Preparation and Crystal Structures of Two 3-Anthracenyl Isoxazolyl Sulfonamides

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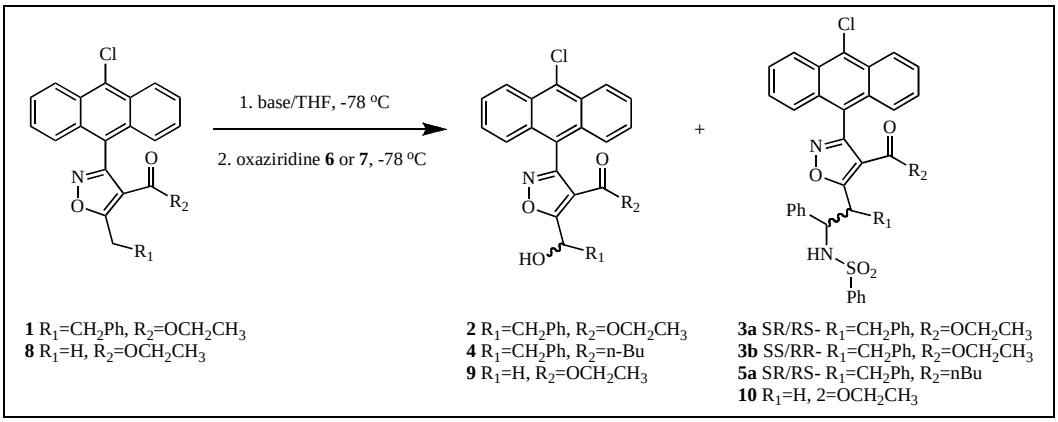

Lateral metalation and oxidation of 3-(9'-anthryl)-isoxazoles **(1)**, using Davis' oxaziridine **(6)**, produced the desired hydroxylation **(2)**, along with sulfonamide adduct **(3)**, and in the case of the use of butyl lithium as base, butyl addition products **(4)** and **(5)**. Structures of isoxazole sulfonamides **(3a)** and **(5a)**, were obtained as the SR/RS-diastereomer, however, studies indicate that this is a consequence of the crystallization process. Metalation studies with isoxazole **(8)** demonstrate that hydroxylation **(9)**, can be carried out cleanly, minimizing formation of **(10)**, using camphorsulfonyloxaziridine **(7)** as an electrophile.

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INTRODUCTION

We previously reported a new class of isoxazoles [1-3], which were subsequently found to exhibit significant anti-cancer activity in the National Cancer Institute's 60 cell line screening protocol [4]. Our working hypothesis is based on the fact that the single-stranded G-rich overhang of the human telomere, or other similar oligonucleotide sequences, can adopt a G-quadruplex (G-4) structure, and stabilization of this G-4 by a small molecule ligand inhibits tumor cell proliferation. Many such ligands have been reported [5-7], among which notably is fluoroquino-benzoxazine CX-3543, which is the first-in-class G-4 binding molecule to advance to clinical trials [8]. This type of molecule bears some similar structural features to our anthracenylisoxazoles. The binding modes of these types of molecules to G-4 are thought to involve π-stacking onto the terminal G-tetrad. We calculated the coordination of G-4 with one of our lead compounds (NSC D 694332), using SGI INSIGHT II [9]. The result showed that the hydrogen on C-10 was proximal to the K^+ in the G-4 cavity, the N of the isoxazole moiety coordinated with the NH_2 group in guanine, and the C-5 methyl on the isoxazole falls into the groove formed by a TTA loop. Most of the reported G-4 ligands have planar structures and are non-chiral. Introduction of a chiral center (*i.e.*, hydroxyl group) for hydrogen bonding to DNA's sugar phosphate backbone should increase G-4 interaction specificity. Furthermore, α-hydroxylation of a substituted isoxazole should help us better understand the physiological behavior of this series of analogues. Based upon the above studies and hypotheses, hydroxylations using oxaziridines were carried out on the C-5 methyl or methylene groups of our substrates. Our results are discussed in this paper.

