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A HIGHLY STEREOSELECTIVE ROUTE TO SUBSTITUTED BIS-TETRAHYDROFURANS FROM 1,5-DIENES.

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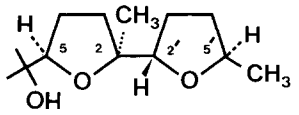
Summary : Bis-tetrahydrofurans 1a and 1b, containing four chiral centers, are obtained with a 90 % isomeric purity from geranyl and neryl chlorides in four steps including two stereoselective cyclizations.

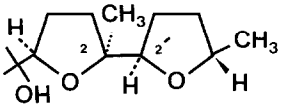
The stereoselective synthesis of bis-tetrahydrofurans with functional groups at positions 5 and 5' is a step towards the elaboration of more complex structures found in natural ionophore antibiotics (1). Many of these structures possess at adjacent positions two tetrahydrofuran rings, one of which has a trans configuration and the other a cis configuration. A typical example is monensin whose total synthesis has recently been carried out (2, 3).

We describe here a method of stereoselective synthesis of bis-tetrahydrofurans 1a and 1b which have this type of structure (Scheme I). These compounds, with four asymetric centers, were obtained, respectively, from geranyl and neryl chlorides by two successive stereoselective cyclizations.

Scheme I



1a



1 b

1) Synthesis of the ring with cis-configuration

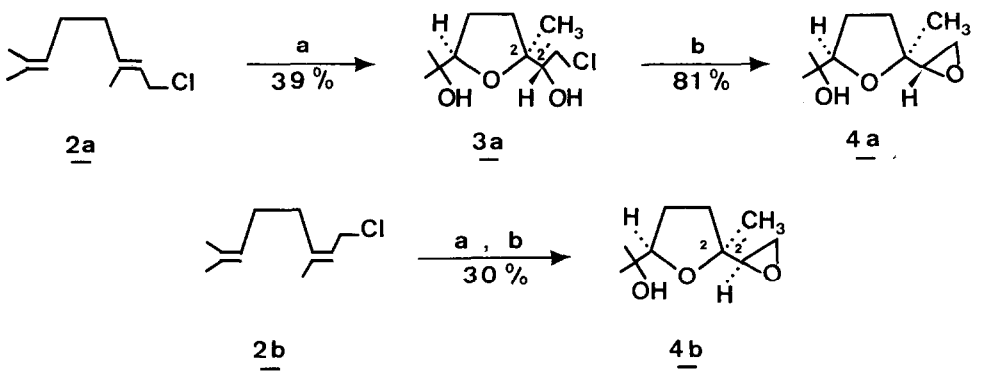
In scheme II are indicated the different steps in this synthesis which led to only a single diastereoisomer of the epoxide of linalool oxide (4a or 4b), in fact controlling the configuration of ring (exclusively cis) as well as the relative configuration of carbons 2 and 2'. The oxidative cyclization of 1,5-diene with potassium permanganate, introduced by Klein and Rojahn (4) is a key-step in this synthesis.

Geranyl chloride 2a (7) was treated with potassium permanganate at -10°C, in 10 % aqueous acetone. The reaction mixture was kept almost neutral by bubbling CO_2. The chlorohy-

drin 3a was obtained in a yield of 39 % following its purification over silicagel (ether/ petroleum ether 50/50). Treatment of the chlorohydrin 3a with an alkali (powdered KOH, 5 h, reflux of ether) gave the epoxide of linalool oxide 4a. In this reaction the stereochemistry of carbon 2' is conserved and its configuration is not only fixed during the cyclization reaction but is also controlled by the choice of the starting diene (4,5). Similarly, neryl chloride 2b afforded the epoxide 4b which is an epimer of 4a. To designate the relative configurations of carbons 2 and 2', the diastereoisomer 4a is named threo and the diastereoisomer 4b erythro.

Assessment of the stereoselectivity of the cyclization reaction with $KMnO_4$ was carried out by comparing, using gas chromatography and a capillary column (Carbowax 20 M, 50 m, 0,25mm), the isomers 4a and 4b to a mixture of the 4 possible diastereoisomers obtained in the epoxidation of linalool oxide cis + trans (8).

