Highly Enantioselective Michael Addition of Malonates to Nitroolefins Catalyzed by Chiral Bifunctional Tertiary Amine–Thioureas Based on Saccharides

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Received 14 June 2008

Abstract: A series of saccharide-derived bifunctional tertiary amine-thioureas for the asymmetric Michael addition reaction have been designed and synthesized. The addition products between malonates and various nitroolefins were obtained in high yields (up to 99%) and excellent enantioselectivities (up to 99% ee).

Key words: asymmetric catalysis, Michael addition, nitroolefins, bifunctional thiourea, saccharides

Asymmetric Michael additions are one of the most valuable C–C bond-forming reactions because they give synthetically useful chiral building blocks.[1] Among the variants of these reactions, Michael additions of carbonyl compounds to nitroolefins normally generate versatile bifunctionalized products.[2] Recently, considerable research efforts have been made toward developing environment-friendly nonmetallic organocatalysts for these processes.[3,4] In this vein, the utilization of chiral bifunctional thioureas has emerged as a viable strategy in the design of efficient organocatalysts.[5] Notable examples include Jacobsen's peptide thioureas[6] and Takemoto's amine thioureas.[7] Following these pioneering work, a number of research group have developed different bifunctional thiourea catalysts for the Michael addition aimed to improving reactivity, broadening substrate scope, and enhancing stereoselectivity.[8]

Two catalytic approaches can be envisaged for organocatalyzed Michael addition to nitroolefins (Figure 1).[2c,5d] Mechanism **A** involves the formation of an enamine intermediate with a chiral primary or secondary amine. This enamine is the nucleophile, which attacks the Michael acceptor.[9] In the second mechanism **B**, the tertiary amine plays the role of chiral base which forms an ion pair between the enolate and the chiral ammonium. The enolate is the nucleophilic species involved in this type of addition reactions.[10] It should be noted that in the catalytic procedures both the amine and the thiourea functionalities are required for the catalytic activity.

As part of our ongoing effort in developing saccharide-substituted thiourea catalysts,[11,12] we realized that these chiral molecules should be tunable and bifunctional organocatalysts. It is well known that the asymmetric Michael addition of malonates to nitroolefins is an important C–C bond-forming reaction that provides access to versatile enantioenriched nitroalkanes.[8m,13]As mentioned above, nitroolefin and malonate could be simultaneously activated by the thiourea-tertiary amine catalyst. Accordingly, we designed and synthesized a series of saccharide-substituted tertiary amine-thiourea compounds **2c**–**h** (Scheme 1),[15] and their catalytic activities were evaluated in the direct Michael addition reactions of malonates to nitroolefins. In this letter, we wish to disclose the preliminary results of this research.

The Michael addition of methyl malonate to nitrostyrene was selected as a model reaction (Scheme 2), and Table 1 summarizes the results. Bifunctional thioureas **2a** and **2b**, which lack tertiary amine moiety, exhibited poor catalytic activity for the addition reaction (entries 1 and 2). To our delight, when the same reactions were carried out in the presence of bifunctional thiourea-tertiary amines **2c**,**d**–**f**,

