Synthesis of 4-substituted-1,2,3-triazole carbanucleoside analogues of ribavirin *via* click chemistry†

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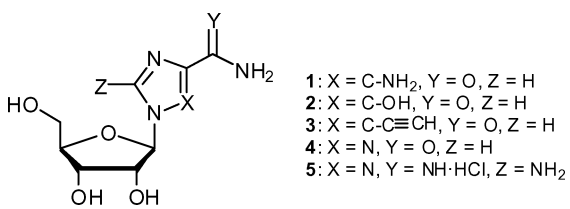
The synthesis and biological evaluation as antiviral agents of a series of racemic 4-aryl-1,2,3-triazolo-2′,3′-dideoxy-2′-iodocarbanucleosides and 4-aryl-1,2,3-triazolo-2′,3′-dideoxy-2′,3′-didehydrocarbanucleosides is presented. These compounds were produced using a click chemistry approach, with the iodoazide **13a** as the key intermediary.

Introduction

The structure of natural nucleosides has been the object of numerous chemical modifications in the search for new therapeutic entities. Among these alterations, those resulting in the modification of the natural nucleobases have ended in the discovery of a series of compounds with a wide range of activities against diverse viruses, such as hepatitis C virus, influenza virus and respiratory syncytial virus.[1] In these group, compounds bearing 5-membered heterocyclic nucleobases such as triazole or imidazole rings, for instance 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide (AICAR, **1**), deserve special attention. Interesting therapeutic properties have also been found in structurally related analogues of **1**, by introduction of modifications at position 4 of the heterocycle, for example brenedin (Mizoribine®, **2**) used as an immunosuppressor for the treatment of transplant patients,[2] or EICAR (**3**), which causes depletion of purine nucleotides, resulting in a broad spectrum of activity against RNA and DNA viruses and tumour cell proliferation.[3]

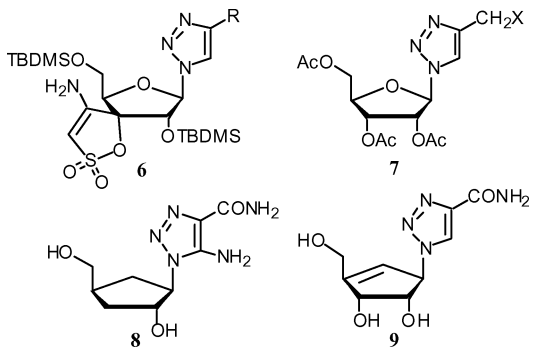
As the result of modifications in other positions of the heterocyclic ring of **1**, new compounds were developed such as ribavirin (Virazole®, **4**),[4] used for the treatment of RSV infections, lassa fever, hepatitis (A, B, and C), measles and mumps, and its analogue TCNR (**5**), a better substrate for human PNP than ribavirin, due to the interaction of the protonated carboxamidine group with the Asn 243 and Glu 201 residues in the PNP active site.[5]



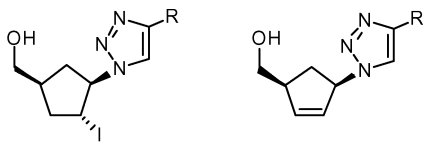
1: X = C-NH_2, Y = O, Z = H
2: X = C-OH, Y = O, Z = H
3: X = C-C≡CH, Y = O, Z = H
4: X = N, Y = O, Z = H
5: X = N, Y = NH·HCl, Z = NH_2

A great number of 1,2,3-triazole derivatives have also been reported as potent antiviral, antimicrobial or antiproliferative agents,[6–8] some interesting examples of the 1,2,3-triazole nucleosides being compounds **6** and **7**, which exhibit anti-HIV activity[9] and cytostatic activity,[10] respectively.

Also in the field of carbanucleosides (substances in which the anomeric oxygen of furanose ring is replaced by a methylene group), the synthesis and biological evaluation of compounds having a 1,2,3-triazole ring as a nucleobase have been reported recently; in the case of **8** moderate antiviral activity against HIV-1 (IC_{50} 43.8 μM) has been found,[11] while **9** showed potent antiviral activity against vaccinia virus (EC_{50} 0.4 μM), but moderate activity against cowpox virus (EC_{50} 39 μM) and severe acute respiratory syndrome coronavirus (SARCoV) (EC_{50} 47 μM).[12]



As a part of our drug discovery program, we report herein a full account of the synthesis and biological evaluation as antiviral agents of 1′-(1,2,3-triazol-1-yl)-2′,3′-dideoxy-2′-iodocarbanucleosides of type **10**, and of 1′-(1,2,3-triazol-1-yl)-2′,3′-dideoxy-2′,3′-didehydrocarbanucleosides of type **11** using a click chemistry approach.



10 (R = CO_2Me, $CONH_2$, Ar) **11** (R = Ar)

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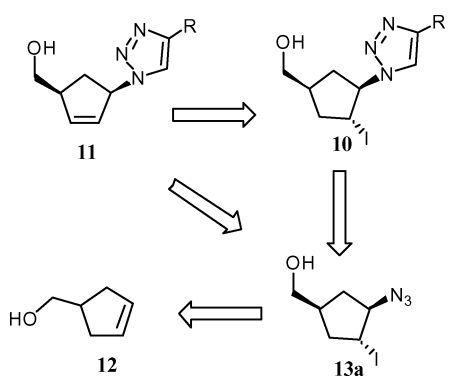
Results and discussion

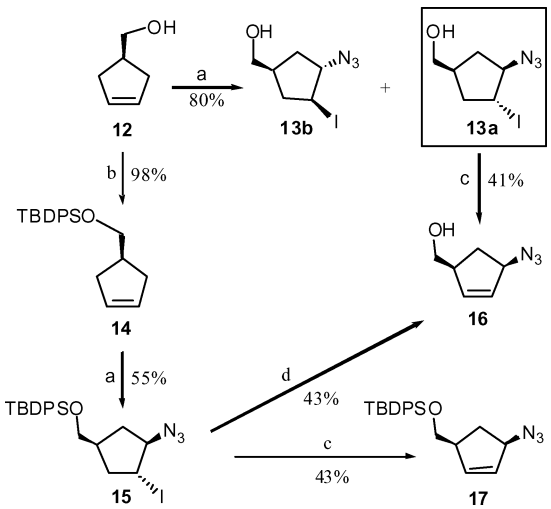
Since the seminal review by Kolb, Finn and Sharpless in which the principles of click chemistry were defined,[13] this new strategy in organic synthesis has been used extensively in the fields of bioconjugation, materials science and drug discovery.[14] The philosophy of this new approach is that "all searches must be restricted to molecules that are easy to make"[13] so they must be synthesized using a group of practical and reliable reactions. Sharpless and co-workers define click reactions as those that "are modular, wide in scope and easy to perform, high yielding, create only inoffensive by-products (which can be removed without chromatography), are stereospecific, simple to perform and that require benign or easily removed solvents".[13] As well, only readily available reagents should be used, and they must be insensitive to oxygen and water. In fact, in several instances water is the ideal reaction solvent, providing the best yields and highest rates.[13] Huisgen's 1,3-dipolar cycloaddition of alkynes and azides yielding triazoles is the premier example of a click chemistry reaction.[15] Azides and alkynes are easy to install, and despite being among the most energetic species known, they are also among the most reactive functional groups in organic chemistry. With the recently discovered dramatic acceleration of azide–alkyne coupling under copper(I) catalysis,[16,17] and the beneficial effects of water,[16] this unique connection process seems to be redefining the concept of a perfect reaction.

As we wished to integrate in some extent the paradigms of the click chemistry philosophy for the preparation of our target compounds, the synthesis was planned as shown in the retrosynthetic analysis (Scheme 1). Starting from commercially available cyclopent-3-enylmethanol **12**, the β-*trans*-iodoazide group could be installed with the desired relative stereochemistry with regard to the hydroxymethyl group by means of a haloazidation reaction of the substrate, leading to **13a**. For our purposes, this 3-azido-4-iodo alcohol constitutes the key intermediate that could allow us to prepare directly the dideoxyiodocarbanucleoside analogues of type **10**, and by a dehydroiodination proccess, before or after the construction of the triazole system, the unsaturated analogues of type **11**. This simple approach does not use protecting groups, and takes advantage of the expected stereoselectivity of the haloazidation reaction and the reliability of Huisgen's 1,3-dipolar cycloaddition of alkynes and azides for the modular construction of the desired compounds.



Scheme 1 Retrosynthetic analysis for the synthesis of target compounds **10** and **11**.

