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SYNTHESIS OF SOME ISOXAZOLIDINE AND ISOXAZOLINE DERIVATIVES USING NITRONE-DERIVED (–)-MENTHONE VIA 1,3-DIPOLAR CYCLOADDITION WITH ALKENES, ALKYNES AND CYCLOALKENES

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Abstract – Cycloaddition reactions between a menthone-based chiral nitrone and alkenes or alkynes under microwave activation afforded a series of enantiopure cycloadducts in good yields and with high stereoselectivity. Removal of the chiral auxiliary under acid-catalysis led to a new series of isoxazolidines and isoxazolines with the control of one, two or three stereogenic centers.

INTRODUCTION

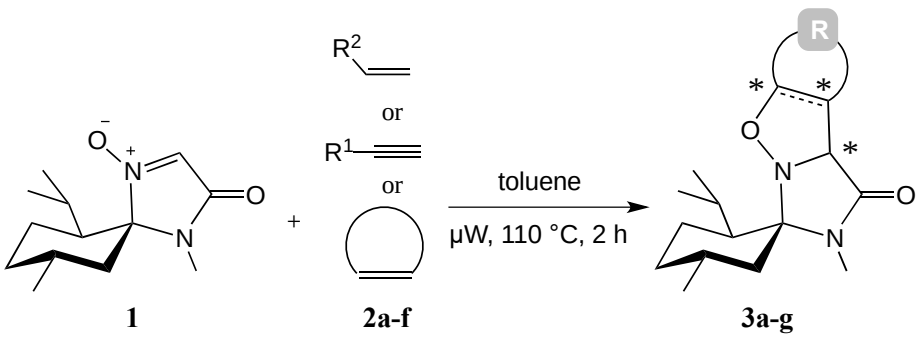
1,3-Dipolar cycloaddition of nitrones with olefinic or acetylenic dipolarophiles are very interesting reactions in organic synthesis[1] due to their efficient induction of stereocenters and the rapid conversion of the resulting isoxazolidines/isoxazolines into synthetically useful natural product precursors.[1f] Up to three contiguous asymmetric carbon centers can be formed through 1,3-dipolar cycloaddition and the challenge of controlling the absolute and relative stereochemistry has attracted much attention in recent years.[2-6] The stereoselective 1,3-dipolar cycloaddition of nitrones to alkenes was applied to produce substituted isoxazolidines[3] as precursors for heterocyclic products. These compounds can be converted into β-amino alcohols,[4] β-lactams,[5] α-amino acids[6] and pyrrolidinones[7] by reductive cleavage of the N-O bond. Consequently, isoxazolidines are used as key intermediates for the synthesis of various natural products[8] or antifungal,[9] anti-inflammatory,[10] anti-mycobacterial,[11] anti-tubercular[12] and antiviral agents.[13] On the

other hand, isoxazolines are cycloadducts obtained from nitrone and alkynes providing additional access to heterocycles of potential biological interest.[14]

In connection with our studies on synthetic molecules with potential applications in the context of type 2 diabetes mellitus,[15] we have developed approaches toward enantiopure natural and unnatural amino acids,[6f-i] such as enantiopure (2*S*,3*R*,4*R*)-[6d] or (2*S*,3*S*,4*R*)-4-hydroxyisoleucine,[6g] (4*S*)-4-hydroxy-L-ornithine,[6f] and cycloalkylglycines.[16] As the simultaneous creation of various chiral centers impacts favorably on atom economy, these cycloaddition approaches are advantageous as compared, such as, with a multi-step route from D-glucose to analogues of (2*S*,3*R*,4*S*)-4-hydroxyisoleucine, a naturally-occurring insulinotropic α-amino acid.[6j] More recently, we have designed a new synthetic route to aziridines via 1,3-dipolar cycloaddition of a menthone-based nitrone[17] to alkynes under microwave irradiation.[18] We report herein the synthesis of isoxazolines and isoxazolidines by 1,3-dipolar cycloaddition of a menthone-based chiral nitrone to substituted or cyclic alkenes and alkynes.

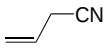
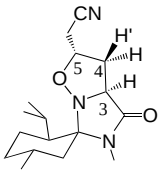
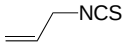
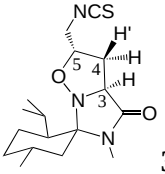
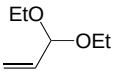
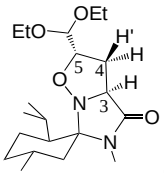
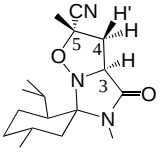
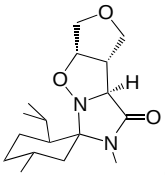
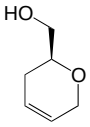
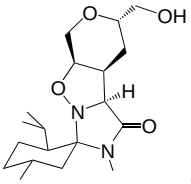
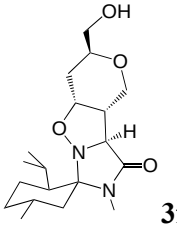
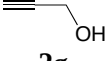
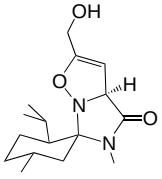
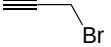
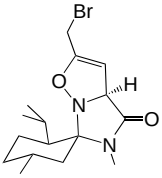
RESULTS AND DISCUSSION

The nitrone **1**[17a] was employed in 1,3-dipolar cycloaddition in the presence of a wide range of alkenes **2a-f** (Scheme 1, Table 1), using toluene as the solvent under microwave irradiation at 110 °C. The reaction was highly regio- and diastereo-selective through the *exo*-approach of the dipolarophile onto the nitrone's less hindered face. Pure and stable cycloadducts were obtained except in the case of methacrylonitrile **2d** (Table 1, Entry 4). The major cycloadduct **3d** was isolated in 70% yield with a chiral tetrasubstituted carbon atom while a minor isomer was detected by TLC (traces). In the case of the cycloaddition of nitrone **1** with cycloalkene **2f**, an almost equimolar mixture of two regioisomers **3f** and **3f'** was obtained with up to three asymmetric centers and with a total yield of 78% (Table 1, Entry 6). The same conditions were used for the condensation with alkynes **2g,h** resulting in the formation of isoxazolines **3g,h** in moderate yields (Table 1, Entries 7 and 8).



