FURTHER FUROCLERODANES FROM *TEUCRIUM* GENUS[#]

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Abstract - The review updates the results reported during the last four years on the chemistry of these diterpenoids.

The interest for the furoclerodane diterpenoids (*neo*-clerodane skeleton) occurring in *Teucrium* species (family Labiatae) seems to meet no pause. The main reason is their powerful insect antifeedant activity. The previous reviews[1-3] are updated by the present report, concerning 19 new taxa (plus five reinvestigated) and 51 new natural products; in particular, some substances with transposed skeletons are attractive for the researcher. This genus is surely one of the richest sources of *neo*-clerodanes.

The new taxa and products will be reported mostly in chronological order, and for the new products the numbering used in the previous reviews[2,3] will be continued.

A paper escaped the previous review[3] and published in 1990 referred to *Teucrium grisebachii* growing in Argentina:[4] two furoclerodanes were isolated: one is the new triacetylteumassilin (**156**), the other is 6-acetylteucjaponin B (**20**), claimed as a new derivative but in the fact previously known.[5]

A reinvestigation of the extract of *Teucrium polium* collected in Armenia (subspecies not indicated) yielded[6] two products named tepolin A and tepolin B; they were assigned the structures (**157**) and (**158**), whose more peculiar detail is the occurrence of not lactonized 12-OH and 9α-COOH.

Another reinvestigation was concerned with *Teucrium pernyi*. From this species, growing in South-East China, the teupernins A (**115**), B (**105**) and C (**106**) had been described by two chinese groups.[3,7,8] In a second time, a product indicated as teupernin D (**155**) had been isolated.[3,9]

Another product was then[10] extracted and also named teupernin D, but its structure, reported as **159**, is quite different and shows an unprecedented carbomethoxy group on C-4. The nomenclature of these two products should be revised. In the same species also the known teucvidin (**91**), teuflin (**93**), montanin D (**46**) and teuscorodonin (**68**) were found.[10]

Structurally more interesting are the nine furoclerodanes isolated[11,12] from *Teucrium brevifolium*, growing in small areas of Greece and collected in the island of Karpathos. Teubrevin A (**160**) has a rearranged skeleton[11] arising from cleavage of the C-5/C-10 bond and formation of a C-1/C-6 linkage; teubrevin B (**161**) is its 8β-OH derivative.[11]

[#] Dedicated to Professor Koji Nakanishi on the occasion of his 75th birthday.

Teubrevin C (**162**), obtained[12] for the first time from a natural source, was found to be identical to the diacetyl derivative of teulepicin (**44**)[2]. Teubrevin D (**163**) is the 8β,10β-dihydroxy derivative of teubrevin C. The *neo*-clerodane absolute stereochemistry of **163** was established from its CD curve.

The structure of teubrevin E was elucidated by careful NMR investigations,[12] proving the occurrence of an eight-membered carbocycle, formed by carbon atomes 1-5, 19 and 9-10, fused at C-4, C-5 with a γ-lactone arising from C-18 and C-6, and bearing a spiro 20,12-γ-lactone; moreover, the carbon atoms 7, 8 and 17 have been lost. The quite novel structure of teubrevin E is therefore represented by **164**.

Extremely similar is the structure[12] of teubrevin F (**165**): it differs from **164** only for the inverted relative configuration at C-9. The two products are therefore epimers at C-9.

Also teubrevin G and teubrevin H are epimers at C-9: instead of the lactone carbonyl C-6, they bear a CH_2-CO-CH_3 side chain formed by C-7, C-8 and C-17, whereas the atoms C-18, C-4, C-5 and C-6 form a furan ring. The structures of these two unusual products are shown[12] by **166** resp. **167**.

Even more complex is the structure of teubrevin I, solved by X-Ray diffraction analysis: it has not only the eight-membered carbocyclic ring, but also a substituted tetrahydropyranone moyety, and a five-membered dioxa ring involving C-4, C-18, O, C-8, O. This fascinating molecular structure is represented[12] by **168**.

Teubrevins E-I (**164-168**, respectively) are the first reported compounds having a rearranged *neo*-clerodane skeleton with an eight-membered ring. Their biogenesis may be rationalized by a mechanistic pathway[12] starting from teubrevin D. The absolute stereochemistry of these products is the one depicted in their formulae, because all of them could be derived biogenetically from the proved *neo*-clerodane structure (**163**) of teubrevin D.

Eight furoclerodanes (teucrolivins A-H, **109-114**, **118-119**) had been reported previously[13-15] from *Teucrium oliverianum* growing in Saudi Arabia. The plant was reinvestigated by another group: teucrolivins A-C (**109**, **110**, **111**) were found again, together with five new compounds (teucrolins A-E) and three diterpene artifacts.[16]

Teucrolin A (**169**) differs from teucrolivin A (**109**) by having an axial 3α-OAc group replacing the ketone carbonyl. Teucrolin B (**170**) has a free 6α-OH and a 12-OH group of unknown configuration. In teucrolin C (**171**) this hydroxy group is oxidized to ketone, whereas the 6α-OH is acetylated to 6α-OAc. Teucrolin D (**172**) is a tetranor-diterpene quite similar to teucrolivin F (**112**), from which differs only by the occurrence of 3α-OAc instead of the keto group. In teucrolin E (**173**) the 4,18-epoxide system is replaced by a 4-CH_2OH and an unusual oxigen bridge between C-4 and C-10, whose stereochemistry was not proved.[17] The artifacts were: 12-*O*-methyl-teucrolin A (**174**), 12-*O*-methyl-teucrolivin A (**175**) and 12-*O*-ethyl-teucrolin A (**176**) arising from alkylation of **169** and **109** by MeOH used for the extraction and by EtOH contained in $CHCl_3$ used for partitioning. This easy alkylation at the tertiary hydroxy group on C-12 is very unusual.

