3 Syntheses

3.1 Synthesis of Stilbene Derivatives

A variety of synthetic methods have been employed to prepare stilbene and stilbene derivatives with substituted aromatic rings. A review article dealing specifically with stilbene synthesis was presented by Becker in 1983, which summarized and classified the vast number of synthetic methods applicable to the synthesis of stilbene and stilbene derivatives substituted in the aromatic ring as four types [Becker, 96]: (1) Stilbenes by oxidation, reduction, or elimination reactions from other diaryl compounds; (2) Symmetric stilbenes by dimerization reactions; (3) Coupling of aromatic compounds with styrenes and other vinylarenes; (4) Condensation of a nucleophilic with an electrophilic arylmethyl compound. Despite great development in the last twenty years this classification covers still a wide range. Among them, however, there are only few reactions which can tolerate a large number of functional groups in different positions on the aromatic ring. Wittig reaction by condensation of a phosphorus-stabilized carbanion with an aryl aldehyde as one method of the type (4), because of the ready availability of the starring materials, the simple and mild reaction conditions and the broad applicable scope, is probably up to now the most popular method for the synthesis of stilbenes. Besides, the one-step reductive coupling from aryl aldehydes to stilbenes as one of the dimerization reactions (2) is often used for the preparation of symmetrical stilbenes.

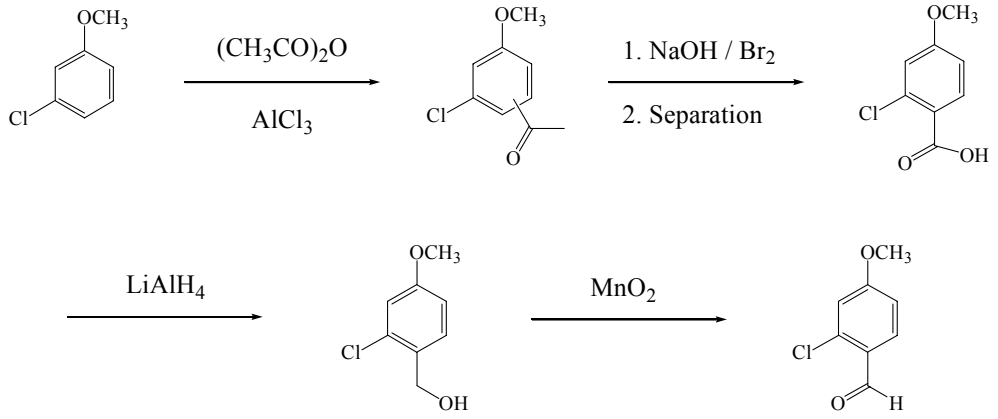
In the present work some asymmetrical dimethoxystilbenes are prepared by Wittig reaction and the others, symmetric dimethoxystilbenes and especially serveral asymmetric hydroxy-methoxy-stilbenes, are obtained by reductive coupling of the corresponding aryl aldehydes with low-valent titanium reagents.

3.1.1 Synthesis of dimethoxystilbenes

3.1.1.1 Preparation of chloro-substituted 4-methoxybenzaldehydes

Several commercially not available aryl aldehydes such as 2-chloro-4-methoxy-benzaldehyde und 2,6-dichloro-4-methoxybenzaldehyde are essential for the preparation of the desired stilbenes either by Wittig reaction or by reductive coupling. These compounds can be synthesized starting from the corresponding chloro-substituted anisoles over multisteps

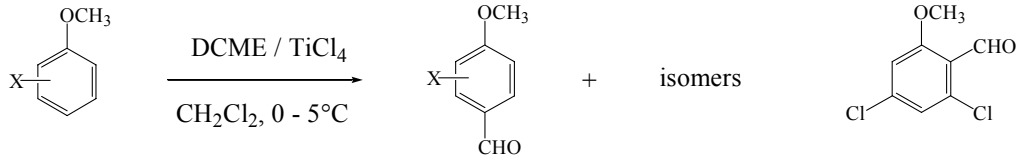
according to earlier publications [von Rauch, 97; Wiglenda, 98]. For example, the synthesis of 2-chloro-4-methoxybenzaldehyde was performed as shown in scheme 9:



Scheme 9

This procedure for preparing the desired benzaldehyde seemed to be strenuous and uneconomical. Therefore we tried to carry out a direct formylation of chloro-substituted anisole with a reactive formylation reagent, *i.e.* the combination of dichloromethyl methyl ether (DCME) and titanium tetrachloride. This well-known reagent has been widely applied to prepare substituted benzaldehydes from corresponding phenyl derivatives [Simchen, 99]. However, to our knowledge, no chloro-substituted benzaldehyde was synthesized by means of this formylation method in the previous literatures.

In fact, the chloro-substituted anisole **1** or **2** could be smoothly formylated with DCME / $TiCl_4$ according to the literature procedure [Fanghänel, 100] to give a mixture of the desired benzaldehyde **3** or **4** and their isomers (Scheme 10).



1, 2 **3, 4** **5**

Compound	1	2	3	4
X	3-Cl	3,5-Cl_2	2-Cl	2,6-Cl_2

Scheme 10

The procedure is very simple. Titanium tetrachloride and dichloromethyl methyl ether were added successively and carefully to a stirred solution of the corresponding chloro-substituted anisole in dry dichloromethane at 0°C. After stirring for 30 minutes at this temperature, the reaction mixture was hydrolyzed by adding chopped ice and then extracted with dichloromethane. The residue obtained from the organic phase was purified or separated by column chromatography on silica gel and recrystallization to gain the desired products.

The benzaldehyde **3** and its isomers could not be separated by column chromatography on silica gel, but through which some unknown colourless substance and polar side products, which are disadvantageous for followed recrystallization, could be removed. Then the benzaldehyde **3** was easily recrystallized from ligroin by cooling in a refrigerator to obtain the analytic pure product as colourless needles. Whereas the benzaldehyde **4** and its isomer **5** could be separated only by chromatography on silica gel with a mixture of dichloromethane and ligroin as eluent.

The benzaldehydes **3**, **4** and **5** were characterized by NMR spectroscopy.

In the ^{1}H NMR spectrum of **3**, a singlet assigned to formyl proton is observed in the typical field at 10.34 ppm. The signals of three aromatic protons appear at 6.90, 6.94 and 7.90 ppm. A singlet at 3.88 ppm indicates the presence of the methoxy group. These are consistent with those described in literature [von Rauch, 97; Wiglenda, 98]. One of the isomers of **3**, as a main by-product, establishes five signal groups at 3.94(s), 6.99, 7.02, 7.77 and 10.40(s) ppm similar to that of **3** in its ^{1}H NMR spectrum taken in $CDCl_3$. It is difficult to purify this by-product, so the position of the formyl group on the phenyl ring remains unconfirmed.

The structures of the benzaldehyde **4** and **5** were simply distinguished by comparing their ^{1}H NMR spectra. A significant difference between them lies in the resonances of the aromatic protons. The two aromatic protons of **4** are chemically equivalent and appear in the ^{1}H NMR spectrum together as a singlet at 6.92 ppm, whereas those of **5** are chemically non-equivalent and appear as two doublets with a coupling of 1.7 Hz separately at 6.91 and 7.07 ppm. The signals of the formyl protons of **4** and **5** are observed in similar shifts at 10.42 and 10.44 ppm, respectively.

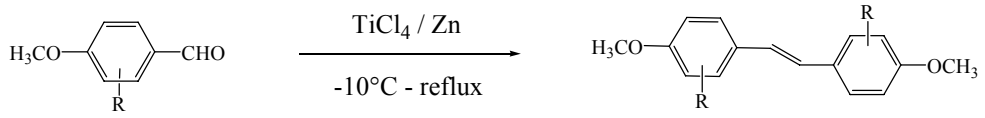
The synthesis of **3** and **4** depicted in scheme 10 is an improvement over the above-mentioned multistep methods.

3.1.1.2 Synthesis of symmetric dimethoxystilbenes

A number of symmetric stilbene derivatives can be synthesized by the "McMurry Reaction", a reductive coupling reaction from aldehydes and ketones with low-valent titanium reagents to alkenes. The "McMurry Reaction" was first reported independently between 1973 and 1974 by Tyrlik, Mukaiyama, and McMuurry *et al*. but greatly extended by McMurry who used $TiCl_3$ / $LiAlH_4$ to generate the low-valent titanium species and further elaborated upon it [Lenoir, 101; McMurry, 102]. Some substituted benzaldehydes having adjacent acyloxy, carbomethoxy or tosyloxy groups have been coupled to corresponding symmetric stilbenes using $TiCl_3$ / Zn-Cu [Castedo, 103]. Several symmetric *E*-polymethoxystilbenes were also obtained by reductive coupling of the corresponding methoxybenzaldehydes with $TiCl_4$ / Zn [Ali, 104].

Aromatic halides do not interfere with the coupling reaction if the correct conditions are used. For example, the coupling of 4-chlorobenzaldehyde with $(cyclopentadienyl)_2Ti(CO)_2$ in THF to 4,4'-dichlorostilbene [Chen, 105] and the coupling from 4-bromobenzaldehyde with $TiCl_3$ / Li to 4,4'-dibromostilbene [Richardson, 106] were reported. In addition, *E*-2,2',6,6'-tetrachloro-4,4'-dimethoxystilbene could also be prepared by the reductive coupling of 2,6-dichloro-4-methoxybenzaldehyde with $TiCl_4$ / Zn in dioxane [Schertl, 92]. But under this condition *E*-2,2',6'-trichloro-4,4'-dimethoxystilbene was observed as a side product by cleavage of one chloro-substituent of the designed product [Schertl, 92].

Based on the above-mentioned published results, several symmetric methoxystilbenes bearing aromatic halides needed in this work were prepared in satisfactory yields from the corresponding benzaldehydes with $TiCl_4$ / Zn (Scheme 11):



3, 4, 6, 7 **8 - 11(*E*)**

Compound	**6**	**7**	**8**	**9**	**10**	**11**
R	H	2-F	H	2-F	2-Cl	2,6-Cl_2

Scheme 11

The classic procedure is that zinc power was added in small portions to a mixture of $TiCl_4$ and the carbonyl materials in a solvent [Mukaiyama, 107; Lenoir, 108]. In order to achieve a more reactive $TiCl_4$ / Zn coupling reagent, we adopted the following procedure modified by Coe et al.[Coe, 109]: $TiCl_4$ was added to a suspension of zinc power in dry tetrahydrofuran

followed by a short reflux period and to which the carbonyl materials was added. Then the reaction mixture was refluxed for 2 - 4 hours. After cooling the mixture was poured into ice-water and worked up. The crude products were purified by recrystallization or column chromatography on silica gel.

The synthesis of stilbenes **8**, **9** and **10** was successfully performed according to this modified procedure without cleavage of halogen atom and exclusively gave *trans* geometry of stilbenes as others reported in literature [Ali, 104; Mukaiyama, 107]. The *E*-form stilbenes **9** and **10** could be easily extracted with diethyl ether after coupling reaction and the crude products were recrystallized from ligroin / tetrahydrofuran, whereas **8** which is only slightly soluble in diethyl ether was extracted with heated dichloromethane instead of diethyl ether and recrystallized from chloroform by cooling in a refrigerator to give the pure product as colourless leaflets. However, the compound **11** surprisingly could not be obtained under the same conditions, under which a product isolated with relative great quantities was also neither the corresponding pinacol nor the chloro-cleavaged stilbene and remained unknown. The preparation of **11** was finally accomplished using $TiCl_4$ / Zn but in dioxane according to the above-mentioned literature procedure [Schertl, 92].

The structures of the stilbenes **8 - 11** were confirmed by NMR and mass spectra as well as elemental analyses.

The ^1H NMR spectra of **8 - 11** show only the resonances of moiety of each compound due to the symmetric character of their structures (see Table 1).

Table 1. ^1H NMR Spectral Properties of Stilbenes **8 - 11**

Compound	Chemical Shifts (ppm, in $CDCl_3$)		
	CH=CH	Aromatic-H	OCH_3
8	6.93(s)	6.88, 7.42	3.82(s)
9	7.13(s)	6.62(dd), 6.70(dd), 7.52(dd)	3.81(s)
10	7.29(s)	6.84(dd), 6.93(d), 7.63(d)	3.81(s)
11	7.05(s)	6.94(s)	3.81(s)

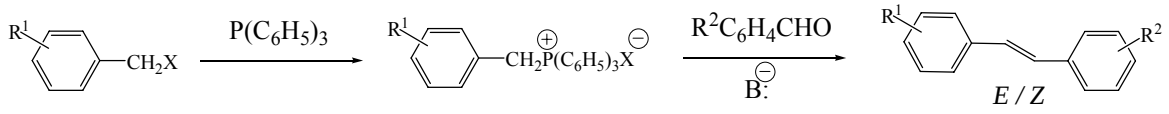
The signals of olefinic protons are shown as a singlet with a chemical shift in the range of 6.93 - 7.29 ppm. The signal of the methoxy group appears as a singlet at 3.81 or 3.82 ppm. Whereas the different signals of aromatic protons indicate the different substituents on the phenyl ring and their figures are consistent with those of the corresponding starting benzaldehyde with only different chemical shifts. For instance, the signals of the aromatic

protons of **9** or **10** are observed as the same three groups as those of the starting benzaldehyde **7** (R = 2-F) or **3** (R = 2-Cl) at higher field (see Table 1) compared with those of **7** at 6.64, 6.78 and 7.83 ppm or **3** at 6.90, 6.94 and 7.90 ppm.
The mass spectra and elemental analyses of **8 - 11** support the above-depicted structures.

3.1.1.3 Syntheses of asymmetric dimethoxystilbenes

An attempt to prepare asymmetric 2-chloro-4,4'-methoxystilbene was carried out as well by reductive coupling from anisaldehyde and benzaldehyde **3** with $TiCl_4$ / Zn in tetrahydrofuran. The desired stilbene was obtained in 24% yield after separation of the formed stilbene mixture by column chromatography on silica gel. An other similar attempt afforded 2,6-dichloro-2'-fluoro-4,4'-dimethoxybenzaldehyde in 15% yield. Compared to the synthesis by Wittig reaction described hereinbelow, the coupling method for the desired asymmetric dimethoxystilbenes seemed not to be of significantly synthetic value on account of the low yields and the difficulties of separation.

The classic version of the Wittig reaction is depicted in scheme 12: Benzyl halide is treated with triphenylphosphine to afford benzyltriphenylphosphonium halide, which is deprotonated using a strong base to the corresponding phosphorus ylid and then treated with aryl aldehyde to yield the stilbene. The stilbene is usually formed as a mixture of (*E*)- and (*Z*)-isomers together with triphenylphosphine oxide.

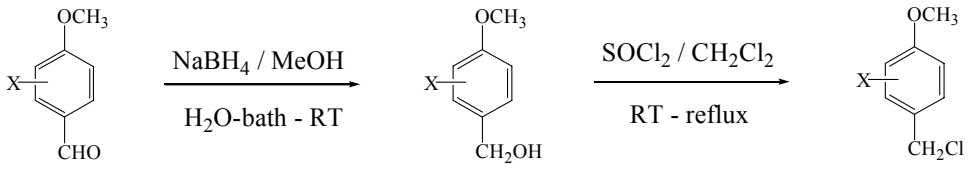


Scheme 12

Several asymmetric dimethoxystilbenes needed in this work have been successfully prepared by Wittig reaction in the literature [Schertl, 92]. Under similar conditions we have synthesized not only these familiar but some new dimethoxystilbenes.

3.1.1.3.1 Preparation of benzyl chlorides

The preparation of the benzyl chlorides required for the following reaction with triphenylphosphine and aryl aldehydes to dimethoxystilbenes is depicted in scheme 13:



3, 12 **13, 14** **15**, **16**

Compound	**12**	**13**	**14**	**15**	**16**
X	F	F	Cl	F	Cl

Scheme 13

It is known that 2-fluoro-4-methoxybenzaldehyde **12** can be reduced with sodium borohydride to the benzyl alcohol **13** [Tierling, 110]. According to this route we have smoothly accomplished the reduction of **12** and **13** with excessive sodium borohydride in methanol at room temperature for 1 hour to obtain the benzyl alcohols **13** and **14** in high yields of 98% (both). Because of the relative vigorous reaction between sodium borohydride and methanol, more sodium borohydride (2 ~ 5 molars to benzaldehyde of 1 molar) was necessary and during the addition of both starting materials to methanol the reaction was controlled by cooling in a water bath. After the complete reaction the mixture was diluted with water and extracted with diethyl ether. The residue obtained from the ethereal phase was analyzed to be the pure product, which could be directly used for the following reactions. Previously the reduction of **12** with sodium borohydride was attempted in ethanol as solvent. Due to the less solubility of sodium borohydride in ethanol the reaction ran slowly and was incomplete in spite of using 2 molars sodium borohydride to 1 molar benzaldehyde **12** and heating. In addition, certain acetal product was found after separation of the mixture of products by column chromatography on silica gel.

In the ^{1}H NMR spectra of **13** and **14**, the disappearance of the formyl signals and the appearance of the signals of a methylene group and a hydroxy group indicate the successful reduction. The signals of the methylene and hydroxy protons are observed to have a great differentiation in the ^{1}H NMR spectra taken in $CDCl_3$ or in DMSO-d_6. In $CDCl_3$ the signals of both groups of **13** appear as two singlets at 1.64 (OH) and 4.68 (CH_2) ppm, whereas in DMSO-d_6 they appear at 5.10 ppm (OH) as a triplet and 4.44 ppm (CH_2) as a doublet with a coupling constant of 5.6 Hz and this coupling disappears after proton exchange of hydroxy group with D_2O. Such a difference is also observed in the ^{1}H NMR spectra of **14**.

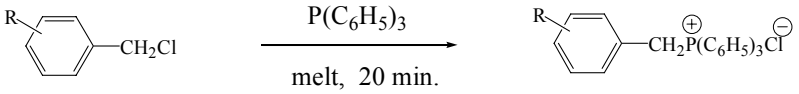
The benzyl alcohols **13** and **14** could be easily converted to the corresponding benzyl chlorides **15** and **16**. In the earlier literature [Gust, 94] a good method for the preparation of

16 was reported by treatment of **14** with hydrochloride gas in dry benzene. In the present work the conversion of the benzyl alcohols **13** and **14** to the benzyl chlorides **15** and **16** was accomplished using thionylchloride in dichloromethane in high yields of 91 - 94% by heating to reflux for 6 hours. The derivation of reagents lay in the easier operation and less danger of thionylchloride and dichloromethane as against hydrochloride gas and dry benzene. After the complete reaction the mixture was neutralized with a solution of 10% $NaHCO_3$ and extracted with diethyl ether. The residue obtained from the ethereal layer was purified by column chromatography on silica gel with a mixture of dichloromethane and diethyl ether (5 : 1) as eluent.

The ^1H NMR spectra of **15** and **16** show the similar signals as those of **13** and **14** only without the signal of hydroxy proton. The mass spectra support the presented structures.

3.1.1.3.2 Preparation of benzyltriphenylphosphonium chlorides

The preparation of the benzyltriphenylphosphonium chlorides **19 - 22** depicted in scheme 14 were performed from the benzyl chlorides **15 - 18** and triphenylphosphine according to the known procedure [Schertl, 92]:



15 - 18 **19 - 22**

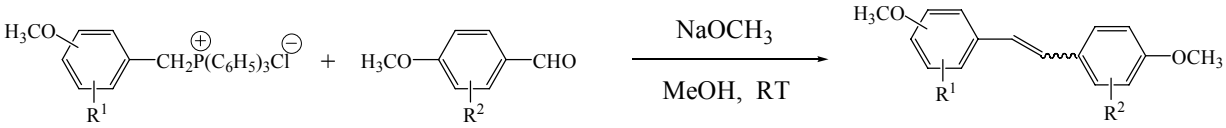
Compound	17	18	19	20	21	22
R	3-OMe	4-OMe	3-OMe	4-OMe	2-F-4-OMe	2-Cl-4-OMe

Scheme 14

The corresponding benzyl chloride and triphenylphosphine were mixed and melted under nitrogen for 20 minutes. After cooling the crude product was purified by treatment with diethyl ether to remove the non-transformed materials. It was found that the suspending and washing procedure got easy and rapid, if the crude product was first dissolved in a little amount of chloroform before the addition of ether. Drying and storage of the product should be under exclusion of air humidity.

3.1.1.3.3 Condensation of benzyltriphenylphosphonium chlorides with benzaldehydes by Wittig reaction to dimethoxystilbenes

The condensation of compounds **19** - **22** with the benzaldehydes **3**, **4**, **6** and **7** were performed in dry methanol in the presence of $NaOCH_3$ at room temperature [Schertl, 92] to give asymmetrical stilbenes **23** - **29** as a mixture of *E* and *Z* isomers as usual (Scheme 15):



19-22 **3, 4, 6, 7** **23-29 *E* / *Z***

Compound	OCH_3	R^1	R^2	Form	Yields* (%)
23	4-	2-F	H	*E* / *Z*	47 / 25
24	4-	H	2-Cl	*E* / *Z*	54 / 7
25	4-	2-F	2-Cl	*E* / *Z*	47 / 35
26	4-	2-F	2,6-Cl_2	*E*	69
27	4-	2-Cl	2,6-Cl_2	*E*	52
28	3-	H	2-F	*E* / *Z*	51 / 30
29	3-	H	2-Cl	*E* / *Z*	52 / 34

* isolated yields without optimization

Scheme 15

The *E*-form stilbenes as major isomers in this conversion were less soluble in methanol than the *Z*-form stilbenes and sedimentated from the reaction solution already in a short time after addition of $NaOCH_3$ (except **28** and **29)**. After the reaction being complete (2 - 24 hours), a quarter volume of water calculated from that of methanol was slowly added under stirring and the resulting mixture was stirred for further 30 minutes, followed by the separation and purification of *E*- and *Z*-form products.

Most of the stilbenes **23*E***, **24*E*, 26*E*** and **27*E*** were precipitated from the solution of methanol and water (4 / 1) as pure crystals, which were isolated by suction filtration and washed with 80% methanol. The filtrates containing the rest of *E*- and *Z*-form stilbenes **23**, **24, 26** and **27** as well as the by-product triphenylphosphine oxide were extracted with diethyl ether, respectively. The separation of the residue from the ethereal layer of **23** by column chromatography on silica gel with a mixture of ligroin and dichloromethane (1 : 1) as eluent

gave only a mixture of *E*- and *Z*-isomer. The crystalline **23*E*** was less soluble in ligroin, while **23*Z*** as oil was well soluble. Thus by repeated treatment of the isomer mixture with ligroin the *E*-isomer was isolated as colorless crystals precipitated in cooled ligroin, while the *Z*-isomer left in the solvent was isolated as colorless oil after removal of the solvent. The residue from the ethereal phase of **24** was suspended in a mixture of ligroin and diethyl ether (5 : 1) and the by-product triphenylphosphine oxide as precipitate was isolated by suction filtration. The filtrate was evaporated and the residue was separated into **24*E*** and **24*Z*** by column chromatography on silica gel with the same mixture as eluent. After isolation of **26*E*** and **27*E***, the rest *E*- and *Z*-isomers of **26** and **27** could be separated according to Schertl *et al* [Schertl, 92]. In the present work, **26*Z*** and **27*Z*** were too little to isolate.

