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ACYLOXY TRI(ISOPROPOXY)TITANIUM REAGENTS FOR REGIOSELECTIVE CLEAVAGE OF 2,3-EPOXYALCOHOLS. A SYNTHESIS OF 2-DEOXY-D-RIBOSE.

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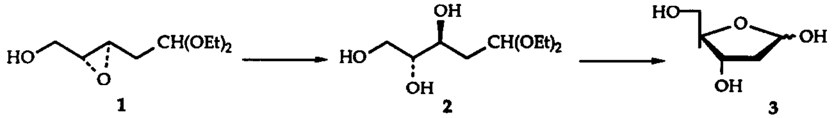
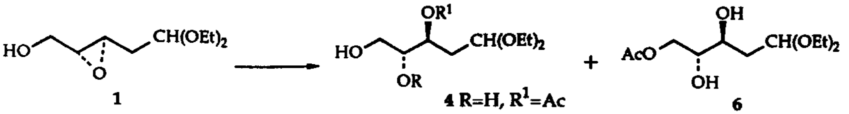
Abstract The cleavage of the oxirane ring of 3,4-anhydro-2-deoxy-D-*threo*-pentose diethyl acetal by various acetic acid derivatives - titanium(IV) isopropoxide combinations are reported in detail The high regioselectivity found with tri(isopropoxy)titanium acetate serves as the basis for a synthesis of 2-deoxy-D-ribose and its ethyl furanosides in high yields and optical purity from non-carbohydrate precursors The synthesis of other acyloxy tri(isopropoxy)titanium reagents is also described

In 1984, we described a two step synthesis of 2-deoxy-D-ribose (**3**) from 3,4-anhydro-2-deoxy-D-*threo*-pentose diethyl acetal (**1**)[1a] by aqueous alkali oxirane ring cleavage of **1** and hydrolysis of the resultant acyclic acetal (**2**)[1b] While the yield of 2-deoxy-D-ribose was high, the optical purity was *ca* 54% The loss of optical purity was due to concomitant isomerisation, *i e*, Payne rearrangement[3], of **1** during the oxirane cleavage process which gave partially racemic **2**



1 **2** **3**

To minimize isomerisation, we decided initially to carry out the cleavage of **1** in a non-aqueous medium with a nucleophilic hydroxide equivalent, for example acetoxy ion, in the presence of titanium (IV) isopropoxide, a well-known promoter of regioselective oxirane ring opening (Table 1)[4] Lithium acetate afforded the highest yields that is probably due to its greater solubility in organic media. Since direct NMR-based analyses of the reaction mixtures, prior to workup, were unsuitable because of considerable signal broadening in the presence of organotitaniums, the analyses were carried out after aqueous workup In all cases, the resulting mixture consisted of 3-, 4- and 5-*O*-acetyl derivatives of 2-deoxy-D-*erythro*-pentose diethyl acetal (2-deoxy-D-ribose diethyl acetal) (**4-6**) The formation of the isomeric acetals is attributed to acetyl migration that occurred during the aqueous sodium bicarbonate workup of the reaction mixture It is well known that acetoxy groups on polyols have a proclivity to migrate from secondary to primary hydroxy group in mild alkaline medium[5]



1

4 R=H, R^1=Ac
5 R=Ac, R^1=H

6

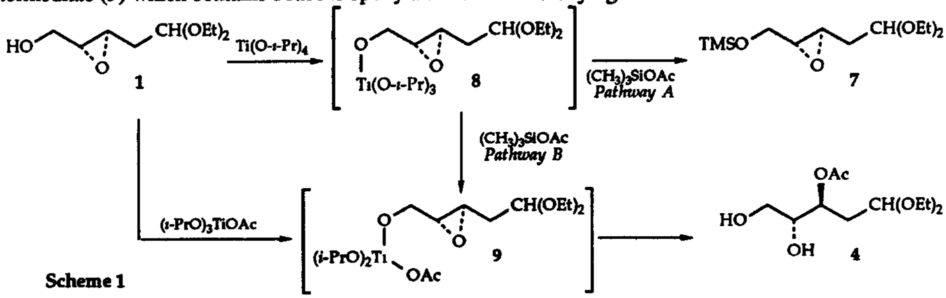
Table 1. Ring Cleavage of 3,4-Anhydro-2-deoxy-D-*threo*-pentose Diethyl Acetal (1) with Metal Acetate - Titanium (IV) Isopropoxide Combinations.

