DICRANENONES – A NEW CLASS OF C_{18} POLYUNSATURATED FATTY ACIDS

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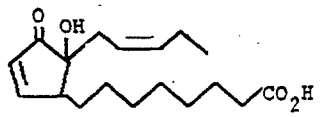
In this review paper we consider questions of the occurrence in nature and the biosynthesis and total chemical synthesis of the dicranenones – new cyclopentanoid C_{18} polyunsaturated fatty acids. A critical evaluation of the stereochemical assignments in this series of compounds is given.

NATURAL SOURCES AND BIOSYNTHESIS OF THE DICRANENONES

In 1981, in a study of extracts of the epigeal parts of Brazilian chrysanthemums of the species Chromoleana morii K. et R., a group of workers from the USA and the FRG isolated a compound to which, on the basis of spectral characteristics and a study of the products of periodate oxidation, they ascribed structure **1**. They called this compound chromoric acid [1].



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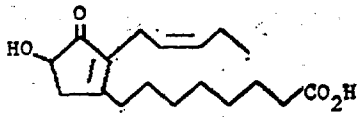

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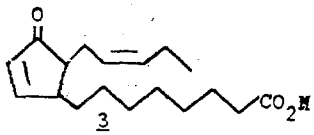
Subsequently, the same authors isolated compound **2** [2] from a chrysanthemum of the species Chromolaena chaslease K. et R., and compounds **3**, and **4** from a chrysanthemum of the species Chromolaena morii [3].



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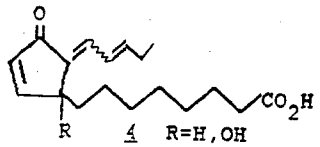
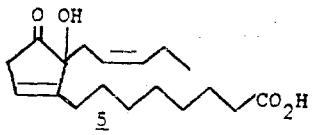


4 R=H, OH



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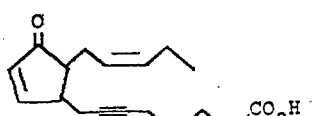
In 1983, a group of Japanese authors reported the isolation, from Japanese mosses of the species Dicranum japonicum and Dicranum scoporium, of compounds **6** and **7**, which were called dicranenone A and dicranenone B_1, respectively [4].



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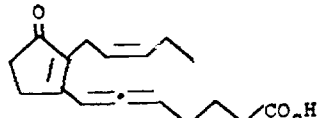

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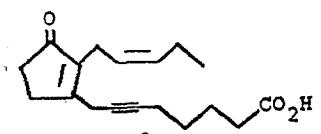
Subsequently, the same authors reported the isolation of dicranenones **8**, **9** and **10**, and also **3**, **6**, and **7** from Japanese mosses of the species Dicranum scabrum, Leucobryum scabrum, Dicranoloma scabrum, and Dicranum majus [5, 6].



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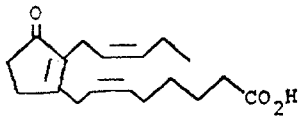

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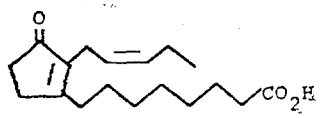

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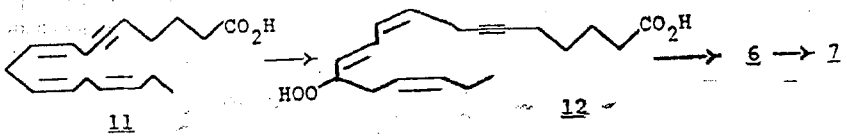
At the present time, 14 compounds of this class have been isolated. A mechanism has been suggested for the biosynthesis of the dicranenones from hexadeca-9Z,12Z,15Z-trien-6-ynoic acid **11**, found as the main component of Japanese mosses [6].

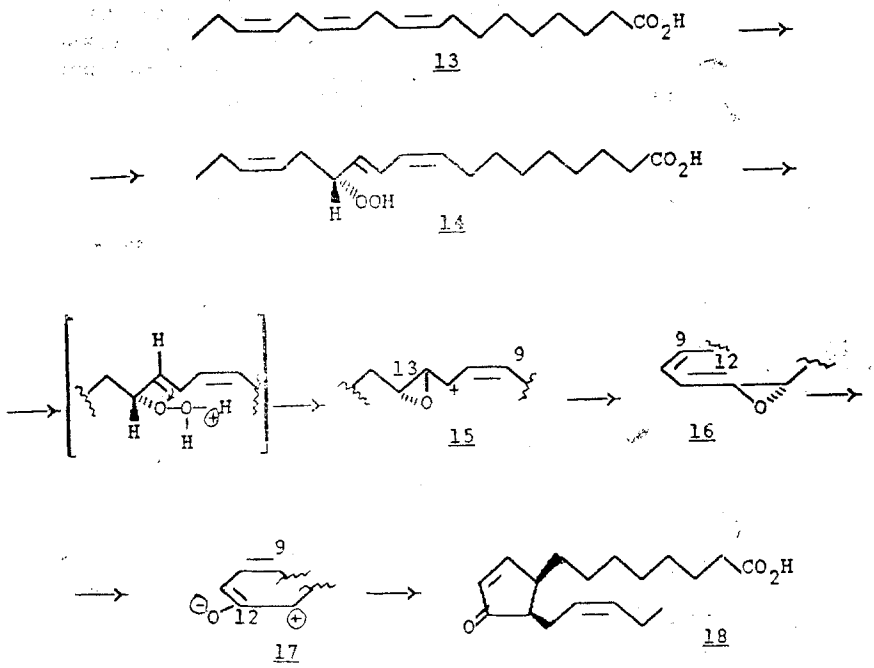


11 **12**

The unsaturated fatty acid **11** is attacked by a lipoxygenase, giving the hydroperoxide intermediate **12**, which, under the action of a cyclase, is cyclized to dicranenone A, **6**. The The conversion of dicranenone A, **6**, into the dicranenone is also, apparently, catalyzed by an enzyme.

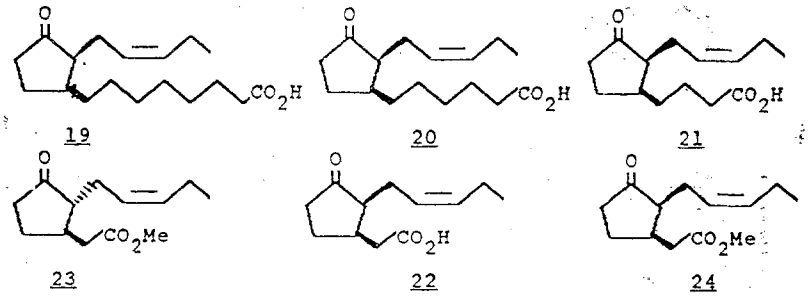
Investigations by Zimmerman et al. showed that the enzyme isomerase isolated from flax seeds is capable of converting linolenic acid **13** into 12-oxophytodienic acid **18** [7-12].

