Available online at www.sciencedirect.com
ScienceDirect
Carbohydrate Research 342 (2007) 1169–1174
Carbohydrate RESEARCH

Synthesis and anti-inflammatory activity of *N*-phthalimidomethyl 2,3-dideoxy- and 2,3-unsaturated glycosides

Xiang-Bao Meng,[a] Dong Han,[a] Su-Na Zhang,[a] Wei Guo,[b] Jing-Rong Cui[b] and Zhong-Jun Li[a,b,*]

[a]*Department of Chemical Biology, School of Pharmaceutical Sciences, Peking University, Beijing 100083, China*
[b]*National Key Laboratory of Natural and Biomimetic Drugs, Peking University, Beijing 100083, China*

Received 14 January 2007; received in revised form 26 February 2007; accepted 6 March 2007
Available online 12 March 2007

Abstract—3,4,6-Tri-*O*-acetyl-D-galactal, 3,4,6-tri-*O*-acetyl-D-glucal and 3,6,2′,3′,4′6′-hexa-*O*-acetyl-D-lactal were reacted with *N*-hydroxymethylphthalimide and boron trifluoride etherate to produce the corresponding phthalimidomethyl unsaturated glycosides via Ferrier rearrangement. When the galactal derivative was used, a non-Ferrier rearrangement product was also isolated as a minor product under classical Ferrier conditions. Phthalimidomethyl deoxy glycosides were readily prepared by hydrogenation of the unsaturated glycosides. Following deacetylation, the anti-inflammatory activities of these compounds were tested on mice and three were found to possess potent activity compared to hydrocortisone sodium succinate (HSS).

Keywords: Phthalimidomethyl sugar derivatives; Glycal; Deoxy-sugar; Anti-inflammation

1. Introduction

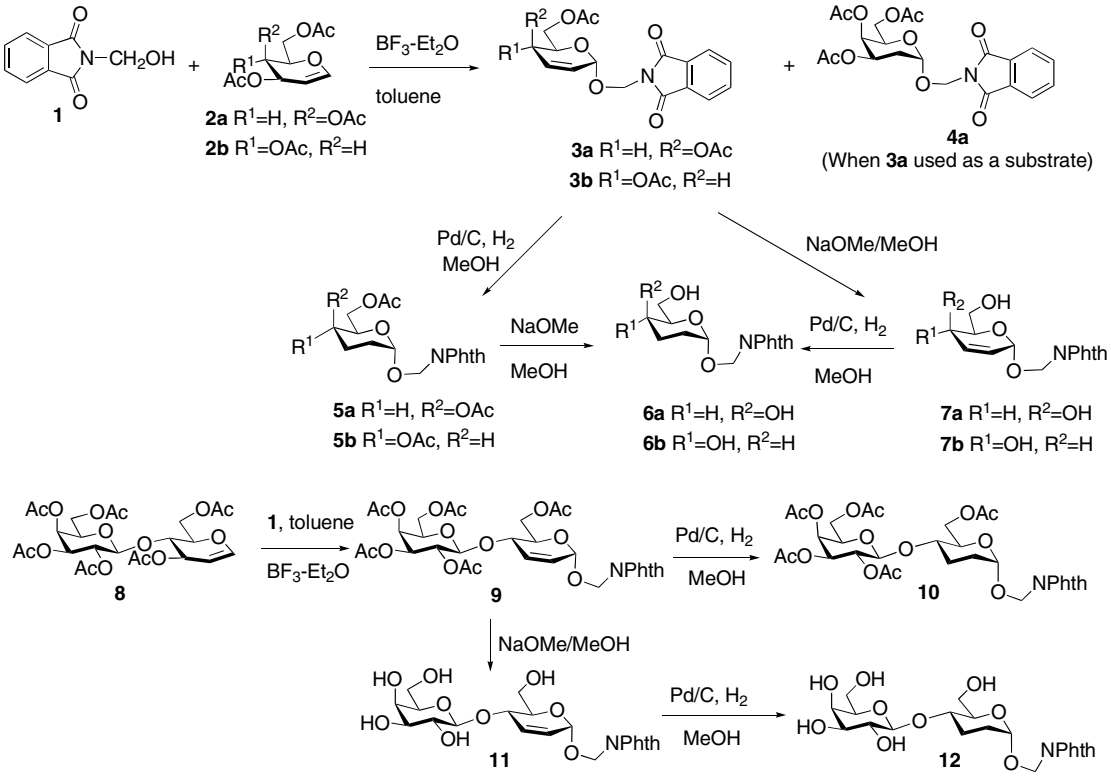
The phthalimido group is a common protecting group for amines and is widely used in carbohydrate chemistry. As a known pharmacophore, the phthalimido moiety also has a wide range of activities such as anti-tumor,[1] anti-convulsant,[2] and anti-inflammatory activity.[3] Systematic investigation of phthalimide analogues revealed that derivatives bearing a spherical alkyl group, such as an adamantyl group or a carboranyl group, possess potent bi-directional TNF-α (tumor necrosis factor-α) production-regulating activity.[4] Recently, the synthesis of *N*-phthalimidomethyl tetra-*O*-acyl-α-D-mamopyranoside derivatives and their hypolipidemic activity was reported.[5] However, the bioactivities of *N*-phthalimidomethyl glycosides have not been fully studied. As the phthalimido moiety is insoluble in water, its conjugation to sugars bearing free hydroxyl groups may enhance their water-solubility, thus making the whole structure more 'drug-like'. Furthermore, the carbohydrate moiety could play an important role in directing the pharmacophore to a specific site in vivo. With these ideas in mind, a series of phthalimidomethyl 2,3-dideoxy sugars and 2,3-unsaturated sugars were designed and synthesized to study the activity of phthalimide derivatives. Their anti-inflammatory activities were tested on mice.

