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PII: S0040-4020(17)30567-7

DOI: 10.1016/j.tet.2017.05.066

Reference: TET 28732

To appear in: *Tetrahedron*

Received Date: 31 March 2017

Revised Date: 15 May 2017

Accepted Date: 19 May 2017

Please cite this article as: Wang Y, Huang G, Hu S, Jin K, Wu Y, Chen F, Enantioselective *β*-hydroxy thioesters formation via decarboxylative aldol reactions of malonic acid half thioesters with aldehydes promoted by chloramphenicol derived sulfonamides, *Tetrahedron* (2017), doi: 10.1016/j.tet.2017.05.066.

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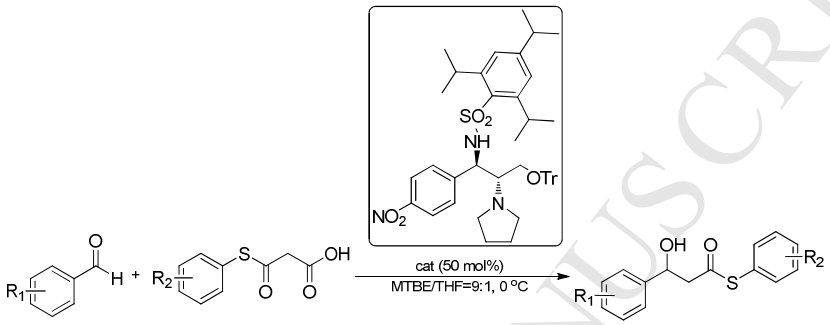

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Enantioselective β-Hydroxy thioesters Formation via Decarboxylative Aldol Reactions of Malonic Acid Half Thioesters with Aldehydes Promoted by Chloramphenicol derived Sulfonamides[1]

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

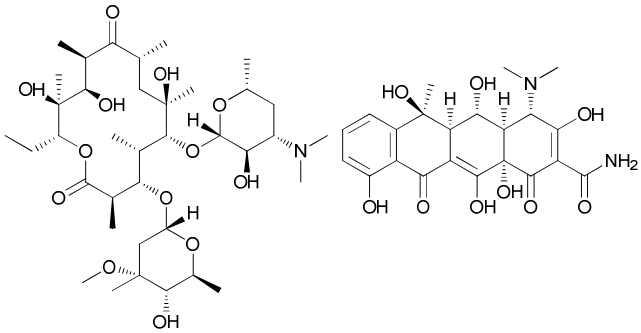
Keywords:
Chloramphenicol base-sulfonamides catalysts
Aldol reaction
Asymmetric catalysis
Chiral β-hydroxy thioesters

ABSTRACT

A highly enantioselective synthesis of chiral β-hydroxy thioesters that uses a decarboxylative aldol reaction of malonic acid half thioesters and aldehydes catalyzed by a chloramphenicol base-derived bifunctional organocatalyst is reported. The resulting chiral β-hydroxy thioesters were obtained in high yields (up to 82%) with good to excellent enantioselectivities (up to 94% ee). The synthetic application of the methodology is illustrated by the asymmetric synthesis of the selective serotonin reuptake inhibitor dapoxetine.

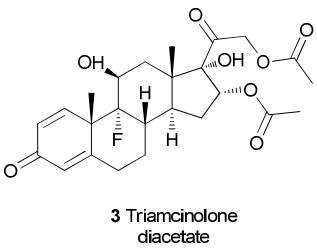
1. Introduction

Chiral β-hydroxy thioesters[2] are important synthetic building blocks in many pharmaceuticals and natural products, including erythromycin (**1**), oxytetracycline (**2**), triamcinolone diacetate (**3**), tephrosin (**4**), atorvastatin (**5**) and fluoxetine (**6**). In the past two decades, tremendous efforts have been devoted to the construction of this class of β-hydroxy thioester motifs using a highly enantioselective catalytic approach. For example, Ikariya and co-workers[3] reported work on the asymmetric synthesis of β-hydroxy thioesters using an asymmetric Mukaiyama aldol reaction catalyzed by a BINOL-Ti complex. Subsequently, Shair[4] and Cozzi[5] and their co-workers independently investigated a direct aldol reaction with malonic acid half thioesters (MAHTs) using a chiral Cu/bis(oxazoline) catalyst to give the corresponding β-hydroxy thioesters; this method required the use of metal catalysts. Recently, Shibata[6] disclosed a metal-free decarboxylative addition reaction of MAHTs with isatins for the synthesis of β-hydroxy thioesters that is catalyzed by cinchona-derived squaramide. Most importantly, when using cinchona-based bifunctional thioureas or sulfonamides as catalysts, the groups of Song[7] and Wennemers[8] obtained β-hydroxy thioesters with up to 96% and 99% ee, respectively. Despite considerable progress, however, the inaccessibility and high cost of the catalysts used in these protocols limits their use in industrial applications. The ultimate goal of developing a practical and highly effective catalytic system remains elusive forthe construction of chiral β-hydroxy thioester scaffolds using the asymmetric decarboxylative aldol reaction.

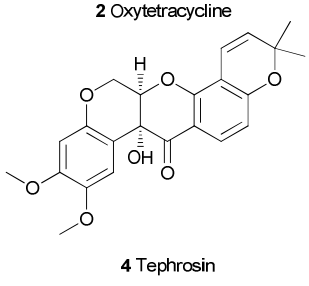


1 Erythromycin

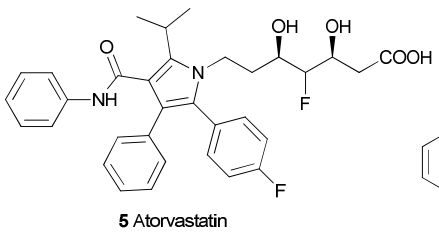
2 Oxytetracycline



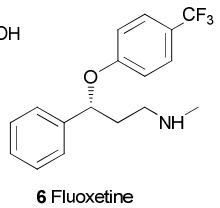
3 Triamcinolone diacetate



4 Tephrosin



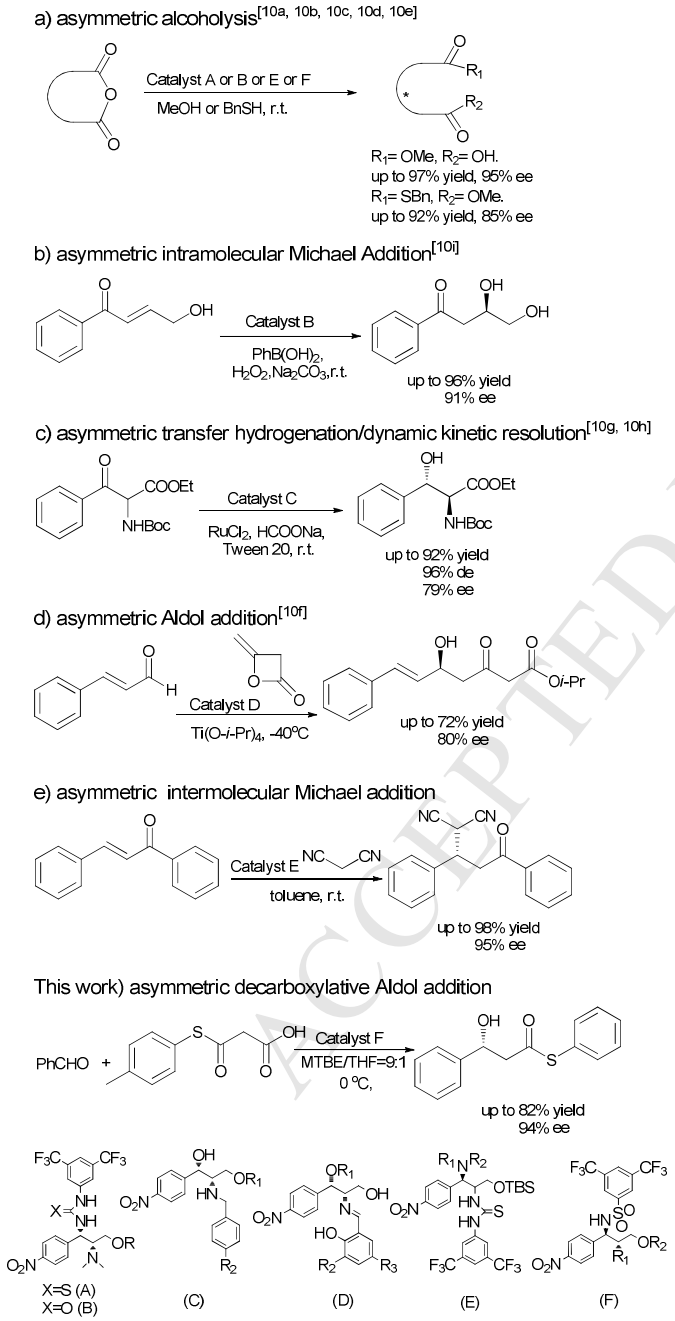
5 Atorvastatin



6 Fluoxetine

Figure 1. Pharmaceuticals and natural products derived from *β*-hydroxy thioesters.

