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SYNTHESIS OF (±)-α-CHAMIGRENE.

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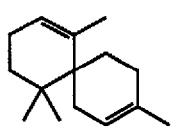
SUMMARY: Regiospecific spiroalkylation of the selectively generated enolate arising from the 1,4-addition of lithium dimethylcuprate to 3-methylcyclohex-2-en-1-one allows an efficient preparation of spiroketones, including a key intermediate for the synthesis of (±)-α-Chamigrene.

We have previously reported a new synthetic approach for the preparation of spiro γ- and δ-lactones in monocyclic, fused bicyclic and bridged tricyclic systems. This methodology, based on the reaction of α,ω-diprimary di-Grignard reagents with cyclic or polycyclic lactones and carboxylic acid anhydrides, provides the advantage of retaining the initial stereochemistry of the substrate[1]. We also demonstrated that primary secondary di-Grignard reagents react with carboxylic esters stereoselectively leading predominantly to the formation of 1-substituted-trans-2-methyl cycloalkanols[2]. More recently we elaborated another procedure based on the dialkylation of esters, using primary secondary α,ω-dibromides, in order to obtain stereoselectively the corresponding 2-alkylated cyclic compounds[3]. Our main objective in this area centers on the synthesis of natural spiro compounds such as sesquiterpenes with spiro[5.4]decane and spiro [5.5]undecane skeletons. The Chamigrene natural unsaturated spiro[5.5]undecanes 1,2 present an interesting synthetic challenge to illustrate our modified methodology.



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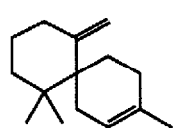

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(±)-α-Chamigrene (1), the parent member of this class and a component of *Schizandra chinesis* Baillon[4], was selected as the focus of these studies because it possesses the structure from which halogenated derivatives, found in marine organisms, could be formed.

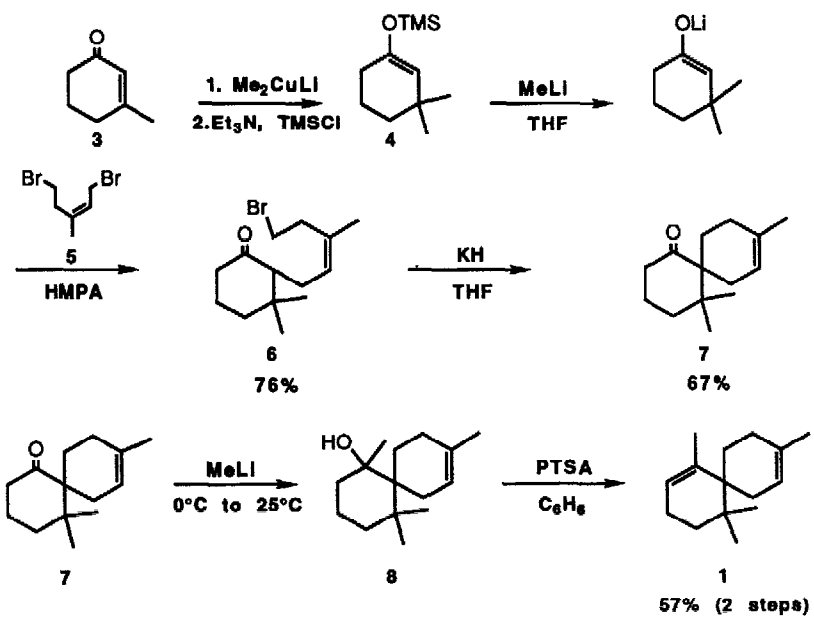
This paper describes an important and most convenient route for the total synthesis of (±)-α-Chamigrene, and provides some indications for the preparation of β-chamigrene (2). Furthermore, previous syntheses of (±)-α-Chamigrene (1) were less satisfactory because of inefficient cyclization processes and the larger number of steps involved[5].

The major advantages and strategic features of this approach are:

1) Spiroannelation (cycloquaternization) is achieved regiospecifically by generating the intermediate silyl enolate 4.

2) Conjugate addition of lithium dimethylcuprate to 3-methylcyclohex-2-en-1-one 3 favors annelation adjacent to the gem dimethyl group and this allows the substitution of three contiguous carbons.

With regards to the regiospecific spiroannelation of the more sterically encumbered anion, the 1,4-addition of lithium dimethylcuprate[6] transformed quantitatively 3-methylcyclohex-2-en-1-one 3 to 1-trimethylsiloxy-3,3-dimethylcyclohexene 4. As expected[6a] alkylation with (Z)-1,5-dibromo-3-methylpent-2-ene (5) was more rapid than proton exchange. So this moiety in the bifunctionalized substrate 5 readily reacted with 4 in the presence of methyllithium and provided regioselective control of the monoalkylation.



Indeed, examination of the reaction mixture revealed that the alkylation had occurred quantitatively and that only one compound could be detected; after isolation, purification and characterization by ^{1}H- and ^{13}C-NMR it was confirmed that it was the desired 3,3-dimethyl-2(cis-3-methyl-5-bromo-2-ene)pentyl cyclohexanone(6)[7]. This investigation disclosed that the spiroannelation is indeed completely regioselective and that, therefore other substances can be prepared by this method.

