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# First green protocols for the large-scale preparation of γ-diisoeugenol and related dihydro(1*H*)indenes via formal [3+2] cycloaddition reactions

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ABSTRACT

*Trans*-isoeugenol and related styrenes (*trans*-isohomogenol or O-benzylated isoeugenol), important components of the essential oil of various tropical plants, dimerize easily in the presence of catalytic amounts of $BF_3{\cdot}OEt_2$ in poly(ethylene glycol) with $M_n = 400$ (PEG-400) or $SiO_2$–$OSO_3H$ in MeCN via formal [3+2] cycloaddition reaction to give respective natural products (diisoeugenol and its O-substituted analog) with the 1,2-*trans*-2,3-*trans*-configuration in excellent yields. γ-Diisoeugenol scale-up preparation has also been described.



There are numerous secondary metabolites produced by oxidative dimerization of two phenylpropanoid units, for example, lignans, which show an enormous structural diversity.[1–3] Among them, polyfunctionalized dihydro(1*H*)indene derivatives occupy a considerable place in synthetic and pharmacological researches. Simple compounds such as lignan-like molecules,- asarone dimers **1**,[4] isosafrole dimers **2**,[4] diisoeugenols **3**,[5] and metanetholes **4**[6] (Fig. 1) serve as suitable models in drug development.

α-Diastereomer of the diisoeugenol and its derivatives exhibit diverse promising biological activities, for example, antioxidant,[7] anti-inflammatory,[8] cytotoxic,[9] spasmolytic, and hypertensive,[10] including thromboxane formation inhibition.[11] Another diisoeugenol isomer with γ-configuration can protect perfumes from deterioration.[12] Natural asarone and metanethole dimers also possess γ-configuration.[13]

However, natural sources do not provide commercially useful quantities of these derivatives. Moreover, although polyfunctionalized dihydroindene derivatives such as dimer **3** are molecules of pharmacological importance, there are a few number of methods developed for their synthesis.[14] Among them, a simple dimerization reaction of the *trans*-isoeugenol or similar prop-1-enylbenzenes could serve as suitable process to develop a scale-up preparation of these lignan-like molecules.

Typically, these traditional dimerization reactions employ the use of toxic and volatile halogenated organic solvents ($CH_2Cl_2$ and $CHCl_3$) and hazardous, corrosive reagents ($H_2SO_4$, HCl, or $CF_3COOH$).[15,16] Moreover, these reagents are decomposed during aqueous workup and hence, they cannot be recovered and recycled in subsequent runs.

The replacement of these potentially hazardous solvents and stoichiometric reagents by environmentally benign solvents and sustainable reagents is one of the major issues of green chemistry. In this context, the utilization of reaction media with environmentally acceptable alternatives such as poly(ethylene glycol) (PEG) is an area of tremendous importance in modern organic synthesis. PEG is known to be inexpensive, thermally stable, recoverable, biologically compatible, and non-toxic.[17] PEG is most commonly employed as a support or a phase-transfer catalyst in various organic transformations.[18] Its use as a solvent in organic reactions is relatively recent.[19] This is despite the fact that the toxicity data of some alternative solvent (ionic liquid solvents) are for the most part unknown, while complete toxicity profiles are available for a range of PEG molecular weights; some of them are already approved for internal consumption by the US FDA.[17] Sustainable reagents such as recyclable heterogeneous solid-supported sulfuric acid ($SiO_2$–$OSO_3H$) or perchloric acid ($HClO_4$–$SiO_2$) also play an important role in the development of practical and environmentally friendly procedures for some transformations.[20]

It is noteworthy that dimerization reactions of the *trans*-isoeugenol in the presence of catalytic amounts of $BF_3{\cdot}OEt_2$ in PEG-400 or recyclable heterogeneous solid-supported sulfuric acid ($SiO_2$–$OSO_3H$) in MeCN have not been used in the preparation of lignan-like molecules. Given the aforementioned valuable properties of this family of compounds as pharmaceuticals, an efficient, low cost, and environmentally friendly procedure for the dihydro(1*H*)indene