A reinvestigation of *Teucrium lamiifolium* allowed the isolation[18] of a glucoside, teulamioside (**177**); the glucose moiety is bonded to the 18β hydroxy group of an 18,19 hemiacetale system. Teulamioside is the second glucoside until now isolated from *Teucrium* species out of the 206 *neo*-clerodanes occurring in this genus. The already known[2] teuspinin (**62**) and montanin E (**51**) were also detected. *Teucrium trifidum*, growing in southern Africa, yielded[19] two neo-clerodanes. The first was the already known[3] 4α,18-

epoxytafricanin A (**116**), whereas the second was new and assigned the name teutrifidin and the structure (**178**). It differs from **116** only for the occurrence of a 7β-OH group.

Five *neo*-clerodanes were extracted[20] from *Teucrium polium* ssp. *aurasianum* growing in Algeria. One was the previously described[3] teumicropodin (**142**). Another is 3-deacetylteumicropodin (**179**), whereas the three remaning are products of progressive deacetylation of teupyreinidin (**29**), i.e. 3,20-bisdeacetylteupyreinidin (**180**), 6,20-bisdeacetylteupyreinidin (**31**) and 3,6,20-trisdeacetylteupyreinidin (**181**). The authors claimed that the product formerly[2,5] reported as 6,20-bisdeacetylteupyreinidin (**31**) was on the contrary the 3,20-bisdeacetyl derivative (**180**).

Two species originating from Australia were studied: *Teucrium racemosum* yielded[21] the chlorine-containing teuracemin (**182**), together with the known teutrifidin (**178**), 4α,18-epoxytafricanin A (**116**) and 20-oxoteuflavin (**117**). *Teucrium corymbosum* gave[22] the 19-nor-*neo*-clerodane teucorymbin (**183**) and the three known 19-acetylgnaphalin (**22**), teucjaponin A (**18**) and 6-acetylteucjaponin B (**20**).

Four new *neo*-clerodanes were found in *Teucrium yemense*, collected in Saudi Arabia.[23] The first is 6β-acetyl-3β-hydroxyteucroxylepin (**184**), with the rare δ-lactone between C-20 and C-19. Teucryemin (**185**) and 19-acetylteucryemin (**186**) have the usual γ-lactone system between C-20 and C-12, with 12S configuration. On the contrary, teucryeminone (**187**) has the infrequent 12R configuration.

Very fascinating is the structure of teubetonin (**188**), a rearranged homo-*neo*-clerodane derivative isolated[24] from *Teucrium betonicum* growing in the island of Madera (Portugal). Indeed, teubetonin has a C-18/C-19 chain bonded to C-4 and an unprecedented CH_2OH group on C-7. An hypothesis on its biogenesis proposes an aldol condensation of a 6-keto precursor and formaldehyde. The same species contained also six already known furoclerodanes: 19-acetylgnaphalin (**22**), teucvin (**89**), teucrin H2 (**76**), teucrin E (**72**), 6β-hydroxyteuscordin (**80**) and 6α-hydroxyteuscordin (**79**).

Four new products have been isolated[25] from *Teucrium alyssifolium* growing in Turkey. They are alysin A (**189**), alysin B (**190**), 3-deacetylalysin B (**191**) and alysin C (**192**). All the products show an unusual linkage between C-8 and C-16 (indicated in the original paper as C-14): this rearrangement constitutes a new variant of the *neo*-clerodane skeleton.

Recently, two more furoclerodanes were extracted[26] from the above species: alysin D (**193**) and alysin E (**194**). Both products show the unusual bond between C-8 and C-16, characteristic of this species.

Extraction of *Teucrium chamaedrys* ssp. *syspirense* , also growing in Turkey, yielded[27] the 19-nor-diterpene syspirensin A (**195**) and the diterpene syspirensin B (**196**). In the latter product is remarkable the transformation of the furan ring into a chain with primary hydroxy groups on C-15 and C-16, and a C-13/C-14 double bond.

Also *Teucrium sandrasicum* occurs in Turkey. From its aerial parts three new *neo*-clerodanes were isolated:[28] sandrasin A (**197**), 6-deacetylsandrasin A (**198**) and sandrasin B (**199**). The first and second products show a 10β-OH group, whereas sandrasin B has the epoxy group opened to give 4α-OH and 4β-CH_2OH, the hydroxy group on C-10 having 10α-OH configuration. Moreover, the three substances are reported to have the rare 12R configuration.

The investigation of *Teucrium sandrasicum* was resumed recently[29] by another group: six new *neo*-clerodane diterpenoids were isolated, teusandrin A to teusandrin F. It is probable that teusandrin A and teusandrin B are identical with sandrasin A and 6-deacetylsandrasin A, previously reported:[28] however, the

