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Scope of the formal [3+2] cycloaddition for the synthesis of five-membered ring of functionalized indanes

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ABSTRACT

We report our research about the synthesis of functionalized indanes in the pentagonal ring by a formal [3+2] cycloaddition using benzhydrols and styrene derivatives with electron-withdrawing groups joined to C-β, such as carboxyl, carboxymethyl, carbonyl of ketones, and nitro groups. We also report the configurational assignment of the indanic structures synthesized using several experiments of NMR.

1. Introduction

The dihydroindene ring system is a structural subunit found in a large number of naturally occurring compounds with anti-tumor activity, such as 'secaloside' A (I).[1] In addition, several synthetic compounds with this skeleton, show a broad range of biological activities, such as the hydroxylated derivative of 3-(3,4-dichlorophenyl)-1-*N*-methylindanamine (II), which has high affinity for the serotonin transporter, dopamine, and norepinephrine.[2] Furthermore, indan-2-carboxylic acid with aryl groups at C-1 and C-3, such as compounds SB-209670 and SB-217242 (III),[3] are potent antagonists of endothelin receptors. Endothelin ET-1 and closely related compounds, such as the isopeptides ET-2 and ET-3, cause a profound vasoconstriction and mitogenic activity in the cardiovascular system[4,5] and play an important role in the pathogenesis of cardiovascular diseases (Fig. 1).

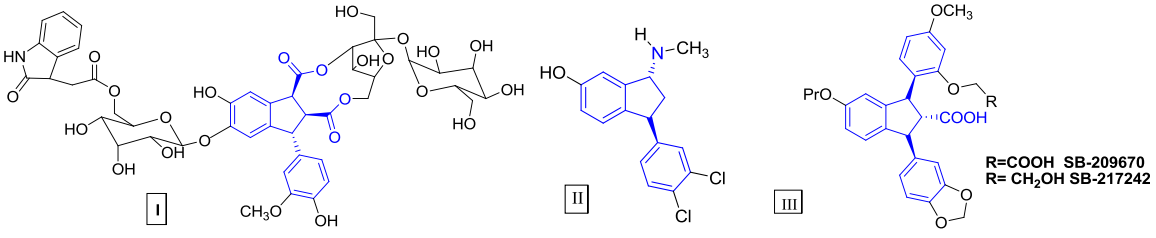

Fig. 1. Natural and synthetic products with dihydroindene ring system.

A variety of synthetic strategies to obtain this type of systems have been developed. These range from the dimerization of propenylbenzenes in acid medium[6] to multi-step synthesis of polycyclic indane structures,[7] among other syntheses.[8] The synthesis of functionalized indane structures in the pentagonal ring is complex, requires several steps, and generally results in low total yield.

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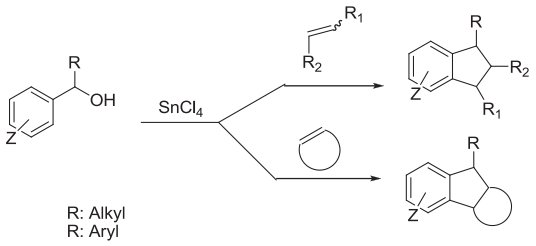
Therefore, the discovery of new synthetic strategies has become an interesting challenge. A reaction that has been very successful in the synthesis of highly substituted indanes[9] and indanic structures in three and tetracyclic systems[10] has been the formal [3+2] cycloaddition (FCA [3+2]) from benzyl alcohols and benzhydrols with styrenes, stilbenes, and cycloalkenes. This reaction offers the possibility to form three stereogenic centers in one step, exhibiting excellent regiochemistry (Scheme 1).[9,10]

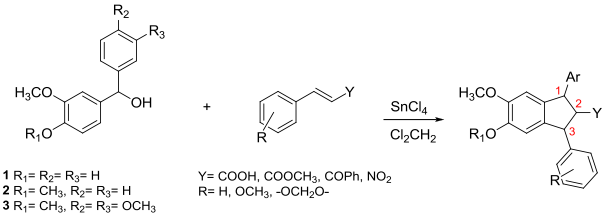


Scheme 1. Formal [3+2] cycloaddition.

In this paper, we report our research and results that led to the synthesis of functionalized indanes in the pentagonal ring, using benzhydrols and styrene derivatives with electron-withdrawing groups joined to C-β, such as carboxyl, carboxymethyl, carbonyl of ketones, and nitro groups. We also report the configurational assignment of the indanic structures synthesized using ^{1}H and ^{13}C NMR analysis and a set of two-dimensional experiments (NOESY, ROESY, HMQC, and HSQC).

2. Results and discussion

The benzhydrols (**1**–**3**) and substituted styrenes used were synthesized according to techniques previously described.[11] The catalyst used for the cycloaddition reaction was $SnCl_4$,[9,12] and methylene chloride as solvent (Scheme 2). The temperature and reaction time are indicated in each case. Other acid catalysts, which had shown good results in obtaining indanic structures [$H_3PMo_{12}O_{40}$ (MPA), MPA supported on C (MPA/C), $H_3PW_{12}O_{40}$ (TPA), TPA supported on SiO_2 (TPA/S)],[13] as well as other catalysts, such as $AlPMo_{12}O_{40}$ (MPAl) and $HClO_4$ supported on SiO_2 ($HClO_4$/S) were also tested in this work.



Scheme 2. Synthesis of functionalized indanes in the pentagonal ring.

2.1. Reaction of benzhydrols with styryl carboxylic acids, esters, and ketones

Table 1 shows the results obtained from benzhydrols **1**, **2** and carbonyl derivatives of styrenes.

Alcohol **2** did not react with cinnamic acid (**4**) (entry 1); instead, substituted cinnamic acids **5** and **6** showed a very good performance. In these cases, a mixture of diastereoisomers were obtained: 1,2-*cis*-2,3-*trans* (**7** and **9**) and *trans*–*trans* (**8** and **10**), in a proportion 2:1, respectively (entry 2, 3).

The reaction between benzhydrol **2** and methyl cinnamate (**11**) afforded indane **12** with trans–trans configuration as a single product, whereas with the substituted esters **13** and **14**, mixtures of diastereomers *trans*–*trans* (**16** and **18**) and 1,2-*cis*-2,3-*trans* (**15** and **17**) were obtained (entry 4–6).

A single stereoisomer (trans–trans configuration) was obtained from chalcone **19** and benzydrols **1** and **2** (entry 7,8), while three indane diastereoisomers were obtained from chalcones **22** and **23**. The main product in both cases presented the *trans*–*trans* configuration (**24** and **27**), while the minority products presented the 1,2-*cis*-2,3-*trans* (**25** and **28**) and 1,2-*trans*-2,3-*cis* (**26** and **29**) configurations (entry 9,10).

This reaction was also performed using other acid catalysts (Table 2). We tested this catalyst with benzhydrol **2** and cinnamic acid **5**, which turned out to be one of the most reactive in previous reactions. Chloroform was used as a solvent at reflux temperature for 24 h with substoichiometric amounts of catalyst. The products obtained in all the cases were the same as those obtained using $SnCl_4$ as catalyst and in the same rate (Table 2 entry 2).

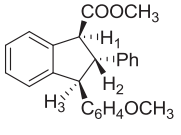
2.2. Reaction of benzhydrols 1, 2, and 3 with nitrostyrenes

Table 3 shows the results obtained by the reaction between benzhydrols and nitrostyrenes **30** and **31**. Nitrostyrene **30** did not react with any of the benzhydrols used. However, nitrostyrene **31** reacted with benzhydrols **1** and **2**, giving two stereoisomers, *trans*–*trans* (**32** and **33**) and 1,2-*cis*-2,3-*trans* (**34** and **35**), in identical proportion (entry 3,4). When the reaction was carried out at rt, a third minor isomer, 1,2-*trans*-2,3-*cis* diastereomer (**36** and **37**) (entry 5,6), was obtained. The reaction between **3** and **31** afforded indanes **38** and **39** (2:1 ratio) (entry 7).

2.3. Structural and configurational assignment of the indanes obtained

The regiochemistry of reaction FCA [3+2] and the stereochemical assignment of all compounds were carried out taking into consideration the data NMR spectra (chemical shifts, coupling constants, and a set of two-dimensional experiments: NOESY, ROESY, HMQC, HSQC). Table 4 summarizes the chemical shift data of protons, carbons, and coupling constants of the compounds obtained from benzhydrols and cinnamic acids, methyl esters, and ketones.

