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A greener enantioselective synthesis of the antiviral agent North-methanocarbathymidine (N-MCT) from 2-deoxy-D-ribose

Olaf R. Ludek and Victor E. Marquez*

Laboratory of Medicinal Chemistry, Center for Cancer Research, National Cancer Institute at Frederick, National Institutes of Health, Frederick, MD 21702, USA

Abstract

An enantioselective synthesis of suitably protected (1*R*,2*S*,4*S*,5*S*)-4-amino-1-(hydroxymethyl)bicyclo[3.1.0]hexan-2-ol, a key starting material for the synthesis of conformationally locked carbocyclic nucleosides, including the antiviral active North-methanocarbathymidine, is reported. Starting from 2-deoxyribose the target Boc-protected amine was prepared in 33% overall yield under conditions that are ecologically friendlier than previous methods.

Keywords

Conformationally locked carbocyclic nucleosides; North-methanocarbathymidine; antiviral; enantioselective synthesis

1. Introduction

The antiviral active and conformationally locked nucleoside, North-methanocarbathymidine (N-MCT, **1**), belongs to a group of carbocyclic nucleosides constructed on a bicyclo[3.1.0]hexane scaffold.¹ This scaffold was devised as a strategy to lock the embedded cyclopentane ring of N-MCT into a permanent North envelope (*2E*) conformation as it is defined in the pseudorotational cycle.² The antiviral activity of N-MCT is dependent on type I thymidine kinase (TK) from herpes simplex viruses (HSV-1 and HSV-2),³⁻⁵ as well as from type II TK expressed in cowpox6 and vaccinia viruses.⁷ Once phosphorylated to the 5'-triphosphate level, N-MCTTP inhibits viral DNA synthesis. The compound reduces the mortality of mice infected with orthopoxviruses when administered intraperitoneally,⁶ as well as when given orally to mice infected with HSV-1, even when treatment is initiated 76 h post-infection.⁸ In addition, N-MCT has shown excellent in vitro activity against Kaposi's sarcoma-associated herpesvirus (KSHV), displaying greater potency than the reference compounds ganciclovir and cidofovir.⁹ These combined properties suggest that N-MCT is bioavailable, safe, and orally effective, thus warranting further development.

*Corresponding author: Victor E. Marquez (marquezv@mail.nih.gov).

Supplementary data: Supplementary data associated with this article can be found in the online version at

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We recently reported an improved synthesis of N-MCT involving the elaboration of the thymine ring from a suitable pseudosugar precursor.¹⁰ Both convergent and linear strategies were compared side by side, but the linear strategy of building the pyrimidine ring from the corresponding carbobicyclic amine was found to more selective and easier to execute, plus the overall yield was comparable to that using a convergent approach. Therefore, the linear approach was selected for the large-scale synthesis of N-MCT. We now wish to report a novel enantioselective route towards the other half of the molecule, the carbobicyclic amine. This new synthesis circumvents many of the drawbacks encountered with other strategies reported earlier.

Historically, our first approach (Route A, Figure 1) was based on the orthogonally protected hexanol **2**—derived from the chiral cyclopentenone precursor (**3a**)—that was used in the synthesis of neplanocin A.^{11, 12} In this methodology, a regioselective cleavage of the contiguous *O*-isopropylidenetriol system with trimethylaluminum and a two-step radical deoxygenation to remove the extra hydroxyl group were necessary. This route, however, was unattractive from an economical and ecological point of view (4% overall yield, 13 steps from *D*-ribose). Formation of the equivalent cyclopentenone precursor (**3b**) by Jeong et al.¹³ using ring-closing metathesis (RCM) was a significant improvement. However, for the purpose of synthesizing a 2'-deoxy analogue, such as N-MCT, the issue of removing the additional hydroxyl function still remained.

Another strategy that we utilized was based on the enantiomerically pure cyclopentenol **5** that was developed by Roberts et al.¹⁴ for the synthesis of 2'-deoxycarbanucleosides (Route B, Figure 1). This approach was very attractive because **5** could be used as a common precursor for making both North- and South-locked bicyclo[3.1.0]hexane nucleosides.^{15, 16} Although **5** could be obtained with excellent optical purity (>97% ee), the synthesis is extremely sensitive to air, moisture, and temperature, plus the overall yield is not optimal. Starting from cyclopentadiene—the precursor of **5**—the critical intermediate (1*S*,2*R*,4*S*,5*R*)-4-(benzyloxy)-5-(benzyloxymethyl)bicyclo[3.1.0]hexan-2-ol (**4**) was obtained in 10% overall yield after ten steps. To our knowledge, no alternative synthesis of cyclopentenol **5** has been reported thus far.

Since the availability of **5** was a limiting factor, we next designed a very simple chemical approach towards the requisite racemic, bicyclo[3.1.0]hexane system that relied on a practical and efficient enzymatic step for chiral resolution (Route C, Figure 1). The bicyclic system ($\pm$) **7** was formed in one step by a metal catalyzed keto-carbene cycloaddition after diazotation of the β -keto ester ($\pm$) **8**, which was easily obtained by an aldol reaction from cheap ethyl acetoacetate and acrolein.¹⁷ However, despite the straightforwardness of this approach, half of the material was lost during the resolution of enantiomers, thus drastically reducing the overall yield of the diacetate **6** (13%, 8 steps).

