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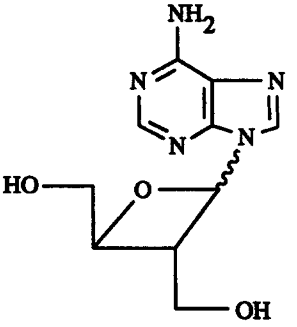
A SHORT SYNTHESIS OF (±)-OXETANOCIN

Robert Hambalek[1] and George Just*
Department of Chemistry, McGill University
Montréal, Québec, Canada H3A 2K6

Summary: The photoadduct 9b of 2-methylfuran and propionyloxyacetaldehyde was transformed in a one-pot reaction to 10d, which gave oxetanocin and its epimer 1α as described[5].

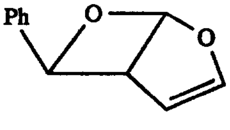
Oxetanocin 1β, a novel nucleoside isolated from *Bacillus megaterium* NK 84-0218 by Shimada et al.[2], has been shown to inhibit the infectivity of human immunodeficiency virus[3]. Total syntheses of oxetanocin have been described by Niitsuma et al.[4], Nishiyama et al.[5] and Norbeck and Kramer[6], who took as starting points cis-2-buten-1,4-diol, glucose and adenosine respectively. We report a very short synthesis of key intermediates 10, which have been transformed to oxetanocin 1β and its anomer 1α by Nishiyama et al.[5] using the classical Vorbrüggen methodology[7]. The synthesis relies on the well-known regio and stereoselectivity of the photoaddition of furans with aldehydes[8,9], which provides oxetanes with the substituents at C-3 and C-4 in a trans arrangement.

Irradiation of benzaldehyde and furan gave photoadduct 2, which upon ozonolysis and dimethyl sulfide reduction provided aldehyde formate 3. Attempts to selectively reduce or acetalise model compound 3 failed in our hands. Since we had noticed that 2-benzoyloxy and 2-acetoxy oxetanes were considerably more stable than the corresponding 2-formyloxy oxetanes[10], we next proceeded to synthesize 7. Irradiation of 2-phenylfuran and aldehyde 4a, obtained by ozonolysis of 1-O-benzoyl-3-methyl-2-buten-1-ol, did not give a cycloadduct.



1β, oxetanocin

1α, epioxetanocin



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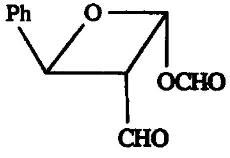

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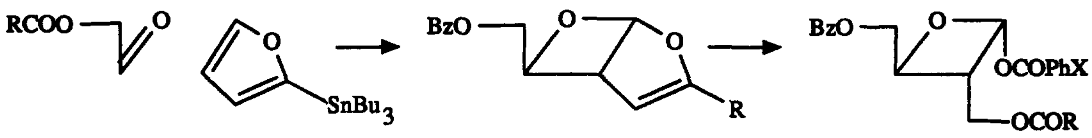


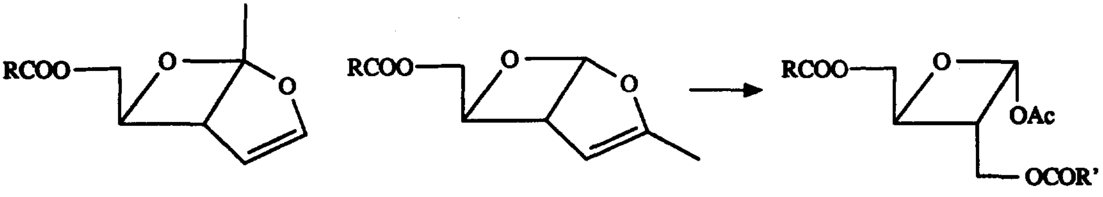
4a, R = Ph
4b, R = Et

5

6a, R = $SnBu_3$
6b, R = Ph
6c, R = $p$$NO_2$-Ph

7a, X = H, R = CH_3
7b, X = $p$$NO_2$, R = CH_3

However, when using tributyl(2-furyl)stannane as the furan component as described by Schreiber[11], photoadduct 6a was isolated in 10-15% (50-55%)[14] yield. Palladium catalyzed arylation using iodobenzene or *p*-bromonitrobenzene transformed 6a to 6b and 6c in 85% and 91% yield, respectively. Ozonolysis of 6b and 6c in CH_2Cl_2 at -78°C, followed by reduction with dimethyl sulfide and reduction of the aldehyde function with sodium borohydride on alumina gel, gave after acylation, stable triacyloxy oxetanes 7a and 7b in 33% and 25% yield, respectively. All of these anomeric benzoates were stable to mixtures of N-benzoyl-disilyladenine/trimethylsilyl trifluoromethanesulfonate or $SnCl_4$ for up to 48 h in refluxing 1,2-dichloroethane.



