Pergamon

Tetrahedron Letters, Vol. 35, No. 41, pp. 7629-7632, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01658-5

An Enantiomerically Pure Epoxyorganolithium Reagent for the Synthesis of Oligo(tetrahydrofurans) by an Epoxide-Cascade Reaction

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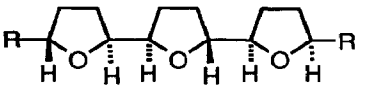
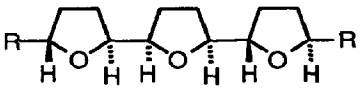
Abstract: *Enantiomerically pure oligo(tetrahydrofurans) **17** and **18** have been prepared using an epoxide cascade reaction. The polyepoxide precursors **13** and **14** were synthesized using the enantiomerically pure epoxyorganolithium reagent **3**. Thus, addition of **3** to the THF aldehyde **11** gave alcohol **12** with a high Cram selectivity of 95:5.*

The stereoselective synthesis of 2,5-linked oligo(tetrahydrofurans) (oligo-THFs) is of twofold interest: On one hand oligo-THFs are the key components of the Annonaceous acetogenins, a pharmacologically important class of natural products. [1] On the other hand oligo-THFs represent potential building blocks for a membrane bound ion-channel active polyether helix. [2] As part of our ongoing studies in the oligo-THF area, [3] we were looking for a synthetic route to two THF-trimers with particular stereostructures - compounds of type **1** (*trans-syn-trans-anti-cis*) and **2** (*trans-syn-cis-anti-trans*). Here we introduce the use of the enantiomerically pure epoxyorganolithium reagent **3** to solve this synthetic problem.



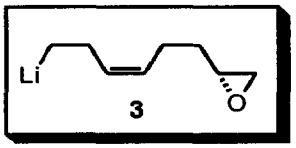
1

trans - syn - trans - anti - cis



2

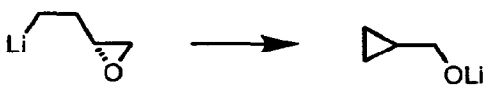
trans - syn - cis - anti - trans



3

The compatibility of an epoxide and an organolithium function in the same reagent depends on the distance between them. [4] For shorter distances it is impossible to avoid - even at very low temperatures - the intramolecular attack of the carbanion on the epoxy ring (e.g. **4** -> **5**, Scheme 1). [5]

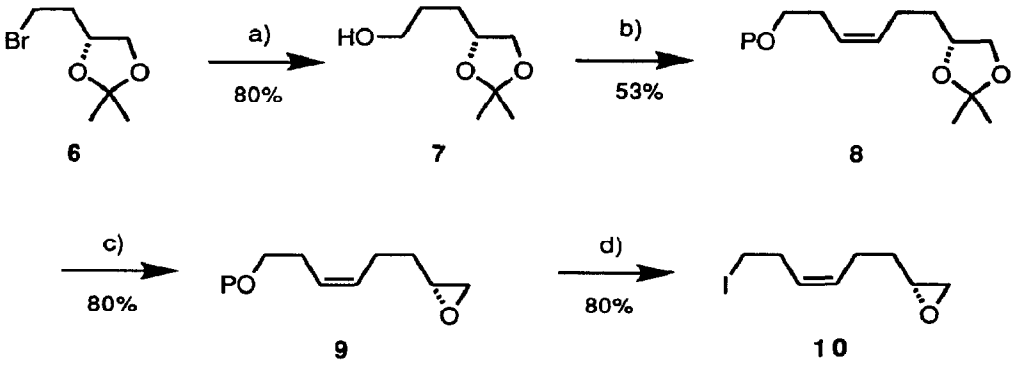
Scheme 1



4 **5**

We hoped that the distance in **3** would be large enough to prevent such an intramolecular side reaction.

The preparation of the organolithium reagent **3** was envisaged by lithium-halogen exchange, thus the corresponding enantiomerically pure iodide **10** was synthesized (Scheme 2).

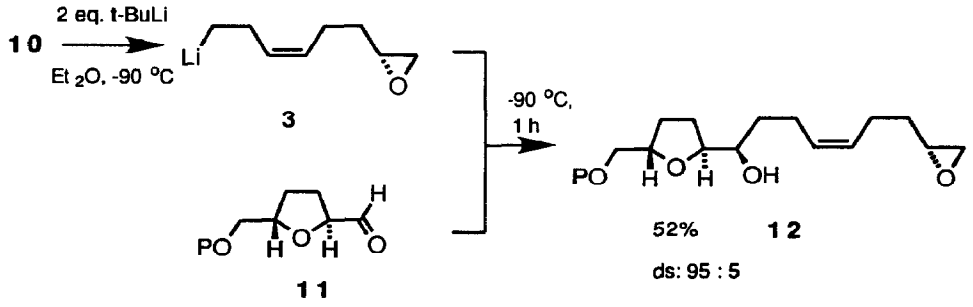


Scheme 2 (P = TBDPS)

a) i: NaCN, DMSO; ii: NaOH, H_2O; iii. $LiAlH_4$, Et_2O; b) i: $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, - 78 °C to rt; ii: NaHMDS, THF, - 78 °C, $TBDPSOCH_2CH_2CH_2P(Ph)_3Br$ c) i: HOAc, H_2O, THF; ii: $MesSO_2Cl$, pyridine, 0 °C; iii: K_2CO_3, MeOH; d) i: nBu_4NF, THF; ii: tosyl chloride, pyridine; iii: LiI, THF.

