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# Tetrahydrothiopyran-4-one as Five Carbon Source for Scalable Synthesis of (±)-Tapentadol

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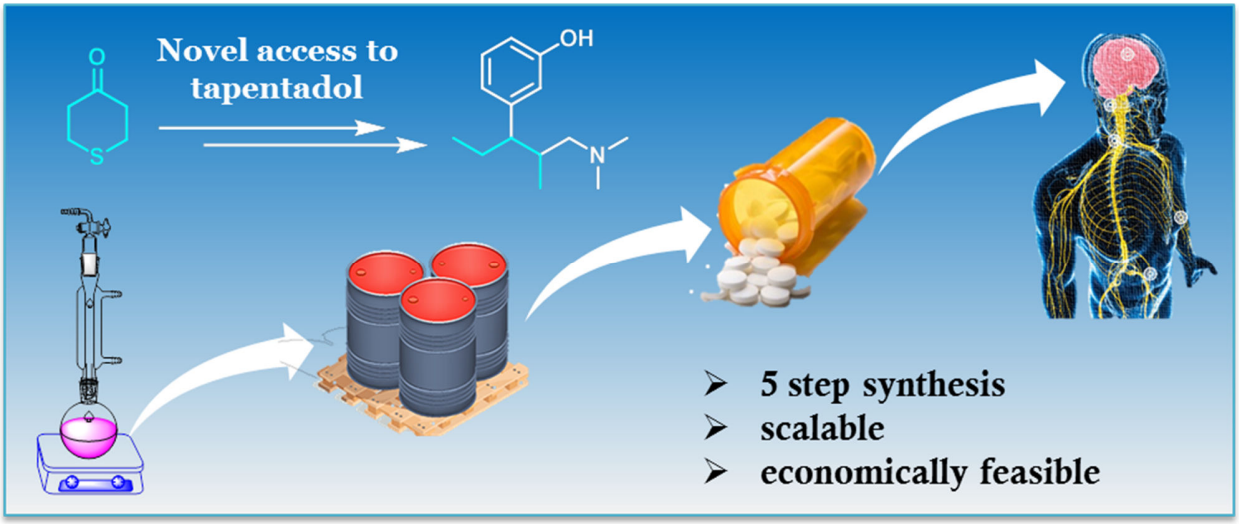
**TOC Figure**


Novel access to tapentadol
O
S
OH
N
5 step synthesis
scalable
economically feasible

**ABSTRACT**: The improved process for synthesis of (±)-tapentadol, the FDA approved analgesic drug is achieved from tetrahydrothiopyran-4-one as the 5-carbon source.

**KEYWORDS**: tapentadol, tetrahydrothiopyran-4-one, analgesic, Grignard addition

## INTRODUCTION

Pain management involves complex biological processes. There are a good numbers of drugs available in the market for the treatment of this unpleasant feeling. The biological process of pain engage interactions of emotions, senses and behavior.[1]

Currently the pain symptoms are treated by many approaches. They are classified into anesthetics, non-steroidal anti-inflammatory drugs, opioids, anti-depressants and others. Morphine (**1a**) (**fig. 1**) is on the top of the pain treatment in adverse cases.[2] However, this is an addictive chemical and also patients can have withdrawal symptoms once treatment is stopped.

Codeine (**1b) (Fig. 1**) is also an approved drug, which works by a similar mechanism like morphine and is less addictive compared to morphine.[3] Tramadol (**2**), which is a synthetic equivalent of codeine, was introduced as a pain killer in the mid-1990s. This works by combining weak μ-opioid and mono-aminergically (noradrenaline and serotonin) mediated mechanisms.[4] The next generation molecule discovered was tapentadol (**3**) by Grünenthal (German pharmaceutical company),[5,6] which works as a dual action analgesic and is used in nociceptive and neuropathic pain. The innovators process involved classical Grignard chemistry and reduction.[7] The total synthesis of tapentadol was recently reviewed.[8, 9]