configuration at C-12 of teusandrins A and B is certainly 12*S*, and not 12*R* as suggested for sandrasin A and 6-deacetylsandrasin A. Therefore the structures of these four products are worthy to be confirmed.
Teusandrin C (**200**) has an oxetane ring in which the C-4, C-5 and C-19 carbons are involved, and a 4β-CH_2OH group. Teusandrin D (**201**) is identical apart from the lack of the 8β-OH group. Teusandrin E (**202**) shows a 4β,10β ether bridge, forming an oxetane ring that involves C-4, C-5 and C-10. Teusandrin F (**203**) differs from teusandrin E only by having an equatorial 6α-OH hydroxy group instead of the keto group. From the same species also two known diterpenoids were isolated:[28] teucjaponin B (**19**) and 6-acetylteucjaponin B (**20**).
A new derivative, teucriasiatin (**204**) occurs[30] in *Teucrium asiaticum*, collected in the island of Majorca, Spain: it shows an hemiacetalic 20α-OH group. It can be remembered that a previous paper[3,31] had reported the occurrence of only the two already known *neo*-clerodanes auropolin (**25**) and teuflin (**93**). Quite recently, another product was isolated, teucrasiolide: its structure[32] is remarkable for the occurrence of an until now unprecedented C-11/C-12 *trans* olefinic double bond, of a 7α-(20α-*O*-acetyl)hemiacetal bridge, and for the change of the furan ring into an α,β-unsaturated γ-lactone involving the C-13, C-14, C-15 and C-16 carbons and having an acetoxyl substituent at its γ-position. The product occurs as a mixture of epimers at C-15; owing to the poor stability of the crude product, it was isolated as its triacetyl derivative (**205**), the unstable precursor having no acetoxyl substituent.
Three *neo*-clerodanes were isolated[33] from *Teucrium nudicaule*, collected in Northern Chile: two of them are the already described triacetylteumassilin (**156**) and 6-acetylteucjaponin B (**20**). The third is the new 12-epi-teupyreinin (**206**) showing the usual 12*S* configuration.
At the end, the stereostructure of montanin E (**51**) was confirmed by X-Ray diffraction.[34]
Several other *Teucrium* taxa were examinated during the last years, and many already known *neo*-clerodanes were isolated. *Teucrium montanum* ssp. *pannonicum* yielded[35] auropolin (**25**) and montanin H (**135**). *Teucrium alpestre* (from Crete island, Greece) contained[36] teupyrenone (**32**), 3-acetylteumicropin (**140**), teumicropin (**139**) and 3-*O*-deacetylteupyrenone (**141**). *Teucrium cuneifolium* (from Crete island, Greece) gave[36] only 3-*O*-deacetylteupyrenone (**141**). *Teucrium divaricatum* ssp. *villosum* (from Karpathos island, Greece) yielded[36] teuflin (**93**), teuscordinone (**82**), teuflidin (**95**), montanin D (**46**), teucrin A (**97**), dihydroteugin (**78**), 6β-hydroxyteuscorodin (**80**) and teugin (**77**). Teucrin A (**97**) was extracted[37] also from a sample of the same species harvested near Istanbul. From *Teucrium flavum* ssp. *hellenicum* (from Greece) teucvidin (**91**), 12-epi-teucvidin (**145**) and teuflin (**93**) were isolated.[36] *Teucrium rivas-martinezii* (from Spain) yielded[30] 19-acetylgnaphalin (**22**) and 19-acetylteulepicin (**45**). *Teucrium divaricatum* ssp. *divaricatum* (from Greece) contained[30] only teucrin A (**97**). Eventually, *Teucrium haenseleri* (from Portugal) was shown[38] to contain 19-acetylgnaphalin (**22**), eriocephalin (**13**), isoeriocephalin (**16**) and 20-deacetyleriocephalin (**14**).
Also in these last years several interesting papers appeared concerning researches aiming at modifying the structures (rings and functional groups) of natural *Teucrium* furoclerodanes, on the purpose of obtaining semisynthetic, non-natural derivatives with increased antifeedant activity. The substrates used for these researches were eriocephalin (**13**),[39,40] montanin C (**8**),[41] teucrin P1 (**24**),[41] teupolin III (**50**),[41] 19-acetylgnaphalin (**22**),[34] teucjaponin A (**18**),[34] teucjaponin B (**19**),[34] teucroxylepin (**129**),[34] teucvidin (**91**),[42] capitatin (**5**)[40] and montanin E (**51**).[34]

As far as we know, no researches either for total synthesis or for the biogenetic mechanism were attempted on the furoclerodanes from *Teucrium.*

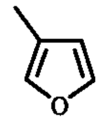
The antifeedant activity of natural furoclerodanes and their derivatives was reported in some other papers.[33, 34, 39, 41, 42, 43]

Another field of interest arose from the casual discovery of the toxicity of teucrin A. The extract of *Teucrium chamaedrys*, its furoclerodane fraction, and teucrin A were found to cause irreversible liver necrosis on mice:[44] several cases of heavy intoxication were reported in men when herbalist preparations of this species were used for weight control.[45] It is possible that all the furoclerodanes from *Teucrium* are toxic.[36]

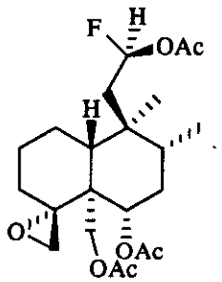
Table 1 report the structures of the 51 new neo-clerodanes isolated since the third review.[3] The symbol F = β-furyl.

Table 2 lists the 108 *Teucrium* taxa (species, subspecies, chemotypes) investigated till now, in alphabetical order, and the *neo*-clerodanes isolated from each taxon, indicated by the numbering adopted in the two previous[2, 3] and in the present review. The names of the taxa are those indicated in the original papers. However, some changes were reported[46] for the systematic taxonomy of *Teucrium* species in recent years: *T. belion* [3] and *T. polium* ssp. *belion* [3] are now called *T. puechiae*; *T. polium* ssp. *pilosum* [2] is now *T. decaisnei*; *T. scorodonia* ssp. *euganeum* [2] is now *T. siculum*; *T. polium* ssp. *expansum* [3] is *T. expansum*; *T. polium* ssp. *vincentinum* [3] is *T. vincentinum*; *T. polium* ssp. *capitatum* [2] is *T. capitatum* .

