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TRISUBSTITUTED OXETANES FROM 2,7-DIOXA-BICYCLO-[3,2,0]-HEPT-3-ENES

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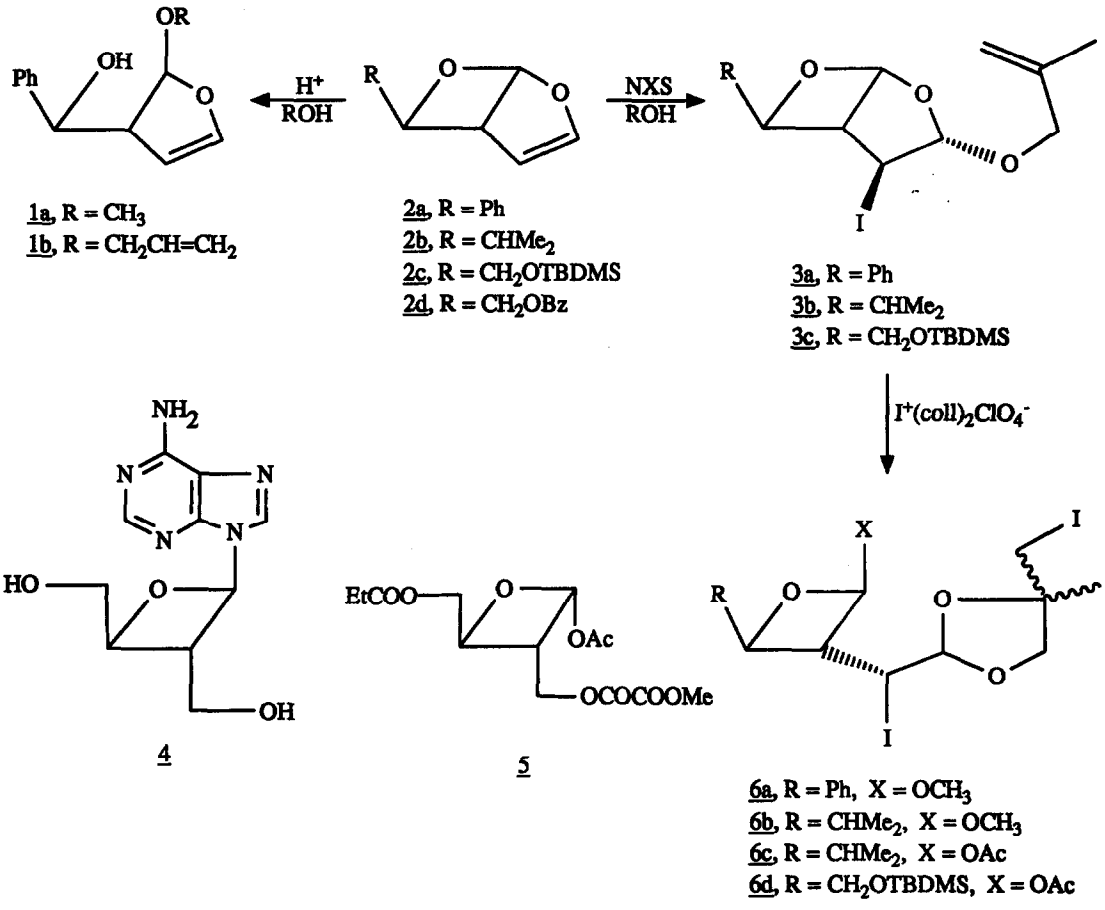
Summary: Photoadducts of aldehydes with furan were transformed to substituted monocyclic oxetanes, using a modification of the Fraser-Reid-Mootoo glycosidation procedure[10].

The photocycloaddition of aldehydes with furan[2,3] leads to adducts 2 which incorporate many of the stereochemical features that characterize oxetanocin 4, a metabolite isolated by Shimada et al.[4,5] and shown to possess antibacterial, antiviral and antitumor activity. Oxetanocin has been synthesized in relatively low yield from glucose by Niitsuma et al.[6], and from cis-2-buten-1,4-diol by Nishiyama et al.[7]. The synthesis more recently described by Norbeck and Kramer[8] proceeds in higher yield, but takes as its starting point, adenosine.

