trahedron Vol. 39, No. 19, pp. 3039 to 3048, 1983
inted in Great Britain.

0040-4020/83 $3.00 + .00

GUAIANOLIDES 1. PERHYDROAZULENIC LACTONES AS INTERMEDIATES FOR TOTAL SYNTHESIS

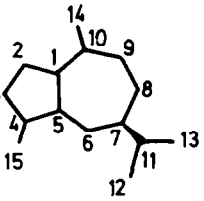
A.A. Devreese, M. Demuynck, P.J. De Clercq[1] and M. Vandewalle*

State University of Ghent, Department of Organic Chemistry
Laboratory for Organic Synthesis,
Krijgslaan, 281 (S.4), B-9000 GENT (Belgium)

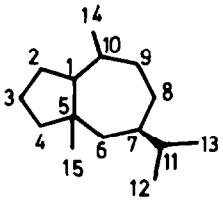
(*Received in UK* 9 *June* 1983)

Abstract - The synthesis of potential guaianolide precursors 31-34 is described, involving as a key-step the reductive opening of keto-epoxides 21-26. The latter products were obtained from the common intermediate 13 (and 14).

Several years ago we embarked on a general pro-ram directed at the total synthesis of guaianoli-es and pseudoguaianolides, two series of sesqui-erpene lactones characterized by a perhydroazu-enic skeleton[2]. These compounds are widely istributed in nature and many members display nteresting biological activities[3]. Comparison f individual members within both series reveals n impressive diversification both in the array f functional groups located on the skeleton and n the stereochemistry. Despite numerous stu-es in relation to their interconversion, no to-l synthesis had been reported prior to 1976.

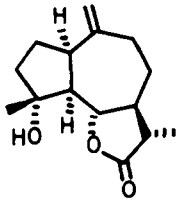


guaiane

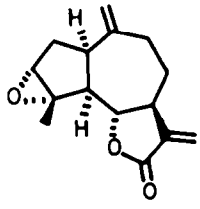


pseudoguaiane

eudoguaianolides were the first to yield to to-l synthesis. Various diversified approaches r the construction of the angularly substi-ted perhydroazulene ring system have since lminated in the synthesis of no less than 18 fferent pseudoguaianolides[4]. In sharp contrast ttle progress has been made in the total syn-esis of guaianolides. For a long time the only isting methods involved structural rearrange-ments of naturally occurring sesquiterpenes of other series, i.e., eudesmanolides and germa-cranolides[5]. We recently reported preliminary results on the total synthesis of two guaiano-lides, compressanolide (1) and estafiatin (2), via a route in which the perhydroazulene ske-leton was constructed in an early stage[6,7]. During the course of our work the synthesis of a non-naturally occurring guaianolide has been described involving the rearrangement of a functionalized decalin intermediate[8].



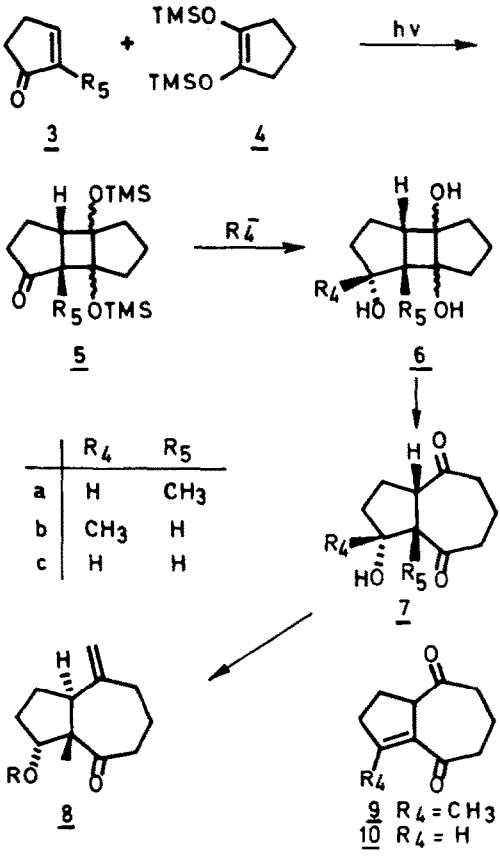
1



2

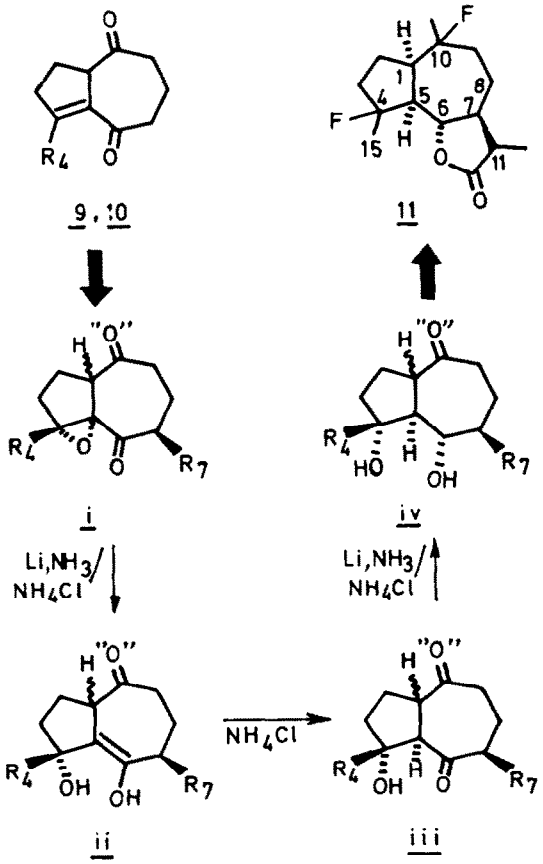
We originally devised a direct method for the construction of perhydroazulenes (i.e., 7)[9], with in mind as ultimate goal the development of routes to both guaianolides and pseudoguaiano-lides (scheme 1). The method involves a pho-tocycloaddition of 1,2-bis(trimethylsilyloxy)-cyclopentene (4) to a cyclopentenone 3, fol-lowed by nucleophilic addition (R_4) to the ke-tone 5 and α-diol cleavage of the resulting triol 6. This affords a short and efficient access to perhydroazulenediones 7 which posess

essential elements of functionality for the construction of members of both series. Our syntheses of pseudoguaianolides have all centered on the key intermediate 8, readily available from 7a, via a sequence involving protection of the hydroxyl group, epimerization at C-1 and selective Wittig reaction[10]. In this and the following paper we wish to describe our synthetic studies which eventually led to the first total syntheses in the guaianolide series, i.e., compressanolide (1) and estafiatin (2).