1,2-Haloazides are usually prepared by addition of Br–NaN_3,[18] NBS–NaN_3,[19] I_2–AgN_3,[20] or ICl–NaN_3[21] to a C=C double bond in the precursor. In our case, treatment of the alcohol **12** with ICl and NaN_3 led to a mixture of iodoazido alcohols **13** (80% chemical yield) (Scheme 2), with **13a** as the major product (^{1}H-NMR). Although full separation of these diastereomers proved to be very difficult, a pure sample of **13a** and a little **13b**-enriched sample were obtained after column chromatography of the crude mixture of the iodoazides using ethyl acetate–hexane 10 : 1 as eluent.



Scheme 2 *Reagents and conditions*: a) NaN_3, ICl, r.t., 24 h; b) TBDPSCl, imidazole, CH_2Cl_2; c) DABCO, benzene, reflux, 25 h; d) KOH, EtOH, reflux, 18 h.

The synthesis of the unsaturated carbanucleoside analogues of type **11** could be tackled starting from the 3-azido-4-iodo alcohol **13a** or its protected derivative **15** by two alternative routes: construction of the corresponding triazole moiety followed by dehydroiodination, or *vice versa*, initial dehydroiodination leading to the alkenes **16** or **17**, followed by construction of the heterocycle on the corresponding unsaturated iodoazido substrate.

As we wished to evaluate whether the protection of the hydroxyl group in compound **12** would be advantageous for further transformations leading to the target compounds, this was subjected to reaction with TBDPSCl and imidazole in CH_2Cl_2 at room temperature, yielding in a nearly quantitative fashion the silyl ether **14** (98%), which was then transformed into the iodoazide **15** by using the above-mentioned method, yielding in this case the desired compound with a lower yield (55%) than the reaction with the unprotected substrate **12**. Moreover, the major product **15** was accompanied, as in the preceding case, by a minor compound that could not be separated by conventional purification methods for its unambiguous identification.

Diverse conditions were tried for the dehydroiodination of compounds **13a** and **15**, namely KOH/EtOH,[22] DABCO in benzene,[23] and DBU in benzene,[24] at reflux in the corresponding solvent, leading in all cases to the isolation of the 2′,3′-unsaturated derivative **16** or **17** resulting from E2 elimination reaction of the 2-H and 3-I atoms on the carbocycle.

Analysis of these results (summarized in Table 1) illustrates that the reaction on all occasions takes place with only low to

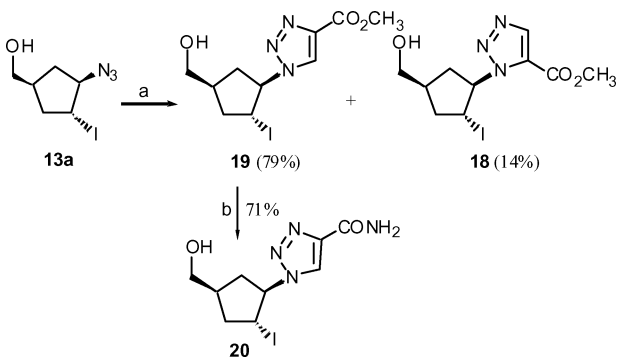
Table 1 Dehydroiodination of **13a** and **15**

Entry	Substrate (equiv.)	Base (equiv.)	Solvent	Time/h	Product (yield (%))
1	**13a** (1)	KOH (1.1)	Ethanol	0.5	**16** (25%)
2	**13a** (1)	DABCO (4)	Benzene	144	—[a]
3	**13a** (1)	DABCO (1 + 1)	Benzene	18 + 70	**16** (24%)
4	**13a** (1)	DABCO (2 + 1 + 1)	Benzene	3 + 15 + 7	**16** (41%)
5	**13a** (1)	DBU (1.5)	Benzene	96	**16** (26%)
6	**15** (1)	DABCO (2 + 1)	Benzene	42 + 13	**17** (43%)
7	**15** (1)	KOH (1.1)	Ethanol	18	**16** (43%)

[a] Complex mixture.

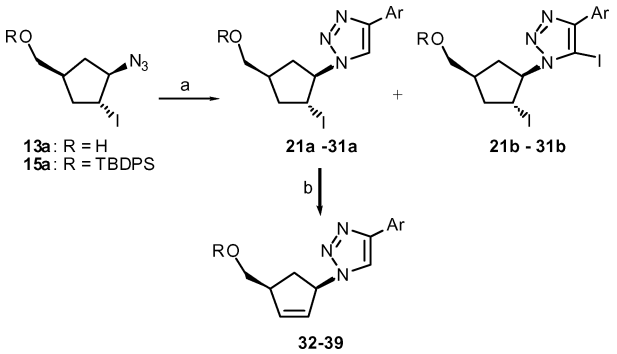
moderate yields, the best results (43% yield) being achieved when compound **15** is used as substrate;‡ however, protection of the hydroxyl group in **12** increases the length of the synthetic route, upsetting the proposed click chemistry strategy. In any case, the overall yield of the process starting from the alcohol **12** is lower for the protected route than for the sequence where the protection step is avoided (23% *vs.* 33%). On the other hand, some erratic results should be noted. For instance, when DABCO was used as the base (entries 2, 3 and 4 in Table 1), addition of extra quantities of the reagent once the reaction had started led to increased yields, while increased reaction times resulted in decreased yields. These disappointing results forced us to postpone the dehydroiodination process to a later step in the synthesis.

The construction of the triazole moiety was initially explored using the thermal 1,3-dipolar cycloaddition with excess methyl propiolate as reagent,[25] yielding a mixture of the 4- and 5-substituted triazoles, **19** (79%) and **18** (14%), which were easily separated by column chromatography. Finally, treatment of **19** with aqueous ammonia led to the amide **20** in good yield (71%) (Scheme 3).



Scheme 3 *Reagents and conditions*: a) methyl propiolate, 50 °C, 4 h; b) NH_4OH, MeOH, r.t., 4.5 h.

The synthesis of the 4-aryl-1,2,3-triazolyl dideoxyiodocarbanucleosides of type **10** (**21a–31a**, Scheme 4) was initially planned not only to obtain the target compounds for their potentially interesting biological activities but, as different terminal aryl alkynes were to be used as dipolarophiles, to study the effect of the presence of electron-donating/withdrawing groups attached to the aromatic ring on the progress of these cycloadditions, as well as to gain insight on the optimization on the reaction conditions.



Scheme 4 *Reagents and conditions*: a) aryl alkyne, CuI, DIPEA, THF; b) base, solvent, reflux.

In our first attempt to construct the triazole moiety from **13a** and phenylacetylene, the Sharpless conditions for the Cu(I)-catalysed Huisgen 1,3-dipolar cycloaddition reaction were used,[17] with CuI as the copper(I) source, Et_3N as the base and $CH_3CN–H_2O$ as the solvent; this protocol led to an unresolved complex reaction mixture. When a larger amount of CuI was used, with DIPEA as the base in THF as solvent, the triazole **21a** was obtained (Table 2, entry 1). The use of this methodology in the reaction of the azides **13a** and **15** with different terminal alkynes produced only one of the possible regioisomers, as expected (Table 2). Furthermore, in some of the experiments (entries 3, 5, 13, 15 and 18), a small amount of the corresponding triazole iodinated in position 5 of the heterocycle was isolated (compounds **22b**, **23b**, **27b**, **28b**, **30b**). This fact can be linked to the large amount of CuI used in method A, but it also seems to be related to other reaction conditions: these derivatives were generally isolated when the reaction proceeded easily at room temperature, but they were not when the transformation was appreciably slower and needed to be heated for completion (Table 2, entries 8, 10, 11 and 20).

When the cycloaddition is carried out using a catalytic amount of CuI (Table 2, method B), the 4-aryl-1,2,3-triazole dideoxyiodocarbanucleosides **21a–31a** are the sole isolated products of the reaction, with better yields than using method A. On only one occasion, a very small amount of the corresponding iodinated compound **23b** was isolated from an experiment carried out at room temperature (Table 2, entry 6).

