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A practical and enantioselective synthesis of tapentadol

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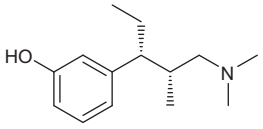
ABSTRACT

A practical and enantioselective synthetic method for tapentadol has been described. Starting from inexpensive and readily available (*E*)-3-(3-(benzyloxy)phenyl)acrylic acid, tapentadol was prepared in seven steps (44% overall yield and 99.9% de) in more than 100 g batches, without any chromatographic purification. An Evans' chiral auxiliary based conjugate addition and alkylation were used as the key steps.

Introduction

Tapentadol **1** (Fig. 1) is a novel centrally acting analgesic with a dual mode of action: μ-opioid receptor agonism and noradrenaline reuptake inhibition. It was recently reported that tapentadol exerted analgesic effects in patients undergoing moderate to acute, inflammatory, and chronic neuropathic pain.[1–3]



tapentadol **1**

Figure 1. Structure of tapentadol **1**.

Due to the clinical attractiveness of **1** along with its structural uniqueness, its synthesis has attracted the increasing research interest of organic chemists from both academic and industrial laboratories. A variety of synthetic processes for **1** have been developed in recent years. In most of these reports, the attainment of the two contiguous alkyl asymmetric centers in **1** was based on resolution techniques (fractional crystallization or chiral HPLC separation).[4] In such procedures, equivalent amounts of unwanted isomers were also produced, leading to high material waste and low atom efficiency. To the best of our knowledge, only two approaches have been reported for the enantioselective synthesis of **1**.[5,6] However, the industrial applications of these two processes were limited due to their unsatisfactory yields, high reagent costs, and complicated column chromatography procedures. Herein we report an efficient, scalable, and enantioselective synthetic route to **1**.

Results and discussion

As outlined in the retrosynthetic strategy (Scheme 1), key intermediate **2** can be transformed into tapentadol via amination, reduction, and debenzylation. And substituted cinnamic derivative **3** can be prepared effectively from the commercially available material **4**. The most important step is the construction of the two contiguous stereogenic centers by asymmetric conjugate addition and methylation from intermediate **3** to **2**.

Despite the popularity of catalytic enantioselective β-conjugate additions[7] and α-alkylations[8] of carbonyl compounds in recent years, many of these methods are still far from practical due to their substrate limitations. In comparison, Evans' chiral oxazolidinone auxiliaries[9] have demonstrated high levels of diastereoselectivity in a great number of β-conjugate additions[10] and α-enolate alkylations.[11,12] Moreover, commercially available oxazolidinone auxiliaries can be conveniently recovered and recycled. In view of this potential for future industrial applications, we decided to use the Evans' auxiliary protocol for the preparation of **1**.

It is widely accepted that 4-phenyloxazolidin-2-one induces higher levels of stereoselectivity and reactivity compared to 4-benzyloxazolidin-2-one[10] or 4-isopropyloxazolidin-2-one[13] in copper-catalyzed asymmetric 1,4-addition reactions, because of the unique steric hindrance of the phenyl ring. Thus, as shown in Scheme 2, (*R*)-4-phenyloxazolidin-2-one was employed as the chiral auxiliary and acylated by 3′-benzyloxy cinnamoyl chloride[14] in CH_2Cl_2 in the presence of triethylamine (TEA); intermediate **5** was

