JOC Notes

New Ruthenium-Based Protocol for Cleavage of Terminal Olefins to Primary Alcohols: Improved Synthesis of a Bicyclic Nucleoside

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Abstract: A new protocol for the oxidative cleavage of terminal alkenes to give exclusively primary alcohols in high yields is introduced. The protocol is based on RuO_4-mediated dihydroxylation, $NaIO_4$-mediated diol cleavage, and $NaBH_4$-mediated reduction, but the introduction of a reducing step before the diol cleavage removes the formation of byproducts and improves the yield significantly. The new protocol has been developed and used for the improved preparation of a [3.2.0]bicycloarabinonucleoside with important potential in antisense and antigene technology.

The search for therapeutically efficient antisense and antigene oligonucleotides has motivated the synthesis and evaluation of a high number of chemically modified nucleic acid analogues.[1] Bicyclic and thereby conformationally restricted nucleosides have received special attention in the design of oligonucleotides with high-affinity DNA and RNA recognition.[2] As a promising example, the [3.2.0]bicycloarabinonucleoside **1** (Figure 1) is the hitherto most efficient mimic of the interesting *E*-type conformation, and oligodeoxynucleotides containing one or several incorporations of **1** have displayed improved affinity toward both complementary single-stranded DNA and RNA.[3,4] In our continuous search for antisense and antigene compounds and in the investigations of the crucial enzyme RNase H, the nucleoside **1** is, therefore, needed for further examination. However, the preparation of larger amounts of **1** is hampered by its complicated synthesis (Figure 1). Thus, from a D-xylose derivative, the dibenzylated 3′-*C*-vinyl compound **2** was obtained via a stereoselective Grignard reaction and used in the preparation of the *ribo*-nucleoside **3** (R = H). By using the pyrimidine moiety in a 2-2′-anhydro-approach,[5] **3** was converted to its arabino-configured

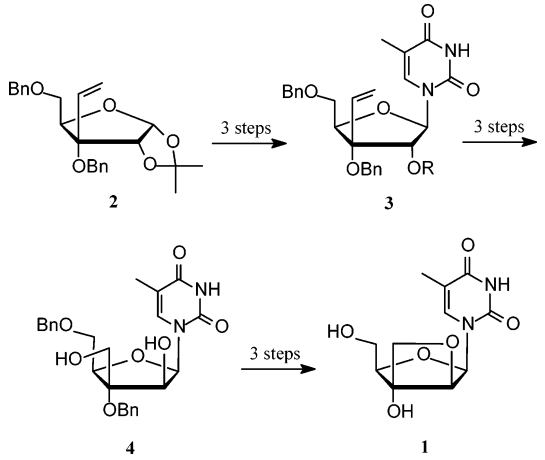

FIGURE 1. Original preparation of the bicyclic nucleoside **1**.[3]

stereoisomer, and the double bond was oxidatively cleaved to give **4**. A selective mesylation and ring-closure afforded after debenzylation **1** in 8.5% yield over the 14 steps.[3] A careful perusal of the reaction sequence reveals that the major bottleneck was the oxidative cleavage of the vinyl group to a hydroxymethyl group using a two-step OsO_4–$NaIO_4$/$NaBH_4$ protocol. This resulted in a poor isolated yield (36%) of the desired product along with the intermediate diol, the starting alkene, and products in which the pyrimidine double bond has been dihydroxylated, as seen with other similar substrates.[6]

To find a better synthetic route toward **1**, we decided to perform the problematic oxidative cleavage step in the beginning of the reaction sequence with the conveniently obtained compound **2**[3] as the substrate. Thus, dihydroxylation of the pyrimidine would be avoided, and better overall yields of the final target molecule were envisioned. Using the standard OsO_4–$NaIO_4$/$NaBH_4$ protocol[7] on **2** resulted in a mixture of the required hydroxymethyl product **5**, the diol **6**, and the starting material **2** (approximate ratio 5:6:3) in 60% yield (Scheme 1). Noting the presence of diol in the product mixture, we thought of first converting **2** into diol **6**, which could subsequently be degraded to **5**. However, the reaction of **2** with OsO_4–NMO[8] did not complete even after multiple additions of OsO_4 over a period of 8 days. Efforts to achieve the desired molecule **5** by an ozonolysis/reduction protocol[9] resulted in complex mixtures in very low yields. The failures of these established procedures forced us to search for an alternative protocol for the conversion of monosubstituted olefins to primary alcohols.

