

Stereoselectivity in Pinacol-Homocoupling Mediated by Samarium Diiodide

Peter Gärtner*, Max Knollmüller, and Joachim Bröker

Institute of Applied Synthetic Chemistry, Vienna University of Technology,
A-1060 Vienna, Austria

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Summary. The stereoselectivity of the pinacol-coupling of various substituted benzaldehydes mediated by samarium diiodide was investigated. The dependence of product-ratios, yields, and stereoselectivities on the substrate, the substrate-reagent-ratio, and the solvent is described.

Keywords. Lanthanides; Aldehydes; Reductions; Hydrobenzoin; Diastereoselectivity.

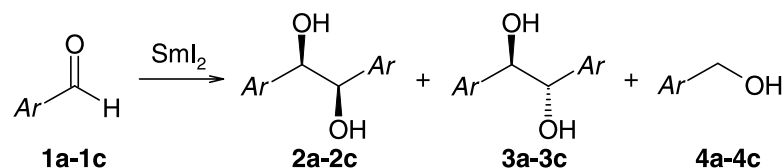
Introduction

Being interested in a general approach to arylsubstituted hydrobenzoin and realizing that not all of these compounds are accessible *via* benzoin-condensation and subsequent reduction in acceptable yields, the direct pinacol-coupling seemed to be a promising alternative. To be even more precise, we expected the application of SmI₂ in the reductive coupling of 4-nitrobenzaldehyde to be a promising way to synthesize 1,2-bis(4-nitrophenyl)ethane-1,2-diol [1]. Furthermore, we found that described stereoselectivities vary in a broad range which seemed to be due to different reaction conditions [1, 2], but no general investigation on this matter has been performed so far. Thus, we decided to test the pinacol-coupling of different nitro-, methoxy-, and unsubstituted derivatives with regard to the dependence of stereoselectivity on the substrate-reagent-ratio as well as other reaction conditions. The results of this study are presented herein.

Results and Discussion

The pinacol-coupling was carried out in two different solvents (*THF* and *MeOH*) using 5 different aromatic aldehydes as substrates (**1a**: *Ar* = *Ph*, **1b**: *Ar* = 2-*MeOPh*, **1c**: *Ar* = 4-*MeOPh*, **1d**: *Ar* = 2-*NO₂-Ph*, **1e**: *Ar* = 4-*NO₂-Ph*).

* Corresponding author. E-mail: peter.gaertner@tuwien.ac.at



Scheme 1

Table 1. Results of the reactions using benzaldehyde (**1a**) or 2- and 4-anisaldehyde (**1b** and **1c**) as substrates following the general procedures for the reactions in *THF* and *MeOH* described in the experimental section

Entry	Ar	Solvent	Yield 2/3 /%	Yield 4 /%	<i>dl/meso</i> -ratio (2:3) ^a
1	<i>Ph</i>	<i>THF</i>	52	18	63:37
2	<i>Ph</i>	<i>MeOH</i>	65	34	68:32
3	<i>2-MeO-Ph</i>	<i>THF</i>	35	29	60:40
4	<i>2-MeO-Ph</i>	<i>MeOH</i>	54	14	62:38
5	<i>4-MeO-Ph</i>	<i>THF</i>	49	27	58:42
6	<i>4-MeO-Ph</i>	<i>MeOH</i>	70	10	52:48

^a *dl/meso*-ratios were determined via ¹H-NMR-spectra of the crude products

Furthermore, additional experiments with different substrate-reagent-ratios were carried out in *THF*.

In the case of benzaldehyde (**1a**) and 2- and 4-methoxybenzaldehyde (**1b** and **1c**) as substrates the reaction lead to a mixture of *meso*- and *dl*-diols (**3a–3c** and **2a–2c**) as well as small amounts of benzyl alcohol (**4a–4c**) (Scheme 1 and Table 1). The yields and stereoselectivities obtained from the reactions in *MeOH* are so far corresponding to Ref. [3].