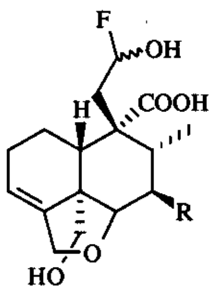
Table 1

F = 

β-furyl

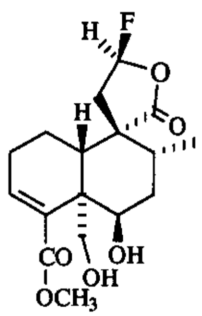


[156] 6,12,19-triacetylteumassilin $C_{26}H_{36}O_8$
T. grisebachii[4]

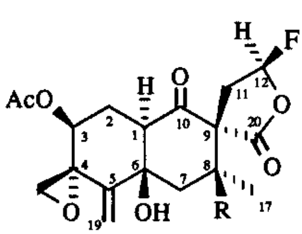


[157] tepolin A R = OH $C_{20}H_{26}O_7$
T. polium[6]

[158] tepolin B R = H $C_{20}H_{26}O_6$
T. polium[6]

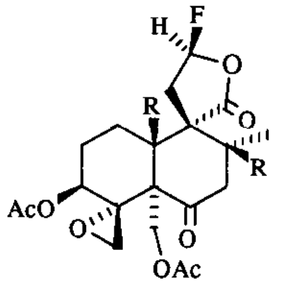


[159] "teupernin D" $C_{21}H_{26}O_7$
T. pernyi[10]



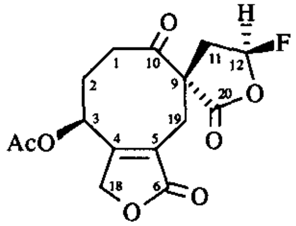
[160] teubrevin A R = H $C_{22}H_{24}O_8$
T. brevifolium[11]

[161] teubrevin B R = OH $C_{22}H_{24}O_9$
T. brevifolium[11]

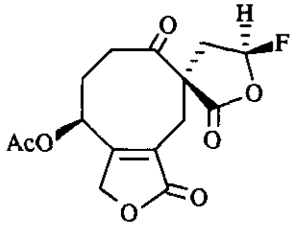


[162] teubrevin C R = H $C_{24}H_{28}O_9$
T. brevifolium[12]

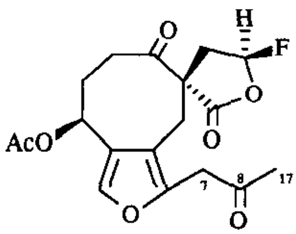
[163] teubrevin D R = OH $C_{24}H_{28}O_{11}$
T. brevifolium[12]



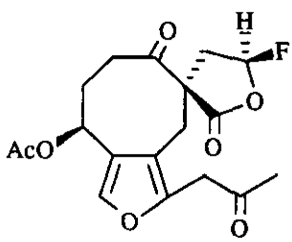
[164] teubrevin E $C_{19}H_{18}O_8$
T. brevifolium[12]



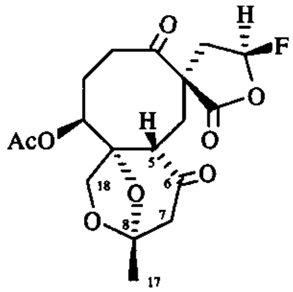
[165] teubrevin F $C_{19}H_{18}O_8$
T. brevifolium[12]



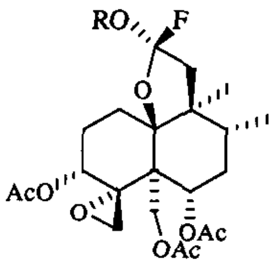
[166] teubrevin G $C_{22}H_{22}O_8$
T. brevifolium[12]



[167] teubrevin H $C_{22}H_{22}O_8$
T. brevifolium[12]



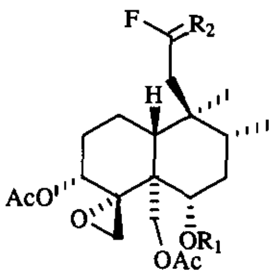
[168] teubrevin I $C_{22}H_{24}O_9$
T. brevifolium[12]



[169] teucrolin A R = H $C_{26}H_{34}O_{10}$
T. oliverianum[16]

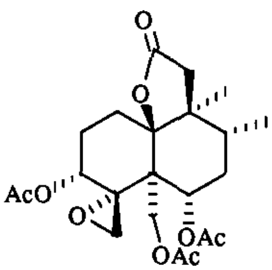
[174] 12-*O*-methylteucrolin A R = Me $C_{27}H_{36}O_{10}$
T. oliverianum[16]

[176] 12-*O*-ethylteucrolin A R = Et $C_{28}H_{38}O_{10}$
T. oliverianum[16]

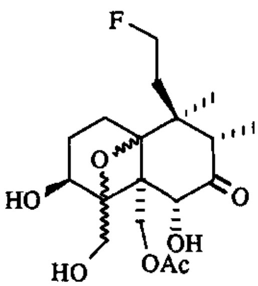


[170] teucrolin B R_1 = H, R_2 = H, OH $C_{24}H_{34}O_8$
T. oliverianum[16]

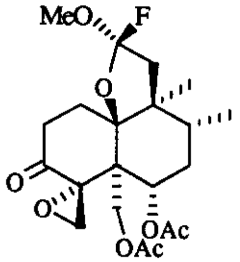
[171] teucrolin C R_1 = Ac, R_2 = O $C_{26}H_{34}O_9$
T. oliverianum[16]