RESULTS AND DISCUSSION

Oxaziridines have been widely investigated and used in organic synthesis as both oxygen and nitrogen transferring reagents for a wide variety of nucleophiles [10]. The unusually high reactivity comes from the presence of an inherently weak N-O bond in a strained three-membered ring [10-13]. Although other nitrogen and oxygen transfer reagents are known, oxaziridine-mediated processes are of interest because they are more easily prepared, more stable and have higher stereoselectivity [14]. In spite of oxaziridines dual reactivity, the predominance of one process over another can be affected by varying the substitution pattern on nitrogen. In general, oxaziridines with small groups on nitrogen (H, Me) act as aminating agents [15], whereas those with bulky or electron-withdrawing groups on nitrogen preferentially transfer the oxygen atom. Electron deficient oxaziridines, such as

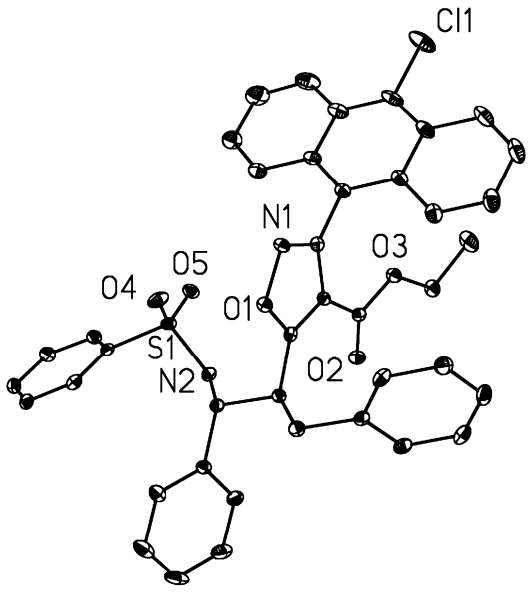


Figure 1. Thermal ellipsoid (30%) diagram of **3a**. Hydrogen atoms have been omitted for clarity. Coordinates have been deposited with CCDC, structure reference 639428.

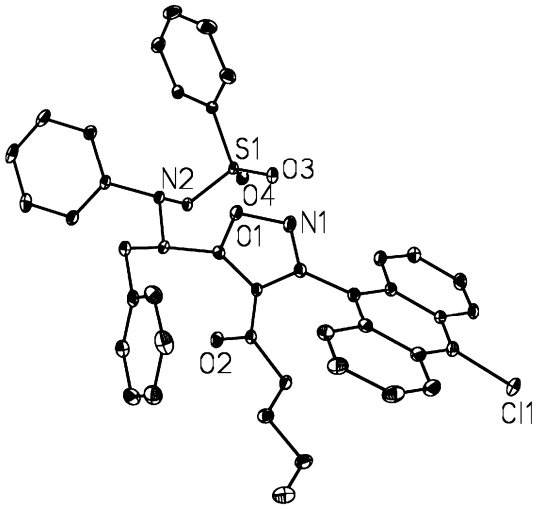


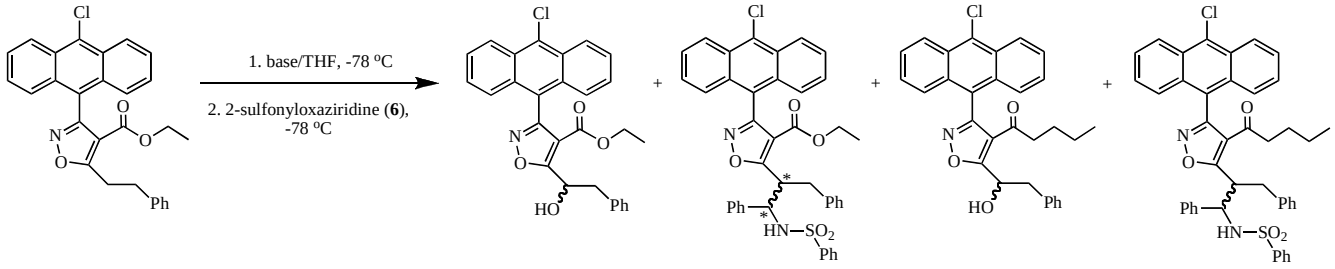
Figure 2. Thermal ellipsoid (30%) diagram **5a**. Hydrogen atoms have been omitted for clarity. Coordinates have been deposited with CCDC, structure reference 639429.

N-sulfonyl oxaziridines, oxaziridinium salts, and perfluorinated oxaziridines have found extensive use as sources of electrophilic oxygen.

