Tetrahedron Letters,Vol.24,No.35,pp 3753-3756,1983
Printed in Great Britain

0040-4039/83 $3.00 + .00

CARBOHYDRATE-LIKE CHIRAL SYNTHONS.
PREPARATION OF (R) γ-HEXANOLIDE, (5R,6S,7S) 6,7-ISOPROPYLIDENDIOXY-δ-OCTANOLIDE AND (+)-EXOBREVICOMIN FROM (2S,3S,4R) 2,3-ISOPROPYLIDENDIOXY-4-BENZYLOXYHEPT-6-ENE

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The C_6, C_7, C_8 and C_9 chiral products (8), (7), (14) and (19), containing one, two and three oxygen-substituted chiral centres, respectively, have been prepared from the carbohydrate-like optically active, C_7 synthon (1).

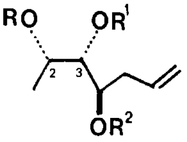
A current approach to the synthesis of enantiomerically pure forms of natural products uses as starting materials alternative to carbohydrates[1] relatively small, highly functionalized, acyclic chiral synthons obtained from readily available, naturally occurring, optically active substances[2] or from the products of biotransformation(s) of non-conventional substrates[3]. The value of this type of synthon, which seems particularly useful for the preparation of molecules containing in their framework relatively few carbon atoms chiral due to oxygen substitution, is enhanced from the fact that an increasing number of them is now becoming available in both the enantiomeric forms[4]. Furthermore, dealing with carbonyl compounds bearing chiral alkoxy substituents in the α and/or β position, it is possible to increase the number of the derived synthons using known methods[5] for stereocontrolled chain elongation through nucleophilic addition onto sp^2 carbon. Recently, we reported obtaining from (2S,3S)-isopropylidendioxy-butyraldehyde the C_7, carbohydrate-like, non-carbohydrate derived, synthon (1) and its C-3 and/or C-4 epimers, respectively, used in the synthesis of the four stereoisomeric 2,6-dideoxysugars of the L-series.[6]

Now, as a further example of the synthetic significance of products like (1), we refer on some transformations of (1), leading, eventually, to the synthesis of the C_6, C_7, C_8 and C_9 products (8), (7), (14) and (19), containing one, two and three oxygen substituted chiral carbon atoms, respectively. Compound (1) can be viewed as a masked form of (R) malaldehyde, in which the two carbonyl may be revealed regioselectively, using different reagents. Thus, the O-benzyl-derivative (2), $[\alpha]_D^{20}$ -39° (c 1, EtOH), obtained in 90% yield from (1) (NaH, $C_6H_5CH_2Cl$, DMF), yielded, on acid hydrolysis, the diol (3), $[\alpha]_D^{20}$ -9° (c 1, EtOH), which, on sequential treatment with HIO_4 in THF and $(C_6H_5)_3P{=}CHCO_2Et$, afforded the doubly unsaturated ester (6), $[\alpha]_D^{20}$ +45° (c 1, $CHCl_3$), in 70% overall yield. The latter material, on basic hydrolysis and hydrogenation (10% Pd/C) gave rise to (*R*) γ-heptanolide (7), $[\alpha]_D^{20}$ +35.7° (c 0.5, MeOH). Conversely, ozonolysis of (2), followed by $NaBH_4$ reduction, afforded the alcohol (9), $[\alpha]_D^{20}$ -12.8° (c 1, $CHCl_3$), which gave (TsCl/pyridine) the tosylate (10), $[\alpha]_D^{20}$ -3.1° (c 1, $CHCl_3$), reduction of which ($LiAlH_4$) yielded compound (11), $[\alpha]_D^{20}$ -34.2° (c 1, $CHCl_3$), in 60% overall yield. The latter compound, on acid hydrolysis, afforded the diol (12), $[\alpha]_D^{20}$ -18.9° (c 1, $CHCl_3$) (90%), converted, in turn, on HIO_4 oxidation, condensation of the intermediate aldehyde with $(C_6H_5)_3P{=}CHCO_2Et$, basic hydrolysis and hydrogenation, into (*R*) γ-hexanolide (8), $[\alpha]_D^{20}$ +52° (c 1, MeOH)[7], in 45% overall.

Chain elongation on the 'right' part of (1) was achieved when the aldehyde obtained on ozonolysis of (1) was condensed with $(C_6H_5)_3P{=}CHCO_2Et$. Product (13) so obtained in 45% yield, on basic hydrolysis and hydrogenation afforded the δ-lactone (14), $[\alpha]_D^{20}$ -28.5° (c 2.5, $CHCl_3$) in 60% overall yield.

