

A 'click chemistry' approach to the straightforward synthesis of new 4-aryl-1,2,3-triazolocarbannucleosides

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Dedicated to Professor Benito Alcaide on the occasion of his 60th birthday

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Abstract

The synthesis and biological evaluation as antiviral agents of a series of racemic 4-aryl-1,2,3-triazolyl carbannucleosides of type (\pm)-**10**/ (\pm) -**11** related to the broad spectrum antiviral agent ribavirin **1** are described. These compounds were produced using a "click chemistry" strategy starting from readily available protected alcohol **13b**. The synthetic approach made use of olefin-based organic reactions for the stereoselective construction of the appropriately functionalized cyclopentane ring moiety followed by copper (I) catalyzed Huisgen 1,3-dipolar cycloaddition of azides and alkynes for the regioselective construction of the heterocyclic triazole moiety.

Keywords: Click chemistry, triazoles, carbannucleosides, antiviral, ribavirin

Introduction

Ribavirin (Virazole[®], **1**, Figure 1)¹ is a broad spectrum antiviral in clinical use for the treatment of RSV infections, lassa fever, hepatitis (A, B, and C), measles and mumps. The structure of this nucleoside analogue consists in a β -D-ribose ring attached to a 1,2,4-triazole derivative replacing the classic purine or pyrimidine base as the aglycon. Other nucleoside analogues owning 5-membered heterocyclic bases, such as imidazoles and triazoles, have displayed interesting biological properties; for instance, brendin (Mizoribine[®], **2**, Figure 1) is currently in clinical use

as an immunosuppressor for the treatment of transplant patients² and EICAR (**3**, Figure 1), causes depletion of purine nucleotides resulting in a broad spectrum of activity against RNA and DNA viruses and tumour cell proliferation.³

In this context, a great number 1,2,3-triazole derivatives have shown a great potential as antiviral, antibacterial or antiproliferative agents,⁴ with 1,2,3-triazolyl nucleoside derivatives such as compounds **4**⁵ and **5**⁶ (Figure 1) exhibiting, respectively, interesting antiviral and cytostatic activities.

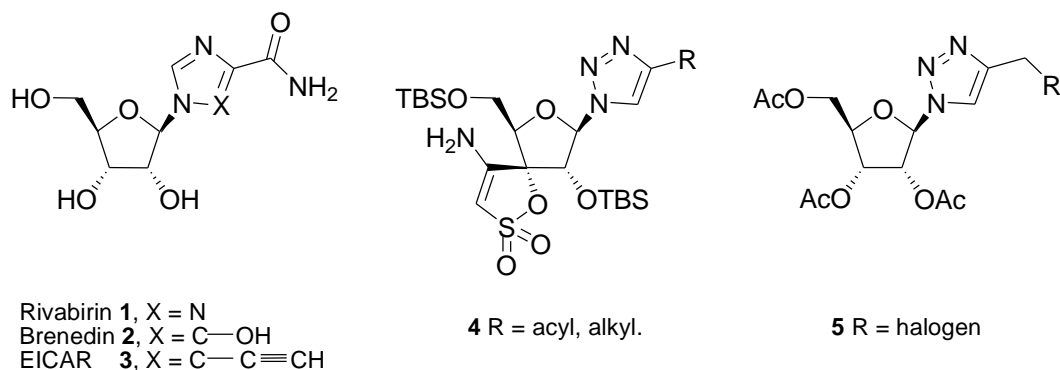


Figure 1. Selected nucleoside analogues with imidazole or triazole bases owning remarkable biological activities.

Furthermore, we and others have recently reported several examples of 1,2,3-triazolyl carbanucleosides owning promising biological activities (Figure 2).⁷ For example, compound (\pm)-**6** (R = 2-C₆H₄OMe) exhibited specific inhibitory potential against TK⁺VZV (EC₅₀ = 11 μ M),⁸ **7** was found to own moderate activity against HIV-1 (IC₅₀ = 43.8 μ M),⁹ and **8**¹⁰ displayed a potent antiviral activity against vaccinia virus (EC₅₀ = 0.4 μ M).

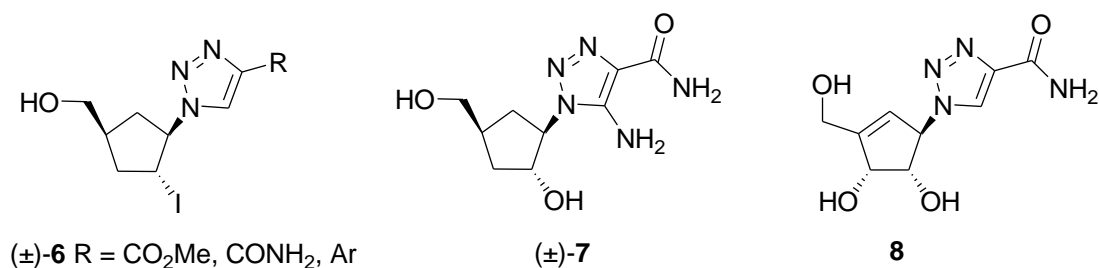


Figure 2. Recently reported 1,2,3-triazolyl carbanucleosides with antiviral activities.

In recent times we have started a research program devoted to the synthesis and biological evaluation as antiviral and antitumoral agents of carbanucleosides produced using, in some extent, the postulates of “click chemistry”. In our previous work,⁸ we reported on a series of racemic 4-aryl-1,2,3-triazolyl 2',3'-dideoxy-2'-iodocarbanucleosides of type (\pm)-**6** (Figure 2) and

4-aryl-1,2,3-triazolyl 2',3'-dideoxy-2',3'-didehydrocarbanucleosides of type (\pm)-**9** (Figure 3). These triazolyl carbanucleosides, structurally related to ribavirin **1**, were produced using an iodoazidation reaction as the key step for the stereoselective construction of the desired functionalized cyclopentane ring, followed by the regioselective assembly of the heterocyclic moiety by a Cu(I) catalysed Huisgen 1,3-dipolar cycloaddition.¹¹

We present here our advances on the topic, reporting the synthesis and biological evaluation as antiviral agents of a series of 4-aryl-1,2,3-triazolyl 3'-deoxycarbanucleosides, of type (\pm)-**10** and (\pm)-**11** (Figure 3). These compounds were designed to explore the effect on the antiviral activities of a different pattern of substitution at position 2' of the carbocycle, as well as the modification of the relative stereochemical configuration of the base with regard to the hydroxymethyl group at position 4' of the pseudosugar.

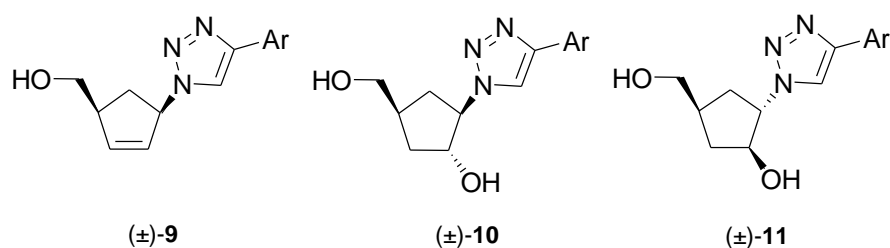
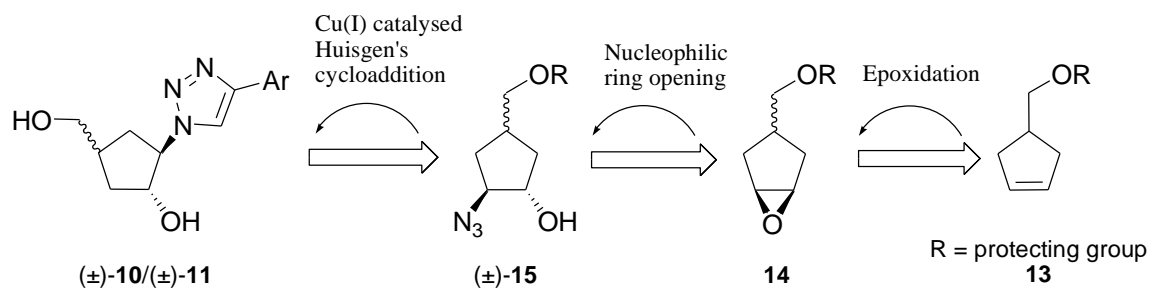


Figure 3. Previously 1,2,3-triazolyl carbanucleosides reported by our group (\pm)-**9**,⁸ and target compounds (\pm)-**10**/ \pm)-**11**.

Results and Discussion

Even when the number of references related to the “click chemistry” topic is increasing exponentially since the seminal review by Kolb, Finn and Sharpless,¹² the original postulates are (in most of the cases) restricted to the use of the ubiquitous Cu(I) catalysed Huisgen’s 1,3-dipolar cycloaddition.¹¹ In a recent review by Moorhouse and Moses,¹³ intelligently entitled: *Click Chemistry and Medicinal Chemistry: A Case of “Cyclo-Addiction”*, the authors stated: *It is important to remember that “click chemistry” was originated before the evolution of the Cu(I) catalyst modification of the Huisgen cycloaddition, and that there are other examples of reactions that meet the “click chemistry” criteria, including mainly olefin based reactions.*

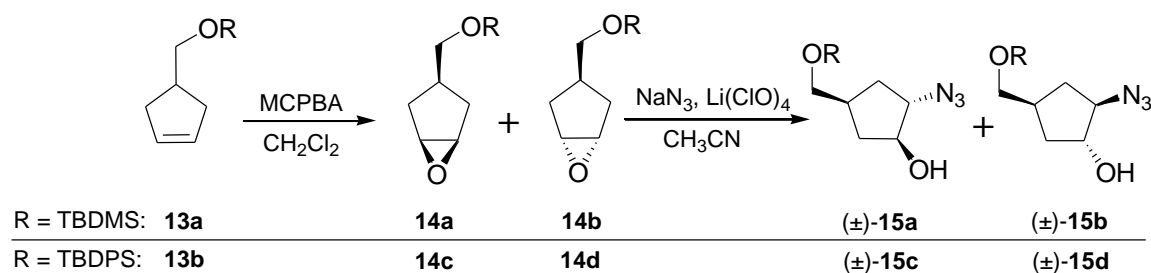
Taking these considerations into account, we felt that our strategy for the rapid synthesis of carbanucleoside derivatives could not be only restricted to the use of the Huisgen cycloaddition for the construction of the heterocyclic base. For this reason, the designed strategy (Scheme 1) for the synthesis of our target compounds was intended to use olefin-based reactions as the key steps for the synthesis of the corresponding pseudosugar scaffold.