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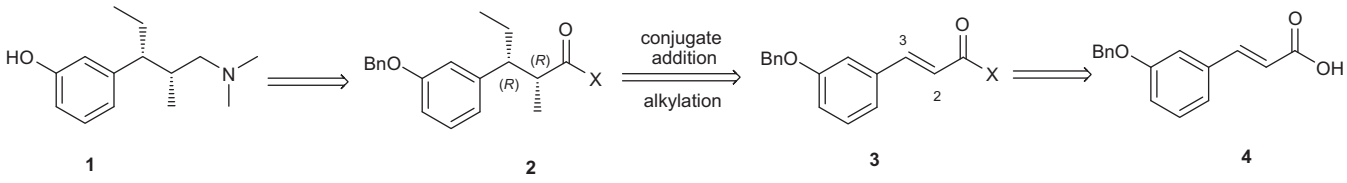
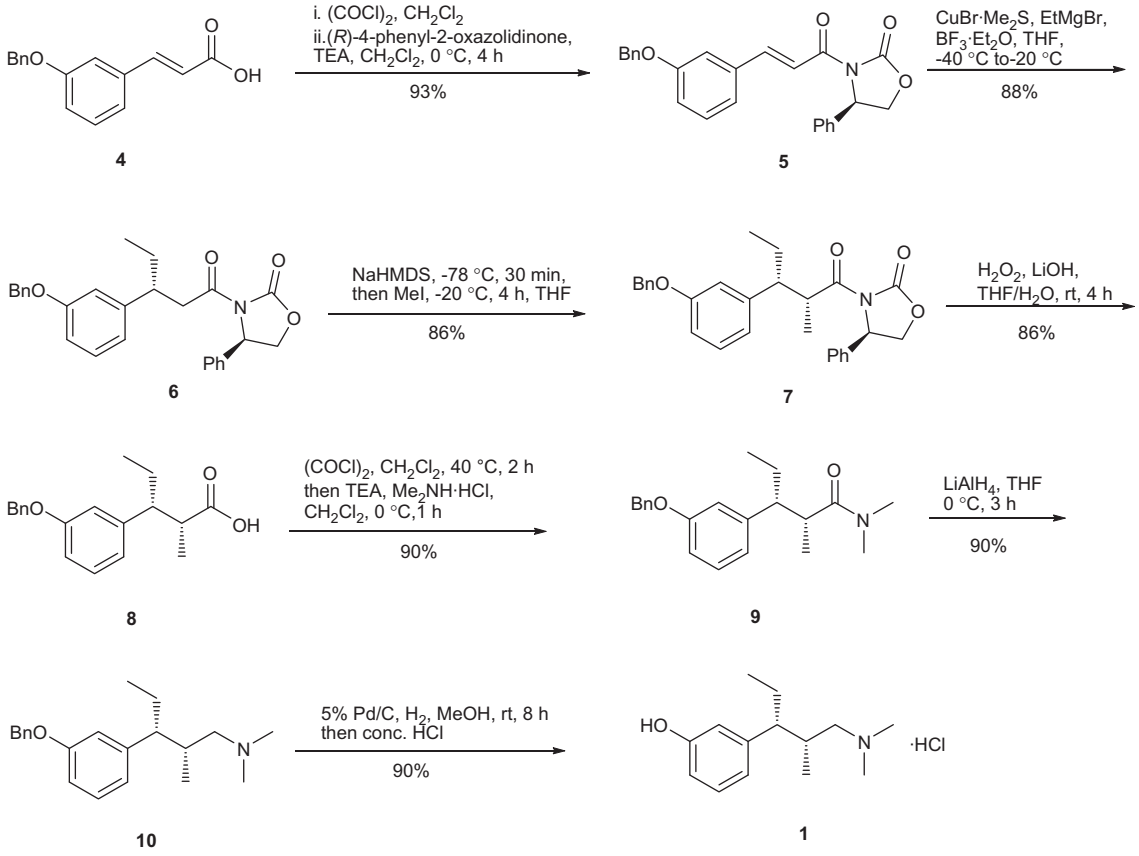


Scheme 1. Retrosynthesis of tapentadol **1**.



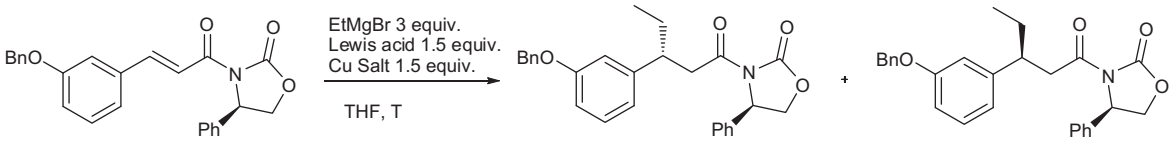
Scheme 2. Synthesis of tapentadol **1**.

obtained in 93% yield after crystallization,[15] requiring no column chromatography purification.[16]

