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SYNTHESIS OF UNSYMMETRICALLY SUBSTITUTED ISOXAZOLES AS INTERMEDIATES FOR BENT-CORE MESOGENS

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ABSTRACT. 3,5-Disubstituted isoxazoles have been designed and synthesized to be used as central units for bent-core mesogens. The substituents at position 3 of the isoxazole ring are either hydroxymethyl or carboxyl, while alkenyl-terminated substituents have been inserted at position 5. A multi-step reaction sequence comprising the *O*-alkylation of 4-hydroxyacetophenone with the suitable alkenyl halide, the Claisen-type condensation with diethyl oxalate and the cyclization to isoxazole led to the isoxazole esters as key intermediates, which were subsequently reduced and hydrolyzed to the corresponding isoxazol-3-ylmethanols and isoxazole-3-carboxilic acids, respectively.

Keywords: *liquid crystals, bent-core, ring closure, isoxazole*

INTRODUCTION

The design of liquid crystals (LCs) having molecular architectures that differ from those of classical calamitic- or discotic-shaped molecules is of great interest. As representatives of unusually shaped molecules with LC properties, bent-core mesogens are a rather recent addition to the LC family [1], and a class of atypical LCs whose unconventional behavior never ceases to amaze [2]. The great majority of bent-core mesogens have a 1,3-phenylene moiety as central unit, but LCs derived from other carbocyclic cores such as 3,4′-disubstituted biphenyls [3,4], 2,7-disubstituted naphthalenes [5,6] or 1,7-disubstituted naphthalenes [7,8] are also well represented. In addition, recent reports that describe the LC properties of bent-core mesogens based on various heterocyclic systems are also available. Whereas examples of bent-core mesogens derived from six-membered heterocycles such as 2,6-disubstituted

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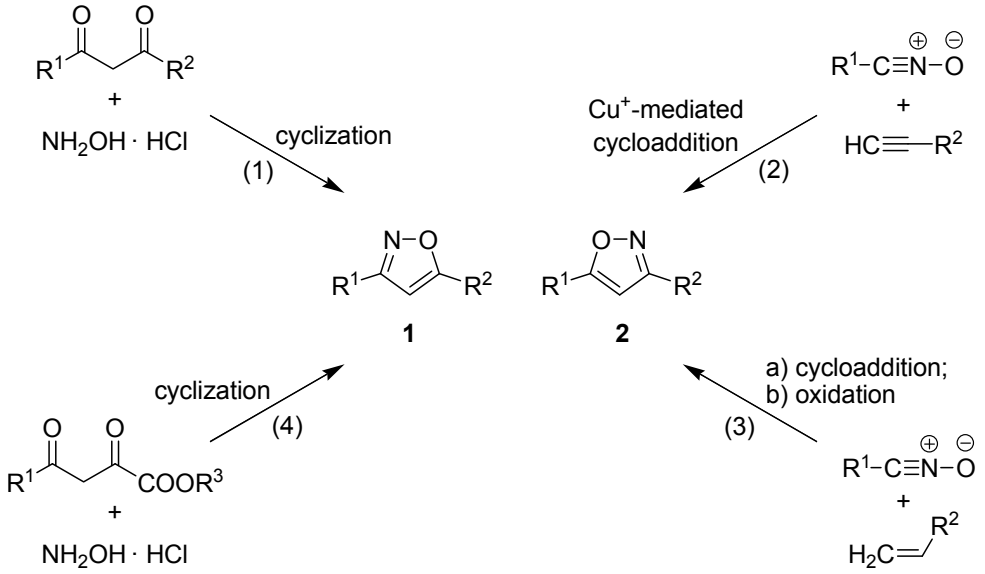
pyridines [9], 2,6-disubstituted pyrimidines [10] or 1,3,5-triazines [11] are so far scarce, bent-core mesogens incorporating various five-membered heterocycles as central structural units (*e.g.*, 1,2,4-oxadiazole [12,13],1,3,4-oxadiazole [14,15],1,3,4-thiadiazole [16,17], 1,2,3-triazole [18,19] or thiophene [20,21])

