行政院國家科學委員會專題研究計畫 成果報告

利用 D-(-)-quinic acid 合成新穎的 azepane 分子以及 amaryllidaceae 類之生物鹼作為 glycosidase 之抑制劑(第 3 年)

研究成果報告(完整版)

計 畫 類 別 ：個別型
計 畫 編 號 ：NSC 95-2113-M-032-004-MY3
執 行 期 間 ：97 年 08 月 01 日至 98 年 07 月 31 日
執 行 單 位 ：淡江大學化學系

計 畫 主 持 人：施增廉

計畫參與人員：碩士班研究生-兼任助理人員：蔣呈凡
碩士班研究生-兼任助理人員：梁名淙
碩士班研究生-兼任助理人員：李恆毅

處 理 方 式 ：本計畫可公開查詢

中 華 民 國 98 年 10 月 02 日

附件一

行政院國家科學委員會補助專題研究計畫 ■ 成 果 報 告 □期中進度報告

利用 D-(－)-quinic acid 合成新穎 azepane 分子以及 amaryllidaceae 類之生物鹼做為 glycosidase 之抑制劑

計畫類別：■ 個別型計畫　□ 整合型計畫
計畫編號：NSC 95 － 2113 － M － 004 － MY3 －
執行期間： 95 年 8 月 1 日至 98 年 7 月 31 日

計畫主持人：施增廉
共同主持人：
計畫參與人員：蔣呈凡 李恆毅 梁名淙

成果報告類型(依經費核定清單規定繳交)：□精簡報告 ■完整報告

本成果報告包括以下應繳交之附件：
□赴國外出差或研習心得報告一份
□赴大陸地區出差或研習心得報告一份
■出席國際學術會議心得報告及發表之論文各一份
□國際合作研究計畫國外研究報告書一份

處理方式：除產學合作研究計畫、提升產業技術及人才培育研究計畫、列管計畫及下列情形者外，得立即公開查詢
□涉及專利或其他智慧財產權，□一年□二年後可公開查詢

執行單位：淡江大學

中 華 民 國 九十八 年 八 月 三 日

本計畫自九十四年八月一日至九十七年七月三十一日，三年主要工作為利用 D-(-)-quinic acid 為起始物，進而合成一系列含氮的七圓環分子，並評估其生物活性。此成果報告包含有四部分：前三部分為以發表或即將發表和尚未完成部分，最後為九十八年七月份參加歐洲有機合成會議之心得報告。

第一部份

這部分已發表在 *Synthetic Communications* **2008,** *38***,** 4139-4149。我們主要目的是，利用 D-(-)-quinic acid 為起始物合成六圓環多氫氧基含氮的化合物。該類分子可視為醣水解酵素之抑制劑，一些抗生素之主要核心部分也含有此架構。

本實驗室已利用 D-(-)-quinic acid 為起始物發表了數篇文章站在這個起點上我們欲將其中的一個氫氧基置換成氮主要目的

Department of Chemistry, Tamkang University, Tamsui, Taipei County, Taiwan 25137, Republic of China

Keywords: aminocyclitol; dihydroxylation; quinic acid

ABSTRACT

As part of our interests in the synthesis of glycosidase inhibitors, we report herein an efficient synthesis of three new polyhydroxylated amino cyclohexane derivatives (aminocyclitols) which may potentially possess important biological activities. The key synthetic steps involve the highly stereoselective dihydroxylation of protected azido cyclohexene derivatives, **5**, **9** and **15** which can be easily prepared from D-(－)-quinic acid. The subsequent hydrogenation step was conducted under acidic condition to provide the target molecules in an efficient manner with high overall yields.

INTRODUCTION

The cyclic polyhydroxylated amines, also known as aminocyclitols, possess a wide variety of biological activities.[1] These sugar-mimetic compounds have attracted much interest because they are not only considered as glycosidase inhibitors but also constituted a key segment of aminoglycoside antibiotics.[2] There were few cases reported in the synthesis of these quercitol-like aminocyclitols. The synthetic tactics were mainly based on either the chiral pool or enantioselestive approaches.[3] In the past few years, we have developed and reported the synthesis of quercitols.[4] Quercitols have been shown to display the biological properties against certain enzymes.[5] Due to the structural similarity between quercitols and aminocyclitols, compounds **4**, **7**, and **13** were selected as intermediates in our synthesis of the title molecules (*vide infra*). The consequent steps were undergone the highly stereoselective dihydroxylation and deprotection to successfully synthesize three new aminocylitols, **1**, **2** and **3** in a very efficient manner.

RESULTS AND DISCUSSION

The synthesis of aminocyclitols **1**, **2** and **3** may be envisioned as shown in Scheme 1 and 2. Our synthetic strategy started with the azido **5** which was prepared from **4** in according to the literature procedure.[6] Compound **5** was subjected to the dihydroxylation under $KMnO_4/MgSO_4$ reaction condition[7] that has been shown to provide a highly diastereoselective adduct **6** as the only isolated product in 60% yield. The resulting stereochemistry of **6** was then determined by the coupling constants observed in COSY and NOESY experiments (Fig. 1a). The observation is in agreement with our previously reported result in the dihydroxylation of **4,** where the resulting stereochemistry of diol is in *trans* relationship to the C5 hydroxyl group.[4] Compound **6** was further hydrogenated over Pd/C under acidic condition to produce the desired aminocyclitol **1** in 85% yield.

Compound **7** was treated with trichloroacetonitrile and DBU to afford **8,** in 86% yield after a simple purification process of this mixture. Compound **8** was subsequently undergone Overman rearrangement[8] after refluxing in xylene to form **9** in 90% yield. Compound **9** was the subjected to the same dihydroxylation condition to isolate the sole stereoisomer **10** in 65% yield (the resulting stereochemistry is illustrated in Fig. 1b). No minor diasteromer was isolated from column chromatography or detected by NMR at this stage. The trichloroacyl and cyclohexyl groups of compound **10** were then removed by following a sequential treatment of base and acid, respectively. In an attempt to perform the deprotection of trichloroacetamide by using K_2CO_3 at ambient temperature,[9] the stable oxazolidinone **11** was formed as the major product. On the other hand, when lithium hydroxide (3 equiv.) was used under refluxing condition for 4h and followed by acidification with 6N HCl, sequentially, compound **2** was produced in 70% yield.

Compound **13** was treated with methanesulfonyl chloride and triethyl amine to give compound **14** (Scheme 2). When compound **14** was heated with sodium azide along with a catalytic amount of 15-crown-5, the unexpected compound **15** was isolated instead of the expected compound **16**. The reaction mechanism was shown to follow a S_N2' pathway and may be rationalized as shown in Fig. 2. Dihydroxylation of compound **15** was shown to give a highly diastereoselective and inseparable mixture based on the analysis of NMR spectrum. An attempt was made to separate these two isomers from their mixtures, by conducting their acetylation reactions. Surprisingly, the major isomer **18** was isolated from this mixture in 70% yield. Its stereochemistry was clearly determined by NMR studies (Fig. 1c). This result suggested that the dihydroxylation of **15** was proceeded in *anti* relationship relative to the azido group to give compound **17** as the main product. The acetylation of minor isomer seems to be unimportant to produce any detectable amount of product from column chromatography. Although the stereoselectivity was not exclusive, the result was still in consistent with our previous report[4] in the dihydroxylation of compound **13** which gave a moderate selectivity depending on the different protecting groups used (Fig. 3). Compound **18** was then subjected to a hydrogenation reaction under acidic condition (6N HCl) to give the resulting aminocyclitols **3,** in 85% yield. With compounds **1**, **2**, and **3** in hand, an attempt was made to utilize of compound **17** to synthesize a piperidine

derivative **19** based on our previous strategy[6] (Scheme 3). Unfortunately, no aminocyclization product **20** was isolated and only the reducing product **21** was obtained.

CONCLUSION

A general route for the synthesis of three new aminocyclitols **1**, **2**, and **3** from D-(－)-quinic acid has been illustrated and successfully carried out. It is shown that the dihydroxylation of compounds **5** and **9** is highly diastereoselective, in accordance with our previous observations. These compounds will be used for biological studies and may be readily served as intermediates for the synthesis of antibiotics.

ACKNODWLEDGES

We are gratefully acknowledged the National Science Council (NSC95-2113-M-032-004-MY3) and Tamkang University for financial support of this work. We also thank the National Center for High-Performing Computing for assistance.

EXPERIMENTAL

Optical rotations were measured on a Horiba Sepa-300. Melting points were determined by Fargo MP-2D and uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on either Bruker 300 or 600 MHz instruments. Chemical shifts were reported in ppm relative to the residual of solvents used ($CDCl_3$: 7.26 ppm (^{1}H), 77.0 ppm (^{13}C); CD_3OD: 4.78 ppm (^{1}H), 49.0 ppm (^{13}C); D_2O: 4.69 ppm (^{1}H)).

(1*R*,2*R*,3*R*,4*R*,5*S*)-5-Azido-1,2-*O*-cyclohexylidene-cyclohexane-1,2,3,4-tetrol (6). Compound **5** (0.280 g, 1.2 mmol) in EtOH (6 mL) was added dropwise of $KMnO_4$ (0.370 g, 2.4 mmol) /$MgSO_4$ (0.289 g, 2.4 mmol) in H_2O (1 mL) solution at 0 ℃. The mixture was allowed to warm up to ambient temperature and stirred for 8 h. At the end of which time, the mixture was filtrated through celite and washed with EtOAc. The organic solvent was removed, diluted with H_2O and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and purified by flash column chromatography (230－400 mesh SiO_2, EtOAc/hexane = 1/4－1/1) to afford **6** (0.194 g, 60%) as a pale yellow syrup. $[\alpha]^{24}_{D}$ +92.4 (*c* 0.6, MeOH). ^{1}H NMR (600 MHz, CD_3OD) δ 4.33 (dd, *J* = 11.7, 5.5 Hz, 1H), 4.13 (dd, *J* = 5.5, 3.8 Hz, 1H), 3.96 (dd, *J* = 3.8, 2.8 Hz, 1H), 3.74 (dd, *J* = 8.0, 2.8 Hz, 1H), 3.65 (ddd, *J* = 13.5, 8.0, 5.6 Hz, 1H), 2.25 (dt, *J* = 14.5, 5.6 Hz, 1H), 1.77 (dt, *J* = 14.5, 6.9 Hz, 1H), 1.70－1.62 (m, 4H), 1.60－1.54 (m, 4H), 1.43－1.37 (m, 2H). ^{13}C NMR (150 MHz, CD_3OD) δ 110.7, 79.0, 73.0, 72.9, 71.8, 60.2, 39.2, 35.9, 32.2, 26.3, 25.2, 24.9. ESI-HRMS calcd for $C_{12}H_{19}N_3NaO_4$ $[M+Na]^+$ 292.1273. Found: 292.1268.

(1*R*,2*S*,5*R*)-5-[(2,2,2-Trichloroethanimidoyl)oxy]-1,2-*O*-cyclohexylidene-3-cyclohexene-1,2,5-triol (8). To a solution of **7** (2.50 g, 11.85 mmol) in CH_2Cl_2 (50 mL) at 0 ℃ was added DBU

(3.60 mL, 23.0 mmol) and trichloroacetonitrile (2.40 mL, 23.0 mmol) and stirred at ambient temperature for 9 h. At the end of which time, the mixture was diluted with $NaHCO_3$ (saturated) and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and purified by flash column chromatography (230－400 mesh SiO_2, CH_2Cl_2/hexane = 1/5－1/3) to afford **8** (3.60 g, 86%) as a pale yellow syrup. Mp = 79.5－80 ℃. $[\alpha]^{25}_D$ +83.1 (*c* 0.42, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (br s, 1H), 6.02 (dd, *J* = 10.2, 2.2 Hz, 1H), 5.90 (ddt, *J* = 11.3, 4.2, 1.4 Hz, 1H), 5.63－5.52 (br m, 1H), 4.55－4.45 (m, 2H), 2.58 (dt, *J* = 13.6, 4.8 Hz, 1H), 1.97 (ddd, *J* = 13.6, 8.5, 2.5 Hz, 1H), 1.60 (br s, 8H), 1.37 (br s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 129.4, 128.5, 109.6, 91.4, 71.7, 71.4, 70.7, 37.5, 35.7, 30.8, 25.0, 24.0, 23.8. HRMS (FAB) calcd for $C_{14}H_{18}Cl_3NO_3$ $[M]^+$ 353.0352. Found: 353.0339.

(1*R*,2*S*,3*R*)-3-[(2,2,2-Trichloroacetyl)amino]-1,2-*O*-cyclohexylidene-4-cyclohexene-1,2-diol (9). A solution of **8** (0.192 g, 0.543 mmol) in xylene (10 mL) was heated to reflux at 150 ℃ for 48 h. At the end of which time, the organic solvent was removed under the reduced pressure and the resulting mixture was purified by flash column chromatography (230－400 mesh SiO_2, CH_2Cl_2/hexane = 1/5－1/3) to afford **9** (0.172 g, 90%) as a white solid. Mp = 113.0－113.5 ℃. $[\alpha]^{26}_D$ –97.7 (*c* 0.65, MeOH). ^{1}H NMR (300 MHz, C_6D_6) δ 6.40－6.25 (br s, 1H), 5.45－5.35 (m, 2H), 4.37－4.27 (m, 1H), 4.03－3.95 (m, 1H), 3.76 (t, *J* = 6.3 Hz, 1H), 2.15－2.06 (m, 2H), 1.80－1.68 (m, 2H), 1.68－1.42 (m, 6H), 1.31－1.11 (m, 2H). ^{13}C NMR (75 MHz, C_6D_6) δ 162.3, 128.2, 127.5, 110.0, 93.9, 77.3, 72.0, 53.0, 38.4, 35.6, 29.0, 26.1, 25.0, 24.7. HRMS (FAB) calcd for $C_{14}H_{18}Cl_3NO_3$ $[M]^+$ 353.0352. Found: 353.0338.

(1*R*,2*S*,3*R*,4*S*,5*R*)-3-[(2,2,2-Trichloroacetyl)amino]-5,6-*O*-cyclohexylidene-cyclohexane-1,2,4,5-tetrol (10). Flash column chromatography (230－400 mesh SiO_2, EtOAc/hexane = 1/4－1/2) afforded **10** as a white solid in 65% yield. Mp = 165.0－165.5 ℃. $[\alpha]^{23}_D$ －148.3 (*c* 1.2, MeOH). ^{1}H NMR (600 MHz, CD_3OD) δ 4.32 (ddd, *J* = 8.8, 4.9, 2.9 Hz, 1H), 4.19 (dd, *J* = 8.6, 4.9 Hz, 1H), 3.96 (dd, *J* = 8.6, 2.3 Hz, 1H), 3.92 (ddd, *J* = 10.2, 5.9, 2.0 Hz, 1H), 3.82 (t, *J* = 2.1 Hz, 1H), 2.14－2.04 (br m, 2H), 1.70－1.63 (m, 2H), 1.62－1.56 (m, 2H), 1.56－1.50 (m, 4H), 1.40－1.32 (br m, 2H). ^{13}C NMR (150 MHz, CD_3OD) δ 164.2, 110.7, 94.1, 76.2, 74.5, 73.4, 68.3, 57.2, 39.3, 36.6, 30.3, 26.3, 25.2, 24.9. ESI-HRMS calcd for $C_{14}H_{20}Cl_3NNaO_5$ $[M+Na]^+$ 410.0283. Found 410.0299.

