Dynamic Kinetic Resolution of β-Azido Alcohols. An Efficient Route to Chiral Aziridines and β-Amino Alcohols

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Enzymatic resolution of β-azido alcohols in combination with ruthenium-catalyzed alcohol isomerization led to a successful dynamic kinetic resolution. A variety of racemic β-azido alcohols were efficiently transformed to the corresponding enantiomerically pure acetates (ee up to 99% and conversion up to 98%). The synthetic utility of this procedure has been illustrated by the practical synthesis of (*S*)-propanolol **I** and (*R*)-β-azido-α-(4-methoxyphenyl)ethanol ((*R*)-**1**c), a direct precursor of denopamine **II**.

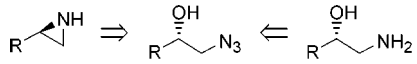
Introduction

The value of enantiopure azido alcohols lies in their utility as direct precursors of aziridines[1] and vicinal amino alcohols[2] (Scheme 1).

During recent years, there has been a growing interest in chiral aziridines due to the increasing importance of functionalized aziridines in organic synthesis[3] and their presence in bioactive molecules (e.g., radiation sensitizers and enzyme inhibitors).[4] Moreover, chiral β-amino alcohols are important structural elements in chiral ligands for asymmetric catalysis[5] as well as in biologically active compounds (e.g., β-adrenergic receptor blockers and immune stimulants).[6] In contrast to chiral 2-amino-1-ols, which are readily available by reduction of α-amino acids,[5a] the corresponding regioisomeric chiral 1-amino-2-ols are not as easy to access. The known approaches to these synthetically valuable compounds include the nitroaldol reaction,[7] hydrocyanation of aldehydes,[8] asymmetric amino- and dihydroxylation,[9] asymmetric hydrogenation,[10] and ring opening of epoxides with amines or amine equivalents.[11]

Several studies dealing with the kinetic resolution (KR) of azido alcohols by lipase-catalyzed esterification have been reported.[12] These studies have shown that azido alcohols are esterified at good reaction rates and good selectivity. However, a major drawback with KR is that the yield is limited to a maximum of 50%. By applying dynamic kinetic resolution (DKR) this limitation can be overcome. To the best of our knowledge the only example of DKR for obtaining vicinal azido alcohols is the expoxide ring opening with trimethylsilyl azide ($TMSN_3$), reported by Jacobsen,[13] in which an epihalohydrin is employed as starting material.

Scheme 1



As a part of our ongoing project on chemoenzymatic DKR of different substrates contaning a *sec*-alcohol moiety,[14] we now report on the efficient synthesis of enantiopure vicinal azido acetates from vicinal azido alcohols **1** via DKR. This procedure is applied to the enantioselective synthesis of different phenyl and aryloxymethyl substituted azido alcohol derivatives, which are important precursors of biologically active compounds.[15] The viability of this strategy is illustrated by the practical syntheses of (*S*)-propanolol **I** (Figure 1), a

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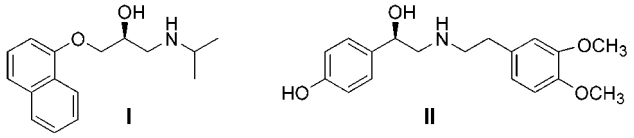


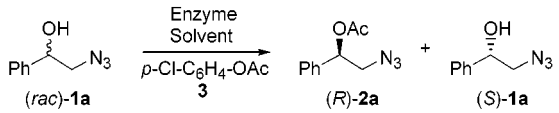
Figure 1.

widely used anti-hypertensive drug (β-blocker),[11b,15d] and (*R*)-β-azido-α-(4-methoxyphenyl)ethanol, a precursor of (*R*)-denopamine **II** (Figure 1) which is a potent orally active β_1 receptor agonist for the treatment of heart failure.[15d]

Results and Discussion

A primary requirement for a successful DKR is that the KR conditions are compatible with the racemization process.[14] Therefore, we screened different commercially available lipases in the kinetic resolution of 2-azido-1-phenylethanol **1a** under different reaction conditions, using *p*-chlorophenyl acetate **3** as acyl donor. The latter is known to be compatible with Ru-catalyzed racemization of alcohols.[14] The results are summarized in Table 1. Although the enzyme *Pseudomonas cepacia* lipase (PS-C type II) showed the highest activity (entry 1), the best enantioselectivity (>99%) was obtained using *Candida antarctica* lipase B (Novozyme 435, N-435) (entry 2).

