Tetrahedron 69 (2013) 1897–1903

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

The first synthesis of 7-(hydroxymethyl)thiepane-3,4,5-triols from D-(−)-quinic acid

Tzenge-Lien Shih *, Wei-Lin Gao

Department of Chemistry, Tamkang University, 25137 Tamsui Dist., New Taipei City, Taiwan

ARTICLE INFO

Article history:
Received 8 October 2012
Received in revised form 10 December 2012
Accepted 18 December 2012
Available online 29 December 2012

Keywords:
Glycosidase inhibitors
D-(−)-Quinic acid
Thiepanes
Thiosugars

ABSTRACT

Seven thiepanes, the seven-membered-ring thiosugars, were first synthesized in 11–12 steps starting from D-(−)-quinic acid. Each thiepane is unique for its flexible conformation with a hydroxymethyl group at its C7 position. The key step was the deprotection of ether groups in compounds **7**, **8**, and **18**–**21** by 1.0 M BCl_3 of CH_2Cl_2 solution at −78 °C to lead to the corresponding thiepanes. These target molecules all exhibited the twisted chair conformation that fully agreed with our previous report.

1. Introduction

Glycosidases are important enzymes that are involved in the hydrolysis of complex carbohydrates.[1] Glycosidase inhibitors are widely used in treatment of diseases, such as diabetes,[2] anti-virus infections,[3] and cancers.[4] Presently, many potent glycosidase inhibitors are either pyrrole- or piperidine-like azasugars. The most notable agents are nojirimycin,[5] 1-deoxynojirimycin (DNJ),[5] and miglitol.[6] as salacinol,[12,13] kotalanol,[13] and other analogues,[14,15] have attracted interests to synthetic communities due to their intriguing structures and biological activities (Fig. 1).[13–17] In addition to the five-membered-ring thiosugar moiety, the thiopyrans and thiepanes could also be incorporated with different sulfate side chains, such as **1**, **2** (Fig. 1).[18] Thiepanes are seemingly as flexible as azepanes (seven-membered-ring azasugars).[19,20] To the best of our knowledge, only few synthetic thiepanes were reported and their syntheses were mainly based on chiral-pool approaches.[21–27]

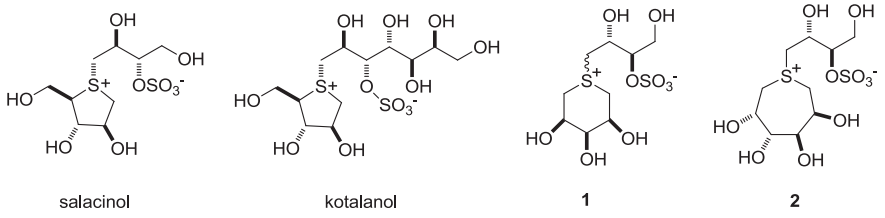


Fig. 1. Structures of salacinol, kotalanol, and analogues **1** and **2**.

Beside the above-mentioned azasugars, the thiosugars were also considered as potential glycosidase inhibitors as well as sugar mimics of nucleoside analogues.[7–11] Recently, five-membered ring thiosugars with various forms of sulfate side chains, such

We have experienced in the synthesis of thiepanes starting from D-(−)-quinic acid.[28] In that report, we obtained not only the required thiepanes but also thiopyrans during the reaction course. Obviously, the intramolecular sulfur displacement of an adjacent hydroxyl group of thiepanes led to the thiopyran formation. Such ring contractions in the formation of thiophenes and thiopyrans from the corresponding either seven- or eight-membered-ring thiosugar derivatives were not unusual as have been

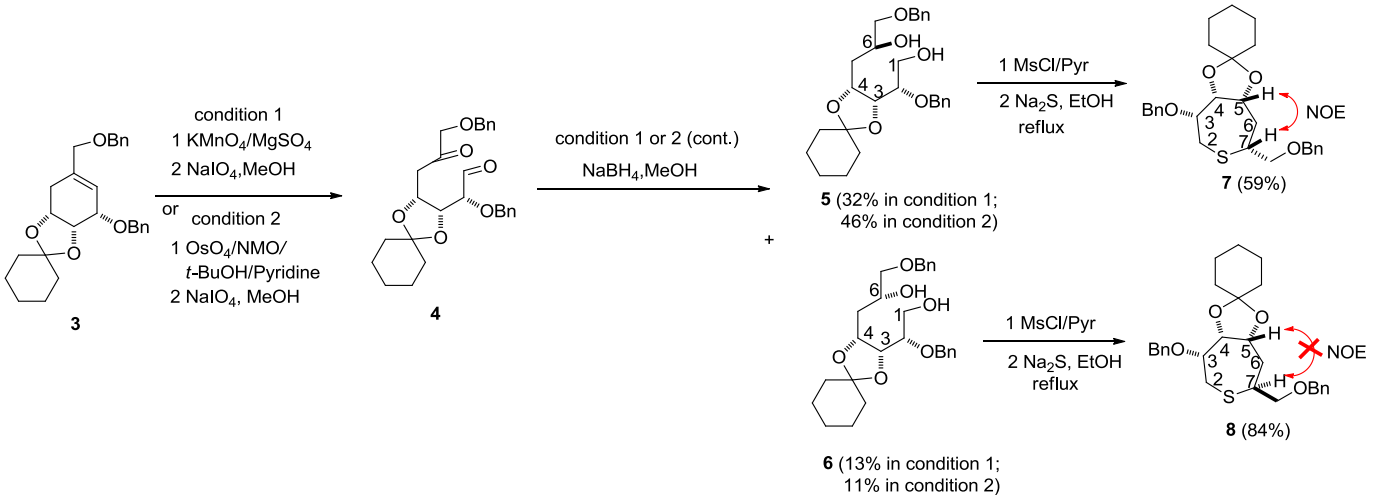
* Corresponding author. Tel.: +886 286315024; fax: +886 226209924; e-mail address: tlshih@mail.tku.edu.tw (T.-L. Shih).

0040-4020/$ – see front matter
http://dx.doi.org/10.1016/j.tet.2012.12.047

reported.[27,30] In order to synthesize thiepanes in higher yields as well as minimize the possibility of ring contraction, we reported herein a straightforward method to synthesize new and unique thiepanes **22**, **23**, and **25**–**29** from D-(−)-quinic acid.

2. Results and discussion

A common intermediate **3**[29] was used for the syntheses of **7** and **8** (Scheme 1). Compound **3** was first subjected to dihydroxylation by $KMnO_4/MgSO_4$ method[31] to afford a diol derivative, which was oxidatively cleaved by $NaIO_4$ to give **4**. The resulting syrup was subsequently reduced by $NaBH_4$ to receive the separable diastereomers **5** (32%, three steps) and **6** (13%, three steps) (vide infra). While OsO_4 and NMO were used as oxidants, the higher yields of **5** (46%) and **6** (11%) were isolated. The absolute stereochemistry at C6 of **5** and **6** was not easily to be confirmed at this stage. Fortunately, their configurations were later determined after methanesulfonation and thiocyclization of compounds **5** and **6** to provide **7** (84%) and **8** (59%), respectively. Many reports have demonstrated that these kinds of thiocyclizations underwent an S_N2 mechanism.[9,12,23,32–34] Therefore, the newly generated stereochemistry at C7 of **7** and **8** were determined by comparison with their cross-coupling patterns between H5 and H7 of NOESY spectra. Compound **7** exhibits space correlation between H5 and H7 but compound **8** does not. Thus we could deduce the C6 configurations of **5** and **6** as shown in Scheme 1.



Scheme 1. Synthesis of thiocyclic compounds **7** and **8**.

