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Chiral amino alcohols bound to diimines, diamines and dendrimers as chiral ligands for the enantioselective ethylation of *N*-diphenylphosphinylimines

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Abstract: Chiral diimines, diamines and dendrimers possessing 2, 4 and 8 ephedrine derivatives are utilized as chiral ligands for the enantioselective addition of diethylzinc to N-diphenylphosphinylimines to afford enantiomerically enriched N-diphenylphosphinylamines in up to 93% e.e. © 1997 Elsevier Science Ltd. All rights reserved.

Dendrimers form a class of compounds with hyper-branched chains and generally consist of a spherical structure possessing terminal functional groups.¹ Therefore it is possible to prepare chiral dendrimers by attaching chiral monomeric ligands to the functional groups at their terminal positions. However, chiral dendrimers² have rarely been utilized in asymmetric synthesis.³ We previously reported an enantioselective alkylation of *N*-diphenylphosphinylimine with dialkylzincs using either monomeric⁴ or polymeric⁵ chiral amino alcohols as chiral ligands. In the reaction, the chiral amino alcohol plays the role of not only chiral ligand but promoter of the nucleophilicity of dialkylzincs.⁶ During the study, we took an interest in the preparation of chiral dendrimers and their use in the enantioselective alkylation of *N*-diphenylphosphinylimine as a chiral ligand.

We report here the preparation of chiral diimines, diamines and dendrimers possessing ephedrine derivatives and their use as chiral ligands in the enantioselective addition of diethylzinc (Et_2Zn) to N-diphenylphosphinylimines.

We plan to connect a chiral amino alcohol moiety and ethylenediamine or Starburst (PAMAM) Dendrimers by the formation of imine. Chiral amino alcohol 3 possessing a formyl group, was synthesized from (1R,2S)-ephedrine 1 (Scheme 1). Reaction of 1 with 4-bromobenzyl bromide in the presence of potassium carbonate afforded N-4-bromobenzylephedrine 2 in 64% yield. The subsequent formylation with n-BuLi and ethyl formate gave (1R,2S)-N-(4-formylbenzyl)ephedrine 3 in 46% yield.



Scheme 1. (i) 4-bromobenzyl bromide, K₂CO₃; (ii) n-BuLi; (iii) ethyl formate.

When ethylenediamine 4 and 3 reacted in refluxing toluene with a Dean-Stark trap, chiral diimine 5a was obtained in 91% yield. Reduction of 5a with sodium borohydride (NaBH₄) afforded chiral diamine 5b in 98% yield (Scheme 2).

Starburst (PAMAM) Dendrimer (Generation 0) 6 with four surface primary amino groups was treated with amino alcohol 3 to afford in 71% yield a chiral imino dendrimer 7a containing four

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Scheme 2.

chiral amino alcohol moieties on its terminal positions (Scheme 3). The subsequent reduction of imine groups of 7a using NaBH₄ afforded the corresponding chiral amino dendrimer 7b in 98% yield.



In a similar manner, starting from Starburst (PAMAM) Dendrimer (Generation 1) 8 with eight surface primary amino groups and chiral amino alcohol 3, chiral imino dendrimer 9a with eight surface amino alcohols was synthesized in 82% yield (Scheme 4). Reduction of the imino groups of 9a with NaBH₄ afforded chiral amino dendrimer 9b possessing eight surface amino alcohols in quantitative yield.

In the presence of **5a,b**, **7a,b**, and **9a,b** as chiral ligands, an enantioselective addition of Et_2Zn to *N*-diphenylphosphinylimine **10a** was examined in toluene at room temperature. The results are shown in Table 1. When chiral diimine **5a** (50 mol%) was employed as the chiral ligand, enantiomerically enriched *N*-diphenylphosphinylamine (*R*)-**11a** with 92% e.e. was obtained in 54% yield (Table 1, entry 1). Because dialkylzinc hardly adds to *N*-alkylimine even in the presence of amino alcohols, the *N*-alkylimine type chiral ligand **5a** was not alkylated during the ethylation reaction of *N*-diphenylphosphinylimine **10a**. The reaction using chiral diamine **5b** as the chiral ligand afforded (*R*)-**11a** with 92% e.e. (entry 2). Chiral ligand **5b** was recovered after quenching. These e.e.s are as high as those observed in the enantioselective ethylation of the same imine **10a** using chiral (1*R*,2*S*)-*N*-benzylephedrine (91% e.e.).^{5c} Thus, chiral diimine **5a** and diamine **5b** with C_2 axes were found to be highly enantioselective chiral ligands in the alkylation of *N*-diphenylphosphinylimine.⁷



Scheme 4.