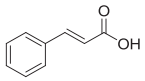
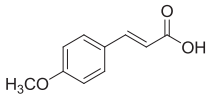
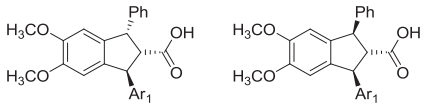
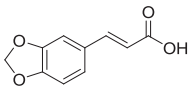
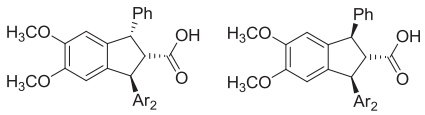
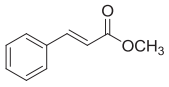
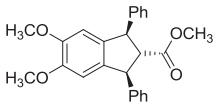
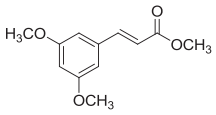
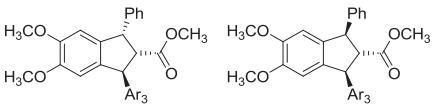
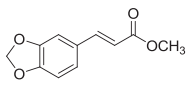
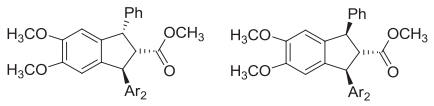
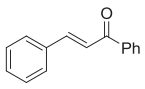
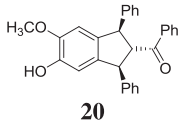
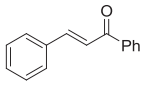
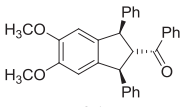
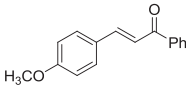
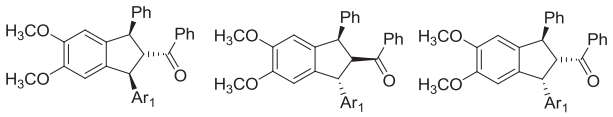
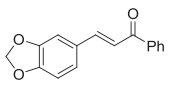
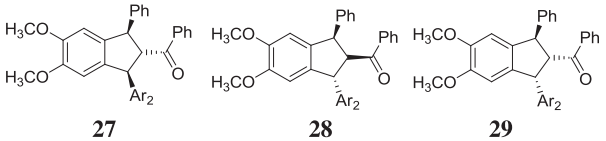
Compounds **8**, **10**, **12**, **16**, **18**, **20**, **21**, **24**, and **27**, showed very similar values of δ_H for the hydrogen atoms H-1 and H-3 ($\Delta\delta \leq 0.05$ ppm). Identical situation was observed for the chemical shifts of the carbon atoms C-1 and C-3 ($\Delta\delta \leq 0.07$ ppm). These data indicate that the regioisomers formed are those with phenyl and/or aryl residues linked to C-1 and C-3. Another evidence that supports the 1,3 diaryl substitution is that the values of δ_C published by Appelbe et al.[14] for *trans*–*trans* methyl 3-(4-methoxyphenyl)-2-phenylindan-1-carboxylate, are markedly different in the chemical shifts from those that appear in Table 4 for the esters **12**, **15**–**18**.



H_1: 4.38 J=10.0 Hz
H_2: 3.98 J=10.3 Hz
H_3: 4.35 J=10.0 Hz
C-1/C-3: 58.21, 59.78
C-2: 52.39
$COOCH_3$: 172.99

Moreover, this regiochemistry is consistent with the study of nucleophilicity of double bond carbons of chalcones **19** and **23**, conducted with the program Spartan 2.0.1.[15] The molecules were optimized using the density functional method (DFT), using the

Table 1
FCA [3+2] of benzhydrols with styryl carboxylic acids, esters, and ketones

Entry	Alcohol	Alkene	Product	Yield %
1	**2**	 **4**	—	
2	**2**	 **5**	 **7** **8** (2:1)[g]	86[a]
3	**2**	 **6**	 **9** **10** (2:1)[g]	88[b]
4	**2**	 **11**	 **12**	61[c]
5	**2**	 **13**	 **15** **16** (1.2:3)[g]	44[d]
6	**2**	 **14**	 **17** **18** (1.3:1)[g]	74[e]
7	**1**	 **19**	 **20**	31[a]
8	**2**	 **19**	 **21**	30[a]
9	**2**	 **22**	 **24** **25** **26** (1.6:1:1)[g]	40[f]
10	**2**	 **23**	 **27** **28** **29** (1.9:1.7:1)[g]	52[f]

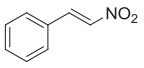
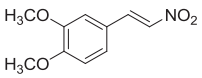
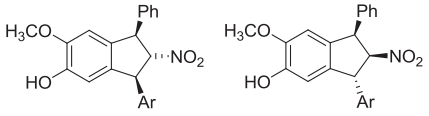
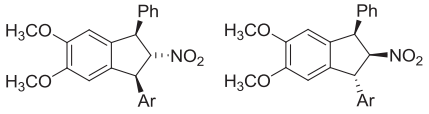
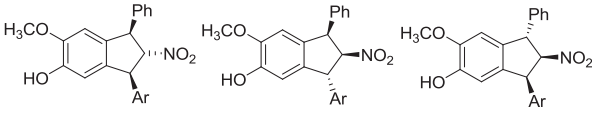
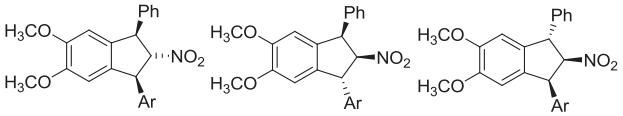
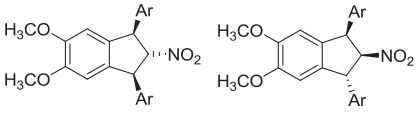
Ar_1=4-methoxyphenyl; Ar_2=3,4-methylenedioxyphenyl; Ar_3=3,5-dimethoxyphenyl.
[g]Ratio was determined by ^1H NMR.
[a] 120 min.
[b] 30 min.
[c] 60 min.
[d] 10 min.
[e] 15 min.
[f] 5 min.

Table 2
FCA [3+2] of benzhydrol **2** and cinnamic acid **5** with different catalysts

Catalysts	Yield (%)
MPA	31.2
TPA	32.0
MPAl	No reaction
MPA/C_2	No reaction
TPA/S	No reaction
$HClO_4$/S	46.4

which are not useful for the configurational assignment of these diastereomers. On the other hand, taking into account the chemical shifts of hydrogen and carbon atoms of these compounds, they can be joined into two groups: (a) compounds in which the values of δ_H of H-1 and H-3 and δ_C of C-1 and C-3 are similar (**8**, **10**, **12**, **16**, **18**, **20**, **21**, **24**, **27**), which might present *cis*–*cis* or *trans*–*trans* stereochemistry; and (b) compounds with different values (**7**, **9**, **15**, **17**, **25**, **26**, **28**, **29**), which would be in agreement with a 1,2-*trans*-2,3-*cis* or

Table 3
FCA [3+2] between benzhydrols and nitrostyrenes

Entry	Alcohol	Alkene	Product	Yield %
1	**1**	 **30**	—	
2	**2**	**30**	—	
3	**1**	 **31**	 **32** **34** (1:1)[c]	50[a]
4	**2**	**31**	 **33** **35** (1:1)[c]	30[a]
5	**1**	**31**	 **32** **34** **36** (1:1:0.08)[c]	56[b]
6	**2**	**31**	 **33** **35** **37** (1:1:0.08)[c]	44[b]
7	**3**	**31**	 **38** **39** (2:1)[c]	52[b]

Ar=3,4-dimethoxyphenyl.
[c]Ratio was determined by ^{1}H NMR.
[a] 0 °C, 120 min.
[b] rt, 60 min.

base B3LyP/6-311+6**, and it was found that the most nucleophilic carbon in both chalcones is the carbon α at the carbonyl group (Fig. 2).

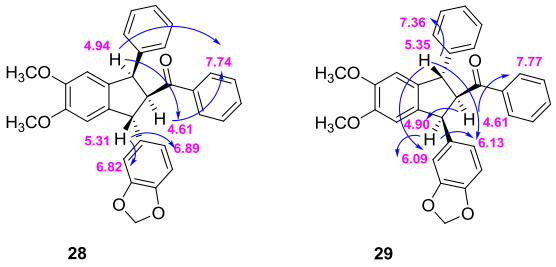
The substitution in the pentagonal ring of the synthesized indanes allows four possible diastereomers: *trans*–*trans, cis*–*cis, trans*–*cis*, and *cis*–*trans*. In previous works, configurational assignment of 1,2,3-triphenyl indanes was based on the coupling constants of the hydrogen atoms of the pentagonal ring[16] and carbon chemical shifts (δ_C).[17] However, the compounds included in Table 4 present very similar values of $J_{1,2}$ and $J_{2,3}$ (9.1–9.9 Hz), 1,2-*cis*-2,3-*trans* configuration. In particular, compound **27** (group a) was assigned the trans–trans configuration taking into account that the signal δ 4.24 ppm (H-2) showed NOE with H_{ortho} (7.23 ppm) of the phenyl group, which is bound at C-1 and the H_{ortho} (6.69 and 6.75 ppm) of the aryl attached to C-3, indicating that H-1 and H-3 are in trans arrangement with H-2 (Fig. 3). By comparison, compounds **20**, **21**, and **24** were assigned identical configuration.

In the case of the diastereomers **28** and **29** (group b), data of HSQC (Table 5) and ROESY (Fig. 4) were used to differentiate between the 1,2-*cis*-2,3-*trans* and 1,2-*trans*-2,3-*cis* isomers.