(1*R*,2*S*,3*S*,4*S*,5*R*)-3-Amino-3-*N*,2-*O*-carbonyl-4,5-*O*-cyclohexylidene-cyclohexane-1,2,4,5-tetrol (11). Flash column chromatography (230－400 mesh SiO_2, EtOAc/hexane = 1/1) afforded **11** in 57% yield as a white solid. Mp = 200 ℃ (decomposed) $[\alpha]^{26}_D$ +13.8 (*c* 0.15, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08 (br s, 1H), 4.85 (dd, *J* = 8.8, 3.7 Hz, 1H), 4.53－4.47 (m, 1H), 4.27－4.14 (m, 2H), 2.60－2.41 (br s, 1H), 2.08 (ddd, *J* = 14.4, 10.4, 5.4 Hz, 1H), 1.79 (dt, *J* = 14.4, 2.5 Hz, 1H), 1.75－1.50 (m, 8H), 1.39 (br s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 109.5, 73.8, 71.6, 63.8, 53.9, 36.7, 33.6, 30.1, 29.9, 25.2, 24.1, 23.7. ESI-HRMS calcd for $C_{13}H_{20}NO_5$ $[M+H]^+$ 270.1341. Found: 270.1341.

(1*R*,2*R*,5*R*)-5-Chloro-1,2-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-diyldioxy]-3-cyclohexene-1,2-diol (14). A solution of **13** (0.345 g, 1.43 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (0.58 mL, 5.73 mmol) and methanesulfonic chloride (0.24 mL, 3.15 mmol), sequentially, and stirred at ambient temperature for 6 h. At the end of which time, the mixture was diluted with CH_2Cl_2 (x2) and washed with saturated $NaHCO_3$ (x2). The organic layer was dried over $MgSO_4$, concentrated and purified by flash column chromatography (230－400 mesh SiO_2, CH_2Cl_2/hexane = 1/4－1/1) to afford **14** (0.368 g, 94%) as a white solid. Mp = 81－84 ℃. $[\alpha]^{26}_D$ +292.0 (*c* 1.3, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ5.75 (d, *J* = 10.9 Hz, 1H), 5.71 (d, *J* = 10.9 Hz, 1H), 4.72 (m, 1H), 4.21 (d, *J* = 9.0 Hz, 1H), 4.12 (ddd, *J* = 12.4, 9.2, 3.7 Hz, 1H), 3.30 (s, 3H), 3.26 (s, 3H), 2.27－2.19 (m, 1H), 2.13 (ddd, *J* = 14.1, 11.7, 5.0 Hz, 1H), 1.34 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ129.7, 128.3, 100.5, 100.1, 69.4, 64.6, 54.4, 47.9 (x2), 35.5, 17.8 (x2).

(1*R*,2*R*,3*S*)-3-Azido-1,2-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-diyldioxy]-4-cyclohexene-1,2-diol (15). To a solution of **14** (0.10 g, 0.380 mmol) in DMF (3.0 mL) was added NaN_3 (0.250 g, 3.81 mmol) and a catalytic amount of 15-crown-5. The resulting mixture was heated at 50－60 ℃ for 12 h. At the end of which time, the mixture was diluted with Et_2O and washed with H_2O. The organic solvent was dried over $MgSO_4$ and removed under the reduced pressure. The resulting mixture was purified by flash column chromatography (230－400 mesh SiO_2, CH_2Cl_2/hexane = 1/4－1/1) to afford **15** (92 mg, 90%) as a white solid. Mp = 53－55 ℃. $[\alpha]^{26}_D$ +239.3 (*c* 3.56, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ5.77－5.67 (m, 1H), 5.46－5.38 (m, 1H), 4.15－4.07 (m, 1H), 3.84 (dt, *J* = 10.1, 5.9 Hz, 1H), 3.77 (dd, *J* = 10.1, 8.3 Hz, 1H), 3.34 (s, 3H), 3.27 (s, 3H), 2.38－2.26 (m, 1H), 2.26－2.12 (m, 1H), 1.35 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 127.4, 124.8, 99.5, 99.2, 73.1, 66.0, 61.0, 48.0, 30.0, 17.7. ESI-HRMS calcd for $C_{12}H_{20}N_3O_4$ $[M+H]^+$ 270.1454. Found: 270.1448.

(1*R*,2*S*,3*R*,4*R*,5*R*)-1,2-*O*-Diacetyl-3-azido-4,5-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-diyldioxy]-cyclohexane-1,2,4,5-tetrol (18). Flash column chromatography (230 － 400 mesh SiO_2, EtOAc/hexane = 1/8) afforded **18** as a white solid in 77% yield. Mp = 82—84 ℃. $[\alpha]^{26}_D$ +99.1 (*c* 1.8, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$) δ5.44 (t, *J* = 3.0 Hz, H-1), 4.69 (dd, *J* = 10.4, 3.2 Hz, H-2), 3.98 (ddd, *J* = 14.5, 10.0, 4.6 Hz, H-5), 3.88 (t, *J* = 10.4 Hz, H-3), 3.55 (t, *J* = 10.4 Hz, H-4), 3.23 (s, -OCH_3), 3.29 (s, -OCH_3), 2.13 (s, -OCOCH_3), 2.10 (s, -OCOCH_3), 2.00 (dt, *J* = 14.2, 4.0 Hz, H-6), 1.69 (ddd, *J* = 14.2, 12.6, 2.5 Hz, H-6), 1.38 (s, CH_3), 1.31 (s, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ169.9, 169.7, 99.9, 99.8, 72.6 (C-4), 72.5 (C-2), 67.7 (C-1), 64.7 (C-5), 60.1 (C-3), 48.1 (-O*C*H$_3$), 48.0 (-O*C*H$_3$), 30.5 (C-6), 20.9 (*C*H$_3$CO-), 20.7 (*C*H$_3$CO-), 17.6 (*C*H$_3$), 17.5 (*C*H$_3$). ESI-HRMS calcd for $C_{16}H_{25}N_3O_8$ $[M+Na]^+$ 410.1539. Found: 410.1544

(1*R*,2*R*,3*R*,4*R*,5*S*)-5-Aminocyclohexane-1,2,3,4-tetrol (1). A solution of **6** (0.299 g, 1.02 mmol) in MeOH (1.0 mL) and 2N HCl (1.0 mL) was hydrogenated over 10% Pd/C (12 mg, 0.01 mmol) for 48 h. At the end of which time, the mixture was filtrated through celite and washed with MeOH. The filtrate was concentrated, washed with Et_2O and H_2O. The aqueous layer was

concentrated and purified by flash column chromatography (230 — 400 mesh SiO_2, MeOH/CH_2Cl_2/10% NH_4OH = 2/10/0.5－2/3.5/0.5) to afford **1** (0.143 g, 85%) as a pale yellow syrup. $[\alpha]^{25}_D$ －44.4 (*c* 0.05, MeOH). ^1H NMR (600 MHz, D_2O) δ 3.95 (ddd, *J* = 11.6, 4.3, 3.2 Hz, 1H), 3.92 (t, *J* = 4.0 Hz, 1H), 3.92－3.87 (br m, 1H), 3.61 (dd, *J* = 10.0, 2.6 Hz, 1H), 3.06 (ddd, *J* = 14.2, 11.5, 4.2 Hz, 1H), 1.89 (dt, *J* = 11.7, 4.3 Hz, 1H), 1.62 (td, *J* = 11.7, 11.7 Hz, 1H). ^{13}C NMR (150 MHz, D_2O) δ 72.0, 71.8, 70.8, 66.0, 48.2, 31.4. ESI-HRMS calcd for $C_6H_{14}NO_4$ $[M+H]^+$ 164.0923. Found: 164.0917.

(1*R*,2*S*,4*S*,5*R*)-3-Aminocyclohexane-1,2,4,5-tetrol (2). A solution of **10** (0.060 g, 0.154 mmol) in MeOH/H_2O (9.0 mL, (v/v)=1/8) was treated with LiOH (0.011 g, 0.462 mmol) and heated to 110—120 ℃ for 4h. The organic solvent was removed under reduced pressure. The resulting solid was diluted with CH_2Cl_2 and H_2O. The aqueous layer was concentrated to afford **12** (85%) as a white solid. To this solid was added 6N HCl and stirred for 12 h. The solution was concentrated and the resulting mixture was purified by flash column chromatography (230－400 mesh SiO_2, MeOH/CH_2Cl_2/10% NH_4OH= 2/10/0.5－2/3.5/0.5) to afford **2** as a pale yellow syrup in 70% yield. $[\alpha]^{24}_D$ －58.1 (*c* 0.53, MeOH). ^1H NMR (600 MHz, D_2O) δ 4.01 (dt, *J* = 6.2, 3.0 Hz, 1H), 3.94 (dd, *J* = 8.1, 2.8 Hz, 1H), 3.92 (dd, *J* = 4.7, 2.8 Hz, 1H), 3.55 (d, *J* = 10.5 Hz, 1H), 2.97－2.93 (m, 1H), 1.87－1.82 (m, 1H), 1.80 (ddd, *J* = 14.5, 12.1, 2.8 Hz, 1H). ^{13}C NMR (150 MHz, D_2O) δ 71.8, 70.5, 68.2, 66.0, 51.3, 32.3. ESI-HRMS calcd for $C_6H_{14}NO_4$ $[M+H]^+$ 164.0923. Found: 164.0871.

(1*R*,2*S*,3*S*,4*S*,5*R*)-3-Aminocyclohexane-1,2,4,5-tetrol (3). Flash column chromatography (230－400 mesh SiO_2, MeOH/CH_2Cl_2/10% NH_4OH= 2/10/0.5－2/3.5/0.5) afforded **3** as a white solid in 85% yield. Mp = 170－180 ℃ (decomposed). $[\alpha]^{24}_D$ －34.5 (*c* 0.44, MeOH). ^1H NMR (600 MHz, D_2O) δ 4.02 (dd, *J* = 6.0, 3.0 Hz, 1H), 3.73 (ddd, *J* = 13.9, 9.2, 4.8 Hz, 1H), 3.59 (dd, *J* = 10.5, 3.0 Hz, 1H), 3.29 (dd, *J* = 9.7, 9.6 Hz, 1H), 3.10 (t, *J* = 10.5 Hz, 1H), 2.07 (ddd, *J* = 14.2, 4.8, 3.9 Hz, 1H), 1.49 (ddd, *J* = 14.2, 12.0, 2.5 Hz, 1H). ^{13}C NMR (150 MHz, D_2O) δ 74.4, 71.1, 68.3, 68.1, 54.4, 34.7. ESI-HRMS calcd for $C_6H_{14}NO_4$ $[M+H]^+$ 164.0923. Found: 164.0871.

REFERENCES AND NOTES

[1] (a) *Iminosugars as glycosidase inhibitors*, Stütz, A., Ed.; Wiley-VHC: Weinheim, **1999**. (b) Berecibar, A.; Crandjean, C.; Siriwardena, A. Synthesis and Biological Activity of Natural Aminocyclopentitol Glycosidase Inhibitors: Mannostatins, Trehazolin, Allosamidins, and Their Analogues. *Chem. Rev*. **1999**, *99*, 779－844.

[2] (a) Flatt, P. M.; Mahmud, T. Biosynthesis of aminocyclitol-aminoglycoside antibiotics and related compounds. *Nat. Prod. Rep.* **2007**, *24*, 358－392. (b) Mahmud, T.; Flatt, P. M.; Wu, X. Biosynthesis of Unusual Aminocyclitol-Containing Natural Products. *J. Nat. Prod.* **2007**, *70*, 1384－1391.

[3] (a) Chakraborty, C.; Vyavahare, V. P.; Dhavale, D. D. Intra-molecular nitrone-olefin cyclization of D-glucose derived allylic alcohol: synthesis of new aminocyclohexitols *Tetrahedron* **2007**, *63*, 11984－11990. (b) Serrano, P.; Casas, J.; Zucco, M.; Emeric, G.; Egido-Gabás, M.; Llebaria, A.;

Delgado, A. Combinatorial Approach to N-Substituted Aminocyclitol Libraries by Solution-Phase Parallel Synthesis and Preliminary Evaluation as Glucocerebrosidase Inhibitors. *J. Comb. Chem.* **2007**, *9*, 43－52. (c) Alegret, C.; Benet-Buchholz, J.; Riera, A. Stereodivergent Syntheses of Conduramines and Aminocyclitols. *Org. Lett.* **2006**, *8*, 3069－3072, (d) Serrano, P.; Llebaria, A.; Delgado, A. Regio- and Stereoselective Synthesis of Aminoinositols and 1,2-Diaminoinositols from Conduritol B Epoxide. *J. Org. Chem.* **2005**, *70*, 7829－7840. (e) Ogawa, S.; Asada, M.; Ooki, Y.; Mori, M.; Itoh, M.; Korenaga, T. Design and synthesis of glycosidase inhibitor 5-amino-1,2,3,4-cyclohexanetetrol derivatives from (－)-*vibo*-quercitol. *Bioorg. Med. Chem.* **2005**, *13*, 4306－4314. (f) Huang, F.; Li, Y.; Yu, J.; Spencer, J. B. Biosynthesis of aminoglycosidase antibiotics: cloning, expression and characterization of an aminotransferase involved in the pathway to 2-deoxystreptamine. *Chem. Commun.* **2002**, 2860－2861. (g) Yu, J.; Spencer, J. B. Convenient synthesis of 2-deoxy-*scyllo*-inosose and 2-deoxy-scyllo-inosamine: two key intermediates on the biosynthetic pathway to aminoglycoside antibiotics. *Tetrahedron Lett.* **2001**, *42*, 4219－4221. (h) Trost, B. M.; Dudash, J. Jr.; Hembre, E. J. Asymmetric Induction of Conduritols via AAA Reactions: Synthesis of the Aminocyclohexitol of Hygromycin A. *Chem. Eur. J.* **2001**, *7*, 1619－1629. (i) Marco-Contelles, J.; Pozuelo, C.; Jimeno, M. L.; Martínez, L.; Martínez-Grau, A. 6-Exo Free Radical Cyclization of Acyclic Carbohydrate Intermediates: A New Synthetic Route to Enantiomerically Pure Polyhydroxylated Cyclohexane Derivatives. *J. Org. Chem.* **1992**, *57*, 2625－2631.

[4] Shih, T.-L.; Lin, Y.-L.; Kuo, W.-S. Highly stereoselective and stereospecific syntheses of a variety of quercitols from D-(－)-quinic acid. *Tetrahedron* **2005**, *61*, 1919－1924.

[5] McCasland, G. E.; Naumann, M. O.; Durham, L. J. Alicyclic carbohydrates. XXXV. Synthesis of proto-quercitol. 220-MHz proton spectrum with the superconducting solenoid *J. Org. Chem.* **1968**, *33*, 4220－4227.

