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Tetrahydrofuran-Podands, Stereoselective Synthesis of trans-2,5-oligo-Tetrahydrofurans

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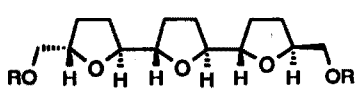
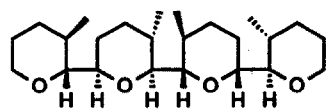
Abstract: Enantiomerically pure THF-podands **1** were synthesized along a linear route starting from lactone **3**. A high degree of stereochemical control was achieved by chelation controlled addition of the functionalized Grignard reagent **7** to α-alkoxy-aldehydes of type **6**.

Oligo-2,5-linked tetrahydrofurans (oligo-THFs) such as **1** receive considerable interest as THF-podands. They share a polyether backbone with the THP-podands of type **2** introduced by Still[1]. In contrast to the THP podands **2**, which possess 2,6-cis-THP units, THF-podands **1** are assembled out of 2,5-trans-THF units. Both podands have in common the potential to differentiate between enantiomeric hosts.



1



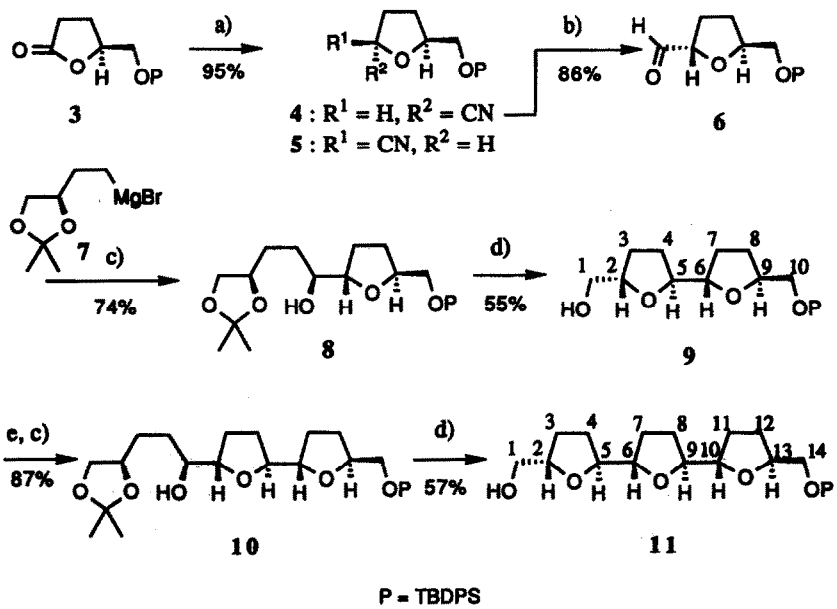
2

While THP-podands **2** were especially designed to have only one preferred conformation[2], oligo-THFs **1** should be more conformationally flexible, thus allowing to bind host molecules in an induced fit mode. The terminal O-functionality in **1** provides the possibility to incorporate these units into larger structures feasible for ion binding and transport.

Furthermore, the oligo-THF moiety represents a structural key feature of the acetogenins[3], a class of natural products with antineoplastic properties. Reported herein is a new stereoselective approach to enantiomerically pure oligo-THFs such as **1**, which differs from previous synthetic work[4] in the field of stereoselective THF synthesis.

Scheme 1 shows our linear approach to oligo-THFs based on successive elaboration of a THF ring to a preexisting chain of THF units. Starting from enantiomerically pure lactone 3[5] the nitriles 4 and 5 were obtained[6] as a 5 : 2 mixture of epimers and easily separated by chromatography. The trans nitrile 4 was converted into its corresponding methyl ester. Subsequent DIBAH-reduction provided trans-aldehyde 6. Reaction of 6 with the Grignard reagent 7[7] in the presence of Cu(I) afforded alcohol 8 with a stereoselectivity of 92:8. Conversion of the acetonide function into an epoxide of proper configuration and intramolecular epoxide opening gave THF-dimer monoalcohol 9. Swern oxidation and another round of the stereoselective Mg/Cu(I) reaction with 7 followed by epoxide formation/opening provided access to the THF-trimer monoalcohol 11.

