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Simple D-glucosamine-based phosphine-imine and phosphine-amine ligands in Pd-catalyzed asymmetric allylic alkylations

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ABSTRACT

A new family of phosphine-imine and phosphine-amine ligands based on D-glucosamine were synthesized in order to probe previous asymmetric allylic alkylation results with those of disaccharide ligands of the same class. In most cases, good-to-excellent activities and enantioselectivities were observed with these ligands with ee's reaching up to 87% in the Pd-catalyzed allylic alkylation reaction of racemic (*E*)-1,3-diphenyl-2-propenyl acetate with dimethyl malonate as the nucleophile.

Carbohydrates represent excellent tools as chiral auxiliaries, reagents, organocatalysts and ligands for asymmetric synthesis,[1] as they can be easily functionalized to provide efficient ligands, which are applicable in a large number of catalytic asymmetric reactions.[2] Derivatives of the most accessible NH_2-containing sugar, D-glucosamine, have been evaluated as chiral ligands in numerous transition metal-catalyzed asymmetric catalysis based on Mn,[3] Ni,[4] V,[5] Cu,[6] Zn,[7] and Pd. With the exception of the few examples studied in the Suzuki–Miyaura[8] and the Mizoroki–Heck[8a,9] reactions, the most studied Pd-catalyzed reactions, applying ligands derived from glucosamine, are the allylic substitution reactions, which represent powerful processes for the asymmetric construction of carbon-carbon and carbon-heteroatom bonds.[10]

The main results in the Pd-catalyzed asymmetric allylations with glucosamine-based ligands are those obtained from diphenylphosphinoaryloxazoline **1**,[11] phosphinite-oxazoline **2**,[12] phosphite-oxazoline **3**,[13] and the phosphite-phosphoramidite **4**[14] (Fig. 1). These ligands provide products of high enantioselectivities (up to 98%) in the allylic alkylation of 1,3-symmetrically disubstituted acetates. A conceptually simpler and more readily available ligand is represented by the phosphine-amide ligands **5** (Fig. 1), which was introduced by us in 2003.[15] Whereas high enantioselectivities can also be obtained with this ligand, they are nevertheless strongly dependent on the C1-alkoxy group and on the anomeric configuration. In order to further probe this class of ligands, these

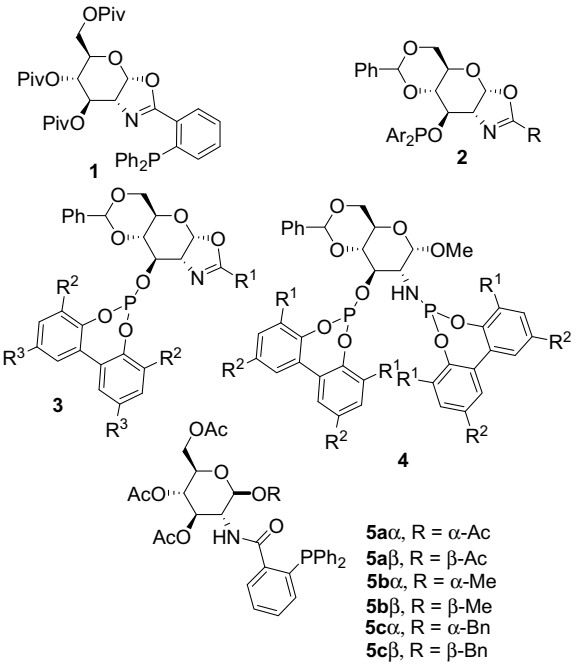

Figure 1. Ligands based on D-glucosamine used in allylic alkylation.