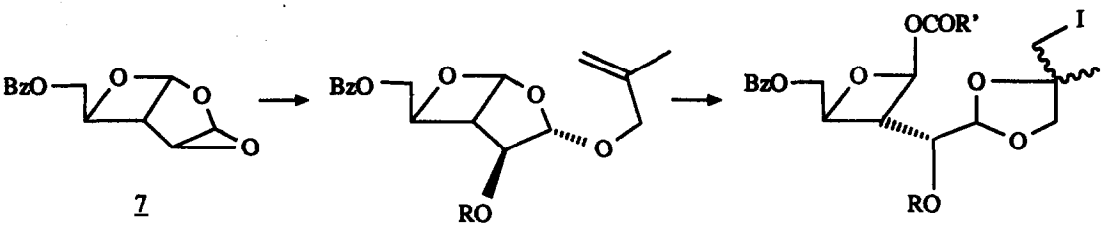
Schreiber[9] used cycloadducts 2 to prepare substituted furans by functionalizing the double bond with *m*-chloroperbenzoic acid and opening the oxetane ring in an acid catalyzed reaction. Any conversion of 2 to oxetanocin, or a precursor thereof, must circumvent this ring opening. In the following, we describe a successful solution of this problem by modifying the recently described glycosidation procedure of Fraser-Reid and Mootoo[10].

Whereas the reaction of photoadduct 2 with hot methanol or allyl alcohol and a catalytic amount of acetic acid gave acetals of structure 1 as established unambiguously by HETCOR carbon-hydrogen correlation, the vinyl ether function of 2 could be transformed to the corresponding bromo or iodo acetal by stirring a 0.2 M solution of 2a, 2b or 2c in the appropriate alcohol with 1 equivalent of N-iodo or N-bromosuccinimide at room temperature for 1-3 h. Iodo acetals 3a, 3b and 3c[11] were obtained in 80-90% yield, and proved to be more stable[12] than the corresponding bromo acetals. Preliminary work on allyl, dimethallyl and methallyl acetals of type 3 indicated that the use of the methallyl derivatives had some advantages and most work was carried out on the latter derivatives.

Using the protocol established by Fraser-Reid and Mootoo[10], iodoacetals 3a and 3b were treated with iodonium di-*sym*-collidine perchlorate (IDCP) and methanol (5 eq.) in benzene and gave 6a and 6b in 30-60% yield as a mixture of inseparable and relatively unstable diastereomers. Reaction with other alcohols such as benzyl alcohol or cyclohexanol, or with acetic acid, proceeded in an analogous manner. All of these compounds decomposed slowly at -10°C and had to be repurified after 1-2 weeks if required for further work. Since 5 had been converted[7] to oxetanocin by reaction with N-benzoyl-disilyladenine and tin tetrachloride, we used these reaction conditions and variations thereof[13] to convert 6c and 6d[11] to an oxetanocin like molecule. However, decomposition occurred before coupling. The instability is probably linked to the presence of the two halogens in 6c and 6d. Attempts to remove the halogen atoms proved to be more difficult than anticipated, and it was decided to carry out further work on systems more closely related to oxetanocin, and in which the iodo function would be replaced by oxygen.



Epoxidation of benzoate 2a with dimethyl dioxirane in acetone[14] gave epoxide 7[11] in almost quantitative yield as a 9:1 mixture of exo and endo isomers, which were unstable to and therefore unseparable by chromatography. Treatment of 7 with 10 equivalents of methallyl alcohol in methylene chloride gave hydroxy acetal 8, which was transformed to acetate, methyl oxalate and benzoate 8a[11]-c by standard procedures. A similar reaction has recently been described by Danishefsky et al.[15]. Treatment of 8a, b and c with IDCP and acetic acid (5 eq.) gave 9a, b and c, whereas the use of benzoic acid as the nucleophile gave 10a, b and c. All of these were obtained in moderate yield. Benzoates 10 had a shelf life of 4-5 weeks at -10°C, whereas the acetates 9 started decomposing after a few days. The nmr data of 9 and 10 were similar to those of the iodo derivatives 6.



7 → 8, R = H; 8a, R = Ac; 8b, R = Bz; 8c, R = COCOOMe → 9, R' = CH_3; 10, R' = Ph; a, R = Ac; b, R = Bz; c, R = COCOOMe

Both 9 and 10 decomposed during attempts to couple with persilylated bases, using Lewis acid catalysis. Attempts to remove the dioxolane ring reductively by means of zinc in methanol lead to unidentified products. Tributyltin hydride mediated deiodination of 10b gave 10b (I = H)[11]. It is stable at -10°C for extended periods of time but could not yet be converted to oxetanocin like material because of rapid decomposition under mildly acidic conditions. Work is in progress to attempt to convert these unstable materials to oxetanocin like molecules or to increase their stabilities by appropriate chemical modifications.