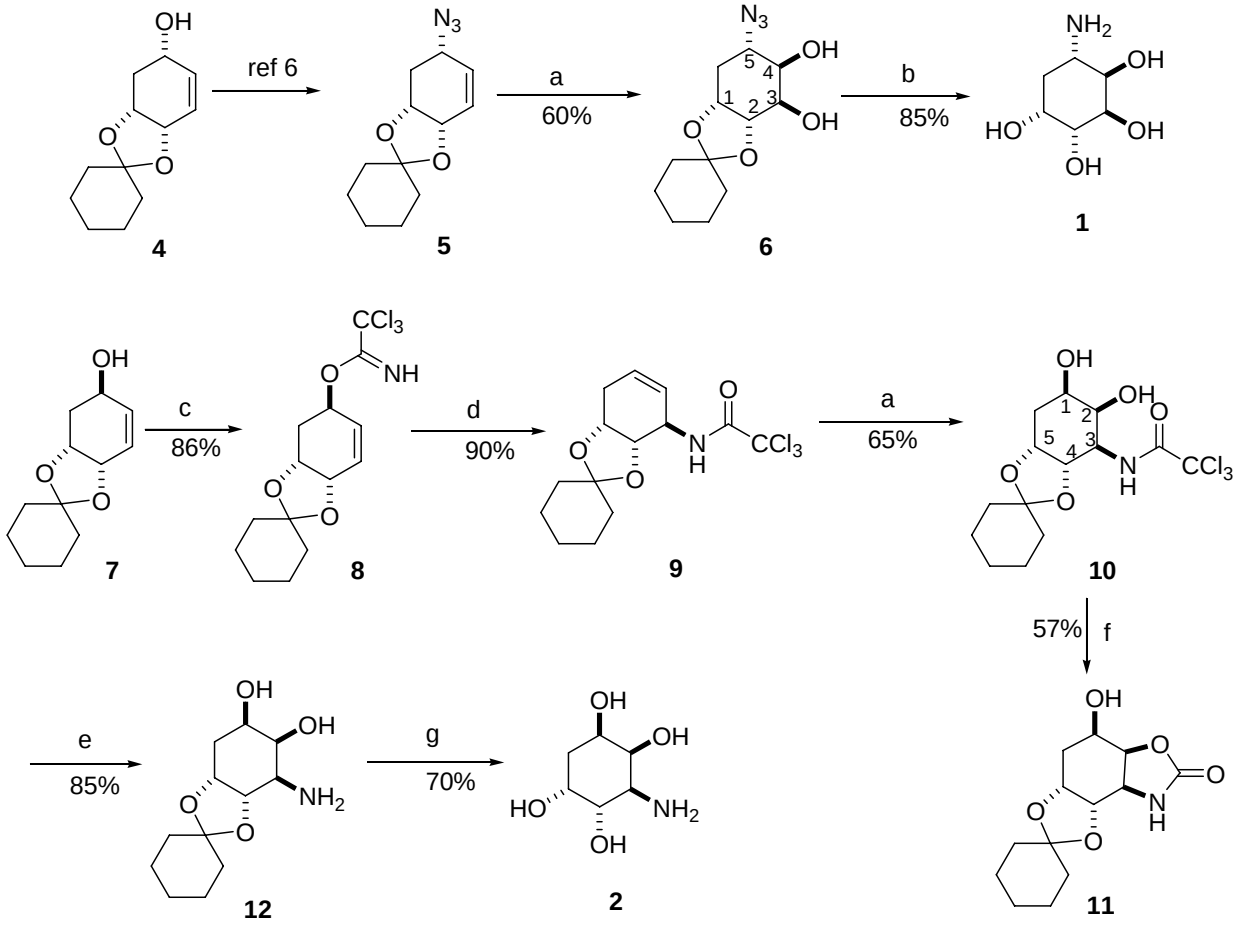
[6] Shih, T.-L.; Kuo, W.-S.; Lin, Y.-L. A facile synthesis of a new trihydroxy piperidine derivative and (+)-*proto*-quercitol from D-(－)-quinic acid. *Tetrahedron Lett.* **2004**, *45*, 5751－5754.

[7] (a) Gültekin, M. S.; Salamci, E.; Balci, M. A novel and short synthesis of (1,4/2)-cyclohex-5-ene-triol and its conversion to (±)-*proto*-quercitol *Carbohydr. Res.* **2003**, *338*, 1615－1619. (b) Salamci, E.; Secen, H.; Sütbeyaz, Y.; Balci, M. A Concise and Convenient Synthesis of DL-*proto*-Quercitol and DL-*gala*-Quercitol *via* Ene Reaction of Singlet Oxygen Combined with [2 + 4] Cycloaddition to Cyclohexadiene. *J. Org. Chem.* **1997**, *62*, 2453－2457. (c) Hudlicky, T.; Thorpe, A. Glycoconjugate Coupling Strategy: Synthesis of a L-***chiro***-Inositol-***gala***-Quercitol Conjugate and the Synthesis of **(+)**-*proto*-Quercitol. *Synlett* **1994**, 899－901. (d) Secen, H.; Salamci, E.; Sütbeyaz, Y.; Balci, M. An Efficient and Stereospecific Synthesis of ***proto***-Quercitol. *Synlett* **1993**, 609－610.

[8] (a) Berger, D.; Overman, L. E.; Renhove, P. A. Enantioselective total synthesis of (+)-isolaurepinnacin. *J. Am. Chem. Soc.* **1993**, *115*, 9305－9306. (b) Overman, L. E. Mercury (II)- and Palladium (II)-Catalyzed [3,3]-Sigmatropic Rearrangements. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 579－586.

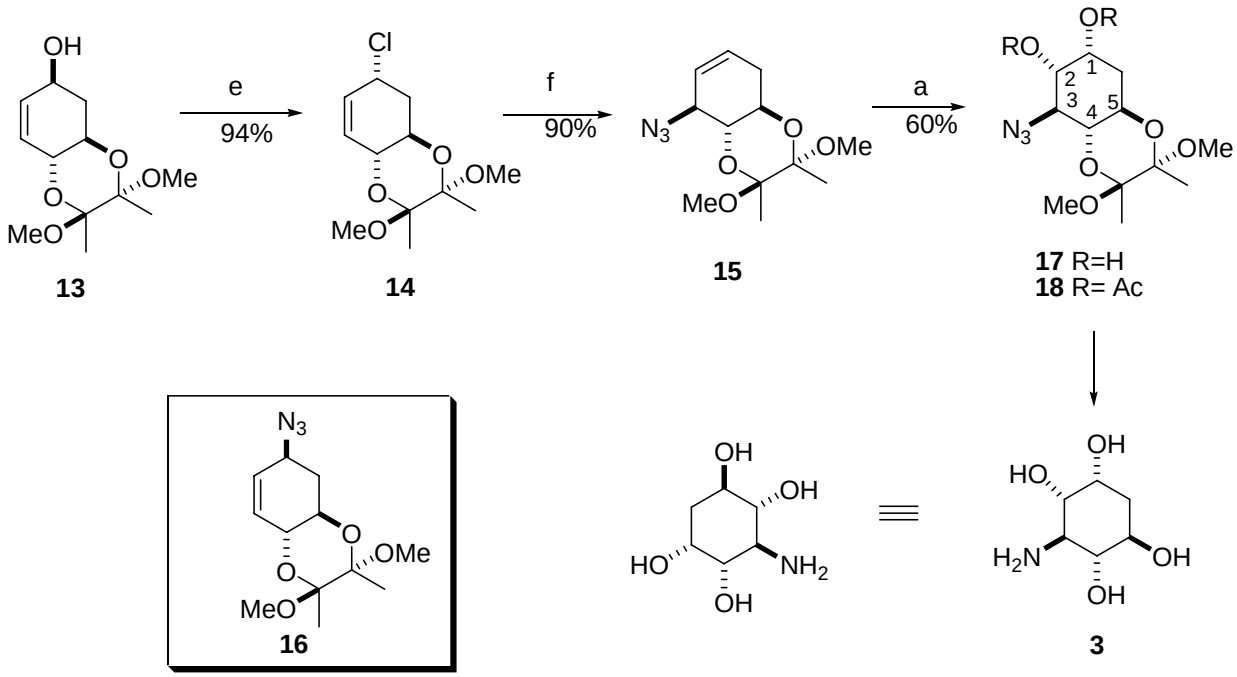
[9] Urabe, D.; Sugino, K.; Nishikawa, T.; Isobe, M. A novel deprotection of trichloroacetamide. *Tetrahedron Lett.* **2004**, *45*, 9405－9407.

Scheme 1. Synthesis of Aminocyclitols 1 and 2 from D-(−)-Quinic Acid



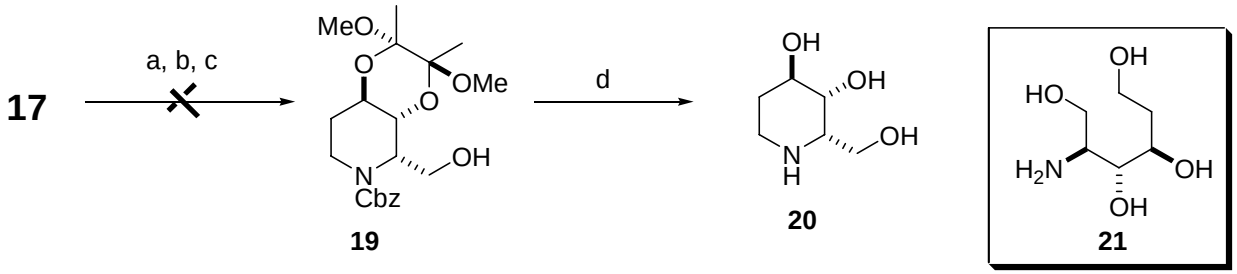
Reagents and conditions: (a) $KMnO_4$ (2 equiv.)/$MgSO_4$ (2 equiv.), EtOH/H_2O = 6/1 (v/v); (b) H_2, Pd/C, MeOH/2N HCl; (c) CCl_3CN, DBU, CH_2Cl_2; (d) xylene, reflux; (e) LiOH (3 equiv.), MeOH/H_2O; (f) K_2CO_3, MeOH; (g) 6N HCl

Scheme 2. Synthesis of Aminocyclitol 3 from D-(−)-Quinic Acid

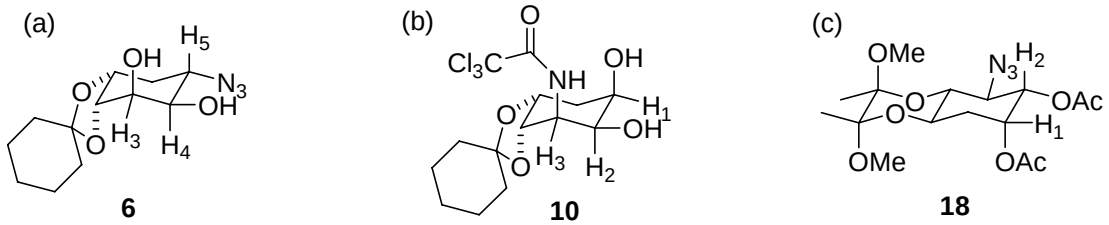


Reagents and conditions: (a) MsCl, CH_2Cl_2, Et_3N; (b) NaN_3, DMF, 15-crown-5 (cat); (c) $KMnO_4/MgSO_4$ then Ac_2O, pyr. (d) H_2/Pd/C, 6N HCl/MeOH

Scheme 3. Attempt in the Synthesis of a Piperidine Derivative 20.



Reagents and conditions: (a) H_2, Pd/C, MeOH then CbzCl, $NaHCO_3$, 1,4-dioxane; (b) $NaIO_4$, MeOH; (c) $NaBH_3CN$, AcOH, MeOH; (d) H_2, Pd/C, 6N HCl



J_{H4-H5} = 8.0 Hz
J_{H3-H4} = 2.8 Hz

J_{H1-H2} = 2.0 Hz

J_{H2-H3} = 10.4 Hz

Fig. 1 Coupling constants account for the determination of stereochemistry of dihydroxylation of **5**, **9** and **15**

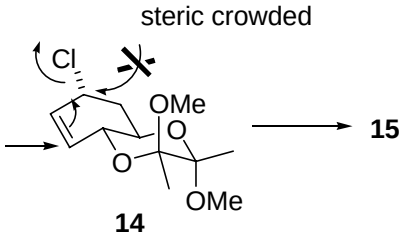


Fig. 2 The plausible mechanism of synthesis of **15**

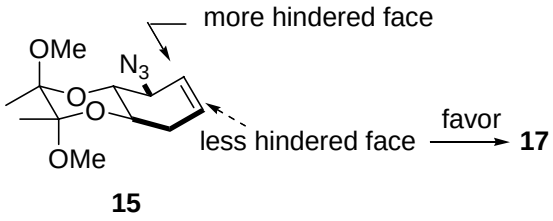


Fig. 3 Steric effect account for the highly diastereoselective dihydroxylation of **15**

第二部份

我們閱讀之文獻顯示，市場上已有氮烷基化六圓環之化合物用於治療糖尿病之藥物。另外，我們猜測若能將七號碳的位置上引入一烷基，或許具有潛力成為藥物，這類分子尚未被合成出。同樣的我們利用了 D-(─)-quinic acid，經約十個合成步驟，分別合成了七號碳及氮烷基化七圓環之化合物，經與中研院生化所林俊宏研究員合作，測試其生物活性，發現其中一個化合物對*β*-galactosidase 具有很好之活性，而且七號碳上必須是丁烷，其絕對構形是 S。經分子模型分析，該烷基恰深入其鄰近之凹槽內，因七圓環具結構靈活性，所以這方面值得進一步探討。我們已整理出結果將近期投稿。

Design and Synthesis of Polyhydroxy 7- and *N*-Alkyl-azepanes as Potent Glycosidase Inhibitors

Tzenge-Lien Shih[a,*], Ming-Tsung Liang[a], Kuen-Da Wu, Zhi-Jay Tu[b], and Chun-Hung Lin[b,*]

a. Department of Chemistry, Tamkang University, Tamsui, Taipei County, Taiwan 25137
b. Institute of Biological Chemistry, Academia Sinica, NanKang, Taipei, 11529 Taiwan

Email:tlshih@mail.tku.edu.tw; chunhung@gate.sinica.edu.tw

Abstract

We report herein the first efficient syntheses of polyhydroxyazepanes that contain an alkyl group at either 7- or *N*-positions. The syntheses were accomplished in eight to ten steps from D-(─)-quinic acid. Among them the polyhydroxy 7-butyl azepane, compound **3**, which adopted the *R*-configuration at C-7 position was shown to give potent inhibition against *β*-galactosidase (IC_{50} = 3 μM). Strongly supported by the analysis of computational modeling, a butyl group fits well to the hydrophobic cavity near the active site of *β*-galactosidase. The preliminary biological data lead us to conclude that the length of alkyl groups with correct stereochemistry at C-7 position is essential for acquiring extra binding affinity. In addition, the polyhydroxy *N*-butyl and -methyl azepanes were also synthesized in similar efficiency in comparison with their biological activities.

Introduction

Polyhydroxypiperidines have attracted immense attention from the synthetic community owing to their biological importance in the development of glycosidase inhibitors.[1] Miglitol™, *N*-hydroxyethyl-deoxynojirimycin (or *N*-hydroxyl-DNJ), is developed to target the intestinal disaccharidase and prescribed for the treatments of type II diabetes[2] (Figure 1). Also *N*-butyl-deoxynojimicycin (NB-DNJ) was used in the treatment of Gaucher disease.[3] The introduction of an alkyl group to the ring nitrogen makes drug molecules more hydrophobic for the purpose of better absorption and delivery.[4] The seven-membered-ring azasugars, so-called

azepanes, have been attracted attention due to the activities of glycosidase inhibitors may be owing to their structural flexibility.[1c] A recent report has revealed that the alkyl groups located in the ring or at nitrogen of azepanes to represent potent inhibition against various enzymes.[5] We have been devoting in the discovery of the potential of azepanes and reported the synthesis of a series of trihydroxyazepanes.[6] We found some candidates shown to be potent glycosidase inhibitors and the activities were compatible to the related piperidines. In continuation of our efforts in the synthesis of various polyhydroxyazepanes, we are interested in several important issues, including how to introduce hydroxyl groups to various positions of the sugar ring with desired stereochemistry and how to enhance the inhibition potency at molecular basis. We report herein the expeditious syntheses of polyhydroxyazepanes that contain an extra methyl or butyl group at either C7- or *N*-positions to compare with the biological activities of the Miglitol or NB-DNJ. Because there is no reported synthesis up to date, it is intriguing to study if the additional alkyl group contributes to the binding affinity.

