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The Isolation and Structures of Novel Neolignans and Neosesquilignans from *Heterotropa takaoi* M.

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Several novel neolignans and neosesquilignans represented by heterotropanone and heterotropatrione, respectively, have been isolated from the plant *Heterotropa takaoi* M. and their structures also been elucidated on the basis of their spectral data closely related to that of asatone. From a biogenetic point of view, furthermore, these neolignans and neosesquilignans were chemically correlated to one another.

In the course of our searching for physiologically active substances in nature, we found two novel neolignans, asatone and isoasatone, in the plant *Asarum teitonense* Hayata (Taiton Kan-aoi in Japanese), the decoction of the stems and rhizomes of which has been used in Taiwan as a remedy for neuralgia by the local people.[1)] In connection with these two interesting neolignans, we further examined chemical components of the plant *Heterotropa takaoi* M. (Hime Kan-aoi in Japanese) and could isolate several new types of neolignan and neosesquilignan. In this paper, we wish to describe the isolation and structures of these compounds. From a biogenetic point of view, furthermore, chemical correlation among them is also presented.

Isolation of Neolignans and Neosesquilignans. Fresh leaves and roots of the above plant, which were collected at Sanage in Aichi Prefecture in April as well as in December, were disintegrated into large amounts of methanol, and then the methanol extract was partitioned between water and ethyl acetate. The ethyl acetate extract was roughly separated by column chromatography [silica gel (Mallinckrodt, 100 mesh)] using hexane–ethyl acetate (1:1) and then ethyl acetate to give several fractions. Each fraction was further separated by a combination of repeated column chromatography (silica gel, Florisil and/or alumina) and preparative TLC (Kieselgel PF_{254}) using hexane, ethyl acetate, chloroform and/or their mixed solvent to afford heterotropanone, isoheterotropanone, isoasatone A, isoasatone B, heterotropan, heterotropatrione and isoheterotropatrione in 0.00023, 0.00074, 0.0041, 0.0012, 0.00048, 0.00042, and 0.0019% yields, respectively,[2)] in addition to asatone as a main product (0.065% yield). All of them are new types of neolignan, of which the last two neolignans are regarded as a new class of neosesquilignan which consists of three C_6–C_3 units.

*The Structures of Heterotropanone (**1**) and Isoheterotropanone (**2**).* Heterotropanone and isoheterotropanone both have the same molecular formula [$C_{24}H_{32}O_7$(*m/e* 432(M^+))] and their spectral data are quite similar to each other, as described in Tables 1 and 2, indicating that these two neolignans must be stereoisomers.

Heterotropanone (**1**), which includes seven oxygen atoms in its molecular formula, has six methoxyl groups (δ 3.28, 3.34, 3.60, 3.82, and 3.84) and one CO group (ν_{max} 1745 cm^{-1}; δ 201.7). The presence of a partial structure [A] including 3,4,5-trimethoxyphenyl group

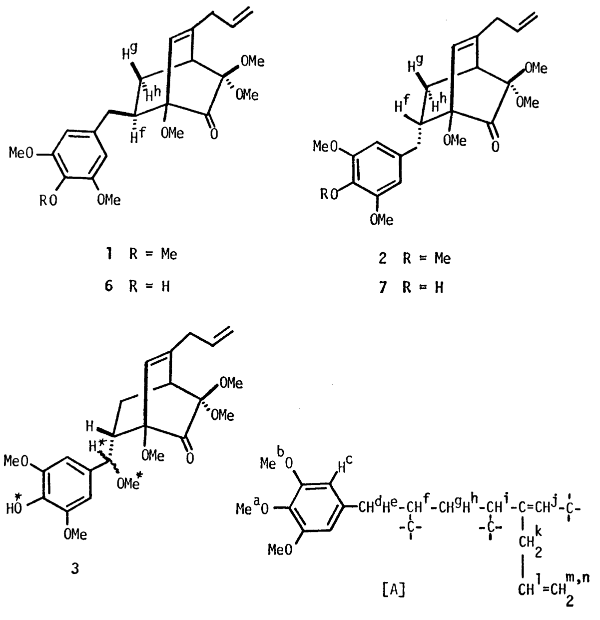


Fig. 1

can be confirmed by analysis of the ^1H NMR spectrum of **1** with aid of double resonance experiments [δ 3.82(H^a), 3.84(H^b), 6.35(H^c), 2.09(H^d),[3)] 3.10(H^e), 2.47(H^f), 1.13(H^g), 1.92(H^h), 2.81(H^i), 5.84(H^j), 2.99(H^k), 5.87(H^l), 5.13(H^m), and 5.15(H^n)]. On irradiation at δ 5.84, particularly, the signals assignable to H^i and H^k became triplet and slightly broad singlet, respectively. Furthermore, the signal at δ 5.84 was changed to slightly broad singlet on irradiation at δ 2.81 as well as at δ 2.99.[4)] As seen in Table 1, these spectral data are quite similar to those of the oxidation product (**3**), which has been electrochemically synthesized from 4-allyl-2,6-dimethoxyphenol,[5)] except for some asterisk-hydrogen atoms in **3**. For example, each δ-value assignable to H^i is in good agreement with one another (δ 2.81 in **1**; δ 2.82 in **2**; δ 2.82 in **3**). Particularly, an exhaustive comparison between **2** and **3** indicates that both compounds adopt the same stereochemistry. Furthermore, the ^{13}C NMR spectra of heterotropanone (**1**) and isoheterotropanone (**2**) indicate that both neolignans with a bicyclic carbon skeleton have the two quaternary carbon atoms (δ 86.1 and 94.2 in **1**; δ 86.5 and 94.7 in **2**), to which three methoxyl groups must be attached, and one CO group (δ 201.7 in **1**; δ 201.0 in **2**) in addition to the carbon atoms included in the partial structure [A]. The close similarity among **1**, **2**, and **3** was further