Based on the above considerations, we now wish to present an enantioselective approach that is inexpensive, environmentally friendlier, easy to handle, and most importantly, highly efficient. The recent publication by Michel and Strazewski on the improved synthesis of chiral

cyclopentenone **3b**¹⁸ and the utilization of natural 2-deoxy-D-ribose as rich chiral pool,¹⁹ prompted us to investigate the possibility of preparing the bicyclic hexanol precursor **4** from this inexpensive building block. The retrosynthetic analysis for this novel route (Figure 2) resembles in great part Jeong's initial approach towards chiral cyclopentenone **3b**.¹³ In a previous communication, we have already shown that compound **4** could be obtained with high stereospecificity from the allylic cyclopentenol **9**,²⁰ which should be accessible from the α,ω -diene **10** via ring closing metathesis (RCM),²¹⁻²⁶ followed by a palladium(II) catalyzed rearrangement of the resulting allylic system.²⁷⁻²⁸ The RCM-precursor **10** is envisaged to arise from the stereospecific addition of a vinyl Grignard reagent to a ketone obtained from the oxidation of the corresponding alcohol **11**. Alcohol **11** is already a known compound that has been synthesized by Herdewijn et al.,²⁹ in four steps starting from 2-deoxy-D-ribose.

2. Results and Discussion

The starting lactol **14** was prepared in three steps from 2-deoxy-D-ribose according to the literature procedure (Scheme 1). Although the synthesis has been described already,³⁰ we would like to comment on the methodology and report some useful modifications (Scheme 1). The purity of **14** greatly depends on reducing the amount of the pyranoside isomer **12'** formed during acetalization under acidic conditions (Table 1). Since the desired furanose form **12** is the kinetic product, while the pyranoside **12'** resembles the thermodynamic product,³¹ we concluded that acetalization at lower temperatures should favor formation of the five-membered isomer **12**. Indeed, lowering the temperature from 20 °C to -20 °C decreased the ratio of **12'** from 15 to 4%, as judged by ¹H NMR of the crude reaction mixture. Therefore, the acidified solution of 2-deoxyribose in methanol was conveniently placed in the freezer overnight and removal of the solvent provided the methyl furanoside **12**, which was sufficiently pure for the next benzylation step to the protected methyl glycoside **13** without any additional workup. We also found it advantageous to perform the final hydrolysis of the methyl glycoside **13** at room temperature in an HCl dioxane-water mixture, instead of refluxing the acetal **13** in an aqueous acetic acid solution. TLC-analysis of the reaction clearly showed fewer side products and the workup involved a simple extraction after neutralization. By applying these modifications, the reported three step procedure was handled as a one-pot reaction with no intermediate chromatography, leading to lactol **14** in 85% overall yield.

Lactol **14** was transformed into the chiral alcohol **11** by a Wittig reaction (91%), using methyltriphenylphosphonium bromide as the olefin-forming reagent (Scheme 1).²⁹ Swern oxidation of the secondary alcohol **11** to the ketone **15** was quantitative and no purification was necessary at this stage. Nevertheless, a small amount of ketone **15** was isolated to determine its stability. After standing in chloroform solution at room temperature for three days, the compound did not show any signs of epimerization/racemization due to a possible keto-enol tautomerism as confirmed by its constant optical rotation. Subsequent Grignard reaction with vinylmagnesium bromide led to the formation of two diastereomeric alcohols (**10a** and **10b**) in various ratios, depending on the solvent employed (Table 2).

Ketone **15** can be considered as an erythrulose analogue and nucleophilic additions of organometallic compounds to the carbonyl group of this carbohydrate have been investigated in detail.³²⁻³³ According to these studies, benzyl protected hydroxyl groups in the α and α' -position compete in chelating the metal and the carbonyl group, leading to poor diastereoselectivities (entries 1 – 4).³⁴⁻³⁶ However, when THF was employed as solvent, we observed a moderate selectivity for one isomer (entry 5). Interestingly, the diastereoselectivity was not influenced by raising the temperature from -78 to -40 °C (entries 6 – 9). Since both diastereoisomers were not separable by chromatography, we were not able to assign the absolute stereochemistry of the major and minor isomers of **10** at this stage. After RCM conversion to the cyclopentenol **16** with Grubbs' second generation catalyst and acetylation of

the tertiary hydroxyl (85%, two steps), both isomers of **17** could be easily separated by column chromatography (Scheme 2). However, nOe experiments on both ring systems were still inconclusive and no absolute configuration could be assigned to either of the two isomers of **17**.