Chloramphenicol base is a byproduct of chloramphenicol production and an important chiral scaffold. Many homogeneous catalysts based on this structural motif have been reported and used in a wide variety of efficient enantioselective and non-enantioselective asymmetric reactions. These reactions have been applied to many pharmaceuticals and natural products, including the asymmetric ring opening of prochiral cyclic anhydrides, asymmetric transfer hydrogenation/dynamic kinetic resolution of *α*-amino-*β*-ketoesters, and catalytic enantioselective aldol reactions of *α*,*β*-unsaturated aldehydes with diketenes (Scheme 1). Continuing our work[9] on the development of organocatalysts and their applications in asymmetric synthesis, we herein report the highly efficient enantioselective synthesis of *β*-hydroxy thioesters from MAHTs and aldehydes using our chiral chloramphenicol derived sulfonamide catalysts in a decarboxylative aldol reaction.

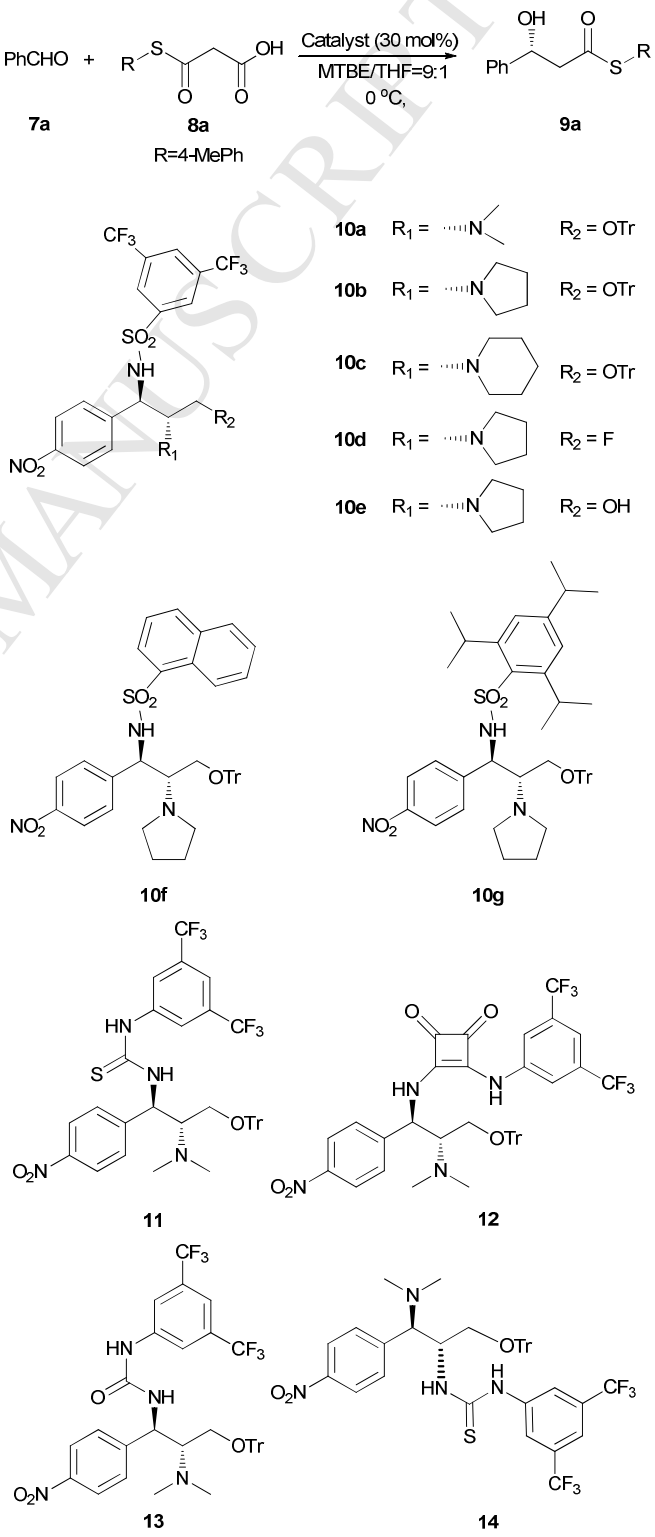


Scheme 1. Various asymmetric reactions catalyzed by our chloramphenicol derived catalysts

2. Results/Discussion

We commenced our evaluation of the catalytic ability of chiral chloramphenicol derived sulfonamide catalysts **10a**-**10g,**

Table 1. Asymmetric decarboxylative aldol reaction between MAHT **8a** and aldehyde **7a** catalyzed by various chloramphenicol derived bifunctional catalysts



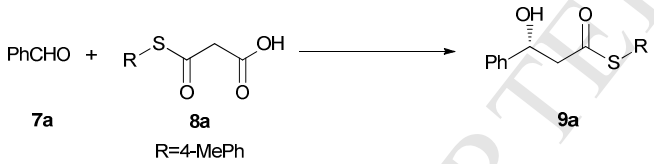
Entry	Catalyst	Time (d)	Yield[a] (%)	Ee[b] (%)
1	**10a**	5	42	74
2	**10b**	8	53	74
3	**10c**	8	20	51
4	**10d**	5	25	62
5	**10e**	5	60	65
6	**10f**	6	85	65
7	**10g**	8	78	86
8	**11**	6	80	5
9	**12**	6	75	11
10	**13**	6	95	2
11	**14**	6	78	7

[a]Yield of isolated product. [b] Determined by HPLC.

11-14 by using thioester **8a** and aldehyde **7a** as model substrates for the decarboxylative aldol reaction. In the presence of organo-catalysts **10a-10g, 11-14** and using MTBE/THF=9:1 as the solvent, desired product **9a** was obtained in good to excellent yields and poor to high ee values (Table 1, entries 1-11). In terms of both isolated yield and ee, the best result was obtained with catalyst **10g**.

With this preliminary result in hand, we investigated further parameters that may affect the efficiency of this transformation, including solvent (entries 1-6, Table 2), catalyst loading (entries 7-9) and temperature (entries 10-11). MTBE/THF (9:1) was the best solvent system among those that we screened. The catalyst loading had a marked effect on the reaction, with 50 mol% organocatalyst giving the best balance in terms of isolated yields and ee values. The reaction temperature had a considerable impact on the reaction rate, isolated yield and ee value. The aldol reaction proceeded slowly in very low yield and enantio-selectivity when it was carried out at –10℃ (entry 11). When the temperature was increased to 0℃ (entry 8), the reaction gave a 76% yield with 88% ee. A slight acceleration in the reaction rate and ee value was observed in the presence of 4 Å molecular sieves (entry 13, Table 2). We therefore decided to run the aldol reaction at 0℃, with 50 mol% of the catalyst and 4 Å molecular sieves in MTBE/THF (9:1).