We conducted lateral metallation on the C-5 methylene group of anthracenylisoxazole (**1**) and quenched with phenylsulfonyloxaziridine (**6**) to introduce a α-hydroxyl group at the isoxazole C-5 position (Scheme 1). It was not without precedent, when using either n-BuLi or Lithium diisopropylamide (LDA) as base, that the hydroxylation was complicated by a side reaction in which the vinylogous lithium enolate added to the sulfonimine, the requisite product resulting from oxaziridine oxygen transfer, even though the reactions were carried out at –78 ºC. The same result was obtained when the anion solution was added to a solution of oxaziridine (reverse addition). When potassium hexamethyldisilazine (KHMDS) was used as base, the sulfonimine addition proceeded in trace amount. These results are similar to what was observed by Davis [14], for simple enolates and indicated that the preference of oxygen transfer over sulfonimine addition from oxaziridine depends on the base used.

After recrystallization, sulfonamides **(3a)** and **(5a)** were obtained as single racemic diastereomers, as determined by single crystal X-ray analysis (Table 1 for the crystallographic data and parameters). The relative configurations shown in Figure 1 and Figure 2 represent the C21S, C29R and C23S, C31R diastereomers of compounds **(3a)** and **(5a)**, respectively. Further experiments were conducted to examine the diasteroselectivity of the reactions producing the sulfonamines (Table 2). For compound **(3)**, the ratio of (S,R)/(R,S) to (S,S)/(R,R) was about 3 to 2. This can be explained from Newman projections (Figure 3) where the hydrogen bond observed in the crystal structure between O2 of the carbonyl and N2 of the sulfonamine for **(3a)** exhibit fewer unfavorable non-bonding interactions for the SR/RS diastereomer after protonation and during crystallization, whereas the precursor vinylogous lithio

Scheme 1



enolate must not be as rigidly organized under the reaction conditions studied. However, this does suggest that useful diasteroselectivites could possibly be obtained, under optimally coordinating reaction conditions, and this issue will be addressed in our ongoing studies.

Another observation from oxaziridine oxidation is that KHMDS was not a good base for oxidation of the C-5 methyl group of **(8)**, in terms of unwanted products that were highly polar and immobile on silica gel. The smaller methyl group on the C-5 position seemed to make the isoxazole prone to putative ring opening in the presence of highly reactive potassium ion. The use of n-BuLi or LDA as base in this reaction for oxidizing the C-5 methyl group of **(8)** with **(6)** resulted in poor yields with the formation of an undesired sulfonamide adduct **(10)** (Scheme 2). To eliminate the addition product, (camphorylsulfonyl)oxaziridine **(7)** was used to oxidize the C-5 methyl group. The desired primary alcohol **(9)** was obtained in 70% isolated yield based on the recovery of starting material, and no adduct was detected (Table 3). This is again analogous to observations by Davis [13,16] for simpler nucleophiles.

Table 1

Crystallographic Data and Structure Refinement Parameters.

	3a	**5a**
CCDC reference	639428	639429
Formula	$C_{41}H_{33}ClN_2O_5S$	$C_{43}H_{37}ClN_2O_4S$
Mol wt	701.20	713.26
Cryst syst, Space grp	Triclinic, P-1	Monoclinic, P2(1)/c
Cryst color and habit	Yellow needle	Yellow fragment
a (Å)	11.035(2)	15.089(3)
b (Å)	11.130(2)	12.830(3)
c (Å)	16.666(3)	18.722(4)
α (°)	72.11(3)	90
β (°)	74.33(3)	93.23(3)
γ (°)	70.28(2)	90
V ($Å^3$)	1801.8(7)	3618.7(13)
Z	2	4
ρ calcd (Mg/m^3)	1.292	1.309
μ (mm^{-1})	0.211	0.210
F(000)	732	1496
Crystal size (mm^3)	0.40 x 0.10 x 0.08	0.26 x 0.24 x 0.17
Θ range (°)	2.00 to 27.50	1.93 to 27.50
Index ranges	-14≤h≤14, -14≤k≤14, -21≤l≤21	-19≤h≤19, -16≤k≤16, -24≤l≤24
No. refl. collected	23677	47185
No. indep. reflections	8253 [R(int) = 0.0346]	8311 [R(int) = 0.0533]
Max. and min. transmission	0.9833 and 0.9202	0.9652 and 0.9475
Data/restraints/param.	8253 / 0 / 452	8311 / 0 / 464
GOF	1.021	1.051
*R_1 [$I>2\sigma(I)$]	0.0483	0.0576
*wR_2 [$I>2\sigma(I)$]	0.1121	0.1319
Largest diff. peak, hole ($eÅ^{-3}$)	0.555, -0.494	0.763, -0.395

