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REMOTE STEREOCHEMICAL CONTROL OF THE RING CONFORMATION OF 2-BROMO-3-METHYL-4-ALKYL-BUTYROLACTONES

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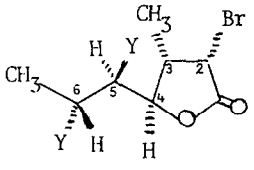
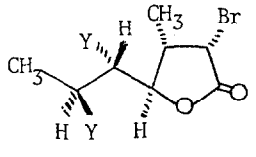
Abstract : *The lactones 2a and 2b are different only by the configuration of the carbon C5 of the side-chain, but present quite different features in the ring conformation. Inspection of the NMR spectra of 2b, compared to 2a, shows a evident flattening of the butyrolactone ring and an axial orientation of the side-chain, which is a new type of this remote effect, with the 3-methyl* trans *to the side-chain. These special features arise from the steric interaction which would occur in the regular conformation between the 3-methyl and the substituents at C5.*

During the synthesis of these lactones, a striking stereochemical behaviour is observed in the course of the addition of a chiral allenic Grignard reagent to a chiral aldehyde or during the hydride reduction of ketones having two asymmetric centres in α and α'.

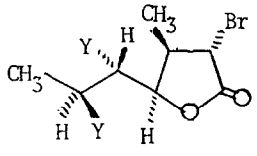
The structural determination of the lactones 1a, 1c and 1d by X-ray diffraction and (or) NMR in solution has shown a stereochemical remote effect of the configuration of the side-chain carbons on the ring conformation [1] :



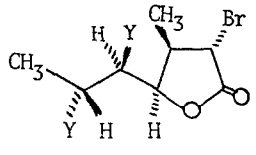
1a Y = Br
2a Y = CH_3



1b Y = Br
2b Y = CH_3

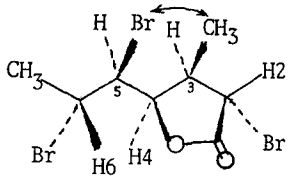


1c Y = Br
2c Y = CH_3

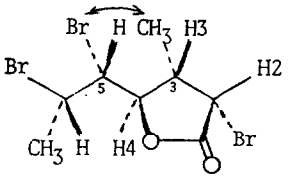


1d Y = Br
2d Y = CH_3

In the case of 1c, the side-chain is equatorial and developed as a planar zig-zag, with an usual value [2] of the puckering of the tetrahydrofuran (THF) ring (τ_m = 35°, in the crystal structure). On the other hand, the chain of the lactone 1d is axial ; it is folded back over the ring and the ring is very flattened (τ_m = 26° : in the absence of substituents [3], the τ_m value is about 32°). This distinctive feature of 1d is simply the result of an 1-3 interaction between Me-3 and Br-5 appearing when the molecular model is built with a planar C2-C6 chain, (fig. 1) similar to that observed in the molecule 1c.



1d

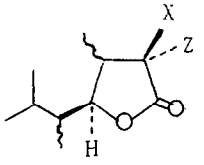


1b

Fig. 1 : The forbidden planar zig-zag conformation of the side-chain in 1d and 1b.

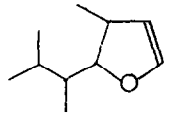
The lactone 1b ought to exhibit the same behaviour in spite of a *trans*-(C3-C4)-stereochemistry but this stereoisomer has not been obtained. Then, we have undertaken the synthesis of lactones 2, with methyls in the side-chain instead of the bromines. This substitution is interesting from two points of view. First, to show that it is not the polar but the steric effect of the bromines which is responsible of the 1d inversion of conformation and overall, it may be a way to obtain the stereoisomer 2b, similar to the missing tribromo-lactone 1b.

The lactones 2a, 2b, 2c and their isomers 3 have been obtained by oxidation of the of the dihydrofuran compounds 4. Their structures were established by NMR study and chemical correlation.



