Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 6759–6769

TETRAHEDRON

Synthesis of fused tetrazole- and imidazole derivatives via iodocyclization

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Received 28 March 2003; revised 25 April 2003; accepted 25 April 2003

This paper is dedicated to Professor K. C. Nicolaou on occasion of receiving the 2003 Tetrahedron Prize

Abstract—The possibility to prepare fused tetrazole- and imidazole derivatives by iodocyclization in moderate to excellent yields is demonstrated. In some examples the cyclizations were not following Baldwin's rules entirely, i.e. *exo*-selectivity. Nucleophilic substitution of the formed iodides gave different results depending on the hardness of the nucleophile. Thus, elimination of the iodide could be a problem but a substitution reaction with ethyl potassium xanthate and a radical reaction using acrylonitrile were tolerated. In addition, we showed that it is possible to selectively use three iodo substituents individually in one of the fused imidazole derivatives.

1. Introduction

The imidazole ring system is an important structural feature in biological systems, natural products and drugs.[1,2] On the other hand, the structurally similar tetrazole functional group is much less abundant but the use is increasing due to the excellent properties as a metabolically stable isosteric replacement for the carboxylic acid moiety[3] and as a *cis*-peptide bond mimetic.[4–6] Tetrazoles have also been used as precursors to other heterocycles[7] and in high energy compounds.[8] A few examples are shown in Figure 1, some of which are used as drugs. Losartan (**1**) is a Angiotensin II antagonist and commonly used for treatment of hypertension. Imidazoles can be found in important fused heterocyclic compounds such as the benzodiazepine antagonist Flumazenil (**3**). Tetrazole **4** has also been found to posses binding affinity to benzodiazepine receptors.[9] Pentylentetrazole (PTZ **2**) has the opposite effect compared to **3** and **4** and is extensively used in models for anxiety, mediated by its unspecific interaction with a number of receptors in the CNS.[10,11] Mannose mimetics **5** and **6** have been reported to be inhibitors of α-mannosidase.[12,13]

Our interest in this area began during our development of a new method for allylation of aromatic systems. We found that tetrazole derivative **7** did not give the expected allylated product **8** but continued to react with the in situ generated Br_2 via a reaction resembling a bromolactonization, thus, forming the fused tetrazole derivative **9**.[14] To our surprise, the halocyclization of olefin substituted tetrazoles had not been reported in the literature. We also noted that available methods for synthesis of this class of compounds had limitations. A common procedure is the azide trapping of a nitrilium cation in the Schmidt rearrangement of ketones, but this method gives regioisomeric mixtures of fused tetrazoles.[9,15,16] Intramolecular approaches via an internal

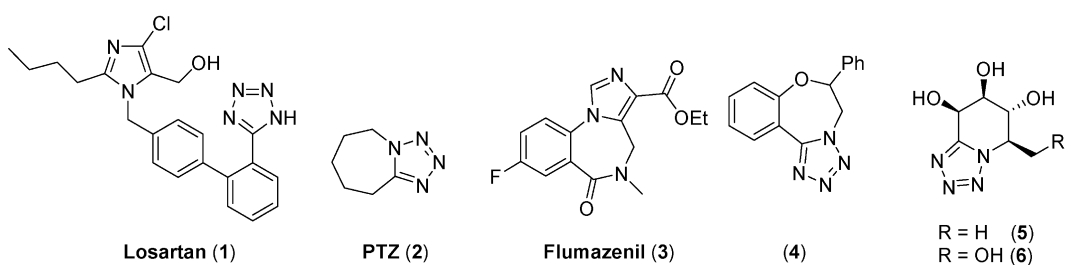

Figure 1. Examples of tetrazole- and imidazole derivatives of pharmacological interest.

Keywords: tetrazoles; nucleophilic substitution; halocyclization.
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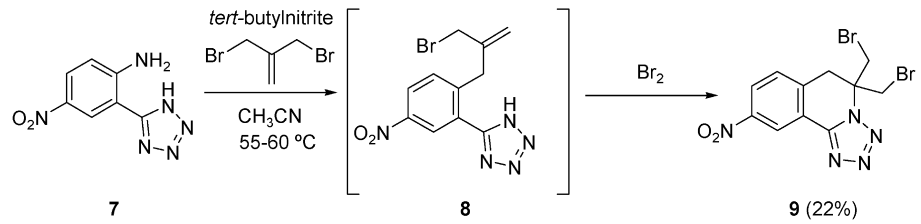
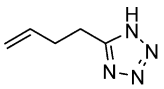
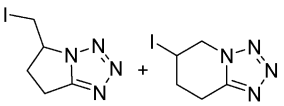
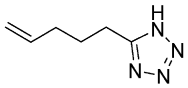
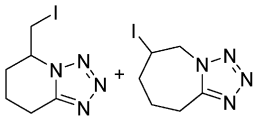
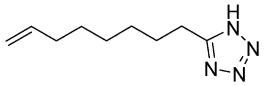
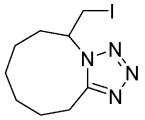
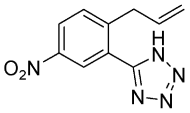
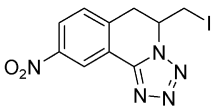
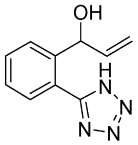
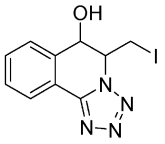
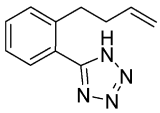
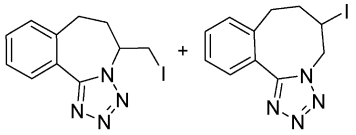
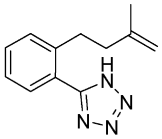
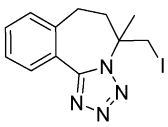
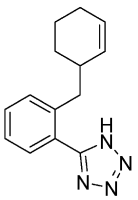
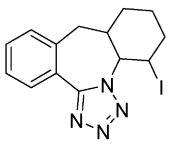
doi:10.1016/S0040-4020(03)00818-4



Scheme 1. Allylation-bromocyclization.

Table 1. Synthesis and iodocyclization of various tetrazole derivatives

Reactant	Yield (%)[a]	Product (%)	Yield (%)[b]
	89 (**10a**)		72 (**11a** and **12**)[c]
	80 (**10b**)[d]		85 (**11b** and **13**)[e]
	96 (**10c**)		41 (**11c**)
	28 (**10d**)		98 (**11d**)
	69 (**10e**)		76 (**11e**)[f]
	90 (**10f**)		98 (**11f** and **14**)[g]
	83 (**10g**)		88 (**11g**)
	63 (**10h**)		93 (**11h**)[h]

[a] Isolated yield of tetrazole derivatives **10a**–**h** at 3 mmol scale if otherwise not stated.
[b] Isolated yields of tetrazole derivatives **11a**–**h** at 0.5 or 0.25 mmol (**11d**) scale. The regioisomeric and diastereoisomeric ratios were determined by ^{1}H NMR spectroscopy.
[c] 1:1 mixture of **11a** and **12**.
[d] The reaction was performed at 10 mmol scale.
[e] The reaction of **10a** gave 85% of **11b** containing 7% of **13**. Recrystallization gave 55% yield of pure **11b**.
[f] Isolated as a mixture of distereoisomers (1.7:1).
[g] The reaction of **10f** gave 98% of **11f** containing 15% of **14**. Column chromatography gave 75% yield of pure **11f**.
[h] Isolated as a mixture of only two distereoisomers according to NOESY spectroscopy (selective *trans* attack). The distereoisomer in which the two bridgehead protons are *syn* is formed to a larger extent (2:1).

[2+3] cycloaddition have also been reported in the synthesis of fused tetrazoles (exemplified by **5** and **6**, Table 1).[12,13,17,18] In a recent example, Demko and Sharpless presented a procedure involving aminonitriles, cyanates and thiocyanates, although the method seems to be limited to the formation of tetrazoles fused to 5- and 6-membered ring systems.[18] Other methods involve azide ion addition to imidoyl chlorides.[19] A vast number of both intra- and intermolecular methods have been developed for the synthesis of fused imidazole derivatives (Scheme 1).[2,20–23]

In this paper we present the synthesis of fused tetrazole derivatives via iodocyclization and some applications of the formed products. An initial study towards the synthesis of fused imidazole derivatives is also described.

2. Results and discussion

Two different methods were used in the synthesis of the tetrazole derivatives **10a–h** containing suitable olefinic substituents (Scheme 2 and Table 1). In the first one, applied in the synthesis of compound **10a–d**, the olefin was already in place and the tetrazole group was synthesized from the corresponding unsaturated nitrile. We employed a recently published method utilizing $Et_3N/H_2SO_4/NaN_3$ in toluene which gave **10a–c** in good to excellent yields.[24] However, this method failed in the synthesis of **10d** probably due to steric hindrance and sensitivity of the allyl functionality. Instead, we applied a method in which catalytic amounts of dibutyltin oxide together with trimethylsilyl azide were used as reagents, although the yield was poor (28%).[25]

In the second method for synthesis of olefinic tetrazoles we started with the tetrazole and then attached the olefinic part. This was made by directed ortho metalation of aryltetrazoles using *sec*-BuLi and TMEDA at −35°C followed by the addition of an appropriate olefinic reagent.[26] As seen in Table 1 (**10e–h**), the yields were often high and the crude products were sufficiently pure to be used directly in the iodocyclization step.