‡ It should be considered that when compound **13a** is subjected to the base-catalysed dehydroiodination process, these reaction conditions could lead as well to an oxonorbornane system, plausibly by cyclization of the deprotonated hydroxymethyl group, thus decreasing the yield of the cycloalkene product.[26]

Table 2 Synthesis of 4-(aryl-1,2,3-triazolyl)-2-iodocarbanucleosides **21a–31a** from azide **13a** and **15** with various terminal aryl alkynes in THF

Entry	Substrate	Ar	Method[a]	*T*	*t*/h	Products (yield (%))[b]
1	**13a**	C_6H_5	A	r.t.	28	**21a** (37) + **13a** (24)
2	**13a**	C_6H_5	B	reflux	28	**21a** (92)
3	**15**	C_6H_5	A	r.t.	23	**22a** (71) + **22b** (13) + **15** (4)
4	**15**	C_6H_5	B	r.t.	112	**22a** (76)
5	**13a**	4-MeC_6H_4	A	r.t.	6	**23a** (60) + **23b** (13)
6	**13a**	4-MeC_6H_4	B	r.t.	76	**23a** (86) + **23b** (0.6) + **13a** (2)
7	**13a**	4-MeC_6H_4	B	reflux	55	**23a** (88) + **13a** (3)
8	**13a**	4-$MeOC_6H_4$	A	reflux	95	**24a** (72)
9	**13a**	4-$MeOC_6H_4$	B	reflux	19	**24a** (81)
10	**13a**	2-$MeOC_6H_4$	A	r.t.	23	—
				reflux	2	**25a** (63)
11	**13a**	2-$NO_2C_6H_4$	A[c]	r.t.	240	—
				reflux	25	**26a** (36)
12	**13a**	2-$NO_2C_6H_4$	B	reflux	54	**26a** (73)
13	**13a**	4-$HOCH_2C_6H_4$	A[d]	r.t.	57	**27a** (48) + **27b** (12)
14	**13a**	4-$HOCH_2C_6H_4$	B	reflux	24	**27a** (69)
15	**13a**	2-$HCOC_6H_4$	A[d]	r.t.	77	**28a** (49) + **28b** (13)
16	**13a**	2-$HCOC_6H_4$	B	reflux	55	**28a** (64)
17	**13a**	2-$NH_2C_6H_4$	B	reflux	40	**29a** (75)
18	**13a**	3-Thienyl	A[d]	r.t.	68	**30a** (57) + **30b** (11)
19	**13a**	3-Thienyl	B	reflux	22	**30a** (89)
20	**13a**	2-Pyridinyl	A[d]	r.t.	120	—
				reflux	53	**31a** (29)
21	**13a**	2-Pyridinyl	B	reflux	56	**31a** (68)

[a] Method A: CuI (1–2 equiv.), DIPEA (50 equiv.). Method B: CuI (0.05–0.1 equiv.), DIPEA (2 equiv.). [b] Isolated yields after column chromatography. [c] CuI (1.5 equiv.). [d] CuI (1 equiv.).

In conclusion, method B led in all cases to better yields of the desired products, showing that the electronic effects of the substituents attached to the aromatic ring of the different aryl alkynes did not greatly affect the progress of the Huisgen 1,3-dipolar cycloaddition between them and the iodoazides **13a** or **15** (Table 2).

The structure of **31a** was unequivocally determined by means of X-ray analysis of a single crystal (Fig. 1). This confirmed the relative configuration of the key intermediate **13a**, and consequently that of the complete series of 4-aryl-1,2,3-triazole dideoxyiodocarbanucleosides **21a–31a**.

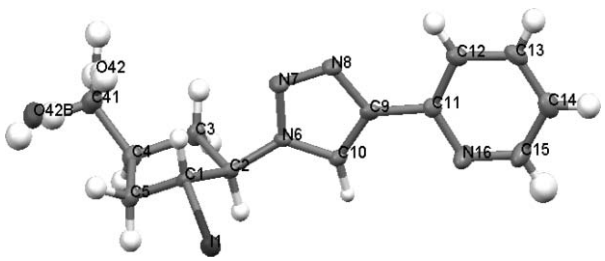
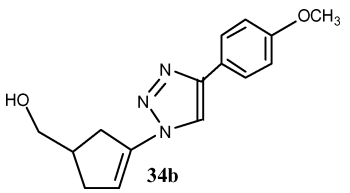


Fig. 1 MERcury ellipsoid projection of the molecular structure of **31a**, with a random atomic numbering scheme. The hydroxylic group linked to C41 showed some disorder with a 50% probability for the two positions (O42 and O42B).

Treatment of the 4-aryl-1,2,3-triazolyl dideoxyiodocarbanucleosides **21a** and **23a–30a** with DABCO in benzene at reflux[23] (Table 3) led in all cases to just one of the possible regioisomers, the 4-aryl-1,2,3-triazolyl 2′,3′-dideoxy-2′,3′-dehydrocarbanucleosides **32–39** resulting from the E2 elimination reaction of the 2-H and 3-I atoms on the carbocycle. On only one occasion, when **24a** was made to react with DBU (3.6 equiv.) in benzene, the regioisomer **34b** was isolated as the sole reaction product (32% yield).

Table 3 Dehydroiodination of compounds **21a**, **23a–28a**, and **30a**

Entry	Compound	Solvent	Base	*T*	*t*/h	Product (%)
1	**21a**	Benzene	DABCO	reflux	168	**32** (80)
2	**23a**	Benzene	DABCO	r.t.	385	**33** (40)
3	**24a**	Benzene	DABCO	reflux	144	**34a** (59)
4	**24a**	Benzene	DBU	reflux	24	**34b** (32)
5	**25a**	Toluene	DABCO	reflux	88	**35** (63)
6	**26a**	Toluene	DABCO	reflux	92	**36** (53)
7	**27a**	Benzene	DABCO	50 °C	108	—
				reflux	168	**37** (38)
8	**28a**	Benzene	DABCO	50 °C	108	—
				reflux	240	**38** (53)
9	**30a**	Benzene	DABCO	80 °C	190	**39** (56)



34b

Antiviral activities

Compounds **21a–28a**, **30a**, **31a**, **23b**, **27b**, **28b**, **30b**, **35**, **36**, **38** and **39** were evaluated for their inhibitory activities against: parainfluenza virus-3, reovirus-1, Sindbis, Coxsackie B4, and Punta Toro virus in Vero cell cultures; herpes simplex virus type 1 (strain KOS), herpes simplex virus type 1 (TK^- KOS ACV), herpes simplex virus type 2 (strain G), vaccinia virus, and vesicular stomatitis virus in human embryonic lung (HEL) cells; and vesicular stomatitis virus, respiratory syncytial virus and

coxsakie B4 virus in human epithelial (HeLa) cells. These activities were compared with those of acyclovir, gancyclovir, brivudin, (*S*)-DPHA, and ribavirin.

Compounds **21a–25a**, **22b** and **35** were also evaluated for their inhibitory activities against cytomegalovirus (CMV Davis strain) and varicella-zoster virus (TK^+VZV, thymidine kinase positive strain, and TK^-VZV, thymidine kinase deficient strain) in human embryonic lung (HEL) cells.

Likewise, compounds **23b**, **26a–28a**, **26b–28b**, **30a**, **31a**, **36**, **38** and **39** were evaluated for their inhibitory activities against feline corona virus and feline herpes virus in Crandell–Rees feline kidney (CRFK) cells.

Most of the compounds did not show any specific antiviral effects (*i.e.* minimal antiviral effective concentration ≤5-fold lower than minimal cytotoxic concentration) against any of the viruses in the assay systems used, except for compound **25a**, which exhibited specific inhibitory potential against TK^+VZV (EC_{50} = 4.5 μg mL^{-1}).

Experimental

(±)-(*c*-3-Azido-*t*-4-iodo-*r*-1-cyclopentyl)methanol (13a) and (±)-(*t*-3-azido-*c*-4-iodo-*r*-1-cyclopentyl)methanol (13b)

To a suspension of NaN_3 (2.31 g, 35.59 mmol) in dry CH_3CN (10 mL) under Ar flux at 0 °C, was added a solution of ICl (2.62 g, 16.13 mmol) in dry CH_3CN (10 mL). This was stirred for 10 min, and then a solution of **12** (0.93 g, 9.49 mmol) in dry CH_3CN (20 mL) was added dropwise. The mixture was allowed to reach room temperature and stirred for 24 hours. The reaction mixture was then poured into H_2O (100 mL) and extracted with diethyl ether (3 × 100 mL). The organic extract was washed successively with 60% $Na_2S_2O_3$ (100 mL), H_2O (2 × 50 mL) and brine (50 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure, leaving a residue (2.36 g) that was column chromatographed (silica gel, hexane–EtOAc 8 : 1 and 5 : 1 as successive eluents). Upon concentration to dryness, the combined early non-void fractions eluted with the first solvent mixture afforded a mixture of the isomeric azidoiodomethanols **13a** and **13b** (2.02 g, 80%), with **13a** as the major compound. A portion of this mixture of isomers was subjected to a second column chromatography on silica gel using hexane–EtOAc 10 : 1 as eluent to give, successively, **13a** (0.36 g) in the first group of fractions, a mixture of **13a** and **13b** (0.86 g) in the second group, and finally a **13b**-enriched group of fractions (0.03 g).

13a: Colourless oil; ν_{max}/cm^{-1} 3350, 2932, 2103, 1350, 1252, 1039; ^1H NMR (300 MHz, $CDCl_3$) δ 1.39–1.46 (1H, m, 2-CH*H*), 1.57 (1H, virtual s, D_2O exch., OH), 2.10–2.25 (2H, m, 2-CH*H* + 5-C*H*H), 2.27–2.35 (1H, m, 5-C*H*H), 2.45–2.55 (1H, m, 1-H), 3.58 (2H, d, *J* 6.3, HOCH_2), 4.11–4.18 (2H, m, 3-H + 4-H) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 27.7 (CH_2), 32.6 (CH), 38.8 (CH_2), 39.3 (CH), 65.7 (CH), 71.2 (CH_2) ppm; HRMS *m*/*z* calcd for $C_6H_{10}IN_3O$, 266.9869; found, 266.9893.

