Easy and regioselective access to dimethyl acetal-protected heterocycles and their efficient allylation reactions mediated by allylaluminum reagent

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Abstract

This paper describes easy access to twelve examples of five- and six-membered heterocycles (monocyclic and fused) containing a dimethyl acetal aldehyde function and/or a trifluoromethyl substituent, in good to excellent yields (72–98%). The dimethyl acetal-protected heterocycles were obtained in one-step *via* regioselective cyclocondensation reactions of 4,6,6-trimethoxy-1,1,1-trifluorohex-3-en-2-one with 1,2-, 1,3- and 1,5-dinucleophiles (hydrazines, hydrazides, hydroxylamine, 1-acetylguanidine and 1,8-diaminonaphthalene). Subsequently, to demonstrate a potential synthetic application, some pyrazole rings containing dimethyl acetal moiety were converted to the respective secondary homoallylic alcohols by efficient allylation reactions employing allylaluminum reagent in 84 to 90% yields.

Keywords: Allylaluminum reagent, dimethyl acetals, heterocycles, homoallylic alcohols, indium

Introduction

Heterocycles are of great importance due to their high applicability in various branches of modern chemistry, specifically in the pharmacological and agricultural field. Since the trifluoromethyl group shows changes in physico-chemical properties such as polarity, lipophilicity and polarizability, chemical behavior,[1] and pharmacological activity of the molecules to which it is connected,[2,3] this substituent has become increasingly popular in heterocyclic compounds synthesized for biological application.[4-6]

Over the last twenty years our research group (NUQUIMHE) has reported on the synthetic potential of *β*-alkoxyvinyl trihalomethyl ketones for obtaining of new trihalomethylated heterocycles,[7-12] as well as other molecules that provide great possibilities for chemical

derivatizations, which lead to a substance, or its structural analogue, with proven applications.[13,14] However, up to 2009,[15] easy and rapid access to trifluoromethylated heterocycles containing a stable dimethyl acetal-protected aldehyde function as a substituent for further chemical transformations has not yet been described.

So, the one-step synthesis of heterocycles that have a protected aldehyde function (such as an acetal moiety) deserves considerable attention. This substituent, which can be easily installed and removed,[16] shows great chemical potential and serves as an intermediate functional group for enabling a wide range of synthetic routes, especially during the total synthesis of complex natural products.

An interesting application for heterocycles with aldehyde moieties would be in the synthesis of homoallyl alcohols, which are usually obtained by an addition reaction of an allylic metal nucleophile with carbonyl compounds such as aldehydes or ketones.[17-21] Homoallyl alcohols are important building blocks or versatile synthons for many biologically active molecules such as macrolides, polyhydroxylated natural compounds, polyether antibiotics,[22-27] and functionalized tetrahydropyrans.[28-30]

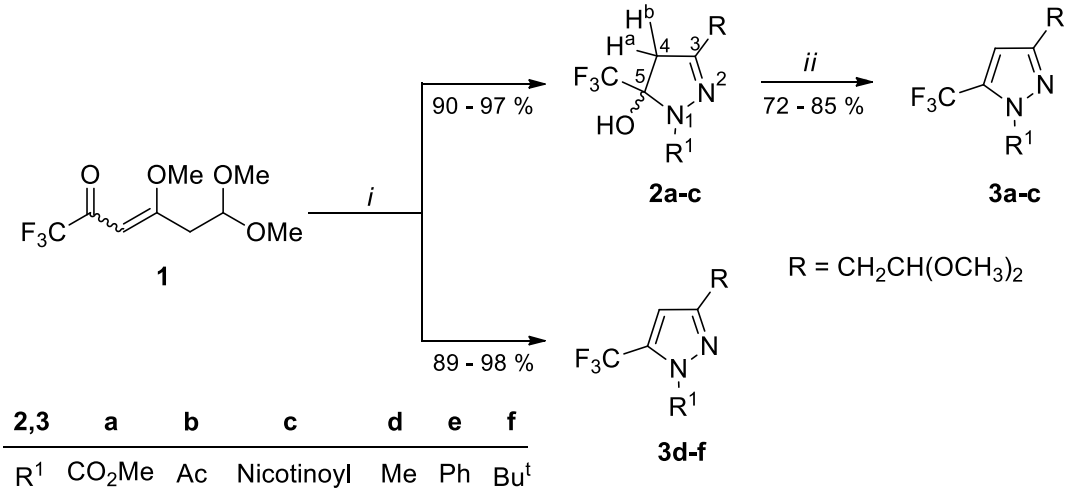
Thus, the aim of this paper is to report the synthesis of new trifluoromethylated heterocycles containing a dimethyl acetal-protected aldehyde function as a substituent from the reactions of 4,6,6-trimethoxy-1,1,1-trifluoro-3-en-2-one (**1**) with hydrazines, hydrazides, hydroxylamine, 1-acetylguanidine and 1,8-diaminonaphthalene, which furnishes examples of new and stable trifluoromethyl-substituted pyrazolines, pyrazoles, isoxazoline, pyrimidine and perimidine. In addition, we will analyze the chemical behavior of the acetal function linked to the heterocyclic alkyl side chain in allylation reactions employing the allylaluminum reagent that furnishes new pyrazolyl homoallyl alcohol scaffolds.

Results and Discussion

4,6,6-Trimethoxy-1,1,1-trifluorohex-3-en-2-one (**1**) was obtained following the method previously reported in 2009 by our research group.[15] Owing to the presence of the dimethyl acetal at the C-6 protecting the aldehyde function, compound **1** presents only two different electrophilic centers at the C-2 and C-4 (*CCC* building block) and not three centers, as would be the case if the C-6 was unprotected. A non-protected aldehyde function at the C-6 could probably lead to a mixture of heterocyles. However, the special chemical feature allows **1** the possibility to exploit it via the regioselective synthesis of many trifluoromethyl and 2,2-dimethoxyethyl-substituted heterocyles for further chemical derivatizations.

Initially, when ketone **1** was treated with three different hydrazides (N,N-1,2-dinucleophiles) at a molar ratio of 1:1, with ethanol as solvent for 20 h at reflux, 3-(2,2-dimethoxyethyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazoles **2a–c** were regiospecifically produced in a one-step reaction in 90–97% yields (Scheme 1). However, when **1** was treated with methyl, *tert*-butyl and phenyl hydrazine in the same reaction conditions as described above, but employing

methanol as solvent, the aromatic pyrazoles **3d-f** were obtained in a single step in 89–98% yields. The absence of a strong electron-withdrawing effect of R^1 is the main factor responsible for this result. So, to obtain pyrazole derivatives from pyrazolines **2a-c**, we used the method described by Padwa,[31] which does not use acidic media and has the advantage of forming heterocycles **3a-c**, thereby maintaining the aldehyde group as a dimethyl acetal and also, in the present case, preventing the loss of the N-1 substituent of the pyrazoline ring in **2a-c**.



