Synthesis and stereochemistry of β-aryl-β-haloacroleins: useful intermediates for the preparation of (*Z*) and (*E*)-2-en-4-ynecarbaldehydes and for the synthesis of rubrolides

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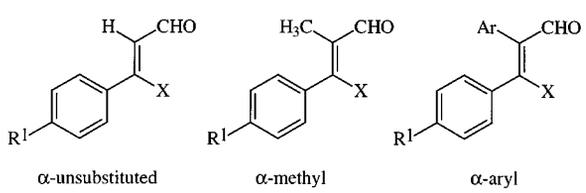
The synthesis of α-substituted β-aryl-β-haloacroleins by two different pathways is presented. The determination of their stereochemistry by NOE experiments is reported for the first time. Furthermore, we describe the preparation of 2-en-4-ynecarbaldehydes and access to rubrolide derivatives from β-aryl-β-haloacroleins.

Introduction

β-Aryl-β-haloacroleins **1** are starting materials for the preparation of numerous heterocycles such as pyrazole,[1] isoxazole,[2] isothiazole,[3] pyrrole,[4] thiophene,[5] selenophene,[6] tellurophene,[7] pyran-2-one,[8] thiopyran-2-one,[9] thiopyran,[10] diazepine,[11] thiazepine,[12] pyrimidine,[13] pyrilium,[14] thiopyrilium salts[15] and quinoline.[16]

Generally, these β-aryl-β-haloacroleins are obtained by two different ways involving the addition of a Vilsmeier–Haack reagent to acetylenic compounds[17] or to α-methylene ketones.[5] These two reactions have already been described, however, little is known about the stereochemistry of the double bond formed. Only a few papers have described the stereochemistry of α-unsubstituted or α-methylated acroleins (Scheme 1): the



Scheme 1 β-Aryl-β-haloacrolein **1**.

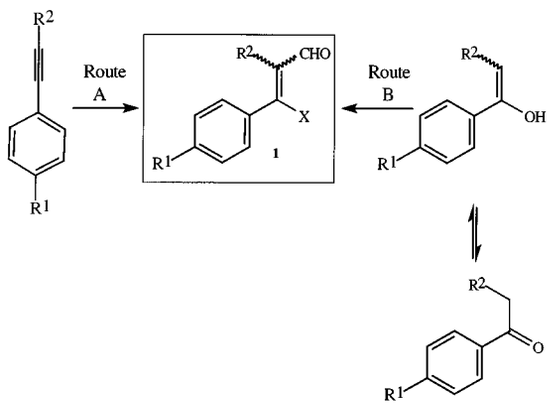
stereochemistry of the carbon–carbon double bond was established through the resonance of the aldehyde proton.[18] In an attempt to prepare junipal, Rossi *et al.*[19] observed and isolated both isomers, (*E*) and (*Z*), of α-methylacroleins, and the stereochemistry was deduced through NMR chemical shifts.

Furthermore, Giles and Marson,[20] in their recent review, only mentioned the possibility of obtaining both isomers (*E*) and (*Z*), but did not report the determination of the stereochemistry with regard to the different substituents.

In the first part of this paper, we describe the preparation of some known and new α-substituted β-aryl-β-haloacroleins **1**, the comparison of the two known access methods (Route A and Route B, Scheme 2) and the determination of the stereochemistry of these compounds by NOE experiments. In the second part, we present the use of these haloacroleins **1** as starting materials for the synthesis of conjugated 2-en-4-ynecarbaldehydes by palladium catalysed cross coupling reactions and for the preparation of biologically active compounds.

Results and discussion

Route A (DMF, $POCl_3$, alkyne) seems to be less efficient than



Scheme 2 Preparation of β-aryl-β-haloacrolein **1**.

Route B (DMF, $POCl_3$, ketone) to prepare acroleins **1** (Table 1). Acrolein **1a** was obtained in 43% yield in DMF at 60 °C (Entry 5). The same reaction run at lower temperature or in refluxing chloroform (Entries 4, 6) gave the unchanged starting material, even after prolonged heating times. When the same strategy was applied to disubstituted alkynes, no reaction was observed even after 20 hours at reflux (Entries 10, 11, 18, 19, 21) which seems to indicate that these alkynes are unreactive towards electrophilic attack from the Vilsmeier–Haack reagent.[19,21] In contrast, acroleins **1a** to **1m** were obtained in good to excellent yields using Route B, depending on the bulkiness of the substituent R^2. As shown in Table 1, the yields decrease from 85–90% (R^2 = H, Entries 1–3) to 57–75% (R^2 = CH_3 or CH_3CH_2, Entries 9, 12–16) and to 55% (R^2 = Ph, Entry 17). Only the more activated β-chloro-α,β-diphenylacrolein **1l** (Entry 20) is obtained with a higher yield (92%).

The results presented in Table 1 also show the influence of the substituent R^2 on the (*Z*/*E*) ratio. The α-unsubstituted acrolein **1a** (R^2 = H) is obtained as a single isomer (*Z*) by Route B. With methyl or ethyl substituents, we observed a decrease of the population of the *Z* isomer to 13–25% (Entries 9, 12–16). The (*Z*/*E*) ratio is dramatically modified with bulkier substituents (R^2 = Ph, Entry 17). The (*E*) isomer was obtained as the single product in one case (R^2 = 4-MeOPh).