2. Results and discussion

Glycals are versatile precursors in oligosaccharide synthesis.[6] In our experiments, *N*-phthalimidomethyl 2,3-unsaturated sugars **3a**, **3b**, and **9** were synthesized through nucleophilic addition of *N*-hydroxymethyl phthalidomide **1** to 3,4,6-tri-*O*-acetyl-D-galactal **2a**, 3,4,6-tri-*O*-acetyl-D-glucal **2b**, or 3,6,2′,3′,4′6′-hexa-*O*-acetyl-D-lactal **8** in the presence of boron trifluoride etherate, resulting in a Ferrier rearrangement (Scheme 1).[7] Although it is known that the 2,3-unsaturated sugars formed by this reaction are usually obtained as an anomeric mixtures, only the α-anomer was obtained in our work. The anomeric configurations of compound **3a**, **3b**,

* Corresponding author. Tel.: +86 10 82801714; fax: +86 10 62367134; e-mail: zjli@bjmu.edu.cn

0008-6215/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2007.03.009

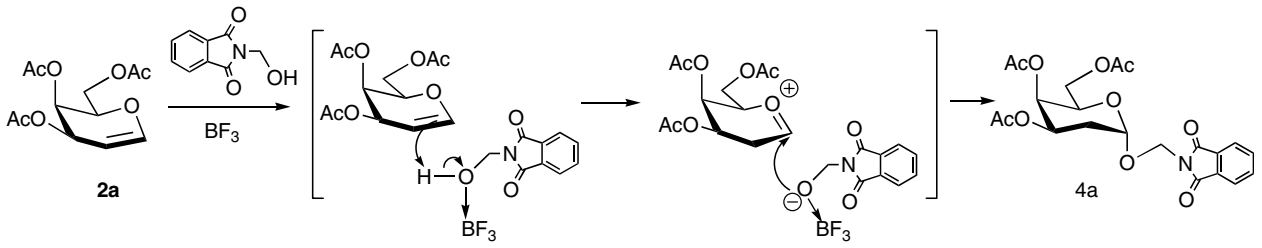


Scheme 1. Synthesis of *N*-phthalimidomethyl 2,3-dideoxy-glycosides and 2,3-unsaturated glycosides.

and **9** were confirmed by NMR spectroscopy. Srivastava et al. had also obtained exclusively the α-anomer in the similar reaction starting from 3,4,6-tri-*O*-acetyl-D-glucal.[5]