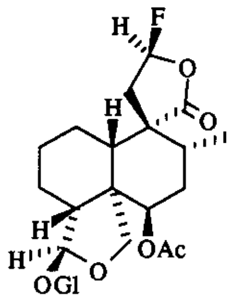
[172] teucrolin D $C_{22}H_{30}O_9$
T. oliverianum[16]



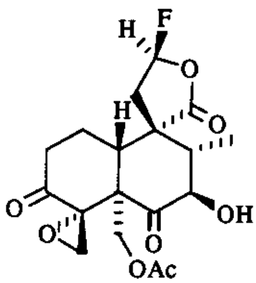
[173] teucrolin E $C_{22}H_{30}O_8$
T. oliverianum[16, 17]



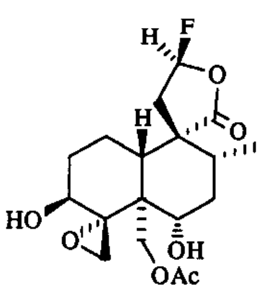
[175] 12-*O*-methylteucrolivin A $C_{25}H_{32}O_9$
T. oliverianum[16, 17]



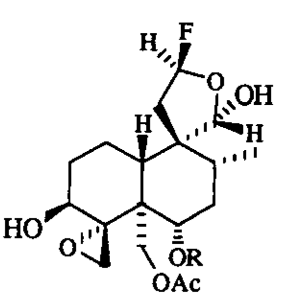
[177] teulamioside $C_{28}H_{38}O_{12}$
T. lamiifolium[18]
Gl = glucose



[178] teutrifidin $C_{22}H_{24}O_9$
T. trifidum[19]

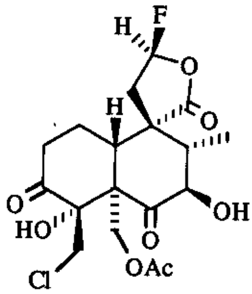


[179] 3-deacetylteumicropodin $C_{22}H_{28}O_8$
T. polium ssp. aurasianum[20]

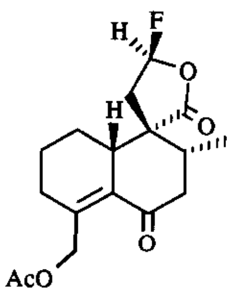


[180] 3,20-bis-deacetylteupyreinidin R = Ac $C_{24}H_{32}O_9$
T. polium ssp. aurasianum[20]

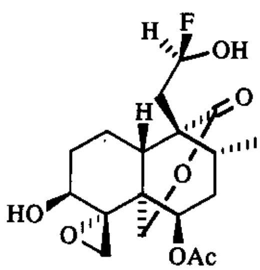
[181] 3,6,20-tris-deacetylteupyreinidin R = H $C_{22}H_{30}O_8$
T. polium ssp. aurasianum[20]



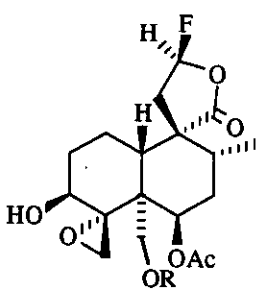
[182] teuracemin $C_{22}H_{25}O_9Cl$
T. racemosum[21]



[183] teucorymbin $C_{21}H_{24}O_6$
T. corymbosum[22]

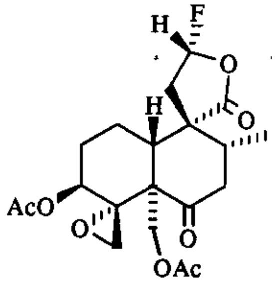


[184] 6β-acetyl-3β-hydroxyteucroxylepin $C_{22}H_{28}O_8$
T. yemense[23]

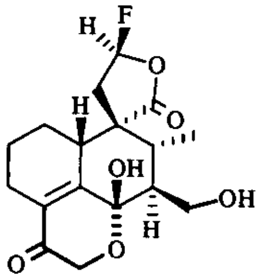


[185] teucryemin R = H $C_{22}H_{28}O_8$
T. yemense[23]

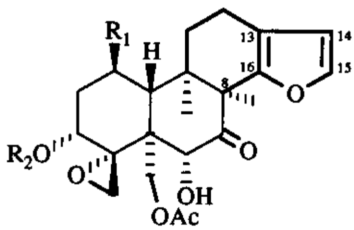
[186] 19-acetylteucryemin R = Ac $C_{24}H_{30}O_9$
T. yemense[23]



[187] teucryeminone $C_{24}H_{28}O_9$
T. yemense[23]

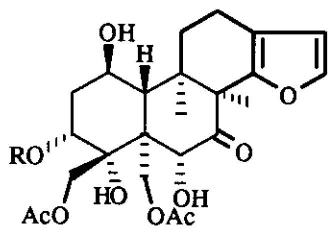


[188] teubetonin $C_{21}H_{24}O_7$
T. betonicum[24]



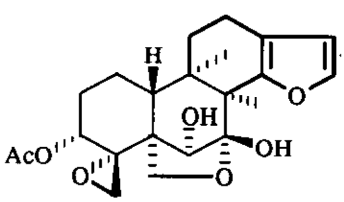
[189] alysin A $R_1 = OH$ $R_2 = Ac$ $C_{24}H_{30}O_9$
T. alyssifolium[25]

[192] alysin C $R_1 = R_2 = H$ $C_{22}H_{28}O_7$
T. alyssifolium[25]

