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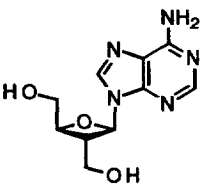
HIGHLY STEREOSELECTIVE SYNTHESIS OF *trans,trans*-4-ARYL-2,3-OXETANEDIMETHANOLS: PREPARATION OF OXETANOCIN A ANALOGUES

MICHAEL E. JUNG* and CHRISTOPHER J. NICHOLS

Department of Chemistry and Biochemistry, University of California, Los Angeles, California, USA, 90095

Summary: A short (5-step) synthesis of the oxetanocin A analogues **12a** and **12b** has been accomplished, with very good stereoselectivity in the key iodocyclization step.

Oxetanocin A (**1**), a naturally occurring antiviral nucleoside isolated in 1986,[1,2] and its analogues[3-10] show activity against HIV,[4,5] HBV,[6,7] HSV,[5,8,9] and cytomegalovirus (CMV).[9,10] Because of its interesting structure as an oxetanose-based nucleoside, oxetanocin A (**1**) has been the target of several published synthetic studies, which use a ring contraction from modified ribose[11] or glucose[12] units, an internal S_N2 displacement of an epoxide[13] or a mesylate,[14] or a [2+2] photocycloaddition[15] in the key step. Our approach was designed to use a cationic iodocyclization[16] to form the oxetane.



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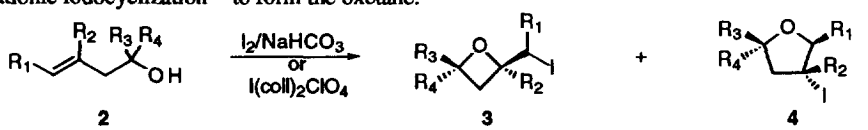


2 **3** **4**

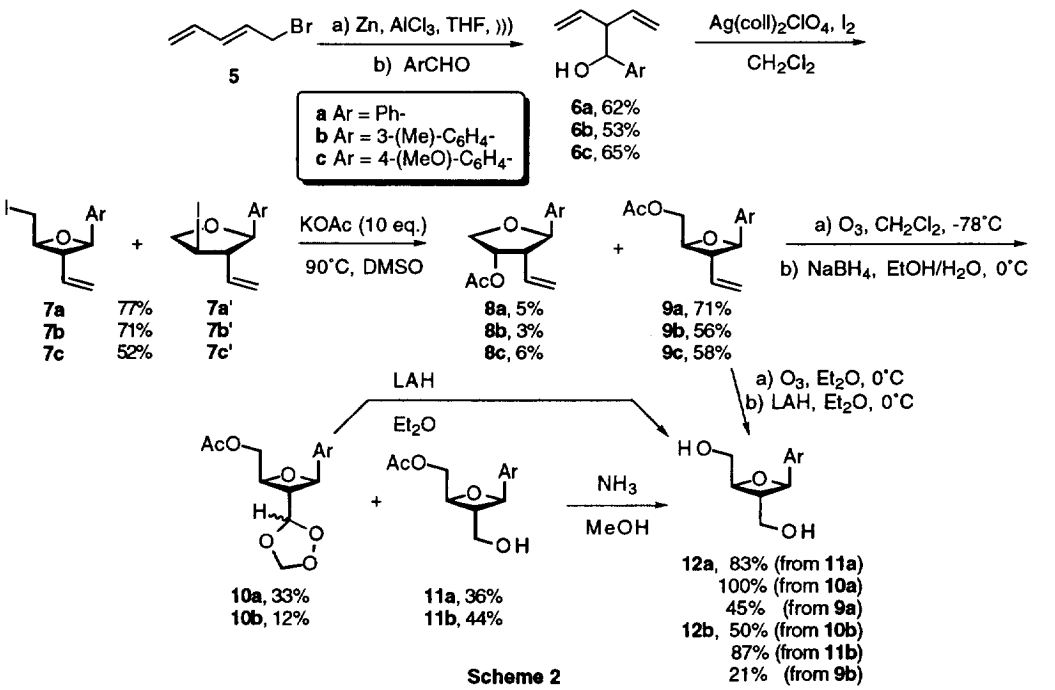
$R_1 = R_2 = H, R_3 = R_4 = Me$ $R_1 = Et, R_2 = R_3 = R_4 = H$
$R_1 = R_3 = R_4 = H, R_2 = Me$ $R_1 = Bu, R_2 = R_3 = H, R_4 = Et$
$R_1 = Et, R_2 = H, R_3 = R_4 = Me$
$R_1 = R_2 = R_3 = R_4 = H$ - 1:1 mixture

