Novel 8-Oxothearspiranes and Dihydro Analogues Possessing a Partly Fluorinated Ring

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Abstract: New spiro compounds, 8-oxothearspiranes analogues and dihydro equivalents possessing a partly fluorinated ring, are obtained from 5-(α-iodoperfluoropropyl)furan-3(2H)-one and unsaturated compounds through an annulation process (favored 6-exo-trig). Yields observed appear as largely depending on the nature of the unsaturated substrate used. For primary alkynols or alkenols or allyl oxycoumarin, the annulation process largely predominates over the radical chain addition process. The contrary is observed when the alkynols or alkenols are tertiary ones.

Key words: idoperfluoropropylfuranone, 8-oxothearspiranes, dihydro-8-oxothearspiranes, annulations, spiro compounds

The spirocyclic ether unit is found in a number of natural products, for example thespirane isolated from tea,1 kuroyurinidine from the bulbs of Fritillaria maximowiczii (a Japanese plant)2 and many others. In this field, formation of the oxaspirodecane skeleton, e.g. thespirane, has received particular attention. Thus 8-oxothearspirane derivatives (Figure 1, compound 1) have been prepared as major coproducts during the synthesis of β-damascenones from 6-hydroxy-7,8-dehydro-α-ionols in studies related to the biosynthesis of damascenones from carotenoids.3 The dihydro equivalents4 (Figure 1, compound 2) have been obtained in studies dealing with the conversion of cyclic ketones into functionalized spirocyclic tetrahydrofurans through a carbene O–H insertion.5 Our aim was to prepare novel 8-oxothearspiranes (Figure 1, compound 3) and their dihydro analogues (Figure 1, compound 4), possessing a partly fluorinared ring.

Recently we reported the synthesis of a partly fluorinared geiparvarin analogue.6 A key intermediate of the synthesis was the furanone 5. In the course of this geiparvarin synthesis, compound 5 was added to 2-methylbut-3-yn-2-ol through a radical chain process and a by-product was observed in low yield. This by-product, an interesting spiro compound possessing a partly fluorinared ring, was derived from a competitive annulation process.

In the present paper, we have developed the study of the annulation process, using alkynols and alkenols as annulating substrates, also varying their substituents to study the possibilities of this process in the synthesis of compounds 3 and 4.

Radical addition of the furanone 5 to alkynols (propargylic alcohol, 2-methylbut-3-yn-2-ol) using the Huang system7 as initiator produced the adducts 6 through a classical chain mechanism with iodine atom transfer8 (only in the Z-form or as a mixture of Z- and E-forms depending on the alkynol used, see footnote 1 in Ref.8), the reduction products 7 through hydrogen atom transfer from the solvent SH, and spiro compounds 3, the new 8-oxothearspiranes (Scheme 1). The formation of 3 may result from a competitive annulation process occurring during the radical chain reaction, as depicted in Scheme 1 (favored 6exo-trig). The molar ratios of 6:7:3 determined by 19F NMR spectra are reported in Table 1. Then, the mixture was treated with zinc in acetic medium9 to reduce the iodide 6 into 7. The crude mixture was composed of compounds 7 and 3, which could be separated by column chromatography in the case of 7b and 3b. Final yields of the spiro compounds 3a and 3b isolated in the pure state (3b) or as a mixture (3a + 7a) are reported in Table 1 (see also experimental part).

Figure 1 The spirocyclic ether unit in natural products, 8-oxothearspiranes 1, dihydro analogues 2, and the fluorinated analogues 3 and 4 synthesized in this work.
Radical addition of the furanone 5 to alkenols (allyl alcohol, 2-methylbut-3-en-2-ol) and 7-allyloxycoumarin using the Huang system as initiator produced the adducts 8 through a classical chain mechanism with iodine atom transfer, the reduction products 9 through hydrogen atom transfer from the solvent SH, and the spiro compounds 4, the fluorinated dihydro-8-oxotheaspiranes (Scheme 2). Again the formation of 4 may result from an annulation process occurring during the radical chain reaction, as depicted on Scheme 2 (favored 6-exo-trig). The molar ratios of 8:9:4 determined by 19F NMR spectra are reported in Table 1. Then, the mixture was treated by zinc in acidic medium in order to reduce the iodide 8 into 9.

