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Use of a Cyclic Sulfite as an Epoxide Surrogate in the Regioselective Synthesis of a Carbocyclic Ring-Enlarged 4',1'a-Methano Oxetanocin Analogue

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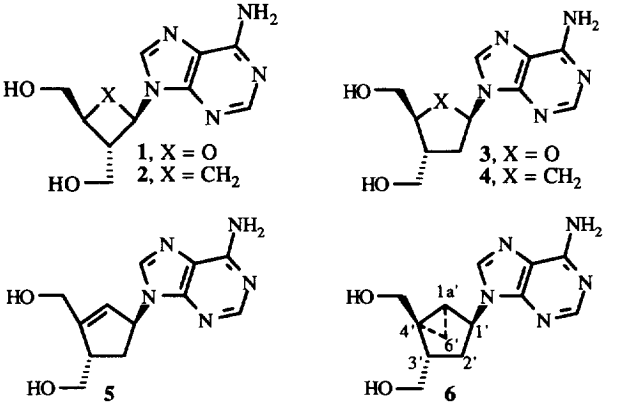
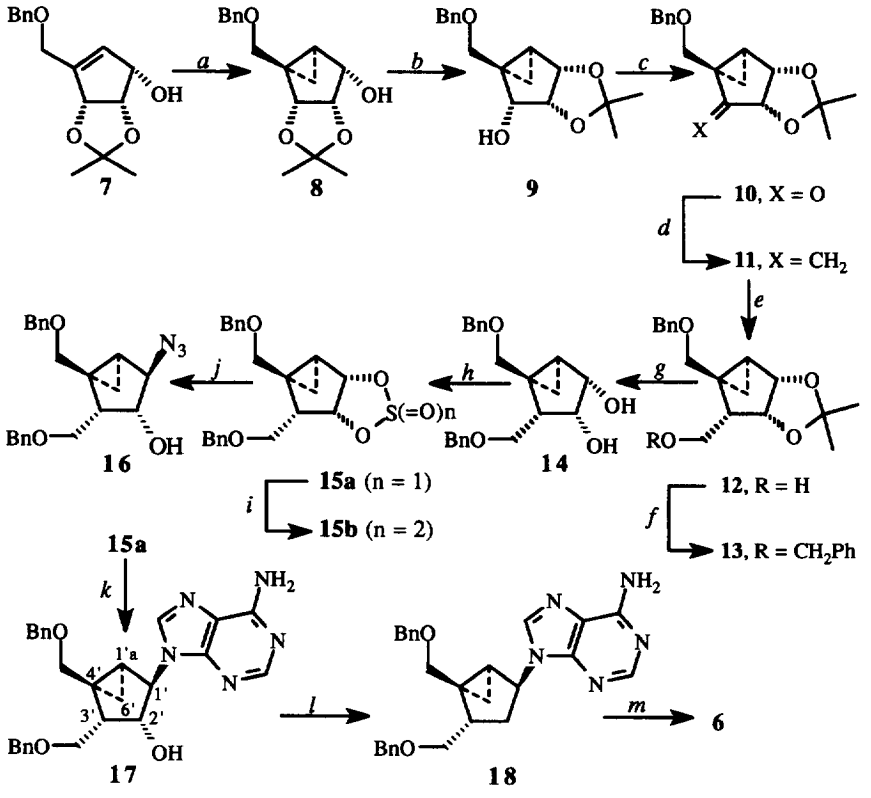
Abstract. Although cyclic sulfites are less reactive than their cyclic sulfate counterparts, the present work shows that cyclic sulfite **15a** is a useful synthon for the convergent synthesis of carbocyclic nucleosides. Target compound **6**, which represents a rigid carbocyclic nucleoside mimic of anti-HIV active 9-[2',3'-dideoxy-3'-*C*-(hydroxymethyl)-β-*erythro*-pentofuranosyl]adenine (**3**), was obtained after regioselective ring opening of **15a** with adenine and radical-induced deoxygenation of the extra hydroxyl group. Elsevier Science Ltd

Carbocyclic nucleosides continue to provide important leads for the development of novel and more specific antitumor and antiviral agents.[1-3] Encouraged by the good anti-HIV activity shown by oxetanocin A (**1**),[4] ring-expanded versions containing adenine (**3**) and cytosine bases were later synthesized, and they too showed significant levels of antiviral activity.[5-7] Later, it was discovered that cyclobutyl nucleosides containing adenine (**2**) and guanine bases were also potent antiviral agents with a much broader spectrum of activity.[8,9] Unfortunately, their ring enlarged versions (e.g., **4**) failed to show any antiviral effectiveness.[10,11] More recently, the synthesis of the cyclopentenyl analogue **5** was reported, but it too lacked anti-HIV activity.[12] In view of our continued interest in bicyclic carbocyclic nucleosides,[13] the synthesis of **6** was undertaken. This target compound was of interest because in terms of conformation it resembles the "northern" sugar puckering characteristic of anti-HIV active **1**.[5,13]