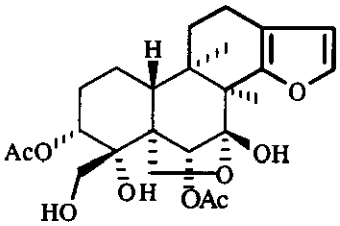


[190] alysin B $R = Ac$ $C_{26}H_{34}O_{11}$
T. alyssifolium[25]

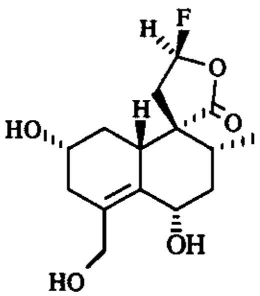
[191] 3-deacetylalysin B $R = H$ $C_{24}H_{32}O_{10}$
T. alyssifolium[25]



[193] alysin D $C_{22}H_{28}O_7$
T. alyssifolium[26]

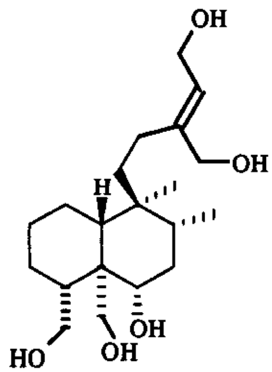


[194] alysin E $C_{24}H_{32}O_9$
T. alyssifolium[26]



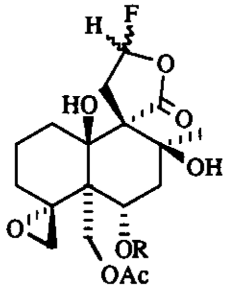
[195] syspirensis A $C_{19}H_{24}O_6$

T. chamaedrys ssp. syspirense[27]

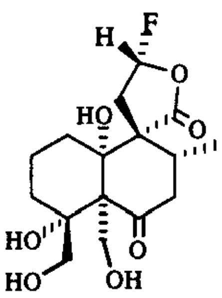


[196] syspirensis B $C_{20}H_{36}O_5$

T. chamaedris ssp. syspirense[27]

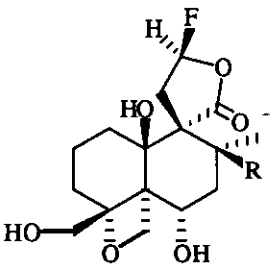


[197]	sandrasin A	12*R*	R = Ac	$C_{24}H_{30}O_{10}$
	teusandrin A	12*S*		
	T. sandrasicum[28, 29]			
[198]	6-deacetylsandrasin A	12*R*	R = H	$C_{22}H_{28}O_9$
	teusandrin B	12*S*		
	T. sandrasicum[28, 29]			



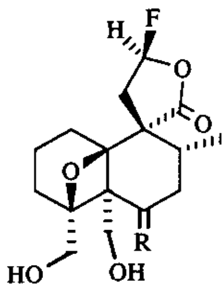
[199] sandrasin B $C_{20}H_{26}O_8$

T. sandrasicum[28]



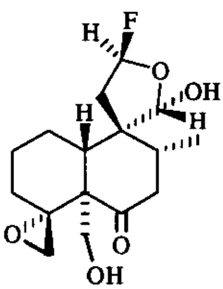
[200] teusandrin C R = OH $C_{20}H_{26}O_8$
T. sandrasicum[29]

[201] teusandrin D R = H $C_{20}H_{26}O_7$
T. sandrasicum[29]

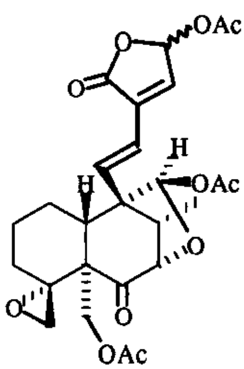


[202] teusandrin E R = O $C_{20}H_{24}O_7$
T. sandrasicum[29]

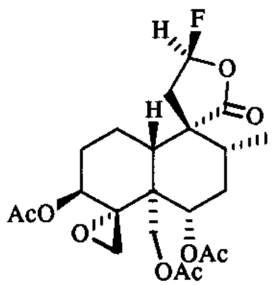
[203] teusandrin F R = α–OH, β–H $C_{20}H_{26}O_7$
T. sandrasicum[29]



[204] teucrasiatin $C_{22}H_{28}O_7$
T. asiaticum[30]



[205] teucrasiolide $C_{26}H_{30}O_{11}$
T. asiaticum[32]



[206] 12-epi-teupyreinin $C_{26}H_{32}O_{10}$
T. nudicaule[33]