Results and Discussion

Our synthetic strategy is straightforward to the target molecules. The alkyl groups at C-7 position were introduced by the lithium reagents at the early stage. Enone **15**[7], prepared in four steps from D-(–)-quinic acid, was treated with $CeCl_3$[8] and then added dropwise by a solution of methyllithium at -78 °C to provide the separable epimeric mixtures of **16** (the major isomer, 82% yield) and **17** (the minor isomer, ～8% yield) which was mixed with a trace amount of other impurities (Scheme 1). The stereochemistry of **16** was elucidated according to the NOESY spectra due to the observation of the cross peak between the methyl group and the hydrogen at C-1 position. It is not surprising that the nucleophile approached from the less hindered side of **15**. The consecutive rearrangement and oxidation reactions occurred to produce enone **20** when the tertiary alcohol **16** or **17** was mixed with pyridinium chlorochromate (PCC) and silica gel[9] in CH_2Cl_2 under refluxing condition. Interestingly the reaction rate was closely related to the stereochemical configuration at C-5 position. When compound **16** was treated with PCC (3 equiv) and refluxed in CH_2Cl_2 for 10 h, compound **20** was obtained in 41% yield (61% yield based on recovery of **16**). In contrast, compound **17** was completely converted into **20** within 1.5 h in 67% yield under the same condition. Steric hindrance was realized to play a determining role in the reactivity because compound **17** was much more reactive owing to the less hindered hydroxyl group. Luch's reduction ($NaBH_4$ and $CeCl_3{\cdot}7H_2O$) of **20** generated the sole product **22** with exclusive stereoselectivity. The allylic alcohol of **22** was protected by using MOMCl and diisopropylethylamine to give **24**. In accordance with our previous report,[7] the double bond of **24** was subjected to dihydroxylation (with $KMnO_4/MgSO_4$), oxidative cleavage (with $NaIO_4$) and reductive aminocyclization (with benzylamine and $NaBH_4$),[6] leading to the separable epimeric products **26** and **27** in 47% and 7% isolated yields (three steps in total), respectively. The assignment of C7-stereochemistry of **26** and **27** was established on the basis of the C7-methyl group and H5 of the former that possessed the special correlation but not for compound **27** by NOESY spectra. The final deprotection of **26** and **27** was carried out individually by

hydrogenation over Pd/C in 2N HCl to afford the desired 7(*R*)-methyl-azepanes-3,4,5-triol **1** (86%) and its 7(*S*)-epimer **2** (92%) respectively.

A similar approach was carried out to introduce a butyl group at 7-position of the azepanes. Compound **18** with the same stereochemical configuration as **16** was obtained in a moderate yield (70%), but the other epimer **19** was isolated only in a trace amount. The PCC oxidation of **18** provided **21** in a moderate yield (47%, 69% based on recovery of **18**). The subsequent steps led to target molecule **3** and **4** were also efficient (Scheme 1).

On the other hand, formation of inseparable diastereomeric mixture **31/32** and **33/34** (ratio of ~1/1) was observed when compound **30**[10] was either methylated or butylated, respectively. In contrast to the successive rearrangement and oxidation of **16**/**17** and **18**/**19** where the steric effect serves as a major factor, the methylation and butylation of the mixtures **31**/**32** and **33**/**34** were relatively faster and were converted to compounds **35** and **36** within 4 h in 85% and 88% yield, respectively. The subsequent reduction provided **37** and **38** and protection with MOM afforded **39** and **40**, respectively. Further dihydroxylation, oxidative cleavage and reductive aminocyclization produced pairs of inseparable diasteromers **41**/**42** and **43**/**44** (ratio of ~10:1) in 43% and 36% total yields, respectively. Efforts have been made to separate each diastereomer after final deprotection still lead to the isolation of product mixtures **5**/**6** and **7**/**8**. The NOESY indicated compounds **5** and **7** to be the major diastereomeric products due to the close relationship between C-7 alky groups and H5, respectively.

Furthermore, six *N*-alkylazepanes **9—14** were prepared from compounds **45**, **46** and **51** in a similar manner, as shown in Scheme 2. The major differences included the oxidant used in the dihydroxylation that was replaced with $RuCl_3$, as well as the amine used in the reductive amination that was substituted with either methylamine or butylamine instead. The yields were comparable to those as in Scheme 1.

Conclusion

We have successfully synthesized a new family of trihydroxyazepanes that contains a methyl or butyl group at either C7- or *N*-positions. The preparation was carried out in a facile manner from D-(－)-quinic acid. The preliminary result in the inhibition activity indicated that the azepane with the butyl substituent and 7*R*-configuration has better inhibition potency against galactosidase, as compared to the methyl homologue. Also the stereochemistry at C-7 is essential and the enhanced inhibition is likely due to extra binding interactions with the hydrophobic residue in the vicinity of the enzyme activity site. In this article, we provide the important information of azepanes regarding to the alkyl substituents at C-7 and *N*-positions and their structure flexibility relative to the corresponding piperidine analogues.

Acknowledgements

Supports provided by the National Science Council (NSC95-2113-M-032-004-MY3) and Tamkang University are gratefully acknowledged. Authors thank the National Center for High-Performing Computing for assistance.

Experimental

Reactions were conducted under anhydrous solvents and an inert atmosphere of nitrogen unless otherwise noted. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on either Bruker 300 or 600 MHz spectrometers. Chemical shifts were reported relative to the residual of deuterium solvents: $CDCl_3$ δ7.26; CD_3OD δ4.89; D_2O δ4.6 ppm for ^{1}H and $CDCl_3$ δ 77.0; CD_3OD δ49.15 ppm for ^{13}C. Optical rotations were measured with Horbia polarimeter.

General procedure of PCC oxidation

To a stirred solution of compound **16** in CH_2Cl_2, for example, was treated with PCC (3 equiv.) and silica gel (same weight as the amount of PCC). The mixture was heated in CH_2Cl_2 under refluxing condition and the reaction was monitored by TLC. The resulting mixture was filtrated through a pad of silica gel, washed by CH_2Cl_2 and purified by flash column chromatography.

General procedure of litheration

$CeCl_3 \cdot 7H_2O$ was heated at 110 ℃under vacuum system (*ca* 10^{-2} mmHg) for 4h in order to remove water. To this dried $CeCl_3$ was added THF and stirred for 20 min. This mixture was sonicated for 1h before cooled to -78 ℃. Three equivalents of corresponding lithium reagent (MeLi or BuLi (1.6 M)) were slowly added to this mixture. Enone in THF was added to the above mixture via cannulation. After the media was stirred for 30 min at that temperature, the reaction was quenched by addition of NH_4Cl (saturated) and allowed to warm to ambient temperature. The mixture was extracted with ether and dried over $MgSO_4$. The resulting crude product was purified by flash column chromatography.

General procedure of dihydroxylation, oxidative cleavage and reductive aminocyclization

This reaction was conducted in a three-step sequence. To the corresponding diene in EtOH and H_2O (v/v=9/1) was treated with $KMnO_4$ (2 equiv.) and $MgSO_4$ (2 equiv.) at 0 ℃. The stirring mixture was allowed to warm up to ambient temperature and stirred for another 10 h. At the end of which time, the reaction mixture was filtrated through celite and the filtrant was concentrated. The crude mixture was extracted with EtOAC and washed with H_2O. The organic layer was dried over $MgSO_4$, filtrated and concentrated. The mixture was no further purification and went on for the next step. To the mixture was dissolved in MeOH and $NaIO_4$ (3 equiv.) was added. The reaction was heated at 50 ℃ for 10 h. The solvent was removed, extracted with EtOAc, and washed with $NaHCO_3$ (sat'd). The organic layer was dried over $MgSO_4$ and concentrated. The

resulting syrup was dissolved in MeOH and 3Å molecular sieve was added. This mixture was cooled to -78 ℃ and a mixture solution of $BnNH_2$/AcOH/MeOH (pH 5─6) was added via cannulation. This solution was stirred for 10 minutes and $NaBH_3CN$ (1 equiv.) was add and stirred for 1 h. The reaction was allowed to warm up to ambient temperature and stirred for another 2 h. At the end of reaction time, the mixture was extracted with EtOAc and washed with $NaHCO_3$ (sat'd). The organic layer was dried over $MgSO_4$ and purified by flash column chromatography.

(1*R*,2*R*)-1,2-*O*-Cyclohexylidene-5-methyl-3-oxo-4-cyclohexene (20). Flash column chromatography (230－400 mesh SiO_2, EtOAc/Hex=1/15－1/4) afforded a white solid. Mp = 115.0－115.5 ℃. $[\alpha]^{23}_D$ －51.2 (*c* 1.3, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92 (s, 1H), 4.59－4.54 (m, 1H), 4.19 (d, *J* = 5.1 Hz, 1H), 2.71 (d, *J* = 4.1 Hz, 1H), 1.97 (s, 3H), 1.63－1.30 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.0, 158.4, 135.4, 125.1, 109.8, 74.2, 72.4, 37.0, 35.4, 32.6, 24.9, 24.4, 23.7. HRMS (ESI) calcd for $C_{13}H_{18}NaO_3$ $[M+Na]^+$ 245.1154. Found: 245.1144.

(1*R*,2*R*)-5-Butyl-1,2-*O*-cyclohexylidene-3-oxo-4-cyclohexene-1,2-diol (21). Flash column chromatography (230－400 mesh SiO_2, EtOAc/Hex=1/20－1/6) afforded a colorless syrup. $[\alpha]^{26}_D$ －32.1 (*c* 1.0, MeOH). ^{1}H NMR (300 MHz, C_6D_6) δ 5.91 (s, 1H), 4.13 (td, *J* = 5.1, 1.6 Hz, 1H), 3.97 (d, *J* = 5.1 Hz, 1H), 2.30 (d, *J* = 19.1 Hz, 1H), 1.91 (dd, *J* = 19.1, 0.8 Hz, 1H), 1.74－1.45 (m, 10 H), 1.22－0.95 (m, 6H), 0.74 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 195.1, 160.7, 125.1, 110.0, 75.4, 73.4, 38.1, 37.7, 36.5, 31.6, 29.2, 25.7, 24.6, 24.5, 22.8, 14.3. HRMS (ESI) calcd for $C_{16}H_{24}NaO_3$ $[M+Na]^+$ 287.1623. Found: 245.1148.

(1*R*,2*S*)-1,2-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-dioxy]-5-methyl-3-oxo-4-cyclohexe (35). Flash column chromatography (230－400 mesh SiO_2, EtOAc/Hex=1/15－1/6) afforded a white solid in 85% yield. Mp = 153.3－153.6 ℃. $[\alpha]^{23}_D$ +39.9 (*c* 1.2, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (s, 1H), 4.18 (d, *J* = 11.3 Hz, 1H), 4.03 (ddd, *J* = 11.3, 9.9, 6.1 Hz, 1H), 3.26 (s, 3H), 3.21 (s, 3H), 2.60－2.43 (m, 2H), 1.97 (s, 3H), 1.38 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.0, 158.1, 126.3, 100.3, 99.3, 74.3, 67.1, 48.5, 48.1, 36.5, 24.5, 17.8 (x2). HRMS (ESI) calcd for $C_{13}H_{20}NaO_5$ ($[M+Na]^+$) 279.1208. Found: 279.1200.

(5*R*,6*S*)-5,6-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-dioxy]-3-butyl-cyclohex-2-enone (36). Flash column chromatography (230－400 mesh SiO_2, EtOAc/Hex=1/15－1/5) afforded a colorless syrup in 88% yield. $[\alpha]^{25}_D$ +40.2 (*c* 2.4, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (s, 1H), 4.19 (dt, *J* = 11.3, 1.1 Hz, 1H), 4.07－3.95 (m, 1H), 3.27 (d, *J* = 1.2 Hz, 3H), 3.21 (d, *J* = 1.2 Hz, 3H), 2.62－2.42 (m, 2H), 2.21 (t, *J* = 7.7 Hz, 2H), 1.50－1.20 (m, 10H), 0.87 (td, *J* = 7.3, 0.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.7, 162.5, 125.7, 100.8, 99.8, 75.0, 67.8, 49.0, 48.6, 38.2, 35.7, 29.6, 22.8, 18.3, 18.2, 14.4. HRMS (ESI) calcd for $C_{16}H_{26}NaO_5$ ($[M+Na]^+$) 321.1678. Found: 321.1670.

(1*R*,2*R*,3*R*)-1,2-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-dioxy]-5-methyl-3-*O*-methoxymethyl-4-cyclohexene-1,2,3-triol (39). Flash column chromatography (230－400 mesh SiO_2, EtOAc/Hex = 1/35－1/15) afforded a colorless syrup in 89% yield. $[\alpha]^{24}_D$ +147.1 (*c* 3.0, MeOH). ^{1}H NMR (300 MHz, C_6D_6) δ 5.31 (br s, 1H), 4.90 (d, *J* = 6.6 Hz, 1H), 4.70 (d, *J* = 6.6 Hz, 1H), 4.36 (dd, *J* = 7.1, 1.8 Hz, 1H), 3.94－3.79 (m, 2H), 3.30 (s, 3H), 3.20 (s, 3H), 3.06 (s, 3H), 2.13 (dd, *J* = 16.0, 9.7 Hz, 1H), 1.99 (dd, *J* = 16.0, 5.5 Hz, 1H), 1.42 (s, 3H), 1.33 (s, 6H). ^{13}C NMR (75 MHz, C_6D_6) δ 133.8, 123.7, 123.5, 99.7, 99.6, 96.9, 75.7, 74.8, 66.6, 55.3, 47.9, 35.6, 23.2, 18.4. HRMS (ESI) calcd for $C_{15}H_{26}NaO_6$ ($[M+Na]^+$) 325.1627. Found: 325.1636.

(1*R*,2*R*,3*R*)-1,2-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-dioxy]-5-butyl-3-*O*-methoxymethyl-4-cyclohexene-1,2,3-triol (40). Flash column chromatography (230－400 mesh SiO_2, EtOAc/Hex =1/25－1/15) afforded a colorless syrup in 94% yield. $[\alpha]^{24}_D$ +88.2 (*c* 1.9, MeOH). ^{1}H NMR (300 MHz, C_6D_6) δ 5.41 (br s, 1H), 4.97 (d, *J* = 6.5 Hz, 1H), 4.76 (d, *J* = 6.5 Hz, 1H), 4.49－4.46 (br m, 1H), 4.01 (dd, *J* = 10.5, 7.6 Hz, 1H), 3.93 (td, *J* = 10.5, 5.8 Hz, 1H), 3.33 (s, 3H), 3.22 (s, 3H), 3.11 (s, 3H), 2.30－2.20 (m, 1H), 2.08 (dd, *J* = 16.3, 5.7 Hz, 1H), 1.78 (dd, *J* = 7.6, 6.6 Hz, 2H), 1.38 (s, 3H), 1.37 (s, 3H), 1.27－1.09 (m, 4H), 0.79 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 138.0, 122.7, 99.8, 99.7, 97.0, 75.9, 75.0, 66.8, 55.4, 48.0, 47.9, 37.3, 34.2, 30.2, 23.0, 18.5, 14.5. HRMS (ESI) calcd for $C_{18}H_{32}NaO_6$ ($[M+Na]^+$) 367.2097. Found: 367.2082.

