The Synthesis of Epiboxidine and Related Analogues as Potential Pharmacological Agents

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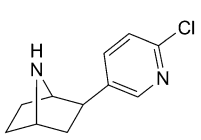
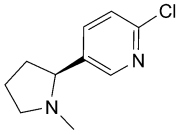
Methyl epiboxidine-*N*-carboxylate (**8**) was synthesized from **7** under reductive *Heck* conditions (*Scheme 2*). The C–C coupling of the new epiboxidine analog **9** with aryl and heteroaryl halides gave by hydroarylation *C*-aryl, *N*-(3-methylisoxazol-5-yl)-substituted tricyclic imides **10a**–**10f** (*Table*). The [3 + 2] cycloaddition of **9** with nitrile oxides yielded the bridged dihydroisoxazole derivatives **11a**–**11d** with potential biological activity (*Scheme 4*).

Introduction. – The discovery of the natural product epibatidine (=(1*R*,2*R*,4*S*)-2-(6-chloropyridin-3-yl)-7-azabicyclo[2.2.1]heptane; **1**) in 1992 [1] and recognition of its powerful analgesic properties has led to a remarkable level of synthetic interest. The fact that epibatidine acts as the nicotinic acetylcholine receptor **2** (nAChR) and is a much more effective ligand than nicotine (= 3-[(2*S*)-1-methylpyrrolidin-2-yl]pyridine) itself has prompted a substantial reappraisal of this receptor [2].

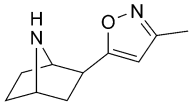
The toxicity of epibatidine itself has encouraged work on structurally related analogues in the search for lower toxicity and also higher discrimination between receptor sub-types. *Daly* and co-workers [3] reported that replacement of the chloropyridinyl moiety of **1** by a methylisoxazolyl moiety gave epiboxidine (= *rac*-2-(3-methylisoxazol-5-yl)-7-azabicyclo[2.2.1]heptane; **3**), which behaved as a potent $\alpha4\beta2$ nicotinic receptor agonist, 10-fold less potent than epibatidine (**1**) as antinociceptive agent but *ca.* 20-fold less toxic. The presence of the 3-methylisoxazol-5-yl moiety was similarly effective in the structure of (*S*)-ABT-418 (**4**) and represents a relatively accessible modification that could be also applied to **1**. The exciting biological properties and unique structure of **3**, combined with its scarcity in nature have aroused the interest of synthetic chemists around the world. So far, some syntheses of epiboxidine and related analogues have been published [4][5]. These syntheses are



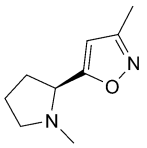
Epibatidine (**1**)



nAChR (**2**)



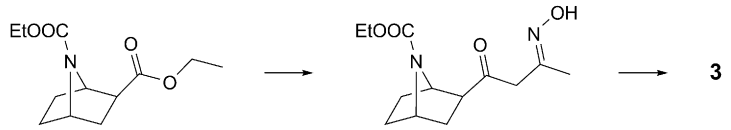
Epiboxidine (**3**)
(racemic)



(*S*)-ABT-418 (**4**)

based on an acetone oxime derivative allowing to construct later on the isoxazole ring at the bicylic system (*Scheme 1*).