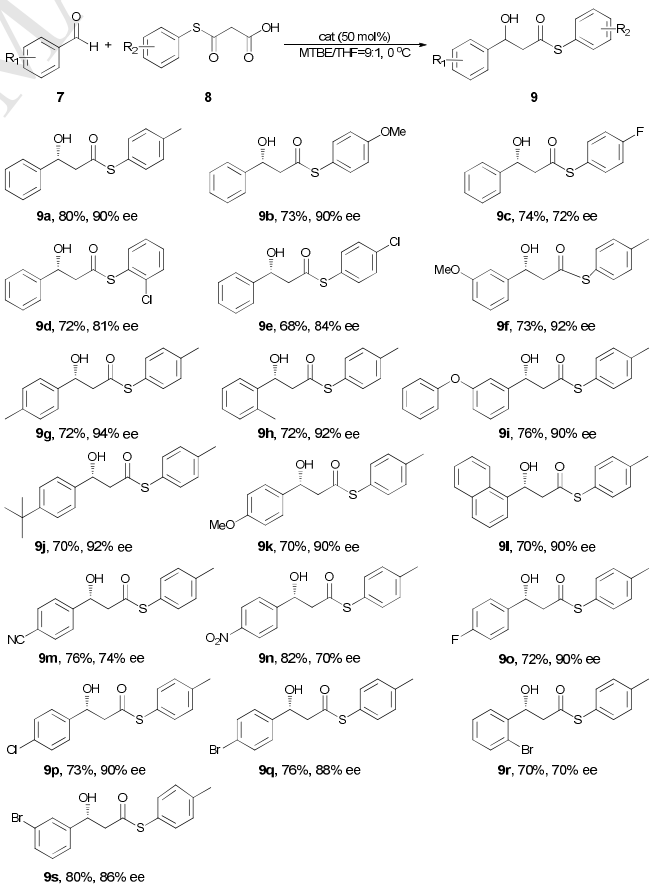
Table 2. Optimization of the reaction conditions



Entry	Solvent	Catalyst loading (%)	T (ºC)	Time (d)	Yield[a] (%)	Ee[b] (%)
1	MTBE/THF(9:1)	30	0	8	78	86
2	MTBE	30	0	8	80	80
3	THF	30	0	8	83	72
4	AcOEt	30	0	8	72	86
5	DCM	30	0	8	10	54
6	acetone	30	0	8	74	82
7	MTBE/THF(9:1)	20	0	13	56	82
8	MTBE/THF(9:1)	50	0	8	76	88
9	MTBE/THF(9:1)	70	0	7	80	80
10	MTBE/THF(9:1)	50	15	4	82	84
11	MTBE/THF(9:1)	50	-10	15	47	55
12	MTBE/THF(9:1)	50[c]	15	3	85	80
13	MTBE/THF(9:1)	50[c]	0	6	80	90
14	MTBE/THF(9:1)	40[c]	0	7	68	88

[a] Yield of isolated product. [b] Determined by HPLC. [c] cat (%) + 4 Å molecular sieves.

A series of *β*-hydroxy thioesters was obtained from a variety of aldehydes and MAHTs with the aim of extending the scope of the methodology under the optimized conditions. As shown in Scheme 2, we found that electron-rich thioesters **9a** and **9b** give high yields (80%, 73%) and excellent ee values (90%, 90%). Electron-deficient thioesters afforded products with ee values lower than 84%. In general, electron-donating groups at the ortho, para or meta positions of the phenyl ring of the aldehydes (**9f-k**) enable the decarboxylative aldol reaction to proceed effectively in high yield (70%-76%) and excellent enantiomeric excess(90%-94% ee). The enantiomeric excess decreases when strongly electron-withdrawing groups, such as *p*-nitro and *p*-cyano groups, are attached to the phenyl ring of the aldehyde. In addition, weakly electron-withdrawing groups are tolerated on the phenyl ring of the aldehyde under the optimized conditions, providing desired products **9o-q** with 88%-90% ee. The electron-



Scheme 2. Substrate scope for *β*-hydroxy thioesters. Reaction conditions: Aldehyde (0.2 mmol), catalyst (10 g. 0.1 mmol), 4 Å molecular sieves (0.1 g) and MAHT (1 mmol) in MTBE/THF (9:1, 1 mL) at 0 ℃

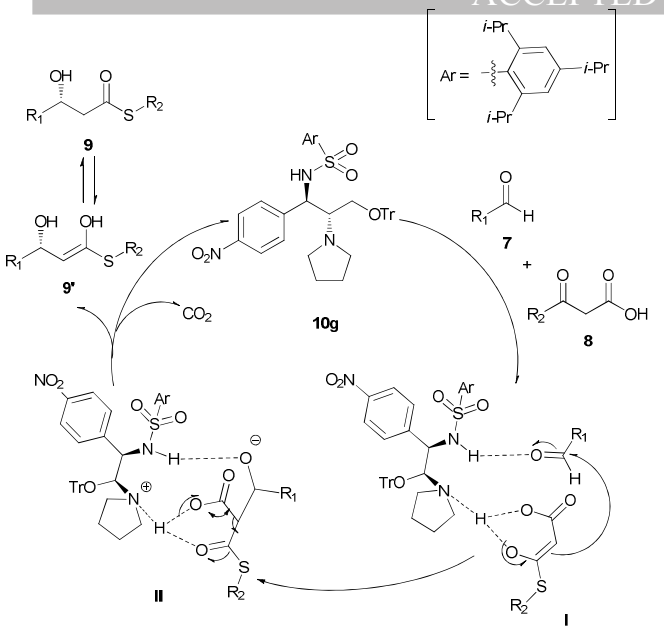
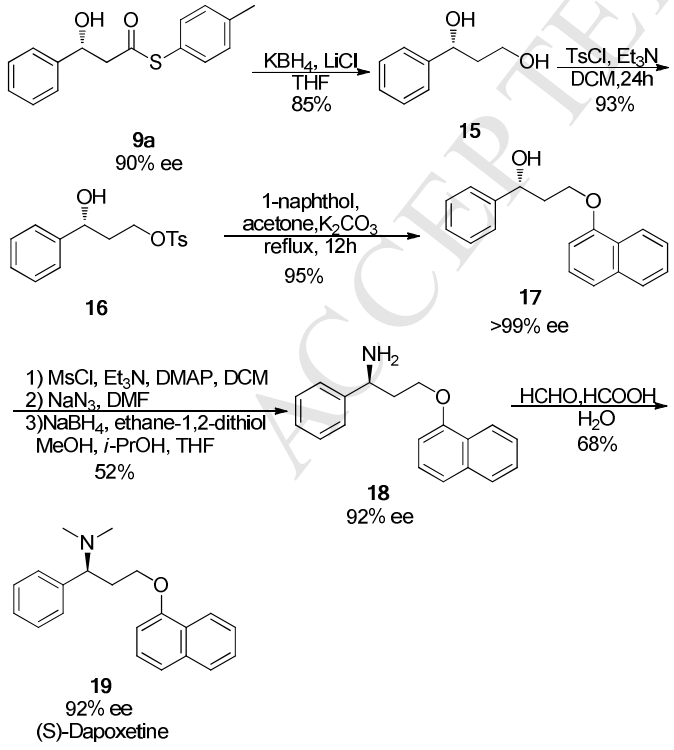


Figure 2. Plausible mechanism for the decarboxylative aldol reaction

withdrawing *p*-bromo group at the 2-positon of the aldehyde had the biggest influence on the aldol reaction, and led to very low enantioselectivities (70% ee). The reaction of 1-naphthaldehyde afforded product **9l** in high yield (70%) with excellent enantioselectivity (90% ee).

Considering the mechanism reported previously by the groups of Song[7] and Wennemers[8], we propose the mechanism shown in Figure 2. The tertiary amine of the chloramphenicol base forms two hydrogen-bonds with the MAHTs because of its basicity. The sulfonamide group acts as a hydrogen-bond donor and activates the aldehyde. Intermediate **I** is converted to complex **II** as a result of the orientation determined by the three hydrogen-bonds. The *β*-hydroxy thioester product is generated from **9'**, which results from the decarboxylation of intermediate **II**. Importantly, only CO_2 is generated as a byproduct in this decarboxylative aldol reaction.



