REVIEW PAPER

The Trachylobane Diterpenes

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The natural occurrence, biosynthesis, chemistry and synthesis, spectroscopic properties and bioactivity of the trachylobane diterpenes have been reviewed.

Keywords: Diterpenes; trachylobane; natural cyclopropane derivatives; spectroscopic properties.

INTRODUCTION

Tetracyclic diterpenes such as *ent*-kaur-16-ene (4), *ent*-beyer-15-ene (5) and *ent*-atis-16-ene (6) are an important group of natural diterpenes. The trachylobane family is related to these compounds and characterized by a pentacyclic carbon skeleton (7) with a tricyclo 3,2,1,0 octane system for the rings C, D, and E. Some authors, using the nomenclature proposed by Rowe (1968), have named this series as *ent*-13,16-cycloatisane. In this paper we have reviewed the natural occurrence, isolation, biosynthesis, chemistry, spectroscopic properties and bioactivity of the trachylobane class of diterpenes.

THE NATURAL SOURCES

All the trachylobane diterpenes isolated so far belong to the *enantio* series. The first diterpenes of this type were found in the resin of *Trachylobium verrucosum* (Leguminosae) by a group led by Professor G. Ourisson (Hugel *et al.*, 1965a, b). This plant is a tropical tree from East Africa and Madagascar. The French authors isolated trachyloban-18-ol (8), trachyloban-18-oic acid (9) and 3 α -hydroxy-trachyloban-18-oic acid (10) from this source. In 1970, Pyrek obtained trachyloban-19-oic acid (13) from *Helianthus annuus* (sunflower) (Pyrek, 1970). Subsequently other species of the Compositae family have been studied. The trachylobane diterpenes which have been isolated so far from the genus *Helianthus* are given in Table 1. Trachylobanic acid (13) and its 9,11-dehydro derivative 19 have been found in *Viguiera bishopii* (Bohlmann *et al.*, 1981). Another species of this genus, *V. pazensis*, contains the trachylobane derivatives 12–18 (Bohlmann *et al.*, 1984). Compound 13 has also been isolated from the roots of *Isotephane heterophylla* (Aguilar *et al.*, 1993).

The hydrocarbon *ent*-trachylobane (7) and its hydroxy derivatives trachinol (20), trachinol acetate (21), trachinodiol (22), trachinodiol 7-monoacetate (23), trachinodiol 7-monoacetate 18-formate (25) and trachinodiol 18-palmitate (26) have been isolated from *Sideritis canariensis* (Labiatae) (González *et al.*, 1971, 1973;

Table 1. Trachylobane diterpenes in the genus *Helianthus*

<i>Helianthus annuus</i>	11–13, 38 (Pyrek, 1970, 1984); 13 (Panizo and Rodríguez, 1979; Mitscher <i>et al.</i> , 1983); 14 (Melek <i>et al.</i> , 1985); 39 (Alfa-tafta and Mullin, 1992)
<i>H. argophyllus</i>	14 (Watanabe <i>et al.</i> , 1982).
<i>H. ciliaris</i>	14 (Bjeldanes and Geissman, 1972)
<i>H. debilis</i>	13 (Beale <i>et al.</i> , 1983)
<i>H. giganteus</i>	13 (Beale <i>et al.</i> , 1983)
<i>H. grosseserratus</i>	14 (Herz and Kumar, 1981)
<i>H. niveus</i>	14 (Ohno and Mabry, 1980)
<i>H. hirsutus</i>	13 (Beale <i>et al.</i> , 1983)
<i>H. occidentalis</i>	14 (Herz <i>et al.</i> , 1983)
<i>H. petiolaris</i>	14 (Herz and Kulanthaivel, 1984)
<i>H. radula</i>	40, 41 (Herz and Kulanthaivel, 1983)
<i>H. rigidus</i>	13, 14 (Herz <i>et al.</i> , 1982, Beale, <i>et al.</i> , 1983)
<i>H. salicifolius</i>	14 (Herz <i>et al.</i> , 1982)
<i>H. tomentosus</i>	13 (Beale <i>et al.</i> , 1983)

Fraga *et al.*, 1991). Other species of this genus endemic to the Canary Islands also contain diterpenes of this type (Fraga *et al.*, 1987, 1991). *ent*-Trachylobane (7) has also been obtained from the essential oil of *Araucaria araucana*. This species also contains the tetracyclic diterpenes *ent*-kaur-16-ene (4), *ent*-beyer-15-ene (5), *ent*-atis-16-ene (6), and the double bond isomers isokaurene (*ent*-kaur-15-ene) and isoatisene (*ent*-atis-15-ene) (Briggs and White, 1975).

