SILVER CATALYZED CYCLIZATION OF ALKYNOIC ACIDS : EFFICIENT SYNTHESIS OF 3-ALKYLIDENEPHTHALIDES, γ-ALKYLIDENEBUTENOLIDES, AND γ-ALKYLIDENEBUTYROLACTONES

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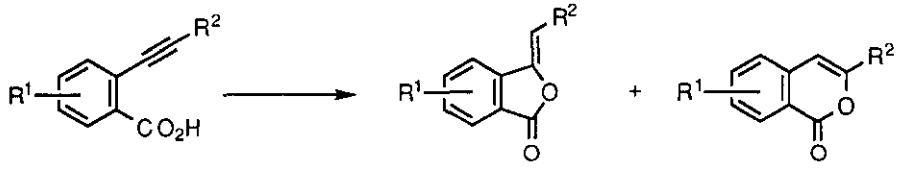
Abstract — The cyclization of 2-pentynylbenzoic acid (**1a**) catalyzed by various silver salts and solvents was investigated. 2-Alkynylbenzoic acids (**1**), 2-alken-4-ynoic acids (**7**), and 4-alkynoic acids (**4**) were effectively cyclized to the corresponding phthalides (**2**), γ-alkylidenebutenolides (**8**), and γ-alkylidenebutyrolactones (**5**) with silver iodide or silver as catalyst in DMF regio- and stereo-selectively in excellent yield, respectively.

3-Alkylidenephthalides (**2**) isolated from rhizomes of *Ligusticum* or *Cnidium* species and roots of *Angelica* species were applied frequently to traditional Chinese medicines. These phthalides (**2**) possess remarkably wide-ranging biological activities and are useful synthetic intermediates.[1a] Therefore, a variety of methods have been reported for the synthesis of **2**.[1] In synthetic point of view, the cyclization of 2-alkynylbenzoic acids (**1**) seems to be an efficient route for the preparation of **2**, the cyclization, however, has received poor attention so far due to the accessible formation of 3-alkylisocoumarins (**3**) in the presence of mineral acid or copper iodide (Scheme 1).[2,3] Although the regioselective cyclization of alkynoic acids (**4**) to γ-alkylidene-

butyrolactones (**5**) with catalysts such as mercuric oxide,[4] silver carbonate,[5] palladium (II)[6], and rhodium (I) complex[7] has been recently described (Scheme 2), these catalysts were not effective for the cyclization of 2-pentynylbenzoic acid (**1a**) to 3-butylidenephthalide (**2a**) in our experiments owing to the predominant formation of 3-propylisocoumarins (**3a**). In this paper, we wish to report a regio- and stereo-selective cyclization of **1** to **2**, **7** to **8**, and **4** to **5** in the presence of silver catalyst in dimethylformamide (DMF).

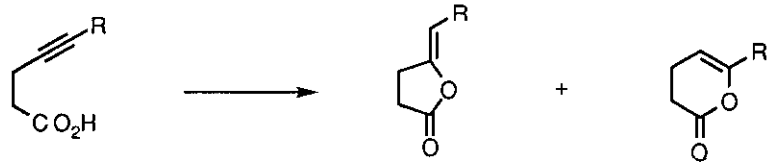
Scheme 1



1 **2** **3**

R^1= H or OR, R^2= Alkyl group

Scheme 2



4 **5** **6**

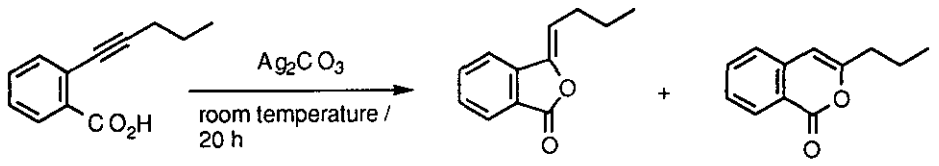
R = Alkyl group

A variety of solvents were tried to achieve reverse selectivity in the cyclization of **1a** catalyzed by silver carbonate. The results are shown in Table 1. Though benzene, dioxane, and dichloromethane did not reverse the regioselectivity, ratio of **2** / **3** was reversed in the reactions in acetonitrile, acetone, and DMF. In particular, DMF was the most effective solvent (ratio of **2** / **3** was 83 / 17).

The cyclization of **1a** catalyzed by various silver salts in DMF was carried out to find the best catalyst. The results are summarized in Table 2. Although some catalysts such as silver chloride, silver bromide, silver iodide, and silver enhanced the regioselectivity, the reaction catalyzed by silver iodide or silver gave the best result in both regioselectivity and chemical yield point of view (ratio of **2** / **3** was 86 / 14 in 90-95% yield).

