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# Exploring the unique reactivities of heterobicyclic tetrazoles—access to functionally diverse and versatile heterocyclic scaffolds

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Dedicated to Professor Larry Overman, friend, scholar, and chemist extraordinaire

ABSTRACT

The benzylic hydrogen atom in oxabicyclic tetrazoles such as (6*R*,8*R*)-(8-phenyl-5,6-dihydro-8*H*-tetrazolo[5,1-*c*][1,4]oxazin-6-yl)-alkanols (**A**, X=$CH_2OH$) is highly acidic, being alkylated in preference to a hydroxymethyl group with NaH and active alkyl halides. The enantioenriched products **B** now contain a phenyl and alkyl group on a stereogenic benzylic carbon atom. The products are subject to β-elimination to give 1-{1-[3-propenyl]-1*H*-tetrazol-5-yl}-1-phenyl-alkanols. Cleavage of the propenyl chain leads to chiral non-racemic 1-phenyl-1-(1*H*-tetrazol-5-yl)-alkanols **C**. Free-radical 'anomeric' azidation of the oxabicyclic tetrazoles followed by reduction and ring closure with inversion of configuration produces azabicyclic tetrazoles **D** as constrained functionalized piperazines.



## 1. Introduction

The tetrazole nucleus has gained importance in recent years due to its utility in wide-ranging areas of applications.[1] In the field of medicinal chemistry, the tetrazole nucleus is often used as a carboxyl group surrogate. Indeed several important drugs contain a tetrazole moiety instead of a carboxyl group in their structures.[2] Substituted tetrazoles are also useful as *cis*-amide isosteres,[3] and as conformationally rigid, flat, space-filling scaffolds.

We recently described a very mild and efficient Lewis acid-mediated stereocontrolled synthesis of novel oxabicyclo tetrazoles from arylidene acetals and alkylidene ketals[4] of 1-azido-2,3-glycerols in the presence of TMSCN (Scheme 1). The stereochemical outcome of the reactions was rationalized on the basis of the existence of proximal **1a**, and distal **1b**, $BF_3$-coordinated acetals in solution.[5] In the presence of TMSCN, the corresponding oxocarbenium ion **2** and **3** would each give diastereomeric cyanohydrins **4**, **5** and **6**, **7** respectively.[6] However, only the cyanohydrins arising from oxocarbenium ion **3** could undergo a [2+3]-cycloaddition to give the *cis*- and *trans*-oxabicyclic tetrazoles **8** and **9** respectively. In actual fact, preponderance of the cis-diastereomer **8** (>10:1 to 20:1) over the trans-isomer **9** is the result of a reversible equilibration of the cyanohydrins **6** and **7** to favor the diequatorial substitution pattern in the cis-isomer **8**. Subjecting cyanohydrins **6** and **7** to $BF_3 \cdot Et_2O$ led to **8** and **9** in the same ratio as in the original reaction. Considering the extremely mild conditions required for these cycloaddition reactions compared to literature precedents,[7] it is clear that the proximity of the reacting azide and nitrile functionalities plays an important role. Fuzed tetrazoles were recently obtained by the intramolecular iodocyclizations of ω-alkenyl tetrazoles.[8]

## 2. Results and discussions

In this paper, we report on a series of site-selective reactions of these oxabicyclic and azabicyclic tetrazoles.[5] In the first of a series of experiments, we studied the O-methylation and O-benzylation of the oxabicyclic tetrazole **8**, in the presence of silver oxide (Scheme 2). Surprisingly, no reaction took place and starting material was recovered. We soon realized that oligomeric tetrazole–Ag complexes[9] may have been formed, rendering the hydroxyl group ineffective as a nucleophile. In the presence of benzyl bromide (1.5 equiv), sodium hydride (2 equiv) and $Bu_4NI$ (0.1 equiv) at −15 °C, compound **8**, underwent partial epimerization within 15 s to a mixture containing 25% of the trans isomer **9**. This was followed by the formation of epimeric *C*,*O*-dibenzyl oxabicyclic tetrazoles **10** and **11** in favor of the trans isomer (5.3:1 with regard to the phenyl group, 46% yield), and the *C*-benzylated products **12** and **13** in a trans/cis ratio of 4:1 (24% yield). The hydroxyethyl analog **14** gave analogous products of C- and O-alkylation, **15** and **16**, albeit with higher ratios of the trans isomer (1:7.5 cis/trans) in both cases. Treatment of the *trans*-hydroxymethyl analogue **9**[5] with NaH/THF and quenching with MeOH resulted in *anti*-protonation to give **8** as the major isomer (4:1 cis/trans). Facile formation of a benzylic carbanion in **8** in the presence of NaH at −15 °C was demonstrated by quenching with MeOD, and recovery of the corresponding deuterated benzylic tetrazole (over 96%

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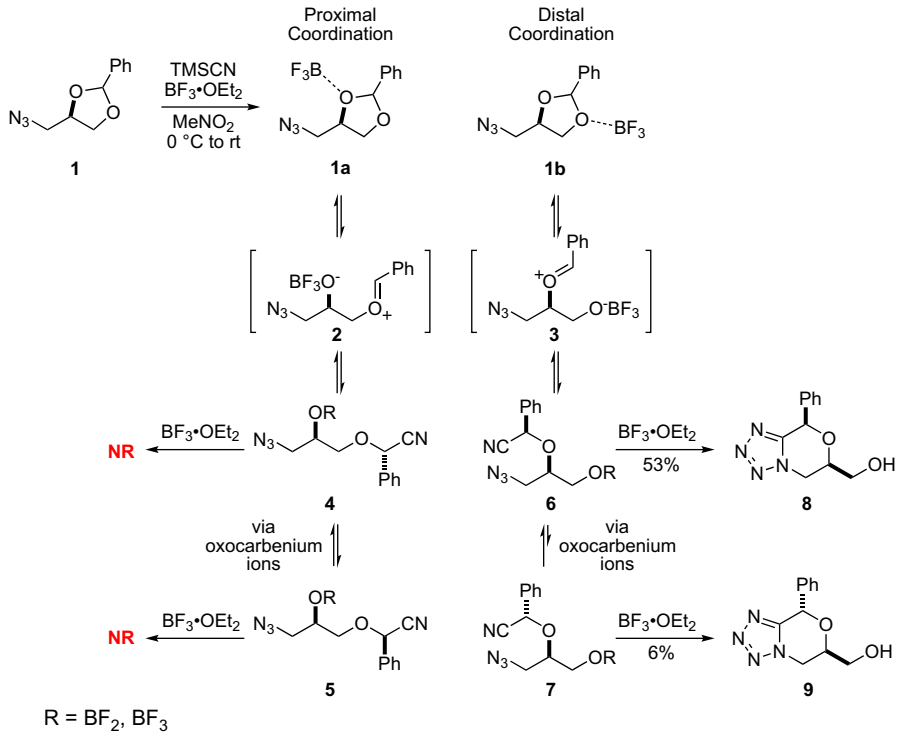
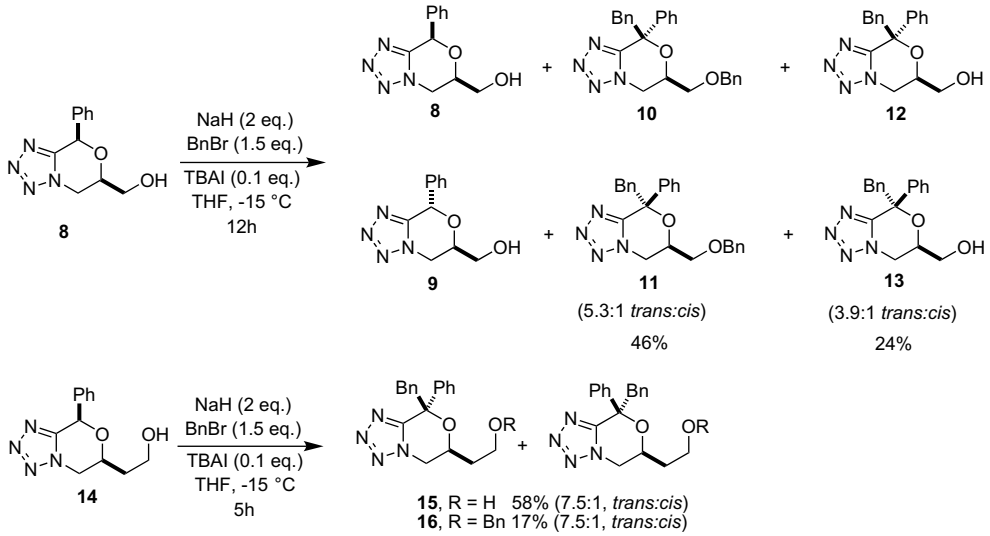



**Scheme 1.** Formation and reaction of isolated cyanohydrins.

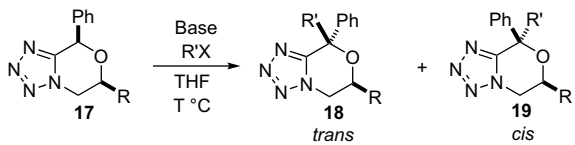



**Scheme 2.** C-Alkylation and epimerization of oxabicyclic tetrazoles.

incorporation). Similar results were obtained in the presence of MeONa and quenching with MeOD.

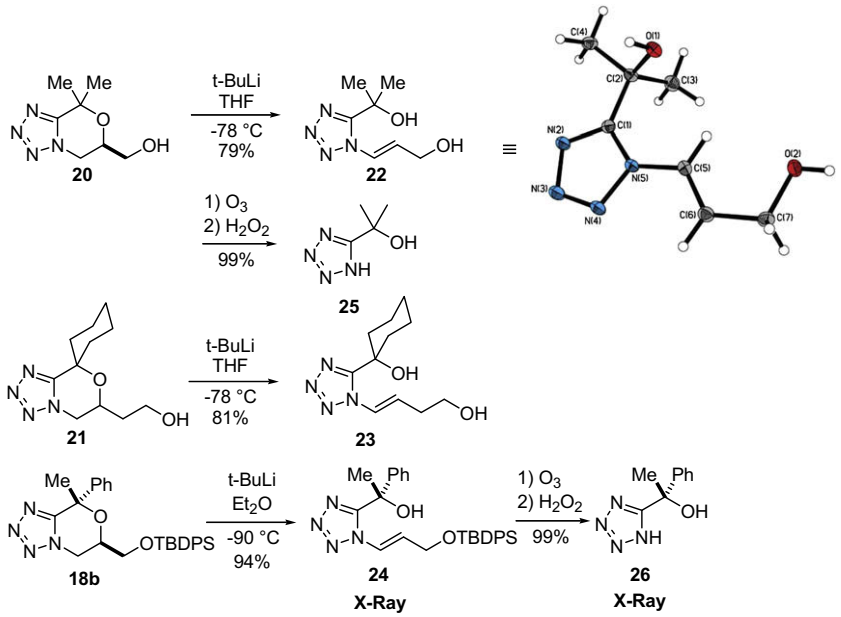
Taking advantage of the reactivity of the benzylic anion in **8**, we treated the *O*-TBDPS ether **17a** (R=$CH_2OTBDPS$, Table 1) with benzyl bromide, methyl iodide, or allyl iodide which led to the preponderant formation of the trans-products as major isomers. With benzyl bromide and LiHMDS as a base, the ratio of trans/cis alkylation products with respect to the phenyl group, was 95:5 as determined by HPLC and isolation of individual isomers **18a** and **19a** (R=$CH_2OTBDPS$). That steric effects (or internal coordination) were not responsible for the selectivity was ascertained in the case of the methyl analog (**17b**, R=Me, compare entry 1 and 3 in Table 1). With the more reactive methyl and allyl iodides, ratios were still in favor of the trans-isomers **18c**, **d** (R′=Me, allyl, Table 1 entries 4, 5), although the nature of the

**Table 1**
C-Alkylation of oxabicyclic benzylic tetrazole anions




| Entry | R | | R′X | Base | *T* (°C) | Y[a] (%) | Products | trans/cis[b] |
|---|---|---|---|---|---|---|---|---|
| 1 | $CH_2OTBDPS$ | **17a** | BnBr | NaH | −5 | 97 | **18a**/**19a** | 86:14 |
| 2 | $CH_2OTBDPS$ | **17a** | BnBr | LiHMDS | −78 | 87 | **18a**/**19a** | 96:4 |
| 3 | Me | **17b** | BnBr | LiHMDS | −78 | 94 | **18b**/**19b** | 95:5 |
| 4 | $CH_2OTBDPS$ | **17a** | Me–I | LiHMDS | −100 | 94 | **18c**/**19c** | 75:25 |
| 5 | $CH_2OTBDPS$ | **17a** | Allyl–I | LiHMDS | −100 | 95 | **18d**/**19d** | 63:37 |

[a] Isolated yield.
[b] HPLC ratio.

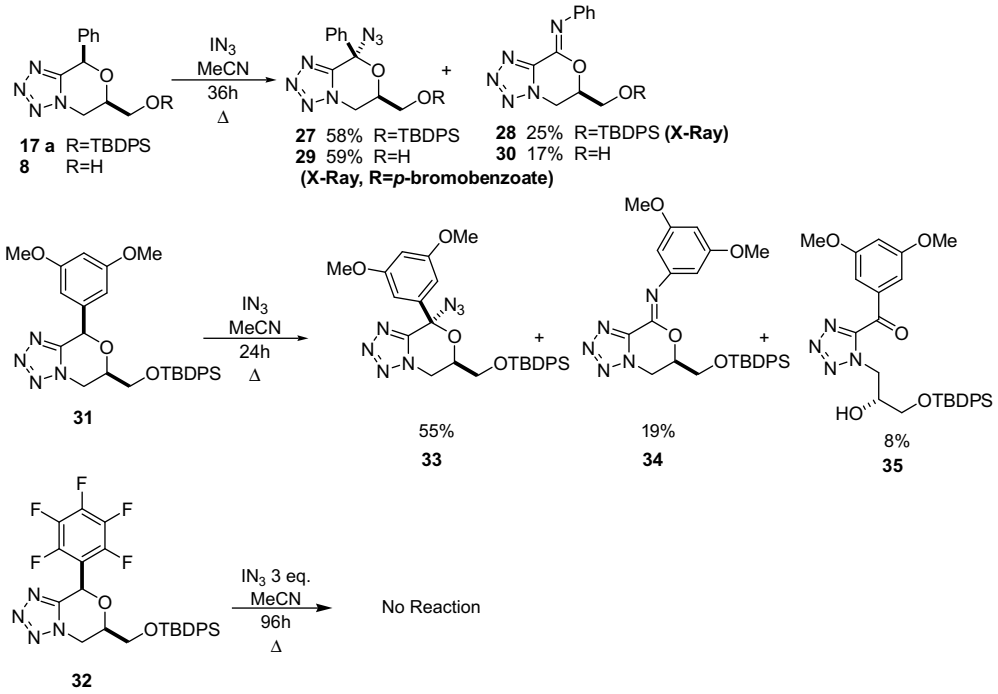



**Scheme 3.** Base-induced fragmentations of oxabicyclic tetrazoles.

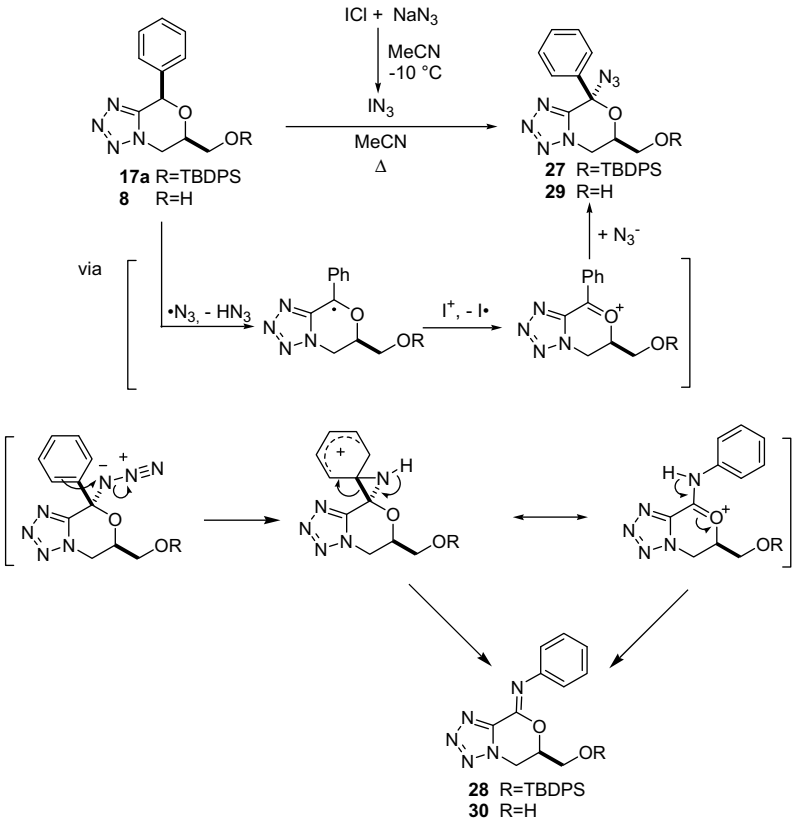
electrophile and the base seem to be playing a role. Thus, unlike the *anti*-selective protonation of Na dianions generated from **8** or **9** in the presence of NaH, alkylation of the benzylic anion (or its delocalized variant on the tetrazole), of **17a** and **17b** occurred to a major extent from the *syn*-side of the hydroxymethyl side-chain to give *trans*-*C*-alkylated products as major isomers. The preponderance of the *trans*-*C*-benzyl isomer **18a** compared to the relatively lower trans/cis ratios of the *C*-methyl **18c** or *C*-allyl **18d** analogs may be due to steric factors associated with the size of the electrophile.