When the reaction was performed with 7-allyloxycoumarin, the reduction product 9c was not formed, and the adduct 8c and the annulation compound 4c were separated directly by column chromatography without reduction of the iodide 8c. When the reaction was performed with 2-(CF2)3:

**Table 1**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkynol</th>
<th>Annulation Compound mol%</th>
<th>Addition Compound mol% (isomer)</th>
<th>Reduced Compound mol%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>propargylic alcohol</td>
<td>3a: 62 (56b)</td>
<td>6a: 2 (Z), 1 (E)</td>
<td>7a: 12 (Z), 23 (E)</td>
</tr>
<tr>
<td>2</td>
<td>2-methylbut-3-yn-2-ol</td>
<td>3b: 18 (12c)</td>
<td>6b: 47 (Z)</td>
<td>7b: 35 (E)</td>
</tr>
<tr>
<td>3</td>
<td>allylic alcohol</td>
<td>4a: 70 (50b)</td>
<td>8a: 15</td>
<td>9a: 15</td>
</tr>
<tr>
<td>4</td>
<td>2-methylbut-3-en-2-ol</td>
<td>4b: traces</td>
<td>8b: 67</td>
<td>9b: 33</td>
</tr>
<tr>
<td>5</td>
<td>7-allyloxycoumarin</td>
<td>4c: 75 (52c)</td>
<td>8c: 25</td>
<td>9c: 0</td>
</tr>
</tbody>
</table>

*NMR yields are given. Final yields of compounds isolated in the pure state when available are given in parentheses.

* Yield relative to the starting furanone 5, on the basis of the NMR analysis and isolated weight of the mixture 3a and 7a or 4a and 9a.

* Yield relative to the starting furanone 5, isolated in the pure state.

* As a mixture of two diastereoisomers (see text).
methylbut-3-en-2-ol, only trace amounts of the cyclization product 4b were detected, and reduction of the iodide 8b resulted in the formation of the expected compound 9b, together with competitive formation of compound 10b from IOH elimination and of compound 11b from H1 elimination (Scheme 3). When the reduction reaction was applied to compound 8a, only the reduction product 9a was formed. Final yields of the spiro compounds 4a and 4c isolated in the pure state (4c) or as a mixture (4a + 9a) are reported in the Table 1 (see also experimental part).

Scheme 3  Reduction of compound 8b

In the two reactions affording annulation compounds, the fluorinated dihydro-8-oxotheaspiranes 4a and 4c were formed as mixtures of two diastereoisomers. Interestingly, in the case of 4c, the two diastereoisomers were resolved by selective crystallization (needles and polyhedra). The big polyhedra appeared as unsuitable for X-ray crystallographic study, being ‘polycrystalline’. On the contrary, the crystal structure of the compounds 4cN (needles form) including the configuration of the spirocyclic unit was determined by X-ray crystallographic analysis (Figure 2). In this diastereoisomer, the coumarinyloxymethyl side chain is in equatorial position, and the C-4 methylene group of the furanone ring is also in equatorial position.

Figure 2  Crystal structure of (5R,10S)-(6,6,7,8,8-hexafluoro-10-methoxyxymethyl-2,2-dimethyl-1-oxaspiro[4.5]-3-oxodecanyl)-chromen-2-one [(5R,10S)-4cN, needles]

