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Convenient efficient synthesis of TAK-779, a nonpeptide CCR5 antagonist: development of preparation of various ammonium salts using trialkylphosphite and *N*-halogenosuccinimide

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Abstract—A convenient and efficient synthesis of TAK-779 (**1a**), a nonpeptide CCR5 antagonist, has been achieved. The new methylation of tertiary amine (**2**) using trimethyl phosphite and *N*-chlorosuccinimide, followed by the addition of HCl led to ammonium chloride (**1a**) in 89% isolated yield without requiring a chromatographic method. By this preparation, ammonium methanesulfonate (**1e**) could be obtained in 75% isolated yield.

1. Introduction

N,*N*-Dimethyl-*N*-[4-[[[2-(4-methylphenyl)-6,7-dihydro-5*H*-benzocyclohepten-8-yl]carbonyl]amino]benzyl]tetrahydro-2*H*-pyran-4-aminium chloride (TAK-779,**1a**)[1] was found as a small molecule nonpeptide CCR5 antagonist (Fig. 1). This compound inhibited macrophage-tropic HIV-1 infection of phytochemagglutinin (PHA)-activated peripheral blood mononuclear cells (PBMCs), and should be a strong candidate for the therapy of HIV-1 infected individuals. The key step is the reaction to form the ammonium moiety, because TAK-779 has an ammonium salt with a chloride anion. The key reaction of the original synthesis employed an anion-exchange with resin from ammonium iodide (**1b**) prepared by the methylation of tertiary amine (**2**) with methyl iodide to ammonium chloride. However, the previous approach suffered from a tedious chromatographic method for the anion-exchange. Hence, an efficient preparation of **1a** on large scale was required to support clinical evaluation. In this paper, we report a highy efficient synthesis of **1a** using commercially available materials.

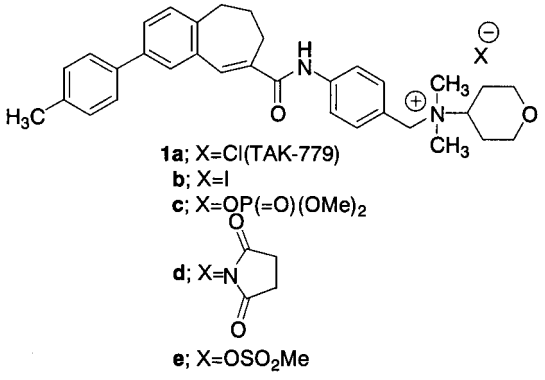

Figure 1.

2. Results and discussion

The synthesis of tertiary amine (**2**) is depicted in Scheme 1. The carboxylic acid (**5**) could be synthesized by the reported procedure[1b–d] via β-ketoester (**7**). However, it was difficult to separate the desired hydroxy-ester (**8**) and hydroxy-hydroxymethyl derivatives (**9**). To solve this problem, we have developed an alternative synthesis of carboxylic acid (**5**) via the aldehyde (**4**),[2] not β-ketoester (**7**). Although many preparations of cyclic α,β-unsaturatedaldehydes using the reduction of α-dialkoxymethyl cyclohexanones,[2a–c] followed by dehydration with acid have been reported, there was only one example using cycloheptanone.[2a] According to the general method,[2a] the dimethoxymethylation of **3** with carbenium ion prepared from methyl orthoformate, BF_3–OEt_2, and *i*-Pr_2NEt at −70°C in dichloromethane as a solvent (entry 1) afforded β-keto-dimethoxymethyl deievative (**10a**), as shown in Table 1. To avoid the hazardous solvent and conditions for large-scale preparation, optimization of the dialkoxymethylation was examined. As a result, the reaction of **3** and 6 equiv. carbenium ion prepared from methyl orthoformate afforded at 0°C in THF a good yield of the target (**10a**). Subsequently, the reduction of **10a** with $NaBH_4$ and the dehydration by

Keywords: trialkylphosphite; *N*-halogenosuccinimide; alkylation; TAK-779.