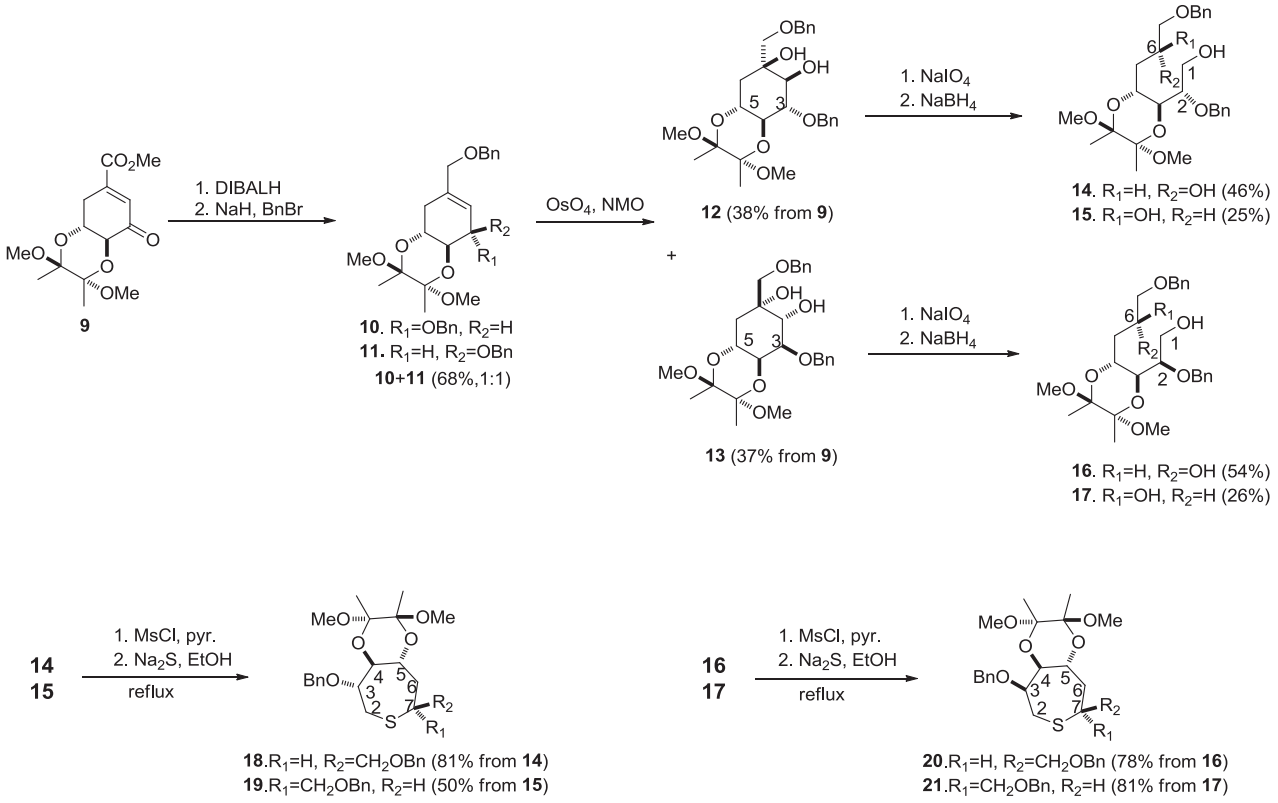
The same strategy was applied to synthesize **18**–**21** (Scheme 2). Compound **9** was reduced by diisobutylaluminium hydride and then protected by benzyl groups to give an inseparable mixture of **10** and **11** (~1:1) in 68% combined yield (two steps).[35,36] Fortunately, the mixture was dihydroxylated to afford the separable stereoisomers **12** (38%) and **13** (37%). The stereochemistry at C3 of **12** and **13** was easily determined according to the comparison of NOESY spectra between H3 and H5 in **12** but not in **13**. When the double bond of compounds **12** was oxidatively cleaved and reduced, two diastereomers **14** (46%) and **15** (25%) were isolated. While compound **13** was treated with the same procedure as above, compounds **16** (54%) and **17** (26%) were obtained (vide infra). Again, their respective stereochemistry could be indirectly deduced after cyclizations of **14**–**17**, which were conducted under the same condition shown in Scheme 1 to afford compounds **18** (81%), **19** (50%), **20** (78%), and **21** (81%), respectively. The resulting stereochemistry at C7 of **18**–**21** was again determined by NMR experiments. The NOE signals were clearly observed between H5 and H7 in **19** and **21** but not in **18** and **20**. These results allowed us to conclude the stereochemistry at C6 of compounds **14**–**17** according to the S_N2 mechanism.

Compound **7**, **18**, and **19** were deprotected by 1.0 M BCl_3 in CH_2Cl_2 at −78 °C[9] to give thiepanes **22** (50%), **25** (45%), and **26** (42%), respectively (Scheme 3). The same procedure was also applied on **8**, however, it afforded a mixture that contained two inseparable compounds **23** and **24** in a ratio of 70:30 that determined by NMR spectroscopy in a 59% combined yield. Obviously, compound **24** was derived from the ring contraction of **23** to give **23a** as an intermediate and followed by the nucleophilic attack by H_2O to afford **24** as indicated (path a).[27,30] Also compound **23** was recovered from **23a** via path b. A very interesting phenomenon was observed in deprotection of compounds **20** and **21**. The benzyl group at C3 of **20** resisted to be cleaved and give **27** (55%) after the other protecting groups were cleaved. Deprotection of **21** also gave the C3 benzyl protected **28** (40%) as well as a fully deprotected **29** (10%) as a minor product. Further attempts to remove the benzyl groups of **27** and **28** by excess equivalents of BCl_3 (10 equiv, 1.0 M in CH_2Cl_2) from −78 °C to ambient temperature were not successful. Compounds **27** and **28** were fully recovered. We attempted to remove the benzyl groups in compounds **7**, **8**, and **18**–**21** by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ (5 equiv)/K_2CO_3) in CH_2Cl_2 under reflux condition. However, only the C8 benzyl groups were removed and the C3 benzyl groups were remained intact in all cases. It is noteworthy that thioadducts **7**, **8**, and **18**–**21** were decomposed when boron tribromide (BBr_3, 3 equiv) was used in CH_2Cl_2 at −78 °C. We found that compounds **7**, **8**, and **18**–**21** might be slightly labile under deprotecting steps to give target molecules in relatively lower yields along with various amounts of complex mixtures in each reaction.

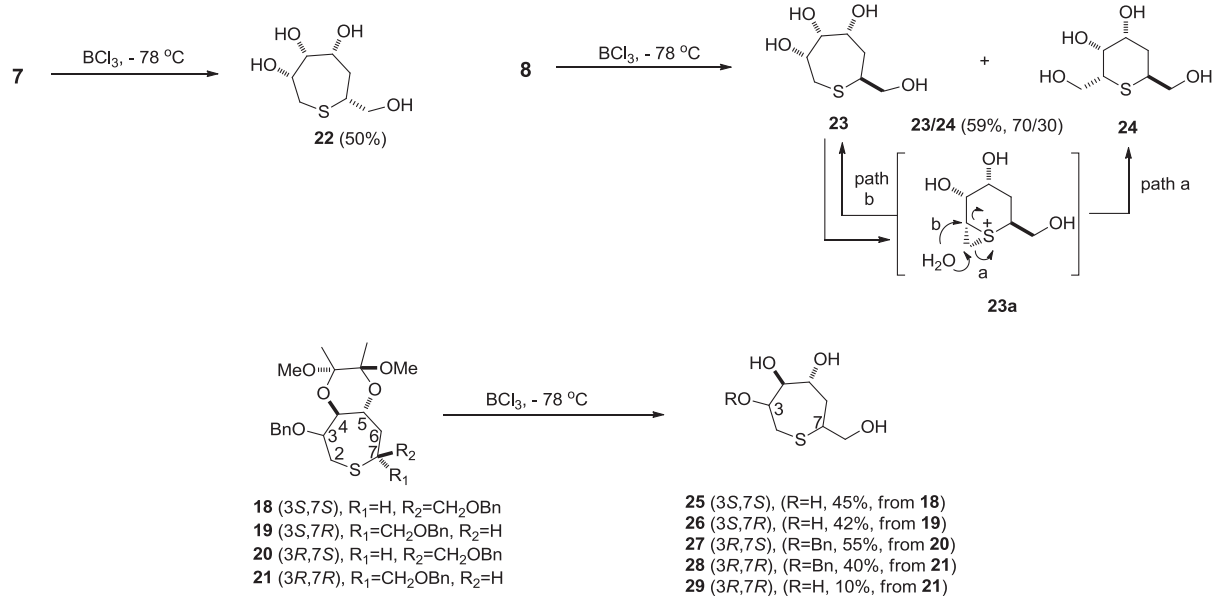
Structural optimizations of compounds **22**, **23**, and **25**–**29** all exhibited the twisted chair conformers. These results were consistent with azepane cases we reported earlier.[37]

3. Conclusion

In conclusion, we have first synthesized a series of 7-(hydroxymethyl)thiepane-3,4,5-triols **22**, **23**, **25**–**29** in 11–12 steps starting from D-(−)-quinic acid. These molecules are not only flexible in structures but also unique with an external hydroxymethyl group



Scheme 2. Syntheses of thiocyclic compounds **18**–**21**.



