extended (**31l**). However, the hydroxyalkyl functionality is an ineffective ester surrogate since **31k** is 20-fold weaker than methyl ester **12a** and offers no significant advantage over **2**.

A lipophilic allyl $\alpha$-substituent is tolerated and **35** is comparable in potency to **2**. However, hybridization of this substituent with the $\alpha$-carboxyethyl ester moiety of

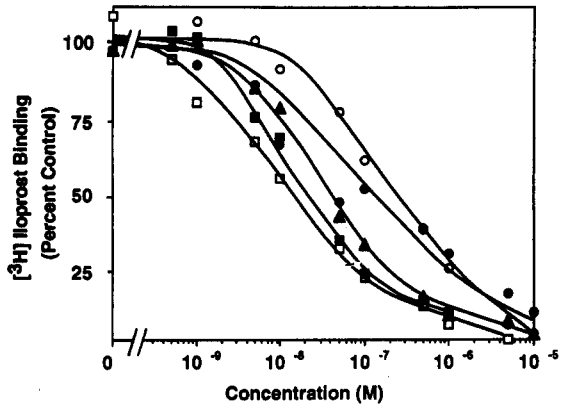



**Figure 1.** Effects of iloprost (▲), **2** (●), **12a** (□), **12b** (■) and **25** (○) on [$^3$H]iloprost binding to isolated human platelet membranes. Binding studies were performed using 5 nM [$^3$H]iloprost at 37 °C, as described previously.[13,15,17]This experiment is representative of three to five such determinations that gave similar results.

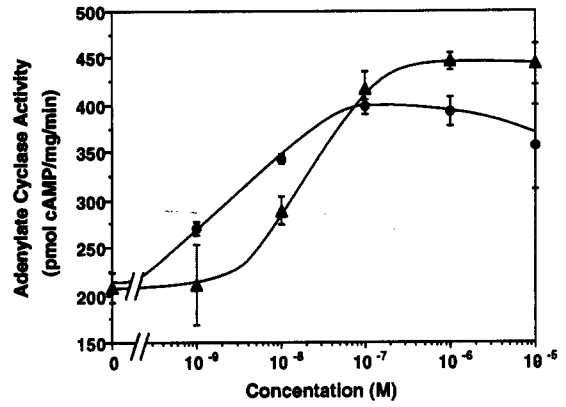



**Figure 2.** Stimulation of human platelet adenylate cyclase activity by **2** (▲) and **12b** (●). Adenylate cyclase activity was determined in the present of 10 μM GTP and the indicated concentrations of **2** and **12b** and was performed according to protocols previously described.[13,15,17] Each point represents the mean ± standard deviation of triplicate determinations within a representative experiment. This figure is representative of six such experiments that gave similar results.

**12b** leads to a compound, **34**, inferior to both as an inhibitor of blood platelet aggregation.

From this series of compounds, the ethyl ester **12b** was selected for more detailed evaluation at the biochemical and pharmacological level since it presents as a potent platelet aggregation inhibitor that would be expected to offer enhanced stability to plasma esterases compared to the more potent methyl analogue **12a**. The increased platelet aggregation inhibitory potency associated with **12b**, compared to **2**, correlates with affinity for the platelet $PGI_2$ receptor, as determined by the ligand binding studies presented in Figure 1. Both **2** and **12b** displace [$^3$H]-iloprost from human platelet membranes in a concentration-dependent fashion with $IC_{50}$'s of 155 ± 97 nM ($n$ = 3) for **2** and 14 ± 10 nM ($n$ = 5) for **12b**, which compares with an $IC_{50}$ of 45 ± 17 nM ($n$ = 4) for unlabeled iloprost in the same experiment. Comparative binding data are also presented in Figure 1 for **12a**, $IC_{50}$ =15 ± 4 nM ($n$ = 3), and **25**, $IC_{50}$ = 163 ± 47 ($n$ = 3). That ester **12b** is also a more potent stimulator of platelet adenylate cyclase than **2** is shown in Figure 2, where the effects of the two compounds are directly compared. The parent structure **2** stimulates adenylate cyclase in a concentration-dependent fashion that is half-maximal at a concentration of 31 ± 10 nM ($n$ = 3) while ester **12b** is 4-fold more effective with an $IC_{50}$ of 8 ± 7 nM ($n$ = 6). For comparison purposes, the $IC_{50}$ recorded for iloprost under these conditions was 24 ± 19 nM (n = 6) (data not shown). However, as with all of the nonprostanoid $PGI_2$ mimetics described to date,[15-17,31] the maximal stimulation of adenylate cyclase by **12b** is less than that observed with iloprost or $PGE_1$ (data not shown) and **12b** is thus classified as a partial agonist at the platelet $PGI_2$ receptor.

The superior activity of ester **12b** compared to **2** as an inhibitor of ADP-induced human platelet aggregation *in vitro* did not translate to a situation involving systemic exposure of the drug. Since the platelet inhibitory properties of this class of nonprostanoid $PGI_2$ mimetic show marked species dependence,[3,13,14,16,31] a heterologous *ex vivo* aggregometry (HEVA) paradigm,[32,33] performed in rats, was employed to evaluate the activity of these compounds *in vivo*. The experimental protocol comprised oral dosing of rats with drug 2 h prior to withdrawing a blood sample which was used to prepare platelet-poor plasma. This was combined with washed human platelets and the extent of aggregation in response to an ADP challenge compared with that in controls from animals dosed with vehicle alone. In this assay, an orally administered dose of 10 mg/kg of **2** inhibited platelet aggregation by 78 ± 20% ($n$ = 21), but in contrast, the same dose of **12b** inhibited platelet aggregation by less than 20% ($n$ = 3). The observed differences in potency between **2** and **12b** are most likely due to metabolic degradation of the ester moiety of **12b** to the corresponding carboxylic acid **12e**, which is over 150-fold weaker as an inhibitor of platelet aggregation *in vitro*. Unfortunately, substituents that would be anticipated to offer enhanced metabolic stability compared to the ethyl ester moiety of **12b** provided no significant advantage over the prototype **2** in the *in vitro* aggregometry assay and were not investigated further.

In summary, the structure–activity relationships that have been devoloped from this study of 4,5-diphenyloxazole derivatives provide further insight into the functional requirements of the nonprostanoid prostacyclin mimetic pharmacophore. The results are consistent with the existence of a pocket on the receptor that accommodates substituents α to the diphenylated oxazole heterocycle. This pocket prefers small, polar functional groups that are capable of engaging in a specific interaction with elements of the receptor protein and compounds able to take advantage of this interaction demonstrate enhanced potency compared to the prototypes **2** and **3**. In contrast,charged or lipophilic substituents are tolerated only poorly and derivatives of **2** presenting this kind of a substituent are only weakly effective as inhibitors of ADP-induced platelet aggregation. The beneficial effect of substitution α to the oxazole ring is most effectively exemplified with derivatives of **2** that incorporate a carbomethoxy (**12a**) or carbethoxy (**12b**) substituent, and these compounds are significantly more potent than the prototype. The introduction of a carbethoxy or nitrile substituent at this site of the *trans*-olefin **3** also leads to compounds with enhanced biological activity, but this does not appear to extend to the *cis*-olefin isomer **4**. Taken together, the structure–activity relationships are suggestive of a role for the polar substituent as a hydrogen-bond acceptor that effectively complements a donor on the receptor. However, this interaction appears to be highly

sensitive to both the stereochemistry of the hydrogen bond acceptor moiety presented by the agonist, with planar functionality optimal, and its orientation relative to the other pharmacophoric elements. The high level of platelet inhibitory activity demonstrated by nitrile **18** suggests that this class of $PGI_2$ mimetic adopts a relatively planar topography and that the hydrogen-bond-accepting atom is optimally located proximate to the junction of the 2-position of the oxazole ring and the side chain tether. These two facets of structure–activity correlations are explored in further detail in the accompanying article.[34]

## Experimental Section

Melting points were recorded on a Thomas-Hoover capillary apparatus and are uncorrected. Proton ($^1$H NMR) magnetic resonance spectra were recorded on either a Bruker AM or a Varian Gemini FT instrument operating at 300 MHz. All spectra were recorded using tetramethylsilane as an internal standard and signal multiplicity was designated according to the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet. Infrared (IR) spectra were obtained using a Perkin-Elmer 1800 FT IR, scanning from 4000 to 400 $cm^{-1}$ and calibrated to the 1601-$cm^{-1}$ absorption of a polystyrene film. Mass spectral data were obtained on a Finnigan Model 4500 GC/MS using electrical or chemical ionization (isobutane) procedures. Fast atom bombardment (FAB) mass spectra were obtained on a Kratos MS 25 spectrometer using *m*-nitrobenzyl alcohol (NOBA) as the matrix. Analytical samples were dried *in vacuo* at 78 °C or in the presence of $P_2O_5$ at room temperature for at least 12 h. Elemental analyses were provided by Bristol-Myers Squibb's Analytical Chemistry Department or Oneida Research Services, Whitesboro, NY. Unless otherwise stated, an extractive workup procedure comprised of extraction of the aqueous layer with solvent (three times), washing the combined extracts with $H_2O$ (usually a single time except where DMF or AcOH was present when the organic phase was washed three times), and drying over $Na_2SO_4$ or $MgSO_4$ prior to evaporation of the solvent *in vacuo*.

