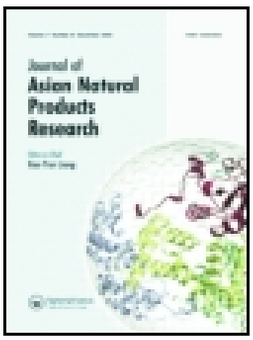

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Synthesis of the impurity F of salbutamol

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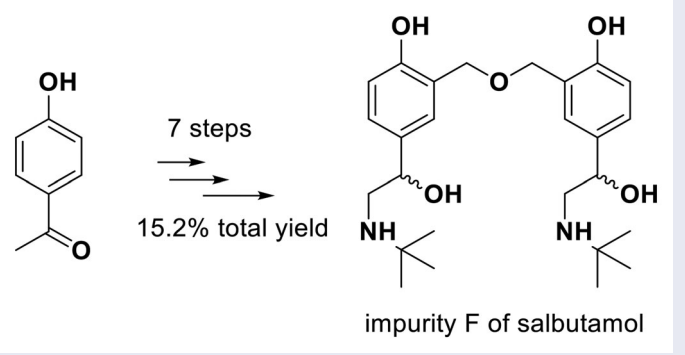
ABSTRACT

First synthesis of the diastereomeric mixture of salbutamol impurity F is described in seven steps by using 4-hydroxyacetophenone as starting material, with 15.2% total yield. The synthesis provides access to multi-gram quantities of impurity F with good purity for reference supplies and further analytical and toxicology investigations.



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KEYWORDS
Salbutamol; impurity F; synthesis

1. Introduction

Sulbutamol sulfate (Figure 1) as a derivative of adrenaline, an important natural human hormone, can be used as a bronchodilator for the treatment of asthma, as well as prevention and relief of bronchospasm induced by exercise [1,2].

It is known that there are several different process impurities associated with the manufacture of sulbutamol sulfate. Ten of the known specified impurities have been mentioned in European Pharmacopoeia 6.0. Their structures and names are showed in Table 1.

According to European Pharmacopoeia 6.0, individual impurity should be $<0.3\%$ and total impurity $<1.0\%$. In the British Pharmacopoeia, the maximum contents of the related impurities are specified to be 0.5%. The United States pharmacopoeia requires that total impurity should not be $>2.0\%$. In recent years, new quantitative

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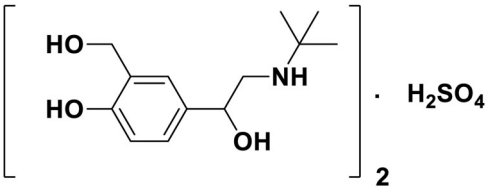
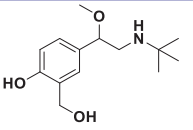
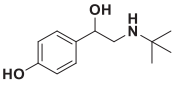
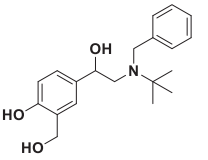
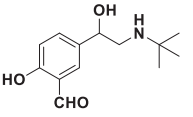
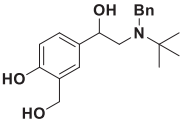
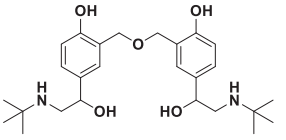
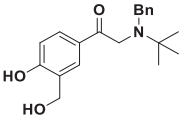
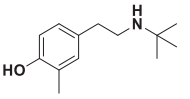
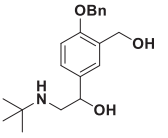


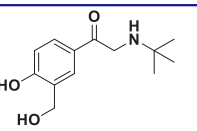
Figure 1. The chemical structure of salbutamol sulfate.