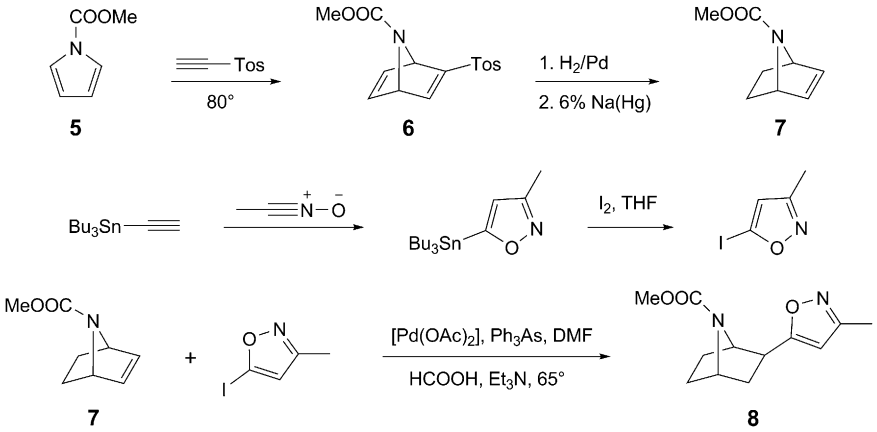
Scheme 1. *Synthesis of Racemic* **3**



Seeden and *Kaufmann* have reported the synthesis of some new epibatidine analogues by the reductive *Heck* reaction, but their compounds were not including the isoxazole ring [6][7]. We therefore became interested in the synthesis of **3** involving the reductive *Heck* reaction in a single synthetic operation with 5-iodo-3-methylisoxazole as reactant in the present work, *i.e.*, we prepared the analog **8**. We then focused on reductive *Heck* reactions of tricyclic molecule containing a strained C=C bond and an *N*-(3-methylisoxazol-5-yl)-substituted imide group (**9**) possessing potential biological activity as epiboxidine analogues. In our previous works, we had already accomplished Pd-catalyzed reductive *Heck* reactions with bicyclic and tricyclic precursors of epibatidine analogues [8–10]. In the present work, we also planned to synthesize dihydroisoxazole derivatives of **9** *via* 1,3-dipolar cycloadditions leading to possibly biologically active molecules including two isoxazole moieties.

Results and Discussion. – Our synthesis of epiboxidine analog **8** started with the reaction of methyl 1*H*-pyrrole-1-carboxylate (**5**) and *p*-toluenesulfonylacetylene (**6**) followed by two reduction steps by using *Kaufmann*'s procedure [7] to give methyl 7-azabicyclo[2.2.1]hept-2-ene-7-carboxylate (**7**; *Scheme 2*). The reagent for the subsequent reductive *Heck* reaction, 5-iodo-3-methylisoxazole, was obtained from 3-methyl-5-(tributylstannyl)isoxazole by using the procedure of *Yamanaka* and co-workers [11], followed by chromatographic purification (silica gel). Finally, treatment of **7** with 5-

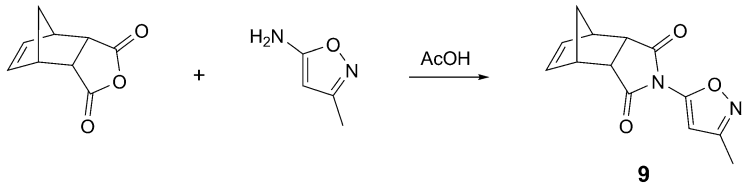
Scheme 2. *Synthesis of Compound* **8**



iodo-3-methylisoxazole under reductive *Heck* conditions and subsequent chromatography (silica gel) gave methyl 2-*exo*-(3-methylisoxazol-5-yl)-7-azabicyclo[2.2.1]heptane-7-carboxylate (= methyl *exo*-epiboxidine-*N*-carboxylate; **8**) in a yield of 61%.

We also synthesized **9** as a new epiboxidine analog from the cyclic anhydride of bicyclo[2.2.1]hept-5-ene-2-*endo*,3-*endo*-dicarboxylic acid (= 3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1,3-dione) and 3-methylisoxazol-5-amine in good yield (90%) after crystallization (*Scheme 3*).

Scheme 3. *Synthesis of Compound* **9**



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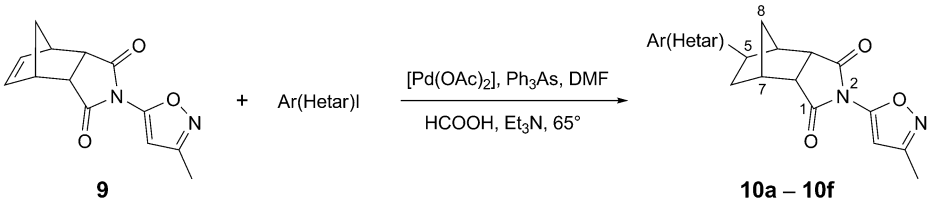
Treatment of **9** with 5-iodo-3-methylisoxazole, 1-iodobenzene, 4-chloro-1-iodobenzene, 2-chloro-5-iodopyridine, 2-iodothiophene, and 4-methoxy-1-iodobenzene under reductive *Heck* conditions and subsequent column chromatography (silica gel) gave **10a**–**10f** as single diastereoisomers in yields of 42–66% after purification (*Table*). The relative configuration for each *Heck* product was inferred from NMR spectra including diagnostic spin–spin interactions. The *exo*-position of the C(5) substituent was confirmed by the fact that H_{endo}–C(5) showed no significant interaction with H–C(7). The geminal H-atoms at C(8) were identified by their vicinal coupling to H–C(7). Additionally, the ^{1}H,^{1}H-COSY plots showed cross-peaks between H–C(3a) and H–C(7a) and between H–C(5) and H–C(6), respectively. In addition to the ^{13}C-NMR, HSQC, and FT-IR data and elemental analyses, which were in agreement with the proposed structures, the mass spectra of all new compounds **10a**–**10f** showed the expected molecular-ion peaks.