The Ferrier rearrangement product **3a** was isolated as the major product contaminated with a byproduct, which was rather difficult to be separate from the mixture. By very careful column chromatography, this byproduct was obtained pure in 10–30% yields from different batches. Based on its NMR and MS data, the structure of this product was assigned as phthalimidomethyl 3,4,6-tri-*O*-acetyl-2-deoxy-α-D-*lyxo*-hexopyranoside, **4a**. Lin et al. hvae also reported similar results.[8] Reports by Ferrier[7] and Wallenfels[9] concluded that the rearrangement product could only be produced in the absence of protic acids whereas in the presence of protic acids addition to the double bond would occur to yield 2-deoxy sugar derivatives. In our case, the 2-deoxy product only occurred with 3,4,6-tri-*O*-acetyl-D-galactal. We suggest a proton first adds to the double bond as a competitive side reaction of Ferrier rearrangement to give the 2-deoxy oxacarbenium ion, which is then trapped by the nucleophile to form predominately the α-anomer, as depicted in Scheme 2. Following the glycosylation reactions, deacetylation products **6**, **7**, **11**, and hydrogenation products **5**, **6**, **10**, **12** were obtained in good yields under conventional conditions.

Most of these synthesized compounds were screened for their activity of inhibiting acute inflammatory response in the xylene-induced mouse ear edema model, and compared to HSS.[10] Intraperitoneal (ip) injection of compounds resulted in mice ear edema inhibition (Table 1). Ear weight reduction induced by compound **3b**, **7b**, and **10** were more significant than the control group.



Scheme 2. A proposed mechanism for non-Ferrier rearrangement reaction of 3,4,6-tri-*O*-acetyl-D-galactal.

Table 1. Effects of synthesized compounds on ear edema in mice[a,b,c]

Compounds	Ear weight difference mass ± SD (mg)	Inhibition ratio (%)
Control	10.9 ± 5.7	—
3a	12.0 ± 5.9	10.3
3b	7.5 ± 4.4*	**49.6**
4a	8.6 ± 2.1*	37.5
5b	9.5 ± 4.4*	36.1
6a	16.1 ± 6.0	0.0
7b	6.1 ± 2.8*	**58.8**
9	8.4 ± 1.8	13.0
10	8.3 ± 4.3*	**45.2**
11	9.9 ± 4.8	0.0
HSS	3.4 ± 1.4	69.0

[a] Eight mice were used in each group.
[b] Dosage 100 mg/kg.
[c] $p < 0.05$ Compared to control group by paired student's *t*-test.

The inhibition ratio on mice was 49.6%, 58.8%, and 45.2% respectively, with the dose of 100 mg/kg. The results suggested that these two 2-deoxy sugar derivatives exhibited considerable anti-inflammatory activity.

In conclusion, the synthesis of a series of *N*-phthalimidomethyl 2,3-dideoxy- and 2,3-unsaturated sugar derivatives was accomplished. Three derivatives were found to have potent anti-inflammatory activity. It is interesting that the unsaturated and deoxy sugar functionalities in these molecules play quite different roles and this merits further investigation.

3. Experimental

3.1. General methods

Solvents were purified by standard procedures. Melting points were measured on an X4 melting point apparatus and are uncorrected. NMR spectra were recorded on Jeol-300 instrument (peaks marked with an asterisk indicate those exchangeable with D_2O). Mass spectra were measured on an IBI-MDS Sciexciex Q-star or an FAB-MS mass spectrometer. Optical rotations were measured at 25 °C using an Optical Activity AA-10R automatic polarimeter. Elemental analyses were performed on a Perkin–Elmer 240 C instrument. TLC was performed on Silica Gel G_{F254} plates (Hai Yang Chemical Factory, Qingdao, Shandong, PR China) with diction by UV fluorescence quenching and by spraying with 10% H_2SO_4. Column chromatography was performed on Silica Gel H 60 (Hai Yang Chemical Factory, Qingdao, Shandong, PR China).

3.2. General procedure for compounds 3a, 3b, 4a, 9

To a stirred solution of glycal **2a**, **2b**,[6] or **8**[11] in dry toluene was added *N*-hydroxymethyl phthalimide **1** (1.1 equiv) under argon at −20 °C, and then $BF_3{\cdot}Et_2O$ (1.5 equiv) was added dropwise. The reaction mixture was stirred at −20 °C for 1.5–6.0 h, and then neutralized with satd aq $NaHCO_3$. The organic layer was washed with water, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel to give the product.

3.3. General procedure for compounds 5a, 7a, 7b, 11

To a solution of compound **3a**, **3b**, **4a**, **10** in dry methanol was added sodium methoxide with stirring. The reaction mixture was stirred at room temperature for 0.5 h, the solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel to give the product.