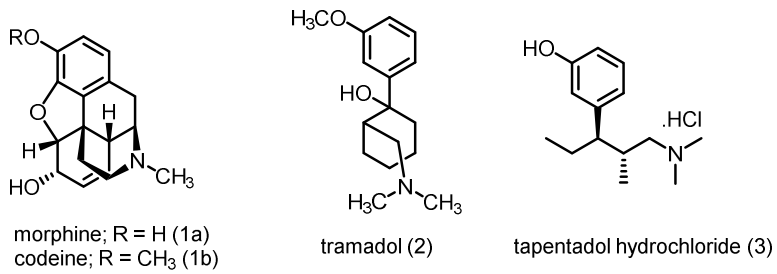
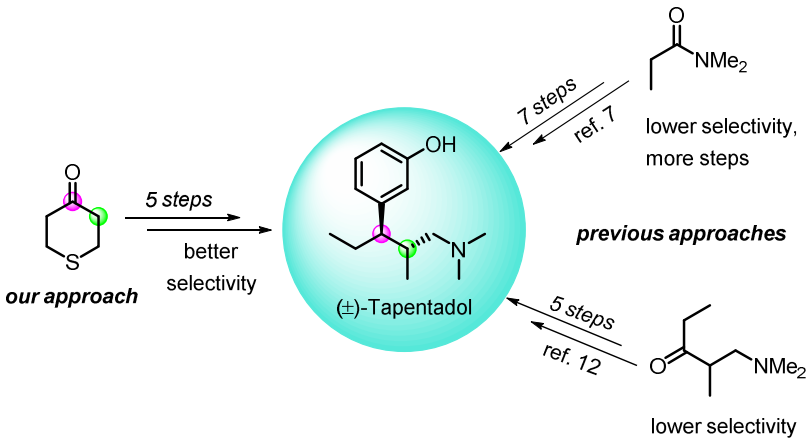



**Figure 1.** Structures of FDA approved analgesic drugs.

Our group has been engaged in developing practical and scalable synthesis of FDA approved drugs *viz*, nebivolol,[10a] asenapine,[10b] zafirlukast,[10c] cephalotaxine,[10d] galanthamine[10e] *etc*. We were intrigued by the excellent properties of tapentadol which has been approved by FDA, for the relief of moderate to severe acute pain.[11] The detailed literature of tapentadol is mostly in the patented domain. The strategies used by most researcher depend on an acyclic approach wherein the Grignard addition of 3-bromoanisole onto ethyl ketone generates diastereomeric mixtures which were carried forward to achieve the target molecule (scheme 1).[7,12]

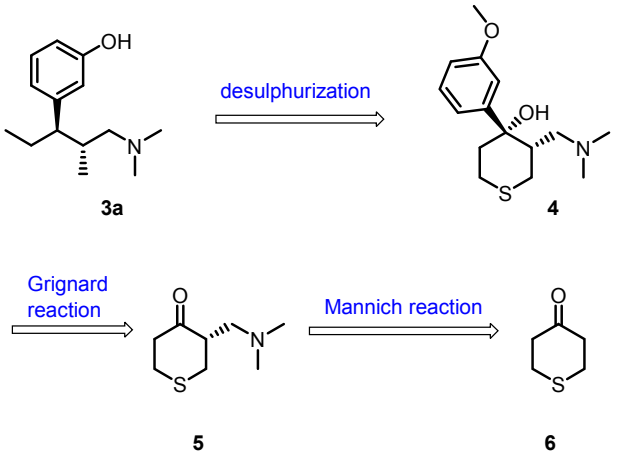
**Scheme 1:** Previous and present approaches for synthesis of tapentadol.




The reactions are mostly based on diethyl ketone (3 - pentanone) or derivatives thereof. 3 - Pentanone being a volatile compound, the quantities required are more and recovery of starting material is less. Use of 4-thiopyranone makes the process more compatible to recover starting material and to reuse it.

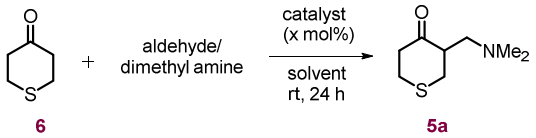
We reasoned, the Grignard addition of bromoanisole onto a cyclic ketone, which upon opening of the cyclic form would be a preferred option for a better diastereo control (scheme 2). It occurred to us that thiopyran-4-one (available at 3-5 USD/Kg on bulk pricing) could be the best five carbon equivalent, in cyclic form, which could be reductively opened after Grignard addition.