On the other hand, in the presence of chiral imino dendrimeric ligand 7a (50 mol%), Et₂Zn added to 10a afforded (R)-11a with moderate enantioselectivity (43% e.e.) (entry 3). The reaction using chiral amino dendrimer 7b as a chiral ligand gave (R)-11a with a similar e.e. (entry 4). Both 7a and 7b were soluble in toluene and worked as homogeneous chiral ligands during the reaction. The enantioselectivity of chiral imino dendrimeric ligand 9a (50 mol%) (entry 5) was comparable to that of 7a and 7b. The use of a lesser amount of chiral amino dendrimer 9b (25 mol%) resulted in the decrease of the yield and e.e. of (R)-11a (entry 6).

Table 1	Enantioselective	ethylation	of	N-diphenylphosphinylimine	10a	using	various	chiral	ligands
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PhN	Ph	-1 7m	chiral ligand	Ph.			
•	0	<u></u>	toluene, r.t.		Et Ö		
10	a				(<i>R</i>)-11a		
				(R)-11a			
entry	chiral ligan	d (mol%)	time / d	yield/%	e.e. / %		
1	5a	50	2	54	92		
2	5b	50	2	46	92		
3	7a	50	2	32	43		
4	7 b	50	2	18	40		
5	9a	50	2	12	39		
6	9b	25	3	8	30		

Molar ratio imine : $Et_2Zn = 1:6$

There was very little difference in the enantioselectivities between the imino type and the corresponding amino type chiral ligands (5a and 5b, 7a and 7b). Because the imino and amino groups are located in the core part of the molecule, the difference in their structure may not affect the enantioselective reaction promoted by the terminal ephedrine derivatives. Unlike cross linked solid polystyrene resin, dendrimeric chiral ligands 7a, b and 9a, b have flexible conformations in organic solvents. Thus, unlike in the reaction using monomeric ligand, the four or eight parts of in situ formed ethylzinc alkoxides of amino alcohols (active chiral sites) cannot operate independently and cannot form an appropriate reaction field for the highly enantioselective addition of Et_2Zn because of the intramolecular interaction among them.

The generality of N-diphenylphosphinylimine is exemplified in the enantioselective ethylation of various N-diphenylphosphinylimines (10a-d) in the presence of 50 mol% of chiral ligands 5a, 5b and 7a (Table 2). Imines 10a,c,d were ethylated to afford 11a,c,d with very high e.e.s in the presence of either chiral 5a or 5b. The e.e.s of the obtained 11d with the p-tolyl substituent using 5a and 5b reached 93% e.e. (entries 4 and 8). On the other hand, the enantioselectivities of 7a were moderate, affording 11d with 56% e.e. (entry 12). It should be noted that enantiomerically enriched 11 is known to be converted into the corresponding enantiomerically enriched amine by acidic hydrolysis.⁸

As described, we prepared chiral diimine 5a and diamine 5b from chiral amino alcohol 3 and chiral dendrimers 7a, b and 9a, b by loading 3 on Starburst (PAMAM) Dendrimers. These compounds were used as chiral ligands for the enantioselective addition of diethylzinc to N-diphenylphosphinylimines 10. In the presence of chiral diimine 5a and diamine 5b, N-diphenylphosphinylamines 11 with >90% e.e. were obtained. Dendrimeric chiral ligands 7a, b and 9a, b afforded 11 with moderate e.e.s. To the best of our knowledge, the present method is the first example of the use of dendrimeric chiral ligands in the enantioselective alkylation of imines.⁹

Experimental

General

¹H-NMR and ¹³C-NMR spectra were recorded on a Bruker DPX300 spectrometer. IR spectra were recorded on a Horiba FT210 spectrometer. Optical rotations were measured using a JASCO DIP-1000 polarimeter. High resolution mass spectra were measured on JEOL JMS-SX102A. Hexane, toluene, and dichloromethane were distilled from CaH₂, and THF and diethyl ether distilled from LiAlH₄ before use. Starburst (PAMAM) Dendrimers were purchased from Sigma Aldrich. *N*-Diphenylphosphinylimines **10a-d** were synthesized according to the literature procedure.¹⁰ All reactions were carried out under an argon atmosphere. HPLC analysis was performed using a chiral column.

