SYNTHETIC STUDY OF ANTI-OBESITY IRIDOID ISOLATED FROM TABEBUIA AVELLANEAE

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*This paper is dedicated to Professor Kiyoshi Tomioka on the occasion of his 70th birthday.

Abstract – Synthetic study toward iridoid 1 with anti-obese activity was performed by utilizing palladium-catalyzed cycloalkenylation reaction, Pd/C-catalyzed debenzylation reaction without hydrogenation and/or isomerization of alkene moiety, and the two-step, one-pot cyclization of diol as key steps.

INTRODUCTION

We have engaged in the studies of the bioactive constituents isolated from Tabebuia avellanedae LORENTZ ex GRISEB (Bignoniaceae) (syn. Tabebuia impetiginosa), which is widespread in South America throughout Brazil to north Argentina and has been well known as a traditional medicine since the Inca Era.1 As a part of our ongoing research projects, we recently reported that T. avellanedae n-BuOH extract decreased body weight in ovariectomized (OVX) mice and reduced the triglyceride (TG) levels in 3T3-L1 cells.2 Further studies revealed that iridoid 1a is considered as one of factors showing an anti-obesity activity in its extract. However, it is unknown exactly how such simple iridoid 1a affects the decreased body weight in OVX mice. Contrarily, the corresponding 4-methoxybenzoyl ester 1b did not affect TG levels in 3T3-L1 cells. These curious results encouraged us to push forward our research program. Here, we describe the concise construction of iridoid frameworks and synthetic studies towards iridoid 1.

RESULTS AND DISCUSSION

The retrosynthesis route is shown in Scheme 1. In this study, the targeted iridoid 1 could be obtained by functional group manipulations of cyclization product 3, which could be synthesized from trans substituted lactone ester 4 by utilizing reported palladium-catalyzed cycloalkenylation reaction.3
The conjugate addition of homoallyl magnesium bromide with enone 5,3 which was synthesized from commercially available 3-butenoic acid and formaldehyde, gave conjugate adduct 6,4 followed by benzyloxycarbonylation of 6 afforded the lactone ester 4a in 96% yield. The Pd-catalyzed cycloalkenylation reaction of lactone ester reported by Toyota et al.5 gave cyclized product 7 as a sole product. The Brønsted acid such as p-toluenesulfonic acid catalyzed olefin isomerization was failed due the occurrence of hydrolysis of the ester moiety rather than the desired reaction. Alternatively, the mixture of 7 with rhodium chloride was refluxed in 1-PrOH, which caused isomerization to the more endocyclic isomer 3a with yield of 62%.6 Next, oxidation of 3a with 15 equiv. of CrO3 followed by hydrogenation catalyzed with Ru[(S,S)-Tsdpen](p-cymene) in a formic acid–triethylamine mixture afforded the secondary alcohol 9.7,8 Decarboxylation of 9 was proved to be challenging with this specific substrate. Our initial attempts for decarboxylation by utilizing thermal conditions,9 or with Raney Nickel10 were failed. Fortunately, treatment of 9 in EtOAc with 20 mol% of Pd/C under hydrogen atmosphere furnished the desired debenzylated compound without hydrogenation and/or isomerization of alkene moiety. Appropriate choice of solvents was crucial for this debenzylation.11 Finally, the corresponding carboxylic acid was converted to 2a by heating the crude mixture in DMSO at 100 °C for 1 h. After protection of the secondary hydroxyl group of 2a as TBS ether, the stereochemistry of 2b was assumed as shown in Figure 1 by NOESY experiments.
Several attempts for the direct reduction of the lactone 2b to ether 12 failed and made us employ a multi-step reaction sequence. To our delight, DIBAL reduction of lactone to diol 11 followed by the two-step, one-pot cyclization\textsuperscript{12} with TsCl and NaH gave the desired ether in satisfactory yield. This reaction probably proceeds through cyclization of monotosylated intermediate. Reaction of 12 with SeO\textsubscript{2} at 40 °C led to the desired aldehyde 13 and C7a-oxidized 14 in 34% and 50% yields, respectively. Further efforts on the conversion of 13 to 1 and SAR study on the anti-obesity activity are currently underway in our laboratory and will be reported in due course.