Crombie and Morgan [13, 14] showed that the process takes place through the protonation of the hydroperoxide **14**, and the rearrangement of the resulting protonated epoxide **15** into the allenic epoxide **16**, the ring-opening of which gives the zwitter-ion **17**, cyclizing into 12-oxophytodienic acid **18**.



13 **14** **15** **16** **17** **18**

The important role of 12-oxophytodienic acid in plant physiology has been confirmed by the detection of a cascade of products formed in the enzymatic reduction and the β-oxidation of the acid **18** [15, 16]. These products include 3-oxo-2-cis-(pent-2Z-enyl)cyclopentyloctanoic acid **20**, 3-oxo-2-cis-(pent-2Z-enyl)cyclopentylhexanoic acid **19**, 3-oxo-2-cis-(pent-2Z-enyl)-cyclopentylbutanoic acid **21**, and epi-jasmonic acid **22**.

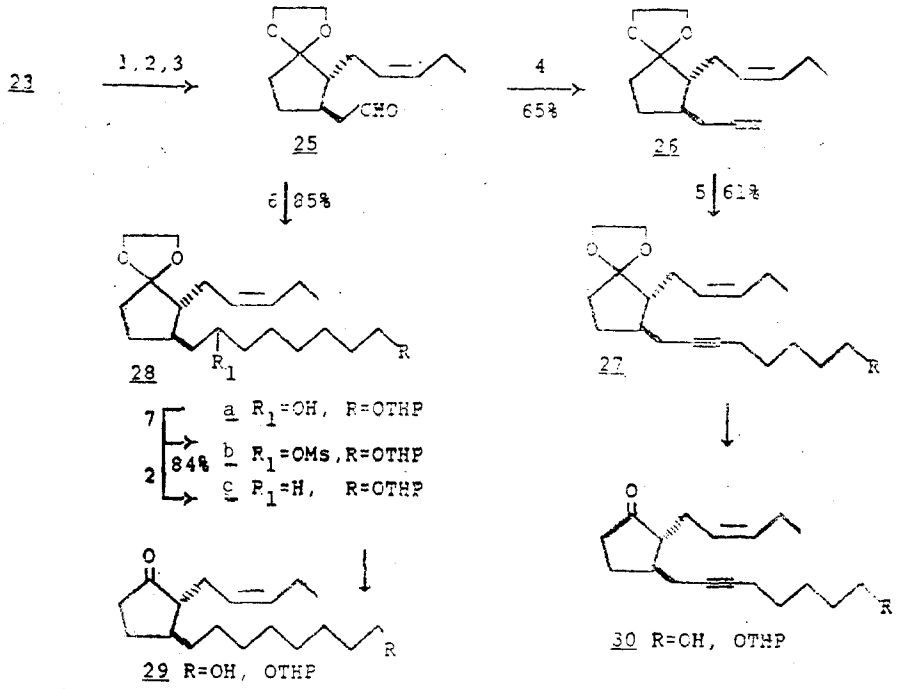


19 **20** **21** **23** **22** **24**

It is interesting to note that although many efforts of chemists have been directed to the synthesis of the trans-jasmonate **24** with the aim of its use in perfumery, it has recently been established that the base of the aroma is due almost completely to methyl (+)-cis-Z-jasmonate **24** [17, 18].

CHEMICAL SYNTHESIS OF THE DICRANENONES

The chemical synthesis of dicranenone A, **6** , and of tetrahydrodicranenone A, **3** , has been undertaken by a group of Japanese researchers using two approaches [5]. The first method was based on the transformation of the side-chains and the cyclic part of methyl jasmonate **23**. The unusual inertness of the acetylene **26** in relation to the alkylation reaction was overcome with the aid of the trialkylborane B $[(CH_2)_5OTHP]_3$ as alkylating agent, with subsequent oxidation of the intermediate boron derivative under the action of iodine. At the same time, treatment of the aldehyde **25** with a Grignard reagent led to the hydroxy derivative **28a**. The hydroxylic function was successfully eliminated by successive treatment with methanesulfonyl chloride in pyridine and the tetrahydroaluminate reduction of the resulting O-methanesulfonate **28b** , giving compound **28c**.



1. $(CH_2OH)_2$, p-TsOH, 70%
2. $LiAlH_4$, 70%
3. Py/CrO_3-HCl/NaOAc, 84%
4. $Ph_3PCH_2Br_2$, t-BuOK, THF, -78°C
5. a) n-BuLi, THF, 0°C
   b) $B[(CH_2)_5OTHP]_3$
   c) I_2, Et_2O, -78°
6. $BrMgC_6H_{12}OTHP$, THF, Δ
7. MsCl/Py, CH_2Cl_2, 83%
8. a) CH_3COOH, H_2O, THF, 45°C
   b) 2,3-dihydropyran, p-TsOH, 20°C

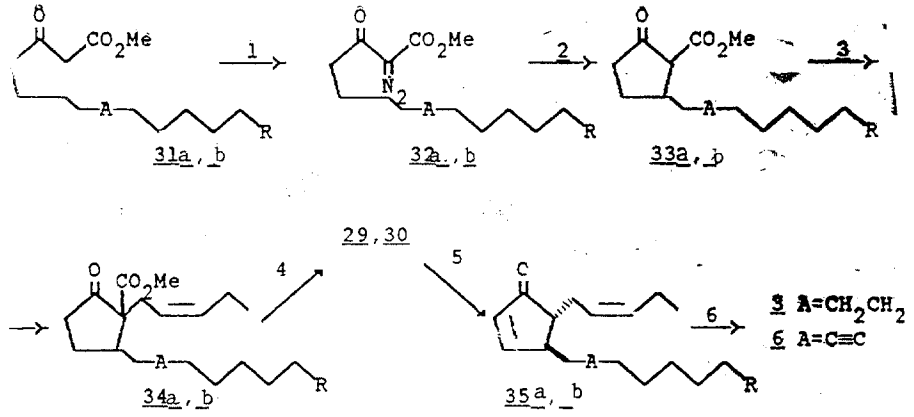
The elimination of the protective groups of compounds **27**, and **28c** with the subsequent reprotection of the hydroxylic functions in the form of the THP ethers led to products **29** and **30**.

According to the same authors [5], compounds **29** and **30**, were obtained by an alternative method from acyclic precursors. Thus, alkylation of methyl acetoacetate with the appropriate C_{10} bromide under the action of two equivalents of a base led to products **31a**, and b with yields of 72 and 71%, respectively.