In the presence of *t*-BuLi at −78 °C, the oxabicyclic tetrazoles **20**, **21**, and **18b** underwent smooth β-elimination to afford the corresponding tertiary alcohols **22**, **23**, and **24** in excellent yields (Scheme 3). Oxidative cleavage of the double bond led to *C*-functionalized 1-*H*-tetrazoles **25**, and **26**, the latter harboring a stereogenic center.[10] Considering that the 1-*H*-tetrazoles are isosteric with carboxylic acids,[1] compound **26** can be regarded as the tetrazole equivalent of α-methyl (*R*)-mandelic acid.

We next explored the reactivity of the benzylic carbon in the oxabicyclic tetrazole **8** and **17** (R=$CH_2$OTBDPS) under free-radical conditions (Scheme 4). Baruah and Bols[11] had shown that *O*-benzylidene acetals undergo an azido Hanessian ring-opening reaction in the presence of $IN_3$ in refluxing MeCN to give ω-azido benzoate esters. Guided by this result, we treated tetrazoles **17** and **8** with $IN_3$ under the same conditions as described by the Danish group. The benzylic azide **27** (58%, 15:1 cis/trans), and the rearranged *N*-phenyloximino ether **28** (25%) were obtained as the major products




**Scheme 4.** Radical azidation on tetrazoles.

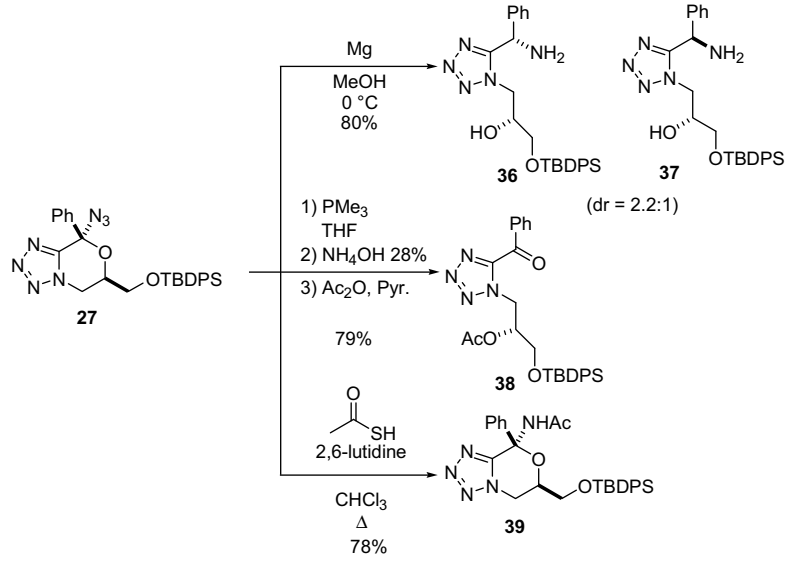



**Scheme 5.** Suggested mechanism of the radical azidation.

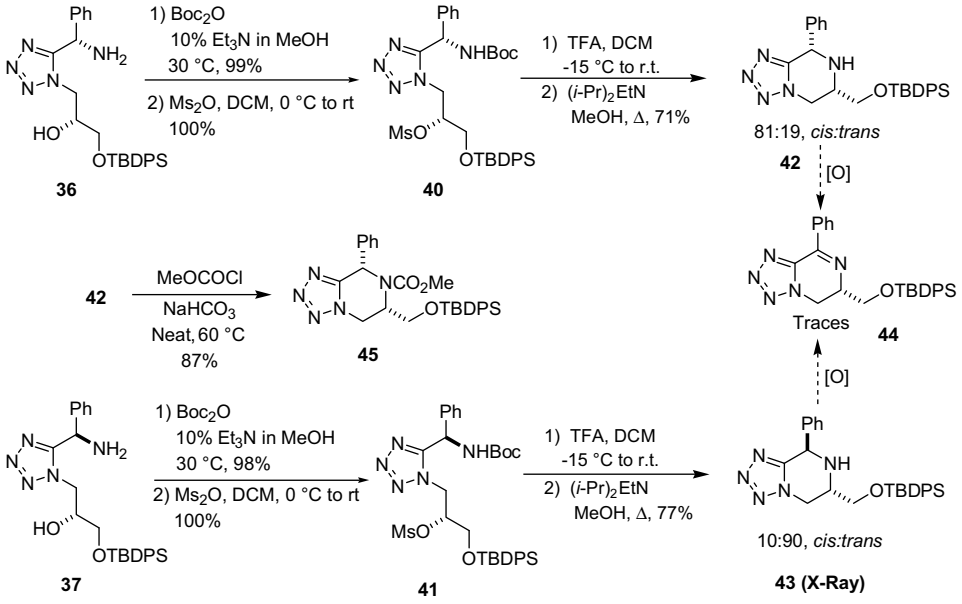
(Scheme 4). The structure of the latter compound was ascertained by a single crystal X-ray analysis. Similar results were obtained in the radical azidation of the hydroxymethyl analogue **8**, giving **29** (X-ray for *p*-bromobenzoate analogue), and **30** in 59% and 15% yields respectively.

A plausible mechanism for this interesting distribution of products is shown in Scheme 5. Thus, abstraction of a benzylic hydrogen radical leads to the corresponding oxocarbenium ion, which is captured by azide ion to give the observed products. The iminolactone could result from participation of the phenyl group with the loss of nitrogen, leading to a new aminophenyl oxocarbenium ion which loses a proton. To shed some light on this proposal, we subjected the 3,5-dimethoxy and 3,5-difluorophenyl tetrazoles **31** and **32** respectively to the same reaction conditions. Whereas **31** led to the same distribution of azido and iminophenyl tetrazoles, **33** and **34** respectively (with traces of the ketone **35**), only starting material was recovered in the case of **32**. Thus, a phenonium ion participation by the aryl group is not unlikely in this reaction.

The reduction of the azide group in **27** under a variety of conditions led to entirely different products (Scheme 6). Treatment of **27** with magnesium powder[12] in MeOH at 0 °C led to the diastereomeric amines **36** and **37** in a ratio of 2.2:1. The assigned stereochemistry to




**Scheme 6.** Functionalized cyclic and acyclic tetrazoles.




**Scheme 7.** Access to functionalized azabicyclic tetrazoles.

**37** was based on subsequent transformations. The imine resulting from the treatment of **27** with $Ph_3P$ under Staudinger conditions[13] was hydrolyzed in the workup process to the ketone which was acetylated to give **38**. Reduction of the azide group with thiolacetic acid[14] in the presence of 2,6-lutidine at reflux temperature in $CHCl_3$ led to the oxabicyclic *N*-acetyl tetrazole **39** in 78% yield.

The aminotetrazole analog **36** was a suitable precursor to access a novel azabicyclic tetrazole nucleus (Scheme 7). Thus, Boc protection and mesylation of **36** afforded **40** in quantitative yield. Cleavage of the *N*-Boc group and treatment with Hünig's base effected intramolecular displacement of the mesylate to give the novel azabicyclic tetrazole **42** as an 81:19 cis/trans mixture. Alternatively, similar treatment of **37** gave **41** and **43** as a 10:90 mixture of cis/trans isomers. The structure and stereochemistry of the major trans-isomer **43** was determined by a single crystal X-ray analysis. Thus, it appears that the α-aminobenzyl tetrazoles are prone to partial epimerization under the conditions of the base-catalyzed azacycle formation. Curiously, the oily tetrazole **42** was slowly transformed to the cyclic imine **44** when exposed to air. The same product was also observed with the crystalline diastereomer **43**, albeit only after several weeks of standing. Protection of the amino group in **42** as the methyl carbamate gave **45**.

Finally, having easy access to the oxabicyclic scaffold **8**, we explored a diversification protocol involving the hydroxymethyl group as shown in Scheme 8. Oxidation of **8** under Jones conditions followed by esterification gave the methyl esther **46** in high overall yield. Tosylation to **47**, displacement with azide to **48** and selective catalytic reduction led to the aminomethyl analog **49** in excellent yield. The easily obtained iodide **50** was transformed into the deoxy **17b**, the endocyclic enol ether **51**, and the exocyclic enol ether **52**, using standard methodology (Scheme 8). Treatment of **50** with Zn dust led to the ring-opened benzylic alcohol tetrazole analog **53**.

## 3. Conclusion

In conclusion, we have uncovered interesting reactivities associated with the benzylic carbon of oxabicyclic tetrazoles exemplified by **8**. Remarkably facile C-alkylation led to the generation of enantioenriched quaternary substituted analogs that undergo β-elimination to the corresponding tertiary alcohols. Oxidative cleavage of the resulting allylic alcohols gives novel chiral, nonracemic 5-substituted 1-*H*-tetrazoles.

Application of a free-radical azidation reaction provides access to benzylic anomeric azides which can be manipulated in a variety of ways, including the formation of hitherto unknown azabicyclic tetrazoles as constrained functionalized piperazines. The oxabicyclic tetrazoles are also amenable to classical chemical modification at the hydroxymethyl (and aromatic group), to provide a host of functionally diverse analogs.[15]

The novel tetrazole analogs described herein will be useful scaffolds in a variety of contexts relative to medicinal chemistry, molecular recognition, catalysis, and related applications.

## 4. Experimental

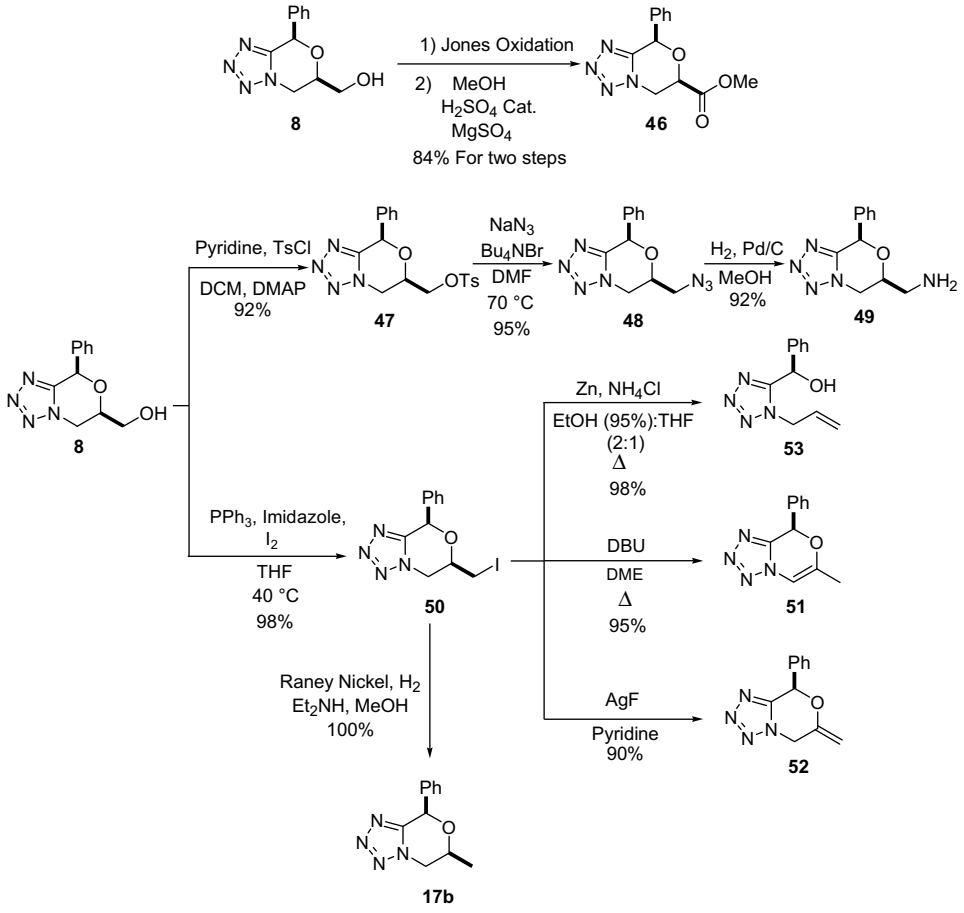
### 4.1. General information

Solvents were distilled under positive pressure of dry argon before use and dried by standard methods; THF and ether, from Na/benzophenone; and $CH_2Cl_2$, from $CaCl_2$. All commercially available reagents were used without further purification. NMR ($^1H$, $^{13}C$) spectra were recorded on AMX-300, ARX-400, AV-700, AV-500, AV-400 and AV-300 spectrometers. Low- and high-resolution mass spectra were recorded on AEI-MS 902, MS-50 or LC-MSD TOF spectrometers using fast atom bombardment (FAB) or electrospray techniques. IR spectra were recorded on a Perkin–Elmer Spectrum One Version B Spectrometer. Analytical thin-layer chromatography was performed on Merck $60F_{254}$ pre-coated silica gel plates. Visualization was performed by ultraviolet light and/or by staining with ceric ammonium molybdate or potassium permanganate. Flash column chromatography was performed using (40–60 μm) silica gel at increased pressure. Normal phase HPLC analyses were performed on Phenomenex Luna 3 μ silica(2) (3 μ silica gel) column for diastereomeric excess. All melting points are uncorrected. All evaporations were carried out under reduced pressure at 40 °C.