Figure 1. NOE correlations of 2b
**EXPERIMENTAL**

$^1$H- and $^{13}$C-NMR spectra were acquired with Bruker-Biospin Avance III 400 MHz NMR spectrometer and taken in CDCl$_3$, unless otherwise noted. Chemical shift values are expressed in ppm relative to internal tetramethylsilane. Coupling constants $J$ values are presented in Hz. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; m, multiplet. IR spectra were recorded with a Shimadzu IRAffinity-1S spectrometer. IR spectroscopy of oil sample was measured as neat liquid film. The wave-numbers of maximum absorption peaks of IR spectroscopy are presented in cm$^{-1}$. MS (ESI) is presented in $m/z$. Extracts were washed with brine and then dried over sodium sulfate. Silica gel column chromatography was used for purification.

**Benzyl 4-(but-3-en-1-yl)-2-oxotetrahydro-$2^H$-pyran-3-carboxylate (4a):** A solution of 6 (1.06 g, 6.88 mmol) in THF (17 mL) was added to a solution of LDA at -78 °C. After 1 h, benzyl chloroformate (1.47 mL, 10.3 mmol) was added dropwise. After it was stirred for 2 h at rt. The mixture was treated with aqueous NH$_4$Cl solution, and then dried over sodium sulfate. The organic extracts were washed with brine, dried over Na$_2$SO$_4$, and then concentrated. The crude product was chromatographed on silica gel. Yield 98% (1.37 g). Yellow oil. R$_f$ (hexane/acetone = 3/1) = 0.35. $^1$H-NMR: $\delta$ 7.39–7.28 (m, 5H), 5.73–5.61 (m, 1H), 5.01–4.93 (m, 2H), 4.40–4.33 (m, 1H), 4.32–4.24 (m, 1H), 3.28 (d, $J = 9.7$ Hz, 1H), 2.44–2.33 (m, 1H), 2.17–1.92 (m, 3H), 1.61–1.44 (m, 2H), 1.42–1.31 (m, 1H). $^{13}$C-NMR: $\delta$ 168.7 (C), 167.4 (C), 137.2 (CH), 135.3 (C), 128.6 (CH), 128.5 (CH), 128.3 (CH), 115.5 (CH$_2$), 68.3 (CH$_2$), 67.5 (CH$_2$), 54.3 (CH), 34.4 (CH), 33.8 (CH$_2$), 30.3 (CH$_2$), 27.1 (CH$_2$). IR: 3066, 3034, 2924, 2855, 1748, 1263, 1192, 914, 843, 756, 698. HRMS (ESI) $m/z$: [M+Na]$^+$ calcd for [C$_{17}$H$_{20}$NaO$_4$]$^+$, 311.1259; Found, 311.1261.

