

Supporting Information for:

Synthesis and Evaluation of Pyridine-Derived Bedaquiline Analogues Containing Modifications at the A-Ring Subunit

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Table S1. Preliminary Screening of Diastereomeric Pairs of 2-Methoxy-5-arylpyridine Bedaquiline Analogues

diastereoisomer A diastereoisomer B

R	<i>M.tb</i> H37Rv % inhibition at 10 μ M ^{a,b}	
	Diastereomer A (<i>R,R-S,S</i>)	Diastereomer B (<i>R,S-S,R</i>)
H (10)	55	100
2,3-benzofused (11)	60	100
4-F (17)	0	100
2-CN (18)	20	90
2-OCF ₃ (19)	65	100
4-CF ₃ (21)	6	100
3-CF ₃ -4-Cl (28)	25	100
3-Me-4-F (30)	7	100

^a Diastereoisomers were separated via preparative HPLC. ^b % inhibition of growth of *M.tb* strain H37Rv, as determined by the resazurin microtitre assay (REMA).

Table S2. Preliminary Screening of Diastereomeric Pairs of 2,6-Dimethoxy-5-arylpyridine Bedaquiline Analogues

diastereoisomer A diastereoisomer B

R	<i>M.tb</i> H37Rv % inhibition at 10 μ M ^{a,b}	
	Diastereomer A (<i>R,R-S,S</i>)	Diastereomer B (<i>R,S-S,R</i>)
OMe (37)	6	100
OCF ₃ (38)	5	100
Cl (40)	5	100