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monosaccharide phosphines were extended to their disaccharide derivatives, as illustrated in Figure 2.[16,17] Of the three classes of disaccharide ligands prepared, the phosphine-imine derivatives **7** rather than the amide **6** or the amines **8** exhibited the highest ee's attaining 99% for the allylic alkylation of racemic (*E*)-1,3-diphenyl-2-propenyl acetate with various nucleophiles. This came as a surprise as (1) phosphine imine ligands are generally not good ligands for these types of palladium-catalyzed reactions as examined with other NH_2-containing sugars[18] and (2) our previous study with ligand **5** showed that it was superior to its corresponding imine-phosphine and amine-phosphine. Suspecting that the role of the reducing sugar of these disaccharide ligands for the good enantioselectivities observed is simple sterical bulk, we have prepared a series of simpler ligands based on 2-amino-2-deoxyglucosides with varying degrees of sterical bulk at the anomeric center and have investigated their activities in asymmetric allylic alkylations of racemic (*E*)-1,3-diphenyl-2-propenyl acetate with dimethyl malonate. The results of this study are communicated in this Letter.

The functionalization of the amino group on the D-glucosamine derivatives provided an easy access to various phosphine-imine ligands,[19] as well as to two phosphine-amine ligands[20] based on the carbohydrate moiety (Scheme 1). The condensation of 2-(diphenylphosphino)-benzaldehyde onto 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose **9a** or alkyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranosides **9b–e** using $MgSO_4$ as the drying agent in toluene furnished the corresponding phosphine-imine derivatives **10** with yields in the range of 63–85%, except from benzyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside **9e** where a yield of 31% was obtained after purification. The reduction of the imino group of the derivatives **10a** and **10b**, using $NaBH_3CN$ in a mixture of acetic acid and methanol, provided the phosphine-amine ligands **11a** and **11b** in quantitative yield.

The starting materials **9** were easily generated from the commercially available D-glucosamine hydrochloride. 1,3,4,6-Tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose **9a** was obtained in three steps according to the literature procedure:[21] protection of the NH_2 group with *p*-anisaldehyde, acetylation of the OH group, removal of the *p*-methoxybenzylidene group with HCl, and a basic washing to give the free amino group. The other glycosides **9b–e** were prepared following the process described by Billing and Nilsson[22] in the case of the methyl glycoside **9b** from 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl bromide hydrobromide

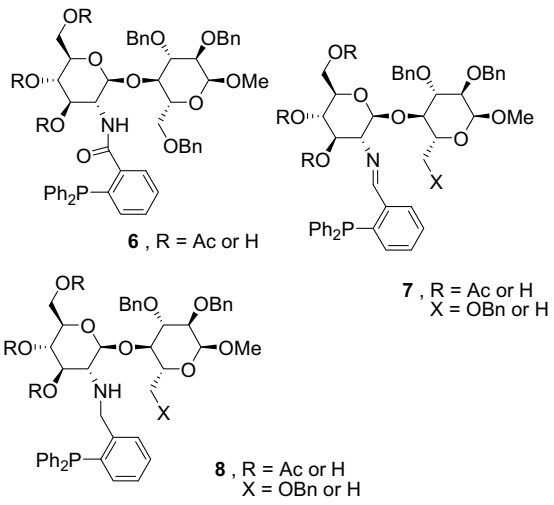
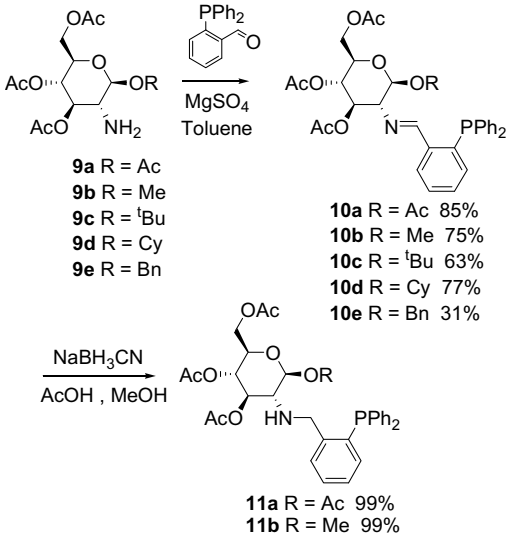


Figure 2. Ligands based on disaccharides with one D-glucosamine unit used in allylic alkylation.