Scheme 1. Retrosynthetic analysis for the synthesis of target compounds $(\pm)\text{-10}/(\pm)\text{-11}$.

As shown in Scheme 1, the synthesis of target compounds $(\pm)\text{-10}/(\pm)\text{-11}$ could be tackled by epoxidation of readily available protected derivatives of cyclopent-3-enylmethanol of general structure **13**, leading to a mixture of epimers **14** that, upon nucleophilic ring opening of the oxirane ring, would lead to a mixture of stereoisomers $(\pm)\text{-15}$. Construction of the heterocyclic base using Cu(I) catalyzed Huisgen 1,3-dipolar cycloaddition,¹¹ and further deprotection of the corresponding hydroxymethyl group, would lead to the target compounds. This synthetic plan would enable us to prepare several racemic 1,2,3-triazolocarbanucleoside derivatives differing in the relative stereochemical configuration of the functional groups attached to positions 1', 2' and 4' in the cyclopentane ring, with derivatives of type $(\pm)\text{-10}$ having a *cis* relationship between the base and the hydroxymethyl group at position 4' (the same relative configuration of natural nucleosides), and derivatives of type $(\pm)\text{-11}$, having a *trans* relationship between the above mentioned substituents.

Starting from readily available known alkenes **13a**¹⁵ and **13b**⁸ (Scheme 2), epoxidation of **13a** using MCPBA led, after purification by flash column chromatography, to a mixture of *cis/trans* epimers **14a/b** in a 1:8 ratio as previously reported,^{14,15} with an improved yield of 91% (69% in the original paper).¹⁵ The reaction of **13b** with MCPBA produced, after chromatographic purification, an 81% yield of a mixture of *cis/trans* epimers **14c/d** in a 1:3.8 ratio (by ¹H-NMR).¹⁶ In both cases, attempts of separation of the mixtures were unsuccessful, leading only to partial resolution of epimers after successive flash column chromatographies.

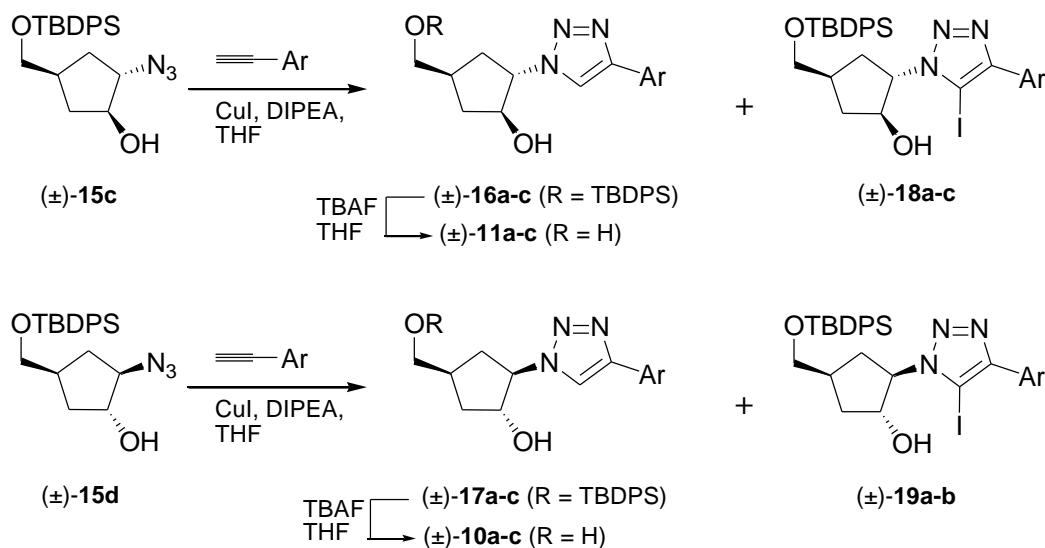


Scheme 2. Epoxidation of alkenes **13** and nucleophilic ring opening with sodium azide of the corresponding epoxides of type **14**.

Concerning the nucleophilic ring opening of the resulting epoxides **14a/b** and **14c/d**, we selected the reaction conditions developed by Crotti et al,¹⁷ that produced mixtures of racemic monoprotected azidoalcohols (\pm)-**15a/b** in a 86% yield and (\pm)-**15c/d** in a 94% yield (Scheme 2). Resolution of those by flash column chromatography was much easier than for the mixtures of epimeric epoxides **14a/b** and **14c/d** (see experimental section), so the needed separation of the corresponding isomers was performed at this stage of the synthetic route.

Since we wished to evaluate the effect on the biological activities of the relative configuration of the base and the hydroxymethyl group on position 4' of the cyclopentane ring of target compounds (\pm)-**10**/ \pm -**11**, we consequently decided to follow the synthetic plan using the TBDPS diastereomeric precursors (\pm)-**15c/d**, as they could be produced in more equitable quantities than their TBDMS (\pm)-**15a/b** counterparts.

Construction of the desired 4-aryl-1,2,3-triazole moiety was achieved (Scheme 3 and Table 1) using Cu(I) catalysed Huisgen's 1,3-dipolar cycloaddition.^{11,18} As expected, this methodology produced only one of the two possible regioisomers (\pm)-**16a-c**/ \pm -**17a-c**). Using large amounts of DIPEA and excess CuI (Method B) the reaction yielded the corresponding 1,2,3-triazole derivatives with good yields (entries 2, 5-7; Table 1). On the contrary, differing from our previous results,⁸ only moderate yields of the desired products (\pm)-**16a-c** (entries 1, 3, 4; Table 1) were obtained using 2 equivalents of the base and a catalytic amount of CuI (Method A). In addition, in most of the cases (entries 1-6, Table 1), a small amount of the corresponding triazole iodinated at position 5 of the heterocycle was isolated (\pm)-**18a-c**/ \pm -**19a-b**).¹⁹ Deprotection of the silyl protecting group using TBAF generated the target compounds (\pm)-**10a-c**/ \pm -**11a-c** in good yields (74-99%).



Scheme 3. Cu(I) catalysed Huisgen's 1,3-dipolar cycloaddition of azides (\pm)-**15c/d** with terminal aryl alkynes (see Table 1 for details) and deprotection of the TBDPS protecting group leading to target compounds (\pm)-**10a-c**/ \pm -**11a-c**.

Table 1. Synthesis of 4-aryl-1,2,3-triazoles (\pm)-**16a-c** and (\pm)-**17a-c**

| Entry | Substrate | Ar | Method ^a | <i>T</i> | <i>t</i> (h) | Products (% yield) ^{b,c} |
|-------|-----------------------|-------------------------------------|---------------------|----------|--------------|---|
| 1 | (\pm)- 15c | C ₆ H ₅ | A | r.t. | 62 | (\pm)- 16a (30) + (\pm)- 18a (13) |
| 2 | (\pm)- 15c | C ₆ H ₅ | B | reflux | 136 | (\pm)- 16a (72) + (\pm)- 18a (3) |
| 3 | (\pm)- 15c | 4-C ₆ H ₄ Me | A | r.t. | 40 | (\pm)- 16b (42) + (\pm)- 18b (4) |
| 4 | (\pm)- 15c | 4-C ₆ H ₄ OMe | A | r.t. | 40 | (\pm)- 16c (23) + (\pm)- 18c (11) |
| 5 | (\pm)- 15d | C ₆ H ₅ | B | reflux | 222 | (\pm)- 17a (64) + (\pm)- 19a (5) |
| 6 | (\pm)- 15d | 4-C ₆ H ₄ Me | B | reflux | 209 | (\pm)- 17b (82) + (\pm)- 19b (5) |
| 7 | (\pm)- 15d | 4-C ₆ H ₄ OMe | B | reflux | 250 | (\pm)- 17c (68) |

^aMethod A: DIPEA (2 eq.), CuI (0.05-0.1 eq.). Method B: DIPEA (50 eq.), CuI (1-2 eq.).

^bIsolated yields after flash column chromatography. ^cFor entries 3 and 4, a 42 % of the starting material (\pm)-**15c** was also recovered.

X-ray analysis of a single crystal of the intermediate (\pm)-**16a** unequivocally confirmed its relative configuration (Figure 4) and, consequently, that of its precursor, (\pm)-**15c**, as well as indirectly those of their respective epimers, (\pm)-**17a** and (\pm)-**15d**, and those of the compounds obtained from each epimeric intermediate, notably both series of target compounds (\pm)-**10a-c**/ \pm)-**11a-c**.

