Tetrahedron Letters Vol. 22, pp 633 - 636 0040-4039/80/0208-0633$02.00/0

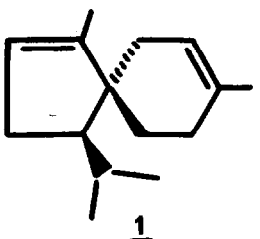
A SYNTHESIS OF (d.l) ACORADIENE III

J. Ficini*, G. Revial, J.P. Genêt

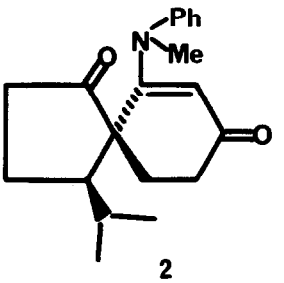
Laboratoire de Chimie Organique de Synthèse
Equipe de Recherche Associée au C.N.R.S.
Université Pierre et Marie Curie
8, rue Cuvier - 75005 Paris.

Summary : A synthesis of (d.l) Acoradiene III (7 steps) starting from N-methyl N-phenyl amino acetylene is described.

We describe here a synthesis of (d,l) acoradiene 1[1], a sesquiterpene present in the essential oil of Vetiveria zizanoides[2] and which possesses the spiro (4.5) decane skeleton of the acoranes.



1



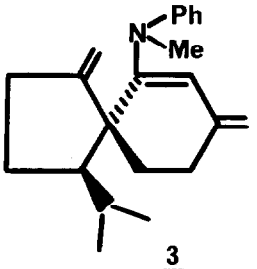
2

One of the difficulties encountered in the synthesis of such spirosesquiterpenes is the control of the stereochemistry of the quaternary spiro center and of the secondary center on the 5-membered ring.

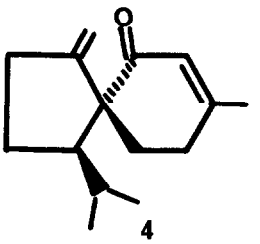
In the preceding paper[3], we presented a method which solves this type of problem since it permits the production of the spiro system 2, the precursor of 1, with complete regio and stereoselectivity.

One can envision several strategies which would transform 2 into acoradiene 1. In the one which we describe here, we first of all, completed the construction of the carbon skeleton of acoradiene by adding the two carbon atoms of the missing methyl groups and then reduced the system to the required oxidation level.

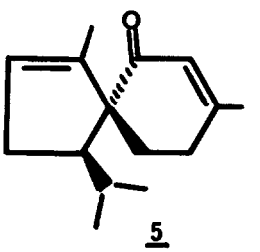
The two carbon atoms are attached by a Wittig reaction on the two carbonyls of 2[4]. Therefore methylene-triphenylphosphorane (3 eq, C_6H_6, reflux 3 days) is reacted with 2[5] to give the dienamine 3 : [IR (neat) : 3060, 3020, 1640, 1615, 1600 cm^{-1} ; NMR ($CDCl_3$) : δ 2.8 (s,3H), 4.5-5 (m,4H), 6 (s,1H) in 90 % yield[6]].



3



4



5

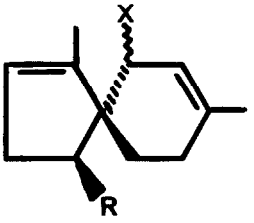
Hydrolysis of 3 (AcOH/AcONa/MeOH/H_2O, 48 hrs reflux) produces, in 95 % yield, the enone 4 : [IR (neat) : 1660, 1600 cm^{-1} ; NMR (CCl_4) : δ 0.7 (d,3H,J = 6 Hz), 0.9 (d,3H,J = 6 Hz), 4.5 (m,1H), 4.7 (m,1H), 5.8 (m,1H)] which by isomerization of the exocyclic methylene cyclopentane to the vinyl methyl (4 ⟶ 5) [pTsOH (5-10 %), C_6H_6, 24 hr reflux] is transformed into the enone 5 [yield : 95 % ; IR : 1600 cm^{-1}, NMR (CCl_4) : δ 0.7 (d,3H, J = 6 Hz) 0.9 (d,3H,J = 6 Hz), 5.4 (m,1H), 5.9 (m,1H), NMR ^{13}C ($CDCl_3$: 202, 160.7, 145.3, 128.2, 127.2, 59.2, 54, 34.3, 29.5, 28.8, 26.7, 24.3, 22.3, 21.7, 15.7 ppm].