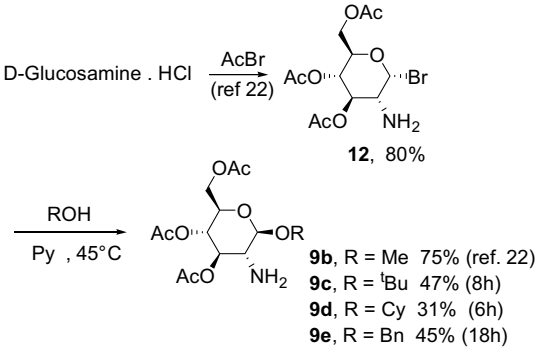


Scheme 1. Preparation of phosphine-imine and phosphine-amine ligands **10** and **11**.

12 (Scheme 2). The treatment of the D-glucosamine by a large excess of acetyl bromide gave the compound **12** in 80% yield. Then, the derivative **12** and pyridine (1.2 equiv) were dissolved in the corresponding alcohol (ROH) to give after a stirring at 45 °C for the desired time, the corresponding alkyl glycosides **9c–e** with yields in the range of 31–47%.

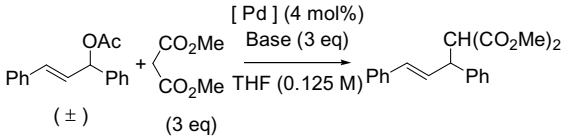
The phosphine-imine and phosphine-amine ligands **10** and **11** were examined in the palladium-catalyzed asymmetric allylic alkylation of racemic (*E*)-1,3-diphenyl-2-propenyl acetate with dimethyl malonate (Table 1). The reactions were performed in THF (0.125 M) at 25 or 60 °C for 24 h, using 2 mol % of $[(\eta^3\text{-}C_3H_5)PdCl]_2$, 4 or 8 mol % of the sugar ligand, 3 equiv of dimethyl malonate, and a mixture of *N,O*-bis(trimethylsilyl)acetamide (BSA) (3 equiv) and KOAc (2 mol %) as the base.[24] The results were compared to those obtained previously using the phosphine-amide, phosphine-imine, and phosphine-amine ligands **5–8**.

We first examined the results obtained using phosphine-imine derivatives **10a–e** as ligands. In the case of a Pd/L ratio of 1/1, after 24 h at 25 °C, the nature of the substituent at the β-anomeric position of the carbohydrate moiety of the ligand had no influence on the reactivity as complete conversion and high yield (97–99%) of the allylic product was obtained. On the other hand, this substituent greatly influenced the enantioselectivity with enantiomeric excesses produced in the range of 38–87% (Table 1, entries 1, 3, 5, 7 and 9). The use of ligands **10c** or **10e**, carrying a *t*-butoxy or benzyloxy group (Table 1, entries 5 and 9), afforded high ee's (87% or 82%,



Scheme 2. Preparation of alkyl glycosides **9b–e**.

Table 1
Palladium-catalyzed asymmetric allylic alkylation of racemic 1,3-diphenylprop-2-enyl acetate with dimethyl malonate[a]



Entry	Ligand	Pd/L	Temp. (°C)	Conv.[b] (yield[c]) (%)	ee[d] (%) Config.[e]
1	**10a**	1/1	25	100 (99)	38 (*R*)
2	**10a**	1/2	25	100 (97)	30 (*R*)
3	**10b**	1/1	25	100 (98)	56 (*S*)
4	**10b**	1/2	25	100 (98)	56 (*S*)
5	**10c**	1/1	25	100 (98)	87 (*S*)
6	**10c**	1/2	25	42 (40)	58 (*S*)
7	**10d**	1/1	25	100 (97)	65 (*S*)
8	**10d**	1/2	25	100 (98)	63 (*S*)
9	**10e**	1/1	25	100 (97)	82 (*S*)
10	**10e**	1/2	25	42 (38)	66 (*S*)
11	**10e**	½	60	100 (97)	60 (*S*)
12	**11a**	1/1	25	100 (98)	32 (*S*)
13	**11a**	½	25	100 (98)	19 (*S*)
14	**11b**	1/1	25	100 (95)	71 (*S*)
15	**11b**	½	25	100 (96)	61 (*S*)

