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A NEW APPROACH TO THE SYNTHESIS OF CHIRAL MULTIFUNCTIONAL CHAIN COMPOUNDS FROM 2,3-O-ISOPROPYLIDENE-D-GLYCERALDEHYDE

JANUSZ JURCZAK,*[a] STANISŁAW PIKUL,[a] AND KJELL ANKNER[b]

[a]Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warszawa, Poland; [b]AB Hässle, 43180 Mölndal, Sweden

Abstract - The strategy of highly stereoselective synthesis of multifunctional "carbohydrate-like" chain compounds starting from 2,3-O-isopropylidene-D-glyceraldehyde (2) is presented and exemplified by the preparation of alcohols 10 and 12 with *arabino* and *ribo* configuration, respectively.

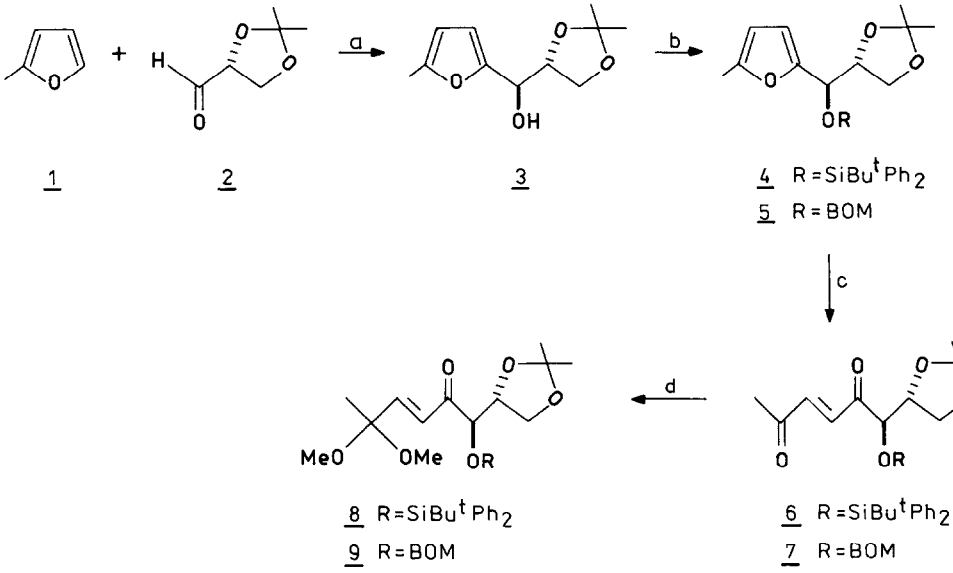
The stereocontrolled synthesis of "carbohydrate-like" frameworks is a crucial problem in the construction of complex polyhydroxylated natural products such as macrolide antibiotics[1] or palytoxin[2] type compounds. Recent reviews[3] survey the efforts of many synthetic chemists in this field. Among methods developed, those leading in acyclic manner to units with more than two consecutive chiral hydroxymethylene centres starting from simple precursors are not very common. Solutions to this problem have recently been given by several groups.[4]

In this communication we report on an alternative method of preparation of synthons having tetraol units with either *arabino* or *ribo* configuration, as well as a synthetically useful α,β-unsaturated ketone system. Our approach is based on the use of 2-methylfuran (1) as a nucleophile, which after addition to a chiral aldehyde can be transformed into a functionalized five-carbon chain unit.

Reaction of 1 with 2,3-O-isopropylidene-D-glyceraldehyde (2)[5] can be carried out on three ways: *(i)* high-pressure reaction of 1 with 2 under 10 kbar in methylene chloride with $ZnCl_2$ added,[6] *(ii)* metallation of 1 with butyllithium followed by addition of $ZnBr_2$ and then reaction with 2 according to Mukaiyama et al.,[7] *(iii)* chloroacetic acid catalyzed reaction of 1 with 2 according to Zamojski et al.[8] In every case, a mixture of diastereoisomers is obtained in good yield (60 - 75%) with high *anti* stereoselectivity (Scheme 1).

