Microwave Accelerated Aza-Claisen Rearrangement

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Abstract: A study of microwave-induced and standard thermal Overman rearrangement of selected allylic trichloroacetimidates 1a-1f, 6-8 to the corresponding acetamides 2a-2f, 9-11 is reported. The microwave-assisted rearrangement of trifluoroacetimidate 13 is also described. Using this methodology, an efficient access to versatile allylic trihaloacetamides building synthons was established.

Keywords: Overman rearrangement; Imidate; Microwave irradiation.

Introduction

The [3,3]-sigmatropic rearrangement of allylic trihaloacetimidates into allylic trihaloacetamides is a useful methodology for the synthesis of nitrogen containing compounds such as amino acids [1-3], modified nucleosides [4,5] or other complex biologically interesting products [6-9]. This transformation is very often involved as the key step in the synthetic approaches and can be accomplished either at elevated temperatures or catalyzed by metal salts such as Hg(OCOCF₃)₂ [10,11], PdCl₂ complexes [12,13] and new Pt(II), Pt(IV), Au(I) and Au(III) catalysts [14] under very mild reaction conditions.
A significant acceleration of aza-Claisen rearrangements was observed using microwave irradiation [15]. This fact eliminated problems with previously required high temperatures and extended reaction times, and also reduced decomposition of the starting materials and products.

Results and Discussion

In this communication, we wish to report on microwave-assisted thermal Overman rearrangement of some selected allylic trihaloacetimidates 1a-f, 6-8, 13 that are derived either from simple allylic alcohols, amino acids or the modified sugars, respectively, and thus illustrate the potential of microwave irradiation to accelerate this reaction.

Scheme 1. Microwave accelerated Overman rearrangement of simple aliphatic imidates.

Table 1. Microwave accelerated Overman rearrangement of simple aliphatic imidates.

| Entry | R          | Conditions                      | Time  | Yield\(^a\) (%) |
|-------|------------|---------------------------------|-------|-----------------|
| 1     | R\(^1\) = H, R\(^2\) = H, R\(^3\) = H (a) | \(\Delta, 140 \, ^\circ\text{C}, \text{o-xylene} \ [10,15]\) | 12 h  | 50              |
|       |            | MW, 140 \, ^\circ\text{C}, \text{o-xylene}, K\(_2\text{CO}_3\) | 10 h  | 65              |
|       |            | MW, 210 \, ^\circ\text{C}, \text{o-xylene}, K\(_2\text{CO}_3\) \(^b\) | 5 min | 70              |
|       |            | \(\Delta, 110^\circ\text{C}, \text{toluene} \ [18]\) | 2 h   | 53              |
|       |            | \(\Delta, 140 \, ^\circ\text{C}, \text{o-xylene}, K\(_2\text{CO}_3\)\) | 2 h   | 60              |
| 2     | R\(^1\) = H, R\(^2\) = H, R\(^3\) = Me (b) | MW, 140 \, ^\circ\text{C}, \text{o-xylene}, K\(_2\text{CO}_3\) \([16]\) | 15 min | 93              |
|       |            | MW, 180 \, ^\circ\text{C}, \text{o-xylene}, K\(_2\text{CO}_3\) \([16]\) | 8 min | 89              |
|       |            | \(\Delta, 140 \, ^\circ\text{C}, \text{o-xylene} \ [10]\) | 2.5 h | 74              |
| 3     | R\(^1\) = H, R\(^2\) = H, R\(^3\) = Bu (c) | MW, 140 \, ^\circ\text{C}, \text{o-xylene}, K\(_2\text{CO}_3\) \([16]\) | 5 min | 97              |
|       |            | MW, 180 \, ^\circ\text{C}, \text{o-xylene}, K\(_2\text{CO}_3\) \([16]\) | 1 min | 94              |
| 4     | R\(^1\) = H, R\(^2\) = H, R\(^3\) = \text{Pent} (d) | \(\Delta, 140 \, ^\circ\text{C}, \text{o-xylene}, K\(_2\text{CO}_3\)\) | 1.5 h | 97              |
|       |            | MW, 140 \, ^\circ\text{C}, \text{o-xylene}, K\(_2\text{CO}_3\) | 5 min | 92              |
|       |            | \(\Delta, 140 \, ^\circ\text{C}, \text{o-xylene} \ [11]\) | 3.5 h | 48              |
| 5     | R\(^1\) = Me, R\(^2\) = Me, R\(^3\) = H (e) | \(\Delta, 140 \, ^\circ\text{C}, \text{o-xylene}, K\(_2\text{CO}_3\)\) | 3.5 h | 80              |
|       |            | MW, 140 \, ^\circ\text{C}, \text{o-xylene}, K\(_2\text{CO}_3\) \([16]\) | 20 min | 85              |
|       |            | MW, 180 \, ^\circ\text{C}, \text{o-xylene}, K\(_2\text{CO}_3\) \([16]\) | 14 min | 84              |
| 6     | R\(^1\) = Me, R\(^2\) = H, R\(^3\) = Me (f) | \(\Delta, 140 \, ^\circ\text{C}, \text{o-xylene}, K\(_2\text{CO}_3\)\) | 45 min | 70              |
|       |            | MW, 140 \, ^\circ\text{C}, \text{o-xylene}, K\(_2\text{CO}_3\) | 45 min | 75              |