Table 1. ^{1}H NMR spectral data of heterotropanone (**1**), isoheterotropanone (**2**), and the anodic oxidation product (**3**)[5]

1	**2**	**3**
1.13 (1H, ddd, J=3, 5, 14 Hz)	1.52 (1H, ddd, J=3, 10, 14 Hz)	1.62 (1H, dd, J=3, 10 Hz)
1.92 (1H, ddd, J=3, 9, 14 Hz)	1.69 (1H, ddd, J=3, 5, 14 Hz)	1.62 (1H, dd, J=3, 8 Hz)
2.09 (1H, d, J=11 Hz)	2.07 (1H, d, J=12 Hz)	
2.47 (1H, m)	2.29 (1H, m)	2.22 (1H, ddd, J=2, 8, 10 Hz)
2.81 (1H, dt, J=2, 3 Hz)	2.82 (1H, dt, J=2, 3 Hz)	2.82 (1H, dt, J=2, 3 Hz)
2.99 (2H, br. d, J=7 Hz)	2.95 (2H, br. d, J=7 Hz)	2.98 (2H, br. d, J=6 Hz)
3.10 (1H, dd, J=3, 11 Hz)	3.12 (1H, dd, J=2, 12 Hz)	
3.28 (3H, s), 3.34 (3H, s)	3.42 (6H, s)	3.22 (3H, s), 3.23 (3H, s)
3.60 (3H, s), 3.82 (3H, s)	3.57 (3H, s), 3.84 (3H, s)	3.32 (3H, s), 3.63 (3H, s)
3.84 (6H, s)	3.87 (6H, s)	3.87 (6H, s)
		4.53 (1H, d, J=2 Hz)
5.13 (1H, tdd, J=1, 2, 9 Hz)	5.10 (1H, tdd, J=1, 2, 9 Hz)	5.16 (1H, br. d, J=10 Hz)
5.15 (1H, tdd, J=1, 2, 17 Hz)	5.12 (1H, tdd, J=1, 2, 17 Hz)	5.21 (1H, br. d, J=17 Hz)
5.84 (1H, br. s)	5.87 (1H, br. s)	5.83 (1H, br. s)
5.87 (1H, tdd, J=7, 9, 17 Hz)	5.79 (1H, tdd, J=7, 9, 17 Hz)	5.85 (1H, tdd, J=6, 10, 17 Hz)
6.35 (2H, s)	6.35 (2H, s)	6.43 (2H, s)

Table 2. ^{13}C NMR spectra of neolignans and neosesquilignans

	1[a]	**2**[a]	**5**	**8**[b]	**14**	**15**	
>C=O					201.3	200.4	(s)
	201.7	201.0	201.4	201.2	201.3	201.6	(s)
HC=C(OMe)-C=O			121.7	122.7	121.1	120.6	(d)
			150.2	150.2	150.2	150.5	(s)
			188.7	187.7	187.9	187.5	(s)
$-CH_2-CH=CH_2$	39.5	39.6	39.0		39.4	39.6	(t)
			41.3	41.5	41.1	41.4	(t)
			116.9		116.7	117.0	(t)
	117.2	117.3	118.2	117.3	117.1	117.4	(t)
	133.9	133.7	133.4		133.8	134.2	(d)
			135.2	135.0	134.8	135.2	(d)
-CH=C<			116.6	116.0	115.8	117.0	(d)
	118.8	120.2			120.7	120.6	(d)
			144.9	141.2	144.0	145.8	(s)
	144.8	146.2			144.0	146.6	(s)
-C(OMe)-	86.1	86.5			85.1	85.7	(s)
			92.1	91.8	91.8	91.6	(s)
$-C(OMe)_2$			93.2	93.3	93.2	93.4	(s)
	94.2	94.7			94.3	94.7	(s)
			98.7	98.5	98.3	98.2	(s)
MeO-	49.2	49.0			48.9	49.4	(q)
			50.1	50.2	49.5	49.4	(q)
			50.1	50.5	49.9	49.8	(q)
			50.2	50.5	49.9	50.3	(q)
			50.2	50.8	50.3	50.7	(q)
	50.7	50.7			50.6	50.7	(q)
	53.7	52.9			52.9	52.3	(q)
			54.8	54.8	54.6	54.7	(q)
			55.5	55.4	55.4	55.4	(q)
-C-			49.8	50.2	49.5	49.8	(s)
-CH-	39.7	41.4			33.0	36.9	(d)
	41.2	41.7			41.1	41.7	(d)
			43.9	39.6	43.9	44.1	(d)
			44.5	43.2	44.6	44.1	(d)
$-CH_2-$	27.1	26.2			28.0	27.1	(t)
	37.4	36.2			36.7	35.6	(t)

a) In the cases of **1** and **2**, the signals corresponding to the aromatic ring are not cited. b) In the case of **8**, the signals due to a 1-propenyl group are observed at δ 18.4(q), 128.2(d), and 128.7(d).

explained by their mass spectra, as follows.