**Ethyl 4,5-Diphenyl-2-oxazoleacetate (7, R = OEt).** Ethyl malonyl chloride (25.68 g, 0.17 mol) was added dropwise to a stirred solution of benzoin (32.90 g, 0.155 mol), pyridine (13.53 g, 0.17 mol), and 4-(dimethylamino)pyridine (catalytic amount) in $CH_2Cl_2$ (300 mL) maintained at 10°C with an ice–water bath. The mixture was stirred for 30 min at 10°C and 2 h at room temperature before being concentrated *in vacuo*. Glacial AcOH (600 mL) and $NH_4OAc$ (59.68 g, 0.775 mol) were added to the residue, and the mixture was heated at reflux. After 2 h, the solution was diluted with $H_2O$ and extracted with $CH_2Cl_2$ to leave an oil which was chromatographed on a column of silica gel using a mixture of hexanes and EtOAc (17:3) as eluent to give **7**, R = OEt (29.62 g, 61%). Recrystallization from a mixture of hexanes and $CH_2Cl_2$ (8:1) gave analytically pure material: mp 71–72 °C; IR (KBr) 1740 ($CO_2Et$) $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.26 (3H, t, $J$ = 7 Hz, $CO_2CH_2CH_3$), 3.91 (2H, s, $CH_2CO_2Et$), 4.22 (2H, q, $J$ = 7 Hz, $OCH_2$), 7.25–7.45 (6H, m, aromatic *H*), 7.50–7.75 (4H, m, aromatic *H*); MS *m/z* 308 ($MH^+$). Anal. ($C_{19}H_{17}NO_3$) C, H, N.

**(*E*)- and (*Z*)-Ethyl α-[[3-[[(1,1-Dimethylethoxy)carbonyl]methoxy]phenyl]methylene]-4,5-diphenyl-2-oxazoleacetate (9ab).** A mixture of **7**, R = OEt (25.00 g, 81 mmol), 1,1-dimethylethyl (3-formylphenoxy)acetate (19.22 g, 81 mmol), piperidine (0.69 g, 8 mmol), *p*-TsOH (catalytic quantity), and toluene (200 mL) was heated at reflux under a Dean–Stark trap. After 18 h, the mixture was cooled, diluted with $H_2O$, and extracted with $CH_2Cl_2$ to afford an oil which was subjected to chromatography on a column of silica gel. Elution with a mixture of hexanes and EtOAc (4:1) afforded **9ab** (41.49 g, 97%) as an oil: IR (film) 1760, 1730 ($CO_2R$) $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.28–1.36 (4H, overlapping triplets, $OCH_2CH_3$), 1.37 (9H, s, $C(CH_3)_3$) of one isomer), 1.47 (9H, s, $C(CH_3)_3$ of other isomer), 4.30 (2H, s, $OCH_2CO_2{}^tBu$), 4.50 (2H, s, $OCH_2CO_2{}^tBu$), 4.33 (2H, q, $J$ = 7 Hz, $OCH_2CH_3$), 4.41 (2H, q, $J$ = 7 Hz, $OCH_2CH_3$), 6.70–7.70 (29H, m, aromatic *H* + 1 olefinic *H* of (*Z*) isomer), 8.07 (1H, s, olefinic *H* of (*E*) isomer); MS *m/z* 526 ($MH^+$). Anal. ($C_{32}H_{31}NO_6$) C, H, N.

**Ethyl α-[[3-(Carboxymethoxy)phenyl]methylene]-4,5-diphenyl-2-oxazoleacetate (10a).** A solution of **9ab** (0.70 g, 1.3 mmol) in $CF_3CO_2H$ (6 mL) was stirred at room temperature for 1 h. The mixture was diluted with EtOAc and $H_2O$, and the organic layer wa separated, washed with $H_2O$ and saturated brine, and dried over $Na_2SO_4$. Evaporation of the solvent left an oil which was chromatographed on a column of silica gel using a mixture of $CHCl_3$ and MeOH (24:1) as eluent to give **10a** (0.41 g, 66%) as a yellow foam: mp 54–56 °C; IR (KBr) 1725 $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.20–1.38 (6H, overlapping t, $OCH_2CH_3$), 4.32 (2H, q, $J$ = 7 Hz, $OCH_2$), 4.39 (2H, q, $J$ = 7 Hz, $OCH_2$), 4.43 (2H, s, $OCH_2CO_2H$), 4.62 (2H, s, $OCH_2$), 6.70–7.75 (11H, m, aromatic *H* + olefinic *H* of (*Z*) isomer), 8.08 (1H, s, olefinic *H* of (*E*) isomer), 8.65 (1H, bs, $CO_2H$); MS *m/z* 470 ($M^+$). Anal. ($C_{28}H_{23}NO_6 \cdot 0.15H_2O$) C, H, N.

**(*E*)- and (*Z*)- α-[[3-(2-Hydroxy-2-oxoethoxy)phenyl]methylene]-4,5-diphenyl-2-oxazoleacetic Acid (10c).** A mixture of **9**, R = OEt, $R^2$ = H, $R^3$ = Me (2.32 g, 5 mmol), a 3 N NaOH solution (6.6 mL, 20 mmol), and MeOH (125 mL) was heated at reflux on a steam bath for 10 min. The mixture was cooled and concentrated *in vacuo* and the residue diluted with $H_2O$ and 2 N HCl solution until pH = 2. The mixture was extracted with $CH_2Cl_2$ to leave a solid which was dissolved in $CH_2Cl_2$. The addition of hexanes gave a yellow solid which was recrystallized from a mixture of $CH_2Cl_2$, hexanes, and MeOH (3:2:1) to furnish **10c** (0.85 g, 39%), mp 178–182°C, as a 3:2 mixture of (*E*) and (*Z*) isomers: IR (KBr) 3060, 2920, 1740, 1720 $cm^{-1}$; $^1$H NMR (DMSO-$d_6$) $\delta$ 4.56 (2H, s, $OCH_2$), 4.69 (2H, s, $OCH_2$), 6.80–7.00 (2H, m, aryl *H ortho* to O), 7.20–7.70 (24H, m, aryl *H* + olefinic *H*), 8.08 (1H, s, olefinic *H cis* to acid); MS *m/z* 442 ($M^+$). Anal. ($C_{26}H_{19}NO_6 \cdot 0.15H_2O$) C, H, N.

**Ethyl α-[[3-[[(1,1-Dimethylethoxy)carbonyl]methoxy]phenyl]methyl]-4,5-diphenyl-2-oxazoleacetate (11, R = OEt, $R^2$ = H, $R^3$ = tBu).** A solution of **9ab** (2.15 g, 4 mmol) in EtOAc (75 mL) was hydrogenated at 30 psi over 10% Pd on C (0.30 g) in a Parr hydrogenation apparatus. After hydrogen uptake ceased, the mixture was filtered through Celite and concentrated to leave an oil which was subjected to chromatography on a column of silica gel. Elution with a mixture of hexanes and EtOAc (9:1) afforded **11**, R = OEt, $R^2$ = H, $R^3$ = tBu (1.05 g, 48%): IR (film) 1745 $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.19 (3H, t, $J$ = 7 Hz, $OCH_2CH_3$), 1.45 (9H, s, $OC(CH_3)_3$), 3.44 (2H, overlapping AB q, $CH_2$-aryl), 4.18 (3H, q, $CHCO_2CH_2CH_3$), 4.43 (2H, s, $OCH_2$), 6.72 (1H, dd, $J$ = 7 Hz, $J'$ = 2 Hz, aryl *H ortho* to O), 6.75 (1H, d, $J$ = 2 Hz, aryl *H ortho* to O), 6.86 (1H, d, $J$ = 7 Hz, aryl *H para* to O), 7.17 (1H, t, $J$ = 7 Hz, aryl *H meta* to O), 7.25–7.42 (6H, m, aromatic *H*), 7.50–7.70 (4H, m, aromatic *H*); MS *m/z* 528 ($M^+$). Anal. ($C_{32}H_{33}NO_6 \cdot 0.15H_2O$) C, H, N.

