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An efficient method for the stereoselective synthesis of *N*-substituted trihydroxypiperidine derivatives promoted by *p*-TsOH

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ABSTRACT

An effective and facile method for the synthesis of *N*-substituted trihydroxypiperidine derivatives is described. The Mannich-type reaction of protected 5-*O*-tosylate pentoses with amines and ketones in the presence of *p*-TsOH provides convenient access to the stereoselective synthesis of *N*-substituted iminosugar *C*-glycosides as potential glucosidase inhibitors in good to excellent yields.

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1. Introduction

Polyhydroxypiperidines, usually referred to as iminosugars (or azasugars), are a family of carbohydrate mimetics in which oxygen present on the ring has been replaced by a nitrogen atom.¹ Since the discovery of the first polyhydroxypiperidine, Nojirimycin, as a powerful glycosidase inhibitor in the 1960s, iminosugars have been attractive target compounds for both synthetic chemists and biochemists.^{2,3} Both naturally occurring (e.g., DNJ, Fagomine) and synthetic polyhydroxylated piperidines display a wide range of interesting biological activities, especially, their inhibitory activity towards carbohydrate-processing enzymes⁴ and have been demonstrated to have a great potential as drugs to treat a variety of carbohydrate-mediated diseases such as diabetes⁵, Gaucher's disease⁶, cancer metastasis⁷, viral infections⁸. For example, iminosugar derivatives *N*-hydroxyethyl-1-deoxynojirimycin (Miglitol)⁹ and *N*-butyl-1-deoxynojirimycin (Zavestca)⁶ have been synthesized as drugs to treat type II diabetes and Gaucher's disease, respectively. In addition, recent biological studies have indicated that *N*-substituted aza-*C*-glycosides, *N*-substituted

iminosugars with a *C*-linked aglycon, often possess improved inhibition specificity and membrane permeability.¹⁰ In addition, properly protected and functionalized iminosugar *C*-glycosides could be useful building blocks for the synthesis of more complex iminosugar conjugates.¹¹ Thus, the design of a simple and efficient approach to synthesize *N*-substituted iminosugars for a wide spectrum of biological evaluation is an important point.¹²

D-ribose tosylate (**1a**) is an important precursor compound for the synthesis of *N*-substituted iminosugar *C*-glycosides. In 2014, Sundarababu Baskaran and co-workers¹³ reported the synthesis of iminosugar aromatic *C*-glycosides from **1a** (Scheme 1a). Also in 2014, Xiang-Guo Hu and co-workers¹⁴ reported the synthesis of trihydroxypiperidine α -iminonitrile which could react with Grignard reagent to afford iminosugar *C*-glycosides catalyzed by AgBF₄ (Scheme 1b). Previously, we have reported the synthesis of *N*-substituted trihydroxypiperidine β -aminoketones from 5-alkylamine-1-*C*-(2'-oxoalkyl)-glycosides, which obtained from D-ribose and D-xylose, by subsequent base-mediated β -elimination and intramolecular Michael addition (Scheme 2)^{1b,2c,10d}, and we found that these compounds have good glucosidase inhibitory activities. Although we successfully obtained the *N*-substituted iminosugar *C*-glycosides, the synthetic route was too long, about 10 steps. Based on the recent report on the simple synthesis of *N*-substituted iminosugar

Fig.1. Natural and synthetic iminosugars as glycosidase inhibitors

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(a) Sundarababu Baskaran, 2014

(b) Xiang-Guo Hu, 2014

Scheme 1 Synthesis of *N*-substituted iminosugar *C*-glycosides from D-ribose tosylate.

C-glycosides from D-ribose tosylate (**1a**), herein, we present a similar strategy to stereoselectively synthesize this type of *N*-substituted iminosugar *C*-glycosides *via* Mannich-type reaction from simple and readily available tosylate (**1a**), amines and ketones (Scheme 2).

Our Previous Work **This Work** **Scheme 2** Synthesis of *N*-substituted trihydroxypiperidine β-aminoketones**2. Results and discussion**

The screening studies were performed with D-ribose tosylate (**1a**), L-1-phenylethylamine (**2a**) and acetone (**3a**) as model substrates. As shown in Table 1, when acetone (**3a**) acted as reagent and solvent, the three-component reaction of **1a** with **2a** promoted by L-proline at room temperature just afforded trace amounts of the desired product **4a** (Table 1, Entry 2), but when warmed to 60 °C, it could afford the corresponding *N*-substituted iminosugar *C*-glycoside **4a** in 89% yield (Table 1, Entry 3). Also, with some other Lewis acids such as BF₃·OEt₂, Cu(OTf)₂, Zn(OTf)₂, AgOTf, TMSOTf, and BiCl₃, the product **4a** could be obtained in good yields at 60 °C (Table 1, Entries 4–9). Interesting, the Brønsted acid *p*-TsOH could produce **4a** in 93% yield, which act as the superior catalyst (Table 1, Entry 10). Screening of solvents showed that acetone gave the best yield of the product, but when other ketones act as the reagent, acetone could not be used as solvent. To our delight, *p*-TsOH could give the product in 89% yield in chloroform (Table 1, Entries 13), so we decided to use acetone and chloroform as solvent respectively when different ketones were used as reagent. When catalyst loading was lowered from 50 mol % to 30 mol %, the yield slightly decreased (Table 1, Entry 17–18). The structure and stereoselectivity of **4a** was confirmed by extensive studies of the NMR spectra.

Under the optimal reaction conditions, we then extended the scope of substrates to different combinations of amines and ketones.¹⁵ The results at this scope are summarized in Table 2. Firstly, various benzylamines including α-substituted chiral benzylamines (**2a**, **2b**), aromatic mono-substituted benzylamines (**2d**, **2e**), aromatic di-substituted benzylamines (**2f–2h**) and benzylamine **2c** with D-ribose tosylate **1a** and acetone **3a**

Table 1 Screening studies of reaction of D-ribose tosylate (**1a**) with L-1-phenylethylamine (**2a**) and acetone (**3a**)^a

Entry	Catalyst	Solvent	T(°C)	Yield (%) ^b
1	—	Acetone	r.t.-60	0
2	L-Proline	Acetone	r.t.	trace
3	L-Proline	Acetone	60	89
4	BF ₃ ·OEt ₂	Acetone	60	88
5	Cu(OTf) ₂	Acetone	60	74
6	Zn(OTf) ₂	Acetone	60	82
7	AgOTf	Acetone	60	75
8	TMSOTf	Acetone	60	78
9	BiCl ₃	Acetone	60	84
10	<i>p</i> -TsOH	Acetone	60	93
11	<i>p</i> -TsOH	THF	60	66
12	<i>p</i> -TsOH	CH ₃ CN	60	47
13	<i>p</i> -TsOH	CHCl ₃	60	89
14	<i>p</i> -TsOH	Toluene	60	47
15	<i>p</i> -TsOH	DMF	60	35
16	<i>p</i> -TsOH	1,4-dioxane	60	Trace
17 ^c	<i>p</i> -TsOH	Acetone	60	86
18 ^c	<i>p</i> -TsOH	CHCl ₃	60	81