13b: Colourless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 1.69 (1H, virtual s, D_2O exch., OH), 1.83–1.87 (1H, m), 1.93–2.03 (1H, m), 2.08–2.33 (1H, m), 2.35–2.44 (1H, m), 2.55–2.65 (1H, m), 3.62–3.64 (2H, m, HOCH_2), 3.96–4.03 (1H, m), 4.11–4.13 (1H, m, 4-H) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 28.2 (CH_2), 31.8 (CH), 39.9 (CH_2), 40.4 (CH), 66.4 (CH), 71.4 (CH_2) ppm; HRMS *m*/*z* calcd for $C_6H_{10}IN_3O$, 266.9869; found, 266.9889.

(±)-*cis*-(4-Azidocyclopent-2-enyl)methanol (16)

Method A. To a solution of **13a** (145 mg, 0.54 mmol) in toluene (4 mL) was added DABCO (122 mg, 1.08 mmol). The reaction mixture was refluxed with magnetic stirring. Extra quantities of DABCO (61 mg, 0.54 mmol, after 3 hours, and 61 mg, 0.54 mmol, after 15 hours), were added to the reaction mixture and the reflux continued for a further 7 hours. Once the reaction was considered complete by TLC analysis, the solvent was evaporated, giving a brownish solid residue. This was purified by chromatography (silica gel, hexane–EtOAc 3 : 1 as eluent). Concentration of the non-void fractions to dryness afforded **16** (31 mg, 41%).

16: Brownish oil; ν_{max}/cm^{-1} 3336, 2926, 2095, 1682, 1651, 1461, 1412, 1366, 1248, 1036; ^1H NMR (300 MHz, $CDCl_3$) δ 1.62 (1H, dt, *J* 14.2 and 4.5, H*H*-5), 1.80 (1H, br s, D_2O exch., OH), 2.46 (1H, dt, *J* 14.2 and 8.4, *H*H-5), 2.88–2.93 (1H, m, H-1), 3.61 (2H, m, OCH_2), 4.43–4.46 (1H, m, H-4), 5.86 (1H, dt, *J* 5.6 and 2.1, H-2), 6.02 (1H, dt, *J* 5.6 and 1.8 Hz, H-3) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 27.7 (CH), 32.8 (CH_2), 39.3 (CH), 65.7 (CH_2), 130.7 (CH), 137.3 (CH) ppm; *m*/*z* (FAB) 139.15 (M, 15%); HRMS *m*/*z* calcd for $C_6H_9IN_3O$, 139.0746; found, 139.0768.

Method B. A solution of **13a** or **15** (1 mmol) and KOH (10 mmol) in EtOH (25 mL) was refluxed for the time specified in Table 1 (entries 1 and 7). Once the reaction was complete, the EtOH was evaporated and the corresponding solid residue dissolved in H_2O (50 mL). This was then acidified to pH 2 with 1 N aqueous HCl solution. The aqueous layer was extracted with EtOAc (3 × 75 mL), the organic layer dried (Na_2SO_4) and the solvent evaporated under reduced pressure, giving a yellow oil that was purified by column chromatography (silica gel, hexane–EtOAc 7 : 1 as eluent). When **13a** was used as the starting material, concentration of the non-void fractions to dryness afforded **16** (25%) presenting spectroscopic characteristics identical to those reported using Method A. The same occurs when **15** is used as the starting material, yielding **16** (43%).

General procedure for the synthesis of (±)-[*c*-4-(4-aryl-1*H*-1,2,3-triazol-1-yl)-*t*-3-iodo-*r*-1-cyclopentyl]methanols 21a–31a

Method A. A suspension of the azidoiodo alcohol **13a** or **15** (1 mmol), aryl alkyne (2 mmol), CuI (1 or 2 mmol) and DIPEA (50 mmol) in dry THF (50 mL), was stirred under the conditions specified in Table 2. The reactions were monitored by TLC until the complete disappearance of the starting material. The yellow solid in suspension was then filtered, the solvents were removed under reduced pressure, and resulting residue was dissolved in EtOAc and washed with water. The organic layer was dried (Na_2SO_4) and the solvent removed under reduced pressure. The obtained residue was purified by column chromatography on silica gel (see below for further details).

Method B. A suspension of the corresponding azidoiodo alcohol **13a** or **15** (1 mmol), aryl alkyne (2 mmol), a catalytic amount of CuI (0.05–0.1 mmol) and DIPEA (2 mmol) in dry THF (50 mL) was stirred under the conditions specified in Table 2. The reactions were monitored by TLC and the work-up carried out in the same manner as for Method A.

(±)-[*t*-3-Iodo-*c*-4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-*r*-1-cyclopentyl]methanol (21a)

Method A: Compound **21a** (37%) was obtained from the non-void fractions eluted with hexane–EtOAc 4 : 1 and 3 : 1, and unreacted **13a** (24%) was recovered from the non-void fractions eluted with CH_2Cl_2. Method B: Compound **21a** (92%) was obtained from the non-void fractions eluted with hexane–EtOAc 1 : 1.

21a: Slightly milky colourless oil, ν_{max}/cm^{-1} 3361, 2930, 1441, 1381, 1232, 1046, 765, 694; ^1H NMR (300 MHz, $CDCl_3$) δ 2.21–2.25 (1H, m, D_2O exch., OH), 2.23 (1H, dt, *J* 13.8 and 7.1, 5-H*H*), 2.30–2.41 (1H, m), 2.43–2.57 (2H, m), 2.58–2.71 (1H, m), 3.72–3.79 (2H, m, HOCH_2), 4.51 (1H, virtual q, *J* 7.2, 3-H), 5.06 (1H, virtual q, *J* 7.8, 4-H), 7.29–7.34 (1H, m), 7.39–7.43 (2H, m), 7.79–7.86 (2H, m), 7.89 (1H, s, 5-$H_{triazole}$) ppm; ^{13}C NMR (75.47, $CDCl_3$) δ 26.6 (CH), 33.6 (CH_2), 39.2 (CH), 40.1 (CH_2), 65.2 (CH_2), 71.4 (CH), 128.3 (CH), 128.8 (CH), 130.3 (C), 147.6 (C) ppm; *m*/*z* (ESI-TOF) 370.04 (M + 1, 100%); HRMS *m*/*z* calcd for $C_{14}H_{16}IN_3O$, 369.0338; found, 369.0357.

(±)-{*t*-3-Iodo-*c*-4-[4-(4-methylphenyl)-1*H*-1,2,3-triazol-1-yl]-*r*-1-cyclopentyl}methanol (23a) and (±)-{[*t*-3-iodo-*c*-4-[5-iodo-4-(4-methylphenyl)-1*H*-1,2,3-triazol-1-yl]-*r*-1-cyclopentyl}methanol (23b)

Method A: The non-void fractions eluting with hexane–EtOAc 2 : 1 afforded **23b** (13%) and those eluting with hexane–EtOAc 3 : 2 afforded **23a** (60%). Method B: The non-void fractions eluting with hexane–EtOAc 3 : 1 afforded **23a** (88%) as a yellow oil that presented identical spectroscopic features to that using Method A.

23a: Yellow oil, ν_{max}/cm^{-1} 3353, 2925, 1498, 1447, 1381, 1230, 1045, 819, 730; ^1H NMR (300 MHz, $CDCl_3$) δ 2.17–2.28 (1H, m), 2.38 (3H, s, CH_3), 2.39–2.56 (4H, m, one of them D_2O exch., OH), 2.58–2.72 (1H, m), 3.73–3.77 (2H, m, HOCH_2), 4.52 (1H, virtual q, *J* 7.3, 3-H), 5.07 (1H, virtual q, *J* 7.6, 4-H), 7.22–7.25 (2H, m), 7.70–7.72 (2H, m), 7.87 (1H, s, 5-$H_{triazole}$) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 21.3 (CH), 26.7 (CH_3), 33.6 (CH_2), 39.2 (CH), 40.1 (CH_2), 65.1 (CH_2), 71.4 (CH), 119.2 (CH), 127.5 (C), 129.5 (CH), 130.2 (C), 147.6 (C) ppm; *m*/*z* (ESI-TOF) 384.05 (M + 1, 100%); HRMS *m*/*z* calcd for $C_{15}H_{18}IN_3O$, 383.0495; found, 383.0518.

