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Towards Synthesis of Atropodiastereomeric Indolostilbenes Hybrids: A New Class of Oligostilbenoids

K. Ahmad, M. Suhaimi, Mohamad N. Azmi, K. Awang, Mohd A. Nafiah

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***Abstract*—**The conceptually construction of axially chiral indolostilbenesi.e*N*-(2-{(E)-2-[2'-(1-Acetyl-1H-indol-2-yl)-3'chloro-4,4',6,6'-tetramethoxy[1,1'-biphenyl]-2yl]ethenyl}phenyl)acetamide and *N*-(2-{(E)-2-[2'-(1-Acetyl-1H-indol-2-yl)-3'-chloro-2,4',6,6'-tetramethoxy[1,1'-biphenyl]-4-yl]ethenyl}phenyl) acetamide are described in this paper. These structure, were obtained by the tactical combination of palladium-catalyzed coupling which produced 10-acetamido-3,5-dimethoxystilbene, follow by $FeCl_3$-induced oxidative cyclization/dimerisation. All structures were unambiguously confirmed by 1D (^1H, ^{13}C) and 2D NMR experiment, (COSY, HMQC, HMBC) and mass spectrometry.

***Keywords*—**Indolostilbene, $FeCl_3$-oxidative cyclization, Oligostilbenooids, Oxidative cyclization/dimerization.

I. Introduction

AMONG polyphenol-based natural products, resveratrol (3,5,4'-*trans*-trihydroxystilbene) and its dimers have attracted considerable attention. For instance, resveratrol itself has demonstrated a potent anti-platelet [1] and anti-cancer agent [2] and its dimeric and polymeric form are reported to exhibit a range of activities e.g inhibition of DNA polymerase [3] and anti-oxidant [4]. The indolines are beginning to attract the attention of synthetic and medicinal chemists.

This is also demonstrated by developments in the recent literature including a major review by Anas & Kagan describing development in the asymmetric syntheses of enantio enriched 2-substituted indolines by means of the kinetic resolution or the use of a chiral auxiliary in stoichiometric or catalytic processes [5].

Velu et al. reported the regio- and stereo-selective syntheses of several dimers by exposing analogues of resveratrol to the ferric chloride ($FeCl_3$) [6] and this study was the latest in the fascinating series of reports relating to stilbenes dimerisation with $FeCl_3$. These stilbenes are usually related in some way to resveratrol or isorhapontigenin. The $FeCl_3$ oxidation chemistry of *ortho*-amidostilbenes is in a more recent development going back to 2004 [7]. However in 2009, the first report of a stilbeneindoline hybrid of unprecedented structure was published [8].

In this paper, the absolute configuration of the derivatization of indolostilbenes A and B will be confirmed by 1D (^1H, ^{13}C) and 2D NMR experiment, (COSY, HMQC, HMBC) and mass spectrometry.

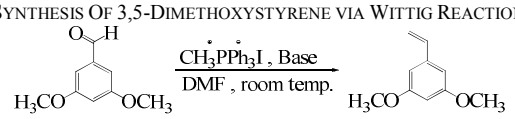
II. Results and Discussion

A. Synthesize of Building Block

We successfully synthesized the building blocks under optimize condition (i.e. 3,5-dimethoxystyrene and 2-iodophenyl-*N*-acetamide). The styrene component is readily obtained by Wittig methodology from the corresponding aldehyde (Table I).

The protecting group can be varied in ways that result in specific radical cation intermediates. The second building block is the protected iodoaniline. The conversion to acetamide requires treatment of the iodoaniline with acetic anhydride under basic conditions[a]. 3,5-dimethoxystyrene was successfully produced in yields of 91.1% (44% in previous report). The yields of the corresponding stilbenes increased pleasingly from 45 % to 97.0 % [8].

TABLE I
Synthesis Of 3,5-Dimethoxystyrene via Wittig Reaction



3,5-Dimethoxybenzaldehyde (A) — 3,5-Dimethoxystyrene

Entry	Base (mol equiv.)	Solvent	Yield[a](%)
A	NaH (3)	DMF[b]	6.6
A	NaH (3)	DMF[c]	16.0
A	t-BuO$^-$ (1)	DMF[b]	0.3
A	t-BuO$^-$ (1)	DMF[c]	91.1

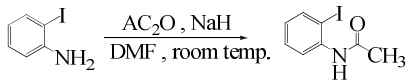
[a] Isolated yields.
[b] The reaction were carried out in non-dry solvent and under nitrogen gas for 24 hrs.
[c] The reaction were carried out in dry solvent and under nitrogen gas for 24 hrs.

K. Ahmad and Mohd A. Nafiah are with the Department of Chemistry, Faculty Science and Mathematics, University Pendidikan Sultan Idris, 35900 TgMalim, Perak. Malaysia (e-mail: kartini@fsmt.upsi.edu.my, azlan@fsmt.upsi.edu.my).

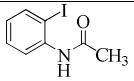
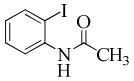
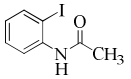
M. Suhaimi was with the Department of Chemistry, Faculty of Science, University of Malaya, 50603 Kuala Lumpur. Malaysia (e-mail: munirah_oni@ siswa.um.edu.my).