Scheme 1

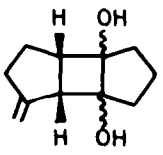
The discrepancy in synthetic results obtained in both series stems, in our experience, from the different position of the 15-methyl group. Its angular location in pseudoguaianolides allows for stereocontrol during the synthesis. Furthermore, as a rule, functionalities in the five- and the seven-membered rings can be delt with separately. In contrast, a general entry to guaianolides has to secure simultaneously both the functionality pattern and the correct stereochemistry along the C-4/C-7 strand. We therefore decided to focus on the strategy as outlined in scheme 2, with lactone 11 representing a structural common denominator in this series. Indeed, most guaianolides possess a cis-fused hydroazulene skeleton with a γ-lactone trans-closed to C-6. Apart from the classical α-methylene moiety on C-11, unsaturations frequently are present at C-4 and at C-10 and further diversity may arise from additional functionalities, especially in the five-membered ring and at C-8. The key-step in the proposed scheme involves the direct conversion of keto-epoxide i to diol iv with lithium in liquid ammonia-ammonium chloride, via alternating reduction and protonation steps[11]. The obtention of the desired stereochemistry at C-5 and at C-6 may be anticipated with some confidence; intramolecular assisted protonation of the intermediate enol ii by the hydroxyl group at C-4 should yield predominantly hydroxy ketone iii, which on further reduction and equilibration of the resulting radical alcohol should give the more stable alcohol iv.



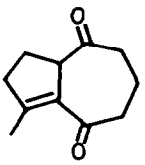
Scheme 2

)nsequently, the trans-relation of R_7 with :spect to the epoxide in i should guarantee ıe crucial stereochemistry at C-5, C-6 and ·7. The stereochemistry at C-1 is of less)ncern provided that at some stage of the :quence, a ketone can be generated at C-10)r epimerization to the cis-fused hydroazu- :ne skeleton, if necessary. Both the ke-)ne at C-10 and the hydroxyl group at C-4)uld then be used for the eventual obten- .on of the desired functionalities of the ırget natural compounds. It should further : noted that at this stage of the planning ıe nature of R_4 in i, i.e., CH_3 or H, is not :ucial, since in the latter case the lacking ·15 group could in principle be introduced : a late stage of the synthesis after oxida- .on to a carbonyl at C-4. In view of the :quired intermediate i, enediones 9 and 10 :e ideal starting substances since they fea- ıre differentiated carbonyl groups, thus al-)wing in principle for selective protection : C-10 and subsequent selective alkylation : C-7.

A three-step procedure to perhydroazulene- .one 9 has already been reported by us in de- ıil (Scheme 1)[9]. It originally involved re- :tion of methylmagnesium bromide in tetrahy- ·ofuran on photoadduct 5b and acid hydroly- .s to 6b, followed by oxidative cleavage th lead tetraacetate in acetic acid at 100°C ıich effected simultaneous dehydratation to 9)verall yield : 47 %). The conversion of ·iol 6b to 9 can also be performed with so- um periodate in ethanol (91 % yield) to 7b,)llowed by dehydratation to 9 with Burgess :agent[13] in benzene (80 % yield). In a simi- .r way triol 6c, obtained from 5b upon lithium anate reduction, is converted to 10 via di- tone 7c (overall yield from 5b : 38 %). Al- ıough originally 7b and 7c could have been luable intermediates as such, we were not le to differentiate between both carbonyl oups except via dehydratation to the cor- sponding enones 9 and 10. Consequently, an ternative two-step sequence for the synthe- s of enedione 9 was developed : treatment of otoadduct 5b with methylenetriphenylphos- orane (generated from sodium tert-amylate toluene) to olefin 12 (74 % yield), fol- wed by lead tetraacetate oxidation in acetic id, which directly yields the conjugated one 9 (71 % yield).

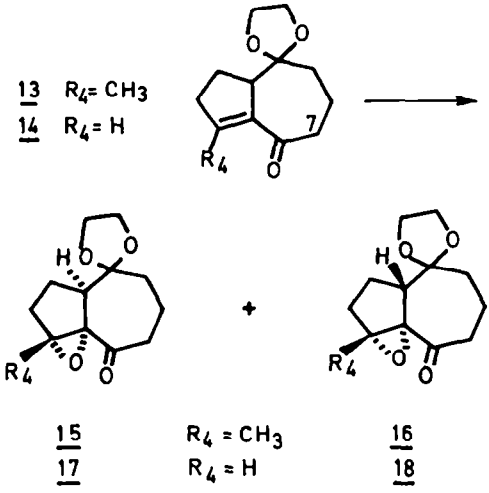


12



9

Selective protection of the C-10 carbonyl-group in diones 9 and 10 was best effected by trans acetalisation with the ethylene ketal of 2-butanone in chloroform (85 % to 13; 65 % to 14). The incorporation of the side-chain at C-7 was first attempted via kinetic deprotonation-alkylation (1-bromo-3-methyl-2-butene) of enone 13; this, however, yielded only complex reaction mixtures. A similar observation has been reported by Posner[8].



We therefore turned our attention first to the epoxidation of the double bond in enones 13 and 14. The results obtained with alkaline peroxides are summarized in table 1 and show that either one of the two epoxides 15 and 16 (or 17 and 18) can be obtained predominantly depending on the oxidant used.

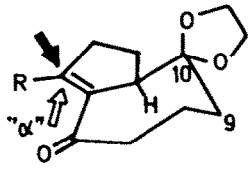
A similar reversal in stereochemical outcome when using alkaline hydrogen peroxide in protic medium (table 1, entries 3 and 7) compared to the use of t-butylhydroperoxide-Triton B[14] in aprotic medium (entries 1, 2 and 4, 5,6) has already been observed before on prostaglandin A derivatives[15].

Table 1

Entry	Substrate	Oxidation conditions	Temp.	Time	15/17[a]	16/18[a]
1	13	t-BuO_2H, Triton B, THF	-30°C → 0°C	4 h	40	17
2	13	$C_6H_5CMe_2O_2H$, Triton B, THF	20°C	5 d	55	3
3	13	H_2O_2, NaOH, MeOH	-30°C → 20°C	8 h	10	70
4	14	t-BuO_2H, Triton B, THF	-30°C → 0°C	4 h	66	19
5	14	$C_6H_5CMe_2O_2H$, Triton B, THF	20°C	1 h	68	16
6	14	$C_6H_5CMe_2O_2H$, Triton B, THF	-10°C	4 h	75	16
7	14	H_2O_2, NaOH, MeOH	-38°C → -10°C	6 h	13	72

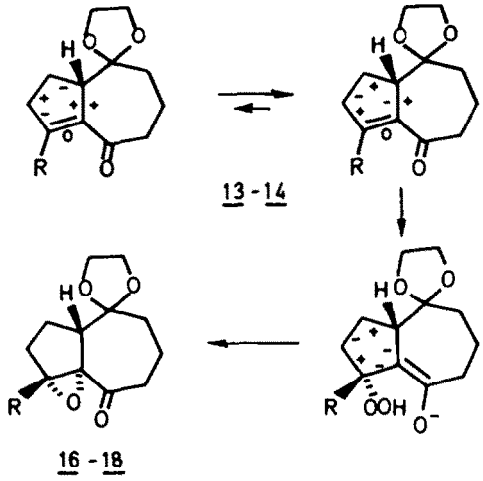
[a] Isolated yield of 15 and 16 from 13, and of 17 and 18 from 14.