The intermediate 5, which is obtained in 80 % overall yield (3 steps) starting from the cycloadduct 2 and in 55 % overall yield (4 steps) starting form N-methyl N-phénylamino acetylene, the starting ynamine, has the stereochemistry of acoradiene 1 and only differs from it by the presence of the carbonyl. Whatever method is envisioned for the reduction of this carbonyl to a methylene group, the process must be totally regioselective.

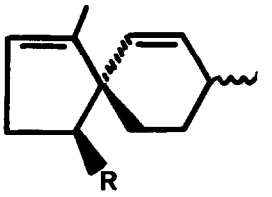
The direct reduction of the carbonyl to a methylene group by the classical methods (Wolff-Kischner, hydrogenolysis of the thioketal) did not fulfill there requirements in our case, because it resulted in rearrangements in poor yield. We then thought about using, instead of the reduction of the carbonyl, the reduction of the corresponding allylic alcohols or their derivatives of type 6[7].

The regioselectivity of the reduction of allylic esters by dissolving metals is often governed by the stability of the olefin formed rather than by steric hindrance of the sites of protonation of the allylic anion or radical intermediates of the reaction[7]. One expected then, a priori, that the reduction of the allylic esters 6 would proceed without

movement of the double bond and would lead to the acoradiene structure (6 : X = H) rather than that of the isomers of type 7 where the double bond is less substituted[7,8].



a : R = iPr ; X = OH
b : R = iPr ; X = $OPO(OEt)_2$
c : R = iPr ; X = OAc
d : R = H ; X = OAc
e : R = H ; X = H



6 7

In fact, this is exactly what is observed when the 5-membered ring of 6 is unsubstituted (R = H). The reduction ($Li,EtNH_2$, 17°C) of the acetate of the spiro alcohol 6d, used as a model, leads as expected only to the diene 6e : [NMR ($CDCl_3$) : δ 5.1-5.4 (m,2H)].

However, the reduction is not as selective when the 5-membered ring of 6 bears an isopropyl substituent (R = iPr). This is the case with the acetate 6c[9] or the phosphate 6b[10] precursors of acoradiene 1. In fact, one obtains, in 95 % yield, in addition to the expected acoradiene 1, its regioisomer 7 (R = iPr)[11] in a 1:1 ratio with the acetate 6c and 2:1 ratio with the phosphate 6b. Acoradiene 1, easily separated from 7 (preparative VPC) is identical (IR, ^1H NMR, ^{13}C NMR, VPC, Mass Spectrum) to an authentic sample[12].

The reasons for the lower regioselectivity of the reduction when the spiro system is substituted (6b or 6c) versus unsubstituted (6d) or when the group being reduced is an acetate 6c instead of a phosphate 6b are not yet clear.

It is possible, in our case, that isomers 1 and 7 are of similar energy when R is isopropyl and when R is a hydrogen, isomer 7 becomes much less stable than 6e[13].

We are studying the different factors which have an effect on the regioselectivity of this reduction.

References and notes :

1) For a known route to this derivative, see : P. Naegeli and R. Kaiser, Tetrahedron Letters, 2013 (1972).

2) a) R. Kaiser and P. Naegeli, ibid, 2009 (1972) ; b) L.H. Zalkow and M.G. Clower, ibid, 75 (1975).

3) J. Ficini, G. Revial and J.P. Genêt, Tetrahedron Letters, preceding article.