Table 2

• T. abutiloides	8, 131, 132, 133
• T. africanum	52, 53
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• T. alpestre	32, 139, 140, 141
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• T. belion	13, 22, 97
• T. betonicum	22, 72, 76, 79, 80, 89, 188
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• T. bidentatum	76, 82, 84, 93, 105
• T. botrys	46, 56, 61, 64, 80, 91
• T. brevifolium	160, 161, 162, 163, 164, 165, 166, 167, 168
• T. buxifolium	22, 45
• T. canadense	9, 54, 89, 91, 93, 131, 148, 149
• T. carolipaui	4, 22
• T. chamaedrys (Bulgarian chemotype)	64, 72, 76, 78, 79, 93, 97
• T. chamaedrys (Italian chemotype)	74, 75, 89, 91, 93, 97
• T. chamaedrys (Moldavian chemotype)	72, 74, 75, 78, 97
• T. chamaedrys (Spanish chemotype)	47, 72, 76, 77, 78, 88, 93, 95, 96, 97, 98
• T. chamaedrys ssp. syspirense	195, 196
• T. cartaginense ssp. homotricum	13, 22
• T. compactum	----
• T. corymbosum	18, 20, 22, 183
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• T. divaricatum ssp. villosum	46, 78, 82, 93, 95, 97
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• T. flavum ssp. flavum	93, 95
• T. flavum ssp. glaucum	33, 90, 93, 103
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• T. grisebachii	20, 156
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• T. heterophyllum	91
• T. hircanicum	22, 76, 94, 95
• T. intricatum	89
• T. japonicum (Japanese chemotype)	18, 19, 89
• T. japonicum (Chinese chemotype)	120
• T. kotschyanum	46, 68, 76, 85, 91, 93, 144, 145, 146, 147
• T. lamiifolium	8, 22, 51, 61, 62, 82, 93, 131, 177
• T. lanigerum	9, 13, 14, 15, 16, 41, 42, 43, 66, 67
• T. lepicephalum	44, 45, 70
• T. leucocladum	8
• T. lucidum	74, 75, 79, 91, 93
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• T. massiliense	8, 18, 22, 34, 35, 36, 37, 136
• T. microphyllum	75, 77, 78, 97
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• T. montanum ssp. pannonicum	25, 135
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• T. montbretii ssp. heliotropifolium	46, 76, 77, 80
• T. montbretii ssp. montbretii	8, 20, 46, 76, 77, 80, 83, 84, 93, 137

• T. montbretii ssp. pamphilicum	----
• T. nudicaule	20, 156, 206
• T. odontites	46, 55, 76
• T. oliverianum	109, 110, 111, 112, 113, 114, 118, 119, 169, 170, 171, 172, 173, 174, 175, 176
• T. oxylepis ssp. marianum	21, 22, 46, 47, 56, 61, 68, 94, 129, 130, 144, 147
• T. pernyi	46, 68, 91, 93, 105, 106, 115, 155, 159
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• T. polium (Bulgarian ssp.)	9, 10, 11, 22, 24, 47, 50, 51, 56, 61, 65, 102, 104
• T. polium (German ssp.)	1, 2, 3
• T. polium (Moldavian ssp.)	24
• T. polium ssp. album	8
• T. polium ssp. aurasianum	31, 142, 179, 180, 181
• T. polium ssp. aureum (Sicilian chemotype)	23, 24
• T. polium ssp. aureum (Spanish chemotype)	22, 25
• T. polium ssp. capitatum	1, 4, 5, 6, 7, 17, 19, 22, 25, 48, 49
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• T. polium ssp. vincentinum	13, 16, 22, 143, 150, 151, 152
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• T. salviastrum	47, 57, 58, 59, 60, 86, 87, 91
• T. sandrasicum	19, 20, 197, 198, 199, 200, 201, 202, 203
• T. scordioides	----
• T. scordium (Bulgarian chemotype)	51, 71, 72, 77, 79, 80, 82, 84, 94
• T. scordium (German chemotype)	20, 30, 31, 47, 72, 73, 77, 78, 79, 80, 81, 82, 83
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• T. scorodonia ssp. scorodonia (Spanish chemotype)	9, 54, 55, 68, 85, 99, 100
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• •T. yemense	**184, 185, 186, 187**

REFERENCES

1. F. Piozzi, *Heterocycles*, 1981, **15**, 1489.
2. F. Piozzi, G. Savona, and B. Rodriguez, *Heterocycles*, 1987, **25**, 807.
3. F. Piozzi, *Heterocycles*, 1994, **37**, 603.
4. C. E. Tonn, J. A. Caltabiano, J. C. Gianello, and O. S. Giordano, *Rev. Latinoamer. Quim.*, 1990, **21**, 52.
5. J. Jakupovic, R. N. Baruah, F. Bohlmann, and W. Quack, *Planta Medica*, 1985, **51**, 341.
6. A. M. Galstyan, A. S. Shashkov, G. B. Oganesyan, V. A. Mnatsakanyan, and E. P. Serebryakov, *Khim. Prir. Soedin*, 1992, **28**, 503.
7. N. Xie, Z. Min, S. Zhao, B. Wu, Q. Zheng, and P. Zhang, *Phytochemistry*, 1991, **30**, 1963.
8. H. Sun, X. Chen, T. Wang, L. Pan, Z. Lin, and D. Chen, *Phytochemistry*, 1991, **30**, 1721.
9. N. Xie, Z. Min, S. Zhao, Y. Lu, Q. Zheng, C. Wang, M. Mizuno, M. Iinuma, and T. Tanaka, *Chem. Pharm. Bull.*, 1992, **40**, 2193.
10. D.-A. Sun and G.-Y. Li, *Phytochemistry*, 1993, **33**, 716.
11. B. Rodriguez, M. C. de la Torre, M. Bruno, C. Fazio, F. Piozzi, G. Savona, A. Perales, and N. A. Arnold, *Tetrahedron*, 1994, **50**, 2289.
12. B. Rodriguez, M. C. de la Torre, M. L. Jimeno, M. Bruno, C. Fazio, F. Piozzi, G. Savona, and A. Perales, *Tetrahedron*, 1995, **51**, 837.
13. M. Bruno, A. A. Omar, A. Perales, F. Piozzi, B. Rodriguez, G. Savona, and M. C. de la Torre, *Phytochemistry*, 1991, **30**, 275.
14. M. C. de la Torre, M. Bruno, F. Piozzi, G. Savona, B. Rodriguez, and A. A. Omar, *Phytochemistry*, 1991, **30**, 1603.
15. M. C. de la Torre, M. Bruno, F. Piozzi, G. Savona, A. A. Omar, A. Perales, and B. Rodriguez, *Tetrahedron*, 1991, **47**, 3463.
16. M. A. Al-Yahya, I. Muhammad, H. H. Mirza, F. S. El-Feraly, and A. T. McPhail, *J. Nat. Prod.*, 1993, **56**, 830.
17. M. A. Al-Yahya, I. Muhammad, H. H. Mirza, F. S. El-Feraly, and A. T. McPhail, *J. Nat. Prod.*, 1995, **58**, 633.
18. P. Y. Malakov, G. Y. Papanov, I. M. Boneva, M. C. de la Torre, and B. Rodriguez, *Phytochemistry*, 1993, **34**, 1095.

