Metalation of 4-Oxazolinyloxazole Derivatives. A Convenient Route to 2,4-Bifunctionalized Oxazoles

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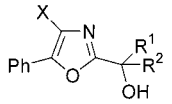
The synthesis of an array of 5-phenyloxazole derivatives bearing a variety of hydroxyalkyl groups at the C-2 position of the heterocyclic nucleus and possessing a formyl or a carboxyl function at C-4 is reported. These bifunctionalized compounds have been efficiently prepared by addition of carbonylated electrophiles to the 2-lithio derivative of 5-phenyloxazole preliminarily equipped with an oxazoline unit at the 4-position of the oxazole nucleus. It is demonstrated that this protocol offers a double advantage since it suppresses the troublesome electrocyclic ring-opening reaction and allows access to the target compounds by simple chemical transformation of the oxazoline ring system.

Introduction

As a part of a program designed to prepare new metallo enzyme inhibitors potentially useful as anticancer drugs, we were recently interested in the synthesis of 5-phenyloxazole derivatives **1a**−**c** and **2c**,**d** (Table 1) bearing a variety of hydroxyalkyl groups at the C-2 position of the heterocyclic nucleus and equipped with a formyl or carboxyl function at C-4.

The emergence of oxazoles as a major class of heterocycles[1] that can be exploited for transformation into more complex heterocycles, for their considerable utility as latent functional group equivalents,[2] and for their presence in a number of interesting and biologically active products[3] has stimulated considerable effort in the development of new synthetic approaches to polysubstituted and diversely substituted models.[4] Paradoxically, many specific, simple examples remain difficult to prepare. This is notably the case of oxazoles functionalized at both the 2- and the 4-positions with differing oxidation states of the appending carbon atoms, which have yet to find important applications in the synthesis of more complex natural products.[5] Classical and most of the long standing synthetic methods leading to substituted oxazoles involve ring-forming reactions.[6] However, they genuinely lack universality and are generally inadequate for the synthesis of models carrying specific substituents, namely sensitive functional groups, on the basic oxazole nucleus. More recently, alternative methods based upon the sequential metalation of the different sites of the heteroring unit have gained interest from the scientific community and are currently the object of intensive synthetic endeavors.[7]

Table 1. Target Compounds 1a−c and 2c,d



1, 2

compd	X	R^1	R^2
1a	CHO	Ph	H
1b	CHO	$CH_3(CH_2)_7$	H
1c	CHO	$(CH_2)_5$	
2c	COOH	$(CH_2)_5$	
2d	COOH	$(CH_3)_2CHCH_2$	H

Results and Discussion

A contentious issue in the elaboration of the diversely functionalized 5-phenyloxazoles **1** and **2** was judging the proper order for the tailored introduction of the func-

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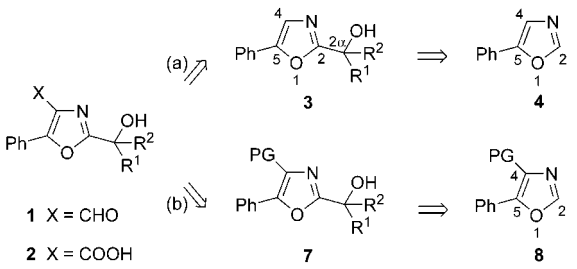
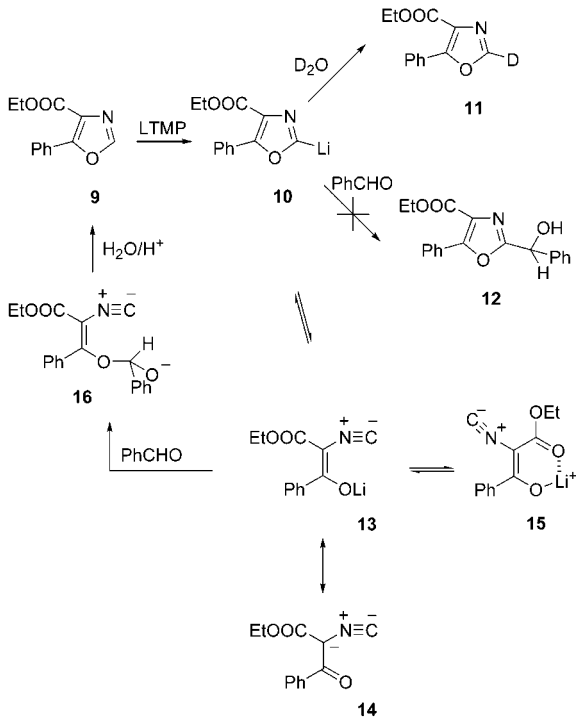
Scheme 1