The diterpene alcohol *ent*-trachyloban-3 β -ol (30) has been obtained from the fruits of *Xylopia aromatica* (Annonaceae) (Moraes and Roque, 1988), whilst the stem bark of another species of this genus, *X. quintasii*, contains 7 β -acetoxy-trachyloban-18-oic acid (27) (Hasan *et al.*, 1982).

The first example to be reported of a trachylobane diterpene in the Hepaticae was the isolation of 3 α ,18-dihydroxy-trachyloban-19-oic acid (32), which was obtained from the liverwort *Jungermannia exsertifolia* (Harrison and Asakawa, 1989).

In our experience the best sources of trachylobane diterpenes are *Helianthus annuus* (sunflower) and *Sideritis canariensis*, the former for the 19-acid 13 and the latter for the 7 β ,18-diol 22. In both plants these metabolites occur with their *ent*-kaur-16-ene analogues, and the best procedure for the separation of these mixtures is chromatography of the corresponding

Scheme 1

Scheme 2

methyl esters or diacetates, respectively, in a silica gel column impregnated with silver nitrate (10%).

Helichrysum fulvum (Compositae) contains the isotrachylobane derivative, helifulvanolic acid (35) (Bohlmann *et al.*, 1979), whilst helifulvanoic acid (36) and helifulvan-19-ol (37) have been found in *H. chionosphaerum* (Bohlmann *et al.*, 1980). The name helifulvane has been assigned to the carbon skeleton of these isotrachylobanes.

THE BIOSYNTHESIS OF THE TRACHYLOBANE DITERPENES

In 1955 Wenkert suggested that the tetracyclic diterpenes might arise by cyclization of suitably oriented pimaradienes, subsequently involving a non-classical carbenium ion 3 with a face-protonated cyclopropyl ring. This could then lead to compounds with the kaurene (4), beyerene (5), atisene (6) and trachylobane (7) skeleta. The last compound, trachylobane, was the deprotonated form of this carbenium ion (Scheme 1) (Wenkert *et al.*, 1955). Ten years later the isolation of the first trachylobane diterpenes (Hugel *et al.*, 1965a) gave support to this hypothesis. However, since the studies of carbenium ion rearrangement, especially of the 2-methoxy-norbornyl ion (Olah *et al.*, 1970), discounting the existence of a non-classical ion in superacid medium, some authors prefer to use rearrangements between the classical carbenium ion or an edge-

protonated cyclopropyl, to explain the formation of the different skeleta of the tetracyclic and pentacyclic diterpenes (Coates and Bertram, 1971; Briggs and White, 1975).

Cell-free enzyme preparations obtained from *Ricinus communis* seedlings convert mevalonate, geranylgeranyl pyrophosphate (1) and copalyl pyrophosphate (2) into *ent*-isopimaradiene, *ent*-kaur-16-ene (4), *ent*-beyer-15-ene (5), *ent*-trachylobane (7) and casbene. However, purification of this kaurene synthetase has shown that separate enzymic proteins are involved in the cyclization reaction of geranylgeranyl pyrophosphate to the different diterpene hydrocarbons, with the exception of *ent*-kaurene and *ent*-trachylobane where no evidence for a separation of the activities was obtained (Robinson and West, 1970a, b).

A soluble cell free enzyme system obtained from *Gibberella fujikuroi* converted mevalonate, geranylgeranyl pyrophosphate (1) and copalyl pyrophosphate (2) into *ent*-kaur-16-ene (4), showing that a free pimaradiene intermediate is not involved in the biosynthesis of 4 (Evans and Hanson, 1972). The same probably occurs in other organisms with the biosynthesis of the tetra- and pentacyclic diterpenes cited here.

Bohlmann *et al.* (1979, 1980) have suggested that the isotrachylobane skeleton (helifulvane), which is represented in nature by 35–37, can be formed by cyclization of an isopimarane carbenium ion such as 43. However, a trachylobane ion such as 45 may also be the precursor of this diterpene skeleton (Scheme 2). This species can also explain the formation in nature of 9,11-dehydrotrachylobane diterpenes such as 19. This has been