Several literature methods for iodocyclization of unsaturated carboxylic acids were tested for the formation of the fused tetrazole derivatives.[27–29] The best result was obtained using $NaHCO_3$, I_2 in dry CH_3CN at 0°C under argone in the dark.[30] As seen in Table 1, good to excellent yields of the products were isolated, which were often pure after work-up. However, it should be mentioned that some of the compounds deteriorated if not carefully handled and they should be stored in the refrigerator. Initially, this method was used in the synthesis of compound **11a–h** but we noticed that some of the reactions gave results, which deviated from the expected halocyclizations. The formation of 4- to 7-membered-ring lactones via halocyclization of ω-unsaturated carboxylic acids has been reported to proceed exclusively via *exo*-cyclization in accordance with Baldwin's rules.[27,28] We could confirm this by using pent-4-enoic acid, which gave only the *exo*-cyclized product. However, some of the tested unsaturated tetrazoles gave considerable amounts of the products resulting from an *endo*-process. For example, when **10a** was subjected to the standard reaction conditions, the expected **11a** was formed in a 1:1 mixture with **12**. It has been reported that the conditions used here would give a kinetically controlled product.[31] By excluding $NaHCO_3$, which has been shown to give thermodynamic control of the reaction,[31] the product from an *endo*-process was favored (3:2). Performing the reaction using the standard procedure at −30°C did not change the *exo*/*endo* selectivity. The cyclization of **10f** also gave the *endo* cyclization product (15%) despite that formation of a 8-membered ring system is disfavored.

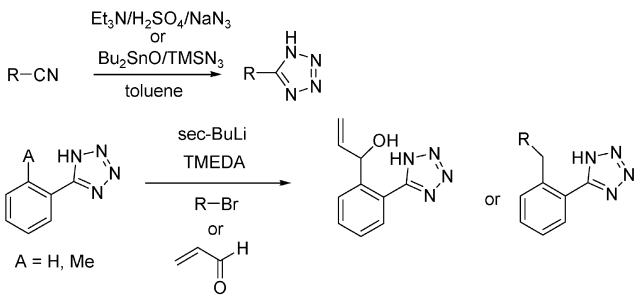
Not surprisingly, **10c** did not give the corresponding product **11c** using the standard procedure. Instead, we used syringe pump technique, which gave a moderate yield of **11c**.[32] Interestingly, only <5% of the *endo* cyclized product could be detected in the crude product while a corresponding iodolactonization typically gives a 1:1 mixture of *endo*/*exo* cyclization.[33]

For reactions which showed some *endo*-selectivity (e.g. **10a**,**10b**,**10e** and **10f**) different methods were tested in order to elucidate if other procedures could give better *exo*-selectivity. However, *exo*-selectivity was improved only for **10e**, which gave 10% *endo*-selectivity using the standard procedure but gave 100% *exo*-selectivity using the biphasic conditions $NaHCO_3/I_2$ in $CHCl_3/H_2O$.

Various degrees of diasteroselectivity have been reported in the iodolactonization reactions.[30,31] Both compound **10e** and **10h** gave poor diastereoselectivity using the standard procedure according to analysis of the crude products by ^1H NMR spectroscopy (1.7:1 and 2:1, respectively).

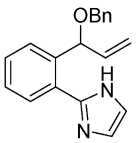
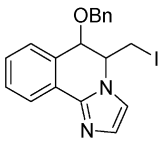
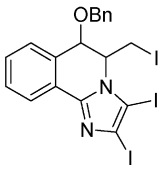
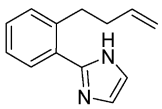
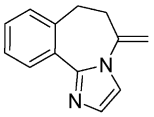
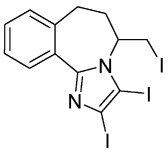
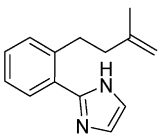
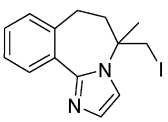
After the synthesis of the fused tetrazoles we turned our attention towards the imidazole derivatives. It was not possible to use the method for the synthesis of **10a–h** to generate imidazole derivatives **15a–c** (Table 2). Instead, **15a–c** were synthesized with an efficient one-pot procedure developed by Demuth Jr. et al.[34] in which 2-phenylimidazole or 2-*o*-tolyl-1*H*-imidazole were treated sequentially with *n*-BuLi/SEMCl(*N*-protection)/*n*-BuLi/TMSCl(C-5 protection)/*n*-BuLi/RBr or RCHO (Scheme 3 and Table 2). The protective groups were then removed by TBAF to give **15a–c** in moderate to good yields considering the number of transformations involved in the sequence. In case of compound **15a**, the hydroxy group was benzylated using NaH/BnBr before the final deprotection.

The large pK_a difference between tetrazole- and imidazole derivatives motivated the change of base to K_2CO_3. However, applying the standard conditions for iodocyclization on **15a** using the stronger base gave, in addition to **16a**, also the tri-iodinated compound **16b** as a 1:1 mixture. Analogously, **15b** and **15c** gave mixtures of mono and tri-iodinated products. The commercial bis(collidine)iodine hexafluorophosphate was also tested in the reaction and we found that it gave cyclization without iodination of the imidazole ring (Table 2). Thus, imidazole derivatives **16a**,**16c** and **16e** were synthesized in good yields. However, the extended reaction times, the large excess of reagent required and the questionable appearance of the reagent (brown powder) prompted reinvestigation with freshly synthesized pure reagent. Consequently, we prepared bis(collidine)iodine hexafluorophosphate (white crystals)



Scheme 2. Synthesis of olefinic tetrazole derivatives.

Table 2. Synthesis and iodocyclization of various imidazole derivatives

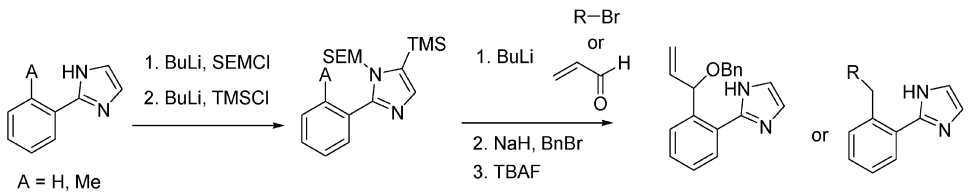
Reactant	Yield (%)[a]	Product (%)	Yield (%)
	44 (**15a**)		63 (**16a**)[b,c]
15a			65 (**16b**)[d,e]
	32 (**15b**)		61 (**16c**)[b,f]
15b			71 (**16d**)[d]
	28 (**15c**)		85 (**16e**)[b]

[a] Isolated yields of imidazole derivatives **15a–c**. The reactions were performed at 4 mmol (**15a**) or 1.5 mmol scale. The regioisomeric and diastereoisomeric ratios were determined by ^{1}H NMR spectroscopy.
[b] The reaction was performed using commercial bis(collidine)iodine hexafluorophosphate.
[c] Isolated as a mixture of diastereoisomers (1.4:1).
[d] The reaction was performed using NIS in DMF.
[e] Isolated as a mixture of diastereoisomers (1:1).
[f] The yield of 5-iodomethyl-6,7-dihydro-imidazo[2,3-*a*][2]benzazepine was determined to be 87% by ^{1}H NMR spectroscopy using anisole as internal standard. **16c** was isolated due to elimination of HI during purification.

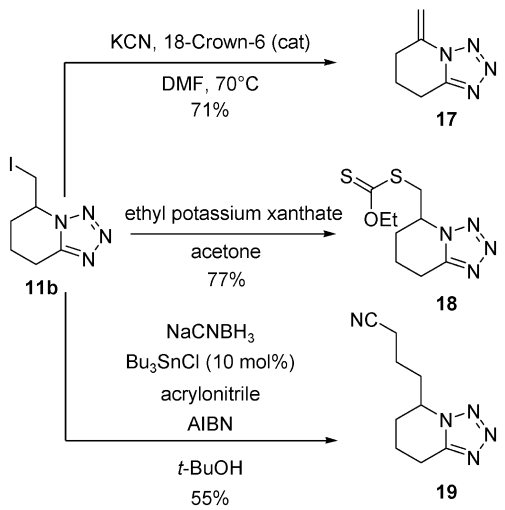
and used it in the reaction with **15a**. To our surprise we now observed iodination of the imidazole ring and the reaction was completed in less than 3 h. The *endo*/*exo* selectivity was poor, however, resulting in a mixture of mono and tri-iodinated products as 7 and 8 membered ring systems.[35] *exo*-Cyclization occurred as the major reaction when NIS was used as cyclization agent as demonstrated for **15a** and **15b** which gave **16b** and **16d**, respectively. In the case of **15b** less than 5% of the *endo* cyclization product could be detected.