^a Reactions were performed with 0.29 mmol of D-ribose tosylate (**1a**), 0.58 mmol of L-1-phenylethylamine (**2a**), 0.87 mmol of acetone (**3a**) and 50 mol % of catalyst in 3.0 mL of solvent; ^b Isolated yield; ^c 30 mol % of catalyst was used; r.t. = room temperature.

could smoothly give the corresponding *N*-substituted trihydroxypiperidine derivatives (**4a–4h**) in good to excellent yields (Table 2, Entries 1–8). Alkylamines such as isobutylamine **2i** could also be employed in the Mannich-type reaction to afford the iminosugar derivative **4i** in 77% yield (Table 2, Entry 9). However, no reaction occurred when aniline and *p*-toluenesulfonamide were used, possibly due to their poor nucleophilicity. Subsequently, we extended this reaction to

Table 2 Synthesis of piperidine derivatives by the Mannich-type reaction of D-ribose tosylate **1a** with amines **2a–2j** and ketones **3a–3d**^{a,b}

Entry	R ₁	R ₂	Product	Yield (%) ^b
1	L-1-Phenylethyl (2a)	Methyl (3a)	4a	93
2	(1R)-2-hydroxy-1-phenylethyl (2b)	Methyl (3a)	4b	99
3	Benzyl (2c)	Methyl (3a)	4c	84
4	4-Methoxybenzyl (2d)	Methyl (3a)	4d	55
5	4-Methylbenzyl (2e)	Methyl (3a)	4e	81
6	3,4-Dichlorobenzyl (2f)	Methyl (3a)	4f	80
7	2-Chloro-4-fluoro-benzyl (2g)	Methyl (3a)	4g	82
8	2,4-Difluorobenzyl (2h)	Methyl (3a)	4h	72
9	Isobutyl (2i)	Methyl (3a)	4i	77
10	L-1-Phenylethyl (2a)	Ethyl (3b)	4j	76
11	4-Methoxybenzyl (2d)	Ethyl (3b)	4k	73
12	4-Methylbenzyl (2e)	Ethyl (3b)	4l	52
13	2-Chloro-4-fluoro-benzyl (2g)	Ethyl (3b)	4m	81
14	2,4-Difluorobenzyl (2h)	Ethyl (3b)	4n	78
15	L-1-Phenylethyl (2a)	Isobutyl (3c)	4o	83
16	Propargyl(2j)	Cyclopropyl (3d)	4p	75

^a All reactions were performed with 0.29 mmol of D-ribose tosylate **1a**, 0.58 mmol of amines **2**, 0.87 mmol of ketones **3** and 50 mol% of *p*-TsOH in 3.0 mL of solvent at 60 °C for 24 h unless otherwise noted; ^b Isolated yield.

other ketones such as 2-butanone **3b**, methylisobutylketone **3c** and cyclopropyl methanone **3d**, which could also give the *N*-

substituted iminosugar C-glycosides **4j–4p** in moderate to good yields with good stereoselectivities (Table 2, Entries 10–16).

Table 3 *p*-TsOH promoted Mannich-type reaction of D-lyxose tosylate **1b** with amines **2** and ketones **3**^{a,b}

^a All reactions were performed with 0.29 mmol of D-lyxose tosylate **1b**, 0.58 mmol of amines **2**, 0.87 mmol of ketones **3** and 50 mol% of *p*-TsOH in 3.0 mL of solvent at 60 °C for 24 h unless otherwise noted; ^b Isolated yield.

Next, the scope of the Mannich-type reaction was further investigated by using D-lyxose tosylate **1b**, and the results are provided in Table 3. Satisfactorily, the D-lyxose tosylate **1b** is also a suitable substrate for the Mannich-type reaction. Under the standard reaction conditions, *N*-substituted trihydroxypiperidine derivatives (**5a–5g**) were obtained in moderate to good yields with good stereoselectivities (61%–94%).

Fig. 2. The conformation and key NOEs of *N*-substituted trihydroxypiperidine derivatives

The stereochemistry of the products were determined by the NMR and NOE spectra (**Fig. 2**). Nojirimycin and 1-deoxynojirimycin are known to exist in ⁴C₁ conformation. However, in case of compounds **4a** and **5b** the presence of –CH₂COCH₃ groups, on adjacent atoms, increases the bulk in the molecule. Therefore, it was thought to derive the conformations of **4a** and **5b** using ¹H NMR spectral data. The coupling constants determined from the 600 MHz ¹H NMR spectra. In case of **4a**, appearance of two distinct doublet of doublets for 1-Ha at δ2.38 (*J*_{1a,1e}=12.2 and *J*_{1a,2}=5.3 Hz) and for 1-He at δ2.51

(*J*_{1e,1a}=12.2 and *J*_{1e,2}=9.3 Hz) were informative. The middle coupling constant (*J*_{1e,2}=9.3 Hz) for the 1-H equatorial proton clearly requires 2-H proton to be equatorial. In substrate **1a**, the relative stereochemistry of the substituents at C-2, C-3 and C-4 is *cis*-form and the same stereochemistry is retained in the product formation. In addition, the small coupling constant between 4-H and 5-H (*J*_{4,5}=3.9 Hz) clearly requires 5-H proton to be equatorial. This confirms that compound **4a** exists in ⁴C₁ conformation and –CH₂COCH₃ substituent at C-5 is axial. In case of **5b**, the appearance of doublet of doublets for 3-H at δ3.80 (*J*_{2,3}=7.6 Hz and *J*_{3,4}=5.4 Hz) indicated the *trans*-diaxial of 2-H and 3-H protons. In addition, 1-Ha appeared as triplet at δ2.39 (*J*_{1a,1e}=*J*_{1a,2}=11.2), wherein the large coupling constant *J*_{1a,2}=11.2 Hz requires *trans*-diaxial relation with 2-H proton. This is clear indicative of the fact that compound **5b** exist in ⁴C₁ conformation. The small coupling constant between 4-H and 5-H (*J*_{4,5}=3.3 Hz) clearly requires 5-H proton to be equatorial and suggestive of the fact that –CH₂COCH₃ substituent at C-5 is axial.

