# Asymmetric Synthesis of 4′-Quaternary 2′-Deoxy-3′-*epi*-β-*C*-Nucleosides

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**Abstract:** An efficient diastereo- and enantioselective synthesis of 4′-quaternary 2′-deoxy-3′-*epi*-β-*C*-nucleosides is described employing the RAMP-hydrazone methodology to establish the first stereocentre. Further key steps include diastereoselective nucleophilic 1,2-additions with Grignard and organocerium reagents.

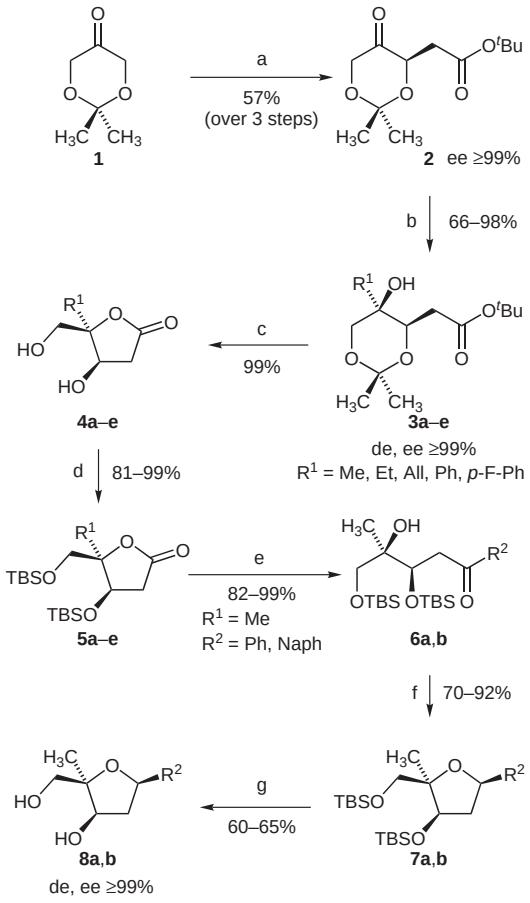
**Key words:** asymmetric synthesis, nucleoside analogues, hydrazones, organocerium reagents, diastereoselective reduction

The synthesis of novel nucleoside analogues has attracted increasing interest in recent years in order to study their behaviour in oligonucleotides or their biological activity.[1–9] A large number of nucleoside analogues have already been synthesised by several groups. Alongside abundant modifications of the structure of nucleobases,[1] a wide variety of sugar analogues have also been developed, most of them severely altering the nucleoside structure and leading to carbocyclic, acyclic, thio or aza nucleosides.[2] Nucleoside analogues with structures closer to the natural building blocks have also been investigated. For example, 4′-quaternary nucleosides have been developed by Marx et al. and proved to lead to superior selectivity compared to natural nucleosides when inserted into oligonucleotides.[3] Other groups have synthesised 4′-quaternary nucleosides in order to study their biological activity[4] or developed syntheses of 4′-branched bicyclic nucleoside analogues.[5] Numerous investigations were reported on *C*-nucleoside synthesis, using various approaches.[6] For instance, in the studies of Kool[7] and Leumann,[8] those nucleoside analogues were introduced into oligonucleotides, which allowed them to study stacking and shape-mimicking effects separately from hydrogen-bonding interactions occurring between natural nucleobases.

Concerning the synthetic aspect, 4′-quaternary 2′-deoxy-3′-*epi*-β-*C*-nucleosides **8** are challenging target molecules for asymmetric synthesis, since they require the formation of three stereocentres, one of them quaternary, in a five-membered ring. We were interested in synthesising these nucleoside analogues as they combine a variety of modifications, which could be of great biological interest. For example, 3′- or 4′-epimers of deoxynucleosides are expected to have a local influence on double helix conformation when inserted into DNA (base-flipping).[9]

We now wish to disclose our syntheses of the β-*C*-nucleosides **8a** and **8b**, which were accomplished in 9 steps in overall yields of 16% and 22%, respectively, starting from 2,2-dimethyl-1,3-dioxan-5-one (**1**)[10] (Scheme 1). First of all the RAMP-hydrazone α-alkylation methodology[11] provided the *tert*-butyl ketoester **2** in a good yield of 57% over 3 steps and with excellent enantioselectivity (ee ≥ 99%).