Mohamad N. Azmi and K. Awang are with the Department of Chemistry, Faculty of Science, University of Malaya, 50603 Kuala Lumpur. Malaysia (e-mail: Mohamad.azmi@siswa.um.edu.my, khalijah@um.edu.my).

TABLE II
SYNTHESIS OF ACETAMIDE FROM 2-IODOANILINE



2-iodoaniline (B) 2-iodophenyl -*N*-acetamide

Entry	Aryl chloride	Base	Solvent	Amide Precursor	Yield[b](%)
B	AC_2O	NaH	DMF	 **AM1**	71.0
B	AC_2O	NaH	DMF	 **AM1**	95.0
B	AC_2O	NaH	DMF	 **AM1**	97.0

[a]All reaction were performed at optimized condition and under nitrogen for 24 hrs.
[b] Isolated yields.

B. Synthesis of 3,5-dimethoxystilbenes

We successfully synthesized the target stilbene under optimize condition (i.e. 3,5-dimethoxystilbene – *trans* product). The stilbene is readily obtained by palladium-cross coupling reaction (Heck coupling) from the corresponding building blocks.

The palladium-catalysed arylation or alkenylation of olefins is referred to as the Heck reaction. This reaction has become one of the most widely used catalytic carbon-carbon bond forming tools in organic synthesis. The reaction is performed in the presence of an organo-palladium catalyst. The halide or triflate is an aryl, benzyl or vinyl compound and the alkene contains at least one proton and is often electron deficient, such as acrylate ester or an acrylonitrile. The catalyst can be tetrakis(triphenylphosphine)palladium (0), palladium chloride or palladium (II) acetate. The ligand can be triphenylphosphine. The base is triethylamine, potassium carbonate or sodium acetate.

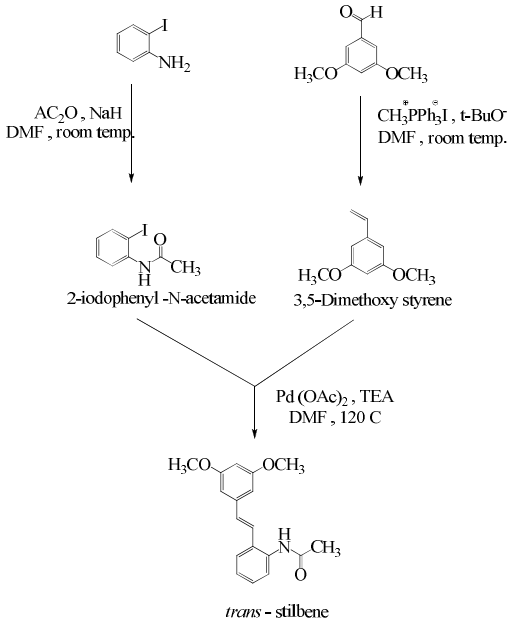
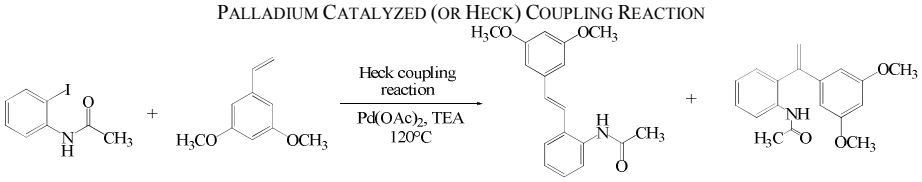


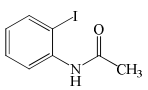
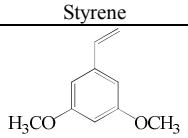
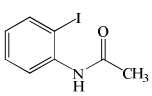
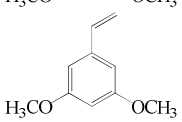
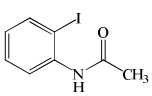
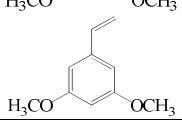
Fig. 1 Synthesis of Stilbene from the Corresponding Building Blocks

Our stilbene was synthesized by applied the modified Heck coupling reaction under nitrogen environment. The 2-iodophenyl-*N*-acetamide was efficiently coupled with the 3,5-dimethoxy styrene in the presence of 1% of palladium (II) acetate[$Pd(OAc)_2$] and three equivalent of triethylamine base in refluxing DMF to afforded the desired *trans*-stilbene in excellence yield (up to 69.1 %) (Table III).

The mechanism of the Heck reaction is not fully understood and the exact mechanistic pathway appears to vary subtly with the changing the reaction conditions. Firstly, a sequence of events beginning with the generation of the active $Pd^{(0)}$ catalyst. The 2-iodophenyl-*N*-acetamide is oxidatively coupling to the coordinatively unsaturated palladium(0) complex and generate a σ–alkenylpalladium (II) complex (Step A) (Fig. 2).