Scheme 3. Syntheses of thiepanes **22**, **23**, **25**–**29**, and thiopyran **24**.

at C7 of thiepane. The most suitable deprotecting agent is boron trichloride that gave the corresponding thiepanes and minimized the possibilities of ring contraction to thiopyrans, except **24**. We find that the fully deprotecting step occurs for compounds **7**, **8**, **18**, and **19** but **20** and **21**. The biological activities of thiepanes will be reported in due course.

4. Experimental section

4.1. General

All chemicals were purchased from commercial providers and used without purification except otherwise mentioned. CH_2Cl_2 was

distilled from CaH_2. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 600 spectrometer, respectively. Chemical shifts were measured in parts per million (ppm) and referenced to the residual C_6D_6 (7.16 ppm for ^1H and 128.0 ppm for ^{13}C) and D_2O (4.63 ppm for ^1H). Optical rotations were measured by Horiba Sepa-300 instrument. HRMS (ESI/FAB) were carried out on model Finnigan MAT 95S.

4.2. General procedures for dihydroxylation, oxidative cleavage, and reduction

(1) Compound **3** (0.11 g, 0.262 mmol) in 95% EtOH was treated with an aqueous solution of $KMnO_4$ (0.169 g, 1.07 mmol)/$MgSO_4$ (0.125 g, 1.04 mmol) (EtOH/H_2O=9:1, v/v, 0.1–0.3 M) at 0 °C. The mixture was stirred at ambient temperature for 24 h. At the end of reaction time, the mixture was passed through a pad of Celite and washed with EtOH. The solution was concentrated, extracted with EtOAc, and dried ($MgSO_4$). This resulting pale yellow syrup in MeOH was treated with $NaIO_4$ (0.96 g, 4.49 mmol) and stirred at ambient temperature for 24 h. At the end of time, the mixture was passed through a pad of Celite and washed with MeOH. The solution was concentrated, diluted with H_2O, extracted with EtOAc, and dried ($MgSO_4$). The resulting syrup **4** was dissolved in MeOH and $NaBH_4$ (4 equiv) was added at 0 °C. Once the reaction was complete, the reaction was quenched by addition of H_2O, concentrated, extracted with EtOAc, and dried over $MgSO_4$. Purification by flash column chromatography (230–400 mesh SiO_2, CH_2Cl_2/EtOAc=20:1→15:1→10:1) provided compounds **5** (32%, three steps) and **6** (13%, three steps), respectively.

(2) Compound **3** (1.970 g, 4.684 mmol) was dissolved in *t*-BuOH/pyridine/H_2O (40.0:4.0:10.0 mL). To this mixture were added 4-methylmorpholine *N*-oxide (1.646 g, 14.051 mmol) and osmium tetroxide (0.1 M solution in THF, 0.94 mL, 2 mol %) and heated at 100 °C for 19 h. At the end of reaction time, to the mixture was added $Na_2S_2O_3$ (saturated) and stirred for 1 h. OsO_4 was removed by filtration through a pad of silica gel and washed with EtOAc. The organic layer was washed with $NaHCO_3$ (saturated), dried with $MgSO_4$, and purified by flash column chromatography (230–400 mesh SiO_2, Hex/EtOAc=3:1→2:1) to provide a white solid. The rest steps included oxidative cleavage and reduction were the same as previous to afford **5** (46%, three steps) and **6** (11%, three steps), respectively.

4.3. General procedure for thiocyclization

To compound **5** (0.0965 g, 0.199 mmol) in pyridine (3 mL) was added methanesulfonyl chloride (0.062 mL, 0.794 mmol) at 0 °C. The reaction mixture was stirred at that temperature for 30 min before this mixture was quenched by slow addition of saturated $NaHCO_3$ solution and EtOAc. The organic layer was separated, washed by $CuSO_4$ saturated solution, and dried ($MgSO_4$) to provide a yellow syrup. To this syrup were added 95% EtOH, Na_2S (0.093 g, 1.194 mmol), 15-crown-6 (*cat*) and heated under reflux condition (110–130 °C, oil bath) for 2 h. At the end of reaction time, the solvent was removed and the resulting mixture was washed with saturated $Na_2S_2O_3$ solution and extracted with EtOAc. The organic layer was dried over $MgSO_4$, concentrated, and purified by flash column chromatography (230–400 mesh SiO_2, Hex/EtOAc=20:1) to afford **7** (59%) in three steps. The same procedure was also accessible for synthesis of **8** (84%).

4.4. General procedure of debenzylation

Compound **7** (0.0286 g, 0.0586 mmol) in CH_2Cl_2, for example, was treated with BCl_3 (1.0 M in CH_2Cl_2, 3 equiv) at −78 °C. The reaction mixture was stirred at that temperature for 4 h followed by addition of MeOH. This mixture was gradually warmed up to ambient temperature and the resulting mixture was concentrated. To this syrup was added MeOH for coevaporation, and this step was repeated for several times. Purification by flash chromatography (230–400 mesh SiO_2, MeOH/CH_2Cl_2=1:10→1:8, 1% NH_4OH) provided **22** (50%) as a clear to pale yellow syrup. The same procedure was also applied in preparation of **23**–**29**.

4.5. (2*S*,3*R*,4*R*,6*R*)-2,7-*O*-Bisbenzyl-3,4-*O*-cyclohexylidene-heptane-1,2,3,4,6,7-pentanol (5)

Purification by flash column chromatography (230–400 mesh SiO_2, EtOAc/CH_2Cl_2=1:20→1:15→1:10→1:5) afforded a clear syrup. Yield=46%. $[\alpha]_D^{26}$ +18.8 (*c* 0.41, EtOAc). ^1H NMR (C_6D_6) δ 7.21 (t, *J*=7.6 Hz, 4H), 7.14–7.00 (m, 6H), 4.62 (ddd, *J*=9.5, 5.6, 3.3 Hz, 1H), 4.37 (d, *J*=11.5 Hz, 1H), 4.30–4.22 (m, 2H), 4.20 (d, *J*=11.5 Hz, 1H), 4.18–4.14 (s, 1H), 3.91–3.82 (m, 2H), 3.44 (dt, *J*=8.2, 3.8 Hz, 1H), 3.33 (dd, *J*=9.3, 4.3 Hz, 1H), 3.23 (dd, *J*=9.3, 6.7 Hz, 1H), 2.49 (d, *J*=4.9 Hz, −OH), 2.00–1.95 (m, −OH), 1.88 (ddd, *J*=13.1, 9.4, 3.2 Hz, 1H), 1.68 (ddd, *J*=13.1, 10.1, 3.2 Hz, 1H), 1.65–1.46 (m, 8H), 1.27–1.16 (m, 2H). ^{13}C NMR (C_6D_6) δ 139.2, 138.8, 130.0–125.0 (*Ar*–), 109.0, 78.1, 77.5, 75.5, 75.0, 73.7, 71.6, 68.6, 62.3, 38.8, 35.6, 34.1, 25.8, 24.9, 24.5. HRMS (ESI) calcd for $C_{27}H_{36}O_6$ ($[M]^+$) 456.2512. Found: 456.2504.

4.6. (2*S*,3*R*,4*R*,6*S*)-2,7-*O*-Bisbenzyl-3,4-*O*-cyclohexylidene-heptane-1,2,3,4,6,7-pentanol (6)

Purification by flash column chromatography (230–400 mesh SiO_2, EtOAc/CH_2Cl_2=1:20→1:15→1:10→1:5) afforded a clear syrup. Yield=11%. $[\alpha]_D^{26}$ +46.4 (*c* 0.25, EtOAc). ^1H NMR (C_6D_6) δ 7.24 (d, *J*=7.5 Hz, 2H), 7.20 (d, *J*=7.5 Hz, 2H), 7.15–7.05 (m, 6H), 4.37–4.28 (m, 4H), 4.18 (dd, *J*=9.2, 5.8 Hz, 1H), 4.15–4.11 (m, 2H), 3.85–3.82 (m, 2H), 3.51 (dd, *J*=9.4, 5.6 Hz, 1H), 3.40 (dd, *J*=9.4, 5.2 Hz, 1H), 3.39–3.36 (m, 1H), 3.22 (s, −OH), 2.00 (dt, *J*=14.0, 3.5 Hz, 1H), 1.84–1.78 (m, 2H), 1.60–1.57 (m, 2H), 1.53–1.41 (m, 6H), 1.20–1.15 (m, 2H). ^{13}C NMR (C_6D_6) δ 139.4, 138.8, 130.0–128.0 (*Ar*–), 109.5, 78.1, 77.3, 77.2, 74.9, 73.8, 71.6, 70.7, 62.0, 38.5, 35.5, 34.3, 25.7, 24.8, 24.4. HRMS (ESI) calcd for $C_{27}H_{36}O_6$ ($[M]^+$) 456.2512. Found: 456.2519.

