



## Short communication

# Antifungal activity of 1'-homo-*N*-1,2,3-triazol-bicyclic carbonucleosides: A novel type of compound afforded by azide-enolate (3+2) cycloaddition



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## ABSTRACT

The first report of 1'-homo-*N*-1,2,3-triazol-bicyclic carbonucleosides (**7a** and **7b**) is described herein. Azide-enolate (3+2) cycloaddition afforded the synthesis of this novel type of compound. Antifungal activity was evaluated *in vitro* against four filamentous fungi (*Aspergillus fumigatus*, *Trichosporon cutaneum*, *Rhizopus oryzae* and *Mucor hiemalis*) as well as nine species of *Candida* spp. as yeast specimens. These pre-clinical studies suggest that compounds **7a** and **7b** are promising candidates for complementary biological studies due to their good activity against *Candida* spp.

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## 1. Introduction

The chemistry and biology of nucleoside analogs has consolidated a very particular and proper field of study in organic and medicinal chemistry [1]. A certain classification of such compounds, convenient for the purpose of the present study, is described in Fig. 1. One of the most important modifications of nucleosides **Aa** [2] has been the replacement of the oxygen atom of the furanose ring with a methylene group, resulting in carbocyclic nucleosides **Ab** [3] (also called 'carbonucleosides' in short form). The recognition of 1,2,3-triazole scaffolds as potent pharmacophores [4] has revolutionized nucleoside analogs allowing for their conversion to the corresponding triazole derivatives **Ba** [5] and **Bb** [6].

1'-Homonucleosides (**Ca** [7] and **Cb** [8]) are a special class of modified nucleosides, in which the nucleobase (Het) and the sugar moiety (at its 1'-position) are separated by a carbon bridge. In addition to greater conformational flexibility and rotational freedom, this gives them more resistance to hydrolytic or enzymatic cleavage compared to the relatively reactive aminal linkage of common nucleosides [9]. Modified triazolic nucleosides **D** [10]

can be found in literature, and the discovery of certain natural bicyclic nucleosides **Ea** [11] (e.g. Ezomycin [12] and Octosyl [13]) along with their potent antifungal activity [14] has sparked new research into the design and synthesis of novel carbonucleoside derivatives **Eb** [15] as well as their 1'-homo mimetics **F** [16].

Sesquiterpene lactones (carbocyclic lactones) are amongst the most abundant natural products. More than 8000 structures have been reported [17], and they have broad structural and functional diversity including their antifungal activity [e.g. Sclareolide [18] (Fig. 2)]. The introduction of these scaffolds to nucleosides analogs (**H** and **I**) has been performed by Castellón [19]. The chemical structure of certain antifungal nucleoside analogs (**J** [20] and **K** [21] among others [22]) has inspired the design and synthesis of 1'-homo-*N*-1,2,3-triazol-bicyclic carbonucleosides **7a** and **7b**. To the best of our knowledge, this type of compound (**G**) has not yet been reported.

