C-Sialylation

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Anomeric Acetates of *N*-Acetylneuraminic Acid are Useful *C*-Sialyl Donors in Samarium-Mediated Reformatsky Coupling Reactions**

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N-Acetylneuraminic acid (Neu5Ac) occurs in a wide range of biologically important glycoconjugates, mostly at the terminal position of oligosaccharides attached to proteins or lipids.[1,2] It is involved in a large number of intercellular events,[2] and molecular tools containing this important motif are needed to devise reagents or probes for biological studies and applications. The α-glycosidic bond of these terminal sialyl residues is, however, fragile in vitro under very mild acidic conditions, and it is cleaved by neuraminidases in vivo. The replacement of the interglycosidic oxygen atom with a carbon atom provides C-linked analogues that are stable towards hydrolysis, as required for various applications such as Neu5Ac-containing antiviral drugs or vaccines.

We have previously established a rapid and stereoselective assembly of C-glycosides through a samarium diiodide[3] promoted Barbier reaction with glycosyl 2-pyridylsulfones without an additive.[4,5] Linhardt and co-workers showed that the procedure worked equally well with **3**, the anomeric 2-pyridylsulfone of Neu5Ac (Scheme 1),[6] as well as with the chlorides (such as **4**) and phenylsulfones of Neu5Ac and other 2-ulosonic esters.[7]

We have also reported that **2**, the anomeric 2-pyridylsulfide *N*-acetyl neuraminic acid derivative, is a useful anionic precursor in a high-yielding samarium-mediated Reformatsky approach for stereoselective α-C-sialylation.[8] All these precursors of the *N*-acetylneuraminyl–samarium(III) species are, in fact, derived from the anomeric acetates **1**. In an effort to simplify further the synthetic sequence, we report herein that these standard peracetylated intermediates, prepared 40 years ago by Kuhn and co-workers,[9] are practical *C*-sialyl donors in samarium-mediated Reformatsky coupling reactions with carbonyl compounds. The possibility of this approach was suggested by the well-documented α-deoxygenation of esters[10] and acetylated carbohydrate lactones[11] with samarium diiodide. This procedure was further devel-

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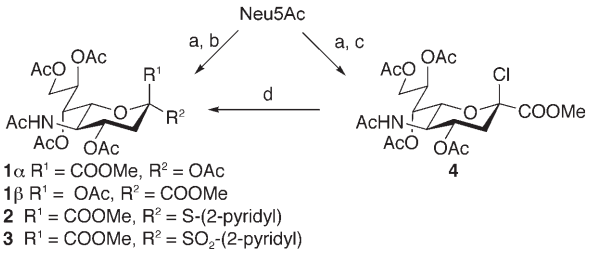
oped by Enholm and co-workers for α-deoxygenation/carbonyl-addition reactions of benzoylated lactones.[12] In an application with O-acetylated 2-ulosonates, Hanessian and Girard have also described an efficient and easy anomeric deoxygenation procedure by using SmI_2.[13] For the success of all of these reactions, additives were needed (namely, hexamethylphosphoramide (HMPA)[10–12] or ethylene glycol[13]).

Standard methyl ester formation and peracetylation of Neu5Ac with acetic anhydride/pyridine provided peracetates **1** as an α/β mixture of ≈1:4 (83% from Neu5Ac; Scheme 1).[9]



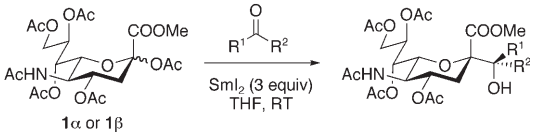
Scheme 1. Synthesis of the Neu5Ac derivatives **1**. a) MeOH, Dowex H^+, room temperature, 24 h; b) Ac_2O, pyridine, room temperature, overnight; 83% from Neu5Ac; c) HCl_g, AcOH/AcCl (1:1), room temperature; d) CsOAc (1.5 equiv), MeCN, room temperature, 74% from Neu5Ac.