The copper-assisted conjugate addition of Grignard reagents to **5** was investigated next, and the results are summarized in Table 1. When we treated **5** with an organocuprate prepared from a $CuBr{\cdot}Me_2S$ complex and ethylmagnesium bromide in THF at −20 °C, intermediate **6** was obtained in 49% yield after recrystallization with moderate diastereoselectivity (entry 1). It has been previously reported that when LiCl is used as an additive, it has a remarkable influence on the diastereoselectivity of many asymmetric conjugate addition reactions.[17] However, excess LiCl only slightly enhanced the yield and diastereoselectivity (entry 2) in our case. Further screening of different additives showed a stronger Lewis acid, such as $BF_3{\cdot}Et_2O$, could dramatically enhance the diastereoselectivity (entry 3 vs entries 1 and 2). When CuBr was used instead of $CuBr{\cdot}Me_2S$, excellent diastereoselectivity was obtained, although the yield of **6** was lower (entry 4 vs entry 3). We also found that both the diastereoselectivity and the yield benefited from lower temperature (entry 5 vs entry 1, entry 6 vs entry 3). When the reaction proceeded in the presence of $BF_3{\cdot}Et_2O$ at −40 °C, the conjugate addition reaction product **6** was obtained in 88% yield after recrystallization with 99.8% ee (entry 6). The slow addition of substrate **5** to the organocuprate reagents was also crucial in guaranteeing reproducible yields and excellent diastereoselectivities. It is noteworthy that only one recrystallization was needed for the purification of **6**, meaning that the reaction can be easily scaled up to hundreds of grams batch.

Encouraged by the success in asymmetric conjugated addition, we focused our efforts toward the optimization of the methylation conditions. No reaction was observed when **6** was treated with LDA in THF at −78 °C (Table 2, entry 1) using MeI as the methylating reagent, while enolate formation of **6** with LiHMDS in THF followed by methylation gave moderate yield and diastereoselectivity (entry 2). The methylation reaction proceeded efficiently to obtain **7** with excellent diastereoselectivity and high yield when employing NaHMDS as the base (entry 3 vs entries 1 and 2). These results are in accordance with a previously proposed conclusion; i.e. that the methylation of a sodium enolate is superior to the corresponding lithium enolate.[11] With NaHMDS as the base, we next screened various methylating reagents, and the experimental results showed that MeBr can lead to an obvious decrease in both yield and diastereoselectivity (entries 6 and 7), while other methylating reagents such as Me_2SO_4, Me_2CO_3, and $MeSO_3Ph$, showed no reactivity (entries 8–10). A higher enolate formation temperature could

Table 1
Optimization of the asymmetric conjugate addition conditions

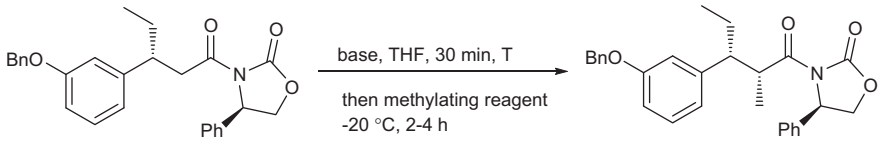


5 6 11

Entry	Cu salt	Lewis acid	Temp (°C)	Yield[a] (%)	ee[b] (%)
1	CuBr·Me_2S	—	−20 °C to 0 °C	49	82
2	CuBr·Me_2S	LiCl	−20 °C to 0 °C	58	86
3	CuBr·Me_2S	BF_3·Et_2O	−20 °C to 0 °C	70	97
4	CuBr	BF_3·Et_2O	−20 °C to 0 °C	59	95
5	CuBr·Me_2S	—	−40 °C to −20 °C	75	96
6	CuBr·Me_2S	BF_3·Et_2O	−40 °C to −20 °C	88	99

[a] Yields after purification by single recrystallization from *i*-PrOH.
[b] ee for the corresponding carboxylic acid derivative of **6** after the removal of the oxazolidin-2-one moiety, determined by chiral HPLC.

Table 2
Optimization of the asymmetric methylation conditions



6 7

Entry	Base	Methylating reagent	Temp of enolate formation (°C)	Yield[a] (%)	*syn*:*anti*[b]	ee[c] (%)
1	LDA	MeI	−78	NR[d]		
2	LiHMDS	MeI	−78	71	90:10	98
3	NaHMDS	MeI	−78	86	99.9:0.1	99
4	NaHMDS	MeI	−40	80	91:9	97
5	NaHMDS	MeI	−20	82	84:16	96
6	NaHMDS	MeBr	−78	74	91:9	97
7	NaHMDS	MeBr	−20	76	90:10	96
8	NaHMDS	Me_2SO_4	−78	NR		
9	NaHMDS	Me_2CO_3	−78	NR		
10	NaHMDS	$MeSO_3Ph$	−78	NR		

