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$CeCl_3 \cdot H_2O$/NaI-Promoted stereoselective synthesis of 2,4-disubstituted chiral tetrahydroquinolines

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Abstract—D-Glycals readily undergo cyclization with aryl amines in the presence of $CeCl_3 \cdot 7H_2O$–NaI under mild and neutral conditions to afford a novel sugar derived tetrahydroquinoline derivatives in good yields with high stereoselectivity. The stereochemistry of the products was assigned by using various NMR studies.
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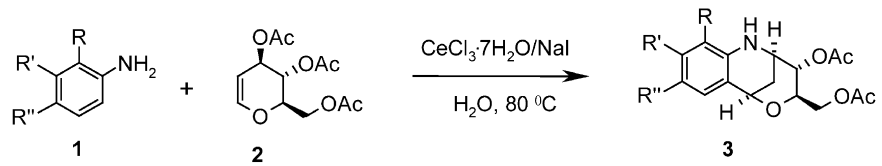
1. Introduction

The tetrahydroquinoline moiety is a core structure in many biologically important natural products[1] such as flindersine, oricine, and veprisine. Derivatives of these alkaloids possess a wide range of biological activities such as psychotropic, antiallergic, and anti-inflammatory behavior[2] and are used as a potential pharmaceuticals.[3] Recently, great attention has been focussed on the use of water as a green solvent in organic synthesis. In addition to its abundance, and for economical and safety reasons, water has naturally become a substitute and an alternative environmentally benign solvent in organic synthesis.[4] The use of aqueous medium as solvent also reduces the harmful effects of organic solvents on the environment. Lanthanide salts are unique Lewis acids that are currently of great research interest.[5] In particular, cerium reagents are relatively non-toxic, readily available at low cost and are fairly stable to air or moisture. Owing to its unique properties, $CeCl_3$ has been extensively used for a variety of organic transformations.[6,7]

2. Results and discussions

In continuation of our interest in the synthesis of *C*- and *O*-glycosides,[8] we herein report a novel approach for the synthesis of sugar derived chiral tetrahydroquinolines from D-glucal and aryl amines. Thus, treatment of 3,4,6-tri-*O*-acetyl-D-glucal **2** with aniline in the presence of an equimolar ratio of $CeCl_3 \cdot 7H_2O$ and NaI in water afforded sugar fused tetrahydroquinoline **3a** in 82% yield (Scheme 1). The reaction proceeded efficiently in water at 80 °C and the product was obtained with high stereoselectivity. The product **3a** was characterized by various NMR experiments like double quantum filtered correlation spectroscopy (DQFCOSY), nuclear Overhauser effect spectroscopy (NOESY), heteronuclear single quantum correlation spectroscopy (HSQC) and $^3J_{CH}$ optimized HMBC experiments. The edited HSQC spectrum showed the presence of two methylene groups in addition to eight methine and two methyl groups. The location of methylene at the bridge head of bicyclononene like structure was confirmed by the presence of small couplings between these protons and the bridge protons H_1 and H_3 J_{1H-2H}=3.7 Hz, J_{1H-2H}=1.8 Hz, J_{2H-3H}=2.4 Hz, and J_{2H-3H}=4.6 Hz. Fusion of the bicyclononene and the aromatic ring at C_{11}–NH was confirmed by NOE between H_1–H_{12} (Fig. 1a).

Further support for the structure came from HMBC peaks between H_1–C_{12}, H_1–C_{11}, H_1–C_{16} and H_{12}–C_1. The two



Scheme 1.

Keywords: D-Glucal; Cerium reagents; Glycal cyclization; Tetrahydroquinolines.
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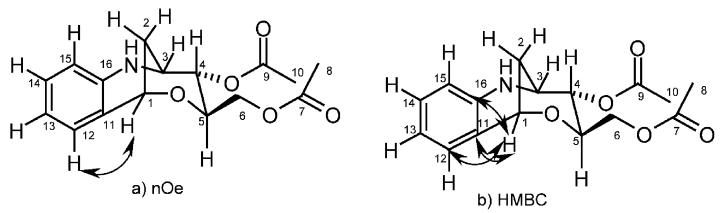
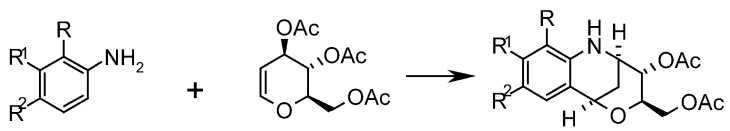