**Benzyl 7-methylene-1-oxohexahydrocyclopenta[c]pyran-7a(1H)-carboxylate (7):** To a solution of 4a (6.87 g, 23.9 mmol) in DMSO (70 mL) were added Pd(OAc)$_2$ (536 mg, 2.39 mmol). The mixture was stirred at 45 °C under 1 atm of oxygen. After 12 h, the mixture was treated with aqueous NaCl solution,
extracted with EtOAc. The organic extracts were washed with brine, dried over Na₂SO₄, and then concentrated. The crude product was chromatographed on silica gel. Recovered 4a 26% (1.81 g). Yield of 7 40% (2.74 g). Yellow oil. R₂f (hexane/EtOAc = 1/1) = 0.5. ¹H-NMR: δ 7.39–7.30 (m, 5H), 5.41 (dd, J = 2.3, 2.3 Hz, 1H), 5.32 (dd, J = 2.3, 2.3 Hz, 1H), 5.24 (ddd J = 12.4, 12.4, 6.2 Hz, 1H), 4.32 (ddd, J = 11.6, 4.4, 4.4 Hz, 1H), 4.17 (ddd, J = 10.2, 11.3, 2.7 Hz, 1H), 3.02–2.95 (m, 1H), 2.59–2.45 (m, 2H), 2.05–1.91 (m, 2H), 1.71–1.62 (m, 1H), 1.55–1.46 (m, 1H). ¹³C-NMR: δ 170.0 (C), 168.1 (C), 146.5 (C), 135.3 (C), 128.6 (CH), 128.4 (CH), 128.0 (CH), 113.4 (CH₂), 67.7 (CH₂), 67.6 (CH₂), 63.6 (C), 42.8 (CH), 31.3 (CH₂), 30.1 (CH₂), 27.0 (CH₂). IR: 2957, 1732, 1654, 1260, 1223, 1188, 908, 783, 745, 698. HRMS (ESI) m/z: [M+Na]+ calcd for [C₁₇H₁₈NaO₄]+, 309.1103; Found, 309.1105.

**Benzyl 7-methyl-1-oxo-3,4,4a,5-tetrahydrocyclopenta[c]pyran-7a(1H)-carboxylate (3a):** A mixture of compound 7 (1.2 g, 4.2 mmol) and rhodium chloride trihydrate (110 mg, 0.42 mmol) in 1-propanol (10 mL) was stirred at 100 °C under an Ar atmosphere. After 7 h, the mixture was concentrated. The crude product was chromatographed on silica gel. Yield 53% (727 mg). Colorless oil. R₂f (hexane/EtOAc = 2/1) = 0.60. ¹H-NMR: δ 7.38–7.29 (m, 5H), 5.74–5.70 (m, 1H), 5.23 (d, J = 12.4 Hz, 1H), 5.15 (d, J = 12.4 Hz, 1H), 4.30 (ddd, J = 3.0, 7.8, 11.4 Hz, 1H), 4.21 (ddd, J = 10.9, 7.3, 3.2 Hz, 1H), 3.04–2.96 (m, 1H), 2.75–2.65 (m, 1H), 2.16–2.03 (m, 2H), 1.87 (dd, J = 3.9, 2.3 Hz, 3H), 1.73–1.64 (m, 1H). ¹³C-NMR: δ 204.8 (C), 172.7 (C), 168.1 (C), 165.0 (C), 134.6 (C), 134.6 (CH), 128.8 (CH), 128.2 (CH), 68.2 (CH₂), 67.0 (CH₂), 63.5 (C), 49.3 (CH₃), 29.2 (CH₂), 14.7 (CH). IR: 2955, 2922, 1732, 1265, 1231, 1179, 1111, 750, 698. HRMS (ESI) m/z: [M+Na]+ calcd for [C₁₇H₁₈NaO₅]+, 323.0895; Found, 323.0887.