## 5. Experimental procedures

### 5.1. General method for the formation of oxabicyclic tetrazoles[5]

To a solution of pure azido acetal at 0 °C in dry nitromethane (0.12 M) (≥99.0% from Aldrich) is added TMSCN (1.2 equiv) then $BF_3 \cdot OEt_2$ dropwise over 2 min. The mixture is stirred at 0 °C for




**Scheme 8.** Side-chain functionalized oxabicyclic tetrazoles.

30 min, then warmed up to room temperature. After 12 h, methanol is added (30 equiv) and the mixture is stirred for 15 min. Evaporation under reduced pressure of the solution yields an oil which can be purified by flash chromatography (EtOAc/hexanes, 80:20). To remove the remaining traces of $BF_3$ complexed to the tetrazole, the solution is filtered on aluminum oxide (activated, basic, Brockmann I) pad with ethyl acetate/MeOH mixture or it was recrystallized from ethyl acetate/MeOH mixture.

*5.1.1. (6R,8R)-(8-Phenyl-5,6-dihydro-8H-tetrazolo[5,1-c][1,4]oxazin-6-yl)-methanol (**8**) and (6R,8S)-(8-phenyl-5,6-dihydro-8H-tetrazolo[5,1-c][1,4]oxazin-6-yl)-methanol (**9**)*

These compounds were obtained according to the general procedure for tetrazoles. From **1**[5] (257 mg, 1.25 mmol) were obtained tetrazoles **8** and **9** as a white solids (cis/trans, 19:1), (273 mg, 94%). Major cis-isomer (**8**): mp 195–197 °C; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ (ppm) 7.48–7.39 (m, 5H), 6.06 (s, 1H), 4.69 (dd, 1H, $J$=2.7, 12.6 Hz), 4.42 (t, 1H, $J$=11.4 Hz), 4.34–4.28 (m, 1H), 3.87 (d, 2H, $J$=4.7 Hz); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ (ppm) 153.1, 136.3, 129.5, 128.3, 128.2, 75.4, 74.8, 62.0, 47.3; FTIR (KBr Disk, cm$^{-1}$) 3348, 3066, 3032, 2993, 2929, 2897, 2872, 1524, 1497, 1477, 1457, 1445, 1429, 1374, 1345, 1280, 1265, 1247, 1153, 1075, 1048, 991, 926, 888, 769, 755; ESI/MS ($m/z$) $[M+1]^+$: 233.1; HRMS (FAB) for $C_{11}H_{12}N_4O_2$: calcd $[M]^+$ 232.0960; found 232.0952; $[\alpha]_D$ −27.3 ($c$ 1.00, MeOH) (>99% ee). Minor trans-isomer (**9**): mp 100–102 °C; $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ (ppm) 7.40–7.32 (m, 5H), 6.45 (s, 1H), 4.62 (dd, 1H, $J$=3.64, 12.8 Hz), 4.33 (dd, 1H, $J$=10.0, 12.8 Hz), 4.12–4.04 (m, 1H), 3.78 (d, 2H, $J$=4.75 Hz); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ (ppm) 151.3, 135.6, 129.2, 129.1, 127.3, 72.3, 68.8, 62.2, 47.5; FTIR (thin film) ($CHCl_3$, cm$^{-1}$) 3390, 3064, 3013, 2934, 1729, 1668, 1598, 1495, 1478, 1448, 1382, 1329, 1274, 1218, 1188, 1150, 1063, 1002, 986, 922, 880, 850, 755, 716, 698; ESI/MS ($m/z$) $[M+1]^+$: 233.1; HRMS (FAB) for $C_{11}H_{12}N_4O_2$: calcd $[M]^+$ 232.0960; found 232.0971; $[\alpha]_D$ −90.4 ($c$ 1.00, MeOH) (>99% ee).

*5.1.2. (6S,8R)-2-(8-Phenyl-5,6-dihydro-8H-tetrazolo[5,1-c][1,4]oxazin-6-yl)-ethanol (**14**)*

This compound was obtained according to the general procedure for tetrazoles. From 4-azidomethyl-2-phenyl-[1,3]dioxane[5] (150 mg, 0.684 mmol) was obtained tetrazole **14** as a white solid (cis/trans, 3:1), (118 mg, 70%). Major cis-isomer: mp 98–100 °C; $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ (ppm) 7.46–7.39 (m, 5H), 6.05 (s, 1H), 4.71 (dd, 1H, $J$=0.99, 9.49 Hz), 4.40–4.33 (m, 1H), 4.35 (dd, 1H, $J$=10.7, 11.7 Hz), 3.81–3.76 (m, 2H), 2.02–1.96 (m, 2H); $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta$ (ppm) 153.2, 136.7, 129.4, 128.7, 128.2, 75.3, 71.5, 57.5, 50.2, 35.5; FTIR (KBr Disk, cm$^{-1}$) 3413, 3060, 3041, 2991, 2942, 1498, 1475, 1458, 1442, 1410, 1385, 1348, 1291, 1246, 1201, 1153, 1096, 1070, 1047, 1028, 997, 897, 747, 694, 679; ESI/MS ($m/z$) $[M+1]^+$: 247.2; HRMS (ESI) for $C_{11}H_{12}N_4O_2$: calcd $[M]^+$ 247.1189; found 247.11832; $[\alpha]_D$ −65.5 ($c$ 1.50, MeOH).

*5.1.3. (trans- and cis-) 8-Benzyl-6-benzyloxymethyl-8-phenyl-5,6-dihydro-8H-tetrazolo[5,1-c][1,4]oxazine (**10**, **11**) and (trans- and cis-) (8-benzyl-8-phenyl-5,6-dihydro-8H-tetrazolo[5,1-c][1,4]oxazin-6-yl)-methanol (**12**, **13**)*

To a solution of tetrazole **8** (50 mg, 0.215 mmol) in THF (1.44 mL (0.15 M)) at −15 °C were added benzyl bromide (38.4 μL, 0.323 mmol, 1.5 equiv) and TBAI (8 mg, 0.0215 mmol, 0.1 equiv),

followed by 60% NaH in mineral oil (17 mg, 0.413 mmol, 2 equiv). The mixture was stirred for 12 h, then quenched with few drops of aqueous $NaHCO_3$. Silica and MeOH were added and the mixture was evaporated under reduced pressure to make a dry solid that was purified by flash chromatography (EtOAc/hexanes, 20:80 to 90:10). For **10**, **11** *C*- and *O*-benzylated products obtained as a colorless gum (40.5 mg, 46%) and as a mixture of diastereomeres (5.3:1): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.84–7.81 (m, 8/25H), 7.69–7.67 (m, 42/25H), 7.44–7.30 (m, 8H), 7.19–7.10 (m, 3H), 7.08–7.06 (m, 42/25H), 6.99–6.97 (m, 8/25), 4.66 (d, 21/25H, $J$=12.1 Hz), 4.64 (d, 21/25H, $J$=12.2 Hz), 4.61 (d, 4/25H, $J$=12.0 Hz), 4.56 (d, 4/25H, $J$=12.1 Hz), 4.73 (dd, 4/25H, $J$=2.98, 12.9 Hz), 4.37 (dd, 21/25, $J$=3.16, 12.6 Hz), 4.18–4.11 (m, 1H), 3.97–3.91 (m, 1H), 3.88 (dd, 21/25H, $J$=5.23, 10.4 Hz), 3.81–3.74 (m, 1H), 3.69 (dd, 4/25H, $J$=5.96, 10.1 Hz), 3.56–3.41 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 152.8, 138.7, 137.1, 134.0, 130.7, 128.4, 128.2, 128.1, 127.6, 127.3, 127.2, 126.5, 125.5, 80.6, 73.3, 69.2, 67.9, 49.5, 47.1; ESI/MS ($m/z$) $[M+1]^+$: 413.2, $[M+Na]^+$: 435.1; HRMS (ESI) for $C_{25}H_{25}N_4O_2$: calcd $[M+1]^+$ 413.1972; found 413.19776; for $C_{25}H_{24}N_4NaO_2$: calcd $[M+Na]^+$ 435.17915; found 435.17983. For **12**, **13** *C*-benzylated products obtained as a colorless gum (16.5 mg, 24%) and as a mixture of diastereomeres (3.9:1): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.81–7.80 (m, 4/10H), 7.66–7.61 (m, 16/10H), 7.42–7.30 (m, 32/10H), 7.22–7.13 (m, 28/10H), 7.06–7.03 (m, 16/10H), 6.97–6.95 (m, 4/10H), 4.48 (dd, 2/10H, $J$=2.74, 12.9 Hz), 4.32 (d, 8/10H, $J$=9.44 Hz), 4.23 (dd, 2/10H, $J$=9.44, 12.9 Hz), 4.08–3.99 (m, 24/10H), 3.95 (dd, 2/10H, $J$=5.74, 10.5 Hz), 3.88–3.84 (m, 12/10H), 3.79 (d, 2/10H, $J$=14.1 Hz), 3.59 (d, 8/10H, $J$=14.0 Hz), 3.54–3.45 (m, 1H), 2.10 (br s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 152.6, 138.6, 134.0, 130.5, 128.4, 128.3, 127.4, 126.7, 125.4, 80.4, 68.6, 62.2, 49.5, 46.0; ESI/MS ($m/z$) $[M+1]^+$: 323.1, $[M+Na]^+$: 345.1; HRMS (ESI) for $C_{18}H_{19}N_4O_2$: calcd $[M+1]^+$ 323.15025; found 323.15178; for $C_{18}H_{18}N_4NaO_2$: calcd $[M+Na]^+$ 345.1322; found 345.13361.

#### 5.1.4. (trans- and cis-) 8-Benzyl-6-(2-benzyloxy-ethyl)-8-phenyl-5,6-dihydro-8H-tetrazolo[5,1-c][1,4]oxazine (**16**) and (trans- and cis-) 2-(8-benzyl-8-phenyl-5,6-dihydro-8H-tetrazolo[5,1-c][1,4]oxazin-6-yl)-ethanol (**15**)

To a solution of tetrazole **14** (50 mg, 0.203 mmol) in THF (1.40 mL (0.15 M)) at −15 °C were added benzyl bromide (36 μL, 0.305 mmol, 1.5 equiv) and TBAI (7.5 mg, 0.0203 mmol, 0.1 equiv), followed by 60% NaH in mineral oil (16.0 mg, 0.406 mmol, 2 equiv). The mixture was stirred for 12 h, then quenched with few drops of aqueous $NaHCO_3$. Silica and MeOH were added and the mixture was evaporated under reduced pressure to make a dry solid that was purified by flash chromatography (EtOAc/hexanes, 20:80 to 90:10) to give **15** and **16** as colorless gums. Major trans-isomer (**16**): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.64–7.61 (m, 2H), 7.37–7.22 (m, 8H), 7.16–7.10 (m, 3H), 7.07–7.04 (m, 2H), 4.51 (d, 1H, $J$=11.7 Hz), 4.46 (d, 1H, $J$=11.7 Hz), 4.29 (dd, 1H, $J$=3.16, 12.7 Hz), 4.09–4.03 (m, 1H), 3.80 (dd, 1H, $J$=10.8, 12.7 Hz), 3.75–3.71 (m, 2H), 3.53 (d, 1H, $J$=13.9 Hz), 3.45–3.42 (d, 1H, $J$=13.9 Hz), 2.13–1.98 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 153.0, 139.3, 137.6, 134.4, 131.0, 128.5, 128.3, 127.7, 127.5, 127.5, 126.7, 125.7, 80.5, 73.1, 66.6, 65.4, 49.8, 49.6, 32.9; FTIR (thin film) ($CHCl_3$, $cm^{-1}$) 3063, 3031, 2925, 2863, 1719, 1495, 1453, 1445, 1366, 1273, 1153, 1132, 1092, 1075, 1028, 768, 748, 699; ESI/MS ($m/z$) $[M+1]^+$: 427.3; HRMS (ESI) for $C_{26}H_{26}N_4O_2$: calcd $[M+1]^+$ 427.21285; found 427.21314. Minor cis-isomer (**16**): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.80–7.77 (m, 2H), 7.39–7.26 (m, 8H), 7.17–7.07 (m, 3H), 6.92–7.90 (m, 2H), 4.58–4.47 (m, 3H), 4.03 (dd, 1H, $J$=10.2, 12.7 Hz), 3.95–3.90 (m, 1H), 3.73 (d, 1H, $J$=14.1 Hz), 3.68–3.62 (m, 2H), 3.46 (d, 1H, $J$=14.1 Hz), 2.14–1.99 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 154.2, 140.4, 137.6, 134.5, 130.3, 128.4, 128.0, 127.8, 127.7, 127.5, 126.9, 125.7, 78.7, 73.1, 68.2, 65.4, 49.9, 47.5, 32.8; FTIR (thin film) ($CHCl_3$, $cm^{-1}$) 3063, 3031, 2925, 2864, 1719, 1496, 1454, 1446, 1365, 1274, 1241, 1146, 1093, 1069, 1030, 750, 700; ESI/MS ($m/z$) $[M+1]^+$: 427.3; HRMS (ESI) for $C_{26}H_{26}N_4O_2$: calcd $[M+1]^+$ 427.21285; found 427.21314. Major trans-isomer (**15**): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 7.61–7.57 (m, 2H), 7.43–7.32 (m, 3H), 7.21–7.12 (m, 3H), 7.06–7.02 (m, 2H), 4.37 (dd, 1H, $J$=3.10, 12.6 Hz), 4.14–4.05 (m, 1H), 3.96–3.92 (m, 2H), 3.89–3.84 (m, 1H), 3.55 (d, 1H, $J$=13.9 Hz), 3.47 (d, 1H, $J$=13.9 Hz), 2.11–1.93 (m, 2H), 1.81 (br s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) 153.5, 139.5, 134.7, 131.4, 130.8, 129.2, 129.1, 128.8, 128.7, 128.2, 127.5, 126.3, 126.2, 81.3, 67.7, 59.2, 50.17, 50.13, 35.4; ESI/MS ($m/z$) $[M+1]^+$: 337.2.

#### 5.1.5. cis-6-(tert-Butyl-diphenyl-silanyloxymethyl)-8-phenyl-5,6-dihydro-8H-tetrazolo[5,1-c][1,4]oxazine (**17a**)

To a solution of tetrazole **8** (1 g, 4.13 mmol) in DMF (14.4 mL (0.3 M)) at room temperature was added imidazole (813 mg, 12.9 mmol, 3 equiv) then, TBDPS-Cl (1.65 mL, 6.46 mmol, 1.5 equiv). The mixture was stirred for 5 h, then quenched with water. The solution was extracted with ether 5 times and extracts were dried on $Na_2SO_4$. Evaporation under reduced pressure yielded an oil which was purified by flash chromatography (EtOAc/hexanes, 25:75 to 35:65) to give **17a** as a white solid (1.80 g, 89%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.69 (d, 4H, $J$=7.54 Hz), 7.50–7.37 (m, 11H), 5.96 (s, 1H), 4.78 (dd, 1H, $J$=2.64, 12.8 Hz), 4.45 (t, 1H, $J$=11.6 Hz), 4.32–4.25 (m, 1H), 4.09 (dd, 1H, $J$=4.67, 10.9 Hz), 3.96 (dd, 1H, $J$=5.99, 10.9 Hz), 1.11 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) 152.6, 136.1, 136.04, 135.96, 133.3, 133.1, 130.5, 129.8, 129.2, 128.40, 128.36, 128.1, 75.5, 74.4, 64.4, 48.1, 27.3, 20.0; FTIR (thin film) ($CHCl_3$, $cm^{-1}$) 3070, 2931, 2857, 1472, 1428, 1391, 1362, 1133, 1113, 1056, 991, 823, 804, 741, 701; ESI/MS ($m/z$) $[M+1]^+$: 471.3; HRMS (ESI) for $C_{27}H_{30}N_4O_2Si$: calcd $[M+1]^+$ 471.22108; found 471.22025.