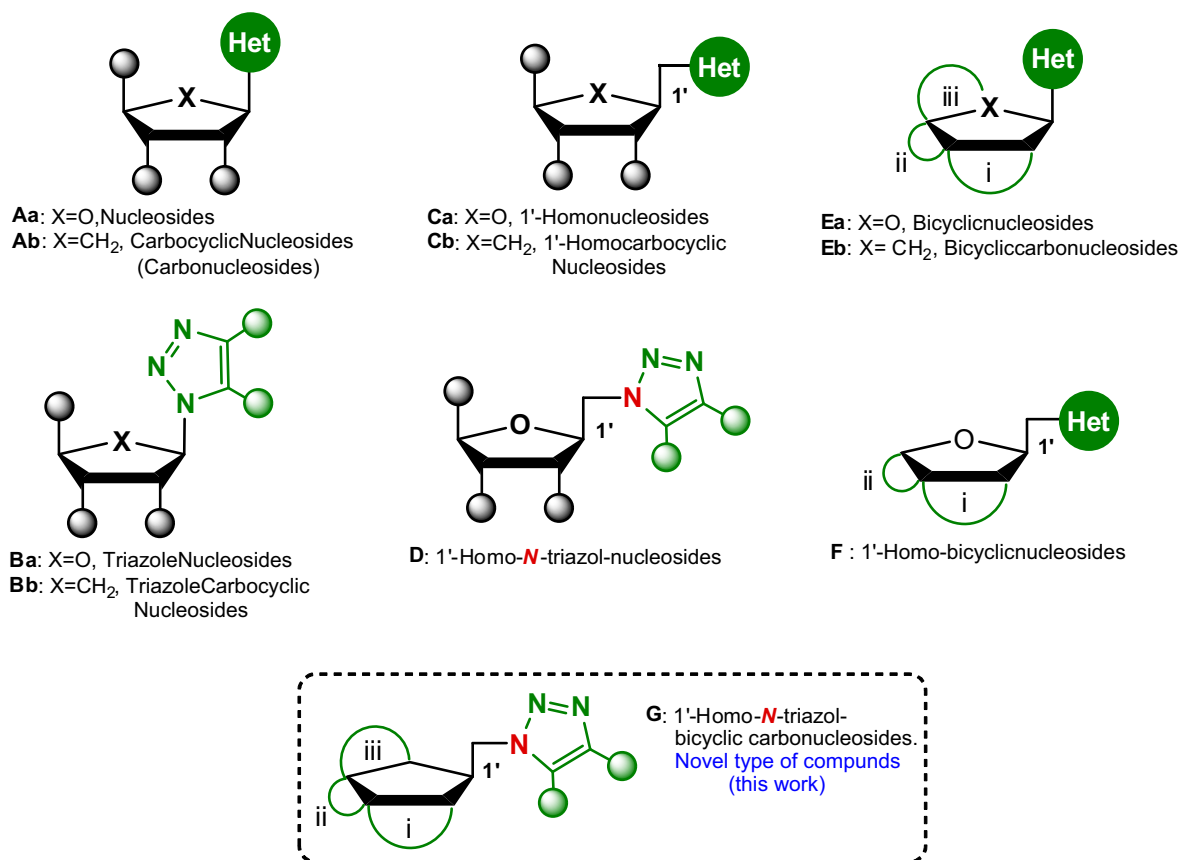
## 2. Results and discussion

## 2.1. Chemistry

The Cu-catalyzed azide-alkyne cycloaddition (CuAAC) has largely been the conventional approach for synthesizing triazole nucleosides [5]. In recent years, azide-enolate (3+2) cycloaddition (AEC) has emerged as a novel and potent tool for the synthesis of

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**Fig. 1.** General classification of nucleoside analogs reported in literature. Possible positions (i, ii, and iii) for bicyclic derivatives E and F are known. A novel type of compound G is herein proposed.

1,2,3-triazole moieties [23]. As a pioneering strategy we describe the synthesis of **7a** and **7b** afforded by a versatile AEC (Scheme 1).

Our initial study began by obtaining silylated 'Corey lactone' **2**, according to our previous report [24], as the key precursor for the present synthesis. This compound is an excellent supplier of the pseudosugar ring (cyclopentane) required for the highly stereospecific configuration of all suitable functional groups. A convenient protection–deprotection strategy for alcohols was planned for the present study involving the esterification of **2** with *p*-phenylbenzoyl chloride (PBCl) in dichloromethane and pyridine to form the ester lactone **3**.

Previously [25], we investigated the AlCl<sub>3</sub>·6H<sub>2</sub>O cleavage of silyl ethers in methanol. Thus, desilylation of **3** was accomplished by such a protocol to afford alcohol **4**, which was functionalized to the corresponding iodide derivative **5** according to the Garegg-Samuelsson procedure (PPh<sub>3</sub>/I<sub>2</sub>/Im/ROH system) [26]. On the other hand, we recently [27] published a straightforward approach to the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles by the coupling of three-components (alkyl halides, sodium azide, and ketones) through an AEC. This method proved to be a very rapid and elegant way to access triazole building blocks **6a** and **6b** by the coupling of acetylacetone and 2-benzoylacetophenone, respectively. Finally, transesterification of **6a** and **6b** by treatment with DBN in MeOH gave the corresponding carbonucleosides **7a** and **7b**.