The bromide **6** [3b] was converted into the higher homologous alcohol **7** by standard procedures. Swern oxidation of **7** and subsequent Z-selective Wittig reaction [6] gave the olefin **8**. Stereocontrolled transformation of the acetonide group into an epoxide produced the epoxy olefin **9**. Cleavage of the silylether in **9** and conversion of the resulting alcohol into an iodide gave compound **10**. [7]

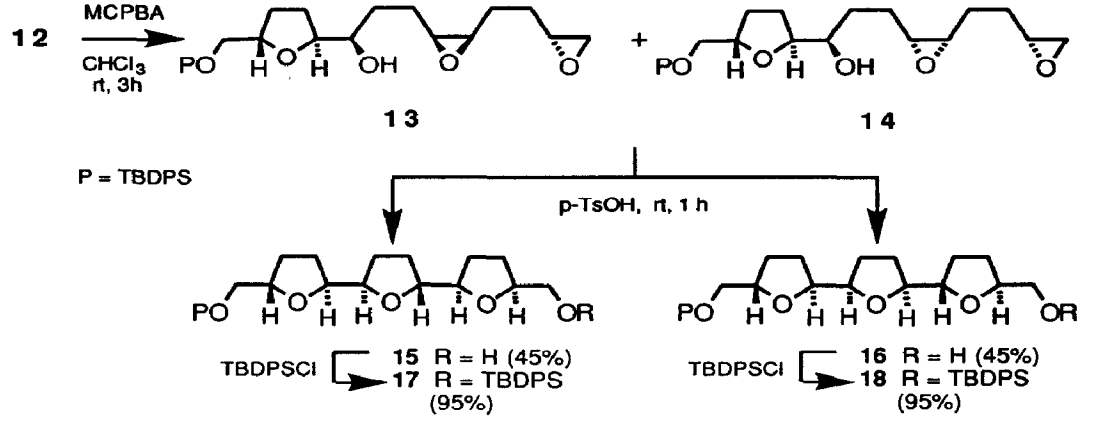
When the iodide **10** was treated with 2 equiv. of t-BuLi in Et_2O at - 90 °C, a clean iodine-lithium exchange occurred (Scheme 3). The resulting epoxyorganolithium reagent **3** was allowed to react with the THF aldehyde **11** to yield the alcohol **12** in 52 % yield. The Cram selectivity of 95:5 in this addition reaction is remarkably high. [8]



Scheme 3 P = TBDPS

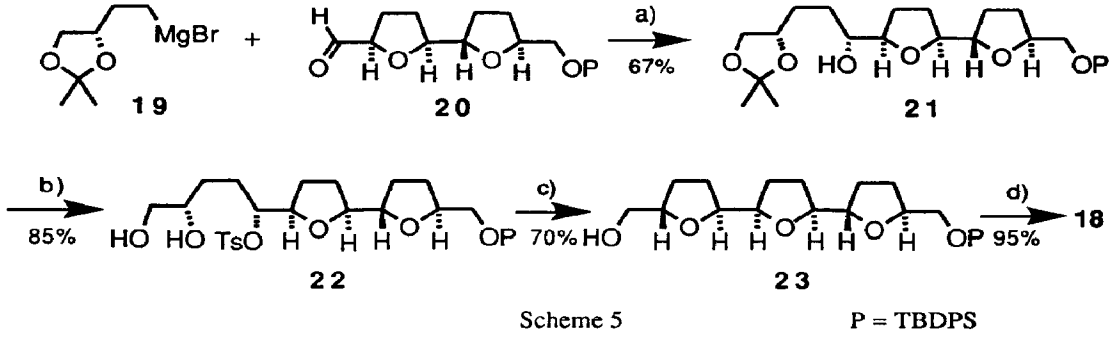
No byproduct from an intramolecular attack of the organolithium function on the epoxide and/or the double bond was observed.

Epoxidation of the monoepoxy-olefin alcohol **12** gave a 1 : 1 mixture of the two diepoxy alcohols **13** and **14** (scheme 4). These were directly submitted to an epoxide-cascade cyclization [9] by addition of p-toluene sulfonic acid to the reaction mixture. The two THF-trimer alcohols **15** and **16** were obtained, which could be separated by silica gel chromatography. Both alcohols were converted separately into the disilylethers **17** and **18**.



Scheme 4

To unambiguously assign the stereostructure of the oligo THFs **17** and **18**, an independent synthesis of the THF-trimer **18** was carried out (scheme 5). For this purpose, we used an established [3a,b] linear strategy for oligo-THF synthesis.



