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STEREOCHEMICALLY CONTROLLED SYNTHESIS OF UNSATURATED 2,5-DIALKYL FURANES

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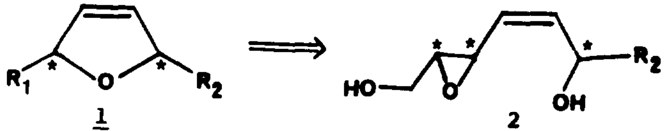
Abstract: The directing effect of a benzoate group in an acid-catalysed intramolecular nucleophilic opening over an epoxyalcohol benzoate is used in the enantioselective preparation of α,α'-dialkyl furanes

In our current syntheses of marine natural products$^{2)}$ we were very interested in the total synthesis of 2,5-dialkyl-3,4-unsaturated furanes 1 as building blocks for a wide number of these compounds bearing the furane unit.$^{3)}$

Having in mind the possibility of synthesizing chiral 2,3-epoxyalcohols by asymmetric epoxidation,$^{4)}$ an obvious way to construct the desired ring is by an intramolecular opening of the epoxide using a secondary nucleophilic oxygen with the proper stereochemistry and fitted at the correct position in the linear chain, considering that such an opening would occur by an "exo"-attack, giving rise to the smallest possible ring$^{5)}$ (Scheme I).



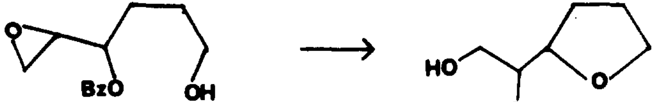
1 2

Scheme I

Unfortunately, the olefinic-2,3-epoxyalcohols 2 are unstable species and are almost inaccessible by asymmetric epoxidation.$^{6)}$ In this communication we report a way to overcome this problem, based on an observed directing effect of the benzoate group in an intramolecular nucleophilic opening over a 1,2-epoxyalcohol benzoate, describing, as a model, the synthesis of the four diastereoisomers of 4 in their enantiomeric forms (Scheme II).

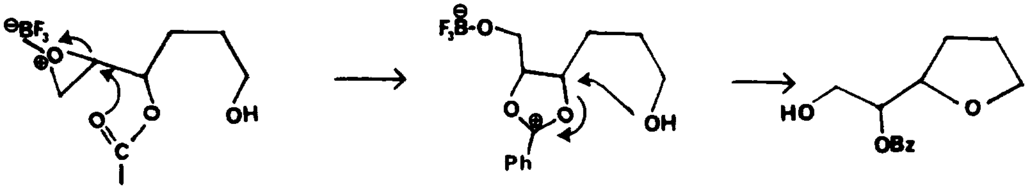
3 Scheme II 4

When the 1,2-epoxyalcohol benzoate 5 (erythro or threo) is submitted to Lewis acid treatment ($BF_3.OEt_2$ (1 equiv.), CH_2Cl_2, 0°C, 10 min.) a clean five member ring formation occurs$^{7)}$(Scheme III).



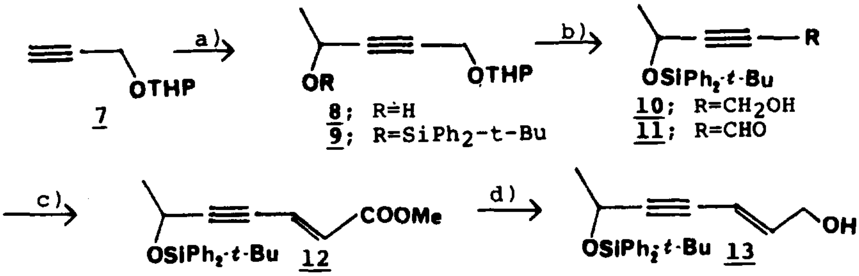
5 Scheme III 6

Clearly such an opening of the epoxide must be the result of a nucleophilic participation of the carbonyl group of the benzoate assisted by the phenyl group which must stabilize the positive charge generated (Scheme IV).



Scheme IV

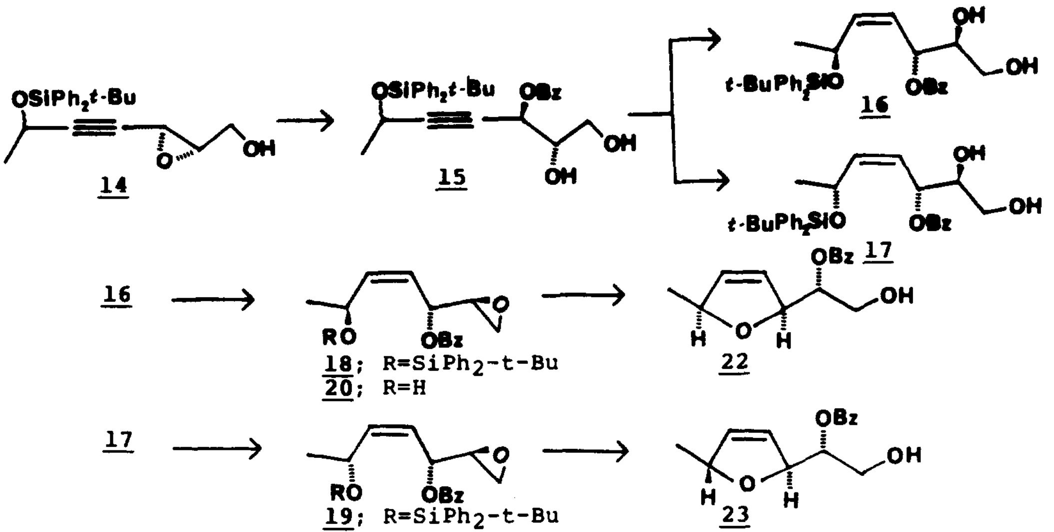
For the synthesis of the epoxides 3 an allylic alcohol 13 was prepared from propargyl-O-THP ether 7 as starting material (Scheme V)