Scheme 3. Asymmetric synthesis of (+)-dapoxetine **19**

We demonstrate the value of our methodology by carrying out the asymmetric synthesis of (+)-dapoxetine, a selective serotonin reuptake inhibitor, from primary alkyl substrates in very few steps. The reduction of chiral *β*-hydroxy thioester **9a** with $LiBH_4$, which was prepared in situ from KBH_4 and anhydrous LiCl in THF at 70□, provided (R)-1-phenylpropane-1,3-diol 15 in 85% yield. The 1,3-diol smoothly underwent hydroxyl tosylation with TsCl to form (R)-3-hydroxy-3-phenyl-propyl-4-methylbenzenesulfonate(**16**), which then successfully underwent nucleophilic substitution with 1-naphthol in the presence of K_2CO_3 to afford (R)-3-(naphthalen-1-yloxy)-1-pheny lpropan-1-ol(**17**) in excellent yield. The (S)-3-(naphthalen-1-yloxy)-1-phenylpropan-1-amine(**18**) was formed by electro-philic substitution, azidated, and reduced of the *O*-mesylated derivative (**17**). Finally, (+)-dapoxetine **19** was generated in 68% yield by refluxing with aqueous formaldehyde solution and formic acid for 10 h (Scheme 3).

3. Conclusion

In summary, chiral bifunctional chloramphenicol derived sulfonamide organocatalyst **10g** displayed high catalytic activity in the asymmetric aldol reaction of MAHTs with aldehydes. Various *β*-hydroxy thioesters were obtained in high yields and excellent enantioselectivities under mild conditions. The reaction was successfully applied to the construction of 1,3-diols in the synthesis of (+)-dapoxetine without loss of enantioselectivity. Further investigations aimed at exploring the scope of this methodology are currently in progress in our laboratory.

4. Experimental section

Unless otherwise specified, all reagents and solvent were obtained from commercial sources and used without further purification. MTBE was distilled from calcium hydride; THF was distilled from sodium–benzophenone. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR were recorded on a Bruker Avance 400 spectrometer using TMS or $CDCl_3$ as internal standards. Optical rotations were measured by a JASCO P1020 digital polarimeter. EI-MS were recorded on an Agilent 6890N/5975 spectrometer and ESI-MS were recorded on a Waters Micromass Quattro Micro spectrometer. HRMS were recorded on a Bruker micrOTOF spectrometer.HPLC analysis were performed with Daicel Chiralpak AD-H column (25 cm × 4.6 mm × 5 μm) and Chiralpak OD-H column (25 cm × 4.6 mm × 5 μm). The enantiomericratios, expressed as % ee, were determined by HPLC analysis as specified in the individual experimental descriptions and verified using the appropriate racemic mixtures.

General procedure for preparation of chloramphenicol derived bifunnctional organocatalysts.

All the chloramphenicol derived bifunnctional organocatalysts **10a-10g**, **11-14** were prepared by known procedure[9b]. The characterization results of new catalysts **10f** and **10g** were as below.

*N-((1R,2R)-1-(4-nitrophenyl)-2-(pyrrolidin-1-yl)-3-(trityloxy) p-ropyl)-naphthalene-1-sulfonamide (**10f**).*

Yellow solid, mp 98-100°C. ^{1}HNMR (400 MHz, $CDCl_3$): δ =8.00 (s, 1H), 7.84 (dd, J = 7.5, 6.0 Hz, 2H), 7.75 – 7.54 (m, 6H), 7.19

– 7.05 (m, 18H), 4.21 (d, J = 9.1 Hz, 1H), 3.10 (dd, J = 10.4, 5.3 Hz, 1H), 2.98 (d, J = 8.3 Hz, 2H), 2.56 (d, J = 18.5 Hz, 4H), 1.70 (d, J = 6.4 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 146.94 , 146.60 , 143.04 , 136.34 , 134.53 , 131.70 , 129.14 , 129.00 , 128.90 , 128.76 , 128.43 , 127.84 , 127.71 , 127.63 , 127.17 , 123.08 , 122.32 , 87.60 , 63.82 , 59.02 , 58.43 , 57.56 , 48.19 , 23.65 , 18.42 . HRMS (ESI) calcd for $C_{42}H_{39}N_3O_5S$ $[M + H]^+$ 698.2683 , found 698.2701.

*2,4,6-triisopropyl-N-((1R,2S)-1-(4-nitrophenyl)-5,5,5-triphen-yl-2-(pyrrolidin-1-yl)pentyl)benzenesulfonamide (**10g**).*

Light yellow solid, mp 93-95°C. ^{1}HNMR (400 MHz, $CDCl_3$): δ= 7.81 (d, J = 8.3 Hz, 2H), 7.18 (s, 17H), 6.98 (s, 2H), 5.27 (s, 1H), 4.53 (d, J = 9.4 Hz, 1H), 3.99 (dt, J = 13.1, 6.5 Hz, 2H), 3.23 (dd, J = 9.7, 4.6 Hz, 1H), 3.04 (dd, J = 17.5, 7.4 Hz, 2H), 2.83 (d, J = 6.1 Hz, 3H), 2.69 (d, J = 6.7 Hz, 2H), 1.76 (d, J = 2.7 Hz, 4H), 1.25 (d, J = 6.6 Hz, 6H), 1.19 (d, J = 6.8 Hz, 6H), 1.10 (d, J = 6.6 Hz, 6H).^{13}CNMR (100 MHz, $CDCl_3$): δ= 152.95, 149.79, 147.18, 146.94, 143.13, 133.65, 128.93, 128.49, 127.73, 127.18, 123.17, 122.89, 87.62, 64.08, 59.26, 57.49, 48.16, 34.15, 29.61, 29.09, 25.07, 24.60, 23.85, 23.67, 23.57. HRMS (ESI) calcd for $C_{47}H_{55}N_3O_5S$ $[M + H]^+$ 774.3943, found 774.3943.

General procedure for preparation of malonic acid half thioesters (MATHs).

MAHTs **20a**, **20b**, **20c**, **20d**, **20e** were prepared by known procedure[10]. The characterization results of **20a**, **20b**, **20c**, **20d**, **20e** were as below.

*3-oxo-3-(p-tolylthio)propanoic acid(**20a**).*

^{1}HNMR (400 MHz, $CDCl_3$): δ =10.27 (s, 1H), 7.34 (d, J = 7.8 Hz, 2H), 7.25 (d, J= 7.8 Hz, 2H), 3.71 (s, 2H), 2.39 (s, 3H).^{13}CNMR (100 MHz, $CDCl_3$): δ =190.25 , 171.30 , 140.36 , 134.36 , 130.19 , 122.93 , 48.18 , 21.29 .HRMS (ESI) calcd for $C_{10}H_{10}O_3S$ $[M + H]^+$ 211.0423, found 211.0423.

*3-((4-methoxyphenyl)thio)-3-oxopropanoic acid(**20b**).*

^{1}HNMR (400 MHz, $CDCl_3$): δ= 9.69 (s, 1H), 7.27 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 3.73 (s, 3H), 3.61 (s, 2H).

*3-((4-fluorophenyl)thio)-3-oxopropanoic acid(**20c**).*

^{1}HNMR (400 MHz, $CDCl_3$): δ =10.68 (s, 1H), 7.42 (dd, J = 8.3, 5.4 Hz, 2H), 7.13 (t, J = 8.5 Hz, 2H), 3.72 (s, 2H).

*3-((2-chlorophenyl)thio)-3-oxopropanoic acid(**20d**).*

^{1}HNMR (400 MHz, $CDCl_3$): δ= 12.95 (dd, J = 4.0, 1.8 Hz, 1H), 7.65 (dd, J = 19.9, 7.7 Hz, 2H), 7.54 (t, J = 7.7 Hz, 1H), 7.46 (t, J = 7.5 Hz, 1H), 3.87 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 188.81, 168.89 , 167.54 , 138.00 , 137.76 , 132.52 , 130.67 , 128.48 , 126.80 , 49.66 . HRMS (ESI) calcd for $C_9H_7ClO_3S$ $[M + Na]^+$ 252.9697, found 252.9697.

*3-((4-chlorophenyl)thio)-3-oxopropanoic acid(**20e**).*

^{1}HNMR (400 MHz, $CDCl_3$): δ =13.05-12.73 (m, 1H), 7.60 (s, 2H), 7.50 (s, 2H), 3.85 (s, 2H).

General procedure for catalytic aldol reaction

The procedure was used for all the substrates. To a stirring solution of MAHT (**8**, 1mmol), catalyst (**10g**, 774mg, 0.1mmol) and 4Å molecular sieve (0.1g) in anhydrous MTBE/THF (9:1, 1ml), aldehyde (**7**, 0.2mmol) was added at 0°C and stirred for 8 days. The *β*-hydroxy thioester (**9**) was achieved by flash chromatography (Petroleum Ether/EtOAc = 10:1 to 4:1).