Table 4
Chemical shifts of hydrogen, carbon, and coupling constants of indanes substituted

	Compound	H-1	H-2	H-3	$J_{1,2}$	$J_{2,3}$	C-1	C-2	C-3
Triphenyl indanes	*trans–trans*	4.51	3.44	4.51	10.2	10.2	58.4	67.6	58.4
	cis–cis	4.88	4.05	4.88	7.2	7.2	56.2	62.8	56.2
	cis–trans	4.74	4.04	4.76	8.2	10.1	54.1	62.1	56.1
Acids	**7**[b]	4.76	3.65	4.83	9.2	9.8	52.8	63.4	51.1
	8[a]	4.58	3.19	4.61	9.2	9.8	54.4	65.3	54.7
	9[b]	4.74	3.64	4.83	9.8	9.8	52.7	63.2	51.6
	10[a]	4.65	3.00	4.68	9.9	9.9	53.9	65.0	54.3
Esters	**12**[a]	4.66	3.27	4.66	9.6	9.6	54.8	65.7	54.8
	15[b]	4.78	3.64	4.90	9.2	9.2	53.4	61.1	51.2
	16[a]	4.58	3.24	4.61	9.6	9.6	54.5	64.9	54.6
	17[b]	4.78	3.64	4.90	9.3	9.5	53.2	61.4	51.2
	18[a]	4.56	3.19	4.61	9.5	9.8	54.3	65.5	54.2
Ketones	**20**[a]	4.73	4.27	4.76	9.2	9.4	54.9	68.0	55.1
	21[a]	4.80	4.27	4.80	9.2	9.2	55.1	68.2	55.1
	24[a]	4.80	4.26	4.77	9.2	9.1	54.5	68.4	55.1
	25[b]	4.94	4.62	5.31	9.2	9.2	54.7	64.4	50.8
	26[b]	5.36	4.63	4.93	9.2	9.2	50.5	64.3	54.1
	27[a]	4.76	4.24	4.76	9.2	9.2	54.9	68.3	55.2
	28[b]	4.94	4.61	5.31	9.0	9.5	54.7	64.3	50.4
	29[a]	5.35	4.61	4.90	9.0	9.8	50.5	64.2	54.5

[a] *trans–trans* or *cis–cis* configuration.
[b] 1,2-*cis*-2,3-*trans* or 1,2-*trans*-2,3-*cis* configuration.



28 **29**

Fig. 4. NOEs data of compounds **28** and **29**.

to δ 4.90 ppm. Thus, the H-1/H-3 atoms present a *trans*-configuration, whereas the H-2/H-3 atoms present a *cis*-configuration (1,2-*trans*-2,3-*cis*). Using a similar study, in compound **28** the signal at δ 4.94 ppm was assigned to H-1 and the signal at δ 5.31 ppm was assigned to H-3. Therefore, the configuration of diastereomer **28** is 1,2-*cis*-2,3-*trans*. For compounds **25** and **26**, the configuration was assigned by comparison.

The configuration of acids **7** and **8** was assigned by HMQC (Table 6) and NOESY data (Fig. 5).

In compound **7**, H-2 (3.65 ppm) showed NOE with the signal at δ 4.76 ppm and the H_{ortho} (7.19 ppm) of the aryl group attached to C-3. The signal at δ 4.83 ppm showed NOE with H_{ortho} (6.98 ppm) of

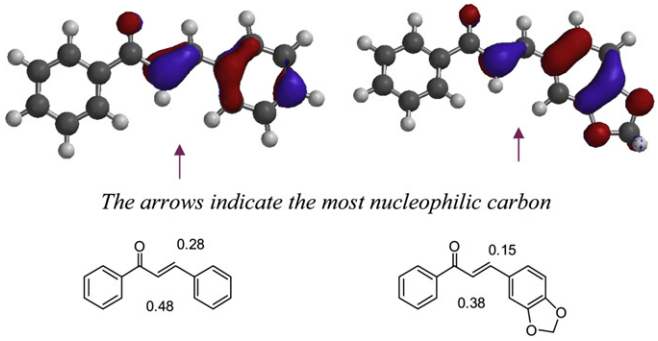


Fig. 2. Results of the study of nucleophilicity of compounds **19** and **23**.

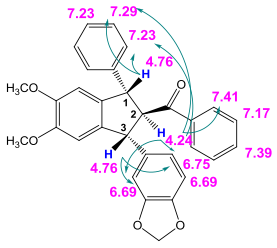


Fig. 3. NOEs data of compound **27**.

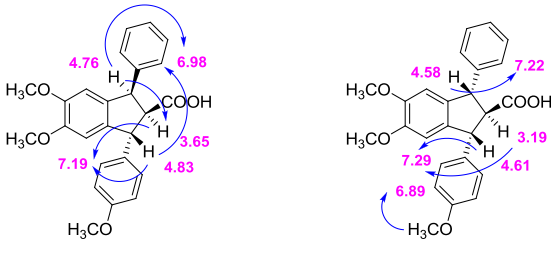
Table 5
Correlation C–H for compounds **28** and **29** (HSQC)

Compound **28**		Compound **29**	
C- (ppm)	H- (ppm)	C- (ppm)	H- (ppm)
54.7	4.94 (d)	50.5	5.35 (d)
64.3	4.61 (t)	64.2	4.61 (t)
50.4	5.31 (d)	54.5	4.90 (d)

The signal at δ 4.90 ppm (doublet) of compound **29** presented NOE with H-2 and the H_{ortho} of the aryl group attached to C-3. The signal at δ 5.35 ppm (doublet) showed NOE with H_{ortho} of the phenyl group attached to C-1 and also with the H_{ortho} of the aryl attached to C-3 (6.09, 6.17 ppm). These correlations indicate that the H-1 signal corresponds to δ 5.35 ppm and that H-3 corresponds

Table 6
Correlation C–H for compounds **7** and **8** (HMQC)

Compound **7**		Compound **8**	
C- (ppm)	H- (ppm)	C- (ppm)	H- (ppm)
52.8	4.76 (d)	54.4	4.58 (d)
63.4	3.65 (t)	65.3	3.19 (t)
51.1	4.83 (d)	54.7	4.61 (d)



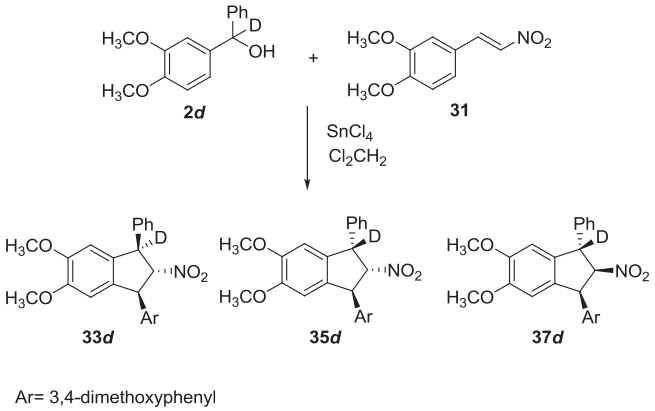
7 **8**

Fig. 5. NOEs data of compounds **7** and **8**.

the phenyl group attached to C-1 and with the H_{ortho} (7.19 ppm) of the aryl group attached to C-3, indicating that H-1 and H-3 are in trans-configuration to each other. Based on these data, the configuration of **7** is 1,2-*cis*-2,3-*trans*. Therefore, the configuration of **8**

is *trans*–*trans*, and it was assigned because of the great similarity between the chemical shift values of C-1 and C-3 and the correlations observed in the NOESY (Fig. 5). Considering the NMR data of compounds **7** and **8** it was possible to establish the configuration trans–trans of compounds **10**, **12**, **16**, **18** and the configuration 1,2-*cis*-2,3-*trans* of diastereomers **9**, **15**, and **17**.

The configuration of compounds **32**–**39** could not be assigned based on the coupling constants $J_{1,2}$ and $J_{2,3}$ because the values were very similar (8.3–8.8 Hz). In order to identify unambiguously the H-1 and H-3 atoms of the three diastereomeric nitroindanes, we performed the FCA [3+2] using alcohol **2** deuterated in the bibenzylic carbon (**2d**). The reaction between 3,4-dimethoxybromobenzene with *n*-butyllithium and subsequent treatment with deuterated benzaldehyde (C_6H_5CDO) gave rise to the deuterated alcohol **2d**. The reaction of FCA [3+2] between **2d** and **31** at rt afforded a mixture of the three products **33d**, **35d**, and **37d** (Scheme 3).



Scheme 3. Synthesis of deuterated nitroindanes.

The chemical shifts of the bibenzylic hydrogens of **33d**, **35d**, and **37d** allowed an unambiguous assignment of H-1 and H-3 (Table 7). The configuration of the nitroindanes was assigned by NOESY experiments performed on the main stereoisomers (**33d** and **35d**).

Table 7
^{1}H NMR selected chemical shifts δ (ppm) and J (Hz) of nitroindanes

Compound	H-1	H-2	H-3	$J_{1,2}$	$J_{2,3}$
33	4.93 (d)	4.99 (dd)	4.91 (d)	8.8	8.3
35	4.99 (d)	5.43 (t)	5.17 (d)	8.7	8.5
37	5.19 (d)	5.41 (dd)	4.97 (d)	8.6	8.5
33d	—	5.02 (d)	4.92 (d)	—	8.4
35d	—	5.43 (d)	5.17(d)	—	8.4
37d	—	5.41 (d)	4.97 (d)	—	8.4

The diastereomer **33d** presented the lowest chemical shift for the H-2 (5.02 ppm) (Fig. 6). This is indicative of a cis relationship with the phenyl group attached to C-1 and the aryl group bound to C-3, due to the shielding effect exerted by them. Furthermore, the H-2 presented NOE with the H_{ortho} (δ 6.73 and 6.82 ppm) of the aryl attached at C-3. This correlation confirms that the H-2 and the aryl group bound at C-3 are in a cis arrangement and that the H-3 and H-2 are in a trans relationship (Fig. 7).