Figure 1. Important NOE's and chemical structure of **3a**.

six-membered rings of the bicyclononene moiety have two different conformations. The oxygen containing ring takes a chair form, whereas the other ring with nitrogen and fused to the aromatic ring exists in the half chair form. HMBC peaks between H_2-C_{11} and H_2-C_4 are consistent with the structure. Large coupling constant value of $J_{H4-H5}=10.4$ Hz and a NOESY cross-peak between H_2-H_4 further support the chair form for the ring containing these protons. Ring current effect due to the aromatic ring causes a high field chemical shifts of H_2 ($\delta=1.96$ ppm) and H_5 ($\delta=3.58$ ppm).

Encouraged by the results obtained with aniline, we turned our attention to various aryl amines and glycals. Interestingly, a variety of aryl amines including mono-, and di-substituted anilines reacted smoothly with glucal triacetate under similar conditions to afford the corresponding benzo-fused heterobicycles in good yields. However, 3,4,6-tri-*O*-methyl-D-glucal or 3,4,6-tri-*O*-benzyl-D-glucal did not react with aryl amines under identical reaction conditions (entry **o**, Table 1). The reaction was successful only with glucal triacetate. Furthermore, the reaction did not proceed with 2,6-disubstituted anilines such as 2,6-dicholoroaniline and 2,6-dimethylaniline under the reaction conditions (entry **n**, Table 1). These results clearly indicated that one of the *ortho* positions of aniline should be free from substitution for the success of the reaction. The probable mechanism seems to be addition of aniline to the α,β-unsaturated aldehyde, which is formed in situ from D-glucal and water. Thus, the initially formed 1,4-adduct may undergo an intramolecular cyclization resulting in the formation of fused tetrahydroquinolines (Scheme 2). This method is clean and highly stereoselective, affording sugar fused tetrahydroquinolines in a one-pot operation. The efficacy of various metal halides such as $CeCl_3{\cdot}7H_2O$, YCl_3, $YbCl_3$, $BiCl_3$, and $ZrCl_4$ was studied in water. Among these catalysts, $CeCl_3{\cdot}7H_2O$ was found to be the most effective reagent in terms of conversion and reaction rates. It is important to mention that simple cyclic enol ethers such as 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran gave the corresponding *cis*-fused pyrano- and furano-tetrahydroquinolines, respectively, under similar reaction conditions.[9]

Table 1. $CeCl_3{\cdot}7H_2O$/NaI-promoted synthesis of fused chiral tetrahydroquinolines



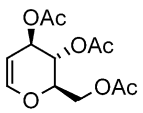
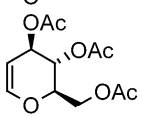
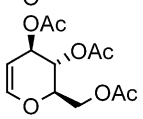
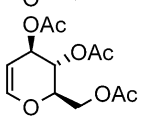
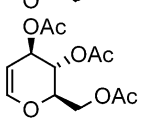
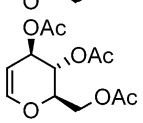
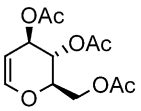
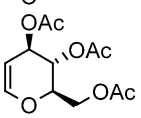
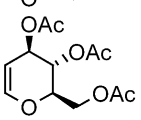
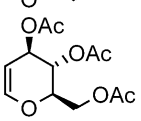
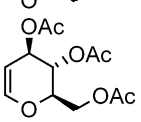
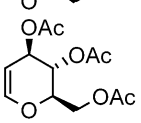
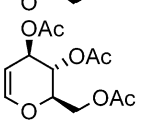
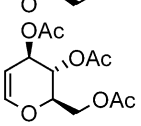
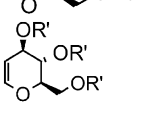
Entry	Aryl amine	D-Glucal	Product[a]	Reaction time (h)	Yield (%)[b]
1a	$R=R^1=R^2=H$		**3a**	7.0	82
1b	$R=R^1=H$; $R^2=Cl$		**3b**	8.0	80
1c	$R=R^1=H$; $R^2=Me$		**3c**	7.5	85
1d	$R=R^1=H$; $R^2=F$		**3d**	9.0	75
1e	$R=R^1=H$; $R^2=Br$		**3e**	8.5	72
1f	$R=R^2=H$; $R^1=Me$		**3f**	7.5	83[c]