23b: Yellow solid, mp 91–93 °C, ν_{max}/cm^{-1} 3333, 2918, 1424, 1336, 1261, 1226, 1036, 815; ^1H NMR (300 MHz,$CDCl_3$) δ 1.60–1.87 (1H, m, D_2O exch., OH), 2.16–2.24 (1H, m, 5-H*H*), 2.45 (3H, s, CH_3), 2.41–2.47 (1H, m), 2.77–2.84 (3H, m), 3.79–3.82 (2H, m, HOCH_2), 4.70 (1H, virtual q, *J* 6.5, 3-H), 5.19 (1H, virtual q, *J* 7.8, 4-H), 7.30–7.26 (2H, m), 7.80–7.84 (2H, m) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 21.3 (CH), 26.3 (CH_3), 33.8 (CH_2), 39.7 (CH_2), 39.8 (CH), 65.3 (CH_2), 71.1 (CH), 129.1 (C), 129.3 (CH), 131.1 (C), 138.7 (C), 147.7 (C) ppm; *m*/*z* (ESI-TOF) 509.95 (M, 100%); $C_{26}H_{32}N_2O_2Si$ (509.1239): calcd. C, 35.39; H, 3.37; N, 8.25; found C, 35.68; H, 3.59; N, 8.54%.

(±)-{*t*-3-Iodo-*c*-4-[4-(4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl]-*r*-1-cyclopentyl}methanol (24a)

Method B: The non-void fractions eluting with hexane–EtOAc 1 : 1 and 1 : 3 afforded **24a** (81%).

24a: Whitish solid, mp 96–98 °C (recrystallised from diethyl ether–hexane), ν_{max}/cm^{-1} 3454, 3130, 2997, 2927, 1497, 1451, 1251, 1176, 1029, 838, 794; ^1H NMR (300 MHz,$CDCl_3$) δ 2.11–2.28 (1H, m), 2.31–2.41 (1H, m), 2.43–2.71 (4H m, one of them D_2O exch., OH), 3.75–3.81 (2H, m, HOCH_2), 3.83 (3H, s, CH_3), 4.52 (1H, virtual q, *J* 7.3, 3-H), 5.05 (1H, virtual q, *J* 7.9, 4-H) 6.93–6.97 (2H, m), 7.72–7.77 (2H, m), 7.82 (1H, s, 5-$H_{triazole}$) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 26.5 (CH), 33.6 (CH_2), 39.0 (CH), 39.8 (CH_2), 55.2 (CH_3), 64.7 (CH_2), 71.2 (CH), 114.2 (CH), 118.8 (CH), 122.8 (C), 126.9 (CH), 147.2 (C), 159.5 (C) ppm; *m*/*z* (ESI-TOF) 400.05 (M + 1, 100%); $C_{15}H_{18}IN_3O_2$ (399.2268). calcd. C, 45.13; H, 4.54; N, 10.53; found C, 45.39; H 4.81; N, 10.67%.

(±)-{*t*-3-Iodo-*c*-4-[(2-nitrophenyl)-1*H*-1,2,3-triazol-1-yl]-*r*-1-cyclopentyl}methanol (26a)

Method B: The non-void fractions eluting with hexane–EtOAc 3 : 2 afforded **26a** (73%).

26a: Yellow oil, ν_{max}/cm^{-1} 3371, 2938, 2896, 1528, 1442, 1358, 1232, 1042, 782; ^1H NMR (300 MHz, $CDCl_3$) δ 2.17–2.28 (1H, m), 2.31–2.44 (3H, m), 2.47–2.72 (2H, m), 3.75 (2H, d, *J* 5.2, HOCH_2), 4.51 (1H, virtual q, *J* 7.3, 3-H), 5.08 (1H, virtual q, *J* 7.9, 4-H), 7.49 (1H, dt, *J* 7.62 and 1.17), 7.64 (1H, dt, *J* 7.6, 1.2), 7.81 (1H, dd, *J* 8.2 and 1.2), 8.0 (1H, s, 5-$H_{triazole}$), 8.04 (1H, dd, *J* 7.8 and 1.2) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 26.4 (CH), 33.5 (CH_2), 39.6 (CH), 39.9 (CH_2), 65.0 (CH_2), 71.5 (CH), 122.9 (CH), 124.0 (CH), 131.1 (CH), 132.5 (CH), 141.7 (C), 148.2 (C) ppm; *m*/*z* (EI 70 eV) 414 (M, 0.5%), 397 (6), 207 (10), 152 (13), 135 (13), 104 (21), 97 (17), 80 (61), 79 (100), 77 (16), 76 (13), 67 (33), 57 (14); HRMS *m*/*z* calcd for $C_{14}H_{15}IN_4O_3$ 414.1984, found, 414.2007.

(±)-{*c*-3-[4-(4-Hydroxymethylphenyl)-1*H*-1,2,3-triazol-1-yl]-*t*-4-iodo-*r*-1-cyclopentyl}methanol (27a) and (±)-{*c*-3-[4-(4-hydroxymethylphenyl)-5-iodo-1*H*-1,2,3-triazol-1-yl]-*t*-4-iodo-*r*-1-cyclopentyl}methanol (27b)

Method A: The non-void fractions eluting with hexane–EtOAc 1 : 2 and 2 : 3 afforded successively **27b** (12%) and **27a** (48%). Method B: The non-void fractions eluting with hexane–EtOAc 1 : 1 afforded **27a** (69%) as a yellow solid that presented identical spectroscopic features to that using Method A.

27a: White solid, mp 114–115 °C (recrystallized from hexane–EtOAc); ν_{max}/cm^{-1} 3250, 2933, 1443, 1200, 1037, 803; ^1H NMR (300 MHz, $CDCl_3$) δ 1.71 (1H, t, *J* 5.9, D_2O exch., OH), 1.8–1.90 (1H, m, D_2O exch.), 2.21–2.65 (5H, m), 3.77–3.80 (2H, m, HOCH_2), 4.53 (1H, virtual q, *J* 7.3, 3-H), 4.72–4.74 (2H, m, HOCH_2Ph), 5.08 (1H, virtual q, *J* 7.6, 4-H); 7.43 (2H, d, *J* 8.3), 7.84 (2H, d, *J* 8.2), 7.92 (1H, s, 5-$H_{triazole}$) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 26.6 (CH), 29.7 (CH_2), 33.6 (CH_2), 39.2 (CH), 40.1 (CH_2), 65.2 (CH_2), 71.4 (CH), 119.5 (CH), 125.9 (CH), 127.5 (CH), 129.7 (C), 137.7 (C), 140.9 (C) ppm; *m*/*z* (EI 70 eV) 399 (M, 6%), 226 (11), 207 (10), 147 (36), 146 (100), 131 (12), 130 (13), 129 (10), 128 (12), 118 (11), 117 (10), 115 (11), 103 (25), 97 (13), 91 (36), 89 (13), 80 (35), 79 (56), 77 (27), 67 (40), 66 (17); $C_{15}H_{18}IN_3O_2$ (399.2268): calcd. C, 45.13; H, 4.54; N, 10.53; found C, 45.38; H, 4.72; N, 10.81%.

27b: White solid, mp 101–102°C (recrystallized from EtOAc); ν_{max}/cm^{-1} 3341, 2923, 1612, 1417, 1229, 1043, 825; ^1H NMR (300 MHz, DMSO-d_6) δ 1.84 (1H, dt, *J* 12.9 and 8.8), 2.26–2.35

(2H, m), 3.24–3.39 (2H, m), 3.4 (2H, t, *J* 8.4, CH_2OH), 4.54 (2H, d, *J* 5.6, HOCH_2), 4.68 (1H, virtual q, *J* 8.4, 4-H), 4.71 (1H, t, *J* 5.3, D_2O exch., OH), 5.13 (1H, virtual q, *J* 8.6, 3-H), 5.24 (1H, t, *J* 5.7, D_2O exch., OH), 7.42 (2H, d, *J* 8.2), 7.82 (2H, d, *J* 7.9) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 24.4 (CH), 33.9 (CH_2), 39.5 (CH), 39.6 (CH_2), 63.6 (CH_2), 64.7 (CH_2), 71.4 (CH), 126.9 (CH), 127.7 (CH), 129.2 (C), 142.4 (C), 148.8 (C), 149.7 (C) ppm; *m*/*z* (EI 70 eV) 273 (12%), 272 (4), 207 (21), 146 (28), 135 (12), 117 (15), 116 (24), 97(22), 91 (22), 90 (14), 89 (20), 80 (56), 79 (93), 77 (22), 69(24), 67 (64), 65 (21), 58 (100), 57 (38), 55 (30), 53 (11); $C_{15}H_{17}I_2N_3O_2$ (525.1233): calcd. C, 34.31; H, 3.26; N, 8.00; found C, 34.69; H, 3.57; N, 8.34%

(±)-2-{1-[*c*-4-(Hydroxymethyl)-*t*-2-iodo-*r*-1-cyclopentyl]-1*H*-1,2,3-triazol-4-yl}benzaldehyde (28a) and (±)-2-{1-[*c*-4-(hydroxymethyl)-*t*-2-iodo-*r*-1-cyclopentyl]-5-iodo-1*H*-1,2,3-triazol-4-yl}benzaldehyde (28b)

Method A: The non-void fractions eluted with hexane–EtOAc 2 : 1 and 3 : 2 afforded successively **28b** (13%) and **28a** (49%). Method B: The non-void fractions eluted with hexane–EtOAc 1 : 1 and 2 : 3 afforded **28a** (64%) as a yellow oil that presented identical spectroscopic features to that using Method A.

