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Regioselective green anomeric deacetylation catalyzed by lanthanide triflates

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Abstract

Lanthanide triflates, especially $Nd(OTf)_3$, efficiently catalyze the regioselective transesterification of anomeric acetates. This method offers an efficient solution for the otherwise difficult removal of methyl uronates anomeric acetates as well as a green alternative to published protocols since the lanthanide catalysts are non-toxic and may be easily recycled and reused.

Keywords: Anomeric deacetylation; Lanthanide triflates; Methyl uronates; Transesterification

Selective anomeric deacetylation is often a key step in oligosaccharide synthesis commonly used for the preparation of anomeric trichloroacetimidate, one of the most used glycosyl donor.[1] A great number of reagents are reported to perform this transformation. Most of them involve selective transamidation using nitrogenous nucleophiles such as benzylamine,[2] hydrazine,[3] and piperidine.[4] Alternative protocols involve transesterification catalyzed by organic tin oxides,[5] solvolysis promoted by tin tetrachloride[6] or conversion to an anomeric halogenide using HBr followed by hydrolysis using silver salts.[7] All these methods use stoichiometric amounts of reagents that are often toxic. Moreover, when applied to compound **1** (an important synthon involved in the synthesis of heparan sulfate fragments),[8] none gave neither satisfactory nor reproducible results. Indeed, conversion to the anomeric bromide with $TiBr_4$[9] followed by hydrolysis using mercuric salts[10] gave high yields on small scales but led to unreproducible yields on larger ones. Transamidation with piperidine proved to be the most reliable method giving the desired compound **2** in reproducible but unsatisfactory 60% yield. Such a low conversion and the more dramatic problems encountered with other nitrogen nucleophiles, may be due to side reactions on the methoxycarbonyl group of **1**. We reasoned that such unwanted transamidation could be avoided by using an acid transesterification. In this regard, HCl in MeOH is known to allow selective hydrolysis of acetate groups in the presence of benzoates,[11] however, we doubted that such reagent could allow the regioselective transesterification of anomeric acetates without competitive formation of methyl glycoside.

Lanthanide triflate $Lx(OTf)_3$ is used as mild Lewis acid in many organic transformations[12] and selective deprotection of the bidentate methoxyacetyl group in the presence of other monodentate ester groups has been achieved by transesterification in MeOH using $Yb(OTf)_3$ as a catalyst.[13] We thus wondered whether $Lx(OTf)_3$ salts could catalyze the regioselective deacetylation of anomeric acetates especially on uronic derivatives.

In view of its importance in ongoing work in our laboratory,[14] methyl-1,2,3-tri-*O*-acetyl-3-*O*-benzyl-β-L-idopyranuronate **1** was selected as a model to screen the efficiency of different lanthanide triflates to catalyze the regioselective transesterification of anomeric acetates with MeOH (Scheme 1). Compound **1** was, thus, treated in MeOH with 5 mol % $Yb(OTf)_3$, $Eu(OTf)_3$, $Sm(OTf)_3$ or $Nd(OTf)_3$. The

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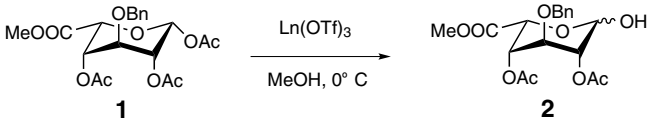


Scheme 1. Regioselective deacetylation of compound **1**.

reactions, followed by TLC led to the exclusive or highly selective formation of a product identified as the hemiacetal **2**. Isolated yields (Table 1) were determined after purification by simple extraction followed by flash chromatography, and showed that quasi-quantitative yields were obtained with Nd^{3+} and Sm^{3+} triflates, while Eu^{3+} and Yb^{3+} salts gave, respectively, 85 and 75% isolated yields.