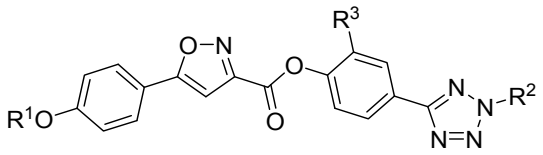


Scheme 1

are abundant. In addition, 3,5-diarylisoxazoles are nowadays well-established mesogens, but structure–property relationships for isoxazole-based LCs still remain fairly uncharted. The difficulty in obtaining only one of the two possible unsymmetrically substituted regioisomers **1** and **2** has initially been a setback in the investigation of the aforementioned relationship. In the early 1990s, the favored approach towards the synthesis of isoxazole-based mesogens was the cyclization of 1,3-diarylpropane-1,3-diones with hydroxylamine (path (1) in Scheme 1), which is an excellent synthetic methodology leading to pure isoxazoles only in the case of identical aryl substituents R^1 and R^2 [22,23], but has been shown to yield mixtures of regioisomeric isoxazoles **1** and **2** when these aryl substituents are different [24,25]. Fortunately, the advent of Cu(I)-catalyzed [3+2]-cycloaddition of nitrile oxides to acetylenes (path (2) in Scheme 1) [26] provided a novel synthetic tool for the regioselective preparation of mesogens having unsymmetrically substituted 3,5-diarylisoxazoles of type **1** as central structural unit [27,28]. A two-step sequential synthetic strategy combining the

cycloaddition of nitrile oxides to alkenes with the oxidation of the resulting isoxazoline (path (3) in Scheme 1) also appears to have been successfully employed for the regioselective preparation of LCs containing unsymmetrically 3,5-disubstituted isoxazoles **1** in their structure [29,30]. Finally, a series of isoxazole-based mesogens of type **2** (R^2 = $COOR^3$) have been generated regioselectively through the ring closure of 4-aryl-2,4-dioxobutanoates using hydroxylamine, followed by the transformation of the ester function at position 3 of the isoxazole ring (path (4) in Scheme 1) [31,32]. Based on the latter synthetic approach, the present paper reports the design, synthesis and structural characterization of novel isoxazoles useful as intermediates in the preparation of LCs.

An initial literature survey has showed that the field of LCs having isoxazole-3-carboxylic acids as central unit is currently underexplored in terms of relationships between the structure and LC properties of these mesogens. Apparently, only a small number of derivatives of type **3** [31,32] and of type **4** [31] (with R^1 and R^2 as long alkyl chains) has been synthesized so far (Fig. 1).



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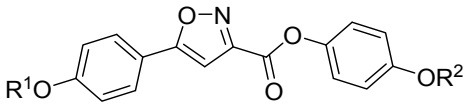

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Figure 1. Examples of bent-core LCs having isoxazole-3-carboxilic acids as central unit.

Prompted by this observation, we have based our design for novel LCs on isoxazole-3-carboxylic acids whose carboxylic group could be converted into an ester function featuring various mesogen moieties such as alkoxyarylethynylaryl [33], alkoxyaryloxycarbonylaryl [4] or alkoxyarylazoaryl [34]. In addition, isoxazol-3-ylmethanols can be easily prepared through the reduction of the corresponding esters. Recently, simple 5-(alkoxyphenyl)isoxazol-3-ylmethanols have been shown to possess mesomorphic properties [35], while their partially hydrogenated counterparts, namely 5-alkoxyphenyl-4,5-dihydroisoxazol-3-ylmethanols, have been successfully employed as platforms for liquid-crystalline

