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Enantioselective Reduction of Diaryl Ketones Catalyzed by a Carbonyl Reductase from *Sporobolomyces salmonicolor* and its Mutant Enzymes

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Abstract: The carbonyl reductase from red yeast *Sporobolomyces salmonicolor* AKU4429 (**SSCR**) and its mutant enzymes effectively catalyzed the enantioselective reduction of diaryl ketones to give the corresponding chiral alcohols. Both conversion and enantioselectivity were dependent on the co-solvent in the reaction medium. Diaryl ketones with a *para*-substituent on one of the phenyl groups were reduced with high enantioselectivity (up to 99% *ee*), which is difficult to achieve using chemical methods such as chiral borane reduction, asymmetric hydrogenation or hydrosilylation. Mutation of **SSCR** at Q245 resulted in a higher amount of (*S*)-enantiomer in the products, and in the case of mutant Q245P with *para*-substituted diaryl ketones as substrate, this effect was so remarkable that the reduction enantiopreference was switched from (*R*) to (*S*). The present study provides valuable information about the catalytic properties of the carbonyl reductase **SSCR** toward the reduction of diaryl ketones, serving as basis for further engineering of this enzyme to develop efficient biocatalysts for highly enantiospecific reduction of diaryl ketones without high electronic dissymmetry or an *ortho*-substituent on one of the aryl groups.

Keywords: bioreduction; diaryl ketones; enantioselectivity; enzyme catalysis; oxidoreductase

Introduction

Chiral diarylmethanols are important intermediates for the synthesis of pharmaceutically interesting molecules, such as (*R*)-neobenodine, (*R*)-orphenadrine, L-cloperastine and (*S*)-carbinoxamine, inspiring considerable efforts to search for methods for the construction of the chiral diarylmethanol core moiety in high optically purity.[1,2] As a result, a high number of publications have appeared in the last 10 years or so to deal with the catalytic asymmetric addition of aryl nucleophiles to aromatic aldehydes with the aim to prepare enantiomerically enriched diarylmethanols.[1,3–10] The aryl nucleophiles are usually the expensive diphenylzinc or arylzinc species formed *in situ* from arylboronic acids or triarylborane with excess of diethylzinc. Rhodium-, titanium- and copper-catalyzed enantioselective aryl transfer reactions to aromatic aldehydes have also been reported and the corresponding arylmetal species have been proposed to be the active nucleophiles.[11–13] However, in many of the described processes, high catalyst loadings (10–20 mol%) and/or addition of additives such as polyethylene glycol ether (PEG) are required to achieve synthetically useful results, since achiral, non-catalytic background aryl addition often leads to a product of low enantiomeric purity.[1,14]

An alternative approach to synthesize enantiomerically enriched diarylmethanols is the reduction of diaryl ketones,[1] which can be achieved chemically and biocatalytically. The asymmetric chemical reductions of diaryl ketones involve chiral borane reduction,[15–17] transition metal-catalyzed hydrogenation,[18–20] hydrogen transfer reduction[21], and hydrosilylation.[22–24] Although these chemical methods have provided a useful access to diarylmethanol with high enantiomeric purity in some cases, their common drawback is the limited substrate range.[1,25] For example, the degree of enantiofacial discrimination in Corey's CBS reduction of diaryl ketones is determined by both electronic and steric effects, requiring that the ketones have an electron donor substituent on one aromatic ring and an acceptor group on the other,[26] or an *ortho*-substituent on one of the aryl

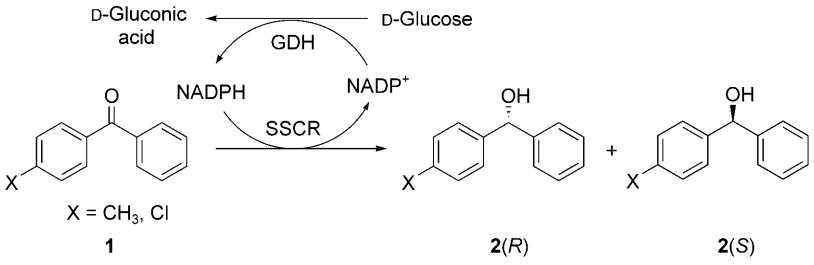
groups.[15] For transition metal-catalyzed hydrogenation and hydrosilylation, the presence of an *ortho*-substituent on one of the aryl groups is necessary for achieving high enantiocontrol in the products. The reduction of diaryl ketones with only a *para*- or *meta*-substituent on one of the aryl groups affords the diarylmethanol in low enantiomeric purity (*ee* often being less than 50%).[18,19,22,24] Therefore, the highly enantioselective reduction of diaryl ketones without high electronic dissymmetry or an *ortho*-substituent on one of the aryl groups has proven to be a significant challenge.[1]