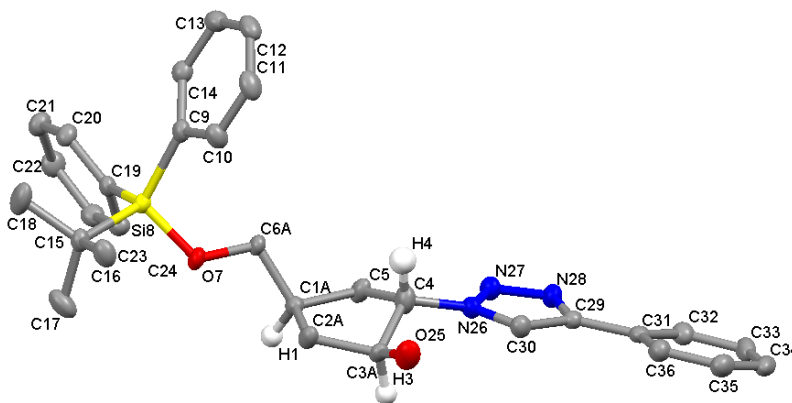


Figure 4. Mercury ellipsoid projection (50% probability) of the molecular structure of compound (\pm)-**16a**, with a random numbering scheme. Hydrogen atoms, except those involved in the relative stereochemical configuration (H1, H3 and H4), are omitted for clarity.²⁰

Target compounds ((\pm)-**10a-c**, (\pm)-**11a-c**), as well as the monoprotected intermediates (\pm)-**16a-c**, and (\pm)-**18a/c**, 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 coxsackie B4 virus in human epithelial (HeLa) cells. These activities were compared with those of acyclovir, ganciclovir, brivudin, (*S*)-DPHA, and ribavirin. Furthermore, the inhibitory activities of (±)-**10a-c**, (±)-**11a-c**, (±)-**16b-c**, and (±)-**18c** against Feline Corona and Feline Herpes viruses in Crandell–Rees feline kidney (CRFK) cells were measured, and the obtained activities compared with those of HHA, UDC and ganciclovir.

Compounds (±)-**10a-c**, (±)-**11a-c**, (±)-**16a-c**, and (±)-**18a/c** were also evaluated for its inhibitory activities against Cytomegalovirus (CMV Davis strain) in HEL cell lines, and the results contrasted with those of ganciclovir and cidofovir. Likewise, these compounds were also evaluated for their inhibitory activities against influenza viruses (Influenza A (H1N1/ H3N2 subtypes) and Influenza B) in MDCK cell lines, and the results compared with those of oseltamivir carboxylate and ribavirin.

In all the cases, these 1,2,3-triazolocarbanucleosides did not show any specific antiviral effects (*i.e.* minimal antiviral effective concentration \leq 5-fold lower than the minimal cytotoxic concentration for the host cell) against any of the viruses in the assay systems used.

More promising results were obtained in the antiviral evaluation of the silylated derivatives (±)-**16a-c** and (±)-**18a/c** against varicella-zoster virus (TK⁺VZV, thymidine kinase positive strain, and TK⁻VZV, thymidine kinase deficient strain) in human embryonic lung (HEL) cells. Even when, strictly speaking, no specific antiviral effects were noted, if the data for the TK⁺VZV (OKA strain) are analysed in more detail, derivative **18a** can be interpreted as specifically antivirally active, if based on a comparison of its EC₅₀ = 5.3 μ M with its MCC > 160 μ M.²¹

Experimental Section

General Procedures. All chemicals used were of reagent grade, obtained from Aldrich Chemical Co. and used without further purification. Starting materials **13a/b** were prepared following previously reported methods.^{8,15} Melting points were measured in a Reichert Kofler Thermopan and are uncorrected. Infrared spectra were recorded in a Perkin-Elmer 1640 FTIR spectrophotometer. ¹H and ¹³C NMR spectra were recorded in a Bruker AMX 300 spectrometer at 300 and 75.47 MHz, respectively, using TMS as internal standard (chemical shifts in δ values, *J* in Hz). Mass spectra were recorded on a Micromass Autoespec (EI and HRMS) and on a Bruker Microtof (ESI-TOF) spectrometers. Microanalyses were performed in a Perkin-Elmer 240B Elemental Analyser at the University of Santiago Microanalysis Service. Analyses indicated by the symbols of elements were within \pm 0.4% of the theoretical values. Flash chromatography was performed on silica gel (Merck 60, 230–240 mesh) and analytical TLC on pre-coated silica gel plates (Merck 60 F₂₅₄, 0.25 mm).

X-Ray crystal structure determination. Single crystals of (±)-**16a** suitable for X-ray diffractometry were obtained by dissolving crystals of the already purified material in the

minimum quantity of cold THF in an open vial that was then placed in a larger container with a little hexane in its bottom; the container was closed, and after a few days in a cool, dark place free from vibrations afforded the desired single crystals. This were mounted in an inert oil and transferred to the cold gas stream of the diffractometer. Empirical formula: $C_{30}H_{35}N_3O_2Si$; formula weight: 497.70; $0.45 \times 0.23 \times 0.10 \text{ mm}^3$; crystal colour: colourless; habit: prismatic; crystal system: triclinic; lattice type: plate; lattice parameters: $a = 7.4396(17) \text{ \AA}$, $b = 9.728(2) \text{ \AA}$, $c = 20.073(5) \text{ \AA}$, $\alpha = 89.570(4)^\circ$, $\beta = 84.621(4)^\circ$, $\gamma = 72.628(4)^\circ$, $V = 1380.0(5) \text{ \AA}^3$; space group: $P-1$; $Z = 2$; $D_{\text{calc}} = 1.198 \text{ Mg/m}^3$; $R1 = 0.0459$, $wR2 = 0.1109$. Diffractometer: Smart-1000 BRUKER.²⁰

Epoxidation of *tert*-butyldimethylsilyl (cyclopent-3-enyl)methyl ether (13a) and *tert*-butyldiphenylsilyl (cyclopent-3-enyl)methyl ether (13b). A solution of the corresponding alkene **13a**¹⁵ or **13b**⁸ (1 mmol) in dry CH_2Cl_2 (5 mL) was slowly added to a well stirred suspension of MCPBA (1.2 mmol) in dry CH_2Cl_2 (5 mL). The reaction mixture was then heated at reflux until complete disappearance of the starting material was detected by TLC. The solution was then cooled to 0°C , the solid in suspension filtered and washed with a small amount of cold CH_2Cl_2 . The filtrate was washed with a 10% aqueous solution of Na_2SO_3 (10 mL), a 10% aqueous solution of NaHCO_3 (10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4) and the solvent concentrated under reduced pressure. The corresponding residue was purified by flash column chromatography (see below for further details).

***cis-tert*-Butyldimethylsilyl (3,4-epoxycyclopentyl)methyl ether 14a and *trans-tert*-butyldimethylsilyl (3,4-epoxycyclopentyl)methyl ether (14b).** A first flash column chromatography of the crude reaction product using CH_2Cl_2 as eluent afforded the pure mixture of the epoxides **14a/b** in a 91% yield, an increase of a 24% in the previously reported yield.^{14,15} A second column chromatography using hexane- CH_2Cl_2 1:1 as eluent afforded successively **14a** (9%), **14a+14b** (60%) and **14b** (31%). The physical data for **14a/b** were coincident with those reported in the bibliography.¹⁵

***cis-tert*-Butyldiphenylsilyl (3,4-epoxycyclopentyl)methyl ether (14c) and *trans-tert*-butyldiphenylsilyl (3,4-epoxycyclopentyl)methyl ether (14d).** The crude reaction mixture was chromatographed (silica gel, hexane-EtOAc 30:1 as eluent). The non-void fractions afforded the pure mixture of epoxides **14c/d** in a 81% yield. Iterative recrystallization (hexane-EtOAc 10:1) of **14c** or **14d**-enriched fractions obtained after the above mentioned chromatography allow us to isolate pure samples of the isomers that were used for the physical characterization of the compounds.

14c. Low melting point white solid. IR (KBr) ν : 3068, 3029, 2951, 2928, 2856, 1429, 1376, 1113, 1016, 997, 841, 828, 790, 744, 704, 688, 616, 506 cm^{-1} . $^1\text{H NMR}$ (CDCl_3) δ : 7.68-7.65 (m, 4H); 7.43-7.35 (m, 6H); 3.52 (d, 2H, $J = 8.1 \text{ Hz}$, OCH_2); 3.46 (virtual s, 2H, 3-H + 4-H); 2.39-2.28 (m, 1H); 1.93 (dd, 2H, $J = 14.9, 1.8 \text{ Hz}$, 5- CHH + 2- CHH); 1.80 (dd, 2H, $J = 14.9, 9.1 \text{ Hz}$, 5- CHH + 2- CHH); 1.07 [s, 9H, $\text{C}(\text{CH}_3)_3$] ppm. MS (EI m/z): 296 [(M+1)-(*tert*-Bu), 3], 295 [(M)-(*tert*-Bu), 13], 265 (17), 247 (17), 217 (13), 200 (18), 199 (100), 197 (13), 187 (15), 183 (17), 181 (21), 139 (23), 135 (13), 104 (17), 91 (10), 77 (20), 57 (20).

14d. Low melting point white solid. IR (KBr) ν : 3047, 2927, 2886, 2855, 1427, 1114, 839, 822, 742, 701, 609 cm^{-1} . ^1H NMR (CDCl_3) δ : 7.66-7.63 (m, 4H); 7.43-7.35 (m, 6H); 3.60 (d, 2H, J = 5.0 Hz, OCH_2); 3.48 (virtual s, 2H, 3-H + 4-H); 2.15-2.04 (m, 3H); 1.56-1.49 (m, 2H); 1.05 [s, 9H, $\text{C}(\text{CH}_3)_3$] ppm. ^{13}C NMR/DEPT (CDCl_3) δ : 136.0 (CH), 134.2 (C), 130.0 (CH), 128.0 (CH), 66.1 (CH_2), 57.6 (CH), 35.7 (CH), 31.1 (CH_2), 27.2 [$\text{C}(\text{CH}_3)_3$], 19.7 [$\text{C}(\text{CH}_3)_3$] ppm. MS (EI m/z): 352 (M, 1), 296 (18), 295 (73), 199 (100), 197 (20), 187 (28), 183 (31), 181 (35), 169 (20), 161 (16), 139 (43), 123 (17), 117 (21), 105 (21), 57 (21).