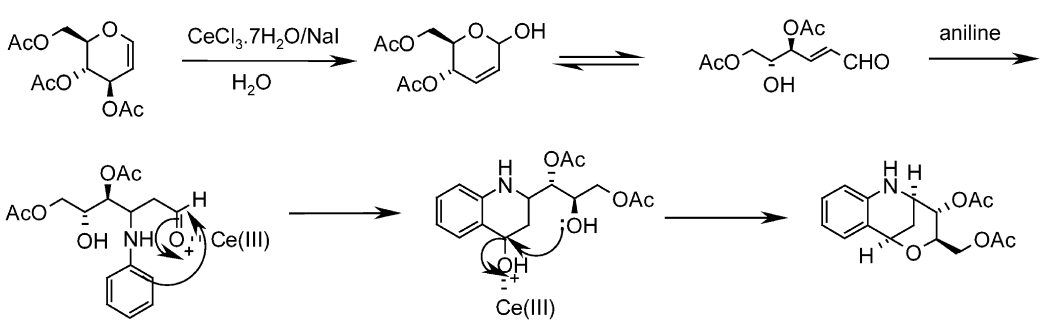
Table 1 (*continued*)

Entry	Aryl amine	D-Glucal	Product[a]	Reaction time (h)	Yield (%)[b]
1g	R=R^1=H; R^2=OMe		**3g**	8.0	70
1h	R=R^2=H; R^1=Cl		**3h**	9.0	80[c]
1i	R=Cl; R^1=Me;=R^2=H;		**3i**	8.5	79
1j	R=Cl; R^1=R^2=H		**3j**	7.5	82
1k	R=Me; R^1=R^2=H		**3k**	8.0	86
1l	R=Br; R^1=H; R^2=nMe		**3l**	9.5	65
1m	α-Naphthalamine		**3m**	8.5	70
1n	2,6-Dichloroaniline		No reaction	8.0	—
1o	Aniline	 R′=Me or Bn	No reaction	9.0	—

[a] Products were characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopy.
[b] Yield refers to pure products after chromatography.
[c] 5–10% other regioisomer was obtained.

Water appears to give the best results as solvent. Finally, we have examined the possibility of $CeCl_3{\cdot}7H_2O$ functioning catalytically or at least, in less than stoichiometric amounts. But best results were obtained with an equimolar ratio of $CeCl_3{\cdot}7H_2O$ and NaI. However, in the absence of NaI the reaction was very slow by $CeCl_3$ alone in refluxing water and took a longer reaction time (15–36 h) to achieve complete conversion. This clearly indicates that the addition of 1 equiv. of NaI is crucial in this transformation. It is well-known in literature that sodium iodide activates the $CeCl_3$ to accelerate the reaction.[6] Although, the reactions proceeded with hydrochloric acid, low conversions (14–25%) were obtained even after long reaction times (15–24 h). The scope and generality of this process is illustrated with respect to various aryl amines and D-glucal (Table 1).

In summary, we describe a novel protocol for the synthesis of sugar derived chiral tetrahydroquinolines from D-glucal



Scheme 2.

and aryl amines using the inexpensive and readily available $CeCl_3{\cdot}7H_2O$/NaI reagent system under mild and neutral conditions. The use of water as solvent makes this method quite simple and a more convenient and environmentally benign process to prepare sugar based heterobicycles in a single-step operation.

3. Experimental

3.1. General

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer FT-IR 240-c spectrophotometer using KBr optics. ^{1}H NMR and ^{13}C spectra were recorded on Gemini-200 and Varian Unity-500 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. The optical rotations were measured on a Jasco Dip 360 Digital polarimeter.