Our result probably originates from steric interference of the β-oriented oxygen atom at C-10 upon peroxide attack from the β-face, thus favoring the formation of cis-epoxides 15 and 17.

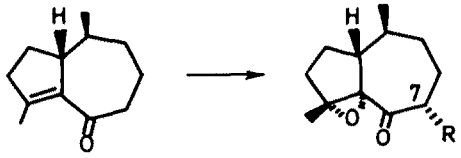


13-14, C_9

Not surprisingly, a higher stereoselectivity is obtained when using the bulkier cumylhydroperoxide reagent instead of t-butylhydroperoxide (cf. entries 4 and 6). On the other hand, the preferred formation of trans-epoxides 16 and 18 upon alkaline hydrogen peroxide reaction probably reflects the preferred quasi-trans conformation of the starting enone, with preferred perpendicular attack at C-4 form the α-side involving the least conformational distortion (scheme 3)[16]. Both isomers being readily separated on silica, a synthetic viable access to both 15 (55 % isolated yield) and 16 (70 % isolated yield) is at hand. In a similar way 17 (75 % yield) or 18 (71 % yield) can be obtained selectively from enone 14. At this point it should be mentioned that both epoxides (cis and trans) are in principle useful for further synthesis, provided that the alkyl group at C-7 can be introduced trans to the epoxide ring (cf. scheme 2). It is interesting to note that in related work of Posner the trans-epoxide 20 was also the major compound formed (67 % compared to 15 % isolated cis-epoxide) upon basic hydrogen peroxide epoxidation of 19[8].



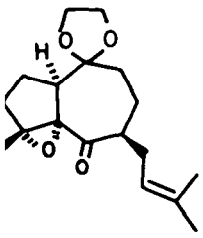
Scheme 3

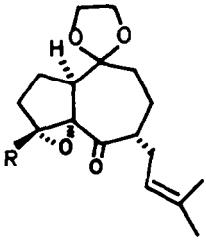


The structural assignment of cis- and trans-epoxides 15 and 16 (i.e., at C-1 and C-4) is unequivocal since both have led to further intermediates whose structures were proven by X-ray.

Deprotonation of epoxide 15 with lithium diisopropylamide followed by addition of 1-bromo-3-methyl-2-butene (1.3 equiv) and hexamethyl-

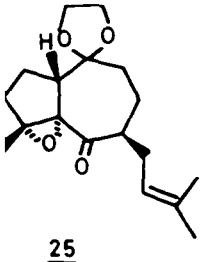
nosphoramide (HMPT) led after purification
n silica to the desired 21 (56 % yield) next
o the C-7 epimer 22 (26 % yield).

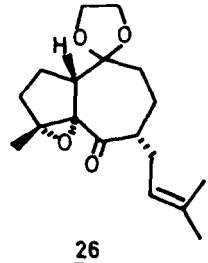




21 R = Me 22
23 R = H 24

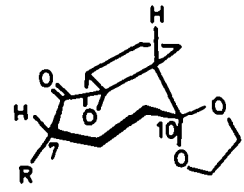
n almost identical result is obtained in the
ase of epoxide 17, leading to 23 and 24 in
5 % and 27 % yield, respectively. Equili-
ration of the undesired isomer 22 (DBU in
ethylene chloride) led to a ca. 1:1 ratio
f 21 and 22, thus allowing for recycling to
1. Under the same conditions the isomeric
oxide 16 gave 25 (60 %) and 26 (16 %).
ne use of an excess of HMPT (20 equiv) gave
owever exclusively and in high yield the un-
sired isomer 26, while no reaction was ob-
rved in the absence of the amide. This
sult is in line with the exclusive forma-
on of 27 (90 % yield) upon similar alky-
tion of 20 in the presence of a large ex-
ss of HMPT as reported by Posner[8].



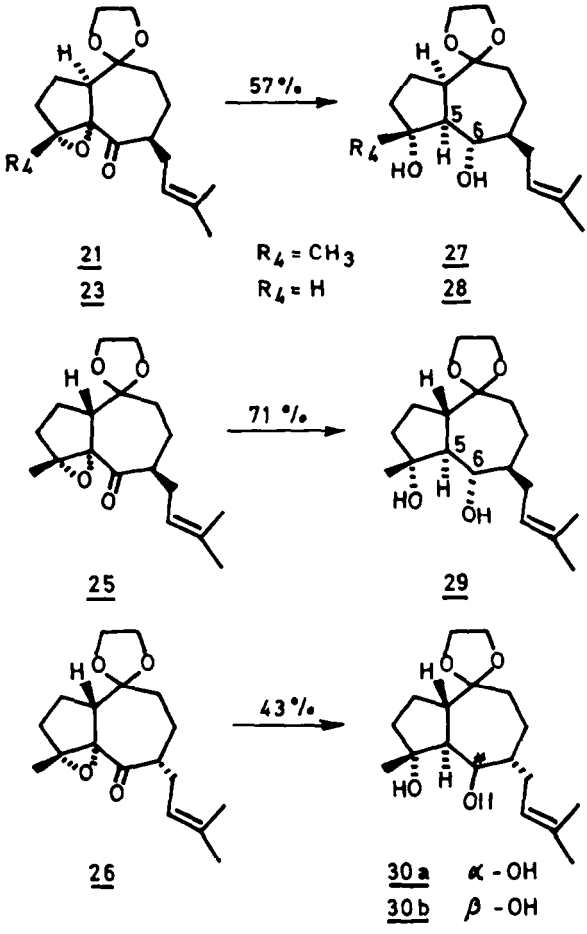


25 26

e known tendency of HMPT for promoting eno-
te equilibration[17] is presumably respon-
ble for the obtention of the more stable
omer 26 when a large excess is used; the
nformations of 26 which are most likely
be populated, i.e., the chair conforma-
on C_{10} and the geometrically close twisted
6^+ and TC_{7-} forms, all possess the α-al-
l group at C-7 in equatorial or isoclinal
sition[18]. Consequently, a reasonably
ereoselective entry is possible towards 21
6 %) and 23 (55 %), 25 (60 %) or 26 (90 %).