Table 2. Enantioselective ethylation of various N-diphenylphosphinylimines 10a-d

			chiral lig	chiral ligand (50 mol%)			H Ph R + N. p-Ph		
	0	- <u>-</u> 124	to	luene, r.t.		Et C)		
	10a-d		1 1a-d						
	imine 1			product 11					
entry 7	R		chiral ligand	time / d		yield/%	e.e. / %		
1	phenyl	10a	5a	2	11a	54	92		
2	l-naphthyl	10b	5a	2	11b	27	74		
3	2-naphthyl	10c	5a	2	11c	52	90		
4	<i>p</i> -tolyl	10d	5a	2	11d	54	93		
5	phenyl	10a	5b	2	11a	46	92		
6	l-naphthyl	10b	5b	2	11b	11	71		
7	2-naphthyl	10c	5 b	3	11c	41	89		
8	<i>p</i> -tolyl	10d	5 b	2	11d	38	93		
9	phenyl	10a	7a	2	11a	32	43		
10	1-naphthyl	10b	7a	3	11b	10	11		
11	2-naphthyl	10c	7a	3	11c	25	47		
12	p-tolyl	10d	7a	4	11d	22	56		

Molar ratio imine : $Et_2Zn = 1:6$

(IR,2S)-N-(4'-Bromobenzyl)ephedrine 2

A mixture of an acetonitrile solution (100 ml) of 4-bromobenzyl bromide (83.3 mmol, 20.8 g), (1*R*,2*S*)-ephedrine (100 mmol, 18.8 g), and potassium carbonate (200 mmol, 27.6 g) was refluxed for 3 h, and then 100 ml of 2 M aq. KOH was added. The acetonitrile layer was separated, the aqueous layer was extracted with dichloromethane (20 ml×3) and the combined organic layer was washed with sat. aq. NaCl. The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. Purification of the crude by recrystallization (hexane) gave 2 (53.2 mmol, 17.8g, 64% yield). Mp 55.5°C; $[\alpha]_D^{26}$ +9.9 (*c* 1.0, CH₃OH); ¹H-NMR (CDCl₃) δ =1.03 (d, 3H, *J*=6.8 Hz), 2.20 (s, 3H), 2.94 (dq, 1H, *J*_d=5.2, *J*_q=6.8 Hz), 3.05–3.25 (bs, 1H), 3.56 (s, 2H), 4.86 (d, 1H, *J*=5.2 Hz), 7.08 (d, 2H, *J*=8.2 Hz), 7.28–7.43 (m, 7H, *J*=8.2 Hz); IR (KBr) 3300 (OH), 1068 (Ph–Br) cm⁻¹; HRMS (EI+) found m/z 332.0649, calcd for C₁₇H₁₉BrNO: (M–1), 332.0650.

(IR,2S)-N-(4'-Formylbenzyl)ephedrine 3

To a THF solution (3 ml) of (1R,2S)-2 (1.5 mmol, 0.502 g), a 1.63 M hexane solution of *n*butyllithium (3.3 mmol, 2.0 ml) was added dropwise at -100° C and the mixture was stirred for 20 min, then ethyl formate (3.3 mmol, 0.244 g, 0.27 ml) was added. The reaction mixture was stirred for 30 min at -100° C. The reaction was quenched by adding 4 M dry HCl in ethyl acetate (4 mmol, 1 ml) at -100° C. Then 20 ml of 1 M aq. NaOH was added and the reaction mixture was left to warm to room temperature. The mixture was filtered and the filtrate was extracted with dichloromethane (10 ml×4). The extract was dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. Purification of the crude on silica gel TLC (developing solvent ethyl acetate:hexane=1:4, then acetone:hexane=1:4) gave 3 (0.68 mmol, 0.194 g, 46% yield). Mp 80.0°C; $[\alpha]_D^{25}$ +10.9 (c 1.0, CH₃OH); ¹H-NMR (CDCl₃) δ =1.08 (d, 3H, J=6.8 Hz), 2.23 (s, 3H), 2.94 (dq, 1H, Jd=5.3, Jq=6.8 Hz), 3.30–3.45 (bs, 1H), 3.68 (s, 2H), 4.85 (d, 1H, J=5.3 Hz), 7.28–7.35 (m, 7H, J=7.9 Hz), 7.79 (d, 2H, J=7.9 Hz), 9.97 (s, 1H); ¹³C-NMR (CDCl₃) δ =10.1, 39.1, 59.1, 64.2, 74.7, 126.7, 127.6, 128.5, 129.4, 130.2, 135.8, 143.2, 147.5, 192.5; IR (neat) 3437 (OH), 3140 (Ph), 1701 (C=O) cm⁻¹; HRMS (EI+) found m/z 282.1484, calcd for C₁₈H₂₁NO₂: (M-1), 282.1494.