Table. *Exploration of Product Formation under Reductive* Heck *Conditions*

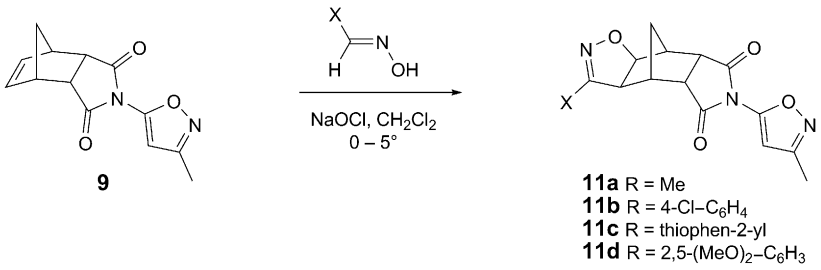


9 **10a – 10f**

Entry	Ar(Hetar)	Product	Yield [%]
1	3-Methylisoxazol-5-yl	**10a**	42
2	Ph	**10b**	66
3	4-Cl–C_6H_4	**10c**	58
4	6-Chloropyridin-3-yl	**10d**	45
5	Thiophen-2-yl	**10e**	52
6	4-MeO–C_6H_4	**10f**	60

Trinorbornene and its derivatives due to their rigid bicyclic skeleton give rise to stereoisomers with fixed spatial orientation of substitutents. The C=C bond in substituted trinorbornenes is quite reactive toward cycloadditions, in particular toward nitrile oxides in 1,3-dipolar additions. We carried out the [3 + 2] cycloaddition of **9** with *in situ* formed nitrile oxides to obtain the target compounds **11a** – **11d** (*Scheme 4*). The ^{1}H-NMR spectra of **11a** – **11d** were in accord with the proposed structures. To identify the configuration of the dihydroisoxazole moiety of the adducts, we studied selective ^{1}H,^{1}H-COSY plots obtained from these compounds.

Scheme 4. *Synthesis of Compounds* **11a** – **11d**



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11a R = Me
11b R = 4-Cl–C_6H_4
11c R = thiophen-2-yl
11d R = 2,5-$(MeO)_2$–C_6H_3

In conclusion, epiboxidine analog **8** was synthesized with 5-iodo-3-methylisoxazole under reductive *Heck* conditions in the presence of Ph_3As as a ligand in a simple way. The Pd-catalyzed hydroarylation of the easily accessible unsaturated tricyclic *N*-(3-methylisoxazol-5-yl)imide **9** was a stereoselective, versatile, and high-yield conversion for the synthesis of aryl and heteroaryl derivatives **10a** – **10f**. Our results also demonstrate that the cycloaddition of **9** to give aryl-substituted bridged dihydroisoxazole derivatives **11b** – **11d** will be useful for the construction of novel heterocycles of potential pharmacological interest.

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Experimental Part

1. *General.* All reactions were conducted under N_2 and carried out in a *Schlenk* system. Column chromatography (CC): silica gel *60*. TLC: silica gel pre-coated (0.2 mm layer) aluminium sheets (*Merck*). M.p.: *Gallenkamp* melting-point apparatus; uncorrected. IR Spectra: *Perkin–Elmer* FT-IR spectrometer; KBr pellets; $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Varian Inova* (500 MHz) spectrometers; in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. GC/MS: *Agilent 6890N* GC system *5973 IMSD*; in *m*/*z*.