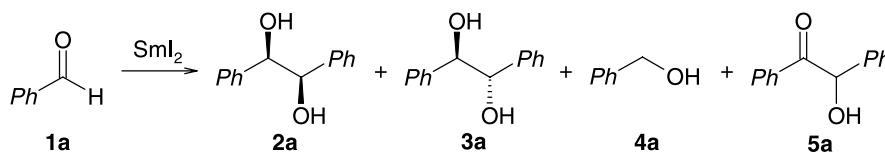
On the contrary, the pinacol-coupling of aromatic aldehydes with 1 equivalent of SmI_2 in *THF* without addition of lewis-acids or complexing-agents is, according to literature, proceeding with only very low stereoselectivity and when 2 equivalents of the reagent are used with benzaldehyde at -78°C no selectivity should be observed [1, 2, 4–6], apart from the fact that **1b** should not give any hydrobenzoin derivative at all [2]. However, although **1b** gave the lowest yield of the desired product compared to aldehydes **1a** and **1c**, it was actually possible to carry out a pinacol-coupling yielding 35% of the corresponding hydrobenzoin with a *dl/meso*-ratio of 1.5:1 (Table 1, entry 3). Further on, the observed diastereoselectivities drop proceeding from benzaldehyde (**1a**) to 2-methoxybenzaldehyde (**1b**) and the *para*-substituted derivative **1c** both in *THF* and *MeOH*. Whereas the drop in selectivity from **1a** to **1b** may be due to an additional complexation of the 2-*OMe*-group such an effect is impossible in **1c** due to steric reasons. Yields of hydrobenzoin tend to be higher when the reaction is carried out in *MeOH* but any further interpretation of the obtained yields and *dl/meso*-ratios regarding the dependence from solvent and substrate seems to be quite difficult, as no obvious trends have been observed.

To investigate the dependence of the achievable diastereoselectivity on the amount of reagent used for the reaction in *THF*, additional experiments, using a

Table 2. Results of experiments using different amounts of 0.1 M SmI₂-solution or SmI₂ generated *in situ*

Entry	Equiv. SmI ₂	Yield 2/3a /%	<i>dl:meso</i> ^a	Yield 4a /%	Yield 5a /%
1	1.5 ^b	52	63:37	18	–
2	2.0 ^b	46 ^c	43:57	–	–
3	3.0 ^b	39	37:63	–	–
4	1.1 ^d	55	43:57	14	30
5	2.0 ^d	95	31:69	–	–
6	3.0 ^d	93	32:68	–	–
7	0.5 ^d	14	71:29	25	31
8	0.8 ^d + 1.2 Sm(0)	82	56:44	18	–
9 ^e	0.1 ^d + 3 Sm(0)	61 ^c	54:46	10	–

^a *dl/meso*-ratios were determined *via* ¹H-NMR-spectra of the crude products; ^b SmI₂ was generated *in situ* from Sm(0) and 1.5 equiv. of 1,2-diiodoethane; ^c approx. 20% of aldehyde were recovered; ^d a commercially available 0.1 M solution of SmI₂ in THF was used; ^e the experiment was carried out at –78°C

**Scheme 2**

commercially available SmI₂-solution, were carried out. This way an accurate amount of reagent could be provided in the reaction mixture. The results of these experiments, using the 0.1 M SmI₂-solution as well as SmI₂ generated *in situ*, are shown in Table 2.

Using a large excess of reagent, the reaction gave a mixture of only *meso*- and *dl*-hydrobenzoin, but equal amounts of reagent and substrate or an excess of substrate lead to mixtures of *meso*- and *dl*-hydrobenzoin, benzyl alcohol and benzoin as the main products (Scheme 2). Furthermore, the *dl/meso*-ratio seems to be highly dependent on the substrate-reagent-ratio. When an excess of reagent is used, the reaction is moderately *meso*-selective (Table 2, entries 5 and 6). With about one equivalent of reagent or less the yield of hydrobenzoin drops and when less than one equivalent of reagent is used, mainly the *dl*-diastereomer is obtained (Table 2, entries 4 and 7). This trend is also obvious in the experiments where SmI₂ was formed *in situ* (entries 1–3). The shift towards *dl*-selectivity (Fig. 1) compared to the experiments with the SmI₂-solution can be explained by a lower amount of reagent actually formed in the reaction mixture. Another explanation could be that only a certain amount of SmI₂ is present in the mixture when the aldehyde is added and it is formed as the reaction proceeds due to shift of equilibrium, providing a lower concentration over the whole reaction time.