Diazotization in the α-position of the β-keto ester followed by cyclization of the resulting diazo compounds **32a**, and b gave the corresponding cyclopentenones **33a**, and b. The alkylation of these compounds took place in the α-position, leading to products **34a**, and b. The

methoxycarbonyl groups were eliminated under mild conditions, giving the key compounds 29 and 30, , identical with the products obtained from methyl jasmonate.

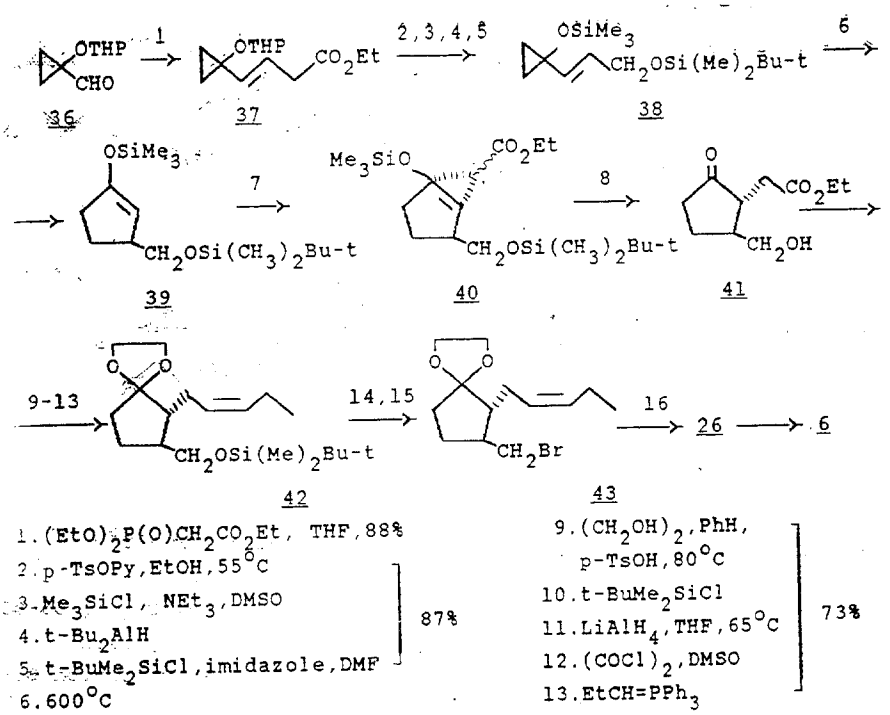
The corresponding dicranenones 3 and 6 were then synthesized from these key synthones by known methods through phenylselenation in the α-positions to the keto groups, followed by the oxidation of the phenyl selenides to the enones 35a, and b. The elimination of the THP protective groups from the terminal hydroxylic functions and their Jones oxidation led to the desired dicranenones 3 and 6.



a A=C≡C R=OTHP
b A=CH_2CH_2 R=OTHP

1.p-$TosN_3$/NEt_3,CH_3CN] 74-87%
2.1-3% $Rh_2(OAc)_4$,CH_2Cl_2]
3.t-BuOK, $BrCH_2CH{=}CHC_2H_5$, $PhCH_3$, Δ, 68-85%
4.NaCN,HMPA, 75°C, 67-75%
5.a)LDA,THF,-78°C
b)PhSeCl
a)H_2O_2/Py,CH_2Cl_2,55-65%
6.b) CH_3OH, p-TsOH
c) Jones oxidation,82-94%

The biotesting of the racemic products obtained showed that they exhibited moderate antihypertensive activity.



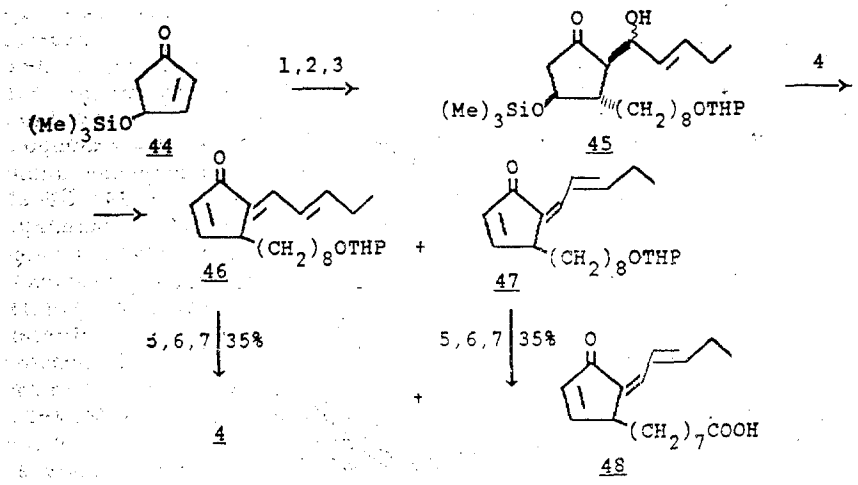
1.$(EtO)_2P(O)CH_2CO_2Et$, THF,88%
2.p-TsOPy,EtOH,55°C
3.Me_3SiCl, NEt_3,DMSO
4.t-Bu_2AlH
5.t-$BuMe_2SiCl$,imidazole,DMF
6.600°C
] 87%

9.$(CH_2OH)_2$,PhH, p-TsOH,80°C
10.t-$BuMe_2SiCl$
11.$LiAlH_4$,THF,65°C
12.$(COCl)_2$,DMSO
13.$EtCH{=}PPh_3$
] 73%

7. $Cu(MeCOCHCOMe)_2$, PhH, 80°C, $N_2CHCO_2C_2H_5$, 75%
8. Me_3SiCl, MeOH, 20°C, 97%
14. p-TsCl, Py, 0°C
15. LiBr, Me_2CO, Δ
16. $LiC{\equiv}CH$, $NH_2(CH_2)_2NH_2$, DMSO, 85%
] 75%

French authors have proposed a method of synthesizing dicranenone A from cyclopropane derivatives [19]. The interaction of the carbanion of triethyl phosphonoacetate [$(Eto)_2P(O)$-CH_2CO_2Et] with the aldehyde **36** gave the trans-vinylcyclopropane **37**. Hydrolysis of the THP ether grouping followed by silylation, reduction of the ester group to an alcohol group, and the introduction of tert-butyldimethylsilyl protection at the allyl alcohol groupings led to the trans-disilyloxyvinylcyclopropane **38**. On flash thermolysis (600°C), the ring expanded, with the formation of a silyl ether of the enolic form of a cyclopentanone **39**. Treatment of the latter with ethyl diazoacetate gave the cyclopropane **40**. Desilylation of compound **40** and and regiospecific cleavage of the cyclopropane ring led to the γ-keto ester **41**. Protection of the carbonyl and hydroxy groups of compound **41**, and reduction of the ester group to an alcohol group followed by its oxidation to an aldehyde group and the Wittig reaction with propylidenetriphenylphosphorane led to the ketal **42**. The subsequent replacement of the protected hydroxylic function by bromine via the corresponding tosyl derivative gave the bromide **43**. Acetylation of the bromide **43** led to the above-described cyclopentanone **26**. The passage from this compound to dicranenone A was achieved by the method described in [5].