**Ethyl α-[[3-(2-Hydroxy-2-oxoethoxy)phenyl]methyl]-4,5-diphenyl-2-oxazoleacetate (12b).** A solution of ethyl α-[[3-[[(1,1-dimethylethoxy)carbonyl]methoxy]phenyl]methyl]-4,5-diphenyl-2-oxazoleacetate (3.74 g, 7 mmol) in $CF_3CO_2H$ (17 mL) was stirred at room temperature. After 1 h, the mixture was diluted with $H_2O$ and extracted with EtOAc to afford an oil which was chromatographed on a column of silica gel using a mixture of $CHCl_3$ and MeOH (97:3) as eluent. Elution gave **12b** as a yellow solid (2.09 g, 62%): mp 140–145 °C; IR (KBr) 1740 $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.19 (3H, t, $J$ = 7 Hz, $CO_2CH_2CH_3$), 3.43 (2H, doublet of AB q, $J$ =14 Hz, $J'$ = 7 Hz, $CH_2$-aryl), 4.17 (2H, q, $J$ = 7 Hz, $OCH_2$), 4.39 (1H, t, $J$ = 7 Hz, $CH{\cdot}CO_2Et$), 4.57 (2H, s, $OCH_2$), 6.75 (1H, dd, $J$ = 7 Hz, $J'$ = 2 Hz, aromatic *H ortho* to O), 6.84 (2H, m, aromatic *H ortho* and *para* to O), 7.16 (1H, t, $J$ = 7 Hz, aromatic *H meta* to O), 7.30–7.75 (10H, m, aromatic *H*); MS *m/z* 472 ($M^+$). Anal. ($C_{28}H_{25}NO_6 \cdot 1.2H_2O$) C, H, N.

**α-[[3-(2-Hydroxy-2-oxoethoxy)phenyl]methyl]-4,5-diphenyl-2-oxazoleacetic Acid, Disodium Salt (12e).** A mixture of **11**, R = OEt, $R^2$ = H, $R^3$ = Me (1.50 g, 3.1 mmol), NaOH (0.245 g, 6.1 mmol), and MeOH (15 mL) was stirred at room temperature for 24 h and at reflux for 18.5 h. The solvent was evaporated to leave **12e** as a solid (1.55 g, 100%): mp indistinct; IR (KBr) 3400, 1610 $cm^{-1}$; $^1$H NMR ($D_2O$) $\delta$ 3.24 (1H, dd, $J$ = 13 Hz, $J'$ = 13 Hz, $CH_2Ar$), 3.38 (1H, dd, $J$ = 13 Hz, $J'$ = 6 Hz, $CH_2Ar$), 4.06 (1H,

dd, $J$ = 13 Hz, $J'$ = 6 Hz, $CHCO_2Na$), 4.26 (2H, s, $OCH_2$), 6.60 (1H, dd, $J$ = 7 Hz, $J'$ = 2 Hz, aromatic *H ortho* to O), 6.70–6.95 (2H, m, aromatic *H ortho* and *para* to O), 7.00–7.40 (11H, m, aromatic *H*); MS *m/z* 342 ($MH^+ - CO_2$ and $CH_2CO_2$). Anal. ($C_{26}H_{19}NO_6Na_2 \cdot 0.65H_2O$) C, H, N.

**4,5-Diphenyl-2-oxazoleacetamide (7, R = $NH_2$).** A mixture of 7, R = OEt (10.24 g, 33 mmol), and $NH_3$ (35 mL) was heated in a bomb at 130 °C for 24 h. After evaporation of the $NH_3$, the residue was chromatographed on a column of silica gel using EtOAc/hexanes (4:1) as eluent to give 7, R = $NH_2$ (3.21 g, 34%): mp 129–133 °C; IR (KBr) 3340, 3200, 1665 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 3.83 (2H, s, $CH_2CONH_2$), 7.27–7.40 (6H, m, aromatic *H*), 6.50–6.68 (4H, m, aromatic *H*); MS *m/z* 279 ($MH^+$). Anal. ($C_{17}H_{14}N_2O_2$) C, H, N.

**(*E*)-and (*Z*)-Ethyl α-[[3-[(1,1-Dimethylethyl)dimethylsiloxy]phenyl]methylene]-4,5-diphenyl-2-oxazoleacetate (14).** A mixture of 7, R = OEt (10.33 g, 33 mmol), 13 (7.94 g, 33 mmol), piperidine (0.29 g, 33 mmol), *p*-TsOH (catalytic quantity), and toluene (120 mL) was heated at reflux under a Dean–Stark trap. After 3 h, the solvent was evaporated and the residual oil chromatographed repeatedly on a column of silica gel using a mixture of hexanes and EtOAc (19:1) as eluent. The less polar material was identified as (*Z*)-14 (5.27 g, 30%) and had mp 97–100 °C: IR (KBr) 1730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.22 (6H, s, $Si(CH_3)_2$), 1.00 (9H, s, $C(CH_3)_3$), 1.34 (3H, t, $J$ = 7 Hz, $OCH_2CH_3$), 4.43 (2H, q, $J$ = 7 Hz, $OCH_2$), 6.86 (1H, dd, $J$ = 7 Hz, $J'$ = 2 Hz, aromatic *H ortho* to O), 6.98 (1H, d, $J$ = 2 Hz, aromatic *H ortho* to O), 7.09 (1H, d, $J$ = 7 Hz, aromatic *H para* to O), 7.24 (1H, t, $J$ = 7 Hz, aromatic *H meta* to O), 7.27–7.45 (6H, m, aromatic *H*), 7.58–7.73 (5H, m, aromatic *H* + olefinic *H*); MS *m/z* 526 ($MH^+$). Anal. ($C_{32}H_{35}NO_4Si$) C, H, N.

The more polar material was identified as the (*E*)-14 (5.78 g, 32%): IR (film) 1725 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.05 (6H, s, $Si(CH_3)_2$), 0.86 (9H, s, $C(CH_3)_3$), 1.32 (3H, t, $J$ = 7 Hz, $OCH_2CH_3$), 4.32 (2H, q, $J$ = 7 Hz, $OCH_2$), 6.76 (1H, t, $J$ = 2 Hz, aromatic *H ortho* to O), 6.83 (1H, dt, $J$ = 8 Hz, $J'$ = 2 Hz, aromatic *H ortho* to O), 6.89 (1H, d, $J$ = 8 Hz, aromatic *H para* to O), 7.17 (1H, t, $J$ = 8 Hz, aromatic *H meta* to O), 7.25–7.40 (6H, m, aromatic *H*), 7.66–7.72 (2H, m, aromatic *H*), 8.08 (1H, s, olefinic *H*); MS *m/z* 526 ($MH^+$). Anal. ($C_{32}H_{35}NO_4Si$) C, H, N.

**(*Z*)-Ethyl α-[[3-(2-Methoxy-2-oxoethoxy)phenyl]methylene]-4,5-diphenyl-2-oxazoleacetate ((*Z*)-9a).** A solution of (*Z*)-14 (1.87 g, 3.6 mmol) in anhydrous THF (60 mL) maintained under an atmosphere of nitrogen was cooled to −30°C and $nBu_4NF$ (1.02 g, 4 mmol) in THF (3.92 mL) added dropwise. The mixture was stirred for 30 min before being diluted with saturated $NH_4Cl$ solution and extracted with $Et_2O$ to give an oil (1.46 g) which was dissolved in $CH_3CN$ (70 mL). Methyl bromoacetate (0.60 g, 3.9 mmol), $K_2CO_3$ (0.59 g, 4.3 mmol), and KI (catalytic quantity) were added, and the mixture was heated at reflux for 1 h. The mixture was filtered through Celite and concentrated and the residual oil subjected sequentially to column and radial chromatography over silica gel using $CHCl_3$ as eluent to give (*Z*)-9a (0.97 g, 56%): IR (film) 1765, 1740, 1215 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.20 (3H, t, $J$ = 7 Hz, $OCH_2CH_3$), 3.79 (3H, s, $CO_2CH_3$), 4.39 (2H, q, $J$ = 7 Hz, $OCH_2CH_3$), 4.62 (2H, s $OCH_2$), 6.90 (1H, dd, $J$ = 7 Hz, $J'$ = 2 Hz, aromatic *H ortho* to O), 6.98 (1H, d, $J$ = 2 Hz, aromatic *H ortho* to O), 7.10 (1H, d, $J$ = 7 Hz, aromatic *H para* to O), 7.23 (0.45H, s, $CHCl_3$), 7.25–7.45 (7H, m, aromatic *H*), 7.55–7.73 (4H, m, aromatic *H*), 7.62 (1H, s, olefinic *H*); MS *m/z* 484 ($MH^+$). Anal. ($C_{29}H_{25}NO_6 \cdot 0.3H_2O \cdot 0.15CHCl_3$) C, H, N.