Biocatalysts have been demonstrated to be highly enantioselective in the reduction of a wide range of ketones including some bulky ones.[27–29] Enzymatic reduction offers a potentially complementary way of achieving highly enantioselective reduction of diaryl ketones that are difficult with chemical catalysts.[30] In this context, a few reports dealing with the biocatalytic reduction of diaryl ketones have appeared. Benzoylpyridines were reduced to the corresponding optically active phenylpyridylmethanols by whole-cell biocatalysts such as immobilized baker's yeast,[31,32] *Rhizopus arrhizus*,[33] *Catharanthus roseus*,[34] *Nicotiana tabacum*[35] and *Camellia sinensis* cell cultures.[36] Preliminary results have shown that selected strains from *Hansenula nonfermentans*, *santamariae*, *ernobii*, *Rhodosporidium toruloides*, *Candida bombi*, and *C. sorbophila* reduced diaryl ketones with high selectivity, producing the alcohol product with $>95\%$ *ee*, but the substrate was not specified and the conversion was less than 12%.[37] *Debaryomyces marama* enantioselectively reduced *p*-chlorobenzophenone to give a 48% yield of the *S*-alcohol with 34% of ketone being recovered.[38] Recently, the reductions of a series of diaryl ketones were tested with commercially available ketoreductases, and high enantioselectivity was obtained in some cases.[30] Since the gene/protein sequences or sources of most of the commercial enzymes are not available, this provides limited information for the further search of more effective ketoreductases for this formidable task. In our previous studies, it has been found that a carbonyl reductase from red yeast *Sporobolomyces salmonicolor* AKU4429 (**SSCR**) catalyzed the highly enantioselective reduction of a wide range of ketones including 2,2-dimethylpropiophenone, 1-phenyl-1-pentanone and cyclopropyl(phenyl)methanone, showing that it is a useful biocatalyst for the reduction of sterically bulky ketones.[28,39] We envisioned that the carbonyl reductase **SSCR** might also take sterically bulky diaryl ketones as substrates. Herein we report that a variety of diaryl ketones were enantioselectively reduced by this carbonyl reductase and its mutant enzyme Q245P.

Results and Discussion

Given that chiral 4-chlorobenzhydrol (**2b**) and 4-methylbenzhydrol (**2c**) are important precursors for the synthesis of (*S*)-cetirizine hydrochloride and (*R*)-neobenodine, respectively, and that the enantioselective reduction of such simple diaryl ketones with a *para*-substituent on one of the aryl groups remains a formidable task, 4-chlorobenzophenone (**1b**) and 4-methylbenzophenone (**1c**) were chosen as substrates and examined using **SSCR** as the catalyst in potassium phosphate buffer with various organic solvents. The organic solvent was added to increase the availability of the highly hydrophobic substrates in the reaction medium. Co-factor NADPH was regenerated with glucose dehydrogenase and D-glucose system, as shown in Scheme 1. The reaction mixtures were shaken at room temperature for 24 h, and then extracted with methyl *tert*-butyl ether. The extracts were dried over anhydrous sodium sulfate and subjected to chiral HPLC analysis. The product alcohols (**2**) were identified by comparison with the authentic samples. The results are summarized in Table 1.

From Table 1, it can be seen that the carbonyl reductase **SSCR** catalyzed the enantioselective reduction of 4-chlorobenzophenone (**1b**) and 4-methylbenzophenone (**1c**) to give the corresponding (*R*)-alcohol products. The co-solvent contained in the reaction medium affected both conversion and enantioselectivity. For both substrates, the reaction in alcoholic solvents (isopropyl alcohol and methanol) gave highest conversion, while highest enantioselectivity was obtained in buffer with THF. Since the addition of THF



Scheme 1. SSCR-catalyzed reduction of diaryl ketones with a glucose dehydrogenase/D-glucose NADPH regeneration system.

