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Brønsted acid catalyzed azlactone ring opening by nucleophiles

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ABSTRACT

Brønsted acid catalyzed azlactone ring opening in the presence of different nucleophiles leading to the efficient synthesis of protected amides and amino esters is presented. Sixteen compounds were synthesized in good to excellent isolated yields. Mechanism investigation by using ESI(+)-MS/MS revealed that the CSA catalyst promotes azlactone activation for electrophilic attack facilitating therefore the attack of the nucleophile that leads to ring opening and protonation.

1. Introduction

Over the past years a major area in organic chemistry has been the development of efficient catalytic reactions able to form biologically functional amino acids and small peptides.[1] For such goal, azlactones have been attractive since they may serve as protected amino acids, which can be used in the synthesis of natural or synthetic bioactive molecules.[2] Our research group has explored the potential of azlactones as pro-nucleophiles in the presence of Michael acceptors by using an organocatalytic approach.[3] The multi-functional heterocyclic azlactone structure, however, confers to such molecules a diverse chemistry reacting as electrophiles via two distinct sites (Fig. 1). This structural versatility is very important since it could be applied in peptide-type synthesis. But azlactone can also suffer nucleophile attack, as shown for instance by Wang and co-workers, who described a Brønsted acid functioning as a catalyst for the asymmetric dynamic kinetic resolution following by opening of azlactone rings in the presence of a nucleophile. However, only a few azlactone rings and a particular alcohol were well tolerated in their optimized reaction condition.[4] Recently, Connon and Palacio showed that cinchona derivatives are suitable organocatalysts for the highly enantioselective dynamic kinetic resolution of azlactones by thiolysis. Moderate to high levels of enantioselectivity were achieved by using this catalytic system.[5]

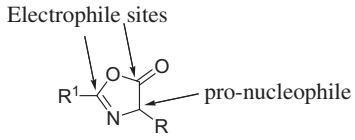

Fig. 1. General structure of azlactones.

We envisioned therefore that the use of Brønsted acid catalysis could be an attractive, metal-free strategy to activate azlactones toward nucleophile attack, and that this reaction could also be useful to prepare protected amino acid derivatives. In this communication, we show that indeed (+/−)-camphorsulfonic acid (CSA) functions as an effective Brønsted acid catalyst for the azlactone ring via nucleophile attack.

2. Results and discussion

Our studies initiated by reacting azlactone[6] **2** and octanol in the presence of 10 mol % of CSA as catalyst. To our delight, the desired product **6** was isolated in 88% yield (Scheme 1). After optimization of the reaction conditions, we found that replacing octanol with DCM as solvent provided the best reaction conditions. We also note that no reaction was observed in the absence of the CSA catalyst.

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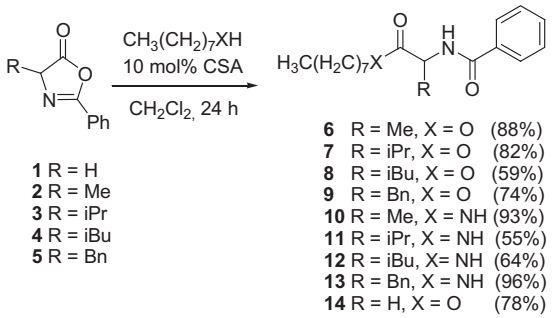
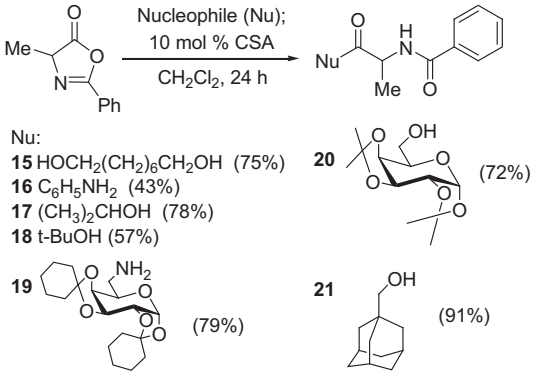


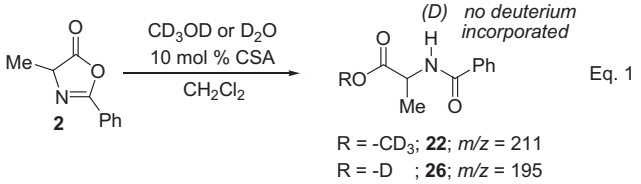
Scheme 1. Opening of the azlactone ring by lipophilic alcohols and amines. Reactions were carried out using 0.2 mmol of azlactone, 0.02 mmol of CSA (10 mol %), and 0.21 mmol of nucleophile (0.2 M in azlactone).