Monoprotected azidodiols (\pm)-15a/b and (\pm)-15c/d. LiClO_4 (25 mmol) and NaN_3 (5 mmol) were added to a solution of the corresponding mixture of epoxides **14a** or **14b** (1 mmol) in dry CH_3CN (10 mL) under Ar atmosphere. The subsequent mixture was stirred at 75°C for 78 hours. Once the reaction was complete, the mixture was cooled to room temperature, diluted with water 50 mL and extracted with ether (3 x 25 mL). The organic layer was dried (Na_2SO_4) and the solvents evaporated under reduced pressure yielding an oily residue that was purified by flash column chromatography (see below for further details).

(\pm)-*t*-2-Azido-*c*-4-(*tert*-butyldimethylsilyloxymethyl)cyclopentan-*r*-1-ol ((\pm)-15a) and (\pm)-*t*-2-azido-*t*-4-(*tert*-butyldimethylsilyloxymethyl)cyclopentan-*r*-1-ol ((\pm)-15b). The crude mixture of isomers (obtained in 86% yield) was subjected to column chromatography on silica gel using hexane–EtOAc 15:1 as eluent to give, successively, (\pm)-15a (24%) in a first group of fractions and a mixture of (\pm)-15a/b (10%) in a second group. A third group of fractions, eluted with hexane–EtOAc 10:1, afforded (\pm)-15b (66%).

(\pm)-15a. Colourless oil. IR (film) ν : 3423, 2931, 2857, 2103, 1466, 1255, 1093, 1033, 836, 778 cm^{-1} . ^1H NMR (CDCl_3) δ : 3.94-3.92 (m, 1H, 1-H); 3.83-3.81 (m, 1H, 2-H); 3.62-3.54 (m, 3H); 2.50-2.39 (m, 1H); 2.26-2.16 (m, 1H); 1.95-1.91 (m, 1H); 1.87-1.83 (m, 1H); 1.54-1.49 (m, 1H); 0.91 [s, 9H, $\text{C}(\text{CH}_3)_3$]; 0.09 [s, 6H, $\text{Si}(\text{CH}_3)_2$] ppm. ^{13}C NMR/DEPT (CDCl_3) δ : 76.3 (CH), 69.5 (CH), 66.0 (CH_2), 37.2 (CH), 35.8 (CH_2), 30.6 (CH_2), 26.3 [$\text{C}(\text{CH}_3)_3$], 18.8 [$\text{C}(\text{CH}_3)_3$], -5.1 [$\text{Si}(\text{CH}_3)_2$], -5.2 [$\text{Si}(\text{CH}_3)_2$] ppm. MS (EI m/z): 272 (M +1, 1), 214 (38), 186 (49), 171 (63), 168 (49), 157 (27), 156 (22), 143 (38), 142 (38), 141 (26), 138 (20), 130 (30), 129 (24), 128 (35), 118 (26), 115 (70), 112 (43), 105 (30), 100 (37), 99 (30), 97 (63), 94 (90), 90 (59), 85 (30), 79 (35), 77 (32), 73 (100). HRMS m/z calcd for $\text{C}_{12}\text{H}_{25}\text{N}_3\text{O}_2\text{Si}$, 271.1716; found, 271.1735.

(\pm)-15b. Colourless oil. IR (film) ν : 3383, 2929, 2857, 2104, 1472, 1256, 1090, 1005, 837, 776 cm^{-1} . ^1H NMR (CDCl_3) δ : 4.10-4.03 (m, 1H, 1-H); 3.70-3.63 (m, 1H, 2-H); 3.49 (d, 2H, J = 6.0 Hz, OCH_2); 2.38-2.29 (m, 1H, 4-H); 2.21-2.06 (m, 1H); 1.86-1.62 (m, 3H); 1.50-1.40 (m, 1H); 0.89 [s, 9H, $\text{C}(\text{CH}_3)_3$]; 0.04 [s, 6H, $\text{Si}(\text{CH}_3)_2$] ppm. ^{13}C NMR/DEPT (CDCl_3) δ : 77.9 (CH), 68.8 (CH), 66.8 (CH_2), 37.0 (CH), 35.2 (CH_2), 31.9 (CH_2), 26.3 [$\text{C}(\text{CH}_3)_3$], 18.7 [$\text{C}(\text{CH}_3)_3$], -5.0 [$\text{Si}(\text{CH}_3)_2$] ppm. Most of this physical data are coincident with the previously reported.¹⁵ MS (EI m/z): 214 [M-(*tert*-Bu), 1], 166 (8), 115 (10), 105 (50), 99 (8), 94 (38), 93 (11), 89 (11), 80 (25), 77 (13), 76 (10), 75 (100), 73 (28), 67 (47). HRMS m/z calcd for $\text{C}_{12}\text{H}_{25}\text{N}_3\text{O}_2\text{Si}$, 271.1716; found, 271.1738.

(±)-*t*-2-Azido-*c*-4-(*tert*-butyldiphenylsilyloxymethyl)cyclopentan-*r*-1-ol ((±)-15c) and (±)-*t*-2-azido-*t*-4-(*tert*-butyldiphenylsilyloxymethyl)cyclopentan-*r*-1-ol ((±)-15d). Partial resolution of the crude mixture of isomers (obtained in 94% yield) was achieved by column chromatography on silica gel using CH₂Cl₂ as eluent to give, successively, (±)-15d (58%) in the first group of fractions, a mixture of (±)-15c/d (17%) in the second group and (±)-15c (25%) in the last group of fractions.

(±)-15c. Colourless oil. IR (film) ν : 3404, 2934, 2879, 2859, 2102, 1428, 1255, 1110, 1029, 821, 741, 702, 611 cm⁻¹. ¹H NMR (CDCl₃) δ : 7.69-7.66 (m, 4H); 7.45-7.37 (m, 6H); 4.09 (dd, 1H, J = 12.6, 6.0 Hz, 1-H); 3.70 (dd, 1H, J = 13.7, 7.5 Hz, 2-H); 3.57 (d, 2H, J = 5.9 Hz, PhCH₂); 2.46-2.36 (m, 1H); 2.21 (dd, 1H, J = 13.3, 7.5 Hz); 2.08 (virtual s, 1H, D₂O exchangeable, OH); 1.87 (q, 1 H, J = 6.9 Hz); 1.76-1.67 (m, 1H); 1.52 (dt, 1H, J = 13.3, 8.3 Hz); 1.08 [s, 9H, C(CH₃)₃] ppm. ¹³C NMR/ DEPT (CDCl₃) δ : 136.0 (CH), 134.1 (C), 134.1 (C), 130.1 (CH), 128.1 (CH), 77.3 (CH), 68.9 (CH), 67.5 (CH₂), 37.1 (CH), 35.2 (CH₂), 32.1 (CH₂), 27.3 [C(CH₃)₃], 19.7 [C(CH₃)₃] ppm. MS (EI m/z): 338 [M-(*tert*-Bu), 14], 232 (31), 200 (18), 199 (100), 197 (17), 183 (21), 181 (26), 176 (11), 161 (16), 139 (10), 135 (11), 105 (17), 77 (11), 57 (22). HRMS m/z calcd for C₂₂H₂₉N₃O₂Si, 395.2029; found, 395.2011.

(±)-15d. Colourless oil. IR (film) ν : 3404, 3069, 2934, 2879, 2859, 2102, 1428, 1110, 702 cm⁻¹. ¹H NMR (CDCl₃) δ : 7.69-7.66 (m, 4H); 7.46-7.38 (m, 6H); 4.03 (virtual s, 1H, 1-H); 3.84 (q, 1H, J = 3.2 Hz); 3.61 and 3.56 (AB part, ABM system, 2H, J = 10.0, 4.0 Hz, PhCH₂); 3.14-3.12 (m, 1H, D₂O exchangeable, OH); 2.45-2.35 (m, 1H); 2.27-2.17 (m, 1H); 2.11-2.02 (m, 1H); 1.87-1.78 (m, 1H); 1.59 (dt, 1H, J = 13.8, 4.3 Hz); 1.09 [s, 9H, C(CH₃)₃] ppm. ¹³C NMR/DEPT (CDCl₃) δ : 136.1 (CH), 136.0 (CH), 133.3 (C), 133.2 (C), 130.3 (CH), 130.3 (CH), 128.2 (CH), 76.8 (CH), 69.1 (CH), 67.1 (CH₂), 37.1 (CH), 35.8 (CH₂), 31.0 (CH₂), 27.3 [C(CH₃)₃], 19.6 [C(CH₃)₃] ppm. MS (EI m/z): 338 [M-(*tert*-Bu), 3], 201 (5), 200 (18), 199 (100), 197 (8), 183 (7), 181 (12), 161 (6), 139 (12), 135 (9), 105 (10), 94 (21), 77 (12), 67 (26), 58 (10), 57 (7). HRMS m/z calcd for C₂₂H₂₉N₃O₂Si, 395.2029; found, 395.2047.

(±)-*t*-4-(*tert*-Butyldiphenylsilyloxymethyl)-*t*-2-(4-aryl-1*H*-1,2,3-triazol-1-yl-*r*-1-cyclopentanols (±)-16a-c and (±)-*c*-4-(*tert*-butyldiphenylsilyloxymethyl)-*t*-2-(4-aryl-1*H*-1,2,3-triazol-1-yl-*r*-1-cyclopentanols (±)-17a-c.

Method A. A suspension of the corresponding monoprotected azidodiols (±)-15c/d (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 1. 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 (Na₂SO₄) 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 monoprotected azidodiols (±)-15c/d (1 mmol), aryl alkyne (2 mmol), CuI (1–2 mmol) and DIPEA (50 mmol) in dry THF (50 mL) was stirred under

the conditions specified in Table 1. The reactions were monitored by TLC and the work-up carried out in the same manner as for Method A.