TABLE III
PALLADIUM CATALYZED (OR HECK) COUPLING REACTION



Amide Precursor	Styrene	Time	Yields (%)
		48	21.0 (*trans*)
		24	69.1 (*trans*)
		26	64.0 (*trans*)

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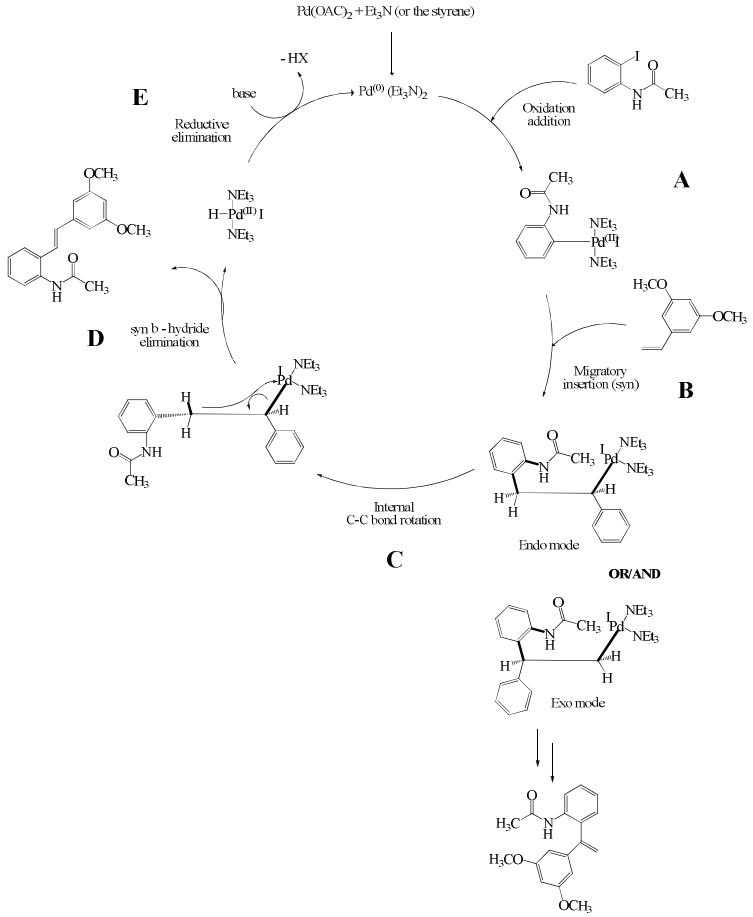

Fig. 2 Mechanism of Formation 3,5-dimethoxystilbene via Heck Reaction

When the alkenyl residue and alkene ligand on palladium are in *cis*-orientation, rotation of the alkene can led to its in-plane coordination and subsequent *syn*-insertion of the σ–alkenylpalladium bond into the C=C double bond occurs to yield a σ–(*β*-alkenyl)alkylpalladium complex via a four-centered transition state (Step B).

The product-yielding *β*–hydride elimination (Step D) can occur only after an internal rotation (Step C) around the former double bond, as it requires at least on *β*–hydrogen to be oriented *syn*-periplanar with the respect to the halopalladium residue. The subsequent *syn*-elimination yielding the 3,5-dimethoxystilbene and a hydridopalladium halide is, however, reversible and therefore the thermodynamically more stable (*E*)-stilbene is generally obtained when the coupling reaction is performed with a terminal alkene (i.e. 3,5-dimethoxystyrene). Reductive elimination of HX from the hydridopalladium halide, aided by the added base, regenerates the active catalyst and thereby (Step E) completes the catalytic cycle.

In the following section, we will attempt (with all due caution) to comment on the mechanistic aspects with one eye on the traditional Heck mechanism (Fig. 2). We will consider alternative modes for the *syn* insertion i.e. *exo* or *endo*; dehydropalladation (E2 Elimination) within a cyclic palladium complex and dehydropalladation (internal base).

In *syn* insertion (Step B) mechanism, two modes of addition can be envisaged. The aryl palladium acetamide complex (or palladacycle) can be attacked by the styrene in either *endo* mode or the *exo* mode (Fig. 3).

An alternative depiction of the mechanism of formation 6 is showed (see Fig. 3). Compound 5 is obtained by "*exo*" carbopalladation of the styrene 2. In this alternative the complex adopts a conformation consistent with *syn* β-hydride elimination via synchronous and non-synchronous pathways. This palladacycle collapses via OAc displacement, rapid hydride transfer and non-synchronous depalladation of the resulting benzyliccarbenium ion.