3.4. General procedure for compounds 5a, 5b, 6a, 6b, 10, 12

To a solution of compound **3a**, **3b**, **7a**, **7b**, **9**, **11** in EtOAc was added 10% Pd/C (0.1 equiv) and the mixture was stirred under hydrogen at 1 atm for 8 h. The mixture was filtered and the filtrate concentrated in vacuo to give a residue that was purified by column chromatography on silica gel to give the product.

3.5. Phthalimidomethyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*threo*-hex-2-enopyranoside (3a)

Chromatographic purification (8:1, petroleum ether–acetone) afforded **3a** (60%) as a colorless solid; mp 101–102 °C; $[\alpha]_D$ −161.9 (*c* 0.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 2.07 (s, 6H, CH_3CO), 4.12 (dd, 2H, $J = 6.9$, 11.4 Hz H-6a), 4.26 (dd, 2H, $J = 5.4$, 11.4 Hz H-6b), 4.40 (m, 1H, H-5), 5.02 (m, 1H, H-4), 5.31 (m, 2H, CH_2), 5.41 (d, 1 H, H-1, $J_{1,2} = 2.7$ Hz), 5.98 (q, 1H, H-2, $J = 3.3$, 9.9 Hz), 6.13 (dd, 1 H, H-3, $J = 5.4$, 9.9 Hz), 7.80 (dd, 2H, $J = 3.0$, 5.7 Hz, Phth), 7.92 (dd, 2H, Phth); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.6, 20.7 (CH_3CO), 62.5 (C-6), 64.4 (C-5), 67.1 (C-4), 93.0 (C-1), 123.7 (C-3), 125.6 (C-2), 129.6, 131.8, 134.4 (Phth), 167.4 (C=O, Phth), 170.2, 170.6 (C=O, Ac); ESI-TOF-MS *m/z*: $[M+Na]^+$ 412.1; $[M+NH_4]^+$ 407.2. Anal. Calcd for $C_{19}H_{19}NO_8$ (389.1): C, 58.61; H, 4.92; N, 3.60. Found: C, 58.63; H, 4.94; N, 3.60.

3.6. Phthalimidomethyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (3b)

Chromatographic purification (3:1, petroleum ether–acetone) afforded **3b** (89%) as white needles; mp 120–121 °C; $[\alpha]_D$ +45.2 (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 2.08, 2.09 (2 s, 6H, 2Ac), 4.14–4.23 (m, 3H), 5.26–5.37 (m, 4H), 5.77–5.82 (m, 1H, H-2), 5.90 (d, 1H, H-3), 7.79 (dd, 2H, $J = 3.0$, 5.7 Hz,

Phth), 7.92 (dd, 2H, Phth); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.7, 20.9, 62.6, 64.7, 64.9, 67.2, 93.5, 123.7, 126.8, 129.7, 131.8, 134.5, 167.3, 170.2, 170.7; FAB-MS *m/z*: $[M-H+K]^+$ 427.4. Anal. Calcd for $C_{19}H_{19}NO_8$ (389.1): C, 58.61; H, 4.92; N, 3.60. Found: C, 58.47; H, 4.74; N, 3.70.

3.7. Phthalimidomethyl 3,4,6-tri-*O*-acetyl-2-deoxy-α-D-*lyxo*-hexopyranoside (4a)

Colorless syrup; $[\alpha]_D$ +0.12 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.96, 2.04, 2.09 (3s, 9H, 3 × Ac), 2.14–2.19 (m, 2H, H-2), 4.00 (dd, 1H, $J = 5.4$, 11.1 Hz, H-6a), 4.12 (dd, 1H, $J = 3.6$, 11.1 Hz, H-6b), 4.26 (t, 1H, $J = 6.6$ Hz, H-5), 5.19–5.34 (m, 4H), 7.79 (dd, 2H, $J = 2.7$, 5.7 Hz, Phth), 7.93 (dd, 2H, Phth); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.6, 20.6, 20.7 (CH_3CO), 29.7 (C-6), 62.0 (O–CH_2–N), 63.9 (C-5), 65.7 (C-4), 66.4 (C-3), 67.1 (C-2), 96.5 (C-1), 123.8, 131.7, 134.5 (Phth), 167.3 (C=O, Phth), 169.8, 170.2, 170.4 (C=O, Ac); ES1-TOF-MS *m/z*: $[M+NH_4]^+$ 467.2, $[M+Na]^+$ 472.1. Anal. Calcd for $C_{21}H_{23}NO_{10}$ (449.1): C, 56.12; H, 5.16; N, 3.12. Found: C, 56.33; H, 4.99; N, 3.10.