2. *Compounds* **8** *and* **9**. *Methyl 2*-exo-*(3-Methylisoxazol-5-yl)-7-azabicyclo[2.2.1]heptane-7-carboxylate* (**8**). As described in *Sect. 3*, from **7** and 5-iodo-3-methylisoxazole. CC (AcOEt/hexane 1 : 2). Yield 61%. Colorless oil. IR: 3012, 2922, 1709, 1605, 1512, 1437, 1396, 1254, 1198, 1024, 880, 772, 737. ^{1}H-NMR: 1.56 – 1.60 (*m*, H–C(5), H–C(6)); 1.75 – 1.83 (*m*, H–C(5), H–C(6), H_{exo}–C(3)); 1.98 – 2.01 (*m*, H_{endo}–C(3)); 2.29 (*s*, Me); 2.93 (*dd*, *J* = 4.8; 8.8, H_{endo}–C(2)); 3.75 (*s*, MeO); 4.11 (br. *s*, H–C(1)); 4.40 (br. *s*, H–C(7)); 5.77 (*s*, =CH). ^{13}C-NMR: 10.85; 28.71; 29.62; 40.25; 44.78; 52.40; 58.15; 62.11; 97.76; 133.80; 153.92; 161.15. GC/MS: 236 (M^+), 178, 110, 82, 69, 55.

rel-*(3a*R,*4*S,*7*R,*7a*S*)-3a,4,7,7a-Tetrahydro-2-(3-methylisoxazol-5-yl)-4,7-methano-1*H*-isoindole-1,3(2*H*)-dione* (**9**). Synthesized from 3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1,3-dione and 3-methylisoxazol-5-amine. CC (AcOEt/hexane 2 : 1). Yield 90%. White crystals. m.p. 135 – 137°. IR: 3134,

3009, 2977, 2940, 2870, 1794, 1717, 1625, 1495, 1414, 1352, 1381, 1165, 1109, 709, 666. ^{1}H-NMR: 1.53 (*d*, *J* = 8.8, H_{anti}–C(8)); 1.72 (*dt*, *J* = 1.9, 10.7, H_{syn}–C(8)); 2.24 (*s*, Me); 3.40 (br. *s*, H–C(4), H–C(7)); 3.43–3.44 (*m*, H–C(3a), H–C(7a)); 6.06 (*s*, =CH); 6.17 (*s*, CH=CH). ^{13}C-NMR: 10.85; 44.78; 45.29; 51.26; 97.76; 133.80; 153.92; 159.73; 172.48. GC-MS: 244 (M^+), 179, 119, 82, 66.

3. *Reductive* Heck *Reactions. General Procedure:* A soln. of [$Pd(OAc)_2$] (5.6 mg, 0.025 mmol) and Ph_3As (33.7 mg, 0.11 mmol) in anh. DMF or DMSO (3 ml) was stirred under N_2 at 65° for 15 min. Then, compound **10** (244 mg, 1 mmol), Et_3N (488 µl, 3.5 mmol), aryl(heteroaryl) iodide (1.5 mmol), and HCOOH (138 mg, 3 mmol) were added. The mixture was stirred for 8–24 h. After cooling to r.t., AcOEt and brine were added. The org. layer was dried ($MgSO_4$) and concentrated, and the residue purified by CC (SiO_2).

rel-*(3a*R*,4*S*,5*S*,7*R*,7a*S*)-Hexahydro-2,5-bis(3-methylisoxazol-5-yl)-4,7-methano-1*H*-isoindole-1,3(2*H*)-dione* (**10a**): CC (AcOEt/hexane 1:1). Yield 42%. Colorless oil. IR: 3169, 3009, 2970, 1795, 1727, 1618, 1600, 1493, 1415, 1346, 1252, 1155, 727, 690. ^{1}H-NMR: 1.65 (*d*, *J* = 10.7, H_{anti}–C(8)); 1.88–1.90 (*m*, CH_2(6)); 1.94 (*d*, *J* = 10.7, H_{syn}–C(8)); 2.18 (*s*, Me); 2.29 (*s*, Me); 2.93–2.96 (*m*, H–C(7), H_{endo}–C(5)); 3.01 (*d*, *J* = 4.8, H–C(4)); 3.27–3.31 (*m*, H–C(3a)); 3.33–3.36 (*m*, H–C(7a)); 5.77 (*s*, =CH); 6.21 (*s*, =CH). ^{13}C-NMR: 11.60; 12.14; 31.71; 35.61; 40.03; 40.44; 45.25; 48.64; 48.84; 99.60; 154.84; 155.99; 161.22; 173.43; 173.58; 174.26. GC/MS: 327 (M^+), 179, 148, 82, 66.