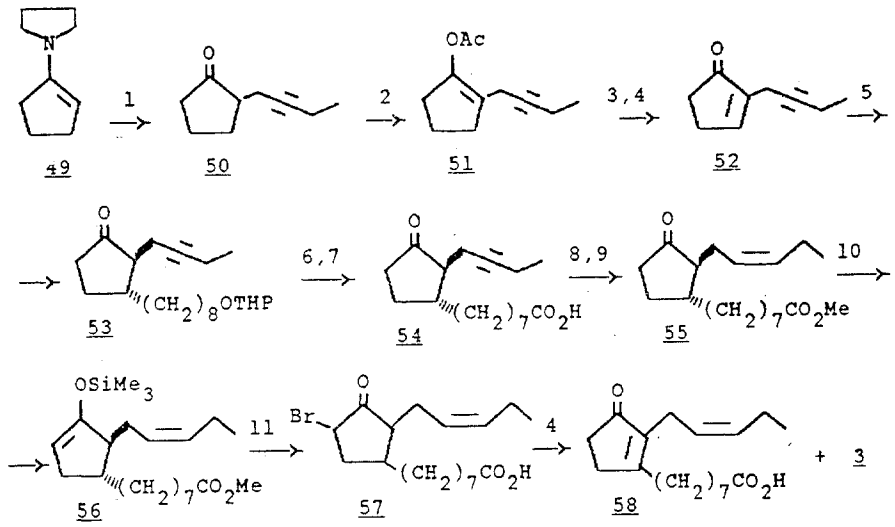
A group of German chemists has proposed a short synthesis of dicranenones containing a dienic system in the ω-chain on the basis of a so-called "three-component coupling process" [20].



1. $ClMg(CH_2)_8OTHP$, CH_2I_2
2. $EtCH{=}CHCHO$, THF, -45°C
3. -78°C
4. Bu_4NF, MsCl, NEt_3
5. p-TsOH, MeOH
6. Py/CrO_3-HCl, NaOAc, CH_2Cl_2
7. Jones oxidation

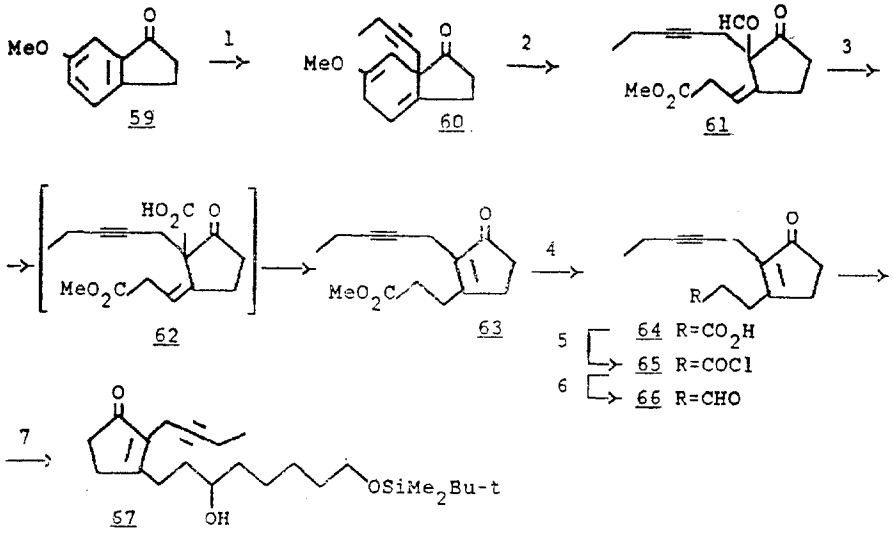
Interaction of the cyclopentenone **44** with a Grignard reagent followed by treatment of the enolate so formed with pent-2E-enal led to compound **45**. Treatment of compound **45** successively with tetrabutylammonium fluoride, methanesulfonyl chloride, and triethylamine gave the cyclopentenone **46**, containing a dienic system with the 14E orientation in the ω-chain. Its formation was accompanied by the apearance of about 10% of the 14Z isomer, **47**. The subsequent oxidation of compounds **46** and **47** led to the dicranenones **4** and **48**. In the course of this work the incorrect assignment made previously [3] for the geometry of the dienic system of compound **48** was rectified.

A synthesis of the tetrahydrodicranenones A and B was proposed by the same authors [20], which started from the cyclopentanone enamine **49**. Alkylation of the latter with a halogenopent-2-yne led to the cyclopentanone **50**. The introduction of the required double bond into the ring was achieved by the bromination of the corresponding enol acetate **52**, followed by the elimination of HBr and the formation of the cyclopentenone **52**. Interaction of cyclopen-



1. $HalCH_2C{\equiv}CC_2H_5$
2. p-TsOH, Ac_2O, 86%
3. Br_2, $CaCO_3$, $CHCl_3$] 66%
4. LiBr, $LiCO_3$, DMF]
5. $ClMg(CH_2)_8OTHP$, Cu_2I_2
6. Amberlist-H-15, MeOH]
7. Jones oxidation] 91%
8. CH_2N_2]
9. H_2, Lindlar catalyst] 81%
10. $LiN(SiMe_3)_2$, Me_3SiCl, 97%
11. NBS