\(^a\)Isolated yield. \(^b\)MW experiments were performed in the presence of a heating bar, Weflon, Milestone.
Thermally driven [3,3]-sigmatropic rearrangements (Scheme 1) were carried out according to the procedure described by Overman [10]. In the microwave-assisted thermal aza-Claisen rearrangement, the imidate was dissolved in o-xylene, powdered anhydrous K₂CO₃ [17] (2 mg/mL) was added, and the solution was heated under sealed vessel conditions. The scope of this method was investigated and all synthesized imidates (only imidates 1e and 1f were not characterized and used immediately to avoid problems connected with their instability) in Table 1 were converted to the corresponding trichloroacetamides 2a–2f in considerably shorter reaction times, compared to the conventional thermal rearrangement. We have observed that the use of microwave irradiation lead to a substantial reduction of the reaction times (from hours to minutes, Table 1, Entry 1-5). On the other hand, the conversion of 1f to compound 2f was achieved at the same reaction time in both cases (the microwave-assisted and standard thermal conditions, Table 1, Entry 6).

Scheme 2. Microwave accelerated Overman rearrangement of the chiral imidates.

Table 2. Microwave accelerated Overman rearrangement of the chiral imidates 6, 7, 8 and 13.

| Entry | Starting material | Conditions | Time | Yielda (%) |
|-------|-------------------|------------|------|------------|
| 1     | Δ, 140 °C, o-xylene, de=10% [12] | MW, 140 °C, o-xylene, K₂CO₃, de=14% [16] | 24 h | 75 |
|       |                   | MW, 200 °C, o-xylene, K₂CO₃, de=12% [16] | 5 min | 80 |
| 2     | Δ, 140 °C, o-xylene, de=10% [12] | MW, 140 °C, o-xylene, K₂CO₃, de=12% [16] | 2 h | 71 |
|       |                   | MW, 200 °C, o-xylene, K₂CO₃, de=13% [16] | 5 min | 68 |
| 3     | Δ, 140 °C, o-xylene, de=2% | MW, 160 °C, o-xylene, K₂CO₃, de=2% | 42 h | 80 |
|       |                   | Δ, 180 °C, o-xylene, K₂CO₃, de = 20% | 1 h | 86 |
| 4     | Δ, 180 °C, o-xylene, de = 19% | MW, 180 °C, o-xylene, de ≈ 18% | 12 h | 31 |
|       |                   | MW, 180 °C, o-xylene, de = 18% | 30 min | 68 |
|       |                   | MW, 180 °C, o-xylene, de = 15% | 1 h | 15 |

aIsolated yields.

In earlier studies was found that Pd(II)-catalyzed Overman rearrangement of trichloroacetimidates 6, 7 derived from primary allylic alcohols with an adjacent centre of chirality proceeded with an excellent diastereoselectivity (de ≥ 98%) [12]. In the next phase of our work we decided to study whether the described microwave-assisted Overman rearrangement could lead to a certain degree of
diastereoselection. The conversion of known allylic alcohols [12,14] into trichloroacetimidates 6-8 was achieved using trichloroacetonitrile and DBU as a base in dichloromethane (Scheme 2). The results of the thermal and microwave induced Overman rearrangements of imidates 6-8 are summarized in Table 2. We have found that microwave irradiation of 6-8 led to the rearranged products 9, 10 [12] and 11 [14] (as the mixtures of diastereoisomers) with substantial shortening of the reaction times (from 24 h to 5 min) with good yields (Table 2), however, it has shown that in these cases microwave-induced rearrangement had practically no influence on the diastereoselectivity of aza-Claisen rearrangement (Table 2).

Scheme 3. Microwave accelerated Overman rearrangement of the sugar trifluoroacetimidate 13.

Finally, we have investigated Overman rearrangement of the sugar allylic trifluoroacetimidate 13 under microwave irradiation. Trifluoroacetimidate 13 was prepared from the corresponding allylic alcohol 12 derived from d-glucose [19] by reaction with CF₃CN in THF (Scheme 3). Rearrangement of 13 afforded trifluoroacetamide 14 as the mixture of diastereoisomers (de=19%) (Scheme 3). In order to determine the best reaction conditions, a series of the thermally and microwave accelerated rearrangements of imidate 13 was performed. Studies showed that microwave irradiation accelerated of the rearrangement 13→14a,b (24 times) in comparison with conventional thermal conditions (Table 2, entry 4) without any improvement in the stereoselectivity. Extension of the reaction time led to the decomposition of product 14.