Based on the above results, a plausible mechanism is proposed for the formation of *N*-substituted trihydroxypiperidine derivatives under the *p*-TsOH promoted conditions (Scheme 3). Firstly, under acidic condition, the tosyl hemiacetal through proton transfer loses a molecule of water to give the cyclic hemiaminal **A**. Then the hemiaminal ring opens to give the open-chain imine intermediate **B**, with subsequent intramolecular S_N2 displacement of the tosylate group to form the electrophilic cyclic iminium ion intermediate **C**. The α-carbon of enolized ketones carries out a preferred “*si*-facial” attack at the iminium ion carbon with a Mannich-type reaction to give rise to the formation of *N*-substituted trihydroxypiperidine derivatives **4**. The alternative “*re*-facial” attack expected to be disfavored due to the steric hindrance of the isopropylidene functionality.¹⁶

Scheme 3 Possible reaction mechanism for the formation of *N*-substituted iminosugar C-glycosides promoted by *p*-TsOH.

3. Conclusion

In conclusion, we have developed a Mannich-type reaction promoted by *p*-TsOH using protected 5-*O*-tosylate pentoses as reagent, which afforded a series of *N*-substituted trihydroxypiperidine derivatives in moderate to good yields with good stereoselectivities (52%–99%). This methodology provides convenient access to the synthesis of a wide variety of *N*-substituted iminosugar derivatives as potential glucosidase

inhibitors. The investigations of the biological activities of these compounds will be undertaken.

4. Experimental section

4.1 General information

All commercially sourced reagents were used as supplied unless otherwise stated. Thin-layer chromatography (TLC) was performed using silica gel GF254 precoated plates (0.20 mm thickness). Visualization on TLC was achieved by UV light (254 nm) and a typical TLC indication solution (5% sulfuric acid in ethanol). Flash chromatography was performed on silica gel 90, 200–300 mesh. Optical rotations were measured on a Perkin Elmer M341 Digital Polarimeter. ^1H and ^{13}C NMR spectra (400 and 100 MHz, respectively) were recorded on a Bruker Avance 400 spectrometer with tetramethylsilane (TMS) as the internal standard (CDCl_3 , $\delta\text{H} = 7.26$ ppm and $\delta\text{C} = 77.0$ ppm). ESI-HRMS spectra were recorded on a BioTOF Q instrument.

4.2 General procedure for preparation of *N*-substituted iminosugar C-glycosides **4** and **5**

To a stirred solution of tosylate **1** (100 mg, 0.29 mmol) in Acetone or CHCl_3 (3 mL) was slowly added amine **2** (0.58 mmol) and ketone **3** (0.87 mmol). Then *p*-TsOH (25 mg, 0.145 mmol) was added to the reaction mixture. The resultant mixture was stirred at 60 °C for 24 h until the reaction was completed as indicated by TLC. The reaction mixture was concentrated in vacuo, and then extracted with saturated aqueous NaHCO_3 and CH_2Cl_2 . The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give **4** or **5** as syrups.

4.2.1. 1-((3*aR*, 4*R*, 7*S*, 7*aS*)-7-hydroxy-2, 2-dimethyl-5-((*R*)-1-phenylethyl)hexahydro-[1,3]dioxolo [4,5-*c*]pyridine-4-yl)propan-2-one (4a**).** Obtained as a colorless syrup (89 mg, 93%); $[\alpha]_{\text{D}}^{20} -25.7$ (c 0.54, CHCl_3); ^1H NMR (600 MHz, CDCl_3) δ 7.35–7.28 (m, 4H), 7.25–7.21 (m, 1H), 4.65 (dd, $J = 6.1$, 3.9 Hz, 1H), 4.45 (dd, $J = 6.2$, 0.5 Hz, 1H), 4.17 (td, $J = 6.6$, 3.9 Hz, 1H), 4.12 (dd, $J = 9.2$, 5.3 Hz, 1H), 3.79 (q, $J = 6.6$ Hz, 1H), 2.87 (dd, $J = 6.9$, 3.4 Hz, 2H), 2.51 (dd, $J = 12.2$, 9.3 Hz, 1H), 2.38 (dd, $J = 12.2$, 5.3 Hz, 1H), 2.19 (s, 3H), 1.46 (s, 3H), 1.37 (d, $J = 6.6$ Hz, 3H), 1.27 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 206.6, 144.8, 128.5, 127.1, 126.7, 112.4, 83.8, 83.1, 81.0, 75.4, 58.5, 46.9, 43.0, 30.6, 26.2, 24.9, 24.4; ESI-HRMS: m/z calcd for $\text{C}_{19}\text{H}_{28}\text{NO}_4$ $[\text{M} + \text{H}]^+$: 334.2013; found: 334.2004.

4.2.2. 1-((3*aR*, 4*R*, 7*S*, 7*aS*)-7-hydroxy-5-((*S*)-2-hydroxy-1-phenylethyl)-2, 2-dimethylhexahydro-[1,3]dioxolo [4,5-*c*]pyridine-4-yl)propan-2-one (4b**).** Obtained as a colorless syrup (100 mg, 99%); $[\alpha]_{\text{D}}^{20} -35.2$ (c 0.71, CDCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.37–7.30 (m, 4H), 7.30–7.26 (m, 1H), 4.68 (dd, $J = 6.0$, 3.9 Hz, 1H), 4.47 (d, $J = 6.1$ Hz, 1H), 4.20 (td, $J = 6.6$, 3.9 Hz, 1H), 4.13 (dd, $J = 8.8$, 5.7 Hz, 1H), 3.79 (dd, $J = 8.8$, 4.1 Hz, 1H), 3.70 (dd, $J = 10.9$, 4.1 Hz, 1H), 3.58 (dd, $J = 10.8$, 8.9 Hz, 1H), 2.89 (d, $J = 6.6$ Hz, 2H), 2.50 (dd, $J = 12.3$, 9.1 Hz, 1H), 2.45 (dd, $J = 12.3$, 5.8 Hz, 1H), 2.20 (s, 3H), 1.48 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 206.8, 140.3, 128.6, 127.7, 127.4, 112.3, 83.7, 83.2, 81.0, 75.4, 67.0, 65.0, 46.8, 43.0, 30.6, 26.2, 24.9; ESI-HRMS: m/z calcd for $\text{C}_{19}\text{H}_{28}\text{NO}_5$ $[\text{M} + \text{H}]^+$: 350.1962; found: 350.1962.