Another objective of this work was to know if the introduced halide could play a role in the stereoselectivity of the Vilsmeier–Haack reaction. The bromo derivatives **1d**, **1e** and **1i**, **1j**, were prepared by using phosphorus oxybromide instead of phosphorus oxychloride. It shows no significant influence of the halide on the (*Z*/*E*) ratio, while a small decrease of

Table 1 Synthesis of β-aryl-β-haloacroleins **1**

Entry	R^1	R^2	X	Route	Compd.	Solvent	Conditions	Yield (%)	*Z*/*E*[a]
1	H	H	Cl	B	**1a**	Ref. 5		90	100:0
2	CH_3O	H	Cl	B	**1b**	Ref. 5		90	100:0
3	Cl	H	Cl	B	**1c**	Ref. 5		85	100:0
4[b]	H	H	Cl	A	**1a**	DMF	20 °C, 20 h	—	—
5	H	H	Cl	A	**1a**	DMF	60 °C, 4 h	43	87:13
6[b]	H	H	Cl	A	**1a**	$CHCl_3$	reflux, 20 h	—	—
7	Cl	H	Br	B	**1d**	DMF	60 °C, 4 h	68	100:0
8	CH_3O	H	Br	B	**1e**	DMF	60 °C, 4 h	71	100:0
9	H	CH_3	Cl	B	**1f**	DMF	60 °C, 4 h	75	13:87
10[b]	H	CH_3	Cl	A	**1f**	DMF	60 °C, 5 h	—	—
11[b]	H	CH_3	Cl	A	**1f**	DMF	reflux, 20 h	—	—
12	CH_3O	CH_3	Cl	B	**1g**	DMF	60 °C, 5 h	69	15:85
13	Cl	CH_3	Cl	B	**1h**	DMF	60 °C, 5 h	72	15:85
14	CH_3O	CH_3	Br	B	**1i**	DMF	60 °C, 5 h	59	20:80
15	Cl	CH_3	Br	B	**1j**	DMF	60 °C, 5 h	57	17:83
16	H	CH_3CH_2	Cl	B	**1k**	DMF	60 °C, 5 h	71	25:75
17	H	Ph	Cl	B	**1l**	DMF	80 °C, 15 h	55	11:89
18[b]	H	Ph	Cl	A	**1l**	DMF	80 °C, 15 h	—	—
19[b]	H	Ph	Cl	A	**1l**	DMF	reflux, 20 h	—	—
20	CH_3O	4-CH_3OPh	Cl	B	**1m**	DMF	80 °C, 15 h	92	0:100
21[b]	CH_3O	4-CH_3OPh	Cl	A	**1m**	DMF	reflux, 40 h	—	—

[a] Based on the integrals of the carbaldehyde proton resonances; stereochemistry determined by NMR NOE experiments. [b] No yields indicated means recovering of the starting material.

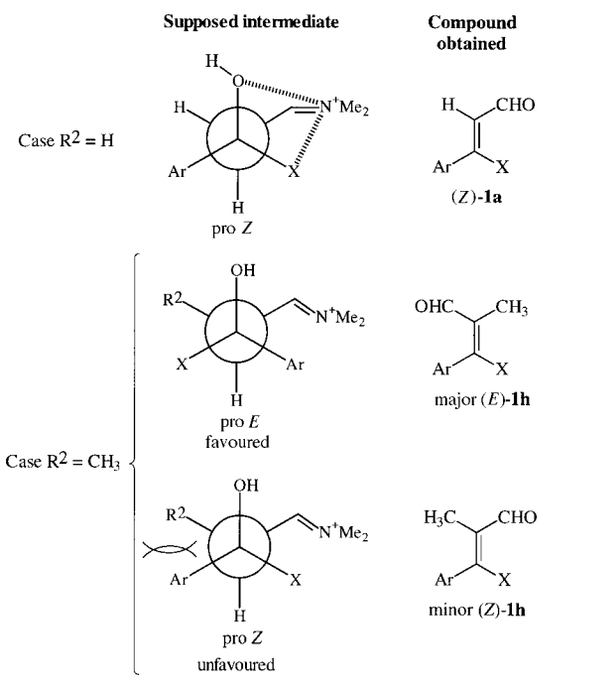
the yields of products **1d**, **1e**, **1i** and **1j** (Entries 7, 8, 14, 15) is observed.

On the other hand variation of the substituents on the starting acetophenones shows little influence on the yields or the stereoselectivity of the Vilsmeier–Haack adduct. Therefore steric factors due to the presence or absence of a substituent in the α-position should be responsible for the observed stereochemistry. In the supposed mechanism for the reaction starting from methylene ketones (Route B), the Vilsmeier–Haack reagent adds to the enol form of the ketone[22] (Scheme 2) leading to the formation of a carbon–carbon single bond (Scheme 3). The β-haloacrolein is obtained after elimination of water and hydrolysis of the iminium salt. When the reaction is carried out with acetophenones (for example compound **1a**, R^2 = H), the *Z* isomer is obtained in a pure form due to a possible stabilisation of the iminium salt by the hydroxy and the halide groups as shown in Scheme 3. With bulkier substituents (for example in compound **1h**, R^2 = CH_3), steric hindrance in the supposed intermediate (before elimination of water) favours the (*E*) isomer, which is obtained as a single isomer in some cases.

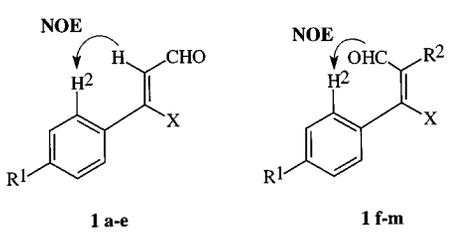
Table 2 shows characteristic resonances of the carbaldehyde protons for compounds **1**. The stereochemistry of these compounds was established by NOE experiments. In the case of α-unsubstituted β-aryl-β-haloacroleins **1a**–**e**, where only one isomer was obtained, NOE experiments have shown a close proximity between H-2,6 and H-α, thus establishing their stereochemistry as the (*Z*) isomer (Scheme 4). For the α-substituted β-aryl-β-haloacroleins **1f**–**k**, upon irradiation of the carbaldehyde proton resonance of the major isomer (δ 9.41–9.49 ppm) enhancements on the H-2,6 signals were observed. These results are only compatible with the structure of the (*E*) isomer of compounds **1f**–**k** (Scheme 4). The ratio of (*E*/*Z*) of compounds **1l,m** was established on the basis of their carbaldehyde protons resonance, because NOE experiments were not possible in these cases due to the presence of equal substituents in the α- and β-positions.