The anomers were easily separated by column chromatography to allow the examination of their individual behaviors in the reductive process. For these preliminary studies, larger amounts of the minor isomer **1α** were more conveniently obtained by cesium acetate treatment of chloride **4**, as described earlier (74% yield from Neu5Ac).[14,15]

Separate treatment of a solution of acetate **1α** or **1β** in the presence of cyclopentanone in THF at 20°C with a *freshly* prepared THF solution of SmI_2[16] gave the *C*-sialyl derivative **5**, with yields of 97% and 82%, respectively (Table 1, entries 1 and 2). In these experiments, reactions occurred at room temperature in the absence of any additive. However, the time needed for the reduction depended on the anomeric configuration of **1**. The equatorial acetate in **1α** reacted in about 20 min, whereas the reaction needed about 2 h to go to completion with the axial acetate in **1β**. As was expected and in agreement with our previously published results, coupling reactions with a symmetric ketone like cyclopentanone gave **5** as a single diastereomer, with an equatorial orientation of the new C–C bond (see below). Coupling with 4-*tert*-butylcyclohexanone proceeded with equal efficiency (yields of 91% and 83%; Table 1, entries 3 and 4).

Cyclohexanecarbaldehyde (2 equiv) was also a good substrate and provided the coupling products **8** in 87% and 83% yield (Table 1, entries 7 and 8). The coupling products both displayed a standard $_5C^2$-chair conformation as determined by ^1H NMR analysis ($J_{3ax,4}$, $J_{4,5}$, and $J_{5,6}$ values of 10.2, 11.8, and 10.5 Hz for one isomer and of 12.0, 10.5, and 10.5 Hz for the other). The expected equatorial orientation of the newly formed C–C bond at the quaternary center was indicated by the large values of $^3J_{C1,H3ax}$.[17] The rate of the acetate reduction was however too slow for coupling with an acyclic ketone such as 3-pentanone or an aliphatic aldehyde such as *n*-octanal; these provided the respective coupling products with much lower efficiency (**7**: 44 and 26% yield; Table 1, entries 5 and 6; **9**: 39 and 33% yield; Table 1, entries 9 and 10). In these reactions, reduction of the carbonyl compound became the major competing pathway.

Table 1: Samarium-induced coupling of acetates **1** with carbonyl compounds.



Entry	Acetate	Carbonyl partner (reaction time)	Product: yield[a] (isomer ratio)
1	**1α**	cyclopentanone (0.3 h)	**5**: 97%
2	**1β**	cyclopentanone (2 h)	**5**: 82%
3	**1α**	4-*tert*-butylcyclohexanone (0.3 h)	**6**: 91%
4	**1β**	4-*tert*-butylcyclohexanone (2 h)	**6**: 83%
5	**1α**	3-pentanone (0.3 h)	**7**: 44%[b]
6	**1β**	3-pentanone (2 h)	**7**: 26%[b]
7	**1α**	cyclohexanecarbaldehyde (0.3 h)	**8**: 87% (1.25:1)
8	**1β**	cyclohexanecarbaldehyde (2 h)	**8**: 83% (1.25:1)
9	**1α**	*n*-octanal (0.3 h)	**9**: 39%[b]
10	**1β**	*n*-octanal (2 h)	**9**: 33% (1:1)[b]

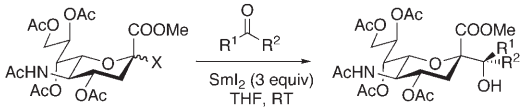
[a] Yields for isolated products after chromatography on silica gel. [b] Together with reduction product **36** (40–44%; $R^1 = H$, see Scheme 5).

With these preliminary results on the separate anomers **1**, we proceeded to investigate the use of the more practical **1α,β** synthetic mixture. Some results obtained for the reductive coupling with the anomeric 2-pyridylsulfide **2**[8] are also reported for comparison (Table 2, Scheme 2).

The SmI_2 treatment of **1α,β** with the same cyclic carbonyl compounds provided results essentially identical to those obtained with the separate anomers in a 2-hour reaction (entries 3 and 4 in Table 1 and entry 3 in Table 2). Under identical conditions, sulfide **2** also provided similar results, although in a very fast reaction, as observed earlier (reduction time <1 min; Table 2, entries 2 and 4). Cyclobutanone was also a good substrate for this reaction and provided the *C*-sialyl compound **11** (88 and 96%; Table 2, entries 5 and 6). Coupling of **1α,β** with 1,4-cyclohexanedione (1.4 equiv) provided 30% of the mono-*C*-sialyl product **12** (Table 2, entry 7), whereas sulfide **2** furnished an 89% yield of the same compound (Table 2, entry 8). Sulfide **2** also provided the bis-*C*-sialyl product **13** in a very high yield (98%) when a limiting amount of the diketone was used (0.45 equiv; Table 2, entry 9). Good coupling yields were obtained with cyclohexanecarbaldehyde (75 and 90%; Table 2, entries 10 and 11).