* $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = \{\Sigma[\ w(F_o^2 - F_c^2)^2]/\ \Sigma\ [w(F_o^2)^2]\}^{1/2}$

Table 2

Hydroxylation of isoxazole (**1**) using lateral metallation and quenching with 2-sulfonyloxaziridine (**6**).

Entry	Base	Isolated Yield, %			
		2	**3***	**4**	**5**
1	n-BuLi	36	10(1.5:1)	18	4
2	LDA	52	11(1.5:1)		
3	KHMDS	81	<3		

* Ratios of diastereomers (SR/RS to SS/RR) before separation for compounds **3** are in parentheses.

Table 3

Hydroxylation of C-5 methyl group of isoxazole (**8**).

Entry	Oxazir-idine	Base	Isolated Yield, %	
			9	**10**
1	**6**	n-BuLi	43	36
2	**6**	LDA	40	24
3	**6**	KHMDS	No desired products found	
4	**7**	n-BuLi	70	Not detected

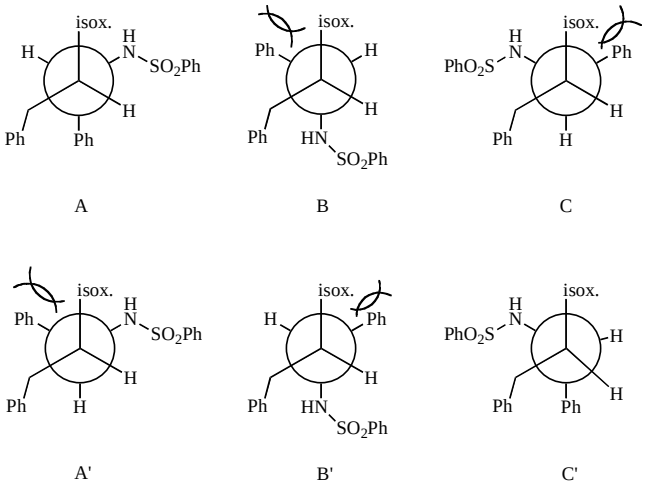
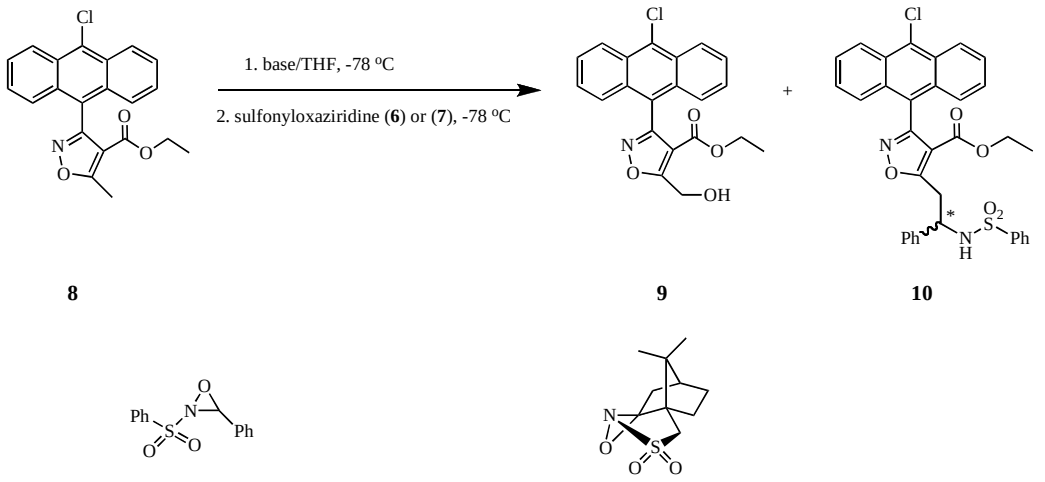


Figure 3. Newman projections of **3** in staggered conformations. Top (A-C): S, R configuration. Bottom (A'-C'): S, S configuration.