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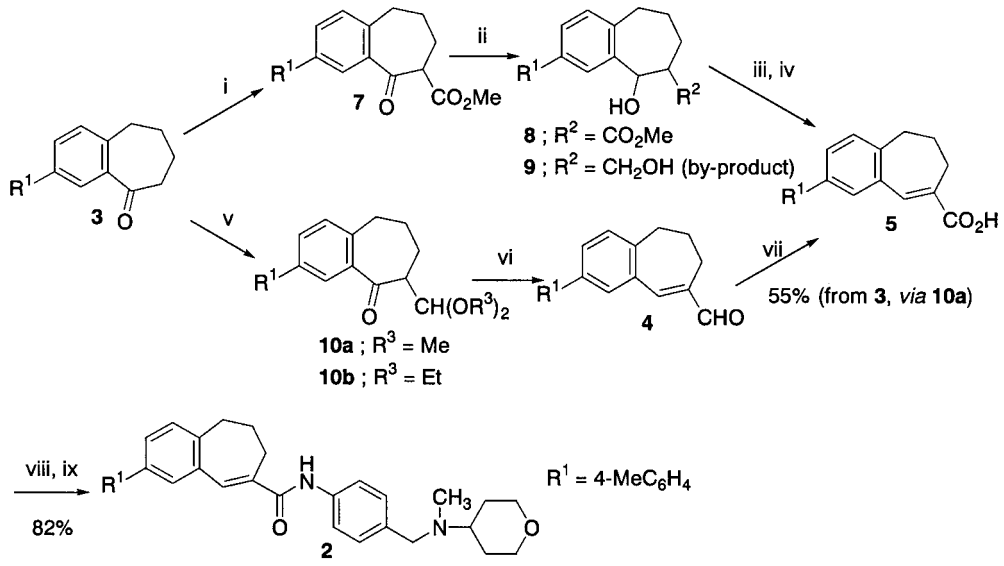


Scheme 1. *Reagents and conditions:* (i) NaOMe, $(MeO)_2CO$; (ii) $NaBH_4$, MeOH; (iii) MsCl, Et_3N, then DBU; (iv) 2N NaOH; (v) $CH(OR^3)_3$, BF_3–OEt_2, *i*-Pr_2Net, THF, −10°C; (vi) $NaBH_4$, then 6N HCl, 65°C; (vii) $NaClO_2$, H_2O_2, toluene–aq. NaH_2PO_4 (pH=2); (viii) $(COCl)_2$, cat. DMF, THF; (ix) **11**, Et_3N.

Table 1. Reaction of **3** with $CH(OR^3)_3$, BF_3–OEt_2 and *i*-Pr_2NEt

Entry	R	Carbenium ion (equiv.)	Solvent	Conditions	Ratio by HPLC[a]	
					3	**10**
1	Me	2	CH_2Cl_2	−70°C, 2 h→0°C, 3 h	14	**10a**; 86
2	Me	2	Toluene	0°C, 3 h	88	**10a**; 12
3	Me	6	THF	0°C, 4 h	12	**10a**; 88
4	Me	4	$CH(OMe)_3$	0°C, 2 h	60	**10a**; 40
5	Et	2	CH_2Cl_2	−30°C, 2 h→rt, 4.5 h	13	**10b**; 87
6	Et	6	THF	0°C, 5 h→rt, 1 h	40	**10b**; 60

[a] Determined at 254 nm.

conc. HCl could lead to **4**. Oxidation of **4** with $NaClO_2$ proceeded quantitatively to give **5** (overall isolated yield was 55% from **3**) in toluene–phosphoric acid buffer (pH=1) at 50°C with addition of H_2O_2 as scavenger of HOCl.[3] On the other hand, the Vielsmeier reaction ($POCl_3$/DMF) of the reductant prepared from **3** with $NaBH_4$ afforded low yield (<15%) of **4**.[2d,e] The reaction of acid-chloride prepared by the treatment of the carboxylic acid (**5**) with a DMF catalytic oxalyl chloride, and 4-[*N*-methyl-*N*-(tetrahydropyran-4-yl)aminomethyl]aniline (**11**) gave **2** in 82% yield.