Scheme 3

Table 2. ^{13}C NMR data of trachylobane derivatives^a

C	Compounds										
	7 ^b	11 ^b	13 ^b	14 ^c	27 ^d	29 ^e	31 ^f	33 ^g	34 ^h	42 ⁱ	54 ^j
1	39.2 ⁱ	39.4 ⁱ	39.5 ⁱ	39.7	38.4	38.2	37.7	37.8	34.2	41.3	35.0
2	18.3	17.9	18.7	19.4	16.1	17.2	23.3	27.8	19.6	18.7	18.1
3	42.2	35.7	37.8	38.5	37.0	36.9	81.1	79.3	37.4	37.8	37.9
4	33.0	38.3	43.7	43.6	46.8	45.5	38.0	53.2	44.2	43.9	43.2
5	56.2	56.8	57.0	54.0	48.8	41.7	55.3	50.6	52.0	56.8	48.6
6	30.2	20.4	21.8	24.9	21.1	30.5	19.9	21.6	20.3	21.3	54.1
7	39.1 ⁱ	39.5 ⁱ	39.2 ⁱ	74.2	78.3	75.4	38.9	38.5	33.2	38.3	174.2
8	40.8	40.7	40.8	47.4	44.3	46.8	40.8	40.3	27.8	39.8	47.3
9	53.4	53.5	52.8	52.2	42.7	47.6	53.1	52.4	49.8	65.5	57.0
10	38.4	38.3	38.9	39.3	37.7	37.8	37.7	38.0	38.7	39.7	44.7
11	19.7	19.9	19.7	22.3	19.2	19.0	19.8	19.8	82.1	211.5	18.7
12	20.7	20.6	20.6	24.0	20.4	20.4	21.3	20.3	28.3	40.2	18.7
13	24.4	24.3	24.3	21.0	23.9	23.9	24.3	24.0	19.9	31.1	21.3
14	33.5	33.4	33.1	32.2	33.1	32.5	33.5	32.9	32.7	34.2	35.0
15	50.6	50.4	50.4	45.4	50.4	45.1	50.4	50.0	26.3	48.5	46.2
16	22.5	22.4	22.4	20.1	22.4	22.9	22.6	22.4	28.0	31.2	25.1
17	20.7	20.6	20.6	20.9	20.5	20.3	20.6	20.4	23.6	19.3	20.7
18	33.5	26.9	28.9	29.2	184.7	178.8	28.0	71.3	29.1	29.8	177.4
19	21.7	65.5	184.7	179.9	28.9	16.4	16.6	176.0	178.3	177.5	17.2
20	14.6	15.1	12.5	13.1	12.5	14.8	14.0	12.5	15.8	14.9	15.6

^a All spectra measured in CDCl_3 unless otherwise stated; ^b Arnone *et al.*, 1979; ^c Measured in $\text{C}_6\text{D}_6\text{N}$, Ohno and Mabry, 1980; ^d Hasan *et al.*, 1982; ^e Fraga *et al.*, 1988; ^f Moraes and Roque, 1988; ^g Harrison and Asakawa, 1989; ^h Bohlmann *et al.*, 1979; ⁱ Herz and Kulanthaivel, 1983; ^j These values may be interchanged.

isolated, together with its possible biogenetic precursor, the trachylobane derivative **13**, from *Viguiera bishopii* (Bohlmann *et al.*, 1981).

The trachylobane skeleton may also be the precursor of *ent*-kaur-11-ene derivatives (Scheme 3). Thus, we have reported (Fraga *et al.*, 1987) that enzymatic abstraction of hydrogen at C-11 in **8**, which assists the cleavage of the cyclopropane ring, can give a carbenium ion at C-16 (**46**). This is then neutralized with water to form the diterpene **47**. These 11-ene derivatives are rare in nature and have only been found in plants that also contain trachylobane diterpenes.

Table 3. ^{13}C NMR Data of trachylobane diterpenes 20–24^{a, b}

C	Compounds				
	20	21	22	23	24
1	39.0	38.7	38.7	38.5	38.3
2	18.1	18.0	17.6	17.3	17.2
3	42.0	41.9	35.1	35.2	35.7
4	32.5	32.3	37.1	36.7	35.9
5	46.9	47.7	39.0	40.6	42.2
6	27.6	25.0	27.1	24.7	25.2
7	76.0	78.4	76.1	78.4	77.8
8	45.3	43.8	45.4	43.8	43.9
9	47.5	48.4	47.5	48.4	48.3
10	38.3	38.1	38.2	37.9	38.1
11	19.3	19.2	19.4	19.2	19.3
12	20.4	20.3	20.7	20.3	20.3
13	24.0	23.7	24.1	23.7	23.8
14	32.7	32.4	32.8	32.4	32.5
15	45.3	45.1	45.4	45.1	45.0
16	22.9	22.7	23.0	22.8	22.7
17	20.6	20.3	20.6	20.3	20.3
18	33.1	32.9	70.6	71.3	72.5
19	21.6	21.2	17.9	17.4	17.3
20	14.5	14.4	15.0	14.8	14.1

^a All spectra measured in CDCl_3 .