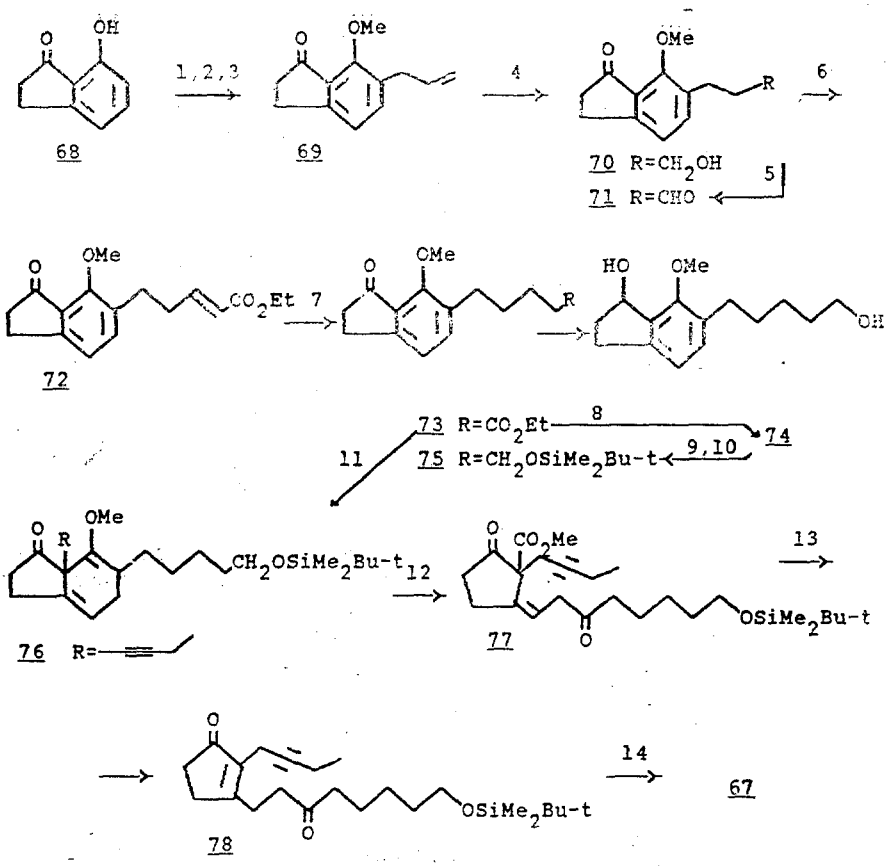
tenone with the appropriate Grignard reagent gave the trans-disubstituted cyclopentenone **53**. Hydrolysis of the THP-protected grouping of compound **53** followed by Jones oxidation led to the acid **54**. Treatment of the latter with diazomethane and reduction of the triple bond on Lindlar catalyst gave compound **55** with good yield. Bromination of the enolic silyl ether **56**, obtained from cyclopentanone **55**, led to the 11-bromoketone **57**, which was converted into the methyl ester of tetrahydrodicranenone A, **3** , after the splitting out of HBr, together with 39% of the corresponding tetrahydrodicranenone B, **58**, formed as a consequence of a migration of the double bond during the reaction.



1.a) K, NH_3, t-BuOH, -78°C
b) LiBr, $ICH_2C{\equiv}CC_2H_5$
2.a) O_3, MeOH
b) Zn, AcOH
3. Jones oxidation, 29%
4. KOH, MeOH, H_2O
5. $(CH_3)_2\overset{+}{N}Cl^{-}{=}CHCl$, PhH
6. $LiAlH(t\text{-}BuO)_3$, THF] 38%
7. $BrMg(CH_2)_5OSiMe_2t\text{-}Bu$, THF]

A group of British chemists have carried out the synthesis of natural tetrahydrodicranenone B, **58**, starting from 6-methoxyindanone, **59** [21-23]. The reductive alkylation of 6-meth-

oxyindanone, **59** , under the conditions of the Birch reaction led to the dihydroindanone **60**. The subsequent selective cleavage of the double bond of the vinyl ester led to the aldehyde **61**. This was immediately oxidized by the Jones method to the acid **61**, which underwent spontaneous decarboxylation with the migration of the double bond from the side-chain into conjugation with the keto group of the ring, giving the cyclopentenone with an overall yield of 29% [21, 22]. Passage from the ester group in the α-chain to an aldehyde group by direct reduction proved difficult, and therefore the ester **62**, was hydrolyzed to the acid **64**, which was converted into its chloride **65**, and this was reduced to the aldehyde **66**. Addition of the appropriate Grignard reagent to the aldehyde **66** gave the alcohol **67**.



1. $BrCH_2CH=CH_2, K_2CO_3, THF$
2. $PhNMe_2, \Delta$
3. $Me_2SO_4, NaOH, H_2O$
4. a) BH_3, THF
   б) $NaOH, H_2O_2$, 96%
5. DMSO, $(COCl)_2, CH_2Cl_2$, $-60^\circ C$, 86%
6. $Ph_3P=CHCO_2Et$, THF, 83%
7. H_2, Pd/C, MeOH, 95%

78%

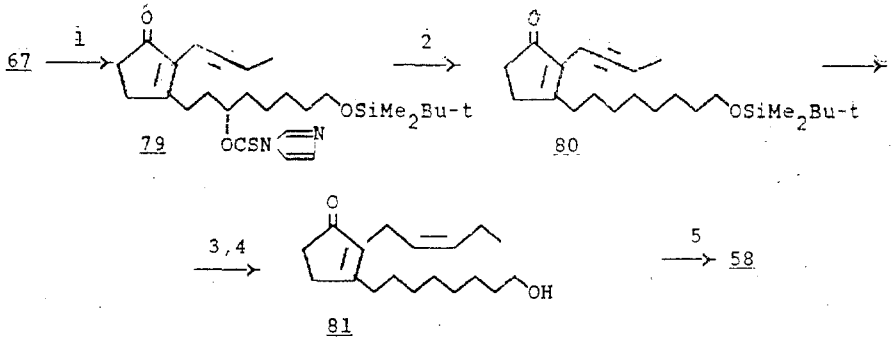
8. $LiAlH_4, Et_2O$
9. MnO_2, CH_2O_2

69%

10. t-$BuMe_2SiCl$, $(i\text{-}Pr)_2NEt$, DMF, 98%
11. a) K, NH_3, t-BuOH, THF, $-78^\circ C$
    b) LiBr, $BrCH_2C{\equiv}CEt$, 42%
12. a) O_3, MeOH
    b) Zn, AcOH, 77%
13. LiI, 2,3-dimethylpyridine, H_2O, 34%
14. $LiAlH(t\text{-}BuO)_3$, THF, 43%