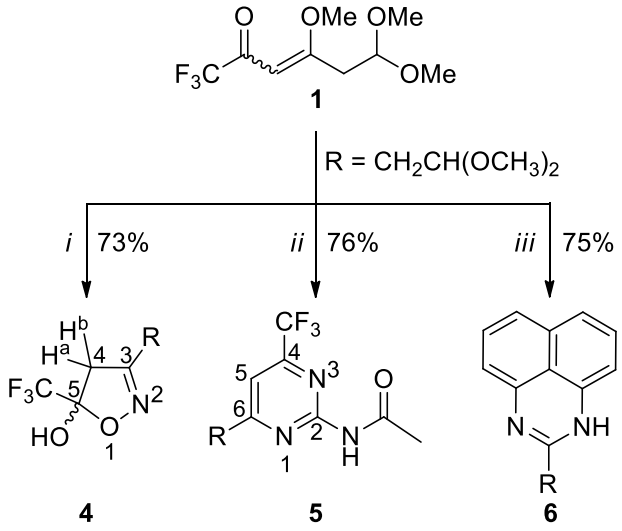
Scheme 1. *Reagents and conditions:* (*i*) NH_2NHR^1, EtOH, 20 h, reflux; (*ii*) NH_2NHR^1, MeOH, 20 h, reflux; *(iii*) $SOCl_2$, Pyridine, Benzene, 1 h, 0–80 ºC.

To increase the scope of the reactions, another azole **4** and azines **5** and **6** were synthesized. For example, the reaction of ketone **1** with a solution of hydroxylamine hydrochloride and pyridine being stirred for 24 h at 45 ºC furnished the 3-(2,2-dimethoxyethyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydroisoxazole of **4** at 73% yield (Scheme 2).

4-Trifluoromethyl-6-(2,2-dimethoxyethyl)-2-acetylaminopyrimidine (**5**) was obtained from the reaction of the ketone **1** with 1-acetylguanidine (Scheme 2) in a one-pot reaction in 76% yield. The reaction was performed in acetonitrile at a molar ratio of 1:1 and the optimal reaction time and temperature were 24 h under reflux. After this, the compound **5** was precipitated and purified by recrystallization from diisopropyl ether, to give a pure yellow solid.

According to Barchet and Merz,[32] 1,8-diaminonaphthalene reacts with ethyl 3-phenyl-acrylate, ethyl 2-benzylacrylate and ethyl 3-(3-pyridyl)acrylate to furnish stable 2(3)-substituted 4,5-dihydro-1*H*-naphtho[1,8-*bc*][1,5]diazocin-4-ones, which were only identified by UV/IR spectroscopy. However, when we tried to obtain a trifluoromethylated eight-membered ring, from the reaction of ketone **1** with 1,8-diaminonaphthalene in chloroform as the solvent at a molar ratio of 1:1 (Scheme 2), the diazocine was not isolated. Instead, we isolated a six-membered ring, a non-trifluoromethylated perimidine **6**, in a one-pot reaction in 75% yield. Thus, the result obtained from the reaction involving ketone **1** and 1,8-diaminonaphthalene

shows that the amino groups attached to positions 1 and 8 of the naphthalene act as the dinucleophiles and attacked only the C-4 of precursor **1**, furnishing the non-trifluoromethyl substituted perimidine **6**. This reaction type, where a nucleophile attacks the C-4 of 4-alkoxy-1,1,1-trifluoroalk-3-en-2-ones has already been reported by us in the synthesis of benzoimidazoles.[33,34]



Scheme 2. *Reagents and conditions*: (*i*) $NH_2OH.HCl$, Pyridine, H_2O, 24 h, 45 ºC; (*ii*) $NH_2(C{=}NH)NHAc$, CH_3CN, 24 h, reflux; (*iii*) 1,8-Diaminonaphthalene, $CHCl_3$, 24 h, reflux.

As seen previously in the introduction, the reaction from the addition of allyl metal nucleophiles to carbonyl compounds is an established way to obtain the homoallylic alcohols. However, to reduce the number of reaction steps, we started the synthesis from dimethyl acetal, employing the method described by Cho *et al.*[35] In this work, the researchers describe an efficient allylation reaction of dimethyl acetals and ketals in aqueous THF media in a single step and under mild conditions, employing indium metal and allylic or propargylic bromides in a 2:1 ratio. The Cho method[35] proved to be a useful tool for direct allylation and propargylation reactions of acetals and ketals in aqueous media.

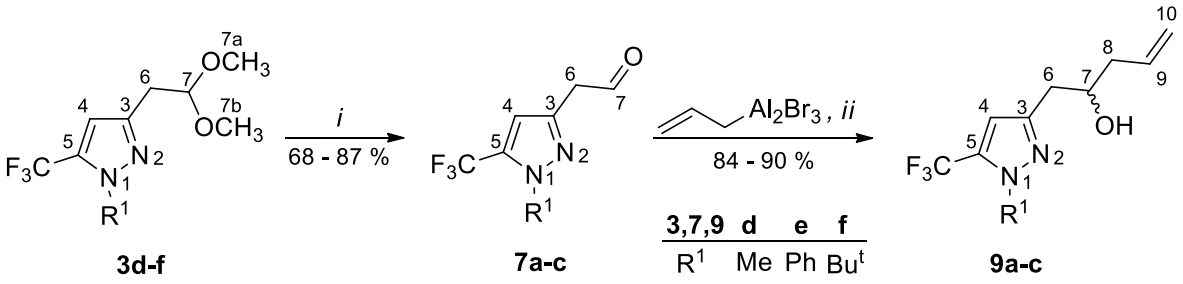
Unfortunately, when we employed the same reaction condition for pyrazole **3d**, using allyl bromide as the halide, no reaction was observed. From the analysis of a previous paper by the same authors,[36] in which the selective deprotection of acetals employing allyl bromide in aqueous media is reported, it became clear that the condition is only selective for acetal groups directly attached to the systems which have high stabilization energy for the methine carbon of the acetal moiety. In our specific case, the likely reason is that the heterocyles **2-6** present a methylene carbon between the dimethyl acetal function and the rings, thus hindering any stabilization by electronic effect related to the acetal moiety.

Owing to this limitation, we deprotected the acetal function and isolated the pyrazol-3-yl-acetaldehydes **7d-f**, employing an adaptation of the method reported by Elisson *et al.*,[37] which was used in previous work reported by us in 2009.[15] This method was applied to pyrazoles **3d-f** and was performed in $CHCl_3$ at 60 °C in the presence of a mixture of trifluoroacetic acid with water at a ratio of 1:1 v/v, which allowed the aldehydes **7d-f** to be obtained as oils in good yields (68–87%) and in a high degree of purity.

Although indium metal is considered to be one of the best choices for performing allylation reactions, its high cost makes the synthetic procedures very expensive, especially when employed in a stoichiometric ratio with carbonyl compounds.

Searching for alternative ways, we followed the method described by Takai *et al.*,[38] in which the desired homoallylic alcohols were accessed by the reaction of allylaluminum with aldehydes.

Thus, the allylaluminum reagent **8** was prepared under argon atmosphere, employing anhydrous THF as the solvent, aluminium flakes (1 mm × 1 mm), allyl bromide and a catalytic amount of indium metal (5 mol%). In accordance with the Takai method,[38] after all metals were consumed (30 min), the aldehyde solutions **7d-f** in anhydrous THF were added to the mixture and stirred for 1 more hour at room temperature. Subsequently, quenching with HCl solution, extraction with diethyl ether, washing with brine, drying over Na_2CO_3, and concentration under reduced pressure, the homoallylic alcohols **9d-f** were obtained as viscous oils in 84–90% yields (Scheme 3).