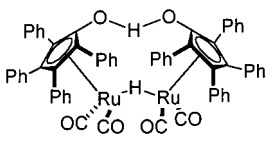
Table 1. Kinetic Resolution of 1a[a]



entry	enzyme	solvent	*t*/h	% **2a**[b]	% ee[c]
1	PS-C	toluene	5	38	93
2	N-435	toluene	5	28	>99
3	PF	toluene	48	8	nm[d]
4	N-435	DIPE[e]	5	31	>99
5	N-435	TBME[f]	5	32	>99

[a] Reactions were performed on a 0.2 mmol scale with 20 mg of enzyme and 3 equiv of **3** in 2 mL of solvent at 60 °C. [b] Determined by NMR. [c] % ee of **2a** determined by HPLC. [d] Not measured. [e] Diisopropyl ether. [f] *tert*-Butyl methyl ether.

Surprisingly, *Pseudomonas fluorescens* lipase (PF), which has been successfully used in the KR of different azido alcohols,[12a] showed very low activity under our conditions. Moreover, these experiments showed that the rate of the kinetic resolution of **1a** is hardly affected by the nature of the nonpolar solvents (entries 2, 4, and 5).



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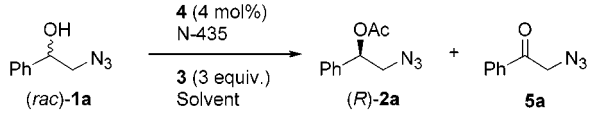
On the basis of our preliminary results on KR, we combined the KR of azido alcohol **1a** using N-435 and the acyl donor **3** with a ruthenium-catalyzed racemization process via hydrogen transfer with catalyst **4**.[16] The results are summarized in Table 2. In all cases, small amounts of ketone **5a**, formed during the hydrogen transfer process,[14] were observed.

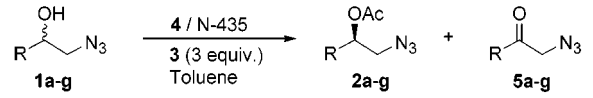
Table 2. Dynamic Kinetic Resolution of 1a[a]



entry	solvent	*T*/°C	*t*/h	% **2a**[b]	% **5a**[b]	% ee[c]
1	toluene	60	48	76	7	>99
2	DIPE	60	48	70	6	>99
3	TBME	60	48	68	6	>99
4[d]	toluene	60	48	78	6	>99
5[e]	toluene	60	48	62	3	92
6[f]	toluene	60	48	89	7	>99
7[f]	toluene	70	36	94	6	>99
8[f]	toluene	80	24	94	6	>99
9[g]	toluene	80	24	94	6	>99

[a] Reactions were performed on a 0.2 mmol scale with 20 mg of N-435, 4 mol % of **4**, and 3 equiv of acyl donor in 2 mL of solvent. [b] Determined by ^{1}H NMR. [c] % ee of **2a** determined by HPLC. [d] 0.02 mmol of NEt_3. [e] 2 equiv of NEt_3. [f] 30 mg of enzyme used. [g] Using the recovered enzyme from entry 8.

Table 3. Dynamic Kinetic Resolution of 1a−g[a]



entry	substrate	R	*t*/h	% **2**[b]	% **5**[b]	% ee[c]
1	**1a**	Ph	24	94 (86)	6	>99 (+)
2	**1b**	*p*-Br-C_6H_4	24	98 (87)	2	>99 (+)
3	**1c**	*p*-MeO-C_6H_4	24	92 (84)	8	>99 (+)
4	**1d**	2-naphthyl	24	95 (85)	5	>99 (+)
5[d]	**1e**	benzyl	48	87 (80)	7	96 (−)
6[e]	**1f**	$PhOCH_2$	72	76 (70)	4	85 (+)
7[e]	**1g**	1-naphthyl-OCH_2	72	75 (71)	5	86 (+)

[a] Reactions were performed on a 0.6 mmol scale with 90 mg of N-435, 4 mol % of **4**, and 3 equiv of acyl donor in 6 mL of solvent at 80 °C. [b] Determined by NMR. Isolated yields in parentheses. [c] % ee of **2** determined by HPLC. Absolute configuration in parentheses. [d] N-435 (15 mg), 6 mol % of **4**. [e] T = 60 °C, N-435 (1.5 mg), 6 mol % of **4**.