a) i)n-BuLi, THF, -78°C, 0.5 hr.; ii) Acetaldehyde, -78°C→r.t., 1 hr.; iii) $ClSiPh_2$-t-Bu, CH_2Cl_2, Imidazole, 2 hrs., 75% overall yield; b) i) HCl(conc.)(cat.), MeOH, RT, 10 hrs., ii) Swern's oxidation,$^{8)}$ 83% overall yield; c) $(MeO)_2P(O)CH_2CO_2Me$, NaH, Benzene, 0°C, 1 hr., 93%; d) DIBAL, ether, 0°C, 0.5 hr., 87%.

Scheme V

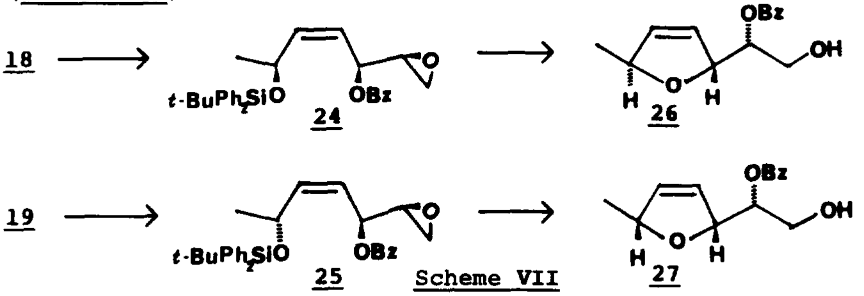
Asymmetric epoxidation of 13$^{4)}$ ($Ti(OPr^i)_4$, L-(+)-diethyl tartrate, tert-butyl hydroperoxide, CH_2Cl_2, -20°C, 3 hrs.) gave the diastereomeric epoxyalcohol 14 in 83% yield (Scheme VI). The application of an isomerization procedure reported recently by us$^{9)}$ gave the diol benzoate 15, which was submitted to selective hydrogenation, in ethyl acetate, using Lindlar's catalyst, giving the diastereomeric mixture 16, |α|$_D^{25}$ +51.8° (c 5.1, $CHCl_3$) and 17, |α|$_D^{25}$ +21.1° (c 4.7, $CHCl_3$) in 77% overall yield, easily separated by column chromatography. The completion of the above-mentioned procedure,$^{9)}$ in both products, afforded the 1,2-epoxyalcohol benzoate 20, |α|$_D^{25}$ +56.9° (c 5.2, $CHCl_3$) and 21, |α|$_D^{25}$ +11.6° (c 0.8, $CHCl_3$)), in 66% and 63% overall yield, respectively (Scheme VI).



Scheme VI

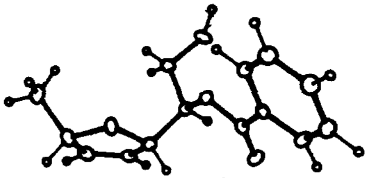
20 was desilylated (n-$Bu_4N^+F^-$, THF, r.t., 3 hrs., 92% yield) and treated with $BF_3.OEt_2$ (-78°C, CH_2Cl_2, 0°C, 15 min.) to yield the furane 22, m.p. 84°C, $|\alpha|_D^{25}$ -51.2°(c 0.56, $CHCl_3$) in almost quantitative yield. Similar treatment with 21 yielded 23, $|\alpha|_D^{25}$ -141°(c 1.0, $CHCl_3$) with an almost similar overall yield.

When the benzoates were removed from 18 and 19 (K_2CO_3, MeOH, r.t., 15 min.) and Mitsunobu's reaction 10) is applied, two threo 1,2-epoxyalcohols 24, $|\alpha|_D^{25}$ -18.9°(c 2.4, $CHCl_3$) and 25, $|\alpha|_D^{25}$ -23.8°(c 2.6,$CHCl_3$) were obtained, which by the above described procedure led to the furanes 26, $|\alpha|_D^{25}$+64.6°(c 0.3, $CHCl_3$) and 27, $|\alpha|_D^{25}$+19.6°(c 0.26, $CHCl_3$), in similar overall yield (Scheme VII)



Scheme VII

The absolute configuration of 22 was determined by X-ray analysis. Crystals of 22 are monoclinic, $P2_1$, a=8.479(1), b=5.714(1), c=13.154(1) Å, β=90.12(6)°, Z=2, Siemens AED4 diffractometer, CuK_α radiation. Structure solved with SHELXS-86. Anisotropic full-matrix l.s. refinement for non hydrogen atoms. Final R=0.059 (738 reflections). Absolute configuration with 18 Bijvoet pairs in the ranges: $10. < F_o < 50.$, $F_o > 5\sigma(F_o)$, $.15 < \sin\theta/\lambda < .50$, averaged Bijvoet differences .24 for the right enantiomer, 28, vs. .27 for the wrong one.



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Full synthetic applications of this kind of substances are in course and will be published elsewhere.

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11) Satisfactory IR and NMR (H^1 and C^{13}) spectroscopic data and high resolution mass spectrometric data for the new products were obtained.

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