Scheme 1

For a homoallylic alcohol **2**, iodoetherification (Scheme 1) typically proceeds through a 5-*endo*-trig pathway to produce a 3-iodotetrahydrofuran **4**.[17-22] Formation of the oxetane **3** has been reported to be preferred only for substrates in which the double bond is *gem*-disubstituted ($R_2 \neq H$),[23] or if there are *gem*-dialkyl substituents[16,24] to accelerate the 4-*exo*-trig mode. For our case, the cyclization substrate would be the homoallylic alcohol **6** (Scheme 2). We predicted that the two substituents, the aryl and vinyl groups, (despite not being geminal) would be enough to favor oxetane formation.

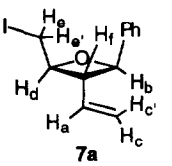
The starting material in each sequence (Scheme 2) is *E*-5-bromo-1,3-pentadiene (**5**).[25] In the presence of zinc and a catalytic amount (*ca.* 10 mol%) of aluminum trichloride,[26] the bromide **5** undergoes a Barbier reaction with a variety of aldehydes (benzaldehyde, *m*-tolualdehyde, *p*-anisaldehyde) to form the racemic dienols **6a-c** in reasonable yield (53-65%). It was found that ultrasound[27] tends to increase the efficiency of the zinc insertion. The key step is the iodocyclization of **6a-c** which gives an inseparable mixture of cyclized products in overall yields of up to 77% with good stereoselectivities. The ratio of the major isomer, the all trans oxetanes **7a-c**, to the next most abundant, the *trans,trans*-2-aryl-3-ethenyl-4-iodotetrahydrofurans **7a'-c'**, is at least 3:1, and in some cases as high as 10:1. There are also other oxetane products in this mixture: in one case reductive deiodination of **7a** with lithium aluminum hydride (LAH) showed four different methyl doublets in the ^{1}H NMR spectrum,[28] indicating that all of the four possible isomeric oxetane products had been formed, in a ratio of 10 : 2 : 1.5 : 1. Thus this iodocyclization allows for establishment of all the relative stereochemistry, analogous to that of oxetanocin A, in one step with good selectivity. The next step, an S_N2 displacement of the iodide with 10 equivalents of potassium acetate, produces the acetates **9a-c** along with a small amount of the 5-membered ring products **8a-c**. At this point the acetates **9a-c** are separable from the other products by column chromatography.

The stereochemistry of the products were assigned by high field proton NMR experiments. Thus a NOESY experiment on the iodide **7a** indicated that the three groups were all trans since there were correlations of proton a



Scheme 2

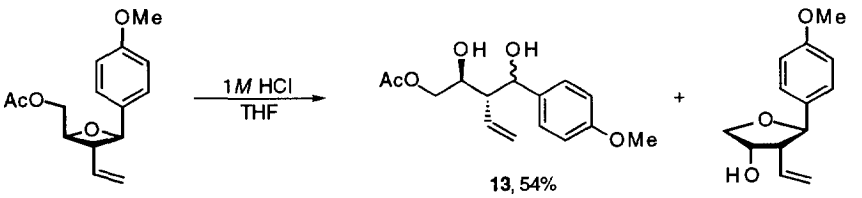
with b and d, proton b with d, proton f with e, e', and the aryl protons, and protons e and e' with the aryl protons. A NOESY experiment on the acetate **8a** showed that the allylic proton was cis to the aryl ring and the proton α to the acetate, confirming that this product had the assigned structure and thereby establishing the stereochemistry of the iodide **7a'**.