Scheme 1

Table 1. 1,3-Dipolar cycloadditions of nitrone **1** with alkenes and alkynes

Entry	Dipolarophile	Cycloadduct	Isolated yield[b] (%)
1	 **2a**	 **3a**	87
2	 **2b**	 **3b**	84
3	 **2c**	 **3c**	84
4	 **2d**	 **3d**	70[a]
5	 **2e**	 **3e**	92
6	 **2f**	 **3f**	42
		 **3f'**	36
7	 **2g**	 **3g**	34
8	 **2h**	 **3h**	42

[a] Traces of second isomer identified from TLC. [b] Yields of the isolated product after silica gel column chromatography.

The stereoselectivity of the cycloaddition results from the fact that terminal alkenes approach to the less hindered face of nitrone **1** on the opposite side of the bulky isopropyl group.[6c,16] This led the alkene substituent to get away from the spirocyclic nitrone according to the *exo*-approach[6g] which was deduced from 1D and 2D NMR experiments.[6c,h] The stereochemistry of isoxazolidines **3a-d** was deduced from NMR experiments and the observed values of the vicinal coupling: $J_{3\text{-}4'}$ ca. 0–2.1 Hz (*anti* relationship), $J_{3\text{-}4}$ ca. 8.7–9.1 Hz (*syn* relationship), $J_{4\text{-}5}$ ca. 0–3Hz (*anti* relationship), $J_{4'\text{-}5}$ ca. 5.8–12.1Hz (*syn* relationship). 2D NOESY experiments provided further data to support the proposed structures (Table 1, Entries 1-4). The structure of cycloadduct **3e** was unambiguously established by X-ray diffraction analysis (Figure 1)[19] and by NMR spectroscopy.

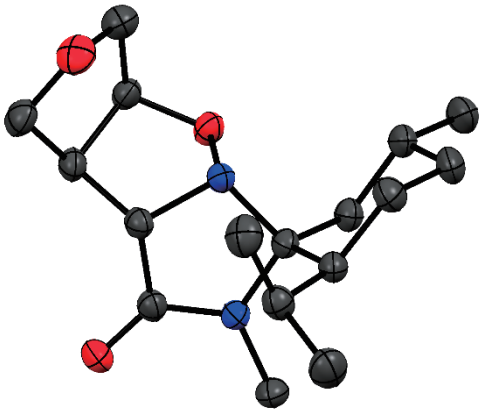


Figure 1

In the case of the regioisomers **3f** and **3f'**, the assignment of their respective structures was based on the chemical shifts of carbons C-4 (δ = 42.4–43.5 ppm) and C-5 (δ = 73.1–76.3 ppm). These results indicated that the carbon C-5 was resonating at lower field hence adjacent to the oxygen atom. Thus, the HMBC experiments were able to define the regiochemistry of compounds **3f** and **3f'** (Figure 2). For example, the observed HMBC correlations between H-3 (δ_H 3.99) and C-8 (δ_C 22.5, at the α position of C-7), on the one hand, and H-4 (δ_H 2.91) and C-7 (δ_C 68.5) on the other hand were of particular significance to determine the position of the isoxazolidine substituents for compound **3f** (see Figure 2 for numbering).

The stereochemistry of compounds **3f** and **3f'** was deduced from extensive NMR investigations. Most relevant data are the coupling constants between H-3 and H-4 ($J_{3,4}$) and between H-4 and H-5 ($J_{4,5}$). For regioisomer **3f**, the coupling constant is $J_{3,4}$ ca. 4.6 Hz (*syn* relationship), $J_{4,5}$ ca. 6.8 Hz (*syn* relationship), whereas for compound **3f'**, the coupling constant is $J_{3,4}$ ca. 0.0 Hz (*anti* relationship), $J_{4,5}$ ca. 6.7 Hz (*syn* relationship). 2D NOESY experiments provided further data to support the proposed structures (Figure 2). Thus, for compound **3f**, five NOESY correlations were observed as expected (H3-H4, H3-H5, H3-isopropyl group, H3-H15'and H4-H5). For compound **3f'**, three NOESY correlations were detected

between H4-H5, H3-H15'and H3-isopropyl group and no correlation between H3-H4 and H3-H5 (Figure 2).

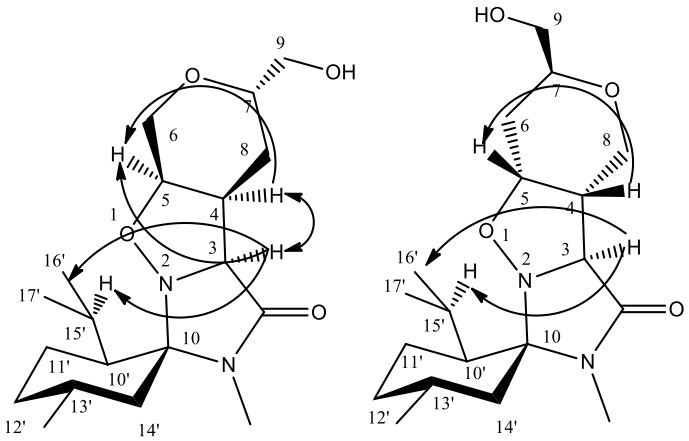
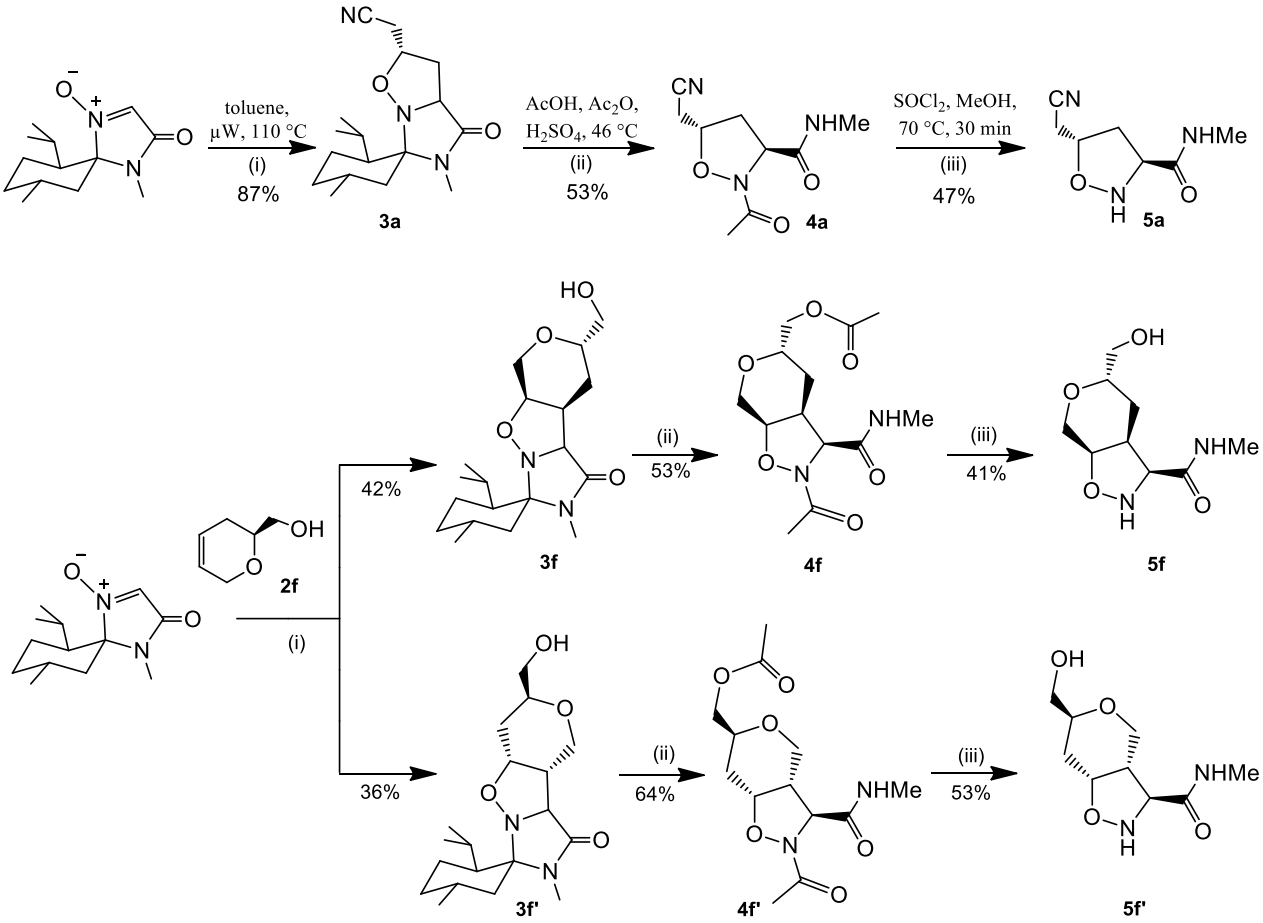