The possibility to introduce an amine functionality is of great importance due to its frequent appearance in drug molecules. Iodides can be easily transformed into nitriles or azides, which are common starting materials for the synthesis of amines. However, applying standard substitution conditions for the formation of nitriles using KCN on **11b** gave the eliminated product **17** as seen in Scheme 4. Also the use of NaN_3 resulted predominately in elimination (4:1 elimination:substitution). On the other hand, the softer nucleophile potassium ethyl xanthate gave **18** as the sole product. It is of course possible to use the elimination product in subsequent reactions but it is clearly a limitation to the synthetic applications of the iodides. However, the convenient access to xanthate derivatives broadens the scope of the fused tetrazoles due to additional chemistry possible with this functional group.[36] Zard and coworkers have developed interesting radical chemistry based on xanthates for the synthesis of tetrazole derivatives.[37] However, it would also be advantageous if the iodides could be used directly in radical reactions, thus, avoiding an additional substitution. We were delighted to see that the radical addition using the methodology developed by Stork et al.[38] gave nitrile **19** in 55% yield (Scheme 4). This reaction shows that the elimination problem can be circumvented. Thus, free radical chemistry appears to be more promising as a method of further derivation.

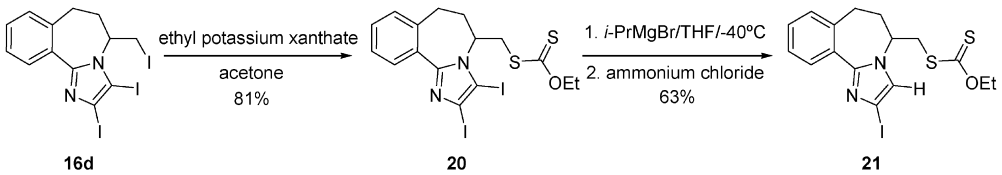
We were also interested in chemoselective manipulation of the three iodides in **16b** and **16d**. As expected it was possible to transform **16d** into ethyl xantate **20** in good yield without affecting the iodides in the imidazole ring (Scheme 5). However, a more delicate problem was to achieve selectivity between the two remaining iodides. It has been demonstrated that protective groups at N-1 capable of coordinating metal reagents can direct metalation to the 5-position in 4,5-dihaloimidazole derivatives.[39] Also with a non-coordinative substituent, such as a vinyl group, the metal–halogen exchange preferably takes place in the 5-position.[40] Yet, to our knowledge ethyl xanthates have not been used as directing groups in metal–halogen exchange reactions. We were also concerned that the metal reagent would react with the xanthate group since it is known that they are sensitive to nucleophiles. However, adding



Scheme 3. Synthesis of olefinic imidazole derivatives.



Scheme 4. Substitutions using hard and soft nucleophiles and radical reaction of **11b**.



Scheme 5. Synthesis and regioselective deiodination of **20**.

i-PrMgBr to **20** in THF at −40°C gave selectively metal–halogen exchange of the iodide in position 3. Subsequent addition of saturated aqueous NH_4Cl to the reaction mixture gave **21**, which was confirmed by NOESY spectroscopy.

In conclusion, we have demonstrated the possibility to prepare fused tetrazole- and imidazole derivatives by iodocyclization in moderate to excellent yields. The cyclization of some of the substrates did not follow Baldwin's cyclization rules entirely i.e. *exo*-selectivity. However, we were in some of these cases able to improve the *exo*-selectivity by using different reaction conditions. Nucleophilic substitution of the formed iodides gave different results depending on the hardness of the nucleophile. Thus, elimination of the iodide could be a problem but substitution was possible with the soft nucleophile ethyl potassium xanthate. Additionally, radical addition to acrylonitrile was performed. Finally, we have demonstrated that it is possible to selectively use two of the three iodo substituents in **16d** for specific reactions.

3. Experimental

3.1. General

HPLC analyses were performed on a HiChrom column (Kromasil 100-5C18, 150×4.6 mm); eluent: CH_3CN (HPLC grade)/H_2O; flow rate 1 mL/min. NMR spectra were recorded on a 400 MHz instrument using $CDCl_3$ or acetone-d_6 as internal standard. Elemental analyses were made by A. Kolbe, Mikroanalytisches Laboratorium, Germany. Chromatographic separations were performed on Matrex Amicon normal phase silica gel 60 (0.035–0.070 mm). Thin-layer chromatography was performed on Merck precoated TLC plates with Silica gel 60 F-254, 0.25 mm. After elution, the TLC plates were visualized with UV light and sprayed with a solution of $KMnO_4$ (10 g), K_2CO_3 (50 g), NaOH (20 mL, 5%) and H_2O (900 mL) followed by heating. Chemicals were reagent grade. All reagents were used as received if not otherwise noted. The allylic bromides were distilled prior to use. Pent-4-enenitrile,[41] non-8-enenitrile,[42] 2-allyl-5-nitrobenzonitrile[43,44] and 2-*o*-tolyl-1*H*-imidazole[45] were synthesized according to literature procedures. Bis(collidine)iodine(I) hexafluorophosphate was either purchased from Aldrich (lot number 10921KI, referred to as commercial quality) and used as received or synthesized according to a literature procedure.[46] *i*-PrMgBr was freshly prepared from 2-bromopropane and magnesium.

3.1.1. 5-But-3-enyl-1*H*-tetrazole (10a). A mixture of concentrated H_2SO_4 (191 mg, 1.95 mmol), triethylamine (0.54 mL, 3.9 mmol), sodium azide (253 mg, 3.9 mmol) and pent-4-enenitrile (244 mg, 3 mmol) in toluene (10 mL) was stirred for 18 h at 100°C. The reaction mixture was cooled to room temperature and then extracted three times with H_2O. The combined aqueous phases were acidified with concentrated HCl and extracted three times with EtOAc. The combined organic phases were dried over Na_2SO_4 and the solvent was removed at reduced pressure to yield 331 mg (89%) of **10a** as pale yellow oil which crystallized in the refrigerator: mp 41–42°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.75–12.25 (br s, 1H), 5.84 (ddt, 1H, J=17.0, 10.3, 6.6 Hz), 5.11–5.05 (dd, 1H, J=17.1, 1.5 Hz), 5.05 (d, 1H, J=10.3 Hz), 3.25 (t, 2H, J=7.5 Hz), 2.65 (br q, 2H, J=7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.4, 135.5, 117.3, 31.5, 23.1. Anal. HRMS (EI^+) calcd for $C_5H_8N_4$ (M): 124.0749. Found: 124.0744.

3.1.2. 5-Pent-4-enyl-1*H*-tetrazole (10b). The reaction was performed according to the synthesis of **10a** using hex-5-enenitrile (10 mmol scale) as starting material which gave 1.10 g (80%) of **10b** as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.50–12.00 (br s, 1H), 5.76 (ddt, 1H, J=17.1, 10.3, 6.6 Hz), 5.05–4.96 (m, 2H), 3.15 (t, 2H, J=7.7 Hz), 2.18 (br q, 2H, J=7.1 Hz), 2.01 (quint, 2H, J=7.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.9, 136.9, 116.3, 33.0, 26.8, 22.9. Anal. HRMS (EI^+) calcd for $C_6H_{10}N_4$ (M): 138.0905. Found: 138.0899.

3.1.3. 5-Oct-7-enyl-1*H*-tetrazole (10c). The reaction was performed according to the synthesis of **10a** using non-8-enenitrile (3 mmol scale) as starting material which gave 520 mg (96%) of **10c** as pale yellow oil, which crystallized in the refrigerator: mp 46–47°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.20–10.90 (br s, 1H), 5.76 (ddt, 1H, J=17.0, 10.3, 6.6 Hz), 4.95 (ddd, 1H, J=17.1, 3.6,

1.6 Hz), 4.90 (br d, 1H, *J*=10.3 Hz), 3.12 (t, 2H, *J*=7.7 Hz), 2.01 (br q, 2H, *J*=6.8 Hz), 1.89 (quint, 2H, *J*=7.5 Hz), 1.45–1.29 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.0, 138.9, 114.6, 33.8, 29.0, 28.7, 28.7, 27.8, 23.6. Anal. HRMS (CI^+) calcd For $C_9H_{17}N_4$ (M+H): 181.1453. Found: 181.1451.

3.1.4. 5-(2-Allyl-5-nitrophenyl)tetrazole (10d). Dibutyltin oxide (109 mg, 0.45 mmol) was added to a mixture of 2-allyl-5-nitrobenzonitrile (568 mg, 3.0 mmol), $TMSN_3$ (1.95 mL, 14.5 mmol) and dry toluene (5 mL). The mixture was heated at 110°C for 23 h before cooling to room temperature followed by the removal of the solvent at reduced pressure. The residue was dissolved in methanol and the solvent was removed at reduced pressure in order to cleave off the TMS-group. Saturated aqueous $NaHCO_3$ and EtOAc were added to the residue and the organic phase was extracted twice with saturated aqueous $NaHCO_3$ followed by acidification of the combined water phases with aqueous concentrated HCl until pH<3. The aqueous phase was extracted three times with EtOAc and the combined organic phases were dried (Na_2SO_4). The solvent was then removed at reduced pressure, which gave 195 mg (28%) of **10d** as pale yellow crystals: mp 157–158°C; ^{1}H NMR (MeOH-d_4, 400 MHz) δ 8.61 (d, 1H, *J*=2.3 Hz), 8.34 (dd, 1H, *J*=8.5, 2.4 Hz), 7.69 (d, 1H, *J*=8.5 Hz), 5.90 (ddt, 1H, *J*=17.0, 10.3, 6.6 Hz), 5.00 (dd, 1H, *J*=10.1, 1.4 Hz), 4.93 (dd, 1H, *J*=17.1, 1.6 Hz), 3.84 (d, 2H, *J*=6.5 Hz), ^{13}C NMR (MeOH-d_4, 100 MHz) δ 157.7, 148.5, 148.0, 136.6, 133.4, 127.3, 126.3, 125.7, 117.5, 38.5. IR (KBr, cm^{-1}) ν 1523 (s), 1347 (s). HRMS (CI^+): calcd for $C_{10}H_{10}N_5O_2$: [(M+H)]: 232.0836. Found: 232.0821.

