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Enantioselective Synthesis of Spiro[4.5]decanone with 2-(S)-Methoxy-1,4-dibromobutane

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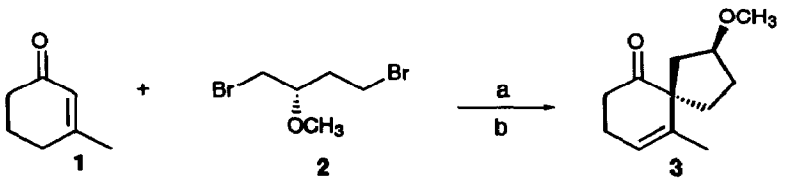
Key Words : Alkylation, chiral dibromide, diisopropoxydimethyltitanium, catalytic hydrogenation, asymmetric spiroannelation.

Abstract: *The reaction of 3-methyl-2-cyclohexen-1-one with 2-(S)-methoxy-1,4-dibromobutane (2) produced spiro[4.5]decanone 3, a key intermediate for the synthesis of spirovetivanes, with regiodifferentiation and stereoselection. Subsequent addition of diisopropoxydimethyltitanium to the carbonyl group furnished compound 6 with diasterofacial selectivity. The same selectivity was observed in the subsequent catalytic hydrogenation.*

The usefulness of allylic-homoallylic dihalides in the stereospecific synthesis of sesquiterpenes of the spirovetivane family,[1] has been demonstrated in the synthesis of (-)-β-vetivone.[2,3] One of the difficulties encountered lies in controlling the stereochemistry of the quaternary spiro center and that of the methyl at C10.[4] The division of spirovetivanes into two groups is based on the stereochemistry of this methyl group at C10 and the more numerous group (β-vetivone) has the β (cis) configuration while in the other group (solavetivone) the methyl is α (trans).

We have observed that the reaction of 3-methylcyclohex-2-en-1-one (**1**) with chiral 2-(S)-methoxy-1,4-dibromobutane (**2**),[5] readily available from L-malic acid, provides a new method for enantioselective spiroannelation. This methodology anticipated that the biselectrophile **2** would favor a regio- and stereochemical control in the sequential attack of the nucleophile, generated at α position from enone **1**.[6] More precisely, this strategy is based on the use of chiral dibromide **2** which permits the control of the relative stereochemistry at C2 and C5 (Scheme 1) by an initial regioselective attack at the less hindered carbone of the biselectrophile.

Scheme 1

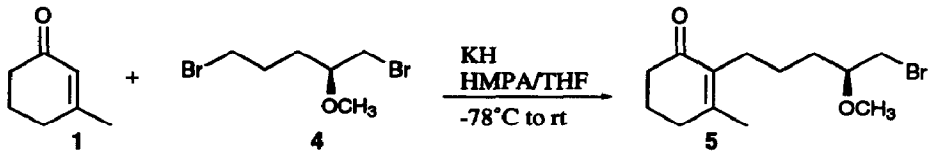


1 **2** **3**

Reagents: a) KH, HMPA / THF, -78°C to 50°C; b) TsOH / Benzene

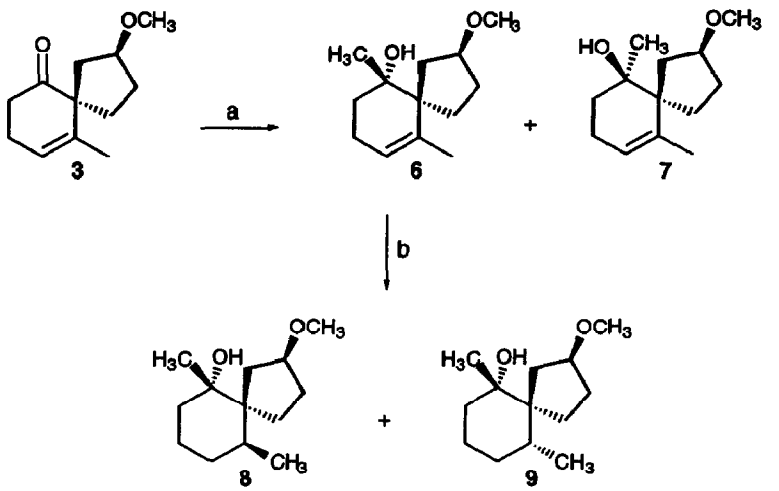
As an intramolecular alkylation (cyclization) is favored in the formation of five-membered rings, the evidence of this regioselectivity was established by the reaction of 3-methylcyclohex-2-en-1-one (**1**) with 2-(S)-methoxy-1,5-dibromopentane (**4**). In this case, alkylation[7] leads to the formation of monoalkylated intermediate **5** (Scheme 2).