Under "standard" conditions (i.e., 60 °C and 4 mol % of **4**), excellent enantioselectivity (>99%) was achieved. However, the efficiency of the process was slightly affected by the solvent (Table 2, entries 1−3). Thus, reaction in toluene gave better conversion than in diisopropyl ether (DIPE) and *tert*-butyl methyl ether (TBME). This can be attributed to the limited solubility of **4** in the latter solvents.

Several attempts to increase the efficiency have been carried out. Although the use of catalytic amounts of triethylamine gave similar results (entry 4, Table 2), the addition of larger amounts had a negative effect on both activity and enantioselectivity (entry 5). The addition of more enzyme increased the activity without loss of enantioselectivity (entry 6). Moreover, increasing the temperature led to significantly higher efficiency of the process (entries 7 and 8). This is mainly due to an increase of the racemization rate. Interestingly, at 80 °C neither deactivation of the enzyme nor loss of ee has been observed. The dynamic kinetic resolution of compound **1a** with the recovered enzyme gave identical results to that of the fresh enzyme, and azido acetate **2a** was obtained in high yield in >99% ee after 24 h (entry 9).

This new procedure was applied to different substrates **1a**−**g** (Table 3). The DKR of various β-azido-α-phenethyl alcohols **1a**−**c** gave high yields in more than 99% ee (Table 3, entries 1−3). These results further indicate that

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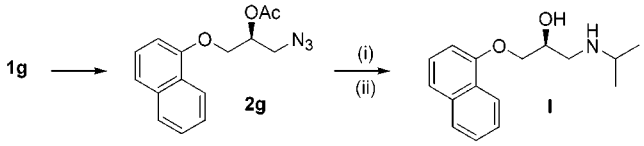
Scheme 2. Synthesis of (*S*)-Propanolol I[a]



[a] Key: (i) LiOH, MeOH, 2 h, rt; (ii) PtO_2, acetone, H_2 (1 atm), 4 h, rt, 98%.

the presence of different substituents in the para position in the aromatic ring does not significantly influence the efficiency of the process. The DKR of *β*-azido-α-(naphth-2-yl)ethyl alcohol **1d** under these conditions also gave enantiopure azido acetate **2d** in high yield (entry 4). For the benzyl (**1e)** and aryloxymethyl derivatives (**1f** and **1g)**, the DKR under the conditions used for **1a**−**d** (i.e., 120 mg N-435/mmol product, 80 °C, 4 mol % **4**) gave the acetates in moderate to low enantioselectivity (around 70% ee for **1e** and around 30% ee for **1f** and **1g**). This is due to the lower enantiopreference of the enzyme for these substrates.[12c] To obtain better enantioselectivity we took full advantage of the DKR. Thus, by reducing the enzyme/ruthenium catalyst ratio the enzymatic acylation became the rate-determining step and the enantioselectivity was therefore substantially improved (entries 5−7).

A wide range of synthetic applications of this dynamic kinetic resolution procedure can be envisaged. For instance, the in situ hydrolysis of acetate **2c** with LiOH in methanol gave quantitatively (*R*)-*β*-azido-α-(4-methoxyphenyl)ethanol (*R*)-**1c**, a precursor of (*R*)-denopamine **II**, in essentially enantiomerically pure form (ee >99%).

This method was extended to the practical synthesis of the anti-hypertensive drug propanolol **I** (Scheme 2). Dynamic kinetic resolution of the racemic azido alcohol **1g** afforded the corresponding azido acetate **2g** in 71% isolated yield and 86% ee (entry 7, Table 3). The transformation to (*S*)-propanolol was performed in a one-pot two-step procedure, hydrolysis with LiOH in methanol followed by azide reduction and in situ reductive alkylation using Adam's catalyst in the presence of acetone.[11b] Recrystallization from cyclohexane gave **I** in almost enantiomerically pure form.