Generally, there have been two kinds of procedures for ammonium chloride prepared from a tertiary amine.[4,5] One is the direct preparation by the reactions of a tertiary amine with alkylchloride[4a–d] that requires unusual equipment. The other is a method where by the ammonium cation having an other anion (Y^-) instead of chloride prepared from a tertiary amine and alkylation reagents exchanged to ammonium chloride, as shown in Fig. 2 (Eqs. (1) and (2)). Although the anion-exchange by resin was popular, it was difficult as the equilibrium lies so far to the right by this protocol. On the other hand, alkylation of a tertiary amine with alkyl oxy-acid ester (RSA), followed by the treatment with HCl smoothly resulted in ammonium chloride, for example, dialkylcarbonate,[4e] alkyl salitylate,[4f] and trialkyl phosphate (Fig. 2 (Eqs. (3) and (4)).[5] To attain our goal, we have attempted a convenient synthesis of ammonium chloride by chemical reaction. The reactions of **2** using methyl salitylate or trimethyl phosphate were examined, since this process was the final stage and the reaction using dimethyl-carbonate required a high-pressure condition. Methylation of **2** with methyl salitylate was not entirely successful, but the reaction of **2** and trimethyl phosphate at 100°C for 6 h, followed the treatment with HCl/IPE led to a mixture of the desired ammonium chloride (**1a**) in 47% yield and benzyl chloride (**12**). In the latter reaction, the HPLC data showed that the resultant prepared from the reaction of a tertiary amine and trimethyl phosphate led to **12** by HCl. From these results, this reaction mechanism was thought to be as shown in Scheme 2, that is, the tertiary amine attacked firstly the phosphorus atom, followed by the transformation to yield ammonium compound (**1c**) and oxyphosphate (**13**),

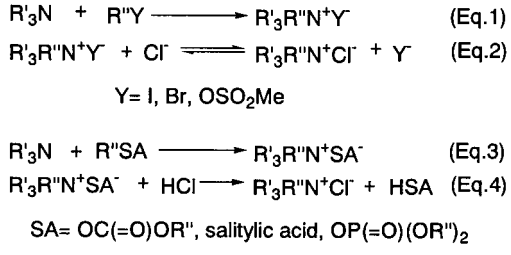
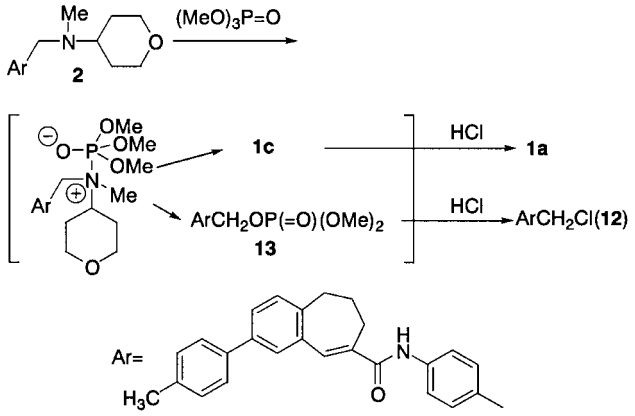
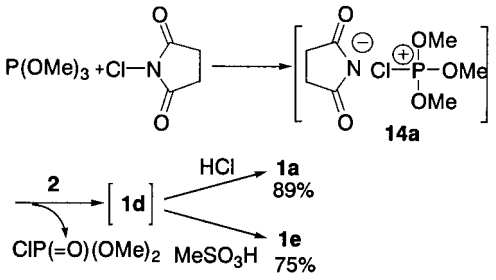


Figure 2.



Scheme 2.



Scheme 3.