**Benzyl 5-hydroxy-7-methyl-1-oxo-3,4,4a,5-tetrahydrocyclopenta[c]pyran-7a(1H)-carboxylate (9):** To a flask were added ketone 8 (310 mg, 1.03 mmol), Ru[(S,S)-Tsdpen]₍p-cymene₎ (62 mg, 0.103 mmol,
10 mol%), formic acid/Et$_3$N (5:2, 7.5 mL). The resulting solution was stirred at 50 °C for 1 d. The reaction mixture was diluted by addition of H$_2$O, and extracted with EtOAc. The organic extracts were washed with brine, and then dried over Na$_2$SO$_4$. The crude product was chromatographed on silica gel. Yield 83% (258 mg). Colorless oil. $R_f$ (hexane/EtOAc = 1/1) = 0.18. $^{1}$H-NMR: δ 7.39–7.30 (m, 5H), 5.87–5.83 (m, 1H), 5.26 (d, $J = 12.3$ Hz, 1H), 4.70 (dd, $J = 6.1$, 6.1 Hz, 1H), 4.37 (ddd, $J = 11.2$, 4.3, 4.3 Hz, 1H), 4.07 (ddd, $J = 11.0$, 11.0, 3.1 Hz, 1H), 3.13 (ddd, $J = 15.4$, 8.5 Hz, 1H), 2.24–2.13 (m, 1H), 1.96–1.87 (m, 4H), 1.84 (d, $J = 7.0$ Hz, 1H). $^{13}$C-NMR: δ 170.3 (C), 169.2 (C), 142.4 (C), 135.0 (C), 133.6 (CH), 128.7 (CH), 128.6 (CH), 128.3 (CH), 74.8 (CH), 68.0 (CH$_2$), 67.7 (CH$_2$), 65.8 (C), 46.2 (CH$_3$), 22.0 (CH$_2$), 15.1 (CH). IR: 3445, 2918, 1730, 1265, 1229, 1186, 1090, 1057, 984, 752, 698. HRMS (ESI) $m/z$: [M+Na]$^+$ calcd for [C$_{17}$H$_{18}$NaO$_5$]$^+$, 325.1052; Found, 325.1064.

5-Hydroxy-7-methyl-4,4a,5,7a-tetrahydrocyclopenta[c]pyran-1(3H)-one (2a): To a solution of 9 (315 mg, 1.04 mmol) in EtOAc (4.0 mL) at rt was added palladium 10% on carbon (220 mg, 0.21 mmol) in one portion. After it was stirred for 1 h at rt. The reaction mixture was filtered through a pad of Celite. The Celite was washed with EtOAc, and the combined organics were concentrated. The crude product was deluted with DMSO (1 mL). The resulting solution was stirred at 100 °C for 1 h. The reaction mixture was diluted by addition of H$_2$O, and extracted with EtOAc. The organic extracts were washed with brine, and then dried over Na$_2$SO$_4$. The crude product was chromatographed on silica gel. Yield 59% (103 mg). Colorless oil. $R_f$ (hexane/EtOAc = 1/1) = 0.10. $^{1}$H-NMR: δ 5.76–5.73 (m, 1H), 4.84–4.79 (m, 1H), 4.36 (ddd, $J = 11.7$, 8.4, 3.0 Hz, 1H), 4.22–4.16 (m, 1H), 3.38–3.33 (m, 1H), 2.89–2.80 (m, 1H), 2.14–2.05 (m, 1H), 1.86–1.84 (m, 3H), 1.80–1.71 (m, 1H), 0.88 (s, 9H), 0.06 (d, $J = 2.5$ Hz, 6H). $^{13}$C-NMR: δ 172.0 (C), 141.9 (C), 131.2 (CH), 75.8 (CH), 67.8 (CH$_2$), 51.2 (CH), 40.1 (CH), 22.3 (CH$_2$), 16.2 (CH). IR: 3420, 2916, 1722, 1395, 1269, 1225, 1169, 1067, 989, 974. HRMS (ESI) $m/z$: [M+Na]$^+$ calcd for [C$_{9}$H$_{12}$NaO$_3$]$^+$, 191.0684; Found, 191.0682.