Finally, chain elongation on the 'right' part of (1), with deoxygenation at position 2 and inversion of configuration at position 3, afforded (+)-*exo*brevicomin (19). The diol (3), on treatment with 1 mol.eq. of benzoyl chloride in CH_2Cl_2-pyridine at r.t. afforded the crystalline 2-O-benzoate (4), m.p. 68°C, $[\alpha]_D^{20}$ +10° (c 1,EtOH), in *ca*. 70% yield. This material, when reacted in pyridine with 5 mol.eq. of TsCl at r.t. one week, afforded the tosylate (5), $[\alpha]_D^{20}$ +2.7° (c 1, EtOH) (80%). Compound (5), on reaction with KOH in ethyleneglycol-water, gave rise to the epoxide (15), $[\alpha]_D^{20}$ +17° (c 1, EtOH), in 70% yield. Regioselective opening of the epoxide (15), using K-selectride gave rise to the deoxygenated *threo* material (16), $[\alpha]_D^{20}$ +2.8° (c 1, EtOH). Benzylation of (16) to (17) and ozonolysis of the latter in CH_2Cl_2 at -40°C and treatment with 1 mol.eq. of $(C_6H_5)_3P{=}CHCOMe$, afforded the C_9 α,β-unsaturated ketone (18), $[\alpha]_D^{20}$ +10.7° (c 1, EtOH). The latter material, on hydrogenation (10% Pd/C, MeOH), yielded (+)-*exo*brevicomin (19), $[\alpha]_D^{20}$ +74° (c 0.7, Et_2O)[8], 93% pure by glc and devoid of the *endo* isomer, in 35% overall from (17).

(*R*) γ-Hexanolide (8), the pheromone of *Trogoderma* species has been prepared previously from the 'chiral pool' component (*S*) glutamic acid[7], whereas (+)-*exo*brevicomin (19), pheromone of *Dendroctonus brevicomis*, was obtained from (*S*,*S*) tartaric acid through different procedures, *D*-glucose, (*R*) 2-benzyloxybutyraldehyde, and by asymmetric epoxidation of a suitable allylic alcohol[8]. The enantiomeric form of the δ-lactone (14) bearing different protective groups, has been recently prepared in high *ee* by asymmetric epoxidation[9] and used as intermediate in the synthesis of the side chain of trichoverrins B. It should be noted that the enantiomer of (1) is formally available from a C_4, 'chiral pool' derived product (*D*-*allo*threonine). The latter



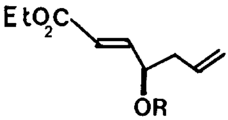
1 $R,R^1 = CMe_2$; $R^2 = H$

2 $R,R^1 = CMe_2$; $R^2 = CH_2C_6H_5$

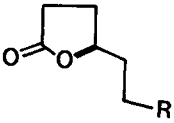
3 $R = R^1 = H$; $R^2 = CH_2C_6H_5$

4 $R = COC_6H_5$; $R^1 = H$; $R^2 = CH_2C_6H_5$

5 $R = COC_6H_5$; $R^1 = Ts$; $R^2 = CH_2C_6H_5$

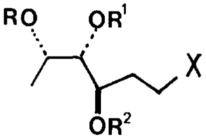


6 $R = CH_2C_6H_5$



7 $R = Me$

8 $R = H$

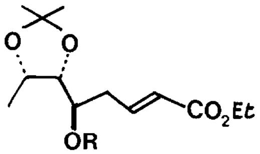


9 $R,R^1 = CMe_2$; $R^2 = CH_2C_6H_5$; $X = OH$

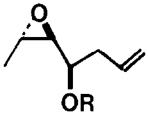
10 $R,R^1 = CMe_2$; $R^2 = CH_2C_6H_5$; $X = OTs$

11 $R,R^1 = CMe_2$; $R^2 = CH_2C_6H_5$; $X = H$

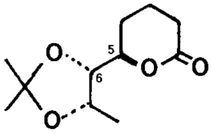
12 $R = R^1 = X = H$; $R^2 = CH_2C_6H_5$



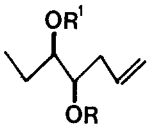
13 $R = CH_2C_6H_5$



15 $R = CH_2C_6H_5$

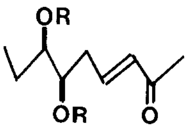


14

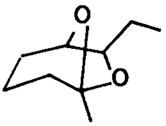


16 $R = CH_2C_6H_5$; $R^1 = H$

17 $R = R^1 = CH_2C_6H_5$



18 $R = CH_2C_6H_5$



19

should allow the synthesis of the octanolide (14) in the required 'natural', absolute configuration.[10]

The preparation of the set of chiral products (7), (8), (14) and (19) from carbohydrate-like (1) through conventional synthetic steps illustrates the usefulness of this type of material in the synthesis of enantiomerically pure forms of natural products.

We thank Farmitalia-Carlo Erba, Milano, for a grant (to C.Z.) and Mrs. Rosanna Bernardi for the glc analyses.

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(Received in UK 23 June 1983)