**Scheme 2:** Retrosynthetic Analysis of Tapentadol.




The original plan was to introduce the dimethylamino methylene group through asymmetric desymmetrization which was not very prudent (Table 1). Attempts to use organocatalytic reactions resulted in good yields with no enantioselectivity. The first step of synthesis, Mannich addition, was carried out using 37% aqueous formaldehyde and 40% aqueous dimethylamine with 4-thiopyranone **6** to yield **5a** in 76% yield.[13] Reaction with *L*- proline did not result in the preferential formation of any one enantiomer, probably due to the catalytic role played by the reagent (dimethylamine). Few other chiral organocatalysts also had the same outcome (see supporting information). A reaction of 100 g scale with optimized conditions gave 74 g of **5a** in 76% yield along with recovery of the starting material (scheme 3).

**Table 1** Screening for optimal reaction conditions[a]

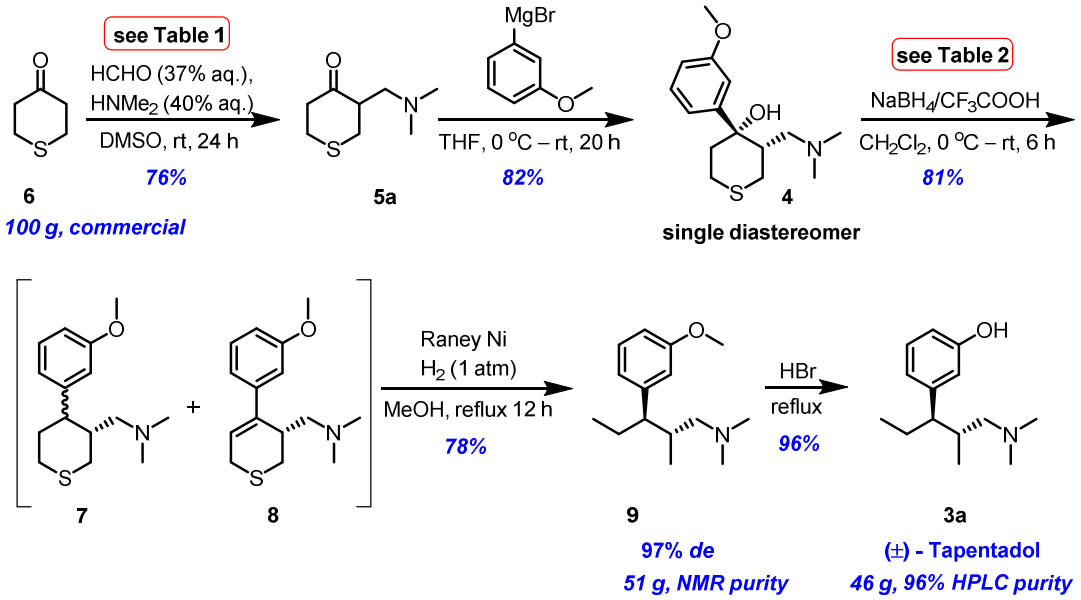



6 5a

| entry | reactants | solvent | catalyst | mol% | yield[b, c] |
|---|---|---|---|---|---|
| 1 | HCHO/aq.$HNMe_2$ | DMSO | *L*-proline | 10 | 75 |
| 2 | HCHO/aq.$HNMe_2$ | DMSO | *L*-proline | 100 | 70 |
| 3 | HCHO/aq.$HNMe_2$ | DMSO | - | - | 76 |
| 4 | HCHO/aq.$HNMe_2$ | DMSO | $CH_3COOH$ | 10 | 70 |
| 5 | $(HCHO)_n/HNMe_2$·HCl | $H_2O$ | HCl | 10 | 68[d] |
| 6 | HCHO/aq.$HNMe_2$ | EtOH | *L*-proline | 10 | n.r |
| 7 | HCHO/aq.$HNMe_2$ | $CH_3OH$ | *L*-proline | 10 | n.r |
| 8 | HCHO/aq.$HNMe_2$ | DMF | *L*-proline | 10 | 62 |

Standard reaction conditions: [a] The reaction was carried out with **6** (0.5 mmol), aldehyde/dimethylamine (0.25 mmol) in solvent (0.2 M) at room temperature for 24 h. [b] Crude product yield [brsm]. [c] *ee* determined by chiral GCMS in case of L-proline catalysed reactions [d] reaction was carried out under reflux for 3 h.