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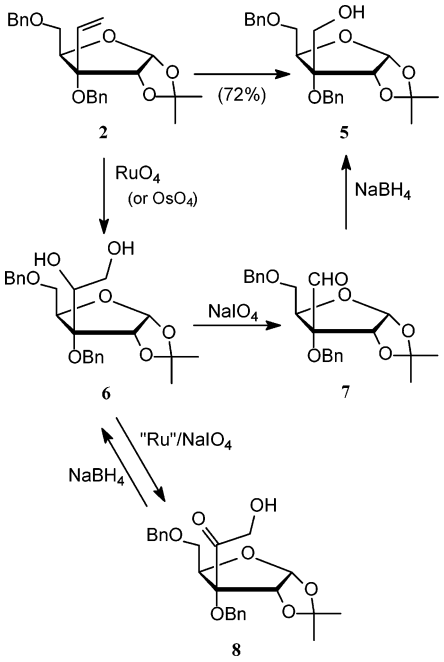
SCHEME 1. Oxidative Cleavage of Alkene 2



Ruthenium tetraoxide (RuO_4) (usually made in situ from $RuCl_3 \cdot xH_2O$ and a cooxidant, normally $NaIO_4$) has long been known for being a much more vigorous oxidant than its osmium analogue.[10] However, its use is mainly limited to the degradation of unsaturated organic compounds to carboxylic acids.[11] Although modified reaction conditions have been reported recently making *cis*-diols as the main product, overoxidation to yield carboxylic acids is usually observed.[12] The problem of overoxidation is especially acute in monosubstituted olefins, and 67% is the best yield of diol reported from any monosubstituted alkene using a catalytic ruthenium procedure.[12] We found that the reaction of **2** under modified conditions[12] (0.07 mol equiv of $RuCl_3 \cdot xH_2O$ and 1.5 equiv of $NaIO_4$ at 0 °C in a biphasic solvent system of ethyl acetate, acetonitrile, and water (in a ratio of 3:3:1)) for 1.5 min leads to complete disappearance of the starting material (Scheme 1). The crude residue obtained after the aqueous workup was treated with $NaIO_4$ in THF−H_2O until TLC indicated no starting diol. After aqueous workup, the residue was redissolved in THF−H_2O and treated with $NaBH_4$ to yield **5**. Surprisingly, HR-MALDI-MS of the crude product showed the presence of some diol **6** in addition to the required hydroxymethyl product **5**. Therefore, the crude product was subjected once again to $NaIO_4$ followed by $NaBH_4$ treatment after which no traces of **6** were detected and **5** was obtained in 26% overall yield from **2** after column chromatography.

To explain the presence of diol **6** after the complete reaction sequence of RuO_4−$NaIO_4$−$NaBH_4$ even though TLC after the treatment of $NaIO_4$ indicated a completed diol cleavage, we purified the crude mixture obtained after the ruthenium treatment of **2** and isolated some α-ketol **8**, aldehyde **7**, and the expected diol **6** (approximate ratio 1:2:6) (Scheme 1). We envisioned that the α-ketol **8**, formed on ruthenium treatment, remained unchanged on $NaIO_4$ treatment and was reconverted into the diol **6** on further reaction with $NaBH_4$. Moreover, we found that it is almost impossible to completely remove ruthenium from the crude reaction mixture even after passing the solution through Celite or treating the mixture with sodium thiosulfate. Therefore, the little ruthenium carried forward in the reaction sequence might be responsible for oxidizing some of the diol **6** to the α-ketol **8** prior to periodate cleavage as well as overoxidizing the aldehyde **7** to carboxylic acid, thus reducing the overall yield of the reaction protocol.[13]