As noticed above with the separate acetates and *n*-octanal, coupling of **1α,β** with aldehyde **14** was not practical (26% yield of **15**; Table 2, entry 12) in comparison with the reaction with sulfide **2**, which furnished **15** in 78% yield. The

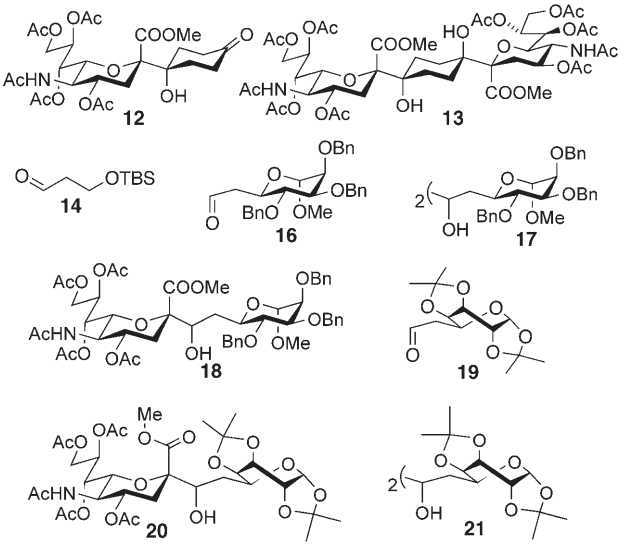
Table 2: Samarium-induced coupling of acetates **1** and pyridylsulfide **2** with carbonyl compounds. The structural formulae of **12**–**14** and **16**–**21** can be found in Scheme 2.



1α,β (X = OAc); **2** [X = αS(2-py)]

Entry	Substrate	Carbonyl partner	Product: yield[a] (isomer ratio)
1	**1α,β**[b]	cyclohexanone	**10**: 79%
2	**2**[c]	cyclohexanone	**10**: 82%
3	**1α,β**	4-*tert*-butylcyclohexanone	**6**: 98%
4	**2**	4-*tert*-butylcyclohexanone	**6**: 96%
5	**1α,β**	cyclobutanone	**11**: 88%
6	**2**	cyclobutanone	**11**: 96%
7	**1α,β**	1,4-cyclohexanedione[d]	**12**: 30%
8	**2**	1,4-cyclohexanedione[d]	**12**: 89%
9	**2**	1,4-cyclohexanedione[e]	**13**: 98%
10	**1α,β**	cyclohexanecarbaldehyde	**8**: 75%
11	**2**	cyclohexanecarbaldehyde	**8**: 90%[f]
12	**1α,β**	**14**	**15**: 26%[g] (1:1)
13	**2**	**14**	**15**: 78%
14	**1α,β**	**16**	(**17**: 56%)[h]
15	**2**	**16**	**18**: 80% (1:1)
16	**1α,β**	**19**	**20**: 30%[h] (1:1)
17	**2**	**19**	**20**: 82% (1:1)

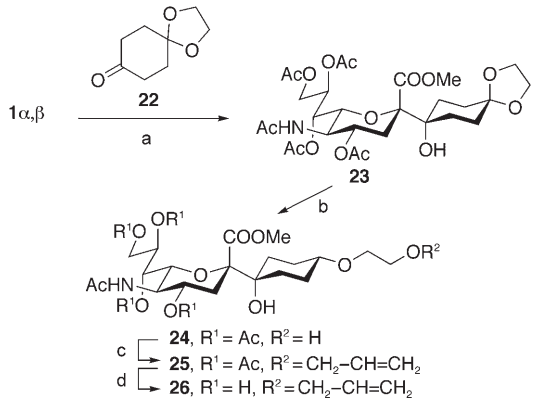
[a] Yields for isolated products after chromatography on silica gel. [b] Used as an α/β mixture with a ratio of 1:4; reaction for 2 h at room temperature. [c] Reaction for about 5 min at room temperature. [d] With 1.4 equivalents of 1,4-cyclohexanedione. [e] With 0.45 equivalents of 1,4-cyclohexanedione. [f] Results taken from reference [8]. [g] Together with reduction product **36** (17%; $R^1 = H$, see Scheme 5). [h] Acetates **1α/β** were recovered (53%, entry 14; 14%, entry 16) with reduction product **36** (24%, entry 14; 21%, entry 16).