Scheme 2

tionalities on the oxazole heterocyclic nucleus. Within this context, it initially appeared that a convenient route to the desired materials **1** and **2** would involve a double sequence of metalation−functionalization of the parent 5-phenyloxazole **4**. This initial conceptual approach was guided by several observations recorded by previous workers on the metalation of oxazoles[8] in conjunction with the known ease of the preparation of 5-aryl-substituted oxazoles,[9] which suggested the simple retrosynthetic Scheme 1 (path a). Schematically, the synthesis entailed the generation of the carbinol derivative **3**, which might have been obtained by hydroxyalkylation of the parent oxazole **4** via its 2-metalated derivative.[8d] Sequential protection followed by metalation at the 4-position of the heterocyclic nucleus and final connection of the appropriate functionality should complete the synthesis of the desired compounds **1** and **2**. Literature precedent gave support to the feasibility of such an approach. The C-2 proton of an oxazole is thermodynamically more acidic than the ortho proton of the phenyl ring in **4**[10] and particularly more than the C-4 proton of the heteroring unit.[11] If C-2 and C-5 are blocked, direct metalation at C-4 can be reasonably expected so that we should be able to sequentially functionalize an intact 5-phenyloxazole in the desired manner. It was, however, anticipated that this strategy would be fraught with difficulties associated with the erratic nature of the metalation processes.[7c] Indeed, attempts to trap 2-lithiooxazoles with electrophiles must contend with the complication due to the presence of valence bond tautomers **5** and **6** (Scheme 2), which can react at the enolate oxygen as well as carbon,[6,8,12] even though this problem has been partly solved recently by the elegant method of Vedejs.[13] Nevertheless, using aromatic aldehydes as electrophiles, variable yields of the normal carbinol adducts have been reported.[8c,e] Above all, the well-known acidity of 2α-methyl protons,[8a,14]

Scheme 3



especially when activated by two aromatic rings, e.g., **3** (R^1 = H, R^2 = aryl), could interfere with the second metalation step since the different CH bonds of oxazole itself and its alkyl derivatives differ considerably in acidity. It is generally believed that the relative acidities follow the trend 2 > 2α > 5 > 4. Finally, the 4-deprotonation of 2,5-disubstituted oxazoles can be complicated by competing reactions, namely addition of the lithiated base to the imine bond of the oxazole ring.[15] Considering then that this strategy would be doomed to failure, we decided to adopt the alternative synthetic tactic depicted in the retrosynthetic Scheme 1 (path b). We opted to introduce specific carbon electrophiles at the 2-position of the oxazole nucleus by metalation of a 5-phenyloxazole precursor **8** pre-equipped at the 4-position with a protective group (PG) liable to give access to the desired functionalities of **1** and **2**.

Critical to the success of this strategy then was the ability to identify a masked carboxaldehyde or carboxylic acid synthon that was capable not only of retaining the required functionalities but also of surviving and, if possible, facilitating the metalation step. For this purpose, we initially chose the readily accessible 4-carbethoxy-5-phenyloxazole (**9**). The first metalation experiments followed literature precedent settling the optimal conditions for the formation of the 2-lithio derivative **10**.[8a] Thus, the 4,5-disubstituted oxazole **9** was deprotonated with LTMP at −78 °C in THF to give a deep red solution that became amber in color on addition of benzaldehyde and that was stirred overnight with gradual warming (Scheme 3). Deuterium quenching studies revealed that the metalation reaction was complete within 5 min and that the only detectable product was the 2-deuterated

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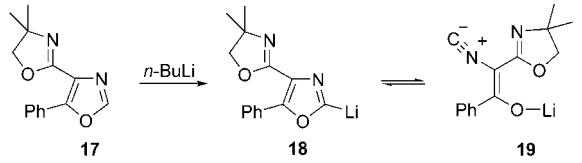
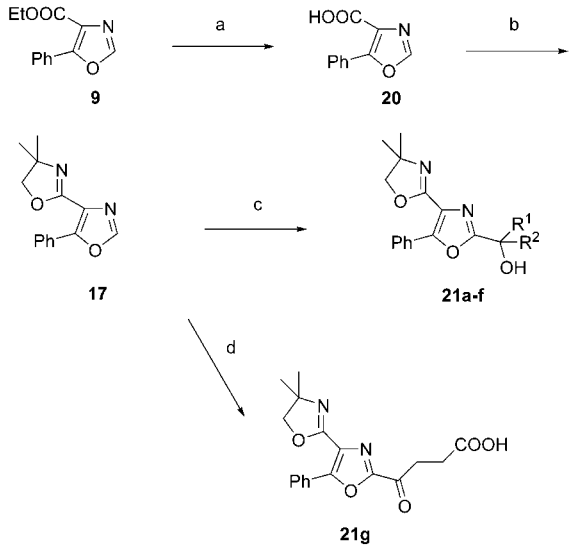
Scheme 4