4.7. (3*R*,4*R*,5*R*,7*S*)-3,7-*O*-Bisbenzyl-4,5-*O*-cyclohexylidene-7-(hydroxymethyl)thiepane-3,4,5-triol (7)

Purification by flash column chromatography (230–400 mesh SiO_2, EtOAc/Hex=1:20→1:18→1:15) afforded a pale yellow syrup. Yield=59%. $[\alpha]_D^{26}$ −6.95 (*c* 1.81, CH_2Cl_2). ^1H NMR (C_6D_6) δ 7.37 (d, *J*=7.4 Hz, 2H), 7.24 (d, *J*=7.4 Hz, 2H), 7.20–7.10 (m, 4H), 7.08 (td, *J*=7.6, 0.8 Hz, 2H), 4.50 (s, 2H), 4.27 (dd, *J*=7.1, 2.8 Hz, 1H), 4.24 (d, *J*=1.2 Hz, 1H), 4.23–4.18 (m, 1H), 3.85 (ddd, *J*=5.3, 5.3, 2.7 Hz, 1H), 3.41 (dd, *J*=9.1, 5.3 Hz, 1H), 3.33 (dd, *J*=9.1, 7.1 Hz, 1H), 2.86 (dd, *J*=15.6, 5.4 Hz, 1H), 2.79 (dd, *J*=13.2, 10.7 Hz, 1H), 2.76–2.73 (m, 1H), 2.53 (ddd, *J*=13.4, 3.8, 3.1 Hz, 1H), 2.35 (dd, *J*=15.4, 5.2 Hz, 1H), 1.92–1.86 (m, 2H), 1.71–1.58 (m, 6H), 1.32–1.28 (m, 2H). ^{13}C NMR (C_6D_6) δ 139.7, 139.3, 129.0–127.0 (*Ar*–), 108.8, 80.4, 78.3, 77.0, 74.4, 73.5, 73.0, 40.3, 37.4, 35.3, 34.7, 29.7, 26.1, 24.8, 24.6. HRMS (ESI) calcd for $C_{27}H_{34}NaO_4S$ ($[M+Na]^+$) 477.2075. Found: 477.2062.

4.8. (3*R*,4*R*,5*R*,7*R*)-3,7-*O*-Bisbenzyl-4,5-*O*-cyclohexylidene-7-(hydroxymethyl)thiepane-3,4,5-triol (8)

Purification by flash column chromatography (230–400 mesh SiO_2, EtOAc/Hex=1:20→1:18→1:15) afforded a pale yellow syrup. Yield=84%. $[\alpha]_D^{25}$ −36.5 (*c* 1.83, CH_2Cl_2). ^1H NMR (C_6D_6) δ 7.29 (d, *J*=7.5 Hz, 4H), 7.18–7.15 (m, 4H), 7.10–7.06 (m, 2H), 4.45–4.41 (m, 1H), 4.42 (d, *J*=12.1 Hz, 1H), 4.32 (d, *J*=12.1 Hz, 1H), 4.27 (d,

J=12.1 Hz, 1H), 4.26 (d, J=12.1 Hz, 1H), 4.10 (ddd, J=8.0, 5.8, 1.9 Hz, 1H), 3.71 (dt, J=8.8, 1.1 Hz, 1H), 3.57–3.52 (m, 2H), 3.45 (dd, J=9.5, 5.4 Hz, 1H), 3.39 (dd, J=9.5, 7.0 Hz, 1H), 2.62–2.57 (m, 2H), 1.79–1.74 (m, 3H), 1.64–1.52 (m, 6H), 1.24–1.20 (m, 2H). ^{13}C NMR (C_6D_6) δ 139.4, 139.2, 130.0–128.0 (*Ar*–), 108.5, 83.1, 80.2, 73.9, 73.8, 73.2, 71.5, 40.0, 39.9, 36.7, 33.9, 28.8, 26.0, 24.7, 24.3. HRMS (ESI) calcd for $C_{27}H_{34}NaO_4S$ ([M+Na]$^+$) 477.2075. Found: 477.2062.

4.9. (1*S*,2*S*,3*R*,4*S*,5*S*)-3,7-*O*-Bisbenzyl-1,2-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-dioxy]-cyclohexane-4,5-diol (12)

Purification by flash column chromatography (230–400 mesh SiO_2, EtOAc/Hex=1:4→1:3→1:2) afforded a colorless syrup. Yield=44%. $[\alpha]_D^{25}$ +94.2 (*c* 0.73, EtOAc). ^{1}H NMR (C_6D_6) δ 7.35 (d, J=7.2 Hz, 2H), 7.18 (d, J=7.2 Hz, 2H), 7.16–7.06 (m, 6H), 5.09 (d, J=11.4 Hz, 1H), 4.69 (d, J=12.0 Hz, 1H), 4.36 (ddd, J=14.4, 9.6, 4.8 Hz, 1H), 4.19 (s, 2H), 3.84 (t, J=9.6 Hz, 1H), 3.77 (t, J=9.0 Hz, 1H), 3.73 (d, J=8.4 Hz, 1H), 3.34 (d, J=9.0 Hz, 1H), 3.17 (m, 4H), 3.10 (s, 3H), 2.55 (s, –OH), 2.09 (dd, J=13.2, 4.8 Hz, 1H), 1.86 (t, J=12.6 Hz, 1H), 1.39 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (C_6D_6) δ 140.2, 138.9, 128.9–128.0 (*Ar*–), 100.1, 99.8, 80.6, 75.5, 75.4, 74.5, 73.9, 73.4, 65.7, 47.9, 35.4, 18.5 (×2). HRMS (FAB) calcd for $C_{27}H_{37}O_8$ [M+H]$^+$ 489.2488. Found: 489.2489.

4.10. (1*S*,2*S*,3*S*,4*R*,5*R*)-3,7-*O*-Bisbenzyl-1,2-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-dioxy]-cyclohexane-4,5-diol (13)

Purification by flash column chromatography (230–400 mesh SiO_2, EtOAc/Hex=1:4→1:3→1:2) afforded a colorless syrup. Yield=27%. $[\alpha]_D^{25}$ +69.1 (*c* 0.57, EtOAc). ^{1}H NMR (C_6D_6) δ 7.36 (d, J=7.4 Hz, 2H), 7.18 (d, J=7.4 Hz, 2H), 7.15–7.06 (m, 6H), 4.94 (d, J=11.6 Hz, 1H), 4.47 (d, J=11.6 Hz, 1H), 4.36 (dd, J=10.3, 2.9 Hz, 1H), 4.22–4.16 (m, 2H), 4.12 (t, J=3.1 Hz, 1H), 4.08 (d, J=11.9 Hz, 1H), 3.99 (d, J=2.9 Hz, 1H), 3.72 (d, J=9.4 Hz, 1H), 3.61 (d, J=9.4 Hz, 1H), 3.11 (s, 3H), 3.10 (s, 3H), 2.92 (s, –OH), 2.77 (s, –OH), 2.18 (t, J=12.5 Hz, 1H), 2.09 (dd, J=12.5, 4.8 Hz, 1H), 1.38 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (C_6D_6) δ 140.0, 138.9, 129–127.9 (*Ar*–), 100.4, 99.9, 79.1, 74.9, 74.7, 74.6, 73.8, 72.5, 71.7, 63.9, 48.0, 47.9, 35.3, 18.5 (×2). HRMS (FAB) calcd for $C_{27}H_{37}O_8$ [M+H]$^+$ 489.2488. Found: 489.2489.