Table 1. Wild-type **SSCR**-catalyzed reduction of 4-chlorobenzophenone (**1b**) and 4-methylbenzophenone (**1c**) in reaction media with different co-solvents.

Solvent in buffer[a]	**1b**		**1c**	
	Conv. [%][b]	*ee* [%][b]	Conv. [%][b]	*ee* [%][b]
No solvent	47	50	45	82
DMSO	97	70	98	80
2-PrOH	93	74	>99	80
Methanol	95	78	>99	84
Butyl acetate	14	62	11	–[c]
MTBE	46	58	52	78
THF	62	88	67	92
THF (20%)	11	–[c]	9	–[c]
THF (30%)	0	–	0	–

[a] Potassium phosphate buffer (100 mM, pH 7.0) containing 10% (v/v) of organic solvent except where indicated otherwise.

[b] Determined by HPLC analysis, the product benzhydrols were (*R*)-enantiomers.

[c] Only (*R*)-enantiomer was observed by chiral HPLC analysis, since the low conversion might result in a trace of (*S*)-enantiomer not being detected, the *ee* value was not reported.

(10%) into the buffer increased the conversion and the enantioselectivity, more THF was added into the buffer in an attempt to further improve the conversion while attaining a higher *ee* value, but lower conversion or no reaction was observed, indicating the enzyme was deactivated rapidly in these cases. Compared to the asymmetric hydrogenation and hydrosilylation of 4-chlorobenzophenone and 4-methylbenzophenone catalyzed by chiral metal catalysts, in which the enantiomeric purity for *p*-chlorobenzhydrol was 0–47% *ee* and the best result for *p*-methylbenzhydrol was 39% *ee*,[8,18,19,24] the carbonyl reductase **SSCR**-catalyzed reduction exhibited much higher stereoselectivity (up to 88 and 92% *ee* for **1b** and **1c**, respectively), and even higher than the best results of the commercially available ketoreductases (64 and 85% *ee* for **1b** and **1c**, respectively),[30] showing the promise of this enzyme toward the reduction of sterically bulky diaryl ketones.

To further explore the substrate scope of this carbonyl reductase, **SSCR** was applied to the reduction of a series of diaryl ketones (Figure 1) in a potassium phosphate buffer containing 10% (v/v) of either methanol or THF, since these two reaction media showed the highest conversion or enantioselectivity. Co-factor NADPH was regenerated with the glucose dehydrogenase and D-glucose system (Scheme 1). The reaction mixtures were shaken at room temperature for 24 h, and then extracted with methyl *tert*-butyl ether. The extracts were dried over anhydrous sodium sulfate and subjected to chiral HPLC analysis. The

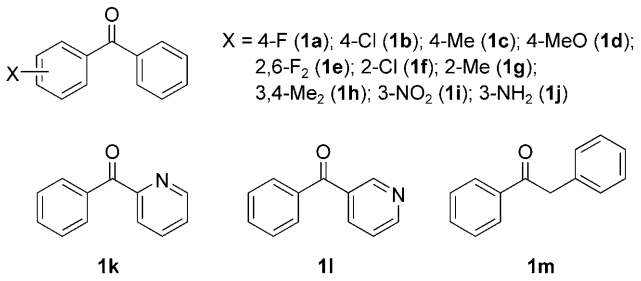


Figure 1. Substituted benzophenones, benzoylpyridines, and benzyl phenyl ketone.

product alcohols were identified by comparison with the authentic samples, and their absolute configurations were determined by comparing the HPLC elution sequence with the literature data using the same type of chiral column,[6,7,17,40–44] and/or by comparison with the enantio-merically enriched sample prepared by literature methods.[30] The results are reported in Table 2.

Table 2. Reduction of diaryl ketones catalyzed by wild-type carbonyl reductase **SSCR**.