Scheme 2. Formulae of some of the compounds given in Table 2.

superiority of sulfide **2** over acetates **1α,β** was also revealed by using the D-mannose-derived aldehyde **16**.[4f] No coupling occurred in the SmI_2-induced reaction with **1α,β**, with the reductive coupling of aldehyde **16** occurring instead to form diol **17**, whereas sulfide **2** supplied the expected compound **18** in 80% yield (Table 2, entries 14 and 15). With the D-galactose-derived aldehyde **19**,[7a] both acetates **1α,β** and sulfide **2** provided the expected compound **20** (in 30 and 82% yield, respectively, Table 2, entries 16 and 17). When acetates **1α,β** are used, the moderate yield is due to the competitive pinacol coupling of aldehyde **19** to diol **21** (30% yield).

The utility of this coupling process with acetates **1α,β** was validated in a fast elaboration of sialoside analogues **24**–**26** (Scheme 3). Coupling of **1α,β** with ketone **22** provided a



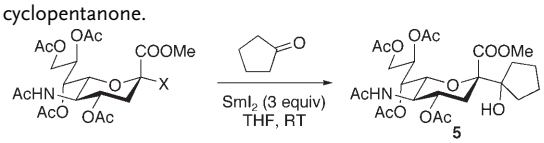
Scheme 3. Synthesis of sialoside analogues. a) SmI_2 (3 equiv), THF, room temperature, 85%; b) $BH_3{\cdot}SMe_2$ (1.2 equiv), TMSOTf (1.2 equiv), −78 °C in CH_2Cl_2, 4 h, 91%; c) allyltrichloroacetimidate (2 equiv), cat. TfOH, cyclohexane/CH_2Cl_2 (2:1), 4 h, 62%; d) K_2CO_3/MeOH, room temperature, overnight, 88%. TMSOTf = trimethylsilyl trifluoromethanesulfonate.

single compound **23** (85% yield). Reductive opening of the acetal furnished selectively the equatorial product **24** (91% yield) which could be allylated to give **25** (62%) and then deprotected to form **26** (88% yield). Compounds such as **24**–**26** constitute valuable building blocks to elaborate multivalent sialosides as robust biological probes or potential inhibitors towards sialic acid binding proteins.[18]

The adequacy of other anomeric substituents was also briefly examined, with the SmI_2-induced coupling with cyclopentanone serving as a reference reaction (Table 3).

Anomeric α-benzoate **27** did not show an improved reduction rate compared to that with acetate **1α** (reduction in 20 min at room temperature; Table 3, entry 2), whereas the reaction with ethyl xanthate **28**[19] was as fast as with 2-pyridylsulfide **2** or its corresponding sulfone (less than 1 min at room temperature; Table 3, entries 3 and 4). Phenylsulfide **29** reacted very slowly (10–20% yield of **5** with 50% of the starting material recovered after 4 h; Table 3, entry 5) and methyl glycoside **30** was unreactive under identical conditions, even after a prolonged time in the presence of SmI_2 (Table 3, entry 7). Increasing the reducing power of SmI_2 by adding HMPA[20] or 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone[21] (DMPU, 8 equiv with respect to SmI_2) restored the reactivity towards phenylsulfide **29**; however, coupling product **5** was obtained in a low yield (25%; Table 3,

Table 3: Samarium-induced coupling of different Neu5Ac glycosides with cyclopentanone.