rel-*(3a*R*,4*S*,5*S*,7*R*,7a*S*)-Hexahydro-2-(3-methylisoxazol-5-yl)-5-phenyl-4,7-methano-1*H*-isoindole-1,3(2*H*)-dione* (**10b**): CC (AcOEt/hexane 2:1). Yield 66%. White crystals. M.p. 118–119°. IR: 3148, 3009, 2922, 1790, 1724, 1607, 1494, 1416, 1349, 1255, 1058, 731, 698. ^{1}H-NMR: 1.55 (*d*, *J* = 10.7, H_{anti}–C(8)); 1.86–1.90 (*m*, H_{syn}–C(8), CH_2(6)); 2.29 (*s*, Me); 2.89–2.93 (*m*, H–C(4), H–C(7), H_{endo}–C(5)); 3.25–3.28 (*m*, H–C(3a)); 3.31–3.34 (*m*, H–C(7a)); 6.21 (*s*, =CH); 7.11–7.14 (*m*, 3 arom. H); 7.22–7.25 (*m*, 2 arom. H). ^{13}C-NMR: 12.15; 32.83; 39.63; 40.64; 42.15; 46.71; 48.90; 49.47; 99.46; 126.60; 127.24; 128.77; 144.13; 155.12; 161.16; 174.13; 174.21. GC/MS: 322 (M^+), 281, 239, 180, 142, 128, 104, 82, 66.

rel-*(3a*R*,4*S*,5*S*,7*R*,7a*S*)-5-(4-Chlorophenyl)hexahydro-2-(3-methylisoxazol-5-yl)-4,7-methano-1*H*-isoindole-1,3(2*H*)-dione* (**10c**): CC (AcOEt/hexane 3:1). Yield 58%. White crystals. M.p. 117–119°. IR: 3135, 3009, 2963, 1794, 1724, 1621, 1493, 1415, 1346, 1256, 1012, 741, 715, 667. ^{1}H-NMR: 1.57 (*d*, *J* = 10.5, H_{anti}–C(8)); 1.81–1.93 (*m*, H_{syn}–C(8), CH_2(6)); 2.29 (*s*, Me); 2.86–2.95 (*m*, H–C(4), H–C(7), H_{endo}–C(5)); 3.26–3.29 (*m*, H–C(3a)); 3.32–3.35 (*m*, H–C(7a)); 6.21 (*s*, =CH); 7.04 (*d*, *J* = 8.8, 2 arom. H); 7.18 (*d*, *J* = 8.8, 2 arom. H). ^{13}C-NMR: 10.92; 31.66; 38.29; 39.33; 40.39; 45.35; 47.52; 48.09; 98.28; 127.36; 127.57; 131.10; 141.39; 153.77; 160.00; 172.82; 172.95. GC/MS: 356.5 (M^+), 331, 315, 273, 176, 139, 103, 82, 66.

rel-*(3a*R*,4*S*,5*S*,7*R*,7a*S*)-5-(6-Chloropyridin-3-yl)hexahydro-2-(3-methylisoxazol-5-yl)-4,7-methano-1*H*-isoindole-1,3(2*H*)-dione* (**10d**): CC (AcOEt/hexane 2:1). Yield 45%. White crystals. M.p. 147–148°. IR: 3151, 3094, 2964, 2886, 1792, 1726, 1621, 1497, 1419, 1349, 1249, 1151, 751, 739, 683, 671. ^{1}H-NMR: 1.63 (*d*, *J* = 10.7, H_{anti}–C(8)); 1.79–1.85 (*m*, H_{syn}–C(8), H_{exo}–C(6)); 1.92–1.98 (*ddd*, *J* = 1.9, 8.8, 14.6, H_{endo}–C(6)); 2.29 (*s*, Me); 2.87–2.92 (*m*, H–C(7), H_{endo}–C(5)); 2.98 (br. *s*, H–C(4)); 3.29–3.32 (*m*, H–C(3a)); 3.36–3.39 (*m*, H–C(7a)); 6.22 (*s*, =CH); 7.19 (*s*, 1 arom. H); 7.40 (*dd*, *J* = 2.9, 8.8, 1 arom. H); 8.17 (*d*, *J* = 2.9, 1 arom. H). ^{13}C-NMR: 12.15; 32.85; 39.58; 39.60; 40.62; 46.19; 48.64; 49.23; 99.58; 124.27; 137.87; 138.39; 148.54; 149.91; 153.90; 154.89; 161.23; 173.61; 173.78. GC/MS: 356 (M^+), 276, 178, 139, 99, 66.