On the basis of these observations, we thought of subjecting the crude mixture, obtained after the ruthenium oxidation, to $NaBH_4$ reduction, predicting that it should reduce any active ruthenium species present as well as reduce the α-ketol **8** to the diol **6** and hence eliminate the hazards of overoxidation on further periodate treatment. The experiments performed on these lines proved our assumption to be correct, as we are able to obtain consistently high yields of **5** (71−72% from **2**) adopting this reaction sequence (Table 1). Another indirect proof was obtained by carrying out a blank experiment where no olefin was added. When the residue obtained after the aqueous workup was treated with $NaBH_4$, a flocculent black powder (presumably inactive ruthenium species) was separated, appearing similar to what we obtained in the experiments using olefins.

The developed protocol worked equally well on a larger scale, and we got consistent yields with 19 mmol of alkene **2**. The remarkable success of this reaction protocol provoked us to apply it to some other carbohydrate substrates (including allyl and vinyl substituents) as well as simple substrates such as styrene and 1-decene (Table 1). The protocol is so predictive that we carried out the reaction sequence on 1-decene without any analytical support like TLC, NMR, etc. and obtained 1-nonanol in 80% yield. This result (Table 1) can only be explained by taking into account that all the α-ketol formed in the dihydroxylation step was recycled back to diol and no more α-ketol was generated in the reaction sequence. Thus, 1-decene has been reported to yield only 67% diol on treatment with RuO_4.[12] We did not examine a series of different protecting groups, as RuO_4 is known to accept a vide range of these,[11,12] whereas the scopes and limitations of $NaBH_4$ reduction is well-known.

Next, we turned our attention to using this protocol on nucleosides themselves (exemplified by **3** (R = Ac)), but as expected, we found that the double bond of the pyrimidine ring undergoes facile dihydroxylation, rendering this protocol unusable on pyrimidine nucleosides.

Having achieved the desired goal of efficient conversion of **2** to **5**, we attempted the synthesis of the target nucleoside **1** as depicted in Scheme 2. Benzoylation of

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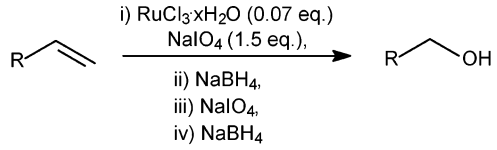
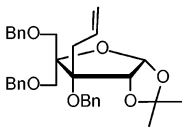
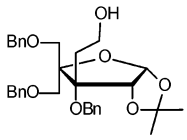
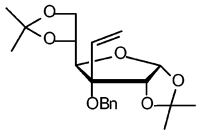
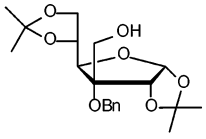
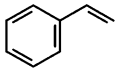
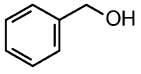
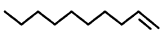
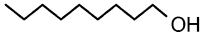
(13) After our work was finished, a report appeared indicating the formation of α-ketols as side products on treating olefins with RuO_4/$NaIO_4$, complementing our presumption; Plietker, B. *Org. Lett.* **2004**, *6*, 289−291.

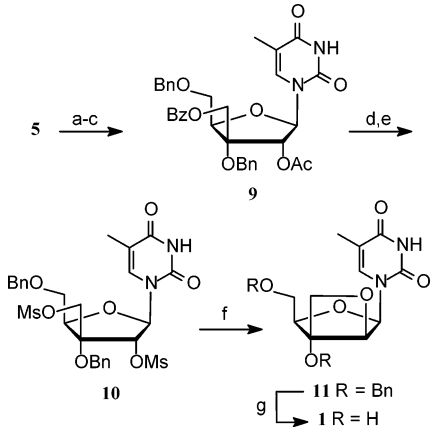
TABLE 1. Oxidative Cleavage of Terminal Olefins[a]



substrate	product	time[b] (h)	yield (%)
2	**5**	2.5	72[c] 71[d]
		2.5	75[c]
		2.5	74[c]
		1.75	79[e]
		1.75	80[e]

[a] See General Procedure in Experimental Section. [b] Overall reaction time. [c] Isolated yield after column purification. [d] Yield at 19 mmol scale. [e] Isolated crude yield.