**Scheme 3:** Synthesis of Tapentadol.

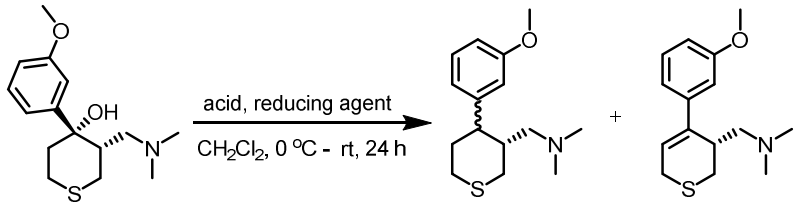



To the Mannich adduct **5a,** was added Grignard reagent of 3-bromoanisole (prepared from magnesium turnings and 3-bromoanisole in THF) to generate a single diastereomeric tertiary alcohol **4** in 82% of crude yield which was used for the next step without purification.[14] The next obvious synthetic

transformation was to deoxygenate the tertiary alcohol in **4**. Here, we screened various acids and reducing agents to eliminate the hydroxyl group without disturbing the adjacent stereocenter (Table 2). Among all conditions, the best was found to be the conversion of compound **4** in TFA/$CH_2Cl_2$ (2:1) solvent in presence of $NaBH_4$ to realize a mixture of **7** & **8** where 8:2 selectivity was observed with 81% yield.[15] After water workup, mixture of **7**/**8** was subjected to desulphurization-hydrogenation, with Raney Ni and $H_2$ at atmospheric pressure in one-pot to produce the methoxy tapentadol **9** with 97% diastereoselectivity (confirmed in the next step) in favor of desired diastereomer. Interestingly, the hydrogenation of double bond in compound **8** also gave **9** with required *anti*-diastereoselectivity. The demethylation of **9** was achieved by refluxing in 48% aqueous HBr to produce the tapentadol **3a** in 96% yield which was confirmed by comparison to a standard using HPLC analysis. Total process for the synthesis of target molecule was achieved without any column chromatography with overall ~ 37% yield.

The advantage of the current strategy using ketone **6** was the higher *de* obtained as compared to previous routes. The synthetic operation from cheaply available tetrahydrothiopyran-4-one **6** provided an added advantage of scale up at a lowest cost than the acyclic strategy. The resolution of the desired mixture is known using L-(-)-dibenzoyltartaric acid.[16]

**Table 2.** Optimization Conditions for Dehydroxylation[a]




**4** **7** **8**

| entry | acid | reducing agent | temp (°C) | time (h) | 7:8[b] | yield (%)[c] |
|---|---|---|---|---|---|---|
| 1 | $BF_3.Et_2O$ | $Et_3SiH$ | rt | 24 | 9:1 | 70 |
| 2 | $BF_3.Et_2O$ | $Et_3SiH$ | 40 | 6 | 1:9 | 83 |
| 3 | TFA | $Et_3SiH$ | rt | 24 | - | - |
| 4 | TFA | $Et_3SiH$ | 40 | 4 | 0:100 | 78 |
| **5**[d] | **TFA** | **$NaBH_4$** | **rt** | **6** | **8:2** | **81** |
| 6 | $BF_3.Et_2O$ | PMHS | rt | 24 | - | - |
| 7 | $BF_3.Et_2O$ | PMHS | 40 | 8 | - | - |
| 8 | 80% $H_2SO_4$ | - | 80 | 4 | 0:100 | 90[e] |

Standard reaction conditions: [a] The reaction was carried out with acid (0.8 mmol), reducing agent (3.0 mmol) in $CH_2Cl_2$ (0.2 M) at room temperature. [b] Determined by LCMS. [c] Combined crude product yield. [d] 15 equiv. of $NaBH_4$ in 0.2 M of TFA/$CH_2Cl_2$ (2:1) solvent. [e] Reaction was carried out without using solvent and product **8** was observed exclusively.