Scheme II

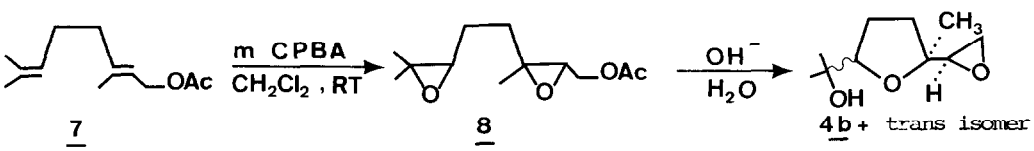


(a) $KMnO_4$, acetone-water (9-1), CO_2 bubbling, -10°C, 2 h.

(b) Powdered KOH, reflux Et_2O, 5 h.

The isomers 4a and 4b did not show cross contamination. On the other hand, the cis-erythro isomer 4b contained only a trace of a product having the same retention time as the trans-isomer, and showed an isomeric purity not less than 98 %. Unfortunatly, the threo-isomers (cis and trans) gave only a single peak ; however, the isomeric purity of the threo isomer 4a could be evaluated in a later stage of the synthesis.

Scheme III



The assignment of configuration is based on previous works in the cyclization of 1,5-dienes with $KMnO_4$ (4-6, 9). The relative configuration of carbons 2 and 2' in 4a (threo) and 4b (erythro) were confirmed by carrying out the reactions indicated in scheme III from geranyl acetate 7. The saponification of the diepoxide of geranyl acetate 8 is known (10) to produce only

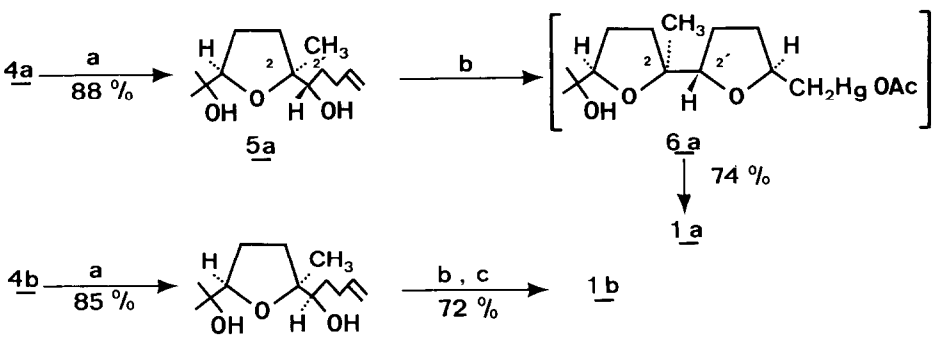
the erythro isomers (mixture of cis + trans) of the epoxide of linalool oxide. On comparing the chromatograms, it is seen that 4b can be correlated with on of the erythro isomers and thus 4a is, in fact, threo (13).

2) Synthesis of the ring with trans configuration

We observed in previous work (11) that heterocyclization with mercuric acetate of a γ,δ-ethylenic alcohol attached to position 2 of a tetrahydrofuran ring produces a new tetrahydrofuran cycle, mainly trans. This method was used to synthesize the second ring of 1a and 1b.

In order to carry out this reaction, the epoxide 4a was converted to the threo γ,δ-ethylenic alcohol 5a by the addition of allylmagnesium bromide (scheme IV). The addition takes place on the less substituted carbon of the epoxide and conserves the stereochemistry of carbon 2' (14).

Scheme IV



(a) ≈MgBr, Et_2O, RT. (b) $Hg(OAc)_2$, water-THF, RT, 1 h. (c) $NaBH_4$, OH^-.

Similar treatment of the mixture of 4 isomers of the epoxide obtained from linalool oxide gave 4 diastereoisomeric ethylenic alcohols and in gas chromatography, the four expected peaks were observed. On comparing these chromatograms to that of the compound 5a threo, it was observed that trans-diastereoisomer was absent, a thing which was impossible to determine at the epoxide 4a stage.