Metal Acetate	Solvent	Reaction conditions		Conversion, %
		Time(hr.)	T,°C	
AcONa	benzene	100	80	25
AcOLi	benzene	100	20	60
AcOLi	benzene	50	80	65
AcONa	THF	100	65	20
AcOLi	THF	100	20	55
AcOLi	THF	50	65	58

However, the possibility of an initial Payne rearrangement of epoxide (1) as well as a non-stereospecific nucleophilic attack could not be excluded Both processes, combined with the acyl migration, would result in loss of optical purity of the acetal (6) We isolated the predominant 5-*O*-acetyl acetal (6) from the mixture and determined its optical purity by the Mosher method[6] It turned out that the conversion of 1 to 6 occurs with minimal loss of optical purity, as evidenced by the absence of isomerisation and nucleophilic attack at both C-3 and C-4 atoms Thus, sequential regioselective cleavage of the epoxide (1), hydrolysis of the resultant acetoxy group and the acetal function afforded 2-deoxy-D-ribose (3) with enantiomeric purity of about 96%

Because the conversion was modest due to the harsh reaction conditions required by the poor solubility of the acetate salts in organic media, milder conditions were sought. Prompted by the report of Wang that oxirane cleavage by trimethylsilyl acetate is facilitated in the presence of chromium (III) reagents[7], we decided to study its use in titanium (IV) isopropoxide-promoted cleavage reactions of oxirane (1) Indeed, trimethylsilyl acetate - titanium (IV) isopropoxide was effective (95% yield) in converting 1 to 4 within 1 5 hr at ambient temperature, but the course of the reaction is dependent on the order of reagent addition For example, initial mixing of trimethylsilyl acetate and titanium (IV) isopropoxide followed by addition of epoxide (1) gave only acetal (4) In contrast, sequential addition of titanium (IV) isopropoxide and trimethylsilyl acetate to epoxide (1) afforded two products acetal (4) and epoxide 5-*O*-trimethylsilyl ether (7) in 1 1 ratio

The results are explained mechanistically as shown in Scheme 1 Mixing of 1 and titanium (IV) isopropoxide results in the initial formation of the titanium epoxyalkoxide (8) In the subsequent addition of trimethylsilyl acetate, an acetoxy group displaces either an epoxyalkoxy (Pathway A) or isopropoxy group (Pathway B) to form the epoxy trimethylsilyl ether (7) or *i*-propoxytrimethylsilane, respectively According to this scheme, epoxide cleavage occurs *via* intermediate (9) which contains both the epoxy alcohol and acetoxy ligands on titanium.



Scheme 1

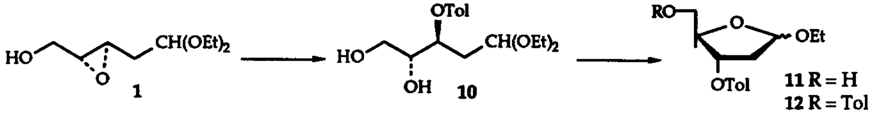
$$Ti(O\text{-}i\text{-}Pr)_4 + (CH_3)_3SiOAc \longrightarrow (i\text{-}PrO)_3TiOAc + i\text{-}PrOSi(CH_3)_3$$

The alternative reaction protocol that includes initial mixing of titanium isopropoxide and trimethylsilyl acetate

(1 1) was studied by means of ^{13}C and ^{29}Si NMR. Spectral monitoring showed gradual disappearance of the silicon and carbon resonances for trimethylsilyl acetate and the appearance of *i*-propoxytrimethylsilane[8] This infers the formation of tri(isopropoxy)titanium acetate, which was not previously used for nucleophilic oxirane ring opening[9] It can be obtained not only as described, but also from acetic acid, acetic anhydride and ethyl acetate We have determined in all cases (except the latter) that the *in situ* formation of tri(isopropoxy)titanium acetate occurs at ambient temperature within 0 5 hour