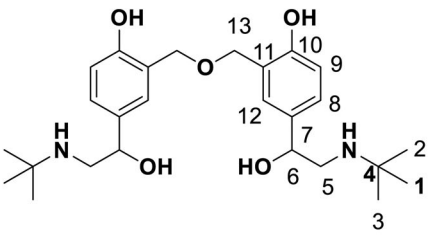
Table 1. The structures and chemical names of the specified impurities in EP 6.0.

Specified impurities	Chemical names	Structures
A	4-(2-tert-butylamino-1-methoxy-ethyl)-2-hydroxymethyl-phenol	
B	4-(2-tert-butylamino-1-hydroxy-ethyl)-phenol	
C	4-[2-(benzyl-tert-butyl-amino)-1-hydroxy-ethyl]-2-hydroxymethyl-phenol	
D	5-(2-tert-butylamino-1-hydroxy-ethyl)-2-hydroxy-benzaldehyde	
E	4-[2-(benzyl-tert-butyl-amino)-1-hydroxy-ethyl]-2-hydroxymethyl-phenol	
F	1,1-[oxybis[methylene(4-hydroxy-1,3-phenylene)]]bis[2-[(1,1-dimethylethyl)amino]ethanol]	
G	2-(benzyl-tert-butyl-amino)-1-(4-hydroxy-3-hydroxymethyl-phenyl)-ethanone	
H	4-(2-tert-butylamino-ethyl)-2-methyl-phenol	
I	1-(4-benzyloxy-3-hydroxymethyl-phenyl)-2-tert-butylamino-ethanol	

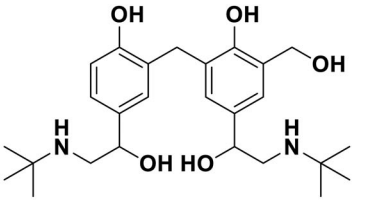
(*continued*)

Table 1. Continued.

Specified impurities	Chemical names	Structures
J	2-tert-Butylamino-1-(4-hydroxy-3-hydroxymethyl-phenyl)-ethanone	



Impurity F



deoxygenated dimer

Figure 2. The chemical structure of impurity F and deoxygenated dimer of salbutamol. Reagents and conditions: (a) 37% HCHO, conc. HCl, 50 °C, 75%; (b) BnCl, K_2CO_3, CH_3CN, reflux, 97%; (c) Ph_3P, CBr_4, DCM, 0 °C-rt, 92%; (d) *t*-BuOK, THF, 0 °C-rt, 63%; (e) NBS, TsOH, CH_3CN, 50 °C, 93%; (f) $NaBH_4$, MeOH, DCM, 0 °C, 98%; (g) *tert*-butylamine, *i*-PrOH, reflux, 48%; (h) Pd/C, THF, rt, 76%.

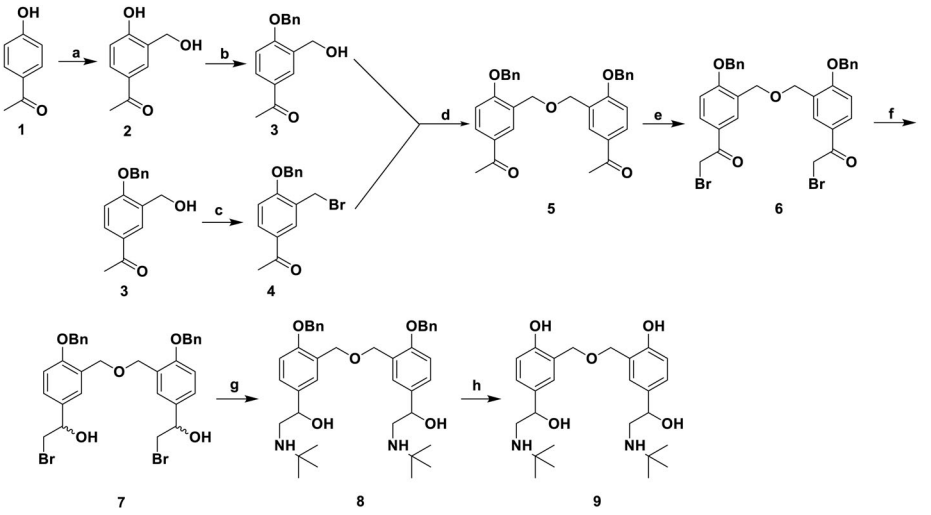
determination of salbutamol sulfate impurities using achiral supercritical fluid chromatography was developed [3]. All of these analyses require impurity references of sulbutamol. Therefore, it is very important to develop convenient synthetic methods of these references.