The reaction was also found to tolerate different azlactones (**1**–**5**); for example, the sterically bulky azlactone **3** provided the desired product **7** in 82% yield. Different lipophilic alcohols and amines could also be used in this reaction condition with medium to high yields (Schemes 1 and 2). Although no diastereoselectivity was observed, sugar-based derivatives were also found to provide the acyclic products in high yields. A secondary alcohol also worked quite well and even a tertiary alcohol was well tolerated, giving the desired product **13** in 57% isolated yield.



Scheme 2. Opening of azlactone ring by others nucleophiles. Reactions were carried out using 0.2 mmol of azlactone, 0.02 mmol of CSA (10 mol %), and 0.21 mmol of nucleophile (0.2 M in azlactone).

We then turned our attention to understanding the basics of this reaction by investigating its mechanism. The transfer of charged reaction intermediates directly from reaction solutions to the gas phase by electrospray ionization (ESI) followed by (tandem) mass spectrometry characterization ESI(+)-MS/MS[7] was therefore used in an attempt to intercept potential intermediates involved in the catalytic cycle. To this end, two experiments were carried out. First, after 5 min of reaction, an aliquot was taken from the crude mixture of azlactone **2** and CD_3OD in the presence of 10 mol % of CSA, diluted in acetonitrile, and directly analyzed by ESI(+)-MS (Eq. 1).



(1)

An ion of m/z 211 corresponding to the final product **22** [**22**+H]$^+$ (Fig. 2A) was intercepted. Its collision-induced dissociation (CID) showed fragment ions of m/z 176, 148, and 105, which were attributed to **23**, **24**, and **25**, respectively (Fig. 2B). In addition, another key species of m/z 408 corresponding to the association of the azlactone and the catalyst, that is, [**2**+CSA+H]$^+$ was also intercepted. Its ESI(+)-MS/MS showed as the unique fragment an ion of m/z 176 due to the neutral loss of CSA (Fig. 2C), which fully agrees with the proposed H-bonded proton dimmer structure in which protonation of **2** occurs at the most basic ring nitrogen.

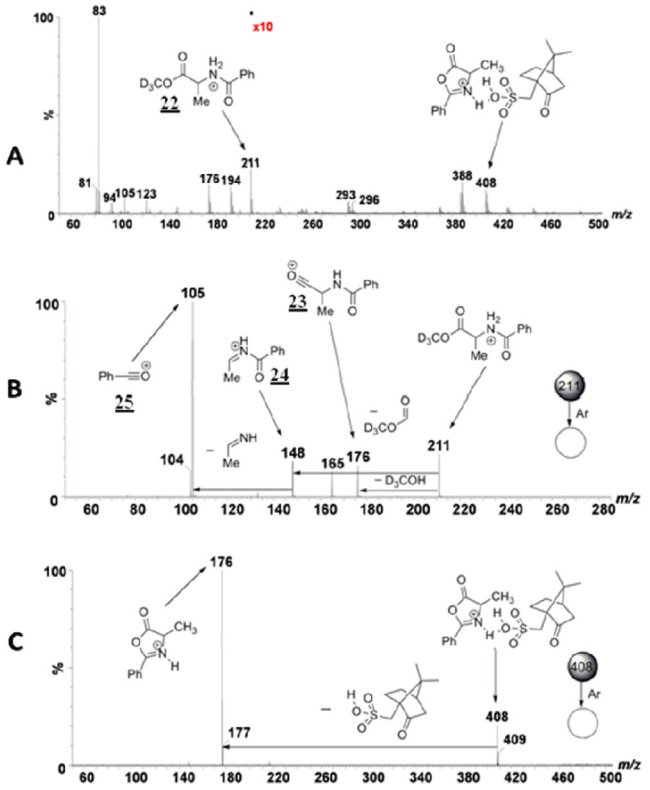
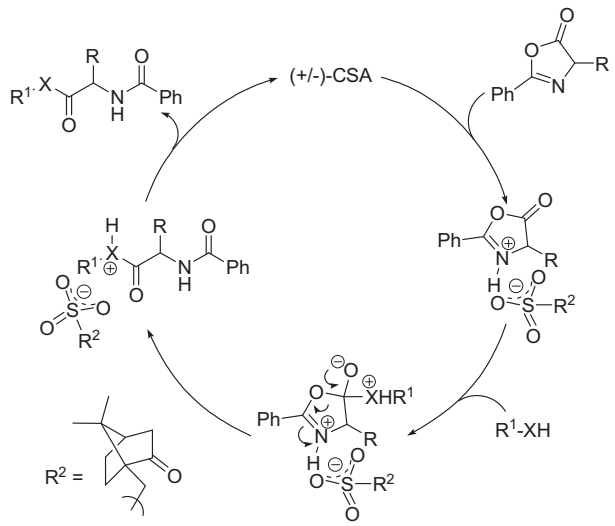