2 : X = H, Z = Br

3 : X = Br, Z = H



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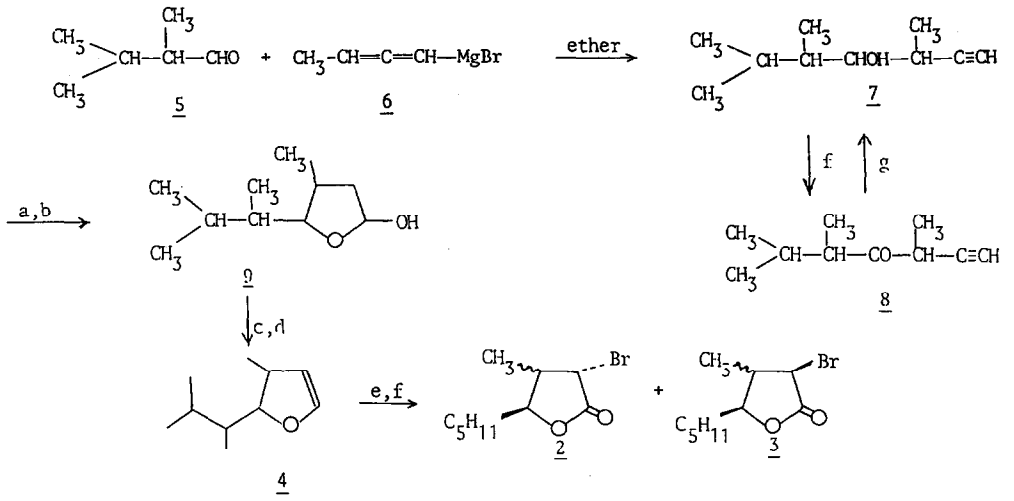
Scheme of Synthesis and Experimental Results.

First, we have prepared the acetylenic alcohols 7, by a Grignard synthesis. In spite of its allenic structure [4], the organo-magnesium derivative 6 of the 3-bromo-1-butyne affords the acetylenic alcohols 7 (scheme 1). These alcohols have three asymetric centers, but a mixture of only three stereoisomers is obtained, with a yield of 76% and a ratio about 7a/7b/7c = 58/30/12.

The two main isomers 7a and 7b were separated by GLC on Carbowax (84°C) and oxidized by the Jones reagent [5]. They gave two different ketones 8a and 8b. The reduction of each of these ketones by $NaBH_4$ affords interesting results : the ketone 8b gives back its starting alcohol 7b only, but 8a gives a mixture of 7a and 7c with a ratio 7a/7c = 10/90 (scheme 2) : the alcohols 7a and 7c have the same relative configuration of the carbons C3 and C5. By oxidation and then reduction of the crude mixture of the alcohols 7, we have obtained a mixture containing 7c as the main isomer (7a/7b/7c = 7/21/72) with a yield of 80%. The ketones 8a and, in particular, 8b are unstable. By heating or by



a) $(iPr-CHCH_3)_2BH$, THF, -10°C ; b) H_2O_2, NaOH, ; c) $(CH_3-CO)_2O$, ether, pyridine ; d) pyrolysis at 200°C ; e) N-bromosuccinimide, DMSO, H_2O ; f) Jones reagent ; g) $NaBH_4$, CH_3OH, H_2O

Scheme 1

contact with silica, they give the allenic ketone and (or) polymers.

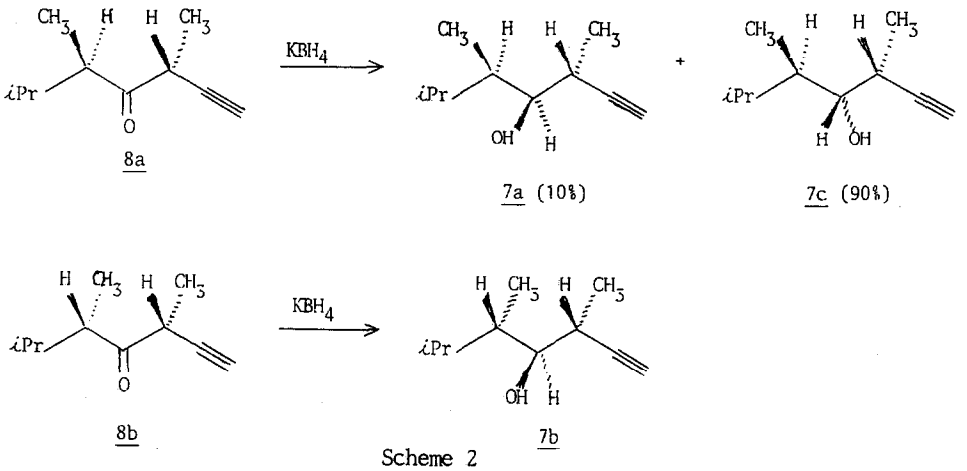
The NMR spectra of the alcohols 7a, 7b and 7c are described in table 1.