4.11. (2*S*,3*S*,4*R*,6*R*)-2,7-*O*-Bisbenzyl-3,4-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-dioxy]-heptane-1,2,3,4,6,7-hexaol (14)

Purification by flash column chromatography (230–400 mesh SiO_2, EtOAc/Hex=1:4→1:3→1:2) afforded a colorless syrup. Yield=46%. $[\alpha]_D^{25}$ +110.7 (*c* 0.38, EtOAc). ^{1}H NMR (C_6D_6) δ 7.31 (d, J=7.6 Hz, 2H), 7.20 (d, J=7.4 Hz, 2H), 7.16–7.12 (m, 4H), 7.11–7.05 (m, 2H), 4.59 (d, J=11.9 Hz, 1H), 4.57 (ddd, J=10.1, 10.1, 2.0 Hz, 1H), 4.46 (d, J=11.9 Hz, 1H), 4.31 (ddd, J=13.0, 6.8, 3.1 Hz, 1H), 4.26 (s, 2H), 3.94 (dt, J=11.5, 5.3 Hz, 1H), 3.85 (dd, J=10.0, 2.7 Hz, 1H), 3.84–3.80 (m, 1H), 3.47 (ddd, J=5.0, 5.0, 2.7 Hz, 1H), 3.30 (dd, J=9.2, 3.8 Hz, 1H), 3.22–3.18 (m, 1H), 3.20 (s, 3H), 3.05 (s, 3H), 2.50 (d, J=3.8 Hz, –OH), 2.12 (t, J=6.4 Hz, –OH), 1.83 (ddd, J=14.1, 10.0, 2.1 Hz, 1H), 1.47 (ddd, J=14.0, 10.2, 2.4 Hz, 1H), 1.31 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (C_6D_6) δ 139.3, 139.2, 130.0–128.0 (*Ar*–), 99.7, 99.2, 78.4, 75.8, 73.7, 73.3, 72.3, 67.1, 65.7, 62.2, 48.1, 48.0, 34.8, 18.3, 18.2. HRMS (FAB) calcd for $C_{27}H_{38}O_8$ [M$^+$] 490.2567. Found: 490.2568.

4.12. (2*S*,3*S*,4*R*,6*S*)-2,7-*O*-Bisbenzyl-3,4-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-dioxy]-heptane-1,2,3,4,6,7-hexaol (15)

Purification by flash column chromatography (230–400 mesh SiO_2, EtOAc/Hex=1:4→1:3→1:2) afforded a colorless syrup. Yield=46%. $[\alpha]_D^{25}$ +122.5 (*c* 0.31, EtOAc). ^{1}H NMR (C_6D_6) δ 7.26 (dd, J=6.8, 4.8 Hz, 4H), 7.14–7.02 (m, 6H), 4.58 (d, J=11.9 Hz, 1H), 4.40 (td, J=9.9, 2.9 Hz, 1H), 4.37 (s, 2H), 4.36 (d, J=10.5 Hz, 1H), 4.30–4.25 (m, 1H), 3.89–3.84 (m, 2H), 3.74 (ddd, J=11.7, 8.0, 4.4 Hz, 1H), 3.51 (ddd, J=9.4, 5.8, 2.0 Hz, 1H), 3.44–3.40 (m, 2H), 3.32 (d, J=1.7 Hz, –OH), 3.03 (s, 6H), 2.06 (t, J=4.1 Hz, –OH), 1.96 (dt, J=14.5, 3.2 Hz, 1H), 1.69 (dt, J=14.5, 8.9 Hz, 1H), 1.22 (s, 3H), 1.18 (s, 3H). ^{13}C NMR (C_6D_6) δ 139.4, 139.2, 130.0–127.0 (*Ar*–), 99.7, 99.3, 77.8, 75.1, 73.8, 73.3, 72.1, 70.2, 69.3, 62.0, 48.1, 48.0, 35.0, 18.2 (×2). HRMS (FAB) calcd for $C_{27}H_{38}O_8$ [M$^+$] 490.2567. Found: 490.2566.

4.13. (2*R*,3*S*,4*R*,6*R*)-2,7-*O*-Bisbenzyl-3,4-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-dioxy]-heptane-1,2,3,4,6,7-hexaol (16)

Purification by flash column chromatography (230–400 mesh SiO_2, EtOAc/CH_2Cl_2=1:8→1:7→1:6→1:4→1:3) afforded a colorless syrup. Yield=54%. $[\alpha]_D^{25}$ +119.4 (*c* 0.58, EtOAc). ^{1}H NMR (C_6D_6) δ 7.27 (d, J=7.6 Hz, 2H), 7.19 (d, J=7.1 Hz, 2H), 7.17–7.12 (m, 4H), 7.12–7.05 (m, 2H), 4.39 (s, 2H), 4.39–4.30 (m, 2H), 4.24 (s, 2H), 4.02 (dd, J=10.1, 4.6 Hz, 1H), 3.96 (dd, J=11.4, 4.5 Hz, 1H), 3.89 (dd, J=11.4, 4.5 Hz, 1H), 3.49 (ddd, J=9.5, 4.8, 1.4 Hz, 1H), 3.25 (dd, J=9.2, 3.7 Hz, 1H), 3.21 (s, 3H), 3.17 (s, 3H), 3.15 (d, J=9.2 Hz, 1H), 2.54 (d, J=11.5 Hz, –OH), 2.38 (s, –OH), 1.82 (t, J=12.3 Hz, 1H), 1.52 (ddd, J=12.3, 10.2, 2.2 Hz, 1H), 1.31 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (C_6D_6) δ 139.2, 139.1, 130.0–127.0 (*Ar*–), 99.2, 99.1, 80.0, 75.7, 73.7, 72.8, 72.2, 67.3, 67.0, 61.7, 48.3, 48.2, 35.4, 18.2, 18.1. HRMS (FAB) calcd for $C_{27}H_{38}O_8$ [M$^+$] 490.2567. Found: 490.2570.

4.14. (2*R*,3*S*,4*R*,6*S*)-2,7-*O*-Bisbenzyl-3,4-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-dioxy]-heptane-1,2,3,4,6,7-hexaol (17)

Purification by flash column chromatography (230–400 mesh SiO_2, EtOAc/CH_2Cl_2=1:8→1:7→1:6→1:4→1:3) afforded a colorless syrup. Yield=26%. $[\alpha]_D^{25}$ +98.0 (*c* 0.54, EtOAc). ^{1}H NMR (C_6D_6) δ 7.27 (dd, J=7.0, 0.5 Hz, 2H), 7.23 (dd, J=7.6, 1.1 Hz, 2H), 7.14–7.05 (m, 6H), 4.42 (d, J=11.7 Hz, 1H), 4.38 (d, J=11.7 Hz, 1H), 4.34 (d, J=12.1 Hz, 1H), 4.31 (d, J=12.1 Hz, 1H), 4.28–4.23 (m, 1H), 4.12 (dd, J=9.2, 3.2 Hz, 1H), 4.09 (dd, J=10.0, 2.9 Hz, 1H), 3.91 (dt, J=11.5, 5.4 Hz, 1H), 3.84 (dt, J=11.5, 5.2 Hz, 1H), 3.47 (dd, J=9.2, 5.9 Hz, 2H), 3.36 (dd, J=9.4, 5.2 Hz, 1H), 3.24 (d, J=1.6 Hz, –OH), 3.14 (s, 3H), 3.03 (s, 3H), 2.27 (t, J=6.1 Hz, –OH), 1.98 (dt, J=14.3, 3.2 Hz, 1H), 1.74 (dt, J=15.0, 8.2 Hz, 1H), 1.24 (s, 3H), 1.20 (s, 3H). ^{13}C NMR (C_6D_6) δ 139.4, 139.1, 130.0–128.0 (*Ar*–), 99.2, 99.1, 79.8, 75.2, 73.8, 72.3, 72.2, 70.3, 69.8, 61.8, 48.2, 35.7, 18.1, 18.0. HRMS (FAB) calcd for $C_{27}H_{38}O_8$ [M$^+$] 490.2567. Found: 490.2563.