The cyclization of 2-alkynylbenzoic acids (**1b-e**) bearing different alkyl group catalyzed by silver iodide or

Table 1. Cyclization of **1a** catalyzed by silver carbonate[a]

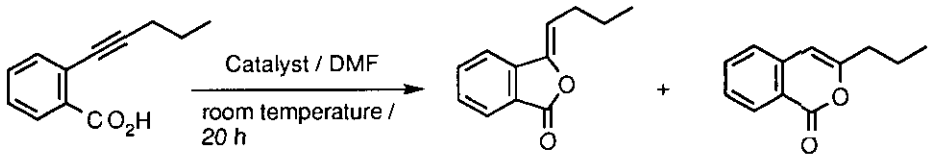


1a **2a** **3a**

Entry	Solvent	Ratio (**2** / **3**)[b]	Yield (%)[c]	Entry	Solvent	Ratio (**2** / **3**)[b]	Yield (%)[c]
1	benzene	23 / 77	93	4	MeCN	64 / 36	71
2	dioxane	16 / 84	85	5	Acetone	75 / 25	80
3	CH_2Cl_2	26 / 74	65	6	DMF	83 / 17	90

a) Ten mol% of Ag_2CO_3 was used. b) Ratio was determined by ^{1}H-nmr analysis. c) Isolated yield.

Table 2. Silver catalyzed cyclization of **1a** in DMF



1a **2a** **3a**

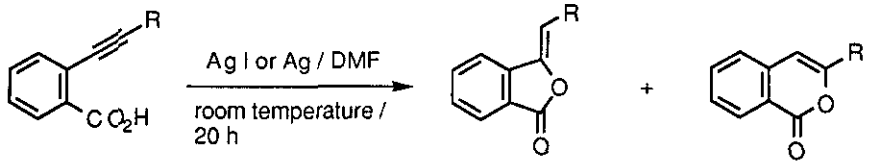
Entry	Catalyst[a]	Ratio (**2** / **3**)[b]	Yield (%)[c]	Entry	Catalyst[a]	Ratio (**2** / **3**)[b]	Yield (%)[c]
1	$AgClO_4$	2 / 98	95	6	Ag_2SO_4	81 / 19	92
2	$AgSO_3CF_3$	4 / 96	90	7	AgCl	86 / 14	61
3	$AgNO_3$	7 / 93	95	8	AgBr	86 / 14	42
4	AgOAc	38 / 62	96	9	AgI	86 / 14	90
5	Ag_2O	40 / 60	97	10	Ag	86 / 14	95

a) Ten mol% of catalyst was used. b) Ratio was determined by ^{1}H-nmr analysis. c) Isolated yield.

silver in DMF was performed to confirm the utility of these catalysts. These reactions proceeded under the mild condition exclusively to afford (Z)-3-alkylidenephthalides (**2b-e**), and it seemed that the regio-selectivity was dependent on the bulkiness of alkyl group. The stereochemistry at C-8 of these phthalides was confirmed by the presence of NOE between the olefinic proton and the aromatic proton. Thus silver iodide and silver were effective in these transformations with high yields and good regio- and stereo-selectivity. The results and the spectral data of these products are summarized in Tables 3 and 4

respectively.

Table 3. Cyclization of **1b-e** catalyzed by silver iodide or silver[a]

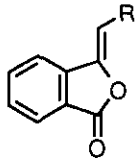


1b-e **2b-e** **3b-e**

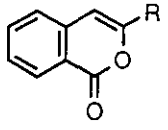
Entry	Substrate	R	AgI		Ag	
			Ratio (**2** / **3**)[b]	Yield(%)[c]	Ratio (**2** / **3**)[b]	Yield (%)[c]
1	**1b**	*n*-C_6H_{13}	86 / 14	89	86 / 14	90
2	**1c**	*c*-C_6H_{11}	90 / 10	94	90 / 10	96
3	**1d**	*t*-C_4H_9	98 / 2	93	98 / 2	95
4	**1e**	Ph	100 / 0	92	100 / 0	96

a) Ten mol% of AgI or Ag was used. b) Ratio was determined by ^{1}H-nmr analysis. c) Isolated yield.