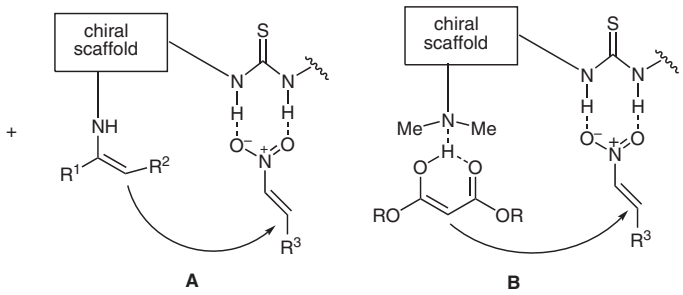
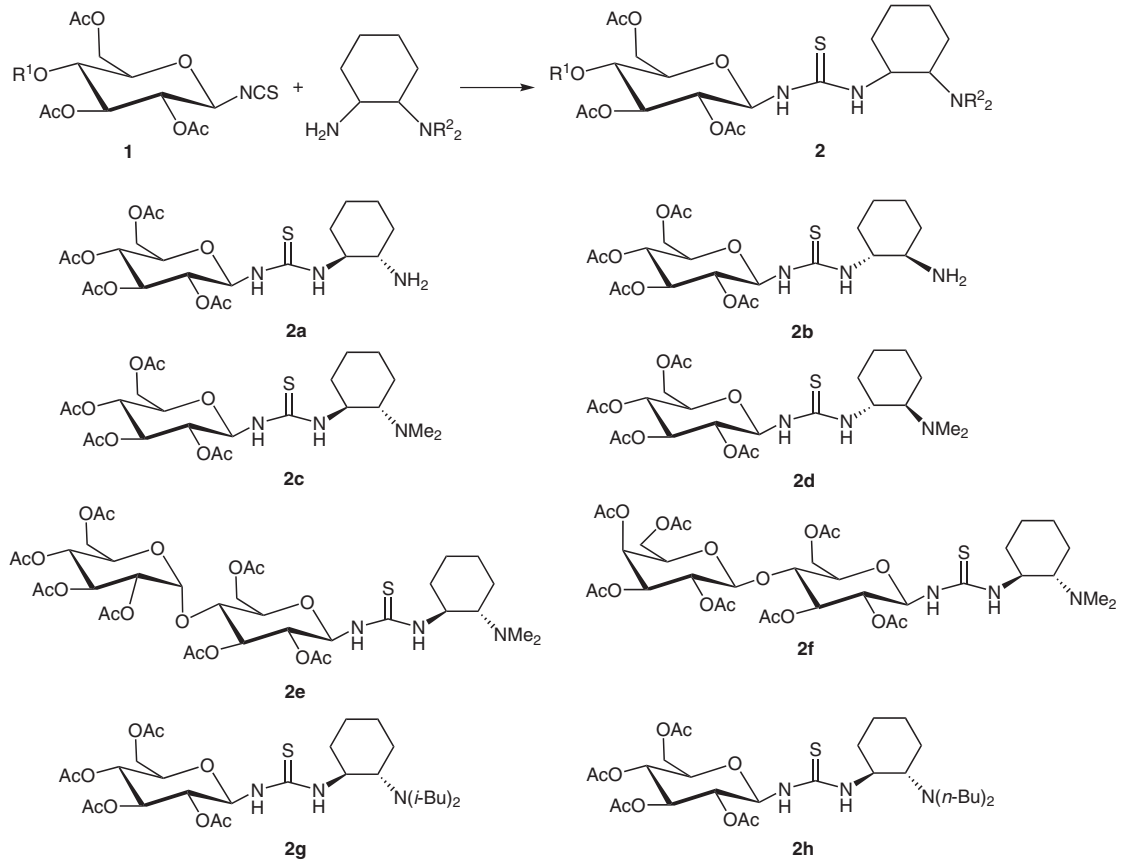


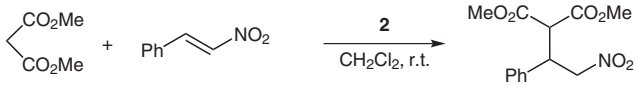
Figure 1 Proposed dual functional activation mechanism

SYNLETT 2008, No. 20, pp 3242–3246
Advanced online publication: 26.11.2008
DOI: 10.1055/s-0028-1087370; Art ID: W09408ST



Scheme 1 Saccharide-substituted thiourea catalysts synthesized and evaluated in the direct Michael reaction

the adduct was produced in excellent yield with high enantioselectivity (entries 3–6). Interestingly, the *S*,*S*-configuration of 1,2-diamino-cyclohexane matched the β-D-glucopyranose to enhance the stereochemical control in this type of addition reaction. It is noteworthy that the alkyl chain of the tertiary amine moiety could influence the catalytic activity and enantioselectivity. The addition reaction did not occur in the presence of organocatalyst **2g** (with *i*-Bu group), while excellent yield and enantioselectivity were obtained by using thiourea **2h** (with *n*-Bu substituent, entries 7 and 8). In addition, the catalyst loading could be reduced to 10 mol% without compromising the enantioselectivity, but the reaction must then be carried out under a longer reaction time (entries 9–11).