In the second step, the hydroboration of the triple bond, followed by an oxidation (H_2O_2, NaOH) of the vinylic boranes leads to the hemiacetals 9 which are the cyclised form of the corresponding γ-aldols [6]. The pyrolysis of the acetates of 9 at about 200°C gives the dihydrofurans 4. Starting from each of two mixtures of the alcohols 7, two mixtures of the dihydrofurans 4a, 4b and 4c were obtained with about the same composition as the alcohols, (yield 38%). These dihydrofurans have been separated by GLC on Silicone SE30 at 96°C. Their NMR spectra are described in table II.

By addition of bromine with N-bromosuccinimide in DMSO containing a trace of water,

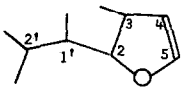
Table I : NMR spectra of the acetylenic alcohols 7 in C_6D_6 at 250 MHz (δ in ppm, internal TMS, J in Hz, room temperature).

	δH1 (JH1H3)	δH3 (JH3H4)	δH4 (JH4H5)	δH5 (JH5H6)	δH6 (JH6Me6)	δMe3 (JH3Me3)	δMe5 (JH5Me5)	δMe6	δOH (JH4OH)
7a	1.69	2.38	3.15	1.24	1.63	0.94	0.76	0.64	1.47
	(2.5)	(5.75)	(5.75)	(1.5)	(7.0)	(6.9)	(7.0)	0.80	(--)
7b	1.66	2.38	2.86	1.53	2.14	1.07	0.49	0.77	1.16
	(2.4)	(2.4)	(9.4)	(2.7)	(7.0)	(7.0)	(7.0)	0.65	(9.0)
7c	1.7	2.36	3.28	1.4	2.4	0.98	0.39	0.67	1.63
	(2.4)	(3.5)	(8.5)	(2.8)	(6.8)	(6.8)	(7.0)	0.78	(3.0)



Scheme 2

Table II : NMR spectra of the dihydrofuran compounds 4 in C_6D_6 at 250 MHz (δ ppm, J in Hz, internal TMS).



	δH5 (JH5H4) (JH5H5)	δH4 (JH4H3)	δH3 (JH3H2)	δH2 (JH2H1')	δH1' (JH1'H2')	δH2' (JH2'Me2')	δMe3 (JH3Me3)	δMe1' (JH1'Me1')	δMe2'
4a	6.30	4.76	2.69	4.12	1.37	1.82	1.04	1.04	1.02
	(2.5) (2.5)	(2.5)	(7.5)	(4.75)	(4.9)	(6.8)	(6.5)	(7.5)	0.96
4b	6.30	4.77	2.69	4.02	1.70	2.22	1.07	0.76	0.96
	(2.7) (2.1)	(2.7)	(6.7)	(8.6)	(4.3)	(6.9)	(6.7)	(7.1)	---
4c	6.36	5.0	2.52	4.05	1.96	2.48	0.89	0.71	1.01
	(2.9) (1.1)	(2.9)	(7.7)	(11.2)	(3.1)	(7.0)	(6.7)	(7.0)	---

the bromohydrines are obtained [7]. An oxidation with the Jones reagent affords the corresponding lactones 2 and 3 [8]. The *trans* dihydrofurans 4a and 4b give a mixture of two lactones (2a/3a = 70/30 and 2b/3b = 65/35) but the *cis* dihydrofuran 4c gives only one lactone, 2c :