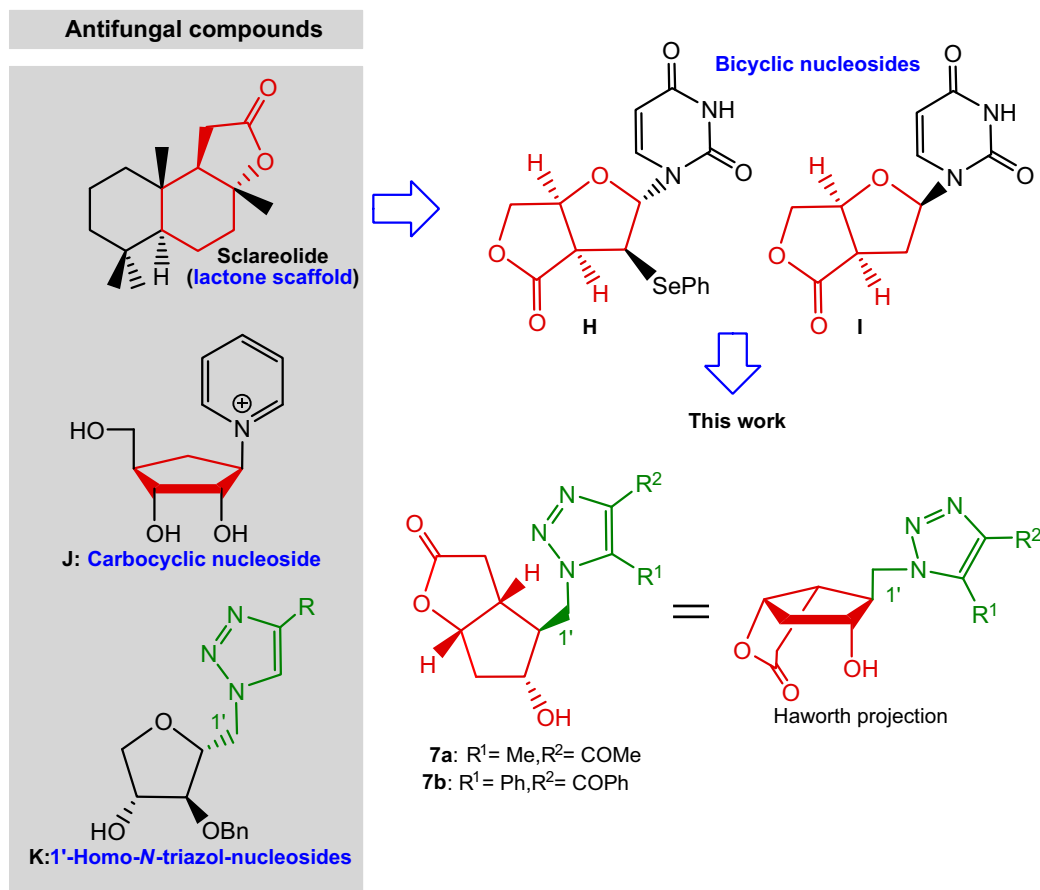
Compounds **7a** and **7b** were evaluated for their *in vitro* antifungal activity against four filamentous fungi (*Aspergillus fumigatus* ATCC-16907, *Trichosporon cutaneum* ATCC-28592, *Rhizopus oryzae* ATCC-10329 and *Mucor hiemalis* ATCC-8690), as well as *Candida utilis* ATCC-9226, *Candida albicans* ATCC-10231 and *Candida*

*tropicalis* ATCC-13803 as yeast specimens. In addition, other strains for *Candida* spp. (*C. lipolytica*, *C. pseudotropicalis*, *C. krusei*, *C. parapsilosis*, *C. glabrata*, and *Candida famata*) were collected from inpatients and evaluated under the aforementioned protocol. CLSI standardized methods were employed to carry out the microbiological tests. We used the M38-A2 [28] microdilution method to determine the sensitivity of filamentous fungi, and the M27-A3 [29] method for *Candida* yeasts. The antifungal activity of compounds **7a** and **7b** was compared with itraconazole, a standard antifungal drug. The minimum inhibitory concentration (MIC) values of compounds and standard drugs, expressed in micrograms per milliliter, were determined in 96-well plates by using RPMI 1640 medium buffered with MOPS (3-[*N*-morpholino]propane sulfonic acid; Sigma-Aldrich).

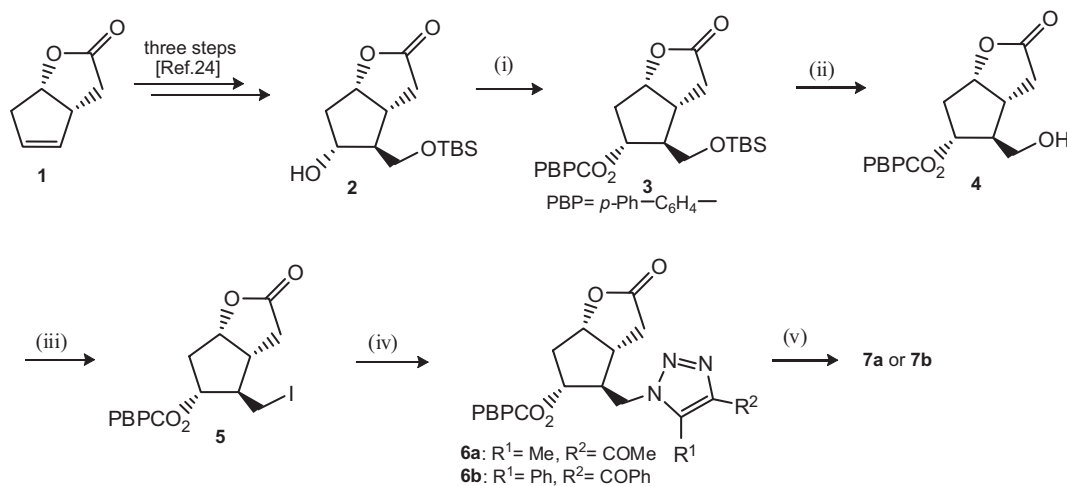
## 2.2. Antifungal activity

The antifungal activity of the evaluated compounds is summarized in Table 1. Compounds **7a** and **7b** showed good activity in some of the yeast strains, including *C. utilis*, *C. lipolytica*, *C. glabrata* and *C. famata*, demonstrating 'sensitivity'<sup>a</sup> according to the parameters of document M27-A3 (Table 2). Only slight

<sup>a</sup> 'S', 'SDD' and 'R' are represented by standardized values (breakpoints) used to appreciate the clinical value of the *in vitro* antifungal testing result and predicting the response of patients infected. Sensitivity is dependent on achieving the maximum dosages in plasma (breakpoints) to obtain optimal response. For itraconazole, an MIC within the susceptible-dose dependent (SDD) range indicates the need for plasma concentrations 0.25–0.5 µg/mL for an optimal response. Actual breakpoints are described in Table 4 (see Ref. [29b]).



