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ENANTIOMERIC SYNTHESIS OF POLYSUBSTITUTED FURANES BY STEREOSELECTIVE INTRAMOLECULAR BROMOETHERIFICATION

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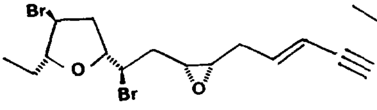
Abstract: The stereoselectively controlled synthesis of 2,5 dialkyl,3-substituted furanes by enantioselective construction of chiral alkenols and stereoselective bromocyclization is described.

As a part of a programme directed towards the total synthesis of several halogenated sesquiterpenoids2) isolated from marine sources,3) we have focussed our attention on a series of compounds containig a five member ring ether including laurepoxide4) 1, kamauselene5) 2, and kamusine 3, (cis and trans).6)



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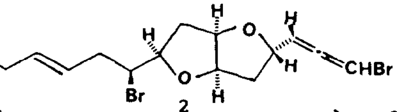

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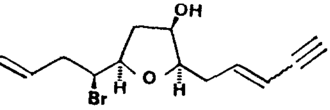

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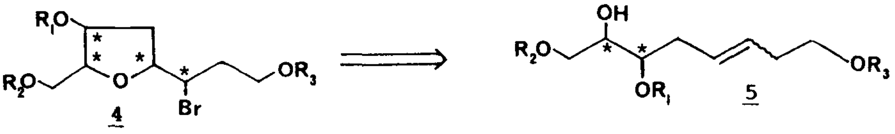
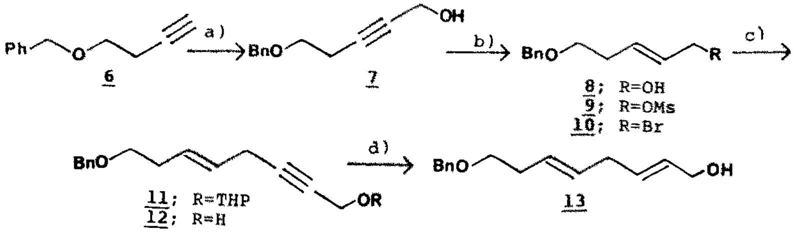
In such compounds the main problem to solve in the total synthesis is the construction of the furan unit with the right configuration of the carbons with substituents including the one with the bromine atom at the linear chain.

In this communication we report our preliminary studies directed to the stereocontrolled synthesis of such units, which may provide a way to the target molecules, and to other related molecular fragments present in more complicated natural products.7) Our strategy is based on the known electrophile-promoted cyclization of γ-hydroxyalkenes7,8,9), directing our results to establishing a way to synthesize with absolute control in all the chiral centres involved, the cyclic product 4 (Scheme I).



Scheme I

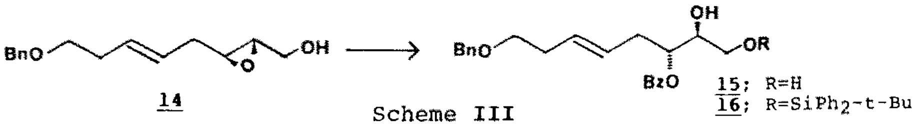
For the synthesis of the proper E-alkene-triol 5 a dienol 13 was prepared from the benzyl ether of 3-butyn-1-ol 6 as starting material (Scheme II).



a) i)n-BuLi, THF, -80°C, 10 min.; ii) $(CH_2O)_n$, -80°C→R.T., 93%; b) i)$LiAlH_4$, THF, R.T., 2 hr., 87%; ii) MsCl, Et_3N, CH_2Cl_2, 0°C, 20 min.; iii) LiBr, DMF, 0°C, 20 min, 85% overall yield; c) i) $LiC{\equiv}CCH_2OTHP$, HMPTA, THF, -60°C→R.T., 10 hr. ii) MeOH, HCl (con., cat.), 73% overall yield; d) $LiALH_4$, ether, 0°C→R.T., 12 hr., 85%.