**(*E*)-Ethyl α-[[3-(2-methoxy-2-oxoethoxy)phenyl]methylene]-4,5-diphenyl-2-oxazoleacetate ((*E*)-9a)** was prepared from (*E*)-14 (2.88 g, 5.5 mmol) via an analogous procedure to that described for (*Z*)-14 to afford (*E*)-9a (2.33 g, 100%): IR (film) 1760, 1715, 1450 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.27 (3H, t, $J$ = 7 Hz, $OCH_2CH_3$), 3.59 (3H, s, $OCH_3$), 4.28 (2H, q, $J$ = 7 Hz, $OCH_2CH_3$), 4.39 (2H, s, $OCH_2$), 5.22 (0.4H, s, $CH_2Cl_2$), 6.73 (1H, d, $J$ = 2 Hz, aromatic *H ortho* to O), 6.85–6.95 (2H, m, aromatic *H ortho* and *para* to O), 7.19 (1H, t, $J$ = 7 Hz, aromatic *H meta* to O), 7.20–7.40 (6H, m, aromatic *H*), 7.53 (2H, m, aromatic *H*), 7.68 (2H, m, aromatic *H*), 8.03 (1H, s, olefinic *H*); MS *m/z* 484 ($MH^+$). Anal. ($C_{29}H_{25}NO_6 \cdot 0.1H_2O \cdot 0.2CH_2Cl_2$) C, H, N.

**2-(Cyanomethyl)-4,5-diphenyloxazole (16).** A mixture of 15 (2.00 g, 6.4 mmol), KCN (0.46 g, 7 mmol), 18-crown-6 (0.17 g, 0.64 mmol), $CH_2Cl_2$ (20 mL), and $H_2O$ (5 mL) was stirred at room temperature for 25 h. The mixture was diluted with $H_2O$ and extracted with $CH_2Cl_2$ to give an oil which was chromatographed on a column of silica gel using a mixture of hexane and EtOAc (17:3) to give the title compound (0.53 g, 32%) as an oil: IR (film) 2265 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 4.00 (2H, s, $CH_2CN$), 7.25–7.45 (6H, m, aromatic *H*), 7.50–7.65 (4H, m, aromatic *H*); MS *m/z* 261 ($MH^+$).

**(*E*)-Methyl [3-[2-cyano-2-(4,5-diphenyl-2-oxazolyl)ethenyl]phenoxy]acetate (17)** was prepared from **16** and **8a** according to the procedure described for the preparation of **9ab** to give 17 (1.28 g, 59%), mp 152–153 °C, after chromatography and subsequent recrystallization from $CH_2Cl_2$/hexanes (1:1): IR (KBr) 2230, 1745 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 3.82 (3H, s, $CO_2CH_3$), 4.71 (2H, s, $OCH_2$), 7.08 (1H, dd, $J$ = 7 Hz, $J'$ = 2 Hz, aromatic *H ortho* to O), 7.25–7.40 (13H, m, aromatic *H*), 7.45–7.75 (6H, m, aromatic *H*), 8.10 (1H, s, olefinic *H*), $^{13}C$ NMR $\delta$ 155.7 (d, $J$ = 7.8 Hz, *OC*=N, indicative of (*E*) geometry); MS *m/z* 437 ($MH^+$). Anal. ($C_{27}H_{20}N_2O_4$) C, H, N.

**(*E*)-[3-[2-Cyano-2-(4,5-diphenyl-2-oxazolyl)ethenyl]phenoxy]acetic Acid (18).** Hydrolysis of 17 according to the procedure described for the preparation of **10b** provided 18 (0.46 g, 63%), mp 154–159°C, after recrystallization from hexane/$CH_2Cl_2$ (5:1): IR (KBr) 3450, 2240, 1740, 1550, 1530 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 4.50 (bs, $H_2O + CO_2H$), 4.64 (2H, s, $OCH_2$), 7.02 (1H, dd, $J$ = 7 Hz, $J'$ = 2 Hz, aromatic *H ortho* to O), 7.10–7.80 (13H, m, aromatic *H*), 7.98 (1H, s, olefinic *H*); MS *m/z* 423 ($MH^+$) (FAB). Anal. ($C_{26}H_{18}N_2O_4 \cdot 0.6H_2O$) C, H, N.

**Methyl [3-[2-[Cyano-2-(4,5-diphenyl-2-oxazolyl)ethyl]phenoxy]acetate (19).** $NaBH_4$ (90 mg, 2.3 mmol) was added to a stirred suspension of 17 (500 mg, 1.15 mmol) in MeOH (10 mL). After 3 h, $NaBH_4$ (50 mg, 1.3 mmol) was added and the mixture stirred at room temperature for 20 h before being poured onto saturated $NH_4Cl$ solution. The mixture was extracted with $CH_2Cl_2$ to give an oil which was chromatographed on a column of silica gel using hexanes/EtOAc (4:1) as eluent to afford 19 (0.25 g, 50%) as an oil: IR (KBr) 2250, 1760 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 3.42 (2H, d of AB q, $J$ = 13.7 Hz, $J'$ = 9 Hz, $J''$ = 6 Hz, $CH_2Ar$), 3.76 (3H, s, $CO_2CH_3$), 4.32 (1H, dd, $J$ = 8 Hz, $J'$ = 6 Hz, *CH*CN), 4.59 (2H, s, $OCH_2$), 6.70–6.95 (2H, m, aromatic *H ortho* and *para* to O), 7.20–7.45 (7H, m, aromatic *H*), 7.50–7.70 (4H, m, aromatic *H*); MS *m/z* 439 ($MH^+$). Anal. ($C_{27}H_{22}N_2O_4 \cdot 0.2H_2O$) C, H, N.

**[3-[2-Cyano-2-(4,5-diphenyl-2-oxazolyl)ethyl]phenoxy]acetic Acid (20).** Hydrolysis of 19 according to the procedure described for the preparation of **10b** provided **20** (0.24 g, 45%), mp 166–171 °C, after recrystallization from $CH_2Cl_2$/hexanes: IR (KBr) 3450, 2250, 1745 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 3.40 (2H, d of AB q, $J$ = 13 Hz, $J'$ = 8.5 Hz, $J''$ = 6.5 Hz, $ArCH_2$), 3.40 (1H, bs, $H_2O + CO_2H$), 4.61 (2H, s, $OCH_2$), 5.17 (1H, dd, $J$ = 8.5 Hz, $J'$ = 6.5 Hz, *CH*CN), 6.75–7.00 (3H, m, aromatic *H ortho* and *para* to O), 7.24 (1H, t, $J$ = 7 Hz, aromatic *H meta* to O), 7.25–7.70 (10H, m, aromatic *H*); MS *m/z* 425 ($MH^+$). Anal. ($C_{26}H_{20}N_2O_4 \cdot 1.5H_2O$) C, H, N.

**2-[2-[3-[(1,1-Dimethylethyl)dimethylsiloxy]phenyl]ethyl]-4,5-diphenyloxazole (22).** A mixture of 21 (20.00 g, 58 mmol), TBDMS chloride (9.71 g, 65 mmol), imidazole (9.97 g, 147 mmol), and dry DMF (125 mL) was stirred at room temperature for 1 h before adding additional TBDMS chloride (1.00 g, 3 mmol). After stirring for 1.5 h, the mixture was diluted with $H_2O$ and extracted with $Et_2O$ to give an oil which was chromatographed on a column of silica gel. Elution with a mixture of hexane and $Et_2O$ (3:1) afforded **22** (22.88 g, 85%).

**3-[2-(Diethylphosphinyl)-2-(4,5-diphenyl-2-oxazolyl)ethyl]phenol (23).** A solution of LDA (1.55 g, 14.5 mmol) in dry THF (50 mL) cooled to −78 °C was added dropwise over 10 min to a stirred solution of **22** (3.00 g, 6.6 mmol) in dry THF (60 mL) maintained at −78 °C under an atmosphere of $N_2$. After 30 min, diethyl chlorophosphate (1.25 g, 1.05 mL, 7 mmol) was added dropwise and the mixture stirred at −78 °C for 15 min before being poured onto a mixture of saturated $NH_4Cl$ solution (60 mL) and $H_2O$ (60 mL). The mixture was extracted with $CH_2Cl_2$ and the residue filtered through a plug of silica gel using $Et_2O$ as eluent to give an oil (3.54 g, 91%) of which 3.20 g was dissolved in dry THF (60 mL). A solution of $nBu_4NF$ (1.84 g, 7 mmol) in THF (7 mL) was added and the mixture stirred at room temperature for 20 min. The solvent was removed the residue diluted with 1 N HCl and extracted with $CH_2Cl_2$ to give an oil.

Chromatography on a column of silica using $Et_2O$ as eluent provided **23** (1.52 g, 58%), mp 107–109 °C, after recrystallization from $CH_2Cl_2$/hexanes: IR (KBr) 3220, 1605, 1460, 1230, 1050, 1025 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.23 (3H, t, $J$ = 7 Hz, $OCH_2CH_3$), 1.27 (3H, t, $J$ = 7 Hz, $OCH_2CH_3$), 3.30–3.60 (2H, m, $CH_2Ar$), 3.90 (1H, ddd, $J$ = 22 Hz, $J'$ = 10 Hz, $J''$ = 5 Hz, $CHP(O)(OEt)_2$), 4.00–4.20 (4H, m, $OCH_2$), 6.61 (2H, m, aromatic *H ortho* and *para* to OH), 6.83 (1H, aromatic *H ortho* to OH), 7.01 (1H, t, $J$ = 8 Hz, aromatic *H meta* to OH), 7.28 (6H, m, aromatic *H*), 7.40–7.60 (4H, m, aromatic *H*), 7.92 (1H, s, O*H*); MS $m/z$ 478 ($MH^+$). Anal. ($C_{27}H_{28}NO_5P$) C, H, N.

