Pergamon

Tetrahedron 56 (2000) 2533–2545

TETRAHEDRON

Regioselective Synthesis of Natural and Unnatural (*Z*)-3-(1-Alkylidene)phthalides and 3-Substituted Isocoumarins Starting from Methyl 2-Hydroxybenzoates

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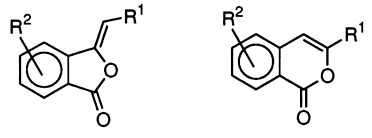
Received 10 December 1999; revised 24 January 2000; accepted 10 February 2000

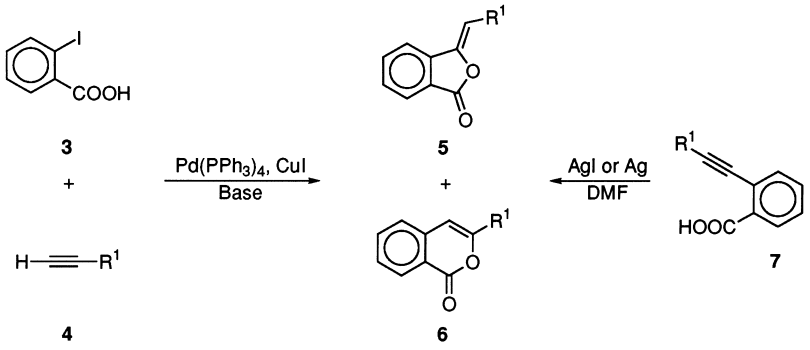
Abstract—(*Z*)-3-(1-Alkylidene)phthalides and 3-substituted isocoumarins, which include compounds bearing a substituent on their benzene ring, have been selectively and efficiently synthesized by a new protocol which involves: (i) the conversion of methyl 2-hydroxybenzoates into the corresponding nonaflates; (ii) Pd-catalyzed alkynylation reactions of these derivatives; (iii) the conversion of the so obtained methyl 2-(1-alkynyl)benzoates into the corresponding carboxylic acids followed by a transition metal-catalyzed heteroannulation reaction. This procedure has been used to prepare either natural products such as senkyunolide B, senkyunolide C, 3-propylisocoumarin and artemidin, or the MEM-ether of senkyunolide E. The regioselectivity of the transition metal-catalyzed cyclization reactions of 2-(1-alkynyl)benzoic acids has proven to be affected either by the catalyst used or the type of 1-alkynyl group present in these carboxylic acids.

Introduction

(*Z*)-3-(1-Alkylidene)phthalides **1** represent an important class of naturally occurring lactones,[1] which are characterized by interesting biological properties. In fact, compounds **1**, which have been isolated from the rhizome of *Cnidium* species or *Ligusticum wallichi*, commonly known as *Senkyu* in Japan, are used in the treatment of anemia and women's disease,[2] as cardiokinetics, antistenocardiacs, antiarrhytmics, vasodilators and coronary artery dilators.[3] Moreover, antispasmodic activity has been observed for a series of synthetic compounds of general formula **1**.[4] A wide range of biological and pharmacological activities are also displayed by 3-substituted isocoumarins of general formula **2**, which correspond to regioisomers of compounds **1**.[5,6] Thus, a number of methods have been reported for the synthesis either of compounds **1**[7,8] or **2**.[9]



1 **2**



Scheme 1.

Keywords: cross-coupling reactions; heteroannulation reactions; regioselectivity; transition metal catalysts.
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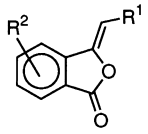
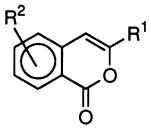
0040–4020/00/$ - see front matter
PII: S0040-4020(00)00125-3

Recently, much attention has been particularly directed to the selective synthesis of 3-ylidenephthalides and 3-substituted isocoumarins, which do not contain a substituent on their benzene ring, by transition metal-catalyzed heteroannulation reactions.[7d,7f,9d,9e] In particular, it has been found that (*Z*)-3-(1-alkylidene)-phthalides **5** and 3-substituted isocoumarins **6** can be obtained as major and minor products, respectively, either by reaction of 2-iodobenzoic acid (**3**) with 1-alkynes (**4**) in the presence of a base and catalytic quantities of $Pd(PPh_3)_4$ and CuI[7f] or by cyclization of 2-(1-alkynyl)benzoic acids **7** in DMF solution in the presence of catalytic amounts of AgI or Ag[7d] (Scheme 1).

However, these transition metal-catalyzed reactions have not been used so far to prepare naturally-occurring (*Z*)-3-(1-alkylidene)phthalides save (*Z*)-3-(1-butylidene)phthalide (**1a**),[7d] a substance which has been isolated from *Levisticum officinale*[1a] and *Apium graveolens dulce*.[10]



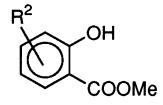
1a : $R^1 = C_3H_7$; R^2 = H
1b : $R^1 = C_3H_7$; R^2 = 4-OMe
1c : $R^1 = C_3H_7$; R^2 = 5-OMe
1d : R^1 = (*E*)-C_2H_5-CH=CH-; R^2 = H
1e : $R^1 = C_2H_5CH(OH)$; R^2 = H
1f : $R^1 = C_2H_5CH(OMEM)$; R^2 = H
1g : $R^1 = C_3H_7$; R^2 = 4-OH
1h : $R^1 = C_3H_7$; R^2 = 5-OH



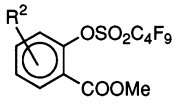
2a : $R^1 = C_3H_7$; R^2 = H
2b : $R^1 = C_3H_7$; R^2 = 5-OMe
2c : $R^1 = C_3H_7$; R^2 = 6-OMe
2d : R^1 = (*E*)-C_2H_5-CH=CH-; R^2 = H
2e : $R^1 = C_2H_5CH(OH)$; R^2 = H
2f : $R^1 = C_2H_5CH(OMEM)$; R^2 = H

It has also been reported that isocoumarins of general formula **6** can be obtained as major products by treatment of **3** with 1-alkynes **4** in the presence of $Pd(PPh_3)_4$, Et_3N and $ZnCl_2$ in DMF,[9e] by reaction of 2-(1-alkynyl)benzoic acids **7** with Et_3N and catalytic amounts of $PdCl_2(CH_3CN)_2$,[9f] by cyclization of compounds **7** in the presence of a mineral acid[11] as well as by CuI-catalyzed cyclization of these carboxylic acids prepared in situ from **3** and 1-alkynylcopper compounds.[9b] However, to the best of our knowledge, no catalytic method has been used so far to prepare 3-substituted isocoumarins of general formula **2** bearing a substituent on their benzene ring.

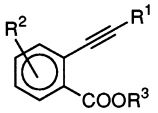
In the context of our studies on the transition metal-catalyzed synthesis of unsaturated lactones,[12] recently we developed a general procedure for the regioselective synthesis either of natural and unnatural 3-substituted isocoumarins **2** or direct precursors to naturally-occurring (*Z*)-3-ylidenephthalides **1** and their structural analogues. The protocol which we used to prepare these compounds involved: (i) the conversion of commercially available and cheap methyl 2-hydroxybenzoates **8** into the corresponding nonaflates **9**; (ii) Pd-catalyzed alkynylation reactions of compounds **9**; (iii) the conversion of the so obtained methyl 2-(1-alkynyl)benzoates **10** into the corresponding carboxylic acids **11** followed by selective 5-*exo*-*dig* or 6-*endo*-*dig* cyclization of these last compounds in the presence of catalytic amounts of Ag powder or $AgNO_3$, respectively.



8a : R^2 = H
8b : R^2 = 3-OMe
8c: R^2 = 4-OMe

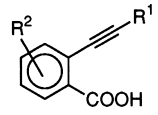


9a : R^2 = H
9b : R^2 = 3-OMe
9c : R^2 = 4-OMe



10 : R^3 = Me
11 : R^3 = H

In this paper we wish to describe in detail these synthetic studies which allowed us to prepare selectively compounds **1a**–**h** and **2a**–**e**. These substances include some natural products, i.e. senkyunolide B (**1g**),[1c] senkyunolide C (**1h**),[1e] senkyunolide E (**1e**),[1c] 3-propylisocoumarin (**2a**)[5c] and artemidin (**2d**).[5b] Moreover, we will show that the regioselectivity of the heteroannulation reactions of carboxylic acids **11a**–**d** and **11f** is strongly affected either by the catalyst used for these reactions, i.e. $AgNO_3$ or Ag powder, or the type of 1-alkynyl group present in these compounds.

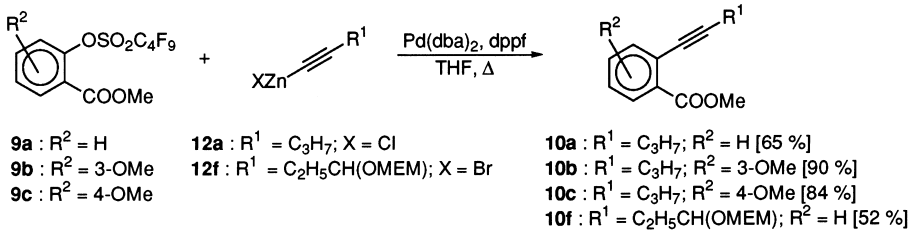


11a : $R^1 = C_3H_7$; R^2 = H
11b : $R^1 = C_3H_7$; R^2 = 3-OMe
11c : $R^1 = C_3H_7$; R^2 = 4-OMe
11d : R^1 = (*E*)-C_2H_5-CH=CH-; R^2 = H
11f : $R^1 = C_2H_5CH(OMEM)$; R^2 = H

Finally, we will report that, whereas saponification of compounds **10**, which have been prepared by Pd-catalyzed reaction of nonaflates **9** with 1-alkynylzinc halides or a 1-alkynylstannane, followed by acidification, affords the desired carboxylic acids **11**, an analogous reaction sequence involving compounds **10**, which have been prepared by treatment of **9** with 1-alkynes **4** in the presence of catalytic amounts of $Pd(PPh_3)_4$ and CuI, provides heteroannulation products which consist of 3-substituted isocoumarins **2** or mixtures of **2** and the corresponding compounds **1**.