We therefore continued with the reaction scheme by separately rearranging the allylic acetates of **17_{major}** and **17_{minor}** using bis(acetonitrile)dichloropalladium(II) and *p*-benzoquinone, which is known to proceed with retention of configuration.^{27, 28} Methanolysis of acetate **18**, derived from **17_{major}**, gave the known alcohol **9**²⁰ and methanolysis of **19** gave the also known epimeric alcohol **20**. This corroborated the desired (3*S*,4*S*)-stereochemistry for the major diastereomer of **10**, which is in accordance with the Felkin-Anh model that favors the *anti*-addition of the Grignard reagent to the carbonyl group in **15**. Cyclopentenol **20** was converted to its regioisomer **9** by a Mitsunobu reaction,^{37, 38} thus contributing to the efficiency of the approach by minimizing the loss of material. Final cyclopropanation was carried out according to the published procedure,²⁰ providing the N-MCT precursor (1*S*,2*R*,4*S*,5*R*)-4-benzyloxy-5-benzyloxymethylbicyclo[3.1.0]hexan-2-ol (**4**) in 43% overall yield.

Previously, we have shown that it is advantageous to construct the thymine heterocycle by a stepwise buildup. Therefore, the bicyclic hexanol **4** was converted to the inverted azide **21** by mesylation and subsequent displacement by sodium azide in 83% yield. Reduction of the azide in presence of di-*tert*-butyldicarbonate (92%) afforded the carbamate **22** as a stable precursor for N-MCT (**1**) synthesis.

In summary we have presented a new and efficient approach towards the prerequisite bicyclo [3.1.0]hexane framework present in the potent antiviral nucleoside N-MCT. Utilizing cheap and plentiful 2-deoxyribose as starting material we were able to introduce the necessary *S*-configuration at C-4 of the precursor, which serves as an anchor for the stepwise buildup of the three remaining stereocenters. We showed how both regioisomers obtained during the addition of vinylmagnesium bromide to ketone **15** could be successfully converted to the N-MCT-precursor **4**, minimizing waste of material and greatly improving the economy of the strategy.

3. Experimental section

3.1 General

All experiments involving water-sensitive compounds were conducted under dry conditions (positive argon pressure) using standard syringe, cannula and septa apparatus. All solvents were purchased anhydrous (Aldrich) and stored over activated molecular sieves. Hexanes, ethyl acetate, methylene chloride, and methanol employed in chromatography were HPLC-grade. Flash chromatography was performed with Teledyne ISCO CombiFlash Companion. Analytical thin layer chromatography was performed on Analtech precoated plates (Uniplat, silica gel GHLF, 250 microns) containing a fluorescence indicator; sugar-containing compounds were visualized with the sugar spray reagent (5 mL of 4-methoxybenzaldehyde, 90 mL of ethanol, 5 mL of concentrated sulfuric acid, and 10 mL of glacial acetic acid) by heating with a heat gun. NMR spectra were recorded using a Varian Inova 400 MHz spectrometer. The coupling constants are reported in Hertz, and the peak shifts are reported in the delta (ppm) scale; abbreviations s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). ESI mass spectra were obtained on an Agilent Technologies 1200 Series LC system coupled to an Agilent G1978A Multimode Ion Source (LC/MSD SL) using the loop injection mode. HRMS Mass spectra (FABMS) were obtained on a VG 7070E mass spectrometer at an accelerating voltage of +8 kV over a limited mass range at 5000 resolution. KCl/NBA was used as the sample matrix, and ionization was effected by a beam of xenon atoms. Optical rotations were measured on a Jasco P-1010 polarimeter at 589 nm. Infrared spectroscopy data

was obtained neat with a Jasco FT-IR/615 spectrometer. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA, 30091.

3.2.1. (4*S*,5*R*)-4-Benzylloxy-5-benzylloxymethyltetrahydrofuran-2-ol (14)—Acetyl chloride (1.0 mL, 14.0 mmol) was slowly added to ice-cold methanol (100 mL) while stirring. The cooling bath was removed and the mixture was stirred for 30 min at room temperature. The mixture was placed in a freezer (−18°C) and after 30 min, 2-deoxyribose (5.00 g, 37.3 mmol) was added in one portion. The yellow solution was kept in the freezer overnight. After neutralization with solid sodium carbonate (1.00 g, 9.43 mmol), the solid was filtered off and the methanolic solution was evaporated under reduced pressure. The crude methyl glycoside **12** was then dissolved in ethyl acetate (100 mL) and filtered again. The solvent was removed *in vacuo* yielding the methyl furanoside **12** (5.53 g, 100%) as a yellow oil.

Under a blanket of argon, the crude methyl glycoside **12** was dissolved in dry THF (100 mL) and sodium hydride (60% in oil, 4.48 g, 112 mmol) was added at 0°C. The cooling bath was removed and the mixture was stirred for 1 h at room temperature. After cooling the mixture to 0°C, benzyl bromide (13.3 mL, 112 mmol) and tetrabutylammonium iodide (TBAI, 400 mg) were added. The cooling bath was removed and the mixture was stirred at room temperature overnight. The reaction was quenched by carefully adding methanol (10 mL) at 0°C and the reaction was stirred at room temperature for 1 h. Water was added (200 mL) and the aqueous phase was extracted with CH₂Cl₂ (3 × 100 mL). The combined organic extracts were dried (MgSO₄) and concentrated, yielding the crude benzylated methyl glycoside **13** (15 g) as yellow oil.