derivative **11** in which the oxazole ring had remained intact. Somewhat surprisingly and disappointingly, no trace of the carbinol adduct **12** could be detected in the reaction mixture that had been treated with benzaldehyde. All that was present were major amounts of recovered **9**. We assumed that the absence of formation of the desired carbinol adduct **12** might not be due to the simple lack of reactivity between the formal carbanion **10** and benzaldehyde, an unprecedented phenomenon, but that a more complex and circuitous mechanism may be involved. This peculiar behavior could tentatively be rationalized by involving a reaction between the aromatic aldehyde and the open-chain tautomer lithio α-isocyano enolate **13** (or **14**) to form the hemiacetal **16**.[8c] Rapid hydrolysis of this isocyanoacetic acid derivative during workup then should regenerate the parent oxazole **9** (Scheme 3). The available evidence was suggestive of an extremely rapid and almost irreversible conversion of **10** to **13** favored by the relative stability of enolate **13** with a coordinated lithium species such as **15** playing a contributing role in this reaction pathway.

Having been thwarted in attempts to use ester **9** as a precursor for the target compounds **1** and **2**, we then opted to modify the temporary protecting auxiliary involved in the original retrosynthetic route (Scheme 1, path b) in order to achieve the challenging 2-hydroxyalkylation of the oxazole precursor **8**. The installation of the oxazoline unit at the 4-position of the oxazole framework originated from the following premises: (i) the oxazoline ring system is easily accessible from the readily available carboxylic acid derivative,[2a] (ii) it not only survives treatment with alkyllithium reagents but also facilitates diverse metalation processes,[16] (iii) it can easily be converted to formyl,[17] carboxyl,[18] and equally nitrile[19] functionalities; (iv) in particular, it could be anticipated that the lithio anion reactivity should be reversed in favor of the 2-lithio intermediate **18** (Scheme 4) (kinetic effect) and that the reactivity of the ring-opening enolate **19**, compared to **15** should be notably decreased (thermodynamic effect). We then embarked on the synthesis of the 4-(4,4-dimethyloxazolin-2-yl)-5-phenyloxazole (**17**). The assemblage of this heterobicyclic compound was readily accomplished by initial saponification of ester **9** to afford acid **20** (Scheme 5). Conversion into the corresponding acid chloride and sequential treatment with 2-methyl-2-aminopropanol and thionyl chloride ensured the formation of the oxazoline ring and thus completed the synthesis of the target compound **17**. Exposure of the heterobicyclic compound **17** to *n*-BuLi (1 equiv) at −78 °C in THF (15 min) furnished an orange solution that was immediately quenched with a variety

Scheme 5[a]



[a] Reagents and conditions: (a) NaOH, EtOH, H_2O, rt, 12 h; (b) (i) $SOCl_2$, (ii) $HOCH_2C(CH_3)_2NH_2$, CH_2Cl_2, NEt_3, rt, 3 h, (iii) $SOCl_2$, rt, 4 h; (c) (i) *n*-BuLi, THF, −78 °C, 15 min, (ii) electrophile, (iii) −78 °C to rt, 1 h, (iv) NH_4Cl saturated, H_2O; (d) (i) *n*-BuLi, THF, −78 °C, 15 min, (ii) $(CH_2CO)_2O$, (iii) rt, 3 h, (iv) NH_4Cl saturated, H_2O.

Table 2. Reaction of 17 with Different Electrophiles

entry	electrophile	R^1	R^2	product	yield (%)
1	PhCHO	Ph	H	**21a**	64
2	$CH_3(CH_2)_7CHO$	$CH_3(CH_2)_7$	H	**21b**	48
3	cyclohexanone	$(CH_2)_5$		**21c**	56
4	$(CH_3)_2CHCH_2CHO$	$(CH_3)_2CHCH_2$	H	**21d**	51
5	$Ph(CH_2)_2CHO$	$Ph(CH_2)_2$	H	**21e**	67
6	$(CH_2O)_2CH(CH_2)_2CHO$	$(CH_2O)_2CH(CH_2)_2$	H	**21f**	34
7	$(CH_2CO)_2O$			**21g**	22