**Methyl 3-[[2-(Diethylphosphinyl)-2-(4,5-diphenyl-2-oxazolyl)ethyl]phenoxy]acetate (24).** A mixture of **23** (4.97 g, 10.4 mmol), methyl bromoacetate (1.75 g, 1.08 mL, 11.4 mmol), $K_2CO_3$ (1.87 g, 12.7 mmol), KI (catalytic quantity), and $CH_3CN$ was heated at reflux for 45 min. The mixture was filtered and concentrated and the residue chromatographed on a column of silica gel using $Et_2O$ as eluent to afford **24** (5.25 g, 92%) as an oil: IR (film) 1765, 1610, 1590, 1450, 1255, 1210, 1160, 1055, 1035 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.27 (3H, t, $J$ = 7 Hz, $OCH_2CH_3$), 1.32 (3H, t, $J$ = 7 Hz, $OCH_2CH_3$), 3.30–3.50 (2H, m, $CH_2Ar$), 3.69 (3H, s, $CO_2CH_3$), 3.73 (1H, ddd, $J$ = 22 Hz, $J'$ = 10 Hz, $J''$ = 5 Hz, $CHP(O)(OEt)_2$), 4.00–4.25 (4H, m, $POCH_2$), 4.47 (2H, s, $OCH_2$), 6.68 (2H, m, aromatic *H ortho* to OH), 6.81 (1H, aromatic *H para* to OH), 7.11 (1H, t, $J$ = 8 Hz, aromatic *H meta* to OH), 7.20–7.35 (6H, m, aromatic *H*), 7.44–7.60 (4H, m, aromatic *H*); MS $m/z$ 550 ($MH^+$). Anal. ($C_{30}H_{32}NO_7P$) C, H, N.

**[3-[2-(Diethylphosphinyl)-2-(4,5-diphenyl-2-oxazolyl)ethyl]phenoxy]acetic Acid (25).** A mixture of **24** (4.00 g, 7.3 mmol), $LiOH \cdot H_2O$ (0.61 g, 14.5 mmol), EtOH (60 mL), and $H_2O$ (10 mL) was stirred at room temperature for 40 min and concentrated and the residue diluted with a 2 N HCl solution. The mixture was extracted with $CH_2Cl_2$ to afford **25** (3.89 g, 100%) as an oil: IR (film) 3000, 2930, 1750, 1610, 1590, 1450, 1210, 1160, 1050, 1035 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.27 (3H, t, $J$ = 7 Hz, $OCH_2CH_3$), 1.29 (3H, t, $J$ = 7 Hz, $OCH_2CH_3$), 3.35–3.50 (2H, m, $CH_2Ar$), 3.90–4.20 (5H, m, $CH.P(O)(OEt)_2$ and $POCH_2$), 4.49 (2H, s, $OCH_2$), 6.71 (2H, m, aromatic *H ortho* and *para* to OH), 6.87 (1H, aromatic *H ortho* to OH), 7.07 (1H, t, $J$ = 8 Hz, aromatic *H meta* to OH), 7.20–7.35 (6H, m, aromatic *H*), 7.40–7.60 (4H, m, aromatic *H*); MS $m/z$ 536 ($MH^+$). Anal. ($C_{29}H_{30}NO_7P \cdot 0.3H_2O$) C, H, N.

**2-[(Methylthio)methyl]-4,5-diphenyloxazole (26, R = $SCH_3$).** A mixture of **5** (35,00 g, 0.17 mol), (methylthio)acetic acid (18.38 g, 0.17 mol), DCC (37.40 g, 0.18 mol), DMAP (catalytic quantity), and $CH_2Cl_2$ (800 mL) was stirred at room temperature. After 15 h, the mixture was filtered and concentrated, and $NH_4OAc$ (63.56 g, 0.83 mol) and AcOH (300 mL) were added. The mixture was heated at reflux for 1 h, cooled, diluted with $H_2O$, and extracted with $Et_2O$ to leave an oil which was chromatographed on a column of silica gel. Elution with a mixture of hexane and $Et_2O$ (3:1) afforded **26**, R = $SCH_3$ (40.69 g, 87%) as a yellow solid. An analytical sample recrystallized from hexane had mp 68–70°C: $^1H$ NMR ($CDCl_3$) $\delta$ 2.26 (3H, s, $SCH_3$), 3.82 (2H, s, $SCH_2$), 7.25–7.40 (6H, m, aromatic *H*), 7.50–7.70 (4H, m, aromatic *H*); MS $m/z$ 282 ($MH^+$). Anal. ($C_{17}H_{15}NOS$) C, H, N.

**3-[2-(4,5-Diphenyl-2-oxazolyl)-2-(methylthio)ethyl]phenol (29, R = $SCH_3$).** nBuLi (5.47 g, 85 mmol) in hexane (34.16 mL) was added dropwise to a solution of **26**, R = $SCH_3$ (20.00 g, 71 mmol), in dry THF (380 mL) maintained at −78 °C under $N_2$. After 25 min, a solution of **28** (23.57 g, 78 mmol) in THF (30 mL) was added dropwise and the mixture stirred at −78°C for 20 min. The solution was stirred at room temperature and additional **28** was added (6.00 g, 20 mmol after 1.5 h and 5.00 g, 16 mmol after a further 1 h). Stirring was continued for 20 min before the mixture was poured onto $H_2O$ and extracted with $CH_2Cl_2$ to leave an oil which was dissolved in dry THF (350 mL). A solution of $nBu_4NF$ (20.46 g, 78 mmol) in THF (78 mL) was added and the mixture stirred at room temperature for 15 min before being poured onto 2 N HCl solution. Extraction with $CH_2Cl_2$ gave an oil which was chromatographed on a column of silica gel using a mixture of hexane and $Et_2O$ (1:1) as eluent to give **29**, R = $SCH_3$ (14.59 g, 52%), as a yellow solid. An analytical sample recrystallized from $CH_2Cl_2$/hexane had mp 146–148°C. IR (KBr) 3400, 3200 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.14 (3H, s, $SCH_3$), 3.28 (2H, *ABX* dq, $J_{AB}$ = 14 Hz, $J_{AX}$ = 8.7 Hz, $J_{BX}$ = 7 Hz, $ArCH_2$), 4.15 (1H, ABX dd, $J_{AX} + J_{BX}$ = 15.7 Hz, $CH_3SCH$), 5.93 (1H, bs, O*H*), 6.58 (2H, m, aromatic *H*), 6.74 (1H, d, $J$ = 7 Hz, aromatic *H*), 7.06 (1H, t, $J$ = 7 Hz, aromatic *H meta* to OH), 7.25–7.40 (6H, m, aromatic *H*), 7.50–7.70 (4H, m, aromatic *H*); MS $m/z$ 388 ($MH^+$). Anal. ($C_{24}H_{21}NO_2S$) C, H, N.

**Methyl [3-[2-(4,5-Diphenyl-2-oxazolyl)-2-(methylthio)ethyl]phenoxy]acetate (30a).** A mixture of **29**, R = $SCH_3$ (14.00 g, 36 mmol), methyl bromoacetate (6.08 g, 3.76 mL, 40 mmol), $K_2CO_3$ (5.49 g, 40 mmol), KI (catalytic amount), and $CH_3CN$ (200 mL) was heated at reflux for 1.5 h, filtered, and concentrated. The residue was chromatographed on a column of silica gel using $Et_2O$/hexane (1:1) as eluent to furnish **30a** (15.88 g, 95%) as an oil. IR (film) 1765, 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.16 (3H, s, $SCH_3$), 3.36 (2H, ABX dq, $J_{AB}$ = 14 Hz, $J'_{AX}$ = 8.3 Hz, $J_{BX}$ = 7.3 Hz, $ArCH_2$), 3.75 (3H, s, $CO_2CH_3$), 4.17 (1H, t, $J$ = 7.5, $CH_3SCH$), 4.55 (2H, s, $OCH_2$), 6.75 (1H, dd, $J$ = 7 Hz, $J'$ = 2 Hz, aromatic *H ortho* to O), 6.80 (1H, d, $J$ = 2 Hz, aromatic *H ortho* to O), 6.89 (1H, d, $J$ = 7 Hz, aromatic *H para* to O), 7.19 (1H, t, $J$ = 7 Hz, aromatic *H meta* to OH), 7.25–7.40 (6H, m, aromatic *H*), 7.50–7.70 (4H, m, aromatic *H*); MS $m/z$ 460 ($MH^+$). Anal. ($C_{27}H_{25}NO_4S$) C, H, N.