Crystallization of the mixture from hexane - ethyl ether afforded pure *anti* isomer 3.[9] Protection of the newly formed hydroxyl functionality by the bulky *tert*-butyldiphenylsilyl group was achieved by heating a standard reaction mixture at 80°C. Under these conditions crystalline 4 was obtained (m.p. 74°C, $[\alpha]_D^{20}$ +91.3° (c 1.04 in $CHCl_3$), 92% yield). Alternatively, the benzyloxymethylene (BOM) protecting group was introduced to compound 3 giving crystalline 5 (m.p. 67°C, $[\alpha]_D^{20}$ +142.9° (c 0.98 in $CHCl_3$), 90% yield). For both, 4 and 5, the furan ring was then oxidatively split to the enedione system using the method recently developed by us.[10] Thus enediones 6 and 7 were obtained with 80 and 78% yield, respectively. Both enediones were subsequently transformed to dimethylketals 8 and 9 using trimethylorthoacetate in methanol and camphorosulphonic acid (CSA) as a catalyst. The reaction proceeded with complete regioselectivity giving 8 and 9 with 77 and 92% yield, respectively. This ketalization reaction was one of the

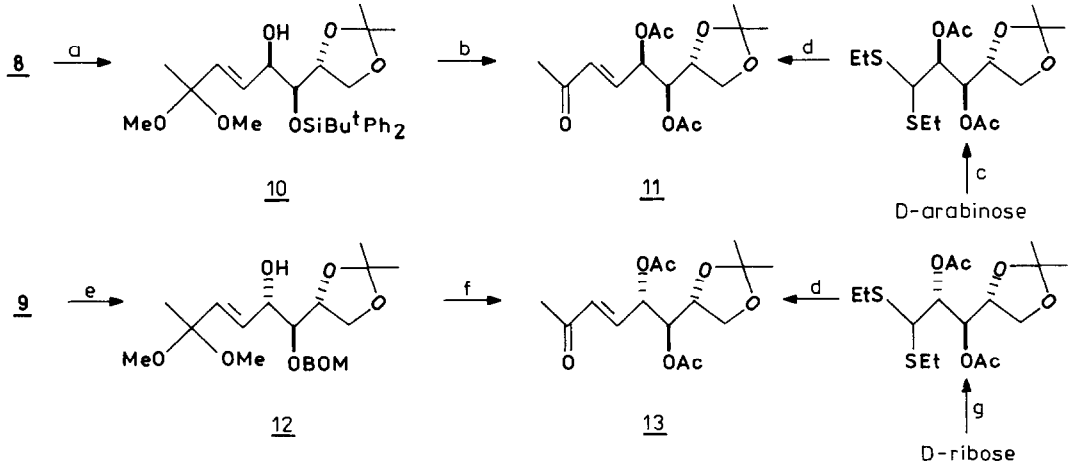
crucial steps in the sequence since it made the differentiation of the two carbonyl groups possible.



1 2 3 4 R=SiBu^{t}Ph$_2$ 5 R=BOM 6 R=SiBu^{t}Ph$_2$ 7 R=BOM 8 R=SiBu^{t}Ph$_2$ 9 R=BOM

Scheme 1. Reagents and reaction conditions: (a) $ZnCl_2$,CH_2Cl_2,10 kbar,RT,24h,*anti*:*syn*=4.5:1; or BuLi,$ZnBr_2$,2,THF,-40°C,5h,*anti*:*syn*=20:1; or $ClCH_2CO_2H$,1(neat),RT,30h,*anti*:*syn*=20:1; (b) 3→4, Bu^{t}Ph$_2$SiCl,imidazole,DMF,80°C,5h; 3→5,BOMCl,DIPEA,CH_2Cl_2,RT,24h; (c) 4→6 and 5→7,Br_2,pyridine,Me_2CO-H_2O,-20°C→RT,3h; (d) 6→8 and 7→9,$MeC(OMe)_3$,MeOH,CSA,0°C,6h.

Having achieved this selective protection, it was then possible to reduce the α,β-unsaturated ketones so obtained using methods which are subject to control by either steric or chelating interactions.[11] Thus, diisobutylaluminium hydride (DIBAL) reduction[12,13] of 8, carried out in ethyl ether at -78°C, gave 10[14] with 75% yield and 20:1 *syn* selectivity[15] (Scheme 2). After



10 11 12 13

Scheme 2. Reagents and reaction conditions: (a) DIBAL,Et_2O,-78°C,0.5h; (b) *i*.Bu_4NF,THF,0°C→RT, 2h; *ii*.Ac_2O,Et_3N,DMAP,CH_2Cl_2,RT,3h; *iii*.CSA,wet Me_2CO,RT,0.5h; (c) see Ref.16; (d) *i*.$HgCl_2$,HgO, Me_2CO-H_2O,60°C,3h; *ii*.Ph_3P=$CHCOCH_3$,PhMe,reflux,2h; (e) $Zn(BH_4)_2$,Et_2O,-20°C,0.5h; (f) *i*.Na,liq. NH_3,THF,0.5h; *ii*.Ac_2O,Et_3N,DMAP,CH_2Cl_2,RT,3h; *iii*.CSA,wet Me_2CO,RT,0.5h; (g) see Ref.17.