Thus, the regioselective cleavage of **1** with an acetoxy group affords an efficient enantioselective synthesis of 2-deoxy-D-ribose However, it was essential that the acetyl group be substituted with other acyl groups, not inclined to migrate under mild alkaline workup conditions For example, the migration rate for the benzoyl group is 30 times less than that for the acetyl group[4] With this in mind, as well as the use of the *p*-toluoyl moiety for hydroxy group protection in nucleoside syntheses, we decided to carry out similar oxirane cleavages with tri(isopropoxy)titanium *p*-toluate

Tri(isopropoxy)titanium *p*-toluate was obtained by treatment of titanium (IV) isopropoxide with either *p*-toluic acid or trimethylsilyl *p*-toluate, as a viscous, moisture sensitive liquid. The cleavage of oxirane **1** with tri(isopropoxy)titanium *p*-toluate afforded only 3-*O*-(*p*-toluoyl)-2-deoxy-D-*erythro*-pentose diethyl acetal (**10**) (96% yield) (Scheme 2) Cyclization of acetal (**10**) led to a mixture of ethyl furanosides (**11**) which were separated by column chromatography and characterized by elemental analysis and NMR spectroscopy (Tables 2-4) Treatment of furanosides (**11**) with *p*-toluoyl chloride gave ethyl 3,5-di-*O*-(*p*-toluoyl)-2-deoxy-D-*erythro*-pentofuranosides (**12**) as intermediates for nucleoside syntheses Thus, the acyloxy tri(isopropoxy)titaniums are excellent reagents for 2,3-epoxyalcohol cleavages as shown for the synthesis of 2-deoxy-D-ribose.



Scheme 2

EXPERIMENTAL

General Methods. Thin-layer chromatography was conducted on Silufol UV$_{254}$ (Kavalier, Czechoslovakia) in methanol chloroform (1 10) with spot detection by heat Column chromatography was done on silica gel Merck 60 Optical rotations were determined with a Perkin-Elmer spectropolarimeter 141 and NMR spectra were recorded with a Bruker CXP-200 (200 MHz, ^{1}H, 50 MHz, ^{13}C) and AM-360 (360 MHz, ^{1}H, 90 MHz, ^{13}C) Enantiomeric purity of >95% was found for **2**, **4-6** and **10** by the procedure of Mosher [6]

Tri(isopropoxy)titanium acetate. *Method A* A mixture of chlorotrimethylsilane (10 8 g, 0 1 mol), anhydrous chloroform (60 ml) and anhydrous sodium acetate (16 0 g, 0 2 mol) was stirred at ambient temperature for *ca* 0 5 h After filtration of the resulting mixture, titanium (IV) isopropoxide (28 4 g, 0 1 mol) was added to the filtrate to form tri(isopropoxy)titanium acetate and sufficient anhydrous chloroform added to afford a 1M solution (100 mL)

Method B A solution of titanium (IV) isopropoxide (2 8 g, 0 01 mol) in anhydrous chloroform (6 ml) was treated with acetic anhydride (1 0 g, 0 01 mol) and sufficient anhydrous chloroform added to afford a 1M solution (10 mL)

Method C differs from method B by the use of acetic acid (0 6 g, 0 01 mol) instead of acetic anhydride

3-*O*-Acetyl-2-deoxy-D-*erythro*-pentose Diethyl Acetal (4). A solution of 3,4-anhydro-2-deoxy-D-*threo*-pentose diethyl acetal (1) (1 9 g, 0.01 mol), anhydrous chloroform (20 ml) and 1M tri(isopropoxy)titanium acetate in chloroform (15 ml) was stirred at ambient temperature for 1h The reaction mixture was quenched with acetone (30 ml) and water (10 ml) and the resultant precipitate was separated by centrifugation After drying of the filtrate with anhydrous magnesium sulfate and concentration *in vacuo*, acetal (4) (2.3 g, 95%) was obtained as a yellow oil (Tables 2-4), $[\alpha]_D^{20}$ -15 6° (*c* 2 05, CH_3OH) Anal Calcd for $C_{11}H_{22}O_6$ C, 52 78, H, 8 86. Found C, 52 85, H, 8 80