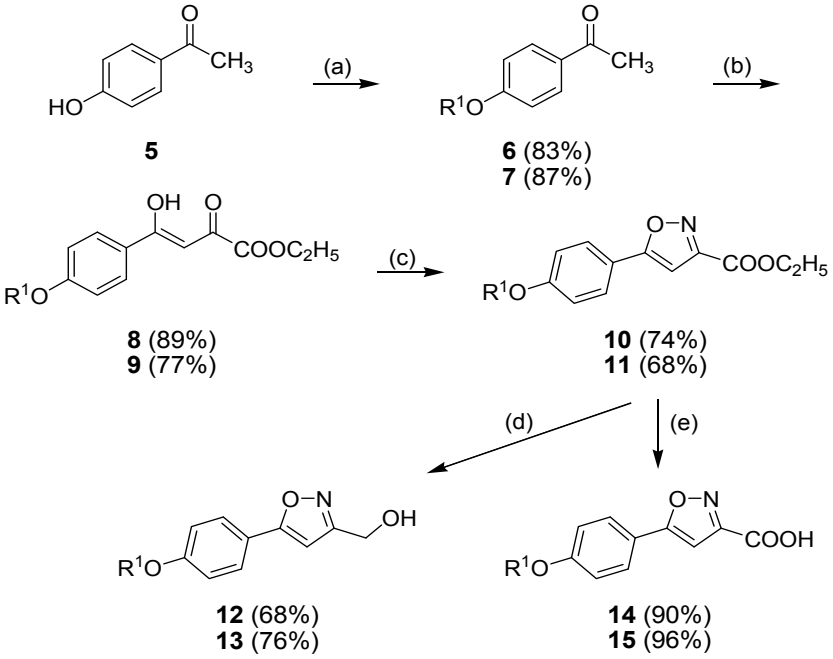
materials [36]. In light of these facts, isoxazol-3-ylmethanols have also been considered as central units in the design of novel bent-core LCs. Finally, the introduction of oligosiloxane or carbosilane units has been shown to have a significant impact on the properties of the mesophases of bent-core molecules [37,38]. To the best of our knowledge, no LCs containing both the isoxazole bent-core central unit and terminal silicon-containing mesogenic moieties have been reported yet. With a view to gain insight on the properties of LCs combining these two features in their structure, the aforementioned isoxazole-3-carboxylic acids and isoxazol-3-ylmethanols have been designed to incorporate terminal alkenyl groups as well. These alkenyl groups have been deemed suitable for the subsequent introduction of silicon-containing units via hydrosilylation.

RESULTS AND DISCUSSION

The multi-step synthesis of the designed isoxazole-derived intermediates for bent-core LCs features in its first stage the introduction of the alkenyl groups through the *O*-alkylation of 4-hydroxyacetophenone **5** either with allyl bromide or with 4-vinylbenzyl chloride in ethanol in the presence of KOH as base (Scheme 2). 4-Allyloxyacetophenone **6** has been previously obtained from the same reagents, but in the presence of K_2CO_3 as base and under various different reaction conditions [39–43]. 4-(4-Vinylbenzyloxy)acetophenone **7** has been previously reported [44], but its complete characterization is presented herein for the first time.

Claisen-type condensation of the resulting acetophenones **6** and **7** with diethyl oxalate in the presence of sodium ethoxide in absolute ethanol afforded 2,4-dioxobutanoates **8** and **9** (Scheme 2). The proton spectra of compounds **8** and **9**, taken in $CDCl_3$, revealed that they exist in solution as one diastereomeric enol form (presumably *Z*). Thus, the presence of a broad singlet in the off-set of the ^{1}H NMR spectra of these compounds has been attributed to the proton of the enolic hydroxyl, while the sharp singlet at approximately 7 ppm is indicative for a proton at an olefinic carbon atom. In addition, no signal associated with the protons in the methylene group between the two carbonyl functions in the diketone tautomer has been noticed in the proton spectrum of compounds **8** and **9**. The preferred existence of compounds **8** and **9** as enol tautomers has been explained through the possibility for the depicted *Z*-diastereomers to form H-chelates through intramolecular hydrogen bonding [45]. In contrast, NMR analysis of structurally similar 1,3-diarylpropane-1,3-diones proved that these compounds exist as mixtures of corresponding tautomeric diketone and enol-ketone in $CDCl_3$ [46].