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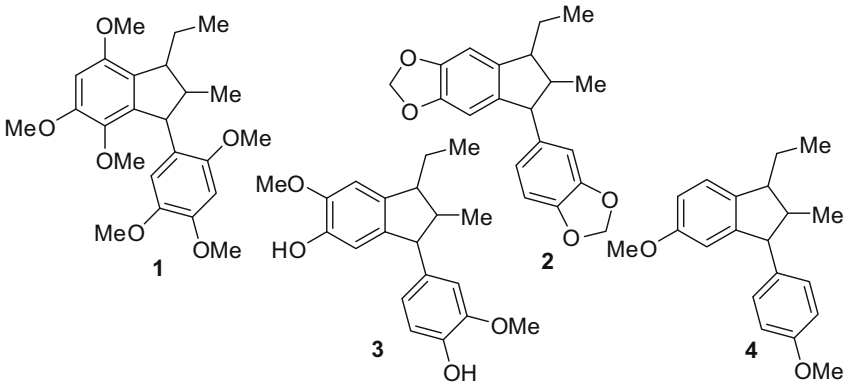



**Figure 1.** Structures of diverse lignan-like molecules **1**–**4** (Stereochemistry was not shown here).[13]

framework would be of great interest for its application to industrial processes.

Bearing this information in mind and in the continuation of our recent works on the chemistry of some prop-1-enylbenzenes as renewable raw materials under green conditions,[21] we wanted to explore an alternative environmentally benign condition for $BF_3{\cdot}OEt_2$ (or $SiO_2$–$OSO_3H$)-promoted dimerization reactions of the *trans*-isoeugenol and related compounds.

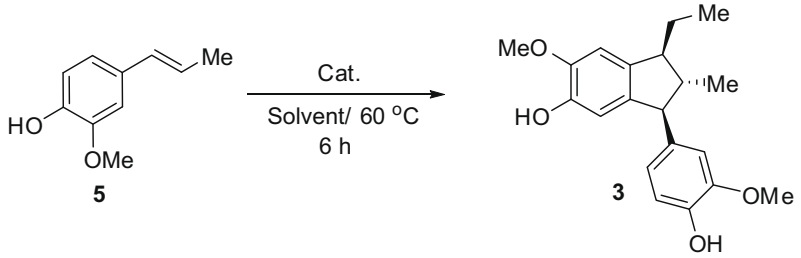
Herein, we wish to report the new and efficient stereoselective synthesis of γ-diisoeugenol and related dihydro(1*H*)indenes and their large-scale preparation under green conditions using PEG-400, commercially available and easily degradable solvent, or silica sulfuric acid ($SiO_2$–$OSO_3H$) support as a recoverable heterogeneous system.

In our initial study, we have investigated dimerization reactions of the *trans*-isoeugenol **5** to obtain the desired product **3** using different conditions (Scheme 1, Table 1). Our attention was addressed to three possible catalysts in this dimerization reaction, $BF_3{\cdot}OEt_2$, $FeCl_3$, and $SiO_2$–$OSO_3H$ in MeCN, a nonhalogenated solvent. After several experiments, we found that (i) catalytic amounts of $BF_3{\cdot}OEt_2$ (10 mol %) favored this condensation only at smooth heating solvent (60 °C) during 10.5 h (Table 1, entry 2); (ii) another Lewis acid, $FeCl_3{\cdot}6H_2O$ (10 mol %) was also very efficient in this process at the same temperature regime and reaction rate (Table 1, entry 4), and (iii) silica sulfuric acid support catalyst, $SiO_2$–$OSO_3H$, was the best reagent catalysing this cycloaddition reaction at room temperature (Table 1, entry 6). All three catalysts gave the same solid product with a fine-defined stereochemistry, respective *r*-1-ethyl-5-hydroxy-*t*-3-(4-hydroxy-5-methoxyphenyl)-6-methoxy-*t*-2-methylindane **3** with the γ-configuration.

It should be noted that a similar Brønsted acid-catalyzed process provided the dimeric product in moderate yields (20–50%) and offered the α-racemate of this phenylindane as major product.[15a] Our method, based on catalysis of common cheap acids ($BF_3{\cdot}OEt_2$, $FeCl_3$, and $SiO_2$–$OSO_3H$) in MeCN, was more efficient (70–80%) and highly stereoselective furnishing the γ-racemate of this phenylindane.

Moreover, the best catalyst ($SiO_2$–$OSO_3H$) was filtered and reused for dimerization reaction without significant loss of activity for three cycles (Table 1, entry 6).