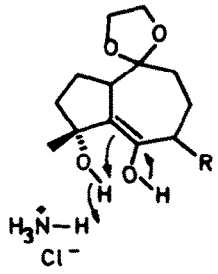
26, C_{10}



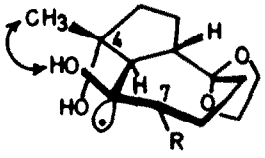
21 $R_4 = CH_3$ 27
23 $R_4 = H$ 28
25 29
26 30a α-OH
30b β-OH

The crucial reductive opening was subse-
quently investigated on the three series of iso-
meric keto-epoxides 21,25 and 26. The one-pot
transformation involves two consecutive treat-
ments of a solution of the keto-epoxide in THF-
liquid ammonia with lithium and intermittent
acidification (NH_4Cl). In every case one dia-
stereoisomeric diol was isolated as major pro-
duct after purification on silica : 27 from 21
(57 % isolated yield), 29 from 25 (71 %) and 30a
from 26 (43 %). It was gratifying to observe
that in all cases internal protonation (cf. cis-
stereochemistry of H-5 with respect to the hy-

droxyl at C-4) was a major stereocontrolling factor (cf. scheme 2)[19]. Thus, subsequent to the reductive cleavage of i and fast protonation on oxygen to enol ii, tautomerization preferentially occurs via intramolecular protonation to ketone iii.



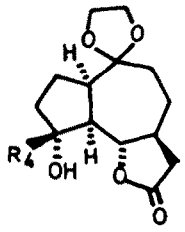
The subsequent in situ reduction is expected to yield the more stable alcohol (i.e., equatorial or isoclinal, trans with the vicinal alkyl substituents at C-5 and C-7) due to equilibration of the intermediate radical alcohol prior to further reduction and protonation. Consequently, the formation of the α-oriented alcohol at C-6 in 27 (28) and 29 is in line with the expectations. The preferred formation of diol 30a upon reductive opening of 26 can be rationalized on conformational grounds. Indeed, molecular model examination of the preferred conformation (i.e., TC_{6+})[18] of diols 30a and 30b, which both can be expected upon reduction of the intermediate hydroxy-ketone (cf. iii), shows a severe non-bonded interaction between the methyl group at C-4 and the β-oriented oxygen at C-6 in 30b, thus favoring formation of 30a.



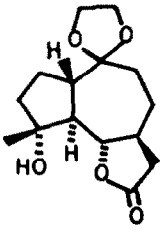
30b, TC_{6+}

The structural determinations of 27 and 29 rest on X-ray studies of further intermediates (i.e., 31 and 32)[20]. The proposed structure 30a is based on the ^1H NMR spectrum of a further lactone (i.e., 33).

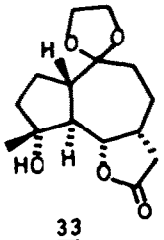
Lactones 31-33 were obtained from 27, 29 and 30a, respectively, by treatment with ozone



31 $R_4 = CH_3$
34 $R_4 = H$

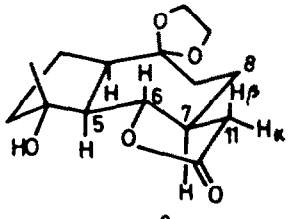


32



33

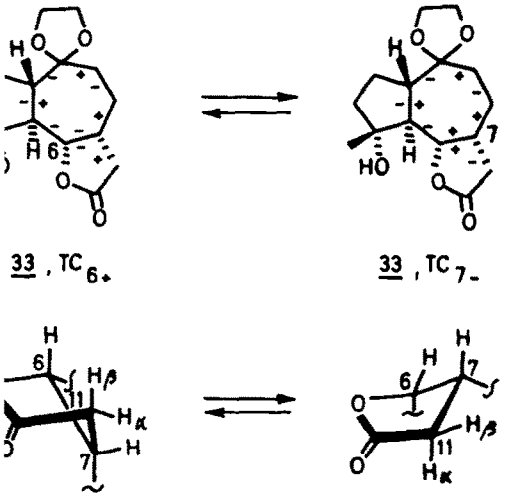
(dimethyl sulfide work-up), immediately followed by Jones oxidation (70-80 % overall yield). The structures of both trans-lactones 31 and 32 were determined by X-ray diffraction[20]. Resonances for the H-5 and H-6 atoms of 31 appear at 2.24 and 4.52 ppm (360 MHz), respectively. The corresponding J values for H-1/H-5, H-5/H-6 and H-6/H-7 are 12.5, 11.0 and 9.5 Hz in accord with the C^8 conformation found in the solid state. The geminal protons H_β-11 and H_α-11 (ABX pattern; 16.8 Hz) resonate at 2.28 and 2.60 ppm, respectively, with J values for H_β-H_7 and H_α-H_7 of 12.5 and 7.5 Hz.



31, C^8

Lactone 33 shows resonances at 2.44 and 4.68 ppm for H-5 and H-6, respectively, with J values for H-1/H-5, H-5/H-6 and H-6/H-7 of 11, 11 and 7.5 Hz, respectively. This strongly suggests both the cis-lactone configuration at 6,7 and the trans-relation between H-5 and H-6, and hence the shown stereochemistry in 33. The occurrence of a cis-lactone is further substantiated by the NMR patterns found for H_α-11 and H_β-11 at 2.24 and 2.86 ppm (ABX; 18

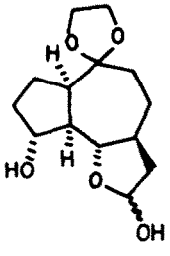
), which show J values of 4.25 and 9.5 Hz
r H_α/H_7 and H_β/H_7, respectively; these J va-
es strongly suggest rapid interconversion in
lution of the two preferred conformers TC_{6+}
d TC_{7-} (scheme 4).



33 , TC_{6+} 33 , TC_{7-}

Scheme 4

In a similar way as described above the nor
oxy-ketone 23 was subjected to reductive ope-
ig conditions, and the major diol (28) ob-
ned after purification directly ozonized
methyl sulfide work-up) to lactol 35 (52 %
rall yield). Subsequent oxidation with
ver carbonate on celite or Jones oxidation
e lactone 34 which showed relevant ab-
ptions in the ^1H NMR indicating an identi-
stereochemistry as for homologue 31 (see
erimental Section).



35

At this point our synthetic scheme has led
the obtention of three key-intermediates
guaianolide syntheses, i.e., 31, 32 and
Lactones 31 and 34 already possess the
rall required stereochemistry (cf. 11).
ther use of 32 however will require an
merization at C-1 at some stage of the
thesis.

EXPERIMENTAL SECTION

The m.ps. are uncorrected. IR spectra were recorded on a Perkin-Elmer 337 spectrometer, mass spectra on a AEI MS-50 spectrometer. The ^1H NMR spectra were recorded at 90 MHz (Varian EM-390) or at 360 MHz (WH-Brucker) in $CDCl_3$ unless otherwise stated with TMS as internal standard. Chemical shifts (δ) are expressed in ppm. Rf values are quoted for Merck silicagel 60 GF_{254} TLC plates of thickness 0.25 mm.