Scheme 3. *Reagents and conditions*: (i) $CHCl_3$,TFA:H_2O (1:1 v/v), 4 h, 60 °C; (ii) THF, 1 h, rt.

The structures of compounds **2-7** and **9** were determined by ^1H, ^{13}C NMR, gas chromatography-mass spectrometry (GC-MS), elemental analyses, high resolution mass spectrometry (HRMS) and by comparison with NMR data of other compounds previously synthesized in our laboratory.[39,40]

The 4,5-dihydropyrazoles **2a-c** and 4,5-dihydroisoxazole **4** show the chemical shifts of the methylene protons of the ring (H-4a and H-4b) to be a characteristic of the AB system and as a doublet on average near δ 3.1 and 3.4 ppm, respectively, with a geminal coupling constant in the range of 18–19 Hz.

In comparison with the compounds **2a-c**, the pyrazoles **3a-f** showed ^1H NMR chemical shifts in $CDCl_3$ for the proton H-4 as a characteristic singlet at an average of δ 6.7 ppm.

The C-5 of the compounds **2-4**, **7** and **9** shows signals in the shape of quartets, with $^{2}J_{C\text{-}F}$ in the range of 33-41 Hz. This characteristic was decisive to confirm the regioselective formation of these heterocicles. This observation was previously described in another work of our research group.[41]

The pyrimidine **5** presents, among other signals, the ^{1}H NMR chemical shifts of the H-5 as a characteristic singlet at δ 7.6 ppm.

The ^{1}H NMR signals for the 2,2-dimethoxyethyl substituent are characterized by the presence of one triplet near δ 4.5–4.9 ppm with a coupling constant of 6 Hz for the methine proton, and a doublet near δ 2.6–3.7 ppm for the methylene protons. Another feature is the appearance of only one singlet resulting from the two equivalent methoxy groups.

The substituted acetaldehyde moiety attached to the C-3 of the pyrazole rings in **7d-f** shows the methylene group as a doublet near δ 3.8 ppm and the proton of the CHO function appears as a triplet near δ 9.7–9.9 ppm; both signals have a sharp coupling constant of 2 Hz.

As expected, the proton spin system of the homoallylic alcohol moiety linked to the C-3 of pyrazoles **9d-f** exhibits a complex set of signals which, according to the Pople notation rules,[42] we have established as ABFMNRXZ system (Figure 1).

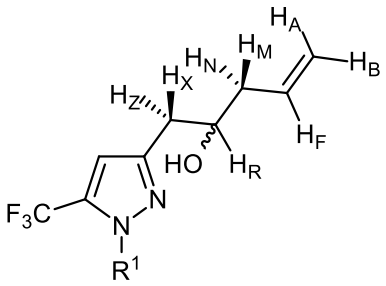


Figure 1. Pople's notation for homoallylic alcohol spin system.

Owing to the diastereotopic methylene groups presenting unresolved signals unlike the other multiplets of the spectrum, they received closer letters (MN and XZ). The CH_2 bonded to the heterocyclic ring shows two doublet of doublets near δ 2.6–2.8 ppm as somewhat separated, while the neighbor to the allylic bond appears as a second order set of signals, near δ 2.1–2.2 ppm.

With three different values of coupling constants, the CH allylic signal shows a doublet of doublets of triplets near δ 5.8–5.9 ppm. The vinylic CH_2 exhibits two doublet of doublets near δ 5.0 ppm, which shows the inner signals overlapping. Nevertheless, the vicinal coupling constants ($^{3}J_{AF}$ = 17 Hz) and ($^{3}J_{BF}$ = 10 Hz) were still observed.

Even though in compound **9d** the proton linked to the asymmetric carbon C-7 appears to overlap with the methyl bonded to N-1, for compounds **9e** and **9f** this signal appears near δ 3.8 ppm, showing a coupling constant of 6 Hz with the two methylene groups and 5 Hz with the

hydroxyl proton. The hydroxyl proton appears near δ 4.6 ppm as a doublet with a coupling constant of 5 Hz.

In all heterocycles, the carbon attached to the CF_3 presents a characteristic quartet in the range of δ 90.5–156.0 ppm with a carbon-fluorine coupling constant ($^2J_{CF}$) in the range of 32–41 Hz. The CF_3 group shows a typical quartet in the range of δ 117.6–125.1 ppm due to the $^1J_{CF}$ in the range of 269–290 Hz.

Conclusions

In summary, we have developed reactions of 4,6,6-trimethoxy-1,1,1-trifluorohex-3-en-2-one (**1**) with representative 1,2-, 1,3- and 1,5-bisnucleophiles to obtain twelve examples of new dimethyl acetal-protected heterocycles that show new regioselective synthetic applications for this dielectrophile precursor as a *CCC* building block in heterocyclic chemistry. Furthermore, to demonstrate a synthetic application, some pyrazole rings containing dimethyl acetal, which have a methylene group between the CHO function and the C-3 of the rings, were converted at excellent yields to the respective homoallylic alcohols by efficient allylation reactions employing allylaluminum reagent in the presence of catalytic amounts of indium metal.

Experimental Section

General. Unless otherwise indicated, all common reagents and solvents were used from commercial suppliers without further purification. All melting points were determined using coverslips on a Microquímica MQAPF - 302 apparatus and are uncorrected. Except for allylic alcohols **9d-f**, for which ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DPX 400 spectrometer (^{1}H at 400.13 MHz and ^{13}C at 100.62 MHz), the ^{1}H and ^{13}C NMR spectra of all other compounds were acquired on a Bruker DPX 200 spectrometer (^{1}H at 100.13 MHz and ^{13}C at 50.32 MHz), using 5 mm sample tubes, 298 K, digital resolution ± 0.01 ppm, in DMSO-d_6 (**4**) and $CDCl_3$ (**2**,**3**, **5**, **7**) using TMS as the internal reference.
Mass spectra were registered in a HP 5973 MSD connected to a HP 6890 GC and interfaced by a Pentium PC. The GC was equipped with a split-splitless injector, autosampler, cross-linked HP-5 capillary column (30 m, 0.32 mm internal diameter), and He was used as the carrier gas. Infrared spectra were recorded as KBr discs using a Bruker Tensor 27 spectrometer over the range 4000 cm^{-1}. The CHN elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer (University of São Paulo, Brazil), and the high resolution mass spectrometry spectra (HRMS) were performed using an Agilent-QTOF 6530 Spectrometer (LARP/UFSM) and LTQ Orbitrap XL ETD Thermo Scientific Spectrometer (National Institute of Technology, RJ, Brazil).

General procedure for the preparation of 5-hydroxy-3-(2,2-dimethoxyethyl)-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazoles 2a-c and 3-(2,2-dimethoxyethyl)-5-trifluoromethyl-1*H*-pyrazoles 3d,e. A solution of 4,6,6-trimethoxy-1,1,1-trifluorohex-3-en-2-one (**1**) (2 mmol; 0.482 g) with hydrazide or hydrazine (2 mmol) in dry EtOH (15 mL) is stirred at 80 °C for 20 h. After the reaction time, the solvent is removed under reduced pressure. The products **2a-c** and **3d-e** are dried under vacuum and isolated as oils (yields of 90-98%).