Conclusions

In summary, a remarkable acceleration of the Overman rearrangement of allylic trihaloimidates to the corresponding allylic trihaloamides was observed using microwave irradiation conditions. The [3,3]-sigmatropic rearrangement carried out under conventional conditions (reflux temperature of the solvent) required long reaction times and produced moderate yields, usually a result of connected with the decomposition of starting materials. This paper demonstrates the practical usability of microwave acerated thermal Overman rearrangement for the synthesis of various amides.

Experimental

All commercially available reagents were used without further purification and solvents were dried according to standard procedures. Column chromatography was carried out on Silica Gel 60 (Merck,
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0.040-0.063 mm, 230-400 mesh). Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} analytical plates; detection was carried out with either UV (254 nm), or spraying with a solution of phosphomolybdic acid, and with a basic solution of KMnO_{4} with subsequent heating. NMR spectra were recorded at room temperature on a Varian Mercury Plus 400 FT NMR spectrometer (^1H at 400.13 MHz and ^13C at 100.6 MHz), in CDCl3 as the solvent (unless otherwise noted) with tetramethylsilane as internal reference. For those fully assigned ^1H- and ^13C-NMR spectra standard NMR (COSY, DEPT, HMQC) experiments were conducted. Optical rotations were measured with a P3002 Krüss polarimeter in chloroform at 25 °C. All moisture-sensitive reactions were performed under a nitrogen atmosphere. Microwave experiments were conducted using a focused microwave system (CEM Discover). Reactions were performed in a glass vessel (10 mL) sealed with a septum. At the end of the reaction the vessels together with their contents were cooled rapidly using a stream of compressed air. The melting points were determined on the Kofler block and are uncorrected.

General procedure for preparation of trichloroacetimidates

To a solution of allyl alcohol in dry dichloromethane were added 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU, 2 eq) and trichloroacetonitrile (2 eq) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. The insoluble material was removed by filtration and the filtrate was concentrated under reduced pressure to give a residue, which was purified by chromatography on silica gel (cyclohexane-ethyl acetate) to afford corresponding imidates 1a-1d, 6, 7, 8.

O-Allyl-2,2,2-trichloroacetimidate

Allyl alcohol (0.50 g, 8.61 mmol), DBU (2.57 mL, 17.22 mmol), trichloroacetonitrile (1.73 mL, 17.22 mmol) in CH_{2}Cl_{2} (20 mL) afforded after flash chromatography (cyclohexane-ethyl acetate, 10:1) compound 1a (1.56 g, 89.5%) as a colorless oil; ^1H-NMR: δ 4.81 (2H, m, CH_{2}), 5.31 (1H, d, J=10.5 Hz, J=1.3 Hz, CH_{2}=), 5.44 (1H, d, d, J=17.2 Hz, J=3.1 Hz, J=1.5 Hz, CH_{2}=), 6.03 (1H, d, d, J=17.2 Hz, J=10.5 Hz, J=5.4 Hz, CH=), 8.32 (1H, bs, NH); ^13C-NMR: δ 69.6, 109.7, 118.5, 131.4, 162.5; Anal. Calcd. for C_{5}H_{6}Cl_{3}NO (202.47): C 29.66, H 2.99, N 6.91; found C 29.53, H 2.87, N 6.74. The procedure and ^1H-NMR spectroscopic data were previously reported [10]. ^13C-NMR data have not been reported before [10].

O-(But-3-en-2-yl)-2,2,2-trichloroacetimidate (1b): But-3-en-2-ol (0.50 g, 6.93 mmol), DBU (1.45 mL, 9.70 mmol, 1.4 eq), trichloroacetonitrile (1.04 mL, 10.4 mmol, 1.5 eq) in CH_{2}Cl_{2} (25 mL) afforded (1.30 g, 87%) of compound 1b after flash chromatography (cyclohexane-ethyl acetate, 5:1) as a pale yellow oil; ^1H-NMR: δ 1.44 (3H, d, J=6.5 Hz, CH_{3}), 5.20 (1H, d, J=10.6 Hz, H_{4}), 5.36 (1H, d, J=17.3 Hz, H_{4}), 5.49 (1H, m, H_{3}), 5.94 (1H, m, H_{2}), 8.29 (1H, bs, NH); ^13C-NMR: δ 19.4, 75.7, 91.8, 115.9, 136.8, 161.8; Anal. Calcd. for C_{6}H_{8}Cl_{3}NO (216.49): C 29.29, H 3.72, N 6.47; found C 29.30, H 3.45, N 6.28. The procedure and ^1H-NMR spectroscopic data have been previously reported [18]. ^13C-NMR data have not been previously reported [18].