In conclusion, we have shown that in the presence of appropriate primary alkenols or alkynols and through radical initiation, the 5-(o-iodoperfluoropropyl)furan-3(2H)-one 5 can be efficiently involved in an annulation process with formation of novel 8-oxotheaspiranes, and their dihydro analogues, possessing a partly fluorinated ring. Thus, in presence of allylic or propargylic alcoholic substrates, radical initiation applied to 5 resulted in the formation of adducts 6 or 8 through a classical radical chain process with iodine atom transfer. The competitive formation of annulation compounds 3 or 4 is very dependent upon the steric hindrance near the oxygen group of the alcoholic substrates. Significant yields (Table 1) are observed with primary alcohols (propargylic or allylic alcohols) or their ether as in the case of 7-allyloxycoumarin (isolated yield: this trans relationship was further supported by NOESY measurements and COSY correlations. In the case of the needle crystals 4cN, the observed nuclear Overhauser effect indicated an interaction between the protons of the C-4 methylene group and the protons of the methylene group of the coumarinyloxymethyl side chain (Figures 1 and 3). In contrast, no nuclear Overhauser effect was detected when the NOESY experiment was performed on the polyhedral crystals 4cP (Figure 3). This is in favor of a cis relationship between the two respective methylene groups, the coumarinyloxymethyl side chain in equatorial position and the furanone methylene in axial position. The ratio observed between the two diastereoisomers was 4cN:4cP = 2:1, attributed to diastereoisomers (5R,10S) + (5S,10R) and (5R,10R) + (5S,10S). In the reaction of 5 with allylic alcohol, a similar ratio of 2:1 between two diastereoisomers was also observed. The relative stereochemistries of these isomers were assigned on the basis of 1H NMR data by comparison with the allyl oxy-coumarin series.

Figure 3  NOESY effects of compounds 4cN and 4cP

In conclusion, we have shown that in the presence of appropriate primary alkenols or alkynols and through radical initiation, the 5-(o-iodoperfluoropropyl)furan-3(2H)-one 5 can be efficiently involved in an annulation process with formation of novel 8-oxotheaspiranes, and their dihydro analogues, possessing a partly fluorinated ring. Thus, in presence of allylic or propargylic alcoholic substrates, radical initiation applied to 5 resulted in the formation of adducts 6 or 8 through a classical radical chain process with iodine atom transfer. The competitive formation of annulation compounds 3 or 4 is very dependent upon the steric hindrance near the oxygen group of the alcoholic substrates. Significant yields (Table 1) are observed with primary alcohols (propargylic or allylic alcohols) or their ether as in the case of 7-allyloxycoumarin (isolated yield:
52%). On the contrary, in the case of tertiary alcohols, the presence of two methyl groups strongly limits (2-methyl-2-pentanol, isolated yield: 12%) or completely inhibits (2-methylbut-3-en-2-ol) the annulation process.

IR spectra were recorded on a Bruker IFS 25 instrument in the transmittance mode. Wavelengths are given in cm$^{-1}$. $^1$H and $^{19}$F NMR spectra were recorded on a Bruker AC 250 spectrometer operating at 250.13 MHz for $^1$H and at 235.36 MHz for $^{19}$F. $^{13}$C NMR spectra were recorded on a Bruker DRX 400 operating at 100.61 MHz. IR spectra were recorded on a Bruker IFS 25 instrument in the transmittance mode. Wavelengths are given in cm$^{-1}. 1$H and $^{19}$F NMR spectra to be a mixture of compounds 3a, 6a and 9a,b in a molar ratio of 62:3:35. The adduct 6a and its reduced form 7a were obtained as a mixture of Z- and E-forms, in a molar ratio of Z:E = 12:23 for compound 6a and Z:E = 12:23 for compound 7a. Then, the general procedure B was applied to the mixture of compounds 3a, 6a and 7a (2.58 mmol). Work-up gave an orange oil (0.74 g, 90%) which was identified as a mixture of two different compounds 3a (56%) and 7a (34%) in a molar ratio of 62:38, with a ratio of Z:E = 13:25 for compound 7a. It has not been possible to separate compounds 3a and 7a. They have been identified from $^1$H and $^{19}$F NMR spectra of the mixture and by comparison with $^1$H and $^{19}$F NMR spectra of equivalent compounds 3b, 6b and 7b obtained in the pure state.