(±)-*c*-4-(*tert*-Butyldiphenylsilyloxymethyl)-*t*-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-*r*-1-cyclopentanol ((±)-16a**) and (±)-*c*-4-(*tert*-butyldiphenylsilyloxymethyl)-*t*-2-(4-phenyl -5-iodo-1*H*-1,2,3-triazol-1-yl)-*r*-1-cyclopentanol ((±)-**18a**).**

Method A. The non-void fractions eluted successively with hexane–EtOAc 7:1 and 4:1 afforded successively (±)-**18a** (13%) and (±)-**16a** (30%).

Method B. The non-void fractions eluting with hexane–EtOAc 7:1 and 4:1 afforded (±)-**18a** (3%) and (±)-**16a** (72%) as a white solid that presented identical spectroscopic features to that using Method A.

(±)-16a. White solid, m.p. = 102-103 °C (recrystallised from THF-hexane). IR (KBr) ν : 3279, 3138, 3069, 2857, 1424, 1109, 1075, 699 cm^{-1} . ^1H NMR (CDCl_3) δ : 7.80 (dd, 2H, $J = 6.9, 1.5$ Hz, 2H); 7.72 (s, 1H, 5- $\text{H}_{\text{triazole}}$); 7.69 (dd, 4H, $J = 6.5, 1.2$ Hz, 4H); 7.49-7.35 (m, 9H); 4.68-4.63 (m, 1H, 1-H); 4.51 (q, 1H, $J = 6.1$ Hz, 2-H); 3.67 (d, 2H, $J = 4.6$ Hz, CH_2O); 3.63 (d, 1H, $J = 5.7$ Hz, D_2O exchangeable, OH); 2.63-2.59 (m, 1H); 2.34 (virtual, 2H, $J = 2.2$ Hz, 3- H_2); 2.23-2.20 (m, 1H); 1.79-1.71 (m, 1H); 1.10 [s, 9H, $\text{C}(\text{CH}_3)_3$] ppm. ^{13}C NMR/DEPT (CDCl_3) δ : 147.4 (C), 135.6 (CH), 133.1 (C), 130.5 (C), 129.9 (CH), 128.8 (CH), 128.1 (CH), 127.8 (C), 125.6 (CH), 119.3 (CH), 77.5 (CH), 67.8 (CH), 66.8 (CH_2), 36.4 (CH), 34.9 (CH_2), 31.2 (CH_2), 26.9 [$\text{C}(\text{CH}_3)$], 19.3 (C) ppm. MS (ESI-TOF m/z %): 498.25 (M+1, 100). Anal. Calcd for $\text{C}_{30}\text{H}_{35}\text{N}_3\text{O}_2\text{Si}$ (497.70): C, 72.40; H, 7.09; N, 8.44. Found: C, 72.76; H, 7.32; N, 8.51.

(±)-18a. White solid, m.p. = 188-190 °C (recrystallised from EtOAc-hexane). IR (KBr) ν : 3391, 2929, 2855, 1425, 1327, 1107, 1006, 798, 699 cm^{-1} . ^1H NMR (CDCl_3) δ : 7.91-7.89 (m, 2H); 7.69-7.66 (m, 4H); 7.46-7.23 (m, 9H); 4.84-4.81 (m, 1H); 4.66-4.63 (m, 1H); 3.67 (d, 2H, $J = 3.9$ Hz, CH_2O); 3.36 (d, 1H, $J = 7.2$ Hz, D_2O exchangeable, OH); 2.77-2.69 (m, 1H); 2.45-2.31 (m, 3H); 1.75 (dt, 1H, $J = 13.7, 5.7$ Hz, 5- HH); 1.10 [s, 9H, $\text{C}(\text{CH}_3)_3$] ppm. ^{13}C NMR/DEPT (CDCl_3) δ : 135.6 (CH), 132.8 (C), 129.9 (CH), 128.5 (CH), 127.8 (CH), 127.5 (CH), 76.8 (CH), 69.0 (CH), 66.7 (CH_2), 37.1 (CH), 35.1 (CH_2), 31.7 (CH_2), 26.9 [$\text{C}(\text{CH}_3)$], 19.2 (C) ppm. Anal. Calcd for $\text{C}_{30}\text{H}_{34}\text{IN}_3\text{O}_2\text{Si}$ (623.60): C, 57.78; H, 5.50; N, 6.74. Found: C, 58.07; H, 5.35; N, 6.99.

(±)-*c*-4-(*tert*-Butyldiphenylsilyloxymethyl)-*t*-2-[4-(4-methylphenyl)-1*H*-1,2,3-triazol-1-yl]-*r*-1-cyclopentanol ((±)-16b**) and (±)-*c*-4-(*tert*-butyldiphenylsilyloxymethyl)-*t*-2-[4-(4-methylphenyl)-5-iodo-1*H*-1,2,3-triazol-1-yl]-*r*-1-cyclopentanol ((±)-**18b**).**

Method A. The non-void fractions eluted with hexane–EtOAc 5:1 afforded successively unaltered (±)-**15c** (42%), (±)-**18b** (4%) and (±)-**16b** (42%).

(±)-16a. White solid, m.p. = 126-127 °C. IR (KBr) ν : 3236, 2930, 2856, 1464, 1428, 1112, 1081, 802, 701 cm^{-1} . ^1H NMR (CDCl_3) δ : 7.69-7.63 (m, 6H); 7.64 (s, 1H, 5- $\text{H}_{\text{triazole}}$); 7.45-7.36 (m, 6H); 7.20-7.19 (m, 2H); 4.65-4.60 (m, 1H, 2-H); 4.50-4.47 (m, 1H, 1-H); 3.65-3.61 (m, 3H, simplified to a duplet once treated with D_2O , $J = 4.0$ Hz, $\text{OCH}_2 + \text{OH}$); 2.59-2.56 (m, 1H); 2.36 (s, 3H, CH_3); 2.34-2.26 (m, 3H); 1.70 (dt, 1H, $J = 13.4, 7.0$ Hz, 5- HH); 1.07 [9H, s, $\text{C}(\text{CH}_3)_3$] ppm. ^{13}C NMR/DEPT (CDCl_3) δ : 147.5 (C), 138.0 (C), 135.6 (CH), 135.6 (CH), 133.1 (C), 133.1 (C), 129.9 (CH), 129.5 (CH), 127.8 (CH), 127.6 (C), 125.5 (CH), 118.9 (CH), 77.4 (CH),

67.7 (CH), 66.8 (CH₂), 36.4 (CH), 34.9 (CH₂), 31.2 (CH₂), 26.9 [C(CH₃)], 21.3 (CH₃), 19.3 (C) ppm. MS (EI *m/z*): 455 (16), 454 (45), 295 (47), 265 (34), 217 (30), 200 (19), 199 (100), 160 (21), 139 (18), 135 (22), 130 (25). Anal. Calcd for C₃₁H₃₇N₃O₂Si (511.26): C, 72.76; H, 7.29; N, 8.21. Found: C, 73.11; H, 7.44; N, 8.38.

(±)-**18b**. White solid, m.p. = 153-154 °C. IR (KBr) *v*: 3323, 2927, 2855, 1109, 819, 701 cm⁻¹. ¹H NMR (CDCl₃) *δ*: 7.80-7.77 (m, 2H); 7.69-7.66 (m, 4H); 7.46-7.37 (m, 6H); 7.23-7.22 (m, 2H); 4.81 (dt, 1H, *J* = 7.8, 4.7 Hz, 2-H); 4.65-4.62 (m, 1H, 1-H); 3.65 (d, 2H, *J* = 4.1 Hz, OCH₂); 2.74-2.71 (m, 1H); 2.45-2.40 (m, 1H); 2.38 (s, 3H, CH₃); 2.37-2.31 (m, 3H, one of them D₂O exchangeable, OH); 1.75 (dt, 1H, *J* = 13.8, 5.8 Hz, 5-*HH*); 1.09 [s, 9H, C(CH₃)₃] ppm. ¹³C NMR/DEPT (CDCl₃) *δ*: 149.7 (C), 138.4 (C), 135.7 (CH), 132.9 (C), 129.9 (CH), 129.2 (CH), 127.8 (CH), 127.5 (CH), 76.7 (CH), 69.0 (CH), 66.7 (CH₂), 37.1 (CH), 35.1 (CH₂), 31.9 (CH₂), 26.9 [C(CH₃)], 21.3 (CH₃), 19.3 (C) ppm. MS (EI *m/z*): 580 (15), 208 (19), 199 (100), 181 (21), 139 (21), 135 (40), 129 (19). Anal. Calcd for C₃₀H₃₄IN₃O₂Si (497.70): C, 57.78; H, 5.50; N, 6.74. Found: C, 58.11; H, 5.82; N, 6.63.

(±)-*c*-4-(*tert*-Butyldiphenylsilyloxymethyl)-*t*-2-[4-(4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl]-*r*-1-cyclopentanol ((±)-**16c**) and (±)-*c*-4-(*tert*-butyldiphenyl-silyloxymethyl)-*t*-2-[4-(4-methoxyphenyl)-5-iodo-1*H*-1,2,3-triazol-1-yl]-*r*-1-cyclopentanol ((±)-**18c**).

Method A. The non-void fractions eluted with hexane–EtOAc 5:1 afforded successively unaltered (±)-**15c** (42%) and (±)-**18c** (11%). A second group of fractions eluted using hexane–EtOAc 3:1 afforded, after evaporation under reduced pressure of the solvents, (±)-**16c** (23%).