4) The reaction can be regioselective if the reaction time is shorter (2 hours instead of 3 days) since the cyclopentane carbonyl, which is more hindered than the cyclohexane carbonyl, does not react under these conditions.

5) J.M. Conia and J.C. Limasset, Bull. Soc. Chim. France, 1936 (1967). Under the conditions described by these authors, there is no enolization of the cyclopentanone.

6) After purification starting with the hydrochloride of 3 (10 % HCl, 20°C) and regeneration of the dienamine (which is not hydrolyzed under these conditions) by a solution of Na_2CO_3.

7) A.S. Hallsworth, H.B. Henbest and T.I. Wrigley, J. Chem. Soc., 1069 (1957).

8) See, for example, in the (4.5) spirodecane series : W.G. Dauben and D.J. Hart, J. Amer. Chem. Soc., 99, 7307 (1977).

9) 6c : [IR (neat) : 1730 cm^{-1} , NMR (CCl_4) : δ 5.1-5.5 (m,3H)] is obtained by esterification (AcCl, pyridine, 0°C) of the alcohol 6a (2 diastereoisomers) [IR (neat) : 3400, 3040 cm^{-1} ; NMR (CCl_4) : δ 3.7-4.1 (m,1H), 5.1-5.5 (m,2H)].

10) 6b is obtained by esterification (methyllithium) $ClP(O)(OEt)_2$ Et_3N,-20°C to 0°C and reduced without purification by the method of : R.E. Ireland, D.C. Muchmore and U. Hengartner, J. Amer. Chem. Soc., 94, 5098 (1972).

11) 7 [(R = isoPr) (2 isomers) ; NMR ($CDCl_3$) : 5.1-5.7 (m,2H), mass spectrum m/e : 204 (M^+ characteristic fragments) : 189, 163, 162, 161 (base peak), 149, 148, 147, 133, 122, 121, 119, 107, 106, 105, 95, 94, 93, 92, 91, 81, 79, 77)] is identical to an authentic sample that we prepared from 5 by reduction (Li, NH_3) followed trapping of the enolate of the corresponding ketone by means of diethylchlorophosphate and reduction of this phosphate by the method of R.E. Ireland and G. Pfister, Tetrahedron Letters, 2145 (1969).

12) We gratefully thank Drs. R. Kaiser and P. Naegeli (Givaudan,Switzerland) for sending us a sample of (±) acoradiene III and its IR, ^1H NMR, and Mass spectra. The ^{13}C NMR spectra recorded at the spectroscopy center (Paris) are likewise identical ($CDCl_3$) : 148.7, 133.8, 123.7, 121.3, 55.2, 48, 34.4, 32.2, 28.9, 28.1, 26.4, 23.6, 22.9, 21.1, 14.9 ppm. We thank Madame Platzer for having recorded these spectra.

13) The energy minimization calculation according to the "Script" method introduced by Dr. N.C. Cohen (Roussel-UCLAF, Romainville, France) (N.C. Cohen, P. Colin, G. Lemoine, to appear later) shows that the strain energy differences between spiroderivatives of types 6 and 7 are very different when R is an isopropyl or a hydrogen. This difference is 2.4 Kcal/mole (in favor of 7) when R is isopropyl while it is practically zero when R is a hydrogen. Taking into account the energy stabilization given to isomers 6 by the presence of a methyl group on a double bond, which does not affect the calculation of the Script method, the difference is energy between 6 and 7 decreases when R is isopropyl and increases when R = H which corresponds with our experimental results ; these results are perfectly rationalized by the calculations if one takes, as an average value for the energy stabilization of a methyl group, a value of 2.3 Kcal/mole see S.J. Rhoads, E.E. Waali, J. Org. Chem., 35, 3358 (1970) . We gratefully thank Dr. Cohen and M.G. Lemoine for having carried out these calculations.

(Received in France 29 October 1980)