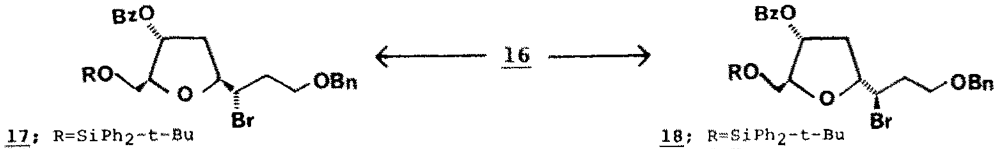
Scheme II

The asymmetric epoxidation[10)] of 13 under stoichiometric conditions (L-(+)-diethyl tartrate, $(CH_3)_3COOH$, CH_2Cl_2, molecular sieves 3Å, -20°C, 2 hr.) yielded the epoxyalcohol **14** $|\alpha|_D^{25}$ -16.5°(c 2.14, $CHCl_3$) (Scheme III) in 88% yield and more than 95% ee. This products was submitted to the titanium tetraisopropoxide-assisted opening of 2,3-epoxyalcohols using benzoic acid as nucleophile[11)] ($TiOPr_4$, PhCOOH, CH_2Cl_2, CH_2Cl_2, R.T., 30 min.) to yield the triol benzoate **15** $|\alpha|_D^{25}$ +4.0°(c 0.9, $CHCl_3$) as the only detectable product. This substance with the well established configuration on the two secondary carbons, was mono-protected at the primary alcohol ($ClSiPh_2$-t-Bu) (1.05 equiv.), DMF, imidazole, 25°C, 12hr.) yielding **16** $|\alpha|_D^{25}$ -3.2°(c 7.5, $CHCl_3$), in an attempt to avoid any nucleophilic competition.



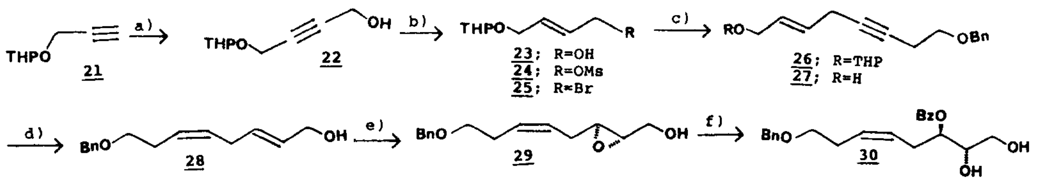
Scheme III

When **16** was treated, in THF and HMPTA (2 equiv.), at -60°C with 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCD) (1.1 equiv.) a 4:1 mixture of **17**:**18** (established by proton-NMR analysis) was obtained in 92% overall yield.[12)] When the mixture was treated, in THF, with $n\text{-}Bu_4NF$, the furans **19** $|\alpha|_D^{25}$ +18.9° (c 2.4, $CHCl_3$) and **20** $|\alpha|_D^{25}$ -15.8° (c 1.5, $CHCl_3$) were readily separated by silica gel column chromatography. When we tried to observe the nucleophilic regioselectivity between the two hydroxy groups by cyclization of **15**, the same ratio and yield of **19** and **20** were observed. The ratio of **19** and **20** was almost inverted (1:2.5) when the cyclization reaction was carried out in CH_2Cl_2 at 0°C (Scheme IV).



Scheme IV

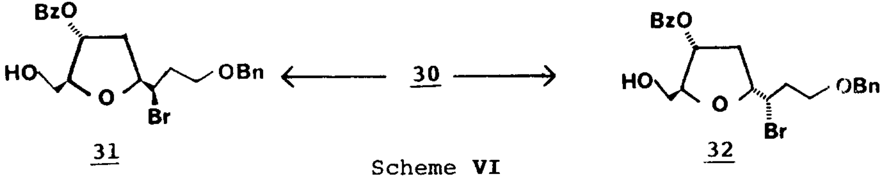
To afford to the diastereoisomers **31** and **32** we prepared the Z-olefin **30** $|\alpha|_D^{25}$-25.0°(c 0.9, $CHCl_3$) according to the Scheme V.



a) i) n-BuLi, THF, -80°C, 15 min.; ii) $(CH_2O)_n$, -80°C---R.T., 93%; b) i) $LiAlH_4$, THF, 0°C, 2 hr., then NaOMe (1.1 equiv.), 83%; ii) MsCl, CH_2Cl_2, 0°C, 20 min; iii) LiBr, DMF, 0°C→R.T., 30 min., 87% overall yield; c) i) $LiC{\equiv}C(CH_2)_2OBn$, Cu_2I_2(cat.), -60°C→R.T., 12 hr., 75%; ii) MeOH, HCl (con., cat.); d) H_2, Lindlar's catalyst, quinoline, MeOH, 83% overall yield; e) $TiOPr^i_4$, L-(+)-diethyl tartrate, TBHP, CH_2Cl_2, -20°C, 88%; f) $TiOPr^i_4$, PhCOOH, CH_2Cl_2, R.T., 81%.