Figure 2. Characteristic NOESY correlations of compounds **3f** (left) and **3f'** (right)

The cycloadducts **3a-d, 3f** and **3f'** were subjected to acidic cleavage with a mixture of acetic acid, acetic anhydride in the presence of a catalytic amount of concentrated sulfuric acid (Scheme 2).[6f] As the result



Scheme 2

of several one-pot reactions (cleavage of the chiral auxiliary and *N*-acetylation), the corresponding isoxazolidines **4a**, **4f,** and **4f'** were isolated in good to moderate yields. These compounds could be characterized by NMR spectroscopy techniques, which indicated their purity, and no epimerization could be detected. In the case of compounds **3b-d**, their action led to a complex mixture of inseparable products. The *N*-deacetylation of **4a** was performed with $SOCl_2$[3,5] in anhydrous methanol to afford compound **5a** in 47% yield (Scheme 2). The same conditions as above were applied to the isoxazolidines **4f** and **4f'** to provide, after the *N*-deacetylation and *O*-deacetylation, **5f** and **5f'** in 41% and 57%, respectively.

In conclusion, the cycloaddition of a spirocyclic nitrone with various alkenes and alkynes afforded the desired isoxazolidines in good yields and with simultaneous creation of two and three adjacent stereogenic centers, respectively. The cycloadducts obtained could be readily characterized by standard multi-dimensional NMR spectroscopies and mass spectrometry. After two steps (cleavage of the chiral auxiliary and hydrolysis with thionyl chloride), the cycloadducts led to novel enantiopure isoxazolidines as precursors of enantiopure unnatural α-amino acids.

EXPERIMENTAL

General procedure for the synthesis of isoxazolidines. In a Biotage Initiator 10 mL vial, nitrone (1 eq.) in anhydrous toluene (4 mL) were introduced. The vial was flushed with argon and dipolarophile (3 eq.) was added. The vial was sealed with a septum cap and was irradiated by microwaves (temperature: 110 °C). TLC monitoring (EtOAc/PE 5/5) showed full conversion after 2 h. After the crude mixture was concentrated and purified by flash column chromatography (silica gel, EtOAc/PE 2/3) to provide the desired isoxazolidine.

(1*S*,2*S*,2'*S*,3a'*S*,5*R*)-2-Isopropyl-5,5'-dimethyl-4'-oxotetrahydro-2'*H*-spiro[cyclohexane-1,6'-imidazo-[1,5-*b*]isoxazol]-2'-yl)acetonitrile (3a): obtained as a yellow solid (450 mg, 87%) following general procedure: toluene (4 mL), alkene **2a** (450 mg), and nitrone **1** (1.68 mmol, 400 mg): mp 63-64 °C (Et_2O); R_f = 0.25 (EtOAc/hexane, 6/4); $[\alpha]_D^{20}$ -91.9 (c 0.81, CH_2Cl_2) {Lit.[20] $[\alpha]_D^{20}$ -89.2 (c 1, CH_2Cl_2)}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81 (d, 3H, J = 6.3 Hz, CH_3), 0.85 (d, 3H, J = 6.8 Hz, CH_3), 0.92 (m, 1H), 0.92 (d, 3H, J = 6.3 Hz, CH_3), 1.26 (t, 1H, J_{gem} = 12.3 Hz), 1.39 (dd, 1H, J = 3.5 Hz, 12.7 Hz), 1.43 (m, 1H), 1.61 (m, 1H), 1.65-1.75 (m, 1H), 1.82 (m, 1H), 1.93-2.01 (m, 1H), 2.03-2.06 (m, 1H), 2.26-2.33 (ddd, 1H, J = 9.5, 6.0 and 6.0 Hz), 2.56-2.69 (dd, 2H, J = 16.8 Hz, 5.3 Hz), 2.73 (s, 3H, NCH_3), 2.77-2.82 (ddd, 1H, J = 8.5, 6.3 and 2.1 Hz), 3.96 (d, 1H, J = 9.1Hz), 4.21 (quin, 1H, J = 12.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.6 (CH_3), 22.3 (CH_3), 22.4, 22.5, 24.3 (CH_3), 24.5, 26.1 (*N*-CH_3), 29.4, 34.7, 37.4, 40.9, 48.2, 65.1, 71.7, 89.0, 116.8 (CN), 172.4 (C=O); HRMS (ESI): *m/z* calcd for $C_{17}H_{28}N_3O_2$ $[M+H]^+$ 306.2176, found 306.2170.