3.1.5. 5-(2-(1-Hydroxy-prop-2-enyl)phenyl)tetrazole (10e). *sec*-BuLi (1.3 M in cyclohexane, 6.9 mL, 9.0 mmol) was added dropwise to a stirred solution of 5-phenyltetrazole (438 mg, 3 mmol) and TMEDA (0.45 mL, 3 mmol) in THF (20 mL) at −35°C under argon atmosphere. The yellow reaction mixture was stirred for 50 min maintaining the temperature followed by addition of acrolein (0.80 mL, 12.0 mmol) in one portion. The temperature of the decolorized reaction mixture was gradually warmed to room temperature. The pH of the reaction mixture was adjusted to pH=2 with dilute aqueous HCl (0.05 M) and the solution was then concentrated at reduced pressure. The residue was extracted twice with EtOAc and the combined organic phases were washed with three portions of dilute aqueous HCl (0.05 M) and then dried (Na_2SO_4). The solvent was removed at reduced pressure followed by column chromatography (heptane/EtOAc/MeOH/AcOH 5:4:1:0.05) of the crude product, which gave 420 mg (69%) of **10e** as a pale yellow oil. ^{1}H NMR (acetone-d_6, 400 MHz) δ 7.81 (dd, 1H, *J*=7.7, 1.3 Hz), 7.71 (dd, 1H, *J*=7.7, 1.3 Hz), 7.58 (dt, 1H, *J*=7.5, 1.4 Hz), 7.47 (dt, 1H, *J*=7.6, 1.4 Hz), 6.01 (ddd, 1H, *J*=17.2, 10.5, 4.8 Hz), 5.74 (dt, 1H, *J*=4.7, 1.8 Hz), 5.19 (dt, 1H, *J*=17.2, 1.8 Hz), 5.01 (dt, 1H, *J*=10.5, 1.8 Hz); ^{13}C NMR (acetone-d_6, 100 MHz) δ 156.2, 143.7, 140.6, 131.9, 130.6, 129.2, 128.6, 123.7, 114.4, 72.1. Anal. HRMS (EI^+) calcd for $C_9H_8ClNO_2$ (M): 202.0855. Found: 202.0856.

3.1.6. 5-(2-(But-3-enyl)phenyl)tetrazole (10f). The reaction was performed according to the synthesis of **10e** starting from 5-(2-methylphenyl)tetrazole (3.0 mmol scale) and using allyl bromide as electrophile.[47] The crude product was recrystallized from heptane/EtOAc to give 540 mg (90%) of **10f** as white crystals: mp 112–113°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.75–11.25 (br s, 1H), 7.61 (dd, 1H, *J*=7.7, 1.0 Hz), 7.45 (dt, 1H, *J*=7.6, 1.3 Hz), 7.36 (br d, 1H, *J*=7.7 Hz), 7.27 (dt, 1H, *J*=7.6, 1.2 Hz), 5.71 (ddt, 1H, *J*=17.1, 10.3, 6.6 Hz), 4.97–4.88 (m, 2H), 2.93 (br t, 2H, *J*=7.7 Hz), 2.28 (br q, 2H, *J*=7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.3, 141.8, 137.6, 131.5, 130.9, 130.0, 126.8, 122.9, 115.8, 35.2, 33.2. Anal. HRMS (EI^+) calcd for $C_9H_8ClNO_2$ (M): 200.1062. Found: 200.1061.

3.1.7. 5-(2-(3-Methyl-but-3-enyl)phenyl)tetrazole (10g). The reaction was performed according to the synthesis of **10e** starting from 5-(2-methylphenyl)tetrazole (3.0 mmol scale) and using methallyl bromide as electrophile. The crude product was recrystallized from heptane/EtOAc to give 535 mg (83%) of **10g** as white crystals: mp 94–95°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61 (m, 1H), 7.50–7.35 (m, 2H), 7.31–7.22 (m, 1H), 4.68 (m, 1H), 4.59 (m, 1H), 3.00 (m, 2H), 2.21 (m, 2H), 1.65 (br quint, 3H, *J*=4.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.2, 144.9, 142.0, 131.3, 130.6, 129.7, 126.5, 122.6, 110.8, 39.1, 32.0, 22.3. Anal. HRMS (EI^+) calcd for $C_9H_8ClNO_2$ (M): 214.1218. Found: 214.1212.

3.1.8. 5-(2-Cyclohex-2-enylmethylphenyl)tetrazole (10h). The reaction was performed according to the synthesis of **10e** starting from 5-(2-methylphenyl)tetrazole (3.0 mmol scale) and using 3-bromocyclohexene as electrophile. The crude product (oil) was crystallized from heptane/EtOAc to give 450 mg (63%) of **10h** as white crystals: mp 97–98°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66 (d, 1H, *J*=7.6 Hz), 7.48 (t, 1H, *J*=7.5 Hz), 7.40–7.25 (m, 2H), 5.75 (m, 1H), 5.48 (br d, 1H, *J*=9.9 Hz), 2.87 (dd, 1H, *J*=13.5, 7.6 Hz), 2.80 (dd, 1H, *J*=13.5, 8.3 Hz), 2.35 (m, 1H), 1.98 (m, 2H), 1.75–1.58 (m, 2H), 1.48 (m, 1H), 1.29 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.2, 140.7, 131.6, 131.2, 130.8, 130.1, 128.7, 126.8, 123.4, 39.9, 36.8, 28.9, 25.4, 20.9. Anal. HRMS (EI^+) calcd for $C_9H_8ClNO_2$ (M): 240.1375. Found: 240.1371.

3.1.9. 5-Iodomethyl-6,7-dihydro-tetrazolo[1,5-*a*]pyrrole (11a) and 6-iodo-5,6,7,8-tetrahydro-tetrazolo[1,5-*a*]pyridine (12). Iodine (382 mg, 1.50 mmol) was added in one portion to stirred solution of **10a** (61 mg, 0.5 mmol) and $NaHCO_3$ (420 mg, 5.0 mmol) in dry CH_3CN (2 mL) under argon atmosphere at 0°C. The red-brown reaction mixture was then stirred for 3 h at 0°C. Saturated aqueous Na_2SO_3 (3 mL) was added to the reaction mixture and H_2O and EtOAc were added to the colorless reaction mixture. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with saturated aqueous $NaHCO_3$ followed by brine. Drying (Na_2SO_4) and removal of the solvent at reduced pressure gave 90 mg (72%) of a mixture (1:1) of **11a** and **12** as white crystals. ^{1}H NMR (acetone-d_6, 400 MHz, **11a**) δ 4.86 (m, 1H), 3.86 (dd, 1H, *J*=11.0, 5.0 Hz), 3.82 (dd, 1H, *J*=11.0, 3.9 Hz), 3.30–2.96 (m, 3H), 2.72 (m, 1H). ^{1}H NMR (acetone-d_6, 400 MHz, **12**) δ 5.05 (m, 1H), 4.96 (dd, 1H, *J*=14.0, 4.3 Hz), 4.78 (dd, 1H, *J*=14.0, 5.0 Hz), 3.30–2.96 (m, 2H), 2.42 (m, 2H); ^{13}C NMR (acetone-d_6, 100 MHz, **11a**+**12**) δ 163.7, 151.2, 57.5, 55.5, 36.5, 31.6, 21.3, 19.4,

18.8, 8.9. Anal. calcd for $C_5H_7IN_4$: C, 24.02; H, 2.82; N, 22.41. Found: C, 24.15; H, 2.86; N, 22.55.

3.1.10. 5-Iodomethyl-5,6,7,8-tetrahydro-tetrazolo[1,5-*a*]pyridine (11b). The reaction was performed according to the synthesis of **11a** starting with **10b** (0.5 mmol scale) which gave 112 mg (85%) of **11b** as a colorless oil containing 7% **13**. Two crystallizations (heptane/EtOAc 3:1) gave 73 mg (55%) of pure **11b** as white crystals: mp 88–89°C. ^{1}H NMR (acetone-d_6, 400 MHz) δ 4.50 (m, 1H), 3.96 (dd, 1H, J=10.8, 5.9 Hz), 3.91 (dd, 1H, J=10.8, 3.2 Hz), 3.13–3.05 (m, 1H), 2.95–2.85 (m, 1H), 2.45–2.35 (m, 1H), 2.25–2.15 (m, 1H), 2.05–1.90 (m, 2H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 153.4, 56.6, 29.6, 21.1, 18.9, 9.0. Anal. calcd for $C_6H_9IN_4$: C, 27.29; H, 3.44; N, 21.22. Found: C, 27.30; H, 3.41; N, 21.29.

