INTRAMOLECULAR ENE REACTION : THE USE OF 1,7-ENYNES IN THE SYNTHESIS OF HYDROXYLATED METHYLENECYCLOHEXANE DERIVATIVES*

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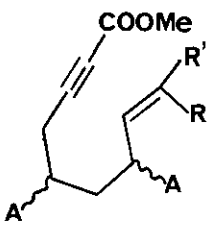
Abstract - The intramolecular ene reaction of 1-7 enynes produces on a preparative scale methylene cyclohexanes in good yields when the double bond is trisubstituted. A protected 1-3 dihydroxy enyne reacts in the same way.

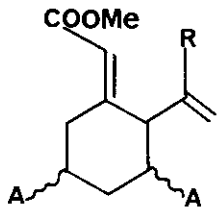
The intramolecular ene reaction of 1,6 enynes is a particularly useful method for the synthesis of five-membered rings[1]. On the other hand, the few studies of the cyclization of 1,7-enynes[2], which were conducted on less than a preparative scale, suggested that the method is not as suitable for the construction of six-membered rings.

In connection with our current interest in the synthesis of certain natural products, we thought it worthwhile to make a more thorough study of the intramolecular ene reaction of 1,7-enynes of type 1 as a route to functionalized six-membered rings.



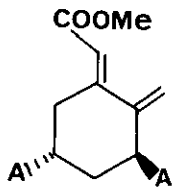
1

a : A=H, R'=Me, R=H
b : A=H, R'=H, R=Me
c : A=H, R=R'=Me
d : A=OSi^{t}BuMe$_2$, R=R'=Me



2

a : A=H, R=H
b : A=H, R=Me
c : A=OSi^{t}BuMe$_2$, R=Me



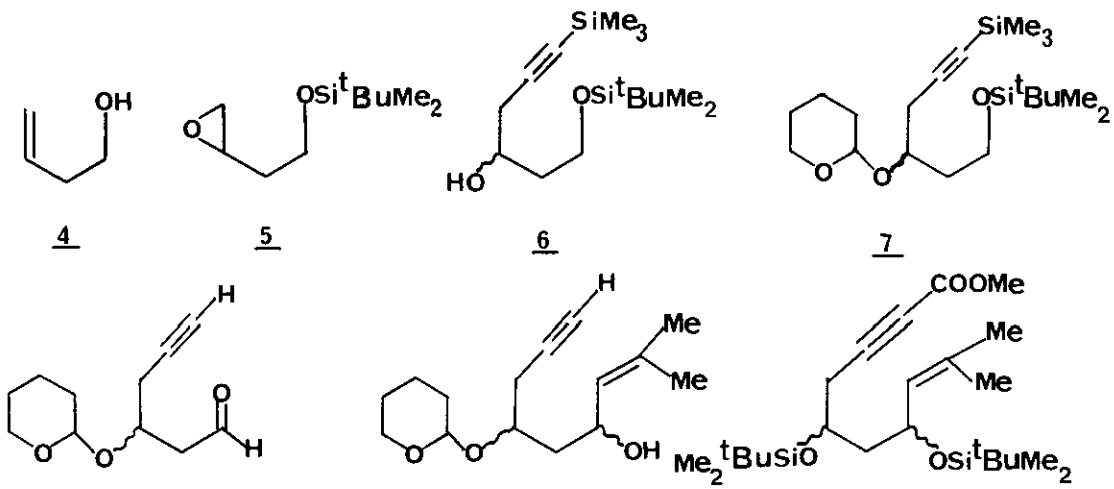
3

A=OSi^{t}BuMe$_2$

Because we had a particular interest in the synthesis of cyclohexane derivatives which might be useful precursors of the A ring of 1S, 25-dihydroxycalciferol, we focussed our attention on two specific goals : 1) To discover the most favorable substitution pattern and geometry of the terminal double bond. 2) To find conditions which would allow the ene reaction to take place without elimination of the protected alcohol functions of 1d.

* This paper is contributed in honor of Professor G.Stork's 65th birthday.