5-Hydroxy-3-(2,2-dimethoxyethyl)-5-trifluoromethyl-4,5-dihydro-1*H*-1-carboxymethylpyrazole (2a). Yield: 93%; 0.56 g; oil. ^{1}H NMR (100 MHz, $CDCl_3$): δ 4.5 (t, 1H, *J* 6.0 Hz, H-7), 3.8 (s, 3H, OMe), 3.4 (d, 1H, *J* 18 Hz, H-4a), 3.3 (d, 1H, *J* 18 Hz, H-4b), 3.4 (s, 6 H, H-7a-b), 2.7 (d, 2H, *J* 6.0 Hz, H-6). ^{13}C NMR (50 MHz, $CDCl_3$): δ 154.4 (C-3), 153.7 (C=O), 123.4 (q, *J* 286 Hz, CF_3), 102.5 (C-7), 90.8 (q, ^2J 33 Hz, C-5), 54.1 (C-2'), 53.7 (C-7a-b), 46.1 (C-4), 33.9 (C-6). GC-MS (EI, 70 eV): *m/z* (%) 269 (24), 237 (10), 75 (100), 47 (24). IR (KBr, ν cm^{-1}): 3414 (OH), 1722 (C=O), 1121 (OMe). Anal Calcd. for $C_{10}H_{15}F_3N_2O_5$ (300): C, 40.00; H, 5.04; N, 9.33. Found: C, 39.69; H, 4.73; N, 9.91%.

5-Hydroxy-3-(2,2-dimethoxyethyl)-5-trifluoromethyl-4,5-dihydro-1*H*-1-acetylpyrazole (2b). Yield: 93%; 0.53 g; oil. ^{1}H NMR (100 MHz, $CDCl_3$): δ 4.5 (t, 1H, *J* 6.0 Hz, H-7), 3.3 (s, 6H, H-7a-b), 3.3 (d, 1H, *J* 19 Hz, H-4a), 3.1 (d, 1H, *J* 19 Hz, H-4b), 2.6 (d, 2H, *J* 6.0 Hz, H-6), 2.3 (s, 3H, Me). ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.6 (C=O), 154.4 (C-3), 125.1 (q, *J* 287 Hz, CF_3), 102.1 (C-7), 90.5 (q, ^2J 34 Hz, C-5), 54.8 (C-7a-b), 46.2 (C-4), 33.8 (C-6), 22.5 (C-2'). GC-MS (EI, 70 eV): *m/z* (%) 284 (M^+, 1), 253 (7), 211 (20), 141 (5), 75 (100). IR (KBr, ν cm^{-1}): 3266 (OH), 1672 (C=O), 1122 (OMe). Anal Calcd. for $C_{10}H_{15}F_3N_2O_4$ (284): C, 42.26; H, 5.32; N, 9.86. Found: C, 42.35; H, 5.27; N, 9.94%.

5-Hydroxy-3-(2,2-dimethoxyethyl)-5-trifluoromethyl-4,5-dihydro-1*H*-1-nicotinoylpyrazole (2c). Yield: 90%; 0.62 g; oil. ^{1}H NMR (100 MHz, $CDCl_3$): δ 9.1 (s, 1H, Py), 8.70-8.72 (m, 1H, Py), 8.1-8.2 (m, 1H, Py), 7.3-7.4 (m, 1H, Py), 4.5 (t, 1H, *J* 6.0 Hz, H-7), 3.4 (d, 1H, *J* 18 Hz, H-4a), 3.3 (d, 6H, *J* 3,0 Hz, H-7a-b), 3.2 (d, 1H, *J* 18 Hz, H-4b), 2.6 (d, 2H, *J* 6.0 Hz, H-6). ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.1(C=O), 155.5, 152.1, 147.7, 137.6, 122.7 (Py), 150.8 (C-3), 120.6 (q, *J* 286 Hz, CF_3), 102.1 (C-7), 92.2 (q, ^2J 34 Hz, C-5), 53.9, 53.7 (C-7a-b), 46.1 (C-4), 33.8 (C-6). GC-MS (EI, 70 eV): *m/z* (%) 347 (M+, 1), 316 (5), 106 (29), 78 (19), 75 (100). IR (KBr, ν cm^{-1}): 3229 (OH), 1641 (C=O), 1121 (OMe). Anal Calcd. For $C_{14}H_{16}F_3N_3O_4$ (347.1): C, 48.42; H, 4.64; N, 12.10. Found: C, 48.30; H, 4.44; N, 12.57%.

3-(2,2-Dimethoxyethyl)-5-trifluoromethyl-1*H*-1-methylpyrazole (3d). Yield: 98%; 0.47 g; oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.3 (s, 1H, H-4), 4.5 (t, 1H, *J* 6.0 Hz, H-7), 3.9 (s, 3H, Me), 3.4 (s, 6H, H-7a-b), 2.9 (d, 2H, *J* 6.0 Hz, H-6).^{13}C NMR (50 MHz, $CDCl_3$): δ 140.9 (q, ^2J 38 Hz, C-5), 139.6 (C-3), 121.3 (q, *J* 268 Hz, CF_3), 104.0 (q, ^3J 2 Hz, C-4), 103.6 (C-7), 53.9 (C-7a-b), 37.1 (Me), 29.9 (C-6). GC-MS (EI, 70 eV): *m/z* (%) 207 (8), 163 (10), 75 (100), 47 (37). HRMS (ESI): *m/z* calcd for $C_9H_{13}F_3N_2O_2$: 239.1007 (M + H). Found: 239.1006.

3-(2,2-Dimethoxyethyl)-5-trifluoromethyl-1*H*-1-phenylpyrazole (3e). Yield: 95%; 0.57 g; oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.5 (5H, Ph), 6.7 (s, 1H, H-4), 4.7 (t, 1H, *J* 6.0 Hz, H-7), 3.4 (s, 6H, H-7a-b), 3.0 (d, 2H, *J* 6.0 Hz, H-6). ^{13}C NMR (50 MHz, $CDCl_3$): δ 148.4 (C-3), 138.9;

129.0; 128.9; 125.4 (Ph), 132.9 (q, ^2J 39 Hz, C-5), 119.6 (q, J 269 Hz, CF_3), 108.7 (q, ^3J 3 Hz, C-4), 103.4 (C-7), 53.2 (C-7a-b), 31.8 (C-6). GC-MS (EI, 70 eV): *m/z* (%) 269 (40), 225 (20), 75 (100). HRMS (ESI): *m/z* calcd for $C_{14}H_{15}F_3N_2O_2$: 301.1164 (M + H). Found: 301.1182.

3-(2,2-Dimethoxyethyl)-5-trifluoromethyl-1*H*-1-*tert*-Butylpyrazole (3f). A mixture of *tert*-butyl hydrazine hydrochloride (2.2 mmol; 0.282 g) and sodium carbonate (2.2 mmol; 0.233 g) in anhydrous MeOH (20 mL) is stirred at rt for 1 h. The mixture is filtered into a glass balloon containing 4,6,6-trimethoxy-1,1,1-trifluorohex-3-en-2-one (**1**) (2 mmol; 0.482 g) and stirred at 65 °C for 20 h. After the reaction time, the solvent is removed under reduced pressure. The solid obtained is solubilized in chloroform and washed with distilled water (3 × 20 mL). The organic layer is stirred with sodium carbonate and the solvent is removed again under reduced pressure. The compound is obtained as a yellow oil at 89% yield.