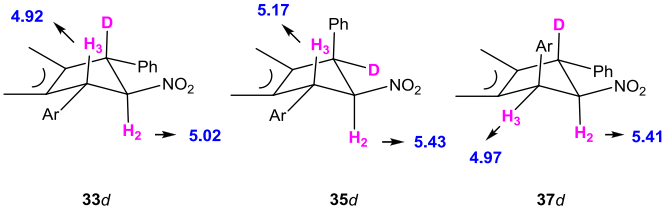


Fig. 6. Chemical shift of the deuterated nitroindanes.

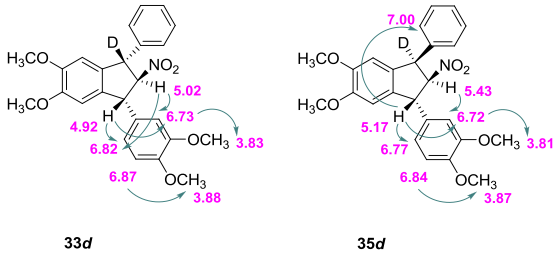


Fig. 7. NOEs data of compounds **33d** and **35d**.

In compound **35d**, the H-2 (δ 5.43 ppm) correlated with the H_{ortho} (δ 6.72 and 6.77 ppm) of the aryl group attached at C-3. Therefore, in this compound, H-2 and H-3 have a *trans* spatial relationship. Moreover, the H-3 (δ 5.17 ppm) showed NOE with H_{ortho} (δ 7.00 ppm) of the phenyl group bound at C-1. This correlation indicates that H-3 and the phenyl group are in cis arrangement and that **35d** has the 1,2-*cis*-2,3-*trans* configuration (Fig. 7).

Finally, by comparison, we were able to assign the configuration *trans*–*trans* to indanes **32**, **33**, and **38**; the configuration 1,2-*cis*-2,3-*trans* to **34**, **35**, and **39**; and the configuration 1,2-*trans*-2,3-*cis* to compounds **36** and **37**.

3. Conclusion

FCA [3+2] of benzhydrols and styrene derivatives with electron withdrawing bound at C-β allowed obtaining indanes functionalized at C-2, with different yields. Several kinds of acids were used to catalyze this reaction. $SnCl_4$ resulted to be the most efficient catalyst of all the catalysts tested.

We observed that the reactivity of benzhydrols against this type of styrenes and the stereoselectivity of the reaction depend of the substitution on the aromatic ring and on the electron-withdrawing group present in the styrenes. The best yields (80%) and the highest stereoselectivity (1,2-*cis*-2,3-*trans* vs *trans*–*trans* (2:1)) were obtained from cinnamic acids **5** and **6** (entry 2,3). Chalcones **22** and **23** and 3,4-dimethoxynitrostyrene **31** (Table 1 entry 9,10 and Table 3 entry 6) afforded a third diastereomer (1,2-*trans*-2,3-*cis*), which was not previously obtained using this type of reaction.

FCA [3+2] allowed the synthesis of endothelin analogs (*trans*–*trans*-1,3-diaryl-2-indane carboxylic acid) in a single step in contrast to other syntheses used. These products can be also obtained by hydrolysis of esters **12** and **15**–**18**.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded ($CDCl_3$) on a Bruker AC 300 spectrometer at 300 and 75 MHz. The bidimensional experiments (NOESY, ROESY, HMQC, and HSQC) were recorded ($CDCl_3$) on an Avance 500 spectrometer. Shifts reported are relative to internal standard $Si(Me)_4$ and coupling constants are reported in hertz. Abbreviations used are as follows: s: singlet, br s: broad singlet, d: doublet, t: triplet, q: quartet, dd: double doublet, dt: double triplet, m: multiplet. Microanalyses were performed by Elemental Analyser Carlo Erba. Preparative thin layer chromatography (p-TLC) was done on Merck Silica Gel 60 GF_{254}; and analytical TLC was performed on Merck aluminum sheets Silica Gel 60 GF_{254}. Commercial compounds were purchased from Aldrich Chemical Co. THF and CH_2Cl_2 were distilled from sodium/benzophenone and CaH_2, respectively. Melting points are uncorrected and were determined in a Thomas Hoover apparatus. In cases were synthetic intermediates or products were isolated by 'aqueous workup (aqueous solution, organic solvent)', the procedure was to quench the reaction mixture with the

indicated aqueous solution, dilute with the indicated organic solvent, separate the organic layer, extract the aqueous layer several times with the organic solvent, dry the combined organic extracts over Na_2SO_4 and remove the solvent under reduced pressure (water aspirator) with a Büchi Rotavapor. Benzhydrolic alcohols **1** and **2** were prepared from corresponding aldehydes and phenylmagnesium bromide.[10] Alcohol **3** was obtained by reduction of 3,3′,4,4′-tetramethoxybenzophenone with $NaBH_4$ in methanol. δ_H (ppm): 2.25 (1H, bs, OH); 3.87 (6H, s, OCH_3); 3.89 (6H, s, OCH_3); 5.77 (1H, s, CHOH); 6.84 (2H, d, J=8.4 Hz, Ar); 6.90 (2H, dd, J=1.5, 8.4 Hz, Ar); 6.94 (2H, d, J=1.5 Hz, Ar). δ_C (ppm): 55.8, 55.9, 79.9, 110.8, 110.9, 119.6, 134.9, 148.3, 148.9. The chalcones **19**, **22**, and **23**[18] were synthesized from acetophenone and the corresponding arylaldehyde.[11] Nitrostyrene **30** and 3.4-dimethoxynitrostyrene **31** were synthesized following standard methodology.[11]

*4.1.1. (3,4-Dimethoxyphenyl)phenylmethanol (**2d**).* To a solution of 3,4-dimethoxybromobenzene (1.0 g, 4.6 mmol) in dry THF (10 mL) was added at −78 °C, a solution of BuLi 1.1 M (5.06 mL) and stirred for 1 h. Then a solution of deuterated benzaldehyde (C_6H_5CDO) in THF (0.47 mL, 4.6 mmol) was added slowly and stirred by 1 h. The mixture at room temperature (rt) was quenched with saturated solution of aqueous ammonium chloride. The aqueous layer was extracted with CH_2Cl_2. Organic layer washed with water, dried with anhydrous Na_2SO_4, and concentrated to give 0.92 g (82%) of alcohol **2d**.

*4.1.2. Methyl 3,5-dimethoxycinnamate (**13**).* A solution of 3,5-dimethoxybenzaldehyde (1.0 g, 6.02 mmol) in dry THF (10 mL) at 0 °C was added to methyl (triphenylphosphoranylidene)acetate (2.58 g, 7.22 mmol), and stirred for 24 h at rt. The solvent was removed, the residue was extracted with boiling hexane (15 mL×3) and then the solvent was evaporated. Recrystallization (ethanol/water) afforded 1.05 g (78.3%) of **13** as a solid, mp: 70–71 °C δ_H (ppm): 3.80 (9H, s, OCH_3), 6.40 (1H, d, J=16.0 Hz, CH=), 6.49 (1H, t, J=2.2 Hz, Ar), 6.66 (2H,d, J=2.2 Hz, Ar), 7.60 (1H, d, J=16.0 Hz, CH=).[19]

*4.1.3. Methyl (3,4-methylenedioxy)cinnamate (**14**).* The same procedure described for the preparation of **13** was carried out with 3,4-methylenedioxybenzaldehyde (0.5 g, 3.6 mmol) and methyl (triphenylphosphoranylidene)acetate (1.30 g, 3.6 mmol). Recrystallization (ethanol/water) afforded 0.48 g (70.6%) of **14**, mp: 125–126 °C δ_H (ppm): 3.78 (3H, s, OCH_3), 6.00 (2H, s, OCH_2O), 6.25 (1H, d, J=15.9 Hz, CH=), 6.81 (1H, d, J=8.0 Hz, Ar), 6.99 (1H, dd, J=1.5, 8.0 Hz, Ar), 7.02 (1H, d, J=1.5 Hz), 7.60 (1H, d, J=15.9 Hz, CH=).

4.2. General procedure for the formal [3+2] cycloaddition of a benzhydrol and a substituted styrene in the presence of $SnCl_4$

*4.2.1. r-1-Phenyl-c-2-carboxy-t-3-(4-methoxyphenyl)-5,6-dimethoxyindane (**7**) and r-1-phenyl-t-2-carboxy-c-3-(4-methoxyphenyl)-5,6-dimethoxyindane (**8**).* 4-Methoxycinnamic acid **5** (0.10 g, 0.58 mmol) and $SnCl_4$ (0.19 g, 0.75 mmol) were sequentially added to a solution of alcohol **2** (0.14 g, 0.58 mmol), in CH_2Cl_2 (10 mL), at rt. The resulting solution was stirred for 2 h at rt and then poured into a rapidly stirred solution of $NaHCO_3$ 5%. Aqueous workup ($NaHCO_3$, CH_2Cl_2) followed by p-TLC (1:1, hexane/ethyl acetate) afforded 0.20 g (85.6%) of **7** and **8** as a 2:1 (solid). Compound **7** δ_H (ppm): 3.65 (1H, t, J=9.5 Hz, C*H*COOH), 3.79 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 4.76 (1H, d, J=9.2 Hz, CHPh), 4.83 (1H, d, J=9.8 Hz, CHAr), 6.49 (1H, s, Ar), 6.65 (1H, s, Ar), 6.87 (2H, d, J=8.0 Hz, Ar), 6.98 (2H, d, J=8.0 Hz, Ar), 7.19 (2H, d, J=8.0 Hz, Ar), 7.30–7.40 (3H, m, Ar). δ_C (ppm): 51.1, 52.8, 55.0, 55.9, 63.4, 107.4, 107.6, 113.8, 127.8, 128.4, 128.7, 129.7, 136.1, 136.8, 137.9, 142.4, 148.7, 148.9, 158.2, 178.8. Compound **8** δ_H (ppm): 3.19 (1H, t, J=9.5 Hz, CHCOOH), 3.75 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 4.58 (1H, d, J=9.2 Hz, CHPh), 4.61 (1H, d, J=9.8 Hz, CHAr), 6.43 (1H, s, Ar), 6.44 (1H, s, Ar), 6.89 (2H, d, J=8.0 Hz, Ar), 7.10 (3H, m, Ar), 7.22 (2H, m, Ar), 7.29 (2H, d, J=8.0 Hz, Ar). δ_C (ppm): 54.4, 54.7, 55.0, 55.9, 65.3, 107.4, 107.6, 113.3, 126.2, 126.5, 128.5, 129.5, 136.0, 137.4, 137.8, 144.3, 148.7, 148.9, 152.2, 181.2. Anal. Calcd for $C_{25}H_{24}O_5$: C, 74.24; H, 5.98. Found: C, 74.26; H, 6.0.