Ketone	THF		Methanol	
	Conv. [%][a]	*ee* [%][a]	Conv. [%][a]	*ee* [%][a]
1a (4-F)	72	44 (*R*)	99	50 (*R*)
1b (4-Cl)	62	88 (*R*)	95	78 (*R*)
1c (4-Me)	67	92 (*R*)	>99	84 (*R*)
1d (4-MeO)	26	96 (*R*)	95	99 (*R*)
1e (2,6-F_2)	49	8 (*S*)	>99	26 (*S*)
1f (2-Cl)	44	74 (*R*)	99	72 (*R*)
1g (2-Me)	8	–[b] (*R*)	61	70 (*R*)
1h (3,4-Me_2)	5	–[b] (*R*)	58	64 (*R*)
1i (3-NO_2)	33	48 (*S*)	81	40 (*S*)
1j (3-NH_2)	50	56 (*R*)	>99	36 (*R*)
1k	>99	99 (*R*)	>99	99 (*R*)
1l	>99	78 (*R*)	>99	82 (*R*)
1m	9	28 (*S*)	85	8 (*R*)

[a] Determined by HPLC analysis.

[b] Only one enantiomer was observed by chiral HPLC analysis, since the low conversion might result in a trace of (*S*)-enantiomer not being detected, the *ee* value was not reported.

Most diaryl ketones showed higher conversion in the medium with methanol as co-solvent. The enantioselectivity was also dependent on the co-solvent in the buffer, although no trend was observed. The *ee* values of product alcohols for some ketones were higher with THF as co-solvent, while others exhibited higher enantioselectivity with methanol as co-solvent. It seems that carbonyl reductase **SSCR** was more enantioselective toward the reduction of diaryl ketones with a *para*-substituent on one of phenyl groups than those with an *ortho*- or *meta*-substituent. This is

quite contrary to the observation in the chiral borane reduction, asymmetric hydrogenation or hydrosilylation of diaryl ketones.[15,19,22,24] For the reduction of *para*-substituted diaryl ketones, the enantioselectivity was increased in the order of $F < Cl < CH_3 < CH_3O$, which was in agreement with the increasing size and electron-donating property of the *para*-substituent. It is worth noting that 4-methoxybenzophenone was reduced to the corresponding (*R*)-alcohol with excellent conversion (95%) and enantiomeric purity (99% *ee*) in buffer containing 10% of methanol. 2-Benzoylpyridine was completely converted to (*R*)-phenylpyridylmethanol in 99% *ee* with THF or methanol as co-solvent.

Recently, three Q245 mutant enzymes (Q245P, Q245L and Q245H) of carbonyl reductase **SSCR** were found to invert the configuration of alcohol products from the (*R*)-enantiomer to the (*S*)-enantiomer for the reduction of *para*-substituted acetophenones.[45] It would be interesting to examine how these mutants affect the reduction of diaryl ketones. Therefore, the catalytic properties of these mutant enzymes were studied using 4-methylbenzophenone (**1c**) and 4-chlorobenzophenone (**1b**) as substrates (Table 3). As indicated by the conversion, the three

Table 3. Reduction of 4-methylbenzophenone (**1c**) and 4-chlorobenzophenone (**1b**) catalyzed by wild-type and mutant **SSCR** enzymes.[a]

Enzyme	**1c**		**1b**	
	Conv [%][b]	*ee* [%][b]	Conv. [%][b]	*ee* [%][b]
wild-type	>99	84 (*R*)	95	78 (*R*)
Q245P	99	48 (*S*)	98	76 (*S*)
Q245L	98	46 (*R*)	>99	28 (*R*)
Q245H	94	46 (*R*)	>99	22 (*S*)

[a] The reaction was carried out in potassium phosphate buffer (100 mM, pH 7.0) with 10% (v/v) of methanol.
[b] Determined by HPLC analysis.

mutant enzymes have comparable activity with wild-type **SSCR** toward the reduction of the two tested diaryl ketones. The *ee* values of alcohol products showed that the ratio of (*S*)-enantiomer increased for the mutant enzymes; thus single site mutation at Q245 to P, L or H favours the formation of the (*S*)-enantiomer compared to their wild-type counterpart. This enantiopreference change was so significant for mutant Q245P that (*S*)-alcohols became the major products. As such, the reduction of other diaryl ketones were also investigated using Q245P mutant enzyme as the catalyst and THF or methanol as co-solvent (Table 4).

From Table 4 it can be seen that Q245P mutation switched the enantiopreference for the reduction of diaryl ketones with a *para*-substituent on one of

Table 4. Reduction of diaryl ketones catalyzed by mutant carbonyl reductase **SSCR** Q245P.