3.8. Phthalimidomethyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*threo*-hexopyranoside (5a)

Chromatographic purification (3:1, petroleum ether–acetone) afforded **5a** (75%) as a white foam; $[\alpha]_D$ +79.9 (*c* 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55–2.00 (m, 4H, H-2, H-3), 2.03 (s, 3H, CH_3CO), 2.08 (s, 3H, CH_3CO), 3.97 (dd, 1H, $J = 6.9$, 11.1 Hz, H-6a), 4.10 (dd, 1H, $J = 6.0$, 11.1 Hz, H-6b), 4.21 (m, 1H, H-5), 4.92 (s, 1H, H-1), 5.19–5.29 (m, 4H), 7.80 (dd, 2H, Phth), 7.92 (dd, 2H, Phth); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.7, 21.2, 22.0, 23.8, 61.5 (O–CH_2–N), 63.2, 63.9, 66.4, 67.5, 95.9 (C-1), 123.7, 131.8, 134.4 (Phth), 167.6 (C=O, Phth), 170.4, 170.7 (C=O, Ac); ESI-TOF-MS *m/z*: $[M+Na]^+$ 413.1. Anal. Calcd for $C_{19}H_{21}NO_8$ (391.1): C, 58.31; H, 5.41; N, 3.58. Found: C, 58.13; H, 5.24; N, 3.40.

3.9. Phthalimidomethyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hexopyranoside (5b)

Chromatographic purification (3:1, petroleum ether–acetone) afforded **5b** (75%) as a white foam; $[\alpha]_D$ +53.3 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.79–2.00 (m, 4H, H-2, H-3), 2.04 (s, 3H, CH_3CO), 2.08 (s, 3H, CH_3CO), 4.01–4.09 (m, 2H), 4.22–4.30 (m, 1H), 4.70–4.75 (m, 1H), 5.15 (s, 1H, H-1), 5.22 (d, 1H, $J = 10.2$ Hz, CH_2), 5.28 (d, 1H, CH_2), 7.80 (dd, 2H, Phth), 7.92 (dd, 2H, Phth); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.7, 21.2, 22.0, 23.8, 61.5 (O–CH_2–N), 62.8, 63.9, 67.4, 69.1, 95.6 (C-1), 123.7, 131.8, 134.4 (Phth), 167.5 (C=O, Phth), 170.0, 170.9 (C=O, Ac); ESI-TOF-MS *m/z*: $[M+NH_4]^+$ 409.2. Anal. Calcd for $C_{19}H_{19}NO_8$ (391.1): C, 58.31; H, 5.41; N, 3.58. Found: C, 58.33; H, 5.54; N, 3.32.

3.10. Phthalimidomethyl 2,3-dideoxy-α-D-*threo*-hexopyranoside (6a)

Chromatographic purification (1:1, petroleum ether–acetone) afforded **6a** (82%) as a white powder; mp 117–119 °C; $[\alpha]_D$ −68.2 (*c* 1.1, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.34–3.37 (m, 1H, H-6a), 3.49–3.52 (m, 1H, H-6b), 3.55–3.61 (m, 1H, H-5), 3.67–3.72 (m, 1H, H-4), 4.09 (t, 1H, OH)*, 4.54 (d, 1H, OH)*, 5.12 (d, 1H, $J = 11.4$ Hz, H-1), 5.20 (m, 2H, CH_2), 5.71 (q, 1H, H-2), 5.92 (q, 1H, H-3), 7.91–7.99 (m, 4H, Phth); ^{13}C NMR (125 MHz, DMSO-d_6): δ 60.7 (O–CH_2–N), 60.9 (C-6), 64.3 (C-5), 72.5 (C-4), 94.2 (C-1), 24.2, 27.3 (C-2, C-3), 130.7, 132.2, 135.1 (Phth), 168.9 (C=O); ESI-TOF-MS *m/z*: $[M+NH_4]^+$ 325.1; $[M+Na]^+$ 330.1. Anal. Calcd for $C_{15}H_{17}NO_6$ (307.1): C, 58.63; H, 5.58; N, 4.56. Found: C, 58.72; H, 5.52; N, 4.53.