4.2.3. 1-((3*aR*, 4*R*, 7*S*, 7*aS*)-5-benzyl-7-hydroxy-2, 2-dimethylhexahydro-[1,3]dioxolo [4,5-*c*]pyridine-4-yl)propan-2-one (4c**).** Obtained as a colorless syrup (78 mg, 84%); $[\alpha]_{\text{D}}^{20} +6.8$ (c 0.50, CDCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.39–7.31 (m, 4H), 7.28–7.22 (m, 1H), 4.73 (dd, $J = 6.1$, 3.9 Hz, 1H), 4.55 (d, $J = 6.1$ Hz, 1H), 4.25–4.17 (m, 2H), 3.84 (q, $J = 13.4$ Hz,

2H), 2.90 (dd, $J = 6.6$, 2.2 Hz, 2H), 2.67 (dd, $J = 12.3$, 9.1 Hz, 1H), 2.59 (dd, $J = 12.3$, 5.1 Hz, 1H), 2.22 (s, 3H), 1.50 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 206.6, 139.8, 128.4, 128.1, 127.1, 112.4, 83.8, 82.7, 81.1, 75.5, 53.6, 48.3, 43.0, 30.6, 26.2, 24.9; ESI-HRMS: m/z calcd for $\text{C}_{18}\text{H}_{26}\text{NO}_4$ $[\text{M} + \text{H}]^+$: 320.1856; found: 320.1858.

4.2.4. 1-((3*aR*, 4*R*, 7*S*, 7*aS*)-7-hydroxy-5-(4-methoxybenzyl)-2, 2-dimethylhexahydro-[1,3]dioxolo [4,5-*c*]pyridine-4-yl)propan-2-one (4d**).** Obtained as a colorless syrup (56 mg, 55%); $[\alpha]_{\text{D}}^{20} +5.0$ (c 0.30, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.31 (d, $J = 8.6$ Hz, 2H), 6.89 (d, $J = 8.6$ Hz, 2H), 4.74 (dd, $J = 6.1$, 3.9 Hz, 1H), 4.55 (d, $J = 6.0$ Hz, 1H), 4.26 (dd, $J = 9.3$, 5.3 Hz, 1H), 4.24–4.17 (m, 1H), 3.89–3.79 (m, 5H), 2.91 (d, $J = 6.6$ Hz, 2H), 2.68 (dd, $J = 12.5$, 9.3 Hz, 1H), 2.62 (dd, $J = 12.5$, 5.2 Hz, 1H), 2.21 (s, 3H), 1.49 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 206.7, 158.7, 131.7, 129.3, 113.8, 112.4, 83.8, 82.6, 81.0, 75.4, 55.3, 52.9, 48.1, 43.0, 30.6, 26.7, 26.2, 24.9; ESI-HRMS: m/z calcd for $\text{C}_{19}\text{H}_{28}\text{NO}_5$ $[\text{M} + \text{H}]^+$: 350.1962; found: 350.1964.

4.2.5. 1-((3*aR*, 4*R*, 7*S*, 7*aS*)-7-hydroxy-2, 2-dimethyl-5-(4-methylbenzyl)hexahydro-[1,3]dioxolo [4,5-*c*]pyridine-4-yl)propan-2-one (4e**).** Obtained as a colorless syrup (79 mg, 81%); $[\alpha]_{\text{D}}^{20} +16.9$ (c 0.68, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.24 (d, $J = 7.9$ Hz, 2H), 7.15 (d, $J = 7.9$ Hz, 2H), 4.73 (dd, $J = 6.1$, 3.9 Hz, 1H), 4.54 (d, $J = 6.1$ Hz, 1H), 4.25–4.17 (m, 2H), 3.82 (q, $J = 13.3$ Hz, 2H), 2.90 (d, $J = 6.7$ Hz, 2H), 2.66 (dd, $J = 12.3$, 9.2 Hz, 1H), 2.58 (dd, $J = 12.4$, 5.1 Hz, 1H), 2.35 (s, 3H), 2.22 (s, 3H), 1.49 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 206.6, 136.8, 136.3, 129.2, 128.2, 112.4, 83.8, 82.4, 81.0, 75.5, 53.0, 47.8, 43.0, 30.6, 26.2, 24.9, 21.1; ESI-HRMS: m/z calcd for $\text{C}_{19}\text{H}_{28}\text{NO}_4$ $[\text{M} + \text{H}]^+$: 334.2013; found: 334.2016.

4.2.6. 1-((3*aR*, 4*R*, 7*S*, 7*aS*)-5-(3,4-dichlorobenzyl)-7-hydroxy-2, 2-dimethylhexahydro-[1,3]dioxolo [4,5-*c*]pyridine-4-yl)propan-2-one (4f**).** Obtained as a colorless syrup (90 mg, 80%); $[\alpha]_{\text{D}}^{20} +8.8$ (c 0.61, CDCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.46 (d, $J = 1.4$ Hz, 1H), 7.41 (d, $J = 8.2$ Hz, 1H), 7.19 (dd, $J = 8.2$, 1.5 Hz, 1H), 4.73 (dd, $J = 5.9$, 4.0 Hz, 1H), 4.53 (d, $J = 6.0$ Hz, 1H), 4.25–4.14 (m, 2H), 3.79 (s, 2H), 2.90 (d, $J = 6.5$ Hz, 2H), 2.63 (dd, $J = 12.2$, 9.3 Hz, 1H), 2.55 (dd, $J = 12.3$, 5.0 Hz, 1H), 2.22 (s, 3H), 1.50 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 206.5, 140.4, 132.4, 130.8, 130.4, 129.9, 127.3, 112.5, 83.7, 82.7, 81.1, 75.4, 52.3, 48.2, 42.9, 30.6, 26.2, 24.9; ESI-HRMS: m/z calcd for $\text{C}_{18}\text{H}_{24}\text{Cl}_2\text{NO}_4$ $[\text{M} + \text{H}]^+$: 388.1077; found: 388.1081.

4.2.7. 1-((3*aR*, 4*R*, 7*S*, 7*aS*)-5-(2-chloro-4-fluorobenzyl)-7-hydroxy-2, 2-dimethylhexahydro-[1,3]dioxolo [4,5-*c*]pyridine-4-yl)propan-2-one (4g**).** Obtained as a colorless syrup (88 mg, 82%); $[\alpha]_{\text{D}}^{20} +7.8$ (c 0.36, CDCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.40 (dd, $J = 8.5$, 6.2 Hz, 1H), 7.12 (dd, $J = 8.5$, 2.6 Hz, 1H), 6.98 (td, $J = 8.3$, 2.6 Hz, 1H), 4.74 (dd, $J = 6.0$, 3.9 Hz, 1H), 4.56 (d, $J = 6.1$ Hz, 1H), 4.28–4.13 (m, 2H), 3.92–3.84 (m, 2H), 2.90 (dd, $J = 6.6$, 2.3 Hz, 2H), 2.66 (dd, $J = 12.2$, 9.1 Hz, 1H), 2.58 (dd, $J = 12.2$, 5.1 Hz, 1H), 2.22 (s, 3H), 1.50 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 206.6, 133.3, 130.9, 117.0, 116.7, 114.1, 113.8, 112.5, 83.8, 82.8, 81.1, 75.5, 50.3, 48.3, 43.0, 30.6, 26.2, 24.9; ESI-HRMS: m/z calcd for $\text{C}_{18}\text{H}_{24}\text{ClFNO}_4$ $[\text{M} + \text{H}]^+$: 372.1372; found: 372.1375.