As shown in Table 2, the carbaldehyde protons resonance of the (*Z*) isomers are higher than that of the (*E*) isomers. Moreover, Entries 4, 5, 9 and 10 show a decrease of 0.13 to 0.21 ppm of this resonance, when chlorine is replaced by bromine.

In the second part of this paper, we show the ability of these β-haloacroleins to undergo palladium mediated cross coupling reactions. In our first attempt and as expected, the palladium catalysed coupling sequence applied to β-aryl-β-chloroacrolein

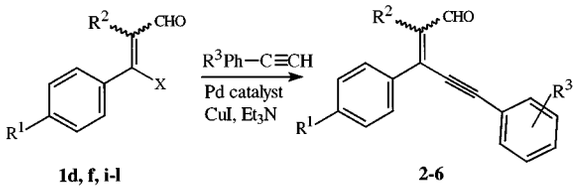


Scheme 3 Supposed intermediates in the reaction of Vilsmeier–Haack reagent with acetophenones (Case R^2 = H) and propiophenones (Case R^2 = CH_3).



Scheme 4 NOE experiments on compounds **1a** to **m**.

1f failed, due to the well known lesser reactivity of chlorine atoms in metal mediated coupling sequences (Table 3, Entry 1). Therefore the acrolein **1f** undergoes cross coupling if refluxed with sodium iodide and anhydrous nickel bromide prior to the coupling sequence (Scheme 5). This activation method, described by Bozell[23] on chloroarenes, leads to the more



Scheme 5 Preparation of 2-en-4-ynecarbaldehydes **2**–**6**.

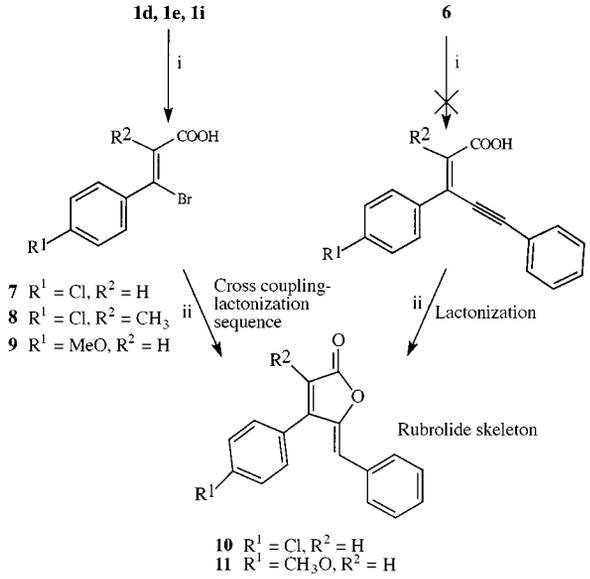
reactive iodoacrolein intermediate. In this case a mixture of (*Z*) and (*E*) isomers of the 2-en-4-ynecarbaldehydes is obtained independently of the stereochemistry of the parent β-aryl-β-chloroacroleins **1**. The intermediate iodoacroleins are probably being produced without selectivity in the described conditions. Our attempt to isolate these iodo derivatives failed. In contrast, Sonogashira's[24] reaction conditions applied to the bromo derivatives **1d**, **1i** and **1j**, **1l** show good selectivity: the starting material stereochemistry is retained in the 2-en-4-ynecarbaldehydes **2**–**6**.

As recently described by Negishi,[25] substituted 2-en-4-yne compounds are efficient starting materials for the preparation of rubrolide derivatives.[25] In the last part of this paper, we will show that the 2-en-4-ynecarbaldehydes **2**–**6** or the parent acroleins **1** prepared in this study are valuable, easy available intermediates for the preparation of the biologically interesting rubrolide derivatives. These rubrolides are available through lactonization of 2-en-4-ynoic acid or in a two step cross coupling–lactonization sequence starting from cinnamic acids **7**–**9** as proposed in Scheme 6.

The oxidation of carbaldehydes **1d, 1e** and **1j** using the procedure of Dalcanale and Montanari[26] gave the corresponding cinnamic acids **7**, **8** and **9** in good yields (91%, 85% and 82%, respectively). An essential difference to Negishi's[25] method, is in the strategy we used to allow the introduction of substituents in the α-position. The cross coupling, lactonization sequence applied to cinnamic acids **7** and **8** under Negishi[25] conditions using tetrakis(triphenylphosphine)palladium (TPP_4Pd), copper iodide, triethylamine in acetonitrile at room temperature, leads to the desired rubrolides **10** (R^1 = Cl; R^2 = H) in 81% yield and

Table 2 Characteristic resonances of the carbaldehyde protons of acroleins **1**

Entry	R^1	R^2	X	Compound	δ (*E*)	δ (*Z*)
1	H	H	Cl	**1a**	—	10.21
2	CH_3O	H	Cl	**1b**	—	10.25
3	Cl	H	Cl	**1c**	—	10.21
4	Cl	H	Br	**1d**	—	10.05
5	CH_3O	H	Br	**1e**	—	10.41
6	H	CH_3	Cl	**1f**	9.45	10.36
7	CH_3O	CH_3	Cl	**1g**	9.49	10.38
8	Cl	CH_3	Cl	**1h**	9.48	10.39
9	CH_3O	CH_3	Br	**1i**	9.39	10.25
10	Cl	CH_3	Br	**1j**	9.38	10.18
11	H	CH_2CH_3	Cl	**1k**	9.41	10.34
12	H	Ph	Cl	**1l**	9.67	10.60
13	CH_3O	4-CH_3OPh	Cl	**1m**	9.65	—



Scheme 6 *Reagents and conditions*: i: H_2O_2, H_2O, NaH_2PO_4, $NaClO_2$, MeCN, room temperature; ii: TPP_4Pd, CuI, Et_3N, MeCN, room temperature.