**Fig. 2.** The current antifungal compounds Sclareolide, J and K as well as H and I inspired the design of novel nucleoside analogs 7a and 7b.



**Scheme 1.** Reagents and conditions: (i) PBCl (1.1 eq), Py anh., DCM, r.t., N<sub>2</sub>, 1 h, 90%. (ii) AlCl<sub>3</sub>·6H<sub>2</sub>O cat, MeOH, 60 °C, 12 h, 93%. (iii) PPh<sub>3</sub> (2.5 eq), I<sub>2</sub> (2.0 eq.), Im (2.5 eq.), MeCN anh., 80 °C, N<sub>2</sub>, 3 h, 85%. (iv) For **6a**: NaN<sub>3</sub> (1.1 eq), DMF anh., 60 °C, N<sub>2</sub>, 6 h, then acetylacetone (1.1 eq), DBU (1.1 eq), 12 h, 60 °C, 72%. For **6b**: NaN<sub>3</sub> (1.1 eq), DMF anh., 60 °C, N<sub>2</sub>, 6 h, then 2-benzoylacetophenone (1.1 eq), DBU (1.1 eq), 12 h, 60 °C, 67%. (v) Both **7a** and **7b**: DBN cat, MeOH, r.t. 12 h, 87% and 81% respectively.

antifungal activity against *C. albicans*, *C. tropicalis*, *C. pseudotropicalis*, *C. krusei*, and *C. parapsilosis* was observed. Whereas there was evident resistance by *M. hiemalis*, slight activity was found against the rest of the filamentous fungi tested (*A. fumigatus*, *T. cutaneum*, and *R. oryzae*).

### 3. Conclusion

In conclusion, we report the first synthesis of a novel type of compound, represented by 1'-homo-N-1,2,3-triazol-bicyclic carbocyclic nucleosides **7a** and **7b**, which showed good activity against

**Table 1**  
In vitro antifungal activities of synthesized compounds (MIC, µg/mL).

| Comp.                 | Yeast fungi    |                 |                |                 |                 |                |                 |                |                | Filamentous fungi |                |                |                |
|-----------------------|----------------|-----------------|----------------|-----------------|-----------------|----------------|-----------------|----------------|----------------|-------------------|----------------|----------------|----------------|
|                       | <i>C. alb.</i> | <i>C. trop.</i> | <i>C. uti.</i> | <i>C. lipo.</i> | <i>C. pseu.</i> | <i>C. kru.</i> | <i>C. para.</i> | <i>C. gla.</i> | <i>C. fam.</i> | <i>M. hie.</i>    | <i>A. fum.</i> | <i>T. cut.</i> | <i>R. ory.</i> |
| <b>1</b>              | 0.25           | 0.5             | 0.12           | 0.12            | 0.5             | 4              | 2               | 0.5            | 0.06           | >16               | 4              | 8              | 4              |
| <b>2</b>              | 2              | 2               | 0.12           | 0.12            | 1               | 4              | 4               | 0.5            | 0.5            | >16               | 8              | >16            | 8              |
| Standard <sup>a</sup> | 0.03           | 0.25            | 0.25           | 0.03            | 0.12            | 0.25           | 0.12            | 0.06           | 0.06           | 4                 | 0.5            | 2              | 1              |

Abbreviations: *C. alb.*, *Candida albicans*; *C. trop.*, *Candida tropicalis*; *C. uti.*, *Candida utilis*; *C. lipo.*, *Candida lipolytica*; *C. pseu.*, *Candida pseudotropicalis*; *C. kru.*, *Candida krusei*; *C. para.*, *Candida parapsilosis*; *C. gla.*, *Candida glabrata*; *C. fam.*, *Candida famata*; *M. hie.*, *Mucor hiemalis*; *A. fum.*, *Aspergillus fumigatus*; *T. cut.*, *Trichosporon cutaneum*; *R. ory.*, *Rhizopus oryzae*.

<sup>a</sup> Itraconazole.