Fig. 2. (A) ESI(+)-MS of the azlactone **2** and CD_3OD reaction solution in the presence of CSA as catalyst; (B) ESI(+)MS/MS of the ion of m/z 211; (C) ESI(+)-MS/MS of the ion of m/z 408.

In the second experiment, D_2O was used as the nucleophile. As before, the two ions [**2**+CSA+H]$^+$ of m/z 408 and [**26**+H]$^+$ of m/z 195 were intercepted (Eq. 1). No H/D exchange for these two ions was noted, which suggested that de-protonation, the last reaction step, is also promoted by the catalyst. The mechanism seems therefore to proceed through azlactone activation via N-protonation and CSA binding at the NH$^+$ center (ion pairing), which facilitates nucleophilic attack at the carbonyl carbon and then the final CSA protonation (Scheme 3).

3. Conclusion

Efficient Brønsted acid catalyzed azlactone ring opening via electrophilic attack in the presence of different nucleophiles has been presented. Several amines and alcohols can be applied in this reaction condition, providing protected amino esters and amides derivatives in good to excellent yields. Mechanism investigation via ESI(+)-MS/MS revealed azlactone activation by the catalyst CSA to form an ion pairing intermediate, following by nucleophilic attack. No H/D exchange occurs when D_2O is used with no deuterium incorporation in the final product, suggesting that CSA is responsible for the protonation and de-protonation step. The development of



Scheme 3. Mechanism hypothesis for the azlactone activation following by nucleophilic attack.

an enantioselective version is ongoing and will be reported in due course.

4. Experimental section

4.1. General remarks

Unless otherwise noted, all reagents were obtained commercially and used without further purification. Unless otherwise noted, all reaction mixtures were carried out in flame-dried glassware under a positive pressure of dry nitrogen. Analytical thin layer chromatography (TLC) was performed on Merck precoated glass-backed TLC plates (silica gel 60 F_{254}) and visualized by UV lamp (254 nm). Yields refer to chromatographically purified and spectroscopically pure compounds, unless stated otherwise. ^{1}H and ^{13}C spectra were recorded on a Bruker DPX-300 spectrometer. Chemical shifts are reported in parts per million (ppm). ^{1}H NMR spectra were referenced to $CDCl_3$ (7.26 ppm) and ^{13}C NMR spectra were referenced to $CDCl_3$ (77.23 ppm). All ^{13}C spectra were measured with complete proton decoupling. Peak multiplicities are designated by the following abbreviations: s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet; br, broad; q, quartet; qu, quintet; and *J*, coupling constant in hertz (Hz). High-resolution mass spectra as well as mechanism investigation were acquired in the positive ion mode using a mass spectrometer Micromass (Manchester, UK) QTof instrument of ESI-QTof configuration with 5000 mass resolution and 50 ppm mass accuracy in the TOF mass analyzer. The following typical operating conditions were used: 3 kV capillary voltage, 8 V cone voltage, and desolvation gas temperature of 100 °C. Tandem ESI-MS/MS were collected after 4–32 eV collision-induced dissociation (CID) of mass-selected ions with argon. Mass-selection was performed by Q1 using a unitary *m*/*z* window, and collisions were performed in the rf-only hexapole collision cell, followed by mass analysis of product ions by the high-resolution orthogonal reflectron TOF analyzer.

