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NON-CARBOHYDRATE BASED SYNTHESIS OF NATURAL LTB_4

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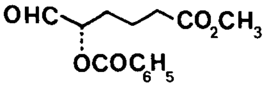
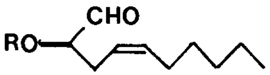
The synthesis of the C_6(2S) and C_{10}(2R) aldehydes (1) and (2), intermediates in reported syntheses of LTB_4 (3), from the C_4 aldehyde (4) through the alcohols (5) and (9) is described.

The chemotactic factor LTB_4 (3) has been recently obtained in the optically active form through procedures using naturally occurring pentoses as starting materials. The C_4 aldehydo ester (1) and the aldehyde (2) are key intermediates in convergent syntheses of (3).[1] Product (1) has been prepared in 9 steps from 2-deoxyribose[2], and, similarly, 9 steps were required for the conversion of L-arabinose into the C_{10} moiety (2).[3]

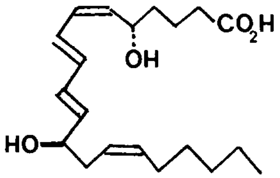
We now present a synthesis of optically pure (1) and (2) from the (2S,3S) C_4 aldehyde (4)[4], obtained upon ozonolysis of protected (2S,3R) 5-phenylpent-4-en-2,3-diol, prepared in fermenting baker's yeast from cinnamaldehyde.[5] The present procedure involves as relevant intermediates the (4S) and (4R) alcohols (5) and (9), respectively, obtained upon addition of suitable carbon nucleophiles onto the carbonyl carbon of the chiral aldehyde (4), bearing in α and β positions two oxygen functions embedded in a pentacyclic ketal framework, and differs from the reported ones because not one of the chiral centres present in the precursor (4) is actually incorporated into products (1) and (2)



(1)



(2) R= $SiPh_2Bu^t$



(3)

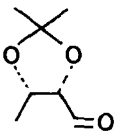
To this end, the (4S) alcohol (5)•, obtained[6] upon addition of the Grignard reagent from

1-bromopent-4-ene onto (4) and separated from the (4*R*) diastereoisomer (6) (ratio (5):(6), *ca.* 6:4) by SiO_2 column chromatography was *O*-benzoylated (C_6H_5COCl/pyridine, 90%) and oxidised (O_3, CH_2Cl_2, -78°C; Ph_3P, 40°C, then Jones reagent, -10°C, 70%) to the acid (7), $[\alpha]_D^{20}$ -4° (c 4, $CHCl_3$), yielding, in turn, with ethereal diazomethane the methyl ester (8), $[\alpha]_D^{20}$ -1.2° (c 10, $CHCl_3$), quantitatively. Controlled acid hydrolysis of (8) (2% HCl in MeOH, r.t. overnight in 1M solution, 85%) afforded the diol (15), $[\alpha]_D^{20}$ -12.7° (c 1.7, $CHCl_3$), oxidised (HIO_4 in dry THF) to the required product (1), $[\alpha]_D^{20}$ -34° (c 2.5, $CHCl_3$) (lit.[2] -33°) in 43% overall yield from the adduct (5).

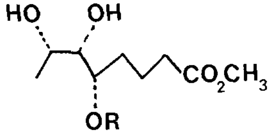
The synthesis of the (2*R*) aldehyde (2) from the C_4 aldehyde (4) was achieved in two ways. Firstly, the C_7, carbohydrate-like, (4*R*) product (10), obtained from (4) upon addition of diallylzinc (ratio with the (4*S*)-isomer, *ca.* 95:5)[7], once protected (BDPSiCl, DMAP, Et_3N, r.t. 3 days, 80%) to (13), $[\alpha]_D^{20}$ -38.4° (c 2, $CHCl_3$), afforded, on ozonolysis and Ph_3P treatment (85%) the C_6 aldehyde (14), $[\alpha]_D^{20}$ +11.4° (c 16, THF). The latter material, on reaction with $Ph_3P{=}CHC_5H_{11}$ ($(Ph)_3C_6H_{13}\overset{+}{P}\overset{-}{Br}$, t-ButOK, THF-DMF, -100°C, 45%) gave rise to the C_{12} product (16), $[\alpha]_D^{20}$ -44.8° (c 3, $CHCl_3$), 95% pure by glc, in 30% overall yield from (10). Selective acid hydrolysis of (16) (0.05M solution in 3:1 MeCN-50% aqueous acetic acid, 80°C, 4 h, 90%) gave rise to the diol (17), $[\alpha]_D^{20}$ -41.8° (c 1.3, $CHCl_3$), eventually converted upon HIO_4 oxidation into the required product (2), $[\alpha]_D^{20}$ -21.3° (c 1, $CHCl_3$) (lit.[3] -18°).