rel-*(3a*R*,4*S*,5*S*,7*R*,7a*S*)-Hexahydro-2-(3-methylisoxazol-5-yl)-5-(thiophen-2-yl)-4,7-methano-1*H*-isoindole-1,3(2*H*)-dione* (**10e**): CC (AcOEt/hexane 3:1). Yield 52%. White crystals. M.p. 127°. IR: 3148, 3009, 2978, 2950, 1792, 1721, 1611, 1492, 1415, 1349, 1253, 1162, 1141, 741, 697, 674. ^{1}H-NMR: 1.60 (*d*, *J* = 10.7, H_{anti}–C(8)); 1.85–2.01 (*m*, H_{syn}–C(8), CH_2(6)); 2.28 (*s*, Me); 2.92 (br. *s*, H–C(4), H–C(7)); 3.11 (*dd*, *J* = 4.8, 8.8, H_{endo}–C(5)); 3.24–3.28 (*m*, H–C(3a)); 3.30–3.34 (*m*, H–C(7a)); 6.21 (*s*, =CH); 6.74 (*d*, *J* = 3.9, 1 arom. H); 6.85 (*dd*, *J* = 4.8, 8.8, 1 arom. H); 7.07 (*d*, *J* = 4.8, 1 arom. H). ^{13}C-NMR: 12.15; 35.23; 38.34; 40.00; 40.29; 48.04; 48.63; 49.04; 99.48; 123.78; 123.92; 127.06; 148.97; 154.99; 161.16; 173.85; 173.87. GC/MS: 327 (M^+), 179, 148, 82, 66.

rel-*(3a*R*,4*S*,5*S*,7*R*,7a*S*)-Hexahydro-5-(4-methoxyphenyl)-2-(3-methylisoxazol-5-yl)-4,7-methano-1*H*-isoindole-1,3(2*H*)-dione* (**10f**): CC (AcOEt/hexane 2:1). Yield 60%. White crystals. M.p. 122°. IR: 3169, 3066, 3009, 2963, 2888, 2836, 1787, 1719, 1594, 1510, 1494, 1419, 1345, 1249, 1034, 821, 741, 726.

^{1}H-NMR: 1.53 (*d*, *J* = 10.7, H_{anti}–C(8)); 1.84–1.87 (*m*, H_{syn}–C(8), CH_2(6)); 2.28 (*s*, Me); 2.84–2.86 (*m*, H–C(7), H_{endo}–C(5)); 2.92 (br. *s*, H–C(4)); 3.24–3.27 (*m*, H–C(3a)); 3.30–3.33 (*m*, H–C(7a)); 3.71 (*s*, MeO); 6.21 (*s*, =CH); 6.77 (*d*, *J* = 8.8, 2 arom. H); 7.03 (*d*, *J* = 8.8, 2 arom. H). ^{13}C-NMR: 10.93; 31.67; 38.28; 39.38; 40.21; 45.78; 47.66; 48.21; 54.27; 98.21; 112.89; 126.99; 134.99; 153.90; 157.11; 159.92; 172.93; 173.03 GC/MS: 352 (M^+), 334, 311, 269, 231, 199, 172, 158, 121, 103, 82, 65.

4. *1,3-Dipolar Cycloaddition Reactions: General Procedure.* To a soln. of oxime (1.3 mmol) in CH_2Cl_2 was added **9** (1 mmol), and the soln. was cooled to 0°. Aq. NaOCl soln. (5.25%; 3.5 g, 2.5 mmol) was added dropwise over 30 min, and the mixture was stirred overnight (0° to r.t.). The mixture was extracted with either CH_2Cl_2 (3 × 10 ml) or Et_2O and dried ($MgSO_4$). The solvent was evaporated and the residue purified by CC.