Reaction products were isolated by the addition of water and extraction with the specified solvent. The combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed from the filtered solution on a rotary evaporator. Column chromatographic separations were performed on silica gel with EtOAc-isooctane (ratio given between brackets) as eluent unless otherwise stated.

1-Methyl-2,3,5,6-tetrahydroazulene-4-(3aH), 8(7H)-dione (9).

- Method via 7b.

To a soln of ketone 5b (50.0 g; 0.15 mol) in THF (320 ml) was added a soln of 1.4 M methyllithium in ether (129 ml; 0.18 mol) at -79°C over a period of 1 h. After completion of the reaction (TLC monitoring) MeOH (16 ml) was added. After 30 min 6 N HCl (40 ml) was added at -30°C and the reaction mixture was stirred for another 3 hrs. Work-up and column chromatography (EtOAc-isooctane, 7:3) yielded triol 6b (23.6 g) in 78 % yield. Rf (EtOAc) 0.37 and 0.15; IR 3400 cm^{-1}; MS m/z 198 ($M^+\cdot$).

To a soln of triol 6b (0.5 g; 2.5 mmol) in EtOH (10 ml) was added a 0.1 M soln of $NaIO_4$ (1.07 g; 5 mmol) in the dark. After stirring for 15 min the soln is concentrated in vacuo and the aqueous phase extracted with $CHCl_3$. Work-up and column chromatography (EtOAc-isooctane, 1:1) yielded diketone 7b (0.45 g) in 91 % yield. Rf (EtOAc) 0.35; m.p. 83°-84°C; IR 3464, 1710, 1683 cm^{-1}; NMR 1.4 (3H, s); MS m/z 196 (M^+, 10), 138 (38), 110 (29), 97 (61), 43 (100).

To a soln of dione 7b (15 g; 0.076 mol) in benzene (50 ml) was added a soln of Burgess reagent ($MeOOCNSO_2N^+Et_3$; 18 g; 0.076 mol) in benzene (150 ml). After stirring for 2 h at 50°C, the mixture was poured into a satd soln of NH_4Cl and extracted with ether. Work-up and column chromatography (ether-hexane, 7:3) gave 9 (10.9 g) in 80 % yield. Rf (ether) 0.56; UV (MeOH) 253 nm; IR 2950, 1710, 1675, 1610 cm^{-1}; NMR 4.02 (m, 1H), 2.19 (s, 3H); MS m/z 178 ($M^+\cdot$, 3), 94 (5), 77 (7), 28 (100).

- Method via 12.

To a suspension of methylenetriphenylphosphorane (from methyltriphenylphosphoniumbromide (5.9 g; 16.6 mmol) and a 1.74 M sodium tert-amylate soln in toluene (9.2 ml; 16.0 mmol)) in toluene was added at 20°C a soln of 5b (3.69 g; 11.32 mmol) in toluene (5 ml). After 24 hrs the reaction mixture was poured into a satd NH_4Cl soln. A soln of 6 N HCl (10 ml) in MeOH (20 ml) was then added. After stirring for another 3 hrs the reaction was worked up. Purification by column chromatography (ether-isooctane, 1:1) gave olefin 12 (1.51 g) in 74 % yield, as a mixture of two diastereoisomers. Rf (ether-isooctane, 1:1) 0.22; IR 3460, 3000, 1655, 920 cm^{-1}; NMR 5.21 (1H, m), 4.92 (1H, m), 2.79 (1H, br d, J = 6.5 Hz), 2.4 (3H, m), 2.29 (1H, br s), 2.24 (1H, br s), 2.05 (1H, m). Rf (ether-isooctane, 1:1) 0.11; IR 3460, 3400, 1665, 890 cm^{-1}; NMR 5.07 (1H, m), 4.90 (1H, m) 3.90 (1H, br s), 3.75 (1H, br s), 3.09 (1H, br

d, J = 11 Hz), 2.84 (1H, ddd, J = 5.5, 8.0, 11.0 Hz), 2.47 (2H, m), 2.00 (2H, m), 1.79 (2H, m); MS m/z 180 (M^+, < 1), 162 (10), 100 (100).

A suspension of diol 12 (0.85 g; 4.72 mmol) and lead tetraacetate (2.6 g; 5.88 mmol) in glacial acetic acid (16 ml) was stirred for 2 hrs at 25°C. The mixture was poured into water and extracted with ether. The combined ether extracts were washed with satd $NaHCO_3$ soln, followed by the usual work-up. Purification by column chromatography (ether-hexane, 2:8) gave 9 (0.6 g) in 71 % yield.

2,3,5,6-Tetrahydroazulene-4(3aH),8(7H)-dione (10).

To a suspension of $LiAlH_4$ (10 g; 0.263 mol) in ether (1 l) was added dropwise a soln of 5b (100 g; 0.306 mol) in ether (100 ml). After stirring for 30 min, the mixture was cooled (0°C) and treated dropwise with a satd Na_2SO_4 soln (18 ml). After stirring for 30 min, the mixture is kept at r.t. for 12 hrs. After filtration and washing with ether (5 x), the combined organic phases are concentrated in vacuo. The residue was dissolved in MeOH (100 ml), and the soln acidified with HCl to pH 4. Water was added (25 ml) and the soln stirred for 3 hrs. After the addition of solid $NaHCO_3$, the soln was concentrated and MeOH (300 ml) added. The suspension was then filtered and the MeOH concentrated in vacuo to yield 200 g of crude triol 6c.

A portion of the above triol (56.4 g; 0.306 mol) was dissolved in EtOH (450 ml) and treated with a 0.5 M soln of sodium periodate (1 l). After stirring for 20 min at room temperature, the salts were filtered off and the filtrate concentrated in vacuo. To the residue was added a satd NaCl soln. Extractive work-up with EtOAc gave 61 g of crude diketone 7c.

To a soln of this diketone in benzene (60 ml) was added dropwise a soln of Burgess reagent (54.7 g, 0.23 mol) in benzene (600 ml) at 20°C. After stirring for 1 hr at 70°C, the soln was poured into a satd NH_4Cl soln (200 ml). After extractive work-up with ether and chromatography (hexane-ether, 4:1) there was obtained pure enone 10 (18.2 g) in 38 % yield. Rf (ether) 0.64; UV (MeOH) 251 nm; IR 1710, 1677, 1600 cm^{-1}; NMR 6.93 (1H, m), 4.1 (1H, m); MS m/z 164 (M^+·, 52), 94 (76), 66 (100).

1-Methyl-2,3,5,6-tetrahydroazulene-4(3aH),8(7H)-dione 8-ethylene ketal (13).