Ring closure to isoxazoles **10** and **11** was achieved through a [3+2]-cyclization of 2,4-dioxobutanoates **8** and **9**, respectively, with hydroxylamine hydrochloride (Scheme 2). Despite the presence of two potential oximation sites in their structure, aroylpyruvic esters similar to **8** or **9** have been long known to preferentially lead to esters of 5-aryl-isoxazole-3-carboxylic acids [47], presumably owing to their aforementioned preferred enolic form that is stabilized through an intramolecular hydrogen bonding. Treatment of esters **8** and **9** with hydroxylamine hydrochloride in refluxing ethanol at low pH for a short time, followed by neutralization with a mild base such as alkaline carbonates or bicarbonates, afforded the desired isoxazoles **10** and **11** in good yields [48]. Recrystallization from ethanol gave the pure samples of these key intermediates, which were fully characterized and subsequently used in the preparation of the target compounds, the isoxazolylmethanols **12** and **13** and the isoxazole acids **14** and **15** (Scheme 2).



6, 8, 10, 12, 14: R^1 = allyl;
7, 9, 11, 13, 15: R^1 = 4-vinylbenzyl

(a): allyl bromide, EtONa, EtOH, reflux, 2 h (for **6**), or 4-vinylbenzyl chloride, KOH, EtOH, reflux, 2 h (for **7**);
(b) diethyl oxalate, EtONa, EtOH, reflux, 2 h;
(c) hydroxylamine hydrochloride, EtOH, reflux, 2 h;
(d) $NaBH_4$, EtOH, rt, overnight;
(e) $LiOH \cdot H_2O$, THF:MeOH:water, rt, overnight.

Scheme 2

Transformation of esters of isoxazole-3-carboxylic acids into corresponding methanols has been reported to proceed through the general, well-established approach that uses $LiAlH_4$ in THF [49] or diethyl ether [50], and although most of these processes have been conducted at low temperature, examples of similar reactions at room temperature are also available [35]. However, even a weaker reducing agent such as $NaBH_4$ was found to be effective in this particular transformation [48], and $NaBH_4$ appears to be the favorite reducing agent for isoxazole esters [51–53], presumably because of its well-known advantages over $LiAlH_4$ (increased stability, easy handling, use of non-anhydrous solvents). Esters **10** and **11** have been completely reduced to methanols **12** and **13**, respectively, by treatment with an excess of $NaBH_4$ in ethanol at room temperature for 24 h. Because of its better solubility in ethanol, the volume of solvent employed in the reduction of ester **10** under these conditions was smaller than that required in the case of ester **11**. An attempt at reducing ester **11** in the same volume of ethanol used for ester **10** led to an incomplete reaction. Nonetheless, either the extension of the reduction time for ester **11** up to 48 h when a smaller volume of ethanol was used, or the use of larger volumes of ethanol when the reaction time was 24 h drives the reaction to completion. As the reduction started, ester **10** was gradually consumed, and the initial suspension soon turned into a clear solution before the salt of the alcohol began to separate. In the case of ester **11**, no clear solution was obtained during the reduction, even when a large volume of ethanol was used. Crude methanols **12** and **13** were isolated in quantitative yield and practically pure by diluting the reaction mixture with water and slowly lowering the pH with dilute HCl under efficient stirring. Alcohol **12** was very soluble in common organic solvents, and the analytical sample was obtained by recrystallization from a mixture of 2-propanol and hexanes, albeit with a significant loss; on the other hand, alcohol **13** could be recrystallized from 2-propanol alone prior to analysis. The structure of methanol **12** was confirmed by its NMR spectra, which were recorded in $CDCl_3$. The proton spectrum presented a sharp singlet integrating for two protons at 4.78 ppm (protons in the methylene group adjacent to hydroxyl) and a somewhat broad singlet integrating for one proton at 2.72 ppm (proton in the hydroxyl), whereas the ^{13}C NMR spectrum had a peak at 57 ppm assigned to the carbon atom of the carbinol moiety. No peak for the hydroxyl proton of alcohol **13** could be evidenced in its proton spectrum recorded in DMSO-d_6, but the protons and the carbon atom in the methylene group of the carbinol function were assigned the signals at 5.17 ppm and 55 ppm, respectively.