*4.2.2. r-1-Phenyl-c-2-carboxy-t-3-(3,4-methylenedioxyphenyl)-5,6-dimethoxyindane (**9**) and r-1-phenyl-t-2-carboxy-c-3-(3,4-methylenedioxyphenyl)-5,6-dimethoxyindane (**10**).* General procedure was carried out with alcohol **2** (0.14 g, 0.58 mmol), 3,4-methylenedioxycinnamic acid **6** (0.11 g, 0.58 mmol), and $SnCl_4$ (0.19 g, 0.75 mmol) during 30 min at rt p-TLC (1:1, hexane/ethyl acetate) afforded 0.106 g (88.2%) of **9** and **10** as a 2:1 mixture (solid). Compound **9** δ_H (ppm): 3.64 (1H, t, J=9.8 Hz, CHCOOH), 3.68 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 4.74 (1H, d, J=9.8 Hz, CHPh), 4.83 (1H,d, J=9.8 Hz, CHAr), 5.86 (1H, s, OCH_2O), 5.89 (1H, s, OCH_2O), 6.50 (1H, s, Ar), 6.64 (1H, s, Ar), 6.65–6.82 (2H, m, Ar), 6.9–7.3 (6H, m, Ar). δ_C (ppm): 51.6, 52.7, 55.9, 63.2, 100.7, 107.4, 107.6, 108.0, 109.0, 121.9, 126.8, 127.8, 128.4, 136.6, 137.4, 137.8, 146.0, 147.5, 148.7, 148.8, 148.9, 178.4. Compound **10** δ_H (ppm): 3.00 (1H, t, J=9.9 Hz, CHCOOH), 3.62 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 4.65 (1H, d, J=9.9 Hz, CHPh), 4.68 (1H, d, J=9.9 Hz, CHAr), 5.83 (1H, s, OCH_2O), 5.84 (1H, s, OCH_2O), 6.40 (1H, s, Ar), 6.47 (1H, s, Ar), 6.65–6.82 (2H, m, Ar), 6.9–7.3 (6H, m, Ar). δ_C (ppm): 53.9, 54.3, 55.9, 65.0, 100.7, 107.4, 107.6, 108.8, 109.1, 121.6, 126.5, 128.4, 128.7, 136.8, 138.8, 142.1, 144.1, 147.5, 148.7, 148.8, 148.9, 180.6. Anal. Calcd for $C_{25}H_{22}O_6$: C, 71.76; H, 5.30. Found: C, 71.78; H, 5.32.

*4.2.3. r-1,c-3-Diphenyl-t-2-methoxycarbonyl-5,6-dimethoxyindane (**12**).* General procedure was carried out with alcohol **2** (0.10 g, 0.39 mmol), methyl cinnamate **11** (0.075 g, 0.46 mmol), and $SnCl_4$ (0.13 g, 0.51 mmol) during 1 h at rt p-TLC (Cl_2CH_2) afforded 0.087 g (60.4%) of **12** (pale yellow solid), mp: 160–161 °C δ_H (ppm): 3.27 (1H, t, J=9.6 Hz, $CHCOOCH_3$), 3.61 (3H, s, $COOCH_3$), 3.76 (6H, s, OCH_3), 4.66 (2H, d, J=9.6 Hz, CHPh), 6.45 (2H, s, Ar), 7.30 (5H, m, Ar), 7.38 (5H, m, Ar). δ_C (ppm): 52.1, 54.8, 56.5, 65.7, 107.9, 127.5, 128.9, 129.1, 136.7, 143.5. 149.5, 174.6. Anal. Calcd for $C_{25}H_{24}O_4$: C, 77.30; H, 6.23. Found: C, 77.32; H, 6.25.

*4.2.4. r-1-Phenyl-c-2-methoxycarbonyl-t-3-(3,5-dimethoxyphenyl)-5,6-dimethoxyindane (**15**) and r-1-phenyl-t-2-methoxycarbonyl-c-3-(3,5-dimethoxyphenyl)-5,6-dimethoxyindane (**16**).* General procedure was carried out with alcohol **2** (0.10 g, 0.40 mmol), methyl 3,5-dimethoxycinnamate **13** (0.09 g, 0.41 mmol), and $SnCl_4$ (0.09 g, 0.34 mmol) during 10 min at rt. p-TLC ($CHCl_2$) afforded 0.08 g (43.7%) of **15** and **16** as a 1:2.3 (white solid). Compound **15** δ_H (ppm): 3.28 (3H, s, $COOCH_3$), 3.64 (4H, overlap with OCH_3, $CHCOOCH_3$), 3.70 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.78 (1H, d, J=9.2 Hz, CHPh), 4.90 (1H, d, J=9.2 Hz, CHAr), 6.36 (1H, t, J=2.2 Hz, Ar), 6.39 (2H, d, J=2.2 Hz, Ar), 6.54 (1H, s, Ar), 6.62 (1H, s, Ar), 7.10–7.30 (5H, m, Ar). δ_C (ppm): 51.2, 51.5, 53.8, 55.4, 55.7, 55.9, 56.0, 61.1, 99.0, 106.6, 107.4, 111.8, 125.0, 127.1, 128.5, 129.4, 136.0, 145.5, 145.9, 148.8, 149.2, 160.8, 171.9. Compound **16** δ_H (ppm): 3.24 (1H, t, J=9.2 Hz, $CHCOOCH_3$), 3.51 (3H, s, OCH_3), 3.61 (3H, s, $COOCH_3$), 3.63 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 4.58 (1H, d, J=9.6 Hz, CHPh), 4.61 (1H, d, J=9.6 Hz, CHAr), 6.08 (1H, s, Ar), 6.39 (1H, t, J=2.1 Hz, Ar), 6.48 (1H, s, Ar), 6.66 (2H, d, J=2.1 Hz, Ar), 7.10–7.30 (5H, m, Ar). δ_C (ppm): 54.5, 54.6, 55.5, 55.8, 56.0, 56.1, 56.2, 64.9, 98.9, 106.5, 107.4, 107.5, 127.6, 128.4, 131.0, 136.5, 136.7, 143.6, 144.3, 147.3, 147.5, 160.9, 174.3. Anal. Calcd for $C_{27}H_{28}O_6$: C, 72.30; H, 6.29. Found: C, 72.32; H, 6.31.

*4.2.5. r-1-Phenyl-c-2-methoxycarbonyl-t-3-(3,4-methylenenedioxyphenyl)-5,6-dimethoxyindane (**17**) and r-1-phenyl-t-2-methoxycarbonyl-c-3-(3,4-methylenedioxyphenyl)-5,6-dimethoxyindane*

(***18***). General procedure was carried out with alcohol **2** (0.10 g, 0.40 mmol), methyl 3,4-methylenedioxyphenylcinnamate **14** (0.085 g, 0.41 mmol), and $SnCl_4$ (0.09 g, 0.34 mmol) during 15 min at rt. p-TLC ($CHCl_2$) afforded 0.13 g (73.4%) of **17** and **18** as a 1.3:1 (white solid). Compound **17** δ_H (ppm): 3.29 (3H, s, $COOCH_3$), 3.64 (1H, t, *J*=9.5 Hz, $CHCOOCH_3$), 3.77 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 4.78 (1H, d, *J*=9.3 Hz, CHPh), 4.90 (1H, d, *J*=9.5 Hz, CHAr), 5.90 (1H, d, *J*=1.5 Hz, OCH_2O), 5.91 (1H, d, *J*=1.5 Hz, OCH_2O), 6.51 (1H, s, Ar), 6.62 (1H, s, Ar), 6.77 (3H, m, Ar), 7.16–7.36 (5H, m, Ar). δ_C (ppm): 51.2, 53.2, 55.9, 56.0, 56.1, 61.4, 100.9, 107.4, 107.5, 107.6, 108.3, 122.0, 128.4, 128.5, 128.7, 135.8, 137.0, 137.2, 141.0, 143.0, 149.5, 149.1, 149.2, 171.9. Compound **18** δ_H (ppm): 3.19 (1H, t, *J*=9.6 Hz, $CHCOOCH_3$), 3.59 (3H, s, $COOCH_3$), 3.72 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.56 (1H, d, *J*=9.5 Hz, CHPh), 4.61 (1H, d, *J*=9.8 Hz, CHAr), 5.94 (1H, d, *J*=1.5 Hz, OCH_2O), 5.96 (1H, d, *J*=1.5 Hz, OCH_2O), 6.41 (1H, s, Ar), 6.45 (1H, s, Ar), 6.71 (1H, d, *J*=1.2 Hz, Ar), 6.96 (2H, m, Ar), 7.16–7.36 (5H, m, Ar). δ_C (ppm): 51.2, 54.2, 54.3, 55.9, 56.0, 65.5, 101.0, 108.4, 108.5, 108.7, 108.8, 121.8, 127.0, 128.2, 128.3, 136.2, 136.3, 136.9, 143.0, 146.7, 147.9, 148.0, 149.3, 174.2. Anal. Calcd for $C_{26}H_{24}O_6$: C, 72.21; H, 5.59. Found: C, 72.23; H, 5.61.