Ketone	THF		Methanol	
	Conv. [%][a]	*ee* [%][a]	Conv. [%][a]	*ee* [%][a]
1a (4-F)	68	24 (*S*)	>99	18 (*S*)
1b (4-Cl)	88	74 (*S*)	98	76 (*S*)
1c (4-Me)	79	52 (*S*)	99	48 (*S*)
1d (4-MeO)	70	76 (*S*)	98	78 (*S*)
1e (2,6-F_2)	77	70 (*S*)	>99	60 (*S*)
1f (2-Cl)	66	12 (*R*)	>99	16 (*R*)
1g (2-Me)	25	20 (*R*)	91	44 (*R*)
1h (3,4-Me_2)	40	36 (*S*)	94	32 (*S*)
1i (3-NO_2)	68	10 (*S*)	93	16 (*S*)
1j (3-NH_2)	13	32 (*S*)	90	34 (*S*)
1k	>99	90 (*R*)	>99	90 (*R*)
1l	>99	74 (*R*)	>99	70 (*R*)
1m	7	12 (*R*)	66	8 (*S*)

[a] Determined by HPLC analysis.

phenyl groups, similar to the observation in the reduction of *para*-substituted acetophenones.[45] The effect on the enantioselectivity of those substrates with only an *ortho*- or *meta*-substituent was less significant, and the increase in favour of forming the (*S*)-enantiomer was not great enough to invert the enantiopreference of the reduction, except for 3-aminobenzophenone.

A few chiral diaryl methanols such as (*R*)-4-methylbenzhydrol, (*R*)-4-methoxybenzhydrol, (*R*)-phenyl-(2-pyridyl)methanol and (*R*)-phenyl-(3-pyridyl)methanol were prepared in good yield and enantiomeric purity using wild-type **SSCR** enzyme in potassium phosphate buffer containing 10% (v/v) methanol (Table 5). This provides a sustainable alternative method for the synthesis of these pharmaceutically important compounds.

Table 5. Preparation of a few diarylmethanols.

Diarylmethanol	Yield [%]	*ee* [%][a]
(*R*)-Methylbenzhydrol	89	84
(*R*)-Methoxybenzhydrol	87	99
(*R*)-Phenyl-(2-pyridyl)methanol	81	99
(*R*)-Phenyl-(3-pyridyl)methanol	84	82

[a] Determined by chiral HPLC analysis.

Conclusions

In summary, the enantioselective reduction of diaryl ketones catalyzed by carbonyl reductase **SSCR** and its mutant enzymes was performed effectively in potassium phosphate buffer containing an organic solvent (10% v/v) to give the corresponding enantiomerically enriched alcohols. Both conversion and enantioselectivity were dependent on the co-solvent in the buffer.

Contrary to the results obtained by chemical methods such as chiral borane reduction, asymmetric hydrogenation or hydrosilylation, which exhibited low enantioselectivity (<47%) toward the reduction of diaryl ketones with a *para*-substituent on one of phenyl groups, these diaryl ketones were reduced with high enantioselectivity (up to 99% *ee*). The mutant enzymes of **SSCR** at Q245 showed a tendency in favour of forming the (*S*)-enantiomer. Especially for mutant Q245P with *para*-substituted diaryl ketone as a substrate, the product enantiopreference is switched from (*R*) to (*S*). The present study demonstrates that carbonyl reductase **SSCR** is a valuable biocatalyst toward the reduction of diaryl ketones, and could serve as a promising starting enzyme for further engineering with the aim to development of efficient biocatalysts for highly enantiospecific reduction of diaryl ketones without high electronic dissymmetry or an *ortho*-substituent on one of the aryl groups, which remains a formidable challenge in organic synthesis.

Experimental Section

The chiral HPLC analysis was performed on an Agilent 1200 high-performance liquid chromatography system with a Chiracel OD-H chiral column. A mixture of hexane and isopropyl alcohol of different ratios was used as eluent (hexane/isopropyl alcohol: 80/20 for **2j**; 90/10 for **2l**; 95/5 for **2b**, **2c**, **2f**, **2g**, **2h**, **2i**, and **2m**; 98/2 for **2a**, **2d**, **2e** and **2k**). All the ketone substrates were obtained from commercial sources. The racemic alcohol standard samples were prepared *via* the reduction of diaryl ketones with sodium borohydride at room temperature. The optically active diaryl methanol standard samples were prepared by the literature method using commercially available enzymes.[30] The carbonyl reductase **SSCR** and its mutant enzymes were prepared on a gram-scale as previously reported.[39,45]