3.2. General procedure

A mixture of 3,4,6-tri-*O*-acetyl-D-glucal (2 mmol), aniline (3 mmol), $CeCl_3{\cdot}7H_2O$ (2 mmol) and NaI (2 mmol) in water (10 mL) was stirred at 80 °C temperature for the specified time as required to complete the reaction (Table 1). After complete conversion, as indicated by TLC, the reaction mixture was extracted with ethyl acetate (2×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford the pure tetrahydroquinoline derivative. Spectral data for products.

3.2.1. Compound 3a. Colourless liquid, $[\alpha]_D^{27}$=95.5 (c=1.0, $CHCl_3$), IR (KBr): ν_{max}: 3427, 2935, 2857, 1730, 1607, 1461, 1365, 1257, 1098, 835 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16 (dt, J=1.5, 7.9 Hz, 1H, H13), 7.13 (dd, J=1.5, 7.9 Hz, 1H, H15), 6.69 (dt, J=1.5, 7.9 Hz, 1H, H14), 6.61 (dd, J=1.5, 7.9 Hz, 1H, H12), 4.84 (dd, J=3.1, 10.4 Hz, 1H, H4), 4.81 (dd, J=1.8, 3.7 Hz, 1H, H1), 4.44 (brs, 1H, NH), 4.19 (dd, J=4.2, 12.0 Hz, 1H, H6), 3.99 (dd, J=2.2, 12.0 Hz, 1H, H6′), 3.84 (ddd, J=2.4, 3.1, 4.6 Hz, 1H, H3), 3.58 (ddd, J=2.1, 4.2, 10.4 Hz, 1H, H5), 2.29 (ddd, J=2.4, 3.7, 13.2 Hz, 1H, H2), 2.10 (s, 3H, CH_3-10), 2.06 (s, 3H, CH_3-8), 1.96 (ddd, J=1.8, 4.6, 13.2 Hz, 1H, H2). ^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): δ 170.8, 169.8, 145.0, 130.5, 129.9, 118.8, 117.2, 112.9, 71.8, 68.5, 67.4, 63.0, 46.6, 27.9, 21.0, 20.7. FAB Mass: 305 M$^+$, 259, 191, 144, 130, 119, 91, 69, 57. HRMS calcd for $C_{16}H_{19}NO_5$: 305.1263. Found: 305.1281.

3.2.2. Compound 3b. Pale yellow liquid, $[\alpha]_D^{27}$=93.5 (c=2.0, $CHCl_3$), IR (KBr):ν_{max}: 3409, 2928, 1728, 1607, 1495, 1372, 1242, 1045, 870 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.05–7.20 (m, 2H), 6.50–6.57 (m, 1H), 4.75 (dd, J=3.2, 10.5 Hz, 1H), 4.65 (dd, J=1.8, 3.8 Hz, 1H), 4.32 (brs, 1H, NH), 4.25 (dd, J=4.2, 12.0 Hz, 1H), 4.0 (dd, J=2.1, 12.0 Hz, 1H), 3.78 (ddd, J=2.5, 3.2, 4.5 Hz, 1H), 3.60 (ddd, J=2.1, 4.2, 10.3 Hz, 1H), 2.23 (ddd, J=2.5, 3.8, 13.0 Hz, 1H), 2.10 (s, 3H), 2.05 (s, 3H), 1.90 (ddd, J=1.8, 4.5, 13.0 Hz, 1H). ^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): δ 170.8, 169.8, 143.5, 129.7, 121.4, 119.9, 115.0, 114.1, 71.5, 68.0, 67.4, 62.9, 46.4, 27.5, 20.9, 20.7. FAB Mass: 340 M$^+$, 325, 309, 295, 281, 267, 251, 221, 207, 191, 164, 147, 133, 117, 91, 77. HRMS calcd for $C_{16}H_{18}ClNO_5$: 339.08735. Found: 339.08313.