8a, R = Ph
8b, R = Et

9a, R = Ph
9b, R = Et

10a, R = Ph, R' = Ph
10b, R = Ph, R' = CH_3
10c, R = Ph, R' = $COOCH_3$
10d, R = Et, R' = $COOCH_3$

We next investigated the photoaddition of 2-methylfuran with benzoyloxyacetaldehyde. Irradiation of a benzene solution of 2-methylfuran and 4a gave a mixture of regioisomers 8a and 9a, which could be isolated by flash chromatography (EtOAc/petroleum ether/NEt_3)[13]. In the absence of NEt_3, 8a decomposed and the desired photoadduct 9a[12] was isolated in 25-30% (45-50%)[14] yield. In a one-pot reaction, 9a was transformed to 10a-c by the following sequence: A methylene chloride solution of 9a (10 mmolar) was ozonized at -78°C, and the ozonide reduced with dimethyl sulfide (10 eq., -78°C → 23°C, 18 h). Addition of $NaBH_4$ on alumina gel (2.5 eq., 23°C, 18 h), followed by filtration and acylation of the alcohol function (10a: PhCOCl, NEt_3, DMAP; 10b: Ac_2O, pyridine, DMAP; 10c MeOCOCOCl, NEt_3, DMAP) gave 10a[12], 10b and 10c in 30%-55% yield. As described by Nishiyama[5] et al., reaction of 10a with N-benzoyl-disilyladenine and $SnCl_4$ gave epioxetanocin 1α as the only isolated product in 70% yield. Similar results were obtained when acetate 10b was used as the carbohydrate component. Applying the Vorbrüggen coupling to methyl oxalate 10c gave 1β and 1α in a 1:9 ratio in 70% yield.

Irradiation of a benzene solution of propionyloxyacetaldehyde 4b, obtained by ozonolysis of 1-O-propionyl-3-methyl-2-buten-1-ol, with 2-methylfuran gave, after column chromatography[13], 9b[12] in 20-25% (35-40%)[14] yield. Ozonolysis, followed by reduction and acylation as described for 9a, gave 10d[12] in 45% yield. It was identical in all respects with the product prepared by Nishiyama et al.[5]. Its conversion to a 3:1 mixture of 1β/1α proceeded as described[5].

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References and Footnotes

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12. All compounds were characterized by LRMS, HRMS and ^1H, ^{13}C, HETCOR, APT and COSY NMR. Only selected data are cited. **9a**: {^1H-NMR (200 MHz, CD_2Cl_2): δ 1.94 [dd, 3H, Me], 3.73 [dddd, 1H, H5], 4.47 [A of ABX, 1H, $H6'_a$], 4.52 [B of ABX, 1H, $H6'_b$], 4.77 [dddd, 1H, H6], 5.01 [dd, 1H, H4], 6.31 [dd, 1H, H1], 7.44-8.11 [m, 5H, phenyl], $J_{1\text{-}5}$ = 4.4 Hz, $J_{1\text{-}6}$ = -0.9 Hz, $J_{4\text{-}Me}$ = -1.4 Hz, $J_{4\text{-}5}$ = 2.8 Hz, $J_{5\text{-}Me}$ = 1.4 Hz, $J_{5\text{-}6}$ = 2.2 Hz, $J_{6\text{-}6'a}$ = 4.4 Hz, $J_{6\text{-}6'b}$ = 2.9 Hz, $J_{6'a\text{-}6'b}$ = -12.5 Hz; ^{13}C-NMR (75.4 MHz, CD_2Cl_2): δ 13.91 [CH_3], 48.12 [C5], 66.48 [C6'], 88.76 [C6], 98.91 [C4], 108.51 [C1], 128.83, 129.88, 130.27, 133.52 [phenyl], 158.45 [C3], 166.44 [CO]; LRMS (CI-NH_3): m/e 264 [$M+NH_4^+$, 1.70%], 247 [MH^+, 0.75%], 229 [MH^+ - H_2O, 100%]; HRMS (CI-NH_3): m/e calcd. for $C_{14}H_{13}O_3$ [MH^+ - H_2O], 229.0865; found, 229.0864}. **9b**: {^1H-NMR (200 MHz, CD_2Cl_2): δ 1.15 [t, 3H, CH_3CH_2], 1.92 [dd, 3H, CH_3], 2.40 [q, 2H, CH_3CH_2], 3.59 [dddd, 1H, H5], 4.22 [A of ABX, 1H, $H6'_a$], 4.26 [B of ABX, 1H, $H6'_b$], 4.63 [dddd, 1H, H6], 4.97 [dd, 1H, H4], 6.22 [dd, 1H, H1], $J_{1\text{-}5}$ = 4.4 Hz, $J_{1\text{-}6}$ = -0.8 Hz, $J_{4\text{-}Me}$ = -1.4 Hz, $J_{4\text{-}5}$ = 2.7 Hz, $J_{5\text{-}Me}$ = 1.4 Hz, $J_{5\text{-}6}$ =