In 2011, Sharma et al. [4] firstly produced impurity F accompanied with other two impurities by heating salbutamol base with NaOH in MeOH and got it by preparative HPLC with 87.93% purity. However, there are some confusion in their spectral data especially for the carbon of position 13 (C-13) in their structure's determination (Figure 2). The chemical shift of C-13 was assigned to be 58 ppm, which is very inconsistent with the chemical shift of carbon connected with oxygen of benzyl ether (about 70 ppm) [5].

In order to get unambiguous structure of impurity F reported by Sharma et al. and also provide an easy access to this compound for further analytical and toxicology investigations, we describe the first total synthesis of impurity F of salbutamol. The synthesis provides multi-gram quantities of impurity F with good purity for reference supplies. The structures of intermediate and impurity F were confirmed by ^{1}H, ^{13}C NMR and HRMS.

2. Results and discussion

In 2002, Nizar Haddad et al. [6] first synthesized deoxygenated "side-by-side" dimer of salbutamol (Figure 2) by using 4-bromophenol as starting material. In their process, tributylvinyltin was coupled with bromide to introduce the vinyl group, which can subsequently be functionalized to the key part 2-(tert-butylamino)ethan-1-ol of salbutamol. However, as very toxic and dangerous compounds, tributylvinyltin should be avoided to use in the synthesis process as much as possible. It should be feasible



Scheme 1. Synthetic route of the impurity F. Reaction conditions:(i) *i*-PrOH, reflux, 7 h.

to use safer and commercial unavailable vinyl boric acid and its esters instead of tributylvinyltin or avoid the vinyl intermediate.

The impurity F of salbutamol is the diastereomeric O-dimer mixture of salbutamol and symmetric without considering the chiral center. With avoiding using vinyl intermediate in mind, the total synthetic route was designed by using 1-(4-hydroxyphenyl)ethan-1-one as starting material containing the carbonyl group which can be easily transformed to the key part 2-(tert-butylamino)ethan-1-ol of salbutamol and the synthetic route is showed in Scheme 1.

According to the method reported by Chris Meier et al. [7], 1-(4-hydroxy-3-(hydroxyl methyl)phenyl)ethan-1-one **2** was obtained in 75% yield by reaction of 1-(4-hydroxy phenyl)ethan-1-one **1** with 37% formaldehyde solution and concentrated HCl at 50 °C for 5 h and subsequent hydroxylation with $CaCO_3$ in the mixture of THF/water. Selective protection of phenolic hydroxyl group of **2** by benzyl group afforded compound **3** in 97% yield. Bromination of hydroxyl group of benzyl alcohol **3** by Appel reaction [8] afforded bromide **4** in 92% yield.

2.1. The synthesis of compound 5

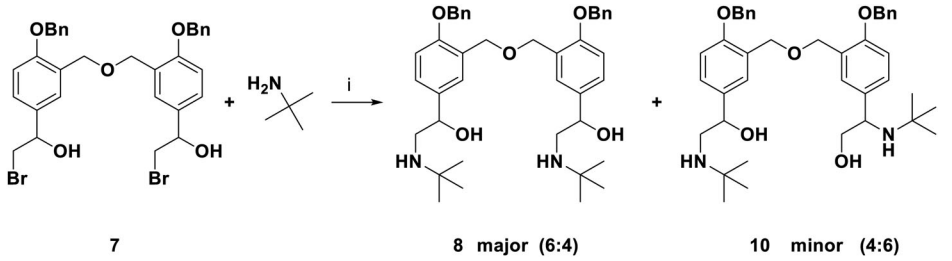
In our synthetic route of impurity F, the key step is the synthesis of compound **5** by using classic Williamson ether reaction which normally works under alkaline condition. In the structures of intermediates **3** and **4**, the carbonyl group easily condensed by aldol condensation under Williamson ether condition. In order to avoid the possible aldol reaction, the reaction condition was optimized.