A soln of 9 (10.0 g; 0.056 mol) and butan-2-one ethylene ketal (46.8 g; 0.4 mol) in $CHCl_3$ (150 ml), containing catalytic amounts of p-TsOH and oxalic acid, was stirred for 24 hrs at 35°C. After the addition of a satd $NaHCO_3$ soln, the organic phase was separated and the water phase extracted with ether. Classical work-up and chromatography (ether-hexane, 1:9) to 13 (10.6 g) in 85 % yield. Rf (ether) 0.58; UV (MeOH) 257 nm; IR 1670, 1610 cm^{-1}; NMR 3.94 (4H, m), 3.36 (1H, m), 2.11 (3H, s); MS m/z 222 (M^+·, 15), 166 (10), 99 (100).

2,3,5,6-Tetrahydroazulene-4(3aH), 8(7H)-dione 8-ethylene ketal (14)

Prepared from diketone 10 as described for 13 (65 % yield). Rf (ether) 0.68; UV (MeOH) 250 nm; IR 1680, 1605 cm^{-1}; NMR 6.95 (1H,m), 4.02 (4H, m), 3.33 (1H, m); MS m/z 208 (M^+·, 8), 179 (18), 99 (100).

The epoxides 15, 16 and 17, 18.

Cumenylhydroperoxide-Triton B method.

To a soln of the enone 13 (6.34 g; 28.6 mmol) in THF (300 ml) is added cumylhydroperoxide (35 ml of a 80 % soln in cumene) and Triton B (28 ml). After stirring at 20°C for 3 hrs under nitrogen cumylhydroperoxide (17 ml) and Triton B (7 ml) were further added. After stirring for 6 days the soln was poured into a satd NH_4Cl soln (100 ml) and the aqueous phase extracted with ether (2 x 200 ml) and $CHCl_3$ (2 x 200 ml). After usual work-up and purification by column chromatography there was obtained 3.73 g of cis-epoxide 15 (55 % yield) and 0.22 g of trans-epoxide (3 % yield).

To a cooled (-10°C) soln of the enone 14 (3 g, 14.6 mmol) in THF (80 ml) was added at once cumylhydroperoxide (80 % soln in cumene, 4 ml) and Triton B (2 ml) under nitrogen. After stirring for 4 hrs a satd Na_2SO_3 soln (10 ml) was added and the mixture was stirred for 30 min. The aqueous phase was extracted with ether and the combined organic phases further worked-up as usual. Both isomeric epoxides were separated by elution chromatography on silicagel to yield 2.47 g (75 %) of cis-epoxide 17 (eluted with hexane-ether, 4:1) and 0.53 g (16 %) of trans-epoxide 18 (eluted with hexane-ether, 1:1).

Sodium hydroxide-Hydrogen peroxide method.

To a soln of enone 13 (8.5 g; 38 mmol) in MeOH (160 ml) was added at -20°C a soln of 3 N NaOH (4.4 ml; 13.2 mmol) and 30 % H_2O_2 (16 ml). After 4 and 8 hrs stirring at -20°C a soln of 3 N NaOH (4.4 ml) was added to the mixture. After stirring for 14 hrs at 0°C the excess of H_2O_2 was destroyed by the addition of a soln of Na_2SO_3. After concentration in vacuo, the water phase was extracted with EtOAc. Work-up and column chromatography (ether-isooctane, 1:1) gave 15 (0.9 g) and 16 (6.4 g) in 10 % and 70 % yield, respectively.

To a cooled (-30°C) soln of enone 14 (1.16 g; 5.57 mmol) in methanol (20 ml) was added 30 % H_2O_2 (1.6 ml) and 15 % NaOH (0.8 ml) under nitrogen. After stirring for 4 hrs at -30°C and 1 hr at -10°C, a satd soln of Na_2SO_3 (7 ml) was added and stirring was continued at 0°C for 2 hrs. After concentration in vacuo, water (10 ml) was added and the aqueous phase extracted with CH_2Cl_2 (3 x, 100 ml). After usual work-up, the residue was recrystallized from hexane-CH_2Cl_2 yielding 0.81 g of trans-epoxide 18. Further purification of the mother liquor on silicagel (hexane-ether, 2:1) gave a further 0.079 g of 18 (combined yield : 72 %) and 0.164 g of 17 (13 %).

For 15 : Rf (ether) 0.50; m.p. 103°-104°C; IR 2950, 1720, 1115 cm^{-1}; NMR 3.97 (4H, m), 2.71 (1H, dd, J = 8.5, 2.5 Hz), 1.42 (3H, s); MS m/z 238 (M^+·, 17), 223 (15), 130 (30), 99 (100).

For 16 : Rf (ether) 0.36; m.p. 109-110°C; IR 2950, 1720, 1060 cm^{-1}; NMR 4.04 (1H, m), 3.94 (3H, m), 2.82 (1H, dd, J = 7, 11 Hz), 1.42 (3H, s); MS m/z 238 (M^+, 89), 168 (25), 121 (50), 99 (100). Found : C, 65.0; H, 7.71, $C_{13}H_{18}O_4$ requires : C, 65.6; H, 7.74.

For 17 : Rf (ether) 0.64; IR 2990, 1720 cm^{-1}; NMR 4.03 (1H, m), 3.94 (4H, m); MS m/z 224 (M^+, 9), 209 (20), 196 (24), 99 (100).

For 18 : Rf (ether) 0.42; IR 2980, 1720 cm^{-1}; NMR 4.11 (1H, m), 3.95 (3H, m), 3.71 (1H, s);

m/z 224 (M^+, 6), 194 (16), 99 (100).

Alkylation of epoxides 15, 16 and 17.

a soln of LDA (24 mmol) in THF (60 ml), a ln of the epoxide (4.4 g; 18.5 mmol) in THF)0 ml) was added dropwise at -78°C. After irring at -78°C for 1 hr, the mixture was ɔught to -45°C for 1 hr. A soln of 1-bromo-methyl-2-butene (2.86 ml; 24 mmol) in HMPA .5 ml) was added at -78°C and the mixture irred for 10 min at -78°C. After a further irring for 2 hrs at -25°C, the mixture was ured into a satd NH_4Cl soln and the pro-ct isolated with ether. Purification by lumn chromatography (EtOAc-isooctane, 1:3) elded 25 (60 %) and 26 (16 %) from epoxide , or 21 (56 %) and 22 (25.6 %) from epo-le 15 (chromatography with ether-hexane, :85), or 23 (55 %) and 24 (27 %) from oxide 17 (chromatography with EtOAc-iso-ane, 1:9).

: 21 : Rf (ether-isooctane, 1:1) 0.4; ɔ. 74°C; IR 1720, 1115 cm^{-1}; NMR 5.06 (1H, , 3.97 (2H, m), 3.91 (2H, m), 2.73 (1H, dd, = 8.5, 2.5 Hz), 1.70 (3H, s), 1.60 (3H, s), 65 (3H, s); MS m/z 306 (M^+, 8), 181 (61), (100).