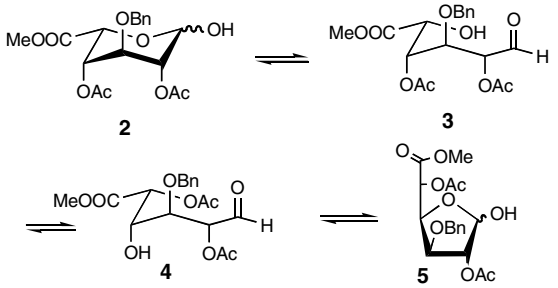
To our surprise, the lower yields obtained with $Yb(OTf)_3$ and $Eu(OTf)_3$ were not due to a diminished regioselectivity, a lower conversion or an over-deacetylation, but to the rearrangement of the pyranosyl derivative **2** into the furanosyl isomer **5**, whose structure was unambiguously established by NMR (COSY and ^{1}H–^{13}C HSQC).[15] Since methyl 1,2,5-tri-*O*-acetyl-3-*O*-benzyl-α,β-L-idofuranonate has already been characterized,[9] a small amount of **5** was acetylated. The ^{1}H and ^{13}C NMR data of the result product were identical to those already published. As shown in Scheme 2, we propose that the isomerisation of compound **2** into the furano derivative **5** proceeds via a migration of an acetyl group between position 4 and position 5 in the open form of these hemiacetals. It seems thus that Yb^{3+} and Eu^{3+} are better catalysts than Sm^{3+} or Nd^{3+} in promoting such acetyl migration leading to a greater amount of furanosyl compound **5**. Therefore, it may be proposed that the higher yields obtained with Sm^{3+} and Nd^{3+} are due to their lower ability to catalyze the unwanted isomerisation of pyranose **2** into furanose **5**. A preparative reaction was then carried on 11 mmol (4.7 g) of compound **1** using $Nd(OTf)_3$ and gave **2** in 90% yield.[16] The treatment of the reaction is very simple and the catalyst may be easily recycled from the aqueous phase and reused, after evaporation of the water, at least 3 times without loss of activity.

Having found an effective protocol for the preparation of compound **2**, we wondered whether other methyl uronates could also be regioselectively deacetylated using Nd^{3+} catalyzed transesterification. So, methyl 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranuronate **6**[17] and methyl

Table 1
Yields obtained for the anomeric deacetylation of compound **1** depending on the lanthanide catalyst used

Lanthanide	Reaction time[a] (min)	Yields[b] (%)
$Yb(OTf)_3$	180	70
$Eu(OTf)_3$	90	85
$Sm(OTf)_3$	90	92
$Nd(OTf)_3$	90	95

[a] Reactions were carried out in anhydr MeOH (2.4 mL) containing (50 mg, 0.11 mmol) and 5 mol % $Lx(OTf)_3$ at 0 °C.
[b] Isolated yields after purification.

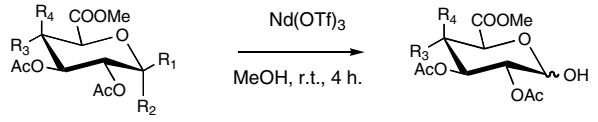


Scheme 2. Proposed mechanism for the in situ formation of **5**.

1,2,3,4-tetra-*O*-acetyl-α-D-galactopyranuronate **7** [18] were treated in the conditions used for compound **1**, without further optimisation of the reaction conditions (Scheme 3). Hemiacetals **8** and **9** were obtained in respective 88% and 75% isolated yields, showing the efficiency of the method on other methyl uronates than **1**. Such results are similar to the one obtained when Bu_2SnO or Bu_3SnOMe are used as catalyst.[5] However, it is worth noting that, in this later case, stoichiometric amounts of tin derivatives were used and not recycled, whereas, in our case, 5 mol % of recyclable and environmentally friendly[12] $Nd(OTf)_3$ was sufficient.

To test whether the electronic effect of the carboxymethyl group in the uronate substrates has an impact on the regioselectivity of the reaction, 1,2,3,4-tetra-*O*-acetyl-β-D-xylopyranose **10** was used as the next substrate (Scheme 4). As for compound **1**, a set of $Lx(OTf)_3$ salts were screened to test their efficiency in the anomeric deacetylation reaction. No major difference between them was detected since 80–85% isolated yields of **14** were obtained irrespective of the catalyst used (Table 2). Thus, as expected, the presence of a carboxymethyl group in position 5 of a peracetylated sugar is not a prerequisite to the regioselectivity and efficiency of $Lx(OTf)_3$ mediated anomeric deacetylation.