The mass spectra of both heterotropanone (**1**) and isoheterotropanone (**2**) have two characteristic peaks at *m/e* 223 and 181, and the corresponding peaks are observed at *m/e* 223 and 197 in **3**. The common fragment ion at *m/e* 223 must be formed by retro-Diels-Alder reaction of **1**, **2**, and **3** on electron impact. Finally, the stereostructures of these two neolignans (**1** and **2**) were elucidated by a comparison of their ^{1}H NMR spectra.

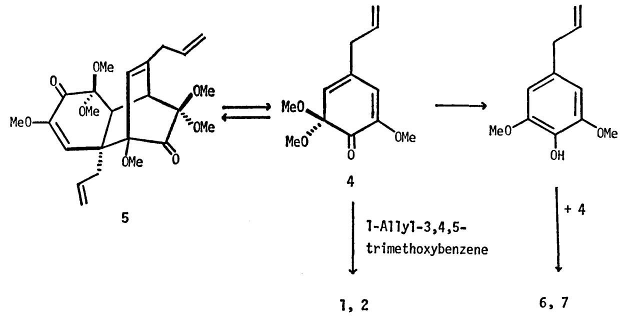
Of the two protons (H^g and H^h) in **1**, the signal at higher magnetic field (δ 1.13) can be assigned to H^g, whose coupling constant with H^f is 5 Hz, indicating that the relationship between H^g and H^f must be in a trans configuration. In the case of **2**, the corresponding one is 10 Hz, indicating that the dihedral angle between H^g and H^f is ≈0°. From the above results, the stereostructures of heterotropanone and isoheterotropanone can be represented by **1** and **2**, respectively.

From a biogenetic point of view, these two neolignans seem to be produced *in vivo* from elemicin and an unstable dienone (**4**). Thus, they were synthesized by means of retro-Diels-Alder reaction of asatone (**5**) generating the desirable dienone (**4**), as follows.[6]

A mixture of asatone (1 equiv.) and 1-allyl-3,4,5-trimethoxybenzene (4 equiv.) in a sealed tube was heated at 175—180 °C for 1.5 h to afford heterotropanone (**1**) and isoheterotropanone (**2**) in 14 and 13% yields, respectively.[7] In addition, 4-allyl-2,6-dimethoxyphenol, demethylheterotropanone (**6**) and demethylisoheterotropanone (**7**) were also obtained in *ca.* 3, 1—2 and 1—2% yields, respectively. These two compounds (**6** and **7**) were readily converted into heterotropanone (**1**) and isoheterotropanone (**2**) in almost quantitative yields, using CH_2N_2 in ether containing methanol. Clearly, the dienone (**4**) as an important intermediate was competitively decomposed into 4-allyl-2,6-dimethoxyphenol, as shown in Scheme 1. Similarly, when heated in mesitylene, instead of 1-allyl-3,4,5-trimethoxybenzene (160—165 °C, 2.5 h), asatone (**5**) was also converted into **6**, **7**, and 4-allyl-2,6-dimethoxyphenol in 19, 18, and 27% yields, respectively.

*The Structures of Isoasatone A (**8**) and Isoasatone B (**9**).* Isoasatone A, which has the same molecular formula ($C_{24}H_{32}O_8$) as that of asatone (**5**),[1] shows the IR and mass spectra (ν_{max} 1745, 1720, and 1640 cm^{-1}; *m/e* 448 and 224) similar to those of asatone, indicating a close similarity of these two neolignans. In fact, on catalytic hydrogenation in ethyl acetate over 10% Pd–C, isoasatone A (**8**) was readily converted into tetrahydroasatone (**10**)[1] in 61% yield. As seen in Tables 2 and 3, however, only one different point is that isoasatone A has one 1-propenyl group (^{1}H NMR δ 1.73, 5.97, and 6.27; ^{13}C NMR δ 18.4, 128.2, and 128.7) instead of one of the two allyl groups in asatone (**5**). Particularly, the partial structure [B] including the 1-propenyl group in **8** was confirmed by the following double resonance experiments. On irradiation at δ 1.73, the olefinic proton signal at δ 6.27 was collapsed to a doublet (J=16 Hz) forming an AB system with the signal at δ 5.97, and the broad doublet at δ 5.66 was changed to a sharp doublet (J=2 Hz). On the other hand, the presence of the remaining allyl group is also confirmed by comparison of the ^{1}H NMR signals assignable to the methylene group (H^a and H^b) between **5** and **8**, as described in Table 3 (δ 2.15 and 2.60—2.95 in **5**; δ 2.34 and 2.76 in **8**). This is also supported by comparison of the δ-values of the allyl groups in the ^{13}C NMR spectra of **1**, **2**, **5** and **8** (see Table 2). Thus, the structure of isoasatone A can be represented by **8**.