Conclusion

We have developed a chemoenzymatic DKR to obtain vicinal azido acetates in good to high yields and with high enantioselectivity. The efficiency of the process together with the easy transformation of these azido acetates to *β*-amino alcohols and aziridines should make the present method an attractive alternative to existing methods for obtaining the latter two classes of compounds in enantiomerically pure form.

Experimental SectionProcedures

General Experimental Procedures. All reactions were carried out under dry argon atmosphere in oven-dried glassware. Solvents were purified by standard procedures. Solvents for HPLC use were spectrometric grade. All other reagents are commercially available and were used without further purification. Compounds **5a**−**d** were prepared according to literature procedures.[17] Racemic azido alcohols **1a**−**d** were prepared from the corresponding azido ketones **5** by reduction with sodium borohydride under standard conditions. Azido alcohols **1e**−**g** were prepared by ring opening of the corresponding epoxide by sodium azide in the presence of ammonium chloride.[18] Novozym-435 (*Candida antarctica* Lipase B) was a generous gift from Novo Nordisk A/S, Denmark. Lipase PS-C type II was a generous gift from Amano Pharmaceutical Co. Ltd, Japan.

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 100 MHz, respectively. Solvents for extraction and chromatography were technical grade and distilled before use. Column chromatography was performed with Merck 60 silica gel. The enantiomeric excess of azido acetates **2a**−**g** was determined by analytical HPLC employing a Daicel, Chiracel OD-H column using racemic compounds as references. The flow parameters and retention times were as follows: **2a**, 17.1 (*R*), 19.2 (*S*) (*n*-hexane/2-propanol = 60:40, 0.5 mL/min, 254 nm); **2b**, 53.9 (*R*), 58.3 (*S*) (*n*-hexane/2-propanol = 99.6:0.4, 0.5 mL/min, 254 nm); **2c**, 18.3 (*R*), 19.8 (*S*) (*n*-hexane/2-propanol = 60:40, 0.5 mL/min, 254 nm); **2d**, 57.7 (*R*), 67.6 (*S*) (*n*-hexane/2-propanol = 99.5:0.5, 0.5 mL/min, 254 nm); **2e**, 20.5 (*S*), 27.8 (*R*) (*n*-hexane/2-propanol = 99.5:0.5, 0.5 mL/min, 254 nm). **2f**, 36.7 (*S*), 38.5 (*R*) (*n*-hexane/2-propanol = 95:5, 0.5 mL/min, 254 nm); **2g**, 43.9 (*S*), 46.8 (*R*) (*n*-hexane/2-propanol = 90:10, 0.5 mL/min, 254 nm).

General Procedure for the DKR of Azido Alcohols. (*R*)-1-Azido-2-acetoxy-2-phenylethane ((*R*)-2a). In a typical experiment, ruthenium catalyst **4** (32.5 mg, 4 mol %) and Novozym-435 (90 mg) were placed in a Schlenk flask under argon. A solution of **1a** (97.9 mg, 0.6 mmol) and **3** (336 mg, 1.8 mmol) in dry toluene (6 mL) under argon (5 min of argon bubbling) was transferred to the ruthenium catalyst and the enzyme. The resulting reaction mixture was stirred at 80 °C for 24 h. The enzyme was then filtered off and washed with toluene (3 × 5 mL), the solvent was evaporated, and the product was purified by flash chromatography (pentane/ethyl acetate 15/1) to yield 105.8 mg (86%) of (*R*)-**2a** in >99% ee. ^{1}H NMR *δ*: 2.14 (s, 3H, CH_3), 3.45 (dd, 1H, CH_2, $^2J_{H-H}$ = 12.9 Hz, $^3J_{H-H}$ = 3.9 Hz), 3.64 (dd, 1H, CH_2, $^2J_{H-H}$ = 12.9 Hz, $^3J_{H-H}$ = 8.4 Hz), 5.92 (dd, 1H, CH, $^3J_{H-H}$ = 8.4 Hz, $^3J_{H-H}$ = 3.9 Hz), 7.36 (m, 5H, CH=). ^{13}C NMR *δ*: 21.6 (CH_3), 55.8 (CH_2), 75.2 (CH), 126.3 (CH=), 128.7 (CH=), 137.8 (C), 170.2 (CO).