The correct (1α,2β,3α)-structure (1,2-*trans*-2,3-*trans*-configuration) of the cyclodimer **3** was possible using $^1H$ NMR and $^{13}C$ NMR




**Scheme 1.** Stereoselective dimerization process of styrene **5** for dihydro(1*H*)indene **3** with the γ-configuration.

**Table 1**
Comparative physicochemical parameters of dimerization process to obtaining **3** in MeCN and in PEG-400

| Entry | Solv. | Cat. | Volume solvent (mL) | Time reaction (h) | Yield (%) |
|---|---|---|---|---|---|
| 1 | PEG | — | 5 | 24 | Nil |
| 2 | MeCN | $BF_3{\cdot}OEt_2$ | 30 | 10.5 | 78 |
| 3 | PEG | $BF_3{\cdot}OEt_2$ | 5 | 5 | 65 |
| 4 | MeCN | $FeCl_3{\cdot}6H_2O$ | 30 | 14 | 70 |
| 5 | PEG | $FeCl_3{\cdot}6H_2O$ | 10 | 12 | 60 |
| 6[a] | MeCN | $SiO_2$–$OSO_3H$ | 30 | 6 | 80 (55)[b] |
| 7 | PEG | $SiO_2$–$OSO_3H$ | 10 | 20 | 55 |

[a] Reaction was run at room temperature.
[b] Yield of the product after third cycle.

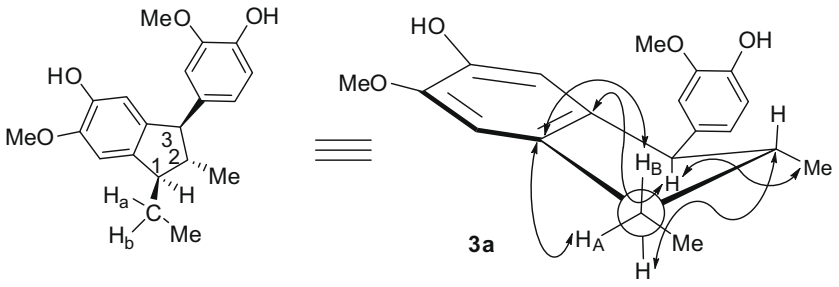



**Figure 2.** Possible conformation of γ-diisoeugenol **3** and its most relevant HMBC correlations.

analysis and a set of two-dimensional experiments (COSY, HMQC, and HMBC).[22] This was corroborated by the protons H-1, H-2, and H-3 coupling constants ($J_{H1,H2}$ = 11.0 and $J_{H2,H3}$ = 9.5 Hz), affirmation enough to indicate the axial–axial (*trans*) relationship to the γ-diisoeugenol **3** (Fig. 2).

The absence of low values for the 1,2- and 2,3-protons also excludes rapid flipping of the envelope conformations of five-membered ring. The HMBC correlations of **3** were very helpful in the assignment of the chemical shifts of this molecule. By analyzing their COSY and HMBC data, it was possible to propose the diastereomer **3a** as a more stable conformer of $MeCH_2$-group at C-1. This proposition is based on the same large range correlation of the protons $H_A$ and $H_B$ with the quaternary carbon at C-7a position.

Next, we wanted to develop a green protocol for the synthesis of this desired particular indane product, taking into consideration that nowadays one of the major objectives for synthetic organic chemistry is the development of environmentally friendly synthetic methods. Thus, PEG-400 was replaced by the conventional organic solvent (MeCN), making these dimerization reactions 'greener'.

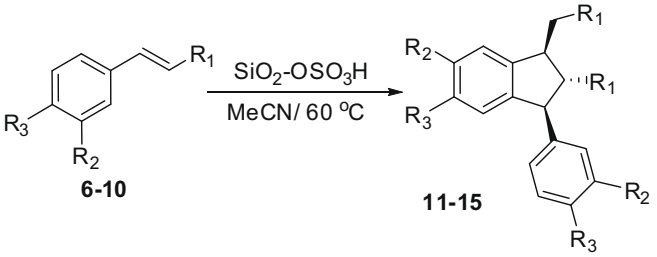
During these experiments, we found that these reactions occurred smoothly in this nonhalogenated and non-toxic solvent in the presence of 10 mol % $BF_3{\cdot}OEt_2$ or $FeCl_3{\cdot}6H_2O$ to give the same product **3** with excellent yields. Using PEG-400 as reaction medium in the cyclodimerization process, reaction time and volume of solvent were reduced considerably (Table 1, entries 3, 5 and 7).