rel-*(3a*R*,4*R*,4a*S*,7a*R*,8*R*,8a*R*)-3a,4,4a,7a,8,8a-Hexahydro-3-methyl-6-(3-methylisoxazol-5-yl)-4,8-methano-5*H*-isoxazolo[4,5-f]isoindole-5,7(6*H*)-dione* (**11a**): CC (AcOEt/hexane 3:1). Yield 64%. White crystals. M.p. 199–203°. IR: 3143, 3008, 2976, 2939, 1794, 1718, 1624, 1495, 1414, 1352, 1323, 1240, 1164, 752, 710, 666. ^{1}H-NMR: 1.56 (*d*, *J* = 10.7, H_{anti}–C(9); 1.75 (*d*, *J* = 10.7, H_{syn}–C(9)); 1.88 (*s*, Me); 2.28 (*s*, Me); 2.90 (*d*, *J* = 4.8, H–C(3a)); 3.09–3.12 (*m*, H–C(4), H–C(8)); 3.25–3.32 (*m*, H–C(4a), H–C(7a)); 4.51 (*d*, *J* = 7.8, H–C(8a)); 6.18 (*s*, =CH). ^{13}C-NMR: 11.90; 12.13; 36.08; 41.72; 44.84; 46.39; 47.06; 56.40; 81.56; 99.74; 154.45; 154.49; 161.25; 172.13; 172.82. GC/MS: 304 (M^+), 282, 207, 178, 113, 85, 57.

rel-*(3a*R*,4*R*,4a*S*,7a*R*,8*R*,8a*R*)-3-(4-Chlorophenyl)-3a,4,4a,7a,8,8a-hexahydro-6-(3-methylisoxazol-5-yl)-4,8-methano-5*H*-isoxazolo[4,5-f]isoindole-5,7(6*H*)-dione* (**11b**): CC (AcOEt/hexane 2:1). Yield 60%. White crystals. M.p. 247–248°. IR: 3154, 3009, 2974, 2951, 1797, 1720, 1610, 1592, 1494, 1417, 1350, 1268, 1090, 830, 749, 713. ^{1}H-NMR: 1.59 (*d*, *J* = 10.7, H_{anti}–C(9)); 1.83 (*d*, *J* = 10.7, H_{syn}–C(9)); 2.29 (*s*, Me); 3.01 (br. *s*, H–C(8)); 3.21 (br. *s*, H–C(4)); 3.32–3.38 (*m*, H–C(4a), H–C(7a)); 3.62 (*d*, *J* = 7.8, H–C(3a)); 4.73 (*d*, *J* = 7.8, H–C(8a)); 6.22 (*s*, =CH); 7.32 (*d*, *J* = 8.8, 2 arom. H); 7.53 (*d*, *J* = 8.8, 2 arom. H). ^{13}C-NMR: 10.91; 35.02; 41.54; 43.62; 45.29; 46.02; 51.60; 82.20; 98.55; 125.35; 127.07; 128.33; 135.55; 153.20; 154.12; 160.06; 170.81; 171.81. GC/MS: 317 (M^+), 301, 287, 271, 216, 191, 151, 111, 82, 66.

rel-*(3a*R*,4*R*,4a*S*,7a*R*,8*R*,8a*R*)-3a,4,4a,7a,8,8a-Hexahydro-6-(3-methylisoxazol-5-yl)-3-(thiophen-2-yl)-4,8-methano-5*H*-isoxazolo[4,5-f]isoindole-5,7(6*H*)-dione* (**11c**): CC (AcOEt/hexane 2:1). Yield 42%. Yellow crystals. M.p. 148°. IR: 3136, 3073, 2963, 1796, 1720, 1612, 1570, 1493, 1417, 1350, 1255, 1056, 713, 677, 665. ^{1}H-NMR: 1.60 (*d*, *J* = 10.7, H_{anti}–C(9)); 1.88 (*d*, *J* = 10.7, H_{syn}–C(9)); 2.29 (*s*, Me); 3.15 (br. *s*, H–C(8)); 3.21 (br. *s*, H–C(4)); 3.31–3.41 (*m*, H–C(4a), H–C(7a)); 3.62 (*d*, *J* = 7.8, H–C(3a)); 4.72 (*d*, *J* = 7.8, H–C(8a)); 6.21 (*s*, =CH); 7.00 (*dt*, *J* = 4.8, 8.8, 1 arom. H); 7.34 (*d*, *J* = 4.8, 1 arom. H); 7.65 (*dd*, *J* = 4.8, 10.7, 1 arom. H). ^{13}C-NMR: 10.90; 35.11; 41.91; 43.58; 44.77; 45.20; 52.83; 82.14; 98.53; 126.54; 127.16; 127.64; 150.98; 153.25; 153.53; 160.04; 171.70; 172.48. GC/MS: 369 (M^+), 355, 281, 207, 179, 163, 82, 66.