Results and Discussion

Commercially available methyl 2-hydroxybenzoates **8a**–**c**, which we used as starting materials for the synthesis of carboxylic acids of general formula **11**, were converted in



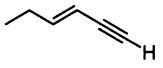
Scheme 2.

quantitative yield into the corresponding crude nonaflates **9a**–**c** by reaction with 1.5 equiv. of NaH in DMF at 0°C followed by treatment with 1.5 equiv. of perfluoro-1-butanesulfonyl fluoride at 0°C for 1.5 h and at room temperature for 3 h. So prepared crude compounds **9a**–**c**, which had chemical purity higher than 96%, were then converted into methyl 2-(1-alkynyl)benzoates of general formula **10** using three different procedures. The first of these (*Procedure A*), which involved the cross-coupling reaction between 1-alkynylzinc halides **12a**,**f** and compounds **9a**–**c** in THF at 65°C in the presence of catalytic amounts of $Pd(dba)_2$ and 1,1′-bis(diphenylphosphino)ferrocene (dppf), gave compounds **10a**, **10b**, **10c** and **10f** in 65, 90, 84 and 52% yield, respectively (Scheme 2).

1-Pentynylzinc chloride (**12a**) was prepared by treatment of 1-pentyne (**4a**) with 1 equiv of ethylmagnesium bromide in THF at 50°C followed by transmetallation of the resulting 1-pentynylmagnesium bromide with 1.3 equiv. of dry $ZnCl_2$ in THF at 0°C. 3-(2-Methoxyethoxymethoxy)-1-pentynylzinc bromide (**12f**) was prepared by treatment of the corresponding 1-alkyne, **4f**, with 1 equiv. of butyllithium in THF at −78°C followed by transmetallation of the resulting 1-alkynyllithium with 1.2 equiv. of dry $ZnBr_2$ in THF. On the other hand, compound **4f** was prepared by reaction of commercially available 1-pentyn-3-ol (**4e**) with 1.5 equiv. of MEM-chloride and 1.5 equiv. of $EtN(i\text{-}Pr)_2$ in CH_2Cl_2 at room temperature.

The second procedure for the synthesis of compounds **10** (*Procedure B*) involved the cross-coupling reaction of nonaflate **9a** with a 1-alkyne **4** in DMF at room temperature in the presence of Et_3N and catalytic amounts of $Pd(PPh_3)_4$ and CuI. Compounds **10a** and **10e** were so prepared in 75 and 84% yield starting from 1-pentyne (**4a**) and 1-pentyn-3-ol (**4e**), respectively, and **9a** (Scheme 3).

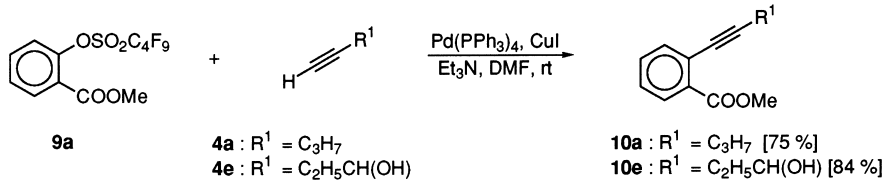
It must be noted that, despite their efficiency, above mentioned *Procedures A* and *B* did not appear suitable to prepare methyl (*E*)-2-(3-hexen-1-ynyl)benzoate (**10d**), which, according to our retrosynthetic analysis, was a precursor to artemidin (**2d**). In fact, these procedures required the use of (*E*)-3-hexen-1-yne (**4d**), which is a previously unreported substance for which an efficient synthesis seemed difficult owing to its volatility.



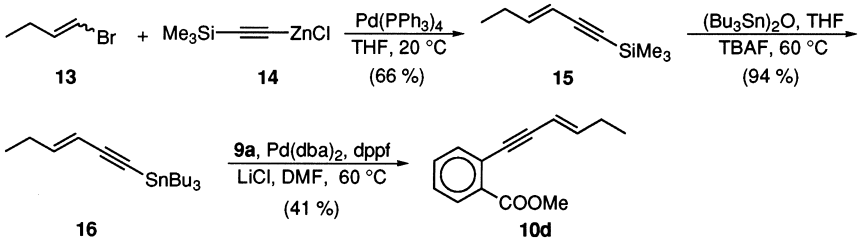
4d

Thus, we prepared compound **10d** by Pd-catalyzed cross-coupling reaction between **9a** and (*E*)-1-tributylstannyl-3-hexen-1-yne (**16**) (*Procedure C*), which was stereoselectively and efficiently synthesized in two steps starting from (*E*)/(*Z*)-1-bromo-1-butene (**13**) (Scheme 4).

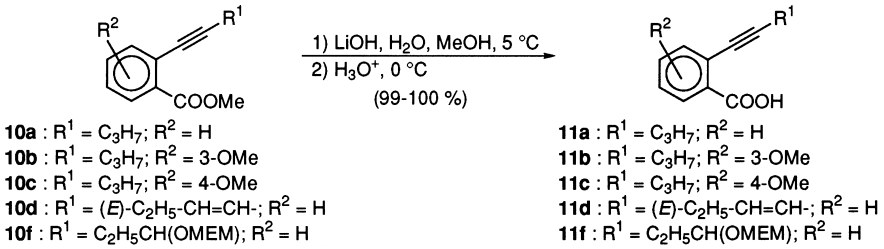
According to a general procedure for the stereoselective synthesis of (*E*)-1-trimethylsilyl-3-en-1-ynes,[13] trimethylsilylethynylzinc chloride (**14**) was reacted with a molar excess of **13** (*E*/*Z*=62/38) in THF at room temperature to give chemically and stereoisomerically pure (*E*)-1-trimethylsilyl-3-hexen-1-yne (**15**) in 66% yield. Using a catalytic method for the direct conversion of 1-alkynylsilanes into the corresponding 1-tributylstannanes,[1g,12f,14] a mixture of 0.46 equiv. of bis(tributyltin)oxide and 1 equiv.



Scheme 3.



Scheme 4.



Scheme 5.

of **15** in dry THF was treated with a catalytic amount of tetrabutylammonium fluoride (TBAF) and the resulting mixture was heated to 65°C for 2.5 h. The volatiles, i.e. THF, the molar excess of **15** and bis(trimethylsilyl)oxide, which was formed in the reaction, were removed in vacuo to give in 94% yield the required organotin derivative **16** having chemical purity higher than 97%. Finally, treatment of **9a** with 1.2 equiv. of **16** in DMF at 60°C in the presence of 4 equiv. of LiCl and catalytic amounts of $Pd(dba)_2$ and dppf provided compound **10d** in 41% yield.

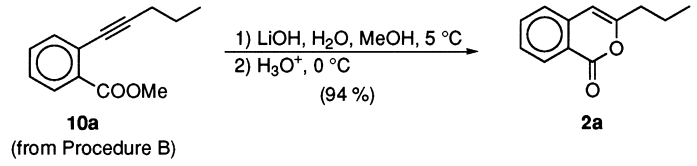
Methanol solutions of **10a**, which was prepared according to *Procedure A*, and compounds **10b**, **10c**, **10d** and **10f** were then reacted with 5 equiv. of an aqueous 2.29 M LiOH solution at 5°C and the resulting lithium carboxylates were treated at 0°C with 10% H_2SO_4 to give the corresponding carboxylic acids, i.e. **11a**, **11b**, **11c**, **11d** and **11f**, respectively, in quantitative yield (Scheme 5).

However, it was found that under these experimental conditions methyl ester **10a**, which had been prepared by *Procedure B*, was unexpectedly converted into 3-propylisocoumarin (**2a**) in 97% yield (Scheme 6).

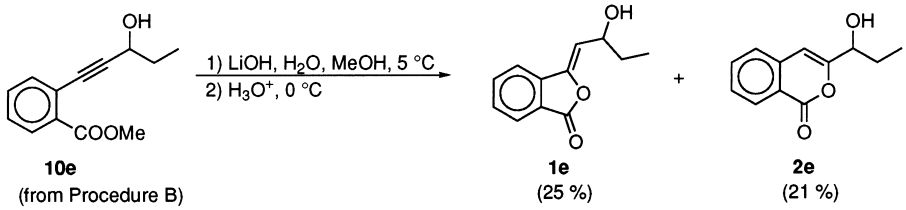
Moreover, saponification of **10e**, which was prepared by *Procedure B*, followed by acidification produced a mixture of senkyunolide *E* (**1e**) and 3-(1-hydroxypropyl)isocoumarin (**2e**) in a ca. 55:45 ratio, respectively (Scheme 7).

It must be noted that these unexpected results parallel those which regard the formation of compounds **1** and **2** by saponification followed by acidification of methyl 2-(1-alkynyl)-benzoates **10**, which had been prepared by reaction of methyl 2-halobenzoates with 1-alkynes in the presence of Et_3N and catalytic amounts of $PdCl_2(PPh_3)_2$ and CuI.[11] A reasonable rationalization for these results could be that (i) traces of Cu(I) salts contaminate either compounds **10** prepared by these alkynylation reactions or the corresponding carboxylic acids **11** and that (ii) these Cu(I) salts promote the 6-*endo*-*dig* and/or the 5-*exo*-*dig* cyclization of compounds **11**. On the other hand, it has been reported that 2-(1-alkynyl)benzoic acids, which are prepared in situ from 2-iodobenzoic acid (**3**) and 1-alkynylcopper compounds undergo CuI-catalyzed cyclization to give 3-substituted isocoumarins **6** or mixtures of **6** and the corresponding 3-ylidenephthalides **5**.[7f]

We next examined the synthesis of some natural and unnatural isocoumarins, i.e. compounds **2a**–**d**, and some direct precursors to natural (*Z*)-3-(1-alkylidene)phthalides, i.e. compounds **1b**, **1c** and **1f**, by transition metal-catalyzed heteroannulation reactions of the carboxylic acids which had been prepared according to *Procedures A* and *C*, i.e. compounds **11a**–**d** and **11f**. As shown in Table 1, these heteroannulation reactions were performed in acetone at room temperature in the presence of 20 mol% $AgNO_3$ (entries 1, 2, 6 and 9), or in DMF at 60°C in the presence of 10 mol% Ag powder (entries 4, 5, 7 and 8). On the other hand, compound **11b** proved also to be able to undergo heterocyclization in toluene solution at 110°C in the presence of 5 mol% *trans*-di(μ-acetato)bis[(di-*o*-tolylphosphino)benzyl]dipalladium(II).[15] The $AgNO_3$-catalyzed

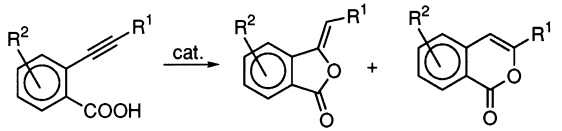


Scheme 6.