Isoasatone B (**9**) with a molecular formula ($C_{24}H_{32}O_9$) has the following spectral data: *m/e* 464(M$^+$), 240 and 224; ν_{max} 3470, 1750, 1720, and 1640 cm^{-1}. As observed in the cases of asatone (**5**) and isoasatone A (**8**), the retro-Diels-Alder reaction of **9** took place on electron impact, leading to the formation of two fragment ions [**C** and **D**], to which the remarkable peaks at *m/e* 240 and 224 are assignable, respectively, suggesting that this neolignan has the same carbon skeleton as those of **5** and **8**. Finally, the structure of isoasatone B was unambiguously established as **9** on the basis of comparison of the ^{1}H NMR spectra between **8** and **9**, as shown in Table 3. Isoasatone B has a HO–CH$_2$–CH=CH– grouping (ν_{max} 3470 cm^{-1};



Scheme 1. Thermal reaction of asatone (**5**) in 1-allyl-3,4,5-trimethoxybenzene.

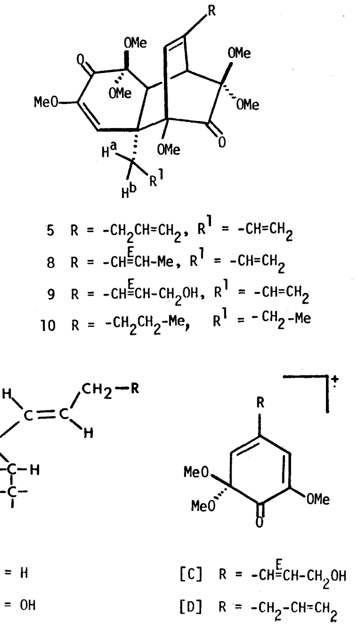


Fig. 2.

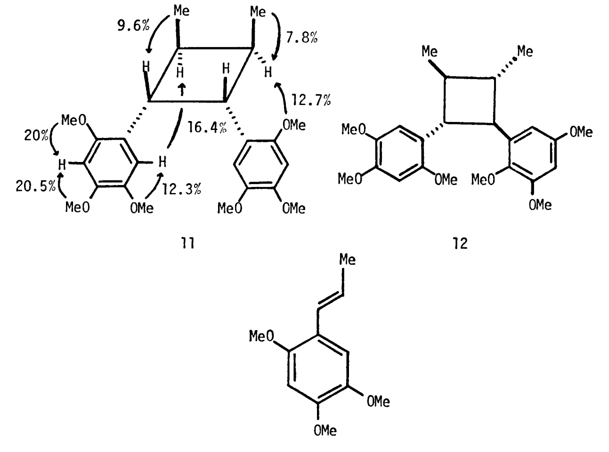
TABLE 3. ^{1}H NMR SPECTRAL DATA OF ASATONE (**5**), ISOASATONE A (**8**), AND ISOASATONE B (**9**)

5	**8**$^{a)}$	**9**
		2.30(1H, br. s, OH)
	1.73(3H, d, J=6 Hz)	
2.15(1H^a, dd, J=14.5, 7.5 Hz)	2.72(1H^a, dd, J=14, 7 Hz)$^{b)}$	2.31(1H^a, dd, J=14, 7 Hz)
2.6—2.95(2H+1H^b, complex)	2.95—3.52(2H+1H$^{b\ b)}$)$^{c)}$	2.80(1H^b, dd, J=14, 8 Hz)
2.88(2H, br. s)		3.35(1H, d, J=2 Hz)
		3.45—3.68(1H)$^{c)}$
3.05(3H, s), 3.31(3H, s)	3.00(3H, s), 3.18(3H, s)	3.10(3H, s), 3.31(3H, s)
3.38(3H, s), 3.42(3H, s)	3.20(3H, s), 3.30(3H, s)	3.45(3H, s), 3.53(3H, s)
3.47(3H, s), 3.60(3H, s)	3.45(3H, s), 3.46(3H, s)	3.55(3H, s), 3.62(3H, s)
		4.30(2H, d, J=4 Hz)
4.90—5.28(4H, complex)	5.23(1H, br. d, J=10 Hz)	5.09(1H, br. d, J=12 Hz)
	5.26(1H, br. d, J=17 Hz)	5.10(1H, br. d, J=16 Hz)
5.39(1H, s)	5.49(1H, s)	5.43(1H, s)
5.55(1H, q, J=2 Hz)	5.66(1H, br. d, J=2 Hz)	5.86(1H, br. d, J=2 Hz)
	5.97(1H, d, J=16 Hz)	6.09(1H, dt, J=16, 4 Hz)
	6.27(1H, dq, J=16, 6 Hz)	6.28(1H, d, J=16 Hz)
5.50—6.20(2H, complex)	6.40(1H, m)	5.92(1H, m)

a) ^{1}H NMR spectrum of **8** was measured in C_6D_6. b) δ($CDCl_3$) 2.34(1H^a, dd, J=14, 7 Hz) and 2.76(1H^b, dd, J=14, 8 Hz). c) Superimposed on MeO signals.

^{1}H NMR δ 2.30, 4.30, 6.09 and 6.28) in the partial structure [**E**], which is also confirmed by the double resonance experiments similar to those of isoasatone A (**8**) having one 1-propenyl group. The other remaining signals in their ^{1}H NMR spectra are quite similar to each other, particularly in the methylene proton signals (H^a and H^b).