SCHEME 2. New Synthesis of Nucleoside 1[a]



[a] Reagents and conditions: (a) BzCl, pyridine; (b) 80% AcOH, then Ac_2O, pyridine; (c) thymine, *N*,*O*-bis(trimethylsilyl)acetamide, CH_3CN, TMS-triflate (69%, three steps); (d) $NaOCH_3$, MeOH; (e) MsCl, pyridine; (f) NaOH, EtOH, H_2O (53%, three steps); (g) H_2, $Pd(OH)_2/C$, EtOH (98%).

the free primary alcohol, acetolysis, acetylation, and coupling with thymine using the silyl Hilbert-Johnson/Birkofer method as modified by Vorbrüggen et al.[14] yielded the nucleoside **9** in 69% yield from **5**. Deprotection of the acetyl and benzoyl groups in a single step followed by complete mesylation afforded the di-*O*-mesylated derivative **10**. Conversion of **10** directly to the desired bicyclic nucleoside **11** proceeded very satisfactory (53% yield from **9**) in a refluxing mixture of 2 M aqueous NaOH and aqueous ethanol. This conversion involves inversion of stereochemistry of the 2′-carbon atom, subsequent cyclization in a one-pot reaction cascade involving the 2-2′-anhydro intermediate,[5] and hydrolysis of this intermediate to give the arabino-configurated nucleoside, which is preorganized for the subsequent formation of a four-membered oxetane ring. A similar tandem reaction has been shown before to form a bicyclic nucleoside with a five-membered ring.[15] Recently, also a bicyclic nucleoside with an oxetane ring has been prepared using reaction conditions that indicate a similar reaction cascade.[16] Finally, debenzylation of **11** afforded **1** in 98% yield.

In conclusion, the use of our new ruthenium protocol for the oxidative cleavage of a double bond to a primary alcohol and the tandem reaction cascade for the ring closure allowed us to develop a significantly improved synthetic sequence for the bicyclic nucleoside **1**. The apparent advantages of the new synthesis are (i) the overall yield of **1** from **2** is 25.8% as compared to 12.5% by the earlier route;[3] (ii) only three steps in the present sequence require column chromatographic separation as compared to eight steps in the earlier route;[3] and (iii) no selective mesylation (and concomitant formation of a dimesyl derative) is required. The preparation of larger amounts of **1** as well as its analogues with other pyrimidine nucleobases is hereby possible, and we are now exploring oligonucleotides containing **1** in biological studies.

In this paper, we have described the first ruthenium-catalyzed protocol (Table 1) for the oxidative cleavage of monosubstituted alkenes to yield exclusively primary alcohols, a process similar to the OsO_4−$NaIO_4/NaBH_4$ protocol or the alternative ozonolysis/$NaBH_4$ protocol, however, with several advantages: (i) the ruthenium reagent is far less expensive as compared to osmium tetraoxide; (ii) $RuCl_3$ is easy to handle, as it is solid, nonvolatile, and stable at room temperature; (iii) the speed of reaction is increased significantly; (iv) the workup is very easy, and even a 19 mmol-scale reaction can easily be completed in 1 day; (v) all of the steps are under aqueous conditions, thus eliminating the need for anhydrous solvents; and (vi) RuO_4 is neither explosive nor poisonous.[17] Obviously, this reaction protocol represents an efficient and intriguing alternative to the osmium- or ozone-based protocols, and we expect it to find wide general application in synthetic chemistry.