Hydrolysis of esters of isoxazole-3-carboxylic acids has been often performed in lower alcohols in the presence of hydroxides of alkaline metals [54–56]. Because of the limited solubility of ester **11** in lower alcohols at room

temperature, we adopted a different procedure, one that employs as solvent a mixture in which tetrahydrofuran is the major component along with methanol and water as minor components, and a twofold excess of LiOH as base [57]. Under these conditions, ester **10** dissolved readily, while ester **11** formed a suspension from which the solid disappeared soon after LiOH had been added. Although the hydrolysis has been reported to proceed swiftly, the reaction mixture was allowed to react overnight. Isoxazole acids **14** and **15** were isolated in excellent yields after treatment of their lithium salts with dilute HCl, and the NMR analysis of the crude compounds showed that they were essentially pure. No trace of the signals associated with the hydrogen atoms in the ethyl moiety of parent esters could be noticed in the ^{1}H NMR spectra of acids **14** and **15** recorded in DMSO-d_6, while a very broad signal in the off-set of these spectra could be assigned to the hydrogen atom in the carboxyl function. The identity of the known isoxazole acid **14** has been also confirmed by comparing its NMR spectra with the data reported in the literature [42].

CONCLUSIONS

Two novel isoxazol-3-ylmethanols and two isoxazole-3-carboxylic acids (one of them being hitherto unknown) have been designed with the view to afford bent-core LCs after derivatization with suitable mesogen moieties. These four isoxazole-based central units feature at one end an alkenyl moiety that is amenable to subsequent hydrosilylation, and either a carboxyl function or a primary alcohol moiety at the other end, which could be each converted into an ester using a plethora of well-established mesogens. The successful multi-step synthesis of these intermediates was accomplished through a sequence involving *O*-alkylation of 4-hydroxyacetophenone, Claisen-type condensation with diethyl oxalate, ring closure to isoxazole and chemical modification of the ester function. The target compounds were obtained with the purity required for intermediates in the synthesis of LCs without any need for chromatographic separations, and with satisfactory total yields of 35% (for isoxazol-3-ylmethanols) and approximately 45% (for isoxazole-3-carboxylic acids) after four synthetic steps.

EXPERIMENTAL SECTION

Melting points were taken on a Mel-Temp II apparatus and are uncorrected. Elemental analysis was conducted in-house, on a Perkin-Elmer 2400 Series II CHNS/O system. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400-MHz spectrometer. The signals owing to residual protons in the deuterated solvents were used as internal standards for the ^{1}H NMR

spectra. The chemical shifts for the carbon atoms are given relative to deuteriochloroform (δ = 77.16 ppm) or dimethyl sulfoxide-d_6 (δ = 39.52 ppm) [58]. The chemical reagents were obtained from Sigma–Aldrich, whereas the solvents were purchased from Chemical Company (Iaşi, Romania), and they were used without purification.

1-[4-(Allyloxy)phenyl]ethanone (6). Sodium (230 mg, 10 mmol) was added to abs. ethanol (15 mL), and the mixture was stirred with cooling in a water bath until sodium was consumed entirely. 4-Hydroxyacetophenone **5** (1.36 g, 10 mmol) was then added, followed by allyl bromide (1.82 g, 15 mmol), and the mixture was heated at reflux temperature for 2 h. The solvent was removed under reduced pressure to give a semisolid, which was partitioned between water (80 mL) containing 5% KOH (2 mL) and chloroform (20 mL). The aqueous phase was further extracted with chloroform (10 mL), then the combined organic phase was washed with water (15 mL) and dried over anhyd. Na_2SO_4. Removal of the solvent under reduced pressure afforded a light yellow oil (1.47 g, 83%), which was sufficiently pure to be used in the next stage. ^{1}H- and ^{13}C NMR spectra of a sample were identical to those reported in literature [42].

1-[4-(4-Vinylbenzyloxy)phenyl]ethanone (7). To a solution of KOH (660 mg, 10 mmol, 85% purity) in 96% ethanol (10 mL), 4-hydroxyacetophenone **5** (1.36 g, 10 mmol) was added, and then the mixture was stirred at room temperature for 5 min. 4-Vinylbenzyl chloride (1.7 g, 10 mmol, 90% purity) was then added, and the reaction mixture was heated at reflux temperature for 2 h. Aqueous 5% KOH (2 mL) was gradually added to the hot mixture, followed by water (50 mL), and the mixture was further stirred at room temperature for 30 min. The resulting solid was filtered, air-dried, and recrystallized from ethanol to give colorless crystals (2.19 g, 87%), mp 108–109 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.55 (s, 3H), 5.12 (s, 2H), 5.28 (d, *J* = 10.8 Hz, 1H), 5.77 (d, *J* = 17.6 Hz, 1H), 6.72 (dd, *J* = 10.8 and 17.6 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.93 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.5, 70.0, 114.5, 114.7, 126.6, 127.8, 130.7, 130.8, 135.8, 136.4, 137.7, 162.7, 196.9. *Anal.* Calcd. for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.75; H, 6.52.