3.1.11. 5-Iodomethyl-6,7,8,9,10,11-hexahydro-5*H*-tetrazolo[1,5-*a*]azonine (11c). Compound **10c** (90 mg, 0.5 mmol) in dry CH_2Cl_2 (1 mL) was added, using a syringe pump, during 48 h to bis(collidine)iodo hexafluorophosphate (400 mg, 0.78 mmol, synthesized according to literature) in dry CH_2Cl_2 (10 mL). The precipitate was filtered off and the remaining solution was concentrated at reduced pressure. Column chromatography (heptane/EtOAc 2:1) of the residue gave 60 mg (41%) of **11c** as white crystals: mp 125–126°C ^{1}H NMR (acetone-d_6, 400 MHz) δ 5.04 (m, 1H), 3.85 (br d, 2H, J=7.2 Hz), 3.38 (ddd, 1H, J=15.1, 8.3, 2.7 Hz), 2.79 (ddd, 1H, J=15.0, 10.4, 2.8 Hz), 2.27–2.14 (m, 2H), 2.00–1.89 (m, 1H), 1.90–1.74 (m, 1H), 1.74–1.60 (m, 1H), 1.55–1.43 (m, 3H), 1.25–1.13 (m, 1H), 0.55–0.40 (m, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 157.8, 61.4, 36.3, 27.6, 26.1, 24.4, 22.5, 6.5. Anal. calcd for $C_9H_{15}IN_4$: C, 35.31; H, 4.94; N, 18.30. Found: C, 35.35; H, 4.86; N, 18.38.

3.1.12. 9-Nitro-5-iodomethyl-5,6-dihydro-tetrazolo[5,1-*a*]isoquinoline (11d). The reaction was performed according to the synthesis of **11a** starting with **10d** (0.25 mmol scale). The crude product was dissolved in acetone and subsequent addition of heptane precipitated 87 mg (98%) of **11d** as white pale yellow crystals: mp 157–158°C. ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.78 (d, 1H, J=2.3 Hz), 8.43 (dd, 1H, J=8.5, 2.4 Hz), 7.90 (d, 1H, J=8.5 Hz), 5.21 (m, 1H), 3.96 (m, 2H), 3.90 (dd, 1H, J=17.2, 6.4 Hz), 3.67 (dd, 1H, J=17.2, 7.4 Hz); ^{13}C NMR (acetone-d_6, 100 MHz) δ 150.5, 148.7, 141.9, 131.7, 127.1, 123.3, 120.5, 55.7, 35.2, 6.1. Anal. calcd for $C_{10}H_8IN_5O$: C, 33.63; H, 2.26; N, 19.61. Found: C, 33.52; H, 2.15; N, 19.52.

3.1.13. 5-Iodomethyl-6-hydroxy-5,6-dihydro-tetrazolo[5,1-*a*]isoquinoline (11e). Compound **10e** (101 mg, 0.50 mmol) was dissolved in H_2O (5 mL) containing $NaHCO_3$ (84 mg, 1.0 mmol). $CHCl_3$ (5 mL) and iodine (382 mg, 1.50 mmol) were added to the reaction mixture and the biphasic solution was vigorously stirred for 5 h at room temperature. Saturated aqueous $NaHCO_3$ (2 mL) followed by saturated aqueous Na_2SO_3 (5 mL) were then added to the reaction mixture. The biphasic mixture was extracted three times with EtOAc and the combined organic phases were washed with saturated aqueous $NaHCO_3$, saturated aqueous Na_2SO_3 and brine. Drying (Na_2SO_4) and concentration at reduced pressure of the organic phase gave 124 mg (76%) of **11e** (white solid) as a diastereoisomeric mixture (1.7:1). ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.12–8.05 (m, 1H), 8.12–8.05 (m, 1H), 7.76 (br d, 1H, J=7.5 Hz), 7.70–7.58 (m, 2H), 7.70–7.58 (m, 2H), 5.53 (d, 1H, J=5.8 Hz), 5.45 (dd, 1H, J=5.3, 3.8 Hz), 5.30 (dd, 1H, J=11.0, 5.7 Hz), 5.02 (m, 1H), 4.94 (dd, 1H, J=10.7, 4.9 Hz), 4.12 (dd, 1H, J=10.2, 5.5 Hz), 3.90 (dd, 1H, J=10.2, 8.7 Hz), 3.81 (dd, 1H, J=11.2, 6.8 Hz), 3.72 (dd, 1H, J=11.2, 5.0 Hz); ^{13}C NMR (acetone-d_6, 100 MHz) δ 150.7, 150.5, 137.9, 137.3, 133.1, 133.0, 130.4, 130.4, 129.7, 129.5, 126.1, 121.3, 120.8, 71.3, 68.9, 62.6, 62.3, 3.1, −2.1. Anal. calcd for $C_{10}H_9IN_4O$: C, 36.61; H, 2.76; N, 17.08. Found: C, 36.74; H, 2.84; N, 16.99.

3.1.14. 5-Iodomethyl-6,7-dihydro-tetrazolo[5,1-*a*][2]-benzazepine (11f). The reaction was performed according to the synthesis of **11a** starting with **10f** (0.5 mmol scale). The crude product was dissolved in heptane/EtOAc (1:1) and filtered through a pad of silica. Concentration of the organic phase at reduced pressure gave 160 mg (98%) of **11f** as a colorless oil containing 15% of **14**. Column chromatography (heptane/EtOAc 3:1) of the crude product gave 122 mg (75%) of pure **11f** as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.31 (dd, 1H, J=7.4, 1.8 Hz), 7.45 (m, 2H), 7.29 (br d, 1H, J=7.4 Hz), 4.88 (m, 1H), 3.73 (m, 2H), 2.99(m, 2H), 2.65 (m, 1H). 2.35 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.9, 140.2, 131.9, 130.6, 129.8, 127.8, 123.0, 60.5, 32.8, 30.5, 7.9. Anal. calcd for $C_{11}H_{11}IN_4$: C, 40.51; H, 3.40; N, 17.18. Found: C, 40.36; H, 3.35; N, 17.22.

3.1.15. 5-Iodomethyl-5-methyl-6,7-dihydro-tetrazolo-[5,1-*a*][2]benzazepine (11g). The reaction was performed according to the synthesis of **11a** starting with **10g** (0.5 mmol scale). Recrystallization (heptane/acetone) of the crude product gave 150 mg (88%) of **11g** as white crystals: mp 118–119°C ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.43 (dd, 1H, J=7.4, 1.9 Hz), 7.43 (m, 2H), 7.27 (dd, 1H, J=6.7, 1.6 Hz), 3.92 (d, 1H, J=10.6 Hz), 3.69 (d, 1H, J=10.6 Hz), 3.09–2.95 (m, 2H), 2.57 (m, 1H), 2.27 (m, 1H), 2.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.8, 141.0, 131.7, 131.0, 129.3, 127.6, 123.2, 64.9, 38.1, 29.4, 28.2, 17.6. Anal. calcd for $C_{12}H_{13}IN_4$: C, 42.37; H, 3.85; N, 16.47. Found: C, 42.67; H, 3.78; N, 16.55.

3.1.16. 5-Iodo-4a,5,6,7,8,8a-hexahydro-benzo[*c*]tetrazolo[5,1-*a*][2]benzazepine (11h). The reaction was performed according to the synthesis of **11a** starting with **10h** (0.5 mmol scale) which gave 170 mg (93%) of **11h** (white solid) as a diastereoisomeric mixture (2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97 (br d, 1H, J=7.5 Hz), 7.74 (br d, 1H, J=7.6 Hz), 7.55–7.39 (m, 4H), 7.32 (br d, 1H, J=7.6 Hz), 7.27 (br d, 1H, J=7.4 Hz), 5.39 (br q, 1H, J=3.3 Hz), 4.94 (br s, 1H), 4.83 (br q, 1H, J=2.8 Hz), 4.54 (br t, 1H, J=3.3 Hz), 3.24 (m, 1H), 3.09 (br d, 1H, J=15.1 Hz), 2.98 (dd, 1H, J=14.8, 5.7 Hz), 2.80–2.62 (m, 3H), 2.45–2.29 (m, 2H), 2.38 (dd, 1H, J=14.8, 9.7 Hz), 2.22–2.10 (m, 1H), 2.10–2.00 (m, 1H), 1.94–1.80 (m, 1H), 1.75–1.58 (m, 2H), 1.75–1.58 (m, 3H), 1.18–1.04 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.5, 153.9, 137.6, 137.5, 132.2, 132.0, 130.7, 130.5, 129.6, 129.4, 127.8, 127.7, 126.2, 124.2, 64.3, 63.0, 40.6, 38.6, 38.0, 37.0, 31.8, 28.4,

27.5, 26.5, 25.7, 24.2, 21.5, 15.2. Anal. calcd for $C_{14}H_{15}IN_4$: C, 45.92; H, 4.13; N, 15.30. Found: C, 46.03; H, 4.15; N, 15.28.