since **2** has the activated benzyl moiety. Subsequently, the treatment of these compounds with HCl might produce both **1a** and **12**. Namely, it is predictable that the reaction might quantitatively give **1a** if the tertiary amine could firstly attack the methyl group of the reagent.[6] In the known Michaelis–Arbuzov reaction,[7] nucleophilic attack of phosphines with an alkyl halide produced an increase in the coordination number to four, and the formation of a phosphonium species led to merely the formation of a tetracoodinate phosphorous(V) species if one of the ligands attached to the phosphorous is an alkoxy group which can undergo facile alkyl–oxygen cleavage. *N*-Halogenosuccinimide instead of alkyl halide also reacted rapidly with tertiary phosphites to give *N*-(dialkylphosphonyl)succinimide passed through a trialkylhalogenophosphonium succinimide salt (**14**).[8] In the case of trimethyl phosphite, the reaction yielded both the Michaelis–Arbuzov type product and *N*-methylsuccinimide,[8e] because a trimethylhalogenophosphonium succinimide salt (**14a**) does not have an α-branch and a succinimide anion attacked the methyl carbon of **14a** (Scheme 3). Therefore, we thought that the addition of tertiary amine (**2**) having stronger basicity generally than a succinimide anion in this reaction might allow a tertiary amine (**2**) to initially attack the methyl group of the intermediate. As a consequence, the reaction might produce an ammonium compound with succinimide aninon (**1d**), followed by the treatment with HCl to give the desired ammonium chloride **1a**. As shown in Table 2, methylation of **2** with trimethyl phosphite and *N*-chlorosuccinimide (NCS) showed good results in most of the solvents. In particular, the reaction of **2**, NCS (3 equiv.), trimethyl phosphite (3 equiv.), and trimethyl phosphate as a solvent at 80°C for 6 h, followed by the addition of HCl/IPE proceeded to give **1a** in 89% isolated yield without a chromatographic method. Moreover, the treatment with methanesulfonic acid gave an ammonium product having a methanesulfonic anion (**1e**) in 75% isolated yield, after methylation of **2** was carried out. In this connection, trimethyl phosphite (3 equiv.) could not entirely react with **2** in AcOBu^t without NCS. Furthermore, 1-methyl-1,3-benzimidazole was also prepared from 1,3-benzimidazole in 27% yield using this methylation.

In conclusion, a convenient efficient synthesis of **1a** has been achieved. The carboxylic acid (**5**) was prepared by dimethoxymethylation of **3**, followed by reduction, dehydration, and oxidation. Ammonium chloride (**1a**) has been obtained in good yield by a new methylation of tertiary amine (**2**) using trimethyl phosphite and NCS.

3. Experimental

3.1. General

Melting points were recorded on a Büchi B-540 micro melting apparatus and were uncorrected. IR spectra were recorded on a Horiba FT-210 spectrophotometer. ^{1}H NMR spectra was recorded on a Bruker DPX-300 spectrometer using tetramethylsilane as an internal standard. HPLC was performed on a YMC-Pack ODS-A302 column (6i.d.×150 mm) with 0.05 M KH_2PO_4 aqueous solution–MeCN (2:8, 3:7, 4:6, and 7:3) at 25°C. Detection was affected with a Shimadzu SPD-10A spectrophotometric detector at 254 nm. Elemental analysis was carried out by Takeda Analytical Research Laboratories Ltd.

3.1.1. 2-(4-Methylphenyl)-6,7-dihydro-5*H*-benzocyclohepten-8-carboxylic acid (5). To a solution of methyl

Table 2. Methylation of **2** with $P(OMe)_3$ and NCS

Entry	$P(OMe)_3$ (equiv.)	NCS (equiv.)	Solvent	Conditions	Ratio by HPLC[a]		Yield (%)[b]
					2	**1a**	
1	3	3	*i*-PrOH	Refluxed, 6 h	62	38	
2	3	3	Toluene	Refluxed, 6 h	17	83	71
3	10	10	THF	Refluxed, 6 h	13	87	30
4	3	3	DMF	80°C, 3 h	41	59	
5	3	3	*n*-BuOAc	Refluxed, 11 h	8	92	78
6	3	3	Diglyme	80°C, 13 h	12	88	80
7	3	3	O=P(OMe)$_3$	80°C, 6 h	1	99	89

[a] Determined at 254 nm.
[b] Isolated yield of **1a**.

orthoformate (25.5 ml, 240 mmol) and THF (80 ml) at −10°C, BF_3–OEt_2 (36.2 ml, 288 mmol) was dropped, and stirred for 0.5 h at 0°C. A solution of **3** (10.0 g, 40 mmol) and THF (20 ml), and *i*-Pr_2NEt (61.6 ml, 360 mmol) were added to the reaction mixture, and stirred for 5 h under the same conditions. Water (100 ml) was added to the reaction mixture, and extracted with AcOEt (100 ml). After that concentrated in vacuo IPE (100 ml) and silica-gel (20 g) were added and stirred for 15 min. Silica-gel was removed by filtration, and concentrated in vacuo to give a brown oil (**10a**). An analytically pure sample of **10a** was obtained by chromatography on silica-gel with *n*-hexane/AcOEt (8:1) as a brown oil: ^{1}H NMR ($CDCl_3$): δ 1.67–1.75 (2H, m), 2.07–2.13 (2H, m), 2.38 (3H, s), 2.96–2.99 (2H, m), 3.12–3.17 (1H, m), 3.40 (6H, s), 4.90 (1H, d, *J*=6.8 Hz), 7.22–7.26 (3H, m), 7.50 (2H, d, *J*=8.1 Hz), 7.59 (1H, dd, *J*=7.9, 2.0 Hz), 7.83 (1H, d, *J*=2.0 Hz).