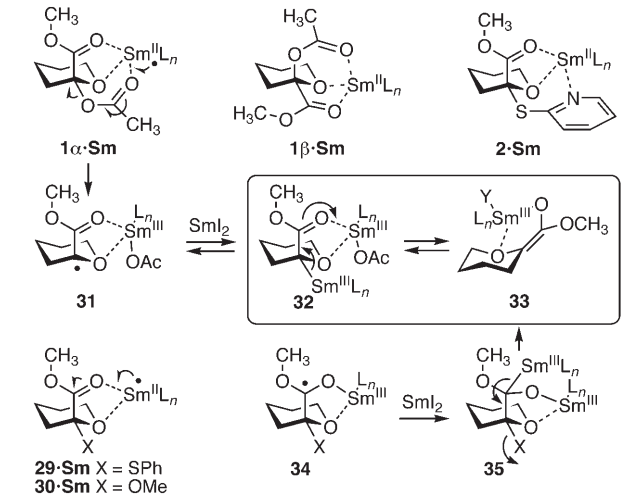
Entry	Substrate	X	Reaction time	Yield of **5**[a]
1	**1α**	OAc	20 min	97%
2	**27**	OBz[b]	20 min	95%
3	**28**	S(CS)OEt	<1 min	94%
4	**2**	SPy[c]	<1 min	76%
5	**29**	SPh	4 h	10–20%[d]
6	**29**	SPh[e]	2 h	25%[f]
7	**30**	OMe[g]	4 h	n.r.[h]

[a] Yields for isolated products after chromatography on silica gel. [b] Bz = benzoyl. [c] Py = 2-pyridyl. [d] 50% of **29** was recovered. [e] With HMPA or DMPU (8 equiv). [f] Together with reduction product **36** (65%; R^1 = H, see Scheme 5). [g] Experiment done with the β anomer. [h] n.r. = not recovered. Only **30** was recovered (97%), even when DMPU (8 equiv) was added.

entry 6), together with the reduction product **36** (R^1 = H in Scheme 4; 65% yield).

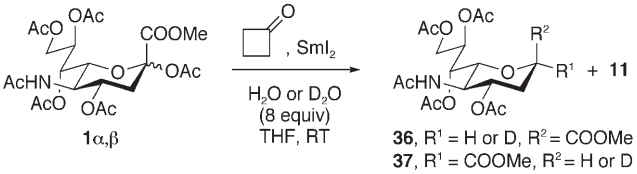
The "room-temperature" conditions reported herein and previously with similar compounds,[6–8] which are possible with the "anion-sensitive" *O*-acetyl protecting groups and an amide proton, may suggest a radical mechanism for the crucial carbon–carbon bond formation.[22] In this report, the behavior of the acetylated Neu5Ac derivatives **1**, **2**, and **27**–**30** with different anomeric substituents also provides information on the possible mechanism. The facile reductive process of acetates **1**, which is possible without an additive, may be facilitated by the chelation of the two carbonyl groups with the samarium atom (Sm^{II}) with an extra complexation of the endocyclic O6 atom as shown in Scheme 4.

This scheme of tight complexation might increase the reducing ability of SmI_2, as most chelating agents do,[23] or facilitate the first electron transfer. It would allow a fast electron transfer within the chelate, which would also be possible with the reactive pyridylsulfide (as in **2**·**Sm** in Scheme 4) but not with the phenylsulfide or the unreactive methyl glycoside (as in **29**·**Sm** and **30**·**Sm** in Scheme 4), unless HMPA or DMPU were present (phenylsulfide **29** only). Owing to the behavior of **29** and **30** in the presence of SmI_2 without an additive, we would favor electron transfer in the carbonyl group of the acetate of **1** (as in **1α**·**Sm** in Scheme 4) rather than in the carbonyl group of the methyl ester (as in **29**·**Sm**/**30**·**Sm** in Scheme 4) because in the latter event, enolate **33** could also be formed by cetyl radical reduction (**34** to **35**) and β elimination of X (**35** to **33**; X = SPh or OMe).



Scheme 4. The proposed complexation scheme for efficient electron transfer and formation of the organosamarium intermediate (in **33**: Y = OAc from **32** or Y = I from **35**). L = ligand.

Finally, addition of H_2O or D_2O (8 equiv with respect to acetates **1**) to the reaction mixture before the introduction of SmI_2 strongly interfered with the coupling reaction with cyclobutanone (Scheme 5). This mostly provided both "protonation" products **36** and **37** in a ratio of 2:1[24] (62–64%; 70% deuterium incorporation), together with coupling product **11** (16–18%). This gives evidence that organosamarium intermediate **32** or the corresponding enolate **33** could be generated and be involved in the carbon–carbon bond forming step, provided that the presence of water does not alter the mechanism.[22e,25]



Scheme 5. Samarium-induced coupling of acetates **1** with cyclobutanone in the presence of water (or D_2O).