Addition of Furanone 5 to Unsaturated Compounds; General Procedure A
To a mixture of Huang system [NaHCO$_3$ (84 mg, 1 mmol) and allyl bromide (Fluka) and 7-hydroxycoumarin (Sigma)] were used as solvents. All chemical shifts are reported in parts per million (ppm) downfield of the standard (TMS and CDCl$_3$) and coupling constants ($J$ values) are given in Hz. MS were recorded using FAB technique. Propargylic alcohol base peak (as 100%). Mass spectra and high-resolution mass spectra (HRMS) were recorded using FAB technique. Propargylic alcohol (Aldrich), 2-methylbut-3-en-2-ol (Aldrich), allyl alcohol (Aldrich), allyl bromide (Fluka) and 7-hydroxycoumarin (Sigma) were used as received. The term 'work-up' implies washing the organic extract with brine, drying (Na$_2$SO$_4$), filtration and concentration of the extract under reduced pressure. Silica gel 40–63 (Prolabo) was used for column chromatography and pre-coated TLC plates SIL (Macherey-Nagel) for chromatography plates. Compounds were detected with UV light (254 nm). PE refers to the fraction with bp 35–60 °C.

Addition of Furanone 5 to 2-Methylbut-3-en-2-ol
Procedure, results and chemical shift correlations of the products obtained from this reaction have been already described and were similar to those given in the Ref.6.

Addition of Furanone 5 to Propargylic Alcohol
General procedure A was applied to the furanone 5 (1 g, 2.58 mmol). Work-up gave an orange oil identified by $^1$H and $^{19}$F NMR to be a mixture of compounds 3a, 6a and 7a in a molar ratio of 62:3:35. The adduct 6a and its reduced form 7a were obtained as a mixture of Z- and E-forms, in a molar ratio of Z:E = 2:1 for compound 6a and Z:E = 12:23 for compound 7a. Then, the general procedure B was applied to the mixture of compounds 3a, 6a and 7a (2.58 mmol). Work-up gave an orange oil (0.74 g, 90%) which was identified as a mixture of two different compounds 3a (56%) and 7a (34%) in a molar ratio of 62:38, with a ratio of Z:E = 13:25 for compound 7a. It has not been possible to separate compounds 3a and 7a. They have been identified from $^1$H and $^{19}$F NMR spectra of the mixture and by comparison with $^1$H and $^{19}$F NMR spectra of equivalent compounds 3b, 6b and 7b obtained in the pure state.

Addition of Furanone 5 to Unsaturated Compounds; General Procedure B
The mixture 6a,b or 9a,b (1 mmol) was poured into EtOH (5 mL), zinc powder (131 mg, 2 mmol) and AcOH (0.25 mL) were added. The resulting solution was stirred for 15 h at reflux, after which time, the excess of zinc was removed by filtration. The EtOH was evaporated to give viscous oil that was taken up in CH$_2$Cl$_2$ (10 mL) for column chromatography and pre-coated TLC plates SIL (Macherey-Nagel) for chromatography plates. Compounds were detected with UV light (254 nm). PE refers to the fraction with bp 35–60 °C.

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Procedure, results and chemical shift correlations of the products obtained from this reaction have been already described and were similar to those given in the Ref.6.
The chemical shift correlations obtained were similar to those given in the Ref.6 (compound numbered 11). The 1H and 19F NMR spectra of equivalent compounds were compared with the above reference. General procedure A was applied to the furanone 5 (2.45 g, 6.31 mmol). Work-up gave an orange oil (4.76 g, 72%), which was identified as a mixture of two different compounds (polyhedra) (Figures 1 and 3).