2,2,2-Trichloro-O-(hept-1-en-3-yl)acetimidate (1c): Hept-1-en-3-ol (0.50 g, 4.38 mmol), DBU (1.31 mL, 8.76 mmol), trichloroacetonitrile (0.88 mL, 8.76 mmol) in CH_{2}Cl_{2} (20 mL) afforded after flash
chromatography (cyclohexane-ethyl acetate, 10:1) compound 1c (1.11 g, 98%) as a pale yellow oil; \(^1\)H-NMR: \(\delta 0.90 (3H, t, J=6.9\) Hz, CH\(_3\)), 1.38 (4H, m, 2 \times CH\(_2\)), 1.74 (2H, m, CH\(_2\)), 5.21 (1H, dd, \(J_{2,1}=10.6\) Hz, \(J_{1,1}=0.7\) Hz, H\(_1\)), 5.36 (2H, m, H\(_1\), H\(_3\)), 5.80 (1H, m, H\(_2\)), 8.27 (1H, s, NH); \(^13\)C-NMR: \(\delta 14.2, 22.6, 27.3, 34.0, 79.7, 92.1, 116.8, 135.8, 162.2;\) Anal. Calcd for C\(_9\)H\(_{14}\)Cl\(_3\)NO\(_2\) (258.57): C 41.76, H 5.41, N 5.41; found C 41.65, H 5.21, N 5.33. The procedure and \(^1\)H-NMR spectroscopic data were reported [10]. \(^13\)C-NMR data have not previously been reported [10].

2,2,2-Trichloro-O-(oct-1-en-3-yl)acetimidate (1d): Oct-1-en-3-ol (0.50 g, 3.90 mmol), DBU (1.17 mL, 7.8 mmol) in CH\(_2\)Cl\(_2\) (20 mL) afforded after flash chromatography (cyclohexane-ethyl acetate, 10:1) compound 1d (0.90 g, 85%) as a pale yellow oil; \(^1\)H-NMR: \(\delta 0.88 (3H, t, J=7.1\) Hz, CH\(_3\)), 1.29-1.47 (6H, m, 3 \times CH\(_2\)), 1.65-1.82 (2H, m, CH\(_2\)), 5.30 (2H, m, H\(_1\), H\(_3\)), 5.86 (1H, m, H\(_2\)), 8.26 (1H, bs, NH); \(^13\)C-NMR: \(\delta 14.2, 79.7, 22.7, 24.8, 31.7, 34.3, 92.1, 116.7, 136.0, 162.2;\) Anal. Calcd. for C\(_{10}\)H\(_{16}\)Cl\(_3\)NO (272.60): C 44.06, H 5.91, N 5.14; found C 43.95, H 5.77, N 5.01.

tert-Butyl N-[(3S,4E)-6-(trichloroacetimidoyloxy)hex-4-en-3-yl]carbamate (6): Compound 3 (0.30 g, 1.393 mmol), DBU (0.42 mL, 2.79 mmol) in CH\(_2\)Cl\(_2\) (15 mL) afforded after flash chromatography (cyclohexane-ethyl acetate, 3:1) compound 6 (0.40 g, 80%) as a colorless oil; \(^1\)H-NMR: \(\delta 0.92 (3H, t, J=7.4\) Hz, CH\(_3\)), 1.44 (9H, s, 3 \times CH\(_3\)), 1.53 (2H, m, CH\(_2\)), 4.08 (1H, m, H\(_3\)), 4.44 (1H, bs, NH), 4.77 (2H, m, H\(_6\)), 5.79 (2H, m, H\(_4\), H\(_5\)), 8.29 (1H, bs, NH); \(^13\)C-NMR: \(\delta 10.1, 28.2, 28.4 (3\times), 53.1, 68.9, 79.4, 123.4, 135.8, 155.4, 162.5;\) Anal. Calcd. for C\(_{13}\)H\(_{21}\)Cl\(_3\)N\(_2\)O\(_3\) (359.68): C 43.37, H 5.83, N 7.78; found C 43.01, H 5.64, N 7.64. \(^1\)H- and \(^13\)C-NMR spectroscopic data have not previously been reported [12].

tert-Butyl N-[(3S,4E)-6-(trichloroacetimidoyloxy)-2-methylhex-4-en-3-yl]carbamate (7): Compound 4 (0.10 g, 0.436 mmol), DBU (0.13 mL, 0.87 mmol) in CH\(_2\)Cl\(_2\) (10 mL) afforded after flash chromatography (cyclohexane-ethyl acetate, 3:1) compound 7 (0.12 g, 74%) as white crystals; m.p. 42 – 43°C; \(^1\)H-NMR: \(\delta 0.89 (3H, m, 2 \times CH\(_3\)), 1.78 (1H, m, CH), 4.04 (1H, m, H\(_3\)), 4.52 (1H, m, NH), 4.80 (2H, m, H\(_6\)), 5.79 (2H, m, H\(_4\), H\(_5\)), 8.30 (1H, bs, NH); \(^13\)C-NMR: \(\delta 18.1, 18.7, 28.4 (3\times), 53.1, 68.9, 79.4, 123.4, 134.5, 155.5, 162.4;\) Anal. Calcd. for C\(_{14}\)H\(_{23}\)Cl\(_3\)N\(_2\)O\(_3\) (373.71): C 44.99, H 6.20, N 7.49; found C 44.78, H 6.05, N 7.21. \(^1\)H- and \(^13\)C-NMR spectroscopic data have not previously been reported [12].