The anhydrous solvents were used to avoid the hydroxylation of bromide **4** under alkaline condition. The effects of different solvents and bases on the reaction were studied, and the results were showed in Table 2. The addition sequence of starting materials especially the base had a significant influence on the yield of the product, and the result indicated that it is better to add base to the mixture of compounds **3**

Table 2. Optimization of the reaction conditions on synthesizing compound **5**.

Entry	Base	Solvent	Yield (%)
1	*t*-BuOK[a]	DMF	58
2	*t*-BuOK[a]	PhF	48
3	*t*-BuOK[a]	Dioxane	53
4	*t*-BuOK[a]	THF	63
5	NaH[a]	THF	54
6	CH_3ONa[a]	THF	32
7	DBU[a]	THF	48
8	NaH[a]	DMF	35
9	NaH[b]	THF	15
10	*t*-BuOK[b]	THF	20

Reaction condition:
[a]Alcohol **3** and bromide **4** were mixed in the solvent, base was added in small portions at 0 °C.
[b]Alcohol **3** and base were mixed and bromide **4** was added in small portions.



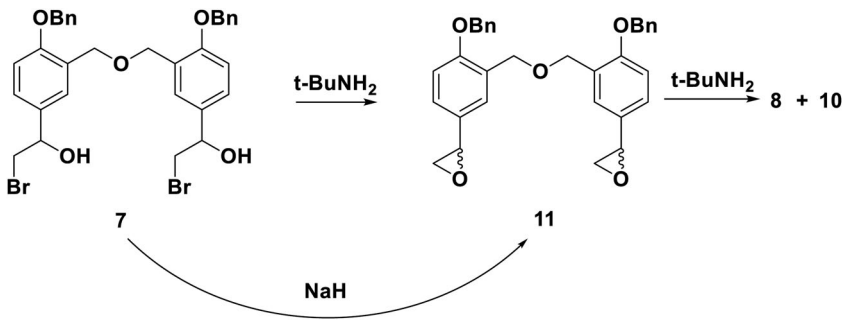
Scheme 2. The reaction of **7** with *t*-$BuNH_2$.

and **4** (Table 2, entry 4, 10 and 5, 9). The yield was 63% when using *t*-BuOK in THF (entry 4); the yield was a little lower when using DMF (*N*,*N*-Dimethylformamide) as solvent (Table 2, entry 1); treatment of **4** with *t*-BuOK in PhF and dioxane respectively gave **5** in 28% and 53% (Table 2, entry 2, 3). Using other bases such as NaH, CH_3ONa and DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene) in THF also gave lower yield (Table 2, entry 5, 6, 7).

The bromination at α position of carbonyl group in compound **5** by using NBS in the presence of TsOH to afford compound **6** in 93% yield. Reduction of the carbonyl group of compound **6** with $NaBH_4$ in the mixture solvent of DCM/MeOH afforded compound **7** in quantitative yield.