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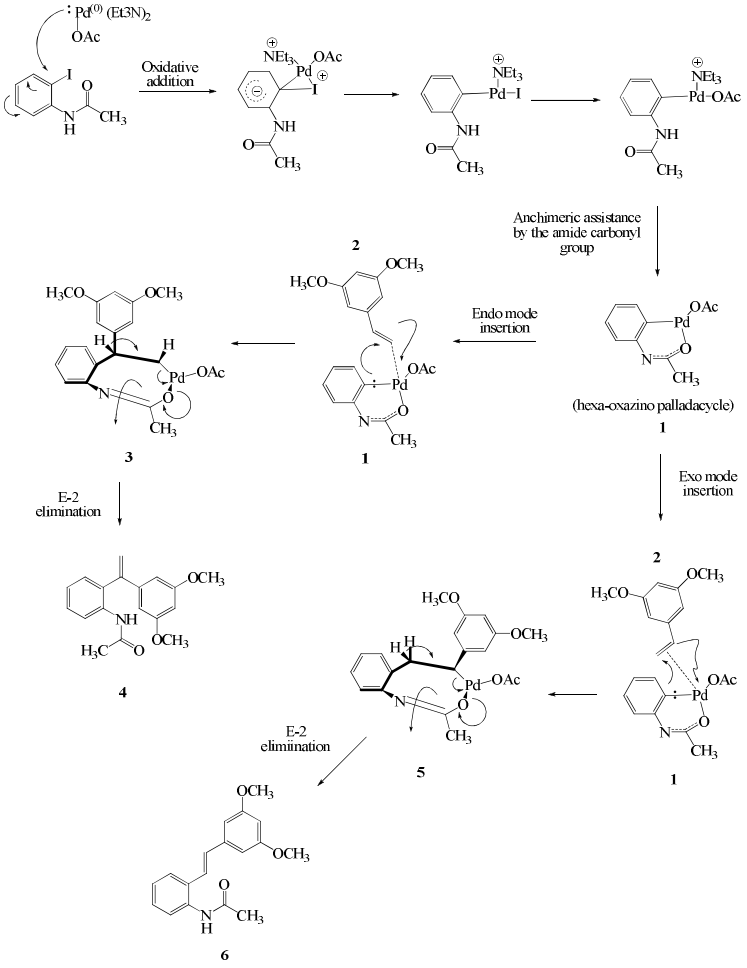

Fig. 3 *Endo*- and *exo*-mode insertion of the styrene into the palladacycle 1 followed by E2 elimination

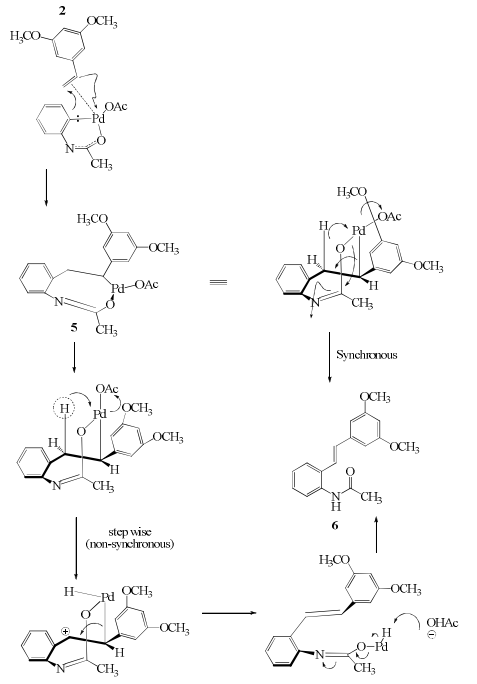

Fig. 4 Alternative proposal - The *syn* β-hydride elimination within an eight membered palladacycle

B. Ferric Chloride Oxidative Coupling on 3,5-Dimethoxystilbenes

The 3,5-dimethoxystilbene was subjected to 'anhydrous' $FeCl_3$ (as opposed to the hydrated salt) oxidation (1:5 molar ratio). The isolable products were the four product; *ortho*acetamidobenzaldehyde10, a dichlorostilbene monomer 11 and two dimers 12 and 13 (Fig. 5), each of the latter contained a clearly intact stilbeneolefinic bond.

We suspect that oxidative cleavage of 18 (for example) leading to water-soluble products (e.g., carboxylic acids) is a major factor for the low yields in these and previously described reactions (Fig. 6).

Previously, this reaction had been done by Kartini et al. and manage to isolate these indolostilbes12 and 13 at a very low yield i.e. 3% and 2% respectively. In this project our focus is to improve the yield by doing some modification on our previous work. For beginning, we repeated this reaction and isolated the indolostilbene 12 and 13 at the 2% and 3% respectively. So, we continue this type of reaction by changing the several parameter i.e. ratio of oxidant ($FeCl_3$), type of solvent, volume of solvent and temperature of reaction. From this reaction and careful examination of the variety of reaction condition leads to a dramatic improvement in yield of the

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indolostilbene 12 and 13 at 11% and a trace amount of *ortho* acetamidobenzaldehyde 10 and a dichlorostilbene monomer 11 (Table IV). In this reaction we used 5.0 equivalent of $FeCl_3$, 50ml dichloromethane and the reaction had been done at room temperature. At this condition we realize the dilute concentration of reaction improve the yield of product and also involve in the radical cations reaction.

In this radical reaction the maximum ratio between stilbene and oxidant is 1:5 and by increasing the ratio of oxidant showed the dramatically decrease of target molecules and also the stilbene will be decomposed. Furthermore, the room temperature and dichloromethane was the good conditions for this reaction because they were responsible to the formation of chlorophenylindole, an intermediate to the formation of indolostilbene12 and 13.

In examining 12 and 13, two stereogenic axes (biaryl linkages) have been installed. This is a unique structural feature (when set in the context of an arrangement incorporating biphenyl, stilbene and indole moieties in the same molecule) although other oxidative methods for constructing the biaryl linkage are known. The spectroscopic analysis had been done and the results had been shown in Table V.