11 (R^1 = MeO; R^2 = H) in 74% yield. When the same strategy was applied to acid **9** neither the desired lactone, nor the Sonogashira coupling product could be observed.

Applying the Dalcanale and Montanari[26] oxidation procedure to 2-en-4-ynecarbaldehyde **6** did not lead to the corresponding 2-en-4-ynoic acid. Treatment of **6** with Ag_2O[27] in Robinson conditions was also unsuccessful.

Conclusion

In conclusion, the configuration of the double bond of β-aryl-β-haloacroleins was determined unequivocally by using NOE experiments. The influence of the α-substituents' bulkiness on the intermediates of the Vilsmeier–Haack reaction, which control the stereochemistry of the created double bond, was also shown. Furthermore, the size of the halide introduced in this reaction had no effect on the stereochemistry of the prepared β-aryl-β-haloacroleins. Finally, β-aryl-β-haloacroleins are readily available starting materials for the preparation of 2-en-4-ynecarbaldehydes by Sonogashira's[24] palladium catalysed coupling reactions. Moreover, they provide an interesting three-step easy access to the biologically active rubrolide derivatives.

Experimental

Mps were determined on a Kofler bench and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in deuterochloroform solution on Bruker AM 250 and AMX 300 spectrometers, at 250.13, 300.13 and 62.89, 75.47 MHz; the chemical shifts (δ) are expressed in ppm relative to internal TMS. Infrared spectra were performed on a Perkin-Elmer FTIR and UV-

Table 3 Synthesis of 2-en-4-ynecarbaldehydes **2**–**6**

Entry	R^1	R^2	X	R^3	Conditions	Compound	Yield (%)	*Z*/*E*[a]
1	H	CH_3	Cl	H	$PdTPP_4$, DMF, CuI, Et_3N	**2**	—	—
2	H	CH_3	Cl	H	NaI, $NiBr_2$, $PdTPP_4$, DMF, CuI, Et_3N	**2**	51	50:50
3	H	Ph	Cl	H	NaI, $NiBr_2$, $PdTPP_4$, DMF, CuI, Et_3N	**3**	27	25:75
4	H	CH_3	Br	H	$PdTPP_4$, DMF, CuI, Et_3N	**2**	59	15:85
5	CH_3O	CH_3	Br	H	$PdTPP_4$, DMF, CuI, Et_3N	**4**	58	20:80
6	Cl	H	Br	2,4-$(CH_3O)_2$	$PdTPP_4$, DMF, CuI, Et_3N	**5**	51	90:10
7	Cl	H	Br	H	$PdTPP_4$, DMF, CuI, Et_3N	**6**	63	100:0

[a] Based on the integrals of the carbaldehyde proton resonances.

visible spectra on a Shimadzu 1250 apparatus; ε values are given in $dm^3\ mol^{-1}\ cm^{-1}$.

β-Halo-β-arylacrolein 1: general procedure

DMF (11 ml) was added to an ice cold solution of phosphoryl chloride (11 ml) and the mixture stirred for 10 minutes. Then the ketone (Route B) or the acetylenic compound (Route A) in 30 ml of the appropriate solvent was added dropwise and the mixture stirred in the conditions described in Table 1. Pouring the reaction mixture into an aqueous sodium acetate solution yielded the β-halo-β-arylacroleins **1**, which were filtered or extracted with ethyl acetate. Purification was accomplished as indicated below.

(*Z*)-β-Chloro-β-phenylacrolein 1a (90%). Purification by distillation: bp 142–143 °C (20 Torr) [lit.[5] 140 °C (20 Torr)]; UV/Vis: λ_{max} (MeOH)/nm 241 (12100); ν_{max}/cm^{-1} 1675; δ_H 6.55 (1H, d, J = 6.2 Hz, H-α), 7.21 (2H, m, H-2,6), 7.40 (3H, m, H-3,4,5), 10.15 (1H, d, J = 6.2 Hz, C*H*O); δ_C 125.7 (C-α), 127.9 (C-2,6), 129.5 (C-3,5), 129.8 (C-4), 135.1 (C-1), 152.7 (C-β), 191.1 (*C*HO).

(*Z*)-β-Chloro-β-(4-methoxyphenyl)acrolein 1b (90%). Purification by recrystallization: mp 57 °C from iPrOH (lit.[5] 57 °C); λ_{max} (MeOH)/nm 259 (13500); ν_{max}/cm^{-1} 1680; δ_H 3.85 (s, 3H, 4-OC*H*$_3$), 6.65 (d, J = 6.0 Hz, 1H, H-α), 7.00 (d, J = 5.8 Hz, 2H, H-3,5), 7.80 (d, J = 5.8 Hz, 2H, H-2,6), 10.25 (d, J = 6.0 Hz, 1H, C*H*O); δ_C 55.3 (4-O*C*H$_3$), 113.7 (C-3,5), 122.1 (C-α), 127.6 (C-1), 128.7 (C-2,6), 151.1 (C-β), 162.4 (C-4), 190.5 (*C*HO).