$NaBH_4$ (4.5 g, 120 mmol) was added to a solution of **10a** and EtOH (180 ml) at room temperature, and stirred for 1 h. 6N HCl aqueous solution (40 ml, 240 mmol) was added to the reaction mixture with ice-bathing, and stirred for 1 h at 65°C. The organic solvent was distilled, and extracted with AcOEt (180 ml). The AcOEt extract was washed with sat. NaCl aqueous solution (90 ml), and concentrated in vacuo to give crude **4** (14.6 g) as a light-brown solid. An analytically pure sample of **4** was obtained by chromatography on silica-gel with *n*-hexane/AcOEt (2:1) as a white solid: ^{1}H NMR ($CDCl_3$): δ 1.99–2.07 (2H, m), 2.40 (3H, s), 2.62 (2H, t, *J*=5.8 Hz), 2.94 (2H, t, *J*=5.3 Hz), 7.23–7.31 (4H, m), 7.47–7.51 (3H, m), 7.59 (1H, d, *J*=1.8 Hz), 9.59 (1H, s).

30 w/w% H_2O_2 solution (5.4 ml, 48 mmol) and $NaClO_2$ (7.2 g, 80 mmol) in water (15 ml) were added to a suspension of crude **4** (described above), 2 mol/l NaH_2PO_4 aqueous solution (40 ml, 88 mmol, adjusted to pH2 with conc. HCl), and toluene–MeOH (2:1, 240 ml). The whole was stirred for 1 h at 50°C, and cooling to room temperature, 10 w/w%$Na_2S_2O_3$ aqueous solution (40 ml) was added to the reaction mixture. 1N KOH aqueous solution (88 ml) was added to the organic solution, and the organic solvent was distilled. The remaining solution was washed with IPE (50 ml×2), adjusted to pH1 with 6N HCl aqueous solution, and extracted with AcOEt (100 ml). The AcOEt extract was washed with sat. NaCl aqueous solution (50 ml), and concentrated in vacuo. The residue was triturated with IPA–water (1:1, 30 ml), collected by filtration. The colorless crystalline solid was dried at 40°C in vacuo to give **5** (6.1 g, yield 55% from **3**). Mp. 186–188°C. Anal. Calcd for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52%. Found: C, 81.91; H, 6.52.). ^{1}H NMR ($CDCl_3$): δ 2.07–2.13 (2H, m), 2.39 (3H, s), 2.67–2.71 (2H, m), 2.86–2.89 (2H, m), 7.20–7.26 (4H, m), 7.43–7.55 (3H, m), 7.91 (1H, s). IR (KBr, cm^{-1}): 2923, 1671.

3.1.2. *N*-[4-[*N*-Methyl-*N*-4-(tetrahydropyranyl)aminomethyl]phenyl]-2-(4-methylphenyl)-6,7-dihydro-5*H*-benzocyclohepten-8-carboxamide (2). Oxalyl chloride (12.6 ml, 144 mmol) was dropped to a solution of **5** (20.0 g, 72 mmol), DMF (0.4 ml) and THF (200 ml) at 20–30°C, and stirred for 2 h at room temperature. The reaction mixture was concentrated in vacuo, and THF (200 ml) was added. After Et_3N (62.0 ml, 446 mmol) was added to a suspension of **11** (23.2 g, 79 mmol) and THF (200 ml) and stirred for 0.5 h at room temperature, a solution of acid chloride was dropped to the whole at 20–30°C with ice-bathing and stirred for 1 h under the same conditions. Water (200 ml) was added to the reaction mixture, which was separated and extracted with AcOEt (200 ml). The organic solution was washed with 10% citric acid aqueous solution (100 ml×2), 5% $NaHCO_3$ aqueous solution (100 ml×2), and sat. NaCl aqueous solution (100 ml), and concentrated in vacuo. After the concentrate was solved by AcOEt (370 ml) under refluxing condition, the solution was cooled to room temperature, stirred for 1 h at room temperature, and stirred for 1 h at 5°C. The solid was collected by filtration, washed with cooled AcOEt (60 ml). The colorless crystalline solid was dried at 40°C in vacuo to give **2** (28.3 g, yield 82%). Mp 162–163°C. Anal. Calcd for $C_{32}H_{36}N_2O_2$: C, 79.96; H, 7.55; N, 5.83%. Found: C, 79.87; H, 7.50; N, 5.67. ^{1}H NMR ($CDCl_3$): δ 1.67–1.79 (4H, m), 2.15–2.19 (2H, m), 2.29 (3H, s), 2.41 (3H, s), 2.66–2.75 (3H, m), 2.87–2.91 (2H, m), 3.34–3.43 (2H, m), 3.59 (2H, s), 4.03–4.08 (2H, m), 7.23–7.34 (4H, m), 7.42–7.59 (7H, m), 7.70 (1H, s). IR (KBr, cm^{-1}): 3300, 1655, 1550.