The results showed that PEG-400 did not act only as non-toxic solvent but could also accelerate the cyclodimerization process. Moreover, isolation of the final product became easy without necessity of common work-up (basic treatment and extraction), using only a column chromatography separation.[23,24] However, it should be noted that PEG-400 worked only as a solvent in this dimerization reaction and did not promote this process (Table 1, entry 1).

Inspired with our findings, we continued this study to demonstrate the synthetic utility of our developed green protocol toward the generation of related dihydro(1*H*)indenes. The following alkenes: styrene **6**, prop-1-enylbenzene **7**, (2-methoxyvinyl)benzene **8**, (*E*)-1,2-dimethoxy-4-(prop-1-enyl)benzene (*trans*-isohomogenol) **9**[25] and O-benzylated *trans*-isoeugenol **10**[26] were chosen as initial substrates.

Thus, these styrenes were investigated in the cyclodimerization process under the best found reaction conditions, ($SiO_2$–$OSO_3H$)/MeCN. Their dimerization reactions were initially run at room temperature; because these all reactions showed no signs of progress after several hours they were heated at reflux (Scheme 2).

The results, summarized in Table 2, revealed that (i) styrenes **6**–**8** were inactive, and did not give respective dimeric products **11–13**; (ii) the dimerization reactions of *trans*-isohomogenol **9** and molecule **10** were very efficient providing only the natural γ-racemate of diisohomogenol **14** and O-benzylated diisoeugenol **15**, respectively.




**Scheme 2.** $SiO_2$–$OSO_3H$-catalyzed dimerization reaction of styrene **6**–**10**.

**Table 2**
$SiO_2$–$OSO_3H$-catalyzed dimerization reactions in MeCN

| Dihydro(1*H*)indenes | $R_1$ | $R_2$ | $R_3$ | Time reaction (h) | Yield (%) |
|---|---|---|---|---|---|
| **11** | H | H | H | 10 | Nil[a] |
| **12** | Me | H | H | 10 | Nil[a] |
| **13** | MeO | H | H | 12 | Nil[a] |
| **14** | Me | MeO | MeO | 12 | 63 |
| **15** | Me | MeO | BnO | 15 | 52 |

[a] GC–MS analysis of the crude reaction products showed only a complex mixture of unidentified compounds.

These results indicated that the dimerization reactions occur better when styrens are activated by two electron-donating groups. The 1,2-*trans*-2,3-*trans*-configuration of these phenylindanes, obtained by this procedure, was also confirmed by their NMR spectra, which were similar to those reported in work.[15a]

Although the best catalyst ($SiO_2$–$OSO_3H$) for the cyclodimerization process resulted less effective in green reaction medium (PEG) than that in organic solvent, we wanted to study the potential of two developed methods toward the large-scale preparation of these pharmacologically important molecules, by use of 10 mol % $F_3{\cdot}OEt_2$/PEG-400 or 10 mol % $FeCl_3{\cdot}6H_2O$/PEG-400 and ($SiO_2$–$OSO_3H$)/MeCN systems. In a similar fashion, we investigated the cyclodimerization process, having more than 5.0 g of the starting material **5**. Fortunately, this process also occurred smoothly giving the same final product **3** with good to excellent yields.

In conclusion, this Letter describes first, green, and convenient protocols for the scale-up preparation of diisoeugenol and its O-substituted analogs with γ-configuration, interesting rigid lignan-like molecules in pharmacological studies. The notable features of developed protocols are mild and green reaction conditions, simplicity in operation, excellent yields and reaction rates, cleaner reaction profiles, and utilization of cheap and cost effective reagents in large-scale preparation. These methods represent greener alternatives to traditional dimerization reactions of the isoeugenol or its O-substituted analogs and could be applicable to a wide range of electron-rich styrenes, and would be attractive process for the pharmaceutical industry.