A wide range of substituents $R^1$ were incorporated into **2** by employing various Grignard reagents, the *tert*-butyl-ester functionality being a good directing group for the formation of the second stereocentre.[12] The diastereomeric excesses ranged from good to excellent (de = 70–98%), and the minor diastereoisomer could easily be separated




**Scheme 1** *Reagents and conditions*: (a) 1. RAMP, benzene, reflux; 2. *t*-BuLi, THF, –78 °C, then *tert*-butylbromoacetate, –100 °C; 3. $O_3$, $CH_2Cl_2$, –78 °C; (b) $R^1MgBr$, THF, –78 °C or –100 °C; (c) 3 N HCl, MeOH, r.t.; (d) TBSOTf, pyridine, THF, 0 °C; (e) $CeCl_3$, $R^2Li$, THF, –110 °C to –99 °C; (f) $Me_4NHB(OAc)_3$, MeCN, AcOH, –30 °C; (g) TFA–$CHCl_3$ (4:1), $CHCl_3$, 0 °C.

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by column chromatography giving access to diastereo- and enantiomerically pure alcohols **3a**–**e** in good to excellent yields (de, ee ≥ 99%). Subsequent cyclisation[13] with methanolic hydrochloric acid led to lactones **4a**–**e** with excellent yields in all cases, followed by transformation to the corresponding TBS ethers **5a**–**e** in very good to excellent yields (Table 1).

For the TBS protection[14] of the secondary alcohol neighbouring a quaternary centre, the use of TBSOTf was necessary, as reaction with TBSCl led to the mono-protected product only, even when the reaction mixture was exposed to harsh conditions (reflux in pyridine). The choice of base was also crucial for the outcome of the reaction. Thus, the use of commonly employed 2,6-lutidine led to elimination, which could be suppressed by using 2,6-di-*tert*-butyl pyridine as reported by Chamberlin et al.[15] Further investigations showed that the far less expensive pyridine was sufficient to obtain the desired products.

**Table 1** Preparation of the Doubly TBS-Protected Lactones **5a**–**e**

| | $R^1$ | Yield of **3** (%) | de,[a,b] ee[c] of **3** (%) | Yield of **5** (% over 2 steps) |
|---|---|---|---|---|
| **a** | Me | 86 | ≥ 99, ≥ 99 | 85 |
| **b** | Et | 66 | ≥ 99, ≥ 99 | 98 |
| **c** | Ph | 88 | ≥ 99, ≥ 99 | 89 |
| **d** | *p*-F–Ph | 98 | ≥ 99, ≥ 99 | 80 |
| **e** | All | 66 | ≥ 99, ≥ 99 | 86 |

[a] Determined by GC (CP-Sil-8).
[b] After column chromatography.
[c] Determined by CSP-GC (Chirasil-dex, Chirasil L-Val).

Subsequently, nucleophilic 1,2-addition of organocerium reagents[16] on the TBS-protected lactone **5a** was performed.[17] The cyclic hemi-acetals formed during the course of this reaction opened to give the γ-hydroxy-ketones **6a**,**b** in good yields. The reaction temperature proved to be very important for the reproducibility of this addition. On the one hand the temperature had to be kept below –105 °C to prevent a second addition to the new keto functionality, on the other hand the ring-opening seemed to only occur at temperatures above –105 °C. At lower temperature only a complex mixture of elimination products along with the desired product was found. For these reasons, our strategy was to perform the reaction at temperatures below –105 °C in order to avoid double addition and then allow the mixture to warm up to –99 °C right before quenching. This led to the satisfying results shown in Table 2.

Reduction was then performed according to Evans et al. with tetramethyl ammonium triacetoxy borohydride,[18] which to our surprise not only led to the cyclised products **7a**,**b** but also showed complete diastereoselectivity towards the β-configuration of the *C*-nucleoside formed (de ≥ 99%).[19] The reaction proceeded smoothly to give protected β-*C*-nucleosides **7a**,**b** in good to excellent yields (Table 2). Investigations with other reducing agents have not resulted in α-nucleosides so far. The relative β-configuration was confirmed by NOE experiments on **7a**.