rel-*(3a*R*,4*R*,4a*S*,7a*R*,8*R*,8a*R*)-3-(2,5-Dimethoxyphenyl)-3a,4,4a,7a,8,8a-hexahydro-6-(3-methylisoxazol-5-yl)-4,8-methano-5*H*-isoxazolo[4,5-f]isoindole-5,7(6*H*)-dione* (**11d**). CC (AcOEt/hexane 2:1). Yield 60%. White crystals. M.p. 178–180°. IR: 3158, 3009, 2962, 2840, 1793, 1728, 1616, 1597, 1491, 1462, 1342, 1261, 1020, 800, 741, 729. ^{1}H-NMR: 1.51 (*d*, *J* = 8.8, H_{anti}–C(9)); 1.83 (*d*, *J* = 11.7, H_{syn}–C(9)); 2.29 (*s*, Me); 2.88 (br. *s*, H–C(8)); 3.15 (br. *s*, H–C(4)); 3.25–3.31 (*m*, H–C(4a), H–C(7a)); 3.71 (*s*, MeO); 3.79 (*s*, MeO); 4.04 (*d*, *J* = 8.8, H–C(3a)); 4.65 (*d*, *J* = 8.8, H–C(8a)); 6.22 (*s*, =CH); 6.81 (*d*, *J* = 8.8, 1 arom. H); 6.88 (*dd*, *J* = 2.9, 8.8, 1 arom. H); 7.33 (*d*, *J* = 2.9, 1 arom. H). ^{13}C-NMR: 10.92; 34.77; 42.03; 43.99; 45.32; 46.13; 53.77; 54.77; 54.80; 81.67; 98.40; 112.01; 112.16; 115.80; 117.53; 150.58; 152.47; 153.53; 154.55; 160.01; 171.24; 171.60. GC/MS: 423 (M^+), 394, 270, 205, 176, 148, 82, 66.

REFERENCES

[1] T. F. Spande, H. M. Garraffo, M. W. Edwards, H. J. C. Yeh, L. Pannell, J. W. Daly, *J. Am. Chem. Soc.* **1992**, *114*, 3475.

[2] J. Cheng, S. Izenwasser, C. Zhang, S. Zhang, D. Wade, M. L. Trudell, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1775.

[3] B. Badio, H. M. Garraffo, C. V. Plummer, W. L. Padgett, J. W. Daly, *Eur. J. Pharmacol.* **1997**, *321*, 189.

[4] L. Rizzi, C. Dallanoce, C. Matera, P. Magrone, L. Pucci, C. Gotti, F. Clementi, M. De Amici, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4651.

[5] C. Dallanoce, P. Magrone, P. Bazza, G. Grazioso, L. Rizzi, L. Riganti, C. Gotti, F. Clementi, K. Frydenvang, M. De Amici, *Chem. Biodiversity* **2009**, *6*, 244.
[6] J.-P. G. Seerden, M. T. M. Tulp, H. W. Scheeren, C. G. Kruse, *Bioorg. Med. Chem.* **1998**, *6*, 2103.
[7] A. Otten, J. C. Namyslo, M. Stoermer, D. E. Kaufmann, *Eur. J. Org. Chem.* **1998**, 1997.
[8] G. Göksu, M. Gul, N. Ocal, D. E. Kaufmann, *Tetrahedron Lett.* **2008**, *49*, 2685.
[9] E. Bagdatli, N. Ocal, D. E. Kaufmann, *Helv. Chim. Acta* **2007**, *90*, 2380.
[10] Ç. Yolacan, E. Bagdatli, N. Ocal, D. E. Kaufmann, *Molecules* **2006**, *11*, 603.
[11] T. Sakamoto, Y. Kondo, D. Uchiyama, H. Yamanaka, *Tetrahedron* **1991**, *47*, 5111.

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