Scheme 5 P = TBDPS

a) i: CuBr • Me_2S, Et_2O, - 78 to 0 °C; b) i: TsCl, pyridine, 0 °C; ii: HOAc, H_2O, THF, rt; c) NaH, THF, 30 °C, 30 min; d) TBDPSCl, imidazole, DMF.

Chelation controlled reaction of the Grignard reagent **19** [10] with THF-dimer aldehyde **20** [3a] gave the alcohol **21**, which was easily transformed into the dihydroxy tosylate **22**. Five-ring selective intramolecular Williamson reaction [11] of **22** yielded the THF-trimer alcohol **23**. After TBDPS protection the disilylether **18** was obtained, which was identical with the compound **18** of the polyepoxide cascade route (scheme 4) by TLC, optical rotation and ^1H as well as ^{13}C-NMR spectra. [7]

In summary, a short and efficient synthetic route towards the two THF-trimers **17** (*trans-syn-trans-anti-cis*) and **18** (*trans-syn-cis-anti-trans*) has been developed. Key steps were the highly Cram-selective addition of the epoxyorganolithium reagent **3** to the THF aldehyde **11** and the polyepoxide cascade reactions of the bisepoxy alcohols **13** and **14**.

Acknowledgement: Financial support by the Deutsche Forschungsgemeinschaft (SFB 260) as well as the Fonds der Chemischen Industrie is gratefully acknowledged.

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7. All new compounds gave satisfactory analytical and spectral data according to their structures. Representative data for compounds **10**, **12**, **17** and **18** (a = 300 MHz, $CDCl_3$, b = 75 MHz, $CDCl_3$):
10: - $[\alpha]_D^{20}$ = + 4.6 (c = 1.00, $CHCl_3$); - ^{1}H NMR (a): δ = 1.51-1.70 (m, 2H), 2.13-2.65 (m, 4H), 2.48 (dd, J = 5.0/2.7 Hz, 1H), 2.75 (t, J = 4.9 Hz, 1H), 2.89-2.95 (m, 1H), 3.14 (t, J = 7.2 Hz, 2H), 5.32-5.41 and 5.51-5.58 (m, 2H); - ^{13}C NMR (b): δ = 5.39, 24.13, 31.46, 32.43, 47.25, 51.93, 128.96, 131.15.
12: - $[\alpha]_D^{20}$ = - 3.8, (c = 1.80, $CHCl_3$). - ^{1}H NMR (a): δ = 1.01 (s, 9H), 1.36-2.23 (m, 12H), 2.43 (dd, J = 5.0/2.7 Hz, 1H), 2.70 (dd, J = 4.9/4.1 Hz, 1H), 2.85-2.91 (m, 1H), 3.61 (d, J = 4.7 Hz, 2H), 3.69-3.84 (m, 2H), 4.04-4.13 (m, 1H), 5.32-5.44 (m, 2H), 7.30-7.38 (m, 6H), 7.59-7.68 (m, 4H). - ^{13}C NMR (b): δ = 19.31, 23.76, 23.82, 25.23, 26.71, 28.26, 32.61 2x, 47.23, 52.01, 66.65, 71.45, 79.96, 82.45, 129.11, 130.20, 127.68, 129.67, 133.74, 135.69.
17: - $[\alpha]_D^{20}$ = + 7.1, (c = 1.37, $CHCl_3$). - ^{1}H NMR (a): δ = 1.05 (s, 18H), 1.55-2.06 (m, 12H), 3.58 (dd, J = 5.3/10.3 Hz, 1H), 3.62 (q, J = 5.6 Hz, 2H), 3.69 (dd, J = 4.1/10.3 Hz, 1H), 3.74-3.83 (m, 3H), 3.84-3.94 (m, 1H), 4.07-4.16 (m, 2H), 7.28-7.40 (m, 12H), 7.63-7.69 (m, 8H). - ^{13}C NMR (b): δ = 19.39, 26.99, 27.62, 28.09, 28.53, 28.62, 28.76, 28.90, 66.62 2x, 79.79, 79.96, 81.73, 82.01, 82.05, 82.49, 127.73, 129.66, 133.93, 134.94, 135.77;
18: - $[\alpha]_{546}^{20}$ = + 0.6, (c = 0.80, $CHCl_3$). - ^{1}H NMR (a): δ = 1.01 (s, 18H), 1.52-2.04 (m, 12H), 3.53-3.64 (m, 3H), 3.68 (dd, J = 4.3/10.2 Hz, 1H), 3.72-3.88 (m, 4H), 4.03-4.11 (m, 2H), 7.28-7.40 (m, 12H), 7.62-7.68 (m, 8H). - ^{13}C NMR (b): δ = 19.10, 26.70, 27.39, 27.77, 27.92, 28.16, 28.73, 28.95, 66.11, 66.33, 79.51, 79.71, 81.49, 81.67, 81.77, 82.32, 127.43, 129.37, 133.65, 135.48.

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(*Received in Germany* 16 *August* 1994; *accepted* 24 *August* 1994)