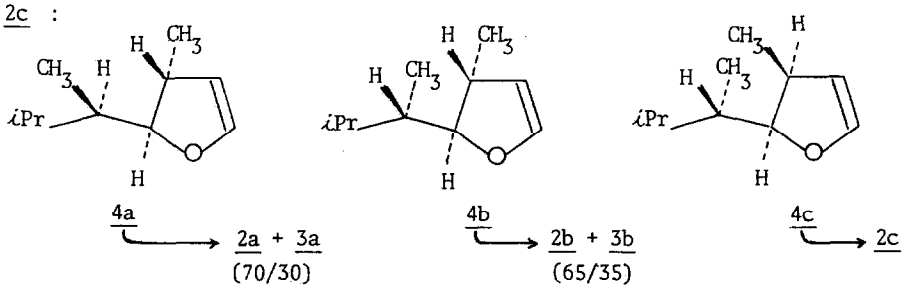
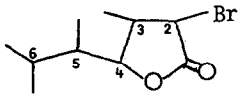


Table III : NMR spectra of the bromolactones 2 and 3 in CD_3COCD_3



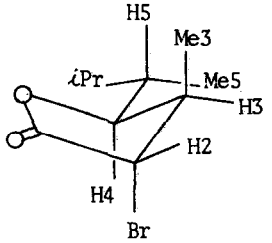
	δH2 (JH2H5)	δH3 (JH3H4)	δH4 (JH4H5)	δH5 (JH5H6)	δH6 (JH6Me6)	δMe3 (JH3Me3)	δMe5 (JH5Me5)	δMe6 ----	Cond.
2a	4.28 (6.25)	2.54 (9.5)	4.66 (2.25)	1.65 (5.75)	1.76 (6.75)	1.15 (6.5)	0.89 (7.25)	0.93 ---	500 MHz
3a	4.37 (10.75)	2.54 (9.75)	4.65 (2.5)	1.69 (5.25)	1.84 (7.0)	0.98 (6.5)	0.94 (7.0)	0.97 0.92	500 MHz
2b	4.83 (6.25)	2.67 (7.6)	4.20 (7.6)	1.81 (4.0)	2.05 (7.0)	1.30 (6.6)	0.97 (7.0)	0.90 1.0	250 MHz
3b	4.67 (9.75)	2.6 (8.1)	4.20 (8.1)	1.81 (4.0)	2.05 (7.0)	1.36 (6.8)	0.96* (7.0)	0.88* 0.94*	500 MHz
2c	4.38 (0)	2.74 (4.25)	4.60 (11.25)	1.88 (2.9)	2.10 (7.0)	1.13 (7.25)	0.84 (7.0)	0.93 1.02	250 MHz

* Interchangeable

Structures of the Lactones and Discussion

Study of the bromo-lactone 2c, obtained from 4c :

The coupling constant JH2H3 = 0 Hz observed in the NMR spectrum of 2c (table III) indicates that Br2 and Me3 are *trans* and essentially axial, : the molecule is in a single conformation. Then, the coupling constant JH3H4 = 4.25 Hz is *cis*, with H3 equatorial and H4 axial : the side-chain is equatorial. We observe also that H4 and H5 are antiperiplanar with a large coupling constant (11.25 Hz). The nuclear Overhauser effect (NOE) shows that Me3 interacts with H2 and H5 and that Me5 interacts with H3 and H4. These observations allow us to propose for 2c the following stereochemical and conformational structure :



2c

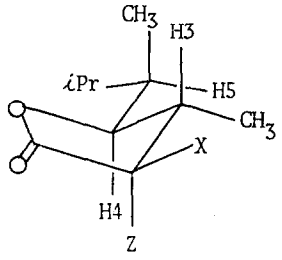
The methyl group and the side-chain on C3 and C4 being *cis* in the starting dihydrofuran 4c, the electrophilic entry of the bromine has taken place only by the opposite face and the lactone 3c is not observed.