#### 5.1.6. trans-8-Benzyl-6-(tert-butyl-diphenyl-silanyloxymethyl)-8-phenyl-5,6-dihydro-8H-tetrazolo[5,1-c][1,4]oxazine (**18a**)

To a solution of tetrazole **17a** (100 mg, 0.212 mmol) in THF (1.4 mL (0.15 M)) at −78 °C was added benzyl bromide (0.028 mL, 0.234 mmol, 1.1 equiv), followed by LiHMDS 1 M in THF (0.256 mL, 0.255 mmol, 1.2 equiv) dropwise. The mixture was stirred for 4 h, then quenched with aqueous $NaHCO_3$. The solution was extracted with ether and extracts were dried on $Na_2SO_4$. Evaporation under reduced pressure yielded an oil which was purified by flash chromatography (EtOAc/hexanes, 15:85 to 30:70) to give **18a** as a colorless gum (103 mg, 87%). Major trans-isomer (**18a**): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 7.79–7.72 (m, 6H), 7.57–7.45 (m, 6H), 7.43–7.35 (m, 3H), 7.19–7.09 (m, 5H), 4.36 (dd, 1H, $J$=2.99, 12.4 Hz), 4.16–4.08 (m, 1H), 4.04–3.89 (m, 3H), 3.57 (d, 1H, $J$=14.0 Hz), 3.48 (d, 1H, $J$=14.0 Hz), 1.15 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) 154.2, 140.0, 136.5, 136.4, 135.3, 133.4, 131.9, 131.0, 129.6, 129.3, 128.8, 128.5, 127.7, 126.8, 81.8, 70.7, 64.7, 50.8, 48.1, 27.6, 20.1; FTIR (thin film) ($CHCl_3$, $cm^{-1}$) 3068, 3032, 2958, 2930, 2893, 2858, 1495, 1471, 1454, 1445, 1428, 1129, 1113, 1087, 1065, 1021, 824, 771, 743, 701; ESI/MS ($m/z$) $[M+1]^+$: 561.3; HRMS (ESI) for $C_{34}H_{36}N_4O_2Si$: calcd $[M+1]^+$ 561.26803; found 561.26858.

#### 5.1.7. trans-8-Benzyl-6-methyl-8-phenyl-5,6-dihydro-8H-tetrazolo[5,1-c][1,4]oxazine (**18b**)

To a solution of tetrazole **17b** (108 mg, 0.499 mmol) in THF (3.33 mL (0.15 M)) at −78 °C was added benzyl bromide (65 μL, 5.49 mmol, 1.1 equiv), followed by LiHMDS 1 M in THF (0.60 mL, 0.60 mmol, 1.2 equiv) dropwise. The mixture was stirred for 4 h, then quenched with aqueous $NaHCO_3$. The solution was extracted with ether and extracts were dried on $Na_2SO_4$. Evaporation under reduced pressure yielded an oil which was purified by flash chromatography (EtOAc/hexanes, 15:85 to 30:70) to give **18b** as a colorless gum (144 mg, 94%) Major trans-isomer (**18b**): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 7.70–7.63 (m, 2H), 7.44–7.33 (m, 3H), 7.19–7.07 (m, 5H), 4.29 (dd, 1H, $J$=3.04, 12.5 Hz), 4.06–3.96 (m, 1H),

3.72 (dd, 1H, *J*=10.7, 12.5 Hz), 3.52 (d, 1H, *J*=13.9 Hz), 3.43 (d, 1H, *J*=13.9 Hz), 1.50 (d, 3H, *J*=6.20 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) 154.0, 140.0, 135.4, 131.9, 129.6, 129.3, 128.5, 127.7, 126.6, 81.6, 66.2, 51.7, 50.8, 18.8; FTIR (thin film) ($CHCl_3$, $cm^{-1}$) 3036, 3032, 2980, 2930, 1495, 1442, 1388, 1373, 1150, 1076, 1018, 959, 771, 748, 700; ESI/MS (*m*/*z*) $[M+1]^+$: 307.1; HRMS (ESI) for $C_{18}H_{18}N_4O$: calcd $[M+1]^+$ 307.15534; found 307.15655.

### 5.1.8. (trans- and cis-) 6-(tert-Butyl-diphenyl-silanyloxymethyl)-8-methyl-8-phenyl-5,6-dihydro-8H-tetrazolo[5,1-c][1,4]oxazine (**18c**, **19c**)

To a solution of tetrazole **17a** (350 mg, 0.744 mmol) in THF (7.4 mL (0.1 M)) at −100 °C was added methyl iodide (51 μL, 0.818 mmol, 1.1 equiv), followed by LiHMDS 1 M in THF (0.892 mL, 0.892 mmol, 1.2 equiv) dropwise. The mixture was stirred for 4 h, then quenched with aqueous $NaHCO_3$. The solution was extracted with ether and extracts were dried on $Na_2SO_4$. Evaporation under reduced pressure yielded an oil which was purified by flash chromatography (EtOAc/hexanes, 15:85 to 30:70) to give **18c** and **19c** as colorless gums (338 mg, 94%). Major trans-isomer (**18c**): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.73–7.69 (m, 4H), 7.54–7.39 (m, 8H), 7.38–7.35 (m, 3H), 4.50 (dd, 1H, *J*=3.42, 12.7 Hz), 4.28 (dd, 1H, *J*=10.8, 12.6 Hz), 4.09–4.05 (m, 1H), 4.02 (dd, 1H, *J*=5.33, 10.7 Hz), 3.89 (dd, 1H, *J*=5.02, 10.8 Hz), 1.94 (s, 3H), 1.12 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 154.2, 140.0, 135.3, 135.1, 132.3, 132.2, 129.71, 129.66, 128.5, 128.0, 127.5, 125.0, 77.8, 68.9, 63.6, 47.2, 30.7, 26.4, 18.9; FTIR (thin film) ($CHCl_3$, $cm^{-1}$) 3071, 2932, 2859, 1494, 1472, 1447, 1428, 1371, 1221, 1166, 1114, 1049, 997, 967, 911, 824, 808, 770, 738, 702; ESI/MS (*m*/*z*) $[M+1]^+$: 485.3; HRMS (ESI) for $C_{28}H_{32}N_4O_2Si$: calcd $[M+1]^+$ 485.2367; found 485.23625. Minor cis-isomer (**19c**): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.78–7.71 (m, 6H), 7.51–7.31 (m, 9H), 4.75 (d, 1H), 4.33–4.25 (m, 2H), 4.10 (dd, 1H, *J*=4.14, 10.7 Hz), 3.99 (dd, 1H, *J*=5.52, 10.7 Hz), 1.96 (s, 3H), 1.13 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 154.9, 141.1, 135.2, 132.3, 132.2, 129.7, 128.0, 127.9, 127.6, 125.1, 69.0, 63.7, 47.8, 26.9, 26.4, 18.9; FTIR (thin film) ($CHCl_3$, $cm^{-1}$) 3072, 2932, 2859, 1496, 1472, 1446, 1428, 1377, 1232, 1114, 1068, 944, 910, 824, 767, 741, 701; ESI/MS (*m*/*z*) $[M+1]^+$: 485.5; HRMS (ESI) for $C_{28}H_{32}N_4O_2Si$: calcd $[M+1]^+$ 485.2367; found 485.23619.

### 5.1.9. (trans- and cis-) 8-Allyl-6-(tert-butyl-diphenyl-silanyloxymethyl)-8-phenyl-5,6-dihydro-8H-tetrazolo[5,1-c]-[1,4]oxazine (**18d** and **19d**)

To a solution of tetrazole **17a** (50.0 mg, 0.106 mmol) in THF (1.1 mL (0.1 M)) at −100 °C was added allyl iodide (10.7 μL, 0.117 mmol, 1.1 equiv), followed by LiHMDS 1 M in THF (138 μL, 0.138 mmol, 1.2 equiv) dropwise. The mixture was stirred for 4 h, then quenched with aqueous $NaHCO_3$. The solution was extracted with ether and extracts were dried on $Na_2SO_4$. Evaporation under reduced pressure yielded an oil which was purified by flash chromatography (EtOAc/hexanes, 15:85 to 30:70) to give **18d** and **19d** as colorless gums (51.5 mg, 95%). Major trans-isomer (**18d**): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 7.78–7.73 (m, 4H), 7.67–7.64 (m, 2H), 7.55–7.35 (m, 9H), 5.67 (ddt, 1H, *J*=7.08, 10.2, 17.2 Hz), 5.07 (dd, 1H, *J*=1.57, 17.4 Hz), 5.03 (d, 1H, *J*=9.05 Hz), 4.50 (dd, 1H, *J*=3.25, 12.5 Hz), 4.30 (dd, 1H, *J*=10.8, 12.5 Hz), 4.17–4.09 (m, 1H), 4.04 (dd, 1H, *J*=5.18, 10.9 Hz), 3.95 (dd, 1H, *J*=4.72, 10.9 Hz), 3.04 (dd, 1H, *J*=7.64, 14.3 Hz), 2.95 (dd, 1H, *J*=6.57, 14.3 Hz), 1.14 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) 154.4, 139.9, 136.5, 136.4, 133.5, 133.4, 131.7, 130.99, 130.91, 129.6, 129.3, 128.8, 126.6, 121.0, 81.4, 70.3, 64.7, 49.0, 48.2, 27.6, 20.1; FTIR (thin film) ($CHCl_3$, $cm^{-1}$) 3071, 2999, 2957, 2931, 2894, 2858, 1642, 1589, 1493, 1472, 1441, 1428, 1159, 1113, 1069, 998, 923, 824, 743, 702; ESI/MS (*m*/*z*) $[M+1]^+$: 511.3; HRMS (ESI) for $C_{30}H_{34}N_4O_2Si$: calcd $[M+1]^+$ 511.25238; found 511.25319. Minor cis-isomer (**19d**): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 7.87–7.84 (m, 2H), 7.77–7.73 (m, 4H), 7.55–7.31 (m, 9H), 5.63–5.49 (m, 1H), 5.04–4.98 (m, 2H), 4.76 (dd, 1H, *J*=2.20, 12.1 Hz), 4.41–4.34 (m, 1H), 4.29 (dd, 1H, *J*=10.3, 12.0 Hz), 4.09 (dd, 1H, *J*=4.36, 10.8 Hz), 4.01 (dd, 1H, *J*=5.75, 10.8 Hz), 3.12 (dd, 1H, *J*=6.69, 14.6 Hz), 3.05 (dd, 1H, *J*=7.02, 14.7 Hz), 1.15 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) 155.5, 140.4, 136.44, 136.41, 133.5, 133.4, 131.5, 131.0, 129.1, 129.0, 128.8, 126.8, 120.8, 79.1, 70.6, 64.7, 48.9, 45.2, 27.6, 20.1; FTIR (thin film) ($CHCl_3$, $cm^{-1}$) 3071, 2956, 2930, 2892, 2857, 1641, 1598, 1494, 1471, 1446, 1428, 1155, 1112, 1073, 1064, 993, 921, 823, 808, 741, 702; ESI/MS (*m*/*z*) $[M+1]^+$: 511.3; HRMS (ESI) for $C_{30}H_{34}N_4O_2Si$: calcd $[M+1]^+$ 511.25238; found 511.25367.

### 5.1.10. (8,8-Dimethyl-5,6-dihydro-8H-tetrazolo[5,1-c][1,4]oxazin-6-yl)methanol (**20**)

This compound was obtained according to the general procedure for tetrazoles. From 4-azidomethyl-2,2-dimethyl-[1,3]dioxolane[5] (2.16 g, 13.7 mmol) was obtained tetrazole **20** as a white solid (1.90 g, 75%): $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ (ppm) 4.62 (dd, 1H, *J*=2.82, 12.2 Hz), 4.32–4.28 (m, 1H), 4.22 (dd, 1H, *J*=10.7, 12.2 Hz), 3.83–3.82 (m, 2H), 1.68 (s, 3H), 1.66 (s, 3H); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ (ppm) 157.8, 74.3, 70.3, 63.1, 48.3, 28.8, 25.9; FTIR (KBr Disk, $cm^{-1}$) 3497, 2995, 2968, 2926, 2886, 1478, 1439, 1411, 1385, 1363, 1343, 1276, 1253, 1237, 1189, 1162, 1142, 1070, 1033, 995, 976, 898, 825, 771; ESI/MS (*m*/*z*) $[M+1]^+$: 185.1; HRMS (ESI) for $C_7H_{12}N_4O_2$: calcd $[M+1]^+$ 185.10330; found 185.10410.

### 5.1.11. 3-[5-(1-Hydroxy-1-methylethyl)-tetrazol-1-yl]propenol (**22**)

To a solution of **20** (147 mg, 0.80 mmol) in THF (8.0 mL (0.1 M)) at −78 °C was added dropwise *t*-BuLi 1.7 M in pentane (1.17 mL, 2.00 mmol, 2.5 equiv). The reaction mixture was stirred 30 min, then quenched slowly with few drops of aqueous $NH_4Cl$. Silica and MeOH were added and the mixture was evaporated under reduced pressure to a dry solid that purified by flash chromatography (EtOAc/hexanes1:1) to give **22** as a white solid (116 mg, 79%): $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ (ppm) 7.81 (dt, 1H, *J*=2.01, 14.0 Hz), 6.75 (dt, 1H, *J*=4.85, 14.0 Hz), 4.33 (dd, 2H, *J*=1.99, 4.85 Hz), 1.70 (s, 6H); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ (ppm) 157.8, 125.8, 121.3, 67.4, 58.7, 27.9; FTIR (thin film) ($CHCl_3$, $cm^{-1}$) 3306, 2991, 2901, 1675, 1459, 1414, 1372, 1260, 1183, 1148, 1105, 1007, 968, 944, 923, 865; ESI/MS (*m*/*z*) $[M+1]^+$: 185.1.

### 5.1.12. 2-(5′,6′-Dihydrospiro[cyclohexane-1,8′-tetrazolo[5,1-c]-[1,4]oxazine]-6′-yl)ethanol (**21**)

This compound was obtained according to the general procedure for tetrazoles. From 2-(azidomethyl)-1,5-dioxaspiro[5.5]undecane[5] (150 mg, 0.71 mmol) was obtained tetrazole **21** as a colorless gum (67 mg, 40%): $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ (ppm) 4.62 (dd, 1H, *J*=3.05, 12.6 Hz), 4.34–4.28 (m, 1H), 4.11 (dd, 1H, *J*=10.6, 12.6 Hz), 3.86–3.83 (m, 2H), 2.21–2.19 (m, 1H), 2.11–2.03 (m, 1H), 1.99–1.94 (m, 2H), 1.87–1.67 (m, 7H), 1.49–1.46 (m, 1H); $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta$ (ppm) 156.8, 74.2, 65.1, 58.9, 50.3, 36.8, 35.4, 32.5, 25.0, 21.0, 20.8; ESI/MS (*m*/*z*) $[M+1]^+$: 239.2.

### 5.1.13. 1-[1-(4-Hydroxy-but-1-enyl)-1H-tetrazol-5-yl]-cyclohexanol (**23**)

To a solution of **21** (40.0 mg, 0.168 mmol) in THF (1.7 mL (0.1 M)) at −78 °C was added dropwise *t*-BuLi 1.7 M in pentane (0.247 mL, 0.420 mmol, 2.5 equiv). The reaction mixture was stirred 30 min, then quenched slowly with few drops of aqueous $NH_4Cl$. Silica and MeOH were added and the mixture is evaporated under reduced pressure to a dry solid that was purified by flash chromatography (EtOAc/hexanes 1:1) to give **23** as a colorless gum (32.2 mg, 81%): $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ (ppm) 7.65 (d, 1H, *J*=12.0 Hz), 6.61 (dt, 1H, *J*=6.2, 12.0 Hz), 3.74 (t, 2H, *J*=6.2 Hz), 2.51–2.43 (m, 2H), 2.03–1.92 (m, 4H), 1.87–1.72 (m, 2H), 1.55–1.72 (m, 3H), 1.45–1.22 (m, 3H); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ (ppm) 159.5, 125.6, 124.4, 70.4, 61.8, 37.7, 34.1, 26.2, 22.2; FTIR (thin film) ($CHCl_3$, $cm^{-1}$) 3339, 3108,

2935, 2858, 1721, 1669, 1448, 1419, 1350, 1261, 1251, 1160, 1140, 1041, 984, 953, 909, 850, 755; ESI/MS (*m*/*z*) $[M+1]^+$: 239.1; HRMS (ESI) for $C_{11}H_{12}N_4O_2$: calcd $[M]^+$ 239.1502; found 239.14972.