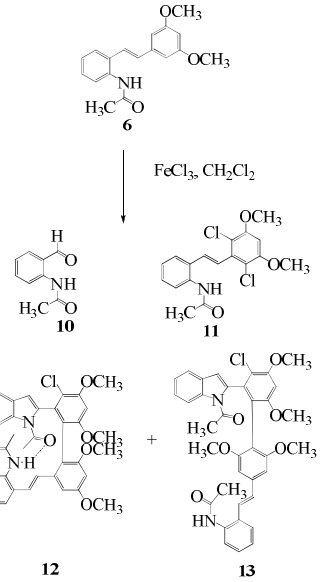


Fig. 5 The effect of 3, 5-dimethoxy substitution on the oxidation dimerization of stilbene

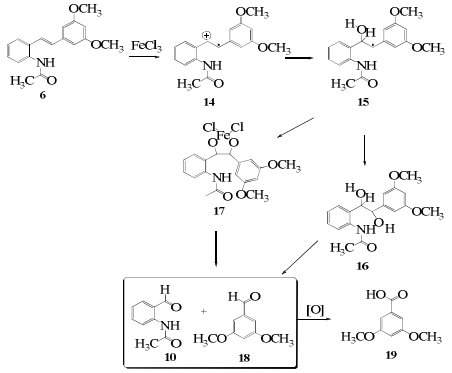
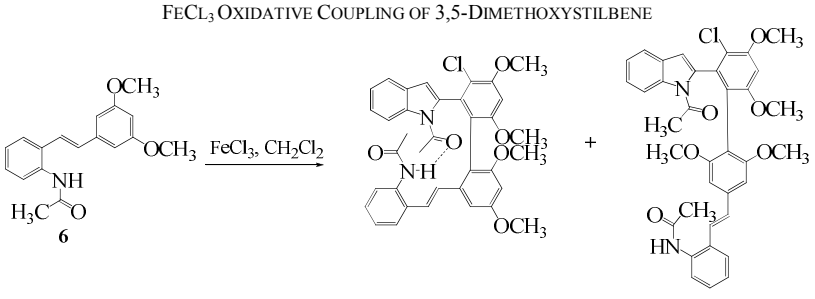


Fig. 6 Possible mechanistic pathways for the oxidative cleavage of stilbene

TABLE IV
$FeCL_3$ OXIDATIVE COUPLING OF 3,5-DIMETHOXYSTILBENE



Entry	Stilbene (equiv)	Conditions	Yield[b] % (Indolostilbene**12**)	(Indolostilbene**13**)
1[a]	1.0	$FeCl_3$ (5.0 equiv), DCM (10 ml), rt	3	2
2	1.0	$FeCl_3$ (5.0 equiv), DCM (10 ml), rt	2	3
3	1.0	$FeCl_3$ (5.0 equiv), DCM (50 ml), rt	11	11
4	1.0	$FeCl_3$ (5.0 equiv), DCM (50 ml), 0-4°C	3	2
5	1.0	$FeCl_3$ (7.0 equiv), DCM (50 ml), rt	5	5
6	1.0	$FeCl_3$ (10.0 equiv), DCM (50 ml), rt	4	4

[a] Data from previous publication.
[b] Isolated yields by column chromatography.

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TABLE V
^{1}H NMR [600 MHZ, δH (*J*, HZ)] AND ^{13}C NMR [150 HZ, δC] IN $CDCL_3$

	Indolostilbene A **12**		Indolostilbene B **13**	
	[M^++Na]= (calculated)		[M^++H]= (calculated)	
No.	^{1}H (*J* Hz)	^{13}C	^{1}H (*J* Hz)	^{13}C
1	-	138.5	-	138.1
2	-	115.6	6.51 (*s*)	101.8
3	-	157.1	-	158.2
4	6.11 (*s*)	97.6	-	113.2
5	-	159.7	-	157.6
6	6.50 (*s*)	102.0	6.51 (*s*)	102.5
7	6.69 (*d*, *J*= 15.8 Hz)	130.6	6.82 (*d*, *J*= 16.4 Hz)	133.1
8	6.87 (*d*, *J*= 15.9 Hz)	128.1	7.00 (*d*, *J*= 15.8 Hz)	123.8
9	-	129.9	-	130.1
10	-	135.1	-	134.6
11	7.87 (*d*, *J*= 7.8Hz)	124.5	7.81 (*d*, *J*= 8.1 Hz)	124.1
12	7.34 (*t*, *J*= 7.0 Hz)	128.1	7.31 (*t*, *J*= 7.0 Hz)	128.4
13	7.13 (*t*, *J*= 7.4 Hz)	126.8	7.13 (*t*, *J*= 8.1 Hz)	125.5
14	7.87 (*d*, *J*= 7.8 Hz)	127.6	7.39 (*d*, *J*= 6.5 Hz)	127.1
1’	-	133.9	-	134.6
2’	-	120.1	-	118.7
3’	-	155.9	-	157.3
4’	6.75 (*s*)	96.9	6.74 (*s*)	97.5
5’	-	155.0	-	155.2
6’	-	115.2	-	115.4
7’	-	135.9	-	135.5
8’	6.45 (*s*)	112.2	6.39 (*s*)	111.3
9’	-	128.5	-	129.0
10’	-	136.0	-	136.9
11’	8.07 (*d*, *J*= 8.2 Hz)	115.3	8.37 (*d*, *J*= 8.2 Hz)	116.9
12’	7.24 (*t*, *J*= 7.8 Hz)	124.4	7.24 (*t*, *J*= 8.0 Hz)	124.6
13’	7.17 (*t*, *J*= 6.6 Hz)	123.1	7.18 (*t*, *J*= 7.0 Hz)	123.1
14’	7.43 (*d*, *J*= 7.4 Hz)	119.9	7.43 (*d*, *J*= 6.6 Hz)	120.2
3-OCH_3	3.61 (*s*)	55.0	3.76 (*s*)	55.7
5-OCH_3	3.70 (*s*)	54.8	3.64 (*s*)	55.2
3’-OCH_3	3.88 (*s*)	56.1	3.80 (*s*)	56.5
5’-OCH_3	4.02 (*s*)	55.9	4.02 (*s*)	56.4
NHCO-CH_3	2.36 (*s*)	23.7	2.19 (*s*)	24.5
NCO-CH_3	1.89 (*s*)	25.9	2.35 (*s*)	25.2
NHC=O	-	169.3	-	168.7
NC=O	-	171.8	-	171.4
-NH	8.92 (s)	-		