In conclusion, a straight forward and rapid synthesis of (±)-tapentadol was achieved, with better diastereoselectivity, from totally different raw materials, which are of commercial relevance.

## EXPERIMENTAL SECTION

***General information*:** Unless otherwise noted, all reagents were used as received from commercial suppliers. $CH_2Cl_2$ was dried in the presence of calcium hydride and distilled prior to use. THF was dried in the presence of sodium metal using benzophenone as indicator and distilled prior to use. Reactions were monitored using thin-layer chromatography ($SiO_2$). TLC plates were visualized with UV light (254 nm), iodine treatment or using ninhydrin stain. Column chromatography was carried out using silica gel (60-120 mesh & 100-200 mesh) packed in glass columns. NMR spectra were recorded at 300, 400, 500

MHz (H) and at 75, 101, 126 MHz (C), respectively. Chemical shifts (δ) are reported in ppm, using the residual solvent peak in $CDCl_3$ (H: $\delta$ = 7.26 and C: $\delta$ = 77.1 ppm) as internal standard, and coupling constants (*J*) are given in Hz. HRMS were recorded using ESI-TOF techniques.

## EXPERIMENTAL SECTION

**3-((Dimethylamino)methyl)tetrahydro-4*H*-thiopyran-4-one (5a):** Tetrahydrothiopyran-4-one (**6**) (100.0 g, 860.7 mmol), formaldehyde (37% aq. Solution, 34.92 mL, 430.3 mmol), dimethylamine (40% aq. Solution, 53.3 mL, 473 mmol) and DMSO (1.5 L) were added to a 5 L reaction vessel equipped with a mechanical stirrer for 24 h. After completion, the reaction mixture was extracted three times with ethyl acetate (1×1.5 L, then 2×1 L). The organic layer was acidified (up to pH 2) using 2N HCl to make it hydrochloride salt which was extracted into water (2×1.5 L). Evaporation of the organic layer gave 35 g of starting material which was recovered and reused. Then to that aqueous layer was added 2N NaOH (up to pH 9) to make it free amine which was extracted into ethyl acetate (3×1 L), concentrated under reduced pressure to give compound **5a** as a brownish oil, 74 g (76% yield based on staring material recovery). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 3.17 (dd, *J* = 13.4, 4.3 Hz, 1H), 2.91-2.97 (m, 3H), 2.88 – 2.81 (m, 1H), 2.78 – 2.73 (m, 1H), 2.71 - 2.66 (m, 2H), 2.43 – 2.37 (m, 1H), 2.21 (s, 6H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 210.0, 58.8, 51.0, 45.8, 43.6, 34.5, 31.1; **IR** (neat) $\upsilon_{max}$ 2940, 2822, 2771, 1701, 1458, 1262, 1038, 850 $cm^{-1}$; **HRMS** (ESI) calcd for $C_8H_{16}NOS$ $[M+H]^+$: 174.0953 ; found: 174.0951.

**3-((Dimethylamino)methyl)-4-(3-methoxyphenyl)tetrahydro-2*H*-thiopyran-4-ol (4):** To a dry 5 L four-neck flask provided with a thermometer, a stirrer, a cooling tube and a dropping funnel were charged activated Mg turnings (12.3 g, 508 mmol) and dry THF (500 mL) followed by drop wise addition of a THF solution (250 mL) of 3-bromoanisole (41.8 mL, 331 mmol) under nitrogen with stirring, where heat generation was observed after 10 min. and then it was allowed to cool for 1 h. After the Grignard reagent was prepared, it was slowly added to the 3-((dimethylamino)methyl)tetrahydro-4H-thiopyran-4-one **(5a)** (44.0 g, 254 mmol) in THF (500 mL) drop wise at 0 °C and the stirring was continued for 12 h at room temperature. After completion of the reaction, sat. $NH_4Cl$ (25 mL) was added to the reaction mixture