Acetyl chloride (15.0 mL, 0.210 mol) was slowly added to ice-cold water (150 mL, containing 1% of acetonitrile) while stirring. The cooling bath was removed and the mixture was stirred for 30 min at room temperature. The crude benzylated methyl glycoside **13** (15 g) in dioxane (300 mL) was added to this aqueous hydrochloric acid solution and the mixture was stirred overnight. After neutralization with saturated NaHCO₃ solution (150 mL), the aqueous phase was extracted with CH₂Cl₂ (3 × 150 mL). The combined organic extracts were dried (MgSO₄) and concentrated. The crude product was purified by flash chromatography on silica gel (EtOAc in hexanes, 30 → 50%) to give lactol **14** (8.91 g, 76%, 3 steps) as a colorless oil, together with unchanged methyl glycoside **13** (1.53 g). From the recovered **13** a repeat hydrolysis gave a second batch of lactol **14** (1.02 g, 9%), raising the overall yield to 85%. The spectroscopic data of lactol **14** were identical to those already reported.^{39,40}

3.2.2. (2*R*,3*S*)-1,3-bis(benzylloxy)hex-5-en-2-ol (11)—A solution of *n*-butyl lithium (1.6 M in hexanes, 23.0 mL, 36.8 mmol) was slowly added to a stirred suspension of methyltriphenylphosphonium bromide (12.5 g, 35.0 mmol) in THF (140 mL) at −78°C under argon. The mixture was allowed to warm to room temperature over 30 min and cooled again to −78°C. A solution of the lactol **14** (5.50 g, 17.5 mmol) in THF (10.0 mL) was added and the reaction mixture was allowed to reach room temperature overnight. The reaction was quenched by carefully adding water (200 mL) and the aqueous layer was extracted with CH₂Cl₂ (3 × 100 mL). The combined organic extracts were dried (MgSO₄) and concentrated. The crude product was purified by flash chromatography on silica gel (EtOAc in hexanes 10 → 30%) to yield the alcohol **11** (5.01 g, 9 %) as a colorless oil. The spectroscopic data were identical to those reported.²⁹

3.2.3. (3*S*,4*S*)-4-Benzylloxy-3-benzylloxymethylhepta-1,6-dien-3-ol (10a) and (3*R*,4*S*)-4-benzylloxy-3-benzylloxymethylhepta-1,6-dien-3-ol (10b)—

Oxalylchloride (2.79 mL, 32.0 mmol) was dissolved in dry CH₂Cl₂ (150 mL) under argon and the solution was cooled to −78°C. DMSO (4.55 mL, 64.0 mmol) was added dropwise and the reaction was stirred for 5 min at the same temperature. Alcohol **11** (5.00 g, 16.0 mmol),

dissolved in 30 mL of dry CH_2Cl_2 , was added to this mixture and the reaction was stirred for 1 h at -78°C . Triethylamine (13.4 mL, 96.0 mmol) was added and the mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched by the slow addition of a saturated ammonium chloride solution (150 mL) and the aqueous phase was extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were dried (MgSO_4) and concentrated to give ketone **15** as oil, which was deemed sufficiently pure to be used in the next step without any further purification. IR (neat): 3073, 3030, 2864, 1730, 1641, 1496, 1454, 1327, 1208, 1098, 1026, 916, 735 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): $\delta = 7.35 - 7.25$ (m, 10H, CH -arom.); 5.76 (dddd, 1H, $J = 17.1, 10.2, 7.1, 7.1$ Hz, $\text{H}-\text{CH}=\text{CH}_2$); 5.12 – 5.03 (m, 2H, $\text{CH}=\text{CH}_2$); 4.54 (AB-system, 2H, $J = 12.0$ Hz, CH_2 -benzyl-A); 4.49 (s, 2H, CH_2 -benzyl-B); 4.30 (s, 2H, OCH_2CO); 4.03 (dd, 1H, $J = 6.5, 5.3$ Hz, CHOBn); 2.55 – 2.40 (m, 2H, $\text{CH}_2\text{CH}=\text{CH}_2$); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 208.2$ (CO); 137.1 (Cq-arom.); 132.6 ($\text{CH}=\text{CH}_2$); 128.5, 128.5, 128.0, 128.0, 127.9 (C-arom.); 118.4 ($\text{CH}=\text{CH}_2$); 82.6 (CHOBn); 73.3, 73.0 (CH_2 -benzyl); 72.5 (OCH_2CO); 35.2 ($\text{CH}_2\text{CH}=\text{CH}_2$); ESI-MS (m/z): 328.2 ($\text{M}+\text{NH}_4^+$), 333.1 ($\text{M}+\text{Na}^+$). A small amount of ketone **15** was purified by silica gel chromatography (EtOAc in hexanes 0 $\rightarrow$ 25%) to monitor its optical rotation. The value of $[\alpha]_{\text{D}}^{20} = -25.18$ ($c = 1.0$, CHCl_3) remained unchanged after 3 days in chloroform solution.