of carbonyl compounds to afford solely and exclusively products of electrophilic substitution at C-2 **21a**−**g** (Scheme 5). Gratifyingly, no complications due to nucleophilic addition to the imine subunit of either of the two heterocycles[15,20] or opening of the oxazole were detected. A variety of electrophiles that can participate in the coupling reaction and a representative series of compounds that have been prepared by this method are presented in Table 2, where it may be seen that this simple procedure affords very satisfactory yields of the hydroxyalkylation products **21a**−**g**. Examination of Table 2 deserves some comment. The method is compatible with a wide variety of carbonyl compounds since the reaction can be indiscriminately performed with aromatic (Table 2, entry 1) and aliphatic (Table 2, entries 2, 4, 5, 6) aldehydes but equally with enolizable ketones (Table 2, entry 3) and succinic anhydride (Table 2, entry 7) albeit in moderate yield. It also allows incorporation of diverse functionalities on the pendant chain at C-2, which can be interesting for further synthetic planning (Table 2, entries 6 and 7). The adoption of the oxazoline protecting auxiliary for the latent functionalities was rewarded here: the carboxylic acid function was easily retrieved by conversion to the methiodide and removal of the oxazolinium moiety by alkaline hydrolysis[20] as exempli-

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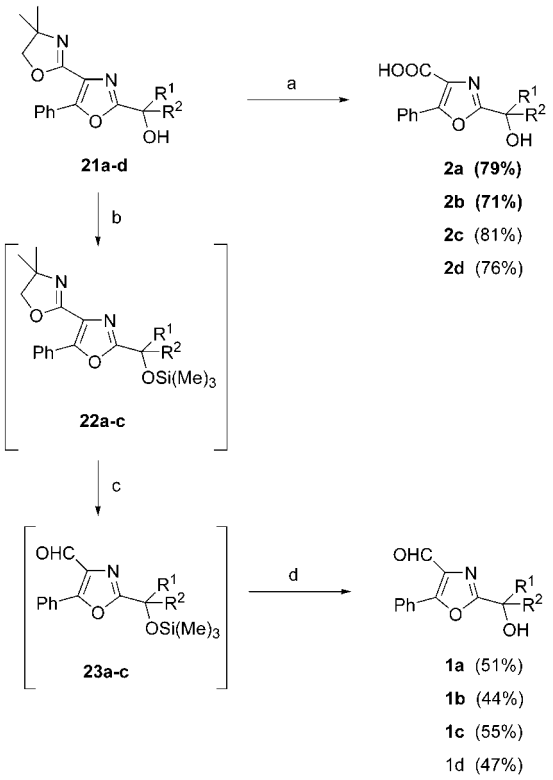
Scheme 6[a]



[a] Reagents and conditions: (a) (i) CH_3I, rt, 12 h, (ii) NaOH (2 N), H_2O; (iii) H_3O^+; (b) (i) HMDS, I_2 (cat.), CH_2Cl_2, (ii) $Na_2S_2O_3$; (iii) $NaHCO_3$ saturated, H_2O; (c) (i) CH_3I, rt, 12 h, (ii) $NaBH_4$, THF−MeOH (4:1), (iii) NH_4Cl saturated, H_2O, (iv) silica gel, CH_2Cl_2 (5% H_2O), rt, 2 h; (d) Bu_4NF, THF, −20 °C, 5 min.

fied by the attainment of **2a**−**d** and particularly of the target 2-hydroxyalkylated 4-oxazole carboxylic acids **2c** and **2d** (Scheme 6). The synthesis of the formyl derivatives **1a**−**d** proved a little more problematic than we had anticipated. Indeed, this required protection of the pendant hydroxy function in **21a**−**d** prior to generation of the formyl functionality. The operation was therefore performed by applying Meyers protocol[17,18] to the O-silylated compounds **22a**−**d**.[21] Reduction and subsequent treatment with silica gel[22] caused release of the formyl function, while sparing the silyl protection and final desilylation of the intermediate **23a**−**d** resulted in the generation of the target bifunctional compounds **1a**−**d**, including the target compounds **1a**−**c**, with satisfactory yields (Scheme 6).

In summary, the synthetic strategy outlined in this paper provides a convenient and efficient synthesis of suitably 2,4-bifunctionalized 5-phenyloxazoles. We have notably demonstrated that incorporation of the oxazoline unit at the 4-position of an oxazole nucleus allows addition of a wide variety of carbonylated electrophiles via the 2-lithio derivative and suppresses the troublesome electrocyclic ring opening reaction. It also demonstrates, if still necessary, the remarkable potential of the oxazoline ring system mainly exploited thus far in nucleophilic aromatic substitutions and in ortho-directed metalation reactions.

Experimental Section

General Methods. Melting points are uncorrected. Infrared spectra were recorded in a KBr pellet. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, with TMS as internal standard. Elemental analyses were performed by the CNRS microanalysis center. CH_2Cl_2 and DMF were distilled from CaH_2 and stored over 3 Å molecular sieves. THF was distilled over sodium benzophenone before use.

Materials. The 5-phenyloxazole-4-carboxylic acid ethyl ester (**9**)[8d] [^{13}C NMR ($CDCl_3$) δ 161.8, 155.4, 149.1, 130.4, 128.35, 128.3, 126.6, 126.5, 61.3, 14.1] and 3-([1,3]dioxolan-2-yl)propanal[23] were synthesized according to previously reported procedures.