*(R)-S-p-tolyl 3-hydroxy-3-phenylpropanethioate(**9a**).*

White solid, mp 85-87 °C. $[\alpha]^D20$ = + 18.24 (c 0.104, $CHCl_3$). ^{1}HNMR (400 MHz, $CDCl_3$): δ =7.37 – 7.19 (m, 9H), 5.18 (dd, J = 8.9, 3.6 Hz, 1H), 3.04 (qd, J = 16.0, 6.2 Hz, 2H), 2.36 (s, 3H). ^{13}CNMR (100 MHz, $CDCl_3$): δ =197.82 , 142.15 , 139.99 , 134.40 , 130.09 , 128.55 , 127.87 ,125.63 , 123.48 , 70.70 , 51.94 , 21.30 .HRMS (ESI) calcd for $C_{16}H_{16}O_2S$ $[M + H]^+$ 207.0944, found 273.0955. ee of **9a** : 90%, determined by HPLC analysis, Daicel, Chiralpak AD-H column (25 cm × 4.6 mm × 5 μm), n-hexane/isopropanol = 95/5, 1 mL/min, 216 nm, 26°C, t_R (major) = 24.682 min, t_R (minor) = 28.651 min.

*(R)-S-p-tolyl 3-hydroxy-3-phenylpropanethioate(**9b**).*

White solid, mp 126-130°C. $[\alpha]^D20$ = + 18.24 (c 0.104, $CHCl_3$). Ref[7]. $[\alpha]^D20$ = + 15.4 (c 0.10, $CHCl_3$). ^{1}HNMR (400 MHz, $CDCl_3$): δ =7.43 – 7.28 (m, 7H), 6.95 (d, J = 8.8 Hz, 2H), 5.21 (dd, J = 8.8, 3.6 Hz, 1H), 3.83 (s, 3H), 3.06 (qd, J = 16.0, 6.2 Hz, 2H). ee of **9b** : 90%, determined by HPLC analysis, Daicel, Chiralpak AD-H column (25 cm × 4.6 mm × 5 μm), n-hexane/isopropanol = 95/5, 1 mL/min, 216 nm, 26°C, t_R (major) = 32.859 min, t_R (minor) = 37.942 min.

*(R)-S-(4-fluorophenyl) 3-hydroxy-3-phenylpropanethioate (**9c**).*

White solid, mp 96-98°C. $[\alpha]^D20$ = + 14.00 (c 0.10, $CHCl_3$). Ref[7]. $[\alpha]^D20$ = + 17.8 (c 0.10, $CHCl_3$). ^{1}HNMR (400 MHz, $CDCl_3$):δ= 7.44 – 7.27 (m，7H), 7.12 (t, J = 8.6 Hz, 2H), 5.22 (dd, J = 9.0, 3.5 Hz, 1H), 3.08 (ddd, J = 19.5, 15.9, 6.3 Hz, 2H). ee of **9c** : 72%, determined by HPLC analysis, Daicel, Chiralpak AD-H column (25 cm × 4.6 mm × 5 μm), n-hexane/isopropanol = 95/5, 1 mL/min, 216 nm, 26°C, t_R (major) = 17.445 min, t_R (minor) = 19.392 min.

*(R)-S-(2-chlorophenyl) 3-hydroxy-3-phenylpropanethioate (**9d**).*

$[\alpha]^D20$ = +22.92 (c 0.288, $CHCl_3$). ^{1}HNMR (400 MHz, $CDCl_3$): δ= 7.52 (t, J = 8.2 Hz, 2H), 7.36 (dd, J = 16.1, 8.5 Hz, 7H), 5.24 (d, J = 8.5 Hz, 1H), 3.11 (ddd, J = 18.5, 15.9, 5.8 Hz, 2H).^{13}CNMR (100 MHz, $CDCl_3$): δ =195.12 , 142.02 , 138.50 , 136.99 , 131.35 , 130.28 , 128.59 , 127.95 , 127.33 , 125.66 , 70.68 , 52.14 .HRMS (ESI) calcd for $C_{15}H_{13}ClO_2S$ $[M + H]^+$ 315.0213, found 315.0217. ee of **9d** : 81%, determined by HPLC analysis, Daicel, Chiralpak AD-H column (25 cm × 4.6 mm × 5 μm), n-hexane/isopropanol = 97/3, 1 mL/min, 216 nm, 30°C, t_R (major) = 42.497 min, t_R (minor) = 45.272 min.

*(R)-S-(4-chlorophenyl) 3-hydroxy-3-phenylpropanethioate (**9e**).*

$[\alpha]^D20$ = +18.18 (c 0.242, $CHCl_3$). ^{1}HNMR (400 MHz, $CDCl_3$): δ =7.37 (dt, J = 14.6, 9.2 Hz, 9H), 5.22 (dd, J = 8.9, 3.0 Hz, 1H), 3.08 (ddd, J = 19.2, 15.9, 6.1 Hz, 2H). ee of **9e** : 84%, determined by HPLC analysis, Daicel, Chiralpak AD-H column (25 cm × 4.6 mm × 5 μm), n-hexane/isopropanol = 98/2, 1 mL/min, 216 nm, 30°C, t_R (major) = 35.706 min, t_R (minor) = 41.740 min.

*(R)-S-p-tolyl 3-hydroxy-3-(3-methoxyphenyl)propanethioate (**9f**).*

White solid, mp 51-53°C. $[\alpha]^D20$ = + 22.03 (c 0.236, $CHCl_3$). ^{1}HNMR (400 MHz, $CDCl_3$): δ =7.28 (dt, J = 12.7, 8.1 Hz, 5H), 6.99 – 6.83 (m, 3H), 5.20 (dd, J = 8.9, 3.6 Hz, 1H), 3.83 (s, 3H), 3.07 (qd, J = 15.9, 6.3 Hz, 2H), 2.40 (s, 3H).^{13}CNMR (100 MHz, $CDCl_3$): δ= 197.70 , 159.76 , 143.85 , 139.93 , 134.36 , 130.05 , 129.55 , 123.48 , 117.85 , 113.46 , 111.01 , 70.57, 55.17 , 51.91 , 21.26 . HRMS (ESI) calcd for $C_{17}H_{18}O_3S$ $[M + H]^+$ 303.1049, found 303.1063. ee of **9f** : 92%, determined by HPLC analysis, Daicel, Chiralpak AD-H column (25 cm × 4.6 mm × 5 μm), n-hexane/isopropanol = 90/10, 1 mL/min, 216 nm, 30°C, t_R (major) = 17.508 min, t_R (minor) = 20.737 min.

*(R)-S-p-tolyl 3-hydroxy-3-(p-tolyl)propanethioate(**9g**).*

White solid, mp 89-90°C. $[\alpha]^{D}20$ = + 10.83 (c 0.24, $CHCl_3$). ^{1}HNMR (400 MHz, $CDCl_3$): δ =7.34 – 7.24 (m, 6H), 7.20 (d, J = 7.9 Hz, 2H), 5.20 (dd, J = 9.0, 3.5 Hz, 1H), 3.07 (ddd, J = 19.5, 15.9, 6.3 Hz, 2H), 2.41 (s, 3H), 2.38 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ =197.79 , 139.94 , 139.22 , 137.58 , 134.40 , 130.07 , 129.21 , 125.58 , 123.55 , 70.58 , 51.97 , 21.29 , 21.08 .HRMS (ESI) calcd for $C_{17}H_{18}O_2S$ $[M + H]^+$ 287.1100, found 287.1100. ee of **9g** : 94%, determined by HPLC analysis, Daicel, Chiralpak AD-H column (25 cm × 4.6 mm × 5 μm), n-hexane/isopropanol = 90/10, 1 mL/min, 216 nm, 30°C, t_R (major) = 12.425 min, t_R (minor) = 13.713 min.