The crude ketone **15** (5.00 g, 16.0 mmol) was dissolved in dry THF (100 mL) under argon and the solution was cooled to -78°C . Vinylmagnesium bromide (1M in THF, 32.0 mL, 32.0 mmol) was added dropwise and the reaction was stirred for 30 min at this temperature. The reaction was quenched by the dropwise addition of a saturated ammonium chloride solution (100 mL) and the aqueous phase was extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were dried (MgSO_4) and concentrated. The crude alcohols were purified by flash chromatography on silica gel (EtOAc in hexanes 10 $\rightarrow$ 30%) to give **10a,b** (4.93 g, 91%) as a 3:1-mixture of diastereomers. A small amount of the major (3*S*,4*S*)-isomer was purified after a second chromatography to give **10a** as a clear oil; $[\alpha]_{\text{D}}^{20} = 0.40$ ($c = 1.0$, CHCl_3); IR (neat): 3550, 3029, 2860, 1870, 1639, 1496, 1454, 1417, 1317, 1191, 1072, 1026, 991, 913, 733 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): $\delta = 7.35 - 7.25$ (m, 10H, CH -arom.); 5.98 (dd, 1H, $J = 17.4, 11.0$ Hz, H-2); 5.90 (dddd, 1H, $J = 17.1, 10.1, 7.1, 7.1$ Hz, H-6); 5.43 (dd, 1H, $J = 17.4, 1.8$ Hz, H-1a); 5.21 (dd, 1H, $J = 11.0, 1.8$ Hz, H-1b); 5.08 (dm, 1H, $J = 17.1$, H-7a); 5.01 (dm, 1H, $J = 10.1$, H-7b); 4.65 (d, 1H, $J = 11.1$ Hz, CHH -benzyl-A); 4.50 (s, 2H, CH_2 -benzyl-B); 4.49 (d, 1H, $J = 11.1$ Hz, CHH -benzyl-A); 3.68 (dd, 1H, $J = 8.2, 4.0$ Hz, H-4); 3.55 (d, 1H, $J = 9.0$ Hz, CHH -OBn); 3.40 (d, 1H, $J = 9.0$ Hz, CHH -OBn); 2.55 (bs, 1H, 3-OH); 2.42 – 2.32 (m, 1H, H-5a); 2.35 – 2.27 (m, 1H, H-5b); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 138.6, 138.3$ (Cq-arom.); 137.6 (C-6); 136.1 (C-2); 128.4, 128.3, 127.9, 127.7, 127.7 (C-arom.); 116.8 (C-1); 114.9 (C-7); 81.0 (C-4); 76.7 (C-3); 74.1, 73.9 (CH_2 -benzyl); 73.5 (CH_2 -OBn); 34.8 (C-5); ESI-MS (m/z): 361.1 ($\text{M}+\text{Na}^+$). Elemental Analysis for $\text{C}_{22}\text{H}_{26}\text{O}_3$: Calculated: C, 78.07; H, 7.74. Found: C, 78.06; H, 7.71.

3.2.4. (1*S*,5*S*)-5-Benzyloxy-1-benzyloxymethylcyclopent-2-enyl acetate (17_{major}) and (1*R*,5*S*)-5-Benzyloxy-1-benzyloxymethylcyclopent-2-enyl acetate (17_{minor})—The two diastereomers **10a,b** (4.80 g, 14.2 mmol) were dissolved in dry, deoxygenated CH_2Cl_2 (400 mL) under argon at room temperature and treated with second generation Grubbs catalyst (600 mg, 0.710 mmol), which was added in one portion. The mixture was heated to reflux for 1 h and cooled to room temperature. After removal of the solvent under reduced pressure, the crude material was redissolved in dry CH_2Cl_2 (50.0 mL) and cooled to 0°C . Triethylamine (19.8 mL, 0.142 mol), *N,N*-dimethylaminopyridine (DMAP, 174 mg, 1.42 mmol) and acetic anhydride (6.71 mL, 71.0 mmol) were added and the mixture was stirred at room temperature overnight. The reaction was diluted with CH_2Cl_2 (200 mL) and the organic phase was extracted with 1*N* HCl (3×100 mL). The aqueous washings were reextracted with CH_2Cl_2 (100 mL) and the combined organic extracts were dried (MgSO_4) and concentrated. The crude acetates were separated by flash chromatography on silica gel

(EtOAc in hexanes 10 → 30%) to yield the (1*S*,5*S*)-diastereomer **17_{major}** (3.20 g, 64%) and the (1*R*,5*S*)-diastereomer **17_{minor}** (1.05 g, 21%) as colorless oils:

17_{minor}: $[\alpha]_D^{20} = 32.48$ ($c=1.0$, CHCl₃); IR (neat): 3073, 3029, 2859, 1733, 1496, 1453, 1365, 1240, 1100, 1017, 734, 696 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.35 – 7.25 (m, 10H, *CH*-arom.); 6.05 (dt, 1H, J = 6.2, 2.0 Hz, H-2); 5.92 (dt, 1H, J = 6.2, 2.4 Hz, H-3); 4.66 (d, 1H, J = 12.0 Hz, *CHH*-benzyl-A); 4.57 (d, 1H, J = 12.0 Hz, *CHH*-benzyl-A); 4.55 (d, 1H, J = 12.0 Hz, *CHH*-benzyl-B); 4.51 (d, 1H, J = 12.0 Hz, *CHH*-benzyl-B); 4.39 (dd, 1H, J = 7.0, 5.0 Hz, H-5); 3.93 (AB-system, 2H, J = 10.0 Hz, CH₂-OBn); 2.70 (dddd, 1H, J = 16.7, 7.0, 2.4, 2.0 Hz, H-4a); 2.33 (ddt, 1H, J = 16.7, 5.0, 2.0 Hz, H-4b); 2.00 (s, 3H, OAc); ¹³C NMR (100 MHz, CDCl₃): δ = 170.3 (C=O); 138.5, 138.4 (Cq-arom.); 133.2 (C-2); 130.8 (C-3); 128.3, 128.2, 127.6, 127.5, 127.4 (C-arom.); 94.4 (C-1); 84.0 (C-5); 73.6, 72.6 (CH₂-benzyl); 68.9 (CH₂-OBn); 37.4 (C-4); 22.0 (CH₃, OAc); ESI-MS (m/z): 375.1 (M+Na⁺). Elemental Analysis for C₂₂H₂₄O₄: Calculated: C, 74.98; H, 6.86. Found: C, 74.72; H, 6.64.

17_{major}: $[\alpha]_D^{20} = -11.03$ ($c=1.0$, CHCl₃); IR (neat): 3029, 2859, 1730, 1496, 1454, 1364, 1243, 1097, 1016, 910, 733, 697 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.35 – 7.25 (m, 10H, *CH*-arom.); 6.03 (dt, 1H, J = 6.1, 2.0 Hz, H-2); 5.93 (dt, 1H, J = 6.1, 2.4 Hz, H-3); 4.56 (AB-system, 2H, J = 12.0 Hz, CH₂-benzyl-A); 4.50 (AB-system, 2H, J = 12.0 Hz, CH₂-benzyl-B); 4.17 (dd, 1H, J = 6.1, 4.4 Hz, H-5); 3.84 (d, 1H, J = 9.7 Hz, *CHH*-OBn); 3.73 (d, 1H, J = 9.7 Hz, *CHH*-OBn); 2.58 – 2.52 (m, 1H, H-4a); 2.51 – 2.45 (m, 1H, H-4b); 2.00 (s, 3H, OAc); ¹³C NMR (100 MHz, CDCl₃): δ = 170.4 (C=O); 138.4, 138.0 (Cq-arom.); 133.6 (C-2); 130.9 (C-3); 128.3, 128.2, 127.9, 127.6, 127.6 (C-arom.); 90.5 (C-1); 79.5 (C-5); 73.4, 72.5 (CH₂-benzyl); 70.7 (CH₂-OBn); 37.5 (C-4); 21.9 (CH₃, OAc); ESI-MS (m/z): 375.1 (M+Na⁺). Elemental Analysis for C₂₂H₂₄O₄: Calculated: C, 74.98; H, 6.86. Found: C, 74.86; H, 6.79.

3.2.5. (1*R*,4*S*)-4-Benzyloxy-3-benzyloxymethylcyclopent-2-enyl acetate (**18**)—

The acetate **17_{major}** (3.10 g, 8.80 mmol) was dissolved in dry THF (60.0 mL) at room temperature under argon and treated with *p*-benzoquinone (761 mg, 7.04 mmol) and PdCl₂(CH₃CN)₂ (228 mg, 0.88 mmol) as catalyst. The mixture was heated to reflux for 4h while the color changed slowly to dark brown. The solvent was evaporated under vacuum and the crude was directly purified by flash chromatography on silica gel (EtOAc in hexanes, 5 → 30%) to give the rearranged acetate **18** (2.82 g, 91%) as a colorless oil; $[\alpha]_D^{20} = 59.60$ ($c=1.0$, CHCl₃); IR (neat): 3029, 2856, 1732, 1496, 1454, 1370, 1237, 1155, 1091, 1025, 913, 851, 735 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.35 – 7.25 (m, 10H, *CH*-arom.); 5.93 – 5.91 (m, 1H, H-2); 5.47 (m, H-1); 4.56 (d, 1H, J = 12.0 Hz, *CHH*-benzyl-A); 4.54 (d, 1H, J = 12.0 Hz, *CHH*-benzyl-B); 4.48 (d, 1H, J = 12.0 Hz, *CHH*-benzyl-A); 4.47 (d, 1H, J = 12.0 Hz, *CHH*-benzyl-B); 4.47 – 4.43 (m, 1H, H-4); 4.19 – 4.17 (m, 2H, CH₂-OBn); 2.75 (overlapped dt, J = 14.5, 7.5 Hz, H-5a); 2.01 (s, 3H, OAc); 1.80 (dt, 1H, J = 14.5, 3.8 Hz, H-5b); ¹³C NMR (100 MHz, CDCl₃): δ = 170.9 (C=O); 147.4 (C-3) 138.3, 138.0, 128.4, 128.3, 128.2 (C-arom.); 127.7 (C-2); 80.4 (C-1); 76.1 (C-4); 72.8, 71.2 (CH₂-benzyl); 66.4 (CH₂-OBn); 37.8 (C-5); 21.2 (CH₃, OAc); ESI-MS (m/z): 370.1 (M+NH₄⁺), 375.1 (M+Na⁺). Elemental Analysis for C₂₂H₂₄O₄: Calculated: C, 74.98; H, 6.86. Found: C, 75.15; H, 7.01.