3.2.3. Compound 3c. Viscous liquid, $[\alpha]_D^{27}$=57.4 (c=0.7, $CHCl_3$), IR (KBr): ν_{max}: 3409, 2926, 1729, 1622, 1510, 1440, 1248, 1045, 815, 758 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.98–6.90 (m, 2H), 6.50 (d, J=8.0 Hz, 1H,), 4.80 (dd, J=3.2, 10.5 Hz, 1H), 4.77 (dd, J=1.7, 3.8 Hz, 1H), 4.40 (brs, 1H, NH), 4.20 (dd, J=4.2, 12.0 Hz, 1H), 3.85 (dd, J=2.1, 12.0 Hz, 1H), 3.78 (ddd, J=2.4, 3.2, 4.5 Hz 1H), 3.50 (ddd, J=2.1, 4.2, 10.5 Hz, 1H), 2.30 (ddd, J=2.4, 3.7, 13.0 Hz, 1H), 2.25 (s, 3H), 2.10 (s, 3H), 2.05 (s, 3H), 1.95 (ddd, J=1.7, 4.5, 13.0 Hz, 1H). ^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): δ 170.6, 170.1, 145.0, 129.6, 127.3, 118.6, 117.4, 112.7, 71.8, 67.4, 65.2, 62.9, 46.6, 29.6, 21.6, 20.8, 20.6. FAB Mass: 319 M$^+$, 281, 207, 158, 144, 105, 91, 73, 57. HRMS calcd for $C_{17}H_{21}NO_5$: 319.1419. Found: 319.1437.

3.2.4. Compound 3d. Oily liquid, $[\alpha]_D^{27}$=67.1 (c=0.75, $CHCl_3$), IR (KBr): ν_{max}: 3356, 2961, 1733, 1505, 1260, 1040, 809 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.78–6.90 (m, 2H), 6.45–6.50 (m, 1H), 4.80 (dd, J=3.1, 10.5 Hz, 1H), 4.70 (dd, J=1.8, 3.8 Hz, 1H), 4.30 (brs, 1H, NH), 4.20 (dd, J=4.2, 12.0 Hz, 1H), 3.90 (dd, J=2.1, 12.0 Hz, 1H), 3.80 (ddd, J=2.5, 3.1, 4.5 Hz, 1H), 3.50 (ddd, J=2.1, 4.2, 10.3 Hz, 1H), 2.25 (ddd, J=2.5, 3.8, 13.1 Hz, 1H), 2.10 (s, 3H), 2.0 (s, 3H), 1.95 (ddd, J=1.8, 4.5, 13.1 Hz, 1H). ^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): δ 170.3, 169.4, 156.9, 141.1, 119.6, 117.2, 116.9, 113.9, 71.7, 68.1, 67.7, 62.9, 46.7, 27.9, 21.0, 20.8. FAB Mass: 323 M$^+$ 267, 221, 191, 147, 133, 73. HRMS calcd for $C_{16}H_{18}FNO_5$: 323.1169. Found: 323.1127.

3.2.5. Compound 3e. Brown liquid, $[\alpha]_D^{27}$=169.2 (c=1.5, $CHCl_3$), IR (KBr): ν_{max}: 3410, 3019, 2955, 1738, 1603, 1490, 1371, 1246, 1046, 813, 757 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10–7.20 (m, 2H), 6.50 (d, J=8.1 Hz, 1H), 4.80 (dd, J=3.2, 10.5 Hz, 1H), 4.70 (dd, J=1.8, 3.8 Hz, 1H), 4.40 (brs, 1H, NH), 4.25 (dd, J=4.2, 12.0 Hz, 1H), 4.10 (dd, J=2.1, 12.0 Hz, 1H), 3.90 (ddd, J=2.5, 3.2, 4.5 Hz, 1H), 3.80 (ddd, J=2.1, 4.2, 10.3 Hz, 1H), 2.30 (ddd, J=2.5, 3.8, 13.0 Hz, 1H), 2.10 (s, 3H), 2.04 (s, 3H), 1.90 (ddd, J=1.8, 4.5, 13.0 Hz, 1H). ^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): δ 170.8, 169.8, 143.9, 132.8, 132.6, 129.1, 120.6, 114.6, 71.5, 68.0, 67.5, 62.9, 46.5, 27.5, 20.9, 20.7. FAB Mass: 383 M$^+$, 368, 340, 327, 289, 265, 239, 224, 219, 191, 165. HRMS calcd for $C_{16}H_{18}BrNO_5$: 383.0368. Found: 383.0393.