3.11. Phthalimidomethyl 2,3-dideoxy-α-D-*erythro*-hexopyranoside (6b)

$[\alpha]_D$ +87.5 (*c* 1.0, CH_3OH). White foam; ^{1}H NMR (300 MHz, D_2O): δ 1.44–1.73 (m, 4H, H-2, H-3), 3.34–3.40 (m, 4H), 4.93 (s, 1H), 5.02 (d, 1H, $J = 11.7$ Hz, O–CH_2–N), 5.07 (d, 1H, O–CH_2–N), 7.61–7.64 (m, 4H, Phth); ^{13}C NMR (75 MHz, D_2O): δ 26.4, 28.8, 61.2, 64.9, 65.5, 74.8, 96.7 (C-1), 124.3, 131.5, 135.7, 170.0 (C=O); ESI-TOF-MS *m/z*: $[M+H]^+$ 308.1; $[M+Na]^+$ 330.1. Anal. Calcd for $C_{15}H_{17}NO_6$ (307.1): C, 58.63; H, 5.58; N, 4.56. Found: C, 58.42; H, 5.35; N, 4.83.

3.12. Phthalimidomethyl 2,3-dideoxy-α-D-*threo*-hex-2-enopyranoside (7a)

Chromatographic purification (1:1, petroleum ether–acetone) afforded **7a** (82%) as a white powder; mp 123–125 °C; $[\alpha]_D$ −55.3 (*c* 1.0, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.24–3.33 (m, 1H, H-6a), 3.45–3.62 (m, 1H, H-6b), 3.64–3.67 (m, 1H, H-5), 3.70–3.74 (m, 1H, H-4), 4.42 (t, 1H, $J = 5.4$ Hz, OH)*, 4.67 (d, 1H, $J = 7.8$ Hz, OH)*, 5.06 (d, 1H, H-1, $J = 11.4$ Hz, CH_2), 5.18 (s, 1H, H-1), 5.19 (m, 1H, CH_2), 5.73 (dd, 1H, $J = 3.0$, 10.2 Hz, H-2), 5.99 (dd, 1H, $J = 5.4$, 10.2 Hz, H-3), 7.86–7.94 (m, 4H, Phth); ^{13}C NMR (75 MHz, DMSO-d_6): δ 60.2 (O–CH_2–N), 60.9 (C-6), 65.0 (C-5), 72.3 (C-4), 94.0 (C-1), 124.2, 127.4, 130.9, 132.0, 135.7 (Phth), 168.4 (C=O); ESI-TOF-MS *m/z*: $[M+NH_4]^+$ 323.2; $[M+Na]^+$ 328.1. Anal. Calcd for $C_{15}H_{15}NO_6$ (305.1): C, 59.01; H, 4.95; N, 4.59. Found: C, 58.79; H, 5.07; N, 4.30.

3.13. Phthalimidomethyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (7b)

White foam, $[\alpha]_D$ +58.6 (*c* 0.7, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6): δ 3.44–3.51 (m, 3H, H-5, H-6), 3.90 (t, 1H, OH)*, 4.50 (t, 1H, OH)*, 5.05 (d, 1H, $J = 6.9$ Hz), 5.10 (d, 1H, $J = 11.1$ Hz, CH_2), 5.17 (s, 1H), 5.19 (d, 1H, CH_2), 5.59–564 (m, 1H, H-2), 5.85 (d, 1H, H-3), 7.87–7.95 (m, 4H, Phth); ^{13}C NMR (75 MHz, DMSO-d_6): δ 60.5 (O–CH_2–N), 61.9 (C-6), 64.3 (C-5), 73.0 (C-4), 92.9 (C-1), 123.5, 124.7, 131.5, 134.8, 135.0 (Phth), 167.4 (C=O); ESI-TOF-MS *m*/*z*: $[M+NH_4]^+$ 323.1. Anal. Calcd for $C_{15}H_{15}NO_6$ (305.1): C, 59.01; H, 4.95; N, 4.59. Found: C, 58.72; H, 5.12; N, 4.53.