Using n-BuLi as the base for metalation of anthryl isoxazole **(8)** has previously been reported to give slightly higher yields than lithium diisopropylamide (LDA) in lateral metallation, without attacking the ester group [9]. However, in this study, when n-BuLi was used as a base for the metallation on the C-5 methylene group of **(1)** (Scheme 2), addition of n-butyl lithium to the ester moiety occurred. In the crystal structure of **(8)**, a relatively strong hydrogen bond between carbon-oxygen double bond and the C-5 methyl hydrogen points the ethoxy group towards the anthracene [3,17], as evidenced in solution by anisotropy in the chemical shift. This orientation shields the carbonyl with the dirigible like anthracenyl moiety, and possibly enhances the reactivity of the C-5 methyl. In contrast, in the presence of phenethyl moiety, the

Scheme 2



6. trans-2-(phenylsulfonyl)-3-phenyloxaziridine

7. (1R)-(-)-(10-camphorsulfonyl)oxaziridine

carbonyl orientation in **(1)** is reversed in the solid state [9]. Thus, in (**1**) the C-5 phenethyl may inhibit the reactivity at that position, and now nucleophilic addition at the carbonyl can compete more favorably.

We continue to be intrigued by the novel chemistry observed in our studies of the lateral metalation and electrophilic quenching of highly functionalized isoxazoles, as well as being motivated by their potentially useful biological activities, and will report on our progress in due course.

EXPERIMENTAL

Mass spectra were obtained on a JEOL JMS-AX505 HA. The NMR spectra (^{1}H and ^{13}C) were obtained on a Bruker Avance 300 Digital NMR (300 MHz) using SGI-IRIX 6.5. The spectra were recorded in deuteriochloroform unless otherwise noted. Elemental analyses were performed by Desert Analytics Laboratory, PO Box 41838, Tucson, Arizona 85717. Single-crystal X-ray analysis was obtained on Bruker (Siemens) SMART APEX instrument. All reactions were performed under Argon atmosphere. Tetrahydrofuran was distilled from sodium-benzophenone immediately before use. Radial chromatography was performed on silica gel (Merck 60 A, 230-400mesh). *trans*-2-Phenylsulfonyl-3-phenyl-oxaziridine was prepared according to previously reported procedure [18]. Ethyl 3-(9'-anthracenyl-10'chloro)-5-methyl-4-isoxazole carboxylate and ethyl 3-(9'-anthracenyl-10'-chloro-)-5-phenylethyl-4-isoxazole carboxylate were synthesized *via* routes developed in our laboratory [3,9]. LDA solution was generated *in situ* by adding n-BuLi (1.2 equiv.) to a solution of freshly distilled diisopropylamine (1.4 equiv.) in THF (*ca*. 0.1 *M*) at 0 ºC and stirred for 10 minutes at 0 ºC before cooling to –78 ºC.

General procedure for hydroxylation. To a stirred solution of ethyl isoxazolecarboxylate in THF (*ca*. 0.1 *M*) at –78 ºC was added base (1.2 equiv.) (n-BuLi or LDA or KHMDS) over 10 minutes. After the reaction mixture was stirred for 30 minutes at -78 ºC, a pre-cooled (-78 ºC) solution of 2-(phenylsulfonyl)-3-phenyloxaziridine (1.2 equiv.) dissolved in THF was added in one portion. After stirring for 2 hours at -78 ºC, the mixture was quenched with saturated aqueous NH_4Cl solution, and warmed up to room temperature. Workup included extraction of aqueous layer with CH_2Cl_2, extraction of the combined organic layers with brine solution, removal of solvent using rotary evaporation. The crude mixture was purified by radial chromatography (hexanes-ethyl acetate, 6:1) to give pure products.

Ethyl 3-(9'-anthracenyl-10'-chloro-)-5-hydroxymethyl-4-isoxazole carboxylate (9). This compound was crystallized as yellow solid from hexanes-ethyl acetate (3:1), mp 129-131 ºC; ^{1}H nmr: δ 0.24 (t, 3H, J=7.1Hz), 3.70 (q, 2H, J=7.1Hz), 4.33 (t, 1H, J=7.2Hz), 5.17 (d, 2H, J=7.2Hz), 7.53 (m, 2H), 7.65 (m, 4H) and 8.61 ppm (d, 2H, J=8.4Hz); ^{13}C nmr: δ 12.55, 57.09, 61.05, 112.53, 121.72, 125.09, 125.67, 126.74, 128.30, 131.15, 131.31, 160.06, 162.42, 178.39; ms: m/z 383 (36, $M+2^+$), 382 (23), 381 (100, M^+), 322 (23), 277 (56), 237 (32), 176 (57). *Anal*. Calcd. for $C_{21}H_{16}NO_4Cl$: C, 66.06; H, 4.22; N, 3.67. Found: C, 65.76; H, 4.47; N, 3.67.