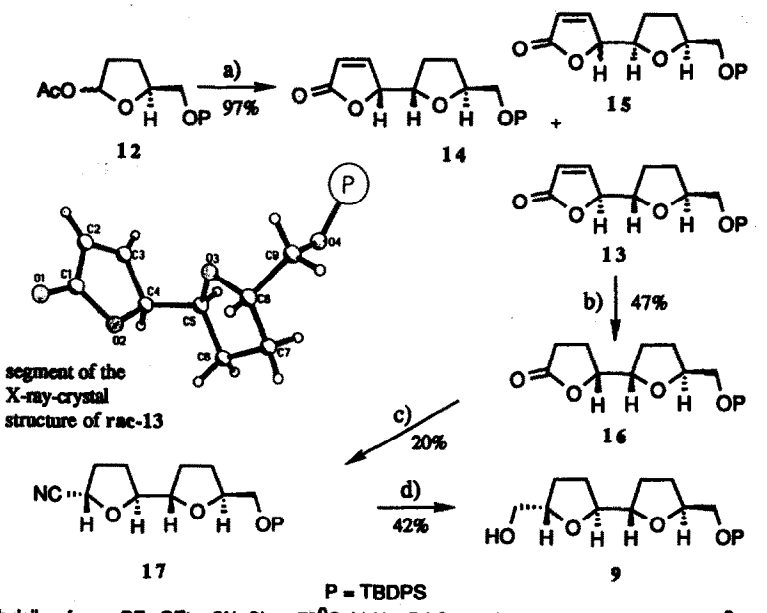
Scheme 1



a) i: DIBAH, toluene, -78^{0}C, ii: Ac_2O, Et_3N, iii: TMSCN, $BF_3{\cdot}OEt_2$, CH_3CN, -20^{0}C; b) i: NaOMe, MeOH, ii: DIBAH, CH_2Cl_2;
c) 7, Et_2O, addition to CuBr·SMe_2 in Et_2O at -40^{0}C; -20^{0}C ,15 min, addition of 6 at -78^{0}C, warm to rt;
d) i: HOAc, H_2O, THF, 9:1:2, ii: MesitylSO$_2$Cl, Py, CH_2Cl_2; iii: K_2CO_3, MeOH then HOAc, CH_2Cl_2; e) Swern oxidation.

The preferred formation of products 8 and 10 was expected according to Cram's cyclic model of chelation control[8]. The relative configuration of the newly formed stereocenter in 8 was secured by correlation with the lactone 13. For this purpose an independent synthesis of compound 9 was carried out as shown in scheme 2. Reaction of acetate 12 with 2-trimethylsiloxyfuran/$BF_3{\cdot}OEt_2$ proceeded smoothly to give a mixture of 13 (threo-trans, 31%), 14 (erythro-trans, 10%) and 15 (threo/erythro-cis, 59%). The compounds 13, 14 and 15 were separated by silica gel chromatography. The assignment of the relative configuration of 13 was unequivocally established by X-ray crystallographic analysis[9].

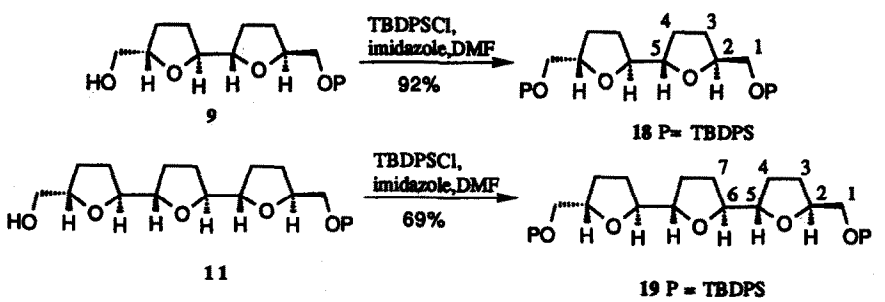
Scheme 2



a) 2-Trimethylsiloxyfuran, $BF_3{\cdot}OEt_2$, CH_2Cl_2, -78°C; b) H_2, Pd/C, AcOEt; c) i: DIBAH, toluene, -78°C, ii: Ac_2O, Et_3N, iii: TMSCN, $BF_3.OEt_2$, CH_3CN, -20°C; d) i: NaOMe, MeOH, ii: $LiAlH_4$, Et_2O.

The dominant formation of the *threo*-products parallels the stereochemical course of the addition of 2-trialkylsiloxyfuran to cyclic N-acyliminium ions[10]. The lactone **13** was subsequently transformed into **9**, thus proving the stereochemical assignments made in scheme 1. Finally, compounds **9** and **11** were TBDPS-protected to afford the C_2-symmetric THF-dimer ***18*** *and THF-trimer* ***19*** respectively (scheme 3).