[a] Yields after purification by single recrystallization from *i*-PrOH.
[b] Dr determined on the corresponding carboxylic acid **8** by HPLC.
[c] ee determined on the corresponding carboxylic acid **8** by chiral HPLC.
[d] NR means no reaction.

speed up the reaction but resulted in a sharp decrease in diastereoselectivity (entries 4 and 5). Taking into consideration the yield, selectivity, and reaction rate, as well as the costs of the reagents, we treated **6** with NaHMDS in THF followed by the addition of 2 equiv of MeI[18] to deliver the α,β-disubstituted imide **7** in 86% yield with excellent dr (>99.9:0.1) after single crystallization from *i*-PrOH. The structure of the key intermediate **7** was determined by single crystal X-ray diffraction.[19] The data indicated that the asymmetric carbons of **7** had a (2*R*,3*R*)-configuration (as shown in Fig. 2). Since imide **7** is the major product in the methylation reaction, we were able to deduce that the conjugate addition of Grignard reagents to **5** furnished **6** as the major isomer.

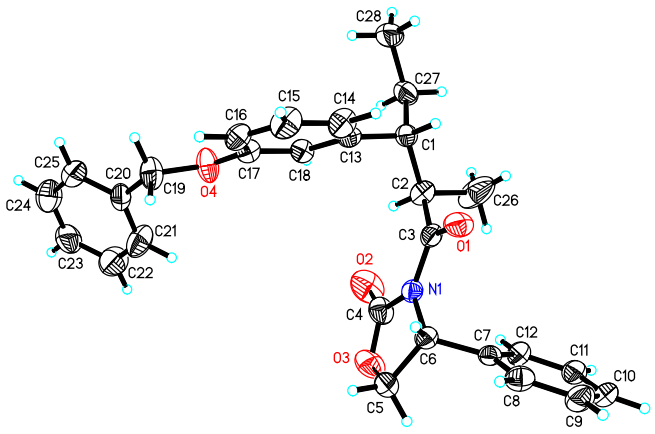


Figure 2. X-ray crystal structure of **7**.

Removal of the chiral auxiliary under base hydrolysis conditions (LiOH/H_2O_2 in H_2O/THF) yielded the α,β-disubstituted acid **8** in 86% yield. This is particularly noteworthy in that the (*R*)-4-phenyloxazolidin-2-one could be recovered in 86% yield after a simple acid-base work-up operation. Treating **8** with oxalyl chloride followed by dimethylamine hydrochloride in the presence of TEA in CH_2Cl_2 afforded the corresponding dimethylamide **9** in 90% yield. Subsequent reduction of amide **9** with $LiAlH_4$ in dry THF gave *o*-benzyl-tapentadol **10**. Debenzylation under a hydrogen atmosphere gave **1** in 90% yield with 99.9% de.[20]

Conclusion

In conclusion, we have successfully implemented an enantioselective synthesis of tapentadol (seven steps, 44% overall yield, >99%

chemical purity and enantiomeric excess) by employing (*E*)-3-(3-(benzyloxy)phenyl)acrylic acid **4** as the starting material. The two contiguous stereocenters in **1** were constructed by (*R*)-4-phenyloxazolidin-2-one induced conjugate addition (88% yield, 99.8% ee) and methylation (86% yield, 99.8% de). No chromatographic purification was required for the entire process and the chiral auxiliaries could be recovered and recycled, which make this synthetic process practical for industrial applications.

Experimental

All reactions, except those involving water, were performed in flame-dried glass charged with nitrogen. Anhydrous THF was distilled from Na/benzophenone ketyl under argon in a recycling still. The copper(I) bromide-dimethyl sulfide complex was purchased from Aldrich. NMR spectra were recorded on a Mercury 300 spectrometer (300 MHz for ^{1}H), and Varian MR-400 (100 MHz for ^{13}C). Chemical shifts are reported in δ ppm referenced to an internal $SiMe_4$ standard for ^{1}H NMR and $CDCl_3$ (δ 77.36) for ^{13}C NMR. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. HPLC analysis was performed on an Agilent 1100 series instrument by using Daicel or DIKMA columns. Melting points are uncorrected. (*E*)-3-(3-(Benzyloxy)phenyl)acrylic acid **4** was prepared from commercially available 3-hydroxybenzaldehyde and had spectral data in agreement with those reported in the literature.[14]