*(R)-S-p-tolyl 3-hydroxy-3-(o-tolyl)propanethioate(**9h**).*

White solid, mp 43-45°C. $[\alpha]^{D}20$ = + 27.78 (c 0.180, $CHCl_3$). ^{1}HNMR (400 MHz, $CDCl_3$): δ= 7.47 (d, J = 7.4 Hz, 1H), 7.29 – 7.09 (m, 7H), 5.39 (dd, J = 8.9, 3.2 Hz, 1H), 3.06 – 2.87 (m, 2H), 2.35 (s, 3H), 2.31 (s, 3H).^{13}CNMR (100 MHz, $CDCl_3$): δ= 198.09 , 140.22, 140.09 , 134.48 , 134.19 , 130.54 , 130.18 , 127.72 , 126.49 , 125.30 , 123.57 , 67.46 , 50.82 , 21.38 , 19.02 . HRMS (ESI) calcd for $C_{17}H_{18}O_2S$ $[M + H]^+$ 287.1100, found 287.1100. ee of **9h** : 92%, determined by HPLC analysis, Daicel, Chiralpak AD-H column (25 cm × 4.6 mm × 5 μm), n-hexane/isopropanol = 90/10, 1 mL/min, 216 nm, 30°C, t_R (major) = 10.774 min, t_R (minor) = 12.807 min.

*(R)-S-p-tolyl 3-hydroxy-3-(3-phenoxyphenyl)propanethioate(**9i**).*

White solid, mp 60-62°C. $[\alpha]^{D}20$ = + 13.14 (c 0.236, $CHCl_3$). ^{1}HNMR (400 MHz, $CDCl_3$): δ= 7.41 – 7.22 (m, 7H), 7.10 (dt, J = 21.1, 7.5 Hz, 5H), 6.96 (dd, J = 8.1, 1.9 Hz, 1H), 5.19 (dd, J = 8.5, 3.8 Hz, 1H), 3.06 (qd, J = 16.0, 6.2 Hz, 2H), 2.40 (s, 3H).^{13}CNMR (100 MHz,$CDCl_3$): δ =197.73 , 157.50 , 156.95 , 144.25 , 140.01 , 134.38 , 130.09 , 129.88 , 129.74 , 123.39 , 123.34 , 120.37 , 118.92 , 118.11 , 116.06 , 70.36 , 51.77 , 21.29 . HRMS (ESI) calcd for $C_{22}H_{20}O_3S$ $[M + H]^+$ 365.1206, found 365.1206. ee of **9i** : 90%, determined by HPLC analysis, Daicel, Chiralpak AD-H column (25 cm × 4.6 mm × 5 μm), n-hexane/isopropanol = 90/10, 1 mL/min, 216 nm, 30°C, t_R (major) = 15.302 min, t_R (minor) = 18.69 min.

*(R)-S-p-tolyl 3-(4-(tert-butyl)phenyl)-3-hydroxypropanethioate (**9j**).*

White solid, mp 74-76°C. $[\alpha]^{D}20$ = + 9.37 (c 0.128, $CHCl_3$). ^{1}HNMR (400 MHz, $CDCl_3$): δ =7.39 (d, J = 8.3 Hz, 2H), 7.33 – 7.27 (m, 4H), 7.24 (d, J = 8.1 Hz, 2H), 5.19 (dd, J = 9.1, 3.3 Hz, 1H), 3.07 (ddd, J = 19.4, 16.0, 6.3 Hz, 2H), 2.39 (s, 3H), 1.32 (s, 9H).^{13}CNMR (100 MHz, $CDCl_3$): δ= 197.91 , 150.95 , 140.00 , 139.16 , 134.44 , 130.11 , 125.51 , 125.43 , 123.58 , 70.55 , 51.92 , 34.54 , 31.32 , 21.33 .HRMS (ESI) calcd for $C_{20}H_{24}O_2S$ $[M + H]^+$ 329.1570, found 329.1584. ee of **9j** : 92%, determined by HPLC analysis, Daicel, Chiralpak AD-H column (25 cm × 4.6 mm × 5 μm), n-hexane/isopropanol = 90/10, 1 mL/min, 216 nm, 30°C, t_R (major) = 9.242 min, t_R (minor) = 10.837 min.

*(R)-S-p-tolyl 3-hydroxy-3-(4-methoxyphenyl)propanethioate(**9k**).*

White solid, mp 89-90°C. $[\alpha]^{D}20$ = + 5.24 (c 0.102, CHCl3). ^{1}HNMR (400 MHz, $CDCl_3$): δ= 7.35 – 7.23 (m, 6H), 6.91 (d, J = 8.6 Hz, 2H), 5.17 (dd, J = 8.9, 3.5 Hz, 1H), 3.82 (s, 3H), 3.06 (ddd, J = 19.4, 15.9, 6.3 Hz, 2H), 2.40 (s, 3H).^{13}CNMR (100 MHz, $CDCl_3$): δ =197.74 , 159.24 , 139.93 , 134.38 , 130.06 , 126.93 , 123.54 , 113.91 , 70.34 , 55.23 , 51.96 , 21.28 .HRMS (ESI) calcd for $C_{17}H_{18}O_3S$ $[M + H]^+$ 303.1049, found 303.1043. ee of **9k** : 90%, determined by HPLC analysis, Daicel, Chiralpak AD-H column (25 cm × 4.6 mm × 5 μm), n-hexane/isopropanol = 90/10, 1 mL/min, 216 nm, 30°C, t_R (major) = 18.684 min, t_R (minor) = 21.201 min.

*(R)-S-p-tolyl 3-hydroxy-3-(naphthalen-1-yl)propanethioate (**9l**).*

White solid, mp 122-124°C. $[\alpha]^{D}20$ = + 8.93 (c 0.168, $CHCl_3$). ^{1}HNMR (400 MHz, $CDCl_3$): δ= 7.87 (d, J = 7.8 Hz, 4H), 7.57 – 7.46 (m, 3H), 7.29 (dd, J = 28.6, 7.9 Hz, 4H), 5.40 (dd, J = 8.8, 3.6 Hz, 1H), 3.17 (qd, J = 16.0, 6.2 Hz, 2H), 2.41 (s, 3H).^{13}CNMR (100 MHz, $CDCl_3$): δ 197.70 , 139.92 , 139.53 , 134.35 , 133.18 , 132.96 , 130.04 , 128.34 , 127.95 , 127.61 , 126.17 , 125.94 , 124.45 , 123.57 , 123.45 , 77.32 , 77.00, 76.68 , 70.76 , 51.86 , 21.25 .HRMS (ESI) calcd for $C_{20}H_{18}O_2S$ $[M + NH_4]^+$ 340.1366, found 340.1366. ee of **9l** : 90%, determined by HPLC analysis, Daicel, Chiralpak AD-H column (25 cm × 4.6 mm × 5 μm), n-hexane/isopropanol = 90/10, 1 mL/min, 216 nm, 30°C, t_R (major) = 17.873 min, t_R (minor) = 22.399 min.

*(R)-S-p-tolyl 3-(4-cyanophenyl)-3-hydroxypropanethioate (**9m**).*

White solid, mp 122-124°C. $[\alpha]^{D}20$ = + 15.84 (c 0.284, $CHCl_3$). ^{1}HNMR (400 MHz, $CDCl_3$): δ= 7.66 (d, J = 8.2 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H), 7.27 (q, J = 8.3 Hz, 4H), 5.33 – 5.20 (m, 1H), 3.11 – 2.98 (m, 2H), 2.40 (s, 3H). ^{13}CNMR (100 MHz, $CDCl_3$): δ =197.59 , 147.37 , 140.25 , 134.32 , 132.35 , 130.17 , 126.35 , 123.00 , 111.56 ,69.89 , 51.38 , 21.29 .HRMS (ESI) calcd for $C_{17}H_{15}NO_2S$ $[M + H]^+$ 298.0896, found 298.0896. ee of **9m** : 74%, determined by HPLC analysis, Daicel, Chiralpak OD-H column (25 cm × 4.6 mm × 5 μm), n-hexane/isopropanol = 90/10, 1 mL/min, 216 nm, 30°C, t_R (minor) = 11.343 min, t_R (major) = 13.651 min.