A comparison of the lactone 2c and the tribromo-lactone 1c shows that the coupling

constants in these two molecules have exactly the same values [1].

Study of the lactones 2a and 3a obtained from 4a.

The two large values of the coupling constants JH2H3 and JH3H4 in 3a (10.75 Hz and 9.75 Hz) show that H2, H3 and H4 are axial : in 3a, Br, Me3 and the side-chain are all equatorial. The relative configuration of C3 and C5 is the same as in 2c but now, H4 and H5 are in a gauche position (JH4H5 =2.5 Hz). The coupling constants in 2a are very similar to those of 3a, except for JH2H3 = 6.25 Hz : Me3 and Br are *cis* with an axial bromine and the rest of the molecule is in the same conformation :



2a : X = H, Z = Br

3a : X = Br, Z = H

In these three molecules, the side-chain is equatorial and there is no 1,3-interaction between the two methyl groups at C3 and C5.

Study of the lactones 2b and 3b obtained from 4b

In the lactone 3b, the coupling constant JH2H3 = 9.75 Hz shows that H2 and H3 are *trans* and biaxial, but JH3H4 = 8.1 Hz is not a characteristic value. The NOE determination in this lactone shows an interaction between H2 and H4 which reveals that H2 and H4 are *cis* and, at least partially, biaxial. The low value of JH3H4 = 8.1 Hz for a biaxial coupling constant may result from a flattening of the ring (similar to that observed for 1d) combined with a rotation of the side-chain (fig. 2).

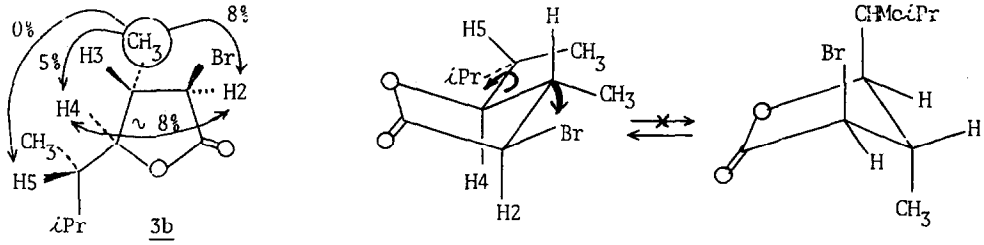


Fig. 2 : NOE and conformation of the lactone 3b.
: (Irradiation of H4 gives also an effect on H5, and less important, on H6).

This behaviour is more evident for 2b in which the *trans* coupling constant JH3H4 = 7.6 Hz has an intermediate value. In these two molecules, the NOE shows that Me3 interacts with H4, with H2, but not with H5.

None of these lactones has crystallised, but especially for 2b, it is quite evident

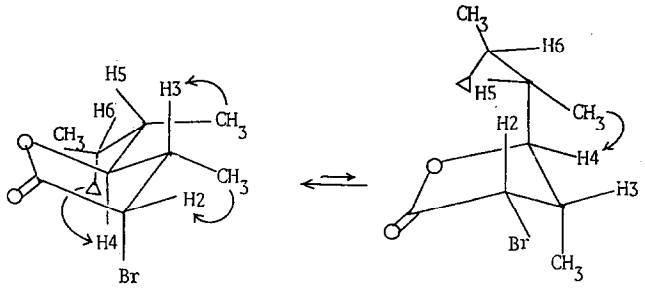
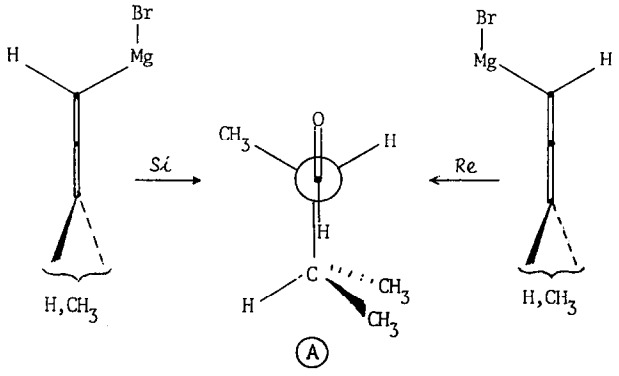


Fig. 3 : Lactone 2b (conformation and observed NOE)

that its structure should be similar to that observed for 1d, with probably an axial side-chain, folded back over the ring, which reduces its puckering and cancels the NOE of Me3 over H5 and H6.