**Table 2**  
Sensitivity of yeast strains according to the document M27-A3: Susceptible (S), dose dependent sensitive (SDD) and resistant (R).

| Compound              | <i>C. alb.</i> | <i>C. trop.</i> | <i>C. uti.</i> | <i>C. lipo.</i> | <i>C. pseu.</i> | <i>C. kru.</i> | <i>C. para.</i> | <i>C. gla.</i> | <i>C. fam.</i> |
|-----------------------|----------------|-----------------|----------------|-----------------|-----------------|----------------|-----------------|----------------|----------------|
| <b>1</b>              | SDD            | SDD             | S              | S               | SDD             | R              | R               | SDD            | S              |
| <b>2</b>              | R              | R               | S              | S               | R               | R              | R               | SDD            | SDD            |
| Standard <sup>a</sup> | S              | SDD             | SDD            | S               | S               | SDD            | S               | S              | S              |

<sup>a</sup> Itraconazole. Interpretive criteria: Breakpoints (MIC, µg/mL) = 0.12 [S], 0.25–0.5 [SDD], 1 [R].

some of the yeast strains tested. Moreover, AEC was employed as a synthetic strategy. These advances make the present study a breakthrough in the field of nucleoside chemistry. The pre-clinical study of these compounds show a good antifungal scope for *Candida* spp., representing new leads for further development of pharmacomodulator in this series.

## 4. Experimental

### 4.1. General

The reagents were purchased from Aldrich Chemical Co. and were used without further purification. Dichloromethane, pyridine, acetonitrile, and dimethylformamide were dried according to literature [30]. **Flash column chromatography:** SiO<sub>2</sub> 60 (230–400 mesh). **TLC:** Silica-gel plates (SiO<sub>2</sub>; 0.20-mm thickness); visualization with UV light at 254 nm or by staining with base soln. of CoCl<sub>2</sub>/H<sub>2</sub>SO<sub>4</sub> ac. (2 g/100 mL H<sub>2</sub>SO<sub>4</sub> 10%) followed by heating ~140 °C. **m.p.:** Fischer-Johns Scientific melting point apparatus; uncorrected. **<sup>1</sup>H and <sup>13</sup>C NMR spectra:** Bruker Avance 300 MHz and a Varian 500 MHz; δ in ppm rel. to Me<sub>4</sub>Si as internal standard, J in Hz. **MS:** Shimadzu GCMS-QP2010 Plus; in m/z (rel.%).

#### 4.1.1. (3aR,4S,5R,6aS)-4-((tert-butyl dimethylsilyloxy)methyl)-2-oxohexahydro-2H-cyclopenta[b]furan-5-yl biphenyl-4-carboxylate (3)

To a solution of Corey lactone-alcohol **2** (2.0 g, 6.98 mmol) in anhydrous dichloromethane (DCM, 15.0 mL) and anhydrous pyridine (Py, 5.0 mL) at room temperature under inert atmosphere was added *p*-phenylbenzoyl chloride (1.66 g, 7.68 mmol). The reaction mixture was stirred for 1 h, and then water (~70 mL) was added to the reaction mixture and washed with DCM (3 × 10 mL). In order to remove the excess Py, the organic layer was washed with CuSO<sub>4</sub> 5% sol. (5–8 × 20 mL until strong blue color of watery layer gradually turned to slightly blue color). The organic layer was dried with anhydrous Na<sub>2</sub>SO<sub>4</sub> and the solvent was concentrated in *vacuo*. The crude product was purified by flash column chromatography to give the white solid **3** (2.94 g, 90%). m.p. 91–95 °C. R<sub>f</sub>: 0.35 (Hex/EtOAc 8:2). <sup>1</sup>H NMR: (300 MHz, CDCl<sub>3</sub>) δ = 8.06 (d, J = 8.4 Hz, 2 Ar–H), 7.64 (dd, J = 15.7, 7.7 Hz, 4 Ar–H), 7.49–7.33 (m, 3 Ar–H), 5.37 (dt, J = 5.8, 2.9 Hz, 1 H), 5.09 (t, J = 5.9 Hz, 1 H), 3.72 (qd, J = 10.2, 4.7 Hz, 2 H), 3.00–2.86 (m, 2 H), 2.65–2.42 (m, 2 H), 2.34 (d, J = 17.2 Hz, 2 H), 0.90 (s, 9 H), 0.07 (s, 6 H) ppm. <sup>13</sup>C NMR: (75 MHz, CDCl<sub>3</sub>) δ = 176.86 (C=O), 165.86

(C=O), 145.84 (C), 139.92 (C), 130.14 (2 CH), 128.89 (2 CH), 128.52 (C), 128.12 (CH), 127.24 (2 CH), 127.12 (2 CH), 85.42 (CH), 78.78 (CH), 63.43 (CH<sub>2</sub>), 55.16 (CH), 40.53 (CH), 39.07 (CH<sub>2</sub>), 36.24 (CH<sub>2</sub>), 25.84 (3 CH<sub>3</sub>), 18.17 (C), –5.53 (2 CH<sub>3</sub>) ppm. MS-EI<sup>+</sup> m/z (%): 409 [C<sub>23</sub>H<sub>25</sub>O<sub>5</sub>Si<sup>+</sup>] (20), 256 (100), 211 (69), 182 (76), 152 (90), 127 (23), 91 (20), 75 (43), 57 [C<sub>4</sub>H<sub>9</sub>] (20).