(*Z*)-β-Chloro-β-(4-chlorophenyl)acrolein 1c (85%). Purification by recrystallization: mp 86 °C from EtOH (lit.[5] 86 °C); λ_{max} (MeOH)/nm 253 (13300); ν_{max}/cm^{-1} 1666; δ_H 6.65 (1H, d, J = 6.0 Hz, H-α), 7.44 (2H, d, J = 9.0 Hz, H-3,5), 7.70 (2H, d, J = 9.0 Hz, H-2,6), 10.21 (1H, d, J = 6.0 Hz, C*H*O); δ_C 124.5 (C-α), 128.4 (C-2,6), 129.2 (C-3,5), 133.9 (C-4), 138.1 (C-1), 150.8 (C-β), 191.2 (*C*HO).

(*Z*)-β-Bromo-β-(4-chlorophenyl)acrolein 1d (68%). Purification by flash chromatography (CH_2Cl_2): mp 63 °C; λ_{max} (MeOH)/nm 295 (6500); ν_{max}/cm^{-1} 1665; δ_H 6.78 (1H, d, J = 6.5 Hz, H-α), 7.42 (2H, d, J = 8.7 Hz, H-2,6), 7.66 (2H, d, J = 8.7 Hz, H-3,5), 10.05 (1H, d, J = 6.5 Hz, C*H*O); δ_C 127.6 (C-α), 128.4 (C-2,6), 129.2 (C-3,5), 135.8 (C-4), 137.9 (C-1), 143.3 (C-β), 193.4 (*C*HO).

(*Z*)-β-Bromo-β-(4-methoxyphenyl)acrolein 1e (71%). Purification by flash chromatography (CH_2Cl_2): mp 42 °C; λ_{max} (MeOH)/nm 299 (8200); ν_{max}/cm^{-1} 1672; δ_H 3.85 (3H, s, 4-OC*H*$_3$), 6.76 (1H, d, J = 6.5 Hz, H-α), 7.04 (2H, d, J = 8.4 Hz, H-2,6), 7.86 (2H, d, J = 8.7 Hz, H-3,5), 10.41 (1H, d, J = 6.5 Hz, C*H*O); δ_C 55.3 (4-O*C*H$_3$), 113.6 (C-3,5), 127.1 (C-α), 128.7 (C-1), 129.1 (C-2,6), 145.1 (C-β), 162.9 (C-4), 193.2 (*C*HO).

β-Chloro-α-methyl-β-phenylacrolein 1f (75%). Purification by distillation: bp 122–124 °C (12 Torr); λ_{max} (MeOH)/nm 252 (7300); ν_{max}/cm^{-1} 1679; (*E*)-*isomer*, δ_H 2.05 (3H, s, α-C*H*$_3$), 7.34–7.39 (5H, m, H-2,3,4,5,6), 9.45 (1H, s, C*H*O); δ_C 12.8 (α-*C*H$_3$), 128.0 (C-2,6), 129.6 (C-3,5), 129.8 (C-4), 135.2 (C-1), 135.7 (C-α), 153.7 (C-β), 189.4 (*C*HO); (*Z*)-*isomer*, δ_H 1.80 (3H, s, α-*C*H$_3$), 10.36 (1H, s, C*H*O); δ_C 13.5 (α-*C*H$_3$), 146.9 (C-β), 191.1 (*C*HO).

β-Chloro-α-methyl-β-(4-methoxyphenyl)acrolein 1g (69%). Purification by recrystallization: mp 40–43 °C (light petroleum); λ_{max} (MeOH)/nm 271 (8400); ν_{max}/cm^{-1} 1681; (*E*)-*isomer*, δ_H 2.07 (3H, s, α-C*H*$_3$), 3.86 (3H, s, 4-OC*H*$_3$), 6.93 (2H, d, J = 8.7 Hz, H-3,5), 7.36 (2H, d, J = 8.7 Hz, H-2,6), 9.49 (1H, s, C*H*O); δ_C 13.5 (α-*C*H$_3$), 55.4 (4-O*C*H$_3$), 113.8 (C-3,5), 128.0 (C-1), 131.8 (C-2,6), 135.6 (C-α), 154.8 (C-β), 161.3 (C-4), 190.5 (*C*HO); (*Z*)-*isomer*, δ_H 1.89 (3H, s, α-C*H*$_3$), 7.43 (2H, d, J = 8.9 Hz, H-2,6), 10.38 (1H, s, C*H*O); δ_C 14.3 (α-*C*H$_3$), 113.7 (C-3,5), 130.4 (C-2,6), 148.0 (C-β), 160.9 (C-4), 192.3 (*C*HO).

β-Chloro-β-(4-chlorophenyl)-α-methylacrolein 1h (72%). Purification by distillation: bp 123–125 °C (0.4 Torr); λ_{max} (MeOH)/nm 266 (8540); ν_{max}/cm^{-1} 1689; (*E*)-*isomer*, δ_H 2.09 (3H, s, α-C*H*$_3$), 7.37 (2H, d, J = 8.7 Hz, H-3,5), 7.43 (2H, d, J = 8.7 Hz, H-2,6), 9.48 (1H, s, C*H*O); δ_C 13.3 (α-*C*H$_3$), 128.7 (C-2,6), 131.3 (C-3,5), 134.1 (C-4), 136.6 (C-1), 136.8 (C-α), 152.8 (C-β), 189.7 (*C*HO); (*Z*)-*isomer*, δ_H 1.85 (3H, s, α-C*H*$_3$), 10.39 (1H, s, C*H*O); δ_C 14.0 (α-*C*H$_3$), 146.6 (C-β), 191.7 (*C*HO).