Stereochemistry of the formation of the alcohols 7.

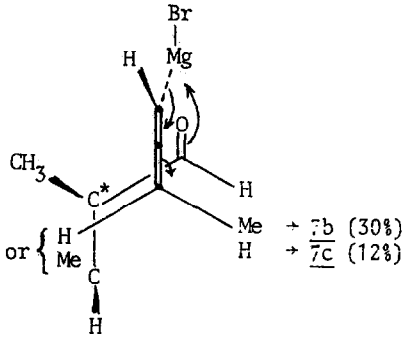
The structure of the alcohols 7a, 7b, 7c is deduced from that of the lactones. The stereochemistry of their formation may be tentatively discussed by consideration of steric effects during the approach of the allenic Grignard reagent having an axial chirality and the aldehyde having an asymmetric α-carbon. Two asymmetric centres are created during the reaction. A good interpretation of the experimental results is obtained by application of the Cram Rules [9]. Taking the aldehyde (of R configuration in the scheme) in the conformation A, we may consider four different approachs :



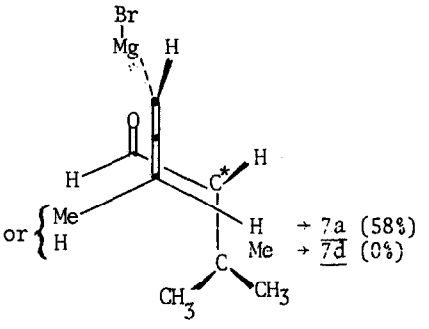
There are two different approaches by the Re-face and two by the Si-face, according to the position of H or Me of the allenic reagent toward H or C* of the aldehyde. The approach by Re-face of the aldehyde (58% 7a) is better than by the Si-face (42%, 7b + 7c) but the conformation of the isopropyl group with hydrogen toward the Si-face makes the formation of 7c (12%) easier than that of the missing alcohol (7d, 0%).

The Felkin-Anh model [10] is also well appropriate to explain why 7a is predominant over 7d (58/0) or 7b over 7c (30/12) but we have not succeded to explain why the formation of 7d (0%) is less probable than 7c (12%). More elaborate study seems necessary.

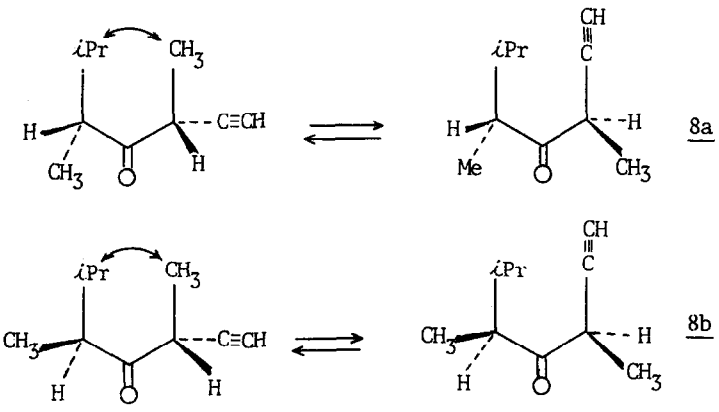
1°/ Approach by the *Si*-face



2°/ Approach by the Re-face



With regard to the reduction of the ketones 8a and 8b, a satisfactory interpretation of the results may be obtained with a model directly related to the Cram's Rule. The large group on C5 is undoubtedly *i*Pr. On C3, we retain Me or C≡CH, because the interaction between *i*Pr and Me may be too unfavourable :



For 8b, the hydride addition by the rear face is the favourable process in the two cases (→ 100% 7b). For 8a, the addition by the front face is only favoured in the first conformation (→ 7c/7a = 90/10).