28a: Yellow oil. ν_{max}/cm^{-1}3353, 2929, 1688, 1602, 1445, 1198, 1044, 827, 769; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.22–2.68 (6H, m, one of them D_2O exch., OH), 3.75–3.78 (2H, m, HOCH_2), 4.53 (1H, virtual q, *J* 7.6, 2-H), 5.11 (1H, virtual q, *J* 7.9, 1-H), 7.48–7.53 (1H, m), 7.62–7.67 (1H, m), 7.71–7.73 (1H, m), 7.96–8.02 (1H, m), 8.05 (1H, s, 5-$H_{triazole}$), 10.37 (1H, s, C*H*O) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 26.5 (CH), 33.5 (CH_2), 39.0 (CH), 40.0 (CH_2), 65.0 (CH_2), 71.5 (CH), 123.2 (CH), 128.7 (CH), 128.9 (CH), 130.1 (CH), 132.8 (C), 133.8 (CH), 144.4 (C), 192.5 (C) ppm; *m*/*z* (EI 70 eV) 370 [(M + 2) − CHO, 16%], 369 [(M + 1) − CHO, 100], 207 (27), 146 (25), 145 (18), 128 (18), 102 (15), 89 (17), 79 (14), 59 (15); HRMS *m*/*z* calcd for $C_{15}H_{16}IN_3O_2$, 397.2109; found, 397.2134.

28b: Yellow solid, mp 73–74°C; ν_{max}/cm^{-1} 3375, 2923, 1688, 1797, 1196, 1039, 823, 769; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.06–2.26 (2H, m, one of them D_2O exch., OH), 2.28–2.46 (1H, m), 2.47–2.59 (1H, m), 2.62–2.75 (1H, m), 3.74–3.79 (2H, m, HOCH_2), 4.70 (1H, virtual q, *J* 7.3, 2-H), 5.13 (1H, virtual q, *J* 7.5, 1-H), 7.56–7.59 (2H, m), 7.66–7.70 (1H, m), 8.06 (1H, d, *J* 8.4), 9.98 (1H, s, C*H*O) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 25.7 (CH), 34.0 (CH_2), 39.6 (CH), 39.7 (CH_2), 65.3 (CH_2), 71.5 (CH), 128.2 (CH), 129.6 (CH), 131.2 (CH), 132.8 (C), 133.7 (CH), 134.5 (C), 148.1 (C), 191.4 (C) ppm; *m*/*z* (ESI-TOF) 523.93 (M + 1, 100%); $C_{16}H_{15}I_2N_3O_2$ (522.9254): calcd. C, 34.44; H, 2.89; N, 8.03; found C 34.68, H 3.10, N 8.34%.

(±)-{*c*-3-[4-(2-Aminophenyl)-1*H*-1,2,3-triazol-1-yl]-*t*-4-iodo-*r*-1-cyclopentyl}methanol (29a)

Method B: The non-void fractions eluted with hexane–EtOAc 1 : 2 and 1 : 3 afforded **29a** (75%).

29a: Brownish oil; ν_{max}/cm^{-1} 3361, 2920, 1619, 1460, 1045, 908, 786, 729; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.17–2.65 (6H, m, one of them D_2O exch., OH), 3.12 (2H, br s, D_2O exch., NH_2), 3.73–3.78 (2H, m, HOCH_2), 4.50 (1H, virtual q, *J* 7.5, 4-H), 5.04 (1H, virtual q, *J* 7.9, 3-H), 6.66 (1H, ddd, *J* 7.6, 2.3 and 1.7), 7.12–7.25 (3H, m), 7.86 (1H, s, 5-$H_{triazole}$) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 26.6 (CH), 33.6 (CH_2), 39.2 (CH), 40.0 (CH_2), 65.1 (CH_2), 71.4 (CH), 112.2 (CH), 115.1 (CH), 116.1 (CH), 119.6 (CH), 129.8 (CH), 131.2 (C), 146.9 (C), 147.6 (C) ppm; *m*/*z* (EI 70 eV) 384 (M, 15%), 256 (16), 160 (16), 132 (44), 131 (100), 117 (38), 104 (26), 85(14), 80 (18), 79 (28), 77 (20), 71 (19), 69 (20), 67 (28), 57 (24); HRMS *m*/*z* calcd for $C_{14}H_{17}IN_4O$, 384.2154; found, 384.2172.

(±)-{*t*-3-Iodo-*c*-4-[4-(3-thienyl)-1*H*-1,2,3-triazol-1-yl]-*r*-1-cyclopentyl}methanol (30a) and (±)-{*t*-3-iodo-*c*-4-[5-iodo-4-(3-thienyl)-1*H*-1,2,3-triazol-1-yl]-*r*-1-cyclopentyl}methanol (30b)

Method A: The non-void fractions eluted with hexane–EtOAc 5 : 1, 3 : 1, 2 : 1 and 1 : 1 afforded successively **30b** (11%) and **30a** (57%). Method B: The non-void fractions eluting with hexane–EtOAc 3 : 1, 2 : 1, and 1 : 1 afforded **30a** (89%) as a yellowish oil that presented identical spectroscopic features to that using Method A.

30a: Yellowish oil; ν_{max}/cm^{-1} 3356, 3126, 2924, 2868, 1596, 1446, 1353, 1314, 1228, 1046, 856, 786, 622; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85–2.06 (1H, m), 2.09–2.31 (3H, m), 2.34–2.51 (1H, m), 3.09 (1H, br s, D_2O exch., OH), 3.53–3.55 (2H, m, HOCH_2), 4.30 (1H, virtual q, *J* 7.8, 3-H), 4.84 (1H, virtual q, *J* 8.1, 4-H), 7.21–7.09 (1H, m), 7.24–7.28 (1H, m), 7.49–7.51 (1H, m), 7.69 (1H, s, 5-$H_{triazole}$) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 26.4 (CH), 33.6 (CH_2), 38.9 (CH), 39.8 (CH_2), 64.7 (CH_2), 71.2 (CH), 119.4 (CH), 121.3 (CH), 125.7 (CH), 126.4 (CH), 131.3 (C), 143.6 (C) ppm; *m*/*z* (EI 70 eV) 375 (M, 43%), 220 (19), 207 (18), 202 (14), 162 (13), 123 (31), 122 (100), 108 (25), 97 (22), 80 (15), 79 (29), 67 (14); HRMS *m*/*z* calcd for $C_{12}H_{14}IN_3OS$, 375.2285; found, 375.2306.

30b: Yellowish solid, mp 95–97°C; ν_{max}/cm^{-1} 3369, 2918, 1651, 1585, 1429, 1148, 1030, 787; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.0 (1H, br s, D_2O exch., OH), 2.12–2.21 (2H, m), 2.34–2.53 (1H, m), 2.54–2.63 (1H, m), 2.66–2.79 (1H, m), 3.77–3.81 (2H, m, HOCH_2), 4.69 (1H, virtual q, *J* 6.6, 3-H), 5.17 (1H, virtual q, *J* 7.2, 4-H), 7.41–7.44 (1H, m), 7.75–7.81 (1H, m), 7.97–7.98 (1H, m) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 25.9 (CH), 33.7 (CH_2), 39.5 (CH_2), 39.6 (CH), 65.2 (CH_2), 70.9 (CH), 122.9 (CH), 125.9 (CH), 126.5 (CH), 130.6 (C), 146.3 (C), 146.4 (C) ppm; *m*/*z* (EI 70 eV) 501 (M, 33%), 346 (27), 248 (62), 247 (100), 218 (20), 207 (63), 123 (24), 122 (74), 121 (45), 97 (26), 95 (34), 94 (14), 80 (42), 79 (83), 67 (28); $C_{12}H_{13}I_2N_3OS$ (500.8869): calcd. C, 28.76; H, 2.61; N, 8.39; found C, 29.08; H, 2.59; N, 8.54%.

(±)-{*t*-3-Iodo-*c*-4-[4-(2-pyridinyl)-1*H*-1,2,3-triazol-1-yl]-*r*-1-cyclopentyl}methanol (31a)

Method A: The non-void fractions eluted with hexane–EtOAc 1 : 1, 2 : 3, and 1 : 3 afforded **31a** (29%). Method B: The non-void fractions eluted with hexane–EtOAc 3 : 1, 2 : 1, and 1 : 1 afforded **31a** (68%) as a white solid that presented identical spectroscopic features to that using method A.