desilylation of 10, followed by acetylation and deketalization, diacetate 11[9] was obtained in 80% yield; it was found to be identical with the sample prepared from natural D-arabinose.[18] This finally established the R absolute configuration of the newly created chiral centre. In contrast, zinc borohydride reduction[13,19] of 9 carried out in ethyl ether at -20°C afforded 12 with 90% yield and 20:1 *anti* selectivity.[15] Removal of BOM protection with sodium in liquid ammonia followed by acetylation and deketalization gave diacetate 13.[9] Again, comparison with the sample prepared from natural D-ribose[20] proved the oposite stereochemical direction of the reduction.

The approach presented here offers a short and convenient synthetic route for the preparation of synthons 10 and 12 from 2,3-O-isopropylidene-D-glyceraldehyde (2). Moreover, the unique pattern of a hydroxyl group protection prepared by us should be very useful in further manipulations on the chiral part of these compounds.

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9. Selected physical and spectral data:
   3: m.p. 63°C; $[\alpha]_D^{20}$ +29.5° (c 1.07 in $CHCl_3$); ^1H NMR, 100 MHz ($CDCl_3$), δ (ppm): 6.14(d,1H), 5.90(d,1H), 4.66(d,1H), 4.32(q,1H), 4.2-3.9(m,2H), 2.90(bs,1H), 2.32(s,3H), 1.42(s,3H), 1.34(s,3H).
   8: oil; $[\alpha]_D^{20}$ +20.4° (c 1.3 in $CHCl_3$); ^1H NMR, 100 MHz ($CDCl_3$), δ (ppm): 7.8-7.5(m,4H), 7.5-7.2(m,6H), 6.73(d,1H), 6.48(d,1H), 4.37(d,1H), 4.22(q,1H), 4.0-3.8(m,2H), 3.14(s,6H),

1.32(s,9H), 1.14(s,9H).

9: oil; $[\alpha]_D^{20}$ -18° (c 1.66 in $CHCl_3$); ^1H NMR, 100 MHz ($CDCl_3$), δ (ppm): 7.35(bs,5H), 6.80 (s,2H), 4.83(s,2H), 4.60(s,2H), 4.5-4.3(m,2H), 4.1-3.8(m,2H), 3.13(s,6H), 1.37(s,3H), 1.30 (s,6H).

11: m.p. 52°C; $[\alpha]_D^{20}$ +32.5° (c 0.9 in $CHCl_3$); ^1H NMR, 500 MHz ($CDCl_3$), δ (ppm): 6.65(dd, J=4.6,J=16.1Hz,1H), 6.11(dd,J=1.7,J=16.1Hz,1H), 5.72(ddd,J=3.1,J=1.7,J=4.6Hz,1H), 5.18(dd, J=7.2,J=3.1Hz,1H), 4.21(ddd,J=5.4,J=6.2,J=7.2Hz,1H), 4.01(dd,J=8.6,J=6.2Hz,1H), 3.83(dd, J=8.6,J=5.4Hz,1H), 2.25(s,3H), 2.16(s,3H), 2.06(s,3H), 1.41(s,3H), 1.34(s,3H).

13: oil; $[\alpha]_D^{20}$ +14.6° (c 1.58 in $CHCl_3$); ^1H NMR, 500 MHz ($CDCl_3$), δ (ppm): 6.74(dd,J=5.8, J=16.1Hz,1H), 6.28(dd,J=1.6,J=16.1Hz,1H), 5.77(ddd,J=3.0,J=5.8,J=1.6Hz,1H), 5.19(dd,J=6.9, J=3.0Hz,1H), 4.15(ddd,J=5.1,J=6.3,J=6.9Hz,1H), 4.03(dd,J=8.6,J=6.3Hz,1H), 3.84(dd,J=8.6, J=5.1Hz,1H), 2.30(s,3H), 2.10(s,3H), 2.08(s,3H), 1.43(s,3H), 1.34(s,3H).

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20. Optical rotation of 13 prepared from D-ribose was $[\alpha]_D^{20}$ +13.0° (c 1.51 in $CHCl_3$).

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