Scheme 3



In summary, this work establishes a linear route to trans-2,5-oligo-THFs, a potential new type of podands. Extension of the synthetic strategy presented here to larger oligo-THF containing structures as well as ion binding and transport studies are currently underway and will be the topics of subsequent reports from this laboratory.

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References and Notes

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6. All new compounds gave satisfactory micro analysis results and spectral data according to their structures. Selected analytical data is given below.
(^{1}H-NMR: 300 MHz, $CDCl_3$, ^{13}C-NMR: 75,5 MHz, $CDCl_3$)
9: $[\alpha]^{20}_D$ = + 5,8 (c = 2,8, $CHCl_3$);
^{1}H-NMR: 0.97 (s, 9H, t-Bu), 1,55-2,00 (m, 8H, H-C(3,4,7,8)), 2,23 (t, OH), 3,41-3,52 (m, 1H, H-C(1)), 3,62-3,68 (m, 1H, H-C(1)), 3,63 (dd, 1H, H-C(10)), 3,71 (dd, 1H, H-C(10)), 3,82-3,98 (m, 2H, H-C(5,6)), 4,15-4,20 (m, 2H, H-C(2,9)), 7,30-7,41 (m, 6H, arom.), 7,62-7,70 (m, 4H, arom.); ^{13}C-NMR: 19,2; 26,8; 27,4; 28,4; 28,7; 64,6; 66,5; 79,7; 79,8; 82,1; 82,2; 127,6; 129,5; 133,6; 135,6.
11: $[\alpha]^{20}_D$ = + 5,1 (c = 0,5, $CHCl_3$);
^{1}H-NMR: 1,01 (s, 9H, t-Bu), 1,54-2,08 (m, 12H, H-C(3,4,7,8,11,12)), 2,43 (t, OH), 3,40-3,77 (m, 2H, H-C(1)), 3,57 (dd, 1H, H-C(14)), 3,65 (dd, 1H, H-C(14)), 3,80-3,98 (m, 4H, H-C(5,6,9,10)), 4,05-4,18 (m, 2H, H-C(2,13)), 7,26-7,42 (m, 6H, arom.), 7,60-7,68 (m, 4H, arom.); ^{13}C-NMR: 19,2; 26,8; 27,4; 27,6; 28,2; 28,3; 28,4; 64,6; 66,5; 79,7; 79,8; 81,7; 81,8; 82,0; 82,1; 127,6; 129,5; 133,8; 135,6.
18*: $[\alpha]^{20}_D$ = - 0,8 (c = 0,5, $CHCl_3$);
^{1}H-NMR: 1,01 (s, 9H, t-Bu), 1,58-2,04 (m, 4H, H-C(3,4)), 3,57 (dd, 1H, H-C(1)), 3,68 (dd, 1H, H-C(1)), 3,82-3,90 (m, 1H, H-C(5)), 4,05-4,16 (m, 1H, H-C(2)), 7,28-7,41 (m, 6H, arom.), 7,60-7,70 (m, 4H, arom.); ^{13}C-NMR: 19,1; 26,7; 28,2; 28,4; 66,5; 79,5; 81,8; 127,5; 129,4; 133,6; 135,5.
19*: $[\alpha]^{20}_D$ = - 5,3 (c = 1,5, $CHCl_3$);
^{1}H-NMR: 0,98 (s, 9H, t-Bu), 1,60-2,04 (m, 6H, H-C(3,4,7)), 3,57 (dd, 1H, H-C(1)), 3,65 (dd, 1H, H-C(1)), 3,84-3,95 (m, 2H, H-C(5,6)), 4,05-4,14 (m, 1H, H-C(2,)), 7,28-7,41 (m, 6H, arom.), 7,60-7,68 (m, 4H, arom.); ^{13}C-NMR: 19,3; 26,9; 28,2; 28,3; 28,5; 66,6; 79,7; 81,7; 81,8; 127,6, 129,5; 133,8; 135,6.
*only one half of the symmetric molecule is assigned; for numbering see schemes 1 and 3.

7. Bromide **7** could be obtained following the procedures for **ent-7** starting from D(+) malic acid instead of L(-) malic acid. For the preparation of **ent-7** see Küchler, B.; Voß, G.; Gerlach, H. *Liebigs Ann. Chem.* **1991**, 545-552.

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9. X-ray crystallographic analysis was carried out on racemic lactone **13**. Further details of the crystal structure are available from the Cambridge Crystallographic Data Centre, University Chemical Lab., Lensfield Road, Cambridge CB2 1EW, U.K.. Requests should be accompained by full literature citation for this communication.

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