Scheme 2



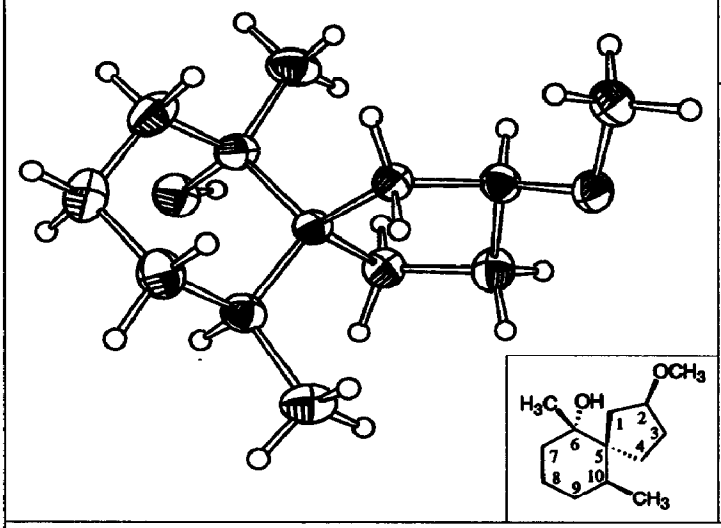
The intramolecular C-alkylation (cyclization), by *in situ* enolization, afforded the functionalized spiroketone as an endo-exo (45:55) isomeric mixture of the desired diastereoisomer in 41% yield.[8] The endo spiroketone **3** was obtained after isomerization of the double bond.[9] Having realized the stereospecific spiroannelation, it was important to determine the absolute configuration of the quaternary center and the following stereoselective transformations were carried out in order to obtain an x-ray crystallographic analysis. Addition of $(CH_3)_2Ti(OiPr)_2$ to spiroketone **3** provided the corresponding tertiary alcohols **6** and **7** in 88% yield with equatorial-axial diastereoselectivity.[10] Analysis of the integrated NMR proton spectra of this mixture provided the stereomer ratio (85 : 15). The major isomer was then separated by flash chromatography and submitted to catalytic hydrogenation using PtO_2 in acetic acid, to give **8** and **9** (90%) in a 5.6:1.0 ratio. These hydrogenated compounds were efficiently separated by column chromatography and the major product (**8**) obtained in crystalline form (Scheme 3).

Scheme 3



Reagents and conditions: a) $(CH_3)_2Ti(iOPr)_2$ / Et_2O; b) H_2, PtO_2 / AcOH

Confirmation of the initial stereochemical assigment (spirocenter) was made from an x-ray crystallographic study of the major isomer, (2S,5S,6S,10S)-(+)-2-methoxy-6,10-dimethylspiro[4.5]decan-6-ol, (8).[11] The ORTEP view and the crystal data of 8 are shown in Figure 1.



Crystal Data	
Chemical formula	$C_{13}H_{24}O_2$
Molecular weight	212.33
Crystal system	Tetragonal
Cell constant	a = b =9.261(2) Å
	c = 29.096(7) Å
Cell volume	V = 2495.5(8) Å^3
Space group	P 4_12_12
	Z = 8
Density	D = 1.130 g.cm^{-1}
Final R value	R < 0.031

Figure 1 : ORTEP view and crystal data of (2S,5S,6S,10S)-(+)-2-methoxy-6,10-dimethyl-spiro[4.5]decan-6-ol (8)

The results obtained by enantioselective spiroannelation can thus be rationalized by assuming that the initial attack takes place at the less hindered electrophilic center and subsequently, that intramolecular alkylation leads to spiroketone 3 as a key intermediate for the preparation of spirovetivane sesquiterpenes. This new method of spiroannelation, as applied to the synthesis of 8, is equally important in that the relative configuration at C10 can be altered as is represented in Scheme 3 or after a Wittig transformation of the carbonyl group followed by a regioselective exocyclic hydrogenation leading to the 5R configuration.

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7. NMR data for compound **5** are as follows: ^{1}H NMR 300MHz, ($CDCl_3$) δ 3.37 (s, 3H); 3.35 (m, 3H); 2.32 (m, 6H); 1.92 (s, 3H); 1.89 (m, 2H); 1.56 (m, 2H); 1.35 (m, 2H); ^{13}C NMR 75.5MHz, ($CDCl_3$) δ: 198.72; 155.51; 135.33; 69.91; 57.29; 37.43; 34.69; 32.81 32.70; 24.91; 24.58; 22.24; 21.23.
8. To a suspension of 3.80 g (94.9 mmol) in 250 ml of anhydrous THF at -78 °C and under nitrogen, was added 16.5 ml (94.9 mmol) of HMPA and 9.59 g (87.07 mmol) of 3-methyl-2-cyclohexen-1-one. This mixture was stirred for 30 min. and a solution of 23.54 g (95.78 mmol) of (S)-2-methoxy-1,4-dibromobutane in 80 ml of anhydrous THF was added during 5 min. The reaction mixture was warmed to rt for 2 h, recooled to -78 °C and a suspension of 3.80 g of KH in 80 ml of anhydrous THF was cannulated during 5 min. This reaction mixture was allowed to warm to rt and then was stirred at 50 °C for 48 h. The reaction was worked up as usual to afford 13.53 g of crude oil which was separated by flash chromatography (silica gel; eluting solvent ethyl acetate-petroleum ether 20:80) to yield 41% of isomeric spiroketone and 20% of 3-methyl-2-cyclohexen-1-one.
   NMR data for compound **3** are as follows: ^{1}H NMR 300MHz, ($CDCl_3$) δ 5.55 (bs, 1H); 3.89 (m, 1H); 3.27 (s, 3H); 2.52 (m, 2H); 2.30 (m, 2H); 1.96 (m ,3H); 1.75 (d, 3H, J=1.48Hz); 1.62 (m, 2H); 1.03 (m, 2H).ppm; ^{13}C NMR 75.5MHz, ($CDCl_3$) δ 213.48; 138.65; 122.39; 82.72; 57.93; 56.39; 38.43; 35.91; 33.04; 31.69; 25.40; 18.63.
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11. Carried out at the Laboratoire de diffraction des rayons X de l'Université de Montréal.

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