We first show that, as expected, enynes such as 1a and 1b, in which the terminal double bond is substituted by a single methyl group, are more difficult to cyclize than the disubstituted enyne 1c : A temperature of 295°C (xylene solution in a sealed tube) is required for the cyclization of 1a and 1b rather than 225°C of 1c. We have also shown that the trans isomer 1a reacts more rapidly and gives a better yield than the cis isomer 1b. It therefore appeared that the best chance of reaching our objective of cyclizing 1,7-enynes having a protected 1,3-diol system would involve the dihydroxyenyne 1d with a terminal isopropylidene group. In the course of this study, we developed a method of thermolysis which we found more effective than heating in a sealed tube : Flash pyrolysis in a quartz tube filled with carborundum, the temperature and pressure being selected so as to minimize exposure of the sensitive enyne and its cyclization product to the high temperature. Our studies were conducted with the model enyne 1d, used as the racemic mixture of the two diastereoisomers[3]. This was synthesized from the commercially available 3-buten-1-ol (4). Oxidation of the tert-butyldimethylsilyl ether of 4 with m-chloroperbenzoic acid gave the epoxide 5[4] which was opened by reaction with lithium trimethylsilylacetylide, in the presence of BF_3 etherate at -78°C[5].



4 5 6 7

8 9 1d

The resulting secondary alcohol 6[6] was protected as its tetrahydropyranyl ether 7[7] and the primary alcohol, liberated by cleavage of its silyl protecting group with tetrabutylammonium fluoride, THF, 0°, 30mn was oxidized to aldehyde 8[8] with PCC[9]. Addition of the Grignard reagent prepared from 1-bromo-2-methylpropene then led to secondary alcohol 9[10]. This was finally led to 1d[11], the required material for our cyclization studies, by protection of the two secondary alcohols as their TBDMS derivatives, followed by carbomethoxylation of the lithio derivative (nBuLi, THF) with methyl chloroformate.

The results we obtained in the cyclization of enynes 1 under various conditions are summarized in the table below which shows that the yield in the formation of annulation products 2 can reach 80%, after silica gel chromatography.

2b ^{1}H NMR (C_6D_6) δ 1.2-3.1 (12H b.b[12] $4CH_2$ and $=-CH_3$, 1C-H), 3.55 (s OCH_3), 4.8 (1H broad s $=C<^{H}_{H}$), 5.02 (1H broad s $=C<^{H}_{H}$), 5.8 (s, $=\underline{CH}-COOMe$) p.p.m.

2c ^{1}H NMR (C_6D_6) 0-0.2 (12H, mixture of stereoisomers 2 $Si(CH_3)_2$), 0.9-1 (18H mixture of stereoisomers 2 $SiC(CH_3)_3$) and 1.5-3 (8H, $=\!\!<^{CH_3}$ and -O-C-$\underline{CH_2}$-C-O, O-C-$\underline{CH_2}$ C$\neg\!\!=$), 3.4 (s OCH_3), 3.6-4.6 (2H mixture of stereoisomers 2 $\underline{H}$-C-O-Si), 4.7-5 (b.b. $=CH_2$), 5.95 (broad s, mixture of ring stereoisomers C$=\underline{CH}$-COOMe). p.p.m.

Enyne 1	Conditions of flash pyrolysis: temperature	pressure	Cyclohexanes 2 yield of purified products	
1a	500°C	300 mm	2a	40%
1b	500°C	300 mm	2a	15%
1c	420°C	300 mm	2b	80%
1d	420°C	200 mm	2c	80%

It is clear that the goal of determining the conditions for the formation of dihydroxylated cyclohexane derivatives by the high temperature cyclization of suitably protected dihydroxy-1,7-enynes has been reached. The work continues still to find a concise route to 1d having the correct relative and absolute stereochemistry such as found in 3, as well as to find a method for the transformation of the isopropenyl group of 2c to the required methylenecyclohexane system of 3.