C. Mechanism Study

The 3,5-dimethoxy derivative produced the aldehyde **10**, dichlorostilbene**11** and the unprecedented indolostilbene dimers 12 and 13. The low yield of the *ortho*-acetamidobenzaldehyde 10 suggested to us the minor pathway for its formation as described in Fig. 6. An alternative pathway that involves the oxygen diradical leading to the dioxetane 21 is shown in Fig. 7.

The dichlorostilbene monomer 11 could be explained as the product of an electrophilic substitution either via an intermolecular pathway (Fig. 8) or the intramolecular alternative (the azaquinodimethyde 24 intermediate) (Fig. 9). Alternatively a radical cation pathway (Fig. 10) may be proposed. Chlorination at C-4 in 6 appears to be prohibited for steric reasons. Figs. 8 and 9 depict an electrophilic chlorination mechanism. An alternative mechanism that depends on prior generation of the radical cation14 and clearly implies the presence of chloro radicals (·Cl) is shown in Fig. 10.

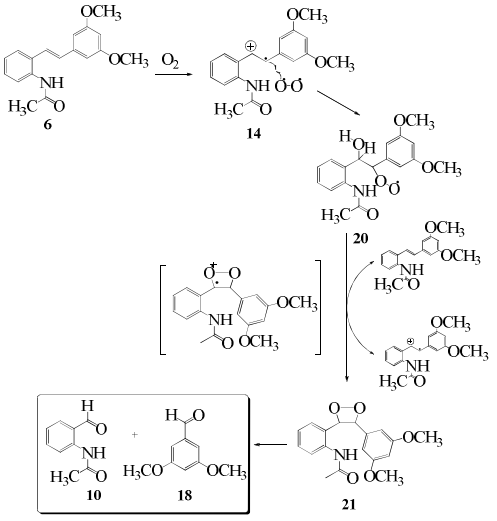

Fig. 7 Hypothesised interaction of the radical cation 14 with the oxygendiradical leading to aldehydes 10 and 18

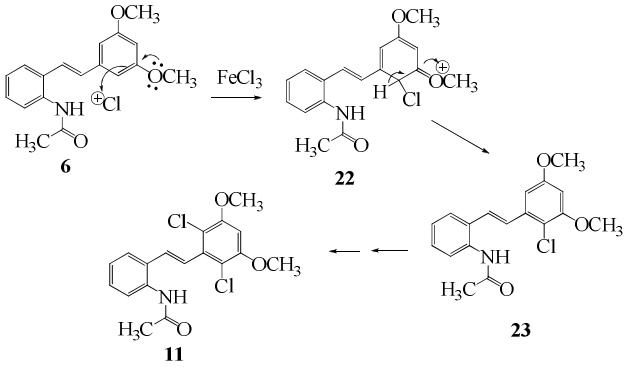

Fig. 8 Mechanistic interpretation of the electrophilic chlorination of stilbene **6**

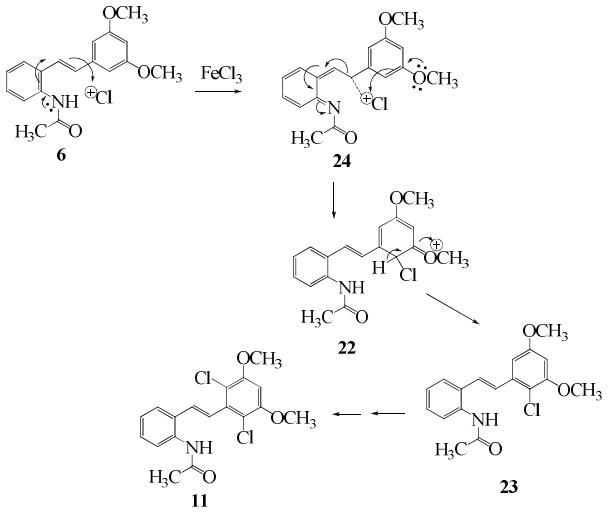

Fig. 9 Indirect pathway (intramolecular)