5-((tert-Butyldimethylsilyl)oxy)-7-methyl-4,4a,5,7a-tetrahydrocyclopenta[c]pyran-1(3H)-one (2b): To a stirred solution of 2a (103 mg, 0.613 mmol) and imidazole (250 mg, 3.68 mmol) in CH$_2$Cl$_2$ (8.0 mL) at 0 °C was added tert-butylchlorodimethylsilane (276 mg, 1.84 mmol) in one portion. After 12 h, the mixture was diluted by addition of brine, and extracted with EtOAc. The organic extracts were washed with brine, dried over Na$_2$SO$_4$, and then concentrated. The crude product was chromatographed on silica gel. Yield 86% (148 mg). Colorless oil. $R_f$ (hexane/EtOAc = 4/1) = 0.30. $^{1}$H-NMR: δ 5.58–5.55 (m, 1H), 4.84–4.79 (m, 1H), 4.36 (ddd, $J = 11.7$, 8.4, 3.0 Hz, 1H), 4.22–4.16 (m, 1H), 3.38–3.33 (m, 1H), 2.89–2.80 (m, 1H), 2.14–2.05 (m, 1H), 1.86–1.84 (m, 3H), 1.80–1.71 (m, 1H), 0.88 (s, 9H), 0.06 (d, $J = 2.5$ Hz, 6H). $^{13}$C-NMR: δ 171.0 (C), 138.9 (C), 131.9 (CH), 76.6 (CH), 67.8 (CH$_2$), 52.2 (CH), 39.5 (CH), 25.9 (CH$_3$), 22.8 (CH$_2$), 18.2 (C), 15.6 (CH$_3$), -4.5 (CH$_3$), -4.9 (CH$_3$). IR: 2955, 2928, 2857, 1734, 1258, 1165, 1078, 835, 775. HRMS (ESI) $m/z$: [M+Na]$^+$ calcd for [C$_{15}$H$_{26}$NaO$_3$Si]$^+$, 305.1549; Found,
To a stirred solution of 2b (62 mg, 0.22 mmol) in dry THF (2.0 mL) at -40 °C was added diisobutylaluminum hydride (17% in toluene) (657 μL, 0.657 mmol). After 1 h at 0 °C, the reaction was quenched by addition of H2O (100 μL) and Na2SO4 (100 mg), and diluted with EtOAc. The mixture was filtered through a pad of Celite. The Celite was washed with EtOAc, and the combined organics were concentrated. The crude product was chromatographed on silica gel. Yield 88% (55 mg). Colorless oil. Rf (hexane/EtOAc = 1/1) = 0.25. 1H-NMR: δ 5.60 (m, 1H), 4.48 (dd, J = 5.2, 2.5 Hz, 1H), 3.72 (t, J = 6.5 Hz, 2H), 3.64 (dd, J = 11.5, 2.3 Hz, 1H), 3.60 (dd, J = 11.5, 2.3 Hz, 1H), 2.49 (m, 1H), 2.37 (m, 1H), 1.80 (m, 3H), 1.83–1.72 (m, 2H), 0.88 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H). 13C-NMR: δ -5.0, -4.1, 15.3, 18.0, 25.7, 29.1, 42.8, 51.6, 57.3, 61.3, 76.2, 128.1, 147.1. IR: 3558, 2953, 2930, 2886, 2859, 1472, 1437, 1254, 1015, 1001, 810, 775. HRMS (ESI) m/z: [M+Na]+ calcd for [C15H30NaO3Si]+, 309.1862; Found, 309.1866.

**tert-Butyldimethyl((7-methyl-1,3,4,4a,5,7a-hexahydrocyclopenta[c]pyran-5-yl)oxy)silane (12):** To a stirred solution of 11 (35 mg, 0.12 mmol) in dry DMF (1.0 mL) at 0 °C was added sodium hydride (60%) (20 mg, 0.49 mmol). After it was stirred for 5 min at 0 °C, p-toluenesulfonyl chloride (34 mg, 0.183 mmol) was added to the reaction. After 3 h at 0 °C, the mixture was diluted by addition of H2O, and extracted with EtOAc. The organic extracts were washed with brine, dried over Na2SO4, and then concentrated. The crude product was chromatographed on silica gel. Yield 55% (18 mg). Colorless oil. Rf (hexane/EtOAc = 4/1) = 0.60. 1H-NMR: δ 5.42 (m, 1H), 4.70–4.68 (m, 1H), 3.79–3.73 (m, 2H), 3.67 (dd, J = 11.4, 5.8 Hz, 1H), 3.52 (dd, J = 8.2, 4.5 Hz, 1H), 3.49 (dd, J = 8.2, 4.5 Hz, 1H), 2.37–2.31 (m, 1H), 1.74 (dd, J = 2.5, 1.5 Hz, 3H), 1.77–1.58 (m, 2H). 13C-NMR: δ -4.8, -4.5, 15.0, 18.2, 23.2, 25.9, 40.3, 45.2, 67.0, 68.7, 78.3, 129.6, 143.6. IR: 2955, 2857, 1508, 1489, 1362, 1256, 1140, 1094, 1067, 878, 835, 773. HRMS (ESI) m/z: [M+Na]+ calcd for [C15H28NaO2Si]+, 291.1756; Found, 291.1760.