β-Bromo-β-(4-methoxyphenyl)-α-methylacrolein 1i (59%). Purification by flash chromatography (CH_2Cl_2): mp 38–41 °C; λ_{max} (MeOH)/nm 287 (10200); ν_{max}/cm^{-1} 1680; (*E*)-*isomer*, δ_H 2.07 (3H, s, α-C*H*$_3$), 3.85 (3H, s, 4-OC*H*$_3$), 6.94 (2H, d, J = 7.6 Hz, H-3,5), 7.37 (2H, d, J = 7.6 Hz, H-2,6), 9.39 (1H, s, C*H*O); δ_C 13.5 (α-*C*H$_3$), 55.4 (4-O*C*H$_3$), 113.7 (C-3,5), 128.0 (C-1), 131.8 (C-2,6), 135.6 (C-α), 154.8 (C-β), 161.3 (C-4), 190.5 (*C*HO); (*Z*)-*isomer*, δ_H 1.90 (3H, s, α-C*H*$_3$), 10.25 (1H, s, C*H*O); δ_C 13.9 (α-*C*H$_3$), 192.1 (*C*HO).

β-Bromo-β-(4-chlorophenyl)-α-methylacrolein 1j (57%). Purification by flash chromatography (CH_2Cl_2): mp 70–73 °C; λ_{max} (MeOH)/nm 281 (10750); ν_{max}/cm^{-1} 1685; (*E*)-*isomer*, δ_H 2.09 (3H, s, α-C*H*$_3$), 7.32 (2H, d, J = 8.5 Hz, H-3,5), 7.38 (2H, d, J = 8.5 Hz, H-2,6), 9.38 (1H, s, C*H*O); δ_C 14.1 (α-*C*H$_3$), 128.4 (C-2,6), 131.7 (C-3,5), 135.8 (C-4), 136.4 (C-1), 139.9 (C-α), 152.9 (C-β), 188.4 (*C*HO); (*Z*)-*isomer*, δ_H 1.77 (3H, s, α-C*H*$_3$), 10.18 (1H, s, C*H*O); δ_C 16.4 (α-*C*H$_3$), 193.9 (*C*HO).

β-Chloro-α-ethyl-β-phenylacrolein 1k (71%). Purification by distillation: bp 135–138 °C (0.1 Torr); λ_{max} (MeOH)/nm 233 (11900); ν_{max}/cm^{-1} 1680; (*E*)-*isomer*, δ_H 1.09 (3H, t, J = 7.5 Hz, C*H*$_3$), 2.59 (2H, q, J = 7.5 Hz, C*H*$_2$), 7.38 (5H, s broad, H-2,3,4,5,6), 9.41 (1H, s, C*H*O); δ_C 11.9 (*C*H$_3$), 20.9 (*C*H$_2$), 128.2 (C-2,6), 129.8 (C-3,5), 130.1 (C-4), 135.5 (C-1), 141.4 (C-α), 154.0 (C-β), 189.8 (*C*HO); (*Z*)-*isomer*, δ_H 0.94 (3H, t, J = 7.4 Hz, C*H*$_3$), 2.25 (2H, q, J = 7.5 Hz, C*H*$_2$), 10.34 (1H, s, C*H*O); δ_C 12.6 (*C*H$_3$), 21.2 (*C*H$_2$), 146.2 (C-β), 191.6 (*C*HO).

β-Chloro-α,β-diphenylacrolein 1l (55%). Purification by recrystallization: mp 159–161 °C from EtOH; λ_{max} (MeOH)/nm 279 (12800); ν_{max}/cm^{-1} 1678; (*E*)-*isomer*, δ_H 7.22–7.31 and 7.43–7.59 (10H, 2 m, aromatic protons), 9.67 (1H, s, C*H*O); δ_C 128.2, 128.4, 128.6, 129.8, 130.2, 130.9, 133.8 and 135.6 (aromatic carbons), 140.7 (C-α), 155.2 (C-β), 189.8 (*C*HO); (*Z*)-*isomer*, δ_H 10.60 (1H s, C*H*O); δ_C 150.5 (C-β), 191.3 (*C*HO).

(*E*)-β-Chloro-α,β-bis(4-methoxyphenyl)acrolein 1m (92%). Purification by recrystallization: mp 128–129 °C from Et_2O; λ_{max} (MeOH)/nm 308 (13600); ν_{max}/cm^{-1} 1681; δ_H 3.85 (3H, s, 4-OC*H*$_3$), 3.88 (3H, s, 4′-OC*H*$_3$), 6.97 (4H, m, aromatic protons), 7.23 (2H, d, J = 8.7 Hz, aromatic protons), 7.51 (2H, d, J = 8.7 Hz, aromatic protons), 9.65 (1H, s, C*H*O); δ_C 55.2 (4′-O*C*H$_3$), 55.5 (4-O*C*H$_3$), 113.7 (C-3′,5′), 113.9 (C-3,5), 126.5 (C-1′), 128.2 (C-1), 131.3 (C-2′,6′), 132.1 (C-2,6), 139.6 (C-α), 154.8 (C-β), 159.5 (C-4′), 161.8 (C-4), 190.6 (*C*HO).

2-En-4-ynecarbaldehydes 2, 4, 5 and 6 from bromoacroleins 1j, 1i and 1d: general procedure

At room temperature and under N_2 atmosphere, tetrakistriphenylphosphine palladium (0.07 g, 6.05×10^{-5} mol) and copper iodide (0.015 g, 7.8×10^{-5} mol) were added to the substituted acetylene (1 mmol) and the appropriate bromoacrolein

1j, **1i** and **1d** (1 mmol) in acetonitrile (20 ml) and triethylamine (6 ml). The reaction mixture was heated at reflux until no starting material appeared on TLC and allowed to cool to room temperature. The reaction was then poured into water (100 ml) and extracted with ethyl acetate. The organic layer was washed with water (3 × 50 ml), dried and evaporated.