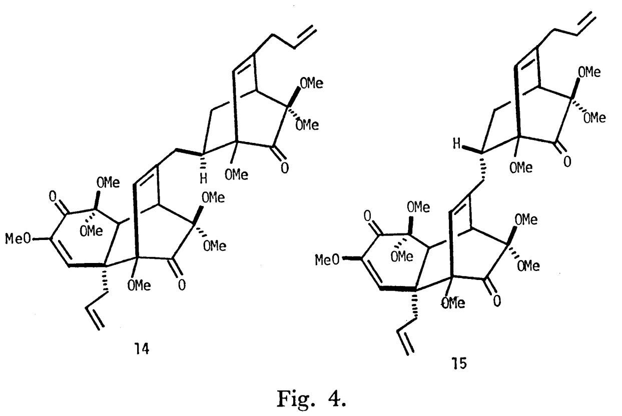
*The Structure of Heterotropan (**11**).* Heterotropan with a molecular formula [$C_{24}H_{32}O_6$ (m/e 416(M$^+$) and 208)] has a symmetric character in its structure, because only a half of the total number of protons and carbon atoms are found in its ^{1}H and ^{13}C NMR spectra: the former indicates the presence of two secondary methyl groups (δ 1.19), six methoxyl groups (δ 3.30, 3.42, and 3.54) and four methine protons (δ 2.78 and 4.15) in addition to two 1,2,4,5-tetrasubstituted aromatic rings (δ 6.11 and 6.66). This result is also compatible with the ^{13}C NMR spectrum of **11**. Thus, two possible stereostructures (**11** and **12**) were deduced from its ^{1}H NMR spectrum with aid of NOE measurements, as shown in **11**. Finally, the stereostructure of heterotropan was proved to be depicted as **11** by the following chemical evidence: E-asarone (**13**) was irradiated in hexane using Pyrex filter at room temperature to afford heterotropan (**11**) as the sole photodimer,[8] in 15% yield.[9]



11 12

13

Fig. 3.



14 15

Fig. 4.

*The Structures of Neosesquilignans, Heterotropatrione (**14**) and Isoheterotropatrione (**15**).* Heterotropatrione and isoheterotropatrione both have the same molecular formula ($C_{36}H_{48}O_{12}$), and their IR, ^{1}H NMR, and mass spectra are quite similar to each other, indicating that they are stereoisomers to each other. Particularly, the ^{1}H and ^{13}C NMR spectra of **14** and **15** indicate the presence of nine methoxyl groups and three CO groups as oxygen-containing functional groups. Furthermore, the same partial structure as that of asatone (**5**) in both **14** and **15** was elucidated by comparing their mass and ^{13}C NMR spectra with those of **5**, as follows.

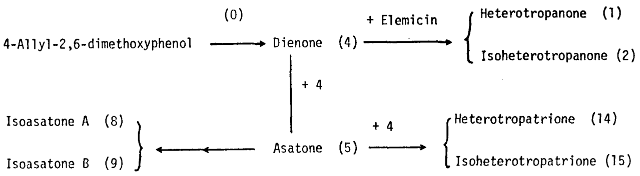
The mass spectra of these two neosesquilignans have a remarkable fragment peak at m/e 448, in addition to the molecular ion peak (m/e 672). The former must be generated by retro-Diels-Alder reaction of the original molecules on electron impact, as seen in the case of asatone [m/e 448(M$^+$) and 224]. As showm in Table 2, the ^{13}C NMR spectra of **14** and **15** include the signals corresponding to those of asatone (**5**). In addition, the remaining signals show the one to one correspondence to each carbon atom of heterotropanone (**1**) as well as of isoheterotropanone (**2**) except for the aromatic ring of **1** and **2**, suggesting that both **14** and **15** have the bicyclo[2.2.2]octane skeleton similar to that of **1** or **2**, as the partial structure.

Thus, there are two possibilities in a combination of the above two moieties. However, of the two allyl groups in asatone (**5**), the angular one must be present in both **14** and **15**, as judged by their ^{13}C NMR spectra which have the signals (δ 41.1, 117.1, and 134.8 in **14**; δ 41.4, 117.4, and 135.2 in **15**) corresponding to those of the angular allyl group in isoasatone A (**8**) (δ 41.5, 117.3, and 135.0). Finally, the stereostructures of heterotropatrione and isoheterotropatrione were elucidated by comparing their ^{1}H NMR spectra with those of heterotropanone (**1**) and isoheterotropanone (**2**) in addition to some chemical evidence, as follows.

Heterotropanone (**1**) has the ^{1}H NMR signals assignable to $\mathrm{H^g}$ at δ 1.13 (1H, ddd, J=3, 5, 14 Hz). In the case of heterotropatrione, the corresponding signal was also observed at δ 0.94 (1H, ddd, J=3, 4, 14 Hz). Accordingly, the stereostructure of heterotropatrione can be represented by **14**.[10] The stereostructure of isoheterotropatrione is also depicted as **15**,[10] on the basis of the ^{1}H NMR signals due to $\mathrm{H^g}$ and $\mathrm{H^h}$ (δ 1.41—1.92), as seen in the case of isoheterotropanone (**2**) which has the corresponding signal ($\mathrm{H^g}$) at δ 1.52 in addition to the signal ($\mathrm{H^h}$) at δ 1.69. In fact, these results were confirmed by the following chemical evidence.

As seen in the case of asatone (**5**) which has been converted into 4-allyl-2,6-dimethoxyphenol on zinc reduction, when treated with active zinc powder in AcOH (60 °C, 1 h), isoheterotropatrione (**15**) was readily converted into demethylisoheterotropanone (**7**) in 58.4% yield, in addition to 4-allyl-2,6-dimethoxyphenol.