slowly at 0 °C and the product 3-((dimethylamino)methyl)-4-(3-methoxyphenyl)tetrahydro-2*H*-thiopyran-4-ol **(4)** was obtained by extraction with ethyl acetate (1×1.5 L, then 1×1 L) followed by concentration to yield yellow oil (58.2 g, 82 %, a single diastereomer). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.28 – 7.24 (m, 1H), 7.16 – 7.03 (m, 2H), 6.77 (dd, *J* = 8.1, 1.8 Hz, 1H), 3.82 (s, 3H), 3.53 (t, *J* = 12.7 Hz, 1H), 3.24 (td, *J* = 13.6, 2.9 Hz, 1H), 2.47 (dd, *J* = 14.0, 4.4 Hz, 1H), 2.40 – 2.34 (m, 2H), 2.27 – 2.20 (m, 2H), 2.08 (s, 6H), 2.03 – 1.94 (m, 2H); **$^{13}$C NMR (125 MHz, $CDCl_3$)** δ 159.8, 151.1, 129.4, 117.3, 111.9, 110.8, 76.2, 62.1, 55.4, 47.9, 46.1, 42.7, 29.4, 24.9; **IR** (neat) $\upsilon_{max}$ 3420, 2923, 2832, 1593, 1471, 1429, 1256, 1042, 925, 756, 698 $cm^{-1}$; **HRMS** (ESI) calcd for $C_{15}H_{24}NO_2S$ $[M+H]^+$: 282.1528 ; found: 282.1525.

**1-(4-(3-Methoxyphenyl) tetrahydro-2*H*-thiopyran-3-yl)-*N, N*-dimethylmethanamine (7):**

To a stirred solution of trifluoroacetic acid (150 mL) under inert conditions was added $NaBH_4$ (91 g, 2.4 mol) slowly at 0 °C followed by addition of a solution of 3-((dimethylamino)methyl)-4-(3-methoxyphenyl)tetrahydro-2*H*-thiopyran-4-ol (**4**) (45.0 g, 160. mmol) in $CH_2Cl_2$ (250 mL) to the reaction at the same temperature. The reaction mixture was allowed to stir for 6 hours at ambient temperature. After completion, reaction mixture was poured into ice water (600 mL) and to the mixture was added saturated $Na_2CO_3$ solution (up to pH 9). The reaction mixture was extracted with $CH_2Cl_2$ (2×200 mL, then 1×100 mL), organic layer was dried and evaporated to give a mixture of products (**7& 8**) as light brown oil, 34.5 g (81%) which was used directly for the next reaction without any further purification. Crude $^1$H NMR showed olefin proton at δ 6.09 – 6.05 ppm as multiplet revealed minor presence of compound 8.

**3-(3-Methoxyphenyl)-*N,N*,2-trimethylpentan-1-amine (9):** The crude 1-(4-(3-methoxyphenyl)tetrahydro-2H-thiopyran-3-yl)-*N,N*-dimethylmethanamine (**7**) (55.0 g, 207 mmol) was dissolved in 750 mL of MeOH and treated with a suspension of Raney Ni (200 g) in 300 mL of MeOH and heated to 80 °C in an autoclave with an internal hydrogen pressure of 1 bar for 12 h. The reaction was monitored by TLC and if necessary another batch of Raney nickel was added. After completion, the

reaction mixture was allowed to settle and the supernatant was removed *via* pipette and filtered through Celite. Additional MeOH (500 mL) was added to the reaction mixture and stirred for 5 min before again being allowed to settle and the supernatant removed. This process was repeated an additional two times and the combined filtrates were concentrated to give 3-(3-methoxyphenyl)-*N*,*N*,2-trimethylpentan-1-amine **(9)** (38 g, 78 %) as yellow oil with 97% diastereomeric excess (based on LCMS analysis).