**[3-[2-(4,5-Diphenyl-2-oxazolyl)-2-(methylthio)ethyl]phenoxy]acetic Acid (31a).** A sample of **30a** (2.00 g, 4.4 mmol) was hydrolyzed according to the general procedure described for the preparation of **25** to give **31a** (1.65 g, 83%) after recrystallization from $CH_2Cl_2$/hexanes: mp 127–129 °C; IR (KBr) 3450, 2910, 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.15 (3H, s, $SCH_3$), 3.34 (2H, ABX dq, $J_{AB}$ = 14 Hz, $J_{AX}$ = 8.6 Hz, $J_{BX}$ = 7.3 Hz, $ArCH_2$), 4.39 (1H, ABX dd, $J_{AX} + J_{BX}$ = 15.9 Hz, $CH_3SCH$), 4.57 (2H, s, $OCH_2$), 6.76 (1H, dd, $J$ = 7 Hz, $J'$ = 2 Hz, aromatic *H ortho* to O), 6.80–6.90 (2H, m, aromatic *H ortho* and *para* to O), 7.16 (1H, t, $J$ = 7 Hz, aromatic *H meta* to OH), 7.25–7.40 (6H, m, aromatic *H*), 7.50–7.70 (4H, m, aromatic *H*), 8.18 (1H, bs, $CO_2H$); MS $m/z$ 446 ($MH^+$). Anal. ($C_{26}H_{23}NO_4S$) C, H, N.

**Methyl [3-[2-(4,5-Diphenyl-2-oxazolyl)-2-(methylsulfinyl)ethyl]phenoxy]acetate (30b).** A solution of **30a** (6.68 g, 14.5 mmol) in MeOH (200 mL) was cooled to −10 °C and a solution of Oxone (10.36 g, 16.9 mmol) in $H_2O$ (100 mL) added in one portion. The mixture was stirred at −10 °C for 10 min and at 0 °C for 1.5 h before being diluted with $H_2O$ and extracted with $CH_2Cl_2$. The residual oil was chromatographed on a column of silica gel using $Et_2O$ as eluent to give **30b** (4.28 g, 61%) as a yellow foam: IR (KBr) 1755, 1580, 1480, 1440, 1205, 1160, 1050 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.61 and 2.68 (3H, s, ratio 1:5, $S(O)CH_3$), 3.40–3.65 (2H, m, $ArCH_2$), 3.72 and 3.75 (3H, s, ratio 5:1, $CO_2CH_3$), 4.24–4.35 (1H, m, $CH_3S(O)CH$), 4.52 and 4.56 (2H, s, ratio 5:1, $OCH_2$), 6.70–6.95 (3H, m, aromatic *H ortho* and *para* to O), 7.16 (1H, t, $J$ = 7 Hz, aromatic *H meta* to OH), 7.25–7.40 (6H, m, aromatic *H*), 7.50–7.70 (4H, m, aromatic *H*); MS $m/z$ 476 ($MH^+$), 412 ($MH^+ - CH_3SOH$). Anal. ($C_{27}H_{25}NO_5S$) C, H, N.

**[3-[2-(4,5-Diphenyl-2-oxazolyl)-2-(methylsulfinyl)ethyl]phenoxy]acetic acid (31b)** was prepared from **30b** (2.75 g, 5.8 mmol) according to the general procedure described for the preparation of **25** to afford **31b** (2.20 g, 82%) as an amorphous solid: mp indistinct; IR (KBr) 3440, 2920, 1740, 1600, 1580, 1480, 1440, 1205, 1160, 1050 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.91 (0.6H, t, $J$ = 7 Hz, $CH_3$ from $Et_2O$), 2.62 and 2.74 (3H, s, ratio 1.2:1, $S(O)CH_3$), 3.40–3.75 (2H, m, $ArCH_2 + OCH_2$ from $Et_2O$), 4.55 and 4.56 (2H, s, ratio 1:1.2, $OCH_2$), 4.60–4.70 (1H, m, $CH_3S(O)CH$), 6.70–7.00 (3H, m, aromatic *H ortho* and *para* to O), 7.12 and 7.20 (1H, t, ratio 1.2:1, $J$ = 7 Hz, aromatic *H meta* to OH), 7.30–7.50 (6H, m, aromatic *H*), 7.50–7.70 (4H, m, aromatic *H*); MS $m/z$ 398 ($MH^+ - CH_3SOH$). Anal. ($C_{26}H_{23}NO_5S \cdot 0.6H_2O \cdot 0.2C_4H_{10}O$) C, H, N.

**Methyl [3-[2-(4,5-Diphenyl-2-oxazolyl)-2-(methylsulfonyl)ethyl]phenoxy]acetate (30c).** A solution of Oxone (24.08 g, 39 mmol) in $H_2O$ (200 mL) was added to a stirred solution of **30a** (6.00 g, 13 mmol) in MeOH (200 mL). After 70 min, the mixture was diluted with $H_2O$ and extracted with $CH_2Cl_2$ and the residue chromatographed on a column of silica gel. Elution with a mixture of $Et_2O$ and hexane (3:2) furnished **30c** (4.48 g, 70%) as an amorphous solid: mp 50–56 °C; IR (KBr) 1755, 1580, 1480, 1440, 1320, 1205, 1140 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 3.07 (3H, s, $SO_2CH_3$), 3.65 (2H, ABX dq, $J_{AB}$ = 13.6 Hz, $J_{AX}$ = 11.5 Hz, $J_{BX}$ = 3.7 Hz, $ArCH_2$), 3.72 (3H, s, $CO_2CH_3$), 4.51 (2H, s, $OCH_2$), 4.59 (1H, ABX dd, $J_{AX} + J_{BX}$ = 15.2 Hz, $CH_3SO_2CH$), 6.73 (1H, dd,

$J$ = 7 Hz, $J'$ = 2 Hz, aromatic *H ortho* O), 6.77 (1H, d, $J$ = 2 Hz, aromatic *H ortho* to O), 6.86 (1H, d, $J$ = 7 Hz, aromatic *H para* to O), 7.17 (1H, t, $J$ = 7 Hz, aromatic *H meta* to OH), 7.25–7.40 (6H, m, aromatic *H*), 7.50–7.70 (4H, m, aromatic *H*); MS $m/z$ 492 ($MH^+$), 412 ($MH^+ - CH_3SO_2H$). Anal. ($C_{27}H_{25}NO_6S \cdot 0.2H_2O$) C, H, N.

**[3-[2-(4,5-Diphenyl-2-oxazolyl)-2-(methylsulfonyl)ethyl]phenoxy]acetic acid (31c)** was prepared by hydrolysis of a sample of **30c** (2.20 g, 4.5 mmol) according to the protocol described for the preparation of **25** to give **31c** (2.00 g, 91%) after recrystallization from $CH_2Cl_2$/hexane: mp 105 °C dec; IR (KBr) 3440, 3170, 3060, 1765, 1580, 1480, 1440, 1310, 1300, 1205, 1140 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 3.03 (3H, s, $SO_2CH_3$), 3.65 (2H, ABX dq, $J_{AB}$ = 11.6 Hz, $J_{AX}$ = 11.6 Hz, $J_{BX}$ = 4 Hz, $ArCH_2$), 4.54 (2H, s, $OCH_2$), 4.90 (1H, ABX dd, $J_{AX} + J_{BX}$ = 15.4 Hz, $CH_3SO_2CH$), 5.27 (0.4H, s, $CH_2Cl_2$), 6.75 (1H, dd, $J$ = 7 Hz, $J'$ = 2 Hz, aromatic *H ortho* O), 6.83 (1H, d, $J$ = 2 Hz, aromatic *H ortho* to O), 6.85 (1H, d, $J$ = 7 Hz, aromatic *H para* to O), 7.15 (1H, t, $J$ = 7 Hz, aromatic *H meta* to OH), 7.25–7.40 (6H, m, aromatic *H*), 7.50–7.70 (4H, m, aromatic *H*), 9.48 (1H, bs, $CO_2H$); MS $m/z$ 478 ($MH^+$), 398 ($MH^+ - CH_3SO_2H$). Anal. ($C_{26}H_{23}NO_6S \cdot 0.2H_2O \cdot 0.2CH_2Cl_2$) C, H, N.

**4,5-Diphenyl-2-oxazolepentanol.** A solution of methyl 4,5-diphenyl-2-oxazolepentanoate (10.66 g, 32 mmol) in $Et_2O$ (100 mL) was added dropwise to a suspension of $LiAlH_4$ (1.21 g, 32 mmol) in $Et_2O$ (200 mL) and the mixture stirred at room temperature for 17 h. The mixture was diluted with $Et_2O$ (100 mL), and $H_2O$ was added dropwise until the salts collected on the bottom of the flask. The mixture was filtered through Celite, the solvent evaporated, and the residue dissolved in $CH_2Cl_2$ and washed with $H_2O$. After drying, the solvent was removed to leave an oil used without further purification. An analytical sample was purified by chromatography on silica gel using a mixture of hexane and EtOAc (11:9) as eluent to give the title compound as a foam: mp 41.5–43 °C; IR (film) 3390, 2940 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.45–1.70 (4H, m, $CH_2$), 1.87 (2H, quintet, $J$ = 7 Hz, $CH_2$), 2.03 (1H, bs, $OH$), 2.85 (2H, t, $J$ = 7 Hz, $CH_2$-oxazole), 3.64 (2H, t, $J$ = 7 Hz, $CH_2OH$), 7.20–7.40 (6H, m, aromatic *H*), 7.50–7.75 (4H, m, aromatic *H*); MS $m/z$ 308 ($MH^+$). Anal. ($C_{20}H_{21}NO_2$) C, H, N.