3.1.17. 2-(2-(1-Benzyloxy-prop-2-enyl)phenyl)imidazole (15a). *n*-BuLi (1.6 M in hexanes, 3 mL, 4.8 mmol) was added to phenylimidazole (577 mg, 4.0 mmol) in THF (15 mL) at −20°C. The yellow reaction mixture was stirred for 1 h followed by addition of (2-chloromethoxyethyl)-trimethylsilane (0.85 mL, 4.8 mmol). The reaction mixture was then stirred at −20°C for 15 min and for 3.5 h at room temperature. The clear yellow solution was then cooled to −78°C and *n*-BuLi (1.6 M in hexanes, 3 mL, 4.8 mmol) was added followed by stirring for 1 h. Chlorotrimethylsilane (0.61 mL, 4.8 mmol) was added and the reaction mixture was stirred an additional hour. The reaction mixture was warmed to −40°C and again treated with *n*-BuLi (1.6 M in hexanes, 3 mL, 4.8 mmol) and then stirred for 2 h. Acrolein (0.32 mL, 4.8 mmol) was added and the reaction mixture was stirred for 1 h in the cold before it was gradually warmed to room temperature and subsequently stirred overnight. The reaction mixture was poured into saturated aqueous ammonium chloride and the aqueous layer was extracted three times with EtOAc. The combined organic phases were washed with brine and dried (Na_2SO_4). Removal of the solvent at reduced pressure gave an oil, which was used directly in the next step. The crude oil, dissolved in dry THF (5 mL), was added dropwise to NaH (176 mg, 60%, 4.4 mmol) in dry DMF (5 mL) at 0°C under argon atmosphere. Benzyl bromide (0.52 mL, 4.4 mmol) was added after 1 h and the stirring was continued for an additional 2 h at room temperature. MeOH (2 mL) was added carefully to the reaction mixture followed by H_2O (20 mL). The aqueous phase was extracted twice with EtOAc and the combined organic phases were washed three times with H_2O and brine. Drying (Na_2SO_4) and concentration at reduced pressure of the organic phase gave an oil which was used unpurified in the next step. Tetrabutylammoniumfluoride trihydrate (6.3 g, 20 mmol) was added to the crude oil dissolved in THF (20 mL) and the reaction mixture was heated at reflux for 3 h. The reaction mixture was then cooled and diluted with pH 7.0 phosphate buffer. The aqueous layer was extracted with three portions of EtOAc and the combined organic phases were washed with pH 7.0 phosphate buffer followed by brine. Drying (Na_2SO_4) and concentration at reduced pressure of the organic phase followed by column chromatography (heptane/EtOAc, 1:1) of the residue gave 510 mg (44%) of **15a** as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (br d, 1H, J=7.6 Hz), 7.45–7.30 (m, 8H), 7.07 (s, 2H), 5.96 (ddd, 1H, J=17.3, 10.5, 5.4 Hz), 5.21 (dt, 1H, J=7.4, 1.7 Hz), 5.15 (dt, 1H, J=17.3, 1.6 Hz), 5.12 (dt, 1H, J=10.5, 1.5 Hz), 4.57 (q, 2H, J=11.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.3, 137.4, 136.5, 135.9, 131.2, 130.9, 129.2, 128.9, 128.8, 128.4, 118.0, 83.0, 70.6. Anal. HRMS (EI^+) calcd for $C_9H_8ClNO_2$ (M): 290.1419. Found: 290.1414.

3.1.18. 2-(2-(But-3-enyl)phenyl)imidazole (15b). The reaction was performed according to the synthesis of **15a** starting from 2-(2-methylphenyl)imidazole (1.5 mmol scale) and using allyl bromide as electrophile except that the crude product, after the addition of allyl bromide, was purified by column chromatography (heptane/EtOAc 4:1) and the benzylation step was omitted. The reaction yielded 96 mg (32%) of **15b** as white crystals: mp 100–102°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 (br d, 1H, J=7.6 Hz), 7.35–7.20 (m, 3H), 7.08 (s, 2H), 5.75 (ddt, 1H, J=17.1, 10.3, 6.7 Hz), 4.98–4.89 (m, 2H), 2.95 (br t, 2H, J=7.8 Hz), 2.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.9, 138.3, 130.4, 130.2, 129.6, 129.3, 126.4, 123.7, 115.3, 35.3, 33.1. Anal. HRMS (EI^+) calcd for $C_9H_8ClNO_2$ (M): 198.1157. Found: 198.1154.

3.1.19. 2-(2-(3-Methyl-but-3-enyl)phenyl)imidazole (15c). The reaction was performed according to the synthesis of **15a** starting from 2-(2-methylphenyl)imidazole (1.5 mmol scale) and using methallyl bromide as electrophile except that the crude product, after the addition of the methallyl bromide, was purified by column chromatography (heptane/EtOAc 4:1) and the benzylation step was omitted. The reaction yielded 90 mg (28%) of **15c** as white crystals: mp 88–89°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (br d, 1H, J=7.4 Hz), 7.33–7.26 (m, 2H), 7.18 (m, 1H), 7.01 (s, 2H), 4.64 (br s, 1H), 4.56 (br s, 1H), 2.95 (m, 2H), 2.13 (m, 2H), 1.62 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.7, 145.7, 141.3, 130.3, 130.2, 129.6, 129.1, 126.1, 122.5, 110.5, 39.4, 32.1, 22.5. Anal. HRMS (EI^+) calcd for $C_9H_8ClNO_2$ (M): 212.1313. Found: 212.1315.

3.1.20. 5-Iodomethyl-6-benzyloxy-5,6-dihydro-imidazo[2,3-*a*]isoquinoline (16a). Bis(collidine)iodine(I) hexafluorophosphate (386 mg, 0.75 mmol, commercial quality) was added to **15a** (73 mg, 0.25 mmol) dissolved in dry CH_2Cl_2 (10 mL). Formation of the product was monitored by HPLC. Additional bis(collidine)iodine(I) hexafluorophosphate (256 mg, 0.50 mmol) was added after 23 h at room temperature. After further 15 days of stirring, saturated aqueous Na_2SO_3 was added and the aqueous phase was extracted twice with ether. The combined organic phases were washed with H_2O and brine and then dried (Na_2SO_4). Removal of the solvent at reduced pressure followed by column chromatography (heptane/EtOAc 1:3) gave 65 mg (63%) of **16a** (pale yellow oil) as a diastereoisomeric mixture (1.4:1). ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.28 (m, 1H), 7.95 (dd, 1H. J=7.6, 1.3 Hz), 7.65–7.25 (m, 18H), 7.17 (d, 1H, J=1.4 Hz), 7.02 (d, 1H, J=1.2 Hz), 5.20–5.05 (m, 3H), 4.80–4.50 (m, 5H), 3.79 (dd, 1H, J=10.2, 5.6 Hz), 3.63 (dd, 1H, J=10.2, 7.5 Hz), 3.40 (dd, 1H, J=10.7, 6.3 Hz), 3.33 (dd, 1H, J=10.7, 7.9 Hz); ^{13}C NMR (acetone-d_6, 100 MHz) δ 141.6, 143.1, 139.1, 138.8, 132.6, 131.5, 130.9, 130.7, 129.8, 129.5, 129.2, 129.1, 128.9, 128.8, 128.6, 128.6, 128.5, 128.3, 127.5, 126.3, 125.6, 124.3, 121.8, 119.7, 76.6, 72.0, 59.5, 2.0. Anal. calcd for $C_{19}H_{17}IN_2O$: C, 54.82; H, 4.12; N, 6.73. Found: C, 54.70; H, 4.21; N, 6.79.

3.1.21. 2,3-Diiodo-5-iodomethyl-6-benzyloxy-5,6-dihydro-imidazo[2,3-*a*]isoquinoline (16b). *N*-iodosuccinimide (0.28 g, 1.25 mmol) was added to **15a** (73 mg, 0.25 mmol) in DMF at room temperature. Stirring was continued for 16 h and then saturated aqueous $NaHCO_3$ and saturated aqueous Na_2SO_3 were added to the reaction mixture. The aqueous phase was extracted twice with EtOAc and the combined organic phases were washed three times with H_2O and once with brine followed by drying (Na_2SO_4). Concentration at reduced pressure of the organic

phase followed by column chromatography (heptane/EtOAc 3:1) of the crude product gave 109 mg (65%) of **16b** (white solid) as a diastereoisomeric mixture (1:1). ^{1}H NMR (acetone-d_6, 400 MHz) δ 7.98 (m, 1H), 7.83 (m, 1H), 7.58 (m, 1H), 7.60–7.25 (m, 15H), 5.39 (br d, 1H, J=6.0 Hz), 5.11 (d, 1H, J=11.5 Hz), 5.09 (s, 1H), 4.97 (d, 1H, J=11.5 Hz), 4.87 (m, 1H), 4.78 (ddd, 1H, J=10.6, 4.1, 1.7 Hz), 4.62 (d, 1H, J=12.0 Hz), 4.53 (d, 1H, J=12.0 Hz), 3.54 (dd, 1H, J=11.4, 4.8 Hz), 3.34 (dd, 1H, J=10.9, 4.1 Hz), 3.30 (dd, 1H, J=11.4, 6.5 Hz), 2.97 (t, 1H, J=10.8 Hz); ^{13}C NMR (acetone-d_6, 100 MHz) δ 148.3, 147.7, 138.7, 138.6, 133.8, 131.6, 131.0, 130.6, 130.3, 130.2, 129.4, 129.2, 129.1, 129.0, 128.9, 128.6, 128.5, 126.3, 126.2, 125.3, 124.3, 123.6, 97.9, 97.3, 85.1, 84.0, 76.7, 76.2, 73.6, 70.7, 62.4, 57.6, 1.2, 0.3. Anal. calcd for $C_{19}H_{15}I_3N_2O$: C, 34.16; H, 2.26; N, 4.19. Found: C, 34.22; H, 2.20; N, 4.14.