**Table 2** *C*-Nucleoside Formation from Lactone **5a**

| | $R^2$ | Yield of **6** (%) | Yield of **7** (%) | Yield of **8** (%) | ee of **8** (%)[a] |
|---|---|---|---|---|---|
| **a** | Ph | 82 | 70 | 65 | ≥ 99 |
| **b** | Naph | 99 | 92 | 60 | ≥ 99 |

[a] Determined by CSP-GC (Chirasil-dex) / HPLC (DAICELAD.M).

In the final deprotection step[20] a screening of typical desilylating agents indicated the sensitivity of the stereocentres. Among the tested reagents only trifluoroacetic acid in chloroform resulted in complete conversion and, more importantly, retention of all stereocentres leading to the desired products **8a**,**b** in good yields and excellent diastereomeric and enantiomeric excesses (de, ee ≥ 99%).[21]

In conclusion, we have developed a highly diastereo- and enantioselective route to 4′-quaternary 2′-deoxy-3′-*epi*-β-*C*-nucleosides, where the substituents at the 4′-position can vary from alkyl and allyl to aromatic. The syntheses of two derivatives (**8a**,**b**) were completed over nine steps in overall yields of 16% and 22%, respectively. We now envisage to apply the SAMP auxiliary to this method in order to synthesise 4′-quaternary 2′-deoxy-4′-*epi*-α-*C*-nucleosides.

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(12) **Typical Procedure for the Grignard Reaction.**
In a dried Schlenk flask, equipped with a magnetic stirrer, the ketone **2** was dissolved in abs. THF (10 mL/mmol) under an argon atmosphere. The solution was cooled to –78 °C or –100 °C, respectively, depending on the Grignard reagent employed, which was then slowly added (2.0 equiv). The mixture was allowed to stir while maintaining the temperature constant for 4 h. The reaction was then stopped by addition of sat. aq solution of $NH_4Cl$ (5 mL/mmol). After warming up to r.t. the precipitate was dissolved by dilution with $H_2O$. The aqueous phase was extracted with $Et_2O$ (50 mL/mmol) and the combined organic layers were washed with brine and dried over $MgSO_4$. Column chromatography (silica gel, $Et_2O$–*n*-pentane) gave the corresponding alcohols **3a**–**e** as colourless crystals.

(13) **Typical Procedure for the Cyclisation.**
The products **3a**–**e** were dissolved in MeOH (3 mL/mmol) and treated with 3 N methanolic HCl (3 mL/mmol, prepared by mixing one part of aq HCl (12 N) with four parts of MeOH). The reaction was stirred at r.t. until TLC control indicated complete conversion of the starting material. All solvents were evaporated under reduced pressure and the product **4a**–**e** was recrystallised from THF–*n*-pentane.

(14) **Typical Procedure for the TBS-Protection.**
To a solution of the diols **4a**–**e** in abs. THF (10 mL/mmol) was added pyridine (6.0 equiv), and the mixture was cooled to 0 °C. Slow addition of TBSOTf (3.0 equiv), followed by 4 h of stirring, gave rise to the product. The reaction was quenched with $H_2O$ (5 mL/mmol), extracted with $Et_2O$ (50 mL/mmol), washed with brine and dried over $MgSO_4$. The products **5a**–**e** were then purified by column chromatography (silica gel, $Et_2O$–*n*-pentane).