4.15. (3*R*,4*S*,5*R*,7*S*)-3-*O*-Benzyl-4,5-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-dioxy]-7-benzyloxymethyl-thiepane-3,4,5-triol (18)

Purification by flash column chromatography (230–400 mesh SiO_2, EtOAc/Hex=1:15→1:10) afforded a colorless syrup. Yield=81%. $[\alpha]_D^{25}$ +87.2 (*c* 0.28, EtOAc). ^{1}H NMR (C_6D_6) δ 7.33 (d, J=7.1 Hz, 2H), 7.23 (d, J=7.1 Hz, 2H), 7.20–7.00 (m, 6H), 4.55 (d, J=11.8 Hz, 1H), 4.39 (d, J=11.8 Hz, 1H), 4.28 (d, J=12.2 Hz, 1H), 4.22 (d, J=12.2 Hz, 1H), 4.17 (d, J=12.2 Hz, 1H), 3.84 (dd, J=9.6, 8.2 Hz, 1H), 3.60 (td, J=8.4, 5.2 Hz, 1H), 3.46–3.41 (m, 1H), 3.35–3.30 (m, 2H), 3.27 (s, 3H), 3.30 (s, 3H), 2.48 (dt, J=15.2, 5.2 Hz, 2H), 2.21 (d, J=15.3 Hz, 1H), 1.89 (ddd, J=15.3, 9.2, 6.3 Hz, 1H), 1.40 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (C_6D_6) δ 140.0, 139.0, 130.0–128.0 (*Ar*–), 99.6, 98.9, 83.6, 78.7, 73.6, 73.5, 72.9, 65.3, 48.1, 47.9, 39.2, 32.8, 28.4, 18.3, 18.1. HRMS (FAB) calcd for $C_{27}H_{36}O_6S$ [M$^+$] 488.2233. Found: 488.2234.

4.16. (3*R*,4*S*,5*R*,7*R*)-3-*O*-Benzyl-4,5-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-dioxy]-7-benzyloxymethyl-thiepane-3,4,5-triol (19)

Purification by flash column chromatography (230–400 mesh SiO_2, EtOAc/Hex=1:18→1:15→1:10) afforded a colorless syrup. Yield=50%. $[\alpha]_D^{25}$ +63.8 (*c* 0.24, EtOAc). ^{1}H NMR (C_6D_6) δ 7.31 (d, J=7.1 Hz, 2H), 7.23 (dd, J=7.5, 0.5 Hz, 2H), 7.20–7.06 (m, 6H), 4.55 (d,

J=11.9 Hz, 1H), 4.37 (d, *J*=11.9 Hz, 1H), 4.26 (d, *J*=12.2 Hz, 1H), 4.24 (d, *J*=12.2 Hz, 1H), 4.13 (t, *J*=9.7 Hz, 1H), 3.83 (t, *J*=8.3 Hz, 1H), 3.63 (ddd, *J*=11.3, 8.2, 3.2 Hz, 1H), 3.31 (dd, *J*=9.2, 4.9 Hz, 1H), 3.27 (s, 3H), 3.17 (t, *J*=8.8 Hz, 1H), 3.08 (s, 3H), 2.92 (ddd, *J*=12.7, 7.1, 5.6 Hz, 1H), 2.59 (dd, *J*=15.4, 11.3 Hz, 1H), 2.39 (dd, *J*=15.4, 6.1 Hz, 1H), 2.36 (dt, *J*=15.4, 3.2 Hz, 1H), 1.77 (ddd, *J*=15.2, 12.3, 9.7 Hz, 1H), 1.42 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (C_6D_6) δ 140.0, 139.2, 130.0–128.0 (*Ar*–), 99.5, 99.0, 84.0, 79.0, 76.1, 73.6, 73.5, 68.5, 48.1, 48.0, 40.7, 34.4, 26.5, 18.2, 18.1. HRMS (FAB) calcd for $C_{27}H_{36}O_6S$ [M^+] 488.2233. Found: 488.2232.

4.17. (3*S*,4*S*,5*R*,7*S*)-3-*O*-Benzyl-4,5-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-dioxy]-7-benzyloxymethyl-thiepane-3,4,5-triol (20)

Purification by flash column chromatography (230–400 mesh SiO_2, EtOAc/Hex=1:18→1:15→1:10) afforded a colorless syrup. Yield=81%. $[\alpha]_D^{25}$ +62.5 (*c* 0.29, EtOAc). ^{1}H NMR (C_6D_6) δ 7.45 (dd, *J*=7.6, 0.5 Hz, 2H), 7.24–7.21 (m, 2H), 7.20 (d, *J*=7.7 Hz, 2H), 7.15–7.10 (m, 3H), 7.07 (t, *J*=7.3 Hz, 1H), 4.81 (d, *J*=11.9 Hz, 1H), 4.62 (d, *J*=11.9 Hz, 1H), 4.45 (dt, *J*=9.5, 4.6 Hz, 1H), 4.24 (d, *J*=1.0 Hz, 2H), 4.21 (dd, *J*=9.8, 2.4 Hz, 1H), 3.79 (ddd, *J*=7.7, 5.5, 2.4 Hz, 1H), 3.48–3.45 (m, 1H), 3.42 (d, *J*=9.1, 7.4 Hz, 1H), 3.35 (dd, *J*=9.1, 5.8 Hz, 1H), 3.10 (s, 3H), 3.06 (s, 3H), 2.73 (dd, *J*=15.2, 7.5 Hz, 1H), 2.55 (dd, *J*=15.2, 5.5 Hz, 1H), 2.28 (ddd, *J*=14.9, 9.7, 5.0 Hz, 1H), 2.14 (ddd, *J*=14.9, 4.3, 2.7 Hz, 1H), 1.39 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (C_6D_6) δ 140.1, 139.3, 130.0–128.0 (*Ar*–), 99.6, 99.5, 78.2, 75.1, 74.9, 73.4, 73.3, 65.8, 47.9, 39.2, 34.2, 31.5, 18.4, 18.3. HRMS (FAB) calcd for $C_{27}H_{36}O_6S$ [M^+] 488.2233. Found: 488.2232.

4.18. (3*S*,4*S*,5*R*,7*R*)-3-*O*-Benzyl-3,4-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-dioxy]-7-benzyloxymethyl-thiepane-3,4,5-triol (21)

Purification by flash column chromatography (230–400 mesh SiO_2, EtOAc/Hex=1:18→1:15→1:10) afforded a colorless syrup. Yield=78%. $[\alpha]_D^{25}$ −5.1 (*c* 0.36, EtOAc). ^{1}H NMR (C_6D_6) δ 7.47 (d, *J*=7.1 Hz, 2H), 7.22 (d, *J*=7.4 Hz, 2H), 7.19 (d, *J*=7.7 Hz, 2H), 7.13–7.05 (m, 4H), 4.78 (d, *J*=12.1 Hz, 1H), 4.68 (d, *J*=12.1 Hz, 1H), 4.38 (ddd, *J*=10.6, 10.6, 3.9 Hz, 1H), 4.24 (s, 2H), 3.93 (td, *J*=4.9, 1.3 Hz, 1H), 3.89 (dd, *J*=9.7, 1.3 Hz, 1H), 3.63–3.58 (m, 1H), 3.42 (dd, *J*=9.3, 5.2 Hz, 1H), 3.30 (dd, *J*=9.3, 7.9 Hz, 1H), 3.05 (s, 6H), 2.86 (dd, *J*=16.6, 4.9 Hz, 1H), 2.63 (ddd, *J*=14.3, 3.7, 1.9 Hz, 1H), 2.50 (dd, *J*=14.4, 3.7 Hz, 1H), 1.99 (dt, *J*=14.3, 10.9 Hz, 1H), 1.38 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (C_6D_6) δ 139.8, 139.3, 130.0–128.0 (*Ar*–), 99.3, 99.0, 78.9, 76.7, 74.9, 73.5, 73.0, 68.2, 48.0, 47.9, 40.3, 39.1, 31.4, 18.3. HRMS (FAB) calcd for $C_{27}H_{36}O_6S$ [M^+] 488.2233. Found: 488.2237.

4.19. (3*R*,4*R*,5*R*,7*R*)-7-(Hydroxymethyl)thiepane-3,4,5-triol (22)

Purification by flash column chromatography (230–400 mesh SiO_2, MeOH/CH_2Cl_2=1:6→1:4, 1% NH_4OH) afforded a pale yellow syrup. Yield=50%. $[\alpha]_D^{25}$ −147.7 (*c* 0.11, MeOH). ^{1}H NMR (D_2O) δ 3.97 (d, *J*=9.8 Hz, 1H), 3.94 (d, *J*=1.5 Hz, 1H), 3.76 (dt, *J*=10.6, 2.9 Hz, 1H), 3.45 (dd, *J*=11.3, 6.1 Hz, 1H), 3.40 (dd, *J*=11.3, 6.7 Hz, 1H), 2.95 (dd, *J*=12.1, 6.2 Hz, 1H), 2.92 (dd, *J*=14.8, 10.8 Hz, 1H), 2.13 (dt, *J*=16.0, 1.7 Hz, 1H), 2.09 (dd, *J*=14.8, 9.8 Hz, 1H), 1.68 (dd, *J*=14.8, 5.6 Hz, 1H). ^{13}C NMR (D_2O) δ 75.9, 74.6, 70.7, 66.6, 42.9, 30.7, 26.4. HRMS (ESI) calcd for $C_7H_{14}O_4S$ [M^+] 194.0613. Found: 194.0617.