Ethyl 3-(9'-anthracenyl-10'-chloro-)-5-(2-phenyl)-2-[(phenylsulfonyl)amino]ethyl-4-isoxazole carboxylate (10). This compound was crystallized as white needles from hexanes-ethyl acetate (3:1), mp 160.5-162.5 ºC (decomposed); ^{1}H nmr: δ 0.26 (t, 3H, J=7.2Hz), 3.69 (m, 3H), 3.90 (dd, 1H, J=14.1, 9.3Hz), 5.11 (ddd, 1H, J=14.1, 8.1, 5.4Hz), 5.83 (d, 1H, J=8.1Hz), 7.20 (m, 5H), 7.38 (m, 2H), 7.50 (m, 4H), 7.64 (m, 3H), 7.72 (m, 2H), 8.60 ppm (d, 2H, J=8.7Hz); ^{13}C nmr: δ 12.65, 34.92, 56.87, 60.59, 113.27, 122.17, 124.85, 124.95, 125.88, 126.01, 126.19, 126.48, 126.61, 126.80, 126.82, 126.95, 128.12, 128.24, 128.27, 128.72, 128.78, 131.03, 131.09, 131.21, 132.38, 139.12, 140.58, 159.93, 161.89, 175.01 ppm; ms: m/z 612 (49.8, $M+2^+$), 611 (54), 610 (94, M^+), 454 (41), 350 (25), 307(11), 246 (100), 154 (93), 131 (89). *Anal*. Calcd. for $C_{34}H_{27}N_2O_5SCl$: C, 66.82; H, 4.45; N, 4.58. Found: C, 66.74; H, 4.47; N, 4.36.

Ethyl 3-(9'-anthracenyl-10'-chloro-)-5-(1''-hydroxy-2-phenylethyl)-4-isoxazole carboxylate (2). This compound was crystallized as yellow flakes from hexanes-ethyl acetate (6:1), mp 123-124 ºC; ^{1}H nmr: δ 0.14 (t, 3H, J=14.0Hz), 3.44 (d, 2H, J=6.5Hz), 3.58 (dq, 2H, J=14.0, 2.1Hz), 4.97 (d, 1H, J=8.5), 5.57 (dd, 1H, J=6.5, 8.5Hz), 7.32 (m, 3H), 7.38 (m, 2H), 7.50

(ddd, 2H, J=10, 5.6, 1.4Hz), 7.57 (ddd, 2H, J=9, 1.25, 0.6), 7.62 (ddd, 2H, J=10, 5.6, 1.4Hz), 8.60ppm (ddd, 2H, J=8.9, 1.25, 0.6Hz); ^{13}C nmr: δ 12.52, 42.41, 61.11, 69.17, 112.05, 122.02, 125.13, 125.17, 125.76, 125.78, 126.73, 126.81, 126.85, 127.17, 128.34, 128.36, 128.62, 129.70, 129.71, 131.18, 131.22, 131.27, 135.98, 160.12, 162.45, 180.01ppm; ms: m/z 473 (55, M+2$^+$), 472(86), 471 (100, M$^+$), 380 (5.3, M$^+$-PhCH$_2$), 306 (26, M$^+$-PhCH$_2$-COOC$_2$H$_5$), 278 (25.5), 176 (10), 91 (17.6). *Anal.* Calcd. for $C_{28}H_{22}NO_4Cl$: C, 71.26; H, 4.70; N, 2.97. Found: C, 71.33; H, 4.52; N, 2.99.