(1*S*,2*S*,3*S*)-1,2-*O*-Cyclohexylidene-5-methyl-4-cyclohexene-1,2,3-triol (22). Flash column chromatography (230－400 mesh SiO_2, EtOAc/Hex=1/16－1/8) afforded a white solid in 86% yield. Mp = 95.0－96.0 ℃. $[\alpha]^{25}_D$ +14.2 (*c* 1.4, MeOH). ^{1}H NMR (300 MHz, C_6D_6) δ 5.55 (t, *J* = 1.1 Hz, 1H), 4.20 (ddd, *J* = 7.5, 4.3, 1.3 Hz, 1H), 4.10 (ddd, *J* = 7.5, 4.4, 2.5 Hz, 1H), 3.99 (ddd, *J* = 9.3, 4.3, 2.2 Hz, 1H), 2.88 (d, *J* = 9.6 Hz, -OH), 2.08 (dd, *J* = 16.2, 2.6 Hz, 1H), 1.62－1.24 (m, 12H), 1.24－1.23 (m, 2H). ^{13}C NMR (75 MHz, C_6D_6) δ 134.1, 126.0, 109.5, 76.6, 73.2, 67.7, 36.7, 34.9, 33.4, 26.0, 24.7, 24.4, 23.9. HRMS (ESI) for $C_{13}H_{20}NaO_3$ ($[M+Na]^+$) 247.1310. Found: 247.1305

(1*S*,2*R*,3*R*)-5-Butyl-1,2-*O*-cyclohexylidene-4-cyclohexene-1,2,3-triol (23). Flash column chromatography (230－400 mesh SiO_2, EtOAc/Hex = 1/25－1/10) afforded a colorless syrup in 87% yield. $[\alpha]^{25}_D$ +14.1 (*c* 1.4, MeOH). ^{1}H NMR (300 MHz, C_6D_6) δ 5.56 (t, *J* = 1.1 Hz, 1H), 4.21 (ddd, *J* = 7.6, 4.4, 1.1 Hz, 1H), 4.11 (dt, *J* = 7.6, 1.7 Hz, 1H), 3.95－3.80 (m, 1H), 2.75 (d, *J* = 15.8, 2.6 Hz, 1H), 2.14 (dd, *J* = 15.8, 2.6 Hz, 1H), 1.91 (t, *J* = 7.0 Hz, 2H), 1.65－1.50 (m, 9H), 1.34－1.20 (m, 6H), 0.86 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 138.2, 125.5, 109.5, 75.8, 73.2, 67.8, 37.5, 36.6, 34.8, 31.9, 30.1, 26.0, 24.7, 24.5, 23.0, 14.5. HRMS (ESI) calcd for $C_{16}H_{27}O_3$ ($[M+H]^+$) 267.1960. Found: 267.1955.

(1*R*,2*R*,3*R*)-1,2-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-dioxy]-5-methyl-4-cyclohexene-1,2,3-triol (37). Flash column chromatography (230－400 mesh SiO_2, EtOAc/Hex = 1/12－1/6) afforded a white solid in 81% yield. Mp = 67.0－68.0 ℃. $[\alpha]^{25}_D$ +160.2 (*c* 1.4, MeOH). ^{1}H NMR (300 MHz, C_6D_6) δ 5.30 (s, 1H), 4.35 (t, *J* = 1.8 Hz, 1H), 3.86 (ddd, *J* = 16.8, 10.5, 6.0 Hz, 1H), 3.76

(dd, J = 10.5, 7.7 Hz, 1H), 3.18 (s, 3H), 3.09 (s, 3H), 2.25—2.10 (m, 2H), 2.00 (dd, J = 16.8, 6.0 Hz, 1H), 1.41 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 133.4, 125.0, 99.8, 99.7, 76.0, 70.9, 66.4, 47.9, 35.9, 23.1, 18.5, 18.4. HRMS (ESI) calcd for $C_{13}H_{22}NaO_5$ ([M+Na]$^+$) 281.1365. Found: 281.1375.

(1*R*,2*R*,3*R*)-1,2-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-dioxy]-5-butyl-4-cyclohexene-1,2,3-triol (38). Flash column chromatography (230—400 mesh SiO_2, EtOAc/Hex = 1/16—1/6) afforded a colorless syrup in 71% yield. $[\alpha]^{25}_D$ +153.0 (*c* 1.7, MeOH). ^{1}H NMR (300 MHz, C_6D_6) δ 5.39 (br s, 1H), 4.43 (br s, 1H), 3.91 (ddd, J = 16.5, 10.5, 6.0 Hz, 1H), 3.82 (dd, J = 10.5, 7.6 Hz, 1H), 3.21 (s, 3H), 3.10 (s, 3H), 2.68 (d, J = 3.6 Hz, -OH), 2.33—2.20 (m, 1H), 2.10 (dd, J = 15.9, 5.8 Hz, 1H), 1.74 (t, J = 7.7 Hz, 1H), 1.45 (s, 3H), 1.42(s, 3H), 1.29—1.05 (m, 4H), 0.79 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 137.4, 124.2, 99.8, 99.7, 76.2, 70.9, 66.6, 48.0, 47.9, 37.1, 34.4, 30.1, 23.0, 18.5, 18.4, 14.5. HRMS (ESI) calcd for $C_{16}H_{28}NaO_5$ ([M+Na]$^+$) 323.1834. Found: 323.1843

(3*S*,4*R*,5*R*)-4,5-*O*-Cyclohexylidene-3,4,5-trihydroxy-3-*O*-methoxymethyl-1-methyl-1-cyclohexene (24). Flash column chromatography (230—400 mesh SiO_2, EtOAc/Hex = 1/20—1/8) afforded a colorless syrup in 98% yield. $[\alpha]^{25}_D$ +20.8 (*c* 1.6, MeOH). ^{1}H NMR (300 MHz, C_6D_6) δ 5.62 (d, J = 1.2 Hz, 1H), 4.75 (d, J = 6.8 Hz, 1H), 4.66 (d, J = 6.8 Hz, 1H), 4.39 (ddd, J = 7.5, 3.7, 2.5 Hz, 1H), 4.14 (ddd, J = 7.4, 5.3, 2.5 Hz, 1H), 3.86 (dt, J = 5.8, 2.1 Hz, 1H), 3.27 (s, 3H), 2.12 (dd, J = 15.6, 2.0 Hz, 1H), 1.79—1.51 (br m, 12H), 1.27—1.22 (m, 2H). ^{13}C NMR (75 MHz, C_6D_6) δ 134.3, 123.7, 109.5, 96.1, 75.8, 73.9, 73.6, 55.5, 36.9, 35.0, 34.1, 26.1, 24.8, 24.6, 23.8. HRMS (ESI) $C_{15}H_{24}NaO_4$ ([M+Na]$^+$) 291.1572. Found: 291.1567.

(1R,2*R*,3S)-5-Butyl-1,2-*O*-cyclohexylidene-3-*O*-methoxymethyl-4-cyclohexene-1,2,3-triol (25). Flash column chromatography (230—400 mesh SiO_2, EtOAc/Hex=1/30—1/15) afforded a colorless syrup in 89% yield. $[\alpha]^{24}_D$ +30.8 (*c* 1.0, MeOH). ^{1}H NMR (300 MHz, C_6D_6) δ 5.64 (d, J = 1.0 Hz, 1H), 4.77 (d, J = 6.7 Hz, 1H), 4.68 (d, J = 6.7 Hz, 1H), 4.42 (ddd, J = 7.4, 3.6, 2.0 Hz, 1H), 4.16 (dd, J = 5.2, 2.6 Hz, 1H), 3.89 (t, J = 1.8 Hz, 1H), 3.30 (s, 3H), 2.19 (dd, J = 15.7, 2.2 Hz, 1H), 1.96 (t, J = 7.4 Hz, 2H), 1.76—1.53 (m, 9H), 1.37—1.20 (m, 6H), 0.85 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 138.5, 123.2, 109.5, 96.1, 75.0, 74.1, 73.5, 55.6, 37.6, 36.7, 34.8, 33.0, 30.2, 26.1, 24.8, 24.6, 23.1, 14.5. HRMS (ESI) calcd for $C_{18}H_{30}NaO_4$ ([M+Na]$^+$) 333.2042. Found: 333.2037.

(3*S*,4*R*,5*R*,7*R*)-*N*-Benzyl-4,5-*O*-cyclohexylidene-3,4,5-trihydroxy-3-*O*-methoxymethyl-7-methylazepane (26). Flash column chromatography (230—400 mesh SiO_2, EtOAc/Hex=1/60—1/20) afforded a pale yellow syrup in 47% yield. $[\alpha]^{25}_D$ —16.5 (*c* 0.9, MeOH). ^{1}H NMR (600 MHz, C_6D_6) δ 7.51 (d, J = 7.3 Hz, 2H), 7.31 (t, J = 7.5 Hz, 2H), 7.21 (t, J = 7.5 Hz, 1H), 4.61 (d, J = 6.8 Hz, 2H), 4.57 (d, J = 6.8 Hz, 2H), 4.53 (d, J = 7.9 Hz, 1H), 4.00 (dt, J = 8.4, 2.3 Hz, 1H), 3.64 (d, J = 14.1 Hz, 2H), 3.58 (d, J = 14.1 Hz, 2H), 3.38—3.30 (m, 2H), 3.22 (s, 3H), 2.89 (dd, J = 14.5, 1.1 Hz, 1H), 2.10—2.06 (br m, 1H), 1.95 (t, J = 6.0 Hz, 2H), 1.96—1.64 (m, 2H), 1.38 (dt, J =

11.7, 5.9 Hz, 2H), 1.10 (d, J = 6.9 Hz, 3H). ^{13}C NMR (150 MHz, C_6D_6) δ 141.5, 129.5－127.4 (signals overlap with C_6D_6), 108.6, 95.8, 79.6, 74.1, 72.6, 55.5, 53.4, 53.0, 51.6, 36.8, 36.3, 34.3, 26.1, 24.8, 24.5, 20.6. HRMS (ESI) calcd for $C_{22}H_{34}NO_4$ ([M+H]$^+$): 376.2482. Found: 376.2526.

(3*S*,4*R*,5*R*,7*S*)-*N*-Benzyl-4,5-*O*-cyclohexylidene-3,4,5-trihydroxy-3-*O*-methoxymethyl-7-methylazepane (27). Flash column chromatography (230－400 mesh SiO_2, EtOAc/Hex=1/60－1/20) afforded a colorless syrup in 7% yield. $[\alpha]^{24}_D$ －54.8 (*c* 0.9, MeOH). ^{1}H NMR (600 MHz, C_6D_6) δ 7.32－7.10 (m, 5H), 4.92 (d, J = 6.6 Hz, 1H), 4.68 (d, J = 6.6 Hz, 1H), 4.64－4.61 (m, 2H), 4.13 (dt, J = 8.2, 2.7 Hz, 1H), 3.51 (d, J = 13.2 Hz, 1H), 3.34 (d, J = 13.2 Hz, 1H), 3.30 (s, 3H), 2.96－2.90 (m, 2H), 2.77－2.72 (m, 2H), 2.15 (ddd, J = 10.1, 6.4, 2.9 Hz, 1H), 2.00－1.89 (m, 2H), 1.85－1.70 (m, 6H), 1.46－1.40 (m, 2H), 0.95 (d, J = 6.3 Hz, 3H). ^{13}C NMR (150 MHz, C_6D_6) δ 140.4, 128.5－127.0 (-Ar), 107.6, 97.4, 78.3, 76.0, 75.7, 59.3, 54.8, 52.9, 49.3, 37.3, 36.8, 33.9, 25.7, 24.3, 24.0, 11.1. HRMS (ESI) calcd for $C_{22}H_{34}NO_4$ ([M+H]$^+$): 376.2482. Found: 376.2325.

(3*S*,4*R*,5*R*,7*R*)-*N*-Benzyl-7-butyl-4,5-*O*-cyclohexylidene-3,4,5-trihydroxy-3-*O*-methoxymethylazepane (28). Flash column chromatography (230－400 mesh SiO_2, EtOAc/Hex=1/50－1/30) afforded a colorless syrup in 25% yield. $[\alpha]^{25}_D$ －32.0 (*c* 0.4, MeOH). ^{1}H NMR (600 MHz, C_6D_6) δ 7.59 (d, J = 7.8 Hz, 2H), 7.33 (t, J = 7.8 Hz, 2H), 7.22 (t, J = 7.2 Hz, 1H), 4.60 (d, J = 8.0 Hz, 1H), 4.56 (d, J = 6.8 Hz, 1H), 4.54 (d, J = 6.8 Hz, 1H), 4.32 (ddd, J = 8.0, 5.2, 2.9 Hz, 1H), 4.04 (dt, J = 9.4, 1.6 Hz, 1H), 3.76 (d, J = 14.1 Hz, 1H), 3.63 (d, J = 14.1 Hz, 1H), 3.56 (dd, J = 14.3, 9.4 Hz, 1H), 3.26 (dd, J = 15.1, 7.4 Hz, 1H), 3.21 (s, 3H), 2.00－1.85 (br m, 3H), 1.80－1.30 (br m, 15H), 1.00 (t, J = 7.3 Hz, 3H). ^{13}C NMR (150 MHz, C_6D_6) δ 141.4, 129.3, 128.9, 127.5, 108.6, 95.8, 79.8, 74.5, 71.4, 57.0, 55.5, 51.4, 50.8, 36.8, 34.8, 34.2, 33.9, 29.8, 26.1, 24.7, 24.4, 23.3, 14.6. HRMS (ESI) calcd for $C_{25}H_{40}NO_4$ ([M+H]$^+$): 418.2957. Found: 418.2924.

(3*S*,4*R*,5*R*,7*S*)-*N*-Benzyl-7-butyl-4,5-*O*-cyclohexylidene-3,4,5-trihydroxy-3-*O*-methoxymethylazepane (29). Flash column chromatography (230－400 mesh SiO_2, EtOAc/Hex=1/50－1/30) afforded a colorless syrup in 14% yield. $[\alpha]^{25}_D$ ＋30.7 (*c* 1.4, MeOH). ^{1}H NMR (600 MHz, C_6D_6) δ 7.35 (d, J = 7.2 Hz, 2H), 7.35－7.26 (m, 2H), 7.21 (t, J = 7.2 Hz, 1H), 4.90 (d, J = 6.7 Hz, 1H), 4.68 (d, J = 6.7 Hz, 1H), 4.61 (ddd, J = 13.9, 10.4, 3.7 Hz, 1H), 4.59 (dd, J = 7.5, 3.0 Hz, 1H), 4.12 (dt, J = 7.5, 2.8 Hz, 1H), 3.63 (d, J = 13.6 Hz, 1H), 3.49 (d, J = 13.6 Hz, 1H), 3.31 (s, 3H), 3.08 (dd, J = 14.8, 1.9 Hz, 1H), 2.79－2.73 (dd+m, J = 14.7, 7.6 Hz, 2H), 2.67 (td, J = 13.2, 10.4 Hz, 1H), 2.27 (ddd, J = 13.2, 5.8, 4.0 Hz, 1H), 2.02－1.90 (m, 2H), 1.88－1.70 (m, 6H), 1.62－1.52 (m, 2H), 1.48－1.37 (m, 2H), 1.37－1.27 (m, 3H), 1.17－1.11 (m, 1H), 0.96 (t, J = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, C_6D_6) δ 141.2, 129.2, 129.0, 128.7, 127.7, 108.2, 97.8, 79.2, 76.6, 76.3, 59.7, 55.4, 50.4, 37.5, 35.6, 34.4, 29.6, 27.9, 26.3, 24.9, 24.7, 23.7, 14.7. HRMS (ESI) calcd for $C_{25}H_{40}NO_4$ ([M+H]$^+$): 418.2957. Found: 418.2957.