Scheme 2 Model reaction for screening of organocatalysts

Subsequently, we investigated the temperature and the solvent effect on the addition reaction. As show in Table 2, the change of temperature did not have a significant effect on the yield and stereoselection of the adduct, but a prolonged reaction time was required at –20 °C (entries 1–5). Notably, the yields and enantioselectivities were highly solvent dependent (entries 1, 4, and 6–10). The reaction proceeded with acceptable rates along with

Table 1 Enantioselective Michael Addition of Dimethyl Malonate to Nitrostyrene Catalyzed by Organocatalysts **2a**–**f**[a]

Entry	Cat. (mol%)	Time (h)	Yield[b] (%)	ee[c,d] (%)
1	**2a** (15)	84	<5	–
2	**2b** (15)	84	<5	–
3	**2c** (15)	24	99	92 (*S*)
4	**2d** (15)	48	99	83 (*R*)
5	**2e** (15)	36	99	88 (*S*)
6	**2f** (15)	84	99	83 (*S*)
7	**2g** (15)	144	0	–
8	**2h** (15)	96	99	99 (*S*)
9	**2h** (10)	144	99	99 (*S*)
10	**2c** (10)	48	99	91 (*S*)
11	**2c** (5)	52	99	89 (*S*)

[a] Conditions: dimethyl malonate (1 mmol), nitrostyrene (0.2 mmol), cat. **2**, CH_2Cl_2 (1 mL), r.t.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] Absolute configuration as determined by comparison with literature HPLC retention times and optical rotation data.[8a]

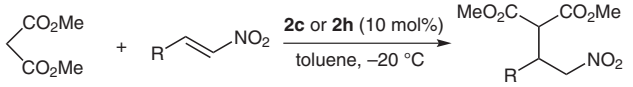
Table 2 Optimizing Reaction Conditions in the Presence of Organocatalyst **2c**[a]

Entry	Solvent/additive	Temp (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	25	24	99	92
2	CH_2Cl_2	0	48	99	93
3	CH_2Cl_2	–20	84	99	94
4	toluene	25	16	99	92
5	toluene	–20	36	99	94
6	Et_2O	25	24	99	92
7	THF	25	36	86	80
8	MeCN	25	36	98	88
9	DMF	25	48	–	–
10	DMSO	25	48	–	–
11	toluene/H_2O (0.1 equiv)	25	36	99	91
12	toluene/AcOH (0.1 equiv)	25	40	98	91
13	toluene/BzOH (0.1 equiv)	25	84	88	92
14	toluene/4 Å MS (10 mg)	25	16	99	81

[a] Conditions (unless stated otherwise): dimethyl malonate (1 mmol), nitrostyrene (0.2 mmol), catalyst **2c** (10 mol%), solvent (1 mL).
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.

high enantioselectivity in less polar aprotic solvents. However, no desired product was observed when more polar DMF or DMSO was used. Among the solvents tested, toluene was found to be the best with respect to catalytic activity and asymmetric induction. The effect of additives in toluene on enantioselectivity was also probed. Water and acid additives neither retarded the process, nor affected ee values (entries 11–13). Interestingly, it was found that molecular sieves (4 Å) decreased the enantioselectivity significantly (entry 14). The detailed mechanism is not known at this moment.[14]

In the presence of catalyst **2c** (or **2h**), the scope of the malonate addition under optimized reaction conditions



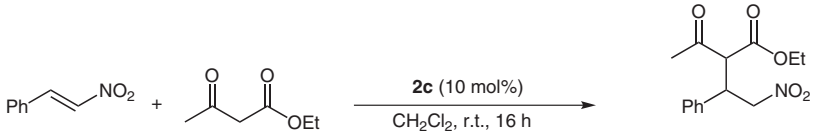
Scheme 3 The reaction of different nitroolefins with malonate catalyzed by **2c** or **2h**

Table 3 Scope of the Enantioselective **2c**- or **2h**-Catalyzed Michael Addition Reaction[a]