Scheme 7.

Table 1. Transition metal-catalyzed heteroannulation of 2-(1-alkynyl)benzoic acids **11**



11 **1** **2**

Entry	Reagent			Catalyst (mol%)	Solvent	Reaction conditions (h/°C)	Products		
	11	R^1	R^2				**1**+**2**	**1**/**2** molar ratio	Yield (%)[a,b]
1	**11a**	C_3H_7	H	$AgNO_3$ (20)	Acetone	24/20	**1a**+**2a**	6/94	88[c]
2	**11b**	C_3H_7	3-MeO	$AgNO_3$ (20)	Acetone	24/20	**1b**+**2b**	6/94	83
3	**11b**	C_3H_7	3-MeO	Palladacycle[d] (5)	Toluene	6/110	**1b**+**2b**[e]	8/80[e]	(>98)
4	**11b**	C_3H_7	3-MeO	Ag (10)	DMF	48/60	**1b**+**2b**	71/29	63[f]
5	**11b**	C_3H_7	3-MeO	Ag (10)	DMF+Et_3N (3 equiv.)	15/50	**1b**+**2b**	34/66	(>98)
6	**11c**	C_3H_7	4-MeO	$AgNO_3$ (20)	Acetone	24/20	**1c**+**2c**	3/97	81
7	**11c**	C_3H_7	4-MeO	Ag (10)	DMF	48/60	**1c**+**2c**	86/14	54[g]
8	**11f**	C_2H_5CH(OMEM)	H	Ag (10)	DMF	48/60	**1f**+**2f**	>99/<1	94
9	**11d**	(E)-C_2H_5-CH═CH–	H	$AgNO_3$ (20)	Acetone	24/20	**1d**+**2d**	72/28	51[h]

[a] Isolated yields of the major products of the reaction mixtures.
[b] Values in parenthesis are referred to GLC conversions.
[c] Compound **1a** was isolated in 5% yield.
[d] This palladacycle was *trans*-di(μ-acetate)-bis[di-*o*-tolilphosphino)benzyl]dipalladium.
[e] The reaction mixture contained a third component which presumably corresponded to the (*E*)-stereoisomer of **1b**.
[f] Compound **2b** was isolated in 19% yield.
[g] Compound **2c** was isolated in 11% yield.
[h] Compound **2d** was isolated in 23% yield.

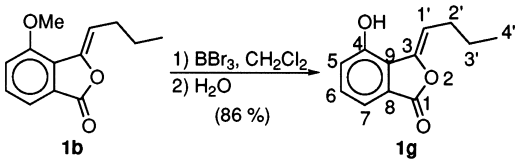
reactions involving **11a**, **11b** and **11c** (entries 1, 2 and 6, Table 1) gave reaction mixtures in which the 3-substituted isocoumarins **2a**, **2b** and **2c**, respectively, were the major products and the stereoisomerically pure (*Z*)-3-(1-alkylidene)phthalides **1a**, **1b** and **1c**, respectively, were the minor products. Purification of these mixtures by MPLC on silica gel allowed isolation of naturally-occurring **2a**, **2b** and **2c** in 88, 83 and 81% yield, respectively. Interestingly, a reaction mixture in which **2b** was the major component and **1b** the minor component was also obtained by Pd-catalyzed heteroannulation of **11b** (entry 3, Table 1). However, this reaction mixture contained a third component which presumably corresponded to the (*E*)-stereoisomer of **1b**.

It was also observed that the regioselectivity of the $AgNO_3$-catalyzed heteroannulation reactions of compounds **11** was affected by the type of 1-alkynyl moieties present in these acids. In fact, in an attempt to synthesize regioselectively artemidin (**2d**), which is an isocoumarin isolated from *Anthemis fuscata*,[5b] by $AgNO_3$-catalyzed lactonization of **11d**, a reaction mixture was obtained in which the major component was stereoisomerically pure (*Z*)-3-{1-[(*E*)-pent-2-enylidene]}phthalide (**1d**) and the minor component was **2d** (entry 9, Table 1). Purification of this mixture by MPLC on silica gel allowed isolation of **1d** and **2d** in 51 and 23% yield, respectively.

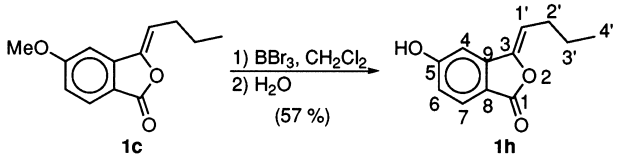
As shown in Table 1, the regioselectivity of the $AgNO_3$-catalyzed ring closure reactions of **11b**, **11c** and **11f** was reversed when the cyclization reactions were catalyzed by Ag powder and were performed in DMF at 60°C. In fact, these last reactions (entries 4, 7 and 8, Table 1) provided reaction mixtures in which the (*Z*)-3-(1-alkylidene)-phthalides were the major products and the corresponding 3-substituted isocoumarins were the minor products. These results were in agreement with those previously reported for the heteroannulation of **11a**.[7d] However, it was observed that the presence of a base could affect the regioselectivity. In fact, the reaction mixture, which was obtained by cyclization of **11b** in DMF in the presence of 3 equiv. of Et_3N and a catalytic quantity of Ag powder, proved to be constituted of a mixture of **1b** and **2b** in which this last compound was the major component (entry 5, Table 1). It is also worth mentioning that the Ag-catalyzed heteroannulation reaction of **11f** proved to be much more regioselective than the corresponding reactions involving **11b** and **11c**. In fact, the reaction involving **11f** gave **1f**, which was the sole product identified in the crude reaction mixture (entry 8, Table 1).

Finally, in order to prepare naturally-occurring senkyunolide B (**1g**), senkyunolide C (**1h**) and senkyunolide E (**1e**), we examined the selective deprotection of the protected hydroxy group present in compounds **1b**, **1c** and **1f**, respectively. Thus, it was found that demethylation of **1b** and **1c** with 2.1–2.5 equiv. of boron tribromide in CH_2Cl_2 at room temperature according to a general procedure[16] provided **1g** and **1h** in 86 and 57% yield, respectively (Schemes 8 and 9).

Unfortunately, attempts to convert **1f** into **1e** by protocols reported in the literature for deprotection of MEM-ethers[17] were fruitless. In fact, treatment of **1f** with 5 equiv. of $TiCl_4$ in CH_2Cl_2 at 0°C for 20 min followed by addition of a large

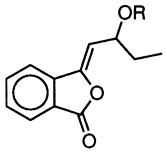


Scheme 8.



Scheme 9.

molar excess of a cold saturated aqueous $NaHCO_3$ solution provided a complex reaction mixture in which **1f** was absent but compound **1e** was the minor product. Interestingly, a GLC/MS analysis of this crude reaction mixture showed that, similarly to **1e**, two other reaction products had a prominent peak at *M*-18.



1e : R = H
1f : R = $CH_2OCH_2CH_2OCH_3$

Moreover, reaction of **1f** with 5 equiv. of $ZnBr_2$ in CH_2Cl_2 for 6 h at room temperature[17] followed by hydrolysis with a saturated aqueous $NaHCO_3$ solution afforded a reaction mixture which contained a compound different from **1e** as the sole reaction product. This unidentified compound was fast running on silica gel chromatography and had a GLC retention time higher than that of **1e**.

In conclusion, we devised a convenient protocol for the synthesis of 2-(1-alkynyl)benzoic acids **11** and we employed the $AgNO_3$-catalyzed cyclization reaction of these carboxylic acids to prepare some 3-substituted isocoumarins of general formula **2**, which include naturally-occurring 3-propylisocoumarin (**2a**) and artemidin (**2d**). On the other hand, by Ag powder-catalyzed heteroannulation reaction of compounds **11** we prepared some precursors to naturally-occurring (*Z*)-3-(1-alkylidene)phthalides **1**. Finally, two of these precursors, i.e. compounds **1b** and **1c**, were converted to naturally-occurring senkyunolide B (**1g**) and senkyunolide C (**1h**), respectively.