^b Data from Fraga, B. M., Hernández, M. G. and Santana, J. M. H., unpublished results.

SPECTROSCOPIC STUDIES

The spectroscopic properties of the cyclopropane ring play an important role in the characterization of trachylobane diterpenes. An absorption at 3020 cm^{-1} in the infrared spectrum is typical of this three-membered ring.

Before high resolution nuclear magnetic resonance (NMR) became available, the confirmation of the structure of the diterpene trachyloban-19-ol (**11**) was carried out by a study of tris(dipivaloyl-methanato)europium-shifted NMR spectroscopy (Achmatowicz *et al.*, 1971). Subsequently, the assignment of the hydrogen signals of the C, D and E rings in the NMR spectrum of this compound was reported (Arnone *et al.*, 1979).

The cyclopropane hydrogens in the ^1H NMR spectrum appear at high field. Thus, in *ent*-trachyloban-19-ol (**11**) the hydrogens in C-12 and C-13 appear as two multiplets at δ 0.56 and 0.81, respectively. This shift to high field is also observed in the ^{13}C NMR spectrum where the resonances of C-12, C-13 and C-16 in this diterpene appear at δ 20.6, 24.3 and 22.4, respectively (Arnone *et al.*, 1979).

The ^{13}C NMR signals of the trachylobane hydrocarbon were assigned taking as models isshwarane sesquiterpene derivatives (Cory and Stothers, 1978). However, some assignments in this work were erroneous. Subsequently a complete assignment of this diterpene was reported using proton single-frequency selective decoupling and shift reagent experiments (Arnone *et al.*, 1979). The elucidation of the structure of several natural trachylobanes has been based on this technique. The assignments of the ^{13}C NMR spectra of some trachylobane derivatives, the isotrachylobane diterpene **34** and the trachylobagibberellin **54**, taken from the literature, are given in Table 2. Taking into

consideration these data, the assignment of the C-12 and C-13 signals in compound 14 must be interchanged. We include in Table 3 the ¹³C NMR spectra of other trachylobane derivatives obtained in our laboratory (Fraga, B. M., Hernández, M. G., and Santana, J. M. H., unpublished results).

X-Ray diffraction studies have permitted the structure of *ent*-15 β -hydroxy-trachyloban-19 oic acid (15) to be resolved as its methyl ester (Ferguson *et al.*, 1982). X-ray crystal structures have also been reported for helifulvanolic (35) and helifulvanic acids (36), two diterpenes with an isotrachylobane skeleton (Bohl-

mann *et al.*, 1979, 1980). Moreover, X-ray analyses of the three trachylobagibberellins **50**, **55** and **59** have been described (Arraez *et al.*, 1985; Fraga *et al.*, 1982; 1988).

CHEMICAL AND SYNTHETIC STUDIES

The first chemical studies of the trachylobane diterpenes were based on the study of the products formed in the opening of the cyclopropane ring by reaction with trifluoroacetic acid (Hugel *et al.*, 1965c). Later, a study of the reaction of *ent*-trachylobane hydrocarbon **7** with dry hydrogen chloride which afforded a mixture of *ent*-kaur-16-ene (**4**) and *ent*-atis-16-ene (**6**) and the double bond isomers, *ent*-kaur-15-ene and *ent*-atis-15-ene, was reported (Appleton *et al.*, 1966). The same mixture was obtained by reaction of *ent*-kaur-16-ene and *ent*-atis-15-ene under the same conditions.

In 1968 Herz and co-workers described the synthesis of the methyl ester of trachyloban-18-oic acid (normal series), the non-natural enantiomer, starting from levopimaric acid (Herz *et al.*, 1968a, b).

The first preparation of a natural *ent*-trachylobane derivative was carried out by Coates and Bertram in 1968. Decomposition under protic conditions of the tosylhydrazone of the methyl ester of 16-keto-*ent*-beyeran-19-oic acid gave methyl *ent*-trachyloban-19-oate and the corresponding *ent*-kaur-15-ene and *ent*-kaur-16-ene derivatives (Coates and Bertram, 1968; 1971).

The synthesis of ($\pm$)-trachylobane was carried out by Kelly *et al.* by two methods in 1973, on the basis of their ($\pm$)-ishwarane sesquiterpene synthesis (Kelly *et al.*, 1972, 1973). Later this Canadian group reported a third and more convenient preparation of trachylobane (Kelly *et al.*, 1975). Finally, a stereoselective synthesis of trachyloban-19-oic acid (**13**), starting from podocarpic acid and based on a vinylphosphonium bicycloannulation method, has been devised (Cory *et al.*, 1980).