#### 4.1.2. (3aR,4S,5R,6aS)-4-(hydroxymethyl)-2-oxohexahydro-2H-cyclopenta[b]furan-5-yl biphenyl-4-carboxylate (4)

To a solution of silyl ether **3** (2.0 g, 4.29 mmol) in methanol (18.0 mL) was added a catalytic amount of AlCl<sub>3</sub>·6H<sub>2</sub>O (0.05 g, 0.2 mmol). The reaction mixture was stirred at 60 °C for 12 h. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography affording a white solid **4** (1.4 g, 93%). m.p. 147–150 °C. R<sub>f</sub>: 0.3 (Hex/EtOAc 2:8). <sup>1</sup>H NMR: (300 MHz, CDCl<sub>3</sub>+(CD<sub>3</sub>)<sub>2</sub>SO) δ = 8.04 (d, J = 8.4 Hz, 2 Ar–H), 7.63 (dd, J = 14.3, 7.6 Hz, 4 Ar–H), 7.50–7.33 (m, 3 Ar–H), 5.43 (dt, J = 5.5, 2.7 Hz, 1 H), 5.10 (t, J = 5.7 Hz, 1 H), 4.55 (t, J = 5.1 Hz, 1 H), 3.60 (td, J = 5.4, 3.2 Hz, 2 H), 3.01–2.86 (m, 2 H), 2.65–2.38 (m, 2 H), 2.38–2.26 (m, 2 H) ppm. <sup>13</sup>C NMR: (75 MHz, CDCl<sub>3</sub>+(CD<sub>3</sub>)<sub>2</sub>SO) δ = 177.00 (C=O), 165.53 (C=O), 145.43 (CH), 139.52 (C), 129.99 (2 CH), 128.86 (2 CH), 128.56 (C), 128.11 (CH), 127.02 (2 CH), 126.85 (2 CH), 85.10 (CH), 78.47 (CH), 61.99 (CH<sub>2</sub>), 55.26 (CH), 40.14 (CH), 38.44 (CH<sub>2</sub>), 36.21 (CH<sub>2</sub>), ppm. MS-EI<sup>+</sup> m/z (%): 353 [M<sup>+</sup>+1] (73), 200 (100), 183 (82), 180 (31), 151 (64), 125 (53), 79 (25), 41 (35).

#### 4.1.3. (3aR,4R,5R,6aS)-4-(iodomethyl)-2-oxohexahydro-2H-cyclopenta[b]furan-5-yl biphenyl-4-carboxylate (5)

To a solution of alcohol **4** (2.0 g, 5.68 mmol), triphenylphosphine (3.72 g, 14.19 mmol), and imidazole (0.96 g, 14.19 mmol) in anhydrous acetonitrile (35.0 mL) was added I<sub>2</sub> (2.88 g, 11.35 mmol). The solution was stirred for 3 h at 80 °C under nitrogen atmosphere. After this time, the reaction mixture was added to brine (~150 mL) and washed with EtOAc (3 × 30 mL). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was evaporated under reduced pressure. The crude was purified by flash column chromatography to afford the white solid **5** (2.2 g, 85%). m.p. 142–145 °C. R<sub>f</sub>: 0.4 (Hex/EtOAc 6:4). <sup>1</sup>H NMR: (300 MHz, CDCl<sub>3</sub>) δ = 8.06 (d, J = 8.4 Hz, 2 Ar–H), 7.76–7.33 (m, 7 Ar–H), 5.33–5.23 (m, 1 H), 5.07 (td, J = 6.4, 1.8 Hz, 1 H), 3.36 (dd, J = 10.3, 5.2 Hz, 1 H), 3.22 (dd, J = 10.3, 7.7 Hz, 1 H), 2.95 (dd, J = 17.8, 10.1 Hz, 1 H), 2.87–2.76 (m, 1 H), 2.66–2.49 (m, 2 H), 2.46–2.27 (m, 2 H) ppm.

$^{13}\text{C}$  NMR: (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 176.11 (C=O), 165.65 (C=O), 146.02 (C), 139.72 (C), 130.19 (2 CH), 128.90 (2 CH), 128.20 (CH), 127.99 (C), 127.21 (2 CH), 127.12 (2 CH), 83.71 (CH), 79.45 (CH), 54.05 (CH), 44.28 (CH), 37.86 ( $\text{CH}_2$ ), 35.72 ( $\text{CH}_2$ ), 7.03 ( $\text{CH}_2$ -I) ppm. MS-EI<sup>+</sup> *m/z* (%): 463 [ $\text{M}+1$ ]<sup>+</sup> (78), 335 (21), 277 (74), 200 (76), 180 (100), 154 (77), 127 (41), 109 (40), 91 (89), 77 (87), 54 (73), 39 (56).