4.2. General procedure for the catalytic azlactone ring opening in the presence of nucleophiles

In a flamed screw cap vial and under nitrogen atmosphere, 0.2 mmol of azlactone was added. After, CH_2Cl_2 was cannulated at the concentration of 0.2 M in azlactone. To this solution, 0.02 mmol (10.0 mol %) of (+/−)-camphorsulfonic acid was added followed by 0.21 mmol of nucleophile. The reaction mixture was kept at room temperature and under nitrogen atmosphere for 24 h. The reaction mixture was then diluted in CH_2Cl_2 (10 mL) and washed with saturated solution of sodium bicarbonate (5 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. After, the crude reaction mixture was purified through silica gel chromatography by using ethyl acetate/hexanes as solvents (up to 25% ethyl acetate/hexanes). The purified products were then fully characterized by the conventional elemental analysis.

4.3. Characterization data

*4.3.1. Octyl 2-(benzamido)propanoate (**6**).* The product was purified by column chromatography on silica gel (elution: hexanes to hexanes/ethyl acetate 25%) to afford product **6** (123 mg, 88%); IR (KBr, cm^{-1}): 3321; 2961; 2930; 2876; 2858; 1741; 1644; 1534; 1170; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7,80–7.78 (m, 2H); 7.51–7.39 (m, 3H); 6.88 (d, 1H, *J*=6.9 Hz); 4.78 (qu, 1H, *J*=7.2 Hz); 4.16–4.01 (m, 2H); 1.62–1.24 (m, 12H); 0.91–0.86 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 173.5; 166.9; 134.1; 131.8; 128.7; 127.2; 68.0; 48.7; 38.9; 30.4; 29.0; 23.9; 23.1; 18.8; 14.2; 11.1; HRMS: calcd for $[C_{18}H_{27}NO_3]^+$ ($[M+H]^+$): *m*/*z* 306.2069, found 306.2075.

*4.3.2. Octyl 2-(benzamido)-3-methylbutanoate (**7**).* The product was purified by column chromatography on silica gel (elution: hexanes to hexanes/ethyl acetate 25%) to afford product **7** (62 mg, 82%); IR (KBr, cm^{-1}): 3313; 2960; 2927; 2873; 2856; 1737; 1647; 1526; 1191; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.82–7.79 (m, 2H); 7.54–7.41(m, 3H); 6.68 (d, 1H, *J*=8.7 Hz); 4.80 (dd, 1H, *J*=8.7 Hz, *J*=4.5 Hz); 4.14–4.02 (m, 2H); 2.34–2.23 (m, 1H); 1.60 (qu, 1H, *J*=6.0 Hz); 1.43–1.24 (m, 9H); 1.02–0.86 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 172.5; 167.4; 134.5; 131.9; 128.8; 127.2; 67.9; 57.7; 38.9; 32.0; 30.5; 29.0; 24.0; 23.0; 19.2; 18.1; 14.2; 11.2; HRMS: calcd for $[C_{20}H_{31}NO_3]^+$ ($[M+H]^+$): *m*/*z* 334.2382, found 334.2433.