THE TRACHYLOBAGIBBERELLINS

Despite the natural occurrence of several structurally similar series of polycyclic diterpenoids related to *ent*-kaur-16-ene, the parent biosynthetic hydrocarbon of gibberellin plant hormones, the gibberellins that have been isolated so far (approximately 90) belong to the *ent*-kaur-16-ene series (see for example the structure **56** of gibberellin A₁₂). However, there is nothing known concerning gibberellin biosynthesis which would preclude the formation of beyeragibberellins, atisagibberellins or trachylobagibberellins in nature. It was therefore interesting to prepare these kinds of gibberellin analogues. We described here only the results obtained in the chemical and microbiological preparation of trachylobagibberellins.

We have synthesized a trachylobagibberellin analogue **50** by rearrangement of a chloro-enol lactone **48** obtained from the natural diterpene trachinodiol (**22**)

(Scheme 4). The stereochemistry obtained at C-4, C-5 and C-6 is opposite to that of natural gibberellins at these centres (Arraez *et al.*, 1985). Later we carried out the partial synthesis of 4-epi-trachylobagibberellin A₁₂ (**55**), also starting from trachinodiol. In this work the stereospecific ring B contraction was carried out by treatment of the bromohydrin **51** with silver oxide to give the aldehyde **52** (Scheme 4) (Fraga *et al.*, 1988).

The trachylobagibberellins have also been obtained by microbiological methods. Thus, TGA₉ (**57**) and TGA₁₂ (**58**) have been prepared by biotransformation of trachyloban-19-oic acid (**13**) with the fungus, *Gibberella fujikuroi* mutant B1-41a. It is interesting to note that the TGA₉ had gibberellin-type biological activity (Bearder *et al.*, 1979). This work was later extended, using different culture conditions, to the preparation in different yields of the trachylobane analogues of GA₄, GA₉, GA₁₄, GA₂₄, GA₂₅, GA₄₀ and GA₄₇. The lactone 7 β -hydroxy-trachylobanolide (**60**) and the triacid **62**, and traces of TGA₁₃, TGA₁₅, *ent*-7 α -hydroxy-trachyloban-19-oic acid (**27**) and *ent*-6 α ,7 α -dihydroxy-trachyloban-19-oic acid (**63**) were also identified in these incubations (Beale *et al.*, 1983).

We have carried out the biotransformation with the wild fungus *G. fujikuroi* of the *ent*-trachylobane hydrocarbon (**7**), obtaining as the main compound the trachylobagibberellin A₄₀ (**58**) (Fraga *et al.*, 1982). In the full paper corresponding to this work, the microbiological transformations of other *ent*-trachylobane derivatives such as trachinol (**20**), trachyloban-19-ol (**11**) and trachinodiol (**22**) were also described. Thus, the first compound was transformed into the trachylobagibberellins A₇, A₉, A₁₃, A₂₅, A₄₀ and A₄₇, and the second into the same TGAs and into the trachylobanolides **60** and **61**, whilst the substance **22** was not transformed into trachylobagibberellins, because the presence of an 18-hydroxyl group inhibits the ring contraction step in the biosynthesis of gibberellins. In this last biotransformation, *ent*-7 α ,18,19-trihydroxy-trachylobane (**64**) was the major metabolite to be obtained (Díaz *et al.*, 1984).

BIOLOGICAL ACTIVITY

ent-Trachyloban-19-oic acid (**13**) and *ent*-kaur-16-en-19-oic acid showed similar antimicrobial properties (Mitscher *et al.*, 1983) against *Staphylococcus aureus* and *Mycobacterium smegmatis*. These two diterpenes inhibit larval development of *Homeosoma electellum* (sunflower moth) and of three Lepidoptera species, *Heliothis virescens*, *H. zea* and *Pectinophora gossypiella* (pink bollworm) (Elliger *et al.*, 1976). The same effect was observed in sunflower moth diets containing 1% ciliaric acid (**14**) and angelylglandifloric acid (Herz *et al.*, 1983). The anti-feedant and toxic effects of floral trachylobane and kaurene diterpenes, in comparison with sesquiterpene lactones, from *Helianthus annuus* on western corn rootworm (*Diabrotica virgifera*) have been studied (Mullin *et al.*, 1991).

Ciliaric acid (**14**) has also shown antifungal properties in assays carried out with *Sclerotium sclerotiorum* and *Verticillium dahliae* (Picman *et al.*, 1990).