3.1.22. 5-Methylene-6,7-dihydro-imidazo[2,3-*a*][2]-benzazepine (16c). The reaction was performed according to the synthesis of **16a** starting from **15b** (0.25 mmol scale). The reaction was stirred for 9 days and 83 mg of a crude product as yellow oil was isolated. The yield of 5-iodomethyl-6,7-dihydro-imidazo[2,3-*a*][2]benzazepine was determined to be 87% by ^{1}H NMR spectroscopy using anisole as internal standard. Column chromatography (heptane/EtOAc 1:1) of the crude oil gave an inseparable mixture of **16c** and 5-iodomethyl-6,7-dihydro-imidazo[2,3-*a*][2]benzazepine as a pale yellow oil. The residual oil was therefore dissolved in acetone and treated with diisopropylamine (0.5 mL) at reflux for 16 h. Concentration of the reaction mixture at reduced pressure followed by column chromatography (heptane/EtOAc 1:3) gave 30 mg (61%) of **16c** as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96 (dd, 1H, J=7.3, 1.8 Hz), 7.30 (m, 2H), 7.18 (br d, 1H, J=7.2 Hz), 7.17 (d, 1H, J=1.3 Hz), 7.15 (d, 1H, J=1.3 Hz), 4.99 (br s, 1H), 4.81 (br s, 1H), 3.07 (m, 2H), 2.87 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.8, 142.9, 138.8, 130.4, 129.5, 129.2, 129.1, 128.7, 127.2, 120.7, 107.0, 36.3, 31.3. Anal. calcd for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.27. Found: C, 79.66; H, 6.24; N, 14.21.

3.1.23. 2,3-Diiodo-5-iodomethyl-6,7-dihydro-imidazo[2,3-*a*][2]benzazepine (16d). The reaction was performed according to the synthesis of **16b** starting from **15b** (1.0 mmol scale). The reaction mixture was stirred for 16 h. Column chromatography (heptane/EtOAc 3:1) of the crude product gave 420 mg (73%, 95% purity according to HPLC analysis) of **16d** as a white solid. Recrystallization from heptane/EtOAc (4:1) gave analytically pure **16d** as white crystals: mp 148–149°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83 (m, 1H), 7.34 (m, 2H), 7.22 (m, 1H), 4.79 (m, 1H), 2.99 (dd, 1H, J=10.5, 7.1 Hz), 2.88 (dd, 1H, J=10.5, 9.1 Hz), 2.79 (m, 2H), 2.67 (m, 1H), 2.31 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.5, 138.6, 130.5, 130.0, 129.2, 129.0, 128.1, 97.0, 86.8, 60.2, 35.9, 30.6, 8.4. Anal. calcd for $C_{13}H_{11}I_3N_2$: C, 27.11; H, 1.93; N, 4.86. Found: C, 27.08; H, 1.86; N, 4.77.

3.1.24. 5-Iodomethyl-5-methyl-6,7-dihydro-imidazo[2,3-*a*][2]benzazepine (16e). The reaction was performed according to the synthesis of **16a** starting from **15c** (0.25 mmol scale). The reaction mixture was stirred for 7 days and purification of the crude product using column chromatography (heptane/EtOAc 1:3) gave 72 mg (85%) of **16e** as a pale yellow oil. ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.01 (m, 1H), 7.37 (d, 1H, J=1.4 Hz), 7.32–7.20 (m, 2H), 7.04 (d, 1H, J=1.4 Hz), 3.55 (d, 1H, J=10.7 Hz), 3.42, (d, 1H, J=10.7 Hz), 2.90–2.78 (m, 2H), 2.49–2.37 (m, 2H), 1.81 (s, 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 147.1, 139.7, 132.6, 132.6, 129.8, 129.1, 128.9, 127.3, 120.9, 60.4, 41.6, 30.5, 29.1, 20.7. Anal. calcd for $C_{14}H_{15}IN_2$: C, 49.72; H, 4.47; N, 8.28. Found: C, 49.82; H, 4.38; N, 8.34.

3.1.25. 5-Methylen-5,6,7,8-tetrahydro-tetrazolo[1,5-*a*]pyridine (17). A mixture of **11b** (66 mg, 0.25 mmol), KCN (49 mg, 0.75 mmol) and 18-crown-6 (3.3 mg, 0.013 mmol) in DMF (2 mL) was stirred for 24 h at 70°C. The reaction mixture was then cooled to room temperature and H_2O was added. The aqueous phase was extracted twice with EtOAc and the combined organic phases were washed twice with H_2O and brine. Drying (Na_2SO_4) and concentration at reduced pressure of the organic phase and column chromatography (heptane/EtOAc 1:3) of the residue gave 24 mg (71%) of **17** as white crystals: mp 55–56°C. ^{1}H NMR (acetone-d_6, 400 MHz) δ 5.76 (br s, 1H), 5.04 (br s, 1H), 3.11 (t, 2H, J=6.4 Hz), 2.80 (m, 2H), 2.05 (m, 2H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 152.5, 138.4, 101.3, 28.8, 21.4, 20.8. Anal. calcd for $C_6H_8N_4$: C, 52.93; H, 5.92; N, 41.15. Found: C, 52.82; H, 5.84; N, 41.22.

3.1.26. *O*-Ethyl *S*-(5,6,7,8-tetrahydro-tetrazolo[1,5-*a*]pyridine-5-yl-methyl) dithiocarbonate (18). Potassium ethyl xanthate (190 mg, 1.5 mmol) was added to **11b** (132 mg, 0.50 mmol) in acetone (5 mL) at room temperature. Stirring was continued for 3 h during which the initial yellow solid disappeared and a white precipitate (KI) was slowly formed. H_2O was then added to the reaction mixture and the aqueous phase was extracted twice with EtOAc. The combined organic phases were washed with H_2O and brine followed by drying (Na_2SO_4). Concentration at reduced pressure of the organic phase and column chromatography (heptane/EtOAc 1:3) of the residue gave 99 mg (77%) of **18** as white crystals: mp 82–83°C ^{1}H NMR (acetone-d_6, 400 MHz) δ 4.85 (m, 1H), 4.68 (q, 2H, J=7.1 Hz), 4.10 (dd, 1H, J=14.3, 4.6 Hz), 3.67 (dd, 1H, J=14.3, 7.5 Hz), 3.10–2.90 (m, 2H), 2.45–2.34 (m, 1H), 2.22–2.13 (m, 1H), 2.07–1.92 (m, 2H), 1.43 (t, 3H, J=7.1 Hz); ^{13}C NMR (acetone-d_6, 100 MHz) δ 214.0, 153.2, 71.6, 56.5, 39.2, 27.7, 21.2, 18.8, 13.9. Anal. HRMS (EI^+) calcd for $C_9H_8ClNO_2$ (M): 258.0609. Found: 258.0600.

3.1.27. 4-(5,6,7,8-Tetrahydro-tetrazolo[1,5-*a*]pyridin-5-yl)-butyronitrile (19). Compound **11b** (132 mg, 0.5 mmol), acrylonitrile (0.33 mL, 5.0 mmol), $NaCNBH_3$ (63 mg, 1.0 mmol), chlorotributylstannane (16 mg, 0.05 mmol) and AIBN (8 mg, 0.05 mmol) were mixed in degassed *tert*-butanol (10 mL) and heated at reflux. The consumption of **11b** was monitored by TLC. After 3 h the reaction mixture was cooled and H_2O was added. The aqueous phase was extracted twice with EtOAc and the combined organic phases were washed with brine and then dried (Na_2SO_4). Concentration at reduced pressure of the organic phase followed by column chromatography (CH_2Cl_2–CH_3CN 4:1) of the crude product gave 53 mg (55%) of **19** as a colorless oil. ^{1}H NMR (acetone-d_6,

400 MHz) δ 4.56 (quint, 1H, J=6.3 Hz), 3.07–2.89 (m, 2H), 2.59 (t, 2H, J=7.0 Hz), 2.35–2.24 (m, 2H), 2.20–2.07 (m, 1H), 2.00–1.77 (m, 5H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 152.5, 119.9, 56.6, 33.8, 27.9, 22.1, 20.8, 18.5, 16.6. Anal. calcd for $C_9H_{13}N_5$: C, 56.53; H, 6.85; N, 36.62. Found: C, 56.38; H, 6.76; N, 36.54.

3.1.28. *O*-Ethyl *S*-(2,3-diiodo-6,7-dihydro-imidazo[2,3-*a*][2]benzazepine-5-yl-methyl) dithiocarbonate (20). The reaction was performed according to the synthesis of **18** starting from **16d** (1.0 mmol scale). The reaction mixture was stirred for 16 h. Recrystallization (heptane/EtOAc 4:1) of the crude pale yellow solid gave 230 mg (81%) of **20** as white crystals: mp 131–132°C ^{1}H NMR (acetone-d_6, 400 MHz) δ 7.68 (m, 1H), 7.42–7.33 (m, 3H), 5.02 (m, 1H), 4.62 (q, 2H, J=7.1 Hz), 3.32 (dd, 1H, J=14.4, 5.3 Hz), 2.94–2.85 (m, 1H), 2.84–2.74 (m, 2H), 2.40–2.29 (m, 1H), 1.37 (t, 3H, J=7.1 Hz); ^{13}C NMR (acetone-d_6, 100 MHz) δ 214.0, 151.8, 139.6, 131.3, 130.7, 130.0, 128.9, 128.0, 97.1, 88.3, 71.3, 58.1, 41.8, 35.9, 30.7, 14.0. Anal. calcd for $C_{16}H_{16}I_2N_2OS_2$: C, 33.70; H, 2.83; N, 4.91. Found: C, 33.82; H, 2.76; N, 4.89.