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N,N'-Bis{4-[N''-(1'S,2'R)-2'-hydroxy-1'-methyl-2'-phenylethyl-N''-methyl]aminomethylbenzylidene}ethylenediamine 5a

A mixture of a toluene solution (10 ml) of ethylenediamine (0.47 mmol, 0.028 g, 0.03 ml) and (1*R*,2*S*)-3 (0.95 mmol, 0.270 g) was refluxed for 8 h with a Dean–Stark trap. The remaining solution was evaporated under reduced pressure. The residue was washed three times with a hot solution of ethyl acetate and hexane (1:10, v/v) and the solvent was dried *in vacuo*. The product **5a** (0.43 mmol, 0.253 g, 91% yield) was obtained. $[\alpha]_D^{23}$ +16.4 (*c* 1.5, CH₃OH); ¹H-NMR (CDCl₃) δ =1.00 (d, 3H×2, *J*=6.8 Hz), 2.18 (s, 3H×2), 2.91 (dq, 1H×2, *J*_q=5.0, *J*_d=6.8 Hz), 3.61 (bs, 4H+1H×2), 3.96 (s, 2H×2), 4.85 (d, 1H×2, *J*=5.0 Hz), 7.24–7.34 (m, 7H×2), 7.62 (d, 2H×2, *J*=8.1 Hz), 8.27 (s, 1H×2); ¹³C-NMR (CDCl₃) δ =10.3, 39.1, 59.3, 62.1, 63.9, 74.2, 126.6, 127.5, 128.5, 128.5, 129.2, 135.4, 142.9, 162.; IR (neat) 3417 (OH), 1647 (C=N) cm⁻¹; HRMS (EI+) found m/z 591.3705, calcd for C₃₈H₄₆O₂N₄: (M+1), 591.3699.

N,N'-Bis{4-[N''-(1'S,2'R)-2'-hydroxy-1'-methyl-2'-phenylethyl-N''-methyl]aminomethylbenzyl}ethylenediamine 5b

To a solution of **5a** (0.45 mmol, 0.263 g) in dichloromethane (5 ml) and methanol (2 ml) was added sodium borohydride (4.5 mmol, 0.171 g), and the mixture was stirred for 2 h. The remaining solution was evaporated under reduced pressure. The mixture was filtered through Celite and washed with dichloromethane. The filtrate was evaporated under reduced pressure, then dried *in vacuo*. The product **5b** (0.44 mmol, 0.261 g, 98% yield) was obtained. $[\alpha]_D^{28}$ +10.5 (*c* 1.1, CH₃OH); ¹H-NMR (CDCl₃) δ =0.97 (d, 3H×2, J=6.8 Hz), 1.65 (br, 1H×2), 2.17 (s, 3H×2), 2.76 (s, 4H), 2.92 (dq, 1H×2, J_q=4.8, J_d=6.8 Hz), 3.58 (br, (2H+1H)×2), 3.75 (s, 2H×2), 4.87 (d, 1H×2, J=4.8 Hz), 7.17–7.33 (m, 9H×2); ¹³C-NMR (CDCl₃) δ =10.4, 39.1, 49.2, 54.0, 59.3, 63.8, 74.0, 126.6, 127.4, 128.4, 128.5, 129.1, 138.5, 139.6, 142.9; IR (neat) 1041, 2792 (NH), 3317 (OH) cm⁻¹; HRMS (EI+) found m/z 595.4026, calcd for C₃₈H₅₀O₂N₄: (M+1), 595.4012.