Cyclization of 5a was carried out with mercuric acetate in a mixture 1 : 1 of water and THF. Reduction in situ of the organomercuric compound 6a afforded a mixture containing 90 % of the isomer 1a (2nd ring with trans configuration) and 10 % of the cis-isomer. Similarly, 1b was obtained from the erythro epoxide 4b with 90 % isomeric purity (15). The assigment of trans configuration to the ring formed in the heterocyclization with mercuric acetate is based on previous works carried out on similar systems in our laboratory (11) and on other systems (12).

Thus, we have synthesized a system of two tetrahydrofurans rings containing four asymetric carbons with a 80 % stereoselectivity and a yield of about 20 % based on the starting diene (16). This method can be applied in the synthesis of structural fragments of

natural products by choosing the appropriate starting diene.

References and Notes

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    b) ibid, submitted to Bull. Soc. Chim. Fr.
12. a) V. Speziale, J. Roussel and A. Lattes, J. Heterocycl. Chem., 11, 771 (1974).
    b) For a discussion of the mechanism and the stereoselectivity of the oxymercuration reaction see : V. Speziale, Thesis, Université de Toulouse (France), n° 846 (1978).
13. 4a : oil ; NMR ($CDCl_3$, δ ppm) 1.07 (3H, s), 1.21 (3H, s), 1.30 (3H, s), 1.55-2.3 (4H, m), 2.6-3.05 (3H, m), 3.45 (1H, s, OH), 3.8 (1H, t, J=6Hz).
    4b : oil ; NMR ($CDCl_3$, δ ppm) 1.15 (3H, s), 1.25 (6H, s), 1.62-2.00 (4H, m), 2.25 (1H, s, OH), 2.50-2.85 (2H, m), 3.07 (1H, t, J=4Hz), 3.8 (1H, t, J=6Hz).
14. 5a : m.p. : 46-47°C ; NMR ($CDCl_3$, δ ppm) 1.14 (3H, s), 1.17 (3H, s), 1.25 (3H, s), 1.35-2.33 (8H, m), 2.47 (2H, s, OH), 3.40 (1H, t, J=6Hz, -CH-OH), 3.80 (1H, t, J=7Hz), 4.90-6.07 (3H, m, vinylic H).
    5b : oil ; NMR ($CDCl_3$, δ ppm) 1.15 (3H, s), 1.17 (3H, s), 1.25 (3H, s), 1.38-2.42 (8H, m), 2.72 (2H, s, OH), 3.58 (1H, dd, J=4 and 9Hz, -CH-OH), 3.80 (1H, t, J=7Hz), 4.90-6.07 (3H, m, vinylic H). The difference between signals of protons on carbon 2' distinguishes easily the compound 5a (threo) from 5b (erythro).
15. 1a : oil ; NMR ($CDCl_3$, δ ppm) 1.10 (3H, s), 1.15 (3H, s), 1.23 (3H, d, J=6,5Hz), 1.26 (3H, s), 1.46-3.30 (8H, m), 3.37 (1H, s, OH), 3.67-4.35 (3H, m). Mass spectrum m/e (rel. intensity) : 228 (M^+, 0.6), 213 (11), 169 (10), 143 (93), 125 (46), 109 (14), 85 (100), 71 (26), 43 (54).
    1b ; oil : NMR ($CDCl_3$, δ ppm) 1.09 (3H, s), 1.14 (3H, s), 1.24 (3H, d, J=6Hz), 1.26 (3H, s), 1.35-2.22 (8H, m), 3.75-4.15 (4H, m). Mass spectrum m/e (rel. intensity) : 228 (M^+, 0.8), 213 (11), 169 (14), 143 (100), 125 (53), 109 (18), 85 (83), 71 (32), 43 (61).
    Satisfactory elemental analysis was obtained for the compounds 1a and 1b.
16. Since the end of our work, a procedure was found (6) to improve the extraction yield of the first cyclization.

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