Table 4. Spectral properties of **2a-e** and **3a-e**



2a-e



3a-e

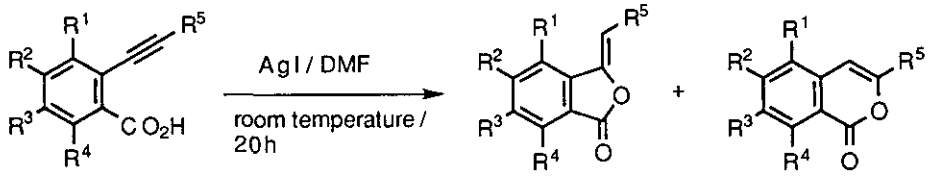
Product	R	ir (KBr) cm^{-1} ν C=O	^{1}H-nmr ($CDCl_3$) δ olefinic proton
2a	*n*-C_3H_7	1777	5.65 (t, J=7.8 Hz)
2b	*n*-C_6H_{13}	1780	5.64 (t, J=7 8 Hz)
2c	*c*-C_6H_{11}	1770	5.50 (d, J=9.5 Hz)
2d	*t*-C_4H_9	1782	5.60 (s)
2e	Ph	1774	6 44 (s)

Product	R	ir (KBr) cm^{-1} ν C=O	^{1}H-nmr ($CDCl_3$) δ olefinic proton
3a	*n*-C_3H_7	1730	6.26 (s)
3b	*n*-C_6H_{13}	1728	6.25 (s)
3c	*c*-C_6H_{11}	1722	6.23 (s)
3d	*t*-C_4H_9	1734	6.31 (s)
3e	Ph	1722	6.97 (s)

The cyclization of 2-alkynylbenzoic acids (**1f-i**) bearing substituent group on the aromatic ring was carried out to explore the limitation of this method as shown in Table 5. Though **1f** (R^5=*n*-C_3H_7) was cyclized

regioselectively to afford (Z)-alkylidenephthalides (**2f**), the regioselectivity of **2** was reduced in the cyclization of **1g-h** (R^5=*n*-C_3H_7) bearing substituent group at C-3. On the other hand, the cyclization of **1i** (R^5=Ph) proceeded exclusively to give **2i** regardless of substituent group at C-3.

Table 5. Cyclization of **1f-i** catalyzed by silver iodide[a]



1f-i **2f-i** **3f-i**

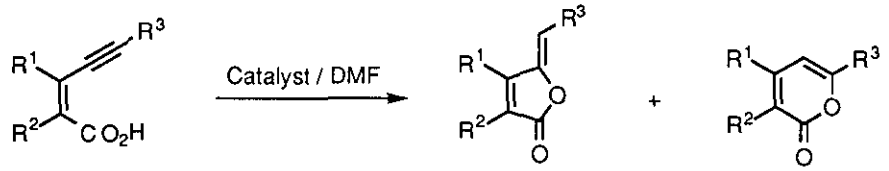
Entry	Substrate	R^1	R^2	R^3	R^4	R^5	Ratio (**2** / **3**)[b]	Yield[c] (%)
1	**1f**	H	OMe	OMe	H	*n*-C_3H_7	90 / 10	95
2	**1g**	-OCH_2O-		H	H	*n*-C_3H_7	56 / 44	93
3	**1h**	OCH_2OMe	OCH_2OMe	H	H	*n*-C_3H_7	41 / 59	90
4	**1i**	-OCH_2O-		H	H	Ph	100 / 0	98

a) Ten mol% of AgI was used. b) Ratio was determined by ^{1}H-nmr analysis. c) Isolated yield.

γ-Alkylidenebutenolides (**8**)[11] and γ-alkylidenebutyrolactones (**5**),[4-7] which have been frequently encountered in natural products, possess significantly diverse biological activities.[8-10] The additional effective use of this method for the synthesis of these lactones was also confirmed. For comparison of catalysts, the cyclization of (Z)-2-alken-4-ynoic acids (**7a-c**) catalyzed by silver iodide, silver or mercuric oxide[11a] in dimethylformamide (DMF) was carried out. When **7a-c** were treated with silver iodide or silver, the cyclization proceeded exclusively to afford γ-alkylidenebutenolides (**8a-c**) which were only Z-olefinic isomer in good yield. On the other hand, the cyclization catalyzed by mercuric oxide provided a mixture of **8** and **9** close to 1 / 1 ratio. The results are summarized in Table 6.

In addition, the cyclization of 4-alkynoic acids (**4a-c**) catalyzed by silver iodide or silver in DMF was performed. In the presence of triethylamine,[12] silver iodide was a more efficient catalyst than silver for the regio- and stereo-selective synthesis of γ-alkylidenebutyrolactones (**5a-c**) having Z-olefinic geometry. The results are shown in Table 7.