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11. All compounds isolated were oils. Their structures were proven by LRMS and HRMS (when possible), ^1H, ^{13}C, COSY, APT and HETCOR NMR. Only selected data are cited. 3c: (^1H-NMR (200 MHz, $CDCl_3$): δ 0.06, 0.07 [2s, 6H, $(CH_3)_3CSIMe_2$], 0.89 [s, 9H, $(CH_3)_3CSiMe_2$], 1.73 [s, 3H, $H_2C=C(CH_3)CH_2O$], 3.89 [A of ABX, 1H, H6'$_a$], 3.71 [B of ABX, 1H, H6'$_b$], 3.76 [t, 1H, H5], 4.12 [dd, br, 2H, H3'$_a$, H3'$_b$], 4.30 [s, 1H, H4], 4.52 [ddd, 1H, H6], 4.89, 4.98 [2s, br, 2H, H3'$_c$, H3'$_d$], 5.75 [d, 1H, H3], 6.03 [d, 1H, H1], J_{1-5} = 4.1 Hz, $J_{3-3'a}$ = -0.5 Hz, $J_{3'a-3'b}$ = -12.7 Hz, J_{5-6} = 4.4 Hz, $J_{6-6'a}$ = 3.5 Hz, $J_{6-6'b}$ = 3.0 Hz, $J_{6'a-6'b}$ = -11.8 Hz;