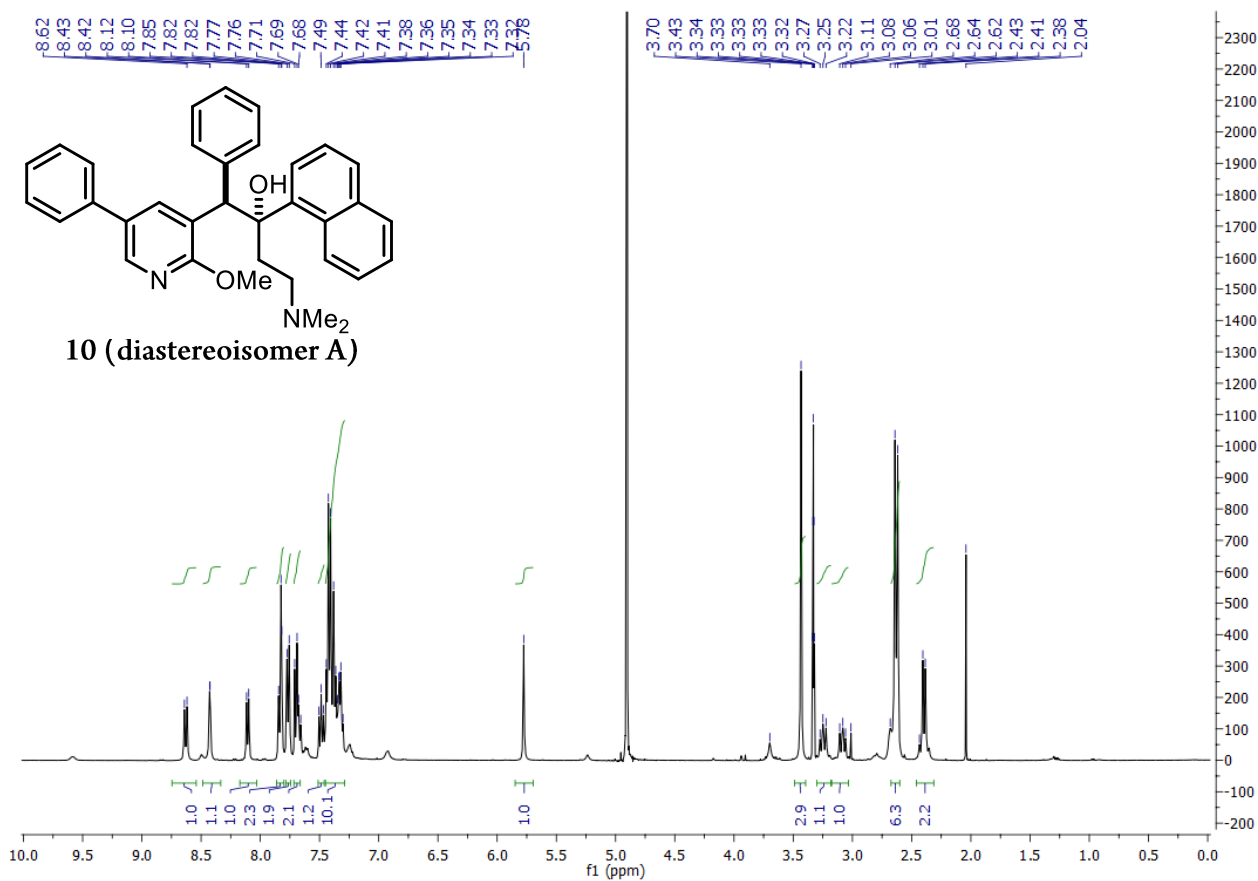
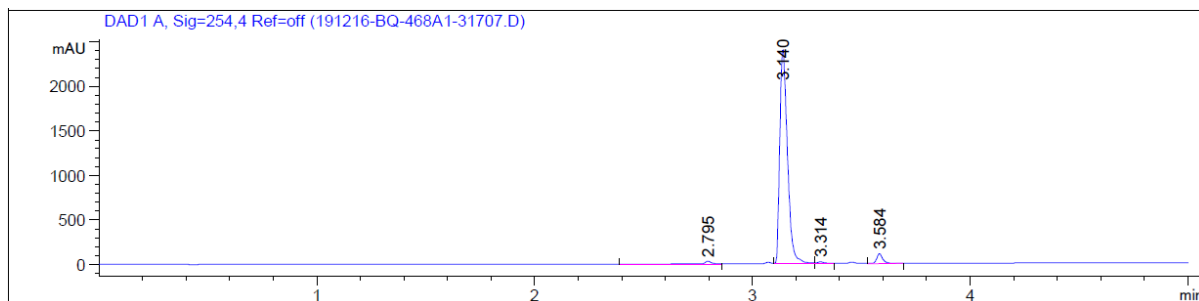
^a Diastereoisomers were separated via preparative HPLC. ^b % inhibition of growth of *M.tb* strain H37Rv, as determined by the resazurin microtitre assay (REMA).

4-(dimethylamino)-1-(2-methoxy-5-phenylpyridin-3-yl)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (10)

Diastereoisomer A:

LCMS (m/z): 503.0

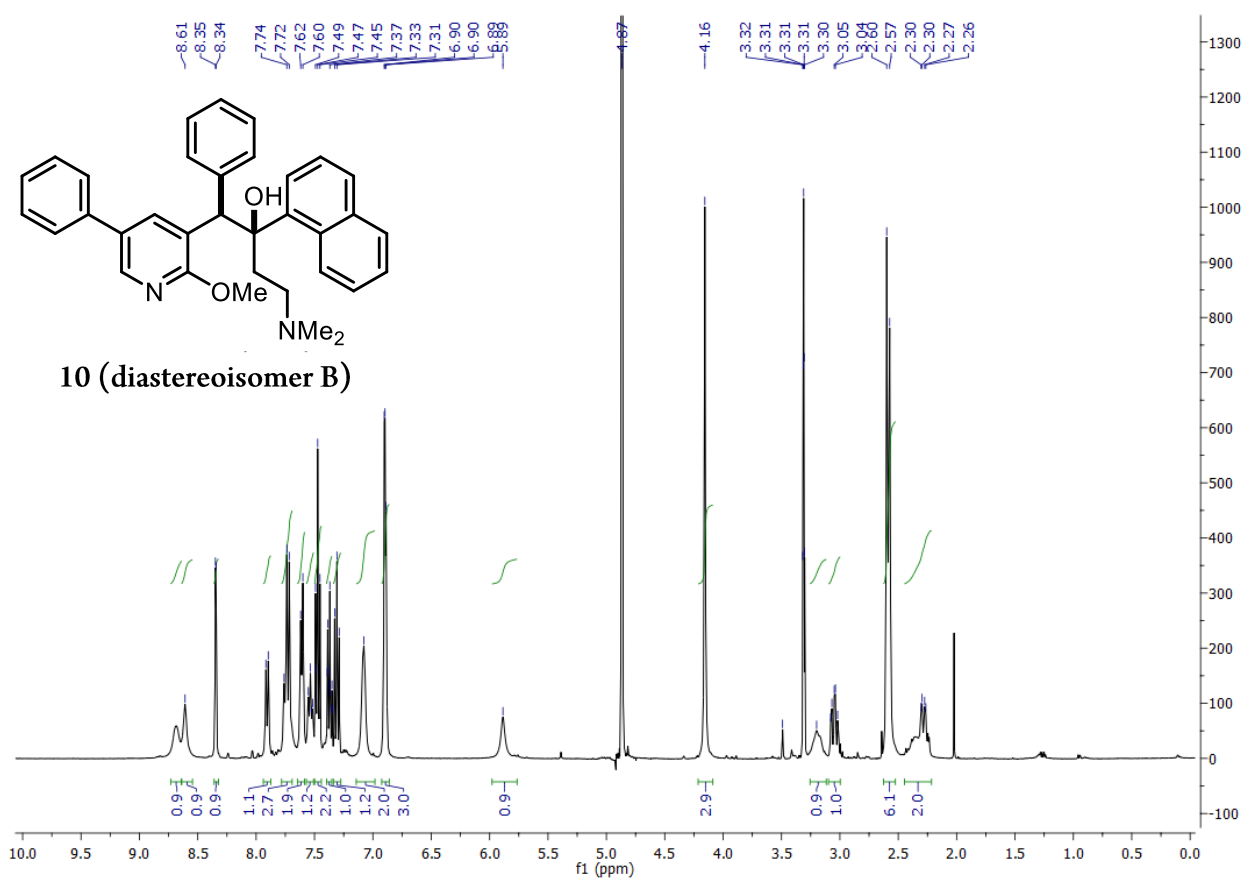
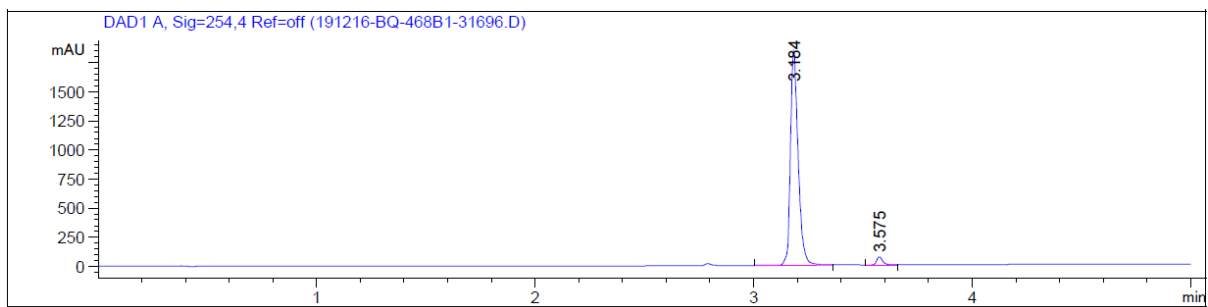
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Diastereoisomer B:

LCMS (m/z): 503.0

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