*4.3.3. Octyl 2-(benzamido)-4-methylpentanoate (**8**).* The product was purified by column chromatography on silica gel (elution: hexanes to hexanes/ethyl acetate 25%) to afford product **8** (142 mg, 59%); IR (KBr, cm^{-1}): 3303; 2958; 2927; 2867; 1749; 1642; 1529; 1162; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.77 (d, 2H, *J*=6.9 Hz); 7.48–7.35 (m, 3H); 6.78 (d, 1H, *J*=8.4 Hz); 4.87–4.80 (m, 1H); 4.10–3.99 (m, 2H); 1.75–1.56 (m, 4H); 1.38–1.23 (m, 9H); 0.97–0.84 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 173.5; 167.2; 134.2; 131.7; 128.6; 127.2; 67.9; 51.5; 42.1; 38.9; 30.5; 29.0; 25.2; 23.9; 23.0; 22.9; 22.3; 14.1; 11.1; HRMS: calcd for $[C_{21}H_{33}NO_3]^+$ ($[M+H]^+$): *m*/*z* 348.2539, found 348.2725.

*4.3.4. Octyl 2-(benzamido)-3-phenylpropanoate (**9**).* The product was purified by column chromatography on silica gel (elution: hexanes to hexanes/ethyl acetate 25%) to afford product **9** (84 mg, 74%); IR (KBr, cm^{-1}): 3330; 2960; 2927; 2873; 2852; 1740; 1644; 1534; 1210; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.64–7.61 (m, 2H); 7.42–7.29 (m, 3H); 7.22–7.03 (m, 5H); 6.59 (d, 1H, *J*=7.5 Hz); 5.03–4.97 (m, 1H); 4.03–3.88 (m, 2H); 3.23–3.10 (m, 2H); 1.51–1.43 (m, 1H); 1.28–1.17 (m, 8H); 0.81–0.76 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 172.0; 167.0; 136.1; 134.2; 131.9; 129.5; 128.7; 127.2; 68.2; 53.8; 38.9; 38.2; 30.5; 29.0; 23.9; 23.1; 14.2; 11.1; HRMS: calcd for $[C_{24}H_{31}NO_3]^+$ ($[M+H]^+$): *m*/*z* 382.2382, found 382.2285.

*4.3.5. N-(1-(Octylcarbamoyl)ethyl)benzamide (**10**).* The product was purified by column chromatography on silica gel (elution: hexanes to hexanes/ethyl acetate 25%) to afford product **10** (219 mg, 93%); IR (KBr, cm^{-1}): 3278; 3071; 2951; 2925; 2858; 1657; 1633; 1546; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.82 (d, 2H, *J*=7.8 Hz); 7.68 (d, 1H, *J*=7.5 Hz); 7.53–7.32 (m, 4H); 4.85 (qu, 1H, *J*=7.2 Hz); 3.32–3.13 (m, 2H); 1.49–1.42 (m, 5H); 1.23–1.19 (m, 10H); 0.82 (t, 3H, *J*=6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 172.7; 167.3; 134.0; 131.7; 128.5; 127.3; 49.4; 39.7; 31.9; 29.5; 29.4; 27.0; 22.7;

18.9; 14.1; HRMS: calcd for $[C_{18}H_{28}N_2O_2]^+$ ($[M+H]^+$): *m*/*z* 305.2229, found 305.2224.

*4.3.6. N-(1-(Octylcarbamoyl)-2-methylpropyl)benzamide (**11**).* The product was purified by column chromatography on silica gel (elution: hexanes to hexanes/ethyl acetate 25%) to afford product **11** (40.6 mg, 55%); IR (KBr, cm^{-1}): 3286; 2960; 2927; 2853; 1648; 1630; 1543; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.83–7.81 (m, 2H); 7.53–7.39 (m, 3H); 7.15 (d, 1H, *J*=8.7 Hz); 6.78–6.75 (m, 1H); 4.50 (t, 1H, *J*=8.4 Hz); 3.38–3.26 (m, 1H); 3.23–3.12 (m, 1H); 2.23–2.12 (m, 1H); 1.49 (qu, 2H, *J*=7.2 Hz); 1.25–1.22 (m, 10H); 0.99 (d, 6H, *J*=6.6 Hz); 0.85 (t, 3H, *J*=6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 171.4; 167.6; 134.3; 131.9; 128.7; 127.3; 59.3; 39.8; 32.0; 31.6; 29.9; 29.6; 29.4; 27.1; 22.8; 19.5; 18.8; 14.3; HRMS: calcd for $[C_{20}H_{32}N_2O_2]^+$ ($[M+H]^+$): *m*/*z* 333.2542, found 333.2569.