Experimental

All boiling and melting points are uncorrected. Precoated Merck 60 F_{254} plastic silica gel sheets were used for TLC analyses. GLC analyses were performed on a Dani GC 1000 instrument with a PTV injector, which was equipped with a Dani data station 86.01. Two types of capillary columns were used: an Alltech AT-1 bonded FSOT column

(30 m×0.25 mm i.d.) and an Alltech AT-35 bonded FSOT column (30 m×0.25 mm i.d.). Purifications by MPLC were performed on a Büchi instrument, using a Bischoff 8100 differential refractometer as detector. GLC/MS analyses were performed using a Q-mass 910 spectrometer interfaced with a Perkin–Elmer 8500 gas-chromatograph. ^{1}H NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer or a Bruker AMX 600 spectrometer using TMS and $CDCl_3$ as an internal standard, respectively. IR spectra were recorded on a Perkin–Elmer 1725-X FT-IR spectrophotometer. All reactions of air- and water-sensitive materials were performed in flame dried glassware under an atmosphere of argon or nitrogen. Air and water sensitive solutions were transferred with hypodermic syringes or double ended needles. Solvents were dried and distilled before use. (*E*)/(*Z*)-1-Bromo-1-butene (**13**) (*E*/*Z*=62/38; bp 90–92°C) was prepared starting from 1,2-dibromobutane according to a previously reported procedure.[18] $Pd(dba)_2$, 1,1′-bis(diphenylphosphino)ferrocene (dppf) and bis(tributyltin)oxide were commercially available. $Pd(PPh_3)_4$ was prepared according to the literature.[19]

General procedure for the synthesis of methyl 2-(perfluoro-1-butanesulfonyloxy)benzoates 9

A dispersion of NaH (60%, 4.50 g, 112.5 mmol) in mineral oil was washed with pentane and the residue was diluted with DMF (220 ml). To the resulting suspension, which was stirred at 0°C, was added dropwise a solution of a methyl 2-hydroxybenzoate **8** (75.0 mmol) in DMF (40 ml) and the mixture was stirred for 0.5 h at 0°C and for 1.5 h at room temperature. To the resulting reaction mixture, which was maintained under stirring at 0°C, was then added dropwise perfluoro-1-butanesulfonyl fluoride (26.05 g, 86.25 mmol) and the mixture was stirred at 0°C for 1.0 h and then at room temperature for 2 h. After this period a GLC analysis of a sample of the reaction mixture, which was hydrolyzed with a saturated aqueous NH_4Cl solution and extracted with Et_2O showed that the reaction was complete. Thus, the reaction mixture was poured into a large excess of a cold saturated aqueous NH_4Cl solution and extracted repeatedly with Et_2O (4×100 ml). The collected organic extracts were washed with water, dried and concentrated in vacuo to give in quantitative yield crude compounds **9** which had chemical purity higher than 96%. Compounds **9a**, **9b** and **9c** were prepared according to this procedure.

Methyl 2-(perfluoro-1-butanesulfonyloxy)benzoate (9a). The crude product, which was obtained in quantitative yield starting from methyl 2-hydroxybenzoate (**8a**) according to the above mentioned procedure, had: mp 41–45°C. MS, *m*/*z* (%): 434 (6), 339 (33), 151 (16), 135 (33), 123 (65), 95 (90), 69 (100). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.10 (1H, dd, *J*=7.7 and 1.7 Hz, H_{arom}), 7.64 (1H, dt, *J*=7.8 and 1.2 Hz, H_{arom}), 7.48 (1H, *pseudo*-t, *J*=7.1 Hz, H_{arom}), 7.30 (1H, t, *J*=7.8 Hz, H_{arom}), 3.97 ppm (3H, s, OMe). This crude compound was used in the next step without any further purification and characterization.

Methyl 3-methoxy-2-(perfluoro-1-butanesulfonyloxy)-benzoate (9b). Crude compound **9b**, which was obtained in quantitative yield from methyl 2-hydroxy-3-methoxybenzoate (**8b**) according to the above mentioned procedure, was purified by MPLC on silica gel, using a mixture of toluene and hexane (80:20) as eluant, to give in 70% yield chemically pure **9b** as a colourless liquid. MS, *m*/*z* (%): 464 (4), 181 (100), 149 (62), 122 (19), 107 (33), 95 (10),j 69 (43). IR (film): ν 1734, 1480, 1426, 1203, 1145, 1064, 763 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.50 (1H, d, *J*=7.9 Hz, H_{arom}), 7.38 (1H, t, *J*=8.0 Hz, H_{arom}), 7.20 (1H, d, *J*=8.0 Hz, H_{arom}), 3.94 (3H, s, OMe), 3.92 ppm (3H, s, OMe). Anal. Calcd for $C_{13}F_9H_9O_6S$: C, 33.63; H, 1.95. Found: C, 33.94; H, 1.98.

Methyl 4-methoxy-2-(perfluoro-1-butanesulfonyloxy)-benzoate (9c). This crude product, which was prepared in quantitative yield starting from methyl 2-hydroxy-4-methoxybenzoate (**8c**) according to the above mentioned procedure, had: mp 55–60°C. MS, *m*/*z* (%): 464 (20), 433 (10), 369 (9), 153 (27), 125 (11), 107 (10), 51 (100). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.06 (1H, d, *J*=8.8 Hz, H_{arom}), 6.95 (1H, dd, *J*=8.8 and 2.4 Hz, H_{arom}), 6.80 (1H, br s, H_{arom}), 3.93 (3H, s, OMe), 3.88 ppm (3H, s, OMe). This crude product was used in the next step without any further purification and characterization.

General procedure for the Pd-catalyzed cross-coupling reactions between 1-pentynylzinc chloride (12a) and the aryl nonaflates 9

A slurry of 1-pentynylzinc chloride (**12a**) in THF was prepared by addition of a 0.64 M THF solution of the corresponding Grignard reagent (50.7 ml, 32.45 mmol) to a solution of dry $ZnCl_2$ (5.74 g, 42.14 mmol) in THF (120 ml), which was stirred at 0°C. After stirring the reaction mixture for additional 30 min, $Pd(dba)_2$ (0.25 g, 0.43 mmol), dppf (0.24 g, 0.43 mmol) and a solution of a crude methyl 2-(perfluoro-1-butanesulfonyloxy)benzoate **9** (21.61 mmol) in THF (30 ml) were sequentially added. The resulting mixture was allowed to warm up to room temperature and then heated to 65°C for 5 h. After usual workup the crude reaction product was diluted with the solvent which was subsequently used for its purification by MPLC on silica gel and filtered over Celite. The filtrate was concentrated in vacuo and the residue was purified by MPLC on silica gel. Compounds **10a**, **10b** and **10c** were prepared according to this procedure.

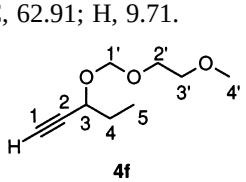
Methyl 2-(1-pentynyl)benzoate (10a). The crude reaction product, which was obtained from the Pd-catalyzed reaction between **12a** and methyl 2-(perfluoro-1-butanesulfonyloxy)-benzoate (**9a**) according to the above mentioned procedure, was purified by MPLC on silica gel, using a mixture of toluene and petroleum ether (70:30) as eluant, to give in 65% yield chemically pure **10a** as a colourless liquid. MS, *m*/*z* (%): 187 (7), 174 (100), 159 (23), 143 (28), 115 (44), 91 (17), 75 (15). IR (film): ν 1734, 1718, 1296, 1251, 1130, 1085, 759 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.88 (1H, d, *J*=7.6 Hz, H_{arom}), 7.53–7.27 (3H, m, H_{arom}), 3.91 (3H, s, OMe), 2.46 (2H, t, *J*=7.3 Hz, H-3′), 1.67 (2H, sext, *J*=7.3 Hz, H-4′), 1.07 ppm (3H, t, *J*=7.3 Hz, H-5′). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.06; H, 6.69.

Methyl 3-methoxy-2-(1-pentynyl)benzoate (10b). The crude reaction product, which was obtained from the

Pd-catalyzed reaction between **12a** and methyl 3-methoxy-2-(perfluoro-1-butanesulfonyloxy)benzoate (**9b**) according to the above mentioned procedure, was purified by MPLC on silica gel using toluene as eluant, to give in 90% yield chemically pure **10b** as a pale yellow liquid. MS, *m/z* (%): 232 (20), 217 (26), 204 (67), 189 (51), 143 (31), 115 (100), 75 (81). IR (film): ν 1732, 1468, 1434, 1306, 1269, 1061, 758 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.41 (1H, d, J=7.7 Hz, H_{arom}), 7.26 (1H, t, J=8.0 Hz, H_{arom}), 7.00 (1H, d, J=8.0 Hz, H_{arom}), 3.90 (3H, s, OMe), 3.89 (3H, s, OMe), 2.52 (2H, t, J=7.0 Hz, H-3′), 1.68 (2H, sext, J=7.0 Hz, H-4′), 1.09 ppm (3H, t, J=7.0 Hz, H-5′). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.78; H, 7.21.

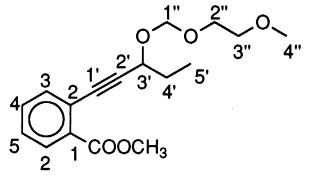
Methyl 4-methoxy-2-(1-pentynyl)benzoate (10c). The crude reaction product, which was obtained from the Pd-catalyzed reaction between **12a** and methyl 4-methoxy-2-(perfluoro-1-butanesulfonyloxy)benzoate (**9c**) according to the above mentioned general procedure, was purified by MPLC on silica gel, using a mixture of hexane and CH_2Cl_2 (50:50) as eluant, to give in 84% yield chemically pure **10c** as a pale yellow liquid. MS, *m/z* (%): 232 (1), 204 (100), 173 (22), 161 (31), 115 (21), 101 (16), 75 (21). IR (film): ν 1729, 1712, 1601, 1286, 1263, 1210, 1136 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.89 (1H, d, J=8.8 Hz, H_{arom}), 7.00 (1H, d, J=2.5 Hz, H_{arom}), 6.82 (1H, dd, J=8.8 and 2.5 Hz, H_{arom}), 3.88 (3H, s, OMe), 3.83 (3H, s, OMe), 2.47 (2H, t, J=7.0 Hz, H-3′), 1.67 (2H, sext, J=7.3 Hz, H-4′), 1.08 ppm (3H, t, J=7.3 Hz, H-5′). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.55; H, 7.05.