REFERENCES

- Achmatowicz, J. A., Ejchart, A., Jurczak, J., Kozerski, L. and Pyrek, J. St. (1971). Confirmation of the structure of a new diterpene trachyloban-19-ol, by tris(dipivaloylmethanato)-europium-shifted nuclear magnetic resonance spectroscopy. *Chem. Commun.*, 98–99.
- Aguilar, M. I., Delgado, G., Bye, R., and Linares, E. (1993). Bisabolenes, polycyclic diterpenoids and other constituents from the roots of *Iostephane heterophylla*. *Phytochemistry* **33**, 1161–1163.
- Alfatafta, A. A. and Mullin, C. A. (1992). Epicuticular terpenoids and an auroane from flowers of *Helianthus annuus*. *Phytochemistry* **31**, 4109–4113.
- Appleton, R. A., McAlees, A. J., McCormick, A., McCrindle, R. and Murray, R. D. H. (1966). The acid-catalysed rearrangement of diterpene hydrocarbons. Part 1. Kaurane, isosatisirane, stachene and trachylobane. *J. Chem. Soc. (C)*, 2319–2322.
- Arnone, A., Mondelli, R. and Pyrek, J. St. (1979). ¹³C NMR studies of trachylobane diterpenes: complete carbon assignment. *Org. Magn. Reson.* **12**, 429–431.
- Arraez, J. D., Fraga, B. M., Gonzalez, A. G., Luis, J. G., Fayos, J. and Perales, A. (1985). Partial synthesis of a trachylobagibberellin analogue. *J. Chem. Soc., Perkin Trans. 1*, 207–211.
- Beale, M. H., Bearder, J. R., MacMillan, J., Matsuo, A. and Phinney, B. O. (1983). Diterpene acids from *Helianthus* species and their microbiological conversion by *Gibberella fujikuroi* mutant B1-41a. *Phytochemistry* **22**, 875–881.
- Bearder, J. R., MacMillan, J., Matsuo, A. and Phinney, B. O. (1979). Conversion of trachylobanic acid into novel pentacyclic analogues of gibberellins by *Gibberella fujikuroi* mutant B1-41a. *J. Chem. Soc., Chem. Commun.*, 649–650.
- Bjeldanes, L. F. and Geissman, T. A. (1972). Constituents of *Helianthus ciliaris*. *Phytochemistry* **11**, 327–332.
- Bohlmann, F., Zdero, C., Zeisberg, R. and Sheldrick, W. S. (1979). Helifulvanolsäure — Ein neues diterpen mit anomalem kohlenstoffgerüst aus *Helechrysom fulvum*. *Phytochemistry* **18**, 1359–1362.
- Bohlmann, F., Abraham, W. R. and Sheldrick, W. S. (1980). Weitere diterpene mit helifulvan-gerüst und andere inhaltsstoffe aus *Helechrysom chionosphaerum*. *Phytochemistry* **19**, 869–871.
- Bohlmann, F., Jakupovic, J., Ahmed, M., Grenz, M., Suding, H., Robinson, H. and King, R. M. (1981). Germacranolides and diterpenes from *Viguiera* species. *Phytochemistry* **20**, 113–116.
- Bohlmann, F., Zdero, C., Schmeda-Hirschmann, G., Jakupovic, J., Castro, V., King, R. M. and Robinson, H. (1984). Heliangolide, trachyloban- und villanovan- derivative aus *Viguiera* arten. *Liebigs Ann. Chem.*, 495–502.
- Briggs, L. H. and White, G. W. (1975). Constituents of the essential oil of *Araucaria araucana*. *Tetrahedron* **31**, 1311–1314.
- Coates, R. M. and Bertram, E. F. (1968). Biogenetic-like rearrangements of tetracyclic diterpenes. A partial synthesis of trachylobane. *Tetrahedron Lett.*, 5145–5148.
- Coates, R. M. and Bertram, E. F. (1971). Biogenetic-like rearrangements of tetracyclic diterpenes. *J. Org. Chem.* **36**, 3722–3729.
- Cory, R. M. and Stothers, J. B. (1978). Carbon-13 spectra of polycyclic systems. Tricyclo[3,2,1,0]octanes as models for some tetracyclic sesquiterpenes and pentacyclic diterpenes. Ishwarane and trachylobane derivatives. *Org. Magn. Res.* **11**, 252–257.
- Cory, R. M., Chan, D. M. T., Naguib, Y. M. A., Rastall, M. H. and Renneboog, R. M. (1980). Vinylphosphonium bicycloannulation of cyclohexenones and its use in a stereoselective synthesis of trachyloban-19-oic acid. *J. Org. Chem.* **45**, 1852–1863.
- Díaz, C. E., Fraga, B. M., Gonzalez, A. G., Gonzalez, P., Hanson, J. R. and Hernandez, M. G. (1984). The microbiological transformation of some trachylobane diterpenoids by *Gibberella fujikuroi*. *Phytochemistry* **23**, 2813–2816.
- Elliger, C. A., Zinkel, D. F., Chan, B. G. and Waiss, A. C. (1976). Diterpene acids as larval growth inhibitors. *Experientia* **32**, 1364–1366.