**5-((tert-Butyldimethylsilyl)oxy)-1,3,4,4a,5,7a-hexahydrocyclopenta[c]pyran-7-carbaldehyde (13):** To a stirred solution of 12 (17 mg, 0.063 mmol) in dioxane (2.0 mL) was added SeO2 (42 mg, 0.38 mmol). After stirred for 3 h at 40 °C, the mixture was diluted by addition of H2O, and extracted with EtOAc. The organic extracts were washed with brine, dried over Na2SO4, and then concentrated. The crude product was chromatographed on silica gel. Yield 34% (6.0 mg). Colorless oil. Rf (hexane/EtOAc = 5/1) = 0.50. 1H-NMR: δ 9.83 (s, 1H), 6.74 (dd, J = 1.9, 1.9 Hz, 1H), 4.88 (ddd, J = 6.5, 1.9, 1.5 Hz, 1H), 4.00 (dd, J = 11.6, 5.6 Hz, 1H), 3.85 (dd, J = 11.6, 5.0 Hz, 1H), 3.78–3.72 (m, 1H), 3.56–3.51 (m, 1H), 2.90–2.86 (m, 1H), 2.48–2.42 (m, 1H), 1.87–1.69 (m, 1H), 0.94 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H). 13C-NMR: δ -4.8 (CH3), -4.6 (CH3), 18.1 (C), 22.8 (CH2), 25.8 (CH3), 40.3 (CH), 66.6 (CH2), 67.9 (CH2), 77.8 (CH), 147.1 (C), 153.7 (CH), 190.5 (CH). IR: 2953, 2927, 2857, 1680, 1103, 1068, 1047, 1004, 839, 775. HRMS
m/z: [M+Na]$^+$ calcd for [C$_{15}$H$_{26}$NaO$_3$Si]$^+$, 305.1549; Found, 305.1546.

5-((tert-Butyldimethylsilyl)oxy)-7-methyl-3,4,4a,5-tetrahydrocyclopenta[c]pyran-7a(1H)-ol: Yield 50% (9.0 mg). Colorless oil. R$_f$ (hexane/EtOAc = 1/1) = 0.40. $^1$H-NMR: δ 5.56 (m, 1H), 4.72 (m, 1H), 3.76 (d, J = 11.4 Hz, 1H), 3.78–3.67 (m, 2H), 3.57 (d, J = 11.4 Hz, 1H), 2.16 (brs, 1H), 2.16–2.06 (m, 1H), 1.99–1.91 (m, 1H), 1.74 (dd, J = 1.4, 1.4 Hz, 1H), 1.66–1.61 (m, 2H), 0.88 (s, 9H), 0.06 (s, 3H), 0.06 (s, 3H). $^{13}$C-NMR: δ -4.7 (CH$_3$), -4.4 (CH$_3$), 12.0 (CH$_3$), 18.1 (C), 22.8 (CH$_2$), 25.9 (CH$_3$), 47.1 (CH), 67.1 (CH$_2$), 74.6 (CH$_2$), 75.8 (CH), 80.0 (C), 130.5 (CH), 146.8 (C). IR: 3383, 2953, 2856, 1251, 1093, 974, 893, 837, 775. HRMS (ESI) m/z: [M+Na]$^+$ calcd for [C$_{15}$H$_{28}$NaO$_3$Si]$^+$, 307.1705; Found, 307.1705.

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REFERENCES AND NOTES


7. Reduction of ketone 8 with NaBH$_4$ gave complex mixture.