[a] [substrate]/[$CH_2(CO_2Me)_2$]/[Base]/[Pd]/[Ligand] = 25/75/75/1/1 or 25/75/75/1/2.
[b] Conversion determined by GC analysis.
[c] Isolated pure product after column chromatography.
[d] Enantiomeric excess determined by HPLC analysis (column Chiralpak AD 0.46 × 25 cm).
[e] The absolute configuration was determined by comparison with an authentic sample (Ref. 24).

respectively), suggesting that the addition of a bulky group at the β-anomeric position of the monosaccharide has a favorable effect on the asymmetric induction as seen in the case of the disaccharide ligands. In the case of a Pd/L ratio of 1/2, total conversion was observed after 24 h at 25 °C, with yields of 97% and 98% when ligands **10a**, **10b**, and **10d** were applied (Table 1, entries 2, 4, and 8). From ligands **10c** and **10e** (Table 1, entries 6 and 10), a low conversion of 42% was determined under the same conditions, and for the ligand **10e** (Table 1, entry 11), it was necessary to perform the allylic alkylation at 60 °C for 24 h to obtain a complete consumption of the starting material conversion. Concerning the enantioselectivity, comparing the results obtained in the case of a Pd/L ratio of 1/1, no change was observed for the ligands **10a**, **10b,** and **10d**, with ee's in the range of 30–63% (Table 1, entries 2, 4, and 8). And when the derivatives **10c** and **10e** were employed as ligands, lower enantioselectivities were noted with a loss of 29% and 16–22%, respectively (Table 1, entries 6, 10 and 11).

In a second study, we investigated the same allylic alkylation reaction using phosphine-amine derivatives **11a** and **11b** as ligand, where the reactions were performed under the same conditions as described for the phosphine-imine ligands **10**. Of the two ligands tested, a total conversion with high yield (95–98%) was observed in the case of both Pd/L ratios of 1/1 and of 1/2 after 24 h at 25 °C (Table 1, entries 12–15). Here, the enantiomeric excess observed was strongly dependent on the choice of the ligand. In the case of ligand **11a** carrying an acetoxy group at the β-anomeric position of the carbohydrate unit and with Pd/L ratios of 1/1 and 1/2, low enantioselectivities were observed: 32% and 19%, respectively (Table 1, entries 12 and 13). More encouraging were the results obtained with the ligand **11b** carrying a methoxy group at the β-anomeric position of the carbohydrate moiety. In these cases, higher enantiomeric excesses were obtained: 71% for a Pd/L ratio of 1/1, and 61% for a Pd/L ratio of 1/2 (Table 1, entries 14 and 15), which are slightly higher than those obtained for the corresponding imine derivative **10b** (entries 3 and 4).

These results were compared with those obtained previously from phosphine-amide ligands **5** and **6**, phosphine-imine ligands **7**, and phosphine-amine ligands **8**. In the case of the phosphine-amide ligand **5**[15] composed of a D-glucosamine unit, the group at the anomeric position has a notable influence on the activity and selectivity of the allylic substitution. For this type of ligand, it was necessary to have an acetoxy group at the anomeric center in a β-orientation to observe a total conversion and an enantioselectivity of 83% in favor of the (*R*)-enantiomer, using dimethyl malonate as nucleophile. On the other hand, with the phosphine-imine ligands **10**, a higher enantioselectivity (87% in favor of the (*S*)-enantiomer) was observed when ligand **10c** was applied, possessing a bulky *t*-butyl group at C1 in the β-position of the monosaccharide unit. Under the same conditions, the ligand **10a** with a β-acetoxy group instead at the anomeric carbon only provided an e.e. of 38% in favor of the (*R*)-enantiomer, suggesting that in the case of the phosphine-imine ligands based on D-glucosamine, it is important to have a bulky C1–O substituent such as a *tert*-butyl group. The more flexible, phosphine-amine ligand as represented by **11b** also provided interesting enantioselectivities, Though further work is required to investigate whether increasing the sterical bulk at C1 will further enhance the ee's of this allylic alkylation using this class of ligands.