3-(2-Methoxyethoxymethoxy)-1-pentyne (4f). A solution of 2-methoxyethoxymethyl chloride (9.99 g, 80.24 mmol) in CH_2Cl_2 (50 ml) was added dropwise to a solution of 1-pentyn-3-ol (**4e**) (4.50 g, 53.49 mmol) and $EtN(i\text{-}Pr)_2$ (10.37 g, 80.24 mmol) in CH_2Cl_2 (50 ml) which was stirred under nitrogen at room temperature. The resulting mixture was stirred for 3 h at room temperature, poured into a large excess of 5% HCl and extracted repeatedly with Et_2O. The collected organic extracts were washed with a saturated aqueous $NaHCO_3$ solution and water, dried and concentrated under reduced pressure. The residue was fractionally distilled to give **4f** (6.60 g, 72% yield) as a colourless liquid. bp 93–94°C/15 Torr. MS, *m/z* (%): 113 (2), 105 (4), 89 (28), 73 (13), 67 (34), 65 (11), 59 (100). ^1H NMR (200 MHz, $CDCl_3$): δ 5.02 (1H, d, J=7.1 Hz, H-1′), 4.73 (1H, d, J=7.1 Hz, H-1′), 4.32 (1H, dt, J=6.4 and 2.2 Hz, H-3), 3.76–3.54 (4H, m, H-2′ and H-3′), 3.40 (3H, s, H-4), 2.41 (1H, d, J=2.2 Hz, H-1), 1.85–1.65 (2H, m, H-4), 1.03 ppm (3H, t, J=7.3 Hz, H-5). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.91; H, 9.71.



4f

Methyl 2-[3-(2-methoxyethoxymethoxy)-1-pentynyl]-benzoate (10f). A 1.91 M hexane solution of butyllithium (18.6 ml, 35.50 mmol) was added dropwise to a solution of 3-(2-methoxyethoxymethoxy)-1-pentyne (**4f**) (6.10 g, 35.42 mmol) in THF (100 ml) which was stirred under argon at −78°C. The resulting mixture was allowed to warm up to 0°C within 1.5 h and then it was cooled to −78°C. A solution of dry $ZnBr_2$ (9.57 g, 42.50 mmol) in THF (50 ml), which was cooled to −20°C, was then added and the mixture was allowed to warm up to 10°C within 2 h. It was then cooled to 0°C and $Pd(dba)_2$ (0.31 g, 0.54 mmol), dppf (0.30 g, 0.54 mmol) and a solution of **9a** (11.83 g, 27.24 mmol) in THF (35 ml) were sequentially added. The resulting mixture was allowed to warm up to room temperature and then it was maintained under reflux for 17 h. After this period the reaction mixture was cooled to room temperature, poured into a large excess of a saturated aqueous NH_4Cl solution and extracted repeatedly with Et_2O (3×100 ml). The collected organic extracts were washed with water, dried and concentrated in vacuo. The residue was purified by MPLC on silica gel, using a mixture of toluene and AcOEt (90:10) as eluant, to give **10f** (4.32 g, 52% yield) as a colourless liquid. MS, *m/z* (%): 276 (1), 217 (28), 201 (15), 187 (15), 89 (13), 59 (100). IR (film): ν 1732, 1295, 1256, 1129, 1110, 1083, 1033 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.92 (1H, dd, J=7.7 and 1.8 Hz, H_{arom}), 7.56–7.32 (3H, m, H_{arom}), 5.18 (1H, d, J=7.0 Hz, H-1″), 4.80 (1H, d, J=7.0 Hz, H-1″), 4.61 (1H, t, J=6.4 Hz, H-3′), 3.91 (3H, s, COOMe), 3.87–3.56 (4H, m, H-2″ and H-3″), 3.40 (3H, s, H-4″), 1.94–1.80 (2H, m, H-4′), 1.11 ppm (3H, t, J=7.3 Hz, H-5′). Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.87; H, 7.51. A GLC analysis showed that **10f** had chemical purity higher than 98%.



10f

Pd(0)/Cu(I)-catalyzed cross-coupling reaction of methyl 2-(perfluoro-1-butanesulfonyloxy)benzoate (9a) with 1-alkynes 4

To a suspension of $Pd(PPh_3)_4$ (1.73 g, 1.50 mmol) and compound **9a** (6.51 g, 15.0 mmol) in deareated dry DMF (60 ml), which was stirred under argon, were sequentially added a 1-alkyne **4** (22.5 mmol), Et_3N (4.18 ml, 30.0 mmol) and CuI (0.57 g, 3.0 mmol) and the resulting reaction mixture was stirred at room temperature for 24 h. It was then poured into a large excess of a saturated aqueous NH_4Cl solution and the resulting mixture, which was stirred in the air for 0.5 h, was extracted repeatedly with Et_2O (4×50 ml). The collected organic extracts were washed with water, dried and concentrated in vacuo. The residue was diluted with the solvent which was subsequently used for its purification by MPLC on silica gel and filtered over Celite. The filtrate was concentrated in vacuo and the residue was purified by MPLC on silica gel. This procedure was employed to prepare compound **10a** and methyl 2-(3-hydroxy-1-pentynyl)benzoate (**10e**) in 75 and 84% yield, respectively. The spectral properties of **10a** were in good agreement with those of the compound which was prepared by Pd-catalyzed cross-coupling reaction between **9a** and **12a**.

Methyl 2-(3-hydroxy-1-pentynyl)benzoate (10e). The crude reaction mixture, which was obtained from the Pd(0)/Cu(I)-catalyzed reaction between **9a** and 3-hydroxy-1-pentyne (**4e**), was purified by MPLC on silica gel, using a mixture of toluene and Et_2O (70:30) as eluant, to give in 84% yield compound **10e** as an orange liquid. MS, *m*/*z* (%): 203 (4), 190 (35), 157 (100), 129 (58), 101 (79), 77 (28), 57 (21). IR (film): ν 1718, 1435, 1298, 1279, 1256, 1084, 759 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.92 (1H, d, J=7.3 Hz, H_{arom}), 7.55–7.35 (3H, br m, H_{arom}), 4.61 (1H, t, J=6.0 Hz, H-3′), 3.91 (3H, s, OMe), 2.75 (1H, br s, OH), 1.85 (2H, quint, J=7.3 Hz, H-4′), 1.10 ppm (3H, t, J=7.3 Hz, H-5′). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.46. Found: C, 71.14; H, 6.25. A GLC analysis showed that **10e** had chemical purity higher than 99%.

(*E*)-1-Trimethylsilyl-3-hexen-1-yne (15). 1-Trimethylsilylacetylene (17.71 g, 180.3 mmol) was added dropwise to a 0.67 M THF solution of ethylmagnesium bromide (269 ml, 180.3 mmol) which was maintained under stirring at 65°C. After the addition was complete, heating was continued for 1 h. The THF solution, which was cooled to 20°C, was then added to a solution of dry $ZnCl_2$ (26.58 g, 195.0 mmol) in THF (180 ml) cooled to 0°C and the resulting mixture was stirred for 0.5 h. A degassed solution of $Pd(PPh_3)_4$ (5.57 g, 4.82 mmol) and (*E*)/(*Z*)-1-bromo-1-butene (**13**) (*E*/*Z*=62/38; 42.0 g, 311.0 mmol) in THF (210 ml), which was prepared immediately prior to use, was added and the resulting mixture was stirred for 58 h at room temperature. It was then poured into a large excess of a saturated aqueous NH_4Cl solution and the resulting mixture was extracted with pentane (4×100 ml). The collected organic extracts were filtered, washed with water, dried and concentrated at 760 Torr. The residue was fractionally distilled using a Fischer Spaltrohr System to give chemically and stereoisomerically pure **15** (18.12 g, 66% yield) as a colourless liquid. bp 73–75°C/25 Torr. (Lit.[20] bp 84–86°C/56 Torr). MS, *m*/*z* (%): 152 (20), 137 (100), 109 (11), 93 (5), 83 (25), 73 (10), 59 (23). ^1H NMR (200 MHz, $CDCl_3$): δ 6.24 (1H, dt, J=15.9 and 6.4 Hz, H-4), 5.48 (1H, dt, J=15.9 and 1.6 Hz, H-3), 2.30–1.95 (2H, m, H-5), 0.99 (3H, t, J=7.4 Hz, H-6), 0.16 ppm (9H, s, $SiMe_3$).

(*E*)-1-Tributylstannyl-3-hexen-1-yne (16). A flame dried reaction vessel, which was maintained under an argon atmosphere, was charged with a degassed solution of compound **15** (3.81 g, 25.00 mmol) in THF (60 ml) and bis(tributyltin)oxide (6.86 g, 11.50 mmol). A 1 M THF solution of TBAF (0.50 ml, 0.50 mmol) was added and the mixture was magnetically stirred at 60°C for 2.5 h, at which time the volatiles were removed in vacuo. The residue was filtered over Celite to give compound **16** (8.49 g, 94% yield) as a yellow liquid. MS, *m*/*z* (%): 313 (41), 311 (34), 257 (40), 255 (33), 199 (100), 197 (78), 121 (60). ^1H NMR (200 MHz, $CDCl_3$): δ 6.20 (1H, dt, J=15.9 and 6.8 Hz, H-4), 5.52 (1H, d, J=15.9 Hz, H-3), 2.11 (2H, quint, J=6.8 Hz, H-5), 1.71–1.45 (6H, br m, H-1′), 1.42–0.81 ppm (24 H, br m, H-2′, H-3′, H-4′ and H-6). GLC and TLC analyses showed that compound **16** had chemical purity higher than 97%. This crude compound was used in the next step without any further purification and characterization.

Methyl (*E*)-2-(3-hexen-1-ynyl)benzoate (10d). A flame dried reaction vessel, which was maintained under an argon atmosphere, was charged with methyl 2-(perfluoro-1-butanesulfonyloxy)benzoate (**9a**) (7.49 g, 17.25 mmol), $Pd(dba)_2$ (0.396 g, 0.689 mmol), dppf (0.760 g, 1.379 mmol), LiCl (2.92 g, 68.99 mmol) and deareated DMF (100 ml) and the mixture was stirred. A deareated solution of **16** (7.64 g, 20.70 mmol) in DMF (30 ml) was then added and the resulting mixture was stirred at 60°C for 80 h. It was then cooled to room temperature, poured into a large excess of a saturated aqueous NH_4Cl solution and extracted repeatedly with Et_2O. The collected organic extracts were washed with water and concentrated in vacuo. The residue was diluted with Et_2O and stirred at 20°C with an aqueous 6 M solution of KF (150 ml) for 24 h. The mixture was then diluted with Et_2O (150 ml), filtered over Celite and the filtrate was extracted with Et_2O (3×50 ml). The collected organic extracts were washed with water, dried and concentrated in vacuo. The residue was purified by MPLC on silica gel, using a mixture of toluene and hexane (60:40) as eluant, to give **10d** (1.51 g, 41% yield) as an orange liquid. MS, *m*/*z* (%): 214 (22), 199 (41), 181 (76), 153 (88), 128 (100), 115 (74). ^1H NMR (200 MHz, $CDCl_3$): δ 7.93 (1H, d, J=7.6 Hz, H_{arom}), 7.55–7.29 (3H, m, H_{arom}), 6.36 (1H, dt, J=15.9 and 6.7 Hz, H-4′), 5.77 (1H, d, J=15.9 Hz, H-3′), 3.93 (3H, s, OMe), 2.21 (2H, *pseudo*-quint, J=7.4 Hz, H-5′), 1.06 ppm (3H, t, J=7.4 Hz, H-6′). Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.58. Found: C, 78.70; H, 6.71.