4.2.6. r-1,c-3-Diphenyl-t-2-benzoyl-5-hydroxy-6-methoxyindane (***20***). General procedure was carried out with alcohol **1** (0.10 g, 0.46 mmol), chalcone **19** (0.15 g, 0.74 mmol), and $SnCl_4$ (0.15 g, 0.60 mmol) during 2 h at rt. p-TLC ($CHCl_3$) afforded 0.06 g (31%) of **20** (yellow solid), mp: 150–152 °C δ_H (ppm): 3.77 (3H, s, OCH_3); 4.27 (1H, dd, *J*=9.2, 9.4 Hz, CHCOPh), 4.73 (1H, d, *J*=9.2 Hz, CHPh), 4.76 (1H, d, *J*=9.4 Hz, CHPh), 5.57 (1H, s, OH), 6.43 (1H, s, Ar), 6.51 (1H, s, Ar), 7.07 (2H, m, Ar), 7.24 (11H, m, Ar), 7.33 (2H, d, *J*=8.6 Hz, Ar). δ_C (ppm): 54.9, 55.1, 56.1, 68.0, 106.9, 110.5, 126.9, 128.0, 128.4, 128.5, 128.6, 128.7, 132.8, 135.9, 137.2, 137.5, 143.2, 143.6, 145.5, 146.6, 201.3. Anal. Calcd for $C_{29}H_{24}O_3$: C, 82.83; H, 5.75. Found: C, 82.85; H, 5.77.

4.2.7. r-1,c-3-Diphenyl-t-2-benzoyl-5,6-dimethoxyindane (***21***). General procedure was carried out with alcohol **2** (0.11 g, 0.46 mmol), chalcone **19** (0.15 g, 0.74 mmol), and $SnCl_4$ (0.15 g, 0.60 mmol) during 2 h at rt. p-TLC ($CHCl_3$) afforded 0.06 g (30%) of **21** (white solid), mp: 153–154 °C δ_H (ppm): 3.76 (6H, s, OCH_3), 4.27 (1H, t, *J*=9.2 Hz, CHCOPh), 4.80 (2H, d, *J*=9.2 Hz, CHPh), 6.46 (2H, s, Ar), 7.10 (2H, m, Ar), 7.23 (11H, m, Ar), 7.33 (2H, d, *J*=8.1 Hz, Ar). δ_C (ppm): 55.1, 56.1, 68.2, 107.4, 126.9, 128.0, 128.5, 128.7, 132.8, 136.4, 137.2, 143.5, 149.1, 201.3. Anal. Calcd for $C_{30}H_{26}O_3$: C, 82.92; H, 6.03. Found: C, 82.94; H, 6.05.

4.2.8. r-1-Phenyl-t-2-benzoyl-c-3-(4-methoxyphenyl)-5,6-dimethoxyindane (***24***), *r-1-phenyl-c-2-benzoyl-t-3-(4-methoxyphenyl)-5,6-dimethoxyindane* (***25***) *and r-1-phenyl-t-2-benzoyl-t-3-(4-methoxyphenyl)-5,6-dimethoxyindane* (***26***). General procedure was carried out with alcohol **2** (0.2 g, 0.82 mmol), chalcone **21** (0.19 g, 0.82 mmol), and $SnCl_4$ (0.09 g, 0.34 mmol) during 5 min at rt p-TLC (70: 30, hexane/ethyl acetate) afforded 0.15 g (39.5%) of **24**, **25** and **26** as a 1.6:1:1 (24/25/26) mixture. p-TLC (80: 20, hexane/ethyl acetate) allowed the separation of **24** (clear oil). Compound **24** δ_H (ppm): 3.78 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.26 (1H, t, *J*=9.2 Hz, CHCOPh), 4.77 (1H, d, *J*=9.1 Hz, CHAr), 4.80 (1H, d, *J*=9.2 Hz, CHPh), 6.49 (2H, s, Ar), 6.82 (2H, d, *J*=8.5 Hz, Ar), 7.14 (2H, m, Ar), 7.17 (2H, m, Ar), 7.24 (3H, m, Ar), 7.28 (2H, m, Ar), 7.34 (1H, m, Ar), 7.39 (2H, d, *J*=8.2 Hz, Ar). δ_C (ppm): 54.5, 55.1, 55.2, 56.1, 68.4, 107.5, 107.6, 114.0, 126.9, 128.5, 128.6, 128.7, 129.5, 132.8, 135.5, 136.3, 136.8, 137.4, 143.6, 149.2, 158.6, 161.6, 163.0, 201.5. Compound **25** δ_H: 3.79 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 4.62 (1H, t, *J*=9.2 Hz, CHCOPh), 4.94 (1H, d, *J*=9.2 Hz, CHPh), 5.31 (1H, d, *J*=9.2 Hz, CHAr), 6.50 (1H, s, Ar), 6.60 (1H, s, Ar), 6.87 (2H, d, *J*=8.8 Hz, Ar), 7.06 (3H, m, Ar), 7.28 (2H, m, Ar), 7.35 (4H, m, Ar), 7.50 (1H, m, Ar), 7.74 (2H, d, *J*=8.6 Hz, Ar). δ_C (ppm): 50.8, 54.7, 55.3, 56.1, 64.4, 107.8, 113.3, 114.0, 126.8, 128.0, 128.2, 128.4, 128.6, 128.8, 132.6, 132.7, 136.0, 136.8, 137.0, 137.6, 140.6, 149.1, 158.4, 198.2. Compound **26** δ_H (ppm): 3.70 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 4.63 (1H, t, *J*=9.2 Hz, CHCOPh), 4.93 (1H, d, *J*=9.2 Hz, CHAr), 5.36 (1H, d, *J*=9.2 Hz, CHPh), 6.54 (1H, s, Ar), 6.55 (1H, s, Ar), 6.60 (5H, m, Ar), 7.28 (2H, m, Ar), 7.35 (4H, m, Ar), 7.50 (1H, m, Ar), 7.74 (2H, d, *J*=8.6 Hz, Ar). δ_C (ppm): 50.5, 54.1, 56.0, 56.1, 64.3, 107.2, 107.3, 113.6, 126.7, 128.0, 128.2, 128.5, 128.6, 129.1, 129.5, 132.3, 136.3, 136.8, 137.6, 137.8, 144.4, 149.2, 158.3, 198.1. Anal. Calcd for $C_{31}H_{28}O_4$: C, 80.15; H, 6.08. Found: C, 80.17; H, 6.10.