(±)-**16c**. Yellowish oil. IR (film) *v*: 2925, 2856, 1616, 1460, 1376, 1255, 1106, 703 cm⁻¹. ¹H NMR (CDCl₃) *δ*: 7.70-7.67 (m, 6H); 7.61 (s, 1H, 5-*H*_{triazole}); 7.48-7.36 (m, 6H); 6.93 (virtual d, 2H, *J* = 8.5 Hz); 4.67-4.60 (m, 1H, 1-H); 4.52-4.50 (m, 1H); 3.84 (s, 3H, OCH₃); 3.81-3.80 (m, 1H, D₂O exchangeable); 3.66 (d, 2H, *J* = 4.4 Hz, OCH₂); 2.60-2.57 (m, 1H); 2.39-2.27 (m, 3H); 1.79-1.64 (m, 1H); 1.09 [s, 9H, C(CH₃)₃] ppm. ¹³C NMR/DEPT (CDCl₃) *δ* (ppm): 159.5 (C), 147.0 (C), 135.6 (CH), 133.1 (C), 129.8 (CH), 127.8 (CH), 127.4 (C), 126.9 (CH), 123.1 (C), 118.6 (CH), 114.2 (CH), 77.4 (CH), 67.8 (CH), 66.9 (CH₂), 55.3 (OCH₃), 36.1 (CH), 34.8 (C(CH₂)), 31.3 (CH₂), 26.9 [C(CH₃)], 19.3 (C) ppm. MS (ESI-TOF *m/z* %): 528.27 (M+1, 100). HRMS: calcd for C₃₁H₃₇N₃O₃Si, 527.2604; found 527.2622).

(±)-**18c**. White solid, m.p. = 167-168 °C. IR (KBr) *v*: 3366, 2929, 2857, 1477, 1245, 1006, 834, 703 cm⁻¹. ¹H NMR (CDCl₃) *δ*: 7.87-7.84 (d, 2H, *J* = 8.8 Hz); 7.69-7.66 (m, 4H); 7.46-7.37 (m, 6H); 7.01 (d, 2H, *J* = 8.8 Hz); 4.85-4.83 (m, 1H, 2-H); 4.66-4.64 (m, 1H, 1-H); 3.86 (s, 3H, OCH₃); 3.67 (d, 2H, *J* = 3.8 Hz, CH₂O); 3.42 (d, 1H, D₂O exchangeable, *J* = 7.3 Hz, OH); 2.79-2.77 (m, 1H); 2.47-2.27 (m, 3H); 1.80-1.76 (m, 1H); 1.11 [s, 9H, C(CH₃)₃] ppm. ¹³C NMR/DEPT (CDCl₃) *δ*: 159.8 (C), 149.6 (C), 135.7 (CH), 132.8 (C), 129.9 (CH), 128.9 (CH), 127.8 (CH), 122.78 (C), 113.9 (CH), 76.8 (CH), 69.0 (CH), 66.7 (CH₂), 55.3 (OCH₃), 37.1 (CH), 35.1 (CH₂), 31.8 (CH₂), 27.0 [C(CH₃)₃], 19.3 (C) ppm. Anal. Calcd for C₃₁H₃₆IN₃O₃Si (653.63): C, 56.96; H, 5.55; N, 6.43. Found: C, 57.21; H, 5.86; N, 6.57.

(±)-*t*-4-(*tert*-Butyldiphenylsilyloxymethyl)-*t*-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-*r*-1-cyclopentanol ((±)-**17a**) and (±)-*t*-4-(*tert*-butyldiphenylsilyloxymethyl)-*t*-2-(4-phenyl-5-iodo-1*H*-1,2,3-triazol-1-yl)-*r*-1-cyclopentanol ((±)-**19a**).

Method B. The non-void fractions eluted with hexane–EtOAc 5:1 afforded (±)-**19a** (5%). A second group of fractions eluted using hexane–EtOAc 2:1 afforded, after evaporation of the solvents under reduced pressure, (±)-**17a** (64%).

(±)-**17a**. Crystalline white solid, m.p. = 110–112 °C (chromatographically purified product washed with acetone). IR (KBr) ν : 3240, 2859, 1461, 1429, 1383, 1114, 1077, 1004, 771, 700 cm^{-1} . ^1H NMR (CDCl_3) δ : 7.79–7.75 (dd, 2H, $J = 6.9, 1.4$ Hz, 2H); 7.73(s, 1H, 5- $\text{H}_{\text{triazole}}$); 7.67–7.64 (m, 4H); 7.46–7.31 (m, 9H); 4.64–4.56 (m, 2H); 3.66 (dd, 2H, $J = 5.4, 1.5$ Hz, OCH_2); 3.03 (s, 1H, D_2O exchangeable, OH); 2.56–2.44 (m, 2H); 2.16–2.02 (m, 2H); 1.96–1.89 (m, 1H); 1.10 [s, 9H, $\text{C}(\text{CH}_3)_3$] ppm. ^{13}C NMR/DEPT (CDCl_3) δ : 146.9 (C), 135.5 (CH), 133.5 (C) 130.2 (C), 129.7 (CH), 128.7 (CH), 128.1 (CH), 127.7 (CH), 125.5 (CH), 119.1 (CH), 76.5 (CH), 68.6 (CH), 67.0 (CH_2), 36.3 (CH), 34.1 (CH_2), 32.9 (CH_2), 26.9 [$\text{C}(\text{CH}_3)_3$], 19.3 (C) ppm. MS (EI m/z): 441 (30), 440 (85), 217 (22), 199 (100), 197 (27), 183 (38), 181 (32), 167 (23), 139 (29), 116 (25), 105 (28), 77 (38), 58 (41). Anal. Calcd for $\text{C}_{30}\text{H}_{35}\text{N}_3\text{O}_2\text{Si}$ (497.25): C, 72.40; H, 7.09; N, 8.44. Found: C, 72.67; H, 7.32; N, 8.69.

(±)-**19a**. Colourless oil. IR (film) ν : 3365, 2928, 2857, 1109, 771 cm^{-1} . ^1H NMR (CDCl_3) δ : 7.91–7.87 (m, 2H); 7.68–7.66 (m, 4H); 7.49–7.35 (m, 9H); 5.01 (q, 2H, $J = 7.2$ Hz, 2-H); 4.71 (dt, 1H, $J = 10.3, 7.2$ Hz, 1-H); 3.66 (d, 2H, $J = 5.7$ Hz, OCH_2); 2.59–2.45 (m, 2H); 2.20–2.11 (m, 1H); 2.03–1.87 (m, 2H); 1.06 [s, 9H, $\text{C}(\text{CH}_3)_3$] ppm. ^{13}C NMR/DEPT (CDCl_3) δ : 135.6 (CH), 133.6 (C), 130.2 (C), 129.7 (CH), 128.6 (CH), 128.5 (C), 127.7 (CH), 127.6 (C), 75.8 (CH), 68.8 (CH), 67.0 (CH_2), 36.6 (CH), 34.4 (CH_2), 33.6 (CH_2), 26.9 [$\text{C}(\text{CH}_3)_3$], 19.3 (C) ppm. MS (EI m/z): 567 [M – (*tert*-Bu), 19], 566 (57), 217 (26), 199 (100), 197 (29), 183 (32), 181 (30), 139 (26), 135 (57), 116, (29), 115 (25), 105 (25), 89 (26), 77 (26). HRMS m/z calcd for $\text{C}_{30}\text{H}_{34}\text{N}_3\text{O}_2\text{Si}$, 623.1465; found, 623.1484.

(±)-*t*-4-(*tert*-Butyldiphenylsilyloxymethyl)-*t*-2-[4-(4-methylphenyl)-1*H*-1,2,3-triazol-1-yl]-*r*-1-cyclopentanol ((±)-**17b**) and (±)-*t*-4-(*tert*-butyldiphenylsilyloxymethyl)-*t*-2-[4-(4-methylphenyl)-5-iodo-1*H*-1,2,3-triazol-1-yl]-*r*-1-cyclopentanol ((±)-**19b**).

Method B. the non-void fractions eluted with hexane–EtOAc 3:1 afforded successively unaltered (±)-**19b** (5%) and (±)-**17b** (82%).

(±)-**17b**: Colourless oil. IR (film) ν : 3352, 3069, 2933, 1463, 1387, 1226, 1109, 1004, 910, 819, 702 cm^{-1} . ^1H NMR (CDCl_3) δ : 7.65 (dd, 4H, $J = 0.8, 7.9$ Hz, 4H); 7.62 (s, 1H, 5- $\text{H}_{\text{triazole}}$); 7.58 (d, 2H, $J = 8.0$ Hz); 7.45–7.35 (m, 6H); 7.19 (d, 2H, $J = 8.0$ Hz, 2-H); 4.62–4.56 (2H, m); 3.65 (dd, 2H, $J = 5.6, 2.3$ Hz, O CH_2); 2.52–2.39 (m, 2H); 2.37 (s, 1H, D_2O exchangeable, OH); 2.37 (s, 3H, CH_3); 2.15–2.05 (m, 2H); 2.00–1.92 (m, 1H); 1.07 [s, 9H, $\text{C}(\text{CH}_3)_3$] ppm. ^{13}C NMR/DEPT (CDCl_3) δ : 147.2 (C), 137.9 (C), 135.5 (CH), 133.5 (C), 129.8 (CH), 129.4 (CH), 127.7 (CH), 127.4 (C), 125.5 (CH), 118.6 (CH), 76.4 (CH), 68.4 (CH), 67.0 (CH_2), 36.3 (CH), 34.1 (CH_2), 32.8 (CH_2), 26.9 [$\text{C}(\text{CH}_3)_3$], 21.2 (CH_3), 19.3 (C) ppm. MS (EI m/z): 455 (36), 454 (100), 199

(39), 197 (12), 183 (16), 181 (15), 135 (18), 115 (15). HRMS m/z calcd for $C_{31}H_{37}N_3O_2Si$, 511.2655; found, 511.2639.