*(R)-S-p-tolyl 3-hydroxy-3-(4-nitrophenyl)propanethioate (**9n**).*

White solid, mp 113-114°C. $[\alpha]^{D}20$ = + 16.01 (c 0.606, $CHCl_3$). ^{1}HNMR (400 MHz, DMSO): δ =8.20 (d, J = 8.5 Hz, 2H), 7.67 (d, J = 8.5 Hz, 2H), 7.26 (s, 4H), 5.97 (d, J = 4.8 Hz, 1H), 5.19 (dd, J = 12.1, 5.4 Hz, 1H), 3.10 – 2.96 (m, 2H), 2.33 (s, 3H).^{13}CNMR (100 MHz, DMSO): δ 194.28 , 151.92 , 146.56 , 139.27 , 134.13 , 129.87 , 127.02 , 123.84 , 123.23 , 68.58 , 52.00 , 20.69 . HRMS (ESI) calcd for $C_{16}H_{15}NO_4S$ $[M + H]^+$ 318.0795, found 318.0803. ee of **9n** : 70%, determined by HPLC analysis, Daicel, Chiralpak OD-H column (25 cm × 4.6 mm × 5 μm), n-hexane/isopropanol = 90/10, 1 mL/min, 216 nm, 30°C, t_R (minor) = 33.757 min, t_R (major) = 41.5 min.

*(R)-S-p-tolyl 3-(4-fluorophenyl)-3-hydroxypropanethioate (**9o**).*

White solid, mp 107-108°C. $[\alpha]^{D}20$ = + 9.09 (c 0.154, $CHCl_3$). ^{1}HNMR (400 MHz, $CDCl_3$): δ= 7.40 – 7.22 (m, 6H), 7.06 (t, J = 8.7 Hz, 2H), 5.19 (dd, J = 8.7, 3.7 Hz, 1H), 3.05 (qd, J = 16.0, 6.3 Hz, 2H), 2.40 (s, 3H).^{13}CNMR (100 MHz, $CDCl_3$): δ =197.85 , 140.16 , 138.04 , 138.01 , 134.46 , 130.21 , 127.51 , 127.4, 123.43 , 115.57 , 115.36 , 70.17 , 51.98 , 21.38 . HRMS (ESI) calcd for $C_{16}H_{15}FO_2S$[M + H]$^+$ 291.0850, found 291.0850. ee of **9o** : 90%, determined by HPLC analysis, Daicel, Chiralpak AD-H column (25 cm × 4.6 mm × 5 μm), n-hexane/isopropanol = 95/5, 1 mL/min, 216 nm, 30°C, t_R (major) = 23.314 min, t_R (minor) = 26.357 min.

*(R)-S-p-tolyl 3-(4-chlorophenyl)-3-hydroxypropanethioate (**9p**).*

White solid, mp 128-130°C. $[\alpha]^{D}20$ = + 12.28 (c 0.228, $CHCl_3$). ^{1}HNMR (400 MHz, DMSO): δ =7.40 (s, 4H), 7.26 (s, 4H), 5.73 (d, J = 4.6 Hz, 1H), 5.10 – 4.98 (m, 1H), 3.04 – 2.92 (m, 2H), 2.34 (s, 3H).^{13}CNMR (100 MHz, DMSO): δ= 194.47, 143.17 , 139.20 , 134.12 , 131.57 , 129.84 , 127.97 , 127.65 , 123.95 , 68.72 , 52.42 , 20.70 .HRMS (ESI) calcd for $C_{16}H_{15}ClO_2S$[M + H]$^+$ 307.0554, found 307.0554. ee of **9p** : 90%, determined by

HPLC analysis, Daicel, Chiralpak AD-H column (25 cm × 4.6 mm × 5 μm), n-hexane/isopropanol = 95/5, 1 mL/min, 216 nm, 30°C, t_R (major) = 23.989 min, t_R (minor) = 27.243 min.

*(R)-S-p-tolyl 3-(4-bromophenyl)-3-hydroxypropanethioate (**9q**).*

White solid, mp 144-145°C. $[\alpha]^D20$ = + 12.78 (c 0.352, $CHCl_3$).

^{1}HNMR (400 MHz, DMSO): δ =7.59-7.15 (m, 8H), 5.73 (s, 1H), 5.03 (s, 1H), 2.98 (s, 2H), 2.33 (s, 3H).^{13}CNMR (100 MHz, DMSO): δ =194.45 , 143.59 , 139.19 , 134.12 , 130.89 , 129.84 , 128.01 , 123.94 , 120.08 , 68.76 , 52.38 , 20.71 . HRMS (ESI) calcd for $C_{16}H_{15}BrO_2S$ $[M + NH_4]^+$ 368.0314, found 368.0312. ee of **9q** : 88%, determined by HPLC analysis, Daicel, Chiralpak OD-H column (25 cm × 4.6 mm × 5 μm), n-hexane/isopropanol = 90/10, 1 mL/min, 216 nm, 30°C, t_R (minor) = 17.811 min, t_R (major) = 20.363 min.

*(R)-S-p-tolyl 3-(2-bromophenyl)-3-hydroxypropanethioate (**9r**).*

White solid, mp 110-112°C. $[\alpha]^D20$ = + 61.90 (c 0.126, $CHCl_3$). ^{1}HNMR (400 MHz, $CDCl_3$): δ =7.59 (dd, J = 37.2, 7.8 Hz, 2H), 7.40 – 7.13 (m, 6H), 5.52 (d, J = 9.2 Hz, 1H), 3.27-3.10 (m, 2H), 2.91 (dd, J = 16.1, 9.4 Hz, 1H), 2.40 (s, 3H).^{13}CNMR (100 MHz, $CDCl_3$): δ =198.04 , 141.02 , 140.02 , 134.41 , 132.64 , 130.10 , 129.13 , 127.80 , 127.33 , 123.38 , 121.27 , 69.69 , 49.95 , 21.30 . HRMS (ESI) calcd for $C_{16}H_{15}BrO_2S$ $[M + NH_4]^+$ 368.0314, found 368.0320. ee of **9r** : 70%, determined by HPLC analysis, Daicel, Chiralpak OD-H column (25 cm × 4.6 mm × 5 μm), n-hexane/isopropanol = 90/10, 1 mL/min, 216 nm, 30°C, t_R (minor) = 10.593 min, t_R (major) = 12.079 min.

*(R)-S-p-tolyl 3-(3-bromophenyl)-3-hydroxypropanethioate(**9s**).*

White solid, mp 84-85°C. $[\alpha]^D20$ = + 15.71 (c 0.49, $CHCl_3$). ^{1}HNMR (400 MHz, $CDCl_3$): δ= 7.56 (s, 1H), 7.44 (d, J = 7.7 Hz, 1H), 7.33 – 7.21 (m, 6H), 5.17 (dd, J = 8.3, 4.0 Hz, 1H), 3.13 (s, 1H), 3.10 – 2.97 (m, 2H), 2.40 (s, 3H).^{13}CNMR (100 MHz, $CDCl_3$): δ =197.69 , 144.44 , 140.08 , 134.37 , 130.87 , 130.11 , 128.78 , 124.23 , 123.24 , 122.64 , 69.94 , 51.67 , 21.29 . HRMS (ESI) calcd for $C_{16}H_{15}BrO_2S$ $[M + NH_4]^+$ 368.0314, found 368.0305. ee of **9s** : 86%, determined by HPLC analysis, Daicel, Chiralpak OD-H column (25 cm × 4.6 mm × 5 μm), n-hexane/isopropanol = 90/10, 1 mL/min, 216 nm, 30°C, t_R (minor) = 16.301 min, t_R (major) = 24.209 min.

General procedure for preparation of (+)-dapoxetine

*(R)-1-phenylpropane-1,3-diol(**15**).*

A mixture of KBH_4 (3.24g, 60mmol) and LiCl (2.54g, 60mmol) was stirred in boiling anhydrous THF under N_2 for 2h. The reaction mixture was cooled to room temperature, and a solution of 9a (5.44g, 20mmol) in THF was added dropwise at 0 °C over 1 h. Striing was continued at room temperature for an additioal 3h. Then water was added and stirred for 1h, extracted with DCM, the combined organic phase was washed with water, dried with Na_2SO_4 and evaporated in vacuo. The crude product was purified by flash chromatography (Petroleum Ether/EtOAc = 10:1 to 4:1) to give (**15**, 2.58g, 85%) as a colorless oil. $[\alpha]^D20$ = + 62.42 (c 0.564, $CHCl_3$). Ref[11a]. $[\alpha]^D20$ = + 59.1 (c 1.00, $CHCl_3$). ^{1}HNMR (400 MHz, $CDCl_3$): δ =7.39 – 7.22 (m，5H), 4.84 (dd, J = 8.5, 4.0 Hz， 1H), 3.85 (s, 2H), 3.78 – 3.62 (m, 2H), 1.98 – 1.77 (m, 2H).