*5.1.14. 1-{1-[3-(tert-Butyl-diphenyl-silanyloxy)-propenyl]-1H-tetrazol-5-yl}-1-phenyl-ethanol (**24**)*

To a solution of **20** (245 mg, 5.06 mmol) in ether (10.1 mL (0.05 M)) at −90 °C was added dropwise *t*-BuLi 1.7 M in pentane (0.446 mL 0.758 mmol, 1.5 equiv). The reaction mixture was stirred 30 min, then quenched slowly with aqueous $NH_4Cl$. The mixture was extracted with ether, then dried on $Na_2SO_4$. After evaporation under reduced pressure, the crude residue was purified by flash chromatography (EtOAc/hexanes 15:85 to 30:70) to give **24** as a white solid (230 mg, 94%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.64–7.62 (m, 2H), 7.60–7.57 (m, 2H), 7.48–7.43 (m, 2H), 7.40–7.27 (m, 10H), 6.55 (dt, 1H, *J*=3.53, 13.7 Hz), 4.30 (ddd, 1H, *J*=2.43, 3.49, 16.4 Hz), 4.22 (ddd, 1H, *J*=2.42, 3.52, 16.4 Hz), 3.64 (br s, 1H), 2.18 (s, 3H), 1.08 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 156.4, 142.2, 135.1, 135.0, 132.5, 132.4, 129.53, 129.48, 128.4, 127.6, 127.5, 127.4, 124.9, 124.1, 120.2, 71.6, 60.8, 31.5, 26.4, 18.8; FTIR (thin film) ($CHCl_3$, $cm^{-1}$) 3325, 3071, 2959, 2932, 2857, 1472, 1448, 1428, 1377, 1134, 1113, 1073, 966, 939, 823, 768, 741, 701; ESI/MS (*m*/*z*) $[M+1]^+$: 485.3; HRMS (ESI) for $C_{28}H_{33}N_4O_2Si$: calcd $[M+1]^+$ 485.23673; found 485.23626; for $C_{28}H_{32}N_4NaO_2Si$: calcd $[M+Na]^+$ 507.21867; found 507.21818.

*5.1.15. 2-(1H-Tetrazol-5-yl)propan-2-ol (**25**)*

Into a solution of **22** (116 mg, 0.63 mmol) in MeOH (2 mL (0.3 M)), was bubbled ozone for 30 min. Then, $H_2O_2$ 30% (300 μL, 2.8 mmol, 4.5 equiv) was added and the solution was stirred for 30 min. After evaporation under reduced pressure, the crude residue was dissolved in water and washed 3 times with DCM. The water solution was lyophilized to give **25** as a white solid (79 mg, 99%): $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ (ppm) 1.65 (s, 6H); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ (ppm) 164.7, 68.7, 30.1; ESI/MS (*m*/*z*) $[M+1]^+$: 129.1.

*5.1.16. 1-Phenyl-1-(1H-tetrazol-5-yl)-ethanol (**26**)*

Into a solution of **24** (36.4 mg, 0.0751 mmol) in formic acid/DCM (4:1) (2.5 mL (0.03 M)), was bubbled ozone for 30 min. Then, $H_2O_2$ 30% (510 μL, 60 equiv) was added and the solution was refluxed for 30 min. $H_2O_2$ 30% (510 μL, 60 equiv) was again added and the solution was refluxed for an extra 30 min. After evaporation under reduced pressure, the crude solid was purified by flash chromatography (MeOH/EtOAc 10:90 to 30:70). Remaining silica in the final product was precipitated in EtOAc/DCM (1:1) solution and filtered on cotton pad to give **26** as a white solid (14.1 mg, 99%): $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ (ppm) 7.52 (d, 2H, *J*=7.32 Hz), 7.35 (t, 2H, *J*=7.52 Hz), 7.29–7.26 (m, 1H), 2.03 (s, 3H); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ (ppm) 163.2, 145.0, 128.4, 127.7, 125.0, 71.2, 29.1; FTIR (thin film) ($CHCl_3$, $cm^{-1}$) 3350, 2986, 2929, 2855, 1548, 1494, 1447, 1373, 1216, 1146, 1073, 1029, 914, 746, 697, 666; ESI/MS (*m*/*z*) $[M+1]^+$: 191.1, $[M+Na]^+$: 213.1; HRMS (ESI) for $C_9H_{11}N_4O$: calcd $[M+1]^+$ 191.09274; found 191.09309; for $C_9H_{10}N_4NaO$: calcd $[M+Na]^+$ 213.07468; found 213.07411.

*5.1.17. cis-8-Azido-6-(tert-butyl-diphenyl-silanyloxymethyl)-8-phenyl-5,6-dihydro-8H-tetrazolo[5,1-c][1,4]oxazine (**27**) and [6-(tert-butyl-diphenyl-silanyloxymethyl)-5,6-dihydro-tetrazolo-[5,1-c][1,4]oxazin-8-ylidene]-phenyl-amine (**28**)*

To a solution of ICl (1.38 g, 8.50 mmol, 2 equiv), in MeCN (14.2 mL (0.3 M)) at −10 °C was added a solution of $NaN_3$ (1.30 g, 20.0 mmol, 4.7 equiv), in MeCN (8.50 mL (0.5 M)). After 15 min, the cooling bath was removed and the tetrazole **8a** (2.17 g, 4.25 mmol) was added. The mixture was heated to reflux for 24 h and a pre-mixed solution of ICl (1 equiv, 0.3 M) and $NaN_3$ (2.4 equiv, 0.5 M) in MeCN, obtained as previously described, was added. The mixture was heated for an additional 12 h, and the solution was cooled down to room temperature, prior to the addition of a 5% $Na_2S_2O_3$ solution. The aqueous phase was extracted with EtOAc (3 times), the combined organic phases were dried with $Na_2SO_4$, and evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexanes, 10:90 to 20:80). For (**27**), a colorless gum (1.26 g, 58%): $^1$H NMR (300 MHz, $CD_2Cl_2$) $\delta$ (ppm) 8.00–7.98 (m, 2H), 7.80–7.78 (m, 4H), 7.54–7.47 (m, 9H), 4.87–4.80 (m, 1H), 4.78 (dd, 1H, *J*=3.23, 15.6 Hz), 4.51 (dd, 1H, *J*=11.1, 12.8 Hz), 4.17 (d, 2H, *J*=4.36 Hz), 1.16 (s, 9H); $^{13}$C NMR (75 MHz, $CD_2Cl_2$) $\delta$ (ppm) 151.5, 136.0, 133.0, 130.7, 130.5, 129.2, 128.37, 128.35, 127.0, 90.8, 70.7, 63.8, 47.6, 27.0, 19.5; FTIR (thin film) (DCM, $cm^{-1}$) 3071, 2931, 2858, 2113, 1449, 1211, 1134, 1113, 1051; ESI/MS (*m*/*z*) $[M+1]^+$: 512.2; HRMS (ESI) for $C_{27}H_{29}N_7O_2Si$: calcd $[M+1]^+$ 512.22248; found 512.22291. For (**28**), a white solid (0.512 g, 25%): $^1$H NMR (300 MHz, $CD_2Cl_2$) $\delta$ (ppm) 7.70–7.61 (m, 4H), 7.57–7.36 (m, 10H), 7.29–7.23 (m, 1H), 5.00–4.92 (m, 1H), 4.86–4.78 (m, 2H), 4.05 (dd, 1H, *J*=3.54, 11.7 Hz), 3.99 (dd, 1H, *J*=3.36, 11.7 Hz), 1.06 (s, 9H); $^{13}$C NMR (75 MHz, $CD_2Cl_2$) $\delta$ (ppm) 146.9, 144.4, 140.8, 136.4, 136.3, 132.9, 132.7, 131.0, 130.9, 129.6, 128.81, 128.79, 126.8, 124.8, 77.1, 64.1, 47.0, 27.2, 19.8; FTIR (thin film) ($CHCl_3$, $cm^{-1}$) 3071, 3052, 2957, 2931, 2892, 2858, 1682, 1590, 1531, 1485, 1472, 1428, 1268, 1220, 1166, 1114, 1047, 1025, 978, 823, 770, 740, 702; ESI/MS (*m*/*z*) $[M+1]^+$: 484.2; HRMS (ESI) for $C_{27}H_{29}N_5O_2Si$: calcd $[M+1]^+$ 484.2163; found 484.21492.

*5.1.18. cis-(8-Azido-8-phenyl-5,6-dihydro-8H-tetrazolo[5,1-c]-[1,4]oxazin-6-yl)-methanol (**29**) and (8-phenylimino-5,6-dihydro-8H-tetrazolo[5,1-c][1,4]oxazin-6-yl)-methanol (**30**)*

To a solution of ICl (5.24 g, 32.2 mmol, 2.5 equiv), in MeCN (43 mL (0.3 M)) at −10 °C was added a solution of $NaN_3$ (4.95 g, 76.2 mmol, 5.9 equiv) in MeCN (26 mL (0.5 M)). After 15 min, the cooling bath was removed and the tetrazole **31** (3.0 g, 12.9 mmol) was added. The mixture was heated to reflux for 36 h, and the solution was cooled down to room temperature, prior to the addition of a 5% $Na_2S_2O_3$ solution. The aqueous phase was then extracted with EtOAc (5 times), the combined organic phases were dried with $Na_2SO_4$ and evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexanes, 50:50 to 75:25). For (**29**), a colorless gum (2.10 g, 59%): $^1$H NMR (300 MHz, $CD_2Cl_2$) $\delta$ (ppm) 7.97–7.94 (m, 2H), 7.54–7.49 (m, 3H), 4.82–4.69 (m, 2H), 4.50 (dd, 1H, *J*=11.1, 13.0 Hz), 4.15 (dd, 1H, *J*=3.87, 12.3 Hz), 4.07 (dd, 1H, *J*=4.49, 12.3 Hz), 2.63 (br s, 1H); $^{13}$C NMR (100 MHz, $CD_2Cl_2$) $\delta$ (ppm) 151.4, 135.9, 130.7, 129.2, 126.9, 90.7, 70.8, 62.3, 47.1; FTIR (thin film) (DCM, $cm^{-1}$) 3401, 2929, 2115, 1449, 1213, 1153, 1056, 1030; ESI/MS (*m*/*z*) $[M+1]^+$: 274.0; HRMS (ESI) for $C_{11}H_{11}N_7O_2$: calcd $[M+1]^+$ 274.10470; found 274.10497. For (**30**), a white solid (0.526 g, 17%): ESI/MS (*m*/*z*) $[M+1]^+$: 246.1; HRMS (ESI) for $C_{11}H_{11}N_5O_2$: calcd $[M+1]^+$ 246.0986; found 246.09839.

*5.1.19. cis-[8-(3,5-Dimethoxy-phenyl)-5,6-dihydro-8H-tetrazolo[5,1-c][1,4]oxazin-6-yl]-methanol*

This compound was obtained according to the general procedure for tetrazoles. From 4-azidomethyl-2-(3,5-dimethoxy-phenyl)-[1,3]dioxolane corresponding to **1**[5] (3.21 g, 12.1 mmol) was obtained tetrazole as a white solid (cis/trans, 19:1), (3.00 g, 85%). Major cis-isomer: $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ (ppm) 6.68 (d, 1H, *J*=2.24 Hz), 6.53 (t, 1H, *J*=2.24 Hz), 6.03 (s, 1H), 4.71 (dd, 1H, *J*=3.24, 12.6 Hz), 4.46 (dd, 1H, *J*=11.1, 11.7 Hz), 4.35–4.30 (m, 1H), 3.90 (d, 2H, *J*=5.08 Hz), 3.79 (s, 6H); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ (ppm) 160.7, 152.2, 137.6, 105.3, 100.4, 74.5, 74.1, 61.1, 54.1, 46.4; FTIR (thin film) ($CHCl_3$, $cm^{-1}$) 3402, 2937, 2842, 1598, 1463, 1432, 1345, 1297, 1205, 1156, 1062, 832; ESI/MS (*m*/*z*) $[M+1]^+$: 293.1, $[M+Na]^+$: 315.1; HRMS (ESI) for $C_{13}H_{17}N_4O_4$: calcd $[M+1]^+$ 293.12443; found 293.12389; for $C_{13}H_{16}N_4NaO_4$: calcd $[M+Na]^+$ 315.10638; found 315.10593.

*5.1.20. cis-6-(tert-Butyl-diphenyl-silanyloxymethyl)-8-(3,5-dimethoxy-phenyl)-5,6-dihydro-8H-tetrazolo[5,1-c][1,4]-oxazine (**31**)*

See procedure for (**17a**): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.71–7.68 (m, 4H), 7.50–7.45 (m, 2H), 7.44–7.38 (m, 4H), 6.63 (d, $J$=2.20 Hz), 6.50 (t, $J$=4.52 Hz), 5.89 (s, 1H), 4.77 (dd, 1H, $J$=2.50, 12.8 Hz), 4.45 (dd, $J$=10.8, 11.9 Hz), 4.29–4.23 (m, 1H), 4.09 (dd, 1H, $J$=4.60, 10.9 Hz), 3.97 (dd, 1H, $J$=6.00, 10.9 Hz), 3.78 (s, 6H), 1.11 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 160.6, 151.6, 136.8, 135.24, 135.15, 132.2, 132.0, 129.7, 127.6, 127.5, 105.1, 101.1, 74.8, 73.6, 63.5, 55.1, 47.5, 26.4, 18.9; FTIR (thin film) ($CHCl_3$, cm$^{-1}$) 3071, 3049, 3000, 2932, 2890, 2857, 1599, 1462, 1428, 1359, 1295, 1205, 1157, 1134, 1113, 1062, 911, 823, 806, 737, 703; ESI/MS ($m/z$) $[M+1]^+$: 531.3, $[M+Na]^+$: 553.2; HRMS (ESI) for $C_{29}H_{35}N_4O_4Si$: calcd $[M+1]^+$ 531.24221; found 531.24315; for $C_{29}H_{34}N_4NaO_4Si$: calcd $[M+Na]^+$ 553.22415; found 553.22449.