(*R*,*E*)-3-(3-(3-(Benzyloxy)phenyl)acryloyl)-4-phenyloxazolidin-2-one 5

To a stirred solution of **4** (2 kg, 8 mol) in CH_2Cl_2 (2 L) was added oxalyl chloride (1.4 L, 16 mol) dropwise at 0 °C. The resulting solution was stirred at room temperature for another 4 h and concentrated in vacuo. To a stirred solution of (*R*)-4-phenyloxazolidin-2-one (1.3 kg, 8 mol) and TEA (1.7 L, 12 mol) in CH_2Cl_2 (4.8 L) at 0 °C was added the substituted cinnamic chloride in CH_2Cl_2 (800 mL) dropwise. The mixture was stirred at 0 °C for 1 h and then raised to room temperature for 3 h when a saturated solution of NH_4Cl (600 mL) was added. The aqueous layer was separated, and the organic solution was washed with water (600 mL × 3), brine (800 mL), and dried over Na_2SO_4. The organic solution was evaporated and 2.9 kg of **5** was obtained after recrystallization in EtOH in 93% yield, mp 143–145 °C, $[\alpha]_D^{22} = +4.5$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 (d, *J* = 15.5 Hz, 1H), 7.75 (d, *J* = 15.3 Hz, 1H), 7.30–7.50 (m, 11H), 7.23 (m, 2H), 7.03 (dd, *J* = 2.3, 8.6 Hz, 1H), 5.64 (dd, *J* = 4.0, 9.0 Hz, 1H), 5.15 (s, 2H), 4.85 (t, *J* = 8.9 Hz, 1H), 4.36 (dd, *J* = 3.9, 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 158.9, 153.7, 146.5, 138.9, 136.5, 135.8, 129.8, 129.2, 129.1, 128.6, 128.5, 128.4, 128.1, 127.6, 127.5, 126.0, 125.9, 121.5, 117.4, 117.1, 114.4, 70.0, 69.9, 57.8. HRMS (ESI): Calcd for $C_{25}H_{21}NO_4Na$: 422.1368. Found: 422.1349.

(*R*)-3-{(*R*)-3-[3-(Benzyloxy)phenyl]pentanoyl}-4-phenyloxazolidin-2-one 6

To a suspension of $CuBr{\cdot}Me_2S$ complex (1.2 kg, 6 mol) in dry THF (6 L) at −40 °C under argon was added MgEtBr (4.8 L, 2.5 M in THF, 12 mol) dropwise and the resulting yellow-green mixture was stirred for 25 min. Next, $BF_3{\cdot}Et_2O$ (760 mL, 6 mol) was added dropwise. The resulting mixture was stirred for 25 min before the addition of **5** (1.6 kg, 4 mol) as a solution in THF (12 L), and the resulting slurries were allowed to warm slowly to −20 °C (2 h). A saturated aqueous NH_4Cl solution (0.5 L) was added to quench the reaction and the solvents were evaporated. Next, EtOAc (6 L) and water (2 L) were added to the residue and the resultant suspension was filtered over glass wool, which was rinsed with EtOAc (1 L × 3). The aqueous layer was separated, and the organic solution was washed with 10% aqueous NH_4OH (1 L × 3), water (1 L), and brine (1 L) and dried over Na_2SO_4. The solvent was evaporated off, after which 1.5 kg of **6** was obtained after recrystallization in *i*-PrOH in 88% yield, mp 106–108 °C, $[\alpha]_D^{22} = -91.2$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33–7.55 (m, 8H), 7.15–7.25 (m, 3H), 6.70–6.90 (m, 3H), 5.22 (dd, *J* = 3.7, 8.6 Hz, 1H), 5.15 (s, 2H), 4.56 (t, *J* = 8.9 Hz, 1H), 4.22 (dd, *J* = 3.5, 8.6 Hz, 1H), 3.53 (dd, *J* = 8.9, 16.4 Hz, 1H), 3.24 (d, *J* = 5.6 Hz, 1H), 3.15 (m, 1H), 1.54–1.76 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 158.8, 153.5, 145.3, 138.9, 136.8, 129.2, 129.1, 129.0, 128.6, 128.5, 128.4, 127.8, 127.6, 127.5, 125.9, 125.8, 120.5, 114.3, 112.5, 69.9, 69.8, 57.4, 43.1, 41.4, 29.4, 12.0. HRMS (ESI): Calcd for $C_{27}H_{27}NO_4Na$: 452.1838. Found: 452.1845. Data for **11**: $[\alpha]_D^{22} = -57.0$ (*c* 0.5, $CHCl_3$). ^{1}H NMR(300 MHz, $CDCl_3$): δ 7.25–7.45 (m, 5H), 7.15–7.25 (m, 4H), 6.95–7.01 (m, 2H), 6.75–6.86 (m, 3H), 5.35–5.40 (dd, *J* = 4.1, 8.8 Hz, 1H), 5.05 (s, 2H), 4.60 (t, *J* = 8.7 Hz, 1H), 4.05 (dd, *J* = 4.1, 8.9 Hz, 1H), 3.50–3.60 (m, 1H), 3.05–3.15 (m, 2H), 1.55–1.70 (m, 2H), 0.75–0.80 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 158.7, 153.6, 145.2, 138.8, 137.0, 129.3, 129.0, 128.9, 128.5, 128.4, 128.3, 127.8, 127.5, 127.4, 125.4, 125.3, 120.4, 114.2, 112.8, 69.3, 69.2, 57.5, 43.7, 41.3, 28.9, 11.9. HRMS (ESI): Calcd for $C_{27}H_{27}NO_4Na$: 452.1838. Found: 452.1825.The ee of the corresponding acid from **6** after the removal of the oxazolidin-2-one moiety was determined to be 99.8% by HPLC analysis on a DAICEL CHIRALCEL OD-H column (250 × 4.6 mm, 5 μm), λ = 270 nm, *n*-hexane/*i*-PrOH/formic acid = 75:25:0.1, flow rate = 0.30 mL/min, retention time: 13.16 min (major enantiomer), 14.69 min (minor enantiomer).