*4.3.7. N-(1-(Octylcarbamoyl)-3-methylbutyl)benzamide (**12**).* The product was purified by column chromatography on silica gel (elution: hexanes to hexanes/ethyl acetate 25%) to afford product **12** (153 mg, 64%); IR (KBr, cm^{-1}): 3333; 3244; 2957; 2927; 2853; 1666; 1635; 1540; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.85–7.82 (m, 2H); 7.65 (d, 1H, *J*=8.4 Hz); 7.47–7.32 (m, 4H); 4.81 (q, 1H, *J*=8.1 Hz); 3.31–3.20 (m, 1H); 3.16–3.06 (m, 1H); 1.68 (d, 3H, *J*=4.8 Hz); 1.46 (qu, 2H, *J*=7.2 Hz); 1.28–1.21 (m, 10H); 0.90–0.82 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 172.6; 167.5; 134.1; 131.7; 128.5; 127.5; 52.4; 41.5; 39.7; 31.9; 29.5; 29.4; 29.3; 27.1; 25.1; 22.9; 22.8; 22.5; 14.2; HRMS: calcd for $[C_{21}H_{34}N_2O_2]^+$ ($[M+H]^+$): *m*/*z* 347.2699, found 347.2655.

*4.3.8. N-(1-(Octylcarbamoyl)-2-phenylethyl)benzamide (**13**).* The product was purified by column chromatography on silica gel (elution: hexanes to hexanes/ethyl acetate 25%) to afford product **13** (218 mg, 96%); IR (KBr, cm^{-1}): 3306; 2955; 2924; 2853; 1657; 1635; 1523; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.78 (d, 3H, *J*=7.5 Hz); 7.49–7.33 (m, 3H); 7.21–7.09 (m, 6H); 5.06 (q, 1H, *J*=7.5 Hz); 3.29–2.99 (m, 4H); 1.37–1.18 (m, 12H); 0.87 (t, 3H, *J*=6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 171.3; 167.4; 137.1; 133.9; 131.7; 129.5; 128.5; 127.4; 126.8; 55.2; 39.7; 39.0; 31.9; 29.8; 29.4; 29.3; 27.0; 22.8; 14.2; HRMS: calcd for $[C_{24}H_{32}N_2O_2]^+$ ($[M+H]^+$): *m*/*z* 381.2542, found 381.2653.

*4.3.9. Octyl 2-(benzamido)acetate (**14**).* The product was purified by column chromatography on silica gel (elution: hexanes to hexanes/ethyl acetate 25%) to afford product **14** (284 mg, 78%); IR (KBr, cm^{-1}): 3335; 2958; 2930; 2873; 2859; 1750; 1650; 1540; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.79–7.76 (m, 2H); 7.46–7.33 (m, 3H); 7.11–7.08 (m, 1H); 4.17 (d, 1H, *J*=5.4 Hz); 4.04 (m, 2H); 1.57–1.51 (m, 1H); 1.36–1.24 (m, 11H); 0.84 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 170.3; 167.6; 133.8; 131.7; 128.6; 127.2; 68.0; 41.9; 38.8; 30.4; 28.9; 23.8; 23.0; 14.1; 11.0; HRMS: calcd for $[C_{17}H_{25}NO_3]^+$ ($[M+H]^+$): *m*/*z* 292.1913, found 292.1985.

*4.3.10. 8-Hydroxyoctyl 2-(benzamido)propanoate (**15**).* The product was purified by column chromatography on silica gel (elution: hexanes to hexanes/ethyl acetate 25%) to afford product **15** (96.4 mg, 75%); IR (KBr, cm^{-1}): 3318; 2930; 2855; 1734; 1642; 1537; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.80–7.77 (m, 2H); 7.50–7.38 (m, 3H); 6.94 (d, 1H, *J*=4.8 Hz); 4.76 (qu, 1H, *J*=7.2 Hz); 4.14 (t, 2H, *J*=6.6 Hz); 3.59 (t, 1H, *J*=6.6 Hz); 2.20 (s, 1H); 1.63 (qu, 2H, *J*=6.9 Hz); 1.57–1.48 (m, 5H); 1.30–1.23 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 173.5; 167.1; 134.1; 131.8; 128.7; 127.2; 65.8; 62.9; 48.7; 32.8; 29.8; 29.3; 29.2; 28.6; 25.8; 18.7; HRMS: calcd for $[C_{18}H_{27}NO_4]^+$ ($[M+H]^+$): *m*/*z* 322.2018, found 322.2070.