^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 18.28 [$(CH_3)_3CSiMe_2$], 19.56 [$H_2C=C(CH_3)CH_2O$], 23.73 [C4], 23.73 [$(CH_3)_3CSiMe_2$], 25.83 [$(CH_3)_3CSiMe_2$], 52.79 [C5], 64.15 [$(CH_3)_3CSiMe_2OCH_2$], 71.60 [$H_2C=C(CH_3)CH_2O$], 83.94 [C6], 108.30 [C1], 112.65 [$H_2C=C(CH_3)CH_2O$], 113.98 [C3], 141.21 [$H_2C=C(CH_3)CH_2O$]; LRMS (CI-NH_3): m/e 441 [MH^+, 4.43%], 369 [MH^+ - $H_2C=C(CH_3)CH_2OH$, 100%]; HRMS (CI-NH_3): m/e calcd. for $C_{12}H_{22}O_3ISi$ [MH^+ - $H_2C=C(CH_3)CH_2OH$], 369.0383; found, 369.0383}. **6d**: {LRMS (CI-NH_3): m/e 644 [$M+NH_4^+$, 100.00%], 627 [MH^+, 3.75%]; HRMS (CI-NH_3): m/e calcd. for $C_{18}H_{33}O_6I_2Si$ [MH^+], 627.0135; found, 627.0135}. **6d-minor**: {^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.06, 0.07 [2s, 6H, $(CH_3)_3CSiMe_2$], 0.90 [s, 9H, $(CH_3)_3CSiMe_2$], 1.57 [s, 3H, CH_3], 2.01 [s, 3H, CH_3CO], 3.70 [s, br, 2H, H3'$_e$, H3'$_f$], 3.70 [s, br, 2H, H4'$_a$, H4'$_b$], 3.73 [t, 1H, H3], 3.94 [dd, 2H, H3'$_c$, H3'$_d$], 4.28 [s, 1H, H3'$_a$], 4.41 [dd, br, 1H, H4], 5.75 [s, 1H, H3'$_b$], 6.03 [d, 1H, H2], J_{2-3} = 4.1 Hz, J_{3-4} = 4.3 Hz, $J_{3'c-3'd}$ = -10.0 Hz, $J_{3'e-3'f}$ ~ 0 Hz, $J_{4-4'a}$ = 3.7 Hz, $J_{4-4'b}$ = 3.7 Hz}. **6d-major**: {^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.06, 0.07 [2s, 6H, $(CH_3)_3CSiMe_2$], 0.90 [s, 9H, $(CH_3)_3CSiMe_2$], 1.59 [s, 3H, CH_3], 2.02 [s, 3H, CH_3CO], 3.69 [dd, 2H, H3'$_e$, H3'$_f$], 3.70 [s, br, 2H, H4'$_a$, H4'$_b$], 3.73 [t, 1H, H3], 3.93 [dd, 2H, H3'$_a$, H3'$_b$], 4.29 [s, 1H, H3'$_a$], 4.41 [dd, br, 1H, H4], 5.75 [s, 1H, H3'$_b$], 6.03 [d, 1H, H2], J_{2-3} = 4.1 Hz, J_{3-4} = 4.3 Hz, $J_{3'c-3'd}$ = -9.7 Hz, $J_{3'e-3'f}$ = -2.5 Hz, $J_{4-4'a}$ = 3.7 Hz, $J_{4-4'b}$ = 3.7 Hz}. **7-exo**: {^{1}H NMR (200 MHz, $CDCl_3$): δ 3.58 [t, 1H, H5], 3.83 [d, 1H, H4], 4.46 [A of ABX, 1H, H6'$_a$], 4.56 [B of ABX, 1H, H6'$_b$], 4.77 [ddd, 1H, H6], 5.41 [d, 1H, H3], 5.74 [d, 1H, H1], 7.29-8.06 [m, 5H, phenyl], J_{1-5} = 3.6 Hz, J_{3-4} = 1.4 Hz, J_{5-6} = 3.8 Hz, $J_{6-6'a}$ = 4.0 Hz, $J_{6-6'b}$ = 3.1 Hz, $J_{6'a-6'b}$ = -12.6 Hz; ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 43.57 [C5], 56.68 [C4], 65.21 [CH_2], 75.62 [C6], 82.55 [C3], 107.82 [C1], 128.48, 129.57, 129.79, 133.38 [phenyl], 166.05 [CO]; LRMS (CI-NH_3): m/e 266 [$M+NH_4^+$, 25.83%], 249 [MH^+,100%]; HRMS (CI-NH_3): m/e calcd. for $C_{13}H_{13}O_5$ [MH^+], 249.0762; found, 249.0762}. **8a**: {^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.77 [s, 3H, CH_3], 2.04 [s, 3H, CH_3CO], 3.37 [t, 1H, H5], 4.17 [dd, 2H, br, H3'$_a$, H3'$_b$], 4.46 [A of ABX, 1H, H6'$_a$], 4.56 [B of ABX, 1H, H6'$_b$], 4.88 [ddd, 1H, H6], 4.91, 5.03 [2s, 2H, br, H3'$_c$, H3'$_d$], 5.25 [s, 1H, H4], 5.41 [d, 1H, H3], 6.08 [d, 1H, H1], 7.40-8.10 [m, 5H, phenyl], J_{1-5} = 4.1 Hz, $J_{3-3'a}$ = -0.8 Hz, $J_{3'a-3'b}$ = -12.5 Hz, J_{5-6} = 4.6 Hz, $J_{6-6'a}$ = 4.1 Hz, $J_{6-6'b}$ = 3.4 Hz, $J_{6'a-6'b}$ = -12.4 Hz; ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 19.45 [$OCH_2C(CH_3)=CH_2$], 20.74 [CH_3CO], 47.51 [C5], 65.56 [$CH_2OCOC_6H_5$], 71.49 [$OCH_2C(CH_3)=CH_2$], 76.24 [C6], 77.90 [C4], 107.61 [C1], 109.10 [C3], 112.94 [$OCH_2C(CH_3)=CH_2$], 128.39, 129.64, 130.10, 133.18 [phenyl], 140.94 [$OCH_2C(CH_3)=CH_2$], 166.12 [C_6H_5CO], 169.71 [CH_3CO]; LRMS (CI-NH_3): m/e 363 [MH^+, 1.38%], 291 [MH^+ - $H_2C=C(CH_3)CH_2OH$, 17.17%]}. **10b (I = H)**: {^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.65, 1.66 [2s, 6H, CH_3], 3.56 [t, 1H, H3], 4.03 [dd, 2H, br, H3$_c$, H3$_d$], 4.36 [A of ABX, 1H, H4'$_a$], 4.42 [B of ABX, 1H, H4'$_b$], 4.86 [ddd, 1H, H4], 5.51 [s, 1H, H3'$_a$], 5.64 [d, 1H, H3'$_b$], 6.13 [d, 1H, H2], 7.34-8.12 [m, 15H, phenyl], J_{2-3} = 3.8 Hz, J_{3-4} = 4.6 Hz, $J_{3'c-3'd}$ = -9.8 Hz, $J_{3'b-3'c}$ = -0.9 Hz, $J_{4-4'a}$ = 3.6 Hz, $J_{4-4'b}$ = 3.4 Hz, $J_{4'a-4'b}$ = -12.5 Hz; ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 23.47, 23.53 [CH_3], 47.62 [C3], 65.36 [C4'$_a$], 73.44 [C3'$_c$], 76.30 [C4], 78.34 [C3'$_a$], 81.27 [CMe_2], 107.73 [C2], 110.261 [C3'$_b$], 128.21, 128.33, 128.46, 129.48, 129.70, 129.74, 129.95, 130.02, 131.57, 132.59, 133.23, 133.55 [phenyl], 165.35, 165.63, 166.19 [CO]; LRMS (DCI-NH_3): m/e 547 [MH^+, 0.87%], 425 [MH^+ - C_6H_5COOH, 26.33 %]; HRMS (DCI-NH_3): m/e calcd. for $C_{24}H_{25}O_7$ [MH^+ - C_6H_5COOH], 425.1600; found, 425.1600}.

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