*(R)-3-hydroxy-3-phenylpropyl 4-methylbenzenesulfonate (**16**).*

To a stirring solution of **15** (1.58g, 10mmol) in DCM at 0 °C was added triethylamine (2.1g, 20mmol) and a solution of tosyl chloride (2.18g, 11mmol) in DCM. The reaction mixture was allowed to stried at r.t. for 24h. It was then extracted with ethyl acetate, washed with brine (20 mL), dried with Na_2SO_4 and evaporated in vacuo. The crude product was purified by flash chromatography (Petroleum Ether/EtOAc = 10:1 to 4:1) to give (**16**, 2.95g, 93%) as a colorless oil. $[\alpha]^D20$ = + 17.60 (c 1, $CHCl_3$). Ref[11b]. $[\alpha]^D24$ = + 12.2 (c 5.53, $CHCl_3$).^{1}HNMR (400 MHz, $CDCl_3$): δ =7.77 (d, J = 8.2 Hz, 2H), 7.35 – 7.23 (m, 7H), 4.78 (t, J = 6.7 Hz, 1H), 4.27 (dt, J = 9.9, 6.7 Hz, 1H), 4.08 – 4.01 (m, 1H), 2.44 (s, 3H), 2.01 (dd, J = 12.7, 6.1 Hz, 2H).

*(R)-3-(naphthalen-1-yloxy)-1-phenylpropan-1-ol (**17**).*

A mixture of **16** (2.95g, 9.6mmol), 1-naphthol(1.53g, 10.6mmol) and K_2CO_3 (4.00g, 28.9mmol) in acetone was refluxed for 5h. The reaction mixture was cooled to room temperature and acetone was evaporated. Then water (20 mL) was added and extracted with ethyl acetate (20 mL × 3), washed with brine, dried with Na_2SO_4 and evaporated in vacuo. The crude product was purified by flash chromatography (Petroleum Ether/EtOAc = 10:1 to 4:1) to give **17** as a white solid (2.55g, 95%) .

The optical purity of **17** was further increased to 99% ee by twice recrystallization from dichloromethane and n-hexane. $[\alpha]^D20$ = -24.9 (c 1, $CHCl_3$). Ref[11c]. $[\alpha]^D20$ = -30.5 (c 0.5, $CHCl_3$).^{1}HNMR (400 MHz, $CDCl_3$):δ =8.34 – 8.26 (m, 1H), 7.89 – 7.80 (m, 1H), 7.58 – 7.29 (m, 9H), 6.82 (d, J = 7.5 Hz, 1H), 5.13 (dd, J = 7.8, 5.2 Hz, 1H), 4.34 (dd, J = 13.7, 7.7 Hz, 1H), 4.18 (dd, J = 11.4, 6.8 Hz, 1H), 2.55 (s, 1H), 2.47 – 2.29 (m, 2H). ee of **17** : >99%, determined by HPLC analysis, Daicel, Chiralpak OD-H column (25 cm × 4.6 mm × 5 μm), n-hexane/isopropanol = 92/8, 1 mL/min, 210 nm, 30°C, t_R (major) = 15.42min.

*(S)-3-(naphthalen-1-yloxy)-1-phenylpropan-1-amine (**18**).*

To a solution of alcohol 17 (1 g, 3.6 mmol) in DCM (10 mL) was added triethylamine (0.91 g, 9 mol) and DMAP (4-dimethyl-aminopyridine, 0.01g, 0.08mmol) at 0 °C. Methanesulfonyl chloride (1.03 g, 9 mmol) was added dropwise to the reaction mixture at 0 °C over 20 min. The mixture was stirred at 0 °C for 0.5 h. The reaction mixture was washed with saturated $NaHCO_3$ aqueous (3 x 5 mL), dired over Na_2SO_4 and concentrated under reduced pressure to give orange oil. The crude product was used in the next step without any further purification. The orange oil was dissolved in DMF (10 mL), sodium azide (0.48 g, 7.2 mmol) was added to the reaction mixture in batches at room temperature. The reaction mixture was stirred at 50°C for 16 h. 5 mL H_2O was added to quench the reaction, and the mixture was extracted with CH_2Cl_2 (20 mL). The organic phase was washed by H_2O (5 x 10 mL), brine, dried over Na_2SO_4 and concentrated under reduced pressure to give orange oil. The crude product was used in the next step without any further purification. The residue was dissolved in the mixture of MeOH/i-PrOH/THF 3:5:8 (16 mL). To the solution was added triethylamine (0.73 g, 7.2 mmol) at room temperature, followed by (0.03g, 0.36mmol) 1,3-propanedithiol. The reaction mixture was cooled to 0 °C, (1.36 g, 36 mol) sodium borohydride was added to the reaction mixture at 0 °C in batches. After addition, the reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched by water (10 mL), the solvent was removed under reduced pressure. The residue was dissolved by CH_2Cl_2 (30 mL), the organic phase was washed with H_2O (3 x 10 mL), brine, dried over Na_2SO_4 and concentrated under reduced pressure to give yellow oil. The crude product was purified by flash chromatography using PE/EA 2:1 to give 18 as colorless oil (0.52 g, yield 52%).$[\alpha]^D20$ = + 53.46 (c 1.62, $CHCl_3$). Ref[11d]. $[\alpha]^D22$ = 8.2 (c 0.3, $CHCl_3$).^{1}HNMR (400 MHz, $CDCl_3$): δ = 8.27 (d, J = 4.7 Hz, 1H), 7.79 (s, 1H), 7.37 (ddd, J = 42.9, 29.5, 4.5 Hz, 9H), 6.72 (d,

J = 6.7 Hz, 1H), 4.32 (s, 1H), 4.19 (s, 1H), 4.07 (s, 1H), 2.27 (dd, J = 17.9, 5.8 Hz, 2H).

ee of **18** : 92%, determined by HPLC analysis, Daicel, Chiralpak OD-H column (25 cm × 4.6 mm × 5 μm), n-hexane/isopropanol = 80/20 with 0.1% Et_3N, 0.8 mL/min, 254 nm, 35°C, t_R (minor) = 13.589 min, t_R (major) = 17.649min.

*(+)-dapoxetine(**19**).*

A mixture of 18 (0.5g, 1.8mmol), 37%-40% formaldehyde aqueous solution (0.59ml, 7.2mmol) and formic acid (0.55ml, 14.4mmol) was refluxed for 12h. The reaction mixture was cooled to room temperature and adjusted to pH 8-9 with N N NaOH solution. Then extracted with DCM (10 mL × 3), dried with Na_2SO_4 and evaporated in vacuo. The crude product was purified by flash chromatography (Petroleum Ether/EtOAc = 10:1 to 4:1) to give (19, 0.38g, 68%) . $[\alpha]^D20$ = + 69.2 (c 1, $CHCl_3$). Ref[11a]. $[\alpha]^D20$ = + 65.9 (c 1.00, $CHCl_3$). ^{1}HNMR (400 MHz, $CDCl_3$): δ =8.00 (d, J = 7.2 Hz, 1H), 7.81 – 7.48 (m, 3H), 7.15-7.37 (m, 5H), 6.89 (ddd, J = 25.2, 12.8, 4.6 Hz, 3H), 4.81 – 4.50 (m, 1H), 4.06 (dd, J = 4.5, 3.3 Hz, 1H), 3.27 (d, J = 6.8 Hz, 2H), 2.69-2.22 (m, 1H), 1.58 (s, 6H).

ee of **19** : 92%, determined by HPLC analysis, Daicel, Chiralpak OD-H column (25 cm × 4.6 mm × 5 μm), n-hexane/isopropanol = 99/1 with 0.1% Et_3N, 1 mL/min, 254 nm, 35°C, t_R (minor) = 7.968 min, t_R (major) = 8.758min.

References and notes

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