(1*S*,2*S*,2'*S*,3a'*S*,5*R*)-2-Isopropyl-2'-(isothiocyanatomethyl)-5,5'-dimethyldihydro-2'*H*-spiro[cyclohexane-1,6'-imidazo[1,5-*b*]isoxazol]-4'(5'*H*)-one (3b): obtained as a yellow solid (120 mg, 84%) following general procedure: toluene (4 mL), alkene **2b** (1.68 mmol, 166 mg), and nitrone **1** (0.42 mmol, 100 mg): mp 102-103 °C (Et_2O); R_f = 0.39 (EtOAc/hexane, 6/4); $[\alpha]_D^{20}$ -73.5 (c 0.72, CH_2Cl_2): ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.81 (d, 3H, J = 6.9 Hz, CH_3), 0.86 (d, 3H, J = 6.9 Hz, CH_3), 0.93 (m, 1H), 0.95 (d, 3H, J = 6.3 Hz, CH_3), 1.27 (t, 1H, J_{gem} = 12.6 Hz), 1.37-1.44 (m, 2H), 1.64-1.82 (m, 2H), 1.83-1.87 (m, 1H), 2.01-2.12 (m, 2H), 2.17-2.25 (ddd, 1H, J = 9.6 Hz, 6.3 Hz and 3.0 Hz), 2.72-2.79 (m, 1H), 2.74 (s, 3H, *N*-CH_3), 3.45 (dd, 1H, J = 14.4 Hz, 4.2 Hz), 3.68 (dd, 1H, J = 14.7 Hz, 7.8 Hz), 3.95 (d, 1H, J = 8.7 Hz), 4.17 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.6 (CH_3), 21.3 (CH_3), 21.4 (CH_3), 23.1, 23.3, 25.0 (NCH_3), 28.2, 33.6, 34.1, 39.8, 46.2, 47.0, 64.0, 73.4, 87.9, 132.5 (CNS), 171.4 (C=O); HRMS (ESI): *m/z* calcd for $C_{17}H_{28}N_3O_2S$ $[M+H]^+$ 338.1897, found 338.1890.

(1*S*,2*S*,2'*S*,3a'*S*,5*R*)-2'-(Diethoxymethyl)-2-isopropyl-5,5'-dimethyldihydro-2'*H*-spiro[cyclohexane-1,6'-imidazo[1,5-*b*]isoxazol]-4'(5'*H*)-one (3c): obtained as a white solid (260 mg, 84%) following general procedure: toluene (4 mL), alkene **2c** (3.36 mmol, 436 mg), and nitrone **1** (0.84 mmol, 200 mg); mp 111-112 °C (Et_2O); R_f = 0.31 (EtOAc/hexane, 6/4); $[\alpha]_D^{20}$ -88.3 (c 0.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.72 (d, 3H, J = 6.8 Hz, CH_3), 0.74 (d, 3H, J = 6.8 Hz, CH_3), 0.81 (d, 3H, J = 6.4 Hz, CH_3), 0.88 (m, 1H), 1.07 (t, 6H, J = 7.2 Hz, $2CH_3$), 1.15 (t, 1H, J_{gem} = 12.6 Hz), 1.25 (dd, 1H, J = 12.1 Hz, 3.3 Hz), 1.31 (quin, 1H, J = 6.8 Hz), 1.47-1.52 (m, 1H), 1.55-1.65 (m, 1H), 1.68-1.73 (m, 1H), 1.90-1.98 (m, 2H), 2.21-2.28 (dt, 1H, J = 8.8 Hz, 3.9 Hz), 2.55-2.61 (ddd, 1H, J = 12.0 Hz, 7.7 Hz, 5.8 Hz), 2.63 (s, 3H, NCH_3), 3.37-3.62 (m, 4H, $2CH_2$), 3.75 (m, 1H), 3.83 (d, 1H, J = 8.9 Hz), 4.29 (d, 1H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.1 (CH_3), 15.3 (CH_3), 18.4, 22.1, 22.3, 24.1 (CH_3), 24.2, 25.9 (*N*-CH_3), 29.4, 34.6, 34.9, 40.6, 48.0, 62.7 (CH_2), 65.5, 77.2, 77.3, 87.3, 102.6, 172.8 (C=O); HRMS (ESI): *m/z* calcd for $C_{20}H_{37}N_2O_4$ $[M+H]^+$ 369.2748, found 369.2739.

(1*S*,2*S*,2'*S*,3*a'S*,5*R*)-2-Isopropyl-2',5,5'-trimethyl-4'-oxotetrahydro-2'*H*-spiro[cyclohexane-1,6'-imidazo[1,5-*b*]isoxazole]-2'-carbonitrile (3d): obtained as a amorphous solid (180 mg, 70%) following general procedure: toluene (4 mL), alkene **2d** (3.3 mmol, 225 mg), and nitrone **1** (0.84 mmol, 200 mg); R_f = 0.52 (EtOAc/hexane, 4/6); $[\alpha]_D^{20}$ +49.3 (c 0.85, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.81 (d, 3H, J = 6.6 Hz, CH_3), 0.86 (d, 3H, J = 6.9 Hz, CH_3), 0.93 (m, 1H), 0.96 (d, 3H, J = 6.6 Hz, CH_3), 1.33 (t, 1H, J_{gem} = 12.3Hz), 1.38-1.45 (m, 2H), 1.65 (m, 2H), 1.71 (s, 3H, CH_3), 1.82-1.98 (m, 2H), 2.25-2.31 (m, 1H), 2.54 (dd, 1H, J_{gem} = 12.1 Hz, 8.4 Hz), 2.73 (s, 3H, *N*-CH_3), 3.19 (d, 1H, J_{gem} = 13.2 Hz), 4.08 (d, 1H, J = 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.5, 22.3, 22.4, 22.8 (CH_3), 24.2, 24.3, 26.0 (*N*-CH_3), 29.1, 34.6, 40.8, 44.6, 48.4, 66.4, 72.8, 90.2, 119.3 (CN), 171.0 (C=O); HRMS (ESI): *m/z* calcd for $C_{17}H_{27}N_3NaO_2$ $[M+Na]^+$ 328.1995, found 328.1988.