2.8 Hz, $J_{6\text{-}6'a}$ = 4.4 Hz, $J_{6\text{-}6'b}$ = 3.2 Hz, $J_{6'a\text{-}6'b}$ = -12.4 Hz; ^{13}C-NMR (75.4 MHz, CD_2Cl_2): δ 9.11 [CH_3CH_2], 13.70 [CH_3], 27.57 [CH_3CH_2], 47.89 [C5], 65.80 [C6'], 88.57 [C6], 98.81 [C4], 108.34 [C1], 158.23 [C3], 174.04 [CO]; LRMS (CI-NH_3): m/e 199 [MH^+,0.48%], 181 [MH^+ - H_2O, 100%]; HRMS (CI-NH_3): m/e calcd. for $C_{10}H_{13}O_3$ [MH^+ - H_2O], 181.0865; found, 181.0864}. **10a**: {^{1}H-NMR (200 MHz, CD_2Cl_2): δ 2.10 [s, 3H, OAc], 3.61 [dddd, 1H, H3], 4.52 [A of ABX, 1H, H4'$_a$], 4.64 [B of ABX, 1H, H4'$_b$], 4.65 [A of ABX, 1H, H3'$_a$], 4.70 [B of ABX, 1H, H3'$_b$], 5.05 [ddd, 1H, H4], 6.58 [d, 1H, H2], 7.31-8.19 [m, 5H, phenyl], $J_{2\text{-}3}$ = 6.0 Hz, $J_{3\text{-}3'a}$ = 6.8 Hz, $J_{3\text{-}3'b}$ = 7.7 Hz, $J_{3\text{-}4}$ = 6.2 Hz, $J_{3'a\text{-}3'b}$ = -11.5 Hz, $J_{4\text{-}4'a}$ = 4.4 Hz, $J_{4\text{-}4'b}$ = 3.2 Hz, $J_{4'a\text{-}4'b}$ = -12.6 Hz; ^{13}C-NMR (75.4 MHz, CD_2Cl_2): δ 21.18 [CH_3CO], 40.49 [C3], 61.44 [C3'], 65.85 [C4'], 80.31 [C4], 96.58 [C2], 128.84, 128.90, 129.27, 129.86, 129.91, 130.42, 133.59, 134.14 [phenyl], 166.47 [CO of C4' benzoate], 169.84 [CO of C3' benzoate], 170.98 [CH_3CO]; LRMS (CI-NH_3): m/e 402 [M+NH_4^+, 100%], 385 [MH^+, 6.66%], 325 [MH^+ - AcOH, 58.36%]; HRMS (CI-NH_3): m/e calcd. for $C_{21}H_{21}O_7$ [MH^+], 385.1286; found, 385.1287}. **10d**: {^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.15 [t, 3H, CH_3CH_2], 2.11 [s, 3H, OAc], 2.39 [q, 2H, CH_3CH_2], 3.44 [dddd, 1H, H3], 3.89 [s, 3H, MeO], 4.19 [A of ABX, 1H, H4'$_a$], 4.34 [B of ABX, 1H, H4'$_b$], 4.55 [A of ABX, 1H, H3'$_a$], 4.60 [B of ABX, 1H, H3'$_b$], 4.82 [ddd, 1H, H4], 6.46 [d, 1H, H2], J_{Et} = 7.5 Hz, $J_{2\text{-}3}$ = 5.9 Hz, $J_{3\text{-}3'a}$ = 7.3 Hz, $J_{3\text{-}3'b}$ = 7.2 Hz, $J_{3\text{-}4}$ = 6.2 Hz, $J_{3'a\text{-}3'b}$ = -11.6 Hz, $J_{4\text{-}4'a}$ = 4.3 Hz, $J_{4\text{-}4'b}$ = 3.3 Hz, $J_{4'a\text{-}4'b}$ = -12.7 Hz; ^{13}C-NMR (75.4 MHz, CD_2Cl_2): δ 9.05 [CH_3CH_2], 20.92 [CH_3CO], 27.48 [CH_3CH_2], 39.67 [C3], 53.75 [MeO], 63.00 [C3'], 64.86 [C4'], 79.62 [C4], 95.96 [C2], 157.56, 158.00 [OCOCOOMe], 169.58 [CH_3CO], 174.09 [CH_3CH_2CO]; LRMS (CI-NH_3): m/e 336 [M+NH_4^+, 56.80%], 259 [MH^+ - AcOH, 25.77%]; HRMS (CI-NH_3): m/e calcd. for $C_{13}H_{22}NO_9$ [M+NH_4^+], 336.1296; found, 336.1294}.

13. The optimum conditions for the photochemical reactions were determined to be as follows: A mixture of 2-methylfuran (17.3 mL, 192 mmol) and the aldehyde (96 mmol) in benzene (1875 mL) was cooled to 8°C and saturated with argon. After 1h, the solution was irradiated (W Hanovia lamp equipped with a Vycor filter) for 7 h. Evaporation under reduced pressure, followed by flash chromatography (petroleum ether-ethyl acetate-NEt_3 10:1:0.01 v/v/v) gave only the desired photoadduct and recovered aldehyde.
14. Yields in parenthesis are based on recovered starting material.

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