**$^1$H NMR (500 MHz, $CDCl_3$)** δ 7.20 (t, *J* = 7.8 Hz, 1H), 6.77 – 6.66 (m, 3H), 3.8 (s, 3H), 2.35 – 2.28 (m, 1H), 2.21 (s, 1H), 2.17 (s, 6H), 2.05 – 2.0 (m, 1H), 1.83 – 1.68 (m, 2H), 1.63 – 1.52 (m, 1H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.72 (t, *J* = 7.4 Hz, 3H).; **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 159.5, 146.2, 129.1, 121.1, 114.7, 110.7, 64.9, 55.2, 51.7, 45.9, 36.6, 24.2, 16.1, 12.5.; **IR** (neat) $\upsilon_{max}$ 3171, 2943, 2825, 1593, 1461, 1250, 1040, 780, 706; **HRMS** (ESI) calcd for $C_{15}H_{26}NO$ $[M+H]^+$: 236.2014 ; found: 236.2022.

**3-(1-(Dimethylamino)-2-methylpentan-3-yl)phenol (3a):** A mixture of 3-(3-methoxyphenyl)-*N*,*N*,2-trimethylpentan-1-amine **(9)** (51.0 g, 217 mmol) and aqueous hydrobromic acid (48%, 300 mL) was heated under stirring at 100-110 °C for 3 h and cooled to room temperature. To the reaction mixture was added sodium bicarbonate (up to pH 9), resulting mixture was extracted with ethyl acetate (500 mL). The organic layer was washed with water and dried over anhydrous sodium sulphate and concentrated to give 3-(1-(dimethylamino)-2-methylpentan-3-yl)phenol **(3a)** (46 g, 96 %) as a Pale yellow oil. By HPLC analysis revealed exclusive *anti* diastereomer.

NMR data for 3-(1-(dimethylamino)-2-methylpentan-3-yl)phenol (**3a**) (*anti)*: **$^1$H NMR (500 MHz, $CDCl_3$)** δ 7.12 (t, *J* = 7.8 Hz, 1H), 6.68 – 6.61 (m, 2H), 6.58 (s, 1H), 2.33 – 2.27 (m, 1H), 2.17 (s, 6H), 2.15 – 2.10 (m, 1H), 2.09 – 2.00 (m, 1H), 1.90 – 1.83 (m, 1H), 1.78 – 1.68 (m, 1H), 1.60 – 1.49 (m, 1H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.70 (t, *J* = 7.3 Hz, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 156.5, 146.1, 129.2, 120.3, 115.8, 113.3, 64.8, 51.5, 45.7, 36.6, 23.9, 16.2, 12.4; **IR** (neat) $\upsilon_{max}$ 3391, 2958, 2871, 1695, 1464, 1266, 1029, 775; **HRMS** (ESI) calcd for $C_{14}H_{24}NO$ $[M+H]^+$: 222.1858 ; found: 222.1865.

NMR data for 3-(1-(dimethylamino)-2-methylpentan-3-yl)phenol (**3b**) (*syn)* (obtained from table 2. entry 1 reaction conditions):

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.10 (t, *J* = 7.8 Hz, 1H), 6.65 (dd, *J* = 8.0, 2.1 Hz, 2H), 6.59 – 6.55 (m, 1H), 2.46 – 2.37 (m, 1H), 2.29 – 2.25 (m, 1H), 2.24 (s, 6H), 2.02 – 1.94 (m, 1H), 1.94 – 1.82 (m, 1H), 1.78 – 1.58 (m, 2H), 0.80 – 0.71 (m, 6H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 156.2, 144.6, 128.9, 121.4, 116.0, 113.4, 65.4, 50.7, 45.9, 35.8, 26.8, 15.6, 12.7; **IR** (neat) $\upsilon_{max}$ 3310, 2951, 2865, 1595, 1465, 1263, 1028, 779 $cm^{-1}$; **HRMS** (ESI) calcd for $C_{14}H_{24}NO$ $[M+H]^+$: 222.1858 ; found: 222.1878

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## ASSOCIATED CONTENT

### Supporting Information

Copies of $^1$H and $^{13}$C spectra for all new compounds; this material is available free of charge via the Internet at http://pubs.acs.org.

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## Notes

The authors declare no competing financial interest.

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