2.2. The synthesis of compound 8

As shown in Scheme 2, interestingly, when compound **7** reacted with *t*-$BuNH_2$, two compounds **8** and by-product **10** were obtained in the ratio of 6:4, the structure of by-product **10** was confirmed by the 1D NMR (^1H, ^{13}C and DEPT), 2D NMR (^1H-^1H COSY and HMQC) (all of the original spectrum are supplied in Supporting Information) and HRMS, and the results indicated that the formation of **10** is possible through epoxy intermediate which easily formed under the alkaline condition in the reaction, and then the ring of epoxy was open by *t*-$BuNH_2$ to afford compound **8** and compound **10**. The possible mechanism of reaction of compound **7** with *t*-$BuNH_2$ shown in Scheme 3 was verified by reaction of compound **11** with *t*-$BuNH_2$. Compound **11** was obtained by reacting compound **7** with strong base NaH in DMF



Scheme 3. The possible mechanism of the formation of **10**.

and the ring of epoxy of compound **11** was opened by *t*-$BuNH_2$ to afford compounds **8** and **10** in similar ratio as the reaction of **7** with *t*-$BuNH_2$.

Removal of benzyl group of compound **8** by palladium catalytic hydrogenation in the solvent of THF afforded the product **9** in 76% yield.

2.3. Conclusion

The impurity F of salbutamol was firstly synthesized in seven steps by using 4-hydroxyacetophenone as starting material with 15.2% total yield. The synthesis provides multi-gram quantities of impurity F with good purity for reference supplies and further analytical and toxicology investigations.

3. Experimental

3.1. General experimental procedures

^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker 500 MHz and 125 MHz instruments (Bruker, Rheinstetten, Germany) except compound **10**. ^{1}H-NMR, ^{13}C-NMR, DEPT and 2D NMR spectra of compound **10** were recorded on Bruker 600 MHz instruments (Bruker, Rheinstetten, Germany). Chemical shifts are reported relative to tetramethylsilane as internal standard. Mass spectra were performed on an XEVO g2-XS (Waters Corporation, Worcester, MA, USA) equipped with an ESI source. Reagents were all purchased from commercial suppliers without further purification and anhydrous solvents were dried by the standard procedures before using. Column chromatography was performed with silica gel (200–300 mesh), and analytical thin-layer chromatography (TLC) used 60-GF254.

3.2. Synthesis of 4-acetylsalicyl alcohol (2)

A mixture of 4-hydroxyacetophenone (20.0 g, 14.7 mmol), formaldehyde solution (37%, 50 ml, 66.2 mmol) and concentrated hydrochloric acid (150 ml) was stirred at 50 °C for 5 h. The resulting suspension was cooled to room temperature and filtered, the filter cake was dissolved in THF (250 ml), water (200 ml) and calcium carbonate (20.6 g, 20.6 mmol) was added. The reaction mixture was stirred at room temperature

for 24 h. Concentrated hydrochloric acid was added dropwise to adjust the pH to <7, and the phases were separated with ethyl acetate. The aqueous layer was extracted with ethyl acetate twice, and the combined organic layers were dried with magnesium sulfate. The desired product **2** was obtained by column chromatography (PE/EtOAc = 3:1) as a colorless solid (18.0 g, 75%). ^{1}H NMR(500 MHz, DMSO-d_6): δ 10.35 (s, 1H), 7.95 (s, 1H), 7.72 (dd, J = 8.5, 2.0 Hz, 1H), 6.85 (d, J = 8.5 Hz, 1H), 5.13 (t, J = 5.5 Hz, 1H), 4.49 (d, J = 5.5 Hz, 2H), 2.47 (s, 3H). ^{13}C{^{1}H} NMR(125 MHz, DMSO-d_6): δ 196.2, 158.8, 128.79, 128.72, 128.4, 127.9, 114.2, 57.8, 26.2. HRESIMS: m/z 167.0607 $[M+H]^+$ (calcd for $C_9H_{11}O_3$, 167.0608).