Table 6. Cyclization of **7a-c** catalyzed by silver iodide and silver

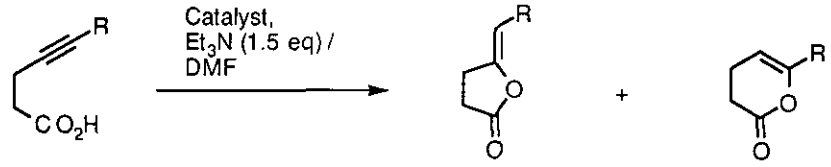


7a-c **8a-c** **9a-c**

Entry	Substrate	R^1	R^2	R^3	Catalyst[a,b]	Temp.,°C	Time, h	Ratio (**8** / **9**)[c]	Yield (%)[d]
1	**7a**	H	H	n-Pr	AgI	100	5	82 / 18	76
2	**7a**	H	H	n-Pr	Ag	100	5	82 / 18	74
3	**7a**	H	H	n-Pr	HgO	150	8	45 / 55	39
4	**7b**	H	H	Ph	AgI	100	5	100 / 0	72
5	**7b**	H	H	Ph	Ag	100	5	100 / 0	76
6	**7b**	H	H	Ph	HgO	150	8	58 / 42	44
7	**7c**	$-(CH_2)_4-$		n-Pr	AgI	r.t.	20	95 / 5	72
8	**7c**	$-(CH_2)_4-$		n-Pr	Ag	r.t.	20	95 / 5	73

a) Ten mol% of AgI or Ag was used. b) One equiv. of HgO was used. c) Ratio was determined by ^{1}H-nmr analysis. d) Isolated yield.

Table 7. Cyclization of **4a-c** catalyzed by silver iodide and silver



4a-c **5a-c** **6a-c**

Entry	Substrate	R	Catalyst[a]	Temp.,°C	Time, h	Ratio (**5** / **6**)[b]	Yield (%)[c]
1	**4a**	H	AgI	100	1	100 / 0	93
2	**4a**	H	Ag	100	17	100 / 0	82
3	**4b**	Me	AgI	100	6	88 / 12	80
4	**4b**	Me	Ag	100	6	-[d]	-[d]
5	**4c**	Ph	AgI	100	3	100 / 0	90
6	**4c**	Ph	Ag	100	24	100 / 0	48

a) Ten mol% was used. b) Ratio was determined by ^{1}H-nmr analysis. c) Isolated yield. d) No reaction.

In conclusion we have demonstrated that the present stereoselective cyclization having highly 5-Exo-Dig

manner catalyzed by silver iodide or silver provided an useful method for the synthesis of (Z)-3-alkylidenephthalides, (Z)-γ-alkylidenebutenolides, and (Z)-γ-alkylidenebutyrolactones. On the other hand, the cyclization having highly 5-Endo-Dig manner catalyzed by silver nitrate, silver trifluoromethanesulfonate or silver perchlorate will be also an efficient method for the synthesis of 3-alkylisocoumarins.

EXPERIMENTAL

Melting points were measured on a YANACO micromelting point apparatus and are uncorrected. Infrared spectra were recorded on a *HITACHI* 270-30 spectrophotometer. Nuclear magnetic resonance spectra were obtained with a JEOL FX-200 or Bruker AM-500 spectrometer using tetramethylsilane as an internal standard. Mass spectra were determined on a Concept 1H or 1S spectrometer. AgI, Ag (powder), and HgO (yellow) were purchased from Wako Pure Chemical Industries, LTD.. Dimethylformamide (DMF) was dried over calcium hydride, distilled and stored over molecular sieves. 4-Pentynoic acid (**4a**) was purchased from Aldrich Chemical Co..

2-Alkynylbenzoic acids. 2-Alkynylbenzoic acids (**1a-e**) were prepared from methyl 2-iodobenzoate according to the method of Villemin[2] followed by hydrolysis with 2N NaOH in methanol. 2-Alkynylbenzoic acids (**1f-i**) were prepared from the corresponding methyl 2-bromobenzoate derivatives[16] according to the method of Castro[3] followed by hydrolysis with 2N NaOH in methanol. (Z)-2-Alken-4-ynoic acids (**7a-b**) were prepared from methyl propiolate according to the method of Lu[13] followed by hydrolysis with 2N NaOH in methanol. 2-Alken-4-ynoic acid (**7c**) was prepared by the method of Yamamoto.[11a] 4-Hexynoic acid (**4b**) was prepared by the method of Gravestock.[14] 5-Phenyl-4-pentynoic (**4c**) was prepared by the method of Johnson[15] followed by oxidation with pyridinium dichromate.