4-*O*-Acetyl- and 5-*O*-Acetyl-2-deoxy-D-*erythro*-pentose Diethyl Acetals (5-6) An identical reaction mixture (*cf* 4) was quenched with acetone (30 ml) and aqueous saturated sodium bicarbonate solution (10 ml) The resulting mixture was stirred for 0.5 h, forming a precipitate that was easily removed by filtration through a pad of Celite After drying of the filtrate with anhydrous magnesium sulfate and concentration *in vacuo*, the residue was chromatographed with chloroform.methanol (25·1) elution to give **3-*O*-acetyl-2-deoxy-D-*erythro*-pentose diethyl acetal (4)** (0 3 g, 11%), **4-*O*-acetyl acetal (5)** (0 3 g, 11%) and **5-*O*-acetyl acetal (6)** (1 7 g, 52%) (Tables 2-4) Acetal (6), $[\alpha]_D^{20}$ -7 8° (*c* 1 45, CH_3OH) Anal. Calcd for $C_{11}H_{22}O_6$ C, 52 78, H, 8 86 Found C, 52 69, H, 8 89

2-Deoxy-D-*erythro*-pentose Diethyl Acetal (2) and **2-Deoxy-D-*erythro*-pentose(2-Deoxy-D-ribose, 3)** A methanolic solution (10 ml) of the acetal mixture (4-6) (2 0 g, 8 0 mmol) and 0 5 M methanolic sodium methoxide (70 mL) was stirred at ambient temperature for 4 h. After concentration *in vacuo*, the residue was filtered through a pad of silica gel with diethyl ether elution (Tables 2-4) [**Acetal (2)**, $[\alpha]_D^{20}$ -23 7° (*c* 1 26, CH_3OH) Anal Calcd for $C_9H_{20}O_5$ C, 51 90, H, 9 68 Found C, 52 15, H, 9 79] The acetal (2) (2 0 g, 1 2 mmol), ion-exchange resin QU-2 (0 2 g) and water (20 ml) was stirred at ambient temperature for 1h, filtered and barium carbonate (0 3 g) was added to the filtrate After stirring for 0 5 h, filtration and evaporation *in vacuo*, the residue was crystallized from methanol:ethyl acetate (1 4) to afford **2-deoxy-D-ribose** (3) (0 61 g, 86%), mp 89-91°C, $[\alpha]_D^{20}$ -56 1° (*c* 2 91, H_2O) [lit $[\alpha]_D^{20}$ -57 2° (*c* 0 5, H_2O)[10]] Anal Calcd for $C_5H_{10}O_4$ C, 44 77, H, 7 52 Found C, 44 59, H, 7 67

Tri(isopropoxy)titanium *p*-toluate was obtained by analogy with tri(isopropoxy)titanium acetate from titanium (IV) isopropoxide and sodium *p*-toluate (Method A) or *p*-toluic acid (Method C)

3-*O*-(*p*-Toluoyl)-2-deoxy-D-*erythro*-pentose Diethyl Acetal (10) A solution of **1** (1 9 g, 0 01 mol), anhydrous chloroform (20 ml) and 1M tri(isopropoxy)titanium *p*-toluate in chloroform (15 mL) was stirred at room temperature for 1h The reaction mixture was quenched with acetone (30 ml) and saturated aqueous sodium bicarbonate (10 ml) and stirred for 3 h The suspension was filtered through a pad of Celite with additional chloroform elution and the filtrate dried over anhydrous magnesium sulfate and concentrated *in vacuo*. **Acetal (10)**(2 9 g, 90%) was obtained as a yellow oil (Tables 2-4), $[\alpha]_D^{20}$ -21 4° (*c* 3 04, CH_3OH) Anal Calcd for $C_{17}H_{26}O_6$ C, 62 56, H, 8 03 Found C, 62 58, H, 7 99.