Addition of Furanone 5 to 7-(Allyloxy)coumarin

The 7-hydroxycoumarin was alkylated with allyl bromide in the presence of anhyd K2CO3 in acetone at reflux to give 7-(allyloxy)coumarin as described in Ref.10. The chemical shift correlations obtained for the 7-(allyloxy)coumarin were similar to those given in the above reference. General procedure A was applied to the furanone 5 (0.73 g, 1.88 mmol). Work-up gave an orange oil identified by 1H and 19F NMR spectra to be a mixture of compounds 4a, 8a and 9a in a molar ratio 70:15:15. Then, general procedure B was applied to the mixture of compounds 4a, 8a and 9a (1.88 mmol). Work-up gave a yellow oil (0.43 g, 72%), which was identified as a mixture of two different compounds (0.43 g, 72%) in a molar ratio of 75:25. The mixture was separated by column chromatography using PE-CHCl3 (50:50) as eluent. Annulation compound 4c (1.53 g, 52%) was obtained as a white powder and addition compound 8c (0.9 g, 24%) was identified in the pure state as a yellow oil. Compound 4c was recrystallized from MeCN to give at the same time two kinds of crystals: fine needles and big polyhedral in a molar ratio of 2:1. They were hand separated and identified as the two diastereoisomers with a weight ratio of 2:1 = (5S,10S) + (5R,10R) (noodles):(5R,10R) + (5S,10S) (polyhedra) (Figures 1 and 3).

7-(5,5-Dimethyl-4-oxo-4,5-dihydrofuran-2-yl)-2,2-dimethylfuran-3-one (11b)

The chemical shift correlations obtained were similar to those given in the Ref.6 (compound numbered 11 in this reference).

Addition of Furanone 5 to Allylic Alcohol

General procedure A was applied to the furanone 5 (0.73 g, 1.88 mmol). Work-up gave an orange oil identified by 1H and 19F NMR spectra to be a mixture of compounds 4a, 8a and 9a in a molar ratio 70:15:15. Then, general procedure B was applied to the mixture of compounds 4a, 8a and 9a (1.88 mmol). Work-up gave a yellow oil (0.43 g, 72%), which was identified as a mixture of two different compounds (0.43 g, 72%) in a molar ratio of 75:25. The mixture was separated by column chromatography using PE-CHCl3 (50:50) as eluent. Annulation compound 4c (1.53 g, 52%) was obtained as a white powder and addition compound 8c (0.9 g, 24%) was identified in the pure state as a yellow oil. Compound 4c was recrystallized from MeCN to give at the same time two kinds of crystals: fine needles and big polyhedral in a molar ratio of 2:1. They were hand separated and identified as the two diastereoisomers with a weight ratio of 2:1 = (5S,10S) + (5R,10R) (noodles):(5R,10R) + (5S,10S) (polyhedra) (Figures 1 and 3).

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The X-Ray diffractions were measured at r.t. on an Bruker-Nonius KappaCCD diffractometer with monochromated MoKα (λ = 0.71073 Å) radiation using the ϕ scan method.12 Lorentz and polarization corrections were applied to the raw data, which were not corrected for absorption.12 The structures were solved by direct methods calculations using SIR92. All non-hydrogen atoms were refined anisotropically through cycles of full-matrix least squares using SHELXL-97. Crystal data: C21H19F6O5, M = 464.35 g·mol⁻¹, colorless prism with dimensions 0.3 × 0.2 × 0.15 mm, monoclinal, space group C 2/c, a = 24.960(3) Å, b = 6.14900(10) Å, c = 26.6520(4) Å, β = 90.00°, γ = 100.3300(5)°, γ = 90.00°, V = 4015.51(10) Å³, Z = 8, D(calcd) = 1.536 mg·cm⁻³, F(000) = 1904, µ = 0.144 mm⁻¹. Unique reflections used were 5150 with R1(F) = 0.0554 and wR2(F²) = 0.1664 [w = 1/[σ²(F²) + (0.1143P)² + 2.348P] where P = (Fo² + Fc²)/2]. Goodness of fit 1.108; maximum/minimum residual density 0.725, −0.628 e Å⁻³.

References
(7) Huang, W. J. Fluorine Chem. 1992, 58, 1.

(12) Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-265643. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223/336033 or e-mail: deposit@ccdc.cam.ac.uk).

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