NOTES AND REFERENCES

1) a) W.D.Huntsman and R.P.Hall, J.Org.Chem., 27, 1988 (1962) ; b) W.D.Huntsman, Int.Sci.Chem.Rep., 6, 151 (1972) ; c) M.Bortolussi, R.Bloch and J.M.Conia, Tetrahedron Lett., 4171 (1973) ; d) G.Saucy, L.H.Chopard, W.Guex, G.Ryser and O.Isler, Helv.Chim.Acta , 41 160 (1958) ; e) C.A.Townsend, T.Scholl, and D.Arigoni, Chem.Commun., 921 (1975) ; f) G.Stork and G.Kraus, J.Amer.Chem.Soc., 98, 6747 (1976).
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2) a) B.B.Snider and T.A.Killinger, J.Org.Chem.,43, 2161 (1978) ; b) B.B.Snider, Acc.Chem.Res., 13, 426 (1980).

3) We warmly thank Mrs Tanier for her very efficient technical assistance in the synthesis of 1d.

4) 81% yield based on 4 : $E_{0.1}$ 55°C ; ^{1}H NMR($CDCl_3$) δ (s $Si(CH_3)_3$), 0.9(s $C(CH_3)_3$), 1.55-1.9(b.b.[12]  CH_2), 2.4-3.2(3H b.b ), 3.75(t CH_2-OSi) p.p.m.

5) M.Yamaguchi and I.Hiroé, Tetrahedron Lett., 391 (1983) ; M.J.Eis, J.E.Wrobel and B.Ganem, J.Am.Chem.Soc., 106, 3693 (1984).

6) 70% yield after purification by silicagel column chromatography (AcOEt/hexane : 1/9) I.R.(neat) 3600-3200-2170 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.05 (s $Si(CH_3)_3$), 0.1 (s $Si(CH_3)_3$), 0.9(s $SiC(CH_3)_3$, 1.8(3H, b.b. $\underline{CH_2}$-CHOH), 2.3(d CH_2-≡), 3.85(3H, b.b. $\underline{CH_2}$-OSi, $\underline{CH}$-OH) p.p.m.

7) 80% after purification by silicagel column chromatography (AcOEt/hexane : 1/7); I.R.(neat) 2170 cm^{-1}.

8) 60% yield after purification by silicagel column chromatography (AcOEt/hexane : 1/2) ; I.R.(neat) 3300-2120-1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4-1.9(6H b.b. $3CH_2$), 1.9-2.1(b.b. ≡-H), 2.2-2.9(4H, b.b, CH_2-≡and $\underline{CH}_2$-CH=O), 3.25-4.5(3H, b.b, $\underline{CH}_2$-O and HC(-O-)-CH_2-≡), 4.7(b.b. $\underline{H}C(O)(O)$), 9.75 (broad s $\underline{H}C(=O)$) p.p.m.

9) According to K.Mori, T.Takigawa and T.Metano, Tetrahedron 35, 933 (1979).

10) 80% yield after purification by silicagel column chromatography (AcOEt/hexane : 1/1) I.R.(neat) 3400-3300-2120 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.4-1.9(14H b.b, 3 $CH_2=C(CH_3)_2$ and O-C-$\underline{CH}_2$-C-O), 2.05(b.b.$\underline{H}$-≡), 2.2-2.6(2H, b.b. $\underline{CH}_2$-≡), 3.4-4.2 (3H b.b. $\underline{CH}_2$-O and $\underline{CH}$(-O-)-CH_2-≡), 4.3-5(2H b.b. O-$\underline{CH}$-O and O-$\underline{CH}$-$C(Me)_2$), 5.3(broad d.$\underline{H}C=C(Me)_2$) p.p.m.

11) 45% yield from 9 after purification by silicagel column chromatography (AcOEt/hexane : 1/9) I.R.(neat) 2230, 1725 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 0.05-0.15(12H mixture of stereoisomers 2 $Si(CH_3)_2$), 0.9(s $SiC(CH_3)_3$), 0.93(s, $SiC(CH_3)_3$), 1.6-1.9 (8H b.b.$=C(CH_3)_2$ and O-C-$\underline{CH}_2$-C(=O)-O), 2.45-2.7 (b.b. $\underline{CH}_2$-≡), 3.8(s, OCH_3), 3.9-4.7(2H mixture of stereoisomers 2$\underline{H}C$-OSi), 5.2 (broad d. $\underline{H}C=$) p.p.m.

12) b.b. means broad band for the compounds described in this communication ; all of them, give a correct elementary analysis.

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