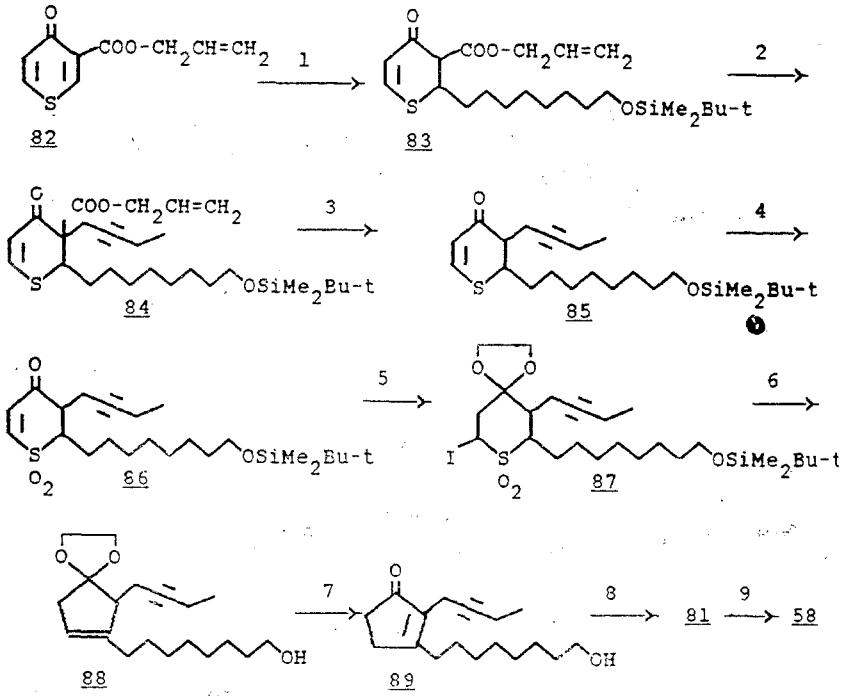
The same compound was obtained by an alternative method from 7-hydroxyindanone, **68**. This was converted into 6-allyl-7-methoxyindanone, **69** , via the O-allyl ether, followed by O—C isomerization and methylation. The hydroboration of the allyl double bond of compound **70**, under strictly controlled conditions led to the alcohol **69** , which was oxidized by Swern's method to the aldehyde **71**. The Wittig olefination of aldehyde **71** led to the alkene **72**, the hydrogenation of which over Pd/C gave the saturated ester **73**. Reduction of the ester to the diol **74** followed by selective oxidation of the secondary alcohol group to a ketone and protection of the primary alcohol group in the form of a silyl ether led to the indanone **75**. Its Birch reduction and subsequent alkylation gave the dihydroindanone **76**, ozonolysis of which led to the cyclopentanone **77**. The splitting out of the methoxycarbonyl group, accompanied by double-

bond migration gave the ketone **78**, which was selectively reduced to the alcohol **67**. Elimination of the alcohol group from position 6 was effected by the radical reduction of the intermediate thiocarbonylimidazolide **79** with tributyltion hydride in the presence of azoisobutyronitrile. The acetylenic bond of the cyclopentenone **80** so obtained was reduced to an olefinic bond, and the silyl protective group was then hydrolyzed off. The alcohol so formed, **81**, could not be oxidized by the Jones reagent, and oxidation was effected with oxygen over Adams catalyst, giving tetrahydrodicranenone B, **58** [23].



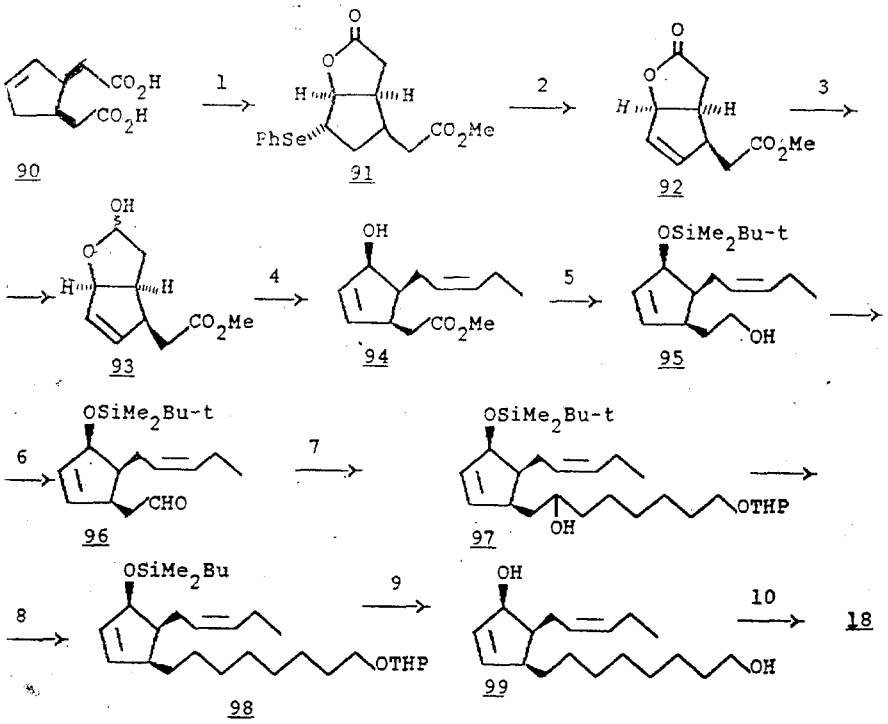
1.1,1'-thiocarbonyldiimidazole
2.Bu_3SnH,aroisobutyronitrile] 33%
3.H_2,Pd/$BaSO_4$
4.AcOH,H_2O,THF] 50%
5.Pt,O_2,$(CH_3)_2CO$, 96%

The synthesis of tetrahydrodicranenone B by means of the Ramberg-Bäcklund reaction has been described by Casy and Taylor [24]. As the starting material they used 3-allyloxycarbonylthiin-4-one, **82**. The conjugate addition of an organocopper reagent gave the 2-substituted β-keto ester **83**, which was alkylated with 1-bromopent-3-yne to give compound **83**. The latter was then decarboxylated to the 2,3-disubstituted derivative **85**.



1.$BrMg(CH_2)_8OSiMe_2t$-Bu,CuBr·Me_2S,60%
2.NaH,$BrCH_2C{\equiv}CC_2H_5$, 82%
3.5% $Pd/(PPh_3)_4$-morpholine, 93%
4.m-chloroperbenzoic acid, 83%
5.Me_3SiI, $(CH_2OH)_2$, H^+, 65%
6.KOt-Bu, -78°C, 65%
7.5% HCl, 95%
8.H_2,10%Pd/C, 85%
9.Pt,$O_2(CH_3)_2CO$,85%

The oxidation of sulfide 85 to sulfone 86 with m-chloroperbenzoic acid followed by the Michael addition of iodine gave the iodosulfone 87. On treatment with potassium tert-butoxide, the Ramber-Bälund precursor so obtained gave the protected cyclopent-3-enone 88, the hydrolysis of which led to the Δ^2-enone 89. The catalytic hydrogenation of this compound gave the Z-alkene 89 contaminated with the E-isomer and with the product having a saturated side-chain. [81] The authors did not carry out the subsequent conversion of compound 81, into tetrahydrodicranenone B, [58] referring to the method described in [21].