Conclusion : we have obtained the two lactones 2a and 2b having very different NMR spectra in solution, corresponding to a change in the ring conformation, due to the steric interaction between the methyl groups at C3 and C5. This is a new case of the remote stereochemical effect of C5 on the ring conformation, already observed with a side chain *cis* to Me3.

During the synthesis of these lactones, we have observed two interesting stereochemical behaviours in nucleophilic additions to carbonyl groups when two chiral entities are concerned :

- a chiral allenic Grignard reagent with an aldehyde having an asymetric center, or
- an hydride with a ketone having two asymetric centers.

The two cases give rise to very diastereoselective processes.

Experimental Section.

Synthesis of the acetylenic alcohols

The Grignard reagent of *3-bromo-1-butyne* (E_{760} = 91-92°C) was prepared in dry ether [4b] and the *2,3-dimethyl-butanal* (E_{760} = 109°C) was added at -20°C : 9 g (0.09 mol) of the aldehyde, dissolved in 27 ml ether, are added to 0.11 mol of the Grignard reagent. The mixture is stirred 1h at -20°C and then neutralised with a solution of 10% acetic acid. A mixture of three alcohols was purified by distillation (E_{15} = 80-85°) with a yield of 76% (10.5 g) and separated by GLC on Carbowax (84°) :

(±)(3R,4S,5R)*3,5,*6-trimethyl-hept-1-yn-4-ol* (7a)
(±)(3R,4S,5S)*3,5,*6-trimethyl-hept-1-yn-4-ol* (7b)
(±)(3R,4R,5R)*3,5,*6-trimethyl-hept-1-yn-4-ol* (7c)

NMR spectra are described in table 1. IR(neat) : 2105 - 2110 (C≡C), 3290 - 3295 (≡CH) and 3380 - 3440 (OH) cm^{-1}.

Synthesis of the acetylenic ketones

A sample of 941 mg of the alcohol 7a was obtained by GLC on Carbowax and dissolved in 18 ml acetone. The Jones reagent (13,1 g $Na_2Cr_2O_7$ + 20.4 g H_2SO_4 96% + 75 ml H_2O) was added drop by drop at 0°C on stirring until we obtained a red coloration. The excess of reagent was then neutralised with 2-propanol. After evaporation of the acetone, the residue was diluted in ether and washed with water. By drying and evaporation of the ether, we obtained 929 mg of the ketone 8a which was directly analysed by GLC on Carbowax at 80°C.

(±)(3R,5R)*3,5,6-trimethyl-hept-1-yn-4-one* 8a $C_{10}H_{16}O$ ($M^{\cdot+}$ = 152.1206 for 152.12011 calc). IR (neat) : 1710(CO), 2105 (CC), 3300 (CH) cm-1, RMN (C_6D_6, 250 MHz, attrib. by selective decoupling, δ ppm, JHz, TMS) : 0.79 (d, 6.7 Hz, 3H); 0.85 (id.); 1.11 (id., Me-5); 1.33 (d, 7Hz, 3H, Me-3); 1.96 (m , 1H, H-6); 2.82 (quint., 6.7Hz, 1H, H-5); 3.15 (dq, 3 and 7 Hz, 1H, H-3) and 2.01 (d, 3Hz, 1H).

The same procedure applied to 260 mg of the alcohol 7b gave about the same yield of 8b.

(±)(3R,5S)*3,5,6-trimethyl-hept-1-yn-4-one* 8b $C_{10}H_{16}O$. IR(neat) : 1710 (CO), 2110 (CC, weak) , 3300 (CH) cm-1 RMN (C_6D_6, 250 MHz, δ ppm, JHz, TMS) : 0.86 (d, 6.7 Hz, 3H); 0.93 (id.); 1.07 (d, 6.9 Hz, 3H); 1.31 (d, 7.1 Hz, 3H); 2.67 (quint., 7.1 Hz, 1H); 3.17 (dq, 3 and 7 Hz, 1H) and 2.05 (d, 3 Hz, 1H).