(3*S*,4*R*,5*R*,7*R*)-7-Methylazepane-3,4,5-triol (1). Flash column chromatography (230－400 mesh

SiO_2, NH_4OH/MeOH/CH_2Cl_2=1/6/25－1/6/15) afforded a pale yellow syrup in 86% yield. $[\alpha]^{25}_D$ －27.3 (*c* 0.8, MeOH). ^1H NMR (600 MHz, D_2O) δ 3.97 (dd, *J* = 4.8, 3.5 Hz, 1H), 3.95 (d, *J* = 2.6 Hz, 1H), 3.69 (ddd, *J* = 10.5, 4.7, 3.0 Hz, 1H), 2.99 (dq, *J* = 7.2, 6.6 Hz, 1H), 2.81 (ddd, *J* = 13.4, 4.7, 0.9 Hz, 1H), 2.69 (dd, *J* = 13.4, 10.5 Hz, 1H), 2.00 (ddd, *J* = 14.4, 9.4, 6.4 Hz, 1H), 1.53－1.47 (m, 1H), 1.00 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (150 MHz, D_2O) δ 76.8, 71.1, 68.3, 50.0, 47.8, 37.1, 22.3. HRMS (ESI) calcd for $C_7H_{16}NO_{3(}$ $[M+H]^+$): 162.1130. Found: 162.1123.

(3*S*,4*R*,5*R*,7*S*)-7-Methylazepane-3,4,5-triol (2). Flash column chromatography (230－400 mesh SiO_2, NH_4OH/MeOH/CH_2Cl_2 = 1/6/25－1/6/15) afforded a colorless syrup in 92% yield. $[\alpha]^{24}_D$ +15.6 (*c* 0.3, MeOH). ^1H NMR (600 MHz, D_2O) δ 4.10 (ddd, *J* = 8.7, 4.6, 1.7 Hz, 1H), 4.03－4.01 (br m, 1H), 3.89 (ddd, *J* = 11.0, 4.1, 2.4 Hz, 1H), 3.40－3.33 (m, 1H), 3.27 (dd, *J* = 13.6, 8.8 Hz, 1H), 3.17 (dd, *J* = 13.6, 4.7 Hz, 1H), 1.99 (dt, *J* = 15.0, 11.0 Hz, 1H), 1.84－1.78 (m, 1H), 1.27 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (150 MHz, D_2O) δ 75.6, 69.5, 65.6, 50.9, 44.5, 34.9, 20.1. HRMS (ESI) calcd for $C_7H_{16}NO_3$ ($[M+H]^+$): 162.1130. Found: 162.1141.

(3*S*,4*R*,5*R*,7*R*)-7-Butylazepane-3,4,5-triol (3). Flash column chromatography (230－400 mesh SiO_2, NH_4OH/MeOH/CH_2Cl_2=1/6/60－1/6/40) afforded a colorless syrup in 90% yield. $[\alpha]^{25}_D$ －10.7 (*c* 0.8, MeOH). ^1H NMR (600 MHz, D_2O) δ 3.98 (dd, *J* = 8.7, 5.1 Hz, 2H), 3.70 (ddd, *J* = 10.6, 4.8, 2.9 Hz, 1H), 2.85 (dd, *J* = 13.3, 4.8 Hz, 1H), 2.81 (dd, *J* = 13.9, 7.1 Hz, 1H), 2.69 (dd, *J* = 13.3, 10.7 Hz, 1H), 1.99 (ddd, *J* = 14.4, 10.0, 6.5 Hz, 1H), 1.56 (ddd, *J* = 14.4, 7.4, 5.1 Hz, 1H), 1.36－1.31 (m, 2H), 1.26－1.21 (m, 4H), 0.81 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (150 MHz, D_2O) δ 77.0, 71.3, 68.5, 54.5, 48.3, 36.3, 35.5, 27.5, 22.0, 12.3. HRMS (ESI) calcd for $C_{10}H_{22}NO_3$ ($[M+H]^+$): 204.1600. Found: 204.1557.

(3*S*,4*R*,5*R*,7*S*)-7-Butylazepane-3,4,5-triol (4). Flash column chromatography (230－400 mesh SiO_2, NH_4OH/MeOH/CH_2Cl_2=1/6/60－1/6/40) afforded a colorless syrup in 91% yield. $[\alpha]^{25}_D$ +17.9 (*c* 1.0, MeOH). ^1H NMR (600 MHz, D_2O) δ 3.98 (br s, 1H), 3.85 (dt, *J* = 11.1, 2.6 Hz, 1H), 3.77 (ddd, *J* = 9.2, 4.0, 2.9 Hz, 1H), 2.92 (dd, *J* = 14.0, 9.2 Hz, 1H), 2.76－2.71 (m, 1H), 2.63 (dd, *J* = 14.0, 4.0 Hz, 1H), 1.83 (dt, *J* = 14.3, 11.0 Hz, 1H), 1.61 (ddd, *J* = 14.3, 4.0, 1.1 Hz, 1H), 1.36－1.31 (m, 2H), 1.25－1.19 (m, 4H), 0.80 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (150 MHz, D_2O) δ 75.7, 70.5, 70.3, 52.5, 44.6, 36.3, 34.8, 27.4, 22.0, 13.3. HRMS (ESI) calcd for $C_{10}H_{22}NO_3$ ($[M+H]^+$): 204.1600. Found: 204.1583.

(3*R*,4*S*,5*R*,7*R*)-7-Methylazepane-3,4,5-triol (5). Flash column chromatography (230－400 mesh SiO_2, NH_4OH/MeOH/CH_2Cl_2=1/6/25－1/6/15) afforded a yellow syrup as a mixture in a ratio of 10:1 in 89% yield. (major isomer) ^1H NMR (600 MHz, D_2O) δ 3.71 (td, *J* = 9.1, 2.2 Hz, 1H), 3.48 (ddd, *J* = 10.4, 8.2, 3.7 Hz, 1H), 3.30 (dd, *J* = 17.5, 9.4 Hz, 1H), 3.09 (dt, *J* = 17.0, 5.5 Hz, 1H), 2.91 (dd, *J* = 13.9, 3.7 Hz, 1H), 2.67 (dd, *J* = 13.9, 10.4 Hz, 1H), 1.96 (ddd, *J* = 15.2, 9.1, 5.6 Hz, 1H), 1.65 (ddd, *J* = 15.2, 4.6, 2.3 Hz, 1H), 1.06 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (150 MHz, D_2O) δ 80.2, 73.2, 68.2, 48.0, 47.6, 37.5, 21.2.

(3*R*,4*S*,5*R*,7*R*)-7-Butylazepane-3,4,5-triol (7). Flash column chromatography (230－400 mesh SiO_2, NH_4OH/MeOH/CH_2Cl_2=1/6/40－1/6/25) afforded a yellow syrup as a mixture in a ratio of 10:1 in 90% yield. (major isomer) ^{1}H NMR (600 MHz, D_2O) δ3.68 (dd, J = 15.7, 8.8 Hz, 1H), 3.48－3.40 (m, 1H), 3.27 (t, J = 8.4 Hz, 1H), 2.91－2.85 (m, 2H), 2.63 (dd, J = 13.4, 10.8 Hz, 1H), 1.93 (ddd, J = 15.2, 9.1, 6.0 Hz, 1H), 1.69 (dd, J = 15.2, 2.2 Hz, 1H), 1.40－1.35 (m, 2H), 1.25 － 1.22 (m, 4H), 0.83 (t, J = 6.8 Hz, 3H). ^{13}C NMR (150 MHz, D_2O) δ80.5, 73.5, 68.3, 52.5, 47.8, 36.0, 35.2, 27.7, 21.9, 23.2.

(3*S*,4*R*,6*S*)-6-*O*-Benzyl-3,4-*O*-cyclohexylidene-1-Methylazepane (**47**). Flash column chromatography (230－400 mesh SiO_2, EtOAc/Hex=1/32－1/4) afforded a pale yellow syrup. $[\alpha]^{25}_D$ +21.0 (*c* 0.6, MeOH). ^{1}H NMR (600 MHz, C_6D_6) δ7.35 (d, J = 7.6 Hz, 2H), 7.29－7.25 (m, 2H), 7.20 (t, J = 7.4 Hz, 1H), 4.43－4.36 (m, 2H), 4.35－4.28 (m, 2H), 3.38 (tdd, J = 11.2, 4.0, 1.3 Hz, 1H), 3.09 (dt, J = 11.6, 2.0 Hz, 1H), 2.84 (ddd, J = 13.3, 4.9, 1.5 Hz, 1H), 2.62－2.52 (m, 2H), 2.32 (t, J = 10.1 Hz, 1H), 2.21 (s, 3H), 2.11 (ddd, J = 13.4, 11.2, 2.0 Hz, 1H), 1.90－1.65 (m, 8H), 1.42－1.35 (m, 2H). ^{13}C NMR (150 MHz, C_6D_6) δ139.2, aromatic, 108.6, 76.4, 74.4, 74.2, 70.3, 65.5, 58.6, 48.0, 37.8, 36.7, 34.4, 25.5, 24.3, 24.0. HRMS (ESI) calcd for $C_{20}H_{30}NO_3$ ($[M]^+$): 332.2220. Found: 332.2181

(3*S*,4*R*,6*R*)-6-*O*-Benzyl-3,4-*O*-cyclohexylidene-1-Methylazepane (**48**)**.** Flash column chromatography (230－400 mesh SiO_2, EtOAc/Hex=1/32－1/4) afforded a pale yellow syrup. $[\alpha]^{26}_D$ －14.9 (*c* 0.6, MeOH). ^{1}H NMR (600 MHz, C_6D_6) δ7.39 (d, J = 7.5 Hz, 2H), 7.29－7.25 (m, 2H), 7.19 (t, J = 7.3 Hz, 1H), 4.77 (t, J = 9.8 Hz, 1H), 4.55 (t, J = 10.0 Hz, 1H), 4.45 (d, J = 12.0 Hz, 1H), 4.40 (d, J = 12.0 Hz, 1H), 3.60－3.53 (br s, 1H), 2.80 (td, J = 16.0, 3.5 Hz, 2H), 2.63 (dd, J = 13.4, 9.4 Hz, 1H), 2.40－2.33 (m, 1H), 2.29 (s, 3H), 2.26 (d, J = 12.8 Hz, 1H), 2.02 (dd, J = 14.0, 9.6 Hz, 1H), 1.92 (dd, J = 10.4, 5.2 Hz, 2H), 1.82 (dt, J = 12.2, 6.1 Hz, 2H), 1.73－1.64 (m, 4H), 1.45－1.35 (m, 2H). ^{13}C NMR (150 MHz, C_6D_6) δ 139.2, 108.2, 76.7, 73.7, 70.2, 63.1, 58.9, 47.7, 38.0, 34.6, 33.6, 25.5, 24.4, 24.0. HRMS (ESI) calcd for $C_{20}H_{30}NO_3$ ($[M^+]$): 332.2220. Found: 332.2205.

(3*S*,4*R*,6*S*)-6-*O*-Benzyl-1-butyl-3,4-*O*-cyclohexylideneazepane (**49**)**.** Flash column chromatography (230－400 mesh SiO_2, EtOAc/Hex=1/32－1/16) afforded a clear syrup. $[\alpha]^{25}_D$ －2.5 (*c* 0.8, MeOH). ^{1}H NMR (600 MHz, C_6D_6) δ7.36 (d, J = 7.4 Hz, 2H), 7.30－7.25 (m, 2H), 7.20 (t, J = 7.3 Hz, 2H), 4.46 (d, J = 12.1 Hz, 1H), 4.43－4.33 (m, 3H), 3.39 (tdd, J = 11.2, 4.1, 1.6 Hz, 1H), 3.19 (ddd, J = 11.7, 3.8, 1.6 Hz, 1H), 3.04 (ddd, J = 13.5, 5.0, 1.6 Hz, 1H), 2.65 (dd, J = 13.6, 10.4 Hz, 1H), 2.56 (ddt, J = 12.8, 5.6, 1.5 Hz, 1H), 2.49 (dd, J = 11.6, 9.9 Hz, 1H), 2.45－2.34 (m, 2H), 2.16 (dt, J = 13.0, 11.2 Hz, 2H), 1.90 (t, J = 5.9 Hz, 2H), 1.82－1.77 (m, 2H), 1.77－1.68 (m, 4H), 1.44－1.33 (m, 4H), 1.30－1.22 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H). ^{13}C NMR (150 MHz, C_6D_6) δ 139.3, aromatic, 108.7, 76.8, 75.0, 74.8, 70.4, 63.8, 59.4, 56.5, 37.9, 37.0, 34.5, 29.7, 25.5, 24.3, 24.0, 20.4, 13.9. HRMS (ESI) calcd for $C_{23}H_{36}NO_3$ ($[M+H]^+$):374.2695. Found: 374.2651.

(3*S*,4*R*,6*R*)-6-*O*-Benzyl-1-butyl-3,4-*O*-cyclohexylideneazepane (50). Flash column chromatography (230−400 mesh SiO_2, EtOAc/Hex=1/32−1/8) afforded a pale yellow syrup. $[\alpha]^{26}_D$ −13.2 (*c* 0.7, MeOH). ^{1}H NMR (600 MHz, C_6D_6) δ 7.41 (d, *J* = 7.6 Hz, 2H), 7.30−7.25 (m, 2H), 7.19 (t, *J* = 7.4 Hz, 1H), 4.78 (t, *J* = 9.5 Hz, 1H), 4.51−4.45 (m, 2H), 4.43 (d, *J* = 12.0 Hz, 1H), 3.66−3.60 (br s, 1H), 2.95−2.87 (m, 2H), 2.67 (dd, *J* = 13.7, 9.5 Hz, 1H), 2.50−2.42 (m, 3H), 2.40−2.32 (m, 1H), 2.09 (dd, *J* = 14.0, 9.5 Hz, 1H), 1.94 (t, *J* = 6.6 Hz, 2H), 1.83 (dt, *J* = 12.1, 5.6 Hz, 2H), 1.76−1.67 (m, 4H), 1.48−1.30 (m, 6H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (150 MHz, C_6D_6) δ 139.3, aromatic, 108.2, 77.1, 73.9, 73.8, 70.2, 61.2, 58.9, 56.7, 38.0, 34.7, 33.8, 30.0, 25.5, 24.4, 24.0, 20.4, 14.0. HRMS(ESI) calcd for $C_{23}H_{36}NO_3$ ($[M+H]^+$): 373.2690. Found: 374.2651.