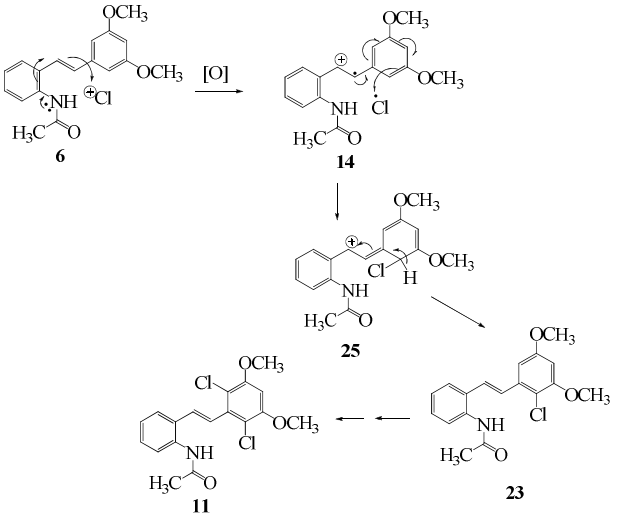

Fig. 10 The chloro-radical alternative

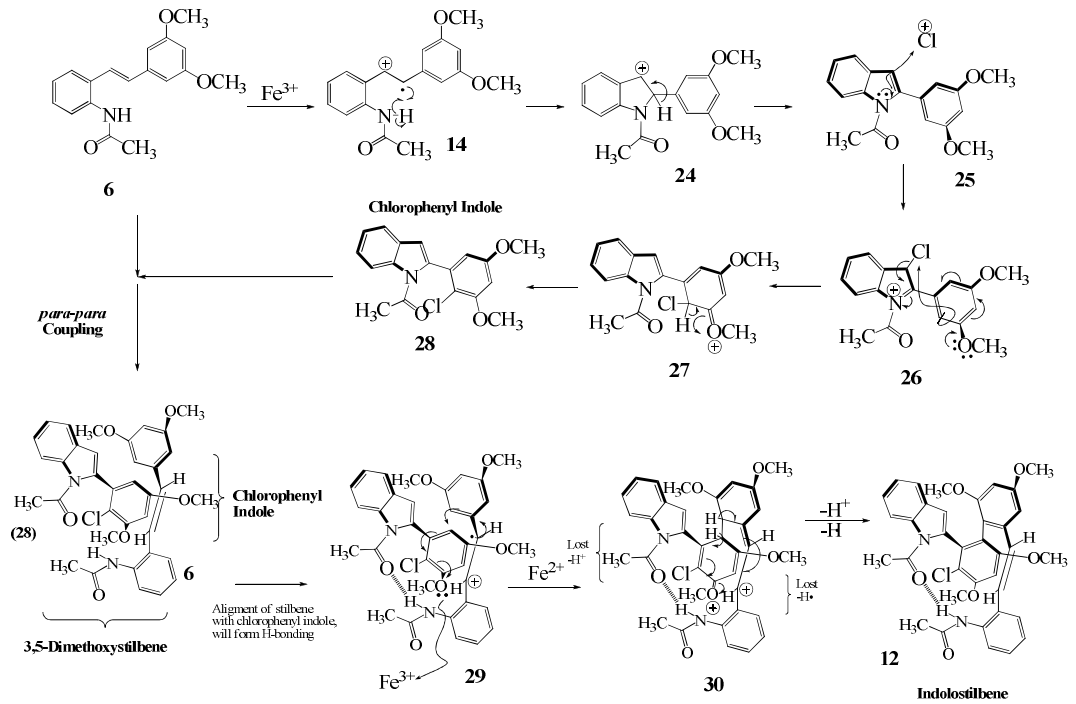

Fig. 11 Oxidative coupling of the stilbene radical cation with **28** leading to Pseudo-macrocycle**12**

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For the formation of indolostilbene **12** and **13**, the 3,5-dimethoxy analogue appears to undergo the deprotonation necessary for indole **25** formation, as opposed to the indoline. This allows us to suggest another way of visualizing the chlorination step. In this alternative, electrophilic chlorination proceeds in contrast to the reactions in Figs. 8-10, via the indolenium species **26**, Fig. 11. Compound **28** is of course a racemate (assuming restricted rotation).

Fig. 11 describes the pathway leading from **28** to the indolostilbene. The alignment of the acetamidostilbene**6** with the chlorophenylindole **28** is guided; it would seem, by hydrogen bonding. Removal of an electron from the olefinic bond of **6** produces the radical cation**29**, which attacks the chlorophenylindole **28** as shown. Removal of an electron from the methoxy lone pair sets up the *para–para* (or *ortho–ortho*) oxidative coupling. This accounts for the installation of the stereogenic axes between rings B and D.

The H-bonded conformational isomer (one of the most stable arrangements but see Fig. 13) (heat of formation of –134.29 kcalmol^{-1}) with a 2.02 Å hydrogen bond length (Fig. 12) is in effect a pseudomacrocycle. An alternative arrangement that has a different stilbene double bond orientation and a H-bond length of 2.20 Å is the conformational isomer (Fig. 13) that has a lower heat of formation (–139.28 kcalmol^{-1}). 3D-representation of these conformations was obtained by PM623/MOPAC200724 determinations and is provided in Figs. 12 and 13.

The formation of the second dimer **13** is the result of an analogous radical cation mediated *ortho–para* coupling (Fig. 15). Intramolecular hydrogen bonding is clearly impossible in this case. The PM623/MOPAC200724 determined heat of formation (the lowest) is -123.41 kcal mol^{-1} (Fig. 14). PM623/MOPAC200724 calculations indicate the most stable conformational isomers.