3.14. Phthalimidomethyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→4)-6-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (9)

Chromatographic purification (1:1, petroleum ether–acetone) afforded **9** (71%) as a white solid; mp 92–93 °C; $[\alpha]_D$ +31.7 (*c* 1.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.97, 2.05, 2.07, 2.10, 2.15 (5s, 15H, CH_3CO), 3.92 (t, 1H, $J = 6.6$ Hz), 4.06–4.28 (m, 6H), 4.56 (d, 1H, H-1′, $J = 7.8$ Hz), 5.00 (dd, 1H, $J = 3.6$, 11.5 Hz), 5.19 (dd, 1H, $J = 7.8$, 10.5 Hz), 5.24 (d, 1H, $J = 10.2$ Hz, CH_2), 5.30 (d, 1H, CH_2), 5.30–5.32 (m, 1H), 5.37 (d, 1H, $J = 2.7$ Hz, H-1), 5.69–5.73 (m, 1H, H-2), 6.10 (d, 1H, $J = 10.2$ Hz, H-3), 7.78 (dd, $J = 3.0$, 5.4 Hz, 2H, Phth), 7.91 (dd, 2H, Phth); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.4, 20.5, 20.7 (CH_3CO), 61.1, 62.7, 64.6, 66.7, 67.7, 68.6, 70.6, 70.7, 72.8, 93.4 (C-1), 102.0 (C′-1), 123.7, 126.0 (C-2, C-3), 131.7, 132.0, 134.4 (Phth), 167.4 (C=O, Phth), 167.4, 169.3, 170.0, 170.2, 170.6 (C=O, Ac); FAB-MS *m*/*z*: $[M+K]^+$ 716.3. Anal. Calcd for $C_{31}H_{35}NO_{16}$ (677.2): C, 54.95; H, 5.21; N, 2.07. Found: C, 54.80; H, 5.33; N, 2.00.

3.15. Phthalimidomethyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→4)-6-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hexopyranoside (10)

Chromatographic purification (5:2, petroleum ether–acetone) afforded **10** (77%) as a colorless syrup; $[\alpha]_D$ +36.2 (*c* 1.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.74–1.86 (m, 4H), 1.98, 2.03, 2.07, 2.10, 2.15 (5s, 15H, CH_3CO), 3.53–3.58 (m, 1H), 3.89–3.98 (m, 2H), 4.05–4.23 (m, 4H), 4.53 (d, 1H, $J = 8.1$ Hz, H-1′), 4.98 (dd, 1H, $J = 3.0$, 10.5 Hz), 5.09–5.27 (m, 4H), 5.37 (d, 1H, $J = 3.3$ Hz), 7.78 (dd, 2H, $J = 3.0$, 5.7 Hz, Phth), 7.92 (dd, 2H, Phth); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.4, 20.5, 20.6, 20.8 (5CH_3CO), 25.7, 28.5, 61.1, 63.2, 63.7, 66.7, 68.6, 69.4, 70.4, 70.8, 76.1, 95.3 (C-1), 102.0 (C′-1), 123.7, 131.7, 134.4 (Phth), 167.4, 169.4 170.0, 170.2, 170.3, 170.7 (C=O); ESI-TOF-MS *m*/*z*: $[M+NH_4]^+$ 697.2, $[M+Na]^+$ 702.2. Anal. Calcd for $C_{31}H_{37}NO_{16}$ (679.2): C, 54.79; H, 5.49; N, 2.06. Found: C, 54.70; H, 5.47; N, 1.99.

3.16. Phthalimidomethyl β-D-galactopyranosyl-(1→4)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (11)

Chromatographic purification (15:1, $CHCl_3$–MeOH) afforded **11** (80%) as a colorless syrup; $[\alpha]_D$ +62.7 (*c* 1.0, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6): δ 3.25–3.56 (m, 9H), 4.09–4.19 (m, 2H, H-1, H′-1), 4.40 (d, 1H, OH)*, 4.53–4.57 (m, 2H, 2 × OH)*, 4.74 (s, 1H, OH)*, 4.96 (s, 1H, OH)*, 5.10–5.21 (m, 3H, O–CH_2–N, H′-3), 5.64 (d, 1H, $J = 10.2$ Hz, H-2), 6.05 (d, 1H, $J = 10.2$ Hz, H-3), 7.87–7.95 (m, 4H, Phth); ^{13}C NMR (75 MHz, DMSO-d_6): δ 60.0, 60.4, 64.4, 68.1, 70.6, 71.2, 73.2, 75.2, 79.2, 93.0 (C-1), 105.0 (C′-1), 123.5, 125.4, 131.5, 133.4, 134.8, 167.4 (C=O); ES1-MS-MS *m*/*z*: $[M+Na]^+$ 490.1, $[M+NH_4]^+$ 485.2, $[M+H]^+$ 468.2. Anal. Calcd for $C_{21}H_{25}NO_{11}$ (467.1): C, 53.96; H, 5.35; N, 3.00. Found: C, 53.63; H, 5.49; N, 2.96.