#### 4.1.4. (3*aR*,4*S*,5*R*,6*aS*)-4-((4-acetyl-5-methyl-1*H*-1,2,3-triazol-1-yl)methyl)-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-5-yl biphenyl-4-carboxylate (6*a*)

The alkyl halide **5** (1.0 g, 2.16 mmol) and sodium azide (0.16 g, 2.38 mmol) were added to anhydrous dimethylformamide (17.0 mL). The reaction mixture was stirred at 60 °C for 6 h under nitrogen atmosphere. After this time, TLC indicated the disappearance of the starting material. Then, acetylacetone (0.24 mL, 2.38 mmol) and DBU (0.36 mL, 2.38 mmol) were added to the reaction mixture which was stirred for 12 h at 60 °C. Brine (~100.0 mL) was added to the reaction mixture and washed with EtOAc (3 × 30 mL). The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent evaporated under reduced pressure. Flash column chromatography afforded the yellow solid **6a** (0.71 g, 72%). m.p. 56–60 °C. R<sub>f</sub>: 0.4 (Hex/EtOAc 3:7).  $^1\text{H}$  NMR: (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.05–7.95 (m, 2 Ar–H), 7.72–7.56 (m, 4 Ar–H), 7.54–7.35 (m, 3 Ar–H), 5.32–5.20 (m, 1 H), 5.18–5.07 (m, 1 H), 4.55–4.30 (m, 2 H), 3.07–2.95 (m, 1 H), 2.93–2.78 (m, 1 H), 2.77–2.52 (m, 8 H), 2.45–2.21 (m, 2 H), 1.45–1.11 (m, 1 H), 0.97–0.82 (m, 1 H) ppm.  $^{13}\text{C}$  NMR: (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 194.03 (C=O), 175.66 (C=O), 165.69 (C=O), 146.27 (C), 143.67 (C), 139.61 (C), 136.81 (C), 130.11 (2 CH), 128.91 (2 CH), 128.26 (CH), 127.48 (C), 127.19 (2 CH), 127.15 (2 CH), 83.26 (CH), 77.13 (CH), 51.66 ( $\text{CH}_2$ ), 48.57 (CH), 41.21 (CH), 37.68 ( $\text{CH}_2$ ), 35.33 ( $\text{CH}_2$ ), 27.58 ( $\text{CH}_3$ ), 9.09 (Ar- $\text{CH}_3$ ) ppm. MS-EI<sup>+</sup> *m/z* (%): 459 [ $\text{M}^+$ ], 181 (15), 149 (14), 91 (12), 71 (22), 57 (42), 48 (100), 41 (50).

#### 4.1.5. (3*aR*,4*S*,5*R*,6*aS*)-4-((4-benzoyl-5-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-5-yl biphenyl-4-carboxylate (6*b*)

The alkyl halide **5** (1.0 g, 2.16 mmol) and sodium azide (0.16 g, 2.38 mmol) were added to anhydrous dimethylformamide (17.0 mL). The reaction mixture was stirred at 60 °C for 6 h under nitrogen atmosphere. After this time, TLC indicated the disappearance of the starting material. Then, 2-benzoylacetophenone (0.54 g, 2.38 mmol) and DBU (0.36 mL, 2.38 mmol) were added to the reaction mixture which was stirred for 12 h at 60 °C. Brine (~100.0 mL) was added to the reaction mixture and washed with EtOAc (3 × 30 mL). The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent evaporated under reduced pressure. Flash column chromatography afforded the slightly yellow solid **6b** (0.84 g, 67%). m.p. 71–76 °C. R<sub>f</sub>: 0.55 (Hex/EtOAc 3:7).  $^1\text{H}$  NMR: (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.24–8.22 (m, 1 Ar–H), 8.22–8.21 (m, 1 Ar–H), 7.93 (d, *J* = 2.0 Hz, 1 Ar–H), 7.91 (d, *J* = 2.0 Hz, 1 Ar–H), 7.65–7.64 (m, 1 Ar–H), 7.63–7.62 (m, 1 Ar–H), 7.61–7.59 (m, 1 Ar–H), 7.61–7.56 (m, 1 Ar–H), 7.58–7.55 (m, 1 Ar–H), 7.53–7.49 (m, 3 Ar–H), 7.50–7.45 (m, 2 Ar–H), 7.48–7.43 (m, 2 Ar–H), 7.46–7.39 (m, 3 Ar–H), 5.16–5.12 (m, 1 H), 5.01 (td, *J* = 6.5, 2.2 Hz, 1 H), 4.53 (dd, *J* = 14.1, 6.9 Hz, 1 H), 4.44 (dd, *J* = 14.2, 7.7 Hz, 1 H), 2.84–2.79 (m, 2 H), 2.63–2.52 (m, 2 H), 2.28–2.21 (m, 1 H), 2.19–2.13 (m, 1 H) ppm.  $^{13}\text{C}$  NMR: (125 MHz,  $\text{CDCl}_3$ )  $\delta$  = 186.10 (C=O), 175.55 (C=O), 165.50 (C=O), 146.22 (C), 143.82 (C), 141.93 (C), 139.71 (C), 136.83 (C), 133.14 (C), 130.61 (2  $\text{CH}_2$ ), 130.37 (CH), 130.15 (2  $\text{CH}_2$ ), 129.54 (2  $\text{CH}_2$ ), 129.16 (2  $\text{CH}_2$ ), 128.93 (2  $\text{CH}_2$ ), 128.28 (C), 128.25 (2  $\text{CH}_2$ ), 127.58 (CH), 127.27 (2  $\text{CH}_2$ ), 127.14 (2  $\text{CH}_2$ ), 125.90 (CH), 82.91 (CH), 77.21 (CH), 51.59 ( $\text{CH}_2$ ), 49.21 (CH), 41.11 (CH), 37.61 ( $\text{CH}_2$ ), 35.12 ( $\text{CH}_2$ ) ppm.