Biogensis of Heterotropanone, Heterotropatrione, and Related Compounds. These novel neolignans and neosesquilignans occurring in the plant *Heterotropa takaoi* M., whose carbon skeleton consists of two or three C_6–C_3 units, are optically inactive and regarded as racemic compounds ($[\alpha]^{23}_{D}$ ±0°), as described in the cases of asatone (**5**) and isoasatone.[1] From a biogenetic point of view, 4-allyl-2,6-dimethoxyphenol is enzymatically oxidized to the optically inactive dienone (**4**), as an important precursor, from which a number of neolignans and related compounds are produced, as shown in Scheme 2. In fact, heterotropanone (**1**) and isoheterotropanone (**2**) both have been produced on Diels-Alder reaction between **4** and elemicin, as demonstrated in Scheme 1. On the other hand, two molecules of the dienone (**4**) react to each other to yield asatone (**5**),[11] from which both isoasatone A (**8**) and isoasatone B (**9**) may be produced. Presumably, further Diels-Alder reaction between asatone (**5**) and the dienone (**4**) affords both heterotropatrione (**14**) and isoheterotropatrione (**15**).



Scheme 2. Biogenesis of neolignans and neosesquilignans.

Experimental

All the melting points were uncorrected. ^{1}H and ^{13}C NMR spectra were taken on JEOL JNM-PS 100 (100 MHz) and JNM-FX 100 (25.0 MHz) spectrometers, respectively, using $CDCl_3$ as solvent, unless otherwise stated. Chemical shifts are given in ppm from TMS as an internal standard. Coupling constants are given in Hz (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet). IR spectra were recorded on a JASCO Model IR-S spectrophotometer. Mass spectra were obtained on a Hitachi RMU-6D mass spectrometer operating with an ionization energy (70 eV). Preparative TLC were carried out on Kieselgel PF_{254} (E. Merck A. G., Germany), unless otherwise stated.

Isolation of Neolignans and Neosesquilignans. Fresh leaves and roots of the plant *Heterotropa takaoi* M. (6.5 kg), which were collected as Sanage in Aichi Prefecture early in April, were pulverized with a mixer and immersed in MeOH (36 l) at room temperature for 45 d, and then filtered. The filtrates were concentrated under reduced pressure below 35 °C to leave a greenish brown residue (343 g) which was partitioned between water and AcOEt. The AcOEt layer was dried over large amounts of Na_2SO_4 and then concentrated under reduced pressure to leave a greenish brown oil (29.4 g) which was directly chromatographed on silica gel (Mallinckrodt, 100 mesh) (1350 g) and eluted successively with 3, 3.8 and 11.6 l of hexane–AcOEt (2:1) to afford three fractions (I, 4.9 g; II, 0.49 g; III, 2.3 g) after removal of the nonpolar fraction containing hydrocarbons using the same eluent (2.4 l). Further successive elution with 3.8 l of hexane–AcOEt (1:1) and then with AcOEt (1.5 l) gave two fractions (IV, 1.1 g; V, 1.0 g). Each fraction was further separated by a combination of repeated column chromatography and preparative TLC, as follows.

The fraction I was allowed to stand at room temperature to give a greenish brown solid, which was crystallized from hexane and collected by filtration to afford asatone (**5**)[1] (3.6 g). The filtrate was chromatographed on Florisil (150 g) using hexane–AcOEt (3:1) to give an oil, which was directly rechromatographed on silica gel (Mallinckrodt, 100 mesh) (50 g) and eluted with the same mixed solvent to afford asatone (600 mg). Further elution with the same mixed solvent gave an almost colorless viscous liquid of heterotropanone (**1**) (15 mg): $[\alpha]^{23}_{D}$ ±0°; IR (film) 1745, 1635, 1590, 1510sh., and 1500 cm^{-1}; MS (70 eV), *m/e* 432 (M^+), 404, 389, 372, 223 and 181. Found: *m/e* 432.2125. Calcd for $C_{24}H_{32}O_7$: M, 432.2148.

The fraction II was chromatographed on silica gel (Mallinckrodt, 100 mesh) (25 g) using $CHCl_3$ to give an oil (33 mg) which was purified by preparative TLC using $CHCl_3$ to afford 3,4-dimethoxybenzaldehyde (15 mg) (IR and ^{1}H NMR spectra). Further elution with the the same solvent also gave an oil (162 mg), which was further subjected to preparative TLC using $CHCl_3$–AcOEt (20:1) to afford asatone (**5**) (47 mg) from the less polar fraction. From the polar fraction, isoheterotropanone (**2**) (43 mg) was obtained as a colorless viscous liquid: $[\alpha]^{23}_{D}$ ±0°; IR (film) 1750, 1640, 1590, 1510sh., and 1505 cm^{-1}; MS (70 eV), *m/e* 432 (M^+), 404, 389, 357, 223, and 181. Found: *m/e* 432.2161. Calcd for $C_{24}H_{32}O_7$: M, 432.2148.