*4.3.11. N-(1-(Phenylcarbamoyl)ethyl)benzamide (**16**).* The product was purified by column chromatography on silica gel (elution: hexanes to hexanes/ethyl acetate 25%) to afford product **16** (130 mg, 43%); IR (KBr, cm^{-1}): 3304; 3253; 3196; 3134; 3064; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.39 (s, 1H); 7.79–7.76 (m, 2H); 7.53–7.50 (m, 3H); 7.46–7.30 (m, 4H); 7.19 (t, 2H, *J*=7.5 Hz); 7.03–6.98 (m, 1H); 5.01 (qu, 1H, *J*=7.2 Hz); 1.50–1.48 (d, 3H, *J*=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 171.1; 168.0; 138.2; 133.8; 132.2; 129.0; 127.4; 124.5; 120.3; 50.3; 18.7; HRMS: calcd for $[C_{16}H_{16}N_2O_2]^+$ ($[M+H]^+$): *m*/*z* 269.1290, found 269.1361.

*4.3.12. Isopropyl 2-(benzamido)propanoate (**17**).* The product was purified by column chromatography on silica gel (elution: hexanes to hexanes/ethyl acetate 25%) to afford product **17** (158 mg, 78%); IR (KBr, cm^{-1}): 3360; 2984; 1747; 1645; 1525; 1174; NMR ^1H (300 MHz, $CDCl_3$) δ (ppm): 7.76–7.73 (m, 2H); 7.44–7.30 (m, 3H); 7.06 (d, 1H, *J*=7.2 Hz); 5.0 (qu, 1H, *J*=6.3 Hz); 4.66 (qu, 1H, *J*=7.2 Hz); 1.43 (d, 3H, *J*=7.2 Hz); 1.22–1.19 (m, 6H); NMR ^{13}C (75 MHz, $CDCl_3$) δ (ppm): 172.8; 166.9; 134.1; 131.6; 128.5; 127.1; 69.2; 48.7; 21.8; 18.4; HRMS: calcd for $[C_{13}H_{17}NO_3]^+$ ($[M+H]^+$): *m*/*z* 236.1287, found 236.1310.

*4.3.13. tert-Butyl 2-(benzamido)propanoate (**18**).* The product was purified by column chromatography on silica gel (elution: hexanes to hexanes/ethyl acetate 25%) to afford product **18** (203 mg, 57%); IR (KBr, cm^{-1}): 3301; 3071; 2984; 2936; 1723; 1630; 1544; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.77–7.74 (m, 2H); 7.45–7.32 (m, 3H); 6.98 (d, 1H, *J*=6.3 Hz); 4.62 (qu, 1H, *J*=6.6 Hz); 1.44–1.42 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 172.6; 166.8; 134.2; 131.6; 128.5; 127.1; 82.1; 49.1; 28.0; 18.7; HRMS: calcd for $[C_{14}H_{19}NO_3]^+$ ($[M+H]^+$): *m*/*z* 250.1443, found 250.1496.