Ethyl 3-*O*-(*p*-toluoyl)-2-deoxy-α,β-D-*erythro*-pentofuranosides (11a-b) An ethanolic solution (10 ml) of acetal (10) (0 8 g, 2 5 mmol) was treated with 0 1 ml of 1% ethanolic hydrogen chloride The reaction mixture was stirred at room temperature for 1 5 h and neutralized with anhydrous potassium carbonate (0 1 g) After filtration and concentration *in vacuo*, the residue was purified by column chromatography with $CHCl_3$ CH_3OH (30 1) elution to afford the individual anomers as syrups (Tables 2-4) **Ethyl-3-*O*-(*p*-toluoyl)-2-deoxy-α-D-*erythro*-pentofuranoside (11a)** (0 28 g, 45%); $[\alpha]_D^{20}$ +75.12° (*c* 10 4, CH_3OH) Anal Calcd for $C_{15}H_{20}O_5$ C, 64 27, H, 7 19 Found C, 64 20; H, 7.22 **β-anomer (11b)** (0 31 g, 50%) $[\alpha]_D^{20}$ -32 02° (*c* 10 5, CH_3OH) Anal. Found C, 64 27; H, 7 19

Ethyl 3,5-di-*O*-(*p*-toluoyl)-2-deoxy-α,β-D-*erythro*-pentofuranosides (12) A cold, well stirred (-5 to 0°C) solution of *p*-toluoyl chloride (0 63 g, 4 1 mmol) and dry pyridine (5 ml) was treated dropwise with a solution of furanosides (**11**) (0 95 g, 3 4 mmol) in dry dichloroethane (10 ml) After stirring at -5 to 0°C for 2 h, the dichloroethane was evaporated and the residue partitioned between cold water and chloroform. The combined extract was dried over anhydrous sodium sulfate and concentrated *in vacuo* Residual pyridine was removed by filtration through a bed of silica gel with chloroform elution to afford furanosides (**12**) (1 2 g, 89%) (Tables 2-4)

Table 2. ^1H NMR Data (δ, p.p.m.) for Compounds 2, 4, 6, 10-12 [in $(CD_3)_2CO$]

Compound	Anomer	H-1	H-2	H-2'	H-3	H-4	H-5	H-5'
2	-	4 75	1.59	2 20	3 65	3 44	3 56	3 68
4	-	4 545	1 85	2 00	5 00	-	-	-
6	-	4 762	1 62	2 02	3 68	3 60	4 04	4 24
10	-	4 625	2 06	2 14	5 286	3 866	3 60	-
11a	α	5 219	2 03	2 42	5 33	4 22	3 73	3 73
11b	β	5 295	2 28	2 39	5 45	4 23	3 68	3 68
12a	α	5 29	2 11	2 57	5 44	4 5	4 5	4 5
12b	β	5 33	2 35	2 49	5 58	4 49	4 5	4 5

Table 3. ^1H NMR Coupling Constants (Hz) for Compounds 2, 4, 6, 10-12 [in $(CD_3)_2CO$]

Compound	$J_{1,2}$	$J_{1,2'}$	$J_{2,3}$	$J_{2',3}$	$J_{2,2'}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$
2	3 8	7 8	9 8	1 7	14 1	6 4	6 2	4 2	10 8
4	4 4	7 1	9 3	5 3	14 5	-	-	-	-
6	4 2	7 1	9 2	2 6	13 9	6 7	8 6	3 0	11 4
10	4 8	6 4	8 4	4 4	14 5	5 0	4 4	6 5	-
11a	0 95	5 25	1 9	7 7	14 3	3 4	3 5	3 5	-
11b	5 3	2 9	4 4	6 9	14 3	2 6	5 1	5 1	-
12a	1 1	5 3	2 2	7 9	14 4	2 1	-	-	-
12b	5 3	2 6	5 2	7 0	14 0	2 0	-	-	-

Table 4. ^{13}C-NMR Data (δ, p.p.m.) for Compounds 2, 4-6, 10-12 [in $(CD_3)_2CO$]

Compound	C-1	C-2	C-3	C-4	C-5	C=O
2	102 03	37 75	70 19	75 33	63 85	-
4	101 24	35 04	72 30	73 76	63 64	170 58
5	101 67	37 91	67 89	78 01	62 03	170 78
6	101 94	37 82	69 59	73 31	66 60	171 20
10	101 32	35 13	72 98	73 93	63 71	166 39
11a	104 40	40 08	75 73	84 96	63 02	166 73
11b	104 84	40 32	76 68	86 00	64 29	166 53
12a	104 35	39 76	75 60	81 70	65 03	166 52
12b	104 97	39 70	76 36	82 40	65 95	166 36

References and Notes

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