Contrary to the hereinabove described stilbenes **23*E***, **24*E***, **26*E*** and **27*E***, the stilbenes **25*E***, **28*E*** and **29*E*** could not simply isolated from the solution of methanol and water. The reaction mixtures were separately extracted with diethyl ether. The stilbenes **25*E*** and **25*Z*** in the ether extract were obtained as described for **23** by column chromatography with ligroin and dichloromethane (3 : 2) as eluent to gain a isomer mixture and followed by repeated treatment with ligroin based on the different solubility of **25*E*** as crystals und **25*Z*** as oil in ligroin. Whereas the separation and purification of **28*E*** and **28*Z*** in the residue of the ethereal phase were performed by column chromatography on silica gel. A mixture of ligroin and dichloromethane (1 : 1) was used as eluent to obtain an isomer mixture, which was separated into pure *E*- and *Z*-isomers as colorless oil with a mixture of ligroin and diethyl ether (5 : 1) as eluent. The same method as described for **28** was employed to obtain **29*E*** and **29*Z*** as colorless oil.

The structures of the stilbenes **23 - 29** were confirmed by NMR and mass spectra as well as elemental analyses.

E or *Z* geometries of these stilbenes were confirmed by their characteristic coupling constants for the olefinic protons of 16.0-16.8 Hz for *E* and about 12 Hz for *Z* in the ^{1}H NMR spectra (see table 2). Among them, the two doublets of olefinic protons of **28*Z*** are superimposed with the signal of an aromatic proton and thus the coupling constant can not be calculated. Especially, the signals of the olefinic protons of **29*Z*** are superimposed with those of an aromatic proton so much so that they can not be distinguished from each other. Therefore, the coupling constant of them can not be listed. Despite the structures of **28*Z*** and **29*Z*** could be confirmed by comparing with their *E*-isomers **28*E*** and **29*E*** as well as by other analytic data (see Figure 16).

Table 2. ^{1}H NMR Spectral Properties of Stilbenes **23 - 29*E***

Compound	CH=CH (2d, ppm)	$J_{CH=CH}$ (Hz)	Compound	CH=CH (2d, ppm)	$J_{CH=CH}$ (Hz)
23*E*	6.99, 7.07	16.5	**23*Z***	6.43, 6.56	12.1
24*E*	6.90*, 7.30	16.3	**24*Z***	6.49, 6.57	12.0
25*E*	7.06, 7.36	16.4	**25*Z***	6.62, 6.65	12.0
26*E*	7.00, 7.19	16.8			
27*E*	6.92*, 7.46	16.6			
28*E*	7.02*, 7.19	16.4	**28*Z***	6.52-6.64*	**
29*E*	6.94*,7.43	16.3	**29*Z***	6.56-6.66*	**

* partially or totally superimposed. ** It can not be calculated from the spectra.

The signals of the methoxy protons of **23 - 29*E*/*Z*** are observed in the range of 3.65 - 3.90 ppm. The figures of the signals of aromatic protons in these stilbenes are similar to those of the starting benzaldehydes. Thus by comparing the signals of the aromatic protons of stilbenes with those of the starting benzaldehydes they might easily be distinguished from each other in their spectra except some seriously superimposed signals. For example, in the ^{1}H NMR spectrum of **25*E*** (see Figure 15), the three groups of signals at 6.63 (dd, $^{3}J_{(H, F)}$ = 12.4Hz), 6.72 (dd) and 7.55 (dd, $^{4}J_{(H, F)}$ = 8.7Hz) ppm are assigned to the protons of the phenyl ring A, while the signals at 6.83 (dd), 6.93 (d) and 7.62 (d) ppm are assigned to the protons of the phenyl ring B.

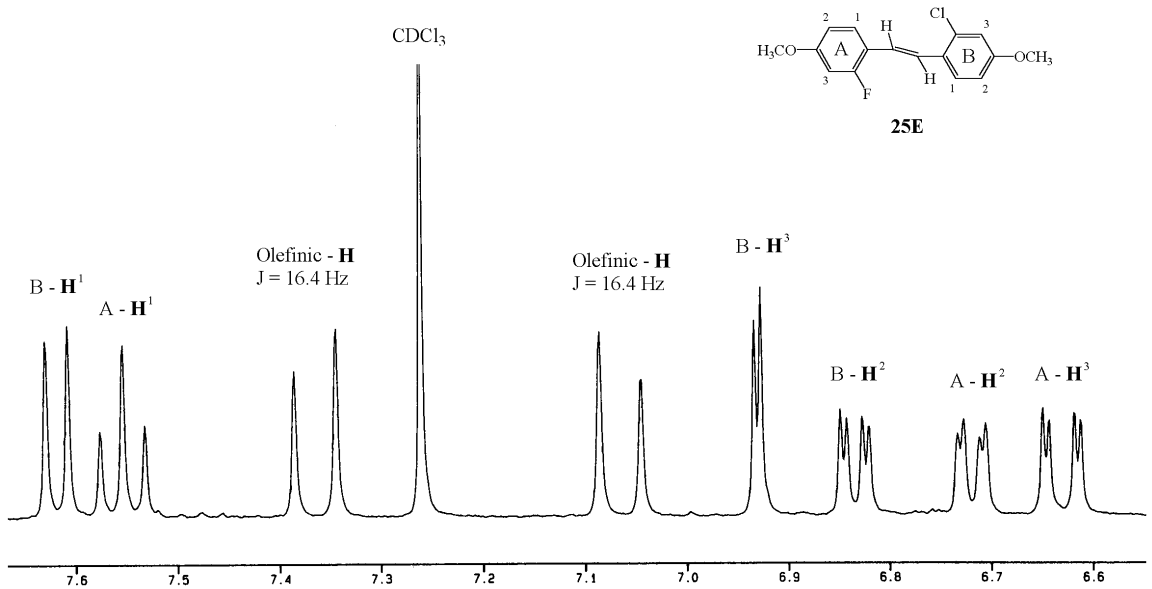
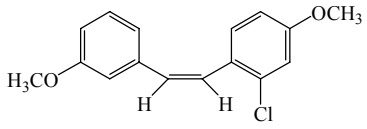


Figure 15. ^{1}H NMR-Spectrum of **25*E*** in $CDCl_3$

Unfortunately, some signals in the ^{1}H NMR-spectra are superimposed, but most of them can be distinguished. For example, in the ^{1}H NMR-spectrum of **29*Z*** taken in $CDCl_3$, the olefinic signals are totally superimposed together with the signals of an aromatic proton. The spectrum shows the resonances of olefinic and aromatic protons together as four signal groups with the integral intensities respectively consistent with three, three, one and two of protons. In order to further assign the signals, a pair of ^{13}C NMR- and ^{1}H-^{13}C-COSY-spectra of **29*Z*** were taken in $CDCl_3$. The ^{13}C NMR-spectrum of **29*Z*** shows sixteen peaks in sum. Two peaks at 55.0, 55.5 ppm were assigned for two methoxy carbons. The signals of two carbons adjacent to the methoxy groups should be observed at about 160 ppm. However, in the range of over 140.0 ppm, only one peak appears at 159.3 ppm. Obviously, the resonances of the both carbons are isochronous. The rest of the ten aromatic and two olefinic carbons give rise to twelve peaks in the range of 112.0 - 139.0 ppm, nine of them with more intensity indicate the presence of the seven aromatic and two olefinic methine carbons. This was confirmed by a ^{1}H-^{13}C-COSY-spectrum (see Figure 16).



29*Z*

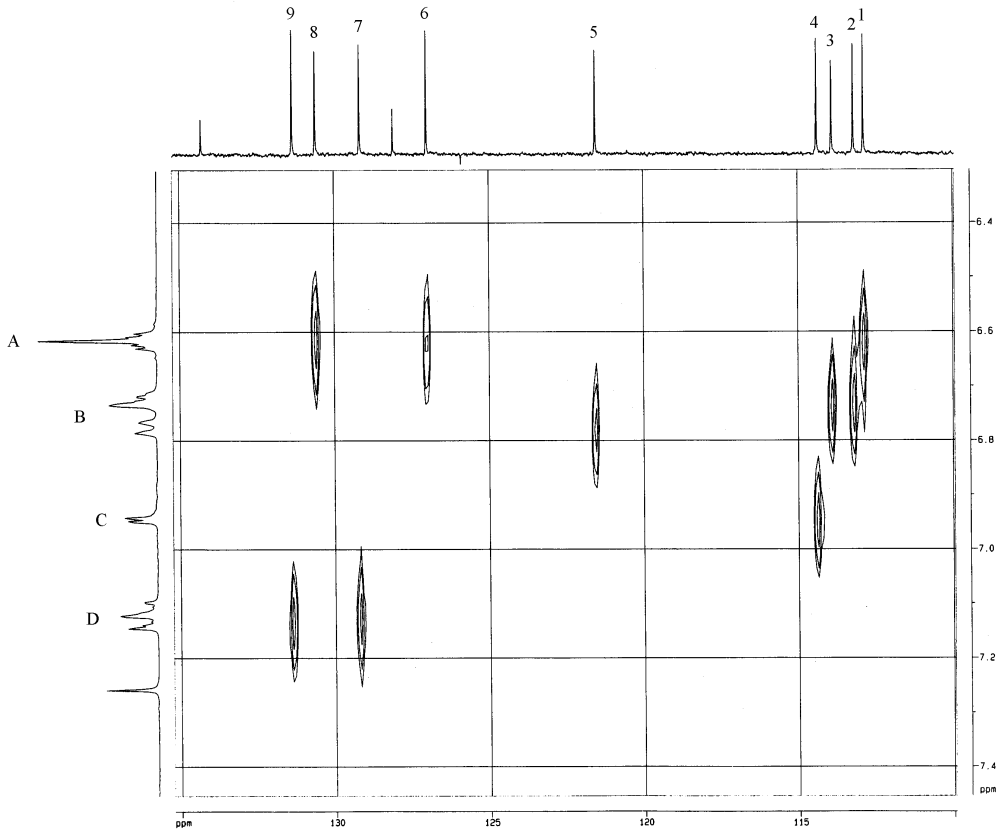


Figure 16. ^{1}H-^{13}C-COSY-Spectrum of **29*Z*** in $CDCl_3$

In the ^{1}H-^{13}C-COSY-spectrum of **29*Z***, nine cross-peaks are observed between the four signal groups A - D of methine protons and the nine peaks 1 - 9 of methine carbons. The signal group A couples with three peaks 1, 6, 8, so does also the group B with three peaks 2, 3, 5, the group C with the peak 4 and the group D with two peaks 7, 9. All these information are consistent with the expected structure, in spite of the fact that the exact position and the coupling constants of the signals of the olefinic protons are still unclear. In this case the confirmation of its "*cis*" geometry was performed only by confirmation of the other "*trans*" isomer.

Further confirmation of the structures of **23 - 29** was obtained from mass spectrometry. The peaks of their molecular ions were separately observed as a base peak (100%) except those of **29*E* / *Z*** (77 / 67%).

3.1.2 Synthesis of hydroxymethoxystilbenes

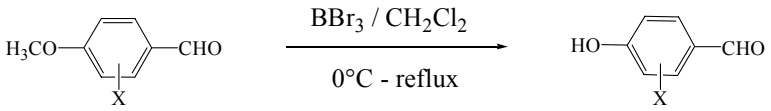
This section relates to the preparation of the stilbenes bearing a hydroxy group in 4-position on one phenyl ring and a methoxy group on the other phenyl ring and containing at least one halide group in 2 or 6 (2' or 6')-position by each stilbene.

3.1.2.1 Preparation of chloro-substituted 4-hydroxybenzaldehydes

Because the benzaldehydes **3** and **4** could be easily prepared by one-step direct formylation, the preparation of the chloro-substituted 4-hydroxybenzaldehydes **30** and **31** was performed by demethylation of the benzaldehydes **3** and **4**.

A large number of reagents, for instance, boron tribromide, dimethylboron bromide, boron trihalide-methylsulfide complex, sodium ethanethiolate / natrium hydride, trimethylsilyl iodide, lithium chloride / DMF, all of which have been elaborated in the review article [Ranu, 111], alkyl thiol / alumium trihalide [Node, 112; Nishide, 113], or their combination were applied to cleave an aryl methyl ether to give an aryl alcohol. Among them, boron tribromide is regarded as one of the favourite ether-cleavage reagents and has been widely used for demethylation of aryl methyl ether. Despite its high efficiency, the primary advantage claimed in favour of boron tribromide is that the cleavage is effected under mild conditions and thus the need for the use of strongly acidic or basic reaction conditions can be avoided [Benton, 114; McOmie, 115]. Boron tribromide cleaves the ether linkage without affecting a large number of functional groups, for example, ester groups, double bonds [Wedemeyer, 116],

halogenic groups and formyl group [Kirk, 117; Borgulya, 118]. The latter specially attracted our attention and stimulated our attempts to prepare the chloro-substituted 4-hydroxy-benzaldehydes.



3, 4 **30, 31**

Compound	**30**	**31**
X	2-Cl	2,6-Cl_2

Scheme 16

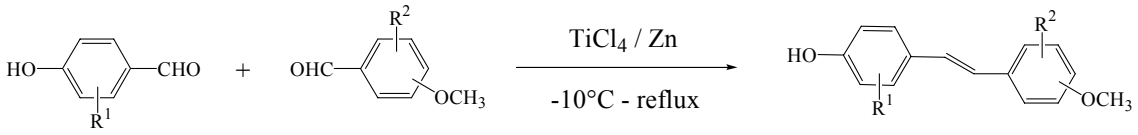
Boron tribromide was added to a stirred solution of the corresponding methoxy-benzaldehyde in dry dichloromethane at 0°C. After stirring at this temperature for 30 minutes, the reaction mixture was stirred at room temperature. Monitoring the demethylation of methoxybenzaldehye **3** by thin layer chromatography (TLC) indicated that the reaction was complete at room temperature after approximately 24 hours. After the reaction being complete, the reaction mixture was poured into ice-water and extracted with diethyl ether. The crude product **30** from the ethereal phase was purified by column chromatography on silica gel with a mixture of dichloromethane and diethyl ether (10 : 1) as eluant. The ether cleavage of **4** was incomplete at room temperature even after 72 hours and thus a further period of reflux was necessary. The crude product **31** obtained by similar procedure as hereinabove described for **30** was suspended in a mixture of dichloromethane and ligroin (5 : 3) and refluxed for 30 minutes. After cooling and filtration, the pure product **31** was gained as pale yellow solid in 78% yield.

The reason why the demethylation of **4** was more difficult than that of **3** might be ascribed to the electron-withdrawing effect of the chloro-substituents. This effect reduces the electron intensity of the oxygen atom of the methoxy group through conjugation of a phenyl ring and thus it becomes more difficult for boron tribromide to attack successfully.

The products **30** and **31** were characterized by NMR and mass spectroscopy as well as elemental analyses. The ^{1}H NMR spectra of **30** and **31** taken in DMSO-d_6 show the deuterium exchangeable hydroxy signal separately as a singlet at 11.11 and 11.45 ppm, the typical formyl signal separately as a singlet at 10.14 and 10.25 ppm, and the signals of aromatic protons similar to that of **3** and **4**. No signal of methoxy protons is observed.

3.1.2.2 Crossed reductive coupling of hydroxybenzaldehydes with methoxybenzaldehydes

After the attempts to prepare dimethoxystilbenes by crossed reductive coupling of different methoxybenzaldehydes with low-valent titanium (Section 3.1.1), we envisaged the possibility of the synthesis of 4-hydroxy-4'(or 2')-methoxystilbenes with the same method. There are three competitive coupling lines starting from two different benzaldehydes, two symmetric and one asymmetric line. First, the formation of at least one of the possible symmetrical stilbenes should be reduced. Due to the weaker electron-donor 4-hydroxy group, compared to the 4-methoxy group, the activity of the formyl group of 4-hydroxybezaldehyde is lower than that of the 4-methoxybenzaldehyde and thus the coupling chance between both 4-hydroxybezaldehydes should be less than the crossed coupling. If a relative sterically hindered 4-methoxybezaldehyde and a sterically convenient 4-hydroxybenzaldehyde are employed to perform the coupling, the crossed coupling product might therefore be a major product. Secondly, the separation of the product mixture should be easier. Based on the different polarity between the hydroxy and the methoxy group which would finally effect the different polarity of the possible products, easier separation of the product mixture would be expected, for example, by means of the different solubility of hydroxy- and methoxystilbenes in either polar or non-polar solvents (such as methanol, ligroin and the like) or in alkali solution, as well as by column chromatography. All these were confirmed by following crossed reductive coupling between hydroxybenzaldehyde and methoxybenzaldehyde (Scheme 17).



30 - 32 **3, 4, 5, 7** **33 - 40**

Compound	R^1	R^2	OCH_3	Form	Yield (%)
32	H				
33	H	2-F	4-	E	47
34	H	2-Cl	4-	E	53
35	H	2,6-Cl_2	4-	E	41
36	H	2,4-Cl_2	6-	E	58
37	2-Cl	2,4-Cl_2	6-	E	21
38	2,6-Cl_2	H	4-	E	21
39	2,6-Cl_2	2-F	4-	E	15
40	2,6-Cl_2	2-Cl	4-	E	18

Scheme 17

The synthesis of **33** - **40** was carried out by means of the above-mentioned modified coupling method [Coe, 109] (see Section 3.1.1.2) and afforded only *E*-form stilbenes. A few noteworthy general points encompassed in the procedure were enumerated as following: (1) The corresponding benzaldehydes as a mixture dissolved in tetrahydrofuran were added to the freshly prepared low-valent titanium reagent; (2) The reaction mixture was first stirred 24 - 48 hours at room temperature before reflux; (3) After the reaction being complete, the mixture was extracted with diethyl ether or a mixture of diethyl ether and ethyl acetate (1 : 1) and 10% brine; (4) The separation and purification of the desired product was performed by column chromatography. Furthermore it had been found that a suitable excess of inexpensive 4-hydroxybenzaldehye **32** was facilitated to obtain an optimum yield of the desired product **33** - **36**, but more excess of **32** was disadvantageous for followed extraction because of the possibility to form the by-product 4,4'-dihydroxystilbene or its polymer derivates.

It can be easily noticed that the yields of stilbenes **33** - **36** are only moderate (41 - 58%), which are, however, over twice as high as that of stilbenes **37** - **40** (15 - 21%). These results are consistent with the foregoing considerations: stilbenes **33** - **36** from sterically convenient

4-hydroxybenzaldehyde **32** afforded higher yields than stilbenes **37 - 40** from the sterically hindered 4-hydroxybezaldehyde **31**.

Certainly, the formation of symmetrical stilbenes was avoided in no case. Some of them were even isolated as major products against the desired asymmetrical stilbenes as minor products. In each case, only dimethoxystilbene as one of two possible symmetrical products was isolated and confirmed, the isolation of another dihydroxystilbene or its polymer was not performed in this work.

The structures of stilbenes **33 - 40** were confirmed by NMR- and mass spectroscopy and elemental analyses. The signals in the ^{1}H NMR-spectra of compounds **33 - 40** were summarized in table 3.

Table 3. ^{1}H NMR Spectral Properties of Stilbenes **33 - 40**

Compound	Chemical shifts in $CDCl_3$ (ppm)			Chemical shifts in DMSO-d_6 (ppm)		
	OCH_3	OH	CH=CH (J, Hz)	OCH_3	OH	CH=CH (J, Hz)
33	3.81	4.73	7.00, 7.03 (16.5)			
34	3.81	4.74	6.90*, 7.30 (16.3)			
35	3.79	5.05	6.93, 7.01 (16.6)	3.81	9.65	6.86, 6.90 (16.6)
36	3.89	4.74	7.12, *** (16.5)	3.90	9.65	6.99, 7.31 (16.5)
37				3.92	10.14	7.03, 7.69 (16.4)
38	3.84	4.94	6.90, 7.03 (16.6)			
39				3.80	10.45	6.89-6.95*
40				3.81	10.49	6.98, 7.27 (16.7)

* superimposed

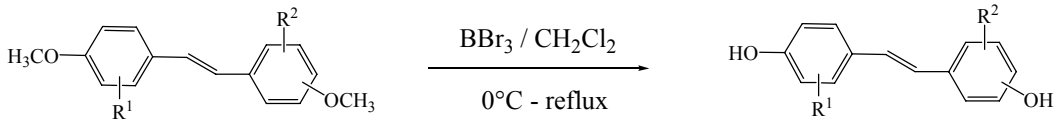
The ^{1}H NMR-spectra of **33 - 44** taken in $CDCl_3$ or DMSO-d_6 show the signal of the methoxy group of each compound as a singlet with chemical shifts in the range of 3.79 - 3.92 ppm. The signal of the hydroxy proton appears in the ^{1}H NMR-spectra taken in $CDCl_3$ as a broad peak centred in the range of 4.73 - 5.05 ppm. Taken in DMSO-d_6, it appears as a singlet in the range of 9.65 - 10.49 ppm. The resonances of the olefinic protons of each compound are positioned in the ^{1}H NMR-spectrum taken in $CDCl_3$ or DMSO-d_6 as two doublets with a coupling constant of 16.3 - 16.7 Hz in the range of 6.80 - 7.80 ppm. These coupling constants are the evidence for the *E* geometries of the obtained stilbenes **33 - 40**. There is here only one compound **39**, of which no coupling constant of the totally superimposed signals of olefinic protons can be given. In view of the knowledge that this procedure affords only *E*-form

stilbenes [Ali, 104; Mukaiyama, 107] and the results of other stilbenes synthesised in this work, the assignation of *E* geometry for **39** should be doubtless. The signals of the aromatic protons of the stilbenes are similar to that of the corresponding starting benzaldehydes.

The IR-spectrum of each stilbene shows a strong absorption in the range of 3300 - 3500 cm^{-1}, which indicates the presence of the hydroxy group. In the mass spectrum of each stilbene, the peak of the molecular ion is observed as the base peak (100%).

3.1.3 Ether cleavage of dimethoxystilbenes to dihydroxystilbenes

The dihydroxystilbenes **41** - **51** were obtained by demethylation of the corresponding dimethoxystilbenes with boron tribromide in dichloromethane as depicted in scheme 18



8 - 11*E*, 23 - 29*E* **41 - 51 (*E*)**

Compound	R^1	R^2	OH	Form	Yield (%)
41	H	H	4-	*E*	98
42	H	2-F	4-	*E*	34
43	H	2-Cl	4-	*E*	45
44	2-F	2-F	4-	*E*	24
45	2-F	2-Cl	4-	*E*	61
46	2-Cl	2-Cl	4-	*E*	74
47	2-F	2,6-Cl_2	4-	*E*	15
48	2-Cl	2,6-Cl_2	4-	*E*	54
49	2,6-Cl_2	2,6-Cl_2	4-	*E*	89
50	2-F	H	3-	*E*	30
51	2-Cl	H	3-	*E*	29

Scheme 18

Similar to the procedure described in chapter 2.1, boron tribromide was added to a stirred solution of the corresponding dimethoxystilbene in dry dichloromethane at 0°C. After stirring

for 30 minutes at 0°C, the reaction mixture was stirred at room temperature for 1 - 48 hours. If the demethylation was incomplete (TLC control), the reaction mixture was refluxed for a further demanded time. The reaction conditions depended to a great extent on the type of ortho-halo-substituents. More halo-substituents ortho to the projected stilbene exerted a greater restrained effect on the ether cleavage due to the stronger electron-withdrawing effect and thus the demethylation needed longer reaction time or higher temperature. The relationship between the reaction time (at room temperature, except specially noted) and the type of ortho-halo-substituents is listed in table 4.