(1*S*,2*S*,5*R*)-2'-(Hydroxymethyl)-2-isopropyl-5,5'-dimethyl-3a'*H*-spiro[cyclohexane-1,6'-imidazo[1,5-*b*]isoxazol]-4'(5'*H*)-one (3g): obtained as a yellow amourphous solid (90 mg, 48%) following general procedure: toluene (4 mL), alkyne **2g** (3.78 mmol, 211 mg), and nitrone **1** (0.63 mmol, 150 mg); R_f = 0.32 (EtOAc/hexane, 6/4); $[\alpha]_D^{20}$ +10.0 (c 0.2, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.79 (d, 3H, *J* = 6.6 Hz, CH_3), 0.85 (d, 3H, *J* = 8.6 Hz, CH_3), 0.89 (d, 3H, *J* = 6.5 Hz, CH_3), 1.21 (t, 2H, *J* = 12.6 Hz), 1.42 (m, 1H), 1.62 (m, 1H), 1.68 (m, 1H), 1.76 (m, 2H), 1.84 (m, 2H), 2.02 (m, 1H), 2.64 (s, 3H, *N*-CH_3), 2.9 (d, 1H, *J* = 4.0 Hz), 3.19 (d, 1H, *J* = 4.0 Hz), 4.38 (d, 1H, *J* = 20 Hz), 4.47 (d, 1H, *J* = 20 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.3, 21.8, 22.3, 24.2, 24.5, 25.5 (*N*-CH_3), 29.0, 34.8, 39.9, 42.0, 46.3, 49.4, 70.3, 85.3, 168.2 (C=O), 203.0; HRMS (ESI): *m/z* calcd for $C_{16}H_{27}N_2O_3$ $[M+H]^+$ 295.2016, found 295.2011.

(1*S*,2*S*,5*R*)-2'-(Bromomethyl)-2-isopropyl-5,5'-dimethyl-3a'*H*-spiro[cyclohexane-1,6'-imidazo[1,5-*b*]isoxazol]-4'(5'*H*)-one (3h): obtained as a amorphous solid (75 mg, 42%) following general procedure: toluene (4 mL), alkyne **2h** (3.78 mmol, 449 mg), and nitrone **1** (0.63 mmol, 150 mg); R_f = 0.71 (EtOAc/hexane, 6/4); $[\alpha]_D^{20}$ +26.8 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.78 (d, 3H, *J* = 6.7 Hz, CH_3), 0.85 (d, 3H, *J* = 8.2 Hz, CH_3), 0.89 (d, 3H, *J* = 6.9 Hz, CH_3), 1.17 (t, 2H, *J* = 12.6 Hz), 1.4 (m, 1H), 1.62 (m, 1H), 1.66 (m,1H), 1.75 (m, 2H), 1.82 (m, 2H), 2.02 (m, 1H), 2.63 (s, 3H, *N*-CH_3), 3.14 (d, 1H, *J* = 4.0 Hz), 3.18 (d, 1H, *J* = 4.0 Hz), 3.93 (d, 1H, *J* = 16 Hz), 4.08 (d, 1H, *J* = 12.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.3, 21.3, 22.2, 24.2, 24.4, 25.5 (*N*-CH_3), 28.0, 34.8, 35.7, 41.0, 41.2, 47.4, 49.5, 85.2, 167.9 (C=O), 196.5; HRMS (ESI): *m/z* calcd for $C_{16}H_{26}$ BrN_2O_2 $[M+H]^+$ 357.1172, found 357.1176.

(1*S*,2*S*,3a'*S*,5*R*,8b'*S*)-2-Isopropyl-5,7'-dimethyltetrahydro-1'*H*-spiro[cyclohexane-1,6'-furo[3,4-*d*]imidazo[1,5-*b*]isoxazol]-8'(7'*H*)-one (3e): obtained as a white solid (120 mg, 92%) following general procedure: toluene (4 mL), alkene **2e** (1.26 mmol, 88 mg), and nitrone **1** (0.42 mmol, 100 mg); mp 137-138 °C; R_f = 0.6 (EtOAc/PE 3/7); $[\alpha]_D^{20}$ +70.6 (c 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.76 (d, 3H, *J* = 6.7 Hz, CH_3), 0.79 (d, 3H, *J* = 6.8 Hz, CH_3), 0.82 (m, 1H), 0,84 (d, 3H, *J* = 6.5 Hz, CH_3), 1.13 (t, 1H, *J* = 12.2 Hz), 1.29 (dd, 1H, *J* = 3.0 Hz, 12.0 Hz), 1.37 (quin., 1H, *J* = 6.7 Hz), 1.49-1.55 (m, 1H), 1.66 (dd, 1H, *J* = 12.8, 3 Hz), 1.75 (m, 1H), 1.87-1.94 (m, 1H), 2.00-2.03 (m, 1H), 2.66 (s, 3H, CH_3), 3.42 (m, 1H), 3.58-3.62 (dd, 1H, *J* = 10.1 Hz, 5.2 Hz), 3.6 (s, 1H), 3.82 (m, 3H), 4.58-4.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.7, 22.2, 22.4, 24.1, 24.4, 25.8 (*N*-CH_3), 28.9, 34.7, 40.9, 48.1, 50.2, 71.5, 73.3, 73.4, 80.5, 88.4, 172.1 (C=O); HRMS (ESI): *m/z* calcd for $C_{17}H_{29}N_2O_3$ $[M+H]^+$ 309.2173, found 309.2177.

(1*S*,2*R*,5*S*,5a'*R*,7'*S*,9a'*S*)-7'-(Hydroxymethyl)-2-isopropyl-2',5-dimethylhexahydrospiro[cyclohexane-1,3'-imidazo[1,5-*b*]pyrano[3,4-*d*]isoxazol]-1'(2'*H*)-one (3f): obtained as a amorphous solid (185 mg, 42%) following general procedure: toluene (4 mL), alkene **2f** (3.78 mmol, 430 mg), and nitrone **1** (1.26 mmol, 300 mg); R_f = 0.53 (EtOAc, 100%); $[\alpha]_D^{20}$ +7.23 (c 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.79 (d, 3H, *J* 6.8 Hz, CH_3), 0.81 (d, 3H, *J* = 6.9 Hz, CH_3), 0.90 (d, 3H, *J* = 6.5 Hz, CH_3), 1.23