3.3. Synthesis of (2-benzyloxy-5-isopropenyl-phenyl)-methanol (3)

To a solution of compound **2** (2.0 g, 12.0 mmol) in acetonitrile (30 ml), benzyl chloride (1.5 g, 12.3 mmol) and potassium carbonate (2.5 g, 18.1 mmol) were added, and the reaction mixture was heated under reflux for 4 h. After being cooled to room temperature, water (40 ml) was added, and the mixture was extracted with EtOAc (2 × 10 ml). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel to afford desired product **3** (3.0 g, 97%). ^{1}HNMR (500 MHz, $CDCl_3$): δ 7.19 (s, 1H), 7.85 (dd, J = 8.5, 2.0 Hz, 1H), 7.35–7.29 (m, 5H), 6.93 (d, J = 8.5 Hz, 1H), 5.13 (s, 2H), 4.72 (s, 2H), 2.51 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 195.9 (1C), 159.1 (1C), 134.9 (1C), 129.4 (1C), 129.0 (1C), 128.6 (1C), 128.0 (1C), 127.8 (2C), 127.4 (1C), 126.3 (2C), 110.1(1C), 69.3 (1C), 60.3 (1C), 25.4 (1C). HRESIMS: m/z 257.1179 $[M+H]^+$ (calcd for $C_{16}H_{17}O_3$, 257.1178).

3.4. Synthesis of 1-(4-benzyloxy-3-bromomethyl-phenyl)-ethanone (4)

A solution of compound **3** (2.0 g, 7.8 mmol) in dry dichloromethane (20 ml) was treated with triphenylphosphine (2.7 g, 10.3 mmol) and carbon tetrabromide (3.4 g, 10.2 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, then saturated aqueous sodium bicarbonate (20 ml) was added. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated under vacuum. The residue was purified by silica gel column chromatography (PE/EA = 3:1) to afford compound **4** as white solid (2.3 g, 92%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.84 (dd, J = 8.5, 2.0 Hz, 1H), 7.43–7.28 (m, 5H), 6.90 (d, J = 8.5 Hz, 1H), 5.18 (s, 2H), 4.55 (s, 2H), 2.50 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 192.2 (1C), 159.2 (1C), 134.9 (1C), 130.4 (1C), 130.1 (1C), 129.4 (1C), 127.7 (2C), 127.2 (1C), 126.1 (2C), 125.7 (1C), 110.7 (1C), 69.4 (1C), 27.1 (1C), 25.2 (1C). HRESIMS: m/z 319.0340 $[M+H]^+$ (calcd for $C_{16}H_{16}BrO_2$, 319.0334).

3.5. Synthesis of 1-{3-[2-(2-acetyl-5-benzyloxy-phenyl)-ethoxymethyl]-4-benzyloxy-phenyl}-ethanone (5)

To a solution of compound **3** (5.0 g, 19.5 mmol) and compound **4** (6.9 g, 21.5 mmol) in anhydrous THF (150 ml) at 0 °C, was added *t*-BuOK (2.4 g, 21.5 mmol) slowly in small portions over 0.5 h. The resulting reaction mixture was allowed to warm to

room temperature and stirred at room temperature overnight. Water (60 ml) and EtOAc (50 ml) were added, the organic layer was separated, and the water phase was extracted with EtOAc (2 × 30 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel using PE/EA/DCM (4:1:0.5) as eluent to afford desired product **5** as white solid (6.35 g, 63%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (s, 2H), 7.84 (dd, J = 8.6, 2.0 Hz, 2H), 7.32–7.25 (m, 10H), 6.90 (d, J = 8.6 Hz, 2H), 5.09 (s, 4H), 4.69 (s, 4H), 2.48 (s, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 195.9 (2C), 158.9 (2C), 135.2 (2C), 129.3 (2C), 128.7 (2C), 128.5 (2C), 127.6 (4C), 127.1 (2C), 126.2 (2C), 126.0 (4C), 110.0 (2C), 69.1 (2C), 66.4 (2C), 25.3 (2C). HRESIMS: m/z 517.1991 $[M + Na]^+$ (calcd for $C_{32}H_{30}O_5Na$, 517.1991).