5-Phenyloxazole-4-carboxylic Acid (20). A solution of NaOH (5.7 g, 142.0 mmol) in water (10 mL) was added to a solution of 5-phenyloxazole-4-carboxylic acid ethyl ester (**9**, 20.5 g, 94.4 mmol) in EtOH (200 mL), and the reaction mixture was then stirred at 20 °C for 12 h. The reaction mixture was concentrated to dryness in vacuo, and aqueous HCl (3N, 100 mL) was added. The resulting precipitate was filtered and dried in vacuo to afford 16.0 g (91%) of **20** as a white solid that was recrystallized from AcOEt: mp 166−168 °C; IR (KBr) 3136, 1710 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.50 (m, 3H), 8.00 (m, 2H), 8.55 (s, 1H), 13.20 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 162.9, 153.8, 150.7, 130.2, 128.5, 128.3, 126.8 (two peaks overlapping). Anal. Calcd for $C_{10}H_7NO_3$: C, 63.49; H, 3.73; N, 7.40. Found: C, 63.36; H, 3.65; N, 7.24.

4-(4,4-Dimethyloxazolin-2-yl)-5-phenyloxazole (17). Compound **20** (10 g, 52.9 mmol) was stirred with thionyl chloride (70 mL) at reflux for 3 h. Excess thionyl chloride was removed in vacuo to give the corresponding acid chloride which was then dissolved in CH_2Cl_2 (100 mL) and added to a mixture of 2-methyl-2-aminopropanol (5.6 g, 63 mmol) and triethylamine (7 g, 70 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The mixture was stirred for 3 h at room temperatur,e and the organic layers were washed with HCl (1 M), water, and brine, dried over $MgSO_4$, and concentrated in vacuo to afford a crude residue that was dissolved in CH_2Cl_2 (50 mL) and then slowly added to thionyl chloride (40 mL) at 0 °C. The resulting solution was stirred at room temperature for 4 h, and thionyl chloride was removed in vacuo. HCl (1 M, 10 mL) was added to the residue, and the resulting solution was washed with ether. The aqueous fraction was made basic with aqueous NaOH (10%) and extracted with Et_2O (3 × 50 mL). The ether solution was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residual solid was recrystallized from cyclohexane to give a white crystalline solid (8.3 g, 65%): mp 68−70 °C; IR (KBr) 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (s, 6H), 4.10 (s, 2H), 7.41−7.44 (m, 3H), 7.90 (s, 1H), 8.07−8.10 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 156.5, 151.9, 149.3, 129.8, 128.3, 127.9, 127.1, 124.3, 79.1, 68.0, 28.3. Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.82; N, 11.55. Found: C, 69.33; H, 5.91; N, 11.33.

General Method for Preparation of [4-(4,4-Dimethyloxazolin-2-yl)-5-phenyloxazol-2-yl] Alcohols 21a−f. A solution of *n*-BuLi (7.75 mL, 12.4 mmol, 1.6 M solution in hexane) was added dropwise, at −78 °C under Ar, over a period of 20 min, to a stirred solution of 4-(4,4-dimethyloxazolin-2-yl)-5-phenyloxazole (**17**, 3.0 g, 12.4 mmol) in THF (30 mL). The solution was stirred for 15 min at this temperature, and a solution of the appropriate electrophile (12.4 mmol) in THF (5 mL) was added by syringe. The reaction was allowed to warm to room temperature over a period of 1 h and then treated with saturated aqueous NH_4Cl (40 mL). The mixture was extracted with Et_2O (3 × 50 mL), and the combined organic phases were washed with HCl (1 M, 3 × 10 mL). The aqueous fraction was made basic by treatment with aqueous NaOH (10%) and then extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated under vacuum to an oily residue that was purified by flash column chromatography on silica gel, using a MeOH/CH_2Cl_2 mixture (5:95) as eluent, and finally recrystallized.

1-[4-(4,4-Dimethyloxazolin-2-yl)-5-phenyloxazol-2-yl]-1-phenylmethanol (21a): white solid; mp 176−179 °C (AcOEt); IR (KBr) 3189, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40

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(s, 6H), 4.10 (s, 2H), 6.01 (s, 1H), 7.30−7.43 (m, 6H), 7.45−7.53 (m, 2H), 7.90−7.98 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 163.2, 156.1, 152.4, 139.1, 129.7, 128.6, 128.4, 128.2, 128.1, 127.1, 126.6, 79.2, 69.7, 67.7, 28.2. Anal. Calcd for $C_{21}H_{20}N_2O_3$: C, 72.33; H, 5.74; N, 8.04. Found: C, 72.23; H, 5.86; N, 8.31.