Table 4. Relationship between Reaction Time and Substituent Type

Dimethoxystilbenes (*E*)	**8**	**23**, **24**, **28**, **29**	**9**, **10**, **25**	**26**, **27**	**11**
Substituent type (X)	-	2-X	2,2'-X_2	2,2',6'-X_3	2,2',6,6'-X_4
Reaction time (hrs)	0.5	5	16	48	48 + 12 (reflux)

The reason why the reaction time was compared and controlled lies in that more than necessary time for complete reaction in many cases had great detrimental effect on the yield of the desired hydroxystilbenes especially containing fewer ortho-halo-substituents. It had been observed that the formed stilbene bearing fewer ortho-halo-substituents was easily polymerised under this condition to give an unknown substance which could be soluble in alkaline solution and alcohol as well as desired products, and could be separated by column chromatography on silica gel. This by-product had no clear melting point and established very complicate signals on its ^{1}H NMR-spectrum and polymolecular peaks in its mass spectrum. Due to this polymerisation the dihydroxystilbenes bearing ortho-fluoro-substituent **42**, **44**, **47** and **50** could be gained only as minor products in 15 - 34% yields.

All of these dihydroxystilbenes **41 - 51** demethylated from the corresponding *E*-dimethoxystilbenes maintained their *E* geometries. Attempts to prepare *Z*-dihydroxystilbenes from the corresponding *Z*-dimethoxystilbenes under the same condition were unsuccessful, from which only geometry-converted *E*-dihydroxystilbenes were isolated as reported in the literature [Schertl, 92].

NMR- and mass spectroscopy as well as elemental analyses were applied to confirm the structures of **41 - 51**. Several known compounds could be simply characterised by comparing their NMR-data with those reported in the literature [Ali, 104; Schertl, 92].

The chemical shifts of the characteristic and comparable signals of hydroxy and olefinic protons in the ^{1}H NMR-spectra of **41 - 51** taken in DMSO-d_6 or CD_3OD are summarized in

table 5. In the ^{1}H NMR-spectra taken in DMSO-d_6, the signals of two hydroxy protons of each stilbene appear as two singlets in the range of 9.42 - 10.50 ppm or are isochronous. The resonances of olefinic protons exhibit for each asymmetrical stilbene two doublets with a coupling constant of 16.3 - 16.7 Hz in the range of 6.80 - 7. 30 ppm and for each symmetrical stilbene a singlet with an integral intensity of two protons in the same range. The ^{1}H NMR-spectra of the symmetrical stilbene **41**, **44** and **46** were taken in CD_3OD, in which the signals of hydroxy protons of stilbenes are not observed due to the exchange of protons with deuterium, the signals of two olefinic protons of each stilbene are observed as a singlet also in the range of 6.80 - 7.30 ppm.

Table 5. ^{1}H NMR Spectral Properties of Stilbenes **41 - 51**

Compound	**Chemical shifts in DMSO-d_6 (ppm)**		**in CD_3OD (ppm)**
	OH	**CH=CH (J, Hz)**	**CH=CH**
41			6.88 (s)
42	9.54, 9.96	6.93, 7.00 (16.5)	
43	9.59, 9.96	6.98, 7.11 (16.3)	
44			7.06 (s)
45	10.05 (2OH)	7.00, 7.23 (16.5)	
46			7.24 (s)
47	10.14, 10.49	6.93, 7.24 (16.7)	
48	10.13, 10.45	6.90, 7.24 (16.6)	
49	10.50 (2OH)	6.93 (s)*	
50	9.42, 9.99	7.02, 7.07 (16.4)	
51	9.43, 10.06	7.03, 7.26 (16.3)	

* superimposed

The mass spectra of **41 - 51** show the peaks of their molecular ion as the base peak. Their elemental analyses support the described structures.

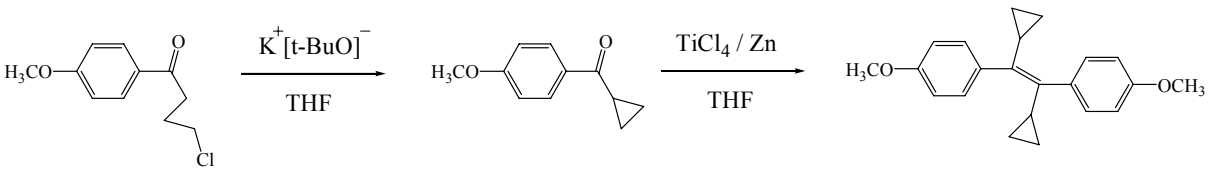
3.2 Preparation of Tetrasubstituted Ethenes containing Two or More Aryl-substituents

3.2.1 Synthesis of 1,2-dialkyl-1,2-diarylethene

3.2.1.1 Preparation of 1,2-dicyclopropyl-1,2-bis(4-methoxyphenyl)ethene

The synthesis of 1,2-dicyclopropyl-1,2-bis(4-methoxyphenyl)ethene **54** is precedented only in one publication [Bennett, 119], where the compounds **54** was prepared by oxidation and coupling of the crude hydrazone [Staudinger, 120; Smith, 121] of cyclopropyl-(4-methoxyphenyl)methanone in 2% yield. The crude hydrazone was obtained from cyclopropanecarbonitrile, which reacted with the Grignard reagent prepared from 1-bromo-4-methoxybenzene to cyclopropyl-(4-methoxyphenyl)methanone and followed by condensation with hydrazine to give hydrazone.

The above-described method seemed to be of little practical value because of the extremely low yield. In this work a new method appearing to be efficient and convenient for preparing compound **54** was designed and successfully performed as shown in scheme 19. The commercially available 3-chloropropyl-(4-methoxyphenyl)methanone **52** was almost quantitatively converted under basic condition to cyclopropyl-(4-methoxyphenyl)methanone **53**, which was coupled with a low-valent titanium reagent to the desired *E* tetrasubstituted ethene **54** in 36% yield.



52 **53** **54**

Scheme 19

The ring closure of **52** to **53** was completed after heating for 3 hours under reflux in the presence of potassium tert-butoxide in tetrahydrofuran. Then the reaction mixture was poured into water and extracted with diethyl ether. The residue obtained from the ethereal phase was analyzed to be a pure oily product **53**, which could be directly used for the following reaction.

The conversion of **52** to **53** gives rise to an obvious change of the ^{1}H NMR signals of the aliphatic side bonded to the carbonyl group (see Figure 17). In the ^{1}H NMR-spectrum of **52** both the α- and γ-methylene groups appear as two triplets at 3.13 and 3.68 ppm, the β-methylene group as a quintet at 2.22 ppm. Whereas in the ^{1}H NMR-spectrum of **53**, only two methylene groups are observed together as two multiplets in higher field at 1.00 and 1.21 ppm and a methine group as a multiplet at 2.63 ppm. The change of a methylene group of **52** to a methine group of **53** and the multiplet features of these three signals in **53** (all three signals couple with each other) indicate the formation of a cyclopropyl ring of **53**. The two protons of each methylene group of the cyclopropyl ring are chemically non-equivalent (see Figure 17). The ^{13}C NMR-spectrum of **53** shows eight peaks, only two of them assigned to cyclopropyl carbons, one peak at 11.2 ppm for two chemically equivalent methylene carbons and the another peak at 16.6 ppm for the methine carbon. One peak at 199.0 ppm is a typical signal for carbonyl carbon and the rest of the signals of methoxy and aromatic carbons appears also in the corresponding field. The mass spectrum and elemental analyses support the structure of **53**.

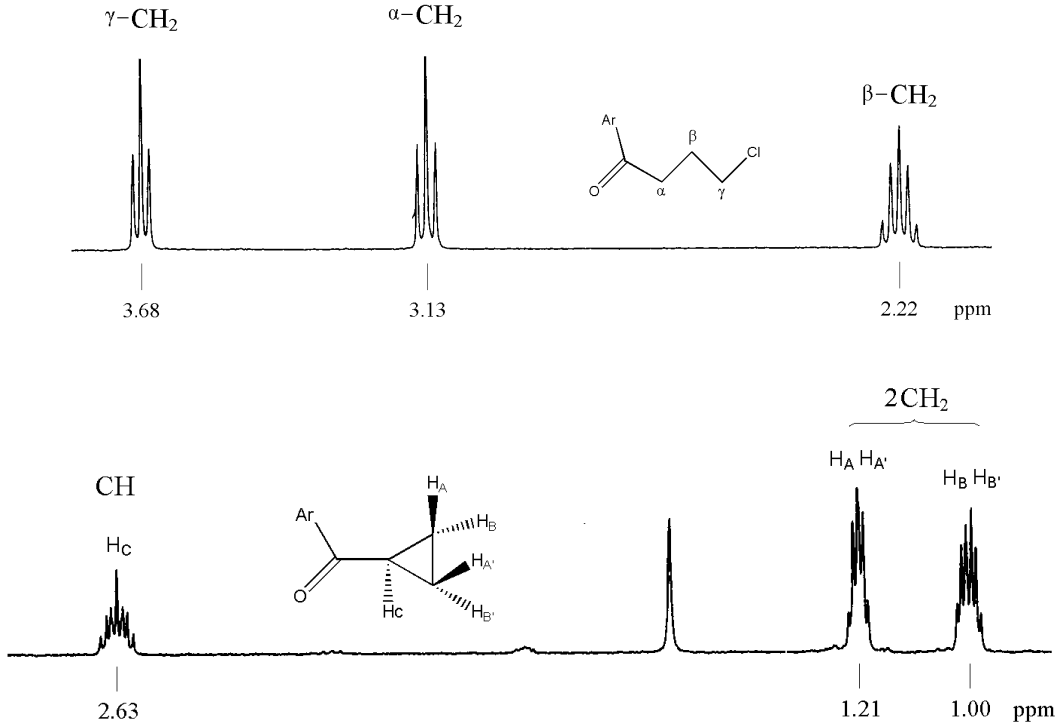


Figure 17. ^{1}H NMR-Spectra of **52** (above) and **53** (below) in $CDCl_3$

The reductive coupling of **53** to **54** was performed in tetrahydrofuran with $TiCl_4$ / Zn according to the procedure as described in section 3.1.1. A solution of **53** in tetrahydrofuran was added to the freshly prepared low-valent titanium reagent and the mixture was refluxed

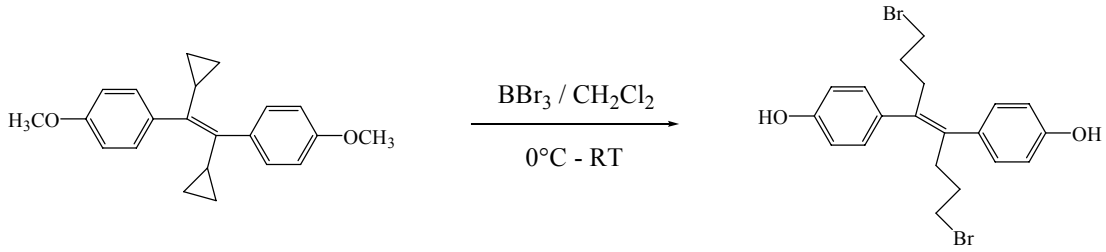
for 4 hours. After cooling the mixture was poured into ice-water and extracted with diethyl ether. The crude product **54** was obtained as an oil after removal of the solvent. It was a mixture of *E* and *Z* isomers. Attempts to separate the mixture by chromatography on silica gel were not entirely successful but did lead to the isolation of the crude product as colourless crystals together with a small amount of oily substance and an oily mixture containing a part of the crystals. The crystals were insoluble in cooled ligroin or ethanol, in which the oil was well soluble. Thus, the crystals were washed with a mixture of ligroin and diethyl ether (5 : 1) to give the pure product **54**. The combined oily mixture was heated in ligroin or alcohol and stood at room temperature over 24 hours, from this a further part of *E* isomer crystallized. Repeated treatments of the mixture with either ligroin or ethanol through heating and cooling gave more crystals. The obtained crystals were further purified by recrystallization with alcohol to afford pure product **54**, which appears to be *E* isomer. The rest of oily substance was still a mixture which could not be separated.

The structure of **54** was confirmed by NMR- and mass spectroscopy as well as elemental analyses. Due to the chemically equivalence of both set delimited by the olefin bond, the resonances of both set are coincident and appear in the NMR-spectra as those of only one set. The ^{1}H NMR-spectrum of **54** shows at 0.12, 0.32 and 1.35 ppm three multiplets with the integral intensity of two, two and one protons, respectively, which are assigned for the two methylene and one methine protons of the cyclopropyl ring. The coupling of carbonyl groups to an olefin bond led to the higher field shifts of the adjacent cyclopropyl proton signals in comparison to those of the starting material **53** (1.00, 1.21 and 2.63 ppm). This is consistent with the fact that the carbonyl group reduces the electronic intensity of the adjacent cyclopropyl ring and the olefin bond improves them. The signal of methoxy protons appears as a singlet at 3.82 ppm. The AA'BB' signals of the aromatic protons appear at 6.88 and 7.09 ppm with a coupling constant of ^{3}J = 8.6 Hz. In the ^{13}C NMR-spectrum of **54** eight peaks appear, two peaks at 4.40 and 15.4 ppm assigned for two methylene and one methine carbons of the cyclopropyl ring, one peak at 55.2 ppm for the methoxy carbon, one peak at 138.0 ppm for the olefinic carbon (carbonyl carbon of **53**, at 199.0 ppm), and the others at 113.1, 131.1 131.4 and 158.0 ppm for the aromatic carbons. In the mass spectrum of **54**, the peak of the molecular ion is observed at m/z 320 (47%), the base peak appears at m/z 292. In addition, the product **54** has a melting point of 175.5 - 176°C, which is consistent with that reported in the literature [Bennett, 119].

Based on all these analytic data, however, the *E* or *Z* geometry of **54** can not be confirmed. It appears to be *E* isomer.

3.2.1.2 Synthesis of 1,2-bis(3-bromopropyl)-1,2-bis(4-hydroxyphenyl)ethene

An attempt to prepare 1,2-dicyclopropyl-1,2-bis(4-hydroxylphenyl)ethene was carried out by ether cleavage of **54** with boron tribromide in dichloromethane. The reaction maintained at room temperature for 48 hours led to much dark material, most of which was insoluble in a mixture of dichloromethane and diethyl ether (3 : 1) and thus was removed by filtration. The solution was stripped of solvent under vacuum, and the residue was separated by column chromatography on silica gel with a mixture of ligroin, diethyl ether and dichloromethane (1 : 1 : 1) as eluent to give in 10% yield a substance, which was characterized to be 1,2-bis(3-brompropyl)-1,2-bis(4-hydroxyphenyl)ethene **55** (Scheme 20):



54 **55**

Scheme 20

Under the used condition, boron tribromide was efficient enough to cleave the linkage of ether, but not mild enough to prevent the opening of cyclopropyl ring.

The structure of **55** was confirmed by ^{1}H NMR- and mass spectra as well as elemental analyses. The ^{1}H NMR-spectrum of **55** taken in DMSO-d_6 shows the hydroxy signal as a singlet at 9.35 ppm, the aromatic methine signals as AA'BB' systems at 6.76 and 6.99 ppm, and three signal groups with the integration of respective two protons at 1.61, 2.22 and 3.27 ppm. No methoxy signal is observed. Obviously, the phenyl methyl ether was successfully demethylated to the phenol and the resonances of both set delimited by the olefin bond are coincident and appear in the ^{1}H NMR-spectrum as those of only one set as other symmetrical stilbenes. The three signal groups relate to two triplets and one multiplet. They have the similar features to those of 3-chloropropyl group of **52** and the integration of respective two protons, these indicate the opening of the cyclopropyl ring during the demethylation of **54**. The possible terminal substituent of the propyl chain is a bromine atom, so the three signals at 1.61, 2.22 and 3.27 ppm should be assigned for 3-bromopropyl group. This was confirmed by the mass spectrum, which shows not only the peak of molecular ion at m/e 454 (84%) and the

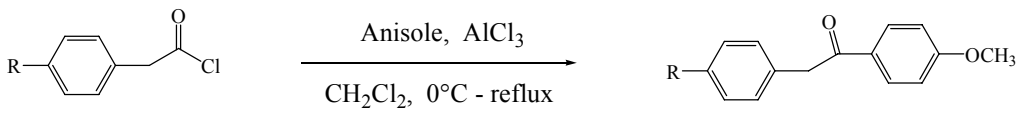
base peak at m/e 107 (100%), but two isotope peaks of HBr^+ at m/e 80 (24%) and 82 (29%). The elemental analyses of **55** support the proposed structure.

3.2.2 Synthesis of 2-alkyl-1,1,2-triarylethene

A convenient and practical method which was used by Dodds et al. [Dodds, 122] to synthesize the stilbestrol series starting from the parent deoxybenzoin was represented by preparation of numerous 2-alkyl-1,1,2-triarylethenes [Schneider, 123 and 124; Lubczyk, 83 and 84]. In the first step the parent deoxybenzoin was treated with alkyl haloride in the presence of a strong base to give an 2-alkyl-1,2-diarylethanone, which was then reacted with a Grignard reagent prepared from aryl bromide and magnesium to afford the corresponding carbinol, followed by dehydration of the carbinol using a strong acid (48% HBr) to yield 2-alkyl-1,1,2-triarylethene. By means of this method, some 2-alkyl-1,1,2-triarylethenes needed in this work were successfully prepared. That in all details will be sequentially described in the following sections. Furthermore, one-pot reductive coupling of carbonyl compounds using low-valent titanium is also a fascinating and powerful method for preparation of 2-alkyl-1,1,2-triarylethenes, some of them have been successfully synthesized in an earlier publication [Coe, 109]. This method is also an alternative for preparing some 2-alkyl-1,1,2-triarylethenes needed in this work.

3.2.2.1 Preparation of deoxybenzoins

The needed deoxybenzoins were obtained by Friedel-Crafts reaction from 2-arylacetyl chloride with anisole in the presence of aluminium chloride [Lubczyk, 83] (Scheme 21):



56, 57 **58, 59**

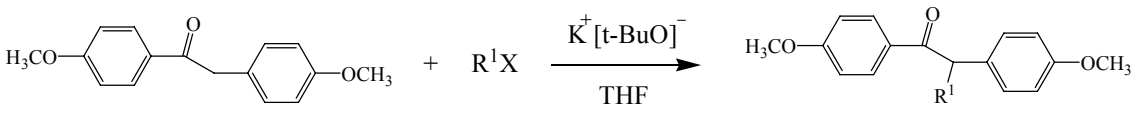
Compound	56	57	58	59
R	H	OCH_3	H	OCH_3

Scheme 21

The 2-arylacetyl chlorides **56** and **57** were separately added to a slurry mixture of aluminium chloride and anisole in dry dichloromethane in an ice-bath, followed by heating to reflux for 2 hours to give the deoxybenzoins **58** and **59**. Under these conditions the desired products were achieved in moderate yields (**58**: 61%; **59**: 57%) and in the meantime a by-product was isolated in each case by column chromatography as a demethylated deoxybenzoin, namely, 1-(4-hydroxyphenyl)-2-phenylethanone by **58** or 1-(4-hydroxyphenyl)-2-(4-methoxyphenyl)ethanone by **59**. The formation of by-products should be ascribed to the demethylating effect of aluminium chloride on the products **58** and **59** [Lednicer, 125].

3.2.2.2 Alkylation of deoxybenzoin

Because of the electron-drawing effect of the carbonyl group, the protons bound to C2 in the deoxybenzoin are acidic and can be easily released under basic condition. Thus the deoxybenzoin is treated with a base to give a carbanion, which is stabilized though conjugate effect of the adjacent phenyl ring and can attack an electrophile to form the corresponding derivative. Based on this principle, the deoxybenzoin **59** was treated with potassium tert-butoxide and alkyl halide **60** - **62** in tetrahydrofuran at room temperature or under reflux to afford the C2-alkyl-substituted 1,2-bis(4-methoxyphenyl)ethanones **63** - **65** as shown in scheme 22:



59 **60 - 62** **63 - 65**

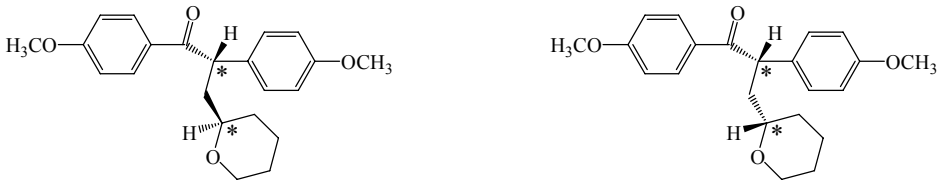
Compound	60	61	62	63	64	65
R^1(X)	CH_3(I)	C_2H_5(I)	Y*(Br)	CH_3	C_2H_5	Y*

* Y = tetrahydropyran-2-yl-methyl-

Scheme 22

1,2-Bis(4-methoxyphenyl)ethenone **59** and potassium tert-butoxide was added to dry tetrahydrofuran and the mixture was stirred for 30 minutes at room temperature. The corresponding alkyl halide was added dropwise under stirring and nitrogen. The deoxybenzoin **59** was reacted rapidly with methyl iodide **60** or ethyl iodide **61** at room temperature

so that the reaction mixture became a suspension during the dropwise addition. After stirring for 1 hour, the reaction was completed and the mixture was extracted with diethyl ether according to the standard procedure. The residue obtained from the ethereal phase was analyzed to be the pure products **63** or **64** gained in almost quantitative yields, which could be directly used for next step without further purification. The conversion of **59** with 2-(bromomethyl)-tetrahydro-2H-pyran **62** into **65** in the presence of potassium tert-butoxide was performed by heating under reflux for 6 hours. The crude product obtained by similar processing as described hereinabove was purified by column chromatography to give the desired product **65** in 44% yield as a mixture of two diastereomeres (Scheme 23), which could be directly used for the next step without separation of the diastereoisomers.



Scheme 23

The structures of **63**, **64** and **65** were confirmed by NMR and mass spectra as well as elemental analyses. In the ^{1}H NMR-spectra of **63** and **64**, the signals of methoxy and aromatic protons are scarcely affected by the group R^1 and appear in typical fields at the same or very similar shifts. The signal of the C2-proton of **63** appears as a quartet at 4.59 ppm due to coupling with methyl protons which exhibits a doublet at 1.48 ppm. The signal of the C2-proton of **64** appears as a triplet at 4.34 ppm due to coupling with the ethyl group which exhibits three signals, a triplet at 0.88 ppm assigned for methyl group and two multiplets separately with the integration of one proton at 1.81 and 2.15 ppm assigned for methylene group. In the structure of **65** two chiral centres exist, which led to two diastereoisomers (see Scheme 23). They were not separated and thus the ^{1}H NMR-spectrum of **65** show all signals as double feature with a ratio of about 1 : 1. The AA'BB' signals of aromatic protons appear at 6.73 - 6.90, 7.16 - 7.24 and 7.89 - 8.03 ppm. The signals of methoxy protons are shown as four singlets at 3.73, 3.75, 3.80 and 3.82 ppm. The proton linkage to C2 exhibits two signal groups at 4.76 - 4.94 ppm. And the signals of tetrahydropyran-2-yl-methyl protons appear as multiple signal groups in the range of 1.15 - 4.02 ppm.