In conclusion, a new and simple class of chiral phosphine-imine and phosphine amine ligands derived from D-glucosamine were easily prepared, and examined in the palladium-catalyzed asymmetric allylic alkylation of racemic (*E*)-1,3-diphenyl-2-propenyl acetate with dimethyl malonate. Good enantioselectivities attaining 87% ee and high conversions were observed with the phosphine-imine ligands bearing a large substituent at the C1 position of the amino sugar. It seems that the size of the group at the β-anomeric position of the monosaccharide **10** has a marked influence on the enantioselectivity, thereby confirming that the reducing sugar of the disaccharide ligands function as a sterically demanding group. Further investigations are now underway to optimize these two ligands in order to provide alternative means for effective asymmetric allylic alkylations from derivatives of a simple and abundant sugar.

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Supplementary data

Supplementary data (experimental details for all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.039.

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19. *General procedure for the synthesis of phosphine-imine ligands* ***10***: The glucopyranoside derivative **9** (0.35 mmol), 2-diphenylphosphinobenzaldehyde (102 mg, 0.35 mmol) and toluene (5 mL) were added to dried $MgSO_4$ under an inert atmosphere. The reactional mixture was stirred at 60 °C for 12 h. After concentration, the residue was purified by flash chromatography to give phosphine-imine derivatives **10**. Data for ligand **10a**: Pale yellow solid (yield 85%); R_f (CH_2Cl_2/MeOH, 30:1) = 0.70; $[\alpha]_D^{25}$ +25.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ 9.04 (d, *J* = 4.9 Hz, 1H), 7.95 (dd, *J* = 6.8, 4.0 Hz, 1H), 7.42–7.15 (m, 12H); 6.94–6.90 (m, 1H), 5.85 (d, *J* = 8.4 Hz, 1H), 5.36 (dd, *J* = 9.4, 9.4 Hz, 1H), 5.10 (dd, *J* = 10.2, 9.4 Hz, 1H), 4.35 (dd, *J* = 12.4, 4.5 Hz, 1H), 4.13 (dd, *J* = 12.1, 1.9 Hz, 1H), 3.93 (ddd, *J* = 10.2, 4.5, 1.9 Hz, 1H), 3.46 (dd, *J* = 9.4, 8.4 Hz, 1H), 2.08 (s, 3H), 2.01 (s, 3H), 1.83 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ 170.7, 169.8, 169.7, 168.8, 163.8 (d, *J* = 25.4 Hz), 139.1 (d, *J* = 18.6 Hz), 137.8 (d, *J* = 21.9 Hz), 136.3 (d, *J* = 5.0 Hz), 136.2 (d, *J* = 5.6 Hz), 134.0 (d, *J* = 3.7 Hz), 133.9, 133.6 (d, *J* = 6.2 Hz), 131.1, 129.3, 128.9 (d, *J* = 5.6 Hz), 128.7 (d, *J* = 10.4 Hz), 128.6 (d, *J* = 3.7 Hz), 127.9 (d, *J* = 5.0 Hz), 92.9, 73.0, 72.6, 72.5, 67.9, 61.6, 20.8, 20.7, 20.6, 20.3; ^{31}P NMR (121 MHz, $CDCl_3$, 298 K): δ −15.7. Anal. Calcd for $C_{33}H_{34}NO_9P$: C, 63.97; H, 5.53. Found: C, 63.88; H, 5.48.