3.2.6. Compound 3f. Viscous liquid, $[\alpha]_D^{27}$=67.5 (c=1.4, $CHCl_3$), IR (KBr): ν_{max}: 3413, 2972, 2854, 1741, 1620, 1583, 1492, 1439, 1371, 1329, 1241, 1171, 1047, 815 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.90 (d, J=8.0 Hz, 1H), 6.50 (d, J=8.0 Hz, 1H), 6.40–6.35 (s, 1H), 4.85 (dd, J=3.1, 10.3 Hz, 1H), 4.75 (dd, J=1.7, 3.8 Hz, 1H), 4.40 (brs, 1H, NH), 4.20 (dd, J=4.2, 12.0 Hz, 1H), 3.90 (dd, J=2.1, 12.0 Hz, 1H), 3.80 (ddd, J=2.4, 3.1, 4.5 Hz 1H), 3.55 (ddd, J=2.1, 4.2, 10.3 Hz, 1H), 2.30 (ddd, J=2.4, 3.7, 13.0 Hz,

1H), 2.25 (s, 3H), 2.10 (s, 3H), 2.05 (s, 3H), 1.90 (ddd, J=1.7, 4.5, 13.0 Hz, 1H). ^{13}C NMR (proton decoupled, 50 MHz, $CDCl_3$): δ 170.3, 169.9, 145.0, 132.5, 127.3, 118.7, 117.5, 112.8, 71.8, 67.4, 65.2, 62.9, 46.6, 29.6, 21.6, 20.7, 20.6. FAB Mass: 319 M^{+1}, 282, 170, 144, 91, 43. HRMS calcd for $C_{17}H_{21}NO_5$: 319.1419. Found: 319.1458.

3.2.7. Compound 3g. Oily liquid, $[\alpha]_D^{25}$=21.5 (c=0.7, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.58–6.65 (m, 2H), 6.40 (d, J=7.9 Hz, 1H), 4.70 (dd, J=3.0, 10.3 Hz, 1H, H4), 4.63 (dd, J=1.7, 3.8 Hz, 1H), 4.15 (dd, J=4.2, 12.0 Hz, 1H), 3.90 (dd, J=2.1, 12.0 Hz, 1H), 3.75 (ddd, J=2.4, 3.0, 4.5 Hz, 1H), 3.65 (s, 3H), 3.45 (ddd, J=2.1, 4.2, 10.3 Hz, 1H), 2.20 (ddd, J=2.4, 3.8, 13.2 Hz, 1H), 2.05 (s, 3H), 2.0 (s, 3H), 1.90 (ddd, J=1.7, 4.5, 13.2 Hz, 1H). ^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): δ 170.9, 169.8, 151.8, 129.7, 123.5, 119.6, 117.0, 114.9, 71.8, 68.7, 67.2, 63.1, 55.8, 46.7, 28.1, 21.0, 20.7. IR (KBr): ν_{max}: 3325, 3015, 1739, 1505, 1462, 1221, 1041, 759 cm^{-1}. FAB Mass: 335 M^+, 281, 267, 249, 221, 207, 191, 177, 160, 147, 133, 117, 105, 91, 73, 65, 55. HRMS calcd for $C_{17}H_{21}NO_6$: 335.13688. Found: 335.13259.

3.2.8. Compound 3h. Light yellow liquid, $[\alpha]_D^{27}$=64.5 (c=2.8, $CHCl_3$), IR (KBr): ν_{max}: 3390, 2926, 2854, 1731, 1599, 1485, 1428, 1371, 1242, 1128, 1047, 846, 760 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15–6.95 (m, 1H), 6.60–6.58 (m, 1H), 6.45–6.40 (m, 1H), 4.73 (dd, J=3.2, 10.5 Hz, 1H), 4.60 (dd, J=1.8, 3.8 Hz, 1H), 4.30 (brs, 1H, NH), 4.23 (dd, J=4.2, 12.0 Hz, 1H), 4.05 (dd, J=2.1, 12.0 Hz, 1H), 3.79 (ddd, J=2.5, 3.2, 4.5 Hz, 1H), 3.60 (ddd, J=2.1, 4.2, 10.3 Hz, 1H), 2.25 (ddd, J=2.5, 3.8, 13.0 Hz, 1H), 2.10 (s, 3H), 2.05 (s, 3H), 1.95 (ddd, J=1.8, 4.5, 13.0 Hz, 1H). ^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): δ 170.5, 169.6, 143.2, 130.4, 121.3, 119.9, 115.2, 114.0, 71.4, 68.0, 67.5, 62.7, 46.3, 27.4, 20.8, 20.6. FAB Mass: 339 M^+, 333, 292, 220, 281, 194, 166, 153, 128, 97, 84, 44. HRMS calcd for $C_{16}H_{18}ClNO_5$: 339.08735. Found: 339.08419.