1. a) PhSeCl, THF
   b) CH_2N_2, 75%
2. a) H_2O_2, THF
   b) KOH, MeOH, 92%
3. $(i\text{-Bu})_2AlH$, -45°C
4. a) $Ph_3P{=}CHEt$, DMSO, 70°C
   b) CH_2N_2
5. a) t-$BuMe_2SiCl$, DMF, imidazole
   b) $(i\text{-Bu})_2AlH$, THF, -78°C, 94%
6. Pyridinium dichromate, CH_2Cl_2, 78%
7. $BrMg(CH_2)_6OTHP$, THF, 92%
8. a) MsCl, Py,
   b) $LiAlH_4$, Et_2O, Δ, 88%
9. a) Bu_4NF, THF, 45°C
   b) Pyridinium toluene-p-sulphonate 56%
10. Pyridinium dichromate, DMF, 20°C 20%

The first synthesis of 12-oxophytodienic acid, 18, was proposed by British chemists in 1988 [25]. The lactonization of the cis-cyclopentenediyldiacetic acid, 90, with the introduction of a double bond by selenation, followed by oxidation, gave the unsaturated lactone 92. Reduction of lactone 92 to lactone 93 and introduction of the latter, without purification, into the Wittig reaction with propylidenetriphenylphosphorane led to the cyclopentenone 94, in the form of a mixture of Z- and E-isomers in a ratio of 85:15. The protection of the alcoholic group in the form of a allyl ether permitted the separation of the isomeric mixture, and the pure Z-isomer was reduced to the alcohol 95. The oxidation of the alcohol 95 so obtained to the aldehyde 96 and treatment with the appropriate Grignard reagent led to compound 97, which was produced in the form of a pair of diastereomers. Treatment of compound 97 with methanesulfonyl chloride and subsequent demesylation and elimination of the protective groups gave the diol 99. The oxidation of this diol, followed by esterification, led to methyl 12-oxophytodienate 18. According to the authors, in its PMR spectrum and chromatographic mobility this compound was identical with a specimen obtained by enzymatic synthesis. At the same time, it was shown that the trans-isomer that was formed on the acid treatment of compound 18, differed chromatographically and spectrally from the natural cis-isomer. It

is quite obvious that this trans- isomer is natural tetrahydrodicranenone A, 3, but, unfortunately, the Crombie and Mistry [25] did not give any spectral characteristics whatever.

It must be mentioned that there are disagreements in the literature about the stereochemistry of a series of natural and synthetic dicranenones and compounds related to them. Thus, the mutual cis-orientation of the α- and ω-chains of 12-oxophytodienic acid, 18, must be regarded as proved, even though from the information about the PMR spectrum given in the literature it is known only that the chemical shift of the proton at C-13 is 2.44 ppm [13, 25]. At the same time, complete details of the PMR spectrum have been given for tetrahydrodicranenone A, 3 , and these reliably show that the mutual trans-orientation of the α- and ω-chains for this compound [3]. This is demonstrated by the SSCC of the protons at C-9 and C-13, which is 2.0 Hz [26], the chemical shifts of these protons being 2.57 and 2.00 ppm, 18 respectively. Thus 12-oxophytodienic acid and tetrahydrodicranenone A, 3 , are stereoisomers.

The Japanese authors who first isolated dicranenone A, 6 , from Japanese mosses, gave detailed spectral characteristics for this compound and, in particular, interpreted the PMR spectrum (400 MHz) completely; however, on the basis of these results they drew the incorrect – in our opinion – conclusion of the trans-orientation of the α- and ω-chains [4, 5]. In the opinion of Ichikawa et al. [4], based on a comparison of angles of rotation and circular dichroism spectra, the stereochemical assignments of the two chiral centers at C-9 and C-13 are analogous to those for prostaglandins of the A series. At the same time, the SSCC of the protons at C-9 and C-13, which is 6.0 Hz, and also the chemical shifts of these protons, which are 3.18 and 2.43 ppm, unambiguously show the mutual cis-orientation of these protons. Thus, according to its PMR spectrum, dicranenone A, 6 , is an acetylenic analog of 12-oxophytodienic acid, 18, and is biosynthetically closer to it than is tetrahydrodicarenone A, 3.

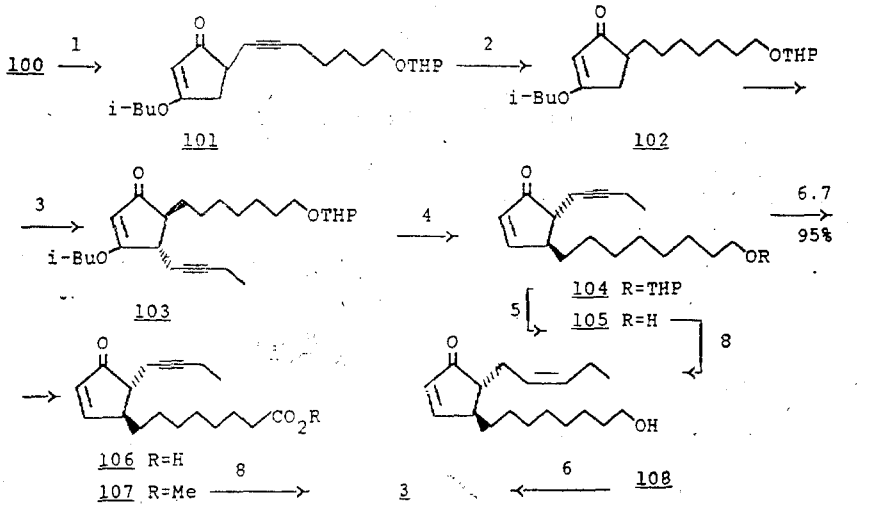
The scheme of synthesis of dicranenone A, , given by the same authors [5] and based on methyl jasmonate, 23 , as the initial compound naturally leads to an end-product with the trans orientation of the α- and ω-chains [4, 5]. An alternative route proposed by the authors leads to intermediates in common with the first scheme. Without giving spectral characteristics, the authors report that the dicranenone A synthesized and also the tetrahydrodicranenone A were completely identical with the natural products according to their IR, PMR, and mass spectra and retention times in HPLC. It is possible to agree with such a statement in relation to tetrahydrodicranenone A, 6 , while this conclusion is a matter of doubt in relation to dicranenone A, 9 .

Olivier and Salaiin [19] have described an approach to the synthesis of dicranenone A, but, again, they give no spectral charcteristics whatever.

We have proposed a convergent method of synthesizing dicranenones that is based on the regio- and stereoselective alkylation of the isobutyl enol ether of cyclopentane-1,3-dione with the appropriate halogen-substituted alkynes and alkenes [27]. The basis of this approach consists in the successive introduction of functionalized side-chains into positions 4 and 5 of the enol ether of cyclopentane-1,3-dione by the use of lithium diisopropylamide (LDA) [28] and lithium bistrimethylsilylamide (LBTMSA) as bases. Subsequent reductive and oxidative transformations permit the production of a series of natural dicranenones and also of their analogs with different degrees of unsaturation of the side-chains.