Yield: 89%; 0.49 g; oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.5 (s, 1H, H-4), 4.6 (t, 1H, J 6.0 Hz, H-7), 3.4 (s, 6H, H-7a-b), 2.9 (d, 2H, J 6.0 Hz, H-6), 1.6 (s, 9H, Bu^t). ^{13}C NMR (50 MHz, $CDCl_3$): δ 144.8 (C-3), 131.5 (q, ^2J 39 Hz, C-5), 121.5 (q, J 269 Hz, CF_3), 110.1 (q, ^3J 4 Hz, C-4), 103.8 (C-7), 53.1 (C-7a-b), 29.9 (Me), 29,5 (C-6). GC-MS (EI, 70 eV): *m/z* (%) 249 (38), 193 (83), 173 (36), 149 (27), 75 (100), 57 (27). HRMS (ESI): *m/z* calcd for $C_{12}H_{19}F_3N_2O_2$: 281.1477 (M + H). Found: 281.1463.

General Procedure for the preparation of 3-(2,2-dimethoxyethyl)-5-trifluoromethyl-1*H*-pyrazoles (3a-c). A solution of 3-(2,2-dimethoxyethyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazoles **2a-c** (2.6 mmol) and pyridine (33.8 mmol) in benzene (50 mL) is cooled to 0 °C and thionyl chloride (16.8 mmol) diluted in benzene (25 mL) is added in drops over a 10 min period. The solution is stirred for an additional 30 min, during which the temperature is allowed to rise to 20 °C. The mixture is then heated under reflux (bath temperature 80 °C) for 1 h and then filtered to remove the pyridine hydrochloride at room temperature. The solution is washed twice with water and dried (Na_2SO_4). The solvent is evaporated to obtain dark oils as pure compounds **3a-c** (yields 72–85%).

3-(2,2-Dimethoxyethyl)-5-trifluoromethyl-1*H*-1-carboxymethylpyrazole (3a). Yield: 85%; 0.48 g; oil. ^{1}H NMR (100 MHz, $CDCl_3$): δ 6.8 (s, 1H, H-4), 4.6 (t, 1H, J 6.0 Hz, H-7), 4.1 (s, 3H, H-2'), 3.3 (s, 6H, H-7a-b), 3.0 (d, 2H, J 6.0 Hz, H-6). ^{13}C NMR (50 MHz, $CDCl_3$): δ 151.6 (C-3), 148.3 (C=O), 134.3 (q, ^2J 41 Hz, C-5), 117.6 (q, J 269 Hz, CF_3), 113.9 (C-4), 102.9 (C-7), 55.2 (C-2'), 53.5 (C-7a-b), 32.1 (C-6). GC-MS (EI, 70 eV): *m/z* (%) 282 (M^+,2), 251 (19), 163 (10), 149 (5), 75 (100). IR (KBr, ν cm^{-1}): 1781 (C=O), 1156 (OMe). Anal Calcd. for $C_{10}H_{13}F_3N_2O_4$ (282.0): C, 42.56; H, 4.64; N, 9.93. Found: C, 42.97; H, 3.95; N, 10.40%.

3-(2,2-Dimethoxyethyl)-5-trifluoromethyl-1*H*-1-acetylpyrazole (3b). Yield: 83%; 0.44 g; oil. ^{1}H NMR (100 MHz, $CDCl_3$): δ 6.7 (s, 1H, H-4), 4.6 (t, 1H, J 6.0 Hz, H-7), 3.3 (s, 6H, H-7a-b), 2.9 (d, 2H, J 6.0 Hz, H-6), 2.7 (s, 3H, H-2'). ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.2 (C=O), 150.8 (C-3), 133.9 (q, ^2J 41 Hz, C-5), 117.9 (q, J 269 Hz, CF_3), 114.1 (C-4), 102.9 (C-7), 53.4 (C-7a-b), 32.1 (C-6), 22.6 (C-2'). GC-MS (EI, 70 eV): *m/z* (%) 266 (M^+, 17), 235 (10), 193 (14), 173

(7), 75 (100). IR (KBr, *v* cm^{-1}): 1672 (C=O), 1131 (OMe). Anal Calcd. for $C_{10}H_{13}F_3N_2O3$ (266.2): C, 45.12; H, 4.92; N, 10.52. Found: C, 45.56; H, 5.12; N, 10.01%.

3-(2,2-Dimethoxyethyl)-5-trifluoromethyl-1*H*-1-nicotinoylpyrazole (3c). Yield: 72%; 0.47 g; oil. ^{1}H NMR (100 MHz, $CDCl_3$): δ 9.2 (d, 1H, Py), 8.81-8.83 (m, 1H, Py), 8.3-8.4 (m, 1H, Py), 7.44-7.47 (m, 1H, Py), 6.9 (s, 1H, H-4), 4.6 (t, 1H, *J* 6.0 Hz, H-7), 3.3 (s, 6H, H-7a-b), 2.9 (d, 2H, *J* 6.0 Hz, H-6). ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.7 (C=O), 153.1, 151.8, 139.0, 127.6, 114.5 (Py), 152.2 (C-3), 134.7 (q, ^2J 41 Hz, C-5), 122.9 (C-4), 120.5 (q, *J* 269 Hz, CF_3), 102.8 (C-7), 53.5 (C-7a-b), 32.1 (C-6). GC-MS (EI, 70 eV): *m/z* (%) 328 (M^+, 1), 298 (4), 106 (22), 78 (19), 75 (100). IR (KBr, *v* cm^{-1}): 1732 (C=O), 1133 (OMe). Anal Calcd for $C_{14}H_{14}F_3N_3O_3$ (329.1): C, 51.07; H, 4.29; N, 12.76. Found: C, 51.21; H, 4.53; N, 12.81%.

5-Hydroxy-3-(2,2-dimethoxyethyl)-5-trifluoromethyl-4,5-dihydroisoxazole (4). To a stirred solution of 4,6,6-trimethoxy-1,1,1-trifluorohex-3-en-2-one (**1**) (2 mmol; 0.482 g) in pyridine (2 mmol; 0.16 mL), add a solution of hydroxylamine hydrochloride (2 mmol; 0.138 g) in H_2O (2 mL). The mixture is then stirred at 45 °C for 24 h. Water (20 mL) is then added and extracted with diethyl ether (3 × 15 mL). The organic layer is dried (Na_2CO_3), filtered and evaporated under reduced pressure. Yield: 73%; 0.35 g; oil. ^{1}H NMR (100 MHz, DMSO-d_6): δ 4.5 (t, 1H, H-7, *J* 5 Hz), 3.3 (s, 6H, H-7a-b), 3.2 (d, 1H, H-4a, *J* 19 Hz), 3.1 (d, 1H, H-4b, *J* 19 Hz), 2.7 (d, 2H, H-6, *J* 5 Hz). ^{13}C NMR (50 MHz, DMSO-d_6): δ 148.1 (C-3), 124.0 (q, CF_3, *J* 283 Hz), 103.1 (q, ^2J 34 Hz, C-5), 102.0 (C-4), 53.7 (C-7a-b), 45.4 (C-4), 31.0 (C-6). GC-MS (EI, 70 eV): *m/z* (%) 212 (48), 192 (9), 75 (100), 47 (30). IR (KBr, *v* cm^{-1}): 3405 (OH), 1121 (OMe). Anal Calcd. for $C_8H_{12}F_3NO_4$ (243.0): C, 39.51; H, 4.97; N, 5.76. Found: C, 38.95; H, 5.01; N, 5.81%.