The strategy for this synthesis involved a convergent approach starting with our versatile cyclopentenone synthon which was quantitatively reduced to the allylic alcohol **7** as reported previously (Scheme 1).[14] Following Altmann's procedure,[15] the corresponding bicyclo[3.1.0]hexane intermediate **8** was easily prepared in 90% yield. Repeated acid-catalyzed equilibration of **8** in acetone favored formation of the isomeric acetonide

Scheme 1



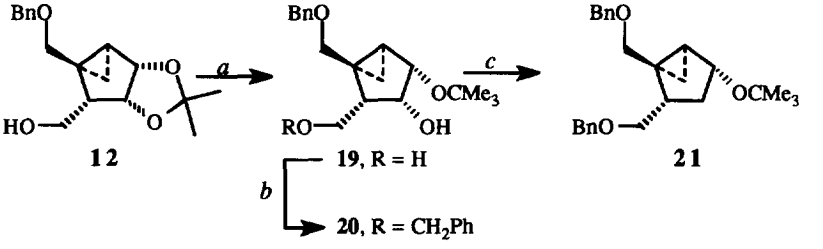
Reagents and Conditions: (*a*) ref. 15. (*b*) *p*-TsOH, acetone, 50 °C, 2 h, 57%. (*c*) Tetrapropylammonium perruthenate(VII), 4-methylmorpholine *N*-oxide, 4 Å mol. sieves, CH_2Cl_2, rt, 100%. (*d*) $CH_3P(C_6H_5)_3Br$, *n*-BuLi, THF, 0 °C, 30 min, 90%. (*e*) 1. BH_3•THF, THF, 0 °C, 3 h. 2. $NaBO_3$•H_2O, rt, 3 h, 90%. (*f*) $PhCH_2Br$, $(n\text{-}Bu)_4NI$, NaH, THF, 80 °C, 88%. (*g*) 1N HCl, MeOH-THF (1:1), 50 °C, 5 h, 100%. (*h*) $SOCl_2$, Et_3N, 0 °C, 3 min, 100%. (*i*) MeCN-CCl_4 (1:1), H_2O, 1.5 mol-% of $RuCl_3$, $NaIO_4$, 0 °C, 1 h, (100%). (*j*) From **15a**: NaN_3, DMF, 105 °C, 6 h, 80%. From **15b**: 1. NaN_3, DMF, 0 °C, 30 min. 2. H_2SO_4, THF, rt, overnight, 47%. (*k*) Adenine, NaH, 18-crown-6, DMF, 120 °C, 72 h, 50%. (*l*) 1. CS_2, NaH, MeI, THF, 0°C to rt. 2. $n\text{-}Bu_3SnH$, Et_3B, benzene, rt, 15 min, 73%. (*m*) Pd-black, 5% HCOOH in MeOH, rt, 3 days, 83%.

9. This compound could be readily oxidized to **10**, which in turn was subsequently converted to the 2-ylidene intermediate **11** after Wittig olefination with methyltriphenylphosphonium bromide. Hydroboration of **11** proceeded with 90% regioselectivity to give **12**, which resulted from the preferential attack of the reagent from the less encumbered convex β-side of **11**. Protection of the newly generated primary alcohol as a benzyl ether (**13**) was then followed by removal of the acetonide and conversion of the *cis*-diol **14** to the corresponding cyclic sulfite **15a**. Being aware of the use of cyclic sulfates and sulfites as surrogate epoxides,[16-18] cyclic sulfite **15a** was readily oxidized to cyclic sulfate **15b** according the procedure of Sharpless and Kim.[18] Cyclic sulfates