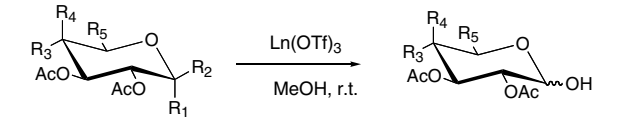
To test further the scope and limitations of our method, we checked if the regioselectivity of the $Lx(OTf)_3$ catalyzed reaction was maintained with sugars containing an acetyl group in a primary position. Peracetylated sugars **11** and **12** were, thus, used as next substrates in the deacetylation reaction (Scheme 4). Once more and in each case, the selectivity for the anomeric acetate was maintained whatever the salt used and good to excellent yields were obtained in both cases. It should be noted that in these cases too, $Nd(OTf)_3$ gave better isolated yields (Table 2). When α-D-glucose pentaacetate **13** was used as substrate, lower isolated yields between 62% and 68% were obtained. Such



6. R_1=OAc, R_2=H, R_3=OAc, R_4=H
7. R_1=H, R_2=OAc, R_3=H, R_4=OAc

8. R_3= OAc, R_4=H
9. R_3= H, R_4=OAc

Scheme 3. Efficient anomeric deacetylation of methyl uronates.



10. R_1 =H, R_2 =OAc, R_3=OAc, R_4 =H,R_5=H
11. R_1 = H, R_2= OAc, R_3=H, R_4=OAc, R_5=CH_2OAc
12. R_1 = H, R_2= OAc, R_3=OAc, R_4=H, R_5=CH_2OAc
13. R_1 = OAc, R_2= H, R_3=OAc, R_4=H, R_5=CH_2OAc

14. R_3 =OAc, R_4 = H, R_5=H
15. R_3 = H, R_4 =OAc, R_5=CH_2OAc
16. R_3= OAc, R_4=H, R_5=CH_2OAc

Scheme 4. A general method for anomeric deacetylation.

Table 2
Yields obtained for anomeric deacetylation depending on the lanthanide catalyst used

Starting material	Products	$Yb(OTf)_3$	$Eu(OTf)_3$	$Sm(OTf)_3$	$Nd(OTf)_3$
10	**14**	85	81	85	81
11	**15**	68	78	82	82
12	**16**	61	62	79	81
13	**16**	67	62	67	68

Reactions were carried out in anhydr MeOH (6 mL) containing starting materials (100 mg) and 5 mol % $Lx(OTf)_3$ at rt. Yields were obtained after purification.

a lower reactivity of α acetates has been previously observed in transesterification promoted by tin oxides.[5]

We have, thus, developed an effective method to selectively deacetylate the anomeric position of carbohydrates. This method, using lanthanide triflate catalyzed transesterification, is especially valuable when working with uronic acids methyl esters for whom more classical methods are inefficient. Different $Lx(OTf)_3$ salts were tested and Nd^{3+} gave better yields in most of the cases and thus seems to be the best catalyst for this reaction. Most importantly, this approach is a green alternative to previously described procedures, thanks to the low toxicity of lanthanide salts, the possibility of recycling the catalyst and the easy and highly tolerant experimental procedure.