4-Trifluoromethyl-6-(2,2-dimethoxyethyl)-2-acetylaminopyrimidine (5). A stirred solution of 4,6,6-trimethoxy-1,1,1-trifluorohex-3-en-2-one (**1**) (2 mmol; 0.482 g) with 1-acetylguanidine (2 mmol; 0.202 g) in dry acetonitrile (15 mL) is heated at 85 °C for 24 h. After the reaction time, the solvent is removed under reduced pressure, and the product **5** is dried under vacuum, isolated as a solid, and purified by recrystallization from di-*iso*-propyl ether. Yellow solid; Yield: 76%; 0.44 g; mp 73-75 ºC; ^{1}H NMR (100 MHz, $CDCl_3$): δ 10.9 (br, 1H, NH), 7.6 (s, 1H, H-5), 4.9 (t, 1H, *J* 6.0 Hz, H-8), 3.2 (s, 6H, H-8a-b), 3.1 (d, 2H, *J* 5 Hz, H-7), 2.2 (s, 3H, Me). ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.5 (C-6), 171.0 (C=O), 157.5 (C-2), 156.0 (q, ^2J 35 Hz, C-4), 121.0 (q, *J* 290 Hz, CF_3), 111.3 (C-5), 102.6 (C-8), 53.0 (C-8a-b), 41.1 (C-7); 25.0 (Me). GC-MS (EI, 70 eV): *m/z* (%) 293 (M^+, 2), 278 (36), 262 (19), 220 (39), 75 (100), 47 (14). IR (KBr, *v* cm^{-1}): 3352 (NH), 1674 (C=O), 1119 (OMe). Anal Calcd. for $C_{11}H_{14}F_3N_3O_3$ (293.1): C, 45.05; H, 4.81; N, 14.33. Found: C, 45.28; H, 4.59; N, 14.47%.

2-(2,2-Dimethoxyethyl)perimidine (6). A stirred solution of 4,6,6-trimethoxy-1,1,1-trifluoro-hex-3-en-2-one (**1**) (2 mmol; 0.482 g) with 1,8-diaminonaphthalene (2 mmol; 0.316 g) in dry chloroform (15 mL) is heated at 60 °C for 24 h. After the reaction time, the solvent is removed under reduced pressure, and the product **6** is dried under vacuum, and isolated as oil. Yield: 75%; 0.38 g; oil. ^{1}H NMR (100 MHz, $CDCl_3$): δ 7.1-7.0 (m, 5H, ArH-perimidine and NH), 6.4 (d, 2H, *J* 6 Hz, ArH-perimidine), 4.65 (t, 1H, *J* 5 Hz, CH), 3.4 (s, 6H, $2CH_3$), 2.6 (d, 2H, *J* 5 Hz, CH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 153.1, 135.0, 128.3, 121.0, 119.4 (perimidine), 103.0 (CH), 54.0

(OMe), 39.0 (CH_2). GC-MS (EI, 70 eV): *m/z* (%) 256 (M^+, 19), 224 (100), 205 (17), 181 (24), 75 (9). IR (KBr, *v* cm^{-1}): 3423 (NH), 1117 (OMe). Anal Calcd. for $C_{15}H_{16}N_2O_2$ (256.1): C, 70.29; H, 6.29; N, 10.93. Found: C, 70.41; H, 6.04; N, 10.58%.

General procedure for the preparation of 2-[5-(Trifluoromethyl)-1*H*-pyrazol-3-yl]acetaldehydes (7d–f). A stirred solution of 3-(1,1-dimethoxyethan-2-yl)-5-trifluoromethyl-1*H*-pyrazole (**3d–f**) (2 mmol) in chloroform (8 mL) is added to a solution of trifluoroacetic acid with water (1:1 v/v) (4 mL). The solution is stirred at 60 °C for 4 h, then washed with water (2 × 15 mL) and dried (Na_2CO_3). The solvent is evaporated and dried under vacuum, resulting in oils as pure products (**7d-f**).

2-[1-Methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]acetaldehyde (7d). Yield: 68%; 0.26 g; oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.7 (t, 1H, *J* 1.0 Hz, H-7), 6.5 (s, 1H, H-4), 3.8 (d, 2H, *J* 1.0 Hz, H-6), 3.8 (s, 3H, Me). ^{13}C NMR (50 MHz, $CDCl_3$) δ 194.8 (CH=O, C-7), 141.3 (q, ^2J 38 Hz, C-5), 135.0 (C-3), 121.0 (q, *J* 268 Hz, CF_3), 105.3 (q, ^3J 2 Hz C-4), 40.1 (C-6), 37.1 (s, CH_3). GC-MS (EI, 70 eV): *m/z* (%) 192 (M^+, 20), 163 (100), 69 (7). HRMS (ESI): *m/z* calcd for $C_7H_7F_3N_2O$:193.0588 (M + H). Found: 193.0583.

2-[1-Phenyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]acetaldehyde (7e). Yield: 87%; 0.44 g; oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.8 (t, 1H, *J* 2.0 Hz, H-7), 7,5 (s, 5H, Ph), 6.7 (s, 1H, H-4), 3.8 (d, 2H, *J* 2.0, H-6). ^{13}C NMR (50 MHz, $CDCl_3$) δ 197.5 (CH=O, C-7), 144.1 (C-3), 138.6; 129.2; 129.0; 125.4 (Ph), 133.5 (q, ^2J 40 Hz, C-5), 119.4 (q, *J* 269 Hz, CF_3), 109.0 (q, ^3J 2 Hz C-4), 42.4 (C-6). GC-MS (EI, 70 eV): *m/z* (%) 254 (M^+, 17), 226 (100), 205 (15), 77 (23). Anal Calcd. for $C_{12}H_9F_3N_2O$ (254): C, 56.7; H, 3.57; N, 11.02. Found: C, 56.32; H, 3.62; N, 10.75%.

2-[1-*t*-Butyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]acetaldehyde (7f). Yield: 71%; 0.33 g; oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.7 (t, 1H, *J* 2.0 Hz, H-7), 6.6 (s, 1H, H-4), 3.7 (d, 2H, *J* 2.0 Hz, H-6), 1.6 (s, 9H, Bu^t). ^{13}C NMR (50 MHz, $CDCl_3$) δ 198.6 (CH=O, C-7), 140.4 (C-3), 132.1 (q, ^2J 39 Hz, C-5), 120.1 (q, *J* 269 Hz, CF_3), 110.4 (q, ^3J 4 Hz, C-4), 63.0 (C *tert*-Butyl), 42.6 (C-6), 29.8 (q, *J* 2 Hz, CH_3 *tert*-Butyl). GC-MS (EI, 70 eV): *m/z* (%) 219 (5), 179 (87), 159 (37), 150 (100), 130 (13), 101 (11), 75 (49), 57 (83). HRMS (ESI): *m/z* calcd for $C_{10}H_{13}F_3N_2O$: 235.1058 (M + H). Found: 235.1053.