Ethyl 4-[4-(allyloxy)phenyl]-4-hydroxy-2-oxobut-3-enoate (8). A solution of sodium ethoxide obtained from sodium (368 mg, 16 mmol) and abs. ethanol (10 mL) was added dropwise to an efficiently stirred solution of 1-[4-(allyloxy)phenyl]ethanone **6** (1408 mg, 8 mmol) and diethyl oxalate (2336 mg, 16 mmol) in abs. ethanol (10 mL) at room temperature. The mixture was heated at reflux temperature for 2 h, cooled to room temperature, and

gradually added to a vigorously stirred mixture of finely chopped ice (50 g) and water (150 g). The pH of the mixture was brought to 1 with 5% HCl, then the solid was filtered and washed thoroughly with water to give off-white crystals (1965 mg, 89%), mp 42–43 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.40 (t, *J* = 7.2 Hz, 3H), 4.39 (q, *J* = 7.2 Hz, 2H), 4.62 (d, *J* = 5.2 Hz, 2H), 5.33 (d, *J* = 10.8 Hz, 1H), 5.43 (dd, *J* = 1.2 and 17.2 Hz, 1H), 5.98–6.11 (m, 1H), 6.97 (s, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 7.97 (d, *J* = 8.8 Hz, 2H), 15.46 (br s, 1H); ^{13}C NMR ($CDCl_3$,100 MHz): δ 14.2, 62.7, 69.1, 97.9, 115.0, 118.5, 127.9, 130.4, 132.4, 162.6, 163.5, 168.3, 190.4. *Anal.* Calcd. for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 64.98; H, 5.72.

Ethyl 4-[4-(4-vinylbenzyloxy)phenyl]-4-hydroxy-2-oxobut-3-enoate (9). The mixture of 1-[4-(4-vinylbenzyloxy)phenyl]ethanone **7** (2016 mg, 8 mmol) and diethyl oxalate (2336 mg, 16 mmol) in abs. ethanol (10 mL) was treated at room temperature with an ethanolic solution of sodium ethoxide that has been previously obtained from sodium (368 mg, 16 mmol) and abs. ethanol (10 mL). The mixture was heated at reflux temperature for 2 h, cooled to room temperature, and gradually added to a vigorously stirred mixture of finely chopped ice (50 g) and water (150 g). Treatment with 5% HCl gave a solid that was filtered, washed thoroughly with water and recrystallized from ethanol to give yellow crystals (2.17 g, 77%) mp 79–80 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.41 (t, *J* = 7.2 Hz, 3H), 4.39 (q, *J* = 7.2 Hz, 2H), 5.14 (s, 2H), 5.28 (d, *J* = 10.8 Hz, 1H), 5.77 (d, *J* = 17.6 Hz, 1H), 6.73 (dd, *J* = 10.8 and 17.6 Hz, 1H), 7.03 (s, 1H), 7.05 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.98 (d, *J* = 8.8 Hz, 2H), 15.46 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.2, 62.6, 70.2, 97.9, 114.6, 115.2, 126.7, 127.9, 128.0, 130.5, 135.5, 136.4, 137.8, 162.6, 163.5, 168.3, 190.4. *Anal.* Calcd. for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72. Found: C, 71.76; H, 5.59.