To find conditions for a *dl*-selective pinacol-coupling leading to a satisfying yield of hydrobenzoin, two experiments with a combination of less than 1 equivalent of SmI₂-solution and an excess of Sm(0) were carried out (Table 2, entries 8

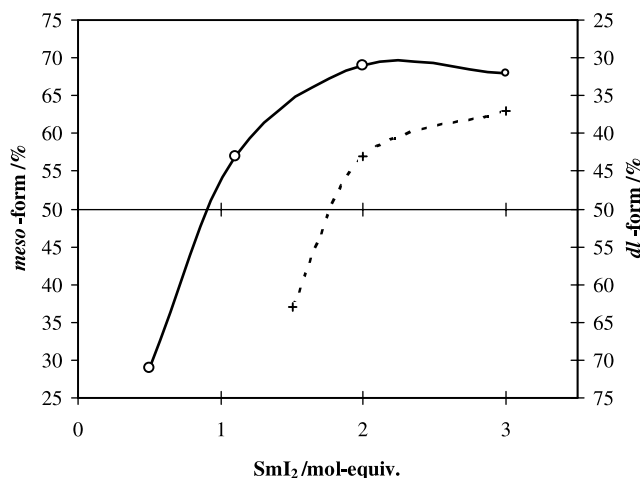


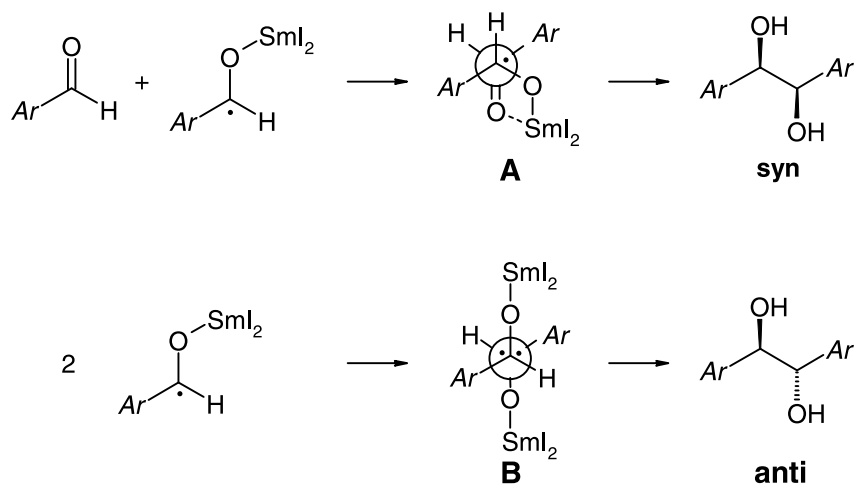
Fig. 1. Dependence of stereoselectivity on amount of SmI₂ (—○—: SmI₂-solution; ---+---: SmI₂ formed *in situ*)

and 9). The use of 0.8 equivalents of SmI₂ together with 1.2 equivalents of Sm(0) lead to much higher yields of hydrobenzoin but a significant loss of selectivity. The use of catalytic amounts of SmI₂ at lower temperature did not improve this result as well.

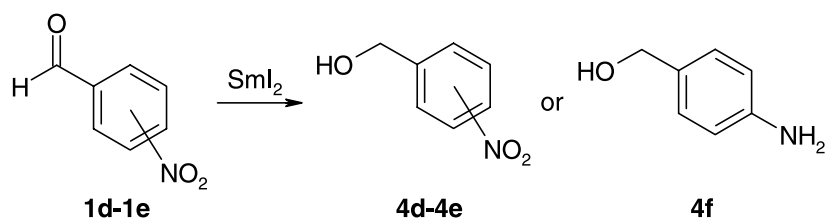
It has to be noted that the pinacol-coupling of benzaldehyde using Sm(0) in *THF*/HCl is already known, hence a direct participation of the samarium-metal present in the reaction mixture is possible [7]. However, considering the poor yields of hydrobenzoin and benzyl alcohol using Sm(0) without addition of any activating reagent as I₂ or HCl, this influence seems to be negligible [7]. As the reaction-times using Sm(0) in *THF*/HCl are at least 24 h, the reaction of remaining aldehyde with excessive samarium-metal during the hydrolysis of the reaction mixture (see experimental section) does not seem to be very likely as well.