The fraction III was roughly separated into two fractions A and B by column chromatography (Mallinckrodt, 100 mesh) (100 g) using hexane–AcOEt (4:1) and then hexane–AcOEt (2:1), respectively. Furthermore, the fraction A was chromatographed on silica gel (Mallinckrodt, 100 mesh; $CHCl_3$ as eluent) (50 g) and then on Florisil (50 g) using $CHCl_3$ as the same eluent to afford a viscous liquid, which was further chromatographed on alumina (Nakarai Chemicals, 100 mesh) (50 g) using hexane–AcOEt (2:1) to afford a crystalline solid of isoasatone A (**8**) (260 mg) in addition to a crude oil which was further purified by repeating preparative TLC [1) alumina, hexane–$CHCl_3$ (3:1); 2) 10% $AgNO_3$–SiO_2, hexane–AcOEt (1:1)] to afford a colorless viscous liquid of heterotropan (**11**) (31 mg), which was crystallized in a refrigerator. Both neoligans are characterized by their physical data: **8**: mp 122—124 °C (from hexane–ether); $[\alpha]^{23}_D$ ±0°; IR (Nujol) 1745, 1720 and 1640 cm^{-1}; MS (70 eV), *m/e* 448(M^+), 416, 384 and 224. Found: *m/e* 448.2117. Calcd for $C_{24}H_{32}O_8$: M, 448.2097. **11**: $[\alpha]^{23}_D$ ±0°; IR (film) 1610, 1590 and 1510 cm^{-1}; ^1H NMR (C_6D_6) δ=1.19 (6H, d, J=6 Hz),[12] 2.78 (2H, m), 3.30 (6H, s), 3.42 (6H, s), 3.54 (6H, s), 4.15 (2H, d, J=5.5 Hz),[12] 6.11 (2H, s) and 6.66 (2H, s); ^{13}C NMR δ=15.1(q), 34.0(d), 42.5(d), 56.1(q), 56.3(q), 56.7(q), 97.7(d), 112.4(d), 122.1(s), 142.3(s), 147.2(s) and 151.6(s). Found: *m/e* 416.2185. Calcd for $C_{24}H_{32}O_6$: M, 416.2199.

The fraction B was further chromatographed on silica gel (Mallinckrodt, 100 mesh) (100 g) using hexane–AcOEt (2:1) to give an oil (217 mg), which was subjected to repeated preparative TLC using hexane–AcOEt (2:1) and then $CHCl_3$–AcOEt (10:1) to give a viscous liquid which was further purified by preparative TLC (10% $AgNO_3$–SiO_2) using $CHCl_3$–AcOEt (10:1) to afford an almost colorless viscous liquid of heterotropatrione (**14**) (27 mg): $[\alpha]^{23}_D$ ±0°; IR (film) 1750br., 1730sh., and 1645 cm^{-1}; ^1H NMR δ=0.94 (1H, ddd, J=3, 4, 13 Hz), 1.94—2.99 (11H, complex), 3.04 (3H, s), 3.25 (3H, s), 3.27 (3H, s), 3.30 (3H, s), 3.34 (3H, s), 3.39 (3H, s), 3.47 (3H, s), 3.51 (3H, s), 3.57 (3H, s), 4.84—5.22 (4H, complex), 5.32 (1H, s), 5.45 (1H, br.s), 5.59 (1H, br.s) and 5.60—6.10 (2H, complex); MS (70 eV), *m/e* 672 (M^+), 644, 640, 565, 448 and 317. Found: *m/e* 672.3147. Calcd for $C_{36}H_{48}O_{12}$: M, 672.3145.

The fraction IV was chromatographed on silica gel (Mallinckrodt, 100 mesh) (30 g) using $CHCl_3$–AcOEt (10:1) to give a pale yellow oil (217 mg), which was subjected to preparative TLC using $CHCl_3$–AcOEt (10:1) to afford an almost colorless viscous liquid of isoheterotropatrione (**15**) (120 mg): $[\alpha]^{23}_D$ ±0°; IR (film) 1760, 1725 and 1645 cm^{-1}; ^1H NMR δ=1.41—1.92 (2H, complex), 2.0—3.0 (10H, complex), 3.05 (3H, s), 3.28 (3H, s), 3.32 (3H, s), 3.33 (3H, s), 3.37 (3H, s), 3.38 (3H, s), 3.40 (3H, s), 3.47 (3H, s), 3.57 (3H, s), 4.88—5.23 (4H, complex), 5.04 (1H, br.s), 5.38 (1H, s), 5.39—6.07 (2H, complex) and 5.84 (1H, br.s); MS (70 eV), *m/e* 672 (M^+), 644, 640, 565, 448, 418, and 343. Found: *m/e* 672.3149. Calcd for $C_{36}H_{48}O_{12}$: M, 672.3145.

The fraction V was subjected to preparative TLC using AcOEt to give a slightly greenish oil, which was further purified by preparative TLC using benzene–acetone (1:1) to give a crystalline solid of isoasatone B (**9**) (76 mg):[13] mp 129—131 °C (from hexane–ether); $[\alpha]^{23}_D$ ±0°; IR (KBr) 3470, 1750, 1720, and 1640 cm^{-1}; MS (70 eV), *m/e* 464(M^+), 432, 400, 368, 327, 240, and 224. Found: *m/e* 464.2058. Calcd for $C_{24}H_{32}O_9$: M, 464.2046.