*5.1.21. cis-8-Azido-6-(tert-butyl-diphenyl-silanyloxymethyl)-8-(3,5-dimethoxy-phenyl)-5,6-dihydro-8H-tetrazolo[5,1-c][1,4]oxazine (**33**), [6-(tert-butyl-diphenyl-silanyloxymethyl)-5,6-dihydro-tetrazolo[5,1-c][1,4]oxazin-8-ylidene]-(3,5-dimethoxy-phenyl)-amine (**34**) and {1-[3-(tert-butyl-diphenyl-silanyloxy)-2-hydroxy-propyl]-1H-tetrazol-5-yl}-(3,5-dimethoxy-phenyl)-methanone (**35**)*

To a solution of ICl (180 mg, 1.11 mmol, 3 equiv) in MeCN (1.23 mL (0.3 M)) at −10 °C was added a solution of $NaN_3$ (171 mg, 2.62 mmol, 7.1 equiv) in MeCN (0.74 mL (0.5 M)). After 15 min, the cooling bath was removed and the tetrazole **31** (196 mg, 0.369 mmol) was added. The mixture was heated to reflux for 24 h, and the solution was cooled down to room temperature, prior to the addition of a 5% $Na_2S_2O_3$ solution. The aqueous phase was then extracted with EtOAc (3 times), the combined organic phases were dried with $Na_2SO_4$ and evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexanes, 10:90 to 20:80). For (**33**), a colorless gum (116 mg, 55%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.76–7.72 (m, 4H), 7.53–7.42 (m, 6H), 7.15 (d, 2H, $J$=2.28 Hz), 6.55 (t, 1H, $J$=2.26 Hz), 4.77–4.71 (m, 2H), 4.43 (dd, 1H, $J$=11.6, 13.5 Hz), 4.16–4.07 (m, 2H), 3.84 (s, 6H), 1.14 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 160.7, 150.7, 137.0, 135.2, 132.0, 129.9, 129.8, 127.69, 127.67, 104.3, 101.8, 89.9, 69.8, 63.0, 55.2, 47.0, 26.4, 18.9; FTIR (thin film) ($CHCl_3$, cm$^{-1}$) 3072, 3001, 2933, 2858, 2116, 1598, 1462, 1427, 1350, 1327, 1298, 1206, 1158, 1134, 1112, 1064, 1043, 1007, 936, 842, 824, 740, 703; ESI/MS ($m/z$) $[M+1]^+$: 572.3, $[M+Na]^+$: 594.3, $[M-N_3]^+$: 529.3; HRMS (ESI) for $C_{29}H_{34}N_7O_4Si$: calcd $[M+1]^+$ 572.24361; found 572.24374; for $C_{29}H_{33}N_7NaO_4Si$: calcd $[M+Na]^+$ 594.22555; found 594.22586. For (**34**), a colorless gum (39 mg, 19%): $^1$H NMR (400 MHz, $CD_2Cl_2$) $\delta$ (ppm) 7.65–7.59 (m, 4H), 7.52–7.35 (m, 6H), 6.49 (d, 2H, $J$=2.28 Hz), 6.38 (t, 1H, $J$=2.26 Hz), 4.94 (dd, 1H, $J$=3.26, 12.9 Hz), 4.86–4.74 (m, 2H), 4.02 (dd, 1H, $J$=4.20, 12.8 Hz), 3.96 (dd, 1H, $J$=3.40, 11.6 Hz), 3.77 (s, 6H), 1.03 (s, 9H); $^{13}$C NMR (100 MHz, $CD_2Cl_2$) $\delta$ (ppm) 160.5, 145.0, 139.8, 137.3, 135.11, 135.06, 131.7, 131.4, 129.7, 129.6, 127.5, 127.4, 101.2, 97.6, 75.8, 62.8, 55.0, 45.8, 26.0, 18.5; ESI/MS ($m/z$) $[M+1]^+$: 544.3, $[M+Na]^+$: 566.3; HRMS (ESI) for $C_{29}H_{34}N_5O_4Si$: calcd $[M+1]^+$ 544.23746; found 544.23764; for $C_{29}H_{33}N_5NaO_4Si$: calcd $[M+Na]^+$ 566.2194; found 566.21934. For (**35**), a colorless gum (16 mg, 8%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.69–6.65 (m, 4H), 7.55 (d, 2H, 2.32 Hz), 7.49–7.34 (m, 6H), 6.82 (t, 1H, $J$=2.30 Hz), 4.98 (dd, 1H, $J$=8.64, 13.8 Hz), 4.84 (dd, 1H, $J$=3.54, 13.8 Hz), 4.17–4.07 (m, 1H), 3.89 (s, 6H), 3.81 (dd, 1H, $J$=4.60, 6.04 Hz), 3.71 (dd, 1H, $J$=4.80, 10.6 Hz), 1.11 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 181.8, 160.8, 150.5, 136.4, 135.4, 134.6, 134.2, 132.3, 132.3, 130.0, 127.80, 127.73, 108.5, 180.1, 70.4, 64.6, 55.6, 51.4, 26.7, 19.1; ESI/MS ($m/z$) $[M+1]^+$: 547.3, $[M+Na]^+$: 569.3; HRMS (ESI) for $C_{29}H_{35}N_4O_5Si$: calcd $[M+1]^+$ 547.23712; found 547.23661; for $C_{29}H_{34}N_4NaO_5Si$: calcd $[M+Na]^+$ 569.21907; found 569.21894.

*5.1.22. cis-(8-Pentafluorophenyl-5,6-dihydro-8H-tetrazolo[5,1-c][1,4]oxazin-6-yl)-methanol*

This compound was obtained according to the general procedure for tetrazoles. From 4-azidomethyl-2-pentafluorophenyl-[1,3]dioxolane corresponding to **1**[5] (0.5 g, 1.69 mmol) was obtained tetrazole as a white solid (cis/trans, 3:1), (266 mg, 49%). Major cis-isomer: $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ (ppm) 6.39 (s, 1H), 4.72 (dd, 1H, $J$=3.77, 13.2 Hz), 4.58 (dd, 1H, $J$=9.56, 13.2 Hz), 4.25–4.22 (m, 1H), 3.99 (dd, 1H, $J$=3.48, 12.2 Hz), 3.91–3.88 (m, 1H), 2.56 (br s, 1H); $^{13}$C NMR (233 MHz, $CDCl_3$) $\delta$ (ppm) 150.0, 145.6 (d, $J$=337 Hz), 142.7 (d, $J$=343 Hz), 137.8 (d, $J$=337 Hz), 109.6, 74.8, 65.0, 62.1, 46.7; FTIR (thin film) ($CHCl_3$, cm$^{-1}$) 3409, 3062, 2932, 1659, 1505, 1435, 1373, 1307, 1268, 1133, 1070, 972, 877, 853, 777, 739; ESI/MS ($m/z$) $[M+1]^+$: 323.0, $[M+Na]^+$: 355.1; HRMS (ESI) for $C_{11}H_8F_5N_4O_2$: calcd $[M+1]^+$ 323.05619; found 323.05627; for $C_{11}H_7F_5N_4NaO_2$: calcd $[M+Na]^+$ 345.03814; found 345.03785.

*5.1.23. cis-6-(tert-Butyl-diphenyl-silanyloxymethyl)-8-pentafluorophenyl-5,6-dihydro-8H-tetrazolo[5,1-c][1,4]oxazine (**32**)*

See procedure for (**17a**): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.67–7.65 (m, 4H), 7.51–7.45 (m, 2H), 7.44–7.37 (m, 4H), 6.31 (s, 1H), 4.78 (dd, 1H, $J$=2.32, 12.9 Hz), 4.46 (ddd, 1H, $J$=0.78, 11.5, 12.9 Hz), 4.30–4.25 (m, 1H), 4.06 (dd, 1H, $J$=4.58, 11.1 Hz), 3.94 (dd, 1H, $J$=5.8, 11.1 Hz), 1.10 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 149.7, 135.2, 135.1, 132.1, 132.0, 129.8, 127.6, 127.5, 74.2, 64.6, 63.1, 47.3, 26.4, 18.9 (Carbons bearing fluorides have not been observed, see 233 MHz carbon NMR for the starting material to see them); FTIR (thin film) ($CHCl_3$, cm$^{-1}$) 3073, 2933, 2860, 1657, 1524, 1512, 1473, 1428, 1362, 1307, 1134, 1113, 1061, 1005, 990, 972, 823, 740, 702; ESI/MS ($m/z$) $[M+1]^+$: 561.2, $[M+Na]^+$: 583.2; HRMS (ESI) for $C_{27}H_{26}F_5N_4O_2Si$: calcd $[M+1]^+$ 561.17397; found 561.17473; for $C_{27}H_{25}F_5N_4NaO_2Si$: calcd $[M+Na]^+$ 583.15591; found 583.15671.

*5.1.24. 1-[5-(Amino-phenyl-methyl)-tetrazol-1-yl]-3-(tert-butyl-diphenyl-silanyloxy)-propan-2-ol (**36** and **37**)*

To a solution of **27** (720 mg, 1.41 mmol) at 0 °C in MeOH (9.4 mL (0.5 M)) was added Mg powder (171 mg, 7.04 mmol, 5 equiv). The mixture was stirred for 12 h, then filtered on a Celite pad. Evaporation under reduced pressure gave an oil which was purified by flash chromatography (EtOAc/hexanes/$NH_3$ 7 M in MeOH, 55:40:5) to give **36** and **37** as colorless gums (547 mg, 80%). Major isomer (**36**): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 7.66–7.60 (m, 4H), 7.44–7.33 (m, 7H), 7.30–7.18 (m, 5H), 5.54 (s, 1H), 4.42 (d, 1H, $J$=11.6 Hz), 4.08–3.98 (m, 2H), 3.71–3.68 (m, 1H), 3.65 (dd, 1H, $J$=5.26, 10.5 Hz), 3.35 (br s, 3H), 1.06 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) 157.9, 139.3, 135.5, 135.4, 132.7, 132.6, 129.9, 129.1, 128.5, 127.8, 127.0, 126.8, 70.6, 65.4, 50.9, 51.6, 26.8, 19.1; FTIR (thin film) (DCM, cm$^{-1}$) 3355, 3296, 3071, 2958, 2931, 2892, 2858, 1589, 1472, 1457, 1428, 1113, 824, 742, 702; ESI/MS ($m/z$) $[M+1]^+$: 488.2; HRMS (ESI) for $C_{27}H_{33}N_5O_2Si$: calcd $[M+1]^+$ 488.24763; found 488.24821. Minor isomer (**37**): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.68–7.64 (m, 4H), 7.48–7.39 (m, 6H), 7.34–7.28 (m, 5H), 5.69 (s, 1H), 4.38–4.30 (m, 2H), 4.14–4.08 (m, 1H), 4.72 (d, 2H, $J$=5.42 Hz), 3.24 (br s, 3H), 1.10 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 157.3, 138.6, 135.4, 135.4, 132.7, 132.6, 129.9, 129.1, 128.5, 127.7, 126.6, 70.0, 64.9, 50.4, 50.2, 26.7, 19.1; FTIR (thin film) ($CHCl_3$, cm$^{-1}$) 3352, 3293, 3071, 2957, 2931, 2858, 1589, 1494, 1471, 1456, 1428, 1113, 824, 741, 702; ESI/MS ($m/z$) $[M+1]^+$: 488.2; HRMS (ESI) for $C_{27}H_{33}N_5O_2Si$: calcd $[M+1]^+$ 488.24763; found 488.24801.

*5.1.25. Acetic acid 2-(5-benzoyl-tetrazol-1-yl)-1-(tert-butyl-diphenyl-silanyloxymethyl)-ethyl ester (**38**)*

To a solution of **27** (90 mg, 0.176 mmol) in THF (0.88 mL (0.2 M)) was added $PMe_3$ (1 M in THF) (193 μL, 0.193 mmol, 1.1 equiv), the mixture was heated at 50 °C for 30 min. The solution was cooled down to room temperature, prior to the addition of a 28% aqueous $NH_4OH$. The mixture was heated and stirred at 35 °C for 2 h, then

extracted with ether and extracts were dried on $Na_2SO_4$. Evaporation under reduced pressure gave an oil which was dissolved in pyridine (0.50 mL (0.5 M)). The solution was cooled at 0 °C and acetic anhydride (33 μL, 2 equiv) was added. After 8 h at room temperature, a solution of HCl 10% was added, and the mixture was extracted with EtOAc. The extracts were washed with a solution of aqueous $NaHCO_3$ and with brine. Processing the organic layer gave an oil which was purified by flash chromatography (EtOAc/hexanes, 15:85) to give **38** as a colorless gum (72.3 mg, 79%): $^1$H NMR (400 MHz, $CD_2Cl_2$) $\delta$ (ppm) 8.42 (d, 2H, $J$=7.72 Hz), 7.79 (t, 1H, $J$=7.44 Hz), 7.74–7.70 (m, 4H), 7.63 (t, 2H, $J$=7.79 Hz), 7.51–7.43 (m, 6H), 5.40–5.35 (m, 1H), 5.21 (dd, 1H, $J$=3.35, 14.25 Hz), 5.14 (dd, 1H, $J$=7.96, 14.25 Hz), 3.90 (dd, 1H, $J$=4.58, 11.19 Hz), 3.84 (dd, 1H, $J$=5.07, 11.17 Hz), 1.75 (s, 3H), 1.14 (s, 9H); $^{13}$C NMR (100 MHz, $CD_2Cl_2$) $\delta$ (ppm) 182.3, 170.1, 150.5, 136.0, 135.9, 135.6, 135.4, 133.2, 133.1, 131.4, 130.3, 129.3, 128.22, 128.20, 72.0, 63.2, 50.2, 26.9, 20.6, 19.5; FTIR (thin film) (DCM, cm$^{-1}$) 3072, 2959, 2932, 2859, 1747, 1668, 1598, 1428, 1276, 1229, 1114, 921; ESI/MS ($m/z$) $[M+1]^+$: 528.2; HRMS (ESI) for $C_{29}H_{32}N_4O_4Si$: calcd $[M+1]^+$ 529.2265; found 529.22714.

### 5.1.26. *cis-N-[6-(tert-Butyl-diphenyl-silanyloxymethyl)-8-phenyl-5,6-dihydro-8H-tetrazolo[5,1-c][1,4]oxazin-8-yl]-acetamide (**39**)*

To a solution of **27** (25.0 mg, 0.0489 mmol) in chloroform (325 μL (0.15 M)) was added 2,6-lutidine (102 μL, 0.879 mmol, 18 equiv), then thioacetic acid (65 μL, 0.909 mmol, 18.6 equiv). The solution was refluxed for 36 h, and the solvent removed under reduced pressure to give an oil which was purified by flash chromatography (EtOAc/hexanes, 45:55). A second flash may be required to remove all the sulfur derivatives. Compound **39** was obtained as a colorless gum (20.1 mg, 78%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.97–7.95 (m, 2H), 7.75–7.69 (m, 4H), 7.51–7.41 (m, 9H), 6.57 (s, 1H), 5.01–4.99 (m, 1H), 4.74 (dd, 1H, $J$=3.36, 12.9 Hz), 4.42 (dd, 1H, $J$=10.8, 12.9 Hz), 4.08–4.00 (m, 2H), 2.03 (s, 3H), 1.12 (s, 9H); $^{13}$C NMR (100 MHz, $CD_2Cl_2$) $\delta$ (ppm) 170.2, 151.7, 138.7, 135.2, 135.1, 132.4, 129.6, 129.2, 128.8, 128.2, 127.5, 126.2, 126.0, 81.0, 70.9, 63.5, 46.6, 26.2, 23.2, 18.7; FTIR (thin film) (DCM, cm$^{-1}$) 3279, 3071, 3050, 2959, 2932, 2858, 1694, 1673, 1538, 1512, 1491, 1472, 1448, 1428, 1282, 1113, 1042, 1029, 741, 702; ESI/MS ($m/z$) $[M+1]^+$: 528.3; HRMS (ESI) for $C_{29}H_{33}N_5O_3Si$: calcd $[M+1]^+$ 528.2425; found 528.24287.