4.2.8. 1-((3*aR*, 4*R*, 7*S*, 7*aS*)-5-(2, 4-difluorobenzyl)-7-hydroxy-2, 2-dimethylhexahydro-[1,3]dioxolo [4,5-*c*]pyridine-4-yl)propan-2-one (4h**).** Obtained as a colorless syrup (74 mg, 72%); $[\alpha]_{\text{D}}^{20} +7.7$ (c 0.60, CDCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.35 (dd, $J = 15.1$, 8.4 Hz, 1H), 6.87 (td, $J = 8.3$, 2.3 Hz, 1H), 6.84–6.77 (m, 1H), 4.73 (dd, $J = 6.1$, 3.9 Hz, 1H), 4.55 (d, $J = 6.1$ Hz, 1H),

4.24–4.15 (m, 2H), 3.88–3.79 (m, 2H), 2.90 (d, $J = 6.6, 1.8$ Hz, 2H), 2.65 (dd, $J = 12.2, 9.1$ Hz, 1H), 2.57 (dd, $J = 12.3, 5.1$ Hz, 1H), 2.22 (s, 3H), 1.50 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 206.6, 103.9, 112.5, 111.2, 104.0, 103.7, 103.5, 83.8, 82.7, 81.1, 75.5, 48.2, 46.4, 43.0, 30.6, 26.2, 24.9; ESI-HRMS: m/z calcd for $\text{C}_{18}\text{H}_{24}\text{F}_2\text{NO}_4$ [$\text{M} + \text{H}$] $^+$: 356.1668; found: 356.1669.

4.2.9. 1-((3*aR*, 4*R*, 7*S*, 7*aS*)-7-hydroxy-5-isobutyl-2, 2-dimethylhexahydro-[1,3]dioxolo [4,5-*c*]pyridine-4-yl)propan-2-one (**4i**). Obtained as a colorless syrup (63 mg, 77%); $[\alpha]_{\text{D}}^{20} +5.2$ (c 0.44, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 4.74 (dd, $J = 6.0, 4.0$ Hz, 1H), 4.56 (d, $J = 6.1$ Hz, 1H), 4.24 (td, $J = 6.6, 4.0$ Hz, 1H), 4.16 (dd, $J = 9.0, 5.1$ Hz, 1H), 2.89 (dd, $J = 6.6, 2.2$ Hz, 2H), 2.66 (dd, $J = 12.4, 9.2$ Hz, 1H), 2.56 (dd, $J = 12.4, 5.1$ Hz, 1H), 2.49–2.35 (m, 2H), 2.20 (s, 3H), 1.76–1.65 (m, 1H), 1.49 (s, 3H), 1.32 (s, 3H), 0.91 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 206.6, 112.4, 83.8, 82.6, 81.1, 75.5, 57.8, 49.3, 43.1, 30.6, 28.2, 26.2, 24.9, 20.5; ESI-HRMS: m/z calcd for $\text{C}_{15}\text{H}_{28}\text{NO}_4$ [$\text{M} + \text{H}$] $^+$: 286.2013; found: 286.2011.

4.2.10. 1-((3*aR*, 4*R*, 7*S*, 7*aS*)-7-hydroxy-2, 2-dimethyl-5-((*R*)-1-phenylethyl)hexahydro-[1,3]dioxolo [4,5-*c*]pyridine-4-yl)butan-2-one (**4j**). Obtained as a colorless syrup (76 mg, 76%); $[\alpha]_{\text{D}}^{20} -24.6$ (c 0.69, CDCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.40–7.33 (m, 4H), 7.28–7.22 (m, 1H), 4.68 (dd, $J = 5.9, 4.0$ Hz, 1H), 4.47 (d, $J = 6.1$ Hz, 1H), 4.21 (td, $J = 6.6, 4.0$ Hz, 1H), 4.14 (dd, $J = 9.1, 5.3$ Hz, 1H), 3.80 (q, $J = 6.4$ Hz, 1H), 2.87 (d, $J = 6.6$ Hz, 2H), 2.58–2.47 (m, 3H), 2.39 (dd, $J = 12.2, 5.3$ Hz, 1H), 1.48 (s, 3H), 1.39 (d, $J = 6.6$ Hz, 3H), 1.30 (s, 3H), 1.09 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 209.4, 144.9, 128.5, 127.1, 126.7, 112.3, 83.8, 83.1, 81.1, 75.5, 58.5, 47.0, 41.7, 36.6, 26.2, 25.0, 24.5, 7.7; ESI-HRMS: m/z calcd for $\text{C}_{20}\text{H}_{30}\text{NO}_4$ [$\text{M} + \text{H}$] $^+$: 348.2169; found: 348.2173.

4.2.11. 1-((3*aR*, 4*R*, 7*S*, 7*aS*)-7-hydroxy-5-(4-methoxybenzyl)-2, 2-dimethylhexahydro-[1,3]dioxolo [4,5-*c*]pyridine-4-yl)butan-2-one (**4k**). Obtained as a colorless syrup (77 mg, 73%); $[\alpha]_{\text{D}}^{20} +8.7$ (c 0.39, CDCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.29 (d, $J = 8.5$ Hz, 2H), 6.88 (d, $J = 8.6$ Hz, 2H), 4.73 (dd, $J = 6.0, 3.9$ Hz, 1H), 4.54 (d, $J = 6.1$ Hz, 1H), 4.26–4.20 (m, 2H), 3.86–3.77 (m, 5H), 2.87 (d, $J = 6.7$ Hz, 2H), 2.66 (dd, $J = 12.4, 9.4$ Hz, 1H), 2.60 (dd, $J = 12.5, 5.1$ Hz, 1H), 2.50 (q, $J = 7.3$ Hz, 2H), 1.48 (s, 3H), 1.31 (s, 3H), 1.08 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 209.3, 158.9, 129.6, 113.9, 112.4, 83.7, 82.1, 81.1, 75.7, 55.3, 52.5, 47.5, 41.7, 36.5, 26.2, 24.9, 7.7; ESI-HRMS: m/z calcd for $\text{C}_{20}\text{H}_{30}\text{NO}_5$ [$\text{M} + \text{H}$] $^+$: 364.2118; found: 364.2118.