The observed dependence of the obtained diastereoselectivities can be explained by two different and competing reaction-mechanisms following the possible mechanisms proposed in literature (Scheme 3) [2, 5]: If a large excess of reagent is used for the reaction and the substrate is slowly added to the reaction mixture, the aldehyde is quantitatively transformed to the ketyl-radical and the main mechanism is a combination of two ketyl-radicals. In this case, the transition state B seems to be sterically favoured, leading to the *meso*-product. If less than one equivalent of reagent is used and the reagent is added to the substrate, the ketyl-radical reacts mainly with excessive aldehyde. In this case the transition state A is favoured due to the possible coordination of the aldehyde-carbonyl-O with the Sm(III) of the ketyl-radical, leading to the *dl*-form as the main product.

On the other hand, according to Ref. [1], 4-nitrobenzaldehyde (**1e**) should give the corresponding hydrobenzoin in 0.5 minutes and 95% yield, but the reaction of 2- and 4-nitrobenzaldehyde (**1d** and **1e**) with SmI₂ in *THF* and *MeOH*, respectively, yielded only the corresponding benzyl alcohol (**4d** and **4e**) (Table 3). When the usual reaction conditions in *THF* (see experimental



Scheme 3



Scheme 4

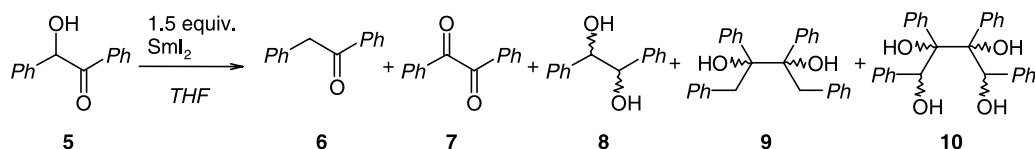
Table 3. Results of the reactions using nitro-derivatives **1d** and **1e** as substrates

Entry	Solvent	Ar	Yield/%
1	<i>THF</i>	2-NO ₂ -Ph	51
2	<i>MeOH</i>	2-NO ₂ -Ph	57
3 ^a	<i>THF</i>	4-NO ₂ -Ph	24
4	<i>MeOH</i>	4-NO ₂ -Ph	42

^a SmI₂ (dissolved in *THF*) was added to a solution of the aldehyde in *THF*

section) were applied to 4-nitrobenzaldehyde (**1e**) the nitro-substituent was reduced as well leading to 4-aminobenzyl alcohol (**4f**). Although the possibility to reduce aromatic nitro-compounds with an excess of SmI₂ in *THF*/H₂O or *MeOH* is already known in literature, this reaction was only observed in case of the *p*-NO₂-derivative in *THF* [8–10]. By inverting the sequence of reagent addition this side-reaction could be prevented and 4-nitrobenzyl alcohol (**4e**) was isolated (Table 3, entry 3).

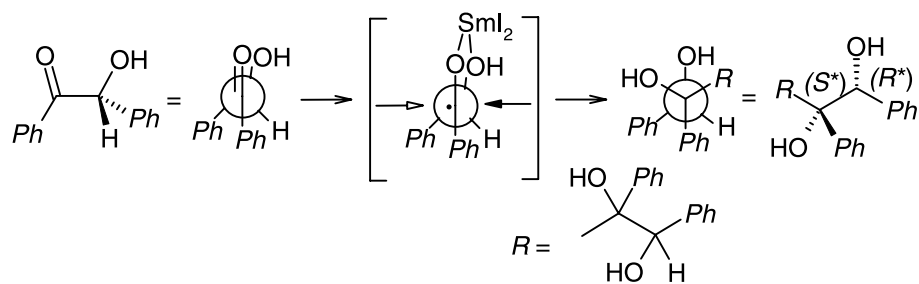
An additional experiment using benzoin as substrate was carried out to investigate if SmI₂ and the conditions used for the pinacol-couplings are applicable for the conversion of benzoin to *meso*- and *dl*-hydrobenzoin. It has to be noted that, according to literature, the reduction of benzoin with a SmI₂-LiNH₂-system in



Scheme 5

THF/MeOH should give a mixture of hydrobenzoin and 1,2-diphenylethanol as the main products together with traces of desoxybenzoin and benzyl alcohol [11]. However, this was not the case when the reaction conditions described herein were applied on benzoin as the substrate (Scheme 5 and experimental section).