(±)-**19b**: Yellowish oil. IR (film) ν : 3330, 2929, 1731, 1428, 1106, 802, 701 cm^{-1} . 1H NMR ($CDCl_3$) δ : 7.78-7.68 (virtual d, 2H, $J = 8.2$ Hz); 7.67-7.62 (m, 4H); 7.43-7.34 (m, 6H); 7.26-7.22 (m, 2H); 4.97 (q, 1H, $J = 7.2$ Hz, 2-H); 4.69 (dt, 1H, $J = 10.1, 7.2$ Hz, 1-H); 3.64 (d, 2H, $J = 5.8$ Hz, OCH_2); 2.61-2.47 (m, 2H); 2.39 (s, 3H, CH_3); 2.15-2.04 (m, 1H); 1.97-1.91 (m, 2H); 1.04 [s, 9H, $C(CH_3)_3$] ppm. ^{13}C NMR/DEPT ($CDCl_3$) δ : 138.5 (C), 135.6 (CH), 133.6 (C), 129.7 (CH), 129.2 (CH), 127.7 (CH), 127.5 (CH), 127.3 (C), 75.8 (CH), 68.8 (CH), 67.0 (CH_2), 36.6 (CH), 34.4 (CH_2), 33.6 (CH_2), 26.9 [$C(CH_3)$], 21.3 (CH_3), 19.3 (C) ppm. MS (EI m/z): 581 (26), 580 [(M-*tert*-Bu), 73], 451 (21), 217 (21), 208 (21), 199 (100), 197 (37), 183 (36), 181 (40), 139 (21), 135 (72), 130 (29), 129 (21), 105 (27), 103 (23), 97 (23), 77 (26). HRMS m/z calcd for $C_{31}H_{36}IN_3O_2Si$, 637.1621; found, 637.1647.

(±)-*t*-4-(*tert*-butyldiphenylsilyloxymethyl)-*t*-2-[4-(4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl]-*r*-1-cyclopentanol ((±)-**17c**).

Method B. The non-void fractions eluted with hexane–EtOAc 1:1 afforded (±)-**17c** (68%).

(±)-**17c**. White solid, m.p. = 107-108 °C. IR (KBr) ν : 3054, 2932, 2857, 1497, 1465, 1429, 1109, 1078, 1027, 705 cm^{-1} . 1H NMR ($CDCl_3$) δ : 7.68-7.65 (m, 4H); 7.60 (s, 1H, 5- $H_{triazole}$); 7.56-7.55 (m, 2H); 7.45-7.35 (m, 6H); 6.90 (virtual d, 2H, $J = 8.7$ Hz, 2-H); 4.63-4.57 (m, 2H); 3.83 (s, 3H, OCH_3); 3.70-3.61 (m, 2H); 2.55-2.37 (m, 2H); 2.16-2.05 (m, 2H); 2.04-1.86 (m, 1H); 1.07 [s, 9H, $C(CH_3)_3$] ppm. ^{13}C NMR/DEPT ($CDCl_3$) δ : 159.5 (C), 146.9 (C), 135.5 (CH), 133.5 (C), 129.7 (CH), 127.7 (CH), 126.8 (CH), 123.0 (C), 118.2 (CH), 114.1 (CH), 76.4 (CH), 68.4 (CH), 67.0 (CH_2), 55.2 (OCH_3), 36.2 (CH), 34.1 (CH_2), 32.8 (CH_2), 26.8 [$C(CH_3)$], 19.2 (C) ppm. MS (EI m/z): 471 (36), 470 [(M-*tert*-Bu), 100], 199 (72), 197 (30), 183 (29), 181 (21), 175 (24), 135 (38), 121 (22), 117 (20). Anal. Calcd for $C_{31}H_{37}N_3O_3Si$ (527.26): C, 70.55; H, 7.07; N, 7.96. Found: C, 70.77; H, 7.21; N, 8.09.

Deprotection of *tert*-butyldiphenylsilyloxymethyl ethers: synthesis of (±)-*t*-4-(hydroxymethyl)-*t*-2-(4-aryl-1*H*-1,2,3-triazol-1-yl)-*r*-1-cyclopentanol (±)-10a-c** and (±)-*c*-4-(hydroxymethyl)-*t*-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-*r*-1-cyclopentanol (±)-**11a-c**.** A solution of the corresponding triazole derivative (±)-**16a-c**/(±)-**17a-c** (1 mmol) and TBAF (1M in THF, 2mmol) in dry THF (15 mL), was stirred at room temperature under Ar atmosphere until complete disappearance of the starting material was detected by TLC. The solvents were then evaporated to dryness under reduced pressure, the residue dissolved in EtOAc (15 mL) and washed with brine (10 mL). The organic layer was dried (Na_2SO_4), evaporated under reduced pressure and the corresponding crude reaction product purified by flash column chromatography using successively EtOAc and acetone as eluents.

(±)-*t*-4-(Hydroxymethyl)-*t*-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-*r*-1-cyclopentanol ((±)-**10a**). 97% Yield, white solid, m.p. = 58-59 °C. IR (film) ν : 3364, 2924, 1650, 1518, 1047 cm^{-1} . 1H NMR ($CDCl_3$) δ : 7.79-7.77 (m, 2H, 2H); 7.76 (s, 1H, 5- $H_{triazole}$); 7.44-7.32 (m, 2H); 7.31-7.25 (m, 1H); 4.74-4.69 (m, 1H, 2-H); 4.49 (virtual q, 1H, $J = 5.8$ Hz, 1-H); 3.76-3.67 (m, 3H, one of them D_2O exchangeable, $HOCH_2 + OH$); 2.67-2.62 (m, 1H); 2.45-2.31 (m, 4H); 1.67 (dt, 1H, $J =$

13.7, 5.9 Hz, 3-*HH*) ppm. ^{13}C NMR/DEPT (CDCl_3) δ : 147.5 (C), 130.4 (C), 128.9 (CH), 128.2 (CH), 125.6 (CH), 119.3 (CH), 77.5 (CH), 68.2 (CH), 65.6 (CH_2), 36.7 (CH), 35.2 (CH_2), 31.5 (CH_2) ppm. MS (EI m/z): 259 (M, 1), 145 (23), 117 (87), 116 (38), 102 (58), 97 (37), 91 (25), 89 (28), 83 (32), 81 (28), 79 (31), 77 (25), 71 (41), 69 (63), 67 (42), 58 (100), 57 (75), 55 (74). Anal. Calcd for $\text{C}_{14}\text{H}_{17}\text{N}_3\text{O}_2$ (259.13): C, 64.85; H, 6.61; N, 16.20. Found: C, 65.12; H, 6.93; N, 16.46.

(\pm)-*t*-4-(Hydroxymethyl)-*t*-2-(4-(4-methylphenyl)-1*H*-1,2,3-triazol-1-yl)-*r*-1-cyclopentanol ((\pm)-10b). 87% Yield, white solid, m.p. = 128-129 °C. IR (KBr) ν : 3284, 2920, 1454, 1382, 1053, 816 cm^{-1} . ^1H NMR (CDCl_3) δ : 7.77 (s, 1H, 5- $\text{H}_{\text{triazole}}$); 7.67 (d, 2H, $J = 8.0$ Hz); 7.20 (d, 2H, $J = 8.0$ Hz); 4.63 (dt, 1H, $J = 7.0, 2.9$ Hz, 2-H); 4.56 (virtual q, 1H, $J = 7.0$ Hz, 1-H); 3.71-3.63 (m, 2H, HOCH_2); 2.74 (b s, 2H, D_2O exchangeable, 2 OH); 2.59-2.50 (m, 2H); 2.36 (s, 3H, CH_3); 2.15-2.01 (m, 2H); 1.99-1.89 (m, 1H) ppm. ^{13}C NMR/DEPT (CDCl_3) δ : 147.6 (C), 138.0 (C), 129.5 (CH), 127.7 (C), 125.6 (CH), 118.9 (CH), 76.9 (CH), 67.9 (CH), 66.1 (CH_2), 36.4 (CH), 32.4 (CH_2), 29.7 (CH_2), 21.3 (CH_3) ppm. MS (EI m/z): 273 (M, 19), 158 (19), 131 (100), 130 (35), 116 (58), 115 (78), 103 (21), 77 (21). Anal. Calcd for $\text{C}_{15}\text{H}_{19}\text{N}_3\text{O}_2$ (273.33): C, 66.91; H, 7.01; N, 15.37. Found: C, 67.22; H, 6.98; N, 15.63.

(\pm)-*t*-4-(Hydroxymethyl)-*t*-2-(4-(4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)-*r*-1-cyclopentanol ((\pm)-10c). 99% Yield, white solid, m.p. = 115-116 °C. IR (KBr) ν : 3350, 3110, 2941, 2885, 1615, 1495, 1444, 1381, 1251, 1051, 1021 cm^{-1} . ^1H NMR (acetone- d_6) δ : 8.28 (s, 1H, 5- $\text{H}_{\text{triazole}}$); 7.80 (d, 2H, $J = 8.8$ Hz); 7.0 (d, 2H, $J = 8.8$ Hz); 4.78-4.70 (m, 1H, 2-H); 4.50-4.47 (m, 1H, 1-H); 3.82 (s, 3H, OCH_3); 3.60-3.57 (m, 2H, HOCH_2); 2.79-2.93 (m, 2H, D_2O exchangeable, 2 OH); 2.52-2.42 (m, 2H); 2.08-2.01 (m, 2H); 2.00-1.80 (m, 1H) ppm. ^{13}C NMR/DEPT (acetone- d_6) δ : 160.7 (C), 147.9 (C), 127.8 (CH), 125.4 (C), 119.9 (CH), 115.3 (CH), 77.7 (CH), 69.7 (CH), 66.7 (CH_2), 55.9 (OCH_3), 38.2 (CH), 36.5 (CH_2), 34.5 (CH_2) ppm. MS (EI m/z): 289 (M, 26), 230 (13), 176 (16), 175 (74), 174 (15), 147 (31), 146 (15), 135 (27), 132 (100), 121 (12), 117 (23), 89 (24), 77 (11). Anal. Calcd for $\text{C}_{15}\text{H}_{19}\text{N}_3\text{O}_3$ (289.33): C, 62.27; H, 6.62; N, 14.52. Found: C, 62.59; H, 6.89; N, 14.36.