#### 4.1.6. (3*aR*,4*S*,5*R*,6*aS*)-4-((4-acetyl-5-methyl-1*H*-1,2,3-triazol-1-yl)methyl)-5-hydroxyhexahydro-2*H*-cyclopenta[*b*]furan-2-one (7*a*)

To a solution of ester **6a** (0.6 g, 1.31 mmol) in MeOH (5.0 mL) was added a catalytic amount of DBN (0.008 mL, 0.065 mmol). The reaction mixture was stirred at room temperature for 12 h. Then solvent was removed under reduced pressure. The crude was purified by flash column chromatography to give the thick yellow oil **7a** (0.32 g, 87%). R<sub>f</sub>: 0.3 (Hex/EtOAc 5:95).  $^1\text{H}$  NMR: (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 4.94 (td, *J* = 6.8, 3.1 Hz, 1 H), 4.42–4.29 (m, 2 H), 4.03 (q, *J* = 6.8 Hz, 1 H), 2.79–2.72 (m, 2 H), 2.69 (s, 3 H), 2.61 (s, 3 H), 2.51 (dt, *J* = 14.9, 6.8 Hz, 1 H), 2.30 (p, *J* = 7.0 Hz, 1 H), 2.26–2.17 (m, 2 H), 2.05 (ddd, *J* = 14.9, 6.8, 3.2 Hz, 1 H) ppm.  $^{13}\text{C}$  NMR: (125 MHz,  $\text{CDCl}_3$ )  $\delta$  = 194.17 (C=O), 176.19 (C=O), 143.68 (C), 137.03 (C), 82.13 (CH), 74.36 (CH), 52.68 ( $\text{CH}_2$ ), 48.08 (CH), 40.51 ( $\text{CH}_2$ ), 40.34 (CH), 34.66 ( $\text{CH}_2$ ), 27.72 ( $\text{CH}_3$ ), 9.13 ( $\text{CH}_3$ ) ppm. MS-EI<sup>+</sup> *m/z* (%): 279 [ $\text{M}^+$ ] (20), 167 (77), 148 (35), 127 (84), 112 (32), 85 (85), 70 (87), 55 (81), 41 (83).

#### 4.1.7. (3*aR*,4*S*,5*R*,6*aS*)-4-((4-benzoyl-5-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)-5-hydroxyhexahydro-2*H*-cyclopenta[*b*]furan-2-one (7*b*)

This compound was prepared from **6b** (0.7 g, 1.2 mmol) according to the synthetic procedure for **7a**. The crude was purified by flash column chromatography to afford the thick yellow oil **7b** (0.392 g, 81%). R<sub>f</sub>: 0.35 (Hex/EtOAc 1:9).  $^1\text{H}$  NMR: (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.96–7.93 (m, 3 Ar–H), 7.69–7.66 (m, 1 Ar–H), 7.64–7.61 (m, 1 Ar–H), 7.50–7.42 (m, 5 Ar–H), 3.57–3.51 (m, 2 H), 3.48–3.41 (m, 3 H), 3.40–3.35 (m, 3 H), 2.63–2.57 (m, 2 H), 2.18 (s, 1 OH), 1.80–1.75 (m, 1 H) ppm.  $^{13}\text{C}$  NMR: (125 MHz,  $\text{CDCl}_3$ )  $\delta$  = 177.34 (C=O), 166.93 (C=O), 143.88 (C), 140.33 (C), 134.53 (C), 131.16 (2 CH), 128.84 (2 CH), 128.47 (2 CH), 127.60 (C), 127.20 (CH), 127.16 (CH), 127.07 (2 CH), 77.42 (CH), 77.22 (CH), 49.62 ( $\text{CH}_2$ ), 45.00 (CH), 37.15 (CH), 35.31 (2 CH), 29.96 ( $\text{CH}_2$ ) ppm. MS-EI<sup>+</sup> *m/z* (%): 351 [ $\text{C}_{19}\text{H}_{17}\text{N}_3\text{O}_4$ ] (38), 52 [ $\text{C}_4\text{H}_4$ ] (14), 183 [ $\text{C}_8\text{H}_4\text{N}_2\text{O}_3$ ] (72), 276 (80), 246 (22), 199 (90), 152 (88), 127 (100), 99 (60), 69 (80), 55 (97).

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## Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.bioorg.2016.09.003>.

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