31a: White solid, mp 151–152°C (recrystallized from EtOAc); ν_{max}/cm^{-1} 3150, 2931, 1600, 1466, 1243, 1134, 1040, 779; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.04–2.14 (1H, m, D_2O exch., OH), 2.16–2.26 (1H, m), 2.32–2.69 (4H, m), 3.75 (2H, d, *J* 5.3, HOCH_2), 4.55 (1H, virtual q, *J* 7.6, 3-H), 5.12 (1H, virtual q, *J* 7.9, 4-H), 7.22–7.28 (1H, m), 7.76–7.81 (1H, m), 8.18 (1H, d, *J* 7.9), 8.29 (1H, s, 5-$H_{triazole}$), 8.57–8.59 (1H, m) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$)

δ 26.0 (CH), 33.8 (CH_2), 39.2 (CH), 40.2 (CH_2), 65.3 (CH_2), 71.5 (CH), 120.3 (CH), 121.7 (CH), 123.0 (CH), 137.0 (CH), 148.2 (C), 149.4 (CH), 150.1 (C) ppm; *m/z* (EI 70 eV) 370 (M, 7%), 340 (27), 243 (15), 215 (15), 207 (16), 147 (42), 120 (15), 119 (24), 118 (75), 117 (100), 104 (10), 91 (14), 90 (16), 80 (18), 79 (31), 78 (14), 67 (14), 58 (13); $C_{13}H_{14}I_2N_4O$ (370.1889): calcd. C, 42.18; H, 4.08; N, 15.13; found C, 42.44; H, 4.23; N, 15.38%.

X-Ray crystal structure determination: Single crystals of compound **31a** suitable for X-ray diffractometry were obtained by iterative recrystallization of the isolated product using MeOH. The desired single crystals were mounted in an inert oil and transferred to the cold gas stream of the diffractometer. Empirical formula: $C_{13}H_{15}IN_4O$; formula weight: 370.19; crystal size: 28 × 0.16 × 0.11 mm^3; crystal colour: colourless; habit: prismatic; crystal system: monoclinic; lattice type: plate; lattice parameters: a = 7.4415(13) Å, b = 21.445(4) Å, c = 8.9163(15) Å, β = 104.154(2)°, V = 1379.0(4) $Å^3$; space group: $P2_1/n$; Z = 4; D_{calc} = 1.782 Mg m^{-3}; $R1$ = 0.0265, $wR2$ = 0.0649. Diffractometer: Smart-1000 BRUKER. CCDC number 651791.†

General procedure for the synthesis of (±)-[*cis*-4-(4-aryl-1*H*-1,2,3-triazol-1-yl)cyclopent-2-enyl]methanol 32–39

A solution of the triazole derivative **21a**, **23a–28a** or **30a** (1 mmol) and DABCO (2 mmol) in dry benzene or toluene (12.5 mL) was stirred under the conditions specified in Table 3 until TLC analysis showed complete disappearance of the starting material. The solvent was then evaporated under reduced pressure and the residue purified by column chromatography on silica gel using the eluent indicated below.

(±)-[*cis*-4-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)cyclopent-2-enyl]methanol (32)

Eluent hexane–EtOAc 2 : 1; milky oil; ν_{max}/cm^{-1} 3356, 2871, 1614, 1434, 1365, 1223, 1041, 764, 693; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66–1.74 (1H, m, D_2O exch., OH), 1.90 (1H, dt, *J* 14.2 and 5.2, 5-CH*H*), 2.86 (1H, dt, *J* 14.2 and 9.0, 5-C*H*H), 2.95–3.13 (1H, m, 1-H), 3.71 and 3.81 (2H, part AB, ABM system, *J* 10.6, 5.0 and 4.8, HOCH_2), 5.78–5.81 (1H, m, 4-H), 5.95 (1H, dt, *J* 5.5 and 2.2, 2-H), 6.18 (1H, dt, *J* 5.5 and 2.1, 3-H), 7.32–7.34 (1H, m), 7.34–7.43 (2H, m), 7.79–7.82 (2H, m), 7.87 (1H, s, 5-$H_{triazole}$) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 30.2 (CH_2), 34.7 (CH_2), 48.0 (CH), 65.4 (CH_2), 66.5 (CH), 118.3 (CH), 126.1 (CH), 128.5 (CH), 129.2 (CH), 130.5 (CH), 131.1 (C), 139.0 (CH), 148.2 (C) ppm; *m/z* (EI 70 eV) 241 (M, 28%), 207 (32), 182 (11), 117 (22), 116 (100), 89(17), 79 (11), 58 (36); HRMS *m/z* calcd for $C_{14}H_{15}N_3O$, 241.2885; found, 241.2907.

(±)-{*cis*-4-[4-(4-Methylphenyl)-1*H*-1,2,3-triazol-1-yl]cyclopent-2-enyl}methanol (33)

Eluent hexane–EtOAc 2 : 1; milky oil; ν_{max}/cm^{-1} 3379, 2920, 1651, 1498, 1454, 1365, 1222, 1042, 799; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92 (1H, dt, *J* 14.2 and 5.3, 5-CH*H*), 1.94–1.99 (1H, m, D_2O exchange, OH), 2.37 (3H, s, CH_3), 2.85 (1H, dt, *J* 14.2 and 9.0, 5-C*H*H), 3.05–3.10 (1H, m, 1-H), 3.69–3.74 (1H, m, HOCH*H*), 3.77–3.82 (1H, m, HOC*H*H), 5.75–5.82 (1H, m, 4-H), 5.95 (1H, dt, *J* 5.6 and 2.2, 2-H), 6.19 (1H, dt, *J* 5.6 and 2.1, 3-H), 7.19–7.22 (2H, m), 7.68–7.70 (2H, m), 7.81 (1H, s, 5-$H_{triazole}$) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 21.3 (CH_3), 34.4 (CH_2), 47.6 (CH), 65.0 (CH_2), 66.1 (CH), 117.6 (CH), 125.6 (CH), 127.8 (C), 129.4 (CH), 130.0 (CH), 137.9 (C), 138.6 (CH), 147.9 (C) ppm; *m/z* (EI 70 eV) 256 (M + 1, 8%), 255 (M, 10), 131 (22), 130 (100), 118 (19), 116 (9), 115 (14), 103 (21), 79 (20), 77 (19), 71 (9), 67 (14), 58 (53), 57 (19); HRMS *m/z* calcd for $C_{15}H_{17}N_3O$, 255.315; found, 255.1368.

(±)-{*cis*-4-[4-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-1-yl]cyclopent-2-enyl}methanol (34a)

Eluent hexane–EtOAc 1 : 2 and 1 : 4; yellow solid; mp 67–68 °C; ν_{max}/cm^{-1} 3324, 2920, 1617, 1559, 1498, 1247, 1103, 1030, 799; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.93 (1H, dt, *J* 14.2 and 5.2, 5-CH*H*), 2.11–2.14 (1H, m, D_2O exch., OH), 2.84 (1H, dt, *J* 14.2 and 9.0, 5-C*H*H), 3.02–3.13 (1H, m, 1-H), 3.68–3.74 (1H, m, HOCH*H*), 3.77–3.79 (1H, m, HOC*H*H), 3.83 (3H, s, CH_3), 5.74–5.82 (1H, m, 4-H), 5.94 (1H, dt, *J* 5.6 and 2.2, 2-H), 6.17 (1H, dt, *J* 5.6 and 2.0, 3-H), 6.90–6.96 (2H, m), 7.70–7.74 (2H, m), 7.77 (1H, s, 5-$H_{triazole}$) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 34.4 (CH_2), 47.6 (CH), 55.3 (CH_3), 65.0 (CH_2), 66.0 (CH), 114.2 (CH), 117.1 (CH), 123.4 (C), 126.9 (CH), 130.0 (CH), 138.5 (CH), 147.6 (C), 159.5 (C) ppm; *m/z* (FAB) 272.12 (M + 1, 11%); $C_{15}H_{17}N_3O_2$ (271.3144): calcd. C, 66.40; H, 6.32; N, 15.49; found C, 66.76; H, 6.65; N, 15.64%.