1,2,3,4-Tetraphenyl-2,3-butanediol (**9**) was most likely formed by the pinacol-coupling of desoxybenzoin **6**. This coupling has been described earlier to take place during the electrolytic reduction of desoxybenzoin in the presence of Fe^{2+} or Cr^{3+} beside the formation of the corresponding alcohol [12]. The NMR-spectrum of this compound corresponds with the data given in literature for the *dl*-diol [13]. We also observed the formation of 1,2,3,4-tetraphenyl-1,2,3,4-butanetetrol (**10**) which is the actual coupling product of **5**. The formation of **10** during the cathodic pinacolisation of benzoin was described already earlier [14]. However, no configuration assignment was performed so far. Although the determination of configuration was beyond the scope of this investigation, a few things can be estimated from NMR results with regard to stereoselectivity. The reduced set of signals gives evidence for a molecule with C_2 - or C_S -symmetry. Thus, relative configuration should be (R^*,R^*,S^*,S^*) or (R^*,S^*,R^*,S^*) in case of C_S -symmetry and (R^*,R^*,R^*,R^*) or (R^*,S^*,S^*,R^*) in case of C_2 -symmetry. As shown in Scheme 6 for the transition-state of (*R*)-benzoin the relative configuration of C1 and C2 should be (R^*,S^*) due to the possible chelation in the transition-state and the following attack of either a second ketyl-radical or a benzoin-carbonyl from the sterically less hindered side. Considering the *dl*-selectivity of the pinacol-coupling of benzaldehyde under the same reaction-conditions (Table 2, entry 1) as well as the predominant configuration of **9** formed in the same reaction-mixture, the relative configuration of C2 and C3 should be *dl* (in this case (S^*,S^*)) as well. Thus, regarding the 4 possibilities mentioned before, (R^*,S^*,S^*,R^*) -configuration seems to be the most likely one.



Scheme 6

Conclusion

Most of the desired hydrobenzoin-derivatives could be synthesized *via* the pinacol-coupling induced by samarium diiodide with satisfactory yields, however, the nitro-substituted compounds gave only the corresponding benzyl alcohols. The stereoselectivity of the reaction could actually be controlled *via* variation of the substrate-reagent-ratio. With an excess of SmI_2 *meso*-hydrobenzoin could be obtained in satisfying yield and moderate diastereoselectivity, whereas subequimolar amounts of SmI_2 gave preferably *dl*-hydrobenzoin. However, yields are lower than for the reaction with an excess of SmI_2 due to obvious reasons. The applicability of SmI_2 as a reducing agent for carbonyl-compounds, like in this case for benzoin, seems to be limited due to the fact that both reduction and reductive coupling of these compounds take place simultaneously, resulting in complex product-mixtures.

Experimental

Diethylether, petrolether and CH_2Cl_2 were distilled before use. Tetrahydrofuran (*THF*) and *MeOH* were degassed under Ar and distilled over Na/benzophenone and Mg, under Ar directly before use. 1,2-Diiodoethane was dissolved in ether and the solution was extracted with a $\text{Na}_2\text{S}_2\text{O}_3$ -solution, washed with brine, dried with anhydrous Na_2SO_4 , and evaporated under slightly reduced pressure. Aldehydes and benzoin were purified by vacuum-distillation directly before use. Commercially available I_2 and Sm (Aldrich, 99.9%, – 40 mesh) were used without further purification. SmI_2 -solution (0.1 M in *THF*) was purchased from Aldrich and stored under Ar. All reactions were carried out under Ar atmosphere.

Meso/dl-ratios were determined from the crude products by integration of the ^1H NMR spectra.

NMR spectra were recorded on a Bruker AC 200 spectrometer operating at 200 MHz (^1H) or 50 MHz (^{13}C) using the solvent peak as reference. The measurements were carried out in CDCl_3 or DMSO-d_6 at 300 K.

Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F₂₅₄ coated aluminum sheets and compounds were visualised with UV-light or staining with 5% phosphomolybdic acid hydrate in ethanol and heating.

Elemental analyses (C, H, N) were conducted at the Institute of Physical Chemistry at the University Vienna, Mikroanalytical Laboratory, their results were found to be in good agreement ($\pm 0.3\%$) with the calculated values.