Ethyl 5-[4-(allyloxy)phenyl]isoxazole-3-carboxylate (10). Ethyl 4-[4-(allyloxy)phenyl]-4-hydroxy-2-oxobut-3-enoate **8** (1656 mg, 6 mmol) and hydroxylamine hydrochloride (500 mg, 7.2 mmol) were heated at reflux temperature in 96% ethanol (10 mL) for 2 h. The mixture, which solidified when it was cooled to room temperature, was diluted with water (80 mL), treated with a solution of Na_2CO_3 (1.59 g, 15 mmol) in water (15 mL), and further stirred at room temperature for 30 min. The solid was filtered, washed with water, air-dried, and slurried into chloroform (15 mL). Gravitational filtration and subsequent removal of chloroform under reduced pressure yielded a light tan solid, which was recrystallized from ethanol to give off-white leaflets (1210 mg, 74%), mp 80–81 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.43 (t, *J* = 7.2 Hz, 3H), 4.46 (q, *J* = 7.2 Hz, 2H), 4.59 (d, *J* = 5.2 Hz, 2H), 5.32 (dd, *J* = 1.2 and

10.4 Hz, 1H), 5.43 (dd, *J* = 1.6 and 17.2 Hz, 1H), 5.98–6.12 (m, 1H), 6.79 (s, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 7.73 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$,100 MHz): δ 14.3, 62.3, 69.0, 98.7, 115.4, 118.3, 119.9, 127.7, 132.7, 157.0, 160.3, 160.7, 171.8. *Anal.* Calcd. for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.69; H, 5.33; N, 5.02.

Ethyl 5-[4-(4-vinylbenzyloxy)phenyl]isoxazole-3-carboxylate (11). Ethyl 4-[4-(4-vinylbenzyloxy)phenyl]-4-hydroxy-2-oxobut-3-enoate **9** (1.76 g 5 mmol) and hydroxylamine hydrochloride (417 mg, 6 mmol) were heated at reflux temperature in 96% ethanol (15 mL) for 2 h. The solvent was removed under reduced pressure, water (70 mL) was added, and the suspension was treated with a solution of Na_2CO_3 (1.27 g, 12 mmol) in water (15 mL). After having been stirred at room temperature for 30 min, the solid was filtered, washed with water and air-dried. The solid was mixed with chloroform (25 mL) and filtered, then the solvent was removed under reduced pressure, and the residue was recrystallized from ethanol to afford colorless leaflets (1190 mg, 68%), mp 119–120 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.44 (t, *J* = 7.2 Hz, 3H), 4.46 (q, *J* = 7.2 Hz, 2H), 5.11 (s, 2H), 5.27 (d, *J* = 10.8 Hz, 1H), 5.77 (d, *J* = 17.6 Hz, 1H), 6.73 (dd, *J* = 10.8 and 17.6 Hz, 1H), 6.80 (s, 1H), 7.05 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.3, 62.3, 70.0, 98.8, 114.5, 115.6, 119.8, 126.6, 127.7, 127.8, 135.9, 136.4, 137.7, 157.0, 160.3, 160.8, 171.8. *Anal.* Calcd. for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.37; H, 5.55; N, 3.89.

{5-[4-(Allyloxy)phenyl]isoxazol-3-yl}methanol (12). Sodium borohydride (152 mg, 4 mmol) was gradually added to a suspension of ethyl 5-[4-(allyloxy)phenyl]isoxazole-3-carboxylate **10** (546 mg, 2 mmol) in 96% ethanol (10 mL), and the mixture was stirred at room temperature overnight (20 h). The resulting thick suspension was diluted with water (50 mL) and treated dropwise with 5% HCl until the pH of the mixture reached 1. The residue was filtered, air-dried and recrystallized from a mixture of 2-propanol and *n*-hexane to give colorless crystals (314 mg, 68%), mp 72–73 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.72 (s, 1H), 4.57 (d, *J* = 5.2 Hz, 2H), 4.78 (s, 2H), 5.32 (dd, *J* = 1.2 and 10.8 Hz, 1H), 5.43 (dd, *J* = 1.2 and 17.2 Hz, 1H), 5.99–6.12 (m, 1H), 6.44 (s, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 7.66 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$,100 MHz): δ 57.1, 69.0, 97.1, 115.2, 118.2, 120.3, 127.5, 132.8, 160.3, 164.3, 170.4. *Anal.* Calcd. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.19; H, 5.79; N, 5.88.