O-[(4S,2E)-4-(tert-Butyldimethylsilyloxy)pent-2-enyl]-2,2,2-trichloroacetimidate (8): Compound 5 (0.35 g, 1.62 mmol), DBU (0.48 mL, 3.24 mmol) in CH\(_2\)Cl\(_2\) (18 mL) afforded compound 8 (0.50 g, 85.5%) as a colorless oil; \(^1\)H-NMR: \(\delta 0.05 (3H, s, CH\(_3\)), 0.06 (3H, s, CH\(_3\)), 0.89 (9H, s, 3 \times CH\(_3\)), 1.23 (3H, d, \(J=6.7\) Hz, CH\(_3\)), 4.35 (1H, m, H\(_4\)), 4.77 (2H, m, H\(_1\)), 5.86 (2H, m, H\(_2\), H\(_3\)), 8.28 (1H, bs, NH); \(^13\)C-NMR: \(\delta -4.8, -4.7, 18.3, 24.1, 25.9 (3 \times C), 68.4, 69.1, 121.4, 139.8, 162.5;\) Anal. Calcd. for C\(_{14}\)H\(_{23}\)Cl\(_3\)NO\(_2\)Si (360.78): C 43.28, H 6.71, N 3.88; found C 43.17, H 6.56, N 3.59. The procedure and \(^1\)H-NMR spectroscopic data were reported before [14]. \(^13\)C-NMR data have not previously been reported [14].
General procedure for Overman rearrangement

Conventional method (Procedure A): To a solution of imidates in dry solvent (see Tables 1, 2) was added anhydrous K₂CO₃ (1.1 eq). The reaction mixture was heated (for temperatures see Tables 1, 2). The solvent was evaporated under reduced pressure and chromatography of the residue on the silica gel (cyclohexane-ethyl acetate) afforded corresponding amides 2a-2f, 9-11, 14 (Tables 1, 2). (B1)

Microwave-assisted synthesis (Procedure B): To a solution of the corresponding imidate in o-xylene in a 10 mL glass pressure microwave tube equipped with a magnetic stirrer bar was added anhydrous K₂CO₃ (1.1 eq) and the tube was closed with a silicon septum. The reaction mixture was subjected to microwave irradiation (power: 300W; for temperatures, reaction times and yields see Tables 1, 2). The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (cyclohexane-ethyl acetate) to give amides 2a-2f, 9-11, 14 (Tables 1, 2). (B2)

N-Allyl-2,2,2-trichloroacetamide (2a): Following general procedure A, 1a (0.30 g, 1.48 mmol), K₂CO₃ (0.23 g, 1.63 mmol) in o-xylene (3 mL) afforded after flash chromatography (cyclohexane-ethyl acetate, 10:1) compound 2a (0.195 g, 65%). 2a: white crystals; m.p. 28 - 32 °C (Ref. [10] m.p. 28–31 °C); ¹H-NMR: δ 3.99-4.02 (2H, m, CH₂), 5.24-5.32 (2H, m, CH₂=), 5.84-5.93 (1H, m, CH=), 6.78 (1H, bs, NH); ¹³C-NMR: δ 43.6, 92.5, 117.8, 132.2, 161.8; Anal. Calcd. for C₅H₆Cl₃NO (202.46): C 29.66, H 2.98, N 7.90; found C 29.59, H 2.83, N 7.75. The procedure and ¹H-NMR spectroscopic data were reported [10]. ¹³C-NMR data have not previously been reported [10].

N-[(E)-But-2-enyl]-2,2,2-trichloroacetamide (2b): Following general procedure A, 1b (0.10 g, 0.462 mmol), K₂CO₃ (70.2 mg, 0.508 mmol) in o-xylene (2 mL) afforded after flash chromatography (cyclohexane-ethyl acetate, 10:1) compound 2b (0.093 g, 93%). Following general procedure B, 1b (0.30 g, 1.386 mmol), K₂CO₃ (0.21 g, 1.525 mmol) in o-xylene (5 mL) afforded after flash chromatography (cyclohexane-ethyl acetate, 10:1) compound 2b (0.18 g, 60%). 2b: white crystals; m.p. 27 - 29 °C (Ref. [10] m.p. 28 – 29 °C); ¹H-NMR: δ 1.72 (3H, d, J=6.5 Hz, CH₃), 3.91 (2H, m, CH₂), 5.50 (1H, m, CH=), 5.74 (1H, m, CH=), 6.68 (1H, bs, NH); ¹³C-NMR: δ 17.7, 43.3, 109.7, 124.8, 130.3, 161.6; Anal. Calcd. for C₆H₈Cl₃NO (216.49): C 33.26, H 3.72, N 6.47; found C 33.14, H 3.55, N 6.38. The procedure, ¹H-NMR and ¹³C-NMR data spectroscopic data have been reported [18].