General Procedure for the preparation of [5-(Trifluoromethyl)-1*H*-pyrazol-3-yl]pent-4-en-2-ols (9d–f). Aluminum flakes (1.2 mmol) and In(0) (5 mol %) are placed in a glass balloon of 10 mL coupled to a Schlenk tube and dried under vacuum (1 mbar) for 5 min with a heat gun. After returning to room temperature, the system is backfilled with argon and a solution of allyl bromide (2 equiv.) in THF (3 mL) is added. The reaction mixture is stirred at room temperature until all aluminium is consumed (30 min). At this point, a solution of **7d-f** (1 mmol) in THF (3 mL) is added and stirred for 1 more hour at room temperature. After a quenching with HCl solution (10%) (5 mL), the reaction mixture is extracted with ether (3 × 20 mL). The combined extracts are washed with brine (3 × 15 mL), dried (Na_2CO_3) and concentrated *in vacuo*, resulting in high pure oil products (**9d-f**).

1-[1-Methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]pent-4-en-2-ol (9d). Yield: 90%; 0.21 g; oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.4 (s, 1H, H-4), 5.8 (ddt, 17, 10, 7 Hz, 1H, H-9), 5.0 (d, 15 Hz, 1H, H-10a), 5.0 (d, 9 Hz, 1H, H-10b), 4.8 (d, 5 Hz, 1H, OH), 3.8 (s, 4H, CH_3 and H-7), 2.8 (dd, 15, 4 Hz, 1 H), 2.7 (dd, 15, 8 Hz, 1H), 2.1 – 2.2 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 142.7 (s, C-3), 138.7 (q, 37 Hz, C-5), 135.0 (s, C-9), 121.5 (q, 268 Hz, CF_3), 116.5 (s, C-10), 103.4 (q, 2 Hz, C-4), 68.8 (s, C-7), 41.1 (s, C-8), 36.8 (s, CH_3), 32.1 (s, C-6). GC-MS (EI, 70 eV): *m/z* (%) 216 (16), 193 (10), 163 (100), 145 (13), 71 (5). HRMS (ESI): *m/z* calcd for $C_{10}H_{13}F_3N_2O$: 235.1058 (M + H). Found: 235.1049.

1-[1-Phenyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]pent-4-en-2-ol (9e). Yield: 84%; 0.24 g; oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.4-7.5 (m, 5H, Ph), 6.9 (s, 1H, H-4), 5.8 (ddt, 17, 10, 7 Hz, 1H, H-9), 5.0 (d, 17 Hz, 1H, H-10a), 5.0 (d, 10 Hz, 1H, H-10b), 4.6 (d, 5 Hz, 1H, OH), 3.8 (m, 1H, and H-7), 2.7 (dd, 15, 5 Hz, 1 H), 2.6 (dd, 15, 8 Hz, 1 H), 2.2 - 2.1 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.7 (s, C-3), 138.5; 129.0; 125.2 (Ph), 135.3 (s, C-9), 131.1 (q, 38 Hz, C-5), 119.6 (q, 268 Hz, CF_3), 116.3 (s, C-10), 109.0 (q, 2 Hz, C-4), 69.01 (s, C-7), 41.1 (s, C-8), 34.8 (s, C-6). GC-MS (EI, 70 eV): *m/z* (%) 296 (M^+, 3), 279 (6), 255 (100), 226 (68), 205 (23), 187 (34), 179 (19), 77 (17). HRMS (ESI): *m/z* calcd for $C_{15}H_{15}F_3N_2O$: 297.1214 (M + H). Found: 297.1221.

1-[1-*t*-Butyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]pent-4-en-2-ol (9f). Yield: 87%; 0.24 g; oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.7 (s, 1H, H-4), 5.8 (ddt, 17, 10, 7 Hz, 1H, H-9), 5.0 (d, 17 Hz, 1H, H-10a), 5.0 (d, 10 Hz, 1H, H-10b), 4.6 (d, 5 Hz, 1H, OH), 3.7 (m, 1H, H-7), 2.6 (dd, 14, 5 Hz, 1 H), 2.5 (dd, 14, 7 Hz, 1 H), 2.1 – 2.2 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.9 (s, C-3), 135.5 (s, C-9), 129.6 (q, 38 Hz, C-5), 120.3 (q, 268 Hz, CF_3), 116.3 (s, C-10), 110.2 (q, 3 Hz, C-4), 69.1 (s, C-7), 61.8 (s, CH *tert*-butyl), 41.1 (s, C-8), 34.8 (s, C-6), 29.3 (q, 2 Hz, CH_3). GC-MS (EI, 70 eV): *m/z* (%) 235 (3), 220 (12), 179 (100), 150 (72), 130 (11), 57 (70). HRMS (ESI): *m/z* calcd for $C_{13}H_{19}F_3N_2O$: 299.1347 (M + Na). Found: 299.1342.

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References

1. Martins, M. A. P.; Pereira, C. M. P.; Sinhorin, A. P.; Rosa, A.; Zimmermann, N. E. K.; Bonacorso, H. G.; Zanatta, N. *Magn. Res. Chem.* **2002**, *40*, 182. http://dx.doi.org/10.1002/mrc.987

2. de Souza, F. R.; Fighera, M. R.; Lima, T. T. F.; de Bastiani, J.; Barcellos, I. B.; Almeida, C. E.; de Oliveira, M. R.; Bonacorso, H. G.; Flores, A. E.; de Mello, C. F. *Pharmacol. Biochem. Behav*. **2001**, *68*, 525. http://dx.doi.org/10.1016/S0091-3057(01)00453-1
3. Souza, F. R.; Souza, V. T.; Ratzlaff, V.; Borges, L. P.; Oliveira, M. R.; Bonacorso, H. G.; Zanatta, N.; Martins, M. A. P.; Mello, C. F. *Eur. J. Pharmacol.* **2002**, *451*, 141. http://dx.doi.org/10.1016/S0014-2999(02)02225-2
4. Park, B. K.; Kitteringham, N. R.; O'Neill, P. M. *Annu. Rev. Pharmacol. Toxicol*. **2001**, *41*, 443. http://dx.doi.org/10.1146/annurev.pharmtox.41.1.443
5. O'Hagan, D.; Rzepa, H. S. *Chem. Commun.* **1997**, 645. http://dx.doi.org/10.1039/a604140j
6. Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. http://dx.doi.org/10.1021/jm800219f
7. Martins, M. A. P., Machado, P.; Rosa, F. A.; Cunico, W.; Bonacorso, H. G.; Zanatta, N. *Mini-Rev. Org. Chem.* **2008**, *5*, 53. http://dx.doi.org/10.2174/157019308783498214
8. Zanatta, N.; Schneider, J. M. F. M.; Schneider, P. H.; Wouters, A. D.; Bonacorso, H. G.; Martins, M. A. P.; Wessjohann, L. A. *J. Org. Chem.* **2006**, *71*, 6996. http://dx.doi.org/10.1021/jo061058k
9. Zanatta, N.; Flores, D. C.; Madruga, C. C.; Flores, A. F. C.; Bonacorso, H. G.; Martins, M. A. P. *Tetrahedron Lett.* **2006**, *47*, 573. http://dx.doi.org/10.1016/j.tetlet.2005.11.035
10. Bonacorso, H. G.; Marques, L. L. M.; Zanatta, N.; Martins, M. A. P. *Synth. Commun.* **2002**, *32*, 3225. http://dx.doi.org/10.1081/SCC-120013748
11. Bonacorso, H. G.; Cechinel, C. A.; Deon, E. D.; Sehnem, R. C.; Luz, F. M.; Martins, M. A. P.; Zanatta, N. *Arkivoc* **2009**, (*ii*), 174. http://dx.doi.org/10.3998/ark.5550190.0010.218
12. Bonacorso, H. G.; Lourega, R. V.; Deon, E. D.; Zanatta, N.; Martins, M. A. P. *Tetrahedron Lett.* **2007**, *48*, 4835. http://dx.doi.org/10.1016/j.tetlet.2007.05.072
13. Milano, J.; Marchesan, S.; Rossato, M. F.; Sauzem, P. D.; Machado, P.; Beck, P.; Zanatta, N.; Martins, M. A. P.; Mello, C.; Rubin, M. A.; Ferreira, J.; Bonacorso, H. G. *Eur. J. Pharmacol.* **2008**, *581*, 86. http://dx.doi.org/10.1016/j.ejphar.2007.11.042
14. Zanatta, N.; Alves, S.; Coelho, H.; Borchhardt, D. M.; Machado, P.; Flores, K. M.; Silva, F. M.; Spader, T. B.; Santurio, J. M.; Bonacorso, H. G.; Martins, M. A. P.; *Bioorg. Med. Chem.* **2007**, *15*, 1947. http://dx.doi.org/10.1016/j.bmc.2007.01.003