General Procedure for the Pinacol-Coupling Carried Out in THF

A solution of 141 mg of 1,2-diiodoethane (0.50 mmol) in 2 cm³ of *THF* was added dropwise to a suspension of 100 mg of samarium (0.67 mmol) in 1 cm³ of *THF*. (After the addition of 10% of the diiodoethane solution the mixture was stirred until the blue colour of SmI_2 in *THF* was apparent and the remaining reagent was added afterwards.) After 30 minutes a solution of the aldehyde (0.33 mmol) in *THF* was added and the reaction was stirred until the blue colour of SmI_2 disappeared. The reaction mixture was quenched with 0.1 N HCl and extracted with ether. The combined organic phases were washed with 10% $\text{Na}_2\text{S}_2\text{O}_3$ -solution and brine, dried with anhydrous Na_2SO_4 , filtered, and evaporated to dryness. The crude product was purified by flash chromatography (petrolether:ether 20:1 → ether).

Experiments with Different Substrate-Reagent-Ratio Using Sm(0) and 1,2-Diiodoethane

The procedure described above was only slightly modified: 1.34 mmol of samarium and 1.0 mmol of 1,2-diiodoethane were used for the *in-situ*-synthesis of the reagent. 0.5 and 0.33 mmol of benzaldehyde were added to the mixture.

Experiments with Different Substrate-Reagent-Ratio Using 0.1 M SmI₂-Solution

When an excess of reagent was used for the reaction, the SmI₂-solution (2–9 cm³, depending on the substrate-reagent-ratio) was placed in the reaction-vessel without further dilution and the corresponding amount of benzaldehyde dissolved in THF was added. In the case of 0.5 equivalents of SmI₂ the reagent was added slowly to the aldehyde dissolved in THF. For the experiments with additional Sm(0) the aldehyde was added to the stirred suspension of samarium in the SmI₂-solution. The initially blue reaction mixture immediately turned yellow, but the blue colour returned during the reaction time of 12 h. In all cases the workup was carried out as described above.

General Procedure for the Pinacol-Coupling Carried Out in MeOH

A solution of 99 mg of iodine (0.39 mmol) in 0.5 cm³ of MeOH was added dropwise to a mixture of 100 mg of samarium (0.67 mmol) and the aldehyde (0.39 mmol) in 2 cm³ of MeOH. During the exothermic reaction the colour of the reaction mixture turned from brown to light orange and the reaction mixture was stirred until the TLC showed no further change. The reaction mixture was quenched with 0.1 N HCl, MeOH was evaporated, and the residue was extracted with ether. The combined organic phases were washed with 10% Na₂S₂O₃-solution and brine, dried with anhydrous Na₂SO₄, filtered, and evaporated to dryness. The crude product was purified by flash chromatography (petrolether:ether 20:1 → ether).

Reaction of Benzoin with SmI₂ in THF

A solution of 141 mg of 1,2-diiodoethane (0.50 mmol) in 2 cm³ of THF was added dropwise to a suspension of 100 mg of samarium (0.67 mmol) in 1 cm³ of THF. (After the addition of 10% of the diiodoethane solution the mixture was stirred until the blue colour of SmI₂ in THF was apparent and the remaining reagent was added afterwards.) After 30 minutes a solution of 71 mg of benzoin (0.33 mmol) in THF was added and the reaction was stirred until the blue colour of SmI₂ disappeared. The reaction mixture was quenched with 0.1 N HCl and extracted with ether. The combined organic phases were washed with brine, dried with anhydrous Na₂SO₄, filtered, and evaporated to dryness. The crude product (82 mg) was purified by flash chromatography (petrolether:ether 20:1 → ether) yielding 13 mg of the substrate (**5**), 5 mg (9%) of desoxybenzoin (**6**), 5 mg (9%) of benzil (**7**), 8 mg (13%) of 1,2-diphenyl-1,2-ethandiol (**8**), 10 mg (9%) of *dl*-diol **9** [13], and 12 mg (10%) of 1,2,3,4-tetraphenyl-1,2,3,4-butanetetrole (**10**) as a white solid.

1,2,3,4-Tetraphenyl-1,2,3,4-butanetetrole (10; C₂₈H₂₆O₄)

Mp.: 145–151°C; ¹H NMR (200 MHz, CDCl₃, 25°C): δ = 2.26, 4.59 (2bs, 4OH), 5.88 (s, 2CHOH), 7.01–7.32 (m, 20aromatic-H); ¹³C NMR (50 MHz, CDCl₃, 25°C): δ = 77.09 (s, Ph-COH), 82.60 (d, Ph-CHOH), 127.02, 127.37, 127.59, 128.83 (4d, Ph-C), 140.53, 140.31 (2s, Ph-C-1); M = 436.52.

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