1-[4-(4,4-Dimethyloxazolin-2-yl)-5-phenyloxazol-2-yl]-nonan-1-ol (21b): yellow oil; IR (KBr) 3351, 1661 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7.0 Hz, 3H), 1.20−1.28 (m, 12H, CH_2), 1.40 (s, 6H), 1.83−1.89 (m, 2H), 4.09 (s, 2H), 4.84 (t, J = 6.5 Hz, 1H), 7.40−7.44 (m, 3H), 8.10−8.13 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 164.4, 156.7, 152.0, 129.7, 128.3, 128.0, 127.5, 79.2, 67.7 (two peaks overlapping), 35.6, 31.8, 30.9, 29.4, 29.3, 28.3, 25.0, 22.6, 14.1. Anal. Calcd for $C_{23}H_{32}N_2O_3$: C, 71.84; H, 8.39; N, 7.29. Found: C, 71.76; H, 8.31; N, 7.33.

1-[4-(4,4-Dimethyloxazolin-2-yl)-5-phenyloxazol-2-yl]-cyclohexanol (21c): white solid; mp 119−120 °C (hexane/toluene); IR (KBr) 3356, 1662 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 6H), 1.49−2.05 (m, 10H), 4.06 (s, 2H), 7.32−7.41 (m, 3H), 8.00−7.98 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 167.2, 156.7, 151.7, 129.6, 128.8, 128.3, 127.4, 124.3, 79.1, 70.7, 67.8, 36.3, 28.3, 25.1, 21.6. Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.57; H, 7.11; N, 8.23. Found: C, 70.49; H, 7.0; N, 8.31.

1-[4-(4,4-Dimethyloxazolin-2-yl)-5-phenyloxazol-2-yl]-3-methylbutan-1-ol (21d): white solid; mp 93−95 °C (cyclohexane); IR (KBr) 3354, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95−1.01 (m, 6H), 1.40 (s, 6H), 1.70−1.95 (m, 3H), 4.10 (s, 2H), 4.98−5.01 (m, 1H), 7.39−7.41 (m, 3H), 8.03−8.06 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 164.7, 156.8, 152.0, 129.7, 128.3 (two peaks overlapping), 128.0, 127.2, 79.2, 67.8, 65.9, 44.4, 28.3, 24.3, 23.1, 21.8. Anal. Calcd for $C_{19}H_{24}N_2O_3$: C, 69.42; H, 7.31; N, 8.52. Found: C, 69.20; H, 7.45; N, 8.33.

1-[4-(4,4-Dimethyloxazolin-2-yl)-5-phenyloxazol-2-yl]-3-phenylpropan-1-ol (21e): white solid; mp 107−110 °C (cyclohexane); IR (KBr) 3361, 1654 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 6H), 2.20−2.31 (m, 2H), 2.75−2.92 (m, 2H), 4.10 (s, 2H), 4.89 (t, J = 6.5 Hz, 1H), 7.10−7.30 (m, 5H), 7.40−7.51 (m, 3H), 7.95−8.03 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 164.3, 156.8, 152.1, 141.1, 129.7, 128.5, 128.4, 128.3, 128.1, 127.2, 126.0, 124.2, 79.2, 67.7, 66.6, 37.0, 31.3, 28.3. Anal. Calcd for $C_{23}H_{24}N_2O_3$: C, 73.38; H, 6.42; N, 7.42. Found: C, 73.05; H, 6.45; N, 7.39.

1-[4-(4,4-Dimethyloxazolin-2-yl)-5-phenyloxazol-2-yl]-3-([1,3]dioxolan-2-yl)propan-1-ol (21f): white solid; mp 92−94 °C (cyclohexane); IR (KBr) 3374, 1661 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 6H), 1.82−2.20 (m, 4H), 3.78−4.00 (m, 4H), 4.10 (s, 2H), 4.85−5.03 (m, 2H), 7.42−7.52 (m, 3H), 7.97−8.09 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 164.0, 156.7, 153.1, 129.7, 128.3, 128.1, 127.1, 103.8, 79.2, 67.8, 67.4, 64.9, 65.0, 29.5, 29.2, 28.3. Anal. Calcd for $C_{20}H_{24}N_2O_5$: C, 64.50; H, 6.50; N, 7.52. Found: C, 64.49; H, 6.79; N, 7.22.