3.6. Synthesis of 1-(4-benzyloxy-3-{2-[5-benzyloxy-2-(2-bromoacetyl) phenyl]-ethoxymethyl}-phenyl)-2-bromo-ethanone (6)

To a solution of compound **5** (2.0 g, 4.0 mmol) in acetonitrile (20 ml), were added NBS (*N*-bromosuccinimide) (1.5 g, 8.2 mmol) and *p*-toluene sulfonic acid monohydrate (1.6 g, 8.2 mmol). Then the reaction mixture was stirred at 50 °C overnight. Water (40 ml) and EtOAc (20 ml) were added, the organic layer was separated, and the water phase was extracted with EtOAc (2 × 10 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel using DCM/PE (1:1) as eluent to afford desired product **6** (2.4 g, 93%). ^{1}H NMR(500 MHz, $CDCl_3$): δ 8.13 (s, 2H), 7.94 (d, J = 8.6 Hz, 2H), 7.37–7.33 (m, 10H), 6.98 (d, J = 8.6 Hz, 2H), 5.16 (s, 4H), 4.76 (s, 4H), 4.39 (s, 4H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 190.1 (2C), 160.5 (2C), 136.0 (2C), 130.6 (2C), 129.8 (2C), 128.7 (4C), 128.3 (2C), 127.7 (2C), 127.1 (4C), 126.9 (2C), 111.3 (2C), 70.3 (2C), 67.4 (2C), 30.8 (2C). HRESIMS: m/z 673.0198 $[M + Na]^+$ (calcd for $C_{32}H_{28}O_5Br_2Na$, 673.0201).

3.7. Synthesis of 1-(4-benzyloxy-3-{2-[5-benzyloxy-2-(2-bromo-1-hydroxyethyl)-phe nyl]-ethoxymethyl}-phenyl)-2-bromoethanol (7)

To a solution of compound **6** (2.0 g, 3.1 mmol) in CH_2Cl_2/MeOH (1:1, 20 ml) at 0 °C, was added $NaBH_4$ (0.24 g, 6.2 mmol), and the reaction mixture was stirred at room temperature for 1 h. Water (50 ml) and CH_2Cl_2 (20 ml) were added, the organic layer was separated, and the water phase was extracted with CH_2Cl_2 (2 × 20 ml). The combined organic layers were washed with water (2 × 20 ml), dried over $MgSO_4$, filtered, and concentrated under vacuum to afford the crude product **7** (1.96 g, 98%), which was used for next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (s, 2H), 7.39–7.29 (m, 12H), 6.90 (d, J = 8.4 Hz, 2H), 5.08 (s, 4H), 4.84 (m, 2H), 4.73 (s, 4H), 3.58–3.54 (m, 2H), 3.52–3.48 (m, 2H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 155.1 (2C), 135.9 (2C), 131.6 (2C), 127.5 (4C), 126.9 (2C), 126.7 (2C), 126.1 (4C), 125.7 (2C), 125.1 (2C), 110.7 (2C), 72.5 (2C), 69.0 (2C), 66.6 (2C), 39.1 (2C). HRESIMS: m/z 677.0518 $[M + Na]^+$ (calcd for $C_{32}H_{32}O_5Br_2Na$, 677.0514).

3.8. Synthesis of 1-{4-benzyloxy-3-[2-benzyloxy-5-(2-tert-butylamino-1-hydroxyethyl)-benzyloxymethyl]-phenyl}-2-tert-butylamino-ethanol (8) and its isomer (10)

