Celery and More Phthalide Lactones—Chemistry and Flavor

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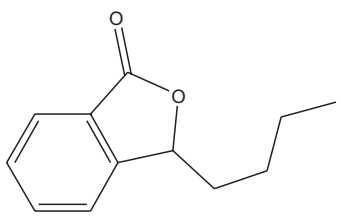
Apium graveolens Linn. (*Apiaceae*) is commonly known as celery.[1] It is an erect, annual or biennial herb. The roots are numerous, succulent and well developed. The stem branches are angular or fistular, and are conspicuously jointed. The leaves are oblong to obovate, pinnate or trifoliolate. The leaflets are ovate to suborbicular and three-lobed. The flowers are white or greenish white and very small. The fruit is a schizocarp consisting of two mericarps, suborbicular to ellipsoid, grayish brown to brown with pale ridges, aromatic and slightly bitter.[2]

Celery contains a few phthalide-derived lactone molecules. One of the most significant contributors to the celery flavor is celery lactone—3-n-butylphthalide (FEMA# 3334, CAS# 6066-49-5; **F-1**). This lactone occurs both in celery and lovage[a]. It has an aromatic spicy, celery- and lovagelike odor and flavor, and it is used in spicy and vegetable soup flavorings.

Another phthalide lactone derivative in celery is 3-propylidenephthalide (CAS# 17369-59-4; **F-2**). This unsaturated side chain phthalide occurs also in celery and lovage. It has a spicy, strongly celerylike odor and flavor, with green, sweet and lovage with vegetative and herbal nuances. Spicy (celery, lovage) flavorings can use 3-propylidenephthalide, as can maple and brown sugar, herbal notes and celery tonics.

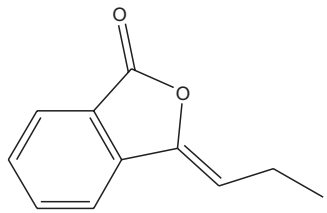
[a] Some of the information on organoleptic properties and uses are taken from FRM 2001 *Database of Flavour Raw Materials*, Boelens Aroma Chemicals Information Services, The Netherlands.

3-n-Butylphthalide **F-1**



3-n-Butylphthalide
FEMA# 3334 CAS# 6066-49-5

3-Propylidenephthalide **F-2**



3-Propylidenephthalide

Celery contains several additional lactones in which the aromatic ring is partly hydrogenated: sedanolide (CAS# 6415-59-4), ligustilide (CAS# 4431-01-0), sedanenolide (CAS# 63038-10-8), ligustilide B (CAS# 166733-97-7) and ligustilidiol (CAS# 88551-87-5) (**F-3**).

Physical Data for 3-n-Butylphthalide

Appearance: Colorless clear oily liquid

Molecular formula: $C_{12}H_{14}O_2$

M.W.: 190.24

Specific gravity: 1.6510 to 1.0695 25°C

Refractive index: 1.5180 to 1.5320 20°C

Acid value: 1.00 max. mgKOH/g

Flash point: 128°C TCC (263°F)