Entry	R	Time (h)	Yield[b] (%)	ee[c] (%)
1	Ph	36 (144)	99 (99)	94 (99)
2	4-BrC_6H_4	36 (108)	99	94 (90)
3	2-BrC_6H_4	20 (60)	99	97 (98)
4	4-ClC_6H_4	20 (108)	98 (99)	93 (90)
5	2-ClC_6H_4	36 (60)	99 (99)	95 (97)
6	4-FC_6H_4	36 (60)	97 (99)	92 (92)
7	4-$MeOC_6H_4$	36	99	95
8	4-MeC_6H_4	36	99	92
9	2-naphthyl	36	99	96
10	3-$PhOC_6H_4$	36	99	91
11	2-furyl	36	99	93
12	4-$O_2NC_6H_4$	16 (60)	99 (99)	90 (91)
13	CH=CHPh	84	92	92
14	2-$O_2NC_6H_3CH$=CH	24	86	92
15	4-$MeOC_6H_4CH$=CH	72	91	90
16	*n*-Pr	36	97	90
17	*i*-Bu	48	89	90

[a] Conditions (unless stated otherwise): dimethyl malonate (1 mmol), nitrostyrene (0.2 mmol), catalyst **2c** (10 mol%), toluene (1 mL), –20 °C. The values in parentheses were obtained in the presence of cat. **2h** at r.t.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.

(Scheme 3) is summarized in Table 3. Both electron-rich and electron-deficient nitrostyrenes were excellent Michael acceptors for methyl malonate. The reactions worked extremely well to afford Michael adducts in nearly quantitative yields and excellent enantioselectivities (91–97% ee, entries 1–12). In addition, 1-nitro-4-phenyl butadienes (R: C_6H_4CH=CH, 2-$O_2NC_6H_3CH$=CH, 4-$MeOC_6H_3CH$=CH) were also shown to be highly efficient activated alkenes (entries 13–15). It is noteworthy that no 1,6-addition was observed. Moreover, it was found that the **2c**-catalyzed Michael addition processes were also applicable to the substrates possessing aliphatic-2-substituents in high yields with comparative enantioselectivities (entries 16 and 17).



99%, dr 90:10, 89% ee

Scheme 4 The Michael addition of b-keto ester to nitrostyrene

The scope of this reaction was also extended to the use of β-keto ester (Scheme 4). When β-keto ester was employed, excellent yield with good diastereo- and enantioselectivity at the position β to the nitro group were obtained.

In summary, we have successfully developed another type of saccharide-substituted bifunctional tertiary amine-thioureas, with the catalytic activity being easily tuned by simply changing the amino moiety. These catalysts have proven to be robust and can be efficiently used in the direct Michael additions of malonate to various nitroolefins. Excellent yields and enantioselectivities were obtained under the optimized reaction conditions. Furthermore, β-keto esters were also used as Michael donors to afford adducts in high yield with good diastereo- and enantioselectivity. A full scope of investigation of the strategy is under way in our laboratory.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

The authors are grateful to NFSC (No. 20772091), Tianjin Municipal Science & Technology Commission (07JCZDJC04700), and NCET from the Ministry of Education of China for financial support.

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(15) **A Typical Procedure for the Preparation of Organocatalyst**

To a solution of 1, 2-cyclohexyldiamine (3.6 mmol) in CH_2Cl_2 (20 mL) was added the corresponding saccharide-derived isothiocyanates **1** (3 mmol). The mixture was stirred at r.t. for 3–24 h (TLC) and concentrated. The resulting residue was purified by flash column chromatography with the eluent (EtOAc–Et_3N, 100:1) to give the crude solid. The crude solid was dissolved in a minimal amount of CH_2Cl_2 and slowly precipitated from solution by the addition of PE at 0 °C. Filtration afforded the desired thiourea products **2**.