(*R*)-3-{(2*R*,3*R*)-3-[3-(Benzyloxy)phenyl]-2-methylpentanoyl}-4-phenyloxazolidin-2-one 7

To a solution of **6** (844 g, 2 mol) in dry THF (4 L) at −78 °C was added NaHMDS (2.0 M in THF, 1.1 L, 2.2 mol) dropwise under argon, and the mixture was stirred for 30 min after which MeI (248 mL, 4 mol) was added dropwise and the resulting mixture was slowly warmed to −20 °C. The reaction mixture was quenched by the addition of a saturated aqueous NH_4Cl solution. The volatiles were evaporated and extracted with EtOAc (2 L × 3). The combined organic layers were washed with brine (1 L) and dried over Na_2SO_4. The organic extracts were concentrated in vacuo and 760 g of **7** was obtained after recrystallization in *i*-PrOH in 86% yield, mp 67–69 °C, $[\alpha]_D^{22} = -148.6$ (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.2–7.5 (m, 11H), 6.70–6.95 (m, 3H), 5.10 (s, 2H), 4.82 (dd, *J* = 3.5, 7.5 Hz, 1H), 4.20–4.30 (m, 1H), 3.92–4.04 (m, 2H), 2.68 (dt, *J* = 3.7, 10.3 Hz, 1H), 1.82–2.04 (m, 1H), 1.45–1.65 (m, 1H), 1.20 (d, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8, 158.5, 153.3, 140.6, 139.1, 137.0, 129.1, 129.0, 128.9, 128.6, 128.5, 128.4, 127.8, 127.6, 127.5, 125.6, 125.5, 120.9, 114.4, 113.1, 69.7, 69.6, 57.5, 51.2, 42.4, 24.9, 15.5, 11.4. HRMS (ESI): Calcd for $C_{28}H_{29}NO_4Na$: 466.1994. Found: 466.2022. Data for (*R*)-3-(2*S*,3*R*)-isomer of **7**: mp 120–122 °C, $[\alpha]_D^{22} = -1.4.4$ (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31–7.46 (m, 10H), 7.14 (t, *J* = 7.9 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 6.75 (s, 1H), 6.68 (d, *J* = 7.4 Hz, 1H), 5.47 (dd, *J* = 3.7, 8.7 Hz, 1H), 5.02 (s, 2H), 4.69 (t, *J* = 8.7 Hz, 1 H), 4.33 (dd, *J* = 3.8, 8.9 Hz, 1H), 4.65 (m, 1H), 2.61 (dt, *J* = 3.3, 10.7 Hz, 1H), 1.48 (m, 1H), 1.16–1.28 (m, 1H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.48 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.7, 158.6, 153.5, 143.5, 139.0, 136.9, 129.1, 129.0, 128.9, 128.7, 128.6, 128.5, 127.8, 127.7, 127.6, 126.4, 126.3, 121.3, 115.3, 112.4, 69.8, 69.5, 57.9, 51.5, 42.6, 26.9, 16.4, 11.8. HRMS (ESI): Calcd for $C_{28}H_{29}NO_4Na$: 466.1994. Found: 466.2011.