2-En-4-ynecarbaldehydes 2 and 3 from chloroacroleins 1f and 1l: modified procedure

The appropriate chloroacrolein **1f** and **1l** (1 mmol) was treated with NaI (1.1 mmol) and $NiBr_2$ (0.2 mmol) in DMF at 140 °C for 4 hours. The mixture was then cooled to room temperature and tetrakistriphenylphosphine palladium (0.07 g, 6.05×10^{-5} mol), copper iodide (0.015 g, 7.8×10^{-5} mol), the substituted acetylene (1 mmol) and triethylamine (6 ml) were added. The mixture was then heated overnight at 100 °C, allowed to cool at room temperature and poured into water. Extraction with ethyl acetate afforded the crude product, which was then purified as indicated below.

β-Phenyl-β-phenylethynyl-α-methylacrolein 2 (51–59%). Purification by flash chromatography (CH_2Cl_2): mp 70–72 °C; λ_{max} (MeOH)/nm 313 (14000); ν_{max}/cm^{-1} 1651, 1674, 2195; (*E*)-*isomer*, δ_H 2.24 (3H, s, α-C*H*$_3$), 7.36–7.48 (9H, m, aromatic protons), 9.71 (1H, s, C*H*O); δ_C 12.6 (α-*C*H$_3$), 88.5 (C-γ), 106.1 (C-δ), 121.9, 128.5, 128.6, 129.9, 131.2, 131.6, 134.0, 135.9 and 138.6 (C-α and aromatic carbons), 141.7 (C-β), 191.4 (*C*HO); (*Z*)-*isomer*, δ_H 1.95 (s, 3H, α-C*H*$_3$), 10.58 (s, 1H, C*H*O); δ_C 14.5 (α-*C*H$_3$), 86.1 (C-γ), 100.4 (C-δ), 192.9 (*C*HO).

α,β-Diphenyl-β-phenylethynylacrolein 3 (27%). Purification by flash chromatography (CH_2Cl_2): formed as oil; λ_{max} (MeOH)/nm 318 (13500); ν_{max}/cm^{-1} 1669, 2201; (*E*)-*isomer*, δ_H 7.28–7.49 (15H, m, aromatic protons), 9.61 (1H, s, C*H*O); δ_C 88.2 (C-γ), 105.7 (C-δ), 128.0, 128.2, 128.6, 128.9, 129.2, 129.8, 130.2, 130.9, 131.5, 133.8, 135.6, 140.6 and 141.5 (C-α, C-β and aromatic carbons), 189.6 (*C*HO); (*Z*)-*isomer*, δ_H 10.60 (s, 1H, C*H*O); δ_C 87.1 (C-γ), 101.2 (C-δ), 192.1 (*C*HO).

β-(4-Methoxyphenyl)-β-phenylethynyl-α-methylacrolein 4 (58%). Purification by flash chromatography (CH_2Cl_2): mp 90–92 °C; λ_{max} (MeOH)/nm 322 (25050); ν_{max}/cm^{-1} 1653, 1667, 2191; (*E*)-*isomer*, δ_H 2.22 (3H, s, α-C*H*$_3$), 3.86 (3H, s, 4-OC*H*$_3$), 6.94 (2H, d, *J* = 7.6 Hz, H-3,5), 7.39 (4H, m, aromatic protons), 7.50 (3H, m, aromatic protons), 9.72 (1H, s, C*H*O); δ_C 12.8 (α-*C*H$_3$), 55.4 (4-O*C*H$_3$), 89.1 (C-γ), 105.5 (C-δ), 113.8 (C-3,5), 122.3, 127.8, 128.5, 129.2, 129.8, 130.4, 131.7, and 139.9 (C-α, C-β and aromatic carbons), 160.6 (C-4), 192.6 (*C*HO); (*Z*)-*isomer*, δ_H 2.00 (3H, s, α-C*H*$_3$), 10.57 (1H, s, C*H*O); δ_C 14.6 (α-*C*H$_3$), 86.8 (C-γ), 100.1 (C-δ), 193.9 (*C*HO).

β-(4-Chlorophenyl)-β-(2,4-dimethoxyphenylethynyl)-α-methylacrolein 5 (51%). Purification by flash chromatography (CH_2Cl_2): mp 101–102 °C; λ_{max} (MeOH)/nm 342 (28100); ν_{max}/cm^{-1} 1659, 1677, 2196; (*E*)-*isomer*, δ_H 3.82 (3H, s, 4-OC*H*$_3$), 3.90 (3H, s, 2-OC*H*$_3$), 6.47 (2H, m, aromatic protons), 6.69 (1H, d, *J* = 7.9 Hz, H-α), 7.41 (3H, m, aromatic protons), 7.84 (2H, d, *J* = 8.6 Hz, H-3,5), 10.41 (1H, d, *J* = 7.9 Hz, H-α); δ_C 55.5 and 55.8 (2′ and 4′-O*C*H$_3$), 87.5 (C-γ), 98.3 (C-3′), 103.3 (C-δ), 105.2 (C-5′), 128.5, 128.7, 129.3, 131.2, 134.1, 134.5, 136.9 and 141.8 (C-α, C-β and aromatic carbons), 162.3 (C-4′), 162.7 (C-2′), 191.7 (*C*HO); (*E*)-*isomer*, δ_H 9.69 (1H, d, *J* = 7.9 Hz, H-α); δ_C 92.7 (C-γ), 100.3 (C-δ), 193.8 (*C*HO).

(*Z*)-β-(4-Chlorophenyl)-β-(phenylethynyl)phenylethynylacrolein 6 (63%). Purification by flash chromatography (CH_2Cl_2): mp 115–116 °C; λ_{max} (MeOH)/nm 334 (16100); ν_{max}/cm^{-1} 1665, 2194; (*E*)-*isomer*, δ_H 6.76 (1H, d, *J* = 7.9 Hz, H-α), 7.44 (5H, m, aromatic protons), 7.58 (2H, m, aromatic protons), 7.78 (2H, d, *J* = 8.5 Hz, H-3,5), 10.38 (1H, d, *J* = 7.9 Hz, C*H*O); δ_C 83.7 (C-γ), 102.4 (C-δ), 121.4 (C-1′), 128.3, 128.5, 129.1, 129.9, 130.9, 131.9, 133.9 and 137.1 (C-α and aromatic carbons), 140.8 (C-β), 192.7 (*C*HO).