N,N,N',N'-Tetrakis{3-N''-{2'-N'''-{4''-[N''''-(1'''S,2'''R)-2'''-hydroxy-1'''-methyl-2'''-phenyl-ethyl-N''''-methyl]aminomethylbenzylidene aminoethyl}amino-3-oxopropyl}ethylenediamine 7a

A mixture of a toluene solution (8 ml) of dendrimer (Generation 0) **6** (0.236 mmol, 0.121 g) and (1*R*,2*S*)-**3** (0.945 mmol, 0.268 g) was refluxed for 8 h with a Dean–Stark trap. The remaining solution was evaporated under reduced pressure. The residue was washed three times with hot ethyl acetate and the solvent was dried *in vacuo*. Chiral dendrimer **7a** (0.168 mmol, 0.266 g, 71% yield) was obtained. $[\alpha]_D^{23}$ +10.1 (*c* 1.0, CH₃OH); ¹H-NMR (CDCl₃) δ =1.01 (d, 3H×4, *J*=6.7 Hz), 1.87 (br, 1H×4), 2.18–2.70 (m, 32H), 2.91 (dq, 1H×4, *J*_q=4.9, *J*_d=6.7 Hz), 3.40–3.80 (m, 28H), 4.86 (d, 1H×4, *J*=4.9 Hz), 7.22–7.63 (m, 9H×4), 8.24 (s, 1H×4); ¹³C-NMR (CDCl₃) δ =10.1, 34.4, 39.2, 40.6, 50.9, 51.9, 59.2, 60.8, 63.9, 74.4, 126.3, 126.6, 127.5, 128.4, 128.6, 129.3, 135.1, 143.0, 143.4, 163.1, 173.1; IR (neat) 1651, (C=N), 3443 (OH) cm⁻¹; HRMS (FAB+) found m/z 1577.9838, calcd for C₉₄H₁₂₄N₁₄O₈: (M+1), 1577.9805.

N,N,N',N'-Tetrakis{3-N''-{2'-N'''-{4''-[N''''-(1'''S,2'''R)-2'''-hydroxy-1'''-methyl-2'''-phenyl-ethyl-N''''-methyl]aminomethylbenzyl}aminoethyl]amino-3-oxopropyl}ethylenediamine **7b**

Chiral dendrimer **7b** was synthesized from chiral dendrimer **7a** (0.05 mmol, 0.079 g) according to the same procedure as described in the synthesis of **5b**. Yield of the product **7b** (0.049 mmol, 0.078 g) was 98%. $[\alpha]_D^{21}$ +4.3 (*c* 1.0, CH₃OH); ¹H-NMR (CDCl₃) δ =0.99 (d, 3H×4, *J*=6.5 Hz), 2.10–2.95 (m, 52H), 3.09–3.40 (m, (1H+1H)×4, *J*=6.5 Hz), 3.56–4.14 (m, 16H), 4.85 (br, 1H×4), 7.19–7.31 (m, (9H+1H)×4); ¹³C-NMR (CDCl₃) δ =9.7, 34.1, 38.6, 39.1, 48.3, 50.5, 53.3, 58.7, 63.1, 73.7, 125.8, 126.2, 126.9, 127.9, 128.1, 128.8, 138.4, 138.6, 142.6, 173.0; IR (neat) 1034, 2784 (NH), 3417 (OH) cm⁻¹; HRMS (FAB+) found m/z 1586.0359, calcd for C₉₄H₁₃₂N₁₄O₈: (M+1), 1586.0431.