Compound **2c**: yield 55%; mp 90–92 °C; $[\alpha]_D^{20}$ –0.5 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.94–1.26 (m, 5 H, cyclohexane-H), 1.66–1.88 (m, 3 H, cyclohexane-H), 1.99 (s, 3 H, $COCH_3$), 2.01 (s, 3 H, $COCH_3$), 2.03 (s, 3 H, $COCH_3$), 2.05 (s, 3 H, $COCH_3$), 2.24 (s, 6 H, 2 NCH_3), 2.32 (m, 1 H, NCH), 3.45 (m, 1 H, NCH), 3.81–3.84 (m, 1 H, pyranose-H), 4.09–4.12 (m, 1 H, pyranose-H), 4.27–4.31 (m, 1 H, pyranose-H), 4.93–4.97 (t, 1 H, CH_2), 5.05–5.09 (t, 1 H, CH_2), 5.29–5.33 (m, 2 H, pyranose-H), 5.58–5.60 (br, 1 H, NH), 6.20 (br, 1 H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.85, 170.81, 170.07, 169.85, 83.30, 73.41, 73.5, 73.16, 71.22, 68.50, 61.88, 56.76, 40.46, 32.86, 24.96, 24.58, 22.76, 20.96, 20.94, 20.82, 20.81. IR (KBr): 3352, 2936, 1753, 1542, 1377, 1225, 1035, 910, 758, 601cm^{-1}. ESI-MS: *m/z* = 532.26 [M^+ + 1].

Compound **2d**: yield 50%; mp 83–86 °C; $[\alpha]_D^{20}$ +4.0 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.03–1.30 (m, 4 H, cyclohexane-H), 1.62–1.91 (m, 4 H, cyclohexane-H), 1.99 (s, 3 H, $COCH_3$), 2.01 (s, 3 H, $COCH_3$), 2.03 (s, 3 H, $COCH_3$), 2.05 (s, 3 H, $COCH_3$), 2.24 (s, 6 H, 2 NCH_3), 2.33 (m, 1 H, NCH), 3.45 (m, 1 H, NCH), 3.81–3.84 (m, 1 H, pyranose-H), 4.09–4.12 (m, 1 H, pyranose-H), 4.27–4.32 (m, 1 H, pyranose-H), 4.91–4.99 (t, 1 H, CH_2), 5.04–5.09 (t, 1 H, CH_2), 5.30–5.33 (m, 2 H, pyranose-H), 5.58–5.60 (br, 1 H, NH), 6.20 (br, 1 H NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.86, 170.81, 170.07, 169.86, 83.30, 73.42, 73.16, 71.22, 68.50, 61.88, 56.76, 40.46, 32.86, 24.98, 24.58, 20.96, 20.94, 20.82, 20.81. IR (KBr): 3352, 2939, 1755, 1545, 1378, 1231, 1038, 907, 755, 602 cm^{-1}. ESI-MS: *m/z* = 532.25 [M^+ + 1].

Comound **2e**: yield 30%; mp 94–97 °C; $[\alpha]_D^{20}$ +63.0 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.15–1.29 (m, 5 H, cyclohexane-H), 1.64–1.84 (m, 3 H, cyclohexane-H), 1.96–2.01 (s, 12 H, 4 $COCH_3$), 2.01–2.04 (s, 3 H, $COCH_3$), 2.04–2.07 (s, 3 H, $COCH_3$), 2.07–2.10 (s, 3 H, $COCH_3$), 2.19 (s, 6 H, 2 NCH_3), 2.24–2.38 (br, 1 H, NCH), 2.41–2.92 (br, 1 H, NCH), 3.76–3.82 (d, 1 H, OCH_2, *J* = 7.0 Hz), 3.84–3.89 (d, 1 H, OCH_2, *J* = 10.5 Hz), 3.98–4.04 (d, 2 H, OCH_2, *J* = 8.0 Hz), 4.04–4.10 (m, 1 H, pyranose-H), 4.16–4.27 (m, 3 H, pyranose-H), 4.42–4.46 (d, 1 H, pyranose-H, *J* = 12.5 Hz), 4.74–4.82 (m, 2 H, pyranose-H), 5.00–5.07 (m, 1 H, pyranose-H), 5.28–5.42 (m, 2 H, pyranose-H). ^{13}C NMR (125 MHz, DMSO): δ = 171.00, 170.86, 170.72, 170.60, 170.04, 169.95, 169.65, 95.60, 82.72, 75.51, 73.77, 72.54, 71.86, 70.19, 69.44, 68.62, 68.13, 62.80, 61.55, 60.60, 56.70, 40.34, 32.76, 29.86, 29.53, 25.06, 24.57, 21.25, 21.08, 21.03, 20.89, 20.82, 20.80, 14.39. IR (KBr): 3354, 2938, 1757, 1542, 1372, 1226, 1046, 940, 906, 754, 601 cm^{-1}. ESI-MS: *m/z* = 820.22 [M^+ + 1].