The success of the present synthesis resides in the structure of (Z)-1,5-dibromo-3-methylpent-2-ene which was readily prepared by reduction of the commercially available mixture of (Z) and (E)-dimethyl 3-methylglutaconate (DIBAL ether 90 %). The isomeric diols separated by flash chromatography and the Z-isomer afforded the desired Z-dibromide 5[8] in quantitative yield (Ph_3P, CBr_4).

Conversion of the bromoketone 6 to the key intermediate, trimethyl-spiro-3,3,9-undec-8-en-1-one(7), was quantitatively realized using KH in tetrahydrofuran at room temperature[9]. Under these conditions the reaction was complete in 3 hours, providing the required ketone 7 which, according to its 200MHz NMR spectrum, consists of only one detectable compound. This volatile substance was purified by column chromatography and then treated with an excess of methyllithium in ether for 2 hours at room temperature, affording the tertiary alcohol in nearly quantitative yield. The spectral properties (^{1}H-NMR, IR) of this alcohol 8 were in full agreement with the proposed structure. Subsequent transformation was affected by treatment of the tertiary alcohol with paratoluenesulfonic acid in refluxing benzene for 48 hours. Under these experimental conditions no skeletal rearrangement was observed[5b,10]. More precisely, the crude dehydration product showed by TLC the presence of only two hydrocarbons of which one predominated and was readily isolated by column chromatography on silica gel impregnated with silver nitrate[11]. The spectral data of these compounds are consistent with the structure of α- and β-chamigrenes.

Thus the isolation and identification of the major component as (±)-α-Chamigrene[12] demonstrates the utility of this new and efficient methodology for the synthesis of spiro sesquiterpenes.

Results of the studies on the formation of spiro[5.5]undecane skeleton reported here should allow further applications in the synthesis of naturally occurring spiro[5.4]decanes. We are currently exploring the use of this spiroalkylation process for the synthesis of acoranes.

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6. (a) Binkley, E.S.; Heathcock, C.H. J. Org. Chem., 1975, 40, 2156, and citations therein. (b) 1-Trimethylsiloxy-3,3-dimethylcyclohexene(3), Colorless oil. IR(neat cm^{-1}) 3010, 2950, 2930, 2860, 1660, 1465, 1450, 1430, 1385, 1365, 1340, 1260, 1250, 1210, 1185, 1140, 1060, 990, 965, 890, 880, 840, 750; ^{1}H-NMR ($CDCl_3$ 200MHz) 4.63(s,1H), 1.92(t, 2H, J=6.25Hz), 1.66(m, 2H), 1.32(m, 2H), 0.96(s, 6H), 0.16(s, 9H). ^{13}C-NMR 148.62, 115.69, 37.09, 31.76, 30.62, 29.89, 20.01, 0.37.

7. A typical selective alkylation described here for 7. A solution of 0.688 g of 4 in 14mL of THF was stirred with 3.47mmol of methyllithium on 2h at 25 °C. To the cooled mixture at -20 °C were added 50mL of HMPA and 0.837g of dibromide 5 in 5mL of THF. The reaction mixture was allowed to warm to room temperature, stirred for 20h and treated with ammonium chloride. Column chromatography on silica gel (elution with hexane-ether 90:10) gave 0.740g of bromoketone 6 as a clear colorless oil.

8. (Z)-1,5-dibromo-3-methylpent-2-ene (5): IR ν_{max} (neat cm^{-1}) 3030, 2965, 2940, 2910, 2860, 1650, 1445, 1370, 1295, 1215, 1195, 845; ^{1}H-NMR ($CDCl_3$) 5.86 (t, 1H), 3.97 (d, 2H), 3.43 (t, 2H), 2.68 (t, 2H), 1.78 (s, 3H). ^{13}C-NMR ($CDCl_3$) 138.90, 124.02, 34.76, 29.71, 28.56, 22.94; Exact mass calcd for 239.9149, 241.9129, 243.9109, found 239.9136, 241.9107, 243.9114.
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12. (±)-α-Chamigrene was purified by column chromatography on silica gel containing silver nitrate. Colorless oil: IR ν_{max} (neat cm^{-1}) 3090, 3070, 3035, 3005, 2950, 2920, 2850, 1480, 1450, 1435, 1380, 1370, 845, 675; ^{1}H-NMR ($CDCl_3$) 5.30(s, 1H), 5.12(s, 1H), 2.20 - 1.20(m, 10H), 1.65(s, 3H), 1.60(d, 3H, J=1.46Hz), 0.935 - 0.928(2s, 6H), ^{13}C-NMR ($CDCl_3$) 139.14, 135.37, 133.54, 121.26, 34.58, 33.84, 33.31, 32.27, 30.90, 30.40, 29.40, 28.40, 24.72, 20.34. Exact mass calcd for 204.1879, found 204.1860.

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