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(17) **Typical Procedure for the 1,2-Addition.**
First, $CeCl_3 \cdot 7H_2O$ (2.0 equiv), placed in a Schlenk flask, was dried without stirring at 130 °C in vacuo (approx. 0.05 mbar) for 1 h. It was subsequently ground up by stirring under these conditions for an additional hour. After cooling down to r.t. the flask was filled with argon and abs. THF (4 mL/mmol of $CeCl_3$) was added. The suspension was stirred for at least 1 h and then placed in an ultrasound bath for an extra hour. The mixture was then cooled down to –78 °C and the lithium reagent was added dropwise. After 2 h stirring at low temperature a bright yellow colour indicated the formation of the active cerium reagent. The mixture was then cooled down to –105 °C and lactone **5a** was added in abs. THF (5 mL/mmol), carefully keeping the temperature below –100 °C. After 30 min, the reaction mixture was allowed to warm up to –99 °C and quenched with $H_2O$ (10 mL/mmol). Extraction with $CH_2Cl_2$ (100 mL/mmol) followed by treatment with brine and drying over $MgSO_4$ provided the desired products **6a**,**b**, which could be purified by column chromatography (silica gel, $Et_2O$–*n*-pentane).

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(19) **Typical Procedure for the Reduction According to Evans.**
A suspension of $Me_4NHB(OAc)_3$ (3.0 equiv) in abs. MeCN (5 mL/mmol) was treated with abs. AcOH (5 mL/mmol) under an argon atmosphere. The resulting solution was cooled down to –30 °C and added to a solution of the hydroxyketone **6a**,**b** in abs. MeCN (2.5 mL/mmol). The reaction was left standing overnight at –26 °C. Quenching the reaction with a solution of 10% Na/K-tartrate in $H_2O$ (10 mL/mmol) led to a precipitate, which was dissolved by addition of a sat. aq solution of $Na_2CO_3$. The aqueous phase was extracted with $Et_2O$ (100 mL/mmol) and the combined organic layers were washed with brine and dried over $MgSO_4$. The cyclised products **7a**,**b** were purified by column chromatography (silica gel, $Et_2O$–*n*-pentane).

(20) **Typical Procedure for the Deprotection.**
To the TBS ethers **7a**,**b** in $CHCl_3$ at 0 °C was slowly added a 4:1 mixture of TFA and $CHCl_3$. The reaction progress was monitored by TLC. When the reaction was completed the solvent was evaporated under reduced pressure. Traces of TFA were removed by repeated co-evaporation with MeOH. Column chromatography with $Et_2O$ on silica gel gave rise to the free β-nucleosides **8a**,**b**.

(21) **(2*R*,3*R*,5*R*)-2-(Hydroxymethyl)-2-methyl-5-(1-naphthyl)tetrahydrofuran-3-ol (8b):** mp 118 °C. IR (KBr): ν = 3517, 3325, 3047, 2962, 2913, 2862, 1597, 1508, 1435, 1373, 1340, 1283, 1220, 1101, 1055, 1016, 939, 913, 860, 778, 642, 560, 490 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.57 (s, 3 H, C*H*$_3$), 2.09 (ddd, 1 H, *J* = 12.9, 9.3, 6.6 Hz, ArCHC*H*H), 2.42 (t, 1 H, *J* = 6.2 Hz, $CH_2O$*H*), 2.98 (d, 1 H, *J* = 14.5 Hz, CHO*H*), 3.02 (ddd, 1 H, *J* = 12.9, 6.6, 6.3 Hz, ArCHCH*H*), 3.87 (d, 2 H, *J* = 6.2 Hz, C*H*$_2$OH), 4.36 (dd, 1 H, *J* = 14.5, 6.6 Hz, C*H*OH), 5.67 (dd, 1 H, *J* = 9.3, 6.3 Hz, ArC*H*), 7.45–7.99 (m, 7 H, Ar*H*) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 22.01, 43.67, 66.92, 73.34, 79.74, 83.58, 121.72, 123.06, 125.37, 125.42, 125.90, 127.91, 128.64, 130.46, 133.46, 137.06 ppm. MS (EI): *m/z* (%) = 115 (5), 127 (9), 128 (25), 129 (9), 141 (19), 142 (9), 152 (11), 153 (24), 154 (18), 155 (31), 156 (9), 165 (12), 166 (10), 167 (24), 170 (9), 183 (5), 184 (5), 209 (75), 210 (11), 227 (52), 228 (8), 258 (100), 259 (17). $[\alpha]_D^{25}$ +26.3 (*c* 0.99, $CHCl_3$). Anal. Calcd for $C_{12}H_{16}O_3$: C, 74.39; H, 7.02. Found: C, 74.36; H, 7.19.