4.2.12. 1-((3*aR*, 4*R*, 7*S*, 7*aS*)-7-hydroxy-2, 2-dimethyl-5-(4-methylbenzyl)hexahydro-[1,3]dioxolo [4,5-*c*]pyridine-4-yl)butan-2-one (**4l**). Obtained as a colorless syrup (52 mg, 52%); $[\alpha]_{\text{D}}^{20} +14.9$ (c 0.61, CDCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.27 (d, $J = 7.9$ Hz, 2H), 7.16 (d, $J = 7.8$ Hz, 2H), 4.73 (dd, $J = 5.9, 3.9$ Hz, 1H), 4.54 (d, $J = 6.0$ Hz, 1H), 4.27–4.20 (m, 2H), 3.86 (q, $J = 13.3$ Hz, 2H), 2.88 (d, $J = 6.6$ Hz, 2H), 2.68 (dd, $J = 12.4, 9.4$ Hz, 1H), 2.61 (dd, $J = 12.5, 5.1$ Hz, 1H), 2.50 (q, $J = 7.3$ Hz, 2H), 2.35 (s, 3H), 1.48 (s, 3H), 1.31 (s, 3H), 1.08 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 209.3, 137.1, 129.3, 128.4, 112.4, 83.7, 81.9, 81.1, 75.7, 52.6, 47.3, 41.7, 36.5, 26.2, 24.9, 21.1, 7.7; ESI-HRMS: m/z calcd for $\text{C}_{20}\text{H}_{30}\text{NO}_4$ [$\text{M} + \text{H}$] $^+$: 348.2169; found: 348.2171.

4.2.13. 1-((3*aR*, 4*R*, 7*S*, 7*aS*)-5-(2-chloro-4-fluorobenzyl)-7-hydroxy-2, 2-dimethylhexahydro-[1,3]dioxolo [4,5-*c*]pyridine-4-yl)butan-2-one (**4m**). Obtained as a colorless syrup (89 mg, 81%); $[\alpha]_{\text{D}}^{20} +10.7$ (c 0.65, CDCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.46 (dd, $J = 8.4, 6.2$ Hz, 1H), 7.13 (dd, $J = 8.5, 2.5$ Hz, 1H), 7.00 (td, $J = 8.3, 2.5$ Hz, 1H), 4.74 (dd, $J = 6.0, 3.9$ Hz, 1H),

4.56 (d, $J = 6.1$ Hz, 1H), 4.28–4.18 (m, 2H), 3.93 (s, 2H), 2.88 (d, $J = 6.6$ Hz, 2H), 2.69 (dd, $J = 12.3, 9.2$ Hz, 1H), 2.62 (dd, $J = 12.3, 5.2$ Hz, 1H), 2.51 (q, $J = 7.3$ Hz, 2H), 1.49 (s, 3H), 1.32 (s, 3H), 1.08 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 209.2, 134.4, 131.2, 117.0, 116.8, 114.2, 114.0, 112.5, 83.7, 82.4, 81.1, 75.7, 50.0, 48.0, 41.7, 36.6, 26.2, 24.9, 7.6; ESI-HRMS: m/z calcd for $\text{C}_{19}\text{H}_{26}\text{ClFNO}_4$ [$\text{M} + \text{H}$] $^+$: 386.1529; found: 386.1528.

4.2.14. 1-((3*aR*, 4*R*, 7*S*, 7*aS*)-5-(2, 4-difluorobenzyl)-7-hydroxy-2, 2-dimethylhexahydro-[1,3]dioxolo [4,5-*c*]pyridine-4-yl)butan-2-one (**4n**). Obtained as a colorless syrup (84 mg, 78%); $[\alpha]_{\text{D}}^{20} +5.1$ (c 0.43, CDCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.40–7.31 (m, 1H), 6.90–6.84 (m, 1H), 6.84–6.77 (m, 1H), 4.73 (dd, $J = 6.1, 3.9$ Hz, 1H), 4.55 (dd, $J = 6.1, 0.8$ Hz, 1H), 4.23 (td, $J = 6.6, 4.0$ Hz, 1H), 4.18 (dd, $J = 9.0, 5.1$ Hz, 1H), 3.84 (s, 2H), 2.87 (d, $J = 6.7$ Hz, 2H), 2.65 (dd, $J = 12.2, 9.1$ Hz, 1H), 2.57 (dd, $J = 12.3, 5.1$ Hz, 1H), 2.51 (q, $J = 7.3$ Hz, 2H), 1.50 (s, 3H), 1.32 (s, 3H), 1.09 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 209.3, 130.9, 112.4, 111.1, 103.9, 103.7, 103.4, 82.7, 81.1, 75.6, 48.3, 46.4, 41.7, 36.5, 29.7, 26.2, 24.9, 7.6; ESI-HRMS: m/z calcd for $\text{C}_{19}\text{H}_{26}\text{F}_2\text{NO}_4$ [$\text{M} + \text{H}$] $^+$: 370.1824; found: 370.1826.

4.2.15. 1-((3*aR*, 4*R*, 7*S*, 7*aS*)-7-hydroxy-2, 2-dimethyl-5-((*R*)-1-phenylethyl)hexahydro-[1,3]dioxolo [4,5-*c*]pyridine-4-yl)-4-methylpentan-2-one (**4o**). Obtained as a colorless syrup (90 mg, 83%); $[\alpha]_{\text{D}}^{20} -20.2$ (c 0.62, CDCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.38–7.31 (m, 4H), 7.27–7.22 (m, 1H), 4.68 (dd, $J = 5.9, 4.0$ Hz, 1H), 4.47 (d, $J = 6.1$ Hz, 1H), 4.25–4.18 (m, 1H), 4.11 (dd, $J = 9.1, 5.3$ Hz, 1H), 3.78 (q, $J = 6.5$ Hz, 1H), 2.85 (d, $J = 7.0$ Hz, 2H), 2.52 (dd, $J = 12.0, 9.4$ Hz, 1H), 2.42–2.32 (m, 3H), 2.24–2.10 (m, 1H), 1.48 (s, 3H), 1.36 (d, $J = 6.5$ Hz, 3H), 1.30 (s, 3H), 0.95 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 208.8, 145.3, 128.4, 126.9, 126.6, 112.3, 83.8, 83.2, 81.0, 75.4, 58.5, 52.4, 47.1, 42.6, 26.2, 25.0, 24.6, 24.5, 22.6, 22.5; ESI-HRMS: m/z calcd for $\text{C}_{22}\text{H}_{33}\text{NO}_4$ [$\text{M} + \text{H}$] $^+$: 375.2410; found: 375.2410.