The ^{13}C NMR-spectra of **63**, **64** and **65** show also the expected signals, which are summarized in table 6. The introduced C2-substituents, methyl of **63** and ethyl of **64**, signalize at 19.9 ppm and 14.4 and 29.0 ppm, respectively. Their carbonyl signals are

observed in the typical field at 199.5 and 201.0 ppm. The doubling signals of **65** are an evidence of a mixture of two diastereomers. The tetrahydropyran-2-yl-methyl rest of **65** is responsible for the peaks at 23.4 - 41.5 ppm and 68.3 - 75.8 ppm.

Table 6. ^{13}C NMR Spectral Properties of Compounds **63 - 65**

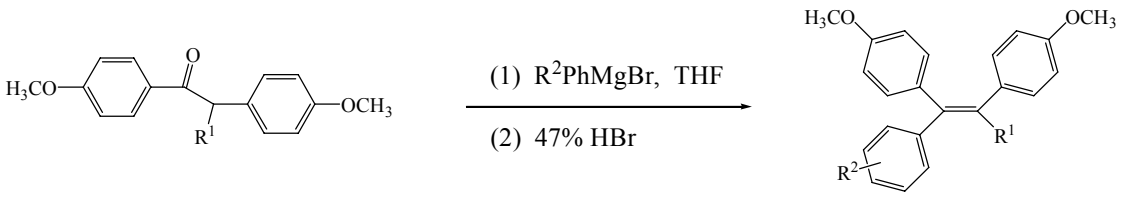
Compound	Chemical shifts in ^{13}C NMR-spectra ($CDCl_3$, ppm)
63	19.9, 47.0, 55.6, 55.8, 114.0, 114.7, 129.1, 129.9, 131.4, 134.4, 158.8, 163.5, 199.5
64	14.4, 29.2, 56.3, 57.3, 57.5, 115.8, 116.3, 131.3, 132.2, 133.0, 134.2, 160.6, 165.3, 201.0
65*	23.4 (2C), 26.2 (2C), 32.3, 32.4, 39.9, 41.5, 47.5, 48.0, 55.1, 55.2, 55.3, 55.4, 68.3, 68.4, 74.5, 75.8, 113.5, 113.6, 114.2 (2C), 129.0, 129.5, 129.7, 130.3, 131.0, 131.1, 131.6, 132.6, 158.4, 158.5, 163.1, 163.3, 198.9, 199.2

* A mixture of two diastereomers

The mass spectra of **63**, **64** and **65** show the peaks of molecular ions respectively at m/z 270 (5%), 284 (8%) and 354 (4%) and the base peaks respectively at m/z 135 ($C_8H_7O_2^+$), 135 ($C_8H_7O_2^+$) and 85 ($C_5H_9O^+$).

3.2.2.3 Preparation of 2-alkyl-1,1,2-triarylethene by Grignard reaction

The preparation of 2-alkyl-1,1,2-triarylethenes from 2-alkyl-deoxybenzoins by Grignard reaction [Lubczyk, 83] was performed in three steps in situ. Firstly aryl bromide was treated with magnesium in tetrahydrofuran to generate the Grignard reagent, with which 2-alkyl-deoxybenzoin was then converted into the corresponding carbinoxy magnesium bromide, which was directly hydrolyzed and dehydrated in situ using 47% hydrobromide acid finally to desired 2-alkyl-1,1,2-triarylethene. According to this procedure, the compounds **66** - **69** were synthesized from **63 - 65** in satisfactory yields as depicted in scheme 24:



63 - 65 **66 - 69**

Compound	66	67	68	69**
R^1	CH_3	C_2H_5	Y*	C_2H_5
R^2	OCH_3	OCH_3	OCH_3	Z*

* Y = tetrahydropyran-2-yl-methyl-; Z = benzo[1,3]dioxole-5-yl-

** A mixture of *trans* and *cis* isomers

Scheme 24

A solution of the corresponding ketone **63 - 65** in tetrahydrofuran was added dropwise under stirring and nitrogen to freshly prepared Grignard reagent and the resulting mixture was refluxed for 1.5 ~ 4 hours. It was noteworthy that the following hydrolysis of carbinoxy magnesium bromide to carbinol and the dehydration of carbinol to the desired product were simultaneously accomplished by using 47% hydrobromide acid without isolation of the carbinol. After dehydration with hydrobromide acid, the crude product **66** was directly precipitated from the reaction mixture, isolated by suction filtration and was purified by recrystallisation from ethanol. The compounds **67 - 69** were extracted with dichloromethane and purified by column chromatography on silica gel, respectively.

The compound **68** whose synthesis started from a mixture of two diastereomers was obtained as a pure substance due to loss of one chiral centre after this conversion. The compound **69** was obtained as a mixture of *E* and *Z* isomers. The separation of two isomers was unsuccessful. The structures of **66 - 69** were confirmed by NMR- and mass spectra as well as elemental analyses.

In the ^{1}H NMR-spectra of **66 - 69**, the signals of the C2-methine protons of the starting materials disappear, while the signals of methoxy, aromatic and C2-substituted group protons are shown in normal fields. The spectrum of **66** shows the signals of three methoxy protons as three singlets at 3.69, 3.75 and 3.82 ppm, aromatic protons as AA'BB' systems in the range of 6.50 - 7.20 ppm, and the C2-methyl group as a singlet at 2.10 ppm. The spectrum of **67** shows the signals of the three methoxy protons as three singlets at 3.68, 3.75 and 3.81 ppm, aromatic

protons as AA'BB' systems in the range of 6.50 - 7.20 ppm, and the signals of the C2-ethyl group as a triplet and a quartet at 0.92 and 2.45 ppm. Similar signals of methoxy and aromatic protons as those of **66** and **67** are also observed in the ^{1}H NMR-spectrum of **68**, while the signals of tetrahydropyran-2-yl-methyl protons appear as more multiplets in the range of 1.00 - 4.00 ppm (see Figure 18). The ^{1}H NMR-spectrum of **69** indicates a mixture of two isomers in a ratio of 10 : 9. Besides the double signals of methoxy, aromatic and C2-ethyl protons, two singlets (integration: 10 : 9) at 5.82 and 5.95 ppm are also observed and assigned for the dioxole methylene group (-OC**H**$_2$O-) of two isomers.

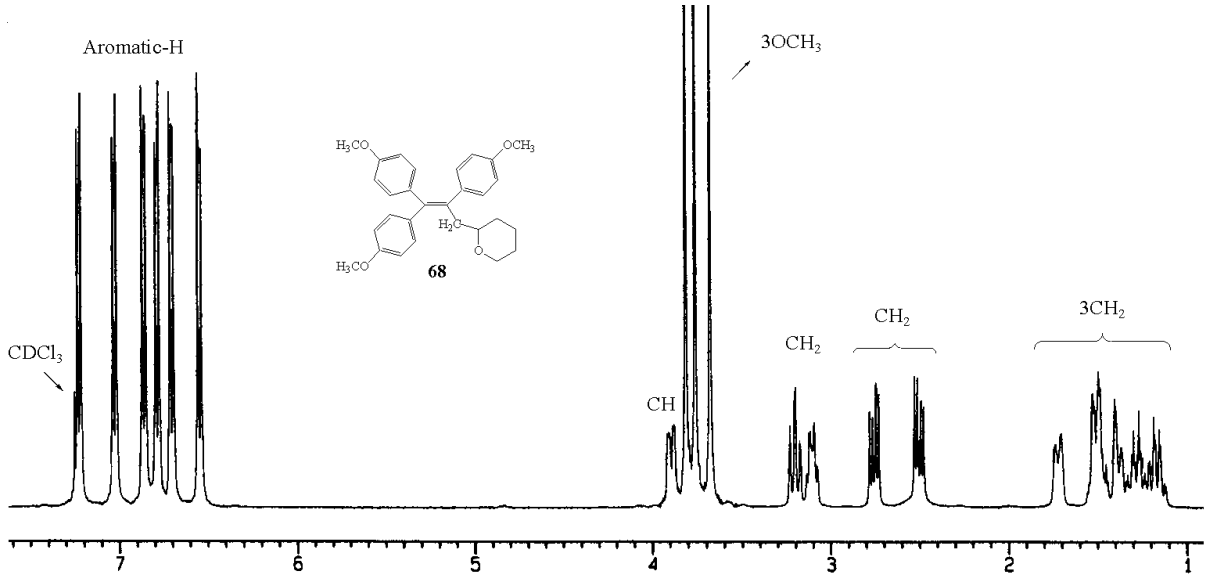


Figure 18. ^{1}H NMR-Spectrum of compound **68** in $CDCl_3$

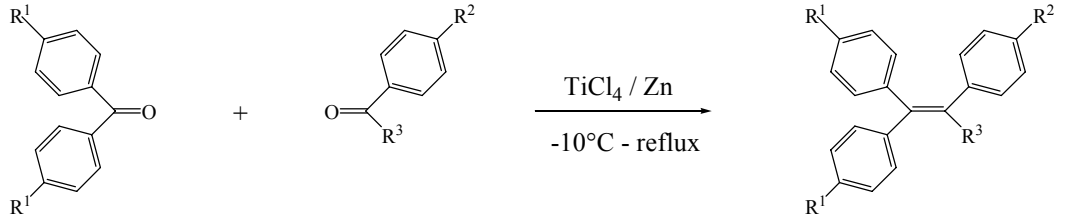
The ^{13}C NMR-spectra of **66** - **69** show the expected peaks. The methoxy carbons of **66** - **68** signalize separately as the same three peaks at 55.0, 55.1, 55.2 ppm. Their aromatic and olefinic carbons exhibit separately fourteen peaks with very similar shifts in the range of 112.7 - 158.2 ppm. In addition, the peaks of the C2-substituted group of each compound are shown as expected, namely, one peak of the methyl carbon of **66** at 23.4 ppm, two peaks of the ethyl carbons of **67** at 13.7 and 28.9 ppm, as well as six peaks of tetrahydropyran-2-yl-methyl carbons of **68** at 23.6, 26.0, 31.7, 42.1 68.4 and 76.2 ppm. The ^{13}C NMR-spectrum of **69** shows in summery forty peaks.

In the mass spectra of **66** - **69** the peaks of the molecular ions are observed at m/z 360 (100%), 374 (100%), 444 (43%) and 388 (100%), respectively. The base peak of **68** appears at m/z 359 (M^{+}-C_5H_9O).

3.2.2.4 Preparation of 2-alkyl-1,1,2-triarylethenes by one-pot reductive coupling

The above described method for the preparation of 2-alkyl-1,1,2-triarylethenes is a classic and efficient method which can be used in many cases. But some compounds having functional groups which are unstable against strong base or acid or Grignard reagent can not be synthesized by means of this method. As an alternative, the reductive coupling of two aryl ketons was proved to be an efficient and very convenient method in some cases [Coe, 109]. Tamoxifen could be obtained by this one-pot reaction from corresponding aryl ketons in 88% yield.

According to the literature procedure [Coe, 109] some desired 2-alkyl-1,1,2-triarylethenes were smoothly prepared as shown in scheme 25:



70, 71 **72 - 74** **75 -77**

Compound	70	71	72	73	74	75	76	77
R^1	H	OCH_3				H	OCH_3	OCH_3
R^2			OCH_3	OH	H	OCH_3	OH	H
R^3			CH_3	CH_3	CF_3	CH_3	CH_3	CF_3

Scheme 25

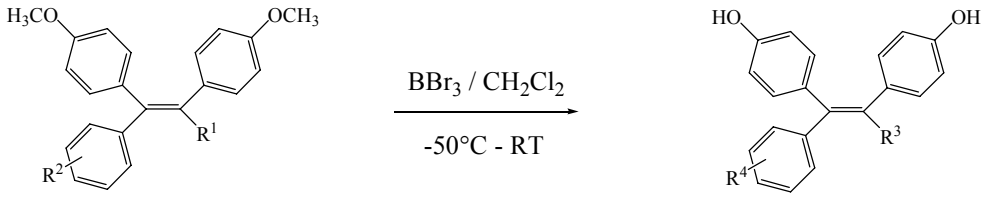
All three compounds **75 - 77** were prepared starting from the commercially available corresponding aryl ketones **70 - 74**. In each case two corresponding ketones were first mixed in tetrahydrofuran and then added to the freshly formed low-valent titanium reagents and heated under reflux for 4 hours. After work-up the crude products were separated by column chromatography on silica gel. In each case symmetrical self-coupling of the starting ketones took place too, but the crossed coupling product was isolated as major product. The yields of **75 - 77** were 74%, 38% and 74%, respectively. So the functional phenol group could be conveniently introduced into the tetrasubstituted ethene during this preparation without protection.

3,3,3-Trifluoro-1,1-bis(4-methoxyphenyl)-2-phenylprop-1-ene **77** was prepared in the literature [Middleton, 126 and 127] by the stepwise replacement of the olefinic fluoro atoms of 2-phenylpentafluoro-1-propene with 4-methoxyphenyl group in a low yield of less than 10%. Obviously, the above-described reductive coupling method is a better alternative to prepare this compound. The product obtained in this work was a viscous orange syrup and it was unfortunately found that this product include still minor impurities which was observed in its NMR-spectra as described in literature [Middleton, 126]. Attempts to purify were unsuccessful.

The ^{1}H NMR-spectrum of **75** shows two singlets, one at 2.11 ppm assigned for the methyl protons and another at 3.75 ppm assigned for the methoxy protons, as well as the signals in the range of 6.66 - 7.38 ppm with an integration of fourteen protons consistent with the aromatic protons. The mass spectrum of **75** shows the molecular ion as the base peak at m/z 300. In the ^{1}H NMR-spectrum of **76** taken in $CDCl_3$ are observed three singlets and three AA'BB' groups. The singlet at 2.10 ppm is assigned for methyl protons, two singlets at 3.70 and 3.82 ppm for two methoxy groups and the three AA'BB' groups in the range of 6.50 - 7.20 ppm for the aromatic protons. The hydroxy proton exhibits a broad and weak signal at 4.72 ppm. The IR-spectrum of **76** shows the typical hydroxy absorption as a broad and medium peak at 3363 cm^{-1}. In its mass spectrum the peak of the molecular ion and the base peak appear at m/z 346 (3%) and 42 (100%), respectively. The elemental analyses of **76** also support the depicted structure.

3.2.2.5 Ether cleavage of 2-alkyl-1,1,2-triarylethenes 66, 68 and 69

The ether cleavage of **66**, **68** and **69** into the hydroxylated derivatives **78** - **80** was performed with boron tribromide in dichloromethane according to the known procedure that have been already used to prepare a number of hydroxylated 2-alkyl-1,1,2-triarylethenes [Lubczyk, 83 and 84].



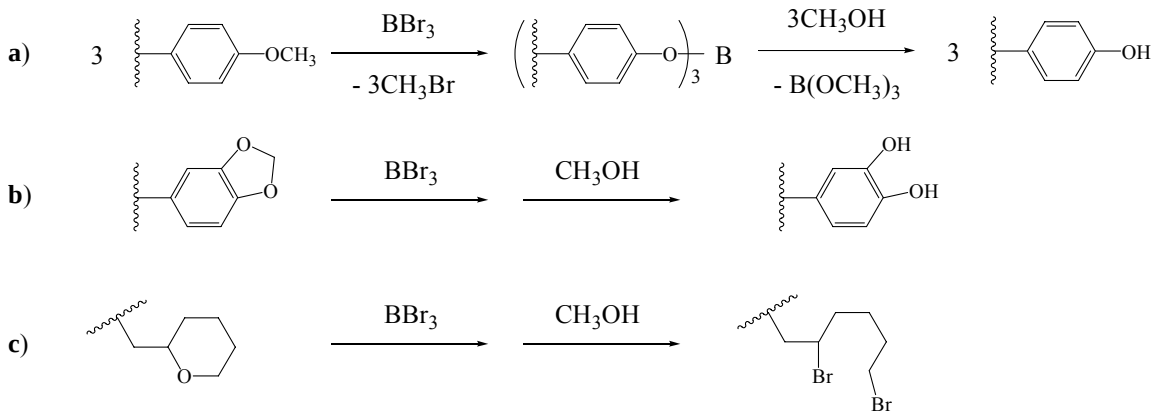
66, 68, 69 **78 -80**

Compound	**66**	**68**	**69**	**78**	**79**	**80**
$R^3(R^1)$	(CH_3)	(Y*)	(C_2H_5)	CH_3	2,6-Br_2-hexyl-	C_2H_5
$R^4(R^2)$	(OCH_3)	(OCH_3)	(Z*)	OH	OH	3,4-$(OH)_2$

* Y = tetrahydropyran-2-yl-methyl-; Z = benzo[1,3]dioxole-5-yl-

Scheme 26

Boron tribromide was added to a solution of the methyl ether protected compound in dichloromethane at –50°C and stirred 2 hours at this temperature and then further 24 ~ 48 hours at room temperature. Methanol was used to hydrolyze the formed complex as depicted in scheme 27a [Benton, 114] and the excess of boron tribromide. The crude products **78** - **80** were purified by column chromatography on silica gel. It is worthy to note that the benzo[1,3]dioxole-5-yl group of **69** was also cleaved to form the 3,4-dihydroxyphenyl group of the product **80** (Scheme 27b). This can be easily understood as the cleavage of a cyclic benzene-1,2-diol ether. More surprisingly, the tetrahydropyran-2-yl-methyl group of **68** was also cleaved to form the 2,6-dibromohexyl group of the product **79** (Scheme 27c). A possible explanation for this conversion is that either boron tribromide or the late-formed hydrobromide cleaved the tetrahydropyran ring into a bromopentanol, followed by substitution of bromo group (HBr) against the hydroxy group to give the corresponding dibromoalkyl group. Hydrobromide was formed by the methylation of boron tribromide.



Scheme 27

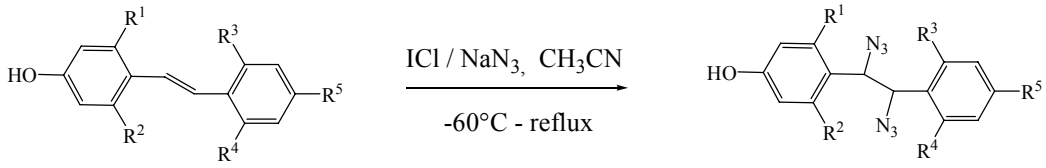
The structures of **78** - **80** are confirmed by ^{1}H NMR- and mass spectra as well as elemental analyses. The ^{1}H NMR-spectrum of **78** is consistent with that described in the literature [Lubczyk, 84]. In the ^{1}H NMR-spectrum of **79** taken in CD_3OD, the signals of the methoxy protons of the starting compound **68** disappear, while the signals of the aromatic protons and the multiplets of the 2,6-dibromohexyl group are observed with changed chemical shifts in comparison to those of the tetrahydropyran-2-yl-methyl group of the starting material **68**. The cleavage of the tetrahydropyran-2-yl-methyl group to the 2,6-dibromohexyl group was deduced and confirmed mainly by mass spectrum and elemental analyses. In the mass spectrum of **79**, the weak parent peak is shown at m/e 546 (0.7%) with two isotopic peaks 544 and 548. The fragments M^+-HBr^+ and M^+-$2HBr^+$ are observed at m/e 466 (2.2%) and 384 (3.1%). The base peak at m/e 94 corresponds to the phenol ion. The isotopic fragment HBr^+ is shown at m/e 82 (29%) and 80 (37%). In addition, the elemental analyses support the structure of 4,8-dibromo-1,1,2-tris(4-hydroxyphenyl)oct-1-ene (**79**). In the ^{1}H NMR-spectrum of the diastereomer mixture **80** taken in CD_3OD, not only the signals of methoxy protons but also the two singlets of the dioxole methylene protons of the starting compound **69** disappear completely. The signals of the aromatic protons and the ethyl protons remain visible. This indicates that, besides the methoxy groups, also the benzo[1,3]dioxole-5-yl group of the starting compound **69** was cleaved by boron tribromide into the 3,4-dihydroxyphenyl group and the compound **80** is still a mixture of hydroxylated *E*- and *Z*-isomers, because all of the shown signals are double so many as that of one isomer. In the mass spectrum of **80**, the peak of the parent ion is shown as the base peak at m/z 348. The elemental analyses of **80** support the described structure.

3.3 Synthesis of Hydroxylated 1,2-Diaryl-1,2-diazidoethane

Organic azides have been widely investigated and used in organic synthesis as precursors for nitrene and amino compounds and as dipole for N-containing heterocyclization. The general synthesis and conversion of organic azides were summarized by Hassner [Hassner, 128]. Only a few methods were employed to prepare aryl-substituted 1,2-diazidoethanes. For example, treatment of styrol with sodium azide in the presence of iron (II) und ammonium persulfat gives 1,2-diazido-1-phenylethane [Minisci, 129]; Enantiomerically pure 1,2-diphenylethane-1,2-diamines were achieved by the conversion of enantiomerically pure 1,2-diphenylethane-1,2-diols to the di-p-toluenesulfonates and subsequent reaction with sodium azide in DMF [Pini, 130]; Especially, a number of 1,2-diaryl-1,2-diazidoethanes as precursors for diamines were synthesized from 1,2-diarylethenes with iodazide [Gust, 94; Müller, 131; Brunner, 132] that was freshly prepared from iodmonochloride and sodium azide according to the method of Fowler *et al* [Fowler, 133]. However, none of them contained 4-hydroxy-substituent in the phenyl ring except only one compound, 1,2-diazido-1-hydroxymethyl-1-p-hydroxyphenylethane, which was prepared by reaction of the corresponding oxirane with sodium azide [Caubere, 134].

Compared to oxirane, substituted stilbene as starting material is obviously convenient and practical for synthesis of 1,2-diaryl-1,2-diazidoethanes bearing a 4-hydroxy-substituent in the phenyl ring. Therefore, some attempts to prepare hydroxylated 1,2-diaryl-1,2-diazidoethanes were carried out in the present work either by ether cleavage of hydroxy-protected 1,2-diaryl-1,2-diazidoethane or by direct azidation of hydroxylated stilbenes.

The debenzylation of 1,2-diazido-1-(4-benzyloxyphenyl)-2-phenylethane (data not shown) was firstly attempted using boron trichloride-dimethyl sulfide complex [Scheurer, 135] in dichloromethane to afford no desired compound. Further attempts by the direct azidation of hydroxylated stilbenes with iodazide based on the known procedure [Gust, 94] were fortunately successful and thus a series of hydroxylated 1,2-diaryl-1,2-diazidoethanes were synthesized as depicted in scheme 28:



33-36*E*, 38*E*, 41*E*, 42*E*, 44-46*E* 48*E*, 49*E*

81 -95

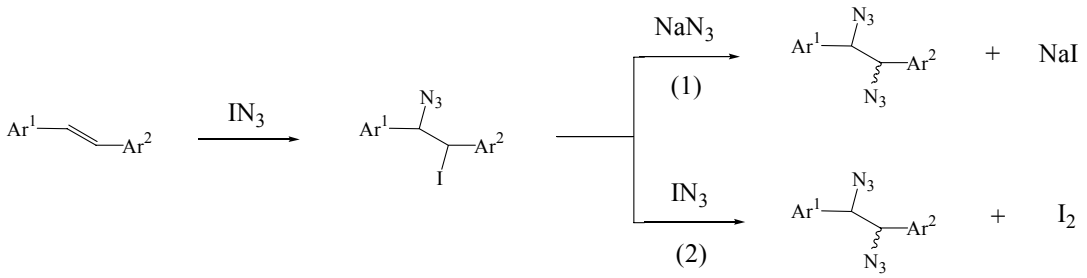
Compound	R^1	R^2	R^3	R^4	R^5	Configuration	Yield* (%)	Mp (°C)
81	H	H	H	F	OCH_3	*threo*	14	oil
82	H	H	H	Cl	OCH_3	*threo*	22	oil
83	H	H	Cl	Cl	OCH_3	*threo*	23	88-89
84	Cl	Cl	H	H	OCH_3	*threo*	6	84-86
85	H	H	Cl	OCH_3	Cl	*threo*	28	oil
86	H	H	H	H	OH	*meso*	37	136(dec.)
87	H	H	H	H	OH	*dl*	31	114(dec.)
88	H	H	H	F	OH	*erythro*	29	114-115
89	H	H	H	F	OH	*threo*	36	oil
90	H	F	H	F	OH	*dl*	26	oil
91	H	F	H	Cl	OH	*erythro/threo*	82	-
92	H	Cl	H	Cl	OH	*meso/dl*	43	-
93	H	Cl	Cl	Cl	OH	*erythro*	46	148-150
94	H	Cl	Cl	Cl	OH	*threo*	32	135-136
95	Cl	Cl	Cl	Cl	OH	*meso*	46	193(dec.)