2,2,2-Trichloro-N-[(E)-hept-2-enyl]acetamide (2c): Following general procedure A, 1c (0.20 g, 0.773 mmol), K₂CO₃ (0.117 g, 0.85 mmol) in o-xylene (2 mL) afforded after flash chromatography (cyclohexane-ethyl acetate, 10:1) compound 2c (0.18 g, 90%). Following general procedure B, 1c (0.40 g, 1.55 mmol), K₂CO₃ (0.236 g, 1.71 mmol) in o-xylene (4 mL) afforded after flash chromatography (cyclohexane-ethyl acetate, 10:1) compound 2c (0.30 g, 75%). 2c: a colorless oil; ¹H-NMR: δ 0.90 (3H, t, J=7.1 Hz, CH₃), 1.28-1.39 (4H, m, 2 x CH₂), 2.02-2.07 (2H, m, CH₂), 3.92 (2H, m, CH₂), 5.44-5.51 (1H, m, CH=), 5.68-5.76 (1H, m, CH=), 6.67 (1H, bs, NH); ¹³C-NMR: δ 14.1, 22.4, 31.3, 32.1, 43.6, 92.8, 123.7, 135.9, 161.8; Anal. Calcd. for C₉H₁₄Cl₃NO₂ (258.57): C 41.77, H 5.45, N 5.41; found C 41.63, H 5.24, N 5.35. The procedure and ¹H-NMR spectroscopic data were reported before [10]. ¹³C-NMR data have not previously been reported [10].


**(E)-2,2,2-Trichloro-(oct-2-enyl)acetamide (2d):** Following general procedure A, 1d (0.40 g, 1.47 mmol), K₂CO₃ (0.224 g, 1.62 mmol) in *o*-xylene (4 mL) afforded after flash chromatography (cyclohexane-ethyl acetate, 10:1) compound 2d (0.37 g, 92.5%). Following general procedure B, 1d (0.40 g, 1.47 mmol), K₂CO₃ (0.224 g, 1.62 mmol) in *o*-xylene (4 mL) afforded after flash chromatography (cyclohexane-ethyl acetate, 10:1) compound 2d (0.39 g, 97.5%).

2d: a colorless oil; 

1H-NMR: δ 0.87 (3H, t, *J* = 7.0 Hz, CH₃), 1.26-1.40 (6H, m, 3 x CH₂), 2.04 (2H, q, *J* = 7.0 Hz, CH₂), 3.93 (2H, t, *J* = 5.9 Hz, CH₂), 5.46 (1H, m, CH=), 5.73 (1H, m, CH=), 6.69 (1H, bs, NH); 13C-NMR: δ 14.6, 22.7, 28.8, 31.6, 32.4, 43.5, 92.8, 123.6, 135.8, 161.7; Anal. Calcd. for C₁₀H₁₆Cl₃NO (272.60): C 44.02, H 5.92, N 5.13; found C 43.90, H 5.84, N 5.04.

2,2,2-Trichloro-N-(2-methylbut-3-en-2-yl)acetamide (2e): Following general procedure A, 1e (0.3 g, 1.30 mmol), K₂CO₃ (0.198 g, 1.43 mmol) in *o*-xylene (3 mL) afforded after flash chromatography (cyclohexane-ethyl acetate, 10:1) compound 2e (0.25 g, 83%). Following general procedure B, 1e (0.5 g, 2.17 mmol), K₂CO₃ (0.33 g, 2.39 mmol) in *o*-xylene (5 mL) afforded after flash chromatography (cyclohexane-ethyl acetate, 10:1) compound 2e (0.40 g, 80%).

2e: white crystals; m.p. 48 – 50 °C (Ref. [11] m.p. 49 – 50 °C); 1H-NMR: δ 1.54 (6H, s, 2 x CH₃), 5.17 (2H, m, H₄), 6.00 (1H, m, H₃), 6.59 (1H, bs, NH); 13C-NMR: δ 26.5 (2 x C), 56.1, 93.4, 113.3, 142.1, 160.4; Anal. Calcd. for C₇H₁₀Cl₃NO (230.52): C 36.43, H 4.32, N 6.07, found C 36.30, H 4.11, N 5.98. The 1H-NMR spectrum was previously reported [11].