(3*R*,4*R*,6*S*)-6-*O*-Benzyl-3,4-dihydroxy-1-*N*-methyl-3,4-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-dioxy] (52). Flash column chromatography (230−400 mesh SiO_2, EtOAc/Hex=1/16−1/2) afforded a clear syrup. $[\alpha]^{26}_D$ +117.6 (*c* 0.7, MeOH). ^{1}H NMR (600 MHz, C_6D_6) δ 7.37 (d, *J* = 7.5 Hz, 2H), 7.29−7.25 (m, 2H), 7.19 (t, *J* = 7.3 Hz, 1H), 4.77 (d, *J* = 12.1 Hz, 1H), 4.36 (d, *J* = 12.1 Hz, 1H), 4.07 (td, *J* = 8.9, 5.9 Hz, 1H), 3.87 (td, *J* = 11.1, 1.7 Hz, 1H), 3.57 (ddd, *J* = 15.4, 10.2, 4.9 Hz, 1H), 3.22 (s, 3H), 3.19 (s, 3H), 2.91 (dd, *J* = 12.8, 5.8 Hz, 1H), 2.75 (dd, *J* = 13.9, 4.8 Hz, 1H), 2.57 (ddd, *J* = 12.8, 8.9, 2.3 Hz, 1H), 2.43 (ddd, *J* = 13.0, 5.5, 1.4 Hz, 1H), 2.31 (s, 3H), 2.26 (ddd, *J* = 13.0, 10.9, 2.5 Hz, 1H), 1.49 (s, 3H), 1.47 (s, 3H). ^{13}C NMR (150 MHz, C_6D_6) δ 139.3, aromatic, 99.0, 98.6, 75.4, 71.9, 70.1, 68.0, 62.9, 61.4, 47.9, 47.4, 47.3, 35.8, 17.8, 17.7. HRMS (ESI) ($[M+H]^+$): 366.2275. Found: 366.2215

(3*R*,4*R*,6*S*)-6-*O*-Benzyl-1-*N*-Butyl-3,4-dihydroxy-3,4-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-dioxy] (53). Flash column chromatography (230−400 mesh SiO_2, EtOAc/Hex=1/30─1/8) afforded a pale yellow syrup. $[\alpha]^{26}_D$ +92.8 (*c* 0.7, MeOH). ^{1}H NMR (600 MHz, C_6D_6) δ 7.39 (d, *J* = 7.2 Hz, 2H), 7.28−7.25 (m, 2H), 7.19 (t, *J* = 7.4 Hz, 1H), 4.48 (d, *J* = 12.1 Hz, 1H), 4.39 (d, *J* = 12.1 Hz, 1H), 4.05 (td, *J* = 9.2, 5.8 Hz, 1H), 3.87 (ddd, *J* = 11.2, 9.5, 1.9 Hz, 1H), 3.57 (dtd, *J* = 15.7, 10.3, 4.7 Hz, 1H), 3.24 (s, 3H), 3.21 (s, 3H), 3.07 (ddd, *J* = 13.0, 5.8, 0.8 Hz, 1H), 2.89 (dd, *J* = 14.1, 4.0 Hz, 1H), 2.65 (td, *J* = 10.5, 4.7 Hz, 2H), 2.55−2.50 (m, 2H), 2.44 (ddd, *J* = 13.1, 5.7, 1.9 Hz, 1H), 2.29 (ddd, *J* = 13.1, 10.7, 8.3 Hz, 1H), 1.50 (s, 3H), 1.49 (s, 3H), 1.48−1.44 (m, 2H), 1.38−1.32 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (150 MHz, C_6D_6) δ 139.4, aromatic, 99.0, 98.6, 75.7, 72.4, 70.1, 68.3, 60.4, 59.5, 58.9, 47.4, 47.3, 35.8, 30.1, 20.4, 17.8, 17.7, 14.0. HRMS (ESI): 408.2744. Found: 408.2729

(3*S*,4*R*,6*S*)-1-*N*-Methylazepane-3,4,6-triol (9). Flash column chromatography (230−400 mesh SiO_2, NH_4OH/MeOH/CH_2Cl_2=1/20/70−1/20/50) afforded a clear syrup in 83% yield. $[\alpha]^{26}_D$ +9.9 (*c* 0.9, MeOH). ^{1}H NMR (600 MHz, D_2O) δ 4.00 (dd, *J* = 9.5, 4.8 Hz, 1H), 3.99−3.95 (m, 1H), 3.89 (ddd, *J* = 9.5, 4.4, 2.9 Hz, 1H), 3.00 (dd, *J* = 13.3, 4.1 Hz, 1H), 2.97 (dd, *J* = 13.8, 3.2 Hz, 1H), 2.88 (dd, *J* = 12.8, 6.3 Hz, 1H), 2.80 (dd, *J* = 12.4, 7.9 Hz, 1H), 2.52 (s, 3H), 2.07−1.96

(m, 2H). ^{13}C NMR (150 MHz, D_2O) δ 69.8, 69.1, 65.1, 63.1, 59.2, 46.9, 36.8. HRMS (ESI) calcd for $C_7H_{16}NO_3$ ($[M+H]^+$): 162.1125. Found: 162.1194.

(3*S*,4*R*,6*R*)-1-*N*-Methylazepane-3,4,6-triol (10). Flash column chromatography (230－400 mesh SiO_2, NH_4OH/MeOH/CH_2Cl_2=1/20/70－1/20/50) afforded a clear syrup in 69% yield. $[\alpha]^{25}_D$ ＋23.6 (*c* 0.5, MeOH). ^{1}H NMR (600 MHz, D_2O) δ 4.07－4.01 (m, 2H), 3.90－3.85 (m, 1H), 2.78 (dd, *J* = 13.7, 5.1 Hz, 1H), 2.66－2.58 (m, 2H), 2.48 (dd, *J* = 13.7, 6.7 Hz, 1H), 2.27 (s, 3H), 2.23 (dt, *J* = 9.4, 4.8 Hz, 1H), 1.65 (ddd, *J* = 14.6, 6.5, 1.8 Hz, 1H). ^{13}C NMR (150 MHz, D_2O) δ 71.5, 68.3, 65.4, 63.4, 60.3, 47.2, 35.9. HRMS (ESI) calcd for $C_7H_{16}NO_3$ ($[M]^+$): 162.1125. Found: 162.1097.

(3*S*,4*R*,6*S*)-1-*N*-Butylazepane-3,4,6-triol (11). Flash column chromatography (230－400 mesh SiO_2, NH_4OH/MeOH/CH_2Cl_2=1/20/70) afforded a clear syrup in 71% yield. $[\alpha]^{26}_D$ －9.4 (*c* 1.3, MeOH). ^{1}H NMR (600 MHz, D_2O) δ 3.89－3.82 (m, 3H), 2.81 (dd, *J* = 13.0, 4.5 Hz, 1H), 2.78 (dd, *J* = 13.8, 3.8 Hz, 1H), 2.60 (dd, *J* = 13.8, 6.7 Hz, 1H), 2.50 (dd, *J* = 13.0, 8.3 Hz, 1H), 2.46 (t, *J* = 8.0 Hz, 2H), 1.98－1.88 (m, 2H), 1.42－1.35 (m, 2H), 1.20 (sextet, *J* = 7.5 Hz, 2H), 0.82 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (150 MHz, D_2O) δ 70.9, 69.1, 66.9, 61.7, 58.3, 57.5, 37.3, 27.6, 20.1, 13.3. HRMS (ESI) calcd for $C_{10}H_{22}NO_3$ ($[M]^+$): 204.1521. Found: 204.1609

(3*S*,4*R*,6*R*)-1-*N*-Butylazepane-3,4,6-triol (12). Flash column chromatography (230－400 mesh SiO_2, NH_4OH/MeOH/CH_2Cl_2=1/20/70) afforded a pale yellow syrup in 67% yield. $[\alpha]^{26}_D$ +1.8 (*c* 0.6, MeOH). ^{1}H NMR (600 MHz, D_2O) δ 4.07－4.01 (m, 2H), 3.90 (s, 1H), 2.90 (dd, *J* = 13.7, 4.7 Hz, 1H), 2.74 (d, *J* = 5.3 Hz, 2H), 2.58－2.50 (m, 3H), 2.34 (ddd, *J* = 14.2, 8.9, 4.6 Hz, 1H), 1.66 (dd, *J* = 14.5, 6.8 Hz, 1H), 1.47－1.37 (m, 2H), 1.21 (sextet, *J* = 7.3 Hz, 2H), 0.83 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (150 MHz, D_2O) δ 71.4, 68.6, 65.4, 60.7, 58.5, 57.4, 36.3, 27.4, 20.0, 13.22. HRMS (ESI) calcd for $C_{10}H_{22}NO_3$ ($[M]^+$): 204.1594. Found: 204.1531.

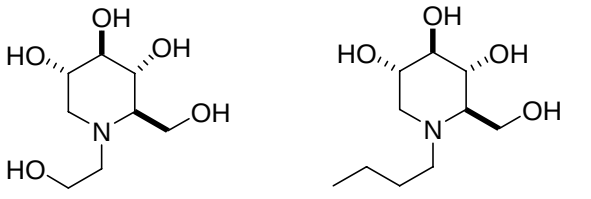
(3*R*,4*R*,6*S*)-1-*N*-Methylazepane-3,4,6-triol (13). Flash column chromatography (230－400 mesh SiO_2, NH_4OH/MeOH/CH_2Cl_2=1/20/70－1/20/50) afforded a white solid in 90% yield. Mp = 215.2－220.2 ℃. $[\alpha]^{25}_D$ －5.7 (*c* 0.7, MeOH). ^{1}H NMR (600 MHz, D_2O) δ 4.25－4.21 (m, 1H), 4.03 (ddd, *J* = 7.3, 7.3, 2.5 Hz, 1H), 3.88 (ddd, *J* = 7.0, 7.0, 5.3 Hz, 1H), 3.50 (d, *J* = 13.6 Hz, 1H), 3.38 (dd, *J* = 13.3, 2.9 Hz, 1H), 3.30－3.21 (m, 2H), 2.28 (ddd, *J* = 14.9, 4.7, 3.7 Hz, 1H), 1.93 (ddd, *J* = 14.9, 8.5, 7.5 Hz, 1H). ^{13}C NMR (150 MHz, D_2O) δ 70.5, 70.2, 63.3, 61.9, 58.0, 46.2, 37.9. HRMS (ESI) calcd for $C_7H_{15}NO_3$ ($[M+H]^+$): 162.1125. Found: 162.1167

(3*R*,4*R*,6*S*)-1-*N*-Butylazepane-3,4,6-triol (14). Flash column chromatography (230－400 mesh SiO_2, NH_4OH/MeOH/CH_2Cl_2=1/20/60-1/20/40) afforded a pale yellow syrup in 88% yield. $[\alpha]^{25}_D$ －17.2 (*c* 0.6, MeOH). ^{1}H NMR (600 MHz, D_2O) δ 4.07 (dddd, *J* = 13.7, 9.7, 7.9, 4.0 Hz, 1H), 3.77 (td, *J* = 7.1, 3.4 Hz, 1H), 3.70 (ddd, *J* = 9.7, 7.7, 3.5 Hz, 1H), 3.13 (dd, *J* = 14.0, 2.5 Hz, 1H), 3.09 (dd, *J* = 13.1, 3.8 Hz, 1H), 2.91 (dd, *J* = 14.0, 6.9 Hz, 1H), 2.86－2.79 (m, 3H), 2.10 (dt,

J = 14.0, 3.5 Hz, 1H), 1.84 (dt, *J* = 14.0, 9.7 Hz, 1H), 1.60－1.47 (m, 2H), 1.27 (sextet, *J* = 7.4 Hz, 2H), 0.85 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (150 MHz, D_2O) δ 72.6, 71.2, 64.9, 60.8, 58.8, 57.2, 38.8, 26.4, 19.6, 13.0. HRMS (ESI) calcd for $C_{10}H_{22}NO_3$ ($[M+H]^+$): 204.1594. Found: 204.1591.

References

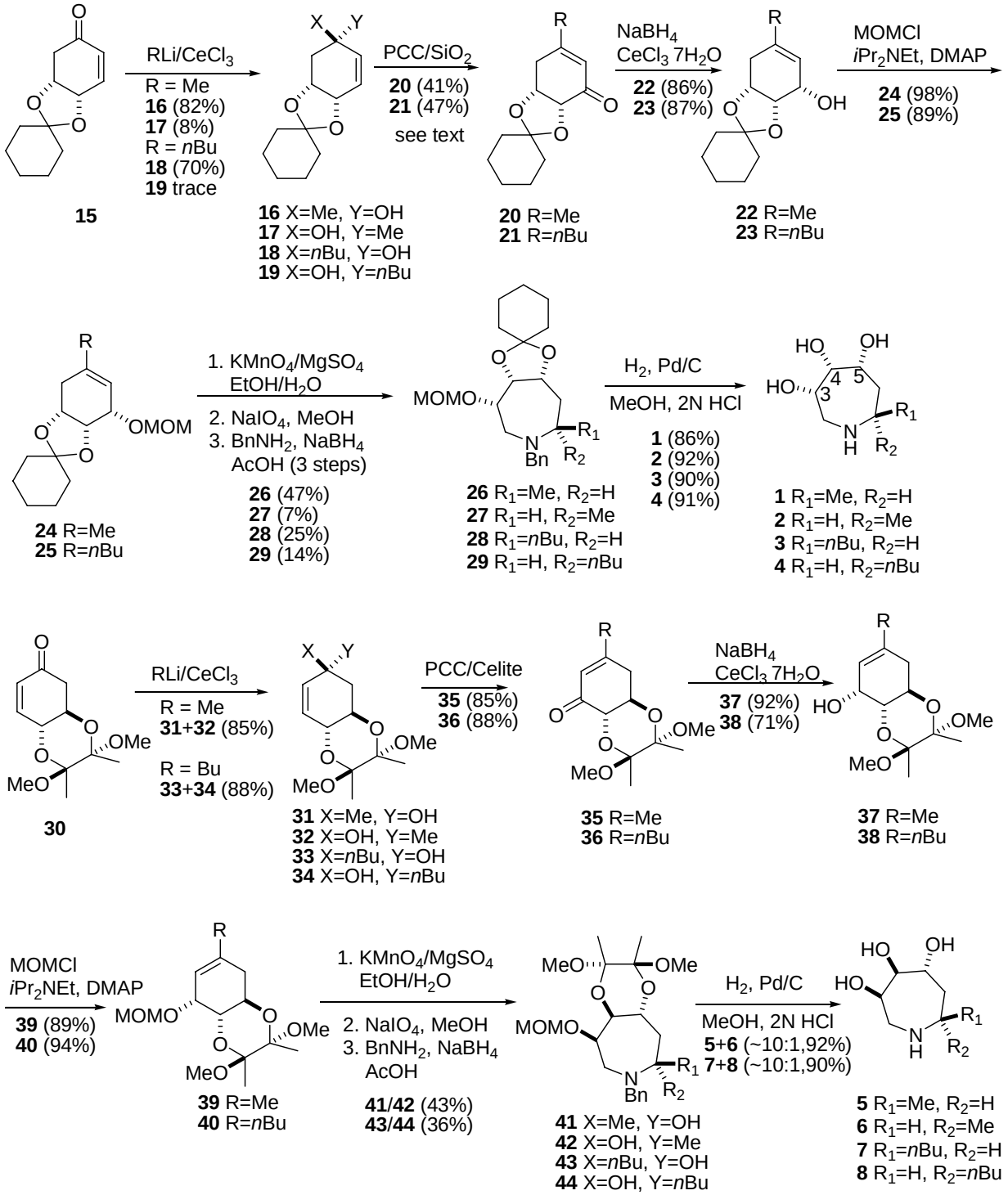
1. (a) Davis, B. G. *Tetrahedron: Asymmetry* **2009**, *20*, 652─671. (b) Bleriot, Y.; Gretzke, D.; Krulle, T. M.; Butters, T. D.; Dwek, R. A.; Nash, R. J.; Asano, N.; Fleet, G. W. J. *Carbohydr. Res.* **2005**, *340*, 2713─2718. (c) Bordier, A.; Compain, P.; Martin, O. R.; Ikedab, K.; Asano, N. *Tetrahedron:Asymmetry* **2003**, *14*, 47─51. (d) Johnson, H. A.; Thomas, N. R. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 237─241. (e) Liu, H.; Liang, X.; Sohoel, H.; Bulow, A.; Bols, M. *J. Am. Chem. Soc.* **2001**, *123*, 5116─5117. (f) Igarashi, Y.; Ichikawa, M.; Ichikawa, Y. *Bioorg. Med. Chem. Lett.* **1996**, *4*, 553─558. (g) Legler, G.; Stiitz, A. E.; Immich, H. *Carbohydr. Res.* **1995**, *272*, 17─30. (h) Kajimoto, T.; Kevin, K. C.; Pederson, R. L.; Zhong, Z.; Ichikawa, Y.; Porco, J. A.; Wong, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6187─6196. (i) Fleet, G. W. J.; Shaw, A. N.; Evans, S. V.; Fellows, L. E. *J. Chem. Soc., Chem. Commun.* **1985**, *13*, 841─842.
2. (a) Winchester, B. G. *Tetrahedron: Asymmetry* **2009**, *20*, 645─651. (b) Scott, L. J.; Spencer, C. M. *Drugs* **2000**, *59*, 521─549.
3. Yu, Z.; Sawkar, A. K.; Whalen, L. J.; Wong, C.-H.; Kelly, J. W. *J. Med. Chem.* **2007**, *50*, 94─100.
4. (a) Compain, P.; Chagnault, V.; Martin, O. R. *Tetrahedron: Asymmetry* **2009**, *20*, 672─711.
5. Li, H.; Liu, T.; Zhang, Y.; Favre, S.; Bello, C.; Vogel, P.; Butters, T. D.; Oikonomakos, N. G.; Marrot, J.; Blériot, Y. *ChemBioChem* **2008**, *9*, 253─260.
6. Shih, T.-L.; Yang, R.-Y.; Li, S.-T.; Chiang, C.-F.; Lin, C.-H. *J. Org. Chem.* **2007**, *72*, 4258─4261.
7. Shih, T.-L.; Kuo, W.-S.; Lin, Y.-L. *Tetrahedron Lett*. **2004**, *45*, 5751─5754.
8. Greeves, N.; Lyford, L. *Tetrahedron Lett*. **1992**, *33*, 4759─4760.
9. Luzzio, F. A.; Moore, W. J. *J. Org. Chem*. **1993**, *58*, 2966─2971.
10. Shih, T.-L.; Lin, Y.-L. *Synth. Commun*. **2005**, *35*, 1809─1817.