* isolated yield without optimisation.

Scheme 28

The preparation of the hydroxylated 1,2-diaryl-1,2-diazidoethanes **81 - 95** was performed by using the corresponding stilbenes and one molar equivalent of iodazide in acetonitrile. The general reaction was described as three steps in situ. Sodium azide was first treated with iodmonochloride in acetonitrile at –10°C to generate fresh iodazide, to which the hydroxylated stilbene was then added at –50 ±10°C. Addition of iodazide to the double bond of the stilbene formed 1,2-diaryl-1-azido-2-iodoethane, which without isolation was reacted with an excess of sodium azide by heating by substitution of N_3^- against I^- finally to give the desired hydroxylated 1,2-diaryl-1,2-diazidoethane.

It was noteworthy and important that the used iodmonochloride in this work was only one molar equivalent to the corresponding stilbene rather than two molar equivalents as by the azidation of stilbenes without 4-hydroxy-substituent [Gust, 94]. Attempts with two molar equivalents of iodmonochloride were unsuccessful, from that no or very little desired products were isolated. A possible explanation for these results might be the different reaction mechanism and the different activities between phenol and methoxyphenyl groups. Both lines had the same reaction mechanism for the formation of the 1,2-diaryl-1-azido-2-iodoethane, which was rapidly completed at low temperature, but the following substitution of N_3^- against I^- to give desired compounds took place in different pathways (Scheme 29):



Scheme 29

The former with one molar equivalent of iodmonochloride is depicted as the line (1): The formed 1,2-diaryl-1-azido-2-iodoethane was reacted with excess of sodium azide under reflux to give 1,2-diazidoethane and sodium iodide; whereas the latter with two molar equivalents of iodmonochloride was accomplished according to the line (2): The formed 1,2-diaryl-1-azido-2-iodoethane was reacted with excess of iodazide to form 1,2-diazidoethane and a by-product iodine [Gust, 94; Müller, 131]. The reason for the unsuccessful azidation of hydroxystilbenes using two molar equivalents of iodazide might lie in the excess of iodazide and the by-product iodine that as oxidants had no effect on methoxystilbenes, but perhaps damaged the hydroxystilbenes or the products hydroxylated 1,2-diaryl-1,2-diazidoethanes. That is to say, some detrimental by-reactions might be in competition with the azidation.

Based on the yields of products and our experience, some generalities about the synthesis of hydroxylated 1,2-diaryl-1,2-diazidoethanes were extracted as following.

(1) Azidation reactivity of stilbenes: Dihydroxylated stilbenes appeared to have more reactivity than monohydroxylated stilbenes. In the synthesis of the monohydroxylated diazidoethanes **81** - **85**, much amount of unreacted stilbenes were separately observed, while no or less unreacted stilbenes were observed in the synthesis of the dihydroxylated compounds **86** - **95**. A possible explanation is that the dihydroxylated stilbene has higher

azidation reactivity and thus its azidation can win the competition with the detrimental by-reactions until iodmonochloride is completely consumed.

(2) Configuration of products: It has been found that both diastereomers of hydroxylated 1,2-diaryl-1,2-diazidoethane are formed, without a diastereomer significantly predominating. This is different from the azidation of dimethoxystilbene with two molar equivalents of iodmonochloride, in which the azidation of stilbene took place with high stereoselectivity, namely, the *E*-stilbenes yielded the *threo*-isomer, while the *Z*-stilbenes mainly afforded the *erythro*-isomers [Gust, 94]. The above-described mechanisms separately contain two steps. Obviously, the same first step is not the reason for the difference of stereoselectivity. Preceding studies on the reaction of olefins with iodazide revealed that such additions occur with a remarkably high degree of stereo- and regioselectivity, suggesting a three-membered-ring iodonium ion intermediate. The greater stability of a three-membered-ring iodonium ion was suggested by the stereospecific anti adition of iodazide to the olefin [Hassner, 136 and 137]. Therefore, the different second steps in the two mechanisms determine the difference of stereoselectivity.

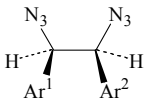
(3) Isolation and yields: The isolation and purification of the *erythro (or meso)* and *threo (or dl)* isomers was performed by column chromatography. If the azidation is complete without the unreacted stilbene remaining, it will be easy to separate the product mixture into two pure diastereomers in higher yields. The diastereomer pairs **86** / **87**, **88** / **89** and **93** / **94** belong to this group. On the contrary, it is difficult to separate the diastereomers from the unreacted stilbene. Due to this, the compounds **81** - **85**, **90** and **95** were partially isolated as one of two diastereomers in lower yields, respectively. The rest of them and their diastereomer partners remained in a mixture with the unreacted stilbene, respectively. In addition, the two mixtures of diastereomers **91** and **92** were only purified but could not be separated into two pure diastereomers by column chromatography after many attempts. After isolation of a sufficient quantity of the compounds **81** - **95** for characterization and biological tests, an optimization of the yields was not carried out.

The structures of the hydroxylated 1,2-diaryl-1,2-diazidoethanes **81** - **95** were confirmed by NMR-, IR- and MS-spectroscopy as well as elemental analyses. The chemical shifts of the comparable signals of the compounds **81** - **95** in their ^{1}H NMR-spectra were sorted out in table 7.

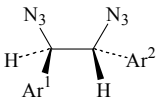
Table 7. ^{1}H NMR Spectral Properties and Configuration of Diazidoethanes **81 - 95**

Compound	Solvent	Chemical shifts (ppm)			Configuration
		OH	CHN_3–CHN_3 (J, Hz)	Ar-H	
81	$CDCl_3$	4.80	4.68, 4.88 (8.5)	6.47-7.15	*threo*
82	$CDCl_3$	4.82	4.71, 5.15 (7.1)	6.75-7.33	*threo*
83	DMSO-d_6	9.54	5.53, 5.58 (10.3)	6.61-7.08	*threo*
84	DMSO-d_6	10.57	5.53, 5.62 (10.3)	6.73-7.19	*threo*
85	DMSO-d_6	9.54	5.27, 5.52 (10.2)	6.60-7.07	*threo*
86	CD_3OD		4.68 (s, 2H)	6.76-7.11	*meso*
87	CD_3OD		4.65 (s, 2H)	6.63-6.95	*dl*
88	DMSO-d_6	9.62, 10.13	5.00, 5.09 (9.0)	6.54-7.31	*erythro*
89	DMSO-d_6	9.51, 10.01	5.07, 5.12 (9.9)	6.41-7.18	*threo*
90	DMSO-d_6	10.05 (2OH)	5.23 (s, 2H)	6.43-7.18	*dl*
91	DMSO-d_6	10.05, 10.08, 10.16 (2OH)	5.26-5.37 (4H)	6.45-7.34	*erythro/threo*
92	CD_3OD		5.31, 5.37 (2s, 4H)	6.67-7.31	*meso/dl*
93	DMSO-d_6	10.27, 10.77	5.75, 5.78 (10.7)	6.90-7.50	*erythro*
	$CDCl_3$	5.06, 5.28	5.61, 5.90 (10.4)	6.88-7.41	
94	DMSO-d_6	10.13, 10.62	5.67, 5.82 (10.5)	6.68-7.39	*threo*
	$CDCl_3$	4.94, 5.18	5.54, 5.87 (10.4)	6.71-7.35	
95	DMSO-d_6	10.81 (2OH)	6.30 (s, 2H)	6.99	*meso*

The characteristic and comparable absorption bands are that of phenolic hydroxy and benzylic protons. In the ^{1}H NMR-spectrum taken in DMSO-d_6, the signals of phenolic hydroxy protons appear as one or two singlets with the expected integral intensity in the range of 9.54 - 10.81 ppm. In $CDCl_3$ they are observed at about 4.80 ppm and in CD_3OD they are exchanged by deuterium. The resonances of the benzylic protons exhibit either two doublets in the range of 4.68 - 5.82 ppm with a coupling constant of 7.1 - 10.7 Hz for each asymmetrical 1,2-diaryl-1,2-diazidoethane or a singlet with a integral intensity of two protons in the range of 4.65 - 6.30 ppm for each symmetrical compound.



erythro
[also: *meso*; *(R,S)/(S,R)*]



threo
[also: *dl*; *(R,R)/(S,S)*]

Scheme 30

The *erythro* (*meso*) / *threo* (*dl*) configuration of the hydroxylated 1,2-diaryl-1,2-diazido-ethanes (Scheme 30) was deduced by comparison of their ^{1}H NMR-spectra with those of other methoxylated 1,2-diaryl-1,2-diazidoethanes described in the literature. In the previous publication, the configuration of *threo*-1,2-diazido-1-(2-methoxyphenyl)-2-phenylethane was confirmed by an X-ray crystal analysis. It was found that the coupling constant of the benzylic protons of the *erythro* isomer shows a higher value (10 Hz) than that of the *threo* isomer (7 Hz) [Müller, 131]. In an other literature, the benzylic protons of the *erythro* / *threo* isomers of 1,2-diazido-1-(2,6-dichloro-4-methoxyphenyl)-2-(2-chloro-4-methoxyphenyl)ethane exhibit a similar coupling constant of about 10 Hz in their ^{1}H NMR-spectra, but that of the *erythro* isomer shows a lower value (9.6 Hz) than that of the *threo* isomer (10.2 Hz) [Gust, 94]. This difference makes it difficult to assign the *erythro* / *threo* configuration of 1,2-diaryl-1,2-diazidoethane based on the coupling constant of the benzylic protons. Moreover, no coupling constant of the benzylic protons is exhibited by symmetrical 1,2-diaryl-1,2-diazidoethane. Fortunately, there is a characteristic property in the ^{1}H NMR-spectrum for the assignment of the *erythro* (*meso*) / *threo* (*dl*) configuration of the 1,2-diaryl-1,2-diazidoethane based on the results described in both publications [Gust, 94; Müller, 131]. The absorption bands of the aromatic protons of the *erythro* (*meso*) isomer appear in lower fields in comparison to that of the *threo* (*dl*) isomer. According to this method, the *erythro* (*meso*) / *threo* (*dl*) configuration of the diastereomer pairs obtained in this work were assigned, e.g. **93** and **94**. The signals of whole aromatic protons of **93** are shifted to the lower fields compared to that of its isomer **94** and so the isomer **93** is assigned to *erythro* form and **94** to *threo* form (see Figure 19 and 20). The R_f values on TLC with a mixture of dichloromethane and diethyl ether (3 : 1) as eluent are 0.73 for the isomer **86** and 0.61 for the isomer **87**. In addition, all the *erythro* (*meso*) isomers were found to have less polarity on TLC than the corresponding *threo* (*dl*) isomers. This has been also used as supplementary method to assign the *erythro* (*meso*) / *threo* (*dl*) stereochemistry of the alone-isolated diastereomer in this work.

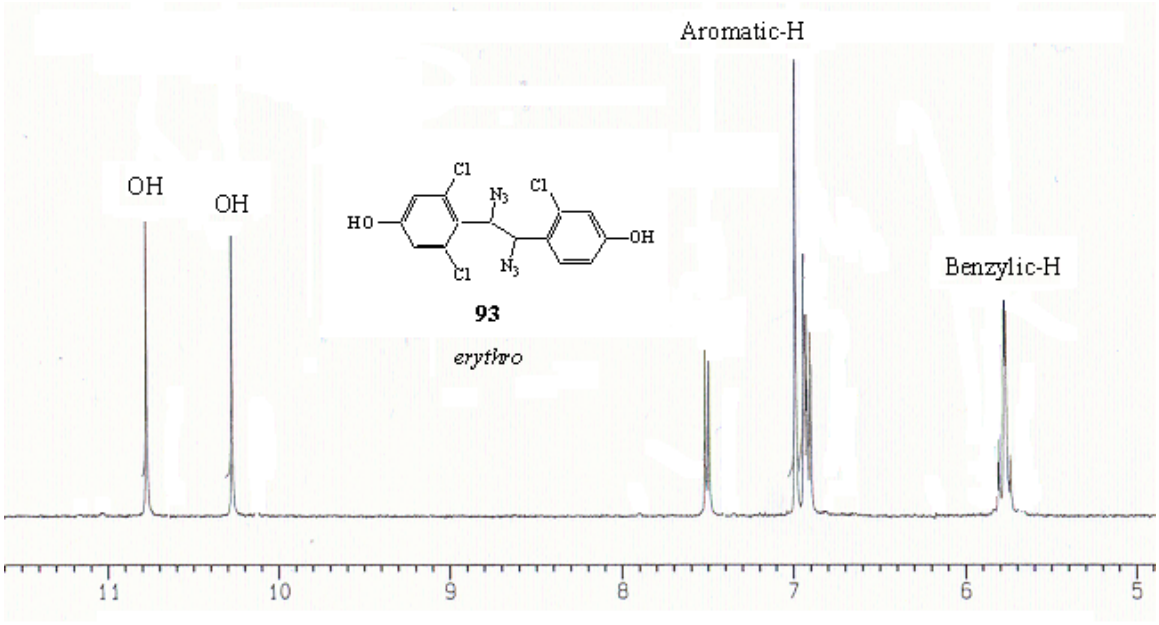


Figure 19. ^{1}H NMR-Spectrum of **93** (*erythro*) in DMSO-d_6.

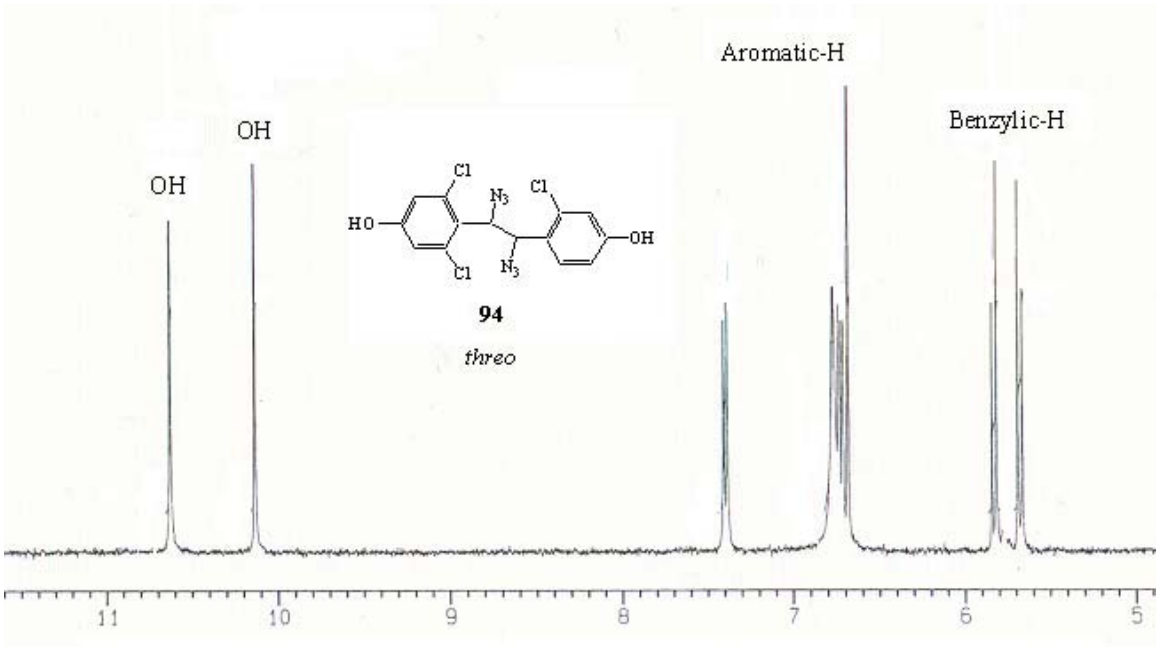


Figure 20. ^{1}H NMR-Spectrum of **94** (*threo*) in DMSO-d_6.

The configuration of the symmetric 1,2-diaryl-1,2-diazidoethanes was also assigned to *meso* or *dl* by comparison of the clearly different chemical shifts of the whole aromatic protons of the diastereomers. For instance, the signals of aromatic protons of **86** are observed at the lower field with the shift values of 6.76 and 7.11 ppm compared to that of its isomer **87** with the shift values of 6.63 and 6.95 ppm (see Figure 21). The R_f values on TLC with a mixture of dichloromethane and isopropanol (20 : 1) as eluent are 0.61 for the isomer **86** and 0.51 for the isomer **87**. And so the diastereomers **86** and **87** were assigned to the *meso* and *dl* configuration, respectively.

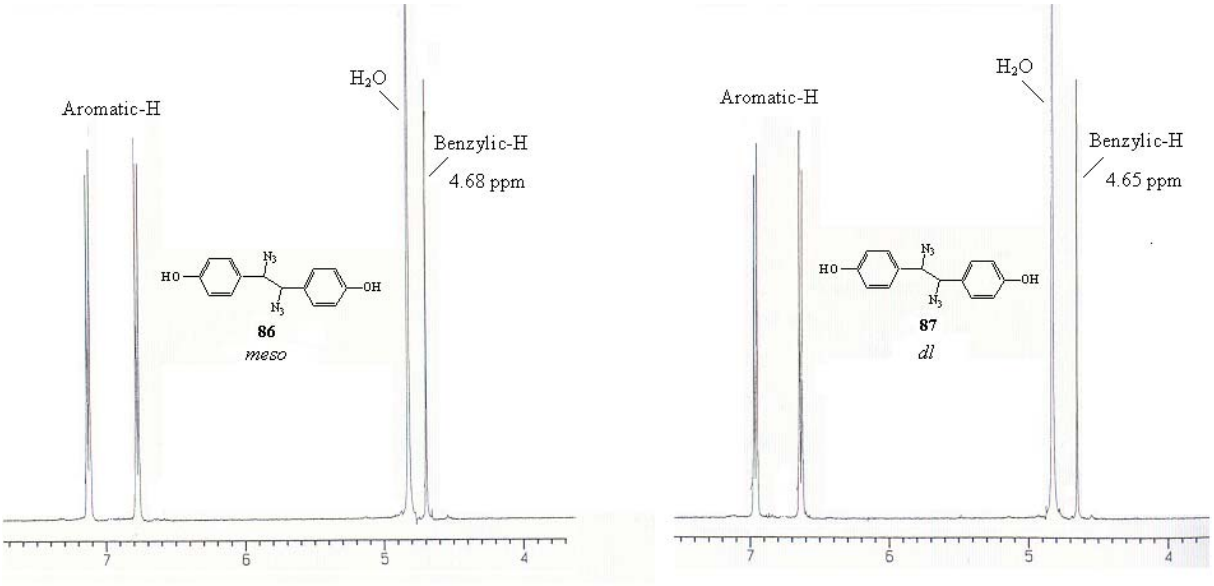


Figure 21. ^{1}H NMR-Spectra of **86** (*meso*, left) and **87** (*dl*, right) in DMSO-d_6.

The assignments of the alone-isolated diastereomers **81** - **85** were performed first by comparison of the relative polarity on TLC with their diastereomers (which remained in a mixture and could not be further separated) and then by comparing their NMR-spectra with those of other methoxylated 1,2-diaryl-1,2-diazidoethanes [Gust, 94; Müller, 131]. For example, **82** was isolated as the second fraction after the other diastereomer (in a mixture). Its ^{1}H NMR-spectrum taken in $CDCl_3$ is depicted in figure 22. The chemical shifts (4.71 and 5.15 ppm) and the low coupling constant (^{3}J = 7.1 Hz) of the benzylic protons of the isomer **82** is consitent with that of the similar *threo*-1,2-diazido-1-(2-methoxyphenyl)-2-phenylethane (4.72 and 5.16 ppm, ^{3}J = 7.0 Hz) [Müller, 131].

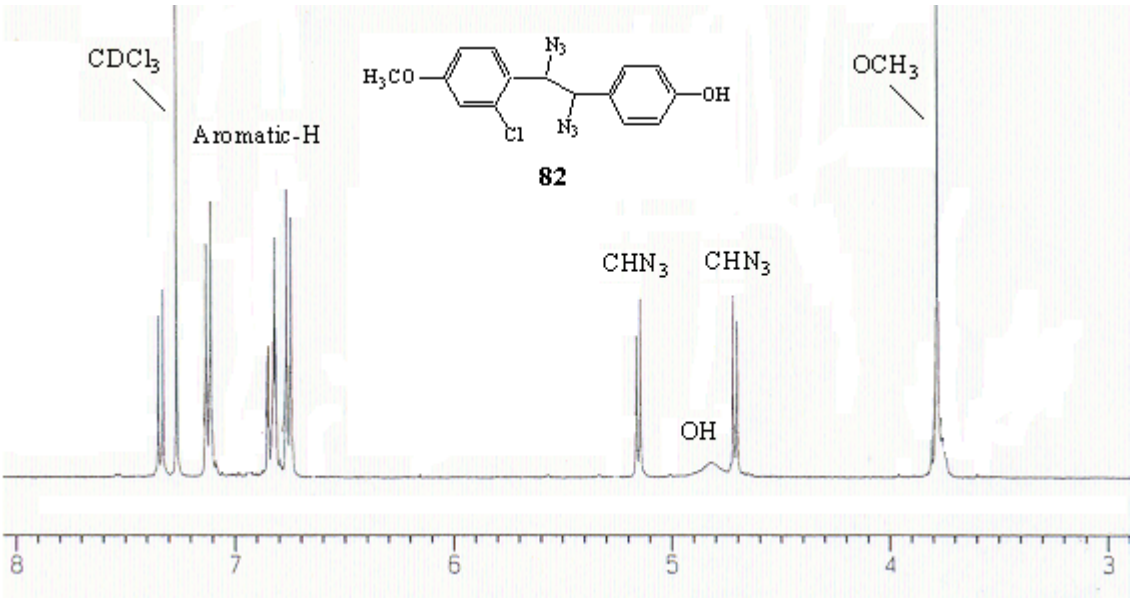
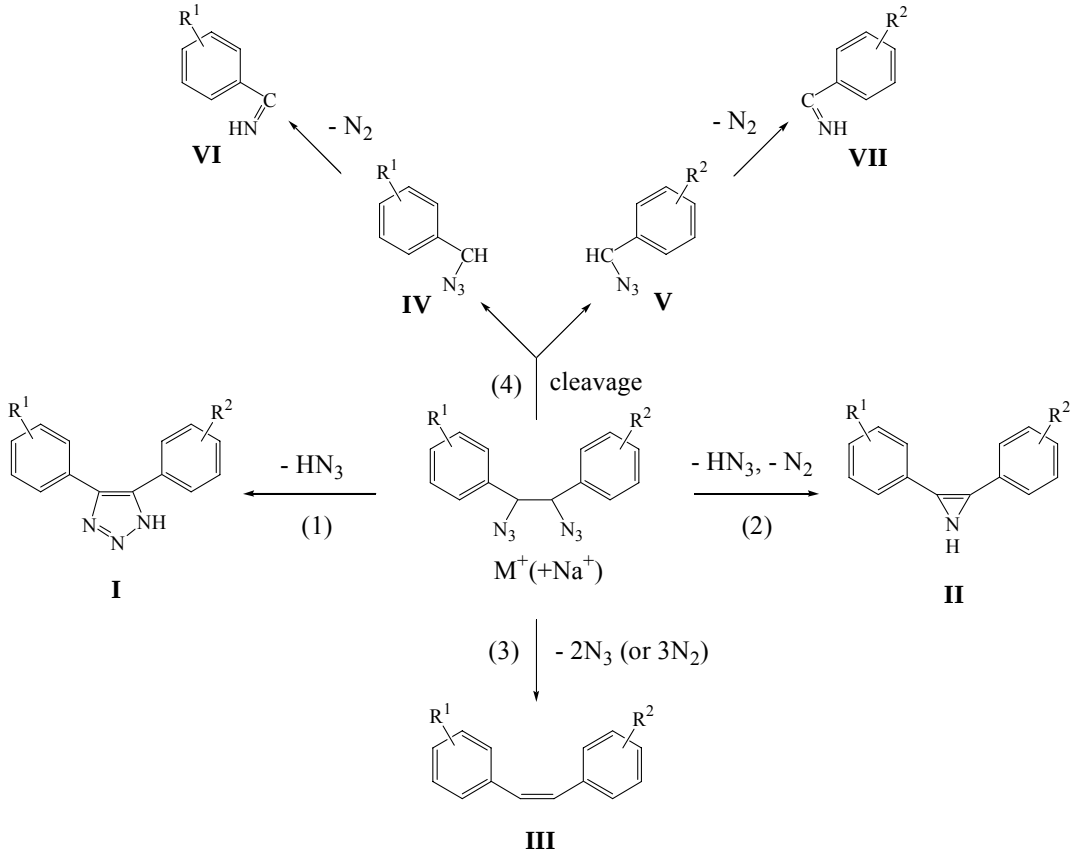


Figure 22. ^{1}H NMR-Spectrum of **82** (*threo*) in $CDCl_3$.