3.2.9. Compound 3i. Brown solid, mp 49–51 °C, $[\alpha]_D^{27}$=28.0 (c=1.6, $CHCl_3$), IR (KBr): ν_{max}: 3417, 2927, 1739, 1622, 1594, 1468, 1370, 1239, 1064, 814, 769 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.05–6.90 (m, 1H), 6.60–6.6.75 (m, 1H), 4.89 (dd, J=3.2, 10.5 Hz, 1H), 4.76 (dd, J=1.8, 3.7 Hz, 1H), 4.35 (brs, 1H, NH), 4.20 (dd, J=4.2, 12.0 Hz, 1H), 3.95 (dd, J=2.2, 12.0 Hz, 1H), 3.85 (ddd, J=2.4, 3.2, 4.6 Hz, 1H), 3.50 (ddd, J=2.1, 4.2, 10.5 Hz, 1H), 2.25 (ddd, J=2.4, 3.7, 13.2 Hz, 1H), 2.15 (s, 3H), 2.10 (s, 3H), 2.05 (s, 3H), 1.93 (ddd, J=1.8, 4.6, 13.2 Hz, 1H, H2). ^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): δ 170.3, 169.5, 134.6, 133.4, 130.2, 127.3, 120.1, 107.4, 71.5, 68.7, 67.6, 63.0, 46.8, 27.9, 21.2, 20.7, 20.3. FAB Mass: 353 M^+, 336, 178, 83, 57, 43. HRMS calcd for $C_{17}H_{20}ClNO_5$: 353.1030. Found: 353.1073.

3.2.10. Compound 3j. Light yellow solid, mp 119–120 °C, $[\alpha]_D^{27}$=52.2 (c=2.0, $CHCl_3$), IR (KBr): ν_{max}: 3412, 2970, 2927, 1727, 1607, 1499, 1256, 1044, 842, 740 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, J=8.0 Hz, 1H), 7.05 (d, J=7.9 Hz, 1H), 6.60 (t, J=7.9 Hz, 1H), 4.90 (dd, J=3.2, 10.5 Hz, 1H), 4.80 (dd, J=1.8, 3.8 Hz, 1H), 4.25 (dd, J=4.0, 12.0 Hz, 1H, H6), 3.98 (dd, J=2.0, 12.0 Hz, 1H), 3.90 (ddd, J=2.3, 3.2, 4.7 Hz, 1H), 3.58 (ddd, J=2.0, 4.0, 10.5 Hz, 1H), 2.30 (ddd, J=2.3, 3.8, 13.2 Hz, 1H), 2.10 (s, 3H), 2.06 (s, 3H), 1.90 (ddd, J=1.8, 4.7, 13.2 Hz, 1H). ^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): δ 170.8, 169.9, 141.0, 129.7, 128.9, 120.2, 117.0, 112.7, 71.3, 68.2, 67.5, 62.9, 46.6, 27.6, 21.0, 20.7. FAB Mass: 340 M^+, 329, 325, 309, 295, 281, 267, 251, 221, 207, 191, 164, 147, 133, 117, 91, 77. HRMS calcd for $C_{16}H_{18}ClNO_5$: 339.08735. Found: 339.08908.