(*R*)-1-Azido-2-acetoxy-2-(*p*-bromophenyl)ethane ((*R*)-2b). ^{1}H NMR *δ*: 2.14 (s, 3H, CH_3), 3.43 (dd, 1H, CH_2, $^2J_{H-H}$ = 12.8 Hz, $^3J_{H-H}$ = 4.4 Hz), 3.60 (dd, 1H, CH_2, $^2J_{H-H}$ = 12.8 Hz, $_3J_{H-H}$ = 7.6 Hz), 5.85 (dd, 1H, CH, $^3J_{H-H}$ = 7.6 Hz, $^3J_{H-H}$ = 4.4 Hz), 7.23 (d, 2H, CH=, $^3J_{H-H}$ = 8.8 Hz), 7.51 (d, 2H, CH=, $^3J_{H-H}$ = 8.8 Hz). ^{13}C NMR *δ*: 21.2 (CH_3), 55.0 (CH_2), 74.2 (CH), 123.0 (C), 128.4 (CH=), 132.2 (CH=), 136.4 (C), 169.9 (CO).

(*R*)-1-Azido-2-acetoxy-2-(*p*-methoxyphenyl)ethane ((*R*)-2c). ^{1}H NMR *δ*: 2.08 (s, 3H, CH_3), 3.39 (dd, 1H, CH_2, $^2J_{H-H}$ = 12.8 Hz, $^3J_{H-H}$ = 4.0 Hz), 3.63 (dd, 1H, CH_2, $^2J_{H-H}$ = 12.8 Hz, $^3J_{H-H}$= 8.0 Hz), 3.80 (s, 3H, CH_3O), 5.86 (dd, 1H, CH, $^3J_{H-H}$ = 8.0 Hz, $^3J_{H-H}$ = 4.0 Hz), 6.90 (d, 2H, CH=, $^3J_{H-H}$ = 6.8 Hz), 7.25 (d, 2H, CH=, $^3J_{H-H}$ = 6.8 Hz). ^{13}C NMR *δ*: 21.3 (CH_3), 55.2 (CH_2), 55.5 (CH_3O), 74.5 (CH), 114.3 (CH=), 128.1 (CH=), 129.4 (C), 160.1 (C), 170.2 (CO).

(*R*)-1-Azido-2-acetoxy-2-(naphth-2-yl)ethane ((*R*)-2d). ^{1}H NMR *δ*: 2.18 (s, 3H, CH_3), 3.52 (dd, 1H, CH_2, $^2J_{H-H}$ = 13.2 Hz, $^3J_{H-H}$ = 4.0 Hz), 3.72 (dd, 1H, CH_2, $^2J_{H-H}$ = 13.2 Hz, $^3J_{H-H}$ = 8.8 Hz), 6.08 (dd, 1H, CH, $^3J_{H-H}$ = 8.8 Hz, $^3J_{H-H}$ = 4.0 Hz), 7.50 (m, 3H, CH=), 7.85 (m, 4H, CH=). ^{13}C NMR *δ*: 21.3 (CH_3), 55.3 (CH_2), 74.9 (CH), 124.0 (C), 126.2 (CH=), 126.8 (CH=), 127.9 (CH=), 128.3 (CH=), 128.9 (CH=), 133.3 (C), 133.5 (C), 134.7 (C), 170.1 (CO).

(*R*)-1-Azido-2-acetoxy-3-phenylpropane ((*R*)-2e). ^{1}H NMR *δ*: 2.07 (s, 3H, CH_3), 2.88 (dd, 1H, CH_2, $^2J_{H-H}$ = 13.5 Hz, $^3J_{H-H}$ = 7.2 Hz), 2.98 (dd, 1H, CH_2, $^2J_{H-H}$ = 13.5 Hz, $^3J_{H-H}$ = 6.3 Hz), 3.26 (dd, 1H, CH_2, $^2J_{H-H}$ = 13.2 Hz, $^3J_{H-H}$ = 5.7 Hz), 3.40 (dd, 1H, CH_2, $^2J_{H-H}$ = 13.2 Hz, $^3J_{H-H}$ = 3.6 Hz), 5.17 (m, 1H, CH), 7.25 (m, 5H, CH=). ^{13}C NMR *δ*: 21.2 (CH_3), 37.8 (CH_2-Ph), 52.6 (CH_2), 73.6 (CH), 127.1 (CH=), 128.9 (CH=), 129.6 (CH=), 136.4 (C), 170.5 (CO).