- Evans, R. and Hanson, J. R. (1972). The formation of (–)-kaurene in a cell-free system from *Gibberella fujikuroi*. *J. Chem. Soc. Perkin Trans. 1*, 2382–2385.
- Ferguson, G., McCrindle, R., Murphy, S. T. and Parvez, M. (1982). Further diterpenoid constituents of *Helianthus annuus*. The crystal and molecular structure of methyl ent-15 β -hydroxytrachyloban-18-oate. *J. Chem. Res. (S)* 200–201, (M) 2009–2033.
- Fraga, B. M., González, A. G., Hernandez, M. G., Hanson, J. R. and Hitchcock, P. B. (1982). The metabolism of the diterpenoid hydrocarbon, ent-trachylobane, by *Gibberella fujikuroi* and the X-ray structure determination of the methyl ester of trachylobagibberellin A₄₀. *Chem. Commun.*, 594–595.
- Fraga, B. M., Hernández, M. G., Fernández, C. and Arteaga, J. M. (1987). Diterpenes from *Sideritis dendrochahorra* and *S. cystosiphon*. *Phytochemistry* **26**, 775–777.
- Fraga, B. M., Guillermo, R., Arraez, J. D., Luis, J. G. and Perales, A. (1988). Partial synthesis of 4-*epi*-trachylobagibberellin A₁₂. *J. Chem. Soc., Perkin Trans. 1*, 1513–1516.
- Fraga, B. M., Guillermo, R., Hernandez, M. G., Mestres, T. and Arteaga, J. M. (1991). Diterpenes from *Sideritis canariensis*. *Phytochemistry* **30**, 3361–3364.
- Gonzalez, A. G., Breton, J. L., Fraga, B. M. and Luis, J. G. (1971). Trachinol and trachinodiol, two new diterpenes from *Sideritis canariensis* Ait. *Tetrahedron Lett.*, 3097–3100.
- Gonzalez, A. G., Fraga, B. M., Hernandez, M. G. and Luis, J. G. (1973). New diterpenes from *Sideritis canariensis* **12**, 1113–1116.
- Harrison, L. J. and Asakawa, Y. (1989). 3 α ,18-Dihydroxytrachyloban-19-oic acid from the liverwort *Jungermannia exsertifolia* subsp. *cordifolia*. *Phytochemistry* **28**, 1533–1534.
- Hasan, C. M., Healey, T. M. and Waterman, P. G. (1982). 7 β -Acetoxytrachyloban-18-oic acid from *Xylopia quintasii*. *Phytochemistry* **21**, 177–179.
- Herz, W. and Kulanthaivel, P. (1983). ent-Kaurenes and trachylobanes from *Helianthus radula*. *Phytochemistry* **22**, 2543–2546.
- Herz, W. and Kulanthaivel, P. (1984). ent-Pimarenes, ent-kaurenes, heliangolides and other constituents of three *Helianthus* species. *Phytochemistry* **30**, 1453–1459.
- Herz, W. and Kumar, N. (1981). Sesquiterpene lactones from *Helianthus grosseserratus*. *Phytochemistry* **20**, 99–104.
- Herz, W., Mirrington, R. N. and Young, H. (1968a). Synthesis of ent-methyl trachylobanate from levopimaric acid. *Tetrahedron Lett.*, 405–407.
- Herz, W., Mirrington, R. N., Young, H. and Lin, Y. Y. (1968b). The synthesis of methyl 13,16-cycloatisan-18-oate (methyl anti-trachylobanate). *J. Org. Chem.* **33**, 4210–4219.
- Herz, W., Govindan, S. V. and Watanabe, K. (1982). Diterpenes of *Helianthus rigidus* and *H. salicifolius*. *Phytochemistry* **21**, 946–947.
- Herz, W., Kulanthaivel, P. and Watanabe, K. (1983). ent-Kauranes and other constituents of three *Helianthus* species. *Phytochemistry* **22**, 2021–2025.
- Hugel, G., Lods, L., Mellor, J. M., Theobald, D. W. and Ourisson, G. (1965a). Diterpènes de *Trachylobium*. I.—Introduction générale. Isolement du kauranol et de huit diterpènes nouveaux. *Bull. Soc. Chim. France*, 2882–2887.
- Hugel, G., Lods, L., Mellor, J. M., Theobald, D. W. and Ourisson, G. (1965b). Diterpènes de *Trachylobium*. II.—Structure des diterpènes tétra- et pentacycliques de *Trachylobium*. *Bull. Soc. Chim. France*, 2888–2894.
- Hugel, G., Lods, L., Mellor, J. M., Theobald, D. W. and Ourisson, G. (1965c). Diterpènes de *Trachylobium*. III.—Réactions des dérivés trachylobaniques. *Bull. Soc. Chim. France*, 2894–2902.
- Kelly, R. B., Zamecnik, J. and Beckett, B. A. (1972). Total synthesis of (±)-ishwarane, a tetracyclic sesquiterpenoid. *Can. J. Chem.* **21**, 3455–3564.
- Kelly, R. B., Eber, J. and Hung, H. K. (1973). Total synthesis of (±)-trachylobane, a pentacyclic diterpenoid with a tricyclicoctane system. *Can. J. Chem.* **51**, 2534–2541.
- Kelly, R. B., Beckett, B. A., Eber, J., Hung, H. K. and Zamecnik (1975). Conversion of bicyclo[2,2,2]octane systems into tri-