(2*R*,3*R*)-3-[3-(Benzyloxy)phenyl]-2-methylpentanoic acid 8

To a solution of **7** (708 g, 1.6 mol) in THF (4 L) and water (1 L) at 0 °C was added dropwise H_2O_2 (0.6 L, 30% in H_2O, 6.4 mol) followed by $LiOH{\cdot}H_2O$ (114 g, 2.8 mol). The mixture was stirred at 0 °C for 1 h and then raised to room temperature over 1 h. After stirring at room temperature for 6 h, the reaction mixture was quenched by the addition of a saturated aqueous $Na_2S_2O_3$ solution. Next, THF was removed by rotary evaporation at 30 °C and the resulting mixture was extracted with CH_2Cl_2 (1.5 L × 4). The combined organic layers were washed with water (500 mL × 2) and brine (500 mL × 2). The organic solution was dried over Na_2SO_4, filtered, and evaporated to give 224 g of chiral oxazolidinone in 86% yield. The aqueous solution was acidified with ice-cooled 1 M aqueous HCl to pH 1–2 and extracted with EtOAc (1 L × 4). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (500 mL) and brine (500 mL), dried over Na_2SO_4, concentrated to yield 408 g of **8** as a white powder in 86% yield, mp 75–77 °C, $[\alpha]_D^{22} = -20.0$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30–7.50 (m, 5H), 7.24 (t, *J* = 7.6 Hz, 1H), 6.70–6.94 (m, 3H), 5.05 (s, 2H), 2.84 (m, 1H), 2.77 (m, 1H), 1.77–1.87 (m, 1H), 1.55–1.68 (m, 1H), 1.10 (d, *J* = 6.8 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.8, 158.5, 144.0, 136.8, 129.0, 128.6, 128.5, 127.8, 127.6, 127.5, 120.9, 115.1, 112.4, 69.6, 48.9, 44.8, 23.7, 13.6, 11.7. HRMS (ESI): Calcd for $C_{19}H_{22}O_3Na$: 321.1467. Found: 321.1472. The dr and ee was determined by HPLC analysis in comparison with authentic racemic materials respectively. HPLC: DIKMA CHIRALPAK AD-H column (250 × 4.6 mm, 5 μm), λ = 270 nm, *n*-hexane/*i*-PrOH/formic acid = 95:5:0.1, flow rate = 0.60 mL/min, retention time: 13.69 min (*anti*-isomer), 14.37 min (*anti*-isomer), 20.02 min (2*S*,3*S*), 25.49 min (2*R*,3*R*).

(2*R*,3*R*)-3-(3-(Benzyloxy)phenyl)-*N*,*N*,2-trimethylpentanamide 9

To a stirred solution of **8** (357 g, 1.2 mol) in CH_2Cl_2 (0.6 L) at room temperature was added dropwise oxalyl chloride (200 mL, 2.4 mol) and the mixture was stirred at 40 °C for 2 h and then concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (400 mL), and at 0 °C, was added to a solution of dimethylamine hydrochloride (196 g, 2.4 mol) and TEA (576 mL, 4 mol) over a period of 1 h. The mixture was stirred at room temperature for 1 h, and then acidified with 1 M aqueous HCl at pH 6–7 at 0 °C. The organic layer was separated and washed with a saturated solution of $NaHCO_3$ (500 mL), brine (500 mL), and dried over Na_2SO_4. Filtration followed by concentration in vacuo afforded 352 g of **9** as a pale yellow oil in 90% yield, $[\alpha]_D^{22} = -46.2$ (*c* 1.0, $CHCl_3$).^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30–7.55 (m, 5H), 7.22 (m, 1H), 6.70–6.82 (m, 3H), 5.05 (s, 2H), 2.80–2.90 (m, 1H), 2.74–2.82 (m, 1H), 2.65 (s, 3H), 2.55 (s, 3H), 1.80–1.92 (m, 1H), 1.44–1.64 (m, 1H), 1.10 (d, *J* = 6.2 Hz, 3H), 0.85 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ175.4, 158.3, 145.2, 137.1, 128.9, 128.5, 128.4, 127.8, 127.5, 127.4, 120.6, 114.4, 112.3, 69.7, 50.0, 41.7, 37.1, 35.3, 23.9, 15.1, 11.9. HRMS (ESI): Calcd for $C_{21}H_{28}NO_2$: 326.2120. Found: 326.2142.