3.1.3. *N*,*N*-Dimethyl-*N*-[4-[[[2-(4-methylphenyl)-6,7-dihydro-5*H*-benzocyclohepten-8-yl]carbonyl]amino]benzyl]-tetrahydro-2*H*-pyran-4-aminium chloride (TAK-779,1a). Trimethyl phosphite (0.37 ml, 3.1 mmol) was added to a solution of **2** (0.50 g, 3.1 mmol), NCS (0.42 g, 1.0 mmol), and trimethyl phophate (5 ml) with ice-bathing, and stirred for 6 h at 80°C. After cooled to rt, 1.8N HCl/IPE (3 ml) and acetone (0.5 ml) were added, and stirred overnight at room temperature. The solid was collected by filtration, washed with acetone–AcOEt (1:3, 4 ml). The colorless crystalline solid was dried at 40°C in vacuo to give **1a** (0.49 g, yield 89%). Mp 222–223°C (decomp.). Anal. Calcd for $C_{33}H_{39}N_2O_2Cl$: C, 74.62; H, 7.40; N, 5.27; Cl, 6.67%. Found: C, 74.37; H, 7.32; N, 5.23; Cl, 6.53.). ^{1}H NMR (DMSO-d_6): δ 1.85–2.18 (6H, m), 2.34 (3H, s), 2.64 (2H, m), 2.78 (8H, m), 3.35 (2H, m), 3.50–3.75 (1H, m), 4.04–4.07 (2H, m), 4.46 (2H, s), 7.26–7.88 (12H, m), 10.22 (1H, s). IR (KBr, cm^{-1}): 1652, 1521.

3.1.4. *N*,*N*-Dimethyl-*N*-[4-[[[2-(4-methylphenyl)-6,7-dihydro-5*H*-benzocyclohepten-8-yl]carbonyl]amino]benzyl]-tetrahydro-2*H*-pyran-4-aminium methanesulfonate (1e). Trimethyl phosphite (0.50 ml, 4.2 mmol) was added to a solution of **2** (1.00 g, 2.1 mmol), NCS (0.56 g, 4.2 mmol), and trimethyl phosphate (4 ml) with ice-bathing, and stirred for 4 h at 80°C. After being cooled to room temperature, $MeSO_3H$ (0.27 ml, 4.2 mmol), IPE (7 ml), and acetone (5 ml) were added, and stirred overnight at room temperature. The solid was collected by filtration, washed with acetone–AcOEt (1:4, 5 ml). The colorless crystalline solid was dried at 40°C in vacuo to give **1e** (0.90 g, yield 75%). Mp 217–219°C (decomp.). Anal Calcd for $C_{34}H_{42}N_2O_5S$: C, 69.12; H, 7.17; N, 4.74; S, 5.43%. Found: C, 69.14; H, 7.19; N, 4.82; S, 5.41. ^{1}H NMR ($CDCl_3$): δ 1.75–2.20 (6H, m), 2.32 (3H, s), 2.34 (3H, s), 2.64 (2H, m), 2.75–3.00 (8H, m), 3.30–3.45 (2H, m), 3.50–3.75 (1H, m), 4.00–4.25 (2H, m), 4.47 (2H, s), 7.25–7.90 (12H, m), 10.30 (1H, s). IR (KBr, cm^{-1}): 1654, 1529, 1517, 1317, 1193, 1180, 1039.

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