{5-[4-(4-Vinylbenzyloxy)phenyl]isoxazol-3-yl}methanol (13). A suspension of ethyl 5-[4-(4-vinylbenzyloxy)phenyl]isoxazole-3-carboxylate **11** (523 mg, 1.5 mmol) in 96% ethanol (25 mL) was gradually treated with $NaBH_4$ (114 mg, 3 mmol), then the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, water (50 mL) was added to the residue, and then the pH of the suspension was slowly brought to 1 with 5% HCl. After having been stirred for 30 min, the solid was filtered, air-dried, and recrystallized from 2-propanol to give colorless crystals (350 mg, 76%), mp 145–146 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 4.53 (d, J = 6.0 Hz, 2H), 5.17 (s, 2H), 5.27 (d, J = 11.2 Hz, 1H), 5.52 (t, J = 6.0 Hz, 1H), 5.85 (d, J = 17.6 Hz, 1H), 6.74 (dd, J = 11.2 and 17.6 Hz, 1H), 6.85 (s, 1H), 7.14 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.80 (d, J = 8.8 Hz, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 55.1, 69.1, 98.2, 114.6, 115.5, 119.9, 126.2, 127.2, 128.0, 136.2, 136.3, 136.8, 159.8, 165.2, 168.7. *Anal.* Calcd. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 73.96; H, 5.77; N, 4.30.

5-[4-(Allyloxy)phenyl]isoxazole-3-carboxylic acid (14). Lithium hydroxide monohydrate (168 mg, 4 mmol) was added to a solution of ethyl 5-[4-(allyloxy)phenyl]isoxazole-3-carboxylate **10** (546 mg, 2 mmol) in a mixture of THF : methanol : water (10 mL, 3 : 1 : 1, v/v/v), and the mixture was stirred at room temperature overnight. The organic solvents were removed under reduced pressure, water (50 mL) was added, and the mixture was gradually treated with 5% HCl until pH reached 1. The solid was filtered, washed thoroughly with water and air-dried to give a colorless powder (440 mg, 90%), mp 176–177 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 4.65 (d, J = 5.2 Hz, 2H), 5.28 (dd, J = 1.2 and 10.4 Hz, 1H), 5.41 (dd, J = 1.2 and 17.2 Hz, 1H), 5.98–6.12 (m, 1H), 7.10 (d, J = 8.8 Hz, 2H), 7.87 (d, J = 8.8 Hz, 2H), 14.02 (br s, 1H, exchangeable with deuterium); ^{13}C NMR (DMSO-d_6,100 MHz): δ 68.4, 99.4, 115.4, 117.8, 127.6, 133.3, 157.8, 160.1, 161.0, 170.8. *Anal.* Calcd. for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.33; H, 4.58; N, 5.44.

5-[4-(4-Vinylbenzyloxy)phenyl]isoxazole-3-carboxylic acid (15). Ethyl 5-[4-(4-vinylbenzyloxy)phenyl]isoxazole-3-carboxylate **11** (349 mg, 1 mmol) was suspended in a mixture of THF : methanol : water (10 mL, 3 : 1 : 1, v/v/v), then $LiOH \cdot H_2O$ (84 mg, 2 mmol) was added, and the resulting solution was stirred at room temperature overnight. The organic solvents were removed under reduced pressure to give a colorless residue, which was suspended in water (50 mL) and gradually brought to pH 1 with 5% HCl. After 30 min, the solid was filtered, washed thoroughly with water and air-dried to yield colorless microcrystals (310 mg, 96%), mp 193–195 °C (dec.); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 5.18 (s, 2H), 5.27 (d, J = 10.8 Hz, 1H), 5.84 (d, J =

17.6 Hz, 1H), 6.74 (dd, *J* = 11.2 and 17.6 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 2H), 7.25 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.88 (d, *J* = 8.8 Hz, 2H), 14.02 (br s, 1H, exchangeable with deuterium); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 69.2, 99.4, 114.6, 115.6, 119.1, 126.3, 127.6, 128.1, 136.2, 136.3, 136.8, 157.8, 160.2, 161.0, 170.8. *Anal.* Calcd. for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found: C, 70.68; H, 4.89; N, 4.03.

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