3.17. Phthalimidomethyl β-D-galactopyranosyl-(1→4)-2,3-dideoxy-α-D-*erythro*-hexopyranoside (12)

Chromatographic purification (15:1, $CHCl_3$–MeOH) afforded **12** (71%) as a colorless syrup; $[\alpha]_D$ +28.3 (*c* 0.8, CH_3OH); ^1H NMR (300 MHz, D_2O): δ 1.59–1.68 (m, 3H), 1.90–1.93 (m, 1H), 3.26–3.32 (m, 1H), 3.39–3.58 (m, 8H), 3.73 (d, 1H, $J = 3.0$ Hz), 4.26 (d, 1H, $J = 7.5$ Hz, H′-1), 4.96 (s, 1H), 5.08 (d, 1H, $J = 11.4$ Hz, O–CH_2–N), 5.11 (d, 1H, O–CH_2–N), 7.67–7.75 (m, 4H, Phth); ^{13}C NMR (75 MHz, D_2O): δ 25.7, 28.4, 50.1, 62.1, 62.8, 65.7, 66.6, 68.2, 69.6, 70.5, 77.7, 92.0 (C-1), 102.1 (C′-1), 121.4, 126.8, 130.0 (Phth), 169.2 (C=O, Phth); ESI-TOF-MS *m*/*z*: $[M+NH_4]^+$ 487.2, $[M+Na]^+$ 482.2. Anal. Calcd for $C_{21}H_{27}NO_{11}$ (469.2): C, 53.73; H, 5.80; N, 2.98. Found: C, 53.83; H, 6.00; N, 3.11.

3.18. General methods for determination of anti-inflammation activity.[10]

Experimental animals were ICR (Institute of Cancer Research) mice provided by the Center for Experimental Animals, Peking University Health Science Center. Only male mice (SPF grade, 4–6 weeks old and weighing between 18 and 22 g) were used in the study. Mice were allowed free access to food and drink and housed at room temperature and at a humidity of 45–55%. Hydrocortisone sodium succinate (HSS) was purchased from Tianjin Biochemical Pharmaceuticals.

Acknowledgement

This work was supported by the National Natural Science Foundation of China (NSFC No. 20372003).

References

1. Chan, C. L.; Lien, E. J.; Tokes, Z. A. *J. Med. Chem.* **1987**, *30*, 509–514.
2. Bailleux, V.; Vallee, L.; Nuyts, J. P.; Vamecq, J. *Biomed. Pharmacother.* **1994**, *48*, 95–101.
3. Lima, L. M.; Castro, P.; Machado, A. L.; Fraga, C. A. M.; Lugnier, C.; Concalves de Moraes, V. L.; Barreiro, E. J. *Bioorg. Med. Chem.* **2002**, *10*, 3067–3073.
4. Hashimoto, Y. *Bioorg. Med. Chem.* **2002**, *10*, 461–479.
5. Srivastava, R. M.; Oliveira, F. J. S.; Da Silva, L. P.; De Freitas Filho, J. R.; Oliveira, S. P.; Lima, V. L. M. *Carbohydr. Res.* **2001**, *332*, 335–340.
6. Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Intl. Ed.* **1996**, *35*, 1380–1419.
7. Ferrier, R. J.; Overend, W. G.; Ryan, Miss A. E. *J. Chem. Soc.* **1962**, 3667–3670.
8. Lin, H.; Du, W.; Chang, C.; Lin, C. *Tetrahedron Lett.* **2005**, *46*, 5071–5076.
9. Wallenfels, K.; Lehmann, J. *Ann.* **1960**, *635*, 166–177.
10. Shen, P. N.; Ruan, K. F.; Wang, Yu L.; Yu, W.; Zhang, W. Q.; Hong, X. K.; Wang, X. H. U.S. Patent 6,787,165, 2004.
11. Stick, R. V.; Stubbs, Keith A.; Tilbrook, D.; Matthew, G.; Watts, A. G. *Aust. J. Chem.* **2002**, 83–86.