Acrylic acids 7–9: general procedure

A solution of $NaClO_2$ (8.0 g, 7×10^{-2} mol) in 70 ml water was added dropwise to a stirred mixture of the appropriate acrolein **1d**, **1e** and **1j** (5×10^{-2} mol) in 50 ml of acetonitrile, NaH_2PO_4 (6 g, 7×10^{-2} mol) in 20 ml of water and 35% H_2O_2 (5 ml, 5.2×10^{-2} mol), keeping the temperature at 10 °C. After 12 h at room temperature a small amount of Na_2SO_3 (0.5 g) was added and the solution acidified with 10% aqueous HCl. The acrylic acids were purified as indicated below.

(*Z*)-β-(4-Chlorophenyl)-β-bromoacrylic acid 7 (91%). Purification by flash chromatography (AcOEt): mp 159–160 °C; λ_{max} (MeOH)/nm 271 (16100); ν_{max}/cm^{-1} 1682, 2568, 2792, 3059; δ_H 6.77 (1H, s, H-α), 7.39 (2H, d, *J* = 8.5 Hz, H-2,6), 7.60 (2H, d, *J* = 8.5 Hz, H-3,5), 10.7 (1H, broad s, COO*H*); δ_C 121.2 (C-α), 128.8 (C-2,6), 129.4 (C-3,5), 137.1 (C-4), 137.6 (C-1), 139.1 (C-β), 169.1 (*C*OOH).

(*Z*)-β-(4-Chlorophenyl)-β-bromo-α-methylacrylic acid 8 (85%). Purification by flash chromatography (MeOH): mp 151 °C (decomp.); λ_{max} (MeOH)/nm 246 (19300); ν_{max}/cm^{-1} 1699, 2545, 2864, 2991; δ_H 3.86 (3H, s, 4-OC*H*$_3$), 6.72 (1H, s, H-α), 6.91 (2H, d, *J* = 8.9 Hz, H-2,6), 7.64 (2H, d, *J* = 8.9 Hz, H-3,5), 9.1 (1H, broad s, COO*H*); δ_C 55.8 (4′-O*C*H$_3$), 113.1 (C-3,5), 121.1 (C-α), 131.4 (C-2,6), 130.6 (C-1), 142.3 (C-β), 164.0 (C-4), 170.2 (*C*OOH).

β-(4-Methoxyphenyl)-β-bromoacrylic acid 9 (82%). Purification by flash chromatography (MeOH): mp 99 °C (decomp.); λ_{max} (MeOH)/nm 233 (18400); ν_{max}/cm^{-1} 1698, 2543, 2854, 2980; (*E*)-*isomer*, δ_H 2.24 (3H, s, α-C*H*$_3$), 7.29 (4H, m, aromatic protons), 11.4 (1H, broad s, COO*H*); δ_C 18.5 (α-*C*H$_3$), 122.5 (C-α), 128.5 (C-2,6), 129.3 (C-3,5), 130.5 (C-4), 134.8 (C-1), 139.2 (C-β), 171.1 (*C*OOH); (*Z*)-*isomer*, δ_H 1.89 (s, 3H, α-C*H*$_3$); δ_C 22.1 (α-*C*H$_3$), 173.3 (*C*OOH).

Rubrolide 10 and 11: general procedure

To a solution of the appropriate acrylic acid **7** and **8** (0.25 mmol) in acetonitrile (5 ml) were added phenylethyne (0.30 mmol), tetrakistriphenylphosphine palladium (12.5×10^{-6} mol), copper iodide (2.4 mg, 12.5×10^{-6} mol), and triethylamine (101 mg, 1 mmol). The mixture was stirred at room temperature for 24 h, concentrated *in vacuo* and purified as indicated below.

(*Z*)-5-Benzylidene-4-(4-chlorophenyl)furan-2(5*H*)-one 10 (81%). Purification by flash chromatography (CH_2Cl_2): mp 178–180 °C; λ_{max} (MeOH)/nm 334 (5850); ν_{max}/cm^{-1} 1766; δ_H 6.12 (1H, s, H-3), 6.19 (1H, s, H-6), 7.34–7.53 (7H, m, aromatic protons), 7.79 (2H, d, *J* = 8.5 Hz, H-3,5); δ_C 112.3 (C-3), 113.7 (C-6), 127.7, 128.2, 128.4, 128.7, 129.9, 130.7, 132.7 and 136.6 (aromatic carbons), 147.6 (C-4), 156.8 (C-5), 168.3 (C-2).

(*Z*)-5-Benzylidene-4-(4-methoxyphenyl)furan-2(5*H*)-one 11 (74%). Purification by flash chromatography (CH_2Cl_2): mp 110–112 °C; λ_{max} (MeOH)/nm 335 (4750); ν_{max}/cm^{-1} 1764; δ_H 3.84 (3H, s, 4-OC*H*$_3$), 6.08 (1H, s, H-3), 6.19 (1H, s, H-6), 7.01 (2H, d, *J* = 8.9 Hz, H-2,6), 7.21–7.53 (5H, m, aromatic protons), 7.77 (2H, d, *J* = 8.9 Hz, H-3,5); δ_C 55.5 (4′-O*C*H$_3$), 113.6 (C-3), 114.6 (C-6), 122.7, 128.8, 129.2, 129.8, 130.1, 130.8, 133.1 and 133.9 (aromatic carbons), 148.2 (C-4), 158.5 (C-5), 169.1 (C-2).

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