: 22 : Rf (ether-isooctane, 1:1) 0.34; 1730, 1020-1100 cm^{-1}; NMR 5.01 (1H, m),) (4H, m), 2.64 (1H, dd, J = 9, 1.5 Hz), 63 (6H, s), 1.31 (3H, s); MS m/z 306 (M^+, , 263 (18), 181 (57), 99 (100).

: 23 : Rf (EtOAc-isooctane, 1:9) 0.12; 1730, 1015-1150 cm^{-1}; NMR 5.06 (1H, m),)5 (1H, s), 3.95 (4H, m), 1.70 (3H, s), 62 (3H, s); MS m/z 292 (M^+, 6), 181 (19), (100).

: 24 : Rf (EtOAc-isooctane, 1:9) 0.08; t 5.01 (1H, m), 3.99 (4H, m), 3.73 (1H, s), 74 (1H, dd, J = 8.5, 1.5 Hz), 1.68 (3H, s), 63 (3H, s).

: 25 : Rf (ether-hexane, 3:1) 0.56; 1730, 1200-1040 cm^{-1}; NMR 5.04 (1H, m),)9 (1H, m), 3.90 (3H, m), 2.67 (1H, dd, = 7.5, 10 Hz), 1.68 (3H, s), 1.61 (3H, s), 35 (3H, s); MS m/z 306 (M^+, 3), 182 (5), (20), 99 (100); Found C, 70.6; H, 8.76; $_{}H_{26}O_4$, requires : C, 69.8; H, 8.76.

: 26 : Rf (ether-hexane, 3:1) 0.42; IR 20, 1460, 1170, 960 cm^{-1}; NMR 5.01 l, m), 4.01 (1H, m), 3.93 (3H, m), 2.86 l, dd, J = 7, 10.5 Hz), 1.68 (3H, s), 63 (3H, s), 1.39 (3H, s); MS m/z 306 , 3), 237 (5), 181 (20), 99 (100).

Reductive opening of keto-epoxides 21, and 26.

a soln of the epoxide 25 (3.4 g, 11 mmol) THF (200 ml) and liquid ammonia (dis-led from Na, 500 ml) was added in one tion at -33°C lithium (0.77 g; 0.11 mol). er 10 min, solid NH_4Cl (6.53 g; 0.12) was added at once. After 10 min ad-ional lithium (0.77 g; 0.11 mol) was led, followed (after 10 min) by NH_4Cl 53 g; 0.12 mol). After stirring for 30 , the ammonia and THF were evacuated and er was added to the residue. After Cl_3 extraction and further work-up, puri-ation by column chromatography (ether-ane, 1:4) gave 29 (2.45 g) in 71 % yield. er the same conditions 30a (42.5 %) was ained from 26 (chromatography with he-e-ether, 2:1), 27 (57 %) from 21 (chroma-raphy with isooctane-ether, 4:1).

: 27 : Rf (isooctane-ether, 1:2) 0.2; 3400, 3000, 2960, 1470, 1390, 1170-1030, , 910 cm^{-1}; NMR 5.21 (1H, m), 3.99 (1H, 3.90 (3H, m), 3.25 (1H, s), 2.68 (1H, s), 2 (1H, ddd, J = 8.5, 9.5, 12 Hz), 2.30 , m), 2.12 (1H, m), 2.04 (1H, dd, J = 10.5, 12.5 Hz), 1.86 (1H, ddd, J = 2.75, 5.0, 13.5 Hz), 1.73 (3H, s), 1.64 (3H, s), 1.34 (3H, s); MS m/z 310 (M^+, 2), 292 (5), 99 (100).

For 29 : Rf (ether) 0.69; m.p. 113°C; IR 3600-3300, 2950, 1480, 1410, 1330, 930 cm^{-1}; NMR 5.19 (1H, m), 4.0 (2H, m), 3.88 (2H, m), 3.42 (1H, ddd, J = 2.75, 8.5, 10.5 Hz), 2.98 (1H, s), 2.92 (1H, d, J = 3 Hz), 2.31 (1H, m), 2.15 (1H, dt, J = 2.75, 10 Hz), 1.93 (1H, t, J = 10.25 Hz), 1.72 (3H, s), 1.64 (3H, s), 1.31 (3H, s); MS m/z 310 (M^+, 5), 292 (40), 99 (100), Found : C, 68.3; H, 9.72, $C_{18}H_{30}O_4$ requires C, 69.4; H, 9.75.

For 30a : Rf (hexane-ether, 1:1) 0.24; IR 3520, 3460, 3000, 1660, 1130-1050 cm^{-1}; NMR 5.17 (1H, m), ∿4 (5H, m), 2.77 (1H, br s), 2.37 (1H, br s), 2.25 (1H, t, J = 10 Hz), 2.04 (1H, dt, J = 3, 10 Hz), 1.72 (3H, s), 1.65 (3H, s), 1.27 (3H, s).

The perhydroazulenic lactones 31-33.

Ozone was led to a cooled (-78°C) soln of diol 29 (2.0 g; 6.5 mmol) in CH_2Cl_2 (2.5 ml) until the soln turned blue. Excess ozone was removed via a stream of nitrogen and to reaction mixture was added Me_2S (5 ml) at -78°C. After stirring for 30 min at room temperature, the soln was concentrated in vacuo and the residue taken in acetone (100 ml). To this cooled (-10°C) soln was added Jones reagent dropwise until the red colour persisted. After addition of isopropanol and $NaHCO_3$, the reaction mixture was concentrated, water was added to the residue and the aqueous phase extracted with CH_2Cl_2. Usual work-up, followed by chromatography (EtOAc-isooctane, 65:35), gave lactone 32 (1.45 g) in 80 % yield.

In a similar way 31 was obtained from diol 27 (80 % yield) and 33 from 30a (70 % yield) after chromatography (ether as eluent).

For 31 : Rf (ether) 0.2; m.p. 158°-160°C; IR 3450, 1795 cm^{-1}; NMR 4.52 (1H, dd, J = 9.5, 11 Hz), 4.02 (1H, m), 3.93 (3H, m), 2.73 (1H, ddd, J = 8.25, 10, 12.25 Hz), 2.60 (1H, ABX, J = 16.8, 7.5 Hz), 2.5 (br s, 1H), 2.28 (1H, ABX, J = 16.8, 12.5 Hz), 2.24 (1H, dd; J = 11.5, 12.5 Hz), 1.34 (3H, 5); MS m/z 282 (M^+, 4), 169 (8), 99 (100).

For 32 : Rf (ether) 0.18; m.p. 132-134°C; IR 3500-3400, 1785 cm^{-1}; NMR ∿4 (5H, m), 2.48 (1H, br s), 1.34 (3H, s); MS m/z 282 (M^+, 10), 254 (20), 99 (100); Found : C, 64.1; H, 7.80; $C_{15}H_{22}O_5$ requires C, 63.88; H, 7.86.