### 5.1.27. *({1-[3-(tert-Butyl-diphenyl-silanyloxy)-2-hydroxy-propyl]-1H-tetrazol-5-yl}-phenyl-methyl)-carbamic acid tert-butyl ester (N-Boc **36**)*

To a mixture of **36** (921 mg, 1.89 mmol) in a solution of 10:90 $Et_3N$/MeOH (19 mL (0.1 M)) was added $Boc_2O$ (618 mg, 2.83 mmol, 2 equiv). The reaction mixture was stirred at 30 °C for 2 h, then evaporated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc/hexanes 30:70) to give the title compound as a colorless gum (1.10 mg, 99%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.67–7.64 (m, 4H), 7.49–7.36 (m, 11H), 6.39 (d, 1H, $J$=7.88 Hz), 5.81 (d, 1H, $J$=7.76 Hz), 5.58 (d, 1H, $J$=12.2 Hz), 4.18–4.09 (m, 2H), 3.75 (dd, 1H, $J$=4.88, 10.6 Hz), 3.70 (dd, 1H, $J$=4.39, 10.8 Hz), 3.63 (br s, 1H), 1.43 (s, 9H), 1.09 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 157.1, 156.1, 137.0, 136.42, 136.38, 133.6, 133.5, 130.9, 130.2, 129.9, 128.8, 128.7, 128.4, 81.8, 72.0, 66.0, 51.9, 50.6, 29.1, 27.7, 20.1; FTIR (thin film) ($CHCl_3$, cm$^{-1}$) 3306, 3072, 2961, 2932, 2859, 1694, 1496, 1472, 1457, 1428, 1393, 1368, 1249, 1167, 1113, 1050, 739, 702; ESI/MS ($m/z$) $[M+1]^+$: 588.2; HRMS (ESI) for $C_{32}H_{41}N_5O_4Si$: calcd $[M+1]^+$ 588.30006; found 588.30004.

### 5.1.28. *({1-[3-(tert-Butyl-diphenyl-silanyloxy)-2-hydroxy-propyl]-1H-tetrazol-5-yl}-phenyl-methyl)-carbamic acid tert-butyl ester (N-Boc **37**)*

See procedure for (*N*-Boc **36**): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.67–7.65 (m, 4H), 7.50–7.34 (m, 11H), 6.38 (d, 1H, $J$=8.20 Hz), 5.96 (d, 1H, $J$=8.09 Hz), 4.48–4.36 (m, 2H), 4.12 (br s, 1H), 3.72 (dd, 1H, $J$=5.12, 10.5 Hz), 3.69–3.66 (m, 1H), 2.48 (br s, 1H), 1.43 (s, 9H), 1.09 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 156.9, 155.9, 137.7, 136.4, 136.4, 133.4, 130.9, 130.0, 129.7, 128.8, 128.4, 81.6, 71.3, 65.7, 50.9, 50.0, 29.1, 27.7, 20.1; FTIR (thin film) ($CHCl_3$, cm$^{-1}$) 3307, 3071, 3051, 2961, 2932, 2893, 2859, 1713, 1699, 1496, 1472, 1456, 1428, 1368, 1249, 1166, 1113, 1049, 824, 739, 702; ESI/MS ($m/z$) $[M+1]^+$: 588.3; HRMS (ESI) for $C_{32}H_{41}N_5O_4Si$: calcd $[M+1]^+$ 588.30006; found 588.30083.

### 5.1.29. *Methanesulfonic acid 2-[5-(tert-butoxycarbonylamino-phenyl-methyl)-tetrazol-1-yl]-1-(tert-butyl-diphenyl-silanyloxymethyl)-ethyl ester (**40**)*

To a solution of the preceding product (1.08 g, 1.83 mmol) in DCM (18.3 mL (0.1 M)) was added $Et_3N$ (0.766 mL, 5.50 mmol, 3 equiv) and the mixture was cooled at 0 °C in an ice bath. $Ms_2O$ (511 mg, 2.93 mmol, 1.6 equiv) was added and the reaction mixture was stirred at room temperature for 24 h. The solution was evaporated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc/hexanes 25:75) to give **40** as a colorless gum (1.22 g, 100%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.68–7.63 (m, 1H), 7.50–7.32 (m, 11H), 6.26 (d, 1H, $J$=7.58 Hz), 5.86 (d, 1H, $J$=7.54 Hz), 5.00 (m, 1H), 4.57 (dd, 1H, $J$=4.89, 15.4 Hz), 4.52 (dd, 1H, $J$=7.97, 15.0 Hz), 3.93 (dd, 1H, $J$=4.13, 11.8 Hz), 3.85 (dd, 1H, $J$=4.22, 11.8 Hz), 2.83 (s, 3H), 1.44 (s, 9H), 1.09 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 155.9, 154.5, 135.5, 135.2, 135.1, 131.9, 131.5, 129.8, 129.2, 129.1, 129.0, 127.7, 127.5, 80.5, 78.0, 63.1, 49.5, 47.2, 37.2, 27.9, 26.4, 18.9; FTIR (thin film) ($CHCl_3$, cm$^{-1}$) 3307, 2931, 2859, 1709, 1467, 1472, 1458, 1428, 1367, 1248, 1178, 1114, 926, 702; ESI/MS ($m/z$) $[M+1]^+$: 666.3; HRMS (ESI) for $C_{32}H_{43}N_5O_6SSi$: calcd $[M+1]^+$ 666.27761; found 666.27728.

### 5.1.30. *Methanesulfonic acid 2-[5-(tert-butoxycarbonylamino-phenyl-methyl)-tetrazol-1-yl]-1-(tert-butyl-diphenyl-silanyloxymethyl)-ethyl ester (**41**)*

See procedure for (**40**): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.70–7.63 (m, 4H), 7.50–7.33 (m, 11H), 6.17 (d, 1H, $J$=7.72 Hz), 5.73 (d, 1H, $J$=7.72 Hz), 4.84 (dd, 1H, $J$=7.75, 14.8 Hz), 4.60 (dd, 1H, $J$=2.97, 14.9 Hz), 3.95 (dd, 1H, $J$=3.85, 11.2 Hz), 3.90 (dd, 1H, $J$=5.50, 11.3 Hz), 2.53 (s, 3H), 1.43 (s, 9H), 1.12 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 155.8, 154.4, 135.2, 135.1, 131.9, 131.8, 129.8, 129.1, 129.0, 127.7, 127.6, 127.5, 80.6, 62.8, 49.0, 47.1, 37.0, 27.9, 26.5, 18.9; FTIR (thin film) ($CHCl_3$, cm$^{-1}$) 3306, 2931, 2858, 1705, 1496, 1472, 1457, 1428, 1367, 1247, 1178, 1114, 924, 739, 702, ESI/MS ($m/z$) $[M+1]^+$: 666.3; HRMS (ESI) for $C_{32}H_{43}N_5O_6SSi$: calcd $[M+1]^+$ 666.27761; found 666.27736.

### 5.1.31. *cis-6-(tert-Butyl-diphenyl-silanyloxymethyl)-8-phenyl-5,6,7,8-tetrahydro-tetrazolo[1,5-a]pyrazine (**42**)*

To a solution of **40** (1.00 g, 1.51 mmol) in DCM (30 mL (0.05 M)) at −15 °C was added TFA (2.33 mL, 30.2 mmol, 20 equiv). The reaction mixture was stirred 3 h at room temperature, then quenched with a minimum of saturated $NaHCO_3$. When effervescence stopped, few drops of ($i$-Pr)$_2$EtN were added, and mixture was dried with $Na_2SO_4$ and filtered on Celite. After evaporation, methanol (150 mL (0.01 M)) and ($i$-Pr)$_2$EtN (0.526 mL, 3.02 mmol, 2 equiv) were added, the reaction mixture was refluxed for 60 h, then evaporated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc/hexanes 20:80 to 30:70) to give **42** as a colorless gum (0.501 g, 71%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.67 (d, 4H, $J$=7.35 Hz), 7.50–7.40 (m, 1H), 5.33 (s, 1H), 4.59 (dd, 1H, $J$=3.81, 12.4 Hz), 4.14 (t, 1H, $J$=11.6 Hz), 3.93–3.87 (m, 2H), 3.58–3.54 (m, 1H), 2.40 (br s, 1H), 1.10 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 153.0, 137.1, 135.18, 135.17, 132.2, 132.1, 129.8, 128.62, 128.59, 127.7, 127.6, 64.2, 56.5, 54.1, 48.1, 26.5, 18.9; FTIR (thin film) ($CHCl_3$, cm$^{-1}$) 3306, 3070, 2930, 2857, 1496, 1471,

1427, 1391, 1362, 1113, 823, 739, 701; ESI/MS ($m/z$) $[M+1]^+$: 470.3; HRMS (ESI) for $C_{27}H_{31}N_5OSi$: calcd $[M+1]^+$ 470.23706; found 470.23741.

### 5.1.32. *trans-6-(tert-Butyl-diphenyl-silanyloxymethyl)-8-phenyl-5,6,7,8-tetrahydro-tetrazolo[1,5-a]pyrazine (**43**)*

See procedure for (**42**): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.67–7.63 (m, 4H), 7.51–7.32 (m, 11H), 5.73 (s, 1H), 4.46 (dd, 1H, $J$=4.46, 12.3 Hz), 4.21 (dd, 1H, $J$=10.0, 12.6 Hz), 3.89 (dd, 1H, $J$=4.53, 10.4 Hz), 3.80 (dd, 1H, $J$=5.64, 10.4 Hz), 4.43–3.39 (m, 1H), 2.68 (br s, 1H), 1.09 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 151.9, 137.2, 135.2, 135.1, 132.0, 129.8, 129.77, 128.5, 127.9, 127.63, 127.59, 126.7, 63.6, 52.3, 48.7, 47.5, 26.4, 18.9; FTIR (thin film) ($CHCl_3$, cm$^{-1}$) 3324, 3070, 2931, 2893, 2858, 1494, 1471, 1449, 1428, 1113, 1090, 823, 736, 701; ESI/MS ($m/z$) $[M+1]^+$: 470.3; HRMS (ESI) for $C_{27}H_{31}N_5OSi$: calcd $[M+1]^+$ 470.23706; found 470.23645.

### 5.1.33. *6-(tert-Butyl-diphenyl-silanyloxymethyl)-8-phenyl-5,6-dihydro-tetrazolo[1,5-a]pyrazine (**44**)*

$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 8.42–8.38 (m, 2H), 7.68–7.60 (m, 4H), 7.59–7.34 (m, 9H), 4.90 (dd, 1H, $J$=6.45, 13.4 Hz), 4.60 (dd, 1H, $J$=9.24, 13.4 Hz), 4.49–4.40 (m, 1H), 4.20 (dd, 1H, $J$=4.23, 10.5 Hz), 3.98 (dd, 1H, $J$=7.37, 10.5 Hz), 1.02 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) 154.4, 145.3, 136.41, 136.37, 134.5, 133.5, 133.2, 132.8, 130.93, 130.89, 129.5, 128.8, 128.7, 65.7, 60.1, 45.6, 27.6, 20.0; FTIR (thin film) ($CHCl_3$, cm$^{-1}$) 3070, 2955, 2930, 2857, 1599, 1571, 1471, 1461, 1437, 1428, 1330, 1151, 1113, 1024, 974, 956, 823, 786, 743, 702, 691; ESI/MS ($m/z$) $[M+1]^+$: 468.2; HRMS (ESI) for $C_{27}H_{30}N_5OSi$: calcd $[M+1]^+$ 468.22141; found 468.22279; for $C_{27}H_{29}N_5NaOSi$: calcd $[M+Na]^+$ 490.20336; found 490.20441.

### 5.1.34. *cis-6-(tert-Butyl-diphenyl-silanyloxymethyl)-8-phenyl-5,6-dihydro-8H-tetrazolo[1,5-a]pyrazine-7-carboxylic acid methyl ester (**45**)*

To a solution of **41** (66 mg, 0.141 mmol) in methyl chloroformate (2.81 mL (0.05 M)) is added $NaHCO_3$ (59 mg, 0.703 mmol, 5 equiv). The solution is stirred at 60 °C and monitored by TLC. Additional reagent was added to complete the reaction. After 24 h, the mixture is filtered and evaporated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc/hexanes 20:80) to give **45** as a colorless gum (64 mg, 87%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.46–7.39 (m, 4H), 7.36–7.28 (m, 6H), 7.26–7.17 (m, 5H), 6.82 (br s, 1H), 5.11 (br s, 1H), 4.96 (dd, 1H, $J$=0.98, 13.3 Hz), 4.41 (dd, 1H, $J$=5.62, 13.3 Hz), 3.84 (s, 3H), 3.35 (dd, 1H, $J$=5.62, 10.4 Hz), 3.15 (t, 1H, $J$=10.2 Hz), 1.01 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 155.5, 149.4, 134.9, 134.85, 131.9, 131.6, 129.7, 129.6, 128.2, 128.0, 127.49, 127.47, 126.1, 61.1, 53.6, 51.9, 44.5, 26.3, 18.6; FTIR (thin film) ($CHCl_3$, cm$^{-1}$) 3070, 2955, 2930, 2857, 1711, 1445, 1428, 1391, 1341, 1307, 1262, 1112, 1076, 739, 701; ESI/MS ($m/z$) $[M+1]^+$: 528.3; HRMS (ESI) for $C_{29}H_{35}N_5O_3Si$: calcd $[M+1]^+$ 528.24254; found 528.24289; for $C_{29}H_{33}N_5NaO_3Si$: calcd $[M+Na]^+$ 550.22449; found 550.22499.

### 5.1.35. *cis-8-Phenyl-5,6-dihydro-8H-tetrazolo[5,1-c][1,4]oxazine-6-carboxylic acid methyl ester (**46**)*

To a solution of **8** (200 mg, 0.861 mmol) in acetone (1.7 mL (0.5 M)) was added an excess of Jones reagent and the mixture was stirred for 30 min. An additional amount of Jones reagent was added and the mixture was stirred again for 30 min. The reaction was quenched with a minimum amount of isopropyl alcohol, then filtered on Florisil and eluted with 1:1 MeOH/acetone eluant. The resulting solution was evaporated under reduced pressure and co-evaporated with dry MeOH. The crude residue was diluted with dry MeOH (29 mL (0.03 M)) and a catalytic amount of conc. $H_2SO_4$ was added with an excess of $Na_2SO_4$ as a drying agent. The mixture was refluxed for 12 h, then evaporated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc/hexanes 30:70) to give **46** as a colorless gum (189 mg, 84%): $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ (ppm) 7.47–7.39 (m, 5H), 6.13 (s, 1H), 4.97 (dd, 1H, $J$=3.81, 11.0 Hz), 4.89 (dd, 1H, $J$=3.11, 12.9 Hz), 4.62 (t, 1H, $J$=11.9 Hz), 3.78 (s, 3H); $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta$ (ppm) 167.7, 152.6, 135.7, 129.8, 128.9, 128.5, 75.7, 72.0, 52.5, 47.1; ESI/MS ($m/z$) $[M+1]^+$: 261.1; HRMS (ESI) for $C_{12}H_{12}N_4O_3$: calcd $[M+1]^+$ 261.09822; found 261.09735.

### 5.1.36. *cis-Toluene-4-sulfonic acid 8-phenyl-5,6-dihydro-8H-tetrazolo[5,1-c][1,4]oxazin-6-ylmethyl ester (**47**)*

To a solution of **8** (1.00 g, 4.31 mmol) in DCM (5.7 mL (0.75 M)) and pyridine (0.90 mL (4.8 M)) was added a catalytic amount of DMAP (42 mg, 0.34 mmol, 0.08 equiv) and TsCl (1.50 g, 6.46 mmol, 1.5 equiv). The solution was stirred 12 h, DCM was added, the organic phase was extracted 3 times with 1 N HCl, washed once with saturated $NaHCO_3$ and once with brine. The organic phase was dried on $Na_2SO_4$ and evaporated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc/hexanes 20:80 to 70:30) to give **47** as a white solid (1.54 g, 92%): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 7.80 (d, 2H, $J$=8.21 Hz), 7.45–7.40 (m, 5H), 7.32 (dd, 2H, $J$=0.51, 8.58 Hz), 5.95 (s, 1H), 4.67 (d, 1H, $J$=12.3 Hz), 4.48–4.29 (m, 4H), 2.45 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) 152.6, 146.6, 135.5, 132.8, 130.9, 130.5, 129.7, 128.9, 128.5, 76.2, 71.9, 68.8, 47.7, 22.6; FTIR (thin film) ($CHCl_3$, cm$^{-1}$) 3066, 3036, 2956, 2924, 1598, 1496, 1473, 1455, 1400, 1360, 945, 907, 816, 755, 698, 666; ESI/MS ($m/z$) $[M+1]^+$: 387.1; HRMS (ESI) for $C_{18}H_{18}N_4O_4S$: calcd $[M+1]^+$ 387.11215; found 387.11407.