(\pm)-*c*-4-(Hydroxymethyl)-*t*-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-*r*-1-cyclopentanol ((\pm)-11a). 93% Yield, white solid, m.p. = 61-62 °C. IR (KBr) ν : 3289, 3083, 2939, 1441, 1107, 1042 cm^{-1} . ^1H NMR (CDCl_3) δ : 7.79-7.75 (m, 2H); 7.77 (s, 1H, 5- $\text{H}_{\text{triazole}}$); 7.44-7.39 (m, 2H); 7.35-7.31 (m, 1H); 4.76-4.69 (m, 1H, 2-H), 4.52-4.46 (virtual q, 1H, $J = 5.8$ Hz, 1-H); 3.76-3.67 (m, 2H, HOCH_2); 2.68-2.59 (m, 1H); 2.45-2.31 (m, 4H, OH); 1.67 (dt, 1H, $J = 13.8, 5.9$ Hz, 3- CHH) ppm. ^{13}C NMR/DEPT (CDCl_3) δ : 147.44 (C), 130.33 (C), 128.85 (CH), 128.22 (CH), 125.64 (CH), 119.35 (CH), 77.52 (CH), 68.25 (CH), 65.62 (CH_2), 36.68 (CH), 35.26 (CH_2), 31.56 (CH_2) ppm. MS (EI m/z): 259 (M, 23), 145 (56), 144 (30), 117 (90), 104 (22), 103 (27), 102 (100), 90 (28), 89 (38), 79 (22), 69 (24), 67 (39), 58 (44), 55 (24). Anal. Calcd for $\text{C}_{14}\text{H}_{17}\text{N}_3\text{O}_2$ (259.13): C, 64.85; H, 6.61; N, 16.20. Found: C, 64.56; H, 6.78; N, 16.15.

(\pm)-*c*-4-(Hydroxymethyl)-*t*-2-(4-(4-methylphenyl)-1*H*-1,2,3-triazol-1-yl)-*r*-1-cyclopentanol ((\pm)-11b). 99% Yield, white solid, m.p. = 119-120 °C. IR (KBr) ν : 3282, 1649, 1517, 1041, 819 cm^{-1} . ^1H NMR (CDCl_3) δ : 7.68 (s, 1H, 5- $\text{H}_{\text{triazole}}$); 7.59-7.24 (m, 2H); 7.16 (d, 2H, $J = 7.8$

Hz); 4.69-4.64 (m, 1H, 2-H); 4.46-4.42 (m, 1H, 1-H); 3.67-3.60 (m, 2H, HOCH₂); 2.60-2.52 (m, 1H); 2.33 (s, 3H, CH₃); 2.38-2.24 (m, 3H); 1.65-1.61 (m, 1H, 3-HH) ppm. ¹³C NMR/DEPT (CDCl₃) δ: 147.6 (C), 138.0 (C), 129.5 (CH), 127.8 (CH), 127.6 (CH), 125.6 (CH), 118.9 (CH), 77.5 (CH), 68.2 (CH), 65.6 (CH₂), 36.7 (CH), 35.3 (CH₂), 31.5 (CH₂), 21.3 (CH₃) ppm. MS (EI *m/z*): 273 (M, 23), 158 (24), 131 (80), 130 (44), 119 (20), 118 (20), 117(23), 116 (83), 115 (100), 103 (25), 91 (20), 79 (21), 77 (28), 69 (25), 67 (32), 57 (25), 55 (27). Anal. Calcd for C₁₅H₁₉N₃O₂ (273.33): C, 66.91; H, 7.01; N, 15.37. Found: C, 67.26; H, 7.33; N, 15.54.

(±)-c-4-(Hydroxymethyl)-t-2-(4-(4-methoxyphenyl)-1H-1,2,3-triazol-1-yl)-r-1-cyclopentanol ((±)-11c). 74% Yield, white solid, m.p. = 124-125°C. IR (KBr) ν: 3282, 1649, 1517, 1041, 819 cm⁻¹. H NMR (CDCl₃) δ: 7.68 (s, 1H, 5-H_{triazol}); 7.59-7.24 (m, 2H); 7.16 (d, 2H, *J* = 7.8 Hz); 4.69-4.64 (m, 1H, 2-H); 4.46-4.42 (m, 1H, 1-H); 3.67-3.60 (m, 2H, HOCH₂); 2.60-2.52 (m, 1H); 2.33 (s, 3H, CH₃); 2.38-2.24 (m, 3H); 1.65-1.61 (m, 1H, 3-HH) ppm. ¹³C NMR/DEPT (CDCl₃) δ: 147.6 (C), 138.0 (C), 129.5 (CH), 127.8 (CH), 127.6 (CH), 125.6 (CH), 118.9 (CH), 77.5 (CH), 68.2 (CH), 65.6 (CH₂), 36.7 (CH), 35.3 (CH₂), 31.5 (CH₂), 21.3 (CH₃) ppm. MS (EI *m/z*): 273 (M, 23), 158 (24), 131 (80), 130 (44), 119 (20), 118 (20), 117 (23), 116 (83), 115 (100), 103 (25), 91 (20), 79 (21), 77 (28), 69 (25), 67 (32), 57 (25), 55 (27). Anal. Calcd for C₁₅H₁₉N₃O₃ (289.33): C, 62.27; H, 6.62; N, 14.52. Found: C, 62.63; H, 6.52; N, 14.68.

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References and Notes

1. Sidwell, R. W.; Huffman, J. H.; Khare, G. P.; Allen, L. B.; Witkowski, J. T.; Robins, R. K. *Science* **1972**, *177*, 705.
2. Wender, P. A.; Touami, S. M., Alayrac, C.; Philipp, U. C. *J. Am. Chem. Soc.* **1996**, *118*, 6522, and references cited therein.
3. Cozzi, P.; Mongelli, N. *Current Pharm. Des.* **1998**, *4*, 181.
4. See for instance: (a) Diana, G. D.; Nitz, T. J. Eur. Pat. 566 199, 1993; *Chem. Abstr.* **1994**, *120*, 164184. (b) Mingdong, C.; Shijie, L.; Guanqpu, Y.; Shiyang, Y.; Xuaoli, D. *Heterocycl. Commun.* **2000**, *6*, 421. (c) Manfredini, S.; Vicentini, C. B.; Manfrini, M.; Bianchi, N.; Rutigliano, A.; Mistiachi C.; Gambari, R. *Bioorg. Med. Chem.* **2000**, *8*, 2343.
5. (a) Alvarez, R.; Velázquez, S.; San-Felix, A.; Aquaro, S.; De Clercq, E.; Perno, C. F.; Karlsson, A.; Balzarini J.; Camarasa, M. J. *J. Med. Chem.* **1994**, *37*, 4185. (b) Velázquez, S.;

- Alvarez, R.; Pérez, C.; Gago, F.; De Clercq, E.; Balzarini J.; Camarasa, M. J. *Antiviral Chem. Chemother.* **1998**, *9*, 481.
6. Alonso, R.; Camarasa, M. J.; Alonso G.; De las Heras, F. G. *Eur. J. Med. Chem.* **1980**, *15*, 105.
 7. The term carbanucleosides (or carbocyclic analogues of nucleosides) is used to define those nucleoside analogues in which the anomeric oxygen of the furanose ring is replaced by a methylene group. For a recent review, see: Casu, F.; Chiacchio, M. A.; Romeo, R.; Gumina, G. *Curr. Org. Chem.* **2007**, *11*, 999, and references cited therein.
 8. Pérez-Castro, I.; Caamaño, O.; Fernández, F.; García, M. D.; López, C.; De Clercq, E. *Org. Biomol. Chem.* **2007**, *5*, 3805.
 9. Saito, Y.; Escuret, V.; Durantel, D.; Zoulim, F.; Schinazi, R. F.; Agrofoglio, L. A. *Bioor. Med. Chem.* **2003**, *11*, 3633.
 10. Cho, J. H.; Bernard, D. L.; Sidwell, R. W.; Kern, E. R.; Chu, C. K. *J. Med. Chem.* **2006**, *49*, 1140.
 11. Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596.
 12. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.
 13. Moorhouse, A. D.; Moses, J. E. *Chem. Med. Chem.* **2008**, *3*, 715.
 14. Agrofoglio, L.; Condom, R.; Guedj, R. *Tetrahedron Lett.* **1992**, *33*, 5503, and references cited therein.
 15. Agrofoglio, L.; Condom, R.; Guedj, R.; Challand, S. R.; Selway, J. *Nucleosides and Nucleotides*, **1994**, *13*, 1147.
 16. Epoxidation of cyclopent-3-enylmethanol derivatives of type **13** with MCPBA is heavily dependent on the substituent on the hydroxymethyl group, as reported by Agrofoglio *et al.*¹⁴ In essence, the *anti:syn* selectivity is correlated with its volume, increasing the steric hindrance on the *syn* face of the cyclopentene ring. When silyl protecting groups are involved, the decreased electronic interactions cause an increased *anti* selectivity for the epoxidation, not related to the volume of the silyl protecting group (the *anti/syn* selectivity was found to be 8.2:1 for TBDMS and 4:1 for TPS). The outcome of the epoxidation of alkene **13b** (R = TBDPS) with MCPBA, leading to a 3.8:1 *anti/syn* selectivity, is in accordance with these results.
 17. Chini, M.; Crotti, P.; Macchia, F. *Tetrahedron Lett.* **1990**, *31*, 5641.
 18. Tornøe, C.W.; Christensen, C.; Mendal, M. *J. Org. Chem.* **2002**, *67*, 3057.
 19. This fact is linked to the *in situ* production of the I⁺ ion during the reaction. For a detailed mechanism see: Li, L.; Zhang, G.; Zhu, A.; Zhang, L. *J. Org. Chem.* **2008**, *73*, 3630.
 20. CCDC 707775 contains the supplementary crystallographic data for compound **11f**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
 21. MCC: Minimum Cytotoxic Concentration that causes microscopically detectable alteration of host cell morphology.