7a

From this point, the success of the reaction sequence depends on the nature of the aryl substituent. Ozonolysis of **9a** followed by sodium borohydride reduction[29] gives a mixture of the alcohol **11a** and the unreduced diastereomeric ozonides **10a**. However, both of these products can be taken to the final 2,3-oxetanedimethanol **12a**, using ammonia in methanol to deprotect the acetate **11a** or LAH to fully reduce the ozonide **10a**. The alkene **9a** could also be converted, albeit in poorer yield, directly to **12a** in a one-pot sequence of ozonolysis followed by LAH reduction. Similar treatment of compound **9b** affords both the ozonide **10b**, which on reduction produces **12b** as expected, and the monoacetate **11b**, which was converted with methanolic ammonia into the final product **12b**. The one-pot conversion of **9b** into **12b** proceeded in 21% yield.

However the olefin **9c**, containing an electron-donating *p*-methoxyphenyl group, could not be carried further in this synthesis because of its propensity to rearrange under the acidic conditions required in the workup of the ozonide reduction. The alkene itself also rearranges in acid. Thus treatment of **9c** with 1*M* HCl in THF produces (Scheme 3) both the diol **13** (with a 3:1 ratio of isomers at C-4) and the ring-enlarged alcohol **14**.[30] Both the proton chemical shifts and the coupling constants of the alcohol **14** matched those of **8a** (except for the protons α to the alcohol and acetate respectively), thereby ensuring the correctness of the structural assignment.[31]



9c **13**, 54% **14**, 3%

Scheme 3

In summary, a short sequence of 5 steps has led to the synthesis of two racemic oxetanocin A analogues, **12a** and **12b**, in 21% and 9% overall yield, respectively. Since the alcohol stereocenter in **6** determines the stereochemistry of the other two stereocenters in **7** (and thus in **12**), if one carried out an enantioselective addition to the aromatic aldehyde to produce this center asymmetrically, then one could effect an enantioselective synthesis of these oxetanocin analogues. Also, if the aryl group in **12** were replaced by appropriate functionality, it could possibly be converted to oxetanocin A. Preliminary investigations in this area are underway.

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28. Partial ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.57 (d, J = 6.1 Hz), 1.48 (d, J = 6.1 Hz), 1.46 (d, J = 6.5 Hz), 1.33 (d, J = 6.5 Hz) in a ratio of 2 : 10 : 1.5 : 1.
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30. Slightly different reaction conditions produce a different mixture of the products **13** and **14**, in which more of the cyclic compound is formed.
31. Proton NMR data: **7a**: 7.40 (5H, m); 6.12 (1H, ddd, J = 17.1, 10.4, 7.9 Hz), 5.36 (1H, d, J = 7.2 Hz), 5.23 (1H, dt, J = 17.1, 1.2 Hz), 5.20 (1H, ddd, J = 10.4, 1.3, 0.8 Hz), 4.70 (1H, ddd, J = 8.0, 6.9, 6.0 Hz), 3.47 (1H, dd, J = 9.8, 5.9 Hz), 3.39 (1H, dd, J = 9.8, 8.0 Hz), 3.09 (1H, qt, J = 7.3, 1.0 Hz). **8a**: 7.28-7.37 (5H, m); 5.83 (1H, ddd, J = 17.3, 10.4, 8.6 Hz), 5.45 (1H, dddd, J = 5.3, 4.4, 1.6, 0.5 Hz), 5.14 (1H, ddd, J = 10.4, 1.6, 0.6 Hz), 4.97 (1H, ddd, J = 17.3, 1.6, 0.9 Hz), 4.84 (1H, d, J = 10.0 Hz), 4.41 (1H, ddd, J = 10.6, 4.4, 0.2 Hz), 4.00 (1H, dd, J = 10.6, 1.6 Hz), 2.78 (1H, b td, J = 9.3, 5.3 Hz), 2.14 (3H, s). **14**: 7.24 (2H, m), 6.86 (2H, m), 5.93 (1H, ddd, J = 17.5, 10.5, 8.1 Hz), 5.26 (1H, ddd, J = 10.5, 1.6, 0.7 Hz), 5.11 (1H, dt, J = 17.5, 1.3 Hz), 4.85 (1H, d, J = 10.0 Hz), 4.48 (1H, m), 4.33 (1H, dd, J = 9.9, 4.2 Hz), 3.98 (1H, dd, J = 9.9, 1.5 Hz), 3.80 (3H, s). 2.69 (1H, b td, J = 9.0, 4.8 Hz), 1.78 (1H, d, J = 3.2 Hz).

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