General Procedure for Silver Catalyzed Cyclization (Method A). A mixture of 2-alkynylbenzoic acids (**1a-i**) (1 mmol) and catalyst (10 mol%) in solvent (2 ml) was vigorously stirred at room

temperature for 20 h under argon atmosphere. The reaction mixture was filtered through celite and the filtrate was poured into water and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated to give a residue. The residue was purified by short column chromatography on silica gel using AcOEt-hexane as eluent to give a mixture of **2** and **3**. The ratio of **2/3** was determined by ^{1}H-nmr analysis. Further, the mixture was purified by flash column chromatography on silica gel eluting with solvent mixture (benzene/hexane or benzene/$CHCl_3$) to separate two isomers.

(Z)-3-Butylidenephthalide (2a) : an oil ; ir (KBr) ν_{max} 1777 (C=O), 1686 (C=C) cm^{-1} ; ^{1}H-nmr ($CDCl_3$) δ 0.99 (3H, t, J=7.3 Hz), 1.56 (2H, tq, J=7.3, 7.3 Hz), 2.46 (2H, dt, J=7.8, 7.3 Hz), 5.65 (1H, t, J=7.8 Hz), 7.51 (1H, ddd,J=7.8, 6.0, 2.4 Hz), 7.60-7.78 (2H, m), 7.89 (1H, ddd, J=7.8, 1.0, 1.0 Hz) ; ms m/z (%) 188 (M^+, 22), 159 (100).

3-Propylisocoumarin (3a) : an oil ; ir (KBr) ν_{max} 1730 (C=O), 1656 (C=C) cm^{-1} ; ^{1}H-nmr ($CDCl_3$) δ 1.00 (3H, t, J=7.3 Hz), 1.74 (2H, tq, J=7.5, 7.3 Hz), 2.51 (2H, t, J=7.5 Hz), 6.26 (1H, s), 7.36 (1H, ddd, J=7.6, 1.5, 1.0 Hz), 7.44 (1H, ddd, J=7.6, 7.6, 1.5 Hz), 7.67 (1H, ddd, J=7.6, 7.6, 1.5 Hz), 8.25 (1H, ddd, J=7.6, 1.5, 1.0 Hz) ; ms m/z (%) 188 (M^+, 74), 83 (100).

(Z)-3-Heptylidenephthalide (2b) : an oil ; ir (KBr) ν_{max} 1780 (C=O), 1686 (C=C) cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 0.89 (3H, t, J=6.4 Hz), 1.20-1.60 (8H, m), 2.48 (2H, dt, J=7.8, 7.3 Hz), 5.64 (1H, t, J=7.8 Hz), 7.50 (1H, ddd, J=8.3, 6.1, 2.0 Hz), 7.60-7.70 (2H, m), 7.90 (1H, ddd, J=7.6, 1.0, 1.0 Hz) ; ms m/z (%) 230 (M^+, 20), 159 (100).

3-Hexylisocoumarin (3b) : an oil ; ir (KBr) ν_{max} 1728 (C=O), 1656 (C=C) cm^{-1} ; ^{1}H-nmr ($CDCl_3$) δ 0.89 (3H, t, J=6.6 Hz), 1.15-1.45 (6H, m), 1.60-1.80 (2H, m), 2.53 (2H, t, J=7.3 Hz), 6.25 (1H, s), 7.35 (1H, d, J=8.1 Hz), 7.44 (1H, ddd, J=8.1, 7.8, 1.5 Hz), 7.67 (1H, ddd, J=7.8, 7.3, 1.5 Hz), 8.25 (1H, ddd, J=7.3, 1.5, 0.7 Hz) ; ms m/z (%) 230 (M^+, 38), 118 (100).

(Z)-3-Cyclohexylmethylidenephthalide (2c) : mp 85-87°C (hexane) ; ir (KBr) ν_{max} 1770 (C=O), 1680 (C=C) cm^{-1} ; ^{1}H-nmr ($CDCl_3$) δ 1.05-1.85 (10H, m), 2.80 (1H, m), 5.50 (1H, d, J=9.5 Hz), 7.50 (1H, ddd, J=7.6, 6.1, 2.0 Hz), 7.55-7.75 (2H, m), 7.89 (1H, ddd, J=7.6, 1.0, 1.0 Hz) ; ms m/z (%) 228 (M^+, 16), 147 (100).

3-Cyclohexylisocoumarin (3c) : mp 91-93°C (hexane) ; ir (KBr) ν_{max} 1722 (C=O), 1647 (C=C) cm^{-1} ; ^{1}H-nmr ($CDCl_3$) δ 1.10-2.10 (10H, m), 2.45 (1H, m), 6.23 (1H, s), 7.37 (1H, d, J=7.8 Hz), 7.44 (1H, ddd, J=7.8, 7.8, 1.2 Hz), 7.67 (1H, ddd, J=7.8, 7.8, 1.5 Hz), 8.25 (1H, d, J=7.8 Hz) ; ms m/z (%) 228 (M^+, 100).