2-(1-Pentynyl)benzoic acid (11a). Compound **10a** (3.0 g, 14.83 mmol), which was prepared by Pd-catalyzed cross-coupling reaction between **9a** and **12a**, was dissolved in methanol (7 ml) and the resulting solution was added to a mixture of an aqueous 2.29 M LiOH solution (32.4 ml, 74.15 mmol) and methanol (90 ml), which was stirred at 5°C. The resulting mixture was stirred at 5°C for 22 h and then concentrated at room temperature under reduced pressure. The residue was diluted with water and extracted with Et_2O (3×75 ml). The aqueous phase was cooled to 0°C, acidified with cold 10% H_2SO_4 and extracted with Et_2O (3×75 ml). The collected organic extracts were washed with water, dried and concentrated in vacuo to give **11a** (2.79 g, quantitative yield) as a solid. mp 35–37°C. ^1H NMR (200 MHz, $CDCl_3$): δ 8.07 (1H, d, J=7.7 Hz, H_{arom}), 7.54–7.36 (3H, m, H_{arom}), 2.48 (2H, t, J=7.0 Hz, H-3′), 1.68 (2H, sext, J=7.1 Hz, H-4′), 1.09 ppm (3H, t, J=7.1 Hz, H-5′). This crude compound was used in the next step without any further purification and characterization.

3-Methoxy-2-(1-pentynyl)benzoic acid (11b). Compound **10b**, which was prepared by Pd-catalyzed cross-coupling reaction between **9b** and **12a**, was converted in 99% yield into the title compound by a procedure similar to that employed to prepare **11a**. Compound **11b**, which was a colourless solid, had: mp 82–86°C. ^1H NMR (200 MHz, $CDCl_3$): δ 10.50 (1H, br s, COOH), 7.65 (1H, d, J=7.9 Hz, H_{arom}), 7.32 (1H, t, J=8.1 Hz, H_{arom}), 7.07 (1H, d, J=8.1 Hz, H_{arom}), 3.91 (3H, s, OMe), 2.54 (2H, t, J=7.0 Hz, H-3′), 1.69 (2H, sext, J=7.3 Hz, H-4′), 1.09 ppm (3H, t, J=7.3 Hz, H-5′). This crude compound was used in the next step without any further purification and characterization.

4-Methoxy-2-(1-pentynyl)benzoic acid (11c). Compound **10c**, which was prepared by Pd-catalyzed cross-coupling reaction between **9c** and **12a**, was converted in quantitative yield into the title compound by a procedure similar to that employed to prepare **11a**. Compound **11c**, which was a colourless solid, had: mp 89–93°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.60 (1H br s, COOH), 8.04 (1H, d, J=8.8 Hz, H-6), 7.02 (1H, d, J=2.6 Hz, H-3), 6.86 (1H, dd, J=8.8 and 2.6 Hz, H-5), 3.84 (3H s, OMe), 2.47 (2H, t, J=7.0 Hz, H-3′), 1.68 (2H, sext, J=7.3 Hz, H-4′), 1.09 ppm (3H, t, J=7.3 Hz, H-5′). This crude compound was used in the next step without any further purification and characterization.

(*E*)-2-(3-Hexen-1-ynyl)benzoic acid (11d). Compound **10d**, which was prepared by Pd-catalyzed cross-coupling reaction between **16** and **9a**, was converted in 99% yield into the title compound by a procedure similar to that employed to prepare **11a**. Compound **11d**, which was a colourless solid, had: mp 93–97°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.30 (1H, br s, COOH), 8.06 (1H, dd, J=8.4 and 1.6 Hz, H_{arom}), 7.70–7.30 (3H, m, H_{arom}), 6.37 (1H, dt, J=15.8 and 6.6 Hz, H-4′), 5.77 (1H, dt, J=15.8 and 1.5 Hz, H-3′), 2.20 (2H, dquint, J=7.4 and 1.5 Hz, H-5′), 1.04 ppm (3H, t, J=7.4 Hz, H-6′). This crude compound was used in the next step without any further purification and characterization.

2-[3-(2-Methoxyethoxymethoxy)-1-pentynyl]benzoic acid (11f). Compound **10f**, which was prepared by Pd-catalyzed cross-coupling reaction between **9a** and **12f**, was converted in quantitative yield into the title compound by a procedure similar to that used prepare **11a**. Crude **11f**, which was a colourless liquid, had: ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.87 (1H, br s, COOH), 8.05 (1H, dd, J=7.7 and 1.5 Hz, H_{arom}), 7.60–7.35 (3H, m, H_{arom}), 5.17 (1H, d, J=7.0 Hz, H-1″), 4.82 (1H, d, J=7.0 Hz, H-1″), 4.61 (1H, t, J=6.4 Hz, H-3′), 3.85–3.50 (2H, m, H-2″ or H-3″), 3.60 (2H, t, J=4.4 Hz, H-3″ or H-2″), 3.41 (3H, s, H-4″), 1.89 (2H, quint, J=7.4 Hz, H-4′), 1.11 ppm (3H, t, J=7.4 Hz, H-5′). This crude compound was used in the next step without any further purification and characterization.

Saponification followed by acidification of compound 10a which was prepared by Pd(0)/Cu(I)-catalyzed reaction between 9a and 4a: synthesis of 3-propyl-isocoumarin (2a)

Compound **10a** (3.0 g, 14.83 mmol), which was prepared by Pd(0)/Cu(I)-catalyzed reaction between **9a** and **4a**, was dissolved in methanol (7 ml) and the resulting solution was stirred at 5°C for 18 h with a 2.29 M aqueous LiOH solution (32.4 ml, 74.15 mmol) and methanol (90 ml). The reaction mixture was concentrated in vacuo at room temperature and the residue was diluted with water and extracted with Et_2O (3×50 ml). The aqueous phase was cooled to 0°C, acidified with cold 10% H_2SO_4 and extracted with Et_2O (3×50 ml). The organic extract was washed with water, dried and concentrated in vacuo. The residue was purified by MPLC on silica gel, using a mixture of toluene and petroleum ether (90:10) as eluant, to give **2a** (2.62, 94% yield) as a light yellow solid. mp 28–30°C. MS, *m*/*z* (%): 188 (36), 159 (14), 131 (38), 118 (100), 103 (15), 89 (60), 77 (16). IR (KBr): ν 1731, 1656, 1160, 1141, 1019, 762, 690 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.25 (1H, d, J=8.0 Hz, H_{arom}), 7.77–7.58 (1H, m, H_{arom}), 7.60–7.30 (2H, m, H_{arom}), 6.26 (1H, s, H-4), 2.51 (2H, t, J=7.5 Hz, H-1′), 1.80–1.65 (2H, m, H-2′), 0.99 ppm (3H, t, J=7.4 Hz, H-3′). These spectral data were in good agreement either with those reported for the natural product[5c] or with those reported for **2a** prepared starting from 2-iodobenzoic acid (**3**).[9b]

Saponification followed by acidification of 10e: synthesis of (*Z*)-3-(2-hydroxy-1-butylidene)phthalide (senkyunolide E) (1e) and 3-(1-hydroxypropyl)isocoumarin (2e)

Compound **10e** (1.0 g, 4.58 mmol), which was prepared by Pd(0)/Cu(I)-catalyzed reaction of **9a** with **4e**, was dissolved in methanol (5 ml) and the resulting solution was stirred at 5°C for 18 h with a 2.29 M aqueous LiOH solution (10 ml, 22.90 mmol) and methanol (25 ml). The reaction mixture was concentrated in vacuo at room temperature and the residue, which was dissolved in water (15 ml), was extracted with Et_2O (3×50 ml). The aqueous phase was cooled to 0°C, acidified with cold 10% H_2SO_4 and extracted with Et_2O (3×50 ml). The organic extract was washed with water, dried and concentrated in vacuo. A GLC analysis of an Et_2O solution of a sample of the residue showed the presence of two compounds in a ca. 55:45 ratio, which were subsequently identified as **1e** and **2e**, respectively. This oily residue was purified by MPLC on silica gel, using a mixture of hexane and AcOEt (70:30) as eluant. Concentration of the first eluted chromatographic fractions allowed to isolate compound **2e** (0.20 g, 21% yield) as an orange oil. MS, *m*/*z* (%): 204 (23), 175 (100), 147 (43), 89 (37), 63 (18), 57 (12), 51 (39). IR (film): ν 1718, 1658, 1605, 1485, 1328, 1024, 759 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.27–8.23 (1H, m, H_{arom}), 7.71–7.39 (3H, m, H_{arom}), 6.56 (1H, s, H-4), 4.42 (1H, dd, J=7.3 and 5.4 Hz, H-1′), 2.50 (1H, br s, OH), 2.05–1.81 (2H, m, H-2′), 1.00 ppm (3H, t, J=7.4 Hz, H-3′). Anal. Calc for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.85; H, 6.04. Concentration of the last eluted chromatographic fractions allowed isolation of compound **1e** (0.23 g, 25% yield) as a pale crystalline solid. mp 86–89°C. MS, *m*/*z* (%): 204 (4), 175 (100), 147 (75), 129 (11), 104 (5), 57 (16), 51 (67). IR (KBr): ν 1770, 1691, 1279, 1256, 1061, 1007, 970, 767, 692 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.91 (1H, dt, J=6.6 and 1.1 Hz, H_{arom}), 7.75–7.50 (3H, m, H_{arom}), 5.66 (1H, d, J=8.5 Hz, H-1′), 4.86 (1H, dt, J=8.5 and 6.6 Hz, H-2′), 2.04 (1H, br s, OH), 1.85–1.60 (2H, m, H-3′), 1.00 ppm (3H, t, J=7.3 Hz, H-4′). These NMR data were in agreement with those of senkyunolide E (**1e**) prepared starting from phthalic anhydride.[21] However, this phthalide was described as a pale yellow oil. Finally, concentration of the intermediate chromatographic fractions allowed to obtain a ca. 1:1 mixture of **1e** and **2e** (0.10 g, 10% yield).