Chiral dendrimer **9a** was synthesized from dendrimer (Generation 1) **8** (0.15 mmol, 0.214 g) and (1*R*,2*S*)-**3** according to the same procedure as described in the synthesis of **7a**. Yield of the product **9a** (0.12 mmol, 0.438 g) was 82%. $[\alpha]_D^{25}$ +11.1 (*c* 1.0, CH₃OH); ¹H-NMR (CDCl₃) δ =1.01 (d, 3H×8, *J*=6.5 Hz), 2.17–2.80 (m, 84H), 2.89 (dq, 1H×8, *J*_q=3.8, *J*_d=6.5 Hz), 3.16 (br, 1H×8), 3.62–3.95 (m, 56H), 4.84 (d, 1H×8, *J*=3.8 Hz), 7.21–7.62 (m, 84H), 8.23 (s, 1H×8); ¹³C-NMR (CDCl₃) δ =10.0, 34.4, 39.2, 40.7, 45.6, 50.7, 51.1, 52.8, 59.1, 60.8, 64.0, 74.5, 126.3, 126.7, 127.4, 128.4, 128.6, 129.3, 135.0, 143.3, 143.5, 163.3, 173.1 (two other signals are not separated); IR (neat) 1658 (C=N), 3432 (OH) cm⁻¹; HRMS (FAB+) found m/z 3551.2, 3552.3, 3553.0, calcd for C₂₀₆H₂₈₀N₃₄O₂₀: (M+1), 3551.2, (M+2), 3552.2, (M+3), 3553.2.

 $\begin{aligned} N,N,N',N'-Tetrakis{3-N''-{2'-N''',N'''-bis{3''-N'''-{2'''-N''''-{4''''-[N'''''-{1''''S,2'''''R)-2'''''-hydroxy-1'''''-methyl-2'''''-phenylethyl-N'''''-methyl]aminomethylbenzyl]aminoethyl}{amino-3''-oxopropyl]aminoethyl}amino-3-oxopropyl]ethylenediamine$ **9b** $\end{aligned}$

Chiral dendrimer **9b** was synthesized from chiral dendrimer **9a** (0.11 mmol, 0.388 g) according to the same procedure as described in the synthesis of **5b**. Yield of the product **9b** (0.11 mmol, 0.394 g) was quantitative. $[\alpha]_D^{23}$ +6.9 (*c* 1.1, CH₃OH); ¹H-NMR (CDCl₃) δ =0.99 (d, 3H×8, *J*=6.6 Hz), 2.17 (s, 3H×8), 2.27 (br, 24H), 2.47 (br, 1H×8), 2.69 (br, 36H), 2.90 (dq, 1H×8, *J*_q=4.1, *J*_d=6.6 Hz), 3.12–3.78 (m, 80H), 4.84 (d, 1H×8, *J*=4.1 Hz), 7.19–7.36 (m, 84H); ¹³C-NMR (CDCl₃) δ =10.0, 34.6, 39.1, 39.4, 48.6, 50.6, 51.1, 53.6, 59.2, 63.6, 74.2, 126.6, 127.3, 128.4, 128.6, 129.2, 138.9, 143.2, 173.2 (six other signals are not separated); IR (neat) 1034, 2823 (NH), 3432 (OH) cm⁻¹; HRMS (FAB+) found m/z 3567.2, 3568.4, 3569.0, calcd for C₂₀₆H₂₉₆N₃₄O₂₀: (M+1), 3567.3, (M+2) 3568.3, (M+3), 3569.3.

Typical procedure for the enantioselective ethylation of N-diphenylphosphinylimine 10a by using chiral ligand 5a

A toluene solution (1 M) of diethylzinc (0.6 mmol, 0.6 ml) was added dropwise to a mixture of toluene solution (1 ml) of **5a** (0.05 mmol, 0.030 g) and imine **10a** (0.1 mmol, 0.031 g). The reaction mixture was stirred for 2 days at room temperature, and then quenched by addition of sat. aq. NaHCO₃. The mixture was filtered and the filtrate was extracted with dichloromethane (10 ml×3). The extract was dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. Purification of the residue on silica gel TLC (developing solvent acetone:hexane=1:1) gave (*R*)-**11a** (0.060 mmol, 0.018 g, 54% yield). Enantiomeric enrichment was determined to be 92% e.e. by HPLC analysis using a chiral column [Daicel Chiralcel OD: 4×250 mm, 254 nm UV detector, room temperature, eluent: 3% 2-propanol in hexane, flow rate: 1.0 ml/min, retention time (min): 13.1 for the major-(*R*)-**11a**, 24.5 for the minor-(*S*)-**11a**; 25.1 for the major-**11b**, 34.5 for the minor-**11b**; 25.1 for the major-**11c**, 36.6 for the minor-**11c**, 18.1 for the major-**11d**, 23.3 for the minor-**11d**].

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