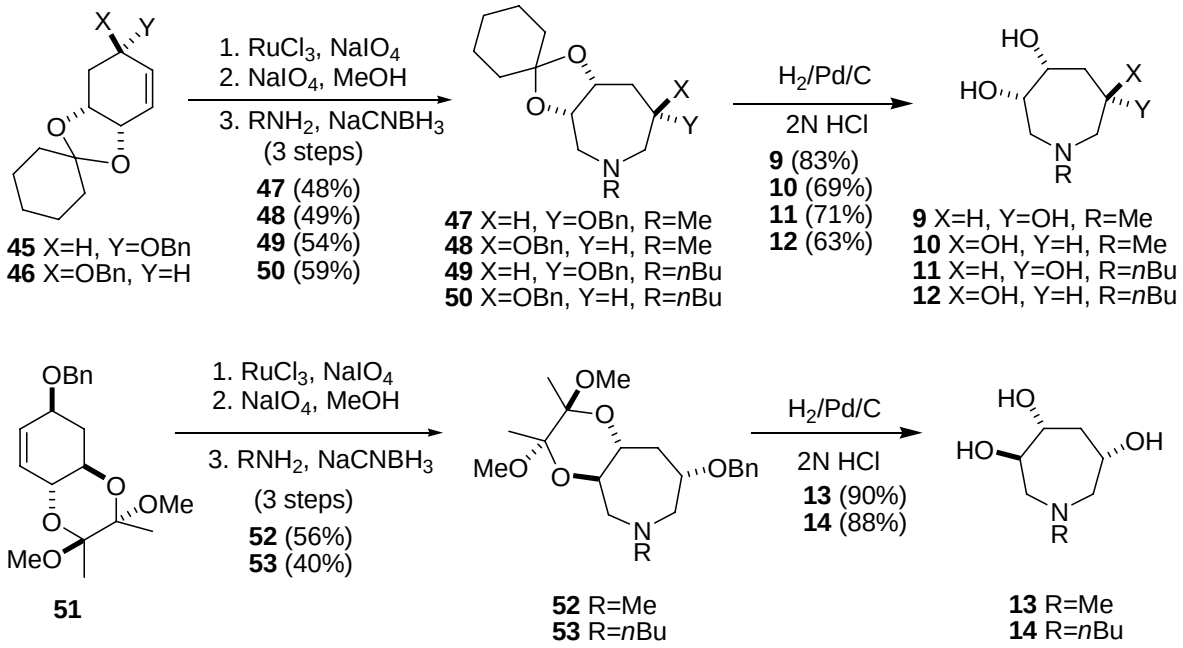
Miglitol (Glyset) NB-DNJ (Zavescal)

Fig. 1 The representative polychydroxylated *N*-alkyl piperidines

Scheme 1 Syntheses of 7-Methyl- and 7-Butylazepanes-3,4,5-triols



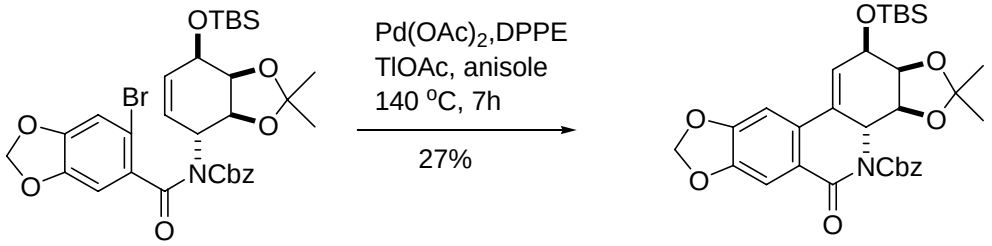
Scheme 2 Synthesis of Polyhydroxylated *N*-Methyl and -Butylazepanes



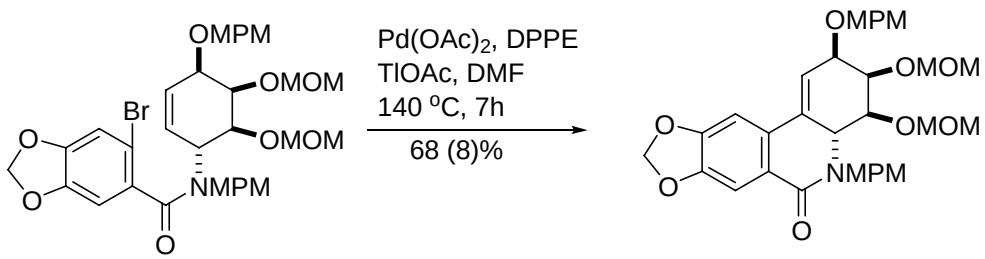
<u>第三部分</u>

我們觀察到 lycoricidine 分子的 C ring 也可以由 D-(－)-quinic acid 而來，lycoricidine 分子是屬於 amaryllidaceae 家族，這一類分子具有抗病毒、昆蟲 antifeedant 等生物活性[1]。早期的合成如 Hodlicky[2] 及 Ogawa[3] 也是利用 Heck 反應來結合 BC 環，但是根據作者報導其產率不具再現性，而且反應時間長是二者共通現象。所以，我們欲利用微波方式促進反應速率。我們分別比較了傳統及微波方式發現，微波具有了絕對優勢，另外，欲控制雙鍵遷移現象與反應的條件非常有關。所以選擇適當方法可讓我們合成 lycoricidine。

Hudlicky, et al



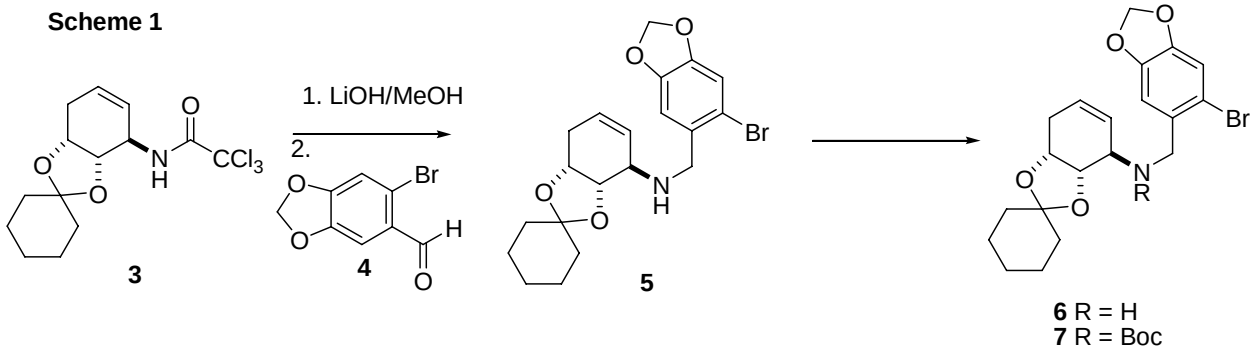
Ogawa, et al

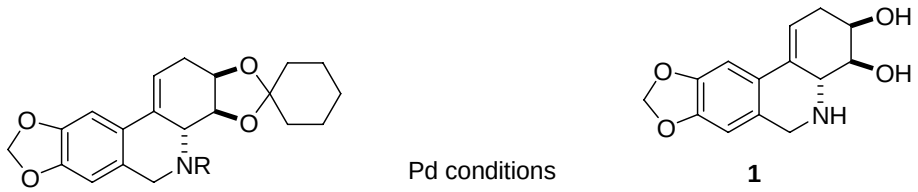


以下計畫尚未全部完成，茲列出部分結果：

化合物 **3** 曾被本實驗室報導過(Scheme 1)，經鹼處理後與化合物 **4** 偶和得到化合物 **5**，我們原先將氮以 Boc 保護，以不同配位基，以傳統油浴方式加熱進行 Heck 反應。文獻方法並不好，回收了部分起始物 **7**。其他二種方式都以化合物 **11** 為唯一產物。有一條件得到化合物 **9**、**11** 的混合物，但以前者為主產物(Table 1)。若化合物氮未經保護，在微波條件下可進行環合反應，整體而言微波反應大大縮減反應時間產率也相對提高了。

Scheme 1





Scheme 2

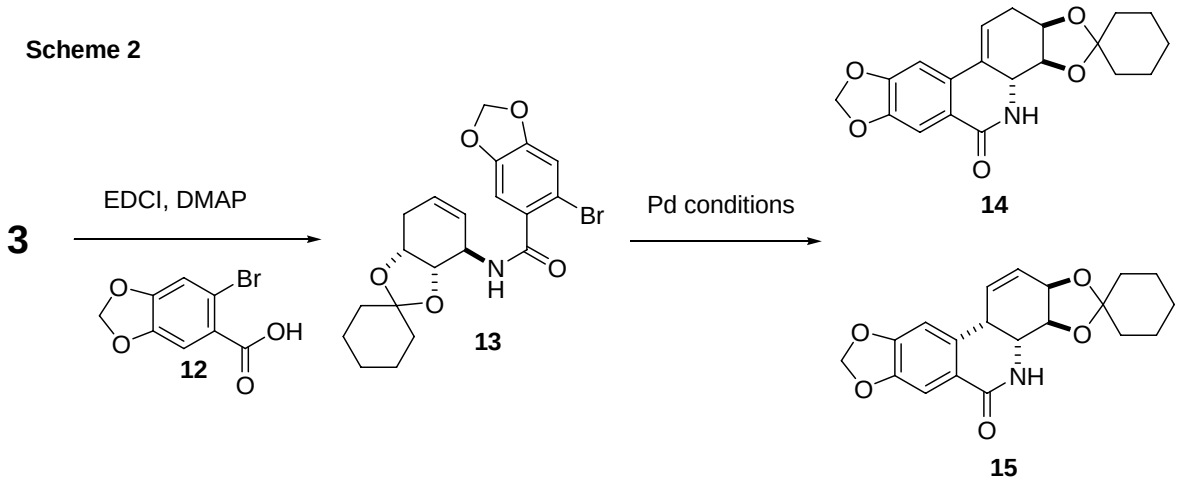


Table 1

cat (mol%)/ligand (mol%)	Reacion conditions	Time	**7**	**8**	**11**
$Pd(OAc)_2$ (15)/PPh_3 (15)	$EtN(iPr)_2$ (1.5eq) 160 ^oC	4h	trace	0%	32%
$Pd(OAc)_2$ (15)/TBAB (15)	NaOAc (5.5 eq) 160 ^oC	4h	0%	45%	15%
$Pd(OAc)_2$ (15)/Tl(OAc) (2eq) DPPE (cat)	DMF, 160 ^oC	4h	37%		31%*
$Pd(OAc)_2$ (15)/PPh_3 (15)	$EtN(iPr)_2$ (1.5eq) **uM,** 160 ^oC	5 min	54	46.5	53.5

* conversion yield ** based on the conversion yield of **1**

我們運用以上條件於真實 lycoricidine 分子(Scheme 2)，化合物 **3**、**12** 進行偶和得到 **13**，先進行微波反應得到主產物 **15**，若能將條件控制好，期望能得到以 **14** 為主產物。

References

1. Martin, S. F. In *The Alkaloids*; Brossi, A. Ed; Academic Press: New York, 1987; Vol 30, pp251-376.
2. Hudlicky, T.; Olivo, H. F. *J. Am. Chem. Soc.* **1992**, *114*, 9694-9696.
3. Chida, N.; Ohtsuka, M.; Ogawa, S. *J. Org. Chem.* **1993**, *58*, 4441-4447

第四部分

參與 21st International Symposium: Synthesis in Organic Chemistry, University of Oxford, UK.

一、參加會議經過

98/7/18 搭機由台北出發至英國倫敦(7/19)再搭乘巴士至牛津，車程約一個半小時。會議於 7/20 早上開始，並於 7/23 結束。7/23 搭巴士從牛津離開至倫敦，接著搭機經香港返回台北。

二、與會心得

此次會議由英國皇家科學會名義，由牛津及劍橋大學每年分別主辦。學術主要之演講者為美國、英國、德國及一名大陸學者。與會人士多為歐洲研究學者及學生，亞洲除了幾位日本學生外，台灣只有我及一名學生與會。報名人數約兩百四十人，實際為約兩百八十人。會議內容已限制在有機合成方面，所以發表之論文也著重在天然物之合成。演講者均將他們近期之研究作一精彩演講，即便是知名的學者無不使出渾身解數，從中我感受到他們對化學的熱情以及學生們以全副精力投注在化學合成。光是這一點，台灣的研究環境及學生對待科學的態度，絕對是望塵莫及。親自聆聽大師的演講比閱讀他們的文章感受又特別深，並也激起很多想法，將來一定可以運用在自己研

究上。

另外值得一提的是，國外辦會議對邀請的知名學者與一般的參與人士均一視同仁，在吃與住方面沒有不同。

除此之外，我感受到國外的學生都非常用功，否則無法做出這麼高水準的研究。反之，台灣的學生可能在研究的決心以及學術熱誠上與他們有一段差距。

計畫成果自評部份

本計畫實施過程中已發表了一篇 *J. Org. Chem.*， 一篇 *Synthetic Communications*，另外一篇正進行中，基本上達成率約 80%。這些年，本實驗室願意加入的學生很少，也許是他們普遍認為有機合成較辛苦，有時候自己也必須親力親為，學生基本上也盡力完成我們交付之任務，過程中，學生也得到完整訓練，差可滿意。我們也希望，這類化合物有一天可用於藥物。