The structures, especially the azido groups of the compounds **81 - 95** are confirmed also by their IR spectra. All of the IR spectra show the strong and characteristic absorption band for the azido groups in the 2108 - 2100 cm^{-1} region, most of them at about 2106 cm^{-1}. The strong and broad absorption bands of the hydroxy groups of **81 - 95** appear in the region of 3440 - 3290 cm^{-1}.

"Fast Atom Bombardment"(FAB)-mass spectra and elemental analyses play a critical role in characterizing **81 - 95**. In the FAB-mass spectra, positive charged molecular ions are mostly formed by taking up protons and alkali ions in the form of $(M+H)^+$, $(M+Na)^+$ or $(M+K)^+$ (Quasi-ion) [Roellgen, 138]. In the determination of all of the compounds **81 - 95**, $(M+Na)^+$ was recorded as quasi-ion. Their fragementation are observed mainly in four patterns (Scheme 31): by the loss of (1) HN_3, (2) HN_3 / N_2 and (3) $2N_3$ to give rise to fragments **I**, **II** and **III**, respectively, as well as (4) with the cleavage of the $C(N_3)$–$C(N_3)$ bond to lead to fragments **IV** and **V**. In addition, the daughter ions **IV** and **V** could be further fragmented to **VI** and **VII** by the loss of N_2, respectively.



Scheme 31: Fragmentation pattern in the FAB-MS of **81 - 95**.

The corresponding quasi-ions $(M+Na)^+$ and fragments **I - VII** in the FAB-mass spectra of **81 - 95** are summaried in table 8. The peaks of the quasi-ions $(M+Na)^+$ are weak (< 10%) but can be readily observed. Most of the daughter ions **I - VII** are shown as (fragment $+H)^+$. For compounds **81**, **86**, **88**, **89**, **91** and **95**, the daughter ion **I** does not appear. Also the fragment **IV** is not observed for compounds **84** and **85**. Nevertheless, FAB-mass spectra are very useful and reliable for characterizing hydroxylated 1,2-diaryl-1,2-diazidoethanes due to the above-described general fragmentation patterns.

Table 8: FAB-MS data of **81 - 85** in Acetonitrile / m-NO_2-Benzyl-OH

Compound	**Quasi-ion and Fragments m/z (%)**								
	$(M+Na)^+$	**I**	**II**	**III**	**IV**	**V**	**VI**	**VII**	**Base Peak**
81	351		258	244	180	148	152	120	231
	(4)		(15)	(25)	(8)	(22)	(60)	(63)	
82	367	301	274	260	196	148	168	120	247
	(6)	(4)	(22)	(28)	(15)	(13)	(81)	(74)	
83	401	336	308	294	230	148	202	120	120
	(8)	(3)	(11)	(14)	(6)	(31)	(41)	(100)	
84	401	336	308	294		162	188	134	121
	(5)	(2)	(5)	(7)		(11)	(13)	(95)	
85	401	336	308	294		148	202	120	107
	(2)	(1)	(6)	(7)		(33)	(11)	(70)	
86	319		226	212	148	148	120	120	120
	(1.4)		(9)	(11)	(24)	(24)	(100)	(100)	
87	319	253	226	212	148	148	120	120	120
	(3)	(1)	(12)	(18)	(19)	(19)	(100)	(100)	
88	337		244	230	166	148	138	120	120
	(3)		(9)	(12)	(14)	(34)	(58)	(100)	
89	337		244	230	166	148	138	120	136
	(5)		(13)	(14)	(10)	(10)	(60)	(72)	

(continued on page 71)

Table 8 (continued from page 70))

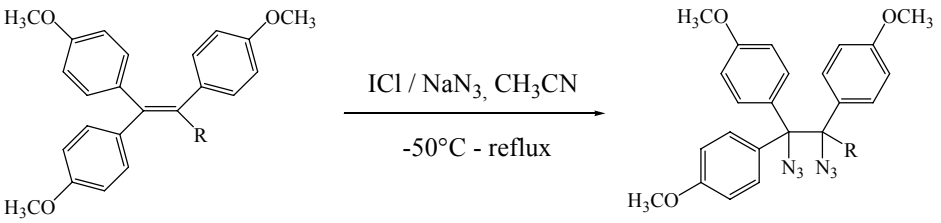
Compound	Quasi-ion and Fragments m/z (%)								
	$(M+Na)^+$	I	II	III	IV	V	VI	VII	Base Peak
90	355	289	262	248	168	168	138	138	138
	(2)	(2)	(21)	(25)	(16)	(16)	(100)	(100)	
91	371		278	264	182	166	154	138	138
	(3)		(13)	(19)	(10)	(27)	(78)	(100)	
92	387	321	294	280	182	182	154	154	154
	(1)	(1)	(8)	(8)	(11)	(11)	(100)	(100)	
93	421	355	328	314	216	182	188	154	154
	(2)	(2)	(4)	(5)	(4)	(8)	(25)	(100)	
94	421	355	328	314	216	182	188	154	154
	(5)	(2)	(3)	(6)	(4)	(9)	(27)	(100)	
95	455		362	348	216	216	188	188	154
	(2)		(2)	(3)	(2)	(2)	(30)	(30)	

The EI-MS analyses is less helpful for characterizing the hydroxylated 1,2-diaryl-1,2-diazidoethane **81** - **95**, since the parent ions of **81** - **95** are unobservable. But these results give an evidence of the lability of the hydroxylated 1,2-diaryl-1,2-diazidoethane in drastic condition and provide an evidence for the presence of different substituents. The dominant fragmentation pattern in the EI-mass spectra of all of these compounds involves cleavage of the both azido groups with the positive charge located on the fragment of M^+-$2N_3$ (**III**), also weak peaks of the fragments M^+-HN_3 (**81**, **82**, **83**, **85**) and M^+-HN_3-N_2 (**81** - **87**, **90**, **92**, **95**) are partially observed. The observed azido-containing daughter ions are at m/e 180 ($C_8H_7FN_3O^+$) for **81**, 196 ($C_8H_7ClN_3O^+$) for **82**, 166 ($C_7H_5FN_3O^+$) for **88**, **90** and **91**, 182 ($C_7H_5ClN_3O^+$) for **91** and **92** and 215 ($C_7H_3Cl_2N_3O^+$) for **93** and **94**. The fragment HN_3^+ at m/e 43 appears as the base peak in the spectra of **87** and **88**.

3.4 Synthesis of Tetrasubstituted 1,2-Diazidoethane

It is known that triaryl-1,2-diazidoethane could be synthesized by azidation of triarylethane with two molar equivalents of iodazide freshly prepared from iodmonochloride and sodium azide in acetonitrile [Gust, 95]. By means of this method two novel 2-alkyl-1,1,2-tris(4-

methoxyphenyl)-1,2-diazidoethanes **96** and **97** were prepared in high yields of 93 and 83% starting from the corresponding substituted ethenes **66** and **67**, respectively:



66, 67 **96, 97**

Compound	**96**	**97**
R	CH_3	C_2H_5

Scheme 32

The starting 2-alkyl-1,1,2-triarylethene was reacted with two molar equivalents of the freshly prepared iodazide in acetonitrile from –50°C to reflux. After the complete reaction, the mixture was extracted with diethyl ether. The combined organic phases were washed with 5% sodium thiosulfate in order to get rid of the by-product iodine, *etc*. After washing with water and drying over sodium sulfate, the residue of the ethereal phase was purified by column chromatography on silica gel with a mixture of ligroin and diethyl ether (3 : 1) to afford the pure product.

^{1}H- and ^{13}C-NMR-, IR- and MS-spectroscopy as well as elemental analyses were used to confirm the structure of two substituted 1,2-diazidoethanes.

The data of ^{1}H NMR-spectra of **66**/**96** and **67**/**97** sorted out in table 9 indicate that, after the conversion of **66** and **67** into **96** and **97**, none of the starting protons disappears and also no signal of new protons appears, but two marked changes of the signal art are observed. First, some of the signals of aromatic protons are out of ordinary AA'BB' systems but a broad band; Secondly, the two protons of the methylene group of **97** are diastereotopic and form an AB system shown as two broad band at 2.22 and 2.50 ppm.

Table 9. Comparison of ^{1}H NMR Spectral Properties of **66**/**96** and **67**/**97**

Compound	Chemical shifts (ppm, in $CDCl_3$)		
	Alkyl (R)	**OCH_3**	**Aromatic-H**
66	2.10 (s, CH_3)	3.69, 3.75, 3.82 (3s)	6.57, 6.70, 6.79, 6.87, 7.05, 7.14
96	1.87 (s, CH_3)	3.79 (s, 6H), 3.80 (s)	6.66-6.80 (m), 6.97, 7.03-7.40 (br.)
67	0.92, 2.45 (C_2H_5)	3.68, 3.75, 3.81 (3s)	6.55, 6.70, 6.78, 6.87, 7.02, 7.14
97	0.79, 2.22, 2.50 (C_2H_5)	3.79 (s, 6H), 3.80 (s)	6.70-6.80 (m), 7.01, 7.18-7.35 (m)

The signals of the aromatic protons of **96** in ^{1}H NMR-spectra taken in DMSO-d_6 at 20°C and 60°C are illustrated with cuts (Figure 23). Four proton signals are shown at 20°C as two broad bands at 7.08 and 7.23 ppm and at 60°C as two doublets at 7.12 and 7.22 ppm. The disorder of these signals at 20°C possibly results from a hindered rotation of the aromatic ring, which rotates freely at higher temperature.

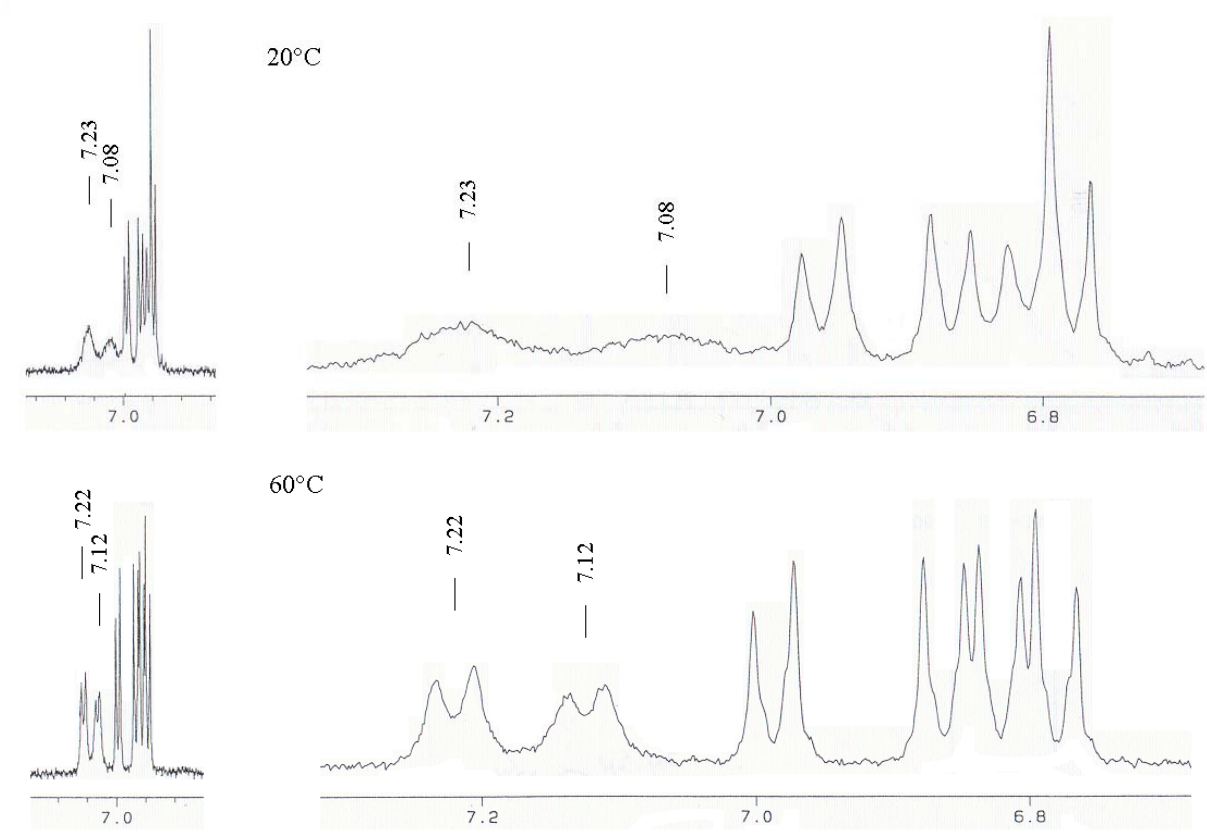
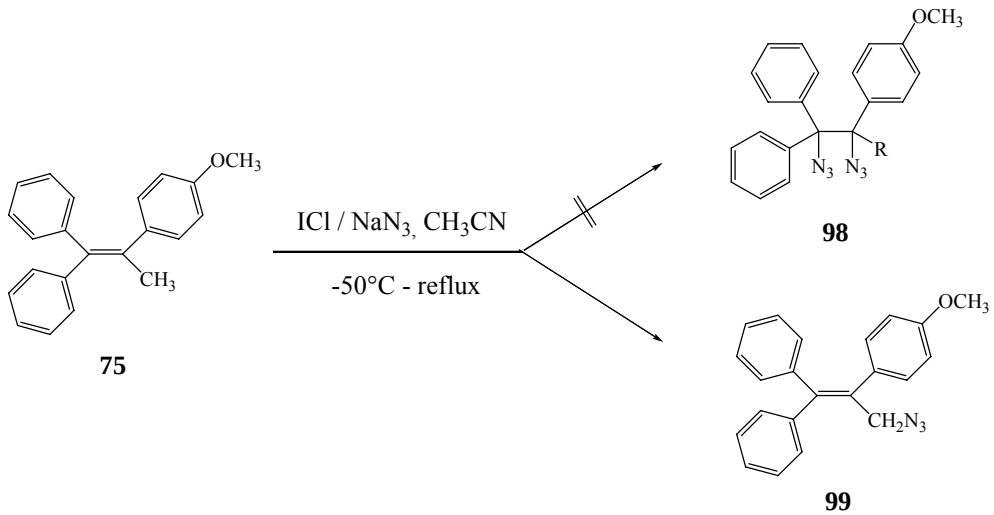


Figure 23. ^{1}H NMR-Spectra of **96** taken in $CDCl_3$ at 20°C (above) and 60°C (below).

The ^{13}C NMR-spectra of **96** and **97** show the expected number of carbon peaks. The aromatic carbons of each compound establish twelve peaks at the range of 112.5 - 159.0 ppm. The carbon signals of the methoxy groups of both compounds appear at 55.2 ppm (each 3C). The signals of the methyl group and the $C(N_3)$–$C(N_3)$ carbons of **96** are observed at 22.5 and 73.5/78.2 ppm, while that of the ethyl group and the $C(N_3)$–$C(N_3)$ carbons of **97** are shown at 8.6, 28.6 and 76.5 (2C) ppm. In the IR-spectra of **96** and **97**, the strong absorption of azido groups is observed at 2106 cm^{-1}. The FAB-mass spectra of **96** and **97** show the quasi-ion $(M+Na)^+$ at m/e 467 (for **96**) and 481 (for **97**). Also the daughter ions M^+-$2N_2$, M^+-N_3-N_2 and M^+-$2N_3$ are observed. In their EI-mass spectra, the observed fragments are at m/e 415 (M^+-N_2-H^+), 388 (M^+-$2N_2$), 360 (M^+-$2N_3$) for **96** and 402 (M^+-$2N_2$), 374 (M^+-$2N_3$) for **97**, while the peaks of their parent ions do not appear. The elemental analyses support the described structure. So two novel 2-alkyl-1,1,2-triaryl-1,2-diazidoethanes **96** and **97** were successfully synthesized by means of a convenient method.

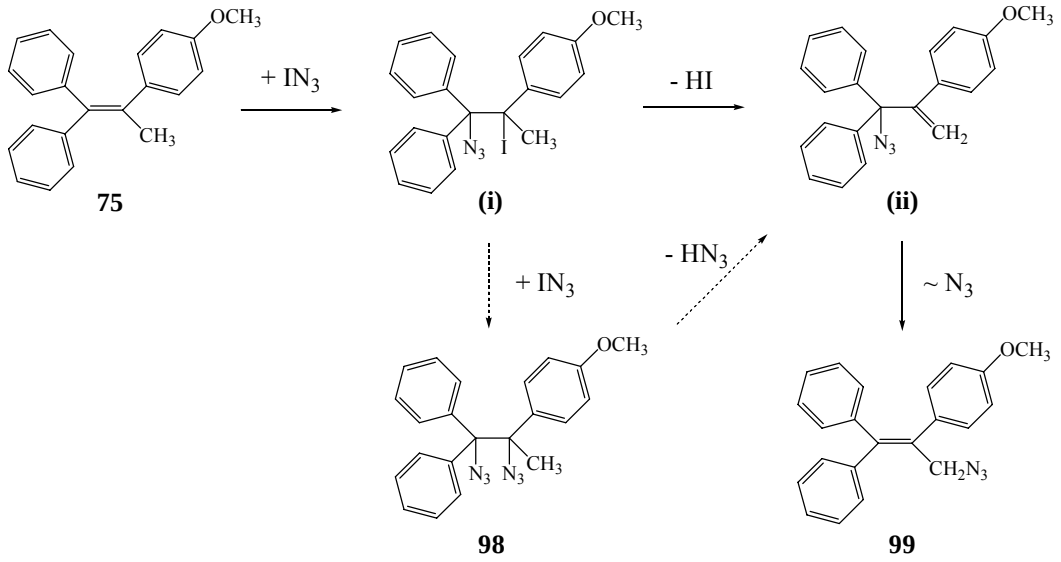
However, when 1,1,2-triarylpropene **75** was treated with freshly prepared iodazide under the same conditions, surprisingly, no corresponding 1,2-diazidoethane **98** was obtained and a new compound, 1,1,2-triaryl-3-azidopropene **99** was isolated in 27% yield, while the starting material **75** was recovered in 23% from the reaction mixture (see Scheme 33).



Scheme 33

Obviously, an elimination and a rearrangement took place after the reaction of **75** with iodazide. Based on similar results [Hassner, 137], a possible pathway for this reaction are suggested as shown in scheme 34. The addition of iodazide to **75** is stereospecific and yields the substituted 1-azido-2-iodopropane **(i)** [Fowler, 133]. The elimination of hydrogen iodide

from **(i)** gives 3-azidopropene **(ii)**, which rearranges to produce **99** [Hassner, 137]. A pathway over 1,2-diazidopropane **98** appears to be implausible. On the one hand, no 1,2-diazidopropane **98** was found in the reaction mixture; On the other hand, so long as **98** was formed, it should be stable under the reaction condition, as was the case with the substituted 1,2-diazidoethane **96** and **97**.

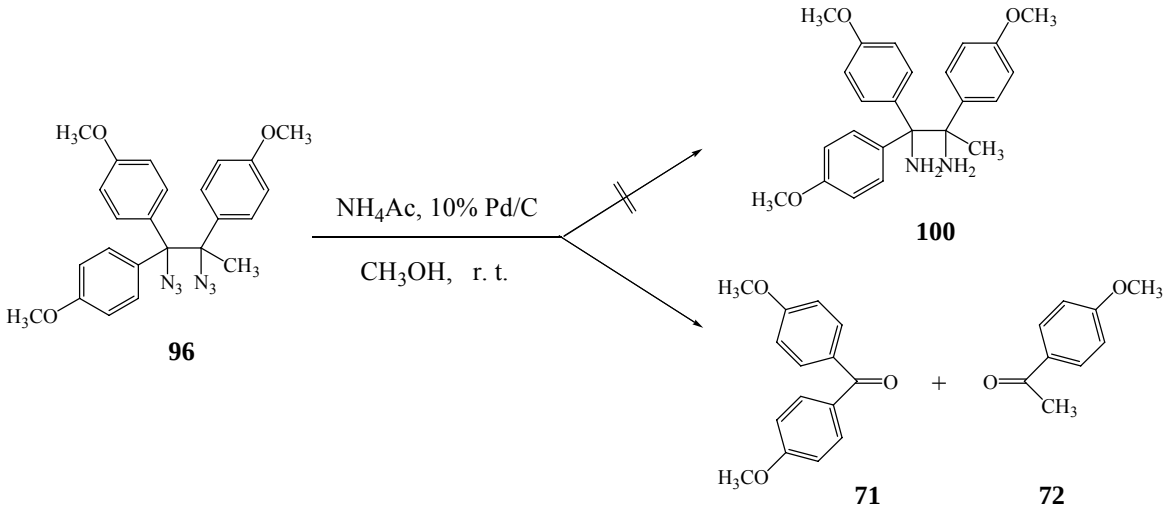


Scheme 34

In the ^{1}H NMR-spectrum of **99**, two singlets at 3.76 and 4.16 ppm are assigned to the methoxy and the methylene group. The aromatic protons signalize at 6.70 - 7.43 ppm. The ^{13}C NMR-spectrum of **99** shows sixteen peaks as expected and the peaks at 54.8 and 55.1 ppm are assigned to the methylene and methoxy carbons, while the others at 113.7 - 158.7 ppm are assigned to olefinic and aromatic carbons. No peak shifted at 60.0 - 90.0 ppm for aliphatic carbon similar to that of **96** / **97** is observed. The mass spectrum of **99** shows the peak of the parent ion also as the base peak at m/e 341. In the IR-spectrum of **99**, the characteristic strong absorption band for the azido group is observed at 2098 cm^{-1}. In addition, the elemental analyses support the structure of **99**.