(d, 1H, *J* = 6.3 Hz), 1.29 (t, 1H, *J* = 12.4 Hz), 1.32 (m, 1H), 1.56 (m, 1H), 1.61 (m, 1H), 1.65 (dd, 2H, *J* = 16.4 Hz, 6.3 Hz), 1.71 (m, 1H), 1.78 (m, 2H), 1.94 (m, 1H), 2.02 (m, 1H), 2.71 (s, 3H, *N*-CH_3), 2.91 (ddd, 1H, *J* = 8.6 Hz, 6.8 Hz, 4.6 Hz), 3.45 (dd, 1H, *J* = 12.0 Hz, 6.8 Hz), 3.47 (s, 1H), 3.51 (d, 1H, *J* = 12.1 Hz), 3.61-3.66 (m, 2H), 3.96 (m, 1H), 3.99 (d, 1H, *J* = 6.8 Hz): ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.4, 22.2, 22.5, 24.1, 24.4, 26.2 (*N*-CH_3), 26.6, 29.6, 34.6, 40.5, 43.5, 48.1, 65.6, 66.1, 68.5, 72.3, 73.1, 90.5, 171.8 (C=O); (SM) $[M+H]^+$ *m/z* 353.0; (CI) [MEAN] 353.2435. HRMS (ESI): *m/z* calcd for $C_{19}H_{32}N_2NaO_4$ $[M+Na]^+$ 375.2254, found 375.2249.

(1*S*,2*R*,5*S*,5a'*R*,8'*S*,9a'*S*)-8'-(Hydroxymethyl)-2-isopropyl-2',5-dimethylhexahydrospiro[cyclohexane-1,3'-imidazo[1,5-*b*]pyrano[4,3-*d*]isoxazol]-1'(2'*H*)-one (3f'): obtained as a amorphous solid (160 mg, 36%) following general procedure: toluene (4 mL), alkene **2f** (3.78 mmol, 430 mg), and nitrone **1** (1.26 mmol, 300 mg); R_f = 0.46 (EtOAc, 100%); $[\alpha]_D^{20}$ +16.32 (c 0.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (d, 3H, *J* = 2.1 Hz, CH_3), 0.83 (d, 3H, *J* = 2.2 Hz, CH_3), 0.90 (d, 3H, *J* = 6.4 Hz, CH_3), 1.24 (m, 1H), 1.30 (t, 1H, *J* = 12.3 Hz), 1.34 (m, 1H), 1.56 (m, 1H), 1.63 (d, 1H, *J* = 12.3 Hz), 1.71 (m, 2H), 1.73 (s, 1H), 1.79 (m, 2H), 1.93 (m, 1H), 2.12 (m, 1H), 2.73 (s, 3H, *N*-CH_3), 2.98 (ddd, 1H, *J* = 6.7 Hz, 3.8 Hz, 3.7 Hz), 3.41 (m, 1H), 3.59 (dd, 2H, *J* = 6.3 Hz, 3.8 Hz), 3.65 (m, 3H), 4.19 (d, 1H, *J* = 13.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 22.2, 22.4, 24.2, 24.4, 26.2 (*N*-CH_3), 27.8, 29.4, 34.8, 40.8, 42.4, 48.1, 65.0, 65.8, 72.3, 73.0, 76.3, 90.6, 171.9 (C=O); HRMS (ESI): *m/z* calcd for $C_{19}H_{32}N_2NaO_4$ $[M+Na]^+$ 375.2254, found 375.2245.

General procedure for removed of chiral auxiliary. Cycloadduct **3a,f** or **3f'** (1 mmol) was dissolved in Ac_2O (3 mL) and AcOH (3 mL) and the mixture was stirred for 10 min at 46 °C. Concentrated H_2SO_4 (3 drops) was added and the mixture was stirred for 6 h at 46 °C. After cooling down to room temperature, the solution was quenched with aqueous 5% NaOH (3 mL). The mixture was then poured slowly into a saturated $NaHCO_3$ aq. solution (100 mL) which was extracted with CH_2Cl_2 (3×10 mL); the combined organic phases were dried ($MgSO_4$). After filtration, and evaporation of the solvents under reduced pressure, the residue was purified by flash chromatography (silica gel, EtOAc/PE 6/4) to afford the desired isoxazolidine.

2-((3*S*,5*S*)-2,3-Diacetylisoxazolidin-5-yl)acetonitrile (4a): obtained as a white solid (110 mg, 53%) following general procedure: Ac_2O (3 mL), AcOH (3 mL), and cycloadduct **3a** (0.98 mmol, 300 mg); mp 158-159 °C; R_f = 0.52 (EtOAc/MeOH, 8/2); $[\alpha]_D^{20}$ -57.5 (c 0.6, MeOH) (Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.21 (s, 3H, CH_3), 2.24-2.31 (ddd, 1H, *J* = 10.0 Hz, 6.5 Hz, 2.8 Hz), 2.63 (dd, 1H, J_{gem} = 17.2 Hz, 6.2 Hz), 2.73 (dd, 1H, J_{gem} = 17.2 Hz, 4.6 Hz), 2.80 (d, 3H, *J* = 4.9 Hz, *N*-CH_3), 3.15 (ddd, 1H, *J* = 10.0 Hz, 6.5 Hz, 2.8 Hz), 4.58-4.64 (m, 1H), 4.89 (dd, 1H, *J* = 5.4, 3.6 Hz), 6.91 (br s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.7, 21.9, 26.6 (*N*-CH_3), 34.6, 58.3, 75.8, 115.6 (CN), 168.5 (C=O), 171.1 (C=O); HRMS (ESI): *m/z* calcd for $C_9H_{13}N_3NaO_3$ $[M+Na]^+$ 234.0849, found 234.0848

(3*S*,3a*S*,5*S*,7a*R*)-2-Acetyl-3-methyl-3-(methylcarbamoyl)hexahydro-2*H*-pyrano[3,4-*d*]isoxazol-6-yl)-methyl acetate (4f): obtained as an amorphous solid (45 mg, 53%) following general procedure: Ac_2O (1.5 mL), AcOH (1.5 mL), and cycloadduct **3f** (0.28 mmol, 100 mg); R_f = 0.37 (EtOAc/MeOH, 9/1); $[\alpha]_D^{20}$ -62.9 (c 0.4, MeOH); ^{1}H NMR (400 MHz, MeOD): δ 1.75 (ddd, 1H, *J* = 11.7 Hz, 8.6 Hz, 3.3 Hz), 1.94 (m, 1H), 2.09 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.79 (d, 3H, *J* = 4.8 Hz, *N*-CH_3), 3.18 (m, 1H), 3.23 (m, 1H), 3.73 (m, 1H, *J* = 12.0 Hz), 4.02 (dd, 2H, *J* = 12.0 Hz, 3.8 Hz), 4.14 (dd, 1H, *J* = 8.6 Hz, 3.2 Hz), 4.32 (s, 1H), 4.57 (m, 1H), 6.97 (s, 1H, NH); ^{13}C NMR (100 MHz, MeOD): δ 20.7, 23.0, 26.5 (*N*-CH3), 26.9, 39.6, 62.2, 65.3, 66.3, 70.3, 75.9, 168.2 (C=O), 170.5 (C=O), 171.0 (C=O); HRMS (ESI): *m/z* calcd for $C_{13}H_{20}N_2NaO_6$ $[M+Na]^+$ 323.1214, found 323.1207.