**Methyl [3-[2-(4,5-Diphenyl-2-oxazolyl)-6-hydroxyhexyl]phenoxy]acetate (30l).** A mixture of 4,5-diphenyl-2-oxazolepentanol (8.29 g, 27 mmol), TBDMS chloride (4.88 g, 32 mmol), imidazole (4.60 g, 67 mmol), and anhydrous DMF (150 mL) was stirred at room temperature under $N_2$. After 6.5 h, the mixture was concentrated, diluted with $H_2O$, and extracted with $CH_2Cl_2$ to give an oil. Chromatography on a column of silica gel using a mixture of hexane and EtOAc (23:1) afforded **26**, R = $(CH_2)_4$-OTBDMS (9.31 g, 82%): IR (film) 2960, 2940, 2850, $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.02 (6H, s, $(CH_3)_2Si$), 0.87 (9H, s, $(CH_3)_3C$), 1.40–1.60 (4H, m, $CH_2$), 1.87 (2H, quintet, $J$ = 7 Hz, $CH_2$), 2.84 (2H, t, $J$ = 7 Hz, $CH_2$-oxazole), 3.62 (2H, t, $J$ = 7 Hz, $CH_2OSi$), 7.20–7.40 (6H, m, aromatic *H*), 7.50–7.75 (4H, m, aromatic *H*); MS $m/z$ 422 ($MH^+$).

A sample of this material (5.00 g, 12 mmol) was dissloved in dry THF (20 mL) and added dropwise to a stirred solution of freshly prepared LDA (1.61 g, 15 mmol) in THF (20 mL) maintained at −78 °C under $N_2$ to give a deep red solution. After 2 h, a solution of **28** (4.47 g, 15 mmol) in THF (5 mL) was added dropwise by syringe to give an amber solution. After 20 min, the mixture was diluted with a saturated $NH_4Cl$ solution and extracted with $Et_2O$ to give an oil. Chromatography on a column of silica gel using a mixture of hexane and EtOAc (49:1) afforded the bis-silyl ether (3.58 g, 47%) as an oil, MS $m/z$ 642 ($MH^+$), which was dissolved in dry THF (50 mL), and a solution of $nBu_4NF$ (3.66 g, 14 mmol) in THF (14 mL) was added. The mixture was stirred at room temperature for 24 h, diluted with a mixture of $Et_2O$ and EtOAc (4:1), and washed with $H_2O$ and a saturated NaCl solution. The organic phase was dried over $MgSO_4$ and concentrated and the residue chromatographed on a column of silica gel. Elution with a mixture of $CHCl_3$ and MeOH (19:1) afforded **29**, R = $(CH_2)_4OH$, as an oil: IR (film) 3250, 2960 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.40–1.45 (4H, m, $CH_2$), 1.51 (2H, quintet, $J$ = 7 Hz, $CH_2$), 2.89 (2H, m, $CH_2Ar$), 3.10 (1H, m, $CH$-oxazole), 3.54 (2H, t, $J$ = 7 Hz, $CH_2OH$), 6.55–6.68 (3H, m, aromatic *H*), 7.05 (1H, t, $J$ = 7 Hz, aromatic *H meta* to OH), 7.20–7.40 (6H, m, aromatic *H*), 7.45–7.65 (4H, m, aromatic *H*); MS $m/z$ 414 ($MH^+$).

A sample of the diol (0.99 g, 2.4 mmol), methyl bromoacetate (0.44 g, 2.9 mmol), $K_2CO_3$ (0.40 g, 3.0 mmol), KI (catalytic quantity), and $CH_3CN$ (25 mL) was heated at reflux for 2.5 h. The mixture was filtered and concentrated and the residue chromatographed on a column of silica gel. Elution with EtOAc afforded **30l** (0.77 g, 66%) as an oil: IR (film) 3400, 2960, 1760 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.37–1.65 (4H, m, $CH_2$), 1.72 (1H, m, $CH_2$), 1.90 (1H, m, $CH_2$), 3.06 (2H, ABX dq, $J_{AB}$ = 13 Hz, $J_{AX}$ = 7.2 Hz, $J_{BX}$ = 7 Hz, $CH_2Ar$), 3.22 (1H, m, $CH$-oxazole), 3.59 (2H, t, $J$ = 7 Hz, $CH_2OH$), 3.75 (3H, s, $CO_2CH_3$), 4.56 (2H, s, $OCH_2$), 6.65–6.85 (3H, m, aromatic *H*), 7.18 (1H, t, $J$ = 7 Hz, aromatic *H meta* to OH), 7.25–7.45 (6H, m, aromatic *H*), 7.45–7.65 (4H, m, aromatic *H*); MS $m/z$ 486 ($MH^+$). Anal. ($C_{30}H_{31}NO_5 \cdot 0.4H_2O$) C, H, N.

**[3-[2-(4,5-Diphenyl-2-oxazolyl)-6-hydroxyhexyl]phenoxy]acetic Acid (31l).** A sample of ester **30l** (0.41 g, 0.9 mmol) was hydrolyzed according to the general procedure described for the preparation of **25** to give **31l** (0.24 g, 60%) as a white foam, mp 55–57°C, after chromatography on a column of silica gel using a mixture of $CHCl_3$ and MeOH (97:3) as eluent: IR (film) 2960, 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.35–1.65 (4H, m, $CH_2$), 1.72 (1H, m, $CH_2$), 1.82 (1H, m, $CH_2$), 3.05 (2H, ABX dq, $J_{AB}$ = 13.6 Hz, $J_{AX}$ = 8.2 Hz, $J_{BX}$ = 6.6 Hz, $CH_2Ar$), 3.35 (1H, m, $CH$-oxazole), 3.56 (2H, t, $J$ = 7 Hz, $CH_2OH$), 4.57 (2H, s, $OCH_2$), 5.24 (2H, bs, $OH$), 6.76 (3H, m, aromatic *H*), 7.15 (1H, t, $J$ = 7 Hz, aromatic *H meta* to OH), 7.25–7.45 (6H, m, aromatic *H*), 7.45–7.65 (4H, m, aromatic *H*); MS $m/z$ 472 ($MH^+$). Anal. ($C_{29}H_{29}NO_5 \cdot 0.5H_2O$) C, H, N.

**β-[(3-Hydroxyphenyl)methyl]-4,5-diphenyl-2-oxazoleethanol (32).** A solution of (*E*)- and (*Z*)-**14** (5.56 g, 10.6 mmol) in EtOAc (175 mL) was hydrogenated at 20 psi over 10% Pd on C (0.96 g) on a Parr hydrogenation apparatus. After $H_2$ uptake had ceased, the mixture was filtered through Celite and concentrated to leave ethyl α-[[3-[(1,1-dimethylethyl)dimethylsiloxy]phenyl]methyl]-4,5-diphenyl-2-oxazoleacetate as an oil (5.58 g, 100%). This was dissolved in $Et_2O$ (100 mL) and added dropwise to a stirred suspension of $LiAlH_4$ (0.60 g, 16 mmol) in $Et_2O$ (150 mL). After 1.5 h, additional $LiAlH_4$ (0.60 g, 16 mmol) was added and the mixture stirred for 94 h and quenched by adding $H_2O$ dropwise until the salts collected on the surface of the flask. The organic layer was filtered through Celite and concentrated and the residue chromatographed on a column of silica gel. Elution with a mixture of hexane and EtOAc (4:1) afforded β-[[3-[(1,1-dimethylethyl)dimethylsiloxy]phenyl]methyl]-4,5-diphenyl-2-oxazoleethanol (2.36 g, 46%) which was dissolved in dry THF (100 mL). A solution of $nBu_4NF$ (1.62 g, 6.2 mmol) in THF (6.2 mL) was added and the mixture stirred at room temperature for 15 min before being diluted with 1 N HCl. The mixture was extracted with $Et_2O$ to give a solid which was recrystallized from a mixture of $CH_2Cl_2$, hexane, and MeOH (4:1:0.5) to give **32** (0.65 g, 36%): mp 176.5–177.5 °C. IR (KBr) 3400, 3200, 3050 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.95 (2H, d, $J$ = 7 Hz, $CH_2Ar$), 3.26 (1H, quintet, $J$ = 7 Hz, $CHCH_2OH$), 3.70 (2H, m, $CH_2OH$), 4.97 (1H, t, $J$ = 5 Hz, $CH_2OH$), 6.50–6.65 (3H, m, aromatic *H*), 7.02 (1H, t, $J$ = 8 Hz, aromatic *H meta* to OH), 7.25–7.60 (10 H, m, aromatic *H*); MS 372 ($MH^+$). Anal. ($C_{24}H_{21}NO_3 \cdot 0.3H_2O$) C, H, N.