3.2.11. Compound 3k. Viscous liquid, $[\alpha]_D^{27}$=83.7 (c=0.8, $CHCl_3$), IR (KBr): ν_{max}: 3422, 2931, 2858, 1734, 1604, 1472, 1367, 1254, 1093, 837 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.98–6.95 (m, 2H), 6.60 (t, J=7.9 Hz, 1H,), 4.82 (dd, J=3.2, 10.5 Hz, 1H), 4.78 (dd, J=1.7, 3.8 Hz, 1H), 4.22 (dd, J=4.2, 12.0 Hz, 1H), 4.20 (brs, 1H, NH), 3.95 (dd, J=2.1, 12.0 Hz, 1H), 3.90 (ddd, J=2.4, 3.2, 4.5 Hz 1H), 3.55 (ddd, J=2.1, 4.2, 10.5 Hz, 1H), 2.30 (ddd, J=2.4, 3.7, 13.0 Hz, 1H), 2.15 (s, 3H), 2.10 (s, 3H), 2.05 (s, 3H), 1.95 (ddd, J=1.7, 4.5, 13.0 Hz, 1H). ^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): δ 170.9, 169.9, 143.0, 130.8, 128.4, 120.1, 118.4, 116.8, 71.7, 68.8, 67.3, 63.1, 46.9, 29.6, 27.9, 21.0, 20.8. FAB Mass: 319 M^+, 281, 207, 158, 144, 105, 91, 73, 57. HRMS calcd for $C_{17}H_{21}NO_5$: 319.1419. Found: 319.1451.

3.2.12. Compound 3l. Yellow solid, mp 165 °C, $[\alpha]_D^{27}$=51.2 (c=1.35, $CHCl_3$), IR (KBr): ν_{max}: 3416, 2965, 2362, 1728, 1618, 1505, 1432, 1373, 1232, 1043, 861 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (s, 1H), 6.90 (s, 1H), 4.85 (dd, J=3.1, 10.4 Hz, 1H), 4.78 (dd, J=1.8, 3.7 Hz, 1H), 4.25 (brs, 1H, NH), 4.20 (dd, J=4.2, 12.0 Hz, 1H), 3.90 (dd, J=2.2, 12.0 Hz, 1H), 3.85 (ddd, J=2.4, 3.1, 4.6 Hz, 1H), 3.50 (ddd, J=2.1, 4.2, 10.4 Hz, 1H), 2.25 (ddd, J=2.4, 3.7, 13.2 Hz, 1H), 2.15 (s, 3H), 2.10 (s, 3H), 2.05 (s, 3H), 1.95 (ddd, J=1.8, 4.6, 13.2 Hz, 1H, H2). ^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): δ 170.5, 169.6, 139.7, 133.4, 130.3, 127.1, 120.2, 107.3, 71.3, 68.5, 67.5, 62.8, 46.9, 27.9, 21.0, 20.8, 20.1. FAB Mass: 397 M^+, 385, 355, 341, 327, 311, 295, 281, 267, 221, 207, 191, 147, 133, 77. HRMS calcd for $C_{17}H_{20}BrNO_5$: 397.05148. Found: 397.05205.

3.2.13. Compound 3m. Viscous oil, $[\alpha]_D^{27}$=85.6 (c=0.5, $CHCl_3$), IR (KBr): ν_{max}: 3400, 2956, 2859, 1730, 1605, 1467, 1254, 1093, 838 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80–7.70 (m, 3H), 7.38–7.45 (m, 2H), 7.10–7.18 (m, 1H), 4.90 (dd, J=3.0, 10.5 Hz, 1H), 4.82 (dd, J=1.7, 3.8 Hz, 1H), 4.40 (brs, 1H, NH), 4.05 (dd, J=4.2, 12.0 Hz, 1H), 3.90 (dd, J=2.0, 12.0 Hz, 1H), 3.84 (ddd, J=2.3, 3.0, 4.6 Hz, 1H), 3.50 (ddd, J=2.0, 4.2, 10.5 Hz, 1H), 2.30 (ddd, J=2.3, 3.8, 13.2 Hz, 1H), 2.10 (s, 3H), 2.04 (s, 3H), 1.96 (ddd, J=1.7, 4.6, 13.2 Hz, 1H). ^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): δ 170.9, 169.7, 143.5, 130.7, 129.6, 124.5, 123.2, 122.8, 122.0, 121.1, 120.3, 119.5, 71.9, 68.4, 67.1, 63.5, 46.7, 28.0, 20.9, 20.5. FAB Mass: 355 M^+, 341, 325, 281, 265, 251, 221, 207, 191, 177, 147, 133, 117, 105, 91, 73, 65, 55. HRMS calcd for $C_{20}H_{21}NO_5$: 355.1419. Found: 355.1458.

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