In the second, more direct approach to (2), the aldehyde (4) was reacted with $BrCH_2C{\equiv}CH$ in the presence of zinc powder in Et_2O at 40°C. A single product, $[\alpha]_D^{20}$ +24.9° (c 2, $CHCl_3$) was obtained in *ca.* 80% yield. This material was assigned the (4*R*) absolute configuration depicted in (9) because, once hydrogenated (H_2, Pd/C) afforded product (11), $[\alpha]_D^{20}$ +3.6° (c 1, $CHCl_3$), identical in every respect to the compound prepared from (10) in similar way. The conversion of (9) into (2) involved *O*-protection to (12), $[\alpha]_D^{20}$ -34.2° (c 2, $CHCl_3$) (75%) and chain elongation (n-BuLi-THF, $C_5H_{11}Br$-HMPTA, 70%) to (18), $[\alpha]_D^{20}$ -44.1° (c 2.5, $CHCl_3$), eventually reduction on Lindlar catalyst, to (16), $[\alpha]_D^{20}$ -46.8° (c 2, $CHCl_3$). The latter material on selective hydrolysis and HIO_4 oxidation afforded optically pure (2) in 28% yield from (4). At this point we have to mentione that addition of $BrCH_2C{\equiv}CC_5H_{11}$ onto (4) in the presence of zinc powder[8] and *O*-protection gave indeed product (18), but the latter was inseparable from substantial amounts of the allenic compound.

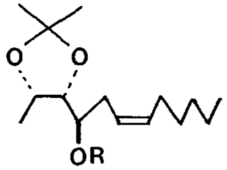
The above results, seen together, indicate the significance of relatively small, highly functionalized chiral synthons like (4) as alternative to carbohydrates as starting materials in the synthesis of enantiomerically pure forms of natural products containing in their framework relatively few oxygen-substituted chiral carbon atoms. Indeed, taking advantage of the increasing knowledge[9] on the steric course of the addition of carbon nucleophiles onto the sp^2 carbon of products like (4), it is possible to obtain educts with a variety of stereochemical situations, as in the present example.



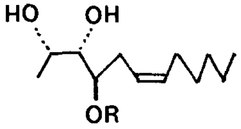
(4)



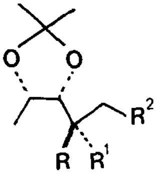
(15) R= COC_6H_5



(16) R= $SiPh_2Bu^t$



(17) R= $SiPh_2Bu^t$



(5) R= H; R^1= OH; R^2= $(CH_2)_2CH{=}CH_2$

(6) R= OH; R^1= H; R^2= $(CH_2)_2CH{=}CH_2$

(7) R= H; R^1= $OCOC_6H_5$; R^2= $(CH_2)_2CO_2H$

(8) R= H; R^1= $OCOC_6H_5$; R^2= $(CH_2)_2CO_2Me$

(9) R= OH; R^1= H; R^2= $C\equiv CH$

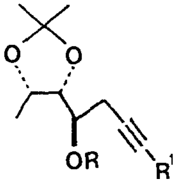
(10) R= OH; R^1= H; R^2= $CH{=}CH_2$

(11) R= OH; R^1= H; R^2= CH_2CH_3

(12) R= $OSiPh_2Bu^t$; R^1= H; R^2= $C\equiv CH$

(13) R= $OSiPh_2Bu^t$; R^1= H; R^2= $CH{=}CH_2$

(14) R= $OSiPh_2Bu^t$; R^1= H; R^2= CHO



(18) R= $SiPh_2Bu^t$; R^1= C_5H_{11}

The addition of the Reformatsky-type reagent obtained from $BrCH_2C\equiv CH$ onto (4) can be modelled after the Roush's proposal recently developed to explain the stereochemistry of the addition of boronates onto the *threo* isomer of (4) (cyclohexylidene derivative instead of isopropylidene)[10] and is coincident with the results obtained with diallylzinc. In the reaction of the Grignard reagent from 1-bromopent-4-ene with (4), yielding the adducts (5) and (6) in *ca.* 6:4 ratio, the metal chelation controlled mode of addition[11] is operating nearby the one mentioned above. Finally, we have to note that the carbonyl carbon of (1) and (2) is the carbonyl carbon of cinnamaldehyde, the precursor of the diol from which (4) has been extruded. A microbially-aided synthesis of (1) has been recently reported.[12]

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•Fully satisfactory spectroscopic and analytical data for the new compounds have been obtained.

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