The two ketones have different retention times on Carbowax (8a, 24 min. and 8b, 27.5 min.). When the reaction was performed with the crude mixture of the alcohols, we obtained the mixture of the two ketones, but we did not succeed any separation (distillation, TLC on silica) and, by equilibration, we obtained the allenic ketone as the major product :

3,5,6-trimethyl-hepta-1,2-dien-4-one. IR (neat) : 1665 (CO), 1925 (=C=, shoulder at 1950), 3045 (=CH_2) cm-1. RMN (C_6D_6, 250 MHz, δ ppm, JHz, TMS) : 0.92 (d, 6.8 Hz, 3H); 0.97 (id.); 1.12 (d, 7 Hz, 3H, Me-5); 2.06 (m, 1H, H-6); 3.11 (m, 1H, H-5) and the A_3X_2 allenic system at 1.91 and 4.7 ppm (3 Hz).

The reduction of the acetylenic ketones gave good yield only by the procedure with $NaBH_4$: the ketone 8a (929 mg) is dissolved in 8 ml of CH_3OH and $NaBH_4$ (116 mg) is dissolved in 1.7 ml of H_2O. The reaction is performed at 0°C and give about 870 mg of the alcohols 7a + 7c (10/90).

Synthesis of the dihydrofuran compounds [6, 11]

The flask containing 4.405 g (0.116 mol.) $NaBH_4$ in 150 ml THF, 20.61 g (0.294 mol.) of *2-methyl-2-butene* and a magnetic stirring bar, is cooled at -10°C and kept under static pressure of nitrogen. From a first pressure-equalizing dropping funnel, a solution of 18.5 ml (0.147 mol.) of freshly distilled BF_3-$O(C_2H_5)_2$ in 18.5 ml of THF is added drop by drop. The mixture is stirred 3h at 0°C and then, cooled at -10°C. From a second funnel, a solution of 9.18 g (0.0584 mol.) of the acetylenic alcohols in 20 ml THF is added slowly. The reaction evolves 1280 ml (0.571 mol.) of hydrogen. After stirring 1h at -10°C, the products were filtered and the filtrate poured in a solution NaOH,1N (147 ml) and oxidized

with 90 ml H_2O_2, 15%. The solution is left overnight at 0 to -10°C, then saturated with NaCl, filtered and worked up with ether and water saturated of NaCl. The *2-isopentanol* is distilled of (E_{15} = 35 - 40°C).

The residue of the crude hemiacetal is diluted with 12 ml ether, 12 ml pyridine and 24 ml acetic anhydride and left one night at 3°C. After evaporation of the solvent, the product is pyrolysed at 200°C (100 mmHg) (E_{100} ≃ 108 - 110°C, 5 g with 70% purity observed by NMR, corresponding to about 38% yield). The three isomers are purified directly by GLC on Silicone SE30 at 96°C (t_R = 16.4 min for 4a, 17.8 min for 4b and 20.2 min for 4c). $C_{10}H_{18}O$ (SM : $M^{\cdot+}$= 154.1363(4a), 154.1361 (4b) and 154.1361 (4c) for 154.13576 calc.).

Preparation of the α-bromobutyrolactones

In a flask containing 173 mg (1.132 m mol) of the dihydrofuran compound in 0.9 ml DMSO with 40 µl H_2O (∿ 2 equiv.) (0°C, N_2), the N-bromosuccinimide (398.9 mg, ∿ 2.24 m mol) is added all at once, under vigourous stirring. The solution becomes orange. After 15 min, a solution $NaHCO_3$ is added until decoloration. After extraction with ether, the crude product (274 mg, 97%) is oxidized with the Jones reagent [5], in acetone at 0°C. The product (184.7 mg) is a mixture of two lactones (2a + 3a or 2b + 3b) or one pure lactone (3c). In case of mixture, the two lactones are separated by thin layer chromatography on Silica (light petroleum/ether = 90/10, 3 elutions). $C_{10}H_{17}O_2Br$ (SM : $M^{\cdot+}$ = 248-250).

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