((3*S*,3a*S*,6*S*,7a*R*)-2-Acetyl-3-(methylcarbamoyl)hexahydro-2*H*-pyrano[3,4-*d*]isoxazol-6-yl)methyl acetate (4f'): obtained as a amorphous solid (48 mg, 64%) following general procedure: Ac_2O (1.5 mL), AcOH (1.5 mL), and cycloadduct **3f'** (0.25 mmol, 90 mg); R_f = 0.31 (EtOAc/MeOH, 9:1); $[\alpha]_D^{20}$ +17.4 (c 0.8, MeOH); ^{1}H NMR (400 MHz, MeOD): δ 1.20 (dd, 1H, *J* = 24 Hz, 12.7 Hz), 1.73 (m, 1H), 2.05 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 2.77 (d, 3H, *J* = 4.8 Hz, *N*-CH_3), 3.20 (m, 1H), 3.53 (m, 1H), 3.69 (dd, 1H, *J* = 12.1 Hz, 1.8 Hz), 4.00-4.07 (m, 2H), 4.14 (m, 1H), 4.22 (d, 1H, *J* = 13.8 Hz), 4.54 (s, 1H), 6.95 (d, 1H, *J* = 2.0 Hz, NH); ^{13}C NMR (100 MHz, MeOD): δ 20.6 (CH_3), 22.9 (CH_3), 26.4 (NCH_3), 27.3, 38.8, 64.9, 66.2, 66.4, 73.3, 75.4, 168.5 (C=O), 170.8 (C=O), 171.4 (C=O); HRMS (ESI): *m/z* calcd for $C_{13}H_{20}N_2NaO_6$ $[M+Na]^+$ 323.1214, found 323.1220.

General procedure for *N*-deacetylation. Freshly distilled MeOH (3 mL) was placed in a dry and argon-flushed 10-mL round-bottom flask. The flask was cooled down to 0 °C and $SOCl_2$ (3 drops) was added dropwise. Stirring was maintained for 5 min and compound **4** (1 eq.) in MeOH (3 mL) was then added dropwise (10 min). After an additional 15 min at 0 °C, the mixture was allowed to warm to room temperature and then heated to reflux for 30 min. The crude mixture was cooled to room temperature and 5% Na_2CO_3 aq. solution (10 mL) was added. This aqueous layer was extracted with EtOAc (3×10 mL); the combined organic phases were dried (Na_2SO_4). After filtration, and evaporation of the solvents under reduced pressure, the residue was purified by silica gel flash chromatography (EtOAc/MeOH 9/1) to afford **5**.

2-((3*S*,5*S*)-3-Acetylisoxazolidin-5-yl)acetonitrile (5a): obtained as a yellow amorphous solid (80 mg, 47%) following general procedure for *N*-deacetylation. R_f = 0.18 (EtOAc/MeOH, 8/2); $[\alpha]_D^{20}$ -21.3 (c 0.58, MeOH); ^{1}H NMR (400 MHz, MeOD): δ 2.24 (m, 1H), 2.62 (m, 1H), 2.70-2.79 (m, 2H, H-6), 2.76 (s, 3H, *N*-CH_3), 3.99 (dd, 1H, *J* = 8.8, 3.3 Hz), 4.39 (quin, 1H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, MeOD): δ 22.7, 26.2 (*N*-CH_3), 39.8, 63.0, 77.0, 118.7 (CN), 172.9 (C=O); HRMS (ESI): *m/z* calcd for $C_7H_{12}N_3O_2$ $[M+H]^+$ 170.0924, found 170.0926.

(3*S*,3a*S*,6*S*,7a*R*)-6-(Hydroxymethyl)-*N*-methylhexahydro-2*H*-pyrano[3,4-*d*]isoxazole-3-carboxamide (5f): obtained as a liquid (12 mg, 41%) following general procedure for *N*-deacetylation; R_f = 0.14 (EtOAc/MeOH, 9:1); $[\alpha]_D^{20}$ -27.2 (c 0.5, MeOH); ^{1}H NMR (400 MHz, MeOD): δ 1.66-1.72 (m, 1H), 185-189 (m, 1H), 1.94 (s, 1H), 2.78 (s, 3H, *N*-CH_3), 2.80 (m, 1H), 3.31 (m, 1H), 3.38 (t, 1H, *J* = 11.4 Hz), 3.45-3.49 (m, 3H), 3.52-3.57 (m, 1H), 4.00-4.05 (m, 1H); ^{13}C NMR (100 MHz, MeOD): δ 26.4 (*N*-CH_3), 28.1 (this peak correspond to two carbon atoms), 49.2, 64.8, 66.0, 67.4, 74.3, 173.7 (C=O); HRMS (ESI): *m/z* calcd for $C_9H_{16}N_2NaO_4$ $[M+Na]^+$ 239.1002, found 239.1004.

(3*S*,3a*S*,5*S*,7a*R*)-5-(Hydroxymethyl)-*N*-methylhexahydro-2*H*-pyrano[4,3-*d*]isoxazole-3-carboxamide (5f'): obtained as a liquid (15 mg, 53%) following general procedure for *N*-deacetylation. Liquid; R_f = 0.18 (EtOAc/MeOH, 9:1); $[\alpha]_D^{20}$ -38.9 (c 0.7, MeOH); ^{1}H NMR (400 MHz, D_2O): δ 1.26 (m, 1H), 1.86-1.93 (m, 1H), 2.81 (s, 3H, *N*-CH_3), 2.85 (m, 1H), 2.98-3.02 (m, 2H), 3.52-3.57 (m, 2H), 3.60-3.71 (m, 1H), 3.80-3.86 (m, 2H), 4.17-4.20 (m, 1H); ^{13}C NMR (100 MHz, D_2O): δ 26.2 (*N*-CH_3), 63.5, 64.4, 64.6, 65.2, 67.4, 73.3, 76.5, 173.7 (C=O); HRMS (ESI): *m/z* calcd for $C_9H_{16}N_2NaO_4$ $[M+Na]^+$ 239.1002, found 239.1009.