More surprisingly, when 1,1,2-triaryl-3,3,3-trifluoroprop-1-ene **77** was treated with freshly prepared iodazide under the same conditions, no new compound was isolated except most of the starting material recovered from the reaction mixture. The reason why trifluoropropene **77** showed such a chemical stability by treating with iodazide lies possibly in the strong electron-withdrawing effect of the trifluoromethyl substituent on the double bond, which is therefore inactive for the addition reagent.

Attempts to reduce 1,1,2-triaryl-1,2-diazidopropane **96** to 1,1,2-triarylpropane-1,2-diamine **100** were unsuccessful. The compound **96** was easily cleaved at the $C(N_3)$–$C(N_3)$ bond into two moieties even by mild reducing agents such as ammonium acetate in the presence of 10% Pd/C in methanol at room temperature (Scheme 35).



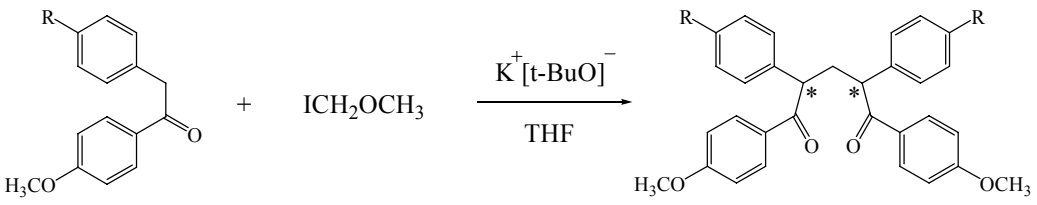
Scheme 35

Also the other methods available for converting diazides to diamines appeared to be ineffective.

3.5 Synthesis of 1,2,3,5-Tetraarylcyclopentene

3.5.1 Preparation of 1,2,4,5-tetraaryl-1,5-pentandione

1,2,4,5-Tetraaryl-1,5-pentandione was a key intermediate for the following reactions. The synthesis of its analogue was often started from deoxybenzoin by a one-step route. For example, 1,2,4,5-tetraphenyl-1,5-pentandione was prepared by treatment of deoxybenzoin either with 30% aqueous formaldehyde solution in the presence of potassium hydroxide [Carpenter, 139; Mackewitz, 140] or with methylene iodide in the presence of sodium ethanolate [Chakravarti, 141]. In the present work a new combination, iodomethyl methyl ether and potassium tert-butoxide, was applied to treat the deoxybenzoin **58** or **59** to give the corresponding diastereomeres **101** / **102** or **103** / **104** as depicted in scheme 36:



58, 59 **101 - 104**

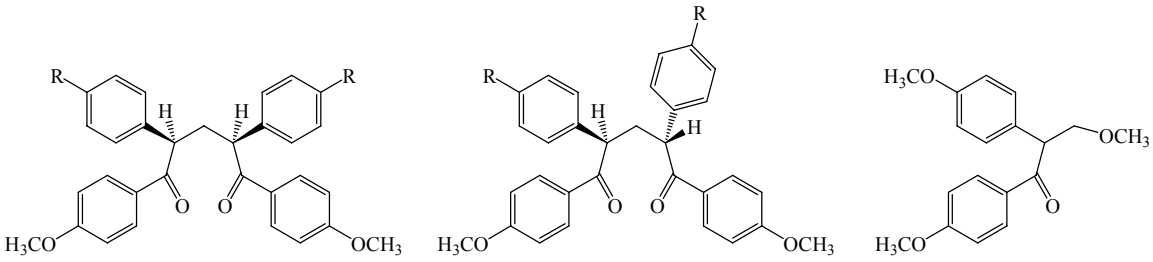
Compound	**101**	**102**	**103**	**104**
R	H	H	OCH_3	OCH_3
Configuration	*(2R,4S)/(2S,4R)*	*(2R,4R)/(2S,4S)*	*(2R,4S)/(2S,4R)*	*(2R,4R)/(2S,4S)*

Scheme 36

The deoxybenzoin was stirred in tetrahydrofuran with potassium tert-butoxide at room temperature for 30 minutes and to which iodomethyl methyl ether was added dropwise. An obvious colour change of the reaction mixture could be observed during the addition of iodomethyl methyl ether, and in the meantime the clear solution became a suspension. The suspensate should be potassium iodide. Monitoring the reaction by TLC indicated that the reaction was complete at room temperature after approximately 2 hours. The reaction mixture was extracted with diethyl ether and the crude product obtained from the ethereal phase was separated by column chromatography on silica gel with dichloromethane as eluent to give two pure diastereomers.

It is well-known that an alkyliodide can be used as an alkylating agent to alkylate the CH-acid compounds in the presence of a strong base. The methyliodide and ethyliodide have been employed to treat the deoxybenzoin **59** in the presence of potassium tert-butoxide to prepare the C2-alkyl-substituted 1,2-bis(4-methoxyphenyl)ethanones **63** and **64** as described in section 3.2.2.2. However, by using iodomethyl methyl ether as an alkylating agent under the same condition the deoxybenzoins **58** and **59** were alkylated to yield the corresponding 1,2,4,5-tetraaryl-1,5-pentandiones **101 - 104** formed from two molecules of deoxybenzoin and one molecule of iodomethyl methyl ether. The later in the presence of potassium tert-butoxide acts as a linkage-methenylating agent with two leaving groups of iodo and methoxy similar to the above-mentioned methylene iodide in the presence of sodium ethanolate [Chakravarti, 141]. Despite one molar excess of iodomethyl methyl ether to deoxybenzoin was used, neither C2-methoxymethylated deoxybenzoin nor C2-iodomethylated deoxybenzoin was observed except the 1,2,4,5-tetraaryl-1,5-pentandione. Therefore it is difficult to suggest a

methenylating mechanism. Because the deoxybenzoin was deprotonized by potassium tert-butoxide and the resulting anion was reacted with iodomethyl methyl ether without stereospecificity, this reaction produced two diastereomers (Scheme 37).



101, 103 *(2R,4S)* **102, 104** *(2R,4R)* **105**

Scheme 37

The structure and the configuration of the diastereomeric products **101** - **104** were deduced and confirmed by NMR- and mass spectra as well as elemental analyses.

The diastereomers **103** and **104** (R = OCH_3) were first synthesized and analyzed. The compound **105** as a product was completely excluded by the results of the taken analyses. In the ^{1}H NMR of **103** / **104**, the signals at the field of 2.29 - 2.90, 3.74 - 3.81, 4.40 - 4.43 and 6.76 - 7.88 ppm are easy to be assigned to the methylene, methoxy protons, aliphatic methine and aromatic protons, respectively. The proportion of the integrations of them is 2 : 12 : 2 : 16 versus 2 : 9 : 1 : 8 that is calculated from the structure **105**. The obtained product possesses at least a methoxy group, an aliphatic methine group and eight aromatic protons more than that of the structure **105**. This result indicates a reaction possibility that the C3-methoxy group of the possible intermediate **105** was substituted by a deprotonized deoxybenzoin anion to form the 1,2,4,5-tetraaryl-1,5-pentandione, of which the proportion of the different protons is consistent with the observed results. This perspective was confirmed by further analyses. In the mass spectra of **103** / **104**, the parent peak is located at m/e 524. The elemental analyses support the structure of 1,2,4,5-tetraaryl-1,5-pentandione. In the ^{13}C NMR-spectra of **103** and **104**, each of them shows thirteen signals including the peak of aliphatic CH at about 38.3 ppm, CH_2 at 50.0 ppm and C=O at 198.8 ppm consistent with that of the pentandiones.

The compounds **101** / **102** and **103** / **104** are two diastereomeric pairs. Their configurations were deduced by a further conversion with retention of the configuration into 1,2,3,5-

tetraarylcyclopentenes, the stereochemistries of which can be confirmed (see Section 3.5.2). The determined point lies in the different signals of the CH_2 protons (see Figure 24 and 25)

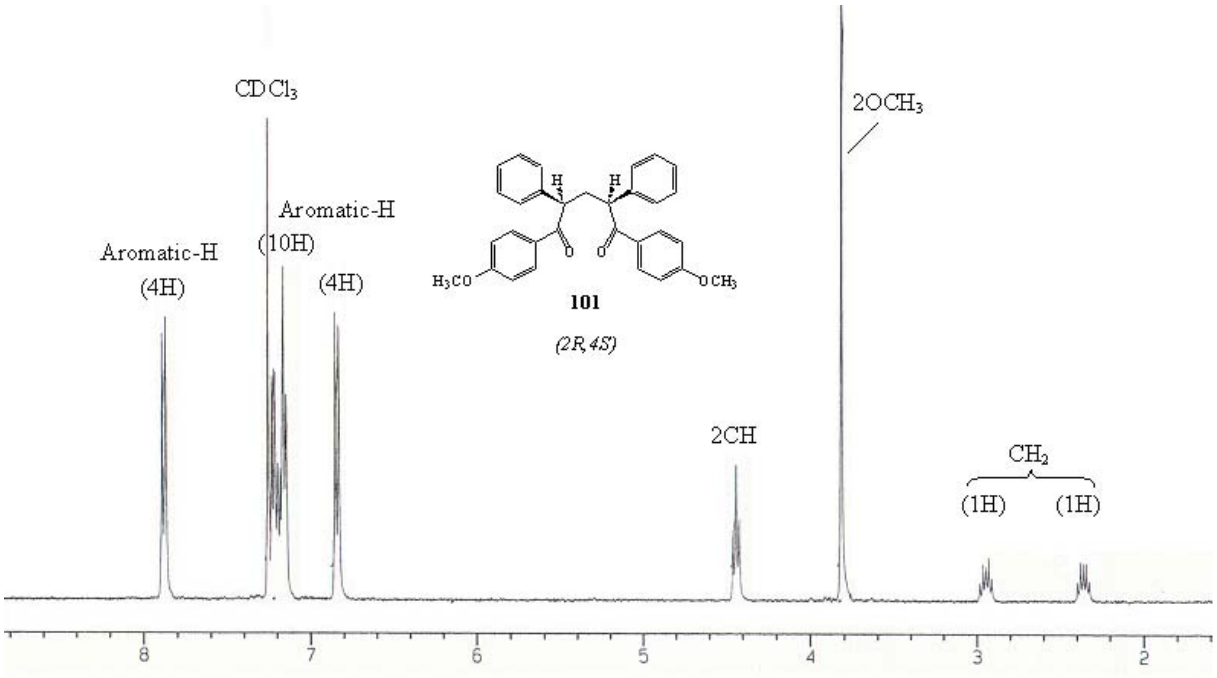


Figure 24. ^{1}H NMR-Spectrum of **101** *(2R,4S)/(2S,4R)* in $CDCl_3$.

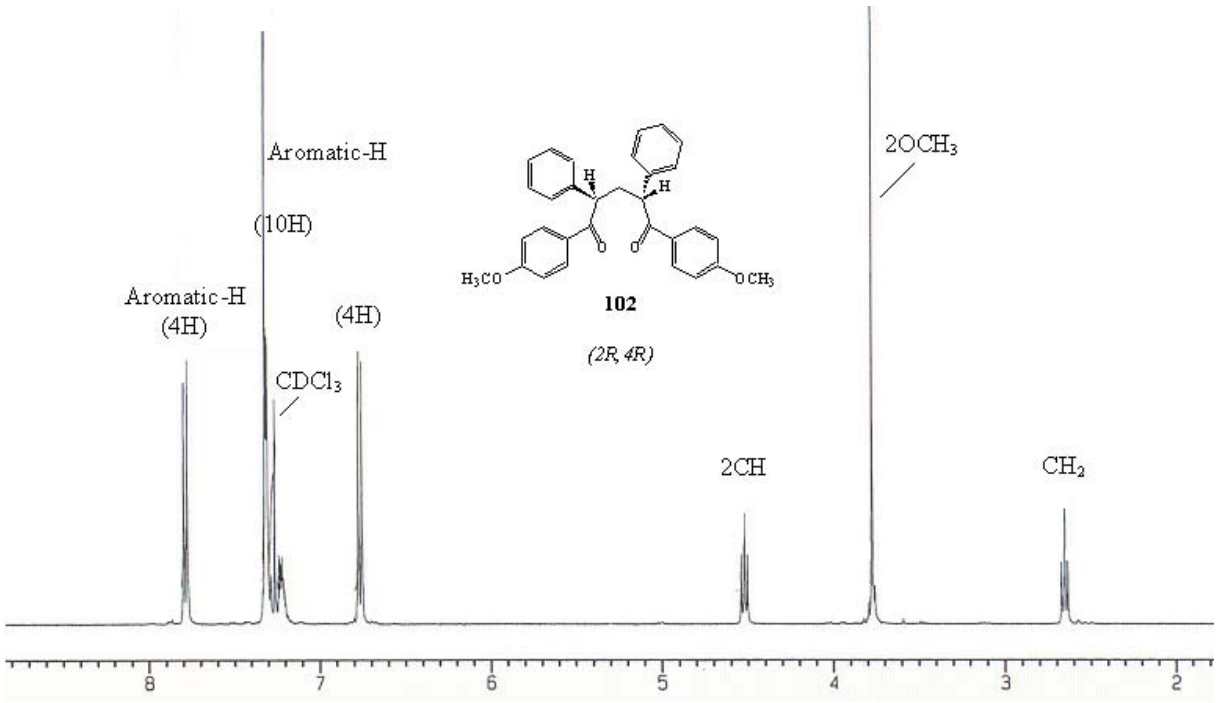


Figure 25. ^{1}H NMR-Spectrum of **102** *(2R,4R)/(2S,4S)* in $CDCl_3$.

In the ^{1}H NMR-spectra of **101** and **102**, the marked difference are the signals of the methylene protons. That of **101** are split into the AB figure shown at 2.29 and 2.90 ppm, because the two protons are diastereotopic and form the AB part of an ABC_2 system (Figure

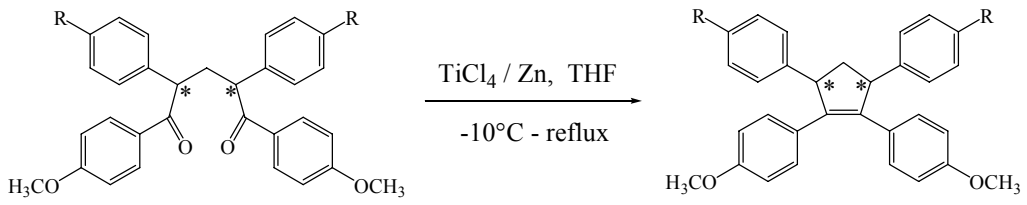
24). While that of **102** are observed as a triplet at 2.59 ppm, because the molecule of **102** possesses a C2 rotation axis through the methylene carbon so that the two methylene protons are chemically equivalent.

In conclusion, this section has provided a novel and convenient method to synthesize the diastereomeric 1,2,4,5-tetraaryl-1,5-pentandiones, which can be separated by column chromatography.

3.5.2 Stereospecific synthesis of 1,2,3,5-tetraarylcyclopentene

The intramolecular coupling of dicarbonyl compounds with low-valent titanium to prepare 1,2,3,5-tetraarylcyclopentene has not yet been reported, but several 1,2-diheteroaryl-cyclopentenes had been synthesized by this method [Huang, 142]. Among those examples, however, there are no examples concerning the isolation of the corresponding diastereomers. In a publication [Benetollo, 143], *(3R,5S)/(3S,5R)*-1,2,3,5-tetraphenylcyclopentene was prepared by catalytic hydrogenation of 1,2,3,4-tetraphenylcyclopentadiene with 10% palladium on charcoal as a catalyst and hydrogen gas under the pressure of 1 bar in acetic acid at 60°C for 67 hours.

By the intramolecular coupling starting from the pure diastereomer of the substituted 1,5-pentandione it is possible to directly prepare isomerically pure cyclopentene. In the last section, the diastereomers of 1,2,4,5-tetraaryl-1,5-pentandiones have been successfully isolated. With the known low-valent titanium reagent [Coe, 109] freshly prepared as described in section 1.1.2 we coupled the isomerically pure 1,5-pentandiones **101** - **103** in tetrahydrofuran under nitrogen atmosphere and reflux to the corresponding isomerically pure 1,2,3,5-tetraaryl-cyclopentenes **106** - **108**, which were obtained in high yields of 81 - 93%:



101 - 103 **106 -108**

Scheme 38

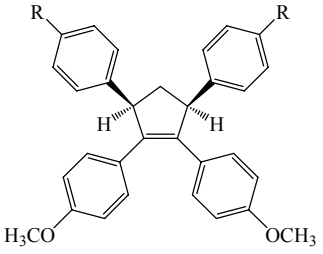
The purification of the crude products is very convenient. After the complete reaction, the reaction mixture was poured into ice-water and extracted with diethyl ether. After diethyl ether being removed, the residue was treated with a suitable solvent, e. g. ligroin or methanol, to give the pure desired product as fine crystals precipitating from the solvent. The crystalline product was collected by suction filtration and dried under vacuum.

The stereochemical assignments for **106 - 108** based on ^{1}H-NMR chemical shifts analogies to the known *cis*- and *trans*-1,2,3,5-tetraphenylcyclopentenes.

The crystal structure of *(3R,5S)/(3S,5R)*-1,2,3,5-tetraphenylcyclopentene had been determined by X-ray analysis [Benetollo, 143]. In its ^{1}H NMR-spectrum taken in $CDCl_3$, the signal of the methylene protons is split into an AB(C_2) system shown at about 2.13 and 3.17 ppm. In the present work, the ^{1}H NMR-spectra of the obtained diastereomers **106** and **108** as well as the starting compounds **101** and **103** show the similar split AB(C_2) signals of the methylene protons to that of the reported diastereomer, while the signals of the methylene protons of the other diastereomer **107** and the starting compound **102** in their ^{1}H NMR-spectra are observed separately as a triplet (see Table 10). So the diastereomers **106**, **108**, **101** and **103** were assigned as the *(R,S)/(S,R)* configuration, whereas the other diastereomeric compounds **107**, **102** and the unused compound **104** were assigned as the *(R,R)/(S,S)* configuration (see Scheme 39 also 38).

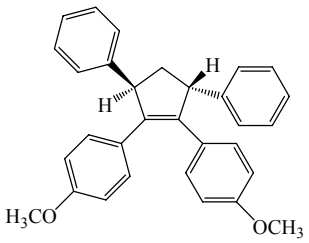
Table 10. ^{1}H NMR Spectral Properties of the Diastereomeric Compounds **101 - 104** and **106 - 108**

Chemical shifts of the CH_2 signals (ppm, in $CDCl_3$)							
Compound	**101**	**102**	**103**	**104**	**106**	**107**	**108**
AB(C_2)	2.36, 2.95		2.29, 2.90		2.02, 3.14		1.95, 3.09
t		2.65		2.59		2.50	



106, 108

(3R,5S)



107

(3R,5R)

Scheme 39

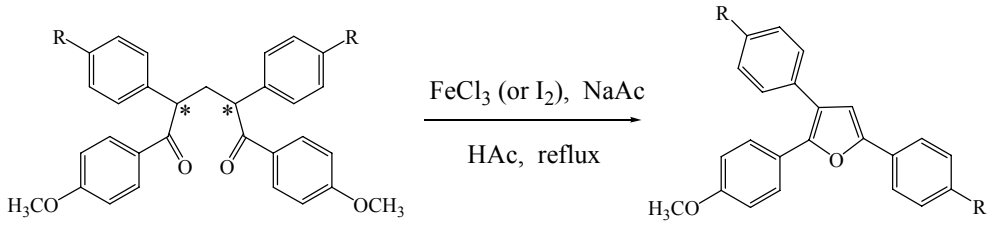
The ^{13}C NMR-spectra of **107 - 108** show the expected signals without the typical carbonyl peaks located at about 198.8 ppm. In the mass spectra of **106 - 108**, all of the parent peaks are observed also as the base peaks. The elemental analyses support the target structures.

Attempts to demethylate these methyl ether protected compounds with boron tribromide to obtain the hydroxylated 1,2,3,5-tetraphenylcyclopentenes were unsuccessful due to the possible rearrangements of the double bond of the cyclopentene [Feutrill, 144]. It was difficult to separate the obtained product mixture into pure products.

3.6 Synthesis of Triarylfuran Derivatives containing Diarylimidazole Unit

3.6.1 Cyclization of 1,2,4,5-tetraarylpentane-1,5-dione to 2,3,5-triarylfuran

2,3,5-Triarylfuran could be synthesised by treatment of appropriate 1,2,4-triaryl-butane-1,4-dione with catalytic p-toluenesulfonic acid in refluxing toluene [Youngdale, 145; Mortensen, 146]. In this work, 1,2,4,5-tetraarylpentane-1,5-dione **102**, **103** (or **104)** prepared from 1,2-arylethenone with iodomethyl methyl ether and potassium tert-butoxide were treated with an oxidant either iron trichloride or iodine in the presence of sodium acetate in acetic acid under reflux to give also 2,3,5-triarylfuran **109** and **110**, respectively.



102, 103 (104) **109, 110**

Compound	109	110
R	H	OCH_3

Scheme 40

The procedure is convenient. The mixture of corresponding 1,2,4,5-tetraarylpentane-1,5-dione, $FeCl_3 \cdot 6H_2O$ (or iodine) and sodium acetate in acetic acid was refluxed for 24 hours. After cooling the mixture was extracted with dichloromethane. The desired 2,3,5-triarylfuran was separated from the obtained residue of the organic phase by column chromatography on

silica gel. The preparation of 2,3,5-triarylfuran **109** was attempted by treating only one isomer **102** of the two corresponding pentane-1,5-diones with $FeCl_3 \cdot 6H_2O$ to gain **109** in a yield of 61%. Employing two diastereomers **103** and **104**, as separately pure isomer or their mixture, we had obtained the same 2,3,5-triarylfuran **110** in yields of 41 - 44%. As oxidant, iron (III) trichloride and iodine had been used separately in those conversion and both of them were effective. In contrast to iodine, however, iron trichloride was preferable because of the simpler working-up and purification of product.

In the ^{1}H NMR-spectra of **109** and **110**, all of the expected signals of methoxy, aromatic and furan-C4-H protons are observed. In the spectrum of **110** (Figure 26), due to the electron-withdrawing effect of the oxygen atom of the furan ring, the methoxy protons of the C2-and C5-anisole groups signalize together in lower field at 3.84 ppm in comparison to that of the other methoxy protons of the C3-anisole group shifted in higher field at 3.81 ppm. These assignments for three methoxy signals are consistent with that of two known similar compounds **111** and **112** (Figure 27). The singlet at 6.63 ppm is assigned to C4-H proton. Three AA'BB' systems of the aromatic protons are shifted in the range of 6.80 - 7.70 ppm.