For 33 : Rf (ether) 0.25; IR 3600-3500, 1790 cm^{-1}; NMR 4.68 (1H, dd, J = 11, 7.5 Hz), ∿4 (4H, m), 2.86 (1H, ABX, J = 18, 9.5 Hz), 2.65 (1H, m), 2.44 (1H, t, J = 10.8 Hz), 2.24 (1H, ABX, J = 18, 4.25 Hz), 1.32 (3H, s); MS m/z 282 (M^+, 7), 223 (28), 99 (100).

Lactone 34.

A soln of keto-epoxide 23 (2.04 g; 7 mmol) was treated with lithium in liquid ammonia/NH_4Cl as described above. The crude diol 28 obtained after work-up was directly treated with ozone as described above. After Me_2S work-up, CH_3OH was added and the mixture stirred for 2 hrs. Purification by column chromatography (isooctane-ether, 1:1) gave lactol 35 (0.967 g) in 51 % overall yield.

For 28 : Rf (ether) 0.73; IR 3350, 1660 cm^{-1}; NMR 5.21 (1H, m), ∿4 (5H, m), 3.66 (1H, s), 2.75 (1H, s), 2.59 (1H, dt, J = 12, 8.5 Hz), 1.73 (3H, s), 1.65 (3H, s); MS m/z 296 (M^+, 1), 278 (13), 99 (100).

For 35 : Rf (ether) 0.28; IR 3550, 3400 cm^{-1}; NMR 5.52 (1H, t, J = 5 Hz), 5.43 (1H, d, J = 4.7 Hz); MS m/z 270 (M^+, 0.5), 252 (6), 237 (8), 155 (22), 99 (100).

To a cooled (0°C) soln of lactol 35 (94 mg;

0.35 mmol) in acetone (3 ml) was added dropwise Jones reagent till disappearance of the green color. After the addition of isopropanol and a satd soln of $NaHCO_3$, the mixture was worked-up with CH_2Cl_2. Column chromatography (isooctane-EtOAc, 2:3) gave lactone 34 (49 mg) in 53 % yield. Rf (EtOAc-isooctane) 4.1; IR 3530, 1795 cm^{-1}; NMR 4.46 (1H, t, J = 10 Hz), 4.09 (1H, br q, J = 7.5 Hz), ~3.95 (4H, m), 2.70 (1H, br, dt, J = 11.5, 9 Hz), 2.65 (1H, br s), 2.61 (1H, ABX, J = 16.8, 7.25 Hz), 2.28 (1H, ABX, J = 16.8, 12.25 Hz), 2.14 (1H, m).

Acknowledgments : We thank the N.F.W.O. and the "Ministerie voor Wetenschapsbeleid" for financial help to the laboratory. A.D. and M.D. are indepted to the I.W.O.N.L. for a graduate scolarship.

References

1. Research Associate of the National Fund for Scientific Research (Belgium).
2. N.H. Fischer, E.J. Olivier, H.D. Fischer, Fortschr. Chem. Org. Naturst. 38, 47 (1979).
3. K.-H. Lee, H. Furukawa, E.-S. Huang, J. Med. Chem. 15, 609 (1972).
4. C.H. Heathcock, S.L. Graham, M.C. Pirrung, F. Plavac, C.T. White, in "The Total Synthesis of Natural Products", vol. 5, J.W. Ap Simon, Ed., Wiley, New York, 1982.
5. See, e.g. : D.H.R. Barton, J.T. Pinhey, R.J. Wells, J. Chem. Soc., 2518 (1964); M. Suchy, V. Herout, F. Sorm, Collect. Czech. Chem. Comm., 29, 1829 (1964); E.H. White, G. Eguchi, J.N. Marx, Tetrahedron 25, 2099 (1969); M. Ando, A. Akahane, K. Tahase, Chem. Lett., 727 (1978); M.T. Edgar, A.E. Greene, P.J. Crabbé, J. Org. Chem. 44, 159 (1979); D.H.R. Barton, O.C. Böckman, P. de Mayo, J. Chem. Soc., 2263 (1960); M. Ogura, G.A. Cordell, N.R. Fainsworth, Phytochemistry, 17, 957 (1978).
6. A.A. Devreese, P.J. De Clercq, M. Vandewalle, Tetrahedron Lett., 21, 4767 (1980).
7. M. Demuynck, A.A. Devreese, P.J. De Clercq, M. Vandewalle, Tetrahedron Lett., 23, 2501 (1982).
8. G.H. Posner, K.A. Babiak, G.L. Loomis, W.J. Frazee, R.D. Mittal, I.L. Karle, J. Am. Chem. Soc., 102, 7498 (1980).
9. D. Termont, P. De Clercq, D. De Keukeleire, M. Vandewalle, Synthesis, 46 (1977).
10. P. De Clercq, M. Vandewalle, J. Org. Chem. 42, 3447 (1977); P. Kok, P. De Clercq, M. Vandewalle, Bull. Soc. Chim. Belg. 87, 615 (1978); P. Kok, P.J. De Clercq, M.E. Vandewalle, J. Org. Chem. 44, 4553 (1979); M. Demuynck, P. De Clercq, M. Vandewalle, J. Org. Chem. 44, 4863 (1979).
11. D.H.R. Barton, R.H. Hesse, M.M. Pechet, E. Rizzardo, J. Am. Chem. Soc. 95, 2748 (1973); P.A. Grieco, M. Nishizawa, T. Oguri, S.D. Burke, N. Marinovic, J. Am. Chem. Soc., 99, 5773 (1977); P.A. Grieco, S. Burke, W. Metz, M. Nishizawa, J. Org. Chem., 44, 152 (1979).
12. cf. H.O. House in "Modern Synthetic Reactions", 2nd Ed., p. 156-158, Ed. W.A. Benjamin, 1972.
13. E.M. Burgess, H.R. Penton, Jr., E.A. Taylor, J. Org. Chem., 38, 26 (1973).
14. N.C. Yang, R.A. Finnegan, J. Am. Chem. Soc., 80, 5845 (1958).
15. E.J. Corey, H.E. Ensley, J. Org. Chem., 38, 3187 (1973).
16. E. Toromanoff, Tetrahedron, 36, 2809 (1980).
17. E.S. Binkley, C.H. Heathcock, J. Org. Chem., 40, 2156 (1975).
18. P.J. De Clercq, J. Org. Chem. 46, 667 (1981).
19. M. Samson, P. De Clercq, M. Vandewalle, Tetrahedron, 31, 1233 (1975); Ibid., 33, 249 (1977).
20. J.P. Declercq, G. Germain, M. Van Meerssche, A. Devreese, P. De Clercq, M. Vandewalle, Bull. Soc. Chim. Belg., 90, 167, 899 (1981).