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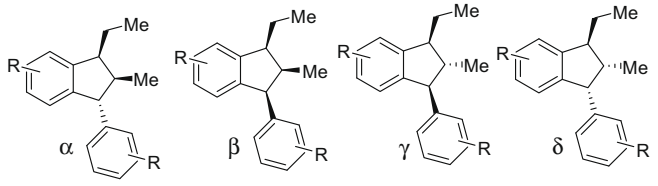
13. There are four possible diastereomers for these structures, namely α (1,2-*cis*-2,3-*trans*), β (1,2-*cis*-2,3-*cis*), γ (1,2-*trans*-2,3-*trans*) and δ (1,2-*trans*-2,3-*cis*), see following figure:

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22. *Selected spectral data for* **3**: *r*-1-ethyl-5-hydroxy-*c*-3-(4-hydroxy-5-methoxyphenyl)-6-methoxy-*t*-2-methylindane (**3**): Mp 184–185 °C. IR(KBr): 3487, 2962, 1265 $cm^{-1}$. $^1H$ NMR (400 MHz; $CDCl_3$; $Me_4Si$), δ (ppm): 0.97 (3H, t, *J* = 7.3 Hz, Me), 1.03 (3H, d, *J* = 6.9 Hz, 2-Me), 1.31–1.44 (1H, m, $CH_2$), 1.65–1.75 (1H, m, $CH_2$), 2.40–2.51 (1H, m, 2-H), 2.85–2.95 (1H, m, 1-H), 3.73 (1H, d, *J* = 9.5 Hz, 3-H) 3.80 (3H, s, $-OCH_{3Ar}$), 3.89 (3H, s, 6-$OCH_3$), 5.51 (1H, s, $OH_{Ar}$), 5.56 (1H, s, 5-OH), 6.48 (1H, s, 4-H), 6.62 (1H, br s, 2-$H_{Ar}$), 6.65 (1H, br d, *J* = 8.0, 6-$H_{Ar}$), 6.77 (1H, br s, 7-H), 6.83 (1H, d, *J* = 8.0, 5-$H_{Ar}$); $^{13}C$ NMR (100 Hz; $CDCl_3$; $Me_4Si$), δ (ppm): 146.4, 145.1, 144.5, 144.1, 139.1, 138.7, 135.8, 121.5, 114.0, 111.0, 110.6, 107.5, 56.7, 56.1, 55.9, 49.2, 48.5, 22.4, 13.8, 12.2. COSY correlations: 0.97/1.31–1.44 [Me/$CH_2$], 0.97/1.65–1.75 [Me/$CH_2$], 1.03/2.40–2.51 [2-Me/2-H], 1.31–1.44/0.97 [$CH_2$/Me], 1.31–1.44/1.65–1.75 [$CH_2$/$CH_2$], 1.31–1.44/2.85–2.95 [$CH_2$/1-H], 1.65–1.75/0.97 [$CH_2$/Me], 1.65–1.75/1.31–1.44 [$CH_2$/$CH_2$], 1.65–1.75/2.85–2.95 [$CH_2$/1-H], 2.40–2.51/1.03 [2-H/2-Me], 2.40–2.51/3.73 [2-H/3-H], 2.85–2.95/1.31–1.44 [1-H/$CH_2$], 2.85–2.95/1.65–1.75 [1-H/$CH_2$], 2.85–2.95/1.65–1.75 [1-H/$CH_2$], 3.73/2.40–2.51 [3-H/2-H], 3.73/6.48 [3-H/4-H], 3.80/6.62 [$OCH_{3Ar}$/2-$H_{Ar}$], 3.89/6.77 [6-$OCH_3$/7-H], 6.48/3.73 [4-H/3-H], 6.62/3.80 [2-$H_{Ar}$/$OCH_{3Ar}$], 6.77/3.89 [7-H/6-$OCH_3$]. HMQC correlations: 0.96/12.2 [Me/$C_{Me}$], 1.03/13.8 [2-Me/$C_{2\text{-}Me}$], 1.31–1.44/22.4 [$CH_2$/$C_{CH2}$], 1.65–1.75/22.4 [$CH_2$/$C_{CH2}$], 2.40–2.51/49.2 [2-H/2-C], 2.85–2.95/48.5 [1-H/1-C], 3.73/56.7 [3-H/3-C], 3.80/55.9 [$-OCH_{3Ar}$/$-OCH_{3Ar}$], 3.89/55.9 [6-$OCH_3$/6-$OCH_3$], 6.48/111.0 [4-H/4-C], 6.65/110.6 [2-$H_{Ar}$/2-$C_{Ar}$], 6.65/121.5 [6-$H_{Ar}$/6-$C_{Ar}$], 6.77/107.5 [7-H/7-C], 6.83/114.0 [5-$H_{Ar}$/5-$C_{Ar}$]. HMBC correlations: 0.96/22.4/48.5 [Me/$C_{CH2}$/1-C], 1.03/48.5/49.2/56.7 [2-Me/1-C/2-C/3-C], 1.31–1.44/12.2/48.5/135.8 [$CH_2$/$C_{Me}$/1-C/7a-C], 1.65–1.75/12.2/48.5/138.7 [$CH_2$/$C_{Me}$/1-C/7a-C], 2.40–2.51/13.8/22.4/48.5/56.7/138.7 [2-H/$C_{2\text{-}Me}$/$C_{CH2}$/1-C/3-C/7a-C], 2.85–2.95/12.2/22.4/49.2/56.7/107.5/138.7 [1-H/$C_{Me}$/$C_{CH2}$/2-C/3-C/7-C/7a-C], 3.73/13.8/49.2/110.6/121.5/135.8/139.1 [3-H/$C_{2\text{-}Me}$/2-C/2-$C_{Ar}$/6-$C_{Ar}$/3a-C/1-$C_{Ar}$], 3.81/146.7 [$CH_3O_{Ar}$/3-$C_{Ar}$], 3.89/146.4/144.5 [6-$OCH_3$/3-C/4-$C_{Ar}$], 5.50/111.0 [$HO_{Ar}$/4-C], 5.56/114.0/144.5 [5-OH/5-$C_{Ar}$/4-$C_{Ar}$], 6.48/56.7/107.5/121.5/138.7/145.1 [4-H/3-C/7-C/6-$C_{Ar}$/7a-C/6-C], 6.62/56.7/121.5/135.8/145.1 [2-$H_{Ar}$/3-C/6-$C_{Ar}$/3a-C/6-C], 6.65/56.7/110.6 [2-$H_{Ar}$/3-C/2-$C_{Ar}$], 6.77/48.5/138.7 [7-H/1-C/7a-C], 6.83/121.5/146.4 [5-$H_{Ar}$/6-$C_{Ar}$/3-C]. MS: *m*/*z* (relative intensity): 328 ($M^+$, 60%), 299 (100), 204 (40), 175 (25). Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.25; H, 8.43.
23. General experimental procedure for synthesis of cyclodimer **3** using PEG-400 as a reaction medium: To a *trans*-isoeugenol (4.62 mmol) in PEG-400 (5 mL), $BF_3{\cdot}OEt_2$ (10 mol %) was added at 0 °C. The reaction mixture was kept slowly to room temperature and continuously stirring. The resulting mixture was stirred at 70 °C for 5 h. After completion of the reaction, as indicated by TLC, a crude product was purified by column chromatography (ethyl acetate–petroleum ether, 1:5) to obtain the respective *r*-1-ethyl-5-hydroxy-*t*-3-(4-hydroxy-5-methoxyphenyl)-6-methoxy-*t*-2-methyl-indane **3**. When MeCN was used, the reaction mixture was treated with a saturated solution of $Na_2CO_3$, and extracted with ethyl acetate (2 × 30 mL), the organic layers were dried over $Na_2SO_4$. The crude product was purified by column chromatography to obtain the respective cyclodimer **3**.
24. General experimental procedure for synthesis of cyclodimer **3** using $SiO_2$–$OSO_3H$/MeCN as a recoverable heterogeneous system prepared from silica gel and chlorosulfonic acid.[20c,b] To a stirred solution of *trans*-isoeugenol (4.62 mmol) in MeCN (30 mL) at rt was added $SiO_2$–$OSO_3H$ (25% W/W). The mixture was stirred at rt until reaction was completed as indicated by TLC.The catalyst was filtered off and washed three times with acetone. The filtrate was concentrated under vacuum to obtain a crude product and was purified by column chromatography (ethyl acetate–petroleum ether, 1:5).
25. *Trans*-isohomogenol (yellowish liquid) was prepared by methylation (MeI/NaOH/$Me_2CO$) of *trans*-isoeugenol.
26. O-benzylated isoeugenol (Mp 51–52 °C) was prepared by benzylation (BnBr/$K_2CO_3$/$Me_2CO$) of *trans*-isoeugenol.