are excellent electrophiles, but are often unstable even under mildly acidic conditions.[19,20] In a model reaction, cyclic sulfate **15b** reacted readily with NaN_3 in DMF at 0 °C, and after hydrolytic cleavage of the monoalkyl sulfate anion, the desired carbocyclic azide **16** was isolated. However, **15b** proved to be quite unstable and we therefore decided to try cyclic sulfite **15a**. Although **15a** was anticipated to be a poorer electrophile than **15b**,[17] it was very stable and easy to store. Thus, the equivalent reaction of **15a** with NaN_3 in DMF required heating to 105 °C, but the reaction was clean, completely regiospecific and efficient. In view of this result, cyclic sulfite **15a** was chosen for the final coupling with adenine in the convergent synthesis of our target compound. In the presence of 18-crown-6, condensation of **15a** with adenine gave the desired product **17** (50%) with recovered starging material **15a** and diol **14** (ca. 40-50%). As before, ring opening of **15a** occurred with complete regioselectivity and the structure of **17** was confirmed unambiguosly by ^1H NMR spectroscopy.[21] After the classical two-step Barton radical deoxygenation procedure,[22] **17** was converted to the protected carbocyclic nucleoside **18**. Catalytic transfer debenzylation of **18** with formic acid over Pd black afforded the target bicyclic carbocyclic adenine nucleoside **6**.[23]

Use of the cyclic sulfate/sulfite chemistry was not part of our original synthetic plan. According to Scheme 2, we first performed a regioselective cleavage of the *O*-isopropylidenetriol **12** with MeMgBr to give the corresponding carbocyclic 4-*tert*-butoxy diol **19**. This compound was selectively monobenzylated, and after radical deoxygenation, it afforded the corresponding carbocyclic sugar **21**. Removal of the *tert*-butyl ether group under a variety of conditions, however, caused extensive decomposition, possibly through an unstable carbocation intermediate.

Scheme 2



Reagents and Conditions: (*a*) MeMgI, benzene:ether (5:1), 70 °C, 48 h, 87%. (*b*) 1. Dibutyltin oxide, toluene, 100 °C, 12 h. 2. $PhCH_2Br$, $(n\text{-}Bu)_4NBr$, 100 °C, 15 h, 92%. (*c*) 1. CS_2, NaH, MeI, THF, 0°C to rt. 2. $n\text{-}Bu_3SnH$, Et_3B, benzene, rt, 15 min, 79%.

Although cyclic sulfites have infrequently been used in organic synthesis,[16,17,24,25] the cyclic sulfite approach described here represents a useful alternative for the convergent syntheses of carbocyclic nucleosides. Even though cyclic sulfite **15a** was less reactive than the cyclic sulfate **15b**, the former was more stable, and the extra hydrolytic step to cleave the monoalkyl sulfate anion (involving treatment with sulfuric acid) was not necessary. The additional stereocenter generated by the cyclic sulfite is irrelevant in terms of our final target, although it is possible that one diastereoisomer reacts more efficiently than the other. Recently, the use of more stable surrogates of cyclic sulfates, such as cyclic thionocarbonates, has been reported to work

advantageously.[19]

Compound **6** had undetectable antiviral activity against HIV in the 0.01-100 μM range in ATH-8 cells, although some cytotoxicity was observed at the highest concentration.[26]

References and Notes:

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21. Due to the rigid nature of the bicyclo[3.1.0]hexane system, the coupling constants are very diagnostic. For example, in **17**, irradiation of the H-3' multiplet at δ 3.05 caused the H-2' doublet at δ 4.12 to coalesce into a singlet. This would not be possible in the case of the alternative regioisomer.
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23. White solid, mp 230 °C (dec.); $[\alpha]_D^{25}$ −10.7 (c 0.15, MeOH; ^{1}H NMR (MeOH-d_6) δ 0.79 (m, 1 H, H-6'a), 0.85 (m, 1 H, H-6'b), 1.65 (m, 2 H, H-5', H-3'a), 1.90 (dd, 1 H, J = 14.8, 8.1 Hz, H-3'b), 2.75 (m, 1 H, H-2'), 3.60 (m, 3 H, CH_2OH, CHHOH), 3.92 (d, 1 H, J = 11.7 Hz, CHHOH), 4.99 (d, 1 H, J = 6.4 Hz, H-4'), 8.20 (s, 1 H, H-2), 8.50 (s, 1 H, H-8); ^{13}C NMR (MeOH-d_6) δ 10.62, 28.00, 35.50, 42.22, 57.28, 62.24, 65.90, 80.00, 120.25, 141.00, 150.10, 153.57, 157.32; FAB MS *m/z* (relative intensity) 276 (MH+, 100), 136 (b + 2 H, 76). Anal. Calcd for $C_{13}H_{17}N_5O_2$: C, 56.72; H, 6.22; N, 25.44. Found: C, 56.89; H, 6.27; N, 25.65. All other intermediates reported in this communication were fully characterized.
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