(Z)-3-(2,2-Dimethylpropylidene)phthalide (2d) : mp 88-90°C (hexane) ; ir (KBr) ν_{max} 1782 (C=O), 1674 (C=C) cm^{-1} ; ^{1}H-nmr ($CDCl_3$) δ 1.32 (9H, s), 5.60 (1H, s), 7.49 (1H, ddd, J=7.6, 6.3, 1.7 Hz), 7.61 (1H, ddd, J=7.6, 1.7, 1.0 Hz), 7.67 (1H, ddd, J=7.6, 6.3, 1.0 Hz), 7.88 (1H, ddd, J=7.6, 1.0, 1.0 Hz) ; ms m/z (%) 202 (M^+, 15), 187 (100).

3-t-Butylisocoumarin (3d) : mp 59-60°C (hexane) ; ir (KBr) ν_{max} 1734 (C=O), 1646 (C=C) cm^{-1} ; ^{1}H-nmr ($CDCl_3$) δ 1.33 (9H, s), 6.31 (1H, s), 7.39 (1H, d, J=7.3 Hz), 7.49 (1H, ddd, J=7.3, 7.3, 1.2 Hz), 7.67 (1H, ddd, J=7.3, 7.3, 1.2 Hz), 8.26 (1H, ddd, J=7.3, 1.2, 0.7 Hz) ; ms m/z (%) 202 (M^+, 1), 149 (100).

(Z)-3-Benzylidenephthalide (2e) : mp 92-94°C (hexane) (lit.,[3] mp 98-99.5°C).

(Z)-3-Butylidene-5,6-dimethoxyphthalide (2f) : mp 129-130°C (AcOEt/hexane) ; ir (KBr) ν_{max} 1752 (C=O), 1688 (C=C) cm^{-1} ; ^{1}H-nmr ($CDCl_3$) δ 0.99 (3H, t, J=7.3 Hz), 1.55 (2H, tq, J=7.6, 7.3 Hz), 2.44 (2H, dt, J=7.8, 7.6 Hz), 3.95 (3H, s), 4.00 (3H, s), 5.49 (1H, t, J=7.8 Hz), 7.00 (1H, s), 7.25 (1H, s) ; ms m/z (%) 248 (M^+, 32), 219 (100).

6,7-Dimethoxy-3-propylisocoumarin (3f) : mp 139-140°C (AcOEt/hexane) ; ir (KBr) ν_{max} 1702 (C=O), 1650 (C=C) cm^{-1} ; ^{1}H-nmr ($CDCl_3$) δ 0.99 (3H, t, J=7.3 Hz), 1.74 (2H, tq, J=7.3, 7.3 Hz), 2.50 (2H, t, J=7.3 Hz), 3.97 (3H, s), 3.99 (3H, s), 6.19 (1H, s), 6.74 (1H, s), 7.63 (1H, s) ; ms m/z (%) 248 (M^+, 100).

The stereochemistry at C-8 of these phthalides (**2a-f**) was confirmed by the presence of NOE between the olefinic proton and the aromatic proton.

(Z)-3-Butylidene-4,5-methylenedioxyphthalide (2g) : mp 118-120°C (AcOEt/hexane) ; ir (KBr) ν_{max} 1764 (C=O), 1694 (C=C) cm^{-1} ; ^{1}H-nmr ($CDCl_3$) δ 0.98 (3H, t, J=7.3 Hz), 1.55 (2H, tq, J=7.3, 7.3 Hz), 2.43 (2H, dt, J=7.8, 7.3 Hz), 5.56 (1H, t, J=7.8 Hz), 6.95 (1H, d, J=8.1 Hz), 7.48 (1H, d, J=8.1

Hz) ; ms m/z (%) 232 (M^+, 25), 203 (100).

5,6-Methylenedioxy-3-propylisocoumarin (3g) : ^{1}H-Nmr ($CDCl_3$) δ 0.99 (3H, t, J=7.3 Hz), 1.73 (2H, tq, J=7.3, 7.3 Hz), 2.49 (2H, t, J=7.3 Hz), 6.15 (2H, s), 6.26 (1H, d, J=0.7 Hz), 6.94 (1H, d, J=8.5 Hz), 7.89 (1H, dd, J=8.5, 0.7 Hz).

(Z)-3-Butylidene-4,5-dimethoxymethoxyphthalide (2h) : ^{1}H-Nmr ($CDCl_3$) δ 0.98 (3H, t, J=7.3 Hz), 1.56 (2H, tq, J=7.3, 7.3 Hz), 2.50 (2H, dt, J=7.8, 7.3 Hz), 3.54 (3H, s), 3.58 (3H, s), 5.32 (2H, s), 5.36 (2H, s), 6.10 (1H, t, J=7.8 Hz), 7.32 (1H, d, J=8.1 Hz), 7.62 (1H, d, J=8.1 Hz) .