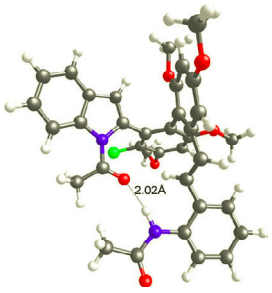

Fig. 12 The 3-D representation (enthalpies of formation data) for the indolostilbeneas Determined by PM6/MOPAC2007

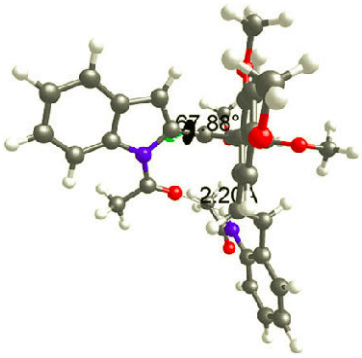

Fig. 13 The 3-D representation (enthalpies of formation data-lower energy) for the indolostilbene (an alternative conformational isomer) as determined by PM6/MOPAC2007

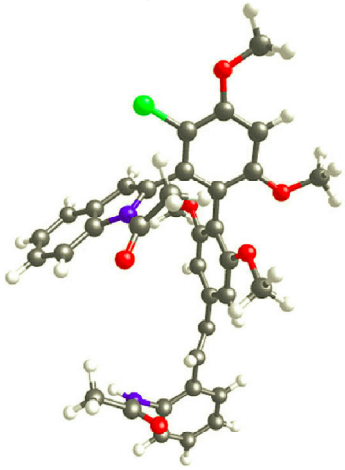

Fig. 14 The 3-D representation (enthalpies of formation data) for the indolostilbene as determined by PM6/MOPAC2007

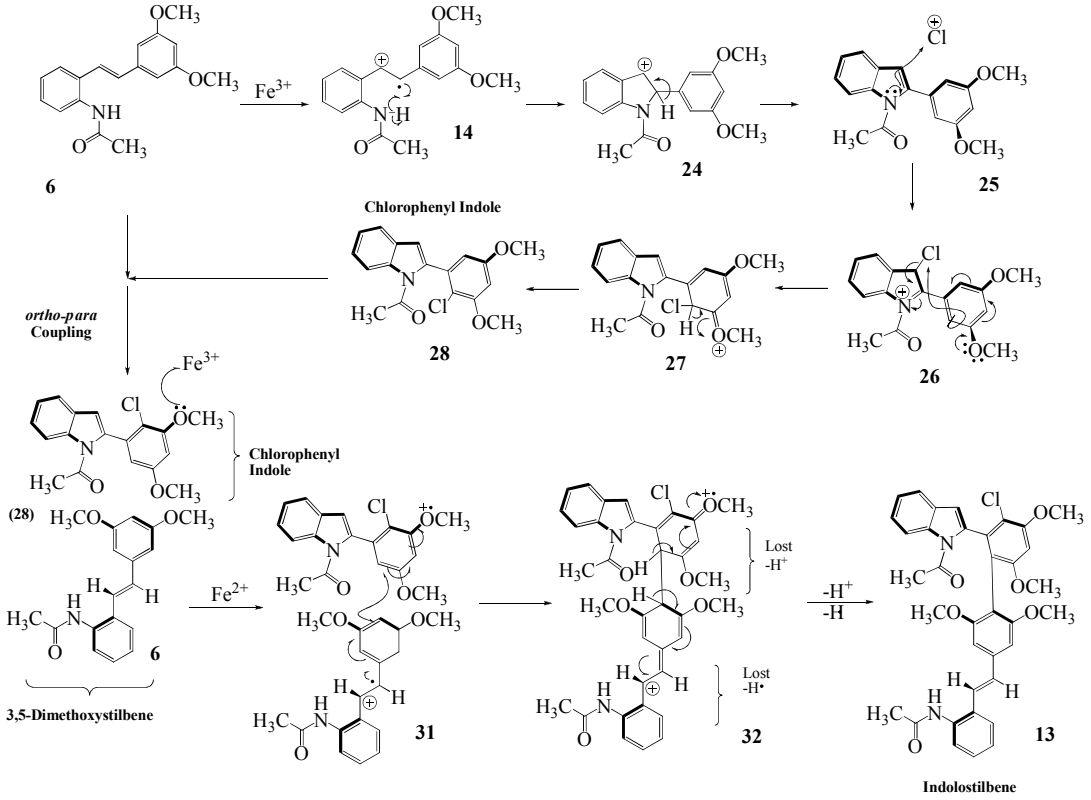

Fig. 15 Oxidative coupling of the stilbene radical cation with **28**leading to indolostilbene**13**

III. Conclusion

This study explains the formation of a new class of axially chiral (racemic) indolostilbenes by a $FeCl_3$-promoted radical cation mediated cascade reaction. We also anticipate that success in generating axially chiral indolostilbenes in good yield would not only demonstrate that this is a valuable procedure for preparing members of this new class of indolostilbenes. An orthogonal arrangement of aromatic rings about a stereogenic axis has been shown to be a critical factor in any biological properties.

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