General Procedure for Enzymatic Reduction of Diaryl Ketones (1-mL scale)

D-Glucose (20 g L^{-1}), D-glucose dehydrogenase (2 g L^{-1}), NADPH (1 g L^{-1}), and **SSCR** or Q245 mutant enzymes (2 g L^{-1}) were dissolved in potassium phosphate buffer (100 mM, pH 7.0), and 0.9 mL of the resulting solution was mixed with 0.1 mL of diaryl ketone solution in the organic solvent (0.1 M). The reaction mixture was shaken for 24 h at room temperature. The mixture was extracted with methyl *tert*-butyl ether (1.0 mL). The organic extract was dried over anhydrous sodium sulfate and subjected to chiral HPLC analysis to determine the conversion and enantiomeric excess. The absolute configurations of product alcohols were identified by comparing the HPLC elution sequence with the literature data using the same type of column,[6,7,17,40–44] and/or by comparing with the enantiomerically enriched sample prepared by literature methods.[30]

General Procedure for Enzymatic Reduction of 4-Methylbenzophenone and 4-Methoxybenzophenone (Preparative Scale)

D-Glucose (20 g L^{-1}), D-glucose dehydrogenase (2 g L^{-1}), NADPH (1 g L^{-1}), **SSCR** mutant enzyme (2 g L^{-1}) were dissolved in potassium phosphate buffer (100 mM, pH 7.0), and 27 mL of the resulting solution were mixed with 3 mL of diaryl ketone solution in methanol (0.1 M). The reaction mixture was shaken at room temperature for 24 h. The mixture was saturated with sodium chloride and extracted with methyl *tert*-butyl ether (3×30 mL). The organic extract was dried over anhydrous sodium sulfate and removal of solvent gave the product alcohols, which were characterized by ^{1}H and ^{13}C NMR analysis.

(*R*)-4-Methylbenzhydrol (2c):[6] Yield: 52.3 mg (89%); ^{1}H NMR (MeOH-d_4): δ=2.29 (s, 1H), 5.74 (s, 1H), 7.09 (m, 2H), 7.21 (m, 3H), 7.28 (m, 2H), 7.32 (m, 2H); ^{13}C NMR (MeOH-d_4): δ=21.1, 76.8, 127.6, 128.0, 129.2, 129.8, 137.9, 143.0, 145.8.

(*R*)-4-Methoxybenzhydrol (2d):[40] Yield: 55.3 mg (87%); ^{1}H NMR (MeOH-d_4): δ=3.75 (s, 3H), 5.71 (s, 1H), 6.85 (m, 2H), 7.20–7.34 (m, H); ^{13}C NMR (MeOH-d_4): δ=55.8, 76.5, 114.6, 127.5, 128.0, 129.0, 129.2, 138.0, 146.2, 160.5.

The procedures for the enzymatic reduction of 2-benzopyridine and 3-benzopyridine were the same as described above except that smaller amounts of enzymes and co-factor were used: D-glucose dehydrogenase (0.2 g L^{-1}), NADPH (0.2 g L^{-1}), **SSCR** enzyme (0.2 g L^{-1}).

(*R*)-Phenyl-(2-pyridyl)methanol (2k):[42] Yield: 44.5 mg (81%); ^{1}H NMR (MeOH-d_4): δ=5.79 (s, 1H), 7.2–7.4 (m, 6H), 7.62 (s, 1H), 7.80 (m, 1H), 8.42 (d, 2H); ^{13}C NMR (MeOH-d_4): δ=77.5, 122.2, 123.8, 127.9, 128.6, 129.4, 138.8, 149.1, 164.8.

(*R*)-Phenyl-(3-pyridyl)methanol (2l):[46] Yield: 46.3 mg (84%); ^{1}H NMR (MeOH-d_4): δ=5.84 (s, 1H), 7.3–7.4 (m, 6H), 7.81 (m, 1H), 8.39 (m, 1H), 9.54 (d, 1H); ^{13}C NMR (MeOH-d_4): δ=74.5, 125.0, 127.6, 128.7, 129.6, 136.5, 142.4, 144.6, 148.6.

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