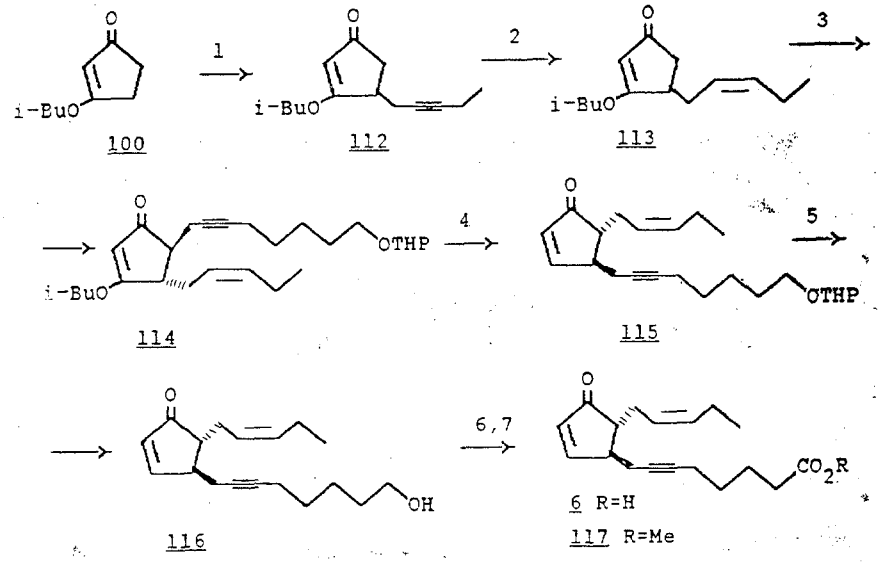
In the first stage, the enol ether 100 was alkylated in the α'-position, giving compound 101, the hydrogenation of which followed by the alkylation of the enol ether 102 in the γ-position led to the vicinally substituted enol ether 103. On reduction of the latter, followed by the elimination of the protective group, the alcohol 105, was obtained, and its further transformatino into (±)-tetrahydrodicranenone A, 3 , presented no difficulties and was achieved by two routes. The oxidation of the terminal hydroxy group of compound 105 by the Jones reagent gave the acid 106, which, after treatment of the reaction mixture with diazomethane, was isolated in the form of its methyl ester 107 . Hydrogenation of the ester 107 then led to the methyl ester of (±)-tetrahydrodicranenone A, 3 [29, 30]. The other route for the passage from alcohol 105 to (±)-tetrahydrodicranenone A, 3 , included the initial reduction of its triple bond to a cis-double bond and the oxidation of the hydroxy group in compound with the Jones reagent. As a result, the ester of 108 identical with that produced by the first method, was obtained [29].

In order to pass to tetrahydrodicranenone B, 111 , the alcohol 105 was stirred with the ion-exchange resin Amberlite-IRA-400 (in the OH^- form) in methanol, giving the 2,3-disubstituted cyclopentenone 109. The oxidation of this compound with the Jones reagent yielded the



1.$LiN(i\text{-}Pr)_2$,THF,-78°C,
$ICH_2C{\equiv}C(CH_2)_5OTHP$, 47%
2.10% Pd/C, 100%
3.$[(CH_3)_3Si]_2NLi$, THF,
-78°C,$ICH_2C{\equiv}CC_2H_5$, 59%

4.$AlH(i\text{-}Bu)_2,C_6H_{14}$,-70°C
5.CH_3COOH,H_2O,40°C, 90%
6.Jones oxidation
7.CH_2N_2
] 86-95%
8.Lindlar catalyst, 95-100%
9.Amberlite-IRA-400(OH^-),MeOH,100%



1.$[(CH_3)_3Si]_2NLi$, THF,
-78°C,$ICH_2C{\equiv}CC_2H_5$, 47%
2.H_2,Lindlar catalyst, 100%
3.$LiN(i\text{-}Pr)_2$,THF,-78°C,
$ICH_2C{\equiv}C(CH_2)_5OTHP$, 65%

4.$AlH(i\text{-}Bu)_2,C_6H_{14}$,-70°C, 98%
5.CH_3COOH,H_2O,40°C
6.Jones oxidation
7.CH_2N_2

acid **110**. Subsequent hydrogenation of the acid over Lindlar catalyst in the presence of quinoline led to the tetrahydrodicranenone **111**, the methyl ester of which, **58**, was formed when the reaction mixture was treated with diazomethane. Another method for using compound **109** presupposes the reduction of the acetylenic bond over Lindlar catalyst with the formation of the olefinic alcohol **81**. which has been described previously [23], followed by oxidation with the Jones reagent to the acid **111** [31].

To obtain dicranenone A, the enol ether **100** was alkylated with 1-iodopent-2-yne using LBTMSA as base. The reaction took place nonselectively, giving a mixture of α'- and γ-substituted products from which the product of γ-alkylation, **112**, was isolated with a yield of 47%. Reduction of the acetylenic bond to an olefinic bond and alkylation of the enol ether **113** in the α'-position led to the vicinally substituted product **114** with the trans position of the introduced substituents. The reduction of the enol ether grouping gave the enone **115**, and elimination of the THP protective group the alcohol **116**, which was oxidized to the acid , isolated in the form of its methyl ester **117** with an overall yield of 80%, calculated on the 1 4 [28, 31].

It must be mentioned that the PMR spectrum of compound **106** differed somewhat from the PMR spectrum obtained by Ichikawa et al. [4] for the methyl ester of natural dicranenone A. From the results of [5], the trans-configura5tion of the side-chains as ascribed to dicranenone A. In [4], chemical shifts and SSCCs are given for all the protons of the molecule of natural dicranenone A. These facts and, in particular, the value of the vicinal SSCC of the methine portions at C-4 and C-5, which is 6 Hz, show the cis-orientation of these protons and, consequently, the cis-orientation of the side-chains. For compounds with the trans-orientation of the side chains in cyclopentenones, this constant does not usually exceed w.0 Hz [32]. This follows from the fact that in the case of the trans-orientation of the substituents the dihedral angle between the protons at C-4 and C-5 is close to 90°C. In our case, the trans-orientation of the side-chains in compound **117** is shown by a SSCC of 1.8 Hz for the protons at C-4 and C-5. In addition to this, the trans-orientation of the side-chains is confirmed by the general stereodirectivity of alkylation reactions of enol ethers of cyclopentane-1,3-diol on the use of the two bases LDA and LBTMSA [33, 34], and also by the close values of the SSCCs of these protons in all the cyclopentenones that we have obtained previously [32, 34-37]. The difference in the stereochemistries of the α- and ω-chains in the methyl ester of natural dicranenone A and the compound **117** that we have obtained explains certain differences in the chemical shifts and multiplicities of the proton signals in the PMR spectra of these compounds.

Thus, it follows from what has been said above that natural dicranenone A apparently has the cis-orientation of the side-chains, while compound **117** that we have synthesized is its analog with the trans-orientation of the α- and ω-chains and may be called (±)-trans-dicranenone A.

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