Acknowledgements

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15. Compound **5** α/β: ^{1}H NMR (360 MHz, $CDCl_3$): δ 5.68 (dd, 1H, $J_{1,2}$ 4.5 Hz, $J_{1,OH}$ 6.0 Hz, H-1β), 5.60 (d, 0.5H, $J_{4,5}$ 6.5 Hz, H-5α), 5.39 (d, 1H, $J_{4,5}$ 3.0 Hz, H-5β), 5.28 (d, 1H, $J_{1,OH}$ 10.0 Hz, H-1α), 5.21 (d, 0.5H, $J_{2,3}$ 1.0 Hz, H-2α), 5.08 (dd, 1H, $J_{2,3}$ 7.0 Hz, H-2β), 4.79 (dd, 10H, $J_{3,4}$ 7.0 Hz, H-4β), 4.73 (d, 0.5H, J_{gem} 11.0 Hz, Ph–CH), 4.67 (d, 1H, J_{gem} 12.0 Hz, Ph–CH), 4.66 (dd, 0.5H, $J_{3,4}$ 6.0 Hz, H-4α), 4.59 (d, 1H, J_{gem} 12.0 Hz, Ph–CH), 4.55 (d, 0.5H, J_{gem} 11.0 Hz, Ph–CH), 4.51 (t, 1H, H-3β), 4.19 (br d, 0.5H, H-3α), 3.74 (s, 3H, $COOCH_3$), 3.66 (s, 1.8H, $COOCH_3$), 3.53 (d, 0.5H, OHα), 3.10 (d, 1H, OHβ), 2.18 (s, 3H, $OCOCH_3$), 2.13 (s, 3H, $OCOCH_3$), 2.11 (s, 3H, $OCOCH_3$). ^{13}C NMR (90 MHz, $CDCl_3$): δ 1 1.2 (C-1α), 94.2 (C-1β), 80.7 (C-3α), 80.0 (C-4α), 79.2 (C-3β), 79.0 (C-2α), 77.2 (C-2β), 75.6 (C-4β), 73.3 (CH_2), 73.0 (CH_2), 70,6 (C-5α, C-5β), 53.0 ($COOCH_3$), 52.5 ($COOCH_3$), 20.8 ($OCOCH_3$), 20.7 ($OCOCH_3$), 20.6 ($OCOCH_3$). $C_{18}H_{22}O_9$ (MW = 382.1): calcd C 56.54, H 5.80; found C 56.22, H 6.04. ESI-MS calcd for $C_{18}H_{22}NaO_9$ $[M+Na]^+$ $m/z = 405.1$; found 405.1.
16. Crystalline methyl-1,2,4-tri-*O*-acetyl-3-*O*-benzyl-β-L-idopyranuronate (**1**) (4.7 g, 11 mmol) was dissolved in MeOH (225 mL) at 0 °C, then 5 mol % $Nd(OTf)_3$ (0.332 g, 0.56 mmol) were added to the mixture. After stirring for 1 h at 0 °C, the reaction was stopped. Water (300 mL) was added and the compound was extracted with CH_2Cl_2 (3 × 200 mL). The organic phase was evaporated and the residue was purified by column chromatography using a toluene: EtOAc gradient (8:2–7:3) to give **1** (3.75 g, 1.7 mmol, 90%). Compound **2** α/β: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.4–7.3 (m, 8H, Ph), 5.33 (br d, 1H, $J_{1,OH}$ 6.0 Hz, H-1α), 5.22 (m, 1H, H-2α), 5.2 (br s, 0.6H, H-1β), 5.16 (m, 0.6H, H-2β), 5.02 (d, 1H, $J_{4,5}$ 2.0 Hz, H-5α), 4.90 (m, 0.6H, H-4β), 4.83 (m, 1H, H-4α), 4.82 (d, 1H, Ph–CHα), 4.78 (d, 1H, Ph–CHα), 4.76 (s, 1.2H, Ph–CH_2β), 4.72 (d, 0.6H, $J_{4,5}$ 2 Hz, H-5β), 4.28 (d, 1H, $J_{1,OH}$ 9.0 Hz, OH-α), 4.2 (t, 0.6H, $J_{2,3} = J_{3,4}$ 3 Hz, H-3β), 3.98 (m, 1H, H-3α), 3.81 (s, 3H, $COOCH_3$), 3.79 (s, 1.8H, $COOCH_3$), 2.2–2 (4s, 9.6H, Ac). ^{13}C NMR (90 MHz, $CDCl_3$): δ 170.3–169.0 (C=O), 128.9–128.0 (Ph), 93.2 (C-1α), 92.1 (C-1β), 73.7 (CH_2), 73.3 (CH_2), 72.9 (C-3β, C-5β), 72.0 (C-3α), 68.3 (C-4β), 67.2 (C-2α, C-2β), 66.8 (C-4α), 65.85 (C-5α), 52.8 ($COOCH_3$), 21.0 ($OCOCH_3$), 20.8 ($OCOCH_3$).
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