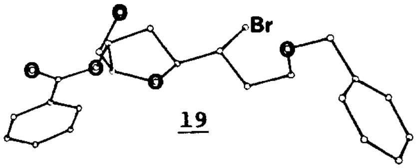
Scheme V

The cyclization of **30**, in the above mentioned conditions led to **31** $|\alpha|_D^{25}$ +4.5°(c 0.5, $CHCl_3$) and **32** $|\alpha|_D^{25}$-4.8°(c 1.2, $CHCl_3$), (THF-HMPTA, -60°C, 5:1 ratio, 87% yield; CH_2Cl_2, 0°C, 1:1 ratio, 75% yield; respectively) (Scheme VI).[13]



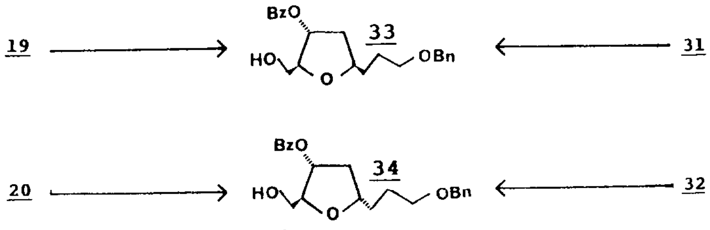
Scheme VI

To establish the relative position of the substituents, **19** was submitted to X-ray analysis, showing a cis-relation between the two alkyl groups. $C_{22}H_{25}O_5Br$, orthorhombic, a=5.063(3), b=20.229(20), c=20.495(8)Å, V=2099.0 Å^3, space group $P22_12_1$, Z=4. Data were measured on a Siemens AED4 diffractometer with Cu-K_α radiation (graphite monochromator) using $\omega:\theta$ scan. The structure was solved by the Patterson method and Fourier synthesis. In the course of the isotropic least squares refinement of the positional parameters on non-hydrogen atoms, an empirical absorption correction was calculated with the DIFABS program (the minimum and maximum corrections were 0.852 and 1.299). Anisotropic temperature factors were used for the refinement of the non-H-atoms. The final discrepancy index was R=0.044 for 1984 observed reflections ($I>3\sigma(I)$, $3°\leq\theta\leq128°$).



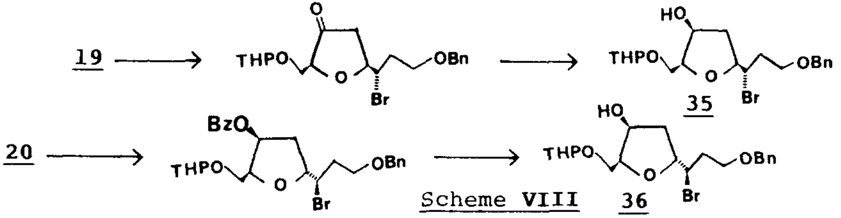
19

The structural correlations of **31** and **19**, and **32** and **20** were established by dehalogenation (n-Bu_3SnH, AIBN, benzene, reflux) yielding **33** $|\alpha|_D^{25}$-2.63°(c 0.4, ether) and **34** $|\alpha|_D^{25}$-12.4°(c 2.7, $CHCl_3$) respectively (Scheme VII).



Scheme VII

To complete the control in all the chiral centres 19 was protected (DHP, PPTS (cat.), CH_2Cl_2, R.T., 5hr.), hydrolysed (NaOMe, CH_2Cl_2, -20^oC, 15 min, 85% in both steps), oxidated (PCC, CH_2Cl_2, mol. sieves, 2 days, 73%) and reduced (DIBAL, ether, -80^oC, 30 min, 85%) to afford the desired epimer 35 $|\alpha|^{25}_{D}+8.4^o$(c 0.6, $CHCl_3$) (Scheme VIII).



Scheme VIII

When 20 was submitted to Mitsunobu's reaction[14)] and hydrolysis the desired epimer 36$|\alpha|^{25}_{D}-5.3^o$(c 0.6, $CHCl_3$) was obtained (Scheme VIII).

Use of the methodology described in this communication is being made in the total synthesis of kamusine[6)] and will be published elsewhere.

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12) A similar ratio is obtained with N-bromo succinimide as bromonium source, however the yields are a little smaller (60-70%). Other solvent systems gave substantial differences (complete details will be given in a forthcoming full paper).
13) A complete homonuclear correlation (COSY) was needed to unequivocally establish the ring size, once the geminal proton to the bromine atom had been assigned by bidimensional heteronuclear spectroscopy.
14) Mitsunobu, O.; **Synthesis**, 1981, 1. The benzoic acid was used as nucleophile.
15) 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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