Preparation of 4-[4-(4,4-Dimethyloxazolin-2-yl)-5-phenyloxazol-2-yl]-4-oxobutanoic Acid (21g). A solution of *n*-BuLi (1.25 mL, 2.0 mmol, 1.6 M solution in hexane) was added dropwise by syringe, at −78 °C under Ar, to a solution of compound **17** (0.48 g, 2.0 mmol) in THF (10 mL). The purple solution was stirred at this temperature for an additional 15 min, and solid succinic anhydride (0.21 g, 2.0 mmol) was added at once. The cyclic anhydride dissolved slowly as the solution turned from purple to orange. Stirring was continued for 3 h at room temperature, and the solution was then treated with saturated aqueous NH_4Cl (40 mL). The mixture was extracted with Et_2O (3 × 20 mL), and the combined organic phases were washed with aqueous NaOH (10%, 20 mL). The aqueous fraction was made acidic (pH 3) with citric acid (10%) and then extracted with Et_2O (3 × 20 mL). The organic layer was then washed with water and brine and dried ($MgSO_4$). The dried extract was concentrated in vacuo to afford a crude residue that was finally purified by recrystallization from AcOEt: white solid (150 mg); mp 188−190 °C; IR (KBr) 3226, 1726, 1707, 1660 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.30 (s, 6H), 2.65 (t, J = 6.6 Hz, 2H), 3.30 (t, J = 6.6 Hz, 2H), 4.15 (s, 2H), 7.54−7.56 (m, 3H), 8.10 (dd, J = 2.5, 7.6 Hz, 2H), 12.35 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 192.7, 174.2, 164.0, 156.4, 155.2, 130.9, 128.8, 128.5, 128.4, 126.2, 79.6, 67.9, 33.9, 33.7, 28.2. Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.10; H, 5.25; N, 8.18. Found: C, 62.94; H, 5.44; N, 8.23.

General Method for Preparation of the Formyl Derivatives 1a−d. A solution of 1,1,1,3,3,3-hexamethylsilazane (HMDS, 0.81 g, 5 mmol) in CH_2Cl_2 (10 mL) was added dropwise over a period of 5 min to a stirred solution of alcohols **21a−d** (6 mmol) and I_2 (1.5 mg, 0.06 mmol) in CH_2Cl_2 (25 mL) under Ar. The solution was stirred for 3 h, and finely powdered $Na_2S_2O_3$ (1.5 g, portion wise) was then added. The mixture was stirred for an additional 30 min, and the white solid was then filtered off and washed twice with CH_2Cl_2 (2 × 10 mL). The solution was concentrated in vacuo to afford a crude residue that was stirred with CH_3I (10 mL) for 24 h. Excess CH_3I was removed under vacuum, and the resulting yellow foam was dissolved in THF/MeOH (10 mL, 4:1) and treated with $NaBH_4$ (345 mg, 9 mmol, portionwise) over a period of 15 min. Stirring was maintained during 2 h at room temperature followed by addition of saturated aqueous NH_4Cl (10 mL). The mixture was stirred for an additional 2 h and then extracted with Et_2O (3 × 30 mL). The combined organic phases were washed with water and brine and dried ($MgSO_4$). Concentration under vacuum left a crude residue that was dissolved in a suspension of silica gel (10 g) in CH_2Cl_2 (25 mL) with a few drops of water, and the mixture was vigorously stirred at room temperature overnight. Filtration and removal of the solvent under vacuum followed by purification by column chromatography on silica gel with CH_2Cl_2 as eluent delivered the silylated compounds **23a−d**, which were identified by ^{1}H NMR spectroscopy [e.g. **23c** ($CDCl_3$) δ 0.00 (s, 9H), 1.19−1.60 (m, 4H), 1.67−1.85 (m, 2H), 1.92−2.25 (m, 4H), 7.50−7.52 (m, 3H), 8.10−8.14 (m, 2H), 10.10 (s, 1H)]. Compounds **23a−d** were used directly in the next step without further purification. Thus compounds **23a−d** were dissolved in THF (10 mL) and treated with Bu_4NF (6.6 mL, 6.6 mmol of 1 M solution in THF) at −20 °C for 5 min. Removal of excess reagents left an oily residue that was finally purified by flash column chromatography on silica gel with a mixture MeOH/CH_2Cl_2 (5:95) as eluent.

2-(Hydroxyphenylmethyl)-5-phenyloxazole-4-carbaldehyde (1a): yellow oil; IR (KBr) 3251, 1692 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.03 (s, 1H), 7.32−7.42 (m, 4H), 7.45−7.54 (m, 4H), 7.96−8.00 (m, 2H), 10.05 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 184.6, 163.4, 156.8, 138.6, 131.4, 129.0, 128.9, 128.1, 127.7, 126.6, 126.0, 70.0. Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.01. Found: C, 73.16; H, 4.52; N, 5.09.