3.2.6. (1*S*,4*S*)-4-Benzyloxy-3-benzyloxymethylcyclopent-2-enyl acetate (**19**)—

The acetate **17_{minor}** (1.00 g, 2.84 mmol) was dissolved in dry THF (20.0 mL) at room temperature under argon and treated with *p*-benzoquinone (245 mg, 2.27 mmol) and PdCl₂(CH₃CN)₂ (73.7 mg, 0.284 mmol) as catalyst. In a similar manner as described for **18**, the rearranged acetate **19** (931 mg, 93%) was obtained as a colorless oil; $[\alpha]_D^{20} = -57.23$ ($c=1.0$, CHCl₃); IR (neat): 3030, 2856, 1730, 1496, 1454, 1370, 1238, 1156, 1069, 1026, 914, 864, 735 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.35 – 7.25 (m, 10H, *CH*-arom.); 5.94 (m, 1H, H-2); 5.75 – 5.70 (m, 1H, H-1); 4.74 (m, 1H, H-4); 4.55 (d, 1H, J = 12.0 Hz, *CHH*-benzyl-A); 4.54 (d, 1H, J = 11.8 Hz, *CHH*-benzyl-B); 4.50 (d, 1H, J = 12.0 Hz, *CHH*-benzyl-A); 4.43

(d, 1H, $J = 11.8$ Hz, CHH-benzyl-B); 4.16 (bs, 2H, $\text{CH}_2\text{-OBn}$); 2.31 (ddd, 1H, $J = 14.7, 7.0, 3.5$ Hz, H-5a); 2.12 (ddd, 1H, $J = 14.7, 6.8, 2.8$ Hz, H-5b); 1.98 (s, 3H, OAc); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 170.9$ (C=O); 148.4 (C-3) 138.2, 138.0, 128.4, 127.7 (C-arom.); 127.6 (C-2); 81.8 (C-1); 78.1 (C-4); 72.8, 71.4 ($\text{CH}_2\text{-benzyl}$); 66.5 ($\text{CH}_2\text{-OBn}$); 37.9 (C-5); 21.2 (CH_3 , OAc); ESI-MS (m/z): 370.1 ($\text{M}+\text{NH}_4^+$), 375.1 ($\text{M}+\text{Na}^+$). Elemental Analysis for $\text{C}_{22}\text{H}_{24}\text{O}_4$: Calculated: C, 74.98; H, 6.86. Found: C, 74.69; H, 6.84.

3.2.7. (1S,2R,4S,5R)-4-benzyloxy-5-benzyloxymethylbicyclo[3.1.0]hexan-2-ol (4)—The bicyclic hexanol **4** was prepared from the allylic acetates **18** and **19** as previously described from the corresponding allylic benzoates.²⁰ All analytical data were identical to those reported before.

3.2.8. (1R,2S,4S,5S)-4-Azido-2-benzyloxy-1-benzyloxymethylbicyclo[3.1.0]hexane (21)—Under a blanket of argon the bicyclic hexanol **4** (800 mg, 2.47 mmol) was dissolved in dry CH_2Cl_2 (25 mL) at 0°C , followed by the addition of triethylamine (1.03 mL, 7.40 mmol) and methanesulfonyl chloride (MsCl , 287 μL , 3.71 mmol). The reaction mixture was stirred for 1 h at 0°C and then poured into a mixture of ice-cold phosphate buffer (pH, 7.2, 100 mL) and Et_2O (100 mL). The aqueous phase was extracted with Et_2O (2×100 mL) and the combined extracts were dried (MgSO_4) and concentrated. The crude mesylate **4a** was used in the next substitution reaction without any further purification (decomposition occurred during chromatography on silica gel). The mesylate **4a** (995 mg, 2.47 mmol) was dissolved in dry DMF (25.0 mL). After the addition of sodium azide (1.61 g, 24.7 mmol), the solution was heated to 60°C and stirred overnight. The reaction was allowed to reach room temperature and poured into a mixture of water (100 mL) and Et_2O (100 mL). The aqueous phase was further extracted with Et_2O (2×100 mL) and the combined organic extracts were dried (MgSO_4) and concentrated. Flash chromatography on silica gel (EtOAc in hexanes 25 $\rightarrow$ 45%) yielded the azide **21** (751 mg, 87%) as a colorless oil.⁴¹ The analytical data were identical to those reported earlier.