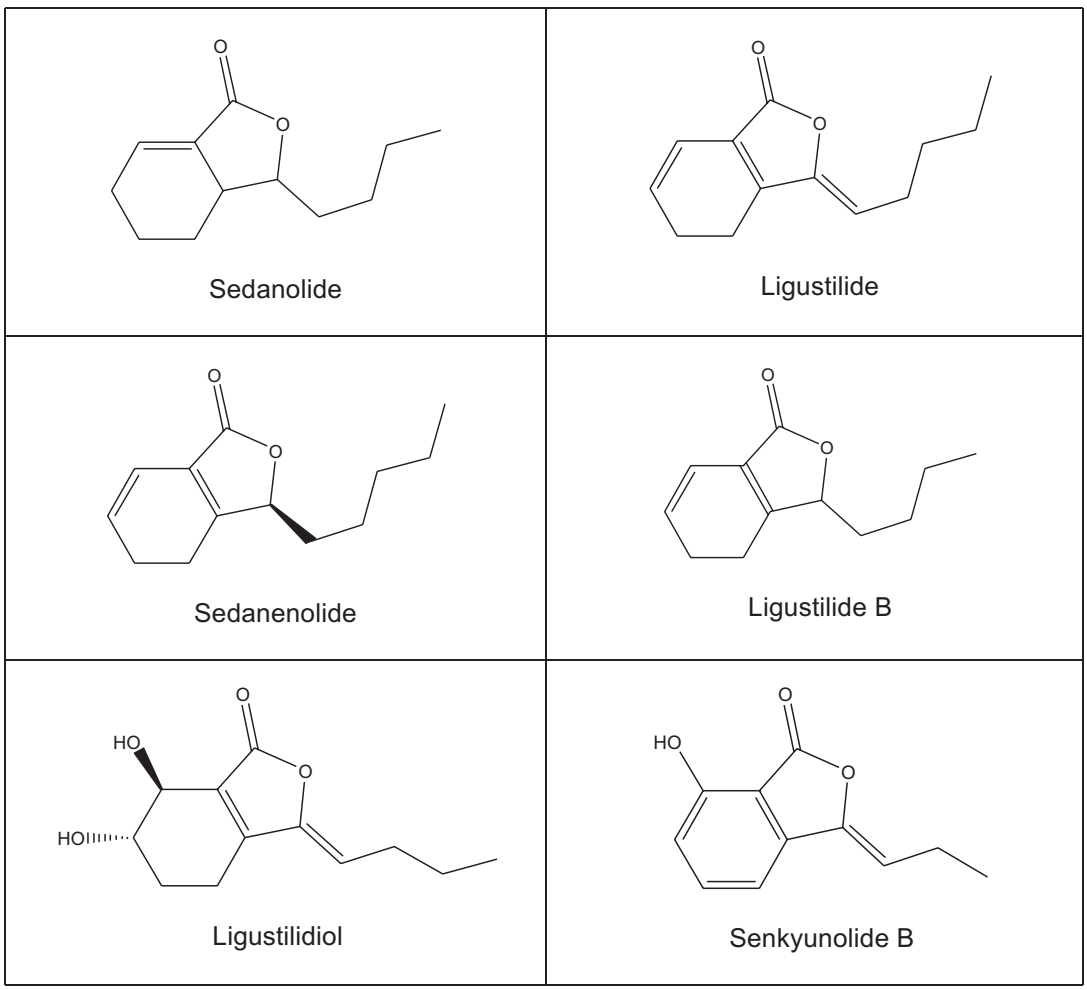
logP (o/w): 2.80

Additional phthalide lactone derivatives that are found in a ligusticum species called *Ligusticum wallichii* (Szechuan lovage) include senkyunolide B (CAS# 93236-67-0), 1(3H)-isobenzofuranone, 6,7-bis(acetyloxy)-3-butylidene-4,5,6,7-tetrahydro-, (3Z,6a,7a)- [CAS# 93236-68-1], 1(3H)-isobenzofuranone, 6,7-bis(benzoyloxy)-3-butylidene-4,5,6,7-tetrahydro-, (3Z,6a,7a)-(CAS# 93236-69-2), (Z)-6,7-*cis*-dihydroxyligustilide (CAS# 93379-53-4) and wallichilide (CAS# 93236-64-7) (**F-4**).[3]

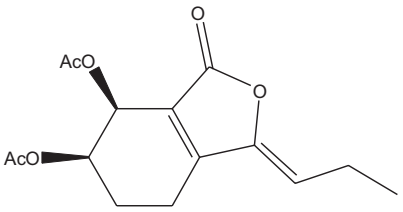
Ligusticum wallichii is a flowering plant in the carrot family best known for its use in traditional Chinese medicine where it is considered one of the 50 fundamental herbs.

T Hasegawa-developed salty taste improvers contain phthalides, e.g., sedanenolide, sedanolide, 3-n-butylphthalide and 3-butylidenephthalide. These phthalides reduce salt stimulation without giving unnecessary taste or flavor to foods including Japanese confectionery, Western confectionery, snacks, flour paste, peanut paste, pickles, *tsukudani* (foods boiled in soy sauce), salted fish, ham, sausage, bacon, *kamaboko* (cured seafood product),

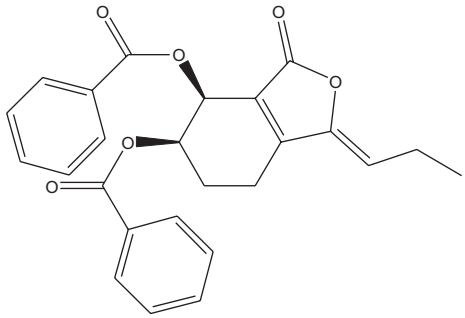
Celery contains several additional lactones in which the aromatic ring is partly hydrogenated **F-3**



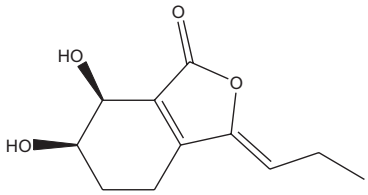
Phthalide lactone derivatives found in a ligusticum species called *Ligusticum wallichii* F-4



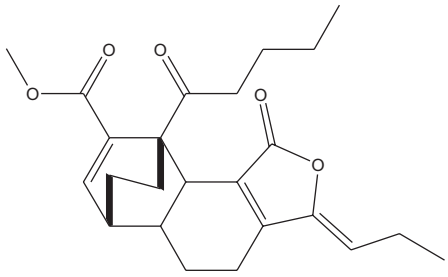
1(3H)-Isobenzofuranone, 6,7-bis(acetyloxy)-3-butylidene-4,5,6,7-tetrahydro-, (3Z,6α,7α)-



1(3H)-Isobenzofuranone, 6,7-bis(benzoyloxy)-3-butylidene-4,5,6,7-tetrahydro-, (3Z,6α,7α)-