Preparation of 3-substituted isocoumarins 2 and (*Z*)-3-(1-alkylidene)phthalides 1 by treatment of 2-(1-alkynyl)-benzoic acids 11 with catalytic amounts of $AgNO_3$ or Ag powder

The $AgNO_3$-catalyzed reactions were performed according to the following procedure. In a typical experiment $AgNO_3$

(0.24 g, 1.41 mmol) was added to a degassed solution of a 2-(1-alkynyl)benzoic acid **11** (7.05 mmol) in dry acetone (70 ml) and the resulting mixture was stirred in the dark under an argon atmosphere for 24 h at room temperature. It was then concentrated in vacuo and the residue, which was diluted with CH_2Cl_2 (40 ml), was filtered over Celite. The filtrate, which was analyzed by TLC and GLC/MS, was concentrated in vacuo and the residue was purified by MPLC on silica gel. Compounds **11a**, **11b**, **11c** and **11d** underwent the Ag(I)-catalyzed cyclization reactions to give mixtures of the corresponding 3-substituted isocoumarins, i.e. **2a**, **2b**, **2c** and **2d**, respectively, and (*Z*)-3-(1-alkylidene)phthalides, i.e **1a**, **1b**, **1c** and **1d**, respectively (entries 1, 2, 6 and 9, Table 1). Nevertheless, the 3-substituted isocoumarins were easily separated from the corresponding (*Z*)-3-(1-alkylidene)phthalides by MPLC on silica gel. The 3-substituted isocoumarins **2a**, **2b** and **2c** were the major products in the case of the Ag(I)-catalyzed cyclization reactions of **11a**, **11b** and **11c**, respectively (entries 1, 2 and 6, Table 1). On the contrary, the Ag(I)-catalyzed cyclization reaction of **11d** afforded a reaction mixture in which the major product was compound **1d** (entry 9; Table 1). On the other hand, the Ag powder-catalyzed heteroannulation reactions were performed according to the following procedure. In a typical experiment, Ag powder (5–8 micron, 0.052 g, 0.48 mmol) was added to a degassed solution of a 2-(1-alkynyl)benzoic acid **11** (4.81 mmol) in dry DMF (32 ml) and the resulting mixture was stirred in the dark at 60°C for 48 h under an argon atmosphere. It was then cooled to room temperature, diluted with water (200 ml) and extracted with CH_2Cl_2 (5×50 ml). The organic extract was washed with brine (2×50 ml), dried and concentrated in vacuo. The residue was purified by MPLC on silica gel. Compounds **11b** and **11c** underwent this Ag-catalyzed reaction to give mixtures containing the corresponding 3-substituted isocoumarins, i.e. **2b** and **2c**, respectively, and the corresponding (*Z*)-3-(1-alkylidene)phthalides, i.e. **1b** and **1c**, respectively, in which these last compounds were the major products (entries 4 and 7, Table 1). On the contrary, the Ag-catalyzed lactonization of **11f** afforded selectively compound **1f** (entry 8, Table 1).

Synthesis of 3-propylisocoumarin (2a) and (*Z*)-3-(1-butylidene)phthalide (1a) by $AgNO_3$-catalyzed lactonization of 11a

GLC analysis of the crude reaction mixture, which was obtained by Ag(I)-catalyzed lactonization of **11a** (entry 1, Table 1), showed the presence of two compounds in a ca. 94:6 molar ratio, which were subsequently identified as **2a** and **1a**, respectively. This mixture was purified by MPLC on silica gel, using a mixture of toluene and petroleum ether (95:5) as eluant. Concentration of the first eluted chromatographic fractions allowed us to isolate in 5% yield **1a** as a colourless oil. MS, *m*/*z* (%): 188 (16), 159 (100), 146 (44), 131 (35), 103 (44), 77 (38), 55 (12). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.88 (1H, d, J=7.7 Hz, H_{arom}), 7.75–7.60 (2H, m, H_{arom}), 7.50 (1H, ddd, J=7.7, 1.0 and 1.0 Hz, H_{arom}), 5.65 (1H, t, J=7.7 Hz, H-1′), 2.46 (2H, dt, J=7.7 and 7.3 Hz, H-2′), 1.56 (2H, tq, J=7.3 and 7.3 Hz, H-3′), 0.99 ppm (3H, t, J=7.3 Hz, H-4′). These NMR data were in agreement with those previously reported.[7d] Concentration of the last eluted chromatographic fractions allowed to isolate in 88% yield stereoisomerically pure **2a**. The physical and spectral properties of this compound were in good agreement with those of **2a** which was prepared by saponification followed by acidification of **10a** which was synthesized by Pd(0)/Cu(I)-catalyzed reaction between **9a** and **4a**.

Synthesis of 5-methoxy-3-propylisocoumarin (2b) and (*Z*)-4-methoxy-3-(1-butylidene)phthalide (1b)

A GLC analysis of the crude reaction mixture, which was obtained by $AgNO_3$-catalyzed heteroannulation reaction of **11b** (entry 2, Table 1), showed the presence of two compounds in a ca. 94:6 ratio, which were subsequently identified as **2b** and **1b**, respectively. This mixture was purified by crystallization from hexane to give in 83% yield chemically pure **2b** as a pale yellow crystalline solid. mp 76–79°C. MS, *m*/*z* (%): 218 (70), 189 (72), 161 (100), 148 (41), 119 (50), 89 (52), 76 (50). IR (KBr): ν 1719, 1651, 1482, 1265, 1139, 1034, 763 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.83 (1H, d, J=7.8 Hz, H_{arom}), 7.37 (1H, t, J=8.0 Hz, H_{arom}), 7.12 (1H, d, J=8.0 Hz, H_{arom}), 6.63 (1H, s, H-4), 3.92 (3H, s, OMe), 2.52 (2H, t, J=7.4 Hz, H-1′), 1.74 (2H, sext, J=7.4 Hz, H-2′), 0.99 ppm (3H, t, J=7.4 Hz, H-3′). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.46. Found: C, 71.61; H, 6.51. On the other hand, a GLC analysis of the crude reaction mixture, which was obtained by cyclization of **11b** in DMF in the presence of a catalytic quantity of Ag powder (entry 4, Table 1), showed the presence of two compounds in a ca. 71:29 ratio, which were subsequently identified as **1b** and **2b**, respectively. This mixture was purified by MPLC on silica gel, using a mixture of CH_2Cl_2 and hexane (60:40) as eluant. Concentration of the first eluted chromatographic fractions allowed to isolate in 63% yield compound **1b** as a pale yellow solid. mp 80–81°C. (Lit.[22] mp 79–81°C). MS, *m*/*z* (%): 218 (18), 189 (100), 161 (18), 131 (18), 105 (33), 91 (15), 76 (35). IR (KBr): ν 1770, 1682, 1496, 1278, 1043, 978, 748 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.49(1H, dd, J=7.4 and 1.5 Hz, H_{arom}), 7.43 (1H, dd, J=7.4 and 1.5 Hz, H_{arom}), 7.13 (1H, dd, J=7.4 and 1.5 Hz, H_{arom}), 5.97 (1H, t, J=7.9 Hz, H-1′), 3.99 (3H, s, OMe), 2.45 (2H, *pseudo*-q, J=7.4 Hz, H-2′), 1.56 (2H, m, H-3′), 0.99 ppm (3H, t, J=7.3 Hz, H-4′). The spectral properties of this compound were in good agreement with those previously reported. On the other hand, concentration of the last eluted chromatographic fractions allowed us to isolate compound **2b** in 19% yield. The spectral properties of this compound were in agreement with those of **2b** prepared by $AgNO_3$-catalyzed cyclization reaction of **11b**.

Synthesis of 6-methoxy-3-propylisocoumarin (2c) and (*Z*)-5-methoxy-3-(1-butylidene)phthalide (1c)

A GLC analysis of the crude reaction mixture, which was obtained by $AgNO_3$-catalyzed cyclization reaction of **11c** (entry 6, Table 1), showed the presence of two compounds in a ca. 97:3 ratio, which were subsequently identified as **2c** and **1c**, respectively. Crystallization of this mixture from hexane allowed to obtain in 81% yield compound **2c** as a pale yellow crystalline solid. mp 69–73°C. MS, *m*/*z* (%): 218 (41), 175 (29), 161 (51), 148 (100), 119 (96), 76 (41), 65 (17). IR (KBr): ν 1718, 1663, 1605, 1574, 1255, 1221,

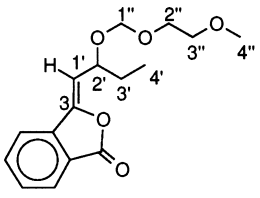
1144 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.17 (1H, d, J=8.8 Hz, H_{arom}), 6.98 (1H, dd, J=8.8 and 2.3 Hz, H_{arom}), 6.73 (1H, d, J=2.3 Hz, H_{arom}), 6.19 (1H, s, H-4), 3.90 (3H, s, OMe), 2.49 (2H, t, J=7.5 Hz, H-1′), 1.83–1.64 (2H, m, H-2′), 0.99 ppm (3H, t, J=7.3 Hz, H-3′). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.46. Found: C, 71.83; H, 6.80.