*4.3.14. N-((1-(6′-Deoxy-1′,2′:3′,4′-di-O-cyclohexylidene-α-D-galactopyrane-6′-yl)carbamoyl)ethyl)benzamide (**19**).* The product was purified by column chromatography on silica gel (elution: hexanes to hexanes/ethyl acetate 25%) to afford product **19** (81.3 mg, 79%); IR (KBr, cm^{-1}): 3425; 3301; 2963; 2933; 2856; 1635; 1260; 1096; 1021; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm, mixture of diastereomers): 7.81 (t, 2H, *J*=6.3 Hz); 7.48–7.35 (m, 3H); 7.28–7.21 (m, 1H); 6.99–6.92 (m, 1H); 5.48 (d, 1H, H_1, *J*=4.8 Hz); 5.45 (d, 1H, $H_{1'}$, *J*=5.1 Hz); 4.73 (qu, 1H, *J*=7.2 Hz); 4.60–4.56 (m, 1H); 4.30–4.26 (m, 1H); 4.17 (d, 1H, *J*=8.1 Hz); 3.87 (d, 1H, *J*=7.5 Hz); 3.77–3.64 (m, 1H); 3.32–3.17 (m, 1H); 1.60–1.34 (m, 23H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm, mixture of diastereomers): 172.9; 172.85; 167.1; 166.9; 134.13; 134.1; 131.7; 131.67; 128.6; 127.3; 127.28; 110.2; 110.16; 109.4; 96.0; 95.98; 71.45; 71.4; 70.6; 70.3; 66.5; 66.4; 49.3; 40.4; 40.3; 35.8; 34.4; 34.38; 34.0; 25.2; 25.1; 24.1; 24.0; 23.8; 23.6; 19.5; 18.9; HRMS: calcd for $[C_{28}H_{38}N_2O_7]^+$ ($[M+H]^+$): *m*/*z* 515.2758, found 515.2974.

*4.3.15. 1′,2′:3′,4′-Di-O-isopropilidene-α-D-galactopyrane-6′-yl-2-(benzamido)propanoate (**20**).* The product was purified by column chromatography on silica gel (elution: hexanes to hexanes/ethyl acetate 25%) to afford product **20** (298 mg, 72%); IR (KBr, cm^{-1}): 3330; 2987; 2936; 1744; 1647; 1072; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm, mixture of diastereomers): 7.74 (d, 2H, *J*=7.2 Hz); 7.43–7.30 (m, 3H); 7.06 (dd, 1H, *J*=7.5 Hz, *J*=2.4 Hz); 5.48–5.44 (m, 2H, H_1, $H_{1'}$); 4.74 (qu, 1H, *J*=7.2 Hz); 4.56–4.51 (m, 2H); 4.37–4.14 (m, 6H); 4.00–3.93 (m, 1H); 3.82–3.62 (m, 3H); 1.46–1.43 (m, 8H); 1.37–1.34 (m, 8H); 1.25–1.23 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm, mixture of diastereomers): 172.9; 172.8; 166.8; 133.9; 131.5; 128.4; 127.1; 109.6; 109.2; 108.7; 108.5; 96.2; 71.3; 70.9; 70.6; 70.55; 70.4; 68.2; 66.0; 65.8; 64.2; 61.8; 48.6; 48.5; 25.9; 25.88; 24.9; 24.33; 24.3; 18.4; HRMS: calcd for $[C_{22}H_{29}NO_8]^+$ ($[M+H]^+$): *m*/*z* 436.1971, found 436.1978.

*4.3.16. Adamantan-1-yl-methyl-2-(benzamido)propanoate (**21**).* The product was purified by column chromatography on silica gel

(elution: hexanes to hexanes/ethyl acetate 25%) to afford product **21** (90 mg, 91%); IR (KBr, cm^{-1}): 3351; 2906; 2847; 1743; 1635; 1168; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.80–7.77 (m, 2H); 7.50–7.37 (m, 3H); 6.95 (d, 1H, J=7.2 Hz); 4.80 (qu, 1H, J=7.2 Hz); 3.80 (d, 1H, J=10.5 Hz); 3.69 (d, 1H, J=7.2 Hz); 2.01–1.96 (m, 3H); 1.73–1.47 (m, 14H); 1.25–1.17 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 173.5; 167.0; 134.2; 131.8; 128.7; 127.2; 75.1; 48.8; 39.3; 37.0; 33.5; 28.1; 18.9; HRMS: calcd for $[C_{21}H_{27}NO_3]^+$ ($[M+H]^+$): m/z 342.2069, found 342.2091.

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Supplementary data

Copies of IR and NMR spectra for the prepared compounds are available free of charge at www.sciencedirect.com. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.11.037.

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