Ethyl 3-(9'-anthracenyl-10'-chloro-)-5-{1(S)-benzyl-2(*R*)-phenyl-[(phenylsulfonyl)amino]ethyl}-4-isoxazole carboxylate (3a). This compound was crystallized as pale yellow needles from hexanes-ethyl acetate (6:1), mp 168.5-169.5 ºC; ^{1}H nmr: δ 0.16 (t, 3H, J=7.1Hz), 2.94 (dd, 1H, J=13.5, 4.8Hz), 3.34 (dd, 1H, J=13.5, 10.8Hz), 3.48 (m, 2H), 4.60 (m, 1H), 5.05 (t, 1H, J=9.1Hz), 5.91 (d, 1H, J=9.1Hz), 7.13 (m, 5H), 7.21 (m, 5H), 7.29 (m, 3H), 7.39 (m, 1H), 7.41 (t, 1H, J=7.3Hz), 7.48 (dd, 2H, J=2.0, 2.6Hz), 7.60 (m, 2H), 7.66 (m, 2H), 8.56 (d, 1H, J=8.8Hz), 8.57 (d, 1H, J=8.8Hz); ^{13}C nmr: δ 12.54, 36.54, 46.69, 60.28, 60.69, 114.47, 122.31, 124.79, 124.87, 125.76, 125.96, 126.32, 126.43, 126.53, 126.61, 126.74, 126.76, 126.86, 128.03, 128.17, 128.20, 128.40, 128.65, 128.69, 128.77, 130.90, 131.01, 131.06, 132.21, 137.81, 138.64, 140.77, 159.62, 161.40, 177.28; ms: m/z 702 (24, M+2$^+$), 701 (28), 700 (41, M$^+$), 455 (10), 246 (100), 131 (53). *Anal.* Calcd. for $C_{41}H_{33}N_2O_5SCl$: C, 70.23; H, 4.74; N, 3.99. Found: C, 69.94; H, 4.85; N, 4.05.

Ethyl 3-(9'-anthracenyl-10'-chloro-)-5-{1(S)-benzyl-2-(S)-phenyl-2-[(Phenylsulfonyl)amino]ethyl}-4-isoxazole carboxylate (3b). This compound was crystallized as pale yellow needles from hexanes-ethyl acetate (6:1), mp 207 ºC (decomposed); ^{1}H nmr: δ 0.20 (t, 3H, J=7.1Hz), 3.33 (t, 1H, J=12Hz), 3.41 (q, 2H, J=7.1Hz), 3.79 (dd, 1H, J=12, 4.8Hz), 4.64 (dt, 1H, J=10.5, 4.8Hz), 5.01 (t, 1H, J=9.7Hz), 5.92 (d, 1H, J=9.3Hz), 6.59 (d, 1H, J=9.0Hz), 6.93 (d, 1H, J=9.0Hz), 7.08 (m, 4H), 7.22 (m, 5H), 7.33 (t, 3H, J=8.0Hz), 7.51 (m, 5H), 7.75 (dd, 2H, J=8.5, 1.2Hz), 8.47ppm (dd, 2H, J=8.8, 0.6Hz); ^{13}C nmr: δ12.74, 37.33, 46.93, 60.03, 113.44, 122.09, 124.87, 124.88, 125.63, 125.74, 126.19, 126.31, 126.46, 126.53, 126.65, 127.20, 127.84, 128.13, 128.13, 128.16, 128.38, 128.43, 128.90, 129.00, 130.81, 130.84, 130.88, 132.60, 138.12, 138.45, 159.48, 160.21, 176.80ppm; ms: m/z 702 (35.3, M+2$^+$), 701 (34.8), 700 (66, M$^+$), 545 (1.6), 455 (27), 351 (7.1), 246 (77), 154 (2.0), 77 (100). *Anal.* Calcd. for $C_{41}H_{33}N_2O_5SCl$: C, 70.23; H, 4.74; N, 3.99. Found: C, 70.05; H, 4.81; N, 4.06.