### 5.1.37. *cis-6-Azidomethyl-8-phenyl-5,6-dihydro-8H-tetrazolo[5,1-c][1,4]oxazine (**48**)*

To a solution of **47** (472 mg, 1.22 mmol) in DMF (12 mL (0.1 M)) was added $NaN_3$ (254 mg, 3.91 mmol, 3.2 equiv) and a catalytic amount of $n$-$Bu_4NBr$ (38 mg, 0.12 mmol, 0.1 equiv). The reaction mixture was then stirred 5 h at 70 °C. After, standing at room temperature, the solution was filtered on a small pad of silica, evaporated under reduced pressure, and the crude residue was dissolved in EtOAc and filtered again. After evaporation, the crude residue was purified by flash chromatography (EtOAc/hexanes 30:70) to give **48** as a colorless gum (298 mg, 95%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.53–7.50 (m, 2H), 7.47–7.41 (m, 3H), 6.04 (s, 1H), 4.62 (d, 1H, $J$=10.2 Hz), 4.45–4.34 (m, 2H), 3.73 (dd, 1H, $J$=3.50, 13.1 Hz), 3.65 (dd, 1H, $J$=4.39, 13.2 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 151.5, 134.5, 129.2, 128.5, 127.1, 74.8, 72.3, 51.2, 46.9; FTIR (thin film) ($CHCl_3$, cm$^{-1}$) 3036, 2925, 2105, 1498, 1473, 1443, 1285, 1246, 1149, 1082, 1058, 1027, 980, 908, 889, 752, 698; ESI/MS ($m/z$) $[M+1]^+$: 258.1; HRMS (ESI) for $C_{11}H_{11}N_7O$: calcd $[M+1]^+$ 258.1097; found 258.10917.

### 5.1.38. *cis-(8-Phenyl-5,6-dihydro-8H-tetrazolo[5,1-c][1,4]oxazin-6-yl)-methylamine (**49**)*

To a solution of **48** (262 mg, 1.02 mmol) in ethanol (14.5 mL (0.07 M)) was added (79 mg (30 mol %)) of 5% Pd/C and hydrogenated under 1 atm of $H_2$. The suspension was then stirred 3 h at room temperature, filtered on Celite and, the resulting solution was evaporated under reduce pressure. The crude residue was filtered on silica by eluting first with EtOAc and then with 30:70 EtOAc/MeOH to give **49** as a slightly yellow gum (218 mg, 92%): $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ (ppm) 7.50–7.47 (m, 2H), 7.44–7.42 (m, 3H), 6.10 (s, 1H), 4.72 (dd, 1H, $J$=2.26, 12.4 Hz), 4.40–4.35 (m, 1H), 3.11–2.99 (m, 2H); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ (ppm) 152.4, 135.7, 128.7, 128.0, 127.5, 74.7, 74.3, 47.2, 42.2; FTIR (thin film) ($CHCl_3$, cm$^{-1}$) 3584, 3378, 3308, 3065, 3035, 3010, 2924, 2876, 1601, 1524, 1498, 1471, 1455, 1444, 1376, 1352, 1287, 1245, 1201, 1148, 1061, 1029, 928, 905, 753, 699; ESI/MS ($m/z$) $[M+1]^+$: 273.1; HRMS (ESI) for $C_{11}H_{13}N_5O$: calcd $[M+1]^+$ 232.1192; found 232.11963.

*5.1.39. cis-6-Iodomethyl-8-phenyl-5,6-dihydro-8H-tetrazolo[5,1-c]-[1,4]oxazine (**50**)*

To a solution of **8** (750 mg, 3.23 mmol) in THF (65 mL (0.05 M)) was added $PPh_3$ (1.86 g, 7.10 mmol, 2.2 equiv), imidazole (703 mg, 1.03 mmol, 3.2 equiv) and $I_2$ (2.05 g, 8.07 mmol, 2.5 equiv). The reaction mixture was stirred 12 h at 35 °C, EtOAc was added and a saturated sodium thiosulfate solution was added to quench the excess of $I_2$. The resulting organic phase was extracted two more times with saturated sodium thiosulfate solution, then, successively washed with 10% HCl, saturated $NaHCO_3$, and finally with brine. The organic phase was then dried on $Na_2SO_4$ and evaporated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc/hexanes 40:60 to 60:40) to give **50** as a colorless gum (1.09 g, 98%): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 7.55–7.48 (m, 2H), 7.47–7.40 (m, 3H), 6.03 (s, 1H), 4.86 (ddd, 1H, $J$=0.93, 2.64, 12.1 Hz), 4.32–4.24 (m, 1H), 4.23–4.15 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) 152.6, 135.8, 130.5, 129.8, 128.5, 76.0, 73.5, 51.2, 2.7; FTIR (thin film) ($CHCl_3$, $cm^{-1}$) 3034, 2958, 2877, 1497, 1472, 1455, 1440, 1368, 1287, 1246, 1201, 1146, 1094, 1074, 1050, 1028, 1005, 903, 749, 698; ESI/MS ($m/z$) $[M+1]^+$: 342.9; HRMS (ESI) for $C_{11}H_{11}IN_4O$: calcd $[M+1]^+$ 343.0050; found 343.00581.

*5.1.40. cis-6-Methyl-8-phenyl-5,6-dihydro-8H-tetrazolo[5,1-c]-[1,4]oxazine (**17b**)*

To a solution of **50** (830 mg, 2.43 mmol) in MeOH (24.3 mL (0.1 M)) was added $Et_2NH$ (359 mg, 4.85 mmol, 2 equiv) and Raney nickel (208 mg (25% w/w)). The reaction mixture was stirred 2 h under $H_2$ (1 atm), filtered on Celite and evaporated under reduced pressure. The crude residue was filtered on silica and eluted with EtOAc/hexanes 1:1 to give **17b** as a colorless gum (0.524 mg, 100%): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 7.41–7.26 (m, 5H), 5.87 (s, 1H), 4.45 (ddd, 1H, $J$=0.98, 2.94, 12.5 Hz), 4.25–4.12 (m, 1H), 4.03 (ddd, 1H, $J$=1.08, 10.7, 12.4 Hz), 1.42 (d, 3H, $J$=6.10 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) 152.0, 135.5, 129.3, 128.7, 127.6, 74.9, 70.0, 66.5, 18.2; FTIR (thin film) ($CHCl_3$, $cm^{-1}$) 3066, 3036, 2984, 2937, 2880, 1497, 1471, 1455, 1445, 1372, 1229, 1154, 1088, 1067, 1045, 1028, 934, 916, 754, 698; ESI/MS ($m/z$) $[M+1]^+$: 217.1; HRMS (ESI) for $C_{11}H_{12}N_4O$: calcd $[M+1]^+$ 217.1083; found 217.10884.

*5.1.41. (1-Allyl-1H-tetrazol-5-yl)-phenyl-methanol (**53**)*

To a solution of **50** (1.45 g, 4.25 mmol) in EtOH/THF (2:1) (159 mL, 0.027 M) was added Zn (2.33 g, 35.7 mmol, 8.4 equiv) and $NH_4Cl$ (0.568 g, 10.6 mmol, 2.5 equiv). The reaction mixture was refluxed 1 h, then filtered on Florisil, and the resulting solution was evaporated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc/hexanes 35:70) to give **53** as a colorless oil (0.90 g, 98%): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 7.42–7.37 (m, 5H), 6.37 (s, 1H), 5.72 (ddt, 1H, $J$=6.20, 10.3, 17.0 Hz), 5.19 (dd, 1H, $J$=0.74, 10.2 Hz), 5.06 (dd, 1H, $J$=0.70, 17.0 Hz), 4.88 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) 156.8, 138.7, 130.6, 129.8, 129.6, 126.9, 121.1, 67.3, 51.2; FTIR (thin film) ($CHCl_3$, $cm^{-1}$) 3307, 3091, 3066, 3033, 2921, 1647, 1495, 1452, 1419, 1251, 1093, 1053, 1028, 989, 938, 725, 699; ESI/MS ($m/z$) $[M+1]^+$: 217.0; HRMS (ESI) for $C_{11}H_{12}N_4O$: calcd $[M+1]^+$ 217.10839; found 217.10906.

*5.1.42. 6-Methyl-8-phenyl-8H-tetrazolo[5,1-c][1,4]oxazine (**51**)*

To a solution of **50** (23 mg, 0.0672 mmol) in DME (0.84 mL (0.08 M)) was added DBU (21 mg, 0.134 mmol, 2 equiv). The reaction mixture was refluxed 1 h, then evaporated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc/hexanes 30:70) to give **51** as a colorless gum (13.7 mg, 95%): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 7.48–7.45 (m, 1H), 6.98 (q, 1H, $J$=1.22 Hz), 6.73 (s, 1H), 2.08 (d, 3H, $J$=1.23 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) 147.6, 146.3, 135.4, 130.7, 129.9, 127.6, 101.2, 75.6, 18.2; FTIR (thin film) ($CHCl_3$, $cm^{-1}$) 3132, 3065, 3036, 2960, 2923, 1672, 1496, 1474, 1456, 1429, 1384, 1342, 1261, 1199, 1110, 1073, 1029, 992, 967, 756, 724, 697; ESI/MS ($m/z$) $[M+1]^+$: 215.1; HRMS (ESI) for $C_{11}H_{10}N_4O$: calcd $[M+1]^+$ 215.09274; found 215.09269.

*5.1.43. 6-Methylene-8-phenyl-5,6-dihydro-8H-tetrazolo[5,1-c]-[1,4]oxazine (**52**)*

To a solution of **50** (116 mg, 0.339 mmol) in dry pyridine (3.4 mL (0.1 M)) was added AgF (86 mg, 0.678 mmol, 2 equiv). The solution was stirred in the dark (covered with aluminum foil) for 24 h. The reaction mixture was then filtered on silica with ether and then evaporated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc/hexanes 15:85 to 25:75) to give **52** as a colorless gum (65.7 mg, 90%): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 7.48–7.37 (m, 5H), 6.36 (s, 1H), 5.18 (dd, 1H, $J$=0.68, 15.0 Hz), 5.11 (d, 1H, $J$=15.0 Hz), 5.03 (s, 1H), 4.88 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) 151.9, 147.6, 135.6, 130.6, 129.8, 128.2, 102.2, 76.2, 48.1; FTIR (thin film) ($CHCl_3$, $cm^{-1}$) 3066, 3035, 3012, 2924, 1667, 1496, 1473, 1455, 1332, 1249, 1079, 1026, 898, 742, 697; ESI/MS ($m/z$) $[M+1]^+$: 215.0; HRMS (ESI) for $C_{11}H_{10}N_4O$: calcd $[M+1]^+$ 215.09274; found 215.09309.

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## Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.06.033.

## References and notes

1. (a) Butler, R. N. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, NY, 1996; Vol. 4; (b) Wittenberger, S. J. *Org. Prep. Proced. Int.* **1994**, *26*, 499 and references cited herein.
2. (a) Carini, D. J.; Duncia, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella, J. B., III; Wells, G. J.; Wexler, R. R.; Wong, P. C.; Yoo, S.-E.; Timmermans, P. B. M. W. M. *J. Med. Chem.* **1991**, *34*, 2525; (b) Carini, D. J.; Duncia, J. V. Eur. Patent 253,310 A2, 1988; See also: (c) Brunner, H. R.; Nussberger, J.; Burnier, M.; Waeber, B. *Clin. Exp. Hypertens.* **1993**, *15*, 1221; (d) Brunner, H. R.; Nussberger, J.; Waeber, B. *J. Hypertens.* **1993**, *11*, S53; (e) Otsuka Pharmaceutical Co., Ltd., Japan, Belg. Patent 878,548, 1979; (f) Hiatt, W. R. *Vasc. Med.* **1997**, *2*, 257; (g) Singh, H.; Chawla, A. S.; Kapoor, V. K.; Paul, D.; Malhotra, K. R. *Prog. Med. Chem.* **1980**, *17*, 151 and references cited therein.
3. For pertinent references, see: (a) Zabrocki, J.; Smith, D. G.; Dunbar, J. B., Jr.; Iijima, H.; Marshall, G. R. *J. Am. Chem. Soc.* **1988**, *110*, 5875; (b) Zabrocki, J.; Dunbar, J. B., Jr.; Marshall, K. W.; Toth, M. V.; Marshall, G. R. *J. Org. Chem.* **1992**, *57*, 202.
4. For pertinent recent references, see: (a) Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1994**, *116*, 7915; (b) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1991**, *113*, 8089; (c) Mori, I.; Ishihara, K.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 6107; (d) Corcoran, R. C. *Tetrahedron Lett.* **1990**, *31*, 2101.
5. Hanessian, S.; Simard, D.; Deschênes–Simard, B.; Chenel, C.; Haak, E. *Org. Lett.* **2008**, *10*, 1381.
6. The four cyanohydrins isomers can be separated by flash column chromatography; see also: (a) Brunel, J.-M.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2752; (b) Gregory, R. H. J. *Chem. Rev.* **1999**, *99*, 3649.
7. (a) Davis, B.; Brandstetter, T.; Smith, C.; Hackett, L.; Winchester, B. G.; Fleet, G. K. *Tetrahedron Lett.* **1995**, *36*, 7507; (b) Davis, B.; Nash, R. J.; Watson, A. A.; Smith, C.; Fleet, G. W. J. *Tetrahedron* **1999**, *55*, 4501; (c) Sharpless, K. B.; Demko, Z. P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2113.
8. Ek, F.; Wistrand, L.-G.; Frejd, T. *Tetrahedron* **2003**, *59*, 6759.
9. (a) Popov, A. I.; Bodner, R. L. *Inorg. Chem.* **1972**, *11*, 1410; (b) Popov, A. I. *Coord. Chem. Rev.* **1969**, *4*, 463; (c) Robinson, S. D.; Moore, D. S. *Adv. Inorg. Chem.* **1988**, *32*, 205.
10. For the related racemic 5-substituted tetrazoles, see: (a) Satoh, Y.; Marcopulos, N. *Tetrahedron Lett.* **1995**, *36*, 1759; (b) Satoh, Y.; Moliterni, J. *Synlett* **1998**, 528.

11. (a) Baruah, M.; Bols, M. *Synlett* **2002**, 1111; (b) Viuf, C.; Bols, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 623.
12. Maiti, S. N.; Spevak, P.; Narender Reddy, A. V. *Synth. Commun.* **1988**, *18*, 1201.
13. (a) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635; (b) Vautier, M.; Knouzi, N.; Carrie, R. *Tetrahedron Lett.* **1983**, *24*, 763.
14. (a) Shangguan, N.; Katukojvala, S.; Grenberg, R.; Williams, L. J. *J. Am. Chem. Soc.* **2003**, *125*, 7754; (b) Rosen, T.; Lico, I. M.; Chu, D. T. W. *J. Org. Chem.* **1998**, *53*, 1580; (c) Fazio, F.; Wong, C.-H. *Tetrahedron Lett.* **2003**, *44*, 9083.
15. For X-ray crystallographic data of compounds **8**, **9**, **14**, **22**, **24**, **26**, **28**, **29** (*p*-bromobenzoate), **43**, see Supplementary data.