4.2.9. r-1-Phenyl-t-2-benzoyl-c-3-(3,4-methylenedioxyphenyl)-5,6-dimethoxyindane (***27***), *r-1-phenyl-c-2-benzoyl-t-3-(3,4-methylenedioxyphenyl)-5,6-dimethoxyindane* (***28***) *and r-1-phenyl-t-2-benzoyl-t-3-(3,4-methylenedioxyphenyl)-5,6-dimethoxyindane* (***29***). General procedure was carried out with alcohol **2** (0.19 g, 0.79 mmol), chalcone **23** (0.2 g, 0.79 mmol), and $SnCl_4$ (0.09 g, 0.34 mmol) during 5 min at rt. p-TLC (70: 30, hexane/ethyl acetate) afforded 0.19 g (51.5%) of **27**, **28** and **29** as a 1.9:1.67:1 (27/28/29) mixture. p-TLC (80: 20, hexane/ethyl acetate) allowed the separation of **27** (white crystalline solid), mp: 75–76 °C. Compound **27** δ_H (ppm): 3.78 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 4.24 (1H, t, *J*=9.2 Hz, CHCOPh), 4.76 (2H, d, *J*=9.2 Hz, CHAr, CHPh), 5.95 (2H, s, OCH_2O), 6.47 (1H, s, Ar), 6.50 (1H, s, Ar), 6.69 (2H, s, Ar), 6.75 (1H, s, Ar), 7.17 (2H, t, *J*=8.2 Hz, Ar), 7.23 (3H, m, Ar), 7.29 (2H, m, Ar), 7.39 (1H, m, Ar), 7.41 (2H, d, *J*=8.5 Hz, Ar). δ_C (ppm): 54.9, 55.2, 56.1, 68.3, 101.0, 107.5, 107.6, 108.4, 122.0, 127.0, 128.1, 128.5, 128.6, 128.7, 132.9, 137.4, 146.5, 147.9, 148.8, 149.2, 151.6, 206.4. Compound **28** δ_H: 3.79 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.61 (1H, t, *J*=9.3 Hz, CHCOPh), 4.94 (1H, d, *J*=9.0 Hz, CHPh), 5.31 (1H, d, *J*=9.5 Hz, CHAr), 5.90 (2H, s, OCH_2O), 6.61 (1H, s, Ar), 6.63 (1H, s, Ar), 6.76 (1H, d, *J*=7.8 Hz, H-6′), 6.82 (1H, d, *J*=1.5 Hz, H-2′), 6.89 (1H, dd, *J*=1.5, 7.8 Hz, H-5′), 7.05 (3H, m. Ar), 7.39 (3H, m, Ar), 7.51 (2H, m, Ar), 7.74 (2H, d, *J*=7.3 Hz, Ar). δ_C (ppm): 50.4, 54.7, 56.1, 64.3, 100.9, 107.3, 107.8, 108.3, 108.9, 122.1, 126.8, 128.2, 128.4, 128.5, 132.8, 136.3, 137.1, 137.6, 137.8, 140.5, 144.0, 147.8, 149.2, 149.3, 198.1. Compound **29** δ_H (ppm): 3.81 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 4.61 (1H, t, *J*=9.3 Hz, CHCOPh), 4.90 (1H, d, *J*=9.0 Hz, CHAr), 5.35 (1H, d, *J*=9.8 Hz, CHPh), 5.82 (1H, d, *J*=1.2 Hz, OCH_2O), 5.84 (1H, d, *J*=1.2 Hz, OCH_2O), 6.09 (1H, dd, *J*=1.5, 7.1 Hz, H-6′), 6.13 (1H, d, *J*=1.5 Hz, H-2′), 6.45 (1H, d, *J*=7.8 Hz, H-5′), 6.59 (1H, s, Ar), 6.62 (1H, s, Ar), 7.05 (3H, m. Ar), 7.39 (3H, m, Ar), 7.51 (2H, m, Ar), 7.77 (2H, d, *J*=7.3 Hz, Ar). δ_C (ppm): 50.5, 54.5, 56.0, 64.2, 100.8, 107.2, 107.5, 107.9, 108.8, 121.7, 126.7, 128.0, 128.6, 128.8, 132.8, 134.4, 136.5, 137.0, 140.6, 146.3, 146.4, 147.4, 149.2, 149.3, 198.0. Anal. Calcd for $C_{31}H_{26}O_5$: C, 77.81; H, 5.48. Found: C, 77.82; H, 5.50.

4.2.10. r-1-Phenyl-t-2-nitro-c-3-(3,4-dimethoxyphenyl)-5-hydroxy-6-methoxyindane (***32***), *r-1-phenyl-c-2-nitro-t-3-(3,4-dimethoxyphenyl)-5-hydroxy-6-methoxyindane* (***34***) *and r-1-phenyl-t-2-nitro-t-3-(3,4-dimethoxyphenyl)-5-hydroxy-6-methoxyindane* (***36***). General procedure was carried out with alcohol **1** (0.13 g, 0.58 mmol), 3,4-dimethoxynitrostyrene **31** (0.19 g, 0.93 mmol), and $SnCl_4$ (0.19 g, 0.75 mmol) during 2 h at 0 °C. p-TLC ($CHCl_3$) afforded 0.11 g (50%) of **32** and **34** as 1:1. p-TLC (70:30, hexane/ethyl acetate) allowed the separation of **32** (pale yellow solid), mp: 118–120 °C and **34** (pale yellow solid), mp: 179–181 °C.

General procedure was carried out with alcohol **1** (0.13 g, 0.58 mmol), 3,4-dimethoxynitrostyrene **31** (0.19 g, 0.93 mmol), and $SnCl_4$ (0.19 g, 0.75 mmol) during 1 h at rt. p-TLC ($CHCl_3$) afforded 0.13 g (56%) of **32**, **34**, and **36** as a 1:1:0.08 (32:34:36) mixture. Compound **32** δ_H (ppm): 3.79 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.90 (1H, d, *J*=8.4 Hz, CHPh), 4.97 (1H, d, *J*=8.2 Hz, CHAr), 5.04 (1H, t, *J*=8.4 Hz, $CHNO_2$), 5.67 (1H, s, OH), 6.44 (1H, s, Ar), 6.58 (1H, s, Ar), 6.73 (1H, d, *J*=1.8 Hz, Ar), 6.83 (2H, m, Ar), 7.27

(3H, m, Ar), 7.36 (2H, m, Ar). δ_C (ppm): 55.3, 55.5, 55.9, 56.0, 56.1, 102.0, 106.9, 110.6, 111.1, 111.4, 120.5, 128.0, 128.3, 129.1, 132.1, 132.2, 133.8, 140.1, 146.3, 147.2, 148.7, 149.3. Compound **34** δ_H (ppm): 3.81 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.98 (1H, d, J=8.7 Hz, CHPh), 5.13 (1H, d, J=9.0 Hz, CHAr), 5.44 (1H, t, J=8.7 Hz, $CHNO_2$), 5.7 (1H, s, OH), 6.62 (1H, s, Ar), 6.64 (1H, s, Ar), 6.71–6.83 (2H, m, Ar), 7.0 (1H, m, Ar), 7.20–7.33 (5H, m, Ar). δ_C (ppm): 52.0, 53.8, 55.9, 56.0, 56.1, 97.5, 107.6, 111.4, 111.5, 120.8, 128.2, 128.6, 128.7, 132.3, 132.4, 133.9, 137.0, 148.7, 149.3, 149.9, 150.0. Compound **36** δ_H (ppm): 3.82 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.95 (1H, d, J=8.7 Hz, CHPh), 5.16 (1H, d, J=9.0 Hz, $CHNO_2$), 5.29 (1H, s, OH), 5.40 (1H, dd, J=7.7, 8.5 Hz, CHAr), 6.51 (1H, s, Ar), 6.54 (1H, s, Ar), 6.71–6.83 (2H, m, Ar), 7.0 (1H, m, Ar), 7.20–7.33 (5H, m, Ar). δ_C (ppm): 52.5, 53.7, 55.8, 56.1, 97.6, 107.6, 111.0, 111.8, 112.0, 121.0, 127.8, 128.5, 129.0, 132.7, 133.9, 140.2, 145.3, 148.9, 149.0, 149.8, 150.0. Anal. Calcd for $C_{24}H_{23}NO_6$: C, 68.40; H, 5.50; N 3.32. Found: C 68.42, H 5.52, N 3.34.

*4.2.11. r-1-Phenyl-t-2-nitro-c-3-(3,4-dimethoxyphenyl)-5,6-dimethoxyindane (**33**), r-1-phenyl-c-2-nitro-t-3-(3,4-dimethoxyphenyl)-5,6-dimethoxyindane (**35**) and r-1-phenyl-t-2-nitro-t-3-(3,4-dimethoxyphenyl)-5,6-dimethoxyindane (**37**).* General procedure was carried out with alcohol **2** (0.14 g, 0.58 mmol), 3,4-dimethoxynitrostyrene **31** (0.19 g, 0.93 mmol), and $SnCl_4$ (0.19 g, 0.75 mmol) during 2 h at 0 °C. p-TLC ($CHCl_3$) afforded 0.07 g (30%) of **33** and **35** as a 1:1 mixture. p-TLC (70:30, hexane/ethyl acetate) allowed the separation of **33** (yellow solid), mp: 285–287 °C and **35** (yellow solid), mp: 170–172 °C.

General procedure was carried out with alcohol **2** (0.14 g, 0.58 mmol), 3,4-dimethoxynitrostyrene **31** (0.19 g, 0.93 mmol), and $SnCl_4$ (0.19 g, 0.75 mmol) during 1 h at rt. p-TLC ($CHCl_3$) afforded 0.10 g (44%) of **33**, **35**, and **37** as a 1:1:0.08 (33:35:37) mixture. Compound **33** δ_H (ppm): 3.76 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.91 (1H, d, J=7.9 Hz, CHAr), 4.93 (1H, d, J=8.8 Hz, CHPh), 4.99 (1H, dd, J=7.9, 8.5 Hz, $CHNO_2$), 6.45 (1H, s, Ar), 6.48 (1H, s, Ar), 6.71 (1H, d, J=1.7 Hz, Ar), 6.85 (2H, m, Ar), 7.25 (2H, m, Ar), 7.36 (3H, m, Ar). δ_C (ppm): 55.5, 55.9, 56.1, 102.2, 107.3, 107.4, 111.0, 111.4, 120.6, 128.0, 128.2, 129.1, 132.4, 132.7, 132.9, 140.0, 148.8, 149.3, 149.8, 149.8. Compound **35** δ_H (ppm): 3.80 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.99 (1H, d, J=8.7 Hz, CHPh), 5.17 (1H, d, J=8.5 Hz, CHAr), 5.43 (1H, t, J=8.7 Hz, $CHNO_2$), 6.54 (1H, s, Ar), 6.66 (1H, s, Ar), 6.71 (1H, d, J=2.0 Hz, Ar), 6.77 (1H, dd, J=2.0, 8.3, Hz, Ar), 6.84 (1H, d, J=8.3 Hz, Ar), 7.0 (2H, m, Ar), 7.25–7.33 (3H, m, Ar). δ_C (ppm): 51.9, 53.6, 53.7, 55.9, 56.0, 56.1, 97.4, 107.5, 110.9, 111.3, 111.4, 120.8, 128.1, 128.4, 128.6, 132.3, 132.4, 133.9, 136.9, 148.6, 149.2, 149.8, 149.9. Compound **37** δ_H (ppm): 3.79 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.97 (1H, d, J=8.5 Hz, CHPh), 5.19 (1H, d, J=7.4 Hz, CHAr), 5.41 (1H, dd, J=7.4, 8.5 Hz, $CHNO_2$), 6.53 (1H, s, Ar), 6.66 (1H, s, Ar), 6.71 (1H, d, J=2.0 Hz, Ar), 6.77 (1H, dd, J=2.0, 8.3 Hz, Ar), 6.84 (1H, d, J=8.3 Hz, Ar), 7.00 (2H, m, Ar), 7.23–7.33 (3H, m, Ar). δ_C (ppm): 52.4, 53.6, 55.7, 55.9, 56.0, 56.1, 97.5, 107.5, 110.9, 111.3, 111.9, 120.9, 127.8, 129.0, 129.1, 132.3, 132.4, 132.6, 140.1, 148.6, 148.8, 149.8, 149.9. Anal. Calcd for $C_{25}H_{25}NO_6$: C, 68.95; H, 5.79; N, 3.22. Found: C, 68.98; H, 5.8; N, 3.24. Compound **33d** δ_H (ppm): 3.76 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.92 (1H, d, J=8.4 Hz, CHAr), 5.02 (1H, d, J=8.4 Hz, $CHNO_2$), 6.46 (1H, s, Ar), 6.49 (1H, s, Ar), 6.73 (1H, d, J=1.8 Hz, Ar), 6.82 (1H, dd, J=1.8, 8.4 Hz, Ar), 6.87 (1H, d, J=8.4 Hz, Ar), 7.28 (2H, m, Ar), 7.35 (3H, m, Ar). Compound **35d** δ_H (ppm): 3.80 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 5.17 (1H, d, J=8.4 Hz, CHAr), 5.43 (1H, d, J=8.4 Hz, $CHNO_2$), 6.55 (1H, s, Ar), 6.65 (1H, s, Ar), 6.72 (1H, d, J=1.7 Hz, Ar), 6.77 (1H, dd, J=1.7, 8.3, Hz, Ar), 6.84 (1H, d, J=8.3 Hz, Ar), 7.0 (2H, m, Ar), 7.25–7.33 (3H, m, Ar).