In conclusion, we have shown that the reductive samariation of the peracetates of methyl *N*-acetyl-neuraminate in the presence of cyclic ketones provides a practical, straightforward, and high-yielding solution for stereoselective α-C-sialylation. Based on experimental evidence, we propose that the key carbon–carbon bond forming step occurs through an organosamarium intermediate. This procedure should prove useful in the fast synthesis of simple molecular modules containing stable bioactive sialoside mimetics for biological research.

Experimental Section

23: A freshly prepared 0.1M solution of SmI_2 in THF (100 mL, 10 mmol of SmI_2) was added to a stirred THF (10 mL) solution mixture of acetates **1α,β** (1.77 g, 3.32 mmol) and ketone **22** (1.00 g, 6.64 mmol) at 20°C under Ar. After the mixture had been stirred for 2 h, saturated aqueous NH_4Cl was added and the reaction mixture was extracted three times with CH_2Cl_2. The combined organic phases were washed twice with water, dried with Na_2SO_4, and evaporated to dryness. Flash chromatography on silica gel (toluene/acetone, 1:1) gave **23** (1.78 g, 85%): ^{1}H NMR ($CDCl_3$, 360 MHz): δ = 5.62 (d, J(NH,5) = 9.5 Hz, 1H, NH), 5.52 (ddd, J(8,7) = 8.1, J(8,9b) = 6.6, J(8,9a) = 2.5 Hz, 1H, H-8), 5.39 (dd, J(7,8) = 8.1, J(7,6) = 1.1 Hz, 1H, H-7), 4.84 (ddd, J(4,3ax) = 11.2, J(4,5) = 10.4, J(4,3eq) = 4.5 Hz, 1H, H-4), 4.43 (dd, J(9a,9b) = 12.4, J(9a,8) = 2.5 Hz, 1H, H-9a), 4.22–3.97

(m, 2H, H-5,6), 4.21 (dd, J(9b,9a) = 12.4, J(9b,8) = 6.6 Hz, 1H, H-9b), 4.05 (m, 4H, $O(CH_2)_2O$), 3.89 (s, 3H, $COOCH_3$), 2.95 (s, 1H, OH), 2.58 (dd, J(3eq,3ax) = 12.8, J(3eq,4) = 4.5 Hz, 1H, H-3eq), 2.27, 2.22, 2.15, and 2.12 (4s, 12H, $OCOCH_3$), 1.96 (s, 3H, $NCOCH_3$), 1.94 (dd, J(3ax,3eq) = 12.8, J(3ax,4) = 11.2 Hz, 1H, H-3ax), 1.93–1.60 ppm (m, 8H, CH_2 of cyclohexyl); ^{13}C NMR ($CDCl_3$, 90 MHz): δ = 170.8, 170.7, 170.5, 170.1, 169.9, and 169.8 (4$OCOCH_3$, $NCOCH_3$, $COOCH_3$), 108.1 (C of cyclohexyl), 85.7 (C2), 74.1 (COH), 73.1, 70.3, 68.7, 67.7 (C4, C6, C7, C8), 64.9, 63.9 (OCH_2CH_2O), 62.9 (C9), 52.2 (CH_3O), 49.0 (C5), 32.9 (C3), 29.9, 29.7, 29.2, and 28.9 (4CH_2 of cyclohexyl), 22.9, 21.1, 20.7, 20.6, and 20.5 ppm (4CH_3OCO, CH_3CON); MS (ES): m/z 654 $[M+Na]^+$; HR-MS (ES): calcd for $C_{28}H_{41}NaNO_{15}$: 654.2368; found: 654.2383.

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[24] These results parallel the reduction results of Hanessian and Girard[13] when they used SmI_2 with ethylene glycol, which provided the two isomers **36** (R^1 = H) and **37** (R^2 = H) in a ratio of 4:1. However, when the reduction of **1** or **2** was carried out without any other electrophile, addition of a proton source (H_2O or ethylene glycol) after the reduction event provided only product **36** (R^1 = H).
[25] As further evidence, the reaction performed in [D_8]THF without an electrophile provided after treatment product **36** without deuterium incorporation (R^1 = H). This indicates that this compound arises from the protonation of an organosamarium intermediate or the corresponding enolate.