2-(1-Hydroxynonyl)-5-phenyloxazole-4-carbaldehyde (1b): yellow oil; IR (KBr) 3275, 1688 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 6.8 Hz, 3H), 1.21−1.25 (m, 12H), 1.92−2.00 (m, 2H), 4.90 (t, J = 6.8 Hz, 1H), 7.46−7.81 (m, 3H), 7.98−8.01 (m, 2H), 10.03 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 184.6, 164.9, 156.5, 133.8, 131.3, 129.0, 127.7, 126.1, 67.4, 35.4, 31.8, 29.4, 29.3, 29.2, 25.0, 22.6, 14.1. Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.21; H, 8.05; N, 4.52.

2-(1-Hydroxycyclohexyl)-5-phenyloxazole-4-carbaldehyde (1c): yellow oil; IR (KBr) 3250, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.56−1.66 (m, 4H), 1.72−1.82 (m, 2H), 1.92−1.98 (m, 2H), 2.08−2.15 (m, 2H), 7.46−7.53 (m, 3H), 8.02−8.06 (m, 2H), 10.07 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 185.0, 166.9, 156.2, 133.9, 129.0, 128.8, 128.4, 126.3, 70.8, 36.4, 25.1, 21.7. Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.92; H, 6.44; N, 5.08.

2-(1-Hydroxy-3-methylbutyl)-5-phenyloxazole-4-carbaldehyde (1d): yellow oil; IR (KBr) 3281, 1687 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.99 (d, J = 6.0 Hz, 6H), 1.77−1.96 (m, 3H), 4.98 (t, J = 8.4 Hz, 1H), 7.46−7.54 (m, 3H), 7.98−8.05 (m, 2H), 10.05 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 184.6, 165.1, 156.5, 133.9, 131.3, 129.0, 127.7, 126.2, 65.9, 44.3, 24.4, 23.1, 21.9. Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.68; H, 6.54; N, 5.28.

General Method for Preparation of Acid Derivatives 2a−d. A mixture of alcohol **21a−d** (3 mmol) in CH_3I (10 mL) was stirred for 24 h at room temperature. CH_3I was then removed under vacuum, and the yellow foam obtained was treated by aqueous NaOH (2 M, 25 mL) over 48 h. The mixture was first washed with Et_2O (3 × 20 mL), and the aqueous

fraction was made acidic by treatment with aqueous HCl (2 M) and then extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and evaporated to give a white solid that was recrystallized from hexane/toluene.

2-(Hydroxyphenylmethyl)-5-phenyloxazole-4-carboxylic acid (2a): white solid; mp 194 °C dec; IR (KBr) 3291, 1692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.19 (s, 1H), 7.23−7.47 (m, 6H), 7.56−7.58 (m, 2H), 8.22−8.31 (m, 2H), 13.12 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 167.4, 162.4, 149.0, 140.0, 133.2, 129.0, 128.4, 128.2, 127.7, 127.4, 126.5, 67.8. Anal. Calcd for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.44; N, 4.74. Found: C, 69.31; H, 4.50; N, 4.98.

2-(1-Hydroxynonyl)-5-phenyloxazole-4-carboxylic acid (2b): white solid; mp 129−130 °C; IR (KBr) 3375, 1688 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (m, 3H), 1.21−1.45 (m, 12H), 1.62−1.90 (m, 2H), 5.83 (br. s, 1H), 7.45−7.65 (m, 3H), 7.90−8.05 (m, 2H), 13.12 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 163.9, 163.1, 153.2, 129.9, 128.4, 128.1, 127.2, 127.0, 65.6, 35.4, 31.8, 29.4, 29.3, 29.2, 25.0, 22.6, 13.9. Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.76; H, 7.45; N, 3.96.

2-(1-Hydroxycyclohexyl)-5-phenyloxazole-4-carboxylic acid (2c): white solid; mp 141−142 °C; IR (KBr) 3350, 1693 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.33−1.43 (m, 4H), 1.66−1.69 (m, 2H), 1.80−1.84 (m, 2H), 1.96−2.03 (m, 2H), 7.44−7.54 (m, 3H), 7.96−8.00 (m, 2H), 13.10 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 166.2, 163.2, 153.4, 130.0, 128.4, 128.2, 127.0, 126.9, 69.0, 35.7, 24.9, 21.6. Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.67. Found: C, 66.95; H, 6.11; N, 4.58.

2-(1-Hydroxy-3-methylbutyl)-5-phenyloxazole-4-carboxylic acid (2d): white solid; mp 145−146 °C; IR (KBr) 3380, 1685 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.90−0.93 (m, 6H), 1.68−1.77 (m, 3H), 4.71 (br. s, 1H), 7.49−7.52 (m, 3H), 7.99−8.03 (m, 2H), 13.10 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 164.9, 163.8, 155.4, 130.4, 128.5, 128.4, 126.6, 65.8, 44.3, 24.4, 23.0, 21.9. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.36; H, 6.15; N, 5.14.

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