(±)-{*cis*-4-[4-(2-Methoxyphenyl)-1*H*-1,2,3-triazol-1-yl]cyclopent-2-enyl}methanol (35)

Eluent hexane–EtOAc 1 : 2; an analytical simple was obtained by a second purification by column chromatography on silica gel using CH_2Cl_2–MeOH 9 : 0.1; slightly milky colourless oil; ν_{max}/cm^{-1} 3364, 2929, 1650, 1544, 1058; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.96 (1H, dt, *J* 14.4 and 5.3, 5-CH*H*), 2.14–2.19 (1H, m, D_2O exch., OH), 2.84 (1H, dt, *J* 14.4 and 8.9, 5-C*H*H), 3.06–3.11 (1H, m, 1-H), 3.81 and 3.72 (2H, part AB, ABM system, *J* 10.6 and 4.8 HOCH_2), 3.91 (3H, s, CH_3), 5.74–5.79 (1H, m, 4-H), 5.97 (1H, dt, *J* 5.6 and 2.2, 2-H), 6.16 (1H, dt, *J* 5.6 and 2.0, 3-H), 6.96 (1H, d, *J* 8.5), 7.04–7.09 (1H, m), 7.27–7.33 (1H, m), 8.08 (1H, s, 5-$H_{triazole}$), 8.31 (1H, dd, *J* 7.6 and 1.8) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 34.5 (CH_2), 47.7 (CH), 55.4 (CH_3), 65.2 (CH_2), 66.9 (CH), 110.7 (CH), 119.5 (C), 121.0 (CH),121.6 (CH), 127.6 (CH), 128.8 (CH), 130.1(CH), 138.2 (CH), 143.1 (C), 155.6 (C) ppm; *m/z* (EI 70 eV) 271 (M, 12%), 212 (14), 147 (20), 146 (100), 132 (21), 119 (31), 89 (15), 79 (17), 77 (14), 67 (16), 65 (11); HRMS *m/z* calcd for $C_{15}H_{17}N_3O_2$, 271.3144; found, 271.3170.

(±)-{*cis*-4-[4-(2-Nitrophenyl)-1*H*-1,2,3-triazol-1-yl)cyclopent-2-enyl}methanol (36)

Eluent hexane–EtOAc 3 : 2 and 1 : 2; colourless oil; ν_{max}/cm^{-1} 3385, 2924, 1617, 1529, 1435, 1360, 1225, 1038, 752; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87–1.95 (1H, m, D_2O exch., OH), 1.93 (1H, dt, *J* 14.4 and 4.8, 5-CH*H*), 2.86 (1H, dt, *J* 14.4 and 9.1, 5-C*H*H), 3.05–3.10 (1H, m, 1-H), 3.67–3.81 (2H, m, HOCH_2), 5.77–5.82 (1H, m, 4-H), 5.93–5.96 (1H, m, 2-H), 6.17–6.20 (1H, m, 3-H), 7.45–7.50 (1H, m), 7.62–7.67 (1H, m), 7.78 (1H, dd, *J* 7.9 and 1.2), 7.94 (1H, s, 5-$H_{triazole}$), 8.04 (1H, dd, *J* 7.9, and 1.5) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 34.4 (CH_2), 47.5 (CH), 64.8 (CH_2), 66.3 (CH), 121.5 (CH), 123.9 (CH), 124.9 (C), 128.8 (CH), 129.7 (CH), 131.0 (CH), 132.4 (CH), 139.0 (CH), 141.9 (C) ppm; *m/z*(EI 70 eV) 286 (M, 1%), 191 (19), 107 (3), 105 (3), 104

(18), 97 (6), 92 (6), 91 (6), 89 (9), 80 (10), 79 (100), 78 (4),77 (21), 76 (13), 67 (61), 66 (26), 65 (17); HRMS *m/z* calcd for $C_{14}H_{14}N_4O_3$, 286.286; found, 286.2882.

(±)-{*cis*-4-[4-(4-Hydroxymethylphenyl)-1*H*-1,2,3-triazol-1-yl]cyclopent-2-enyl}methanol (37)

Eluents hexane–EtOAc 1 : 2 and EtOAc; yellow oil; ν_{max}/cm^{-1} 3357, 2924, 2864, 1651, 1455, 1368, 1221, 1040, 801; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.94 (1H, dt, *J* 14.2 and 5.2, 5-CH*H*), 2.11–2.14 (1H, m, D_2O exch., OH), 2.85 (1H, dt, *J* 14.2 and 9.0, 5-*H*H), 3.03–3.13 (1H, m, 1-H), 3.68 and 3.81 (2H, part AB, ABM system, *J* 10.6 and 4.8, HOCH_2), 4.22–4.20 (1H, m, 4-H), 4.71 (2H, virtual s, PhCH_2OH), 5.95 (1H, dt, *J* 5.6 and 2.2, 2-H), 6.18 (1H, dt, *J* 5.6 and 2.0, 3-H), 7.39 (2H, d, *J* 8.3), 7.78 (2H, d, *J* 8.3), 7.87 (1H, s, 5-$H_{triazole}$) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 29,7 (CH_2), 34.4 (CH_2), 47.6 (CH), 64.9 (CH_2), 66.1 (CH), 118.0 (CH), 125.8 (CH), 127.4 (CH), 130.0 (CH), 130.3 (C), 138.6 (CH), 140.7 (C), 147.5 (C) ppm; *m/z* (EI 70 eV) 271 (M, 9%), 147 (18), 146 (100), 118 (10), 99 (10), 91 (21), 83 (12), 79(29), 77 (15), 71 (26), 69 (21), 65 (13), 58 (30), 57 (29), 55 (11); HRMS *m/z* calcd for $C_{15}H_{17}N_3O_2$, 271.3144; found, 271.3162.

(±)-2-{1-[*cis*-4-(Hydroxymethyl)cyclopent-2-enyl]-1*H*-1,2,3-triazol-4-yl}benzaldehyde (38)

Eluent hexane–EtOAc 2 : 1 and 1 : 2; brown oil; ν_{max}/cm^{-1} 3387, 2925, 1688, 1602, 1455, 1367, 1200, 1039, 769; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.96 (1H, dt, *J* 14.4 and 5.0, 5-CH*H*), 2.21–2.31 (1H, m, D_2O exch., OH), 2.88 (1H, dt, *J* 14.4 and 9.1, 5-*H*H), 3.05–3.11 (1H, m, 4-H), 3.70 and 3.81 (2H, part AB, ABM system, *J* 10.5 and 4.7, HOCH_2), 5.81–5.87 (1H, m, 1-H), 5.94–5.97 (1H, m, 2-H), 6.17–6.20 (1H, m, 3-H), 7.45–7.50 (1H, m), 7.58–7.69 (2H, m), 7.99 (1H, s, 5-$H_{triazole}$), 7.98–8.01 (1H, m), 10.36 (1H, s, CO*H*) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 34.4 (CH_2), 47.5 (CH), 64.6 (CH_2), 66.3 (CH), 121.8 (CH), 128.5 (CH), 128.6 (CH), 129.7 (CH), 130.0 (C), 133.3 (C), 133.7 (CH), 139.8 (CH), 144.6 (C), 192.6 (C) ppm; *m/z* (EI 70 eV) 269 (M, 1%), 242 (15), 241 (90), 146 (29), 145 (100), 144 (21), 130 (16), 128 (15), 118 (28), 117 (41), 102 (30), 90 (37), 89 (66), 79 (57), 77 (30), 67 (62), 66 (28), 65 (23), 63 (19); HRMS *m/z* calcd for $C_{15}H_{15}N_3O_2$, 269.2985; found, 269.3003.

(±)-{*cis*-4-[4-(3-Thienyl)-1*H*-1,2,3-triazol-1-yl]cyclopent-2-enyl}methanol (39)

Eluent hexane–EtOAc 2 : 1; yellow oil; ν_{max}/cm^{-1} 3387, 2925, 1688, 1602, 1455, 1366, 1200, 1039, 769 3402; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.91 (1H, dt, *J* 14.2 and 5.3, 5-CH*H*), 2.21–2.31 (1H, m, D_2O exch., OH), 2.88 (1H, dt, *J* 14.3 and 9.1, 5-*H*H), 3.05–3.11 (1H, m, 4-H), 3.70 and 3.79 (2H, part AB, ABM system, *J* 10.5 and 4.7, HOCH_2), 5.74–5.81 (1H, m, 1-H), 5.92 (1H, dd, *J* 5.6 and 2.2, 2-H), 6.17 (1H, dd, *J* 5.6 and 2.0, 3-H), 7.35 (1H, dd, *J* 5.0 and 3.1), 7.42 (1H, dd, *J* 5.0 and 1.2), 7.66 (1H, dd, *J* 2.9 and 1.2), 7.76 (1H, s, 5-$H_{triazole}$) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 34.6 (CH_2), 47.8 (CH), 65.1 (CH_2), 66.3 (CH), 118.0 (CH), 12.2 (CH), 126.0 (CH), 126.5 (CH), 130.2 (C), 132.2 (C), 138.9 (CH), 144.2 (C) ppm; *m/z* (EI 70 eV) 247 (M, 1%), 122 (11), 118 (29), 88 (10), 85 (15), 71 (23), 69 (20), 58 (100), 57 (32), 55 (17); HRMS *m/z* calcd for $C_{12}H_{13}N_3OS$, 247.3161; found, 247.3179.

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