**Ethyl α-[[3-[2-(1,1-Dimethylethoxy)-2-oxoethoxy]phenyl]methyl]-4,5-diphenyl-α-(2-propenyl)-2-oxazoleacetate (33).** A mixture of **11**, R = OEt, $R^2$ = H, $R^3$ = *t*Bu (3.15 g, 6 mmol), allyl bromide (0.83 g, 6.9 mmol), $K_2CO_3$ (0.74 g, 6.6 mmol), 18-crown-6 (catalytic quantity), and THF (30 mL) was stirred at room temperature for 15 min. The mixture was diluted with EtOAc (350 mL), washed with saturated $NH_4Cl$ solution, dried over $MgSO_4$, and concentrated. The residual oil was chromatographed on a column of silica gel using a mixture of hexane and EtOAc (17:3) as eluent to give **33** (2.45 g, 72%) IR (film) 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.22 (3H, t, $J$ = 7 Hz, $OCH_2CH_3$), 1.41 (9H, s, $OC(CH_3)_3$), 2.84 (2H, d AB q, $J$ = 12.3 Hz, $J'$ = 7.4 Hz, $CH_2C{=}C$), 3.45 (2H, ABq, $J$ = 13.8 Hz, $CH_2$-Ar), 4.19 (2H, m, $CO_2CH_2$), 4.32 (2H, s, $OCH_2$), 5.10–5.20 (2H, m, olefinic *H*), 5.83 (1H, m, olefinic *H*), 6.51 (1H, d, $J$ = 2 Hz, aromatic *H ortho* to O), 6.64 (1H, d, $J$ = 7 Hz, aromatic *H para* to O), 6.73 (1H, dd,

$J$ = 7 Hz, $J'$ = 2 Hz, aromatic *H ortho* to O), 7.10 (1H, t, $J$ = 7 Hz, aromatic *H meta* to O), 7.25 (6H, m, aromatic *H*), 7.50 (2H, m, aromatic *H*), 7.61 (2H, m, aromatic *H*); MS *m/z* 568 ($MH^+$). Anal. ($C_{35}H_{37}NO_6 \cdot 0.25H_2O$) C, H, N.

**Ethyl α-[[3-(2-Hydroxy-2-oxoethoxy)phenyl]methyl]-4,5-diphenyl-α-(2-propenyl)-2-oxazoleacetate (34).** A mixture of **33** (2.15 g, 3.8 mmol) and $CF_3CO_2H$ (20 mL) was stirred at room temperature for 10 min and diluted with EtOAc and $H_2O$ and the organic phase separated. After washing with $H_2O$ and saturated NaCl solution, the organic phase was dried over $Na_2SO_4$ and concentrated to leave an oil which was chromatographed on a column of silica gel using a mixture of $CHCl_3$ and MeOH (99:1) as eluent to afford **34** (1.20 g, 61%): IR (film) 3000, 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.21 (3H, t, $J$ = 7 Hz, $OCH_2CH_3$), 2.84 (2H, d AB q, $J$ = 14.3 Hz, $J'$ = 7.5 Hz, $CH_2C{=}C$), 3.47 (2H, AB q, $J$ = 13.7 Hz, $CH_2$-Ar), 4.18 (2H, m, $CO_2CH_2$), 4.47 (2H, s, $OCH_2$), 5.10–5.20 (2H, m, olefinic *H*), 5.85 (1H, m, olefinic *H*), 6.55 (1H, d, $J$ = 2 Hz, aromatic *H ortho* to O), 6.69 (1H, d, $J$ = 7 Hz, aromatic *H para* to O), 6.74 (1H, dd, $J$ = 7 Hz, $J'$ = 2 Hz, aromatic *H ortho* to O), 7.12 (1H, t, $J$ = 7 Hz, aromatic *H meta* to O), 7.32 (6H, m, aromatic *H*), 7.50 (2H, m, aromatic *H*), 7.60 (2H, m, aromatic *H*); MS *m/z* 512 ($MH^+$). Anal. ($C_{31}H_{29}NO_6 \cdot 0.5H_2O$) C, H, N.

**[3-[2-(4,5-Diphenyl-2-oxazolyl)-4-pentenyl]phenoxy]acetic Acid (35).** A mixture of **34** (1.11 g, 2.2 mmol), a 3 N NaOH solution (3.62 mL, 10.9 mmol), and MeOH (70 mL) was heated at reflux for 18 h and concentrated and the residue diluted with $H_2O$ and a 2 N HCl solution. The mixture was extracted with $CH_2Cl_2$ to give an oil which was dissolved in EtOAc and the mixture heated at reflux for 30 min. The solvent was evaporated to leave **35** (0.90 g, 94%): IR (KBr) 3070, 2930, 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 2.52 (2H, m, $CH_2C{=}C$), 3.04 (2H, ABX dq, $J_{AB}$ = 13.6 Hz, $J_{AX}$ = 8 Hz, $J_{BX}$ = 7.2 Hz, $CH_2$-Ar), 3.49 (1H, quintet, $J$ = 7.5 Hz, CH-oxazole), 4.51 (2H, s, $OCH_2$), 4.95–5.15 (2H, m, olefinic *H*), 5.77 (1H, m, olefinic *H*), 6.67–6.85 (3H, m, aromatic *H*), 7.12 (1H, t, $J$ = 7 Hz, aromatic *H meta* to O), 7.30 (6H, m, aromatic *H*), 7.45–7.60 (4H, m, aromatic *H*) 9.82 (1H, bs, OH); MS *m/z* 440 ($MH^+$). Anal. ($C_{28}H_{25}NO_4 \cdot 0.15H_2O$) C, H, N.

**Blood Platelet Aggregometry.** Platelet-rich plasma (PRP) was prepared from human blood drawn into syringes containing $^1/_{10}$ volume of 3.8% sodium citrate. The blood was then subjected to centrifugation for 10 min at 140*g* and the platelet-rich plasma decanted. The test compound was dissolved in DMSO (5 μL) and added to PRP (0.9 mL) 3 min prior to the addition of ADP (5.86 μM). The aggregometer method of Born,[35] as modified by Mustard et al.,[36] was employed to measure platelet aggregation. Vehicle control trials were performed and compared with the extent of aggregation induced in PRP containing various concentrations of the test compounds. Dose–response curves were thus obtained and $IC_{50}$ values determined. The data presented in Table I are the results of single determinations or the average of duplicates.

**Radioligand Binding Studies.** Radioligand binding assays were performed in 200-μL volumes containing 200 μg of platelet plasma membranes. The isolated membranes were added to a buffer composed of 10 mM $MgCl_2$, 1 mM EGTA, 50 mM Tris/HCl, pH 7.4, with 5 nM [$^3$H]iloprost. The membranes were incubated at 37°C for 90–120 min. After incubation, 5 mL of ice-cold 50 mM Tris/HCl, pH 7.4, was added, the tubes were vortexed, and the samples were rapidly filtered through presoaked Whatman GF/C filters. The filters were then washed four times with 5 mL of ice-cold 50 mM Tris/HCl, pH 7.4, blotted dry on absorbent paper, and counted in a scintillation counter. The specific binding was greater than 90% for [$^3$H]iloprost as determined using excess (10 μM iloprost) cold ligand.

**Determination of Adenylate Cyclase Activity.** Adenylate cyclase activity was assayed in a reaction media (200 μL total volume) containing 30 mM Tris acetate (pH 7.6), 5 mM $Mg(OAc)_2$, 5 mM phosphocreatine, 50 units/mL of creatine phosphokinase, 1 mM EGTA, 1 mM 3-isobutyl-1-methylxanthine, and 0.2 mM adenosine triphosphate (50 cpm/pmol of [α-$^{32}$P]-ATP) with 2 μM guanosine triphosphate. The reaction was initiated by the addition of platelet membrane protein (20 μg) to temperature-equilibrated reaction tubes. The samples were incubated for 15 min at 30°C and the reaction terminated by adding 100 μL of a solution containing 2% SDS, 45 mM ATP, and 1.3 mM cAMP. A 50-μL portion of ($2 \times 10^5$ cpm/mL) [$^3$H]-cAMP stock solution was added to each tube to correct for column recovery. The tubes were boiled for 3 min and then cooled to room temperature. Deionized $H_2O$ (1 mL) was added and the entire sample subjected to chromatography on Dowex AG 50W-X4 and alumina columns. The enzyme activity was linear with respect to time as well as protein concentration under the conditions employed.

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