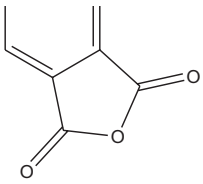


(Z)-6,7-*cis*-Dihydroxyligustilide

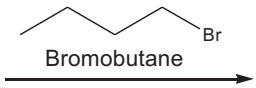


Wallichilide 93236-64-7

A synthetic method of making 3-n-butylphthalide F-5

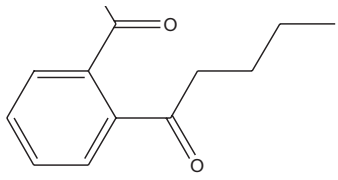


Phthalic anhydride



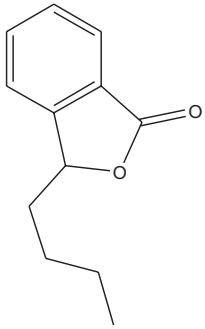
Bromobutane

Mg, THF



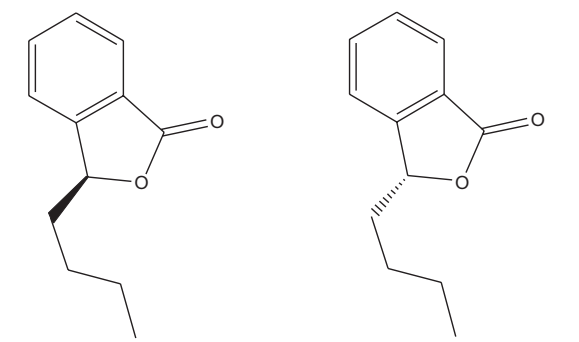
o-Valerylbenzoic acid

$NaBH_4$



3-n-Butylphthalide

3-n-Butylphthalide has two possible enantiomers **F-6**



(S)-3-n-Butylphthalide (R)-3-n-Butylphthalide

curry, miso, soy sauce, mash, sauce, ketchup, mayonnaise, dressing and grilled meat sauce.[4]

According to another T Hasegawa patent, bitterness-masking agents and astringency-masking agents contain phthalides (e.g., sedanenolide, sedanolide, 3-n-butylphthalide and 3-butylidenephthalide) as active components for bitter and astringent foods and drinks (e.g., green tea beverage). The compounds contain 10 ppb to 1% (as phthalides) of the agents.[5]

Another T Hasegawa patent describes phthalide lactones derivatives using sweet taste improvers for foods and drinks with sweet taste. Examples for foods and drinks with sweet taste are fruit juice, vegetable juice, soft drinks, coffee, tea drinks, cocoa, milk, tofu, lactic acid drink, yogurt, jelly, pudding, mousse, chilled desserts, Western confectionery, Japanese confectionery, ice cream, hard candy, nougat, tablet confectionery, chewing gum, jelly beans, fruit-flavor sauce, chocolate sauce, butter cream, fresh cream, jam, confectionery bread, bread, sauce for grilling meat, tomato ketchup, pickled fish products and *tsukudani*. These taste improvers are enhancers of sweet taste and are mainly sedanenolide, sedanolide, 3-n-butylphthalide and 3-butylidenephthalide.[6]

Synthesis of 3-n-Butylphthalide

One of the synthetic methods of making 3-n-butylphthalide (**F-5**) allows halogenated butane to react with a magnesium sheet in the presence of iodine and THF at 120–160°F to obtain a Grignard reagent of halogenated butane, followed by dropping the above Grignard reagent in a mixture of THF, phthalic anhydride and copper salt at -5–20°F. After work up, o-valeryl-benzoic acid crude product is obtained. Mixing with 5% NaOH(aq) under stirring for one hour, cooling to 32°F, slowly adding sodium borohydride at 0–10°C, and further work-up yields 3-n-butylphthalide. According to the authors, this method has advantages of easily obtained raw materials, simple operation, easy industrialization, yields of 50–60% and product purity of 97–98%.[7]

SAR (Structure-activity Relationship) of 3-n-Butylphthalide

Due to the existence of a chiral center at position 3, this phthalide has two possible enantiomers—3R and 3S. (**F-6**)

According to Mosandl et al., (R)-3-n-butylphthalide (CAS# 125412-70-6) has an herbaceous, celerylike odor typical of celery and celeriac[b,8] This enantiomer shows a significantly lower φ value than does the (S)-enantiomer, φ value = 6.96 x 10^5. The (S)-3-n-butylphthalide (3413-15-8) also has an herbaceous, celerylike odor; however, the (S) enantiomer shows a significantly higher φ value than does the (3R)-enantiomer, φ value = 7.04 x 10^8. The authors investigation of the essential oil of celery seed shows enantiomeric distributions in the range of 95:5 in favor of the (S)-enantiomer.

The two enantiomers of 3-n-butylphthalide were resolved through chiral liquid chromatography. The chiral stationary phase was the reaction products of several polysaccharides with benzoyl chloride (CAS# 98-88-4) or phenyl isocyanate (CAS# 103-71-9). According to the authors, this method is quick and simple, and the stationary phase has high column capacity and stability.[9]

[b] Odor descriptions are from *Leffingwell, Flavor-Base 2001—The 3-Butylphthalides, Chirality & Odour Perception*, JC Leffingwell

References

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