2,2,2-Trichloro-N-[(E)-pent-3-en-2-yl]acetamide (2f): Following general procedure A, 1f (0.10 g, 0.434 mmol), K₂CO₃ (66 mg, 0.48 mmol) in *o*-xylene (2 mL) afforded after flash chromatography (cyclohexane-ethyl acetate, 10:1) compound 2f (75 mg, 75%). Following general procedure B, 1f (66 mg, 0.26 mmol), K₂CO₃ (43.5 mg, 0.315 mmol) in *o*-xylene (1 mL) afforded after flash chromatography (cyclohexane-ethyl acetate, 10:1) compound 2f (46 mg, 70%).

2f: white crystals; m.p. 57 – 59 °C (Ref. [20] m.p. 60 °C); 1H-NMR (DMSO [20]): δ 1.31 (3H, d, *J* = 6.8 Hz, CH₃), 1.71 (3H, m, CH₃), 4.43-4.50 (1H, m, H₂), 5.43-5.49 (1H, m, CH=), 5.65-5.75 (1H, m, CH=), 6.52 (1H, bs, NH); 13C-NMR (DMSO [20]): δ 17.9, 20.4, 49.0, 93.0, 127.6, 130.76, 161.03; Anal. Calcd. for C₇H₁₀Cl₃NO (230.52): C 36.44, H 4.37, N 6.07, found C 36.35, H 4.21, N 5.97.

*Methyl (Z)-2,3,4-tri-O-benzyl-6,7-dideoxy-8-(trifluoroacetimidyloxy)-α-D-gluco-oct-6-enpyranoside (13):* To a suspension of NaH (0.09 g, 2.244 mmol, 60% dispersion in mineral oil, freed of oil with anhydrous THF) in dry THF (3 mL) was added allylic alcohol 12 (1.0 g, 2.04 mmol) in dry THF (5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and then treated with gaseous trifluoroacetonitrile (15 g, 0.158 mol, prepared *in situ* by heating trifluoroacetamide (4.57 g, 0.040 mol) and P₂O₅ (11.43 g, 0.012 mol) for 2 h at 150 °C). The solid was removed by filtration and solvent evaporated under reduced pressure. The residue was purified by chromatography on silica gel (hexane-ethyl acetate, 3:1) to afford 0.95 g (79.5%) of compound 13 as a pale yellow oil; 1H-NMR: δ 3.27 (1H, dd, *J*₃,₄=9.6 Hz, J₄,₅=9.1 Hz, H₄), 3.40 (3H, s, OCH₃), 3.52 (1H, dd, *J*₂,₃=9.7 Hz, J₂,₁=3.6 Hz, H₂), 3.99 (1H, dd, *J*₃,₂=9.7 Hz, J₄,₃=9.6 Hz, H₃), 4.45 (1H, ddd, *J*₅,₄=9.1 Hz, J₆,₅=9.0 Hz, *J*₇,₅=1.0, H₅), 4.57 (1H, d, *J*=10.8 Hz, CH₂Ph), 4.57 (1H, d, *J*₂,₁=3.6 Hz, H₁), 4.67 (1H, d, *J*=12.1 Hz, CH₂Ph), 4.70 (1H, ddd, *J*₉,₈=11.9 Hz, J₈,₇=5.4 Hz, *J*₈,₆=1.4 Hz, H₈), 4.79 (1H, d, *J*=10.6 Hz, CH₂Ph), 4.80 (1H, d, *J*=12.1 Hz,
MCH2Ph), 4.82 (1H, J = 10.6 Hz, CH2Ph), 4.96 (1H, J = 10.8 Hz, CH2Ph), 5.01 (1H, dd, J8,8 = 11.9 Hz, J8,7 = 7.4 Hz, J8,6 = 1.4 Hz, JH8), 5.61 (1H, dddd, J7,6 = 11.2 Hz, J6,5 = 9.0 Hz, J8,6 = 1.4 Hz, JH6), 5.81 (1H, dddd, J7,6 = 11.2 Hz, J8,7 = 7.4 Hz, J8,6 = 5.4 Hz, JH7), 5.72-7.37 (15H, m, Ph), 7.22-7.37 (15H, m, Ph), 8.20 (1H, bs, NH); 13C-NMR: δ 55.5, 62.0, 66.8, 73.4, 75.3, 75.8, 79.8, 81.6, 81.9, 98.2, 127.6, 127.7, 127.7, 127.8, 127.9, 128.0, 128.1, 128.3, 128.4, 128.5, 131.2, 138.0, 138.1, 138.6, 157.3, 157.7; Anal. Calcd. for C32H34F3NO6 (585.63): C 65.63, H 5.85, N 2.39; found C 65.59, H 5.80, N 2.31.