Experimental Section

General Procedure for Oxidative Cleavage of Olefins. $NaIO_4$ (1.5 mmol) was stirred in water (2 mL), and the solution was cooled to 0 °C. $RuCl_3 \cdot xH_2O$ (40.6% Ru, obtained from ChemPure, Germany) (0.07 mmol) was added followed by the addition of ethyl acetate (6 mL) and acetonitrile (6 mL), and the mixture was stirred for 5 min at 0 °C. The olefin (1 mmol)

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was added, and the slurry was stirred for 90 s. The reaction was quenched by the addition of a saturated aqueous solution of $Na_2S_2O_3$ (10 mL). Phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was dissolved in a mixture of THF (2.5 mL) and water (2.5 mL). $NaBH_4$ (1 mmol) was added, and a flocculent black powder began to separate after 5 min. The mixture was stirred for 20 min at room temperature, water (5 mL) was added, and the mixture was extracted with dichloromethane (3 × 10 mL). The combined organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (3 × 5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was dissolved in THF (5 mL) and water (5 mL) at 0−5 °C. $NaIO_4$ (2 mmol) was added in small portions, and the solution was stirred for 20 min (followed by TLC, wherever possible) at room temperature. Ehylene glycol (35 μL) was added, and the reaction mixture was diluted with water (7 mL). The mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was redissolved in a mixture of THF (4 mL) and water (4 mL), and $NaBH_4$ (3 mmol) was added. The reaction mixture was stirred at room temperature for 1 h; water (5 mL) was added, and the mixture was extracted with dichloromethane (3 × 10 mL). The combined organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (3 × 5 mL) and dried (Na_2SO_4). After concentration under reduced pressure, the residue was purified by flash chromatography.

3,5-Di-*O*-benzyl-1,2-di-*O*-isopropylidene-3-*C*-hydroxymethyl-α-D-ribofuranose (5). Prepared from 3,5-di-*O*-benzyl-1,2-di-*O*-isopropylidene-3-*C*-vinyl-α-D-ribofuranose (**2**)[3] (2.68 g, 6.76 mmol) as starting material using the general procedure. Column chromatography (eluent: gradient of methanol (0−0.4%) in dichloromethane). The reaction yielded 1.93 g (72%) of a colorless viscous oil: R_f 0.65 (19:1 dichloromethane/methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.23 (m, 10H, Bn), 5.83 (d, 1H, J_{H1-H2} = 3.9 Hz, H-1), 4.71 (d, 1H, J_{gem} = 10.5 Hz, 3-OCH_2Ph), 4.64 (d, 1H, J_{gem} = 11.7 Hz, 5-OCH_2Ph), 4.62 (d, 1H, J_{gem} = 10.5 Hz, 3-OCH_2Ph), 4.56 (d, 1H, J_{gem} = 11.7 Hz, 5-OCH_2Ph), 4.50 (d, 1H, J_{H1-H2} = 3.9 Hz, H-2), 4.22 (m, 1H, H-4), 3.88−3.71 (m, 4H, 2 × H-5, 2 × H-1′), 3.37 (dd, 1H, J = 6.3 Hz, 8.1 Hz, OH), 1.60 (s, 3H, CH_3), 1.37 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 137.2, 128.6, 128.4, 128.1, 128.1, 127.9, 127.7 (Bn), 112.6 (*C*(CH_3)$_2$), 104.6 (C-1), 84.0 (C-3), 81.1 (C-2), 80.1 (C-4), 74.3 (5-OCH_2Ph), 67.5 (3-OCH_2Ph), 66.7 (C-5), 62.0 (C-1′), 27.0 (CH_3), 26.7 (CH_3); HR-MALDI MS *m*/*z* 423.1762 ([M + Na]$^+$, $C_{23}H_{28}O_6Na^+$ calcd 423.1778). Anal. Calcd for $C_{23}H_{28}O_6$ + (1/2)H_2O: C, 67.46; H, 7.13. Found: C, 67.37; H, 6.78.

Acknowledgment. The Danish National Research Foundation is thanked for financial support.

Supporting Information Available: General experimental section, including procedures for the preparation of the compounds in Table 1 and compounds **1** and **9**−**11**, as well as NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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