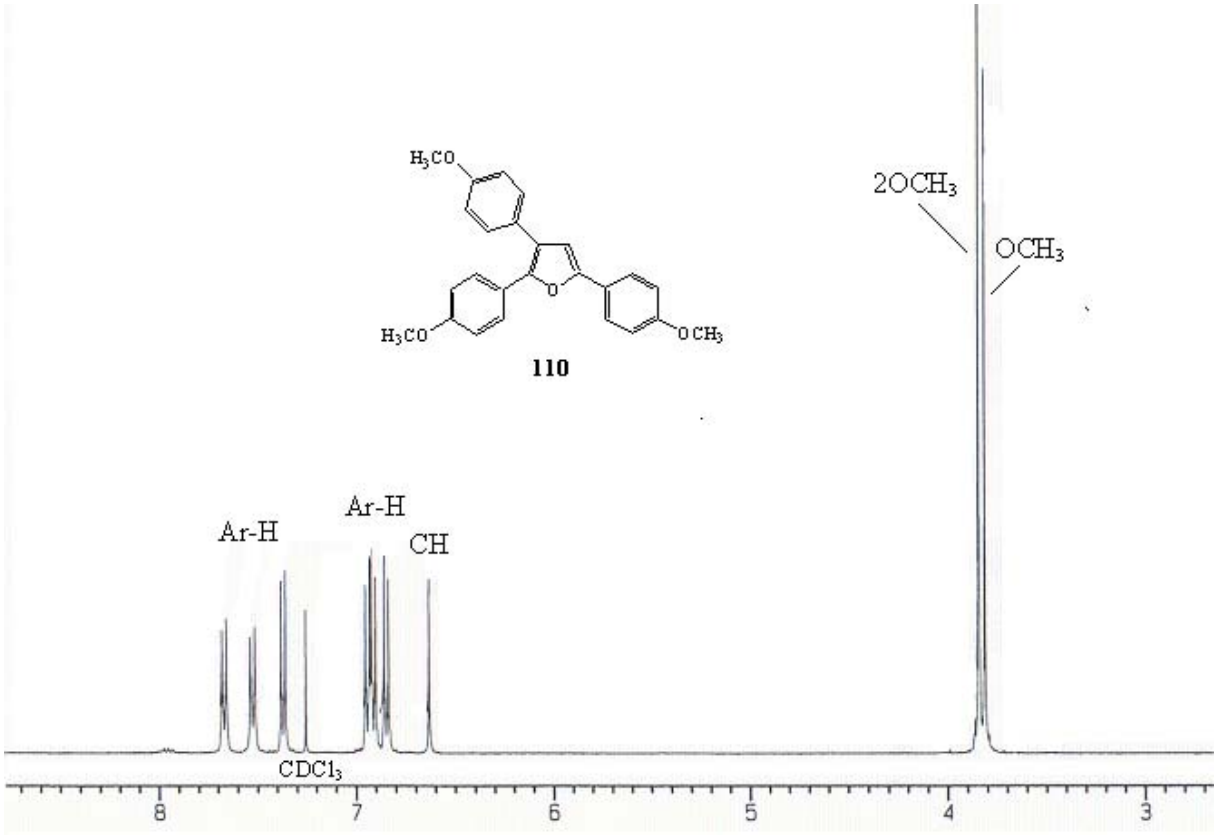


Figure 26. ^{1}H NMR-Spectrum of **110** in $CDCl_3$.

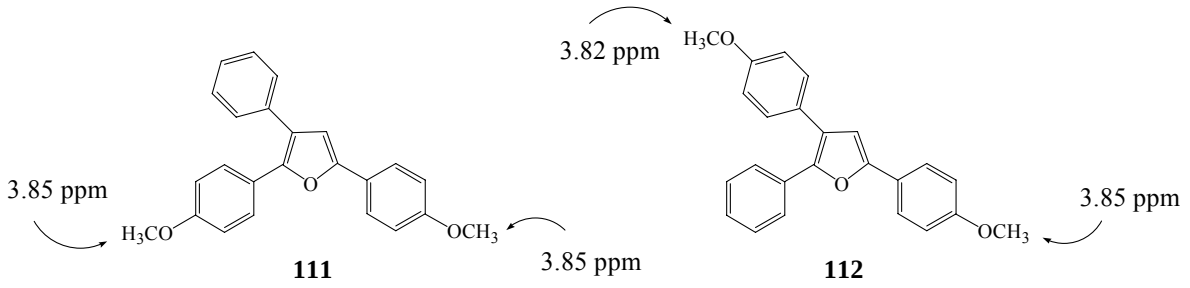


Figure 27. Chemical shifts of the methoxy protons in the ^{1}H NMR-spectra of **111** and **112** in $CDCl_3$ (500MHz) [Mortensen, 146].

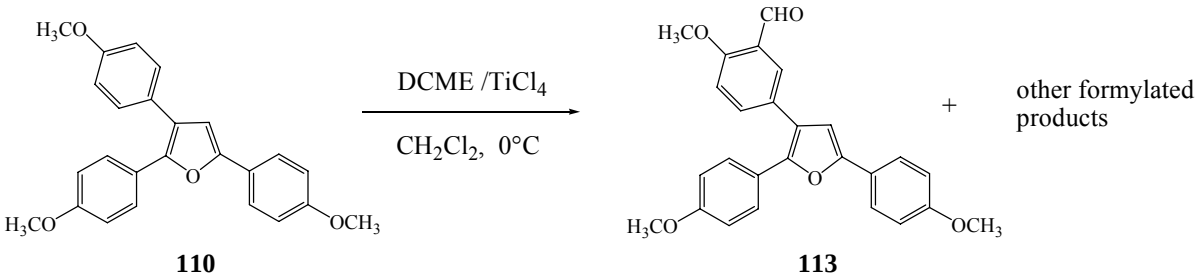
The mass spectra of **109** and **110** show the peaks of the parent ions also as the base peaks at m/e 326 and 386, respectively. The elemental analyses of **109** and **110** are consistent with the described structures.

3.6.2 Selective formylation of 2,3,5-tris(4-methoxyphenyl)furan

Aryl-substituted furan derivatives can be synthesized by cyclization of an appropriate precursor by means of a variety of methods as mentioned in section 3.6.1. If the aryl-substituent bears an active functional group or a voluminous component, however, the preparation and cyclization of precursor can be expected to be difficult. For example, some of the desired compounds in this work are aryl-substituted furan derivatives containing a diaryl-imidazole component. In this case, the direct derivation from the simple aryl-substituted furan is an alternative. 2,3,5-Triarylfuran have been synthesized as described in the last section (3.6.1). If one formyl group can be introduced into the aryl group, then the introduction of an aryl-substituted imidazole component into 2,3,5-triarylfuran can be easily accomplished by condensation of a benzil with the formyl group of the formylated 2,3,5-triarylfuran in the presence of ammonia resource. The foregoing considerations prompt us to investigate the formylation of **110**.

The combination of dichloromethyl methyl ether and titanium tetrachloride is an effective reagent for the formylation, which has been mentioned and applied in section 3.1.1.1. A selective formylation of triarylfuran **110** with this reagent is possible. So 2,3,5-triarylfuran **110** was treated with dichloromethyl methyl ether and titanium tetrachloride in dichloromethane at 0°C for 1 hour. After hydrolysis of the reaction mixture with ice, the mixture was extracted with dichloromethane. The residue obtained from the organic phase was separated by column chromatography on silica gel with a mixture of ligroin and diethyl

ether (1 : 1) as eluent to give in 50% yield a major product, which was characterized as mono-formylated aryl-substituted furan **113**:



110 **113**

Scheme 41

It was noteworthy that some unreacted starting material **110** and multiformylated products were also observed besides the major product **113** in each case. In this conversion, incomplete reaction of **110** and formation of multiformylated products were two contradictory aspects. The attempts to reduce either unreacted starting material or multiformylated products were unsuccessful. Each change on reaction condition convenient to one aspect had always a negative effect on the other aspect. For example, more quantities of formylating reagent and longer reaction time were convenient to complete reaction, but resulted to more multiformylated products. In contrary to this, what was better for reducing multiformylated products, but worse for completing the reaction. Therefore, it was difficult to improve the yield of the desired product. Nevertheless, this selective formylation with a moderate yield was of importance to preparation of **113**.

The ^{1}H NMR-spectrum of **113** (Figure 28) shows a new singlet at 10.45 ppm assigned to the formyl group and the singlet of the C4-H proton at the same shift 6.63 ppm in comparison to that of **110**. Whereas only eleven aromatic protons signalize in the range of 6.84 - 8.15 ppm and three of them signalize separately at three shifts. This indicates that the formylation took place on a phenyl ring. Which phenyl ring was formylated was deduced from the signals of the methoxy protons by comparison with that of **110**. The methoxy protons of the C2-and C5-anisole substituents of **110** signalize together at 3.84 ppm and the other methoxy protons of the C3-anisole group signalize at 3.81 ppm (see Figure 26). In the ^{1}H NMR-spectrum of **113**, also the signals of two methoxy groups are observed together at 3.85 ppm, while the other is shifted at 3.93 ppm. Obviously, the C2-and C5-anisole rests were not formylated and thus the almost unchanged signals of two linked methoxy groups can be still observed. So the C3-

anisole was fomylated and, due to the electron-withdrawing effect of the formyl group, the signal of the corresponding methoxy group is shifted in lower field. As the position of the formyl group adjacent to the methoxy group for results from the orientation of the methoxy group. When the para-position against the methoxy group is occupied, the formylation takes place preferably at the ortho-position to the methoxy group. This has been demonstrated by our previous studies (unpublished results).

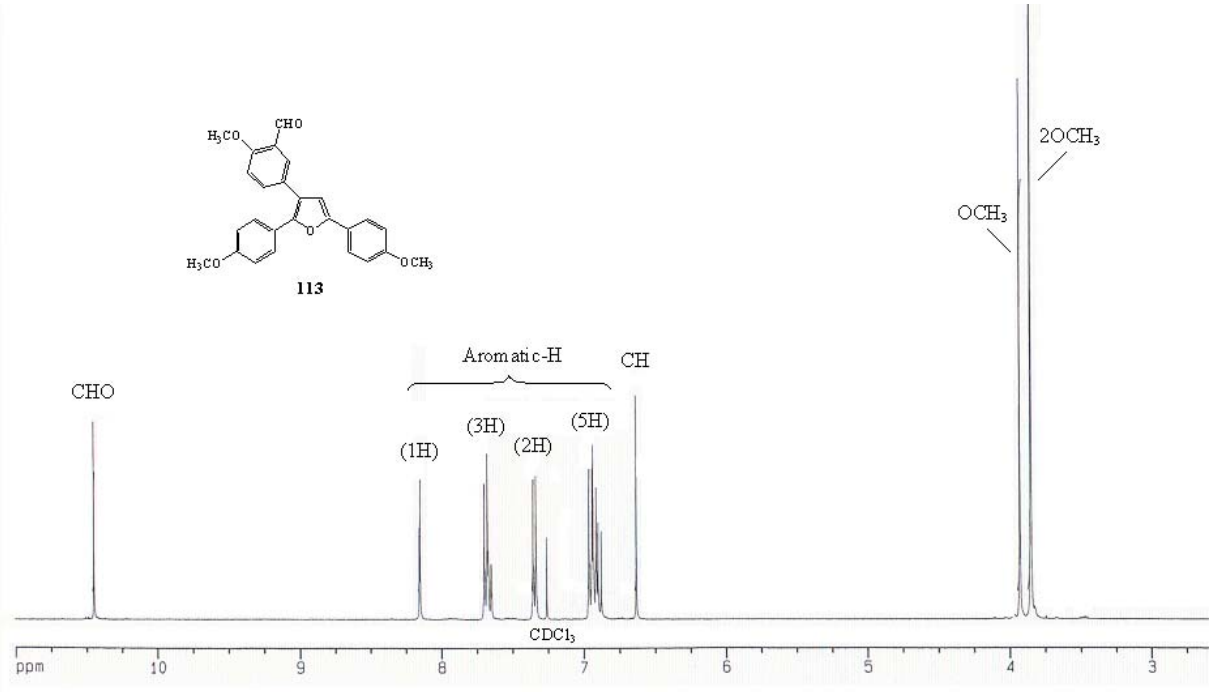


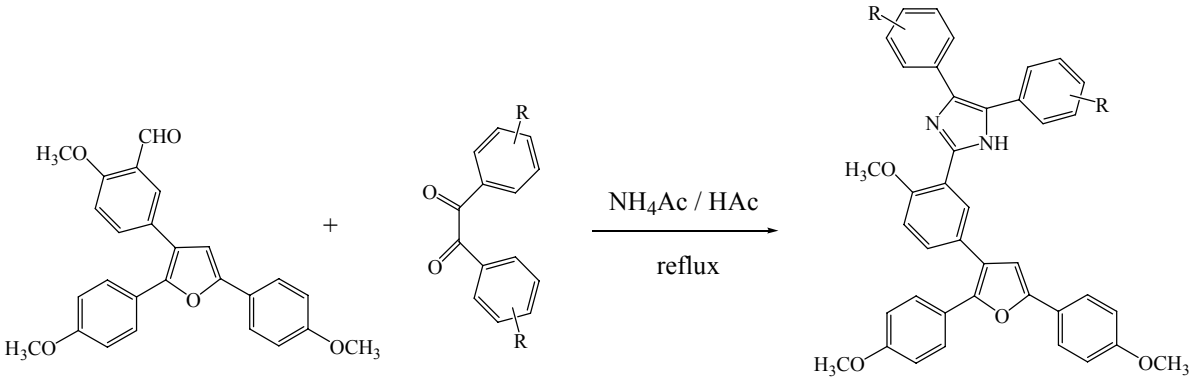
Figure 28. ^{1}H NMR-Spectrum of **113** in $CDCl_3$.

The ^{13}C NMR-spectrum of **113** shows the expected number of carbon signals and the signal of the formyl carbon at 189.5 ppm. In the mass spectrum of **113**, the peak of the parent ion is shown also as the base peak at m/e 414. The elemental analyses support the presented structure of **113**.

3.6.3 Synthesis of triarylfuran derivatives containing diarylimidazole unit

After the successful preparation of furan derivative **113** bearing one formyl group on the side phenyl ring, introduction of an imidazole ring into this furan derivative is expected. An imidazole ring can be formed by cyclization of benzil and an aldehyde in the presence of an ammonia resource according to the classic method [Radziszewski, 147; Davidson, 148; Grimmett, 149; Gust, 150].

Thus a mixture of **113**, one of the commercially available benzils **114 - 116** and ammonium acetate was refluxed in acetic acid for 24 hours. After diluting with water, the reaction mixture was neutralized with ammonia so that the crude product was precipitated and isolated by suction filtration. The dried solid was treated with hot isopropanol to afford the pure product **117 - 119** in yields of 78 - 83%, respectively (see Scheme 42).



113 **114 - 116** **117 - 119**

Compound	**114**, **117**	**115**, **118**	**116**, **119**
R	4-OCH_3	4-F	2-Cl

Scheme 42

The products **117 - 119** were less soluble in hot isopropanol and thus could be purified by treating with isopropanol in order to get rid of unreacted starting materials. Structures of these novel compounds were confirmeded by NMR-spectroscopy.

In the ^{1}H NMR-spectrum of **117** taken in $CDCl_3$ (Figure 29), the protons of five methoxy groups signalize at 3.82 (9H), 3.84 and 3.98 ppm. The singlet at 6.63 ppm is assigned to the furan-H (Ha). The signals of all together nineteen aromatic protons of **117** are shown as two groups at 6.81-6.99 (9H) and 7.40-7.52 (5H) ppm, AA'BB' signals at 7.37 (2H) and 7.71 (2H) ppm and a singlet (doublet) at 8.68 ppm (Hb). The broad deuterium-exchangeable signal at 10.50 ppm is assigned for the NH proton.

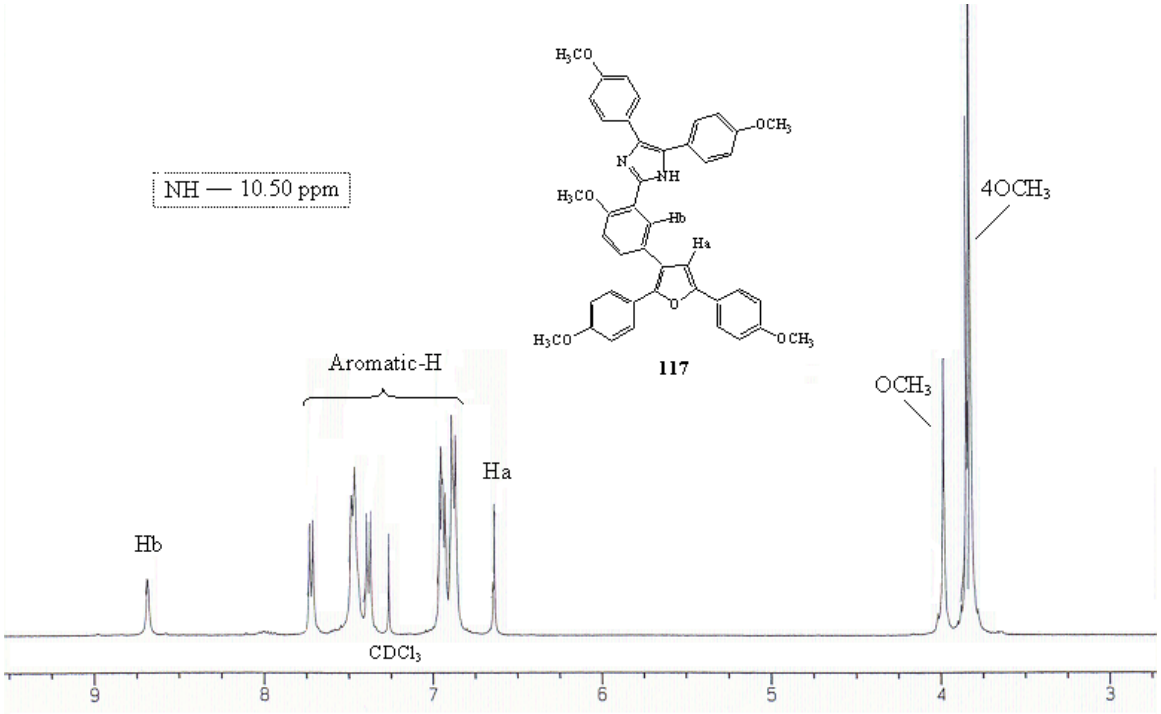


Figure 29. ^{1}H NMR-Spectrum of **117** in $CDCl_3$.

The ^{1}H NMR-spectra of **118** and **119** show the similar signals to that of **117** except the corresponding change of methoxy and aromatic protons. The NH signals of **118** and **119** are observed at 10.65 and 11.60 ppm in their ^{1}H NMR-spectra taken in $CDCl_3$, respectively. A comparison of the ^{1}H NMR spectral properties of **117**, **118** and **119** is listed in table 11.

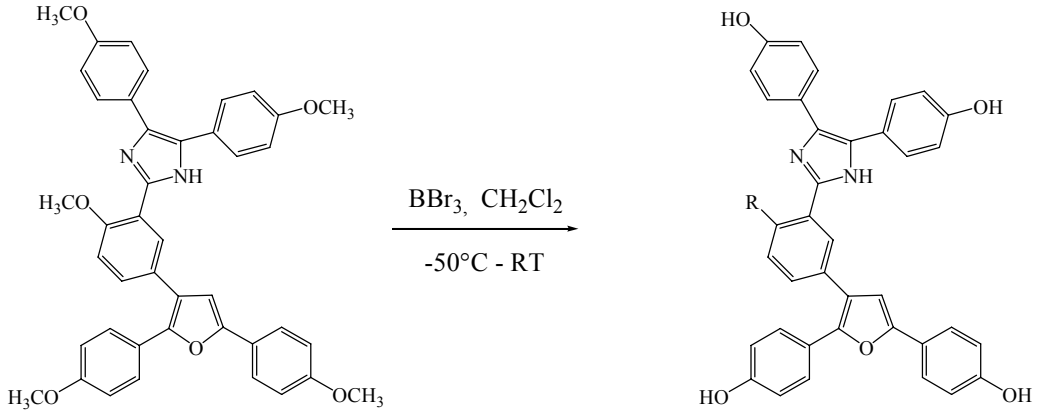
In the IR-spectra of **117** - **119**, the NH absorption is showed significantly as a sharp band of medium strength at 3426, 3431 and 3412 cm^{-1}, respectively. The mass spectra of **117** - **119** show the peak of the parent ion also as the base peak at m/e 664, 640 and 672, respectively. Their elemental analyses are consistent with the described structures.

Table 11. Comparison of ^{1}H NMR Spectral Properties of **117**, **118** and **119**

Compound	**Chemical shifts (ppm, in $CDCl_3$)**		
	OCH_3	**Furan-H**	**Aromatic-H**
117	3.82 (s, 9H), 3.84 (s) 3.98 (s)	6.63 (s)	6.81-6.99 (9H), 7.37 (2H), 7.40-7.52 (5H), 7.71 (2H), 8.68 (1H)
118	3.83 (s), 3.84 (s), 4.00 (s)	6.64 (s)	6.86-7.10 (9H), 7.39 (2H), 7.43-7.55 (5H), 7.70 (2H), 8.67 (1H)
119	3.83 (s), 3.84 (s), 4.05 (s)	6.64 (s)	6.86-6.98 (5H), 7.14-7.48 (13H), 7.74 (2H), 8.86 (1H)

3.6.4 Ether cleavage of tris(4-methoxyphenyl)furan derivatives containing a diarylimidazole unit

In order to obtain hydroxylated triarylfuran drivatives containing a diarylimidazole unit, it was attempted to demethylate compound **117** with boron tribromide. Boron tribromide was added to a solution of **117** in dichloromethane at –50°C and stirred 2 hours at this temperature. Then the reaction mixture was allowed to warm to room temperature and stirred for further 24 hours. After hydrolysis of the reaction mixture with methanol, the solvent was evaporated under vacuum and the residue was first separated by column chromatography on silica gel with acetone as eluent to obtain a mixture, which was then separated by column chromatography with a mixture of diethyl ether and tetrahydrofuran (5 : 1) as eluent into **120** and **121** (Scheme 43).



117 **120, 121**

Compound	120	121
R	OCH_3	OH

Scheme 43

Obviously, compound **120** is an incompletely demethylated product. The reason for this incomplete reaction might be the lack of the reaction time, because much excess of boron tribromide was already used. Due to that the full-hydroxylated product was sufficient for characterization and pharmacological tests, a further attempt to demonstrate this surmise was not performed.

In the ^{1}H NMR-spectrum of **120** taken in CD_3OD, besides the signals of the furan-H at 6.75 ppm and the aromatic protons shifted in the range of 6.76 - 8.23 ppm, a singlet at 3.83 ppm is

shown. This singlet has been assigned to the methoxy group ortho to the imidazol ring because of its lower electron density and more steric hindrance from the imidazole rest in comparison to the others. The ^{1}H NMR-spectrum of **121** taken in CD_3OD shows the signals of the furan-H at 6.69 ppm and the aromatic protons shifted in the range of 6.74 - 8.21 ppm. The OH and NH absorptions of **120** and **121** are observed in their IR-spectra as broad and strong bands at 3428 and 3407 cm^{-1}, respectively. The mass spectra of **120** and **121** show the peak of the parent ion also as the base peak at m/e 608 and 594, respectively. Their elemental analyses support the presented structures.