*Synthesis of Heterotropanone (**1**) and Isoheterotropanone (**2**).* A solution of asatone (**5**) (44.8 mg) in 1-allyl-3,4,5-trimethoxybenzene (165 mg) in a sealed tube was heated at 175—180 °C for 1.5 h and then cooled to leave a pale brown oil, which was separated by preparative TLC using hexane–AcOEt (1:1) to afford 1-allyl-3,4,5-trimethoxybenzene (121 mg), 4-allyl-2,6-dimethoxyphenol (7.8 mg), heterotropanone (**1**) (12 mg), isoheterotropanone (**2**) (11.6 mg), demethylheterotropanone (**6**) (*ca.* 1 mg) and demethylisoheterotropanone (**7**) (*ca.* 1 mg). The first four products were identified by comparing their TLC [hexane–AcOEt (3:1)] and IR spectra with those of each authentic sample. Demethyl compounds (**6** and **7**) were characterized by their spectral data: **6** as a pale yellow oil: IR (film) 3500br., 1750, 1610, and 1520 cm^{-1}; MS (70 eV), *m/e* 418(M^+), 343, 285, and 167. Found: *m/e* 418.2010. Calcd for $C_{23}H_{30}O_7$: M, 418.1991. **7** as an almost colorless oil; IR (film) 3500 br., 1755, 1615, and 1520 cm^{-1}; MS (70 eV), *m/e* 418 (M^+), 343, 285, and 167. Found: *m/e* 418.2012. Calcd for $C_{23}H_{30}O_7$: M, 418.1991. Furthermore, these two phenols (**6** and **7**) were dissolved in excess CH_2N_2 in ether (20 ml) containing MeOH (5 ml), allowed to stand at room temperature overnight and then concentrated under reduced pressure to leave the corresponding methyl ethers (**1** and **2**) in quantitative yields, respectively [TLC (hexane–AcOEt (3:1) and IR spectra].

*Thermal Reaction of Asatone (**5**).* A solution of asatone (39 mg) in mesitylene (1 ml) was gently heated under reflux for 2.5 h, and then concentrated under reduced pressure to leave a pale yellow oil, which was subjected to preparative TLC using hexane–AcOEt (1:1) to afford 4-allyl-2,6-dimethoxyphenol (9.2 mg), demethylheterotropanone (**6**) (7.1 mg) and demethylisoheterotropanone (**7**) (6.0 mg) [TLC (hexane–AcOEt (1:1) and IR spectra].

*Catalytic Hydrogenation of Isoasatone A (**8**).* Catalytic hydrogenation of isoasatone (15 mg) in AcOEt (2 ml) was carried out over 10% Pd–C (5 mg) at room temperature overnight. After filtration of the catalyst, the solvent was evaporated under reduced pressure to leave a white crystalline solid, which was purified by preparative TLC using hexane–AcOEt (3:1) to afford white crystals of tetrahydroasatone (**10**) (9.2 mg) (mp and IR spectrum).[1]

*Synthesis of Heterotropan (**11**).* A solution of *E*-asarone (40 mg) in hexane (5 ml) was irradiated at room temperature for 10 d, using Pyrex filter [apparatus: Eiko-Sha PIH-100, high pressure Hg lamp (100 W)]. The reaction solution was then evaporated under reduced pressure to leave a pale yiellow oil, which was purified by preparative TLC using hexane–AcOEt (3:1). From the more polar fraction corresponding to that of heterotropan (**11**), a colorless viscous liquid (*ca.* 6 mg) was obtained [TLC (hexane–AcOEt (3:1)) and IR spectrum]. From the less polar fraction, a mixture of *E*- and *Z*-asarones (*ca.* 30 mg) was obtained without further purification.

*Zinc Reduction of Isoheterotropatrione (**15**).* A mixture of isoheterotropatrione (115 mg) and activated zinc powder[14] (500 mg) in AcOH (2 ml) was heated at 60 °C, with stirring, for 1 h, and then poured into a lot of water, and then extracted with AcOEt. The extract was successively washed with dil. $NaHCO_3$ aq solution and sat. NaCl aq solution, and then dried over Na_2SO_4. Removal of the solvent under reduced pressure afforded a brown oil (76.7 mg), which was subjected to preparative TLC using $CHCl_3$–AcOEt (10:1). From the less polar fraction, 4-allyl-2,6-dimethoxyphenol (30 mg) was obtained [TLC (hexane–AcOEt (3:1)) and IR spectrum]. From the polar fraction, a colorless viscous liquid (41.8 mg) was obtained, whose TLC (hexane–AcOEt (1:1)) and IR spectrum were completely identical with those of demethylisoheterotropanone (**7**).

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References

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4) The signal at δ 5.87 became sharp doublet of doublet.

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7) 1-Allyl-3,4,5-trimethoxybenzene was recovered in *ca.* 70% yield.

8) A mixture of *E*- and *Z*-asarones was recovered.

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10) Heterotropatrione and isoheterotropatrione both are optically inactive and regareded as racemic compounds, and the diastereoisomeric structures corresponding to **14** and **15** can not be ruled out.

11) Asatone (**5**) has been successfully synthesized on anodic oxidation of 4-allyl-2,6-dimethoxyphenol (See Ref. 5).

12) A virtual coupling is observed.

13) This neolignan has been mainly isolated from the same plant collected early in December.

14) Zinc powder was activated according to the same procedure as described in the following paper: S. Yamamura, M. Toda, and Y. Hirata, *Org. Synth.*, **53**, 86 (1973).