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Supporting Information: Full experimental detail and characterization data. This material can be found via the ''Supplementary Content'' section of this article's webpage.

REFERENCES AND NOTES

1. (a) 1,3-Dipolar Cycloaddition Chemistry, Wiley: New York, 1984; (b) K. V. Gothelf and K. A. Jørgensen, *Chem. Rev.*, 1998, **98**, 863; (c) P. Grünanger and P. Vita-Finzi, 'Isoxazoles. Part One, In The Chemistry of Heterocyclic Compounds, ed. by E. C. Taylor and A. Weissberger, *Interscience*, 1991; (d) C. J. Easton, C. M. M. Hughes, G. P. Savage, and G. W. Simpson, *Adv. Heterocycl. Chem.*, 1994, **60**, 261; (e) W. Carruthers, 'Cycloaddition Reactions in Organic Synthesis', In Tetrahedron Organic Chemistry Series, Volume **8**, ed. by J. E. Baldwin and P. D. Magnus, Pergamon, Oxford, 1990; (f) J. N. Martin and R. C. F. Jones, In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*, Vol. **59**, ed. by A. Padwa and W. H. Pearson, Wiley: Chichester, 2002.
2. S. W. Baldwin and A. Long, *Org. Lett.*, 2004, **6**, 1653; T. B. Nguyen, A. Beauseigneur, A. Martel, R.

D. M. Laurent, and G. Dujardin, *J. Org. Chem.*, 2010, **75**, 611.

3. I. A. Grigorev, Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis, 2nd edn., ed. by H. Feuer, John Wiley and Sons: Hoboken, New Jersey, 2008, 129.
4. For a review, see: S. M. Lait, D. A. Rankic, and B. A. Keay, *Chem. Rev.*, 2007, **107**, 767.
5. R. Hanselmann, J. Zhou, P. Ma, and P. N. Confalone, *J. Org. Chem.*, 2003, **68**, 8739.
6. (a) O. Tamura, T. Shiro, M. Ogasawara, A. Toyao, and H. Ishibashi, *J. Org. Chem.*, 2005, **70**, 4569; (b) F. M. Cordero, S. Bonollo, F. Machetti, and A. Brandi, *Eur. J. Org. Chem.*, 2006, 3235; (c) K. Aouadi, S. Vidal, M. Msaddek, and J.-P. Praly, *Synlett*, 2006, 3299; (d) K. Aouadi, E. Jeanneau, M. Msaddek, and J.-P. Praly, *Synthesis*, 2007, 3399; (e) K. Aouadi, E. Jeanneau, M. Msaddek, and J.-P. Praly, *Tetrahedron: Asymmetry*, 2008, **19**, 1145; (f) K. Aouadi, M. Msaddek, and J.-P. Praly, *Tetrahedron*, 2012, **68**, 1762; (g) K. Aouadi, E. Jeanneau, M. Msaddek, and J.-P. Praly, *Tetrahedron Lett.*, 2012, **53**, 2817; (h) S. Cecioni, K. Aouadi, J. Guiard, S. Parrot, N. Strazielle, S. Blondel, J.-F. Ghersi-Egea, C. Chapelle, L. Denoroy, and J.-P. Praly, *Eur. J. Med. Chem.*, 2015, **98**, 237; (i) K. Aouadi, J. Abdoul-Zabar, M. Msaddek, and J.-P. Praly, *Eur. J. Org. Chem.*, 2014, 4107; (j) K. Aouadi, A.-D. Lajoix, R. Gross, and J.-P. Praly, *Eur. J. Org. Chem.*, 2009, 61.
7. E. C. Argyropoulou, E. M. Xenikaki, X. N. Stampelos, and I. N. Alexopoulou, *Tetrahedron*, 1997, **53**, 707.
8. A. Padwa and W. H. Pearson, 'Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products', Wiley: Chichester, 2002, **59**, pp. 1-81.
9. K. R. R. Kumar, H. Mallesha, and K. S. Rangappa, *Arch. Pharm. Pharm. Med. Chem.*, 2003, **336**, 159.
10. M. J. Green, R. L. Tiberi, R. Friary, B. N. Lutsky, J. Berkenkoph, X. Fernandez, and M. Monahan, *J. Med. Chem.*, 1982, **25**, 1492.
11. R. Raunak, V. Kumar, S. Mukherjee, A. K. Poonam, K. Prasad, C. E. Olsen, S. J. C. Schaffer, S. K. Sharma, A. C. Watterson, W. Errington, and V. S. Parmar, *Tetrahedron*, 2005, **61**, 5687.
12. R. S. Kumar, S. Perumal, K. A. Shetty, P. Yogeeswari, and D. Sriram, *Eur. J. Med. Chem.*, 2010, **45**, 124.
13. B. Loh, L. Vozzolo, B. J. Mok, C. C. Lee, R. J. Fitzmaurice, S. Caddick, and A. Fassati, *Chem. Biol. Drug Des.*, 2010, **75**, 461.
14. (a) J.-P. Freeman, *Chem. Rev.*, 1983, **63**, 241; (b) A. D. MacKenzie, R. A. Sherratt, M. Chigrinova, L. L. Cheung, and J. P. Pezacki, *Curr. Opin. Chem. Biol.*, 2014, **14**, 81.
15. J.-P. Praly and S. Vidal, *Mini-Rev. Med. Chem.*, 2010, **10**, 1102.
16. H. Abda, K. Aouadi, L. Perrin, M. Msaddek, J.-P. Praly, and S. Vidal, *Eur. J. Org. Chem.*, 2014, 6017.

17. (a) A. Vogt, H.-J. Altenbach, M. Kirschbaum, M. G. Hahn, M. S. P. Matthäus, and A. R. Hermann, EP 976721, 2000, *Chem. Abstr*., 2000, **132**, 108296j; (b) B. Westermann, A. Walter, U. Flörke, and H.-J. Altenbach, *Org. Lett*., 2001, **3**, 1375.
18. H. Abda, K. Aouadi, J. Brahmi, M. Msaddek, and S. Vidal, *C. R. Chimie*, 2016, **19**, 274.
19. CCDC 1489217 contains the supplementary crystallographic data of compound **3e**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.
20. J. Brahmi, S. Ghannay, S. Bakari, K. Aouadi, A. Kadri, M. Msaddek, and S. Vidal, *Synth. Commun.*, in press.