4.2.16. 1-Cyclopropyl-2-((3*aR*, 4*R*, 7*S*, 7*aS*)-7-hydroxy-2, 2-dimethyl-5-(prop-2-yn-1-yl)hexahydro-[1,3]dioxolo [4,5-*c*]pyridine-4-yl)ethan-1-one (**4p**). Obtained as a colorless syrup (64 mg, 75%); $[\alpha]_{\text{D}}^{20} -41.4$ (c 0.41, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 4.77 (dd, $J = 6.0, 3.9$ Hz, 1H), 4.58 (d, $J = 6.1$ Hz, 1H), 4.29 (td, $J = 6.5, 3.9$ Hz, 1H), 4.20 (dd, $J = 9.5, 4.7$ Hz, 1H), 3.56 (dd, $J = 17.1, 2.4$ Hz, 1H), 3.45 (dd, $J = 17.1, 2.4$ Hz, 1H), 3.11–2.96 (m, 2H), 2.85 (dd, $J = 12.2, 9.6$ Hz, 1H), 2.66 (dd, $J = 12.2, 4.8$ Hz, 1H), 2.26 (t, $J = 2.4$ Hz, 1H), 2.04–1.94 (m, 1H), 1.50 (s, 3H), 1.33 (s, 3H), 1.13–1.00 (m, 2H), 0.96–0.84 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 208.4, 112.5, 83.8, 82.3, 81.1, 75.5, 72.2, 47.3, 42.3, 37.9, 26.2, 24.9, 21.0, 10.8, 10.7; ESI-HRMS: m/z calcd for $\text{C}_{16}\text{H}_{23}\text{NO}_4$ [$\text{M} + \text{H}$] $^+$: 294.1700; found: 294.1696.

4.2.17. 1-((3*aS*, 4*S*, 7*S*, 7*aR*)-7-hydroxy-2, 2-dimethyl-5-((*R*)-1-phenylethyl)hexahydro-[1,3]dioxolo [4,5-*c*]pyridine-4-yl)propan-2-one (**5a**). Obtained as a colorless syrup (90 mg, 94%); $[\alpha]_{\text{D}}^{20} -25.8$ (c 0.50, CDCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.38–7.30 (m, 4H), 7.27–7.21 (m, 1H), 4.72 (dd, $J = 6.0, 3.7$ Hz, 1H), 4.61 (dd, $J = 6.0, 3.7$ Hz, 1H), 3.91 (td, $J = 6.6, 3.7$ Hz, 1H), 3.83 (q, $J = 6.5$ Hz, 1H), 3.63 (dt, $J = 8.0, 4.1$ Hz, 1H), 2.92 (dd, $J = 6.6, 3.5$ Hz, 2H), 2.82 (dd, $J = 12.3, 8.1$ Hz, 1H), 2.70 (dd, $J = 12.3, 4.6$ Hz, 1H), 2.21 (s, 3H), 1.45–1.35 (m, 6H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 206.4, 144.9, 128.4, 127.0, 126.8, 112.1, 81.1, 81.0, 80.8, 76.9, 58.8, 46.3, 42.5, 30.5, 25.8, 24.8, 24.5; ESI-HRMS: m/z calcd for $\text{C}_{19}\text{H}_{28}\text{NO}_4$ [$\text{M} + \text{H}$] $^+$: 334.2013; found: 334.2017.

4.2.18. 1-((3*aS*, 4*S*, 7*S*, 7*aR*)-7-hydroxy-2, 2-dimethyl-5-(prop-2-yn-1-yl)hexahydro-[1,3]dioxolo [4,5-*c*]pyridine-4-yl)propan-2-

one (**5b**). Obtained as a white solid (60 mg, 77%); $[\alpha]_{\text{D}}^{20} +28.8$ (c 0.25, CHCl_3); ^1H NMR (600 MHz, CDCl_3) δ 4.30 (dd, $J = 5.4$, 3.3 Hz, 1H), 3.88–3.82 (m, 1H), 3.80 (dd, $J = 7.6$, 5.4 Hz, 1H), 3.56 (dd, $J = 17.9$, 2.3 Hz, 1H), 3.38 (dd, $J = 17.9$, 2.3 Hz, 1H), 3.31–3.24 (m, 1H), 2.87 (dd, $J = 16.6$, 9.4 Hz, 1H), 2.83 (dd, $J = 11.7$, 4.6 Hz, 1H), 2.73 (dd, $J = 16.3$, 4.7 Hz, 1H), 2.39 (t, $J = 11.2$ Hz, 1H), 2.27 (t, $J = 2.4$ Hz, 1H), 2.20 (s, 3H), 1.49 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 206.7, 108.9, 79.9, 76.3, 74.7, 74.6, 70.5, 55.5, 54.4, 42.9, 42.3, 30.9, 28.4, 26.0; ESI-HRMS: m/z calcd for $\text{C}_{14}\text{H}_{21}\text{NO}_4$ $[\text{M} + \text{H}]^+$: 268.1543; found: 268.1544.

4.2.19. 1-((3aS, 4S, 7S, 7aR)-7-hydroxy-2, 2-dimethyl-5-((R)-1-phenylethyl)hexahydro-[1,3]dioxolo [4,5-c]pyridine-4-yl)butan-2-one (**5c**). Obtained as a colorless syrup (81 mg, 80%); $[\alpha]_{\text{D}}^{20} -31.8$ (c 0.56, CDCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.38–7.30 (m, 4H), 7.27–7.21 (m, 1H), 4.72 (dd, $J = 5.9$, 3.7 Hz, 1H), 4.61 (dd, $J = 5.9$, 3.7 Hz, 1H), 3.93 (td, $J = 6.8$, 3.8 Hz, 1H), 3.82 (q, $J = 6.5$ Hz, 1H), 3.62 (dt, $J = 7.9$, 4.2 Hz, 1H), 2.90 (dd, $J = 6.5$, 3.5 Hz, 2H), 2.82 (dd, $J = 12.2$, 8.1 Hz, 1H), 2.70 (dd, $J = 12.2$, 4.6 Hz, 1H), 2.50 (q, $J = 7.3$ Hz, 2H), 1.45–1.35 (m, 6H), 1.28 (s, 3H), 1.08 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 209.1, 145.0, 128.4, 126.9, 126.7, 112.1, 81.2, 81.1, 80.8, 77.0, 58.8, 46.3, 41.1, 36.4, 25.8, 24.8, 24.5, 7.6; ESI-HRMS: m/z calcd for $\text{C}_{20}\text{H}_{29}\text{NO}_4$ $[\text{M} + \text{H}]^+$: 347.2097; found: 347.2097.