20. General procedure for the synthesis of phosphine-amine ligands **11**: The phosphine-imine derivative **10** (86 μmol) was dissolved in a mixture of methanol (2.5 mL) and acetic acid (0.25 mL). $NaBH_3CN$ (42 mg, 650 μmol) was added to the previous solution, and the mixture was stirred at room temperature for 15 min before adding water (50 mL) in order to stop the reaction. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic phase was washed with a saturated solution of $NaHCO_3$ and then of brine, dried with Na_2SO_4, and concentrated. The phosphine-amine compound **11** was obtained in quantitative yield without further purification. Data for ligand **11a**: white solid; R_f (CH_2Cl_2/MeOH, 30:1) = 0.63; $[\alpha]_D^{25}$ +20.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ 7.41 (ddd, *J* = 7.7, 4.5, 1.0 Hz, 1H), 7.35–7.30 (m, 7H), 7.23–7.11 (m, 5H), 6.82 (ddd, *J* = 7.6, 4.5, 1.2 Hz, 1H), 5.53 (d, *J* = 8.6 Hz, 1H), 5.09 (dd, *J* = 9.2, 9.0 Hz, 1H), 5.05 (dd, *J* = 9.6, 9.2 Hz, 1H), 4.29 (dd, *J* = 12.5, 4.5 Hz, 1H), 4.05 (dd, *J* = 12.4, 1.9 Hz), 4.01 (br s, 2H), 3.75 (ddd, *J* = 9.6, 4.5, 1.9 Hz, 1H), 2.94 (dd, *J* = 9.0, 8.6 Hz, 1H), 2.10 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ 171.2, 171.1, 170.0, 169.6, 144.6 (d, *J* = 23.6 Hz) 136.8 (d, *J* = 9.9 Hz), 136.7 (d, *J* = 9.8 Hz), 135.5 (d, *J* = 13.7 Hz), 134.3 (d, *J* = 4.4 Hz), 134.0 (d, *J* = 4.9 Hz), 133.8, 129.5, 129.2 (d, *J* = 6.0 Hz), 129.1 (d, *J* = 6.6 Hz), 127.8, 95.4, 74.2, 72.8, 68.7, 62.1, 61.2, 50.8 (d, *J* = 23.6), 21.1, 21.0, 20.7, 20.5; ^{31}P NMR (121 MHz, $CDCl_3$, 298 K): δ −14.9; HRMS (ESI): *m/z* calcd for $C_{33}H_{36}NO_9PNa$ $[M+Na]^+$ 644.2025, found 644.2032.
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23. *General procedure for the allylic alkylation*: In a Schlenk tube, $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (8.8 mg, 24 μmol) and the ligand (48 μmol or 96 μmol) were dissolved in THF (1 mL). After being stirred for 1 h at 25 °C, a solution of racemic (*E*)-1,3-diphenyl-2-propenyl acetate (302 mg, 1.2 mmol) and I THF (1 mL) was added. After 30 min, this solution was transferred to a Schlenk tube containing dimethyl malonate (475 mg, 3.6 mmol), BSA (732 mg, 3.6 mmol), and KOAc (2.5 mg, 24 μmol) in THF (2 mL). The reaction mixture was stirred at the desired temperature for 24 h. The conversion was determined by GC analysis. The mixture was then diluted with diethyl ether (15 mL) and water (5 mL). The organic phase was washed brine and dried over $MgSO_4$. Evaporation of the solvents gave a residue, which was purified by chromatography (petroleum ether/ethyl acetate, 10/1). The enantiomeric excess of dimethyl [(*E*)-1,3-diphenyl-prop-2-en-1-yl]malonate was determined by HPLC analysis: t_R 18 min for (*R*)-isomer and t_S 24 min for (*S*)-isomer. The absolute configuration of the enantiomers was determined by comparison of the retention times with that of an authentic sample[23] and by measurement of the optical rotation of the product. Colorless oil; R_f (Et_2O/EtOAc, 10:1) = 0.40; ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ 7.28–7.20 (m, 10H), 6.50 (d, *J* = 15.6 Hz, 1H), 6.34 (dd, *J* = 15.6, 8.5 Hz, 1H), 4.29 (dd, *J* = 10.9, 8.5 Hz, 1H), 3.95 (d, *J* = 10.9 Hz, 1H), 3.72 (s, 3H), 3.53 (s, 3H). The ^{1}H NMR spectrum is in agreement with the literature (see Ref. 25).
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