5,6-Dimethoxymethoxy-3-propylisocoumarin (3h) : ^{1}H-Nmr ($CDCl_3$) δ 1.00 (3H, t, J=7.3 Hz), 1.74 (2H, tq, J=7.3, 7.3 Hz), 2.51 (2H, t, J=7.3 Hz), 3.52 (3H, s), 3.61 (3H, s), 5.19 (2H, s), 5.31 (2H, s), 6.59 (1H, d, J=0.7 Hz), 7.25 (1H, d, J=8.5 Hz), 8.02 (1H, dd, J=8.5, 0.7 Hz).

(Z)-3-Benzylidene-4,5-methylenedioxyphthalide (2i) : mp 169-171°C (AcOEt/hexane) ; ir (KBr) ν_{max} 1770 (C=O), 1646 (C=C) cm^{-1} ; ^{1}H-nmr ($CDCl_3$) δ 6.27 (2H, s), 6.37 (1H, s), 6.99 (1H, d, J=8.1 Hz), 7.30 (3H, m), 7.54 (1H, d, J=8.1 Hz), 7.80 (2H, m) ; ms m/z (%) 266 (M^+, 100).

5,6-Methylenedioxy-3-phenylisocoumarin (3i) : mp 175-178°C (AcOEt/hexane) ; ir (KBr) ν_{max} 1718 (C=O), 1634 (C=C) cm^{-1} ; ^{1}H-nmr ($CDCl_3$) δ 6.20 (2H, s), 6.96 (1H, s), 6.99 (1H, d, J=7.8 Hz), 7.45 (3H, m), 7.89 (1H, d, J=7.8 Hz), 7.90 (1H, m), 7.95 (dd, J=8.5, 0.7 Hz) ; ms m/z (%) 266 (M^+, 100).

General Procedure for Cyclization (Method B). A mixture of 2-alken-4-ynoic acids (**7a-c**) (1 mmol) and catalyst (10 mol%) in dry DMF (2 ml) was heated at 100 °C under vigorous stirring and argon atmosphere for 5-8 h. The reaction mixture was worked up according to the method A. The residue was purified by flash column chromatography on silica gel eluting with solvent mixture (AcOEt/hexane) to separate two isomers.

(Z)-2,4-Octadien-4-olide (8a) : an oil ; ir (KBr) ν_{max} 1776 (C=O) cm^{-1} ; ^{1}H-nmr ($CDCl_3$) δ 0.96 (3H, t, J=7.3 Hz), 1.52 (2H, tq, J=7.3, 7.3 Hz), 2.39 (2H, dt, J=8.1, 7.3 Hz), 5.31 (1H, t, J=8.1 Hz), 6.15 (1H, d, J=5.4 Hz), 7.34 (1H, d, J=5.4 Hz) ; ms m/z (%) 138 (M^+, 4), 43 (100).

2,4-Octadien-5-olide (9a) : an oil ; ir (KBr) ν_{max} 1734 (C=O) cm^{-1} ; ^{1}H-nmr ($CDCl_3$) δ 0.97 (3H, t, J=7.3 Hz), 1.70 (2H, tq, J=7.6, 7.3 Hz), 2.47 (2H, t, J=7.6 Hz), 5.97 (1H, dd, J=7.3, 1.0 Hz), 6.15 (1H, dd, J=9.3, 1.0 Hz), 7.26 (1H, dd, J=9.3, 7.3 Hz) ; ms m/z (%) 138 (M^+, 24), 95 (100).

(Z)-5-Phenyl-2,4-pentadien-4-olide (8b) : mp 88-89°C (AcOEt/hexane) ; ir (KBr) ν_{max} 1746 (C=O) cm^{-1} ; ^{1}H-nmr ($CDCl_3$) δ 6.04 (1H, s), 6.22 (1H, dd, J=5.4, 0.7 Hz), 7.25-7.45 (3H, m), 7.50 (1H, d, J=5.4 Hz), 7.70-7.85 (2H, m) ; ms m/z (%) 172 (M^+, 89), 43 (100).

The stereochemistry at C-5 of these lactones (**8a-b**) was confirmed by the presence of NOE between the olefinic proton at C-3 and that at C-5.