3-(9'-Anthracenyl-10'-chloro-)-[5-(1''-hydroxy)-phenylisoxazol-4-yl]pentan-1-one (4). This compound was crystallized as pale yellow flakes from hexane-ethyl acetate (6:1), mp 105-106 ºC; ^{1}H nmr: δ 0.28 (t, 3H, J=7.5Hz), 0.53 (m, 2H), 0.99 (m, 2H), 1.53 (t, 2H, J=7.5Hz), 3.40 (t, 2H, J=6.9Hz), 5.21 (d, 1H, J=9.0Hz), 5.46 (dt, 1H, J=9.0, 6.9Hz), 7.35 (m, 5H), 7.56 (m, 4H), 7.68 (m, 2H), 8.65ppm (dd, 2H, J=8.7, 3.0Hz); ^{13}C nmr: δ 12.87, 21.48, 25.20, 40.41, 41.54, 69.31, 119.93, 121.20, 125.20, 125.24, 125.41, 125.45, 127.05, 127.10, 127.16, 127.53, 127.63, 128.45, 128.47, 128.52, 129.56, 131.25, 131.32, 132.25, 136.14, 159.05, 180.15, 197.82; ms: m/z 485 (41, M+2$^+$), 484 (37), 483 (100, M$^+$), 392 (68, M$^+$-PhCH$_2$), 374 (11, M$^+$-PhCH$_2$-H$_2$O), 228 (11), 176 (17). *Anal.* Calcd. for $C_{30}H_{26}NO_3Cl$: C, 74.45; H, 5.41; N, 2.89. Found: C, 74.37; H, 5.41; N, 3.05.

***N*-{2-[3-(9'-Anthracenyl-10'-chloro-)-4-pentanoylisoxazol-5-yl]-1,3-diphenylpropyl}benzenesulfonamide (5)**. This compound was crystallized as yellow cubes from hexanes-ethyl acetate (6:1), mp 173ºC (decomp.); ^{1}H nmr: δ 0.24 (t, 3H, J=7.1Hz), 0.37 (m, 2H), 0.76 (m, 2H), 1.28 (dt, 2H, J=7.1, 2.1Hz), 2.79 (dd, 1H, J=13.2, 4.5Hz), 3.27 (t, 1H, J=13.2Hz), 4.39 (m, 1H), 5.03 (t, 1H, J=9.0Hz), 6.28 (d, 1H, J=9.0Hz), 7.08 (dd, 2H, J=7.5, 1.5Hz), 7.27 (m, 11H), 7.39 (tt, 1H, 10.2, 1.5Hz), 7.45 (ddd, 1H, J=8.7, 6.6, 1.2Hz), 7.63 (m, 6H), 8.59 ppm (dd, 2H, J=8.9, 0.9Hz); ^{13}C nmr: δ 12.93, 21.43, 25.49, 36.35, 40.70, 46.85, 61.12, 121.18, 122.57, 125.06, 125.23, 125.41, 125,58, 126.51, 126.76, 126.87, 127.08, 127.26, 127.87, 128.11, 128.34, 128.36, 128.56, 128.69, 128.74, 131.12, 131.25, 131.92, 132.03, 138.10, 138.80, 141.01, 158.19, 176.68, 197.52 ppm; ms: m/z 714 (50, M+2$^+$), 713 (49.7), 712 (100, M$^+$), 467 (46), 246 (62), 141 (28). *Anal.* Calcd. for $C_{43}H_{37}N_2O_4SCl$: C, 72.41; H, 5.23; N, 3.93. Found: C, 72.34; H, 5.50; N, 3.95.

Procedure for X-ray analysis. Crystals of compound **3a** or **5a** were removed from the flask and covered with a layer of hydrocarbon oil. A suitable crystal was selected, attached to a glass fiber and placed in the low-temperature nitrogen stream [19]. Data were collected at 83(2) K using a Bruker/Siemens SMART APEX instrument (Mo Kα radiation, λ = 0.71073 Å) equipped with a Cryocool NeverIce low temperature device. Data were measured using omega scans of 0.3° per frame for 5 seconds for **3a** and 10 seconds for **5a**, and a full sphere of data was collected. A total of 2132 frames were collected with a final resolution of 0.77 Å for both **3a** and **5a**. The first 50 frames were recollected at the end of data collection to monitor for decay. Cell parameters were retrieved using SMART [20] software and refined using SAINTPlus [21] on all observed reflections. Data reduction and correction for Lp and decay were performed using the SAINTPlus software. Absorption corrections were applied using SADABS [22]. The structure was solved by direct methods and refined by least squares method on F^2 using the SHELXTL program package [23]. The structure was solved in the space group P-1 [P2(1)/c] by analysis of systematic absences. All atoms were refined anisotropically. Both **3a** and **5a** crystallize in non-chiral space groups, which means they are racemic. **3a** is presented as C21, S and C29, R, and **5a** as C23, S and C31, R. No decomposition was observed during data collection.

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