4.20. (3*R*,4*R*,5*R*,7*S*)-7-(Hydroxymethyl)thiepane-3,4,5-triol (23)

Purification by flash column chromatography (230–400 mesh SiO_2, MeOH/CH_2Cl_2=1:6→1:4, 1% NH_4OH) afforded a pale yellow syrup. Major isomer: ^{1}H NMR (D_2O) δ 4.14 (dd, *J*=9.5, 5.8 Hz, 1H), 3.97 (s, 1H), 3.81 (ddd, *J*=11.2, 4.4, 2.5 Hz, 1H), 3.53 (dd, *J*=11.6, 5.2 Hz, 1H), 3.38 (dd, *J*=11.5, 7.0 Hz, 1H), 3.03 (ddd, *J*=11.5, 6.6, 6.2 Hz, 1H), 2.70 (dd, *J*=14.2, 11.3 Hz, 1H), 2.57 (dd, *J*=14.2, 4.2 Hz, 1H), 1.95 (dt, *J*=13.8, 6.4 Hz, 1H), 1.74 (ddd, *J*=13.8, 10.6, 5.7 Hz, 1H). ^{13}C NMR (D_2O) δ 79.9, 74.2, 70.5, 65.3, 46.2, 34.6, 32.9. HRMS (ESI) calcd for $C_7H_{14}O_4S$ [M^+−H] 193.0535. Found: 193.0534.

4.21. (2*R*,3*R*,4*R*,6*S*)-Tetrahydro-2,6-bis(hydroxymethyl)-2*H*-thiopyran-3,4-diol (24)

Minor isomer, structure determination was based on the subtraction of the signals from the mixture spectra with **23**. ^{1}H NMR (D_2O) δ 3.88 (t, *J*=2.3 Hz, 1H), 3.68 (dd, *J*=11.5, 6.0 Hz, 1H), 3.64 (dt, *J*=11.1, 3.4 Hz, 1H), 3.60 (d, *J*=7.6 Hz, 2H), 3.53 (dd, *J*=11.6, 5.3 Hz, 1H), 3.12 (td, *J*=7.9, 2.1 Hz, 1H), 2.92 (ddd, *J*=11.9, 7.7, 4.4 Hz, 1H), 1.95–1.91 (m, 1H), 1.84 (dt, *J*=13.7, 4.1 Hz, 1H). ^{13}C NMR (D_2O) δ 69.0, 67.9, 63.1, 62.2, 45.1, 40.4, 30.4. HRMS (ESI) calcd for $C_7H_{14}O_4S$ [M^+−H] 193.0535. Found: 193.0534.

4.22. (3*R*,4*S*,5*R*,7*S*)-7-(Hydroxymethyl)thiepane-3,4,5-triol (25)

Purification by flash column chromatography (230–400 mesh SiO_2, MeOH/CH_2Cl_2=1:8→1:6, 1% NH_4OH) afforded a colorless syrup. Yield=45%. $[\alpha]_D^{25}$ −15.0 (*c* 0.13, MeOH). ^{1}H NMR (D_2O) δ 3.71 (ddd, *J*=10.1, 5.9, 4.6 Hz, 1H), 3.56 (dt, *J*=11.9, 3.8 Hz, 1H), 3.53 (dd, *J*=11.3, 6.0 Hz, 1H), 3.43 (dd, *J*=11.3, 7.1 Hz, 1H), 3.39 (t, *J*=8.6 Hz, 1H), 3.13 (dt, *J*=12.9, 6.1 Hz, 1H), 2.78 (dd, *J*=15.5, 3.8 Hz, 1H), 2.57 (dd, *J*=15.5, 7.7 Hz, 1H), 1.96–1.92 (m, 2H). ^{13}C NMR (D_2O) δ 78.9, 74.3, 68.4, 64.8, 40.6, 33.7, 30.4. HRMS (FAB) calcd for $C_7H_{14}O_4S$ [M^+] 194.0613. Found: 194.0616.

4.23. (3*R*,4*S*,5*R*,7*R*)-7-(Hydroxymethyl)thiepane-3,4,5-triol (26)

Purification by flash column chromatography (230–400 mesh SiO_2, MeOH/CH_2Cl_2=1:8→1:6, 1% NH_4OH) afforded a colorless syrup. Yield=42%. $[\alpha]_D^{25}$ −78.0 (*c* 0.31, MeOH). ^{1}H NMR (D_2O) δ 3.63 (t, *J*=9.1 Hz, 1H), 3.51 (td, *J*=8.2, 3.1 Hz, 1H), 3.47 (dd, *J*=11.4, 5.9 Hz, 1H), 3.41 (dd, *J*=11.4, 6.5 Hz, 1H), 3.18 (t, *J*=8.4 Hz, 1H), 2.92 (td, *J*=12.0, 5.9 Hz, 1H), 2.73 (dd, *J*=15.4, 9.8 Hz, 1H), 2.39 (dd, *J*=15.4, 3.1 Hz, 1H), 2.02 (dd, *J*=14.9, 5.2 Hz, 1H), 1.66 (ddd, *J*=14.9, 12.3, 10.3 Hz, 1H). ^{13}C NMR (D_2O) δ 81.1, 76.6, 70.6, 66.3, 43.1, 35.6, 28.7. HRMS (FAB) calcd for $C_7H_{14}O_4S$ [M^+] 194.0613. Found: 194.0611.

4.24. (2*S*,4*R*,5*S*,6*S*)-6-(Benzyloxy)-2-(hydroxymethyl)thiepane-4,5-diol (27)

Purification by flash column chromatography (230–400 mesh SiO_2, MeOH/CH_2Cl_2=1:30→1:20, 1% NH_4OH) afforded a colorless syrup. Yield=55%. $[\alpha]_D^{25}$ +29.0 (*c* 0.2, MeOH). ^{1}H NMR (D_2O) δ 7.34–7.24 (m, 5H), 4.54 (d, *J*=11.7 Hz, 1H), 4.49 (d, *J*=11.7 Hz, 1H), 3.92 (td, *J*=7.0, 2.8 Hz, 1H), 3.89–3.85 (m, 2H), 3.49 (dd, *J*=11.3, 5.7 Hz, 1H), 3.41 (dd, *J*=11.3, 6.8 Hz, 1H), 3.04 (ddd, *J*=16.4, 6.2, 4.0 Hz, 1H), 2.86 (dd, *J*=15.0, 7.8 Hz, 1H), 2.62 (dd, *J*=15.0, 3.2 Hz, 1H), 1.98 (ddd, *J*=15.5, 10.3, 2.8 Hz, 1H), 1.90 (ddd, *J*=15.5, 6.4, 3.9 Hz, 1H). ^{13}C NMR (D_2O) δ 137.5, 129.0–128.0 (*Ar*–), 79.2, 74.7, 71.6, 68.6, 65.6, 40.1, 32.8, 27.2. HRMS (FAB) calcd for $C_{14}H_{21}O_4S$ [M+H]$^+$ 285.1161. Found: 285.1161.

4.25. (2*R*,4*R*,5*S*,6*S*)-6-(Benzyloxy)-2-(hydroxymethyl)thiepane-4,5-diol (28)

Purification by flash column chromatography (230–400 mesh SiO_2, MeOH/CH_2Cl_2=1:30→1:20, 1% NH_4OH) afforded a colorless syrup. Yield=40%. $[\alpha]_D^{25}$ −85.7 (*c* 0.22, MeOH). ^{1}H NMR (D_2O) δ 7.35–7.22 (m, 5H), 4.56 (d, *J*=11.5 Hz, 1H), 4.41 (d, *J*=11.5 Hz, 1H), 3.94 (br s, 1H), 3.69 (t, *J*=9.3 Hz, 1H), 3.47–3.35 (m, 3H), 3.05–2.97 (m, 1H), 2.80–2.70 (m, 2H), 2.03 (d, *J*=14.9 Hz, 1H), 1.59 (dd, *J*=14.9, 11.1 Hz, 1H). ^{13}C NMR (D_2O) δ 137.5, 128.7–128.3 (*Ar*–), 77.8, 76.6,

71.5, 70.6, 65.8, 42.0, 36.1, 26.3. HRMS (FAB) calcd for $C_{14}H_{21}O_4S$ $[M+H]^+$ 285.1161. Found: 285.1163.