5-Phenyl-2,4-pentadien-5-olide (9b) : mp 63-64°C (AcOEt/hexane) ; ir (KBr) ν_{max} 1710 (C=O) cm^{-1} ; ^{1}H-nmr ($CDCl_3$) δ 6.29 (1H, dd, J=9.3, 0.7 Hz), 6.66 (1H, dd, J=6.8, 1.0 Hz), 7.40-7.50 (3H, m), 7.43 (1H, dd, J=9.3, 6.8 Hz), 7.80-7.90 (2H, m) ; ms m/z (%) 172 (M^+, 33), 144 (100).

(Z)-3-Butylidene-4,5,6,7-tetrahydrophthalide (8c) : an oil ; ir (KBr) ν_{max} 1770 (C=O) cm^{-1} ; ^{1}H-nmr ($CDCl_3$) δ 0.95 (3H, t, J=7.3 Hz), 1.48 (2H, tq, J=7.3, 7.3 Hz), 1.60-1.85 (4H, m), 2.20-2.45 (6H, m), 5.11 (1H, t, J=7.9 Hz) ; ms m/z (%) 192 (M^+, 36), 163 (100). The stereochemistry at C-8 was confirmed by the presence of NOE between the olefinic proton at C-8 and the protons at C-4.

5,6,7,8-Tetrahydro-3-propylisocoumarin (9c) : an oil ; ir (KBr) ν_{max} 1716 (C=O) cm^{-1} ; ^{1}H-nmr ($CDCl_3$) δ 0.95 (3H, t, J=7.3 Hz), 1.50-1.80 (6H, m), 2.45-2.30 (6H, m), 5.73 (1H, s) ; ms m/z (%) 192 (M^+, 49), 135 (100).

General Procedure for Silver Catalyzed Cyclization (Method C). A mixture of alkynoic acid (1 mmol), AgI (or Ag) (10 mol%), and triethylamine (0.2 ml, 1.5 mmol) in dry DMF (2 ml) was heated at 100 °C under vigorous stirring and argon atmosphere for 1-24 h. The reaction mixture was worked up according to the method A. The residue was purified by flash column chromatography on silica gel eluting with benzene to separate two isomers.

4-Penten-4-olide (5a) : an oil ; ir (KBr) ν_{max} 1808 (C=O) cm^{-1} ; ^{1}H-nmr ($CDCl_3$) δ 2.50-2.75 (2H, m), 2.75-2.95 (2H, m), 4.32 (1H, dt, J=2.0, 2.0 Hz), 4.75 (1H, dt, J=2.0, 2.0 Hz).

(Z)-4-Hexen-4-olide (5b) : an oil ; ir (KBr) ν_{max} 1796 (C=O) cm^{-1} ; ^{1}H-nmr ($CDCl_3$) δ 1.67 (3H, dt, J=6.8, 1.8 Hz), 2.60-2.75 (2H, m), 2.75-2.90 (2H, m), 4.62 (1H, qt, J=6.8, 1.8 Hz) ; ms m/z (%) 112 (M^+, 51), 56 (100).

4-Hexen-5-olide (6b) : an oil ; ir (KBr) ν_{max} 1762 (C=O) cm^{-1} ; ^{1}H-nmr ($CDCl_3$) δ 1.89 (3H, dt, J=1.7, 0.5 Hz), 2.30 (2H, m), 2.58 (2H, tq, J=7.8, 0.5 Hz), 5.00 (1H, qt, J=4.5, 2.0 Hz) ; ms m/z (%) 112 (M^+, 66), 43 (100).

(Z)-5-Phenyl-4-penten-4-olide (5c) : mp 92-93°C (AcOEt/hexane) ; ir (KBr) ν_{max} 1792 (C=O), cm^{-1} ; ^{1}H-nmr ($CDCl_3$) δ 2.65-2.75 (2H, m), 2.90-3.10 (2H, m), 5.54 (1H, t, J=1.7 Hz), 7.15-7.50 (3H, m), 7.50-7.65 (2H, m) ; ms m/z (%) 174 (M^+, 100).

The stereochemistry at C-5 of these lactones (**5b-c**) was confirmed by the presence of NOE between the olefinic proton at C-5 and the protons at C-3.

3-Phenylisocoumarin (3e) : A mixture of **1e** (50 mg, 0.23 mmol) and *p*-toluenesulfonic acid (43 mg, 0.23 mmol) in benzene (0.5 ml) was refluxed for 3 h. The mixture was poured into water and extracted twice with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ solution then brine, dried over $MgSO_4$, and evaporated to give a residue. The ratio of **2e** / **3e** determined by ^{1}H-nmr was 3 / 97. The residue was recrystallized from hexane to give needles of **3e** (38 mg, 76%) : mp 90-91°C (lit.,[17] mp 90-91°C).

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