19. M. T. Davies-Coleman, J. R. Hanson, and D. E. A. Rivett, *Phytochemistry*, 1994, **36**, 1549.
20. S. Ladjel, K. Laamara, M. R. Y. Al-Hillo, and M. Pais, *Phytochemistry*, 1994, **37**, 1663.
21. M. Bruno, C. Fazio, F. Piozzi, G. Savona, B. Rodriguez, and M. C. de la Torre, *Phytochemistry*, 1995, **40**, 505.
22. M. Bruno, C. Fazio, F. Piozzi, B. Rodriguez, and M. C. de la Torre, *Phytochemistry*, 1995, **40**, 1481.
23. E. A. Sattar, J. S. Mossa, I. Muhammad, and F. S. El-Feraly, *Phytochemistry*, 1995, **40**, 1737.
24. H. Gaspar, F. M. S. Brito Palma, M. C. de la Torre, B. Rodriguez, and A. Perales, *Tetrahedron*, 1995, **51**, 2363.
25. G. Topcu, C. Eris, A. Ulubelen, M. Krawiec, and W. H. Watson, *Tetrahedron*, 1995, **51**, 11793.
26. G. Topcu, C. Eris and A. Ulubelen, *J. Nat. Prod.*, 1997, **60**, 1045.
27. I. Calis, E. Bedir, A. D. Wright, and O. Sticher, *J. Nat. Prod.*, 1996, **59**, 457.
28. G. Topcu, C. Eris, C. T. Che, and A. Ulubelen, *Phytochemistry*, 1996, **42**, 775.
29. M. C. de la Torre, B. Rodriguez, M. Bruno, C. Fazio, K. H. C. Baser, and H. Duman, *Phytochemistry,* 1997, **45**, 1653.
30. B. Rodriguez, M. C. de la Torre, M. Bruno, F. Piozzi, N. Vassallo, R. Ciriminna, and O. Servettaz, *Phytochemistry*, 1996, **43**, 435.
31. F. Camps, J. Coll, O. Dargallo, J. Rius, and C. Miravitlles, *Phytochemistry*, 1987, **26**, 1475.
32. B. Rodriguez, M. C. de la Torre, M. Bruno, F. Piozzi, N. Vassallo, R. Ciriminna, and O. Servettaz, *Phytochemistry*, 1997, **45**, 383.
33. O. Gallardo, C. E. Tonn, M. Nieto, G. Morales, and O. S. Giordano, *Nat. Prod. Letters,* 1996, **8**, 189.
34. B. Rodriguez, M. C. de la Torre, A. Perales, P. Y. Malakov, G. Y. Papanov, M. S. J. Simmonds, and W. M. Blaney, *Tetrahedron*, 1994, **50**, 5451.
35. W. Kisiel, F. Piozzi, and J. Grzybek, *Planta Medica*, 1995, **61**, 191.
36. F. Piozzi, M. Bruno, R. Ciriminna, C. Fazio, N. Vassallo, N. A. Arnold, M. C. de la Torre, and B. Rodriguez, *Planta Medica*, 1997, **63**, 483.
37. A. Ulubelen, G. Topcu, and S. Olcal, *Phytochemistry*, 1994, **37**, 1371.
38. H. Gaspar, F. M. S. Brito Palma, M. C. de la Torre, and B. Rodriguez, *Fitoterapia*, 1996, **67**, 188.
39. M. C. de la Torre, G. Dominguez, B. Rodriguez, A. Perales, M. S. J. Simmonds, and W. M. Blaney, *Tetrahedron*, 1994, **47**, 13553.
40. E. Mossner, M. C. de la Torre, and B. Rodriguez, *J. Nat. Prod.*, 1996, **59**, 367.
41. P. Y. Malakov, G. Y. Papanov, B. Rodriguez, M. C. de la Torre, M. S. J. Simmonds, W. M. Blaney, and I. M. Boneva, *Phytochemistry*, 1994, **37**, 147.
42. H.-M. Chen, Z.-D. Min, M. Iinuma, and T. Tanaka, *Heterocycles*, 1996, **43**, 611.
43. M. E. Sosa, C. E. Tonn, and O. S. Giordano, *J. Nat. Prod.*, 1994, **57**, 1262.
44. S. A. Kouzi, R. J. McMurtry, and S. D. Nelson, *Chem. Res. in Toxicology*, 1994, **7**, 850, and bibliography therein.
45. J. Loeper, V. Descatoire, P. Letteron, C. Moulis, C. Degott, P. Dansette, D. Fau, and D. Pessayre, *Gastroenterology*, 1994, **106**, 464, and bibliography therein.

46. W. Greuter, H. M. Burdet, and G. Long, 'Med-Checklist', Vol. 3, Conservatoire et Jardin Botaniques de la Ville de Genève, Genève, 1986, pp. 366-380.

Received, 17th June, 1998