4.26. (3*S*,4*S*,5*R*,7*R*)-7-(Hydroxymethyl)thiepane-3,4,5-triol (29)

Purification by flash column chromatography (230–400 mesh SiO_2, MeOH/CH_2Cl_2=1:8→1:6, 1% NH_4OH) afforded a colorless syrup. Yield=10%. $[\alpha]_D^{22}$ −223.8 (*c* 0.16, MeOH). ^1H NMR (D_2O) δ 4.07 (ddd, *J*=7.4, 3.7, 1.6 Hz, 1H), 3.71 (td, *J*=9.4, 1.4 Hz, 1H), 3.46 (dd, *J*=11.4, 5.9 Hz, 1H), 3.42 (dd, *J*=11.4, 6.5 Hz, 1H), 3.36 (dd, *J*=9.4, 3.4 Hz, 1H), 2.95–2.88 (m, 1H), 2.89 (dd, *J*=15.6, 1.7 Hz, 1H), 2.58 (dd, *J*=15.6, 7.4 Hz, 1H), 2.06 (ddd, *J*=14.9, 4.6, 1.5 Hz, 1H), 1.59 (ddd, *J*=14.9, 11.8, 9.5 Hz, 1H). ^{13}C NMR (D_2O) δ 78.5, 69.8, 69.0, 66.5, 42.4, 36.4, 29.4. HRMS (FAB) calcd for $C_7H_{14}O_4S$ $[M^+]$ 194.0613. Found: 194.0615.

Acknowledgements

The National Science Council (NSC-101-2113-M-032-002) and Tamkang University are gratefully acknowledged for the financial support of this research. Authors thank Prof. Hsiu-Fu Hsu for valuable discussion, the National Center for High-Performing Computing and Instrumentation Center, National Taiwan University for MS experiments.

Supplementary data

Copies of ^1H, ^{13}C NMR spectra and Tables 1–6 for all new products. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.12.047.

References and notes

1. Davies, G. J.; Gloster, T. M.; Henrissant, B. *Curr. Opin. Struct. Biol.* **2005**, *15*, 637–645.
2. Somsák, L.; Nagy, V.; Hadady, Z.; Docsa, T.; Gergely, P. *Curr. Pharm. Des.* **2003**, *9*, 1177–1189.
3. Greimel, P.; Spreitz, J.; Stütz, A. E.; Wrodnigg, T. M. *Curr. Top. Med. Chem.* **2003**, *3*, 513–523.
4. Nishimura, Y. In *Iminosugars from Synthesis to Therapeutic Applications*; Compain, P., Martin, O. R., Eds.; Wiley-VCH: Weinheim, 2007; pp 269–294.
5. Afarinka, K.; Bahar, A. *Tetrahedron: Asymmetry* **2005**, *16*, 1239–1287.
6. Scott, L. J.; Spencer, C. M. *Drugs* **2000**, *59*, 521–549.
7. Dande, P.; Prakash, T. P.; Sioufi, N.; Gaus, H.; Jarres, R.; Berdeja, A.; Swayze, E. E.; Griffey, R. H.; Bhat, B. *J. Med. Chem.* **2006**, *49*, 1624–1634.
8. Yoshimura, Y.; Endo, M.; Sakata, S. *Tetrahedron Lett.* **1999**, *40*, 1937–1940.
9. Yoshimura, Y.; Kitano, K.; Satoh, H.; Watanabe, M.; Miura, S.; Sakata, S.; Sasaki, T.; Matsuda, A. *J. Org. Chem.* **1996**, *61*, 822–823.
10. Selwood, D. L.; Carter, K.; Young, R. J.; Jandu, K. S. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 991–994.
11. Tber, B.; Fahmi, N.-E.; Ronco, G.; Villa, P.; Ewing, D. F.; Mackenzie, G. *Carbohydr. Res.* **1995**, *267*, 203–215.
12. Mohan, S.; Pinto, B. M. *Carbohydr. Res.* **2007**, *342*, 1551–1580.
13. Yoshikawa, M.; Morikawa, T.; Matsuda, H.; Tanabe, G.; Muraoka, O. *Bioorg. Med. Chem.* **2002**, *10*, 1547–1554.
14. Eskandari, R.; Jones, K.; Rose, D. R.; Pinto, B. M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5686–5689.
15. Eskandari, R.; Kuntz, D. A.; Rose, D. A.; Pinto, B. M. *Org. Lett.* **2010**, *12*, 1632–1635.
16. Muraoka, O.; Xie, W.; Osaki, S.; Kagawa, A.; Tanabe, G.; Amer, M. F. A.; Minematsu, T.; Morikawa, T.; Yoshikawa, M. *Tetrahedron* **2010**, *66*, 3717–3722.
17. Yoshikawa, M.; Murakami, T.; Shimada, H.; Matsuda, H.; Yamahara, J.; Tanabe, G.; Muraoka, O. *Tetrahedron Lett.* **1997**, *38*, 8367–8370.
18. Gallienne, E.; Benazza, M.; Demailly, G.; Bolte, J.; Lemaire, M. *Tetrahedron* **2005**, *61*, 4557–4568.
19. Johnson, H. A.; Thomas, N. R. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 237–241.
20. Tilekar, J. N.; Patil, N. T.; Jadhav, H. S.; Dhavale, D. D. *Tetrahedron* **2003**, *59*, 1873–1876.
21. Benazza, M.; Halila, S.; Viot, C.; Danquigny, A.; Pierru, C.; Demailly, G. *Tetrahedron* **2004**, *60*, 2889–2895.
22. Halila, S.; Benazza, M.; Demailly, G. *Carbohydr. Res.* **2003**, *338*, 177–182.
23. Halila, S.; Benazza, M.; Demailly, G. *Tetrahedron Lett.* **2002**, *43*, 815–818.
24. Arcelli, A.; Cerè, V.; Peri, F.; Pollicino, S.; Ricci, A. *Tetrahedron: Asymmetry* **2002**, *13*, 191–196.
25. Halila, S.; Benazza, M.; Demailly, G. *Tetrahedron Lett.* **2001**, *42*, 3307–3310.
26. Arcelli, A.; Cerè, V.; Peri, F.; Pollicino, S.; Sabatino, P. *Tetrahedron: Asymmetry* **2000**, *11*, 1389–1395.
27. Fuzier, M.; Le Merrer, Y.; Depezay, J.-C. *Tetrahedron Lett.* **1995**, *36*, 6443–6446.
28. Shih, T.-L.; Fang, Y.-C. *Synth. Commun.* **2007**, *37*, 3337–3349.
29. Shih, T.-L.; Yang, R.-Y.; Li, S.-T.; Chiang, C.-F.; Lin, C.-H. *J. Org. Chem.* **2007**, *72*, 4258–4261.
30. Cerè, V.; Peri, F.; Pollicino, S. *J. Org. Chem.* **1997**, *62*, 8572–8574.
31. Shih, T.-L.; Li, H.-Y.; Ke, M.-S.; Kuo, W.-S. *Synth. Commun.* **2008**, *38*, 4139–4149 and references cited therein.
32. Muraoka, O.; Yoshikai, K.; Takahashi, H.; Minematsu, T.; Lu, G.; Tanabe, G.; Wang, T.; Matsuda, H.; Yoshikawa, M. *Bioorg. Med. Chem.* **2006**, *14*, 500–509.
33. Gunasundari, T.; Chandrasekaran, S. *J. Org. Chem.* **2010**, *75*, 6685–6688.
34. Zhang, J.; Niu, Y.; Lao, X.; Ye, X.-S. *Tetrahedron* **2012**, *68*, 4242–4247.
35. Alves, C.; Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Tetrahedron* **1999**, *55*, 8443–8456.
36. Shing, T. K. M.; Cui, Y.-X.; Tang, Y. *Tetrahedron* **1992**, *48*, 2349–2356.
37. Yeh, P.-L.; Tai, C.-K.; Shih, T.-L.; Hsiao, H.-L.; Wang, B.-C. *J. Mol. Struct.* **2012**, *1018*, 64–71.