3.1.29. *O*-Ethyl *S*-(2-iodo-6,7-dihydro-imidazo[2,3-*a*][2]benzazepine-5-yl-methyl) dithiocarbonate (21). *i*-PrMgBr (0.5 M in THF, 0.50 mL, 0.25 mmol) was added dropwise to **20** (143 mg, 0.25 mmol) in dry THF at −40°C under argon atmosphere. The disappearance of the starting material was monitored by TLC and after 20 min another portion of *i*-PrMgBr (0.5 M in THF, 0.25 mL, 0.13 mmol) was added. After additional 25 min no starting material remained and saturated aqueous ammonium chloride was added to the reaction mixture and the temperature was gradually increase to room temperature. The aqueous layer was extracted twice with EtOAc and the combined organic phases were washed with brine, dried (Na_2SO_4) and concentration at reduced pressure to give 130 mg of a red oil. Column chromatography (heptane/EtOAc 4:1) of the residual oil gave 70 mg (63%) of **21** as a pale yellow oil. ^{1}H NMR (acetone-d_6, 400 MHz) δ 7.72 (m, 1H), 7.47 (s, 1H), 7.37–7.29 (m, 2H), 4.58 (dq, 2H, J=7.1, 2.2 Hz), 4.51 (m, 1H), 3.58 (dd, 1H, J=14.4, 6.1 Hz), 3.51 (dd, 1H, J=14.4, 8.2 Hz), 2.81 (m, 1H), 2.71 (m, 1H), 2.50 (m, 1H), 2.29 (m, 1H), 1.32 (t, 3H, J=7.1 Hz); ^{13}C NMR (acetone-d_6, 100 MHz) δ 214.0, 149.7, 139.2, 131.1, 130.1, 129.9, 129.2, 127.8, 126.3, 82.1, 71.4, 56.4, 40.1, 36.9, 30.9, 13.8. Anal. calcd for $C_{16}H_{17}IN_2OS_2$: C, 43.25; H, 3.86; N, 6.30. Found: C, 43.20; H, 3.95; N, 6.24.

Acknowledgements

We thank Amersham Health R&D AB, the Swedish Research Council and The Royal Physiographic Society in Lund for financial support and Einar Nilsson for obtaining mass spectral data.

References

1. Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930.
2. Grimmett, M. R. *Compr. Heterocycl. Chem. II* **1996**, *3*, 77–220.
3. Herr, R. J. *Bioorg. Med. Chem.* **2002**, *10*, 3379–3393.
4. Abell, A. D. *Lett. Pept. Sci.* **2002**, *8*, 267–272.
5. Zabrocki, J.; Smith, G. D.; Dunbar, J. B., Jr.; Iijima, H.; Marshall, G. R. *J. Am. Chem. Soc.* **1988**, *110*, 5875–5880.
6. Zabrocki, J.; Marshall, G. R. *Methods Mol. Med.* **1999**, *23*, 417–436.
7. Moderhack, D. *J. Pract. Chem.* **1998**, *340*, 687–709.
8. Ostrovskii, V. A.; Pevzner, M. S.; Kofman, T. P.; Shcherbinin, M. B.; Tselinskii, I. V. *Targets Heterocycl. Syst.* **1999**, *3*, 467–526.
9. Daya, S.; Kaye, P. T.; Mphahlele, M. J. *Med. Sci. Res.* **1996**, *24*, 137–141.
10. Huang, R.-Q.; Bell-Horner, C. L.; Dibas, M. I.; Covey, D. F.; Drewe, J. A.; Dillon, G. H. *J. Pharmacol. Exp. Ther.* **2001**, *298*, 986–995.
11. Jung, M. E.; Lal, H.; Gatch, M. B. *Neurosci. Biobehavioral Rev.* **2002**, *26*, 429–439.
12. Davis, B.; Brandstetter, T. W.; Smith, C.; Hackett, L.; Winchester, B. G.; Fleet, G. W. J. *Tetrahedron Lett.* **1995**, *36*, 7507–7510.
13. Brandstetter, T. W.; Davis, B.; Hyett, D.; Smith, C.; Hackett, L.; Winchester, B. G.; Fleet, G. W. J. *Tetrahedron Lett.* **1995**, *36*, 7511–7514.
14. Ek, F.; Wistrand, L.-G.; Frejd, T. *J. Org. Chem.* **2003**, *68*, 1911–1918.
15. Sakakida, Y.; Kumanireng, A. S.; Kawamoto, H.; Yokoo, A. *Bull. Chem. Soc. Jpn* **1971**, *44*, 478–480.
16. Mphahlele, M. J. *J. Chem. Soc., Perkin Trans. 1: Org. and Bioorg. Chem.* **1999**, 3477–3482.
17. Smith, P. A. S.; Clegg, J. M.; Hall, J. H. *J. Org. Chem.* **1958**, *23*, 524–529.
18. Demko, Z. P.; Sharpless, K. B. *Org. Lett.* **2001**, *3*, 4091–4094.
19. Kadaba, P. K. *J. Org. Chem.* **1976**, *41*, 1073–1075.
20. Joule, J. A.; Mills, K. *Heterocyclic Chemistry*; 4th ed. Blackwell: Oxford, 2000; pp 402–503.
21. Aldabbagh, F.; Bowman, W. R. *Tetrahedron Lett.* **1997**, *38*, 3793–3794.
22. Grimmett, M. R. *Imidazole and Benzimidazole Synthesis*; Academic: San Diego, Califonia, 1997.
23. Korotkikh, N. I.; Aslanov, A. F.; Raenko, G. F.; Shvaika, O. P.; Russ, *J. Org. Chem. (Translation of Zhurnal Organicheskoi Khimii)* **1999**, *35*, 730–740.
24. Koguro, K.; Oga, T.; Mitsui, S.; Orita, R. *Synthesis* **1998**, 910–914.
25. Wittenberger, S. J.; Donner, B. G. *J. Org. Chem.* **1993**, *58*, 4139–4141.
26. Flippin, L. A. *Tetrahedron Lett.* **1991**, *32*, 6857–6860.
27. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, p 363.
28. Dowle, M. D.; Davies, D. I. *Chem. Soc. Rev.* **1979**, *8*, 171–197.
29. Robin, S.; Rousseau, G. *Tetrahedron* **1998**, *54*, 13681–13736.
30. Bartlett, P. A.; Richardson, D. P.; Myerson, J. *Tetrahedron* **1984**, *40*, 2317–2327.
31. Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc* **1978**, *100*, 3950–3952.
32. Roux, M.-C.; Paugam, R.; Rousseau, G. *J. Org. Chem.* **2001**, *66*, 4304–4310.
33. Simonot, B.; Rousseau, G. *J. Org. Chem.* **1993**, *58*, 4–5.
34. Demuth, T. P., Jr.; Lever, D. C.; Gorgos, L. M.; Hogan, C. M.; Chu, J. *J. Org. Chem.* **1992**, *57*, 2963–2965.

35. Despite intense investigation of the commercial reagent, we have not been able to elucidate the exact structure or composition of the specific iodination reagent responsible for the selective synthesis of the mono-iodo products.
36. Zard, S. Z. *Angew.Chem., Int. Ed. Engl.* **1997**, *36*, 673–685.
37. Biadatti, T.; Quiclet-Sire, B.; Saunier, J.-B.; Zard, S. Z. *Tetrahedron Lett.* **1998**, *39*, 19–22.
38. Stork, G.; Sher, P. M. *J. Am. Chem. Soc* **1986**, *108*, 303–304.
39. Abarbri, M.; Thibonnet, J.; Berillon, L.; Dehmel, F.; Rottlaender, M.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 4618–4634.
40. Hartley, D. J.; Iddon, B. *Tetrahedron Lett.* **1997**, *38*, 4647–4650.
41. Hughes, S.; Griffiths, G.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2: Phys. Org. Chem. (1972–1999)* **1987**, 1253–1264.
42. Chan, T. H.; Stossel, D. *J. Org. Chem.* **1986**, *51*, 2423–2428.
43. Ek, F.; Wistrand, L. G. Preparation of Allylic Aromatic Compounds by Reaction of Aromatic Amines with a Nitrite and an Allylic Olefin. EP 1013636, 2000, p 11.
44. Ek, F.; Axelsson, O.; Wistrand, L.-G.; Frejd, T. *J. Org. Chem.* **2002**, *67*, 6376–6381.
45. Anastassiadou, M.; Baziard-Mouysset, G.; Payard, M. *Synthesis* **2000**, 1814–1816.
46. Homsi, F.; Robin, S.; Rousseau, G. *Org. Synth.* **2000**, *77*, 206–211.
47. The reaction mixture became red after the addition of *sec*-BuLi when 5-(2-methylphenyl)tetrazole was used as starting material.