15. Bonacorso, H. G.; Porte, L. M. F.; Cechinel, C. A.; Paim, G. R.; Deon, E. D.; Zanatta, N.; Martins, M. A. P. *Tetrahedron Lett.* **2009**, *50*, 1392. http://dx.doi.org/10.1016/j.tetlet.2009.01.005
16. Mandal, P. K.; Dutta, P.; Roy, S. C.; *Tetrahedron Lett.* **1997**, *38*, 7271. http://dx.doi.org/10.1016/S0040-4039(97)01689-4
17. Luche, J. L.; Damiano, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 7926. http://dx.doi.org/10.1021/ja00547a016
18. Hiyama, T.; Obayashi, M.; Nakamura, A. *Organometallics* **1982**, *1*, 1249. http://dx.doi.org/10.1021/om00069a031
19. Hiyama, T.; Sawahata, M.; Obayashi, M. *Chem. Lett.* **1983**, 1237. http://dx.doi.org/10.1246/cl.1983.1237
20. Mukaiyama, T.; Harada, T.; Shoda, S. *Chem. Lett.* **1980**, 1507. http://dx.doi.org/10.1246/cl.1980.1507
21. Tanaka, H.; Yamashita, S.; Hamatani, T.; Ikemoto, Y.; Torii, S. *Chem. Lett.* **1986**, 1611. http://dx.doi.org/10.1246/cl.1986.1611
22. Nicolaou, K. C.; Kim, D. W.; Baati, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3701. http://dx.doi.org/10.1002/1521-3773(20021004)41:19<3701::AID-ANIE3701>3.0.CO;2-4
23. Nicolaou, K. C.; Ninkovic, S.; Sarabia, F.; Vourloumis, D.; He, Y.; Valllberg, H.; Finlay, M. R. V.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 7974. http://dx.doi.org/10.1021/ja971110h
24. Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2. http://dx.doi.org/10.1016/0040-4020(80)85026-5
25. Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569. http://dx.doi.org/10.1016/S0040-4020(01)91380-8
26. Germay, O.; Kumar, N.; Thomas, E. J. *Tetrahedron Lett.* **2001**, *42*, 4969. http://dx.doi.org/10.1016/S0040-4039(01)00921-2
27. Romo, D.; Meyer, S. D.; Johnson, D. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 9345. http://dx.doi.org/10.1021/ja00073a083
28. Suzuki, Y.; Niwa, E.; Mizukami, M.; Miyashita, M.; Nagumo, S. *Tetrahedron Lett.* **2012**, *53*, 1337. http://dx.doi.org/10.1016/j.tetlet.2011.12.113
29. Kataoka, K.; Ode, Y.; Matsumoto, M.; Nokami, J. *Tetrahedron* **2006**, *62*, 2471. http://dx.doi.org/10.1016/j.tet.2005.12.054
30. Yadav, J. S.; Reddy, B. V.; Reddy, Y. J.; Reddy, N. S. *Tetrahedron Lett.* **2009**, *50*, 2877. http://dx.doi.org/10.1016/j.tetlet.2009.03.176
31. Padwa, A. *J. Org. Chem.* **1965**, *30*, 1274. http://dx.doi.org/10.1021/jo01015a525
32. Barchet, R.; Merz, K. W. *Tetrahedron Lett.* **1964**, *33*, 2239. http://dx.doi.org/10.1016/S0040-4039(00)71694-7

33. Bonacorso, H. G.; Bittencourt, S. R. T.; Wastowski, A. D.; Wentz, A. P.; Zanatta, N.; Martins, M. A. P. *J. Heterocycl. Chem.* **1999**, *36*, 45. http://dx.doi.org/10.1002/jhet.5570360108
34. Martins, M. A. P.; Sinhorin, A. P.; Rosa, A.; Flores, A. F. C.; Wastowski, A. D.; Flores, D.; Beck, P.; Freitag, R. A.; Brondani, S.; Cunico, W.; Bonacorso, H. G.; Zanatta, N. *Synthesis* **2002**, 2353. http://dx.doi.org/10.1055/s-2002-35224
35. Kwon, J. S.; Pae, A. N.; Choi, K. I.; Koh, H. Y.; Kim, Y.; Cho, K. S. *Tetrahedron Lett.* **2001**, *42*, 1957. http://dx.doi.org/10.1016/S0040-4039(01)00042-9
36. Kwon, J. S.; Lee, J. G.; Pae, A. N.; Choi, K. I.; Koh, H. Y.; Kim, Y.; Cho, Y. S. *Bull. Korean Chem. Soc.* **2000**, *21*, 457.
37. Ellison, R.; Lukenbach, E.; Chiu, C. *Tetrahedron Lett.* **1975**, *8*, 499. http://dx.doi.org/10.1016/S0040-4039(00)71904-6
38. Takai, K.; Ikawa, Y. *Org. Lett.* **2002**, *4*, 1727. http://dx.doi.org/10.1021/ol025784v
39. Zanatta, N.; Flores, D.; Madruga, C.; Flores, A. F. C.; Bonacorso, H. G.; Martins, M. A. P. *Tetrahedron Lett*. **2006**, *47*, 573. http://dx.doi.org/10.1016/j.tetlet.2005.11.035
40. Flores, D.; Fiss, G.; Wbatuba, L. S.; Martins, M. A. P.; Burrow, R. A.; Flores, A. F. C. *Synthesis* **2006**, 2349. http://dx.doi.org/10.1055/s-2006-942431
41. Bonacorso, H. G.; Correa, M. S.; Porte, L. M. F.; Pittaluga, E. P.; Zanatta, N.; Martins, M. A. P. *Tetrahedron Lett.* **2012**, *53*, 5488. http://dx.doi.org/10.1016/j.tetlet.2012.07.119
42. Becker, E. *High Resolution NMR Theory and Chemical Application*, 3th Edn., Academic Press, 2000; pp 139–181. http://dx.doi.org/10.1016/B978-012084662-7/50050-8