*4.2.12. r-1-c-3-Bis-(3,4-dimethoxyphenyl)-t-2-nitro-5,6-dimethoxyindane (**38**) and r-1-t-3-bis-(3,4-dimethoxyphenyl)-c-2-nitro-5,6-dimethoxyindane (**39**).* General procedure was carried out with alcohol **3** (0.42 g, 1.37 mmol), 3,4-dimethoxynitrostyrene **31** (0.24 g, 1.37 mmol), and $SnCl_4$ (0.20 g, 0.78 mmol) during 1 h at rt. p-TLC (Cl_2CH_2) afforded 0.35 g (51.5%) of **38** and **39** as a 2:1 (38:39) mixture. p-TLC (70:30, hexane/ethyl acetate) allowed the separation of **38** (cream white solid), mp: 155–156 °C and **39** (white solid), mp: 95–96 °C. Compound **38** δ_H (ppm): 3.80 (6H, s, OCH_3), 3.85 (6H, s, OCH_3), 3.90 (6H, s, OCH_3), 4.92 (2H, d, J=8.1 Hz, CHAr), 5.00 (1H, t, J=8.1 Hz, $CHNO_2$), 6.51 (2H, s, Ar), 6.74 (2H, d, J=1.5 Hz, Ar), 6.83 (2H, dd, J=1.4, 8.1 Hz, Ar), 6.88 (2H, d, J=8.4 Hz, Ar). δ_C (ppm): 55.8, 56.3, 56.4, 56.5, 102.8, 107.8, 111.6, 112.0, 121.0, 132.9, 133.2, 149.2, 149.8, 150.2. Compound **39** δ_H (ppm): 3.79 (3H,s, OCH_3), 3.81 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.95 (1H, d, J=8.5 Hz, CHAr), 5.13 (1H, d, J=7.9 Hz, CHAr); 5.39 (1H, t, J=8.1 Hz, $CHNO_2$), 6.50 (3H, m, Ar), 6.70–6.85 (5H, m, Ar). δ_C (ppm): 52.0, 52.8, 53.6, 55.7, 55.8, 55.9, 56.0, 56.2, 97.6, 107.6, 110.9, 111.3, 111.5, 111.8, 112.0, 120.8, 121.0, 129.2, 132.6, 133.2, 133.8, 148.6, 148.7, 148.8, 149.6, 149.7, 149.8. Anal. Calcd for $C_{27}H_{29}NO_8$: C, 65.44, H 5.90; N, 2.83. Found: C, 65.47; H, 5.93; N, 2.86.

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References and notes

1. Jaun, B.; Martinoni, B.; Marazza, F.; Bertolin, M. *J. Nat. Prod.* **1997**, *60*, 361–365.
2. Yu, H.; Kim, I. Y.; Folk, Y. E.; Tian, X.; Rothman, R. B.; Buamann, M. H.; Dersch, C. M.; Flippen-Anderson, J. L.; Parrish, D.; Jacobson, A. E.; Rice, K. C. *J. Med. Chem.* **2004**, *47*, 2624–2634.
3. Elliot, J. D.; Lago, M. A.; Cousins, R. D.; Gao, A.; Leber, J. D.; Erhard, K. F.; Nambi, P.; Elshourbagy, N. A.; Kumar, C.; Lee, J. A.; Bean, J. W.; DeBrosse, C. W.; Egleston, D. S.; Brooks, D. P.; Feuerstein, G.; Ruffolo, R. R., Jr.; Weintock, J.; Gleason, J. G.; Peishoff, C. E.; Ohlstein, E. H. *J. Med. Chem.* **1994**, *37*, 1553–1557.
4. Yanagisawa, M.; Kurihara, H.; Kimura, S.; Tomote, Y.; Kobayashi, M.; Mitsu, Y.; Yazaki, Y.; Goto, K.; Masaki, T. *Nature* **1988**, *332*, 411–415.
5. (a) Niiyama, K.; Takahashi, H.; Nagase, T.; Kojima, H.; Amano, Y.; Katsuki, K.; Yamakawa, T.; Ozaki, S.; Ihara, M.; Yano, M.; Fukuroda, T.; Nishikibe, M.; Ishikawa, K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3041–3045; (b) Babu, G.; Yu, H.; Yang, S.; Fang, J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1129–1132; (c) Cheng, M.; Yu, H.; Ko, B.; Chang, Y.; Chen, M.; Ho, T.; Tsai, Y.; Fang, J. *Org. Biomol. Chem.* **2006**, *4*, 510–518.
6. Alesso, E. N.; Moltrasio, G. Y.; Mufato, J. D.; Aguirre, J. M. *Aust. J. Chem.* **1992**, *45*, 1753–1758.
7. Bianchi, D. E.; Alesso, E. N.; Moltrasio, G. Y. *OPPI BRIEFS* **1996**, *26*, 198–201.
8. Feraz, H. M. C.; Aguilar, A. M.; Silva, L. F., Jr.; Ciaveiro, M. V. *Quim. Nova* **2005**, *28*, 703–712.
9. (a) Angle, S.; Arnaiz, D. O. *J. Org. Chem.* **1992**, *57*, 5937–5947; (b) Alesso, E.; Torviso, R.; Lantaño, B.; Erlich, M.; Finkielsztein, L.; Moltrasio, G. Y.; Aguirre, J. M.; Brunet, E. *ARKIVOC* **2003** (**s**), 283–297.
10. (a) Lantaño, B.; Aguirre, J. M.; Finkielsztein, L.; Alesso, E.; Brunet, E.; Moltrasio, G. Y. *Synth. Commun.* **2004**, *34*, 625–641; (b) Lantaño, B.; Aguirre, J. M.; Ugliarolo, E. A.; Benegas, L.; Moltrasio, G. Y. *Tetrahedron* **2008**, *54*, 4090–4102.
11. Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Logman Group UK Limited: 1989, pp 1035 and 1039.
12. Angle, S. R.; Louis, M. S. *J. Org. Chem.* **1991**, *56*, 2853–2866.
13. Pizzio, L. R.; Vázquez, P. G.; Cáceres, C. V.; Blanco, M. N.; Alesso, E. N.; Torviso, M. R.; Lantaño, B.; Moltrasio, G. Y.; Aguirre, J. M. *Appl. Catal., A* **2005**, *287*, 1–8.
14. Appelbe, Z.; Casey, M.; Keaveney, C. M.; Kelly, C. J. *Synlett* **2002**, 1404–1408.
15. Spartan'04; wave function, Inc. 18401 Von karman Avenue, Suite 340, Irvine, CA 92612.
16. Marcuzzi, F.; Meloni, G. *J. Chem. Res., Miniprint* **1979**, 2287–2297; *J. Chem. Res., Synop.* **1979**, 184–185.
17. Alesso, E. N.; Finkielsztein, L. M.; Lantaño, B.; Bianchi, D. E.; Moltrasio, G. Y.; Aguirre, J. M. *Aust. J. Chem.* **1997**, *50*, 149–152.
18. Aguire, J. M.; Rossi, A. L.; Mufato, J. D.; Lantaño, B.; Alesso, E. N. *Rev. Latinoam. Quim.* **2006**, *34*, 1–10.
19. Borneman, W. S.; Harley, R. D.; Morrison, W. H.; Akin, D. E.; Ljungdahl, L. G. *Appl. Microbiol. Biotechnol.* **1990**, *33*, 345–351.