(*S*)-1-Azido-2-acetoxy-3-phenoxypropane ((*S*)-2f). ^{1}H NMR *δ*: 2.12 (s, 3H, CH_3), 3.62 (m, 2H, CH_2), 4.12 (m, 2H, CH_2), 5.28 (m, 1H, CH), 6.90 (m, 3H, CH=), 7.30 (m, 2H, CH=). ^{13}C NMR *δ*: 21.2 (CH_3), 51.0 (CH_2), 66.2 (CH_2O), 70.9 (CH), 114.8 (CH=), 121.7 (CH=), 129.8 (CH=), 158.3 (C), 170.5 (CO).

(*S*)-1-Azido-2-acetoxy-3-(1-naphthoxy)propane ((*S*)-2g). ^{1}H NMR *δ*: 2.16 (s, 3H, CH_3), 3.72 (m, 2H, CH_2), 4.30 (m,

2H, CH_2), 5.47 (m, 1H, CH), 6.81 (d, 1H, $^3J_{H-H}$ = 7.2 Hz, CH═), 7.37 (m, 1H, CH═), 7.49 (m, 2H, CH═), 7.81 (m, 1H, CH═), 8.18 (m, 1H, CH═). ^{13}C NMR δ: 21.2 (CH_3), 51.3 (CH_2), 66.6 (CH_2−O), 71.0 (CH), 105.1 (CH═), 121.3 (CH═), 121.9 (CH═), 125.7 (CH═), 125.9 (CH═), 126.8 (CH═), 127.7 (CH═), 134.7 (C), 153.9 (C), 170.5 (CO).

Synthesis of (*S*)-Propanolol (I). To a solution of azido acetate (*S*)-**2g** (285.3 mg, 1 mmol) in methanol (10 mL) was added LiOH (24 mg, 1 mmol). The solution was allowed to stir at room temperature for 2 h. Then PtO_2 (12 mg, 0.05 mmol), 3 Å molecular sieves (0.45 g), and acetone (110 μL, 1.1 mmol) were added. The flask was then flushed with hydrogen at 1 bar, and the reaction was allowed to stir for 4 h at room temperature. The mixture was filtered through Celite and concentrated to dryness affording the compound as a white solid (253 mg, 98%). The resulting solid was recrystallized from cyclohexane. The hydrochloride salt was formed by precipitation from ether using gaseous hydrochloric acid. $[\alpha]^{21}_D = -24.3$ (*c* 1.15 (HCl salt), EtOH) [lit.[19] $[\alpha]^{21}_D = -25.5$ (*c* 1.18 (HCl salt), EtOH). ^{1}H NMR δ: 1.10 (d, 1H, CH_3, $^3J_{H-H}$ = 6.4 Hz), 2.84 (m, 2H, CHN, CH_2N), 2.97 (dd, 1H, CH_2−N, $^3J_{H-H}$ = 3.6 Hz, $^3J_{H-H}$ = 12.0 Hz), 4.10 (m, 1H, CH_2O), 4.18 (m, 2H, CHO, CH_2O), 6.81 (d, 1H, CH═, $^3J_{H-H}$ = 7.6 Hz), 7.36 (t, 1H, CH═, $^3J_{H-H}$ = 8.0 Hz), 7.47 (m, 3H, CH═), 7.80 (dd, 1H, CH═, $^3J_{H-H}$ = 5.6 Hz, $^3J_{H-H}$ = 2.4 Hz), 8.24 (dd, 1H, CH═, $^3J_{H-H}$ = 7.2 Hz, $^3J_{H-H}$ = 3.2 Hz). ^{13}C NMR δ: 23.2 (CH_3), 23.3 (CH_3), 49.2 (CHN), 49.9 (CH_2N), 68.7 (CHO), 71.8 (CH_2O), 105.2 (CH═), 120.8 (CH═), 122.1 (CH═), 125.5 (CH═), 125.8 (C), 126.1 (CH═), 126.7 (CH═), 127.8 (CH═), 134.8 (C), 154.6 (C).

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