On the other hand, a GLC analysis of the crude reaction mixture, which was obtained by cyclization of **11c** in the presence of a catalytic quantity of Ag powder, showed the presence of two compounds in a ca. 86:14 molar ratio, which were subsequently identified as **1c** and **2c**, respectively (entry 7, Table 1). This mixture was purified by MPLC on silica gel, using a mixture of CH_2Cl_2 and hexane (60:40) as eluant. Concentration of the first eluted chromatographic fractions allowed to isolate in 54% yield chemically and stereoisomerically pure **1c** as a pale yellow solid. mp 55–56°C. (Lit.[7c] mp 56–57°C). MS, *m*/*z* (%): 218 (16), 189 (97), 176 (100), 161 (90), 133 (55), 77 (37), 63 (84). IR (KBr): ν 1785, 1617, 1490, 1296, 1063, 859, 775 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.77 (1H, br d, J=9.0 Hz, H_{arom}), 7.10–6.95 (2H, m, H_{arom}), 5.60 (1H, t, J=7.8 Hz, H-1′), 3.92 (3H, s, OMe), 2.44 (2H, *pseudo*-q, J=7.3 Hz, H-2′), 1.70–1.45 (2H, sext, J=7.3 Hz, H-3′), 0.99 ppm (3H, t, J=7.3 Hz, H-4′). The spectral properties of this compound were in agreement with those previously reported.[7c] On the other hand, concentration of the last eluted chromatographic fractions allowed isolation of pure **2c** in 11% yield. The physical and spectral properties of this compound were in agreement with those of **2c** prepared by $AgNO_3$-catalyzed cyclization reaction of **11c**.

Synthesis of (*Z*)-3-{1-[(*E*)-2-penten-1-ylidene]}phthalide (1d) and artemidin (2d)

A GLC analysis of the crude reaction mixture, which was obtained by Ag-catalyzed cyclization reaction of **11d** (entry 9, Table 1), showed the presence of two compounds in a ca. 28:72 molar ratio, which were subsequently identified as **2d** and **1d**, respectively. This crude mixture was purified by MPLC on silica gel, using a mixture of toluene and hexane (90:10) as eluant. Concentration of the first eluted chromatographic fractions allowed to obtain in 51% yield chemically and stereoisomerically pure **1d** as a pale yellow solid. mp 41–43°C. MS, *m*/*z* (%): 200 (100), 185 (26), 157 (56), 144 (20), 129 (36), 115 (20), 76 (20). IR (KBr): ν 1772, 1659, 1279, 1072, 982, 966, 773 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.89 (1H, d, J=7.8 Hz, H-7), 7.67 (1H, m, H-5), 7.65 (1H, m, H-4), 7.49 (1H, ddd, J=7.8, 7.8 and 1.1 Hz, H-6), 6.67 (1H, ddt, J=15.2, 11.0 and 6.5 Hz, H-2′), 6.17 (1H, d, J=11.0 Hz, H-1′), 6.07 (1H, dt, J=15.2 and 6.5 Hz, H-3′), 2.24 (2H, qd, J=7.4 and 6.5 Hz, H-4′), 1.09 ppm (3H, t, J=7.4 Hz, H-5′). A NOESY experiment showed the presence of a cross-peak between the resonances of the H-1′ and H-4 protons. ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.68 (C-1), 143.34 (C-3), 141.24 (C-3′), 139.63 (C-9), 134.20 (C-5), 129.35 (C-6), 125.51 (C-7), 124.19 (C-8), 122.17 (C-2′), 119.63 (C-4), 108.34 (C-1′), 26.27 (C-4′), 13.18 ppm (C-5′). Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 78.05; H, 6.24. On the other hand, concentration of the last eluted chromatographic fraction allowed to isolate in 23% yield chemically pure artemidin (**2d**) as a colourless solid. mp 46–48°C. (Lit.[5b] mp 48°C). MS, *m*/*z* (%): 200 (100), 185 (12), 172 (28), 157 (47), 129 (33), 115 (18), 89 (57). IR (KBr): ν 1729, 1655, 1621, 1059, 972, 961, 759 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.23 (1H, br d, J=8.0 Hz, H-8), 7.64 (1H, ddd, J=7.4, 7.4 and 1.4 Hz, H-6), 7.39 (1H, ddd, J=7.4, 7.4 and 1.4 Hz, H-7), 6.67 (1H, dt, J=15.4 and 6.6 Hz, H-2′), 6.25 (1H, s, H-4), 6.02 (1H, dt, J=15.4 and 1.6 Hz, H-1′), 2.38–2.15 (2H, m, H-3′), 1.09 ppm (3H, t, J=7.5 Hz, H-4′). These spectral properties were in agreement with those previously reported.[9b]

(*Z*)-3-[2-(Methoxyethoxymethoxy)-1-butylidene]phthalide (1f). A GLC analysis of the crude reaction mixture, which was obtained by cyclization of **11f** in DMF in the presence of catalytic quantity of Ag powder (entry 8, Table 1), showed the presence of a single compound which was subsequently identified as **1f**. This crude mixture was purified by MPLC on silica gel, using a mixture of toluene and AcOEt (80:20) as eluant, to give in 94% yield pure **1f** as a colourless liquid. MS, *m*/*z* (%): 263 (4), 203 (20), 187 (57), 159 (16), 115 (11), 89 (100), 59 (45). IR (film): ν 1789, 1110, 1094, 1037, 998, 977, 765 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.95–7.50 (4H, m, H_{arom}), 5.57 (1H, d, J=8.8 Hz, H-1′), 4.86–4.72 (3H, m, H-2′ and H-1″), 3.82–3.52 (4H, m, H-2″ and H-3″), 3.38 (3H, s, H-4″), 1.85–1.65 (2H, m, H-3′), 0.99 ppm (3H, t, J=7.5 Hz, H-4′). Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.89. Found: C, 65.81; H, 6.97.



1f

(*Z*)-3-(1-Butylidene)-4-hydroxyphthalide (senkyunolide B) (1g). A 1.0 M CH_2Cl_2 solution of BBr_3 (10.5 ml, 10.50 mmol) was added to a solution of compound **1b** (1.09 g, 5.0 mmol) in dry CH_2Cl_2 (15 ml), which was stirred at 0°C under an argon atmosphere. The resulting mixture was allowed to warm up to room temperature and stirred for 7.5 h. It was then poured into ice water and extracted with Et_2O (4×75 ml). The organic extract was washed with brine (100 ml), dried and concentrated in vacuo. The solid residue was recrystallized from a mixture of benzene and hexane (3:1) to give compound **1g** (0.88 g, 86% yield) as a colourless crystalline solid. mp 162–164°C (Lit. mp 165–168°C[22]; mp 150–153°C[1c]). MS, *m*/*z* (%): 204 (14), 175 (100), 147 (28), 119 (22), 91 (41), 65 (17), 55 (14). IR (KBr): ν 3233, 1734, 1684, 1467, 1305, 1004, 747 cm^{-1}. ^1H NMR (600 MHz, DMSO-d^6): δ 11.03 (1H, s, OH), 7.42 (1H, dd, J=7.9 and 7.9 Hz, H-6), 7.33 (1H, d, J=7.9 Hz, H-7), 7.22 (1H, d, J=7.9 Hz, H-5), 5.90 (1H, t, J=7.6 Hz, H-1′), 2.36 (2H, q, J=7.6 Hz, H-2′), 1.51 (2H, sext, J=7.6 Hz, H-3′), 0.94 ppm (3H, t, J=7.6 Hz, H-4′). A NOESY experiment showed the presence of cross-peaks between the resonances of the following protons: H-1′ and OH; OH and H-6. ^{13}C NMR (150 MHz, DMSO-d^6): δ 167.34 (C-1), 153.82 (C-4), 145.08 (C-3), 131.86 (C-6), 126.20 (C-8), 125.72 (C-9), 116.22 (C-7), 112.72 (C-1′), 28.52 (C-2′), 23.01 (C-3′), 14.58 ppm (C-4′). The spectral properties of this compound were in agreement with those previously reported.[7e]

(*Z*)-3-(1-Butylidene)-5-hydroxyphthalide (senkyunolide C) (1h). A 1.0 M CH_2Cl_2 solution of BBr_3 (12.5 ml, 12.50 mmol) was added to a solution of **1c** (1.09 g, 5.0 mmol) in dry CH_2Cl_2 (15 ml), which was stirred at 0°C under an argon atmosphere. The resulting mixture was stirred at room temperature for 6 h and worked up according to the same procedure employed in the synthesis of **1g**. The crude reaction product was purified by MPLC on silica gel, using a mixture of petroleum ether and acetone (80:20) as eluant, to give **1h** (0.58 g, 57% yield) as a colourless crystalline solid. mp 117–120°C (Lit.[7c] mp 117–119°C). MS, *m*/*z* (%): 204 (23), 145 (100), 131 (16), 115 (23), 103 (46), 91 (15), 77 (21). IR (KBr): ν 3236, 1753, 1739, 1683, 1620 1591, 1316 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.76 (1H, d, J=8.2 Hz, H-7), 7.03 (1H, d, J=2.0 Hz, H-4), 6.98 (1H, dd, J=8.2 and 2.0 Hz, H-6), 5.57 (1H, t, J=7.6 Hz, H-1′), 2.43 (2H, q, J=7.6 Hz, H-2′), 1.54 (2H, sext, J=7.6 Hz, H-3′), 0.98 ppm (3H, t, J=7.6 Hz, H-4′). A NOESY experiment showed the presence of a cross-peak between the resonances of the H-1′ and H-4 protons. ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.38 (C-1), 161.62 (C-5), 145.47 (C-3), 142.37 (C-4), 127.26 (C-7), 118.15 (C-6), 117.13 (C-8), 109.80 (C-1′), 105.37 (C-4), 27.78 (C-2′), 22.49 (C-3′), 13.80 ppm (C-4′). The spectral properties of **1h** were in satisfactory agreement with those reported either for the product isolated from *Cnidium officinale*[1c] or compound **1h** synthesized from 4-hydroxyphthalic anhydride.[7e]

Acknowledgements

We gratefully acknowledge the financial support from the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) and the University of Pisa.

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