- cyclo[3,2,1,0]octanes: a third synthesis of the diterpenoid trachylobane. *Can. J. Chem.* **53**, 143-147.
- Melek, F. R., Gage, D. A., Gershenzon, J. and Mabry, T. J. (1985). Sesquiterpene lactone and diterpene constituents of *Helianthus annuus*. *Phytochemistry* **24**, 1537-1539.
- Mitscher, L. A., Rao, G. S. R., Vaysoglu, T., Drake, S. and Haas, T. (1983). Isolation and identification of trachyloban-19-oic acid and (-)-kaur-16-en-19-oic acids as antimicrobial agents from the prairie sunflower, *Helianthus annuus*. *J. Nat. Prod.* **46**, 745-746.
- Moraes, M. P. L. and Roque, N. F. (1988). Diterpenes from the fruits of *Xylopiia aromatica*. *Phytochemistry* **27**, 3205-3208.
- Mullin, C. A., Alfatafta, A. A., Harman, J. L., Everett, S. L. and Serino, A. A. (1991). Feeding and toxic effects of floral sesquiterpene lactones, diterpenes and phenolics from sunflower (*Helianthus annuus* L.) on western corn rootworm. *J. Agric. Food Chem.* **39**, 2293-2299.
- Ohno, N. and Mabry, T. J. (1980). Sesquiterpene lactones and diterpene carboxylic acids in *Helianthus niveus* subspecies *canescens*. *Phytochemistry* **19**, 609-614.
- Olah, G. A., White, A. M., DeMember, J. R., Commeyras, A. and Lui, C. Y. (1970). Stable carbonium ions. C. The Structure of norbornyl cation. *J. Am. Chem. Soc.* **92**, 4627-4640.
- Panizo, F. M. and Rodríguez, B. (1979). Algunos componentes diterpénicos del girasol (*Helianthus annuus*). *Anal. Quim.* **75**, 428-430.
- Picman, A. K., Schneider, E. F. and Gershenzon, J. (1990). Antifungal activities of sunflower terpenoids. *Biochem. Syst. Ecol.* **18**, 325-328.
- Pyrek, J. St. (1970). New pentacyclic diterpene acid. Trachyloban-19-oic acid from sunflower. *Tetrahedron* **26**, 5029-5032.
- Pyrek, J. St. (1984). Neutral diterpenoids of *Helianthus annuus*. *J. Nat. Prod.* **47**, 822-827.
- Robinson, D. R. and West, C. A. (1970a). Biosynthesis of cyclic diterpenes in extract from seedlings of *Ricinus communis*. I. Identification of diterpene hydrocarbons formed from mevalonate. *Biochemistry* **9**, 70-79.
- Robinson, D. R. and West, C. A. (1970b). Biosynthesis of cyclic diterpenes in extract from seedlings of *Ricinus communis*. II. Conversion of geranylgeranyl pyrophosphate into diterpene hydrocarbons and partial purification of the cyclization enzyme. *Biochemistry* **9**, 80-89.
- Rowe, J. W. (1968). *The Common and Systematic Nomenclature of Cyclic Diterpenes*, Third Revision, Forest Service U.S. Department of Agriculture, Madison, Wisconsin 53705.
- Watanabe, K., Ohno, N., Yoshioka, H., Gershenzon, J. and Mabry, T. J. (1982). Sesquiterpene lactones and diterpenoids from *Helianthus argophyllus*. *Phytochemistry* **21**, 709-713.
- Wenkert, E. (1955). Structural and biogenetic relationships in the diterpenes series. *Chem. Ind.*, 282-284.