4.2.20. 1-((3aS, 4S, 7S, 7aR)-7-hydroxy-2, 2-dimethyl-5-((R)-1-phenylethyl)hexahydro-[1,3]dioxolo [4,5-c]pyridine-4-yl)-4-methylpentan-2-one (**5d**). Obtained as a colorless syrup (88 mg, 81%); $[\alpha]_{\text{D}}^{20} -30.6$ (c 0.53, CDCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.38–7.30 (m, 4H), 7.27–7.21 (m, 1H), 4.73 (dd, $J = 6.1$, 3.7 Hz, 1H), 4.61 (dd, $J = 6.1$, 3.7 Hz, 1H), 3.95–3.90 (m, 1H), 3.83 (q, $J = 6.6$ Hz, 1H), 3.63 (dt, $J = 8.1$, 4.2 Hz, 1H), 2.95–2.85 (m, 2H), 2.82 (dd, $J = 12.2$, 8.2 Hz, 1H), 2.71 (dd, $J = 12.3$, 4.6 Hz, 1H), 2.38–2.31 (m, 2H), 2.22–2.13 (m, 1H), 1.45–1.37 (m, 6H), 1.27 (s, 3H), 0.94 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 208.5, 144.9, 128.4, 126.9, 126.7, 112.1, 81.1, 80.7, 80.8, 77.0, 58.7, 52.3, 46.3, 42.1, 25.8, 24.8, 24.6, 24.5, 22.6, 22.5; ESI-HRMS: m/z calcd for $\text{C}_{22}\text{H}_{33}\text{NO}_4$ $[\text{M} + \text{H}]^+$: 375.2410; found: 375.2410.

4.2.21. 1-((3aS, 4S, 7S, 7aR)-5-(3,4-dichlorobenzyl)-7-hydroxy-2, 2-dimethylhexahydro-[1,3]dioxolo [4,5-c]pyridine-4-yl)-4-methylpentan-2-one (**5e**). Obtained as a colorless syrup (101 mg, 81%); $[\alpha]_{\text{D}}^{20} -10.9$ (c 0.55, CDCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.47 (d, $J = 1.3$ Hz, 1H), 7.39 (d, $J = 8.2$ Hz, 1H), 7.18 (dd, $J = 8.2$, 1.4 Hz, 1H), 4.76 (dd, $J = 6.0$, 3.7 Hz, 1H), 4.68 (dd, $J = 6.0$, 3.7 Hz, 1H), 3.98–3.90 (m, 1H), 3.81 (q, $J = 13.8$ Hz, 2H), 3.64 (dd, $J = 9.8$, 6.2 Hz, 1H), 2.97–2.80 (m, 4H), 2.39–2.26 (m, 2H), 2.22–2.13 (m, 1H), 1.44 (s, 3H), 1.30 (s, 3H), 0.94 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 208.5, 140.4, 132.3, 130.7, 130.2, 130.0, 127.4, 112.1, 81.1, 81.0, 80.4, 77.0, 52.8, 52.3, 47.6, 42.0, 25.8, 24.8, 24.6, 22.6, 22.5; ESI-HRMS: m/z calcd for $\text{C}_{21}\text{H}_{29}\text{Cl}_2\text{NO}_4$ $[\text{M} + \text{H}]^+$: 429.1474; found: 429.1474.

4.2.22. 1-Cyclopropyl-2-((3aS, 4S, 7S, 7aR)-7-hydroxy-2, 2-dimethyl-5-(4-methylbenzyl)hexahydro-[1,3]dioxolo [4,5-c]pyridine-4-yl)ethan-1-one (**5f**). Obtained as a colorless syrup (64 mg, 61%); $[\alpha]_{\text{D}}^{20} -24.1$ (c 0.29, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.26 (d, $J = 7.9$ Hz, 2H), 7.15 (d, $J = 7.8$ Hz, 2H), 4.74 (dd, $J = 6.0$, 3.6 Hz, 1H), 4.69 (dd, $J = 6.0$, 3.6 Hz, 1H), 3.97–3.90 (m, 1H), 3.90–3.82 (m, 2H), 3.74–3.67 (m, 2H), 3.11–2.87 (m, 4H), 2.35 (s, 3H), 2.01–1.95 (m, 1H), 1.45 (s, 3H), 1.31 (s, 3H), 1.12–1.02 (m, 2H), 0.94–0.87 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 208.2, 137.2, 129.2, 128.6, 112.3, 81.2, 81.1, 79.6, 77.2, 77.1, 53.3, 47.1, 41.7, 25.8, 24.8, 21.1, 20.9, 10.9, 10.7; ESI-HRMS: m/z calcd for $\text{C}_{21}\text{H}_{29}\text{NO}_4$ $[\text{M} + \text{H}]^+$: 360.2169; found: 360.2165.

4.2.23. 1-Cyclopropyl-2-((3aS, 4S, 7S, 7aR)-7-hydroxy-2, 2-dimethyl-5-(prop-2-yn-1-yl)hexahydro-[1,3]dioxolo [4,5-c]pyridine-4-yl)ethan-1-one (**5g**). Obtained as a colorless syrup (55 mg, 65%); $[\alpha]_{\text{D}}^{20} +29$ (c 0.20, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 4.29 (dd, $J = 5.3$, 3.2 Hz, 1H), 3.96–3.85 (m, 1H), 3.82 (dd, $J = 7.6$, 5.4 Hz, 1H), 3.61 (dd, $J = 17.9$, 2.2 Hz, 1H), 3.43 (dd, $J = 17.9$, 2.3 Hz, 1H), 3.36–3.27 (m, 1H), 2.99 (dd, $J = 16.0$, 9.2 Hz, 1H), 2.88 (d, $J = 5.0$ Hz, 1H), 2.85 (dd, $J = 4.6$, 3.4 Hz, 1H), 2.42 (t, $J = 11.2$ Hz, 1H), 2.29 (t, $J = 2.3$ Hz, 1H), 2.06–2.00 (m, 1H), 1.54 (s, 3H), 1.32 (s, 3H), 1.16–1.02 (m, 2H), 0.96–0.87 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 208.8, 108.9, 79.9, 77.2, 76.5, 74.9, 74.6, 70.7, 55.6, 54.7, 43.0, 42.1, 28.5, 26.0, 21.6, 11.0; ESI-HRMS: m/z calcd for $\text{C}_{16}\text{H}_{23}\text{NO}_4$ $[\text{M} + \text{H}]^+$: 294.1700; found: 294.1696.

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