3.2.9. tert-Butyl (1S,2S,4S,5R)-4-benzyloxy-5-benzyloxymethylbicyclo[3.1.0]hexan-2-ylcarbamate (22)—Under a blanket of argon, azide **21** (700 mg, 2.00 mmol) was dissolved in MeOH (30 mL) at room temperature. Di-*tert*-butyldicarbonate ($(\text{Boc})_2\text{O}$, 481 mg, 2.20 mmol) and Lindlar's catalyst (150 mg) were added and the reaction vessel was flushed with H_2 . Stirring at room temperature continued until all starting material was consumed according to TLC-analysis (1.0 h). The solvent was filtered through a short pad of celite and the filtrate was concentrated. The crude was purified by flash chromatography on silica gel (EtOAc in hexanes 15 $\rightarrow$ 35%) to yield the carbamate **22** (788 mg, 93%) as a colorless syrup; $[\alpha]_{\text{D}}^{20} = 30.15$ ($c=1.0$, CHCl_3); IR (neat): 3328, 2976, 2862, 1699, 1496, 1454, 1364, 1243, 1165, 1073, 1027, 909, 779, 696 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): $\delta = 7.35 - 7.25$ (m, 10H, CH-arom.); 4.66 (br d, 1H, $J = 5.7$ Hz, H-2); 4.55 - 4.43 (m, 5H, $2 \times \text{CH}_2\text{-benzyl}$, H-4); 4.03 (bs, 1H, NH); 3.93 (br d, 1H, $J = 10.2$ Hz, CHH-OBn); 3.13 (d, 1H, $J = 10.2$ Hz, CHH-OBn); 1.97 (dd, 1H, $J = 13.9, 7.5$ Hz, H-3a); 1.50 - 1.40 (m, 10H, H-3b, *tert*Bu); 1.26 (m, 1H, H-1); 0.89 (br t, 1H, $J \approx 5$ Hz, H-6a); 0.59 (dd, 1H, $J = 7.5, 5.5$ Hz, H-6b); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 155.0$ (C=O); 138.7, 138.5, 128.4, 128.3, 127.7, 127.6, 127.5, 127.5 (C-arom.); 78.7 ($\text{C}(\text{CH}_3)_3$); 77.4 (C-4); 72.8 ($\text{CH}_2\text{-OBn}$); 71.9, 71.7 ($2 \times \text{CH}_2\text{-benzyl}$); 51.3 (C-2); 35.9 (C-5); 32.3 (C-3); 28.4 ($\text{C}(\text{CH}_3)_3$); 27.1 (C-1); 10.2 (C-6); ESI-MS (m/z): 446.2 ($\text{M}+\text{Na}^+$). HRMS (FAB): $m/z = 424.2054$ (calculated for $[\text{C}_{26}\text{H}_{33}\text{O}_4\text{N}+\text{K}]^+ = 424.2047$).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Synthetic strategies towards N-MCT (**1**)

Figure 2.
Retrosynthetic analysis of the novel strategy towards the N-MCT precursor **4**

Scheme 1.

Reagents and conditions: (a) CH_3COCl , MeOH (Table 1); (b) NaH, BnBr, $n\text{-Bu}_4\text{NI}$, THF; (c) CH_3COCl , H_2O -dioxane (85%, 3 steps); (d) $(\text{Ph})_3\text{PMeBr}$, $n\text{-BuLi}$, THF (91%); (e) $(\text{COCl})_2$, DMSO, Et_3N , CH_2Cl_2 (100%); (f) Table 2; (g) Grubb's catalyst, 2nd generation, CH_2Cl_2 ; (h) Ac_2O , DMAP, Et_3N , CH_2Cl_2 (85%, 2 steps).

Scheme 2.

Reagents and conditions: (a) *p*-benzoquinone, PdCl₂(MeCN)₂, THF (91-93%); (b) 1% NaOH, MeOH (100%); (c) i. (Ph)₃P, DIAD, PhCO₂H, Et₂O; ii. K₂CO₃, MeOH (88%); (d) CH₂I₂, Et₂Zn, CH₂Cl₂ (87%); (e) MsCl, Et₃N, CH₂Cl₂; (f) NaN₃, DMF (83%, 2 steps); (g) H₂, Lindlar catalyst, (Boc)₂O, MeOH (92%).

Table 1Formation of the methyl glycosides **12** and **12'** under acidic conditions.

Experiment	Temperature	Time	Ratio (12/12')	Yield
1	20 °C.	15 min.	85/15	quant.
2	10 °C	30 min.	90/10	quant.
3	0 °C	4 h	93/7	quant.
4	- 20 °C	10 h	96/4	quant.

Table 2Alkylation of ketone **15** with vinylmagnesium bromide in various solvents.

The reaction scheme shows ketone **15** (4,4-dibenzoyloxy-2-penten-2-one) reacting with vinylmagnesium bromide ($\text{CH}_2=\text{CHMgBr}$) in a solvent to yield two diastereomeric products, **10a** and **10b**. Product **10a** is the major isomer, and **10b** is the minor isomer. Both products are 4,4-dibenzoyloxy-2-penten-2-ols.

Entry	Solvent	Temperature	Ratio (major/minor) %	Yield
1	Et_2O	-78 °C	56:44	93%
2	MTBE	-78 °C	56:44	90%
3	CH_2Cl_2	-78 °C	64:36	89%
4	toluene	-78 °C	63:37	93%
5	THF	-78 °C	75:25	91%
6	THF	-70 °C	75:25	93%
7	THF	-60 °C	75:25	88%
8	THF	-50 °C	75:25	92%
9	THF	-40 °C	75:25	93%