(2*R*,3*R*)-3-[3-(Benzyloxy)phenyl]-*N*,*N*,2-trimethylpentan-1-amine 10

To a stirred suspension of $LiAlH_4$ (92 g, 2.4 mol) in dry THF (1 L) was added dropwise a solution of **9** (260 g, 0.8 mol) in dry THF (0.6 L). The reaction mixture was stirred at 0 °C for 3 h and then quenched by the careful addition of 1 M NaOH aqueous solution at 0 °C until yjr evolution of gas ceased. The mixture was filtered and the solid residue rinsed with EtOAc (500 mL). The filtrate was concentrated in vacuo to yield 224 g of **10** as a pale yellow oil in 90% yield, $[\alpha]_D^{22} = -17.6$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.58 (m, 5H), 7.25 (t, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 1H), 6.75 (m, 2H), 5.05 (s, 2H), 2.20–2.34 (m, 2H), 2.21 (s, 3H), 2.14 (s, 3H), 1.80–1.90 (m, 1H), 1.72–1.83 (m, 1H), 1.55–1.66 (m, 1H), 1.42–1.52 (m, 1H), 1.05 (d, *J* = 6.2 Hz, 3H), 0.85 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.7, 145.7, 137.1, 129.2, 128.6, 128.5, 127.9, 127.6, 127.5, 121.2, 115.3, 112.1, 69.9, 64.5, 51.6, 45.4, 45.3, 36.3, 24.3, 16.2, 12.3. HRMS (ESI): Calcd for $C_{21}H_{30}NO$: 312.2327. Found: 312.2310.

3-[(2*R*,3*R*)-1-(Dimethylamino)-2-methylpentan-3-yl] phenol hydrochloride 1

To a stirred solution of **10** (186 g, 0.6 mol) in MeOH (600 mL) was added 5% Pd/C (9 g). A hydrogen atmosphere (1 atm) was applied, and the mixture was stirred at room temperature for 8 h. The mixture was filtered and the solid residue washed with MeOH (250 mL × 3). Next, 12 M HCl (48 mL) was added to the filtrate at 0 °C and then the mixture was stirred for 30 min, concentrated in vacuo to yield 138 g of **1** as white powders after recrystallization in MeOH/diisopropyl ether in 90% yield, mp 198–200 °C, $[\alpha]_D^{22} = -29.6$ (*c* 1.1, MeOH).^{1}H NMR (300 MHz, CD_3OD): δ 7.25 (t, *J* = 7.9 Hz, 1H), 6.60–6.82 (m, 3H), 2.82–2.94 (m, 2H), 2.70–2.80 (br s, 6H), 2.23–2.36 (m, 1H), 2.14–2.28 (m, 1H), 1.80–1.90 (m, 1H), 1.55–1.68 (m, 1H), 1.25 (d, *J* = 6.7 Hz, 3H), 0.85 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 159.7, 145.8, 131.1, 121.0, 117.2, 115.3, 64.6, 53.3, 46.1, 42.1, 35.6, 26.3, 16.4, 12.7. HRMS (ESI): Calcd for $C_{14}H_{24}NO$: 222.1858. Found: 222.1860. The de was determined as 99.9% by HPLC analysis in comparison with authentic racemic materials. HPLC: DIKMA CHIRALPAK AD-H column (250 × 4.6 mm, 5 μm), λ = 270 nm, *n*-hexane/Et_2NH = 100:0.2, flow rate = 0.80 mL/min, retention time: 42.05 min, 44.35 min, 49.16 min (2*R*,3*R*), 54.37 min.

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