A solution of compound **7** (2.0 g, 4.0 mmol) in *tert*-butylamine/*i*-PrOH (1:1, 40 ml) was heated to reflux for 7 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel by using DCM/MEOH/$NH_3{\cdot}H_2O$ (10:1:0.1) as eluent to afford desired product solid **8** (0.94 g) as pale yellow solid and a sticky compound **10** (0.62 g). Compound **8**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (s, 2H), 7.40–7.24 (m, 12H), 6.88 (d, $J = 8.5$ Hz, 2H), 5.07 (s, 4H), 4.74 (s, 4H), 4.54 (m, 2H), 2.83 (m, 2H), 2.57 (m, 2H), 1.07 (s, 18H). $^{13}C\{^1H\}$ NMR(125 MHz, $CDCl_3$): δ 155.6 (2C), 137.3 (2C), 135.2 (2C), 128.5 (4C), 127.7 (2C), 127.4 (2C), 127.1 (4C), 126.8 (2C), 125.9 (2C), 111.7 (2C), 72.1 (2C), 70.1 (2C), 67.77 (2C), 50.30 (2C), 50.33 (2C), 29.2 (6C). HRESIMS: *m/z* 641.3955 $[M + H]^+$ (calcd for $C_{40}H_{53}N_2O_5$, 641.3954).

Compound **10**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.50 (d, $J = 5.4$ Hz, 1H), 7.39–7.25 (m, 12H), 7.13 (d, $J = 7.8$ Hz, 1H), 6.89 (d, $J = 8.4$ Hz, 1H), 6.85 (d, $J = 8.4$ Hz, 1H), 5.07 (s, 2H), 5.05 (s, 2H), 4.75–4.70 (m, 4H), 4.60 (d, $J = 7.2$ Hz, 1H), 3.81 (m, 1H), 3.50 (m, 1H), 3.26 (m, 1H), 2.85 (m, 1H), 2.61 (m, 1H), 1.10 (s, 9H), 1.01 (s, 9H). $^{13}C\{^1H\}$ NMR(150 MHz, $CDCl_3$): δ 155.5 (1C), 155.2 (1C), 137.2 (1C), 136.1 (1C), 136.0 (1C), 135.0 (1C), 128.5 (2C), 127.7 (1C), 127.65 (1C), 127.63 (1C), 127.33 (1C), 127.31 (1C), 127.02 (1C), 126.97 (1C), 126.93 (1C), 126.6 (1C), 126.54 (1C), 126.50 (1C), 125.86 (1C), 125.83 (1C), 111.6 (1C), 111.5 (1C), 71.9 (1C), 70.01 (1C), 69.99 (1C), 67.7 (1C), 67.6 (1C), 66.8 (1C), 58.0 (1C), 51.32 (1C), 51.30 (1C), 50.7 (1C), 50.3 (1C), 30.4 (3C), 28.9 (3C). HRESIMS: *m/z* 641.3956 $[M + H]^+$ (calcd for $C_{40}H_{53}N_2O_5$, 641.3954).

3.9. Synthesis of 1,1-[oxybis[methylene(4-hydroxy-1,3-phenylene)]]bis [2-[(1,1-dimethylethyl)amino]ethanol] (9)

A mixture of compound **8** (2.0 g, 3.1 mmol) and 10% palladium on carbon (0.1 g) in THF (10 ml) was stirred under hydrogen at room temperature overnight. The catalyst was filtered and washed with THF, and the combined filtrate was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel using DCM/MeOH/$NH_3{\cdot}H_2O$ (10:1:0.1) as eluent to afford desired product **9** as white solid (1.1 g, 76%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.25 (s, 2H), 7.05 (d, $J = 7.95$ Hz, 2H), 6.75 (d, $J = 8.2$ Hz, 2H), 4.49 (s, 6H), 2.60 (d, $J = 8.3$ Hz, 4H), 2.47 (d, $J = 1.45$ Hz, 2H), 1.04 (s, 18H). $^{13}C\{^1H\}$ (125 MHz, DMSO-d_6) δ 153.9 (2C), 134.1 (2C), 126.4 (2C), 125.8 (2C), 124.2 (2C), 114.5 (2C), 71.4 (2C), 67.0 (2C), 51.0 (2C), 50.1 (2C), 27.9 (6C). HRESIMS: *m/z* 461.3015 $[M + H]^+$ (calcd for $C_{26}H_{41}N_2O_5$, 461.3015).

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Disclosure statement

No potential conflict of interest was reported by the authors.

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