Compound **2f**: yield 24%; mp 92–94 °C; $[\alpha]_D^{20}$ +14.1 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.97–1.28 (m, 5 H, cyclohexane-H), 1.54–1.87 (m, 3 H, cyclohexane-H), 1.88–2.25 (m, 27 H, 7 CH_3, 2 NCH_3), 2.34–2.51 (m, 1 H, NCH), 3.64–3.71 (m, 1 H, pyranose-H), 3.72–3.89 (m, 2 H, pyranose-H), 4.00–4.17 (m, 4 H, OCH_2), 4.27–4.48 (m, 2 H, pyranose-H), 4.72–4.87 (m, 1 H, pyranose-H), 4.87–4.93 (m, 1 H, pyranose-H), 5.02–5.09 (m, 1 H, pyranose-H), 5.12–5.27 (m, 1 H, pyranose-H), 5.27–5.31 (m, 1 H, pyranose-H), 5.42–5.65 (br, 1 H, NH). ^{13}C NMR (125 MHz, DMSO): δ = 170.97, 170.65, 170.54, 170.34, 170.26, 169.29, 169.11, 100.99, 90.16, 74.00, 73.10, 72.34, 71.19, 70.81, 70.77, 69.29, 69.16, 66.89, 66.83, 61.01, 52.66, 40.15, 34.08, 25.44, 24.80, 24.55., 21.04, 21.02, 20.86, 20.83, 20.81, 20.70, 14.38; IR (KBr): 3357, 2938, 1757, 1542, 1372, 1225, 1046, 940, 906, 754, 602 cm^{-1}. ESI-MS: *m/z* = 820.19 [M^+ + 1].

Compound **2g**: yield 38%; mp 158–160 °C; $[\alpha]_D^{20}$ +57.9 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.75–0.88 (t, 12 H, CH_3), 0.89–1.72 (m, 8 H, cyclohexane-H), 1.72–2.38 (m, 20 H), 3.78–3.88 (m, 1 H, pyranose-H), 3.97–4.11 (m, 1 H, pyranose-H), 4.31–4.44 (m, 1 H, pyranose-H), 4.89–5.12 (m, 2 H, CH_2), 5.25–5.37 (m, 1 H, pyranose-H), 5.66–5.83 (m, 1 H, NH), 6.08–6.23 (m, 1 H, pyranose-H), 6.33–6.61 (m, 1 H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 183.17, 171.38, 170.92, 170.04, 169.89, 82.83, 73.37, 73.14, 70.72, 68.63, 63.84, 61.84, 58.91, 55.05, 32.48, 26.80, 25.85, 24.65, 23.09, 21.36, 20.99, 20.95, 20.83, 20.79. IR (KBr): 3371, 2951, 1751, 1511, 1369, 1232, 1038, 909, 759, 594 cm^{-1}. ESI-MS: *m/z* = 616.4 [M^+ + 1].

Compound **2h**: yield 35%; $[\alpha]_D^{20}$ +23.3 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.79–0.87 (t, 6 H, CH_3), 0.87–1.20 (m, 8 H, CH_2), 1.20–1.35 (7 H, cyclohexane-H), 1.63–1.84 (m, 3 H, cyclohexane-H), 1.94–2.08 (q, 12 H, $COCH_3$), 2.15–2.45 (m, 4 H, NCH_2), 3.30–3.65 (m, 1 H, NH), 3.72–4.34 (m, 3 H, pyranose-H), 4.90–5.71 (m, 4 H, pyranose-H), 6.35–6.60 (m, 1 H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 183.16, 171.59, 170.83, 170.0, 169.81, 90.11, 82.81, 73.35, 73.04, 71.08, 68.61, 63.63, 62.09, 55.53, 49.55, 32.79, 31.41, 25.75, 24.68, 23.64, 20.91, 20.90, 20.83, 20.78, 14.28. IR (KBr): 3362, 2933, 1758, 1543, 1377, 1232, 1039, 912, 751, 610 cm^{-1}. ESI-MS: *m/z* = 616.5 [M^+ + 1].