Methyl 2,3,4-tri-O-benzyl-6-[(trifluoroacetyl)amino]-7,8-dideoxy-D-glycero-α-D-galacto-oct-7-enpyranoside 14a, Methyl 2,3,4-tri-O-benzyl-6-[(trifluoroacetyl)amino]-7,8-dideoxy-L-glycero-α-D-galacto-oct-7-enpyranoside 14b: Following general procedure A, 13 (0.25 g, 0.43 mmol), K2CO3 (65.4 mg, 0.47 mmol) in o-xylene (2 mL) afforded after flash chromatography (hexane-ethyl acetate, 9:1) compounds 14a and 14b (0.08 g, 32%, see Table 4). Following general procedure B, 13 (0.10 g, 0.171 mmol), K2CO3 (26 mg, 0.188 mmol) in o-xylene (2 mL) afforded after flash chromatography (hexane-ethyl acetate, 15:1) compounds 14a and 14b (0.07 g, 70%, see Table 2).

14a: a colorless oil; [α]D25 = -19.6 (c 0.23); 1H-NMR: δ 3.30 (1H, dd, J5,4 = 10.0 Hz, J4,3 = 9.2 Hz, H5), 3.33 (3H, s, OCH3), 3.49 (1H, dd, J3,2 = 9.3 Hz, J2,1 = 3.6 Hz, H3), 3.76 (1H, dd, J5,4 = 10.0 Hz, J6,5 = 1.4 Hz, H5), 4.01 (1H, dd, J3,2 = 9.3 Hz, J4,3 = 9.2 Hz, H4), 4.01 (1H, d, J = 10.1 Hz, CH2Ph), 4.50 (1H, d, J = 10.7 Hz, CH2Ph), 4.56 (1H, d, J = 12.1 Hz, CH2Ph), 4.82 (1H, d, J = 12.1 Hz, CH2Ph), 4.84 (1H, d, J = 10.7 Hz, CH2Ph), 4.90 (1H, d, J = 10.1 Hz, CH2Ph), 4.97 (1H, ddd, J6,6 = 9.4 Hz, J7,6 = 5.4 Hz, JH7), 5.01 (1H, d, J = 10.7 Hz, CH2Ph), 5.01 (1H, dd, J8,7 = 10.3 Hz, J8,6 = 5.4 Hz, H7), 6.17 (1H, d, J = 9.0 Hz, NH), 7.27-7.39 (15H, m, Ph); 13C-NMR: δ 50.8, 55.4, 71.0, 127.8, 2x128.0, 4x128.1, 2x128.4, 2x128.5, 4x128.6, 133.8, 137.9, 137.9, 138.2, 156.6, 157.0; Anal. Calcd. for C32H34F3NO6 (585.63): C 65.63, H 5.85, N 2.39; found C 65.56, H 5.79, N 2.32.

14b: a colorless oil; [α]D25 = +30.5 (c 0.19); 1H-NMR: δ 3.35 (3H, s, OCH3), 3.41 (1H, dd, J5,4 = 10.0 Hz, J4,3 = 9.2 Hz, H4), 3.48 (1H, dd, J3,2 = 9.3 Hz, J2,1 = 3.6 Hz, H3), 3.81 (1H, dd, J5,4 = 10.0 Hz, J6,5 = 2.7 Hz, H5), 4.01 (1H, dd, J3,2 = 9.3 Hz, J4,3 = 9.2 Hz, H4), 4.57 (1H, d, J = 3.5 Hz, H1), 4.61 (1H, d, J = 11.1 Hz, CH2Ph), 4.65 (1H, d, J = 12.1 Hz, CH2Ph), 4.78 (1H, d, J = 11.1 Hz, CH2Ph), 4.81 (1H, d, J = 12.1 Hz, CH2Ph), 4.89 (1H, dd, J6,5 = 9.0 Hz, J6,6 = 8.2 Hz, J7,6 = 8.2 Hz, H5), 4.93 (1H, d, J = 10.8 Hz, CH2Ph), 4.99 (1H, d, J = 10.8 Hz, CH2Ph), 5.25 (1H, dd, J8,7 = 17.1 Hz, J8,6 = 10.0 Hz, H8,7), 5.29 (1H, dd, J8,7 = 10.3 Hz, J8,6 = 10.0 Hz, H8), 5.71 (1H, d, J = 17.1 Hz, J8,7 = 10.3 Hz, J8,6 = 8.2 Hz, H7), 6.70 (1H, d, J = 9.0 Hz, NH), 7.27-7.39 (15H, m, Ph); 13C-NMR: δ 52.4, 55.5, 71.6, 73.8, 74.7, 76.0, 77.8, 80.1, 82.1, 98.5, 121.4, 2x127.8, 128.0, 128.1, 2x128.2, 3x128.3, 2x128.7, 4x128.8, 131.1, 2x138.1, 138.6, 156.3, 156.7; Anal. Calcd. for C32H34F3NO6 (585.63): C 65.63, H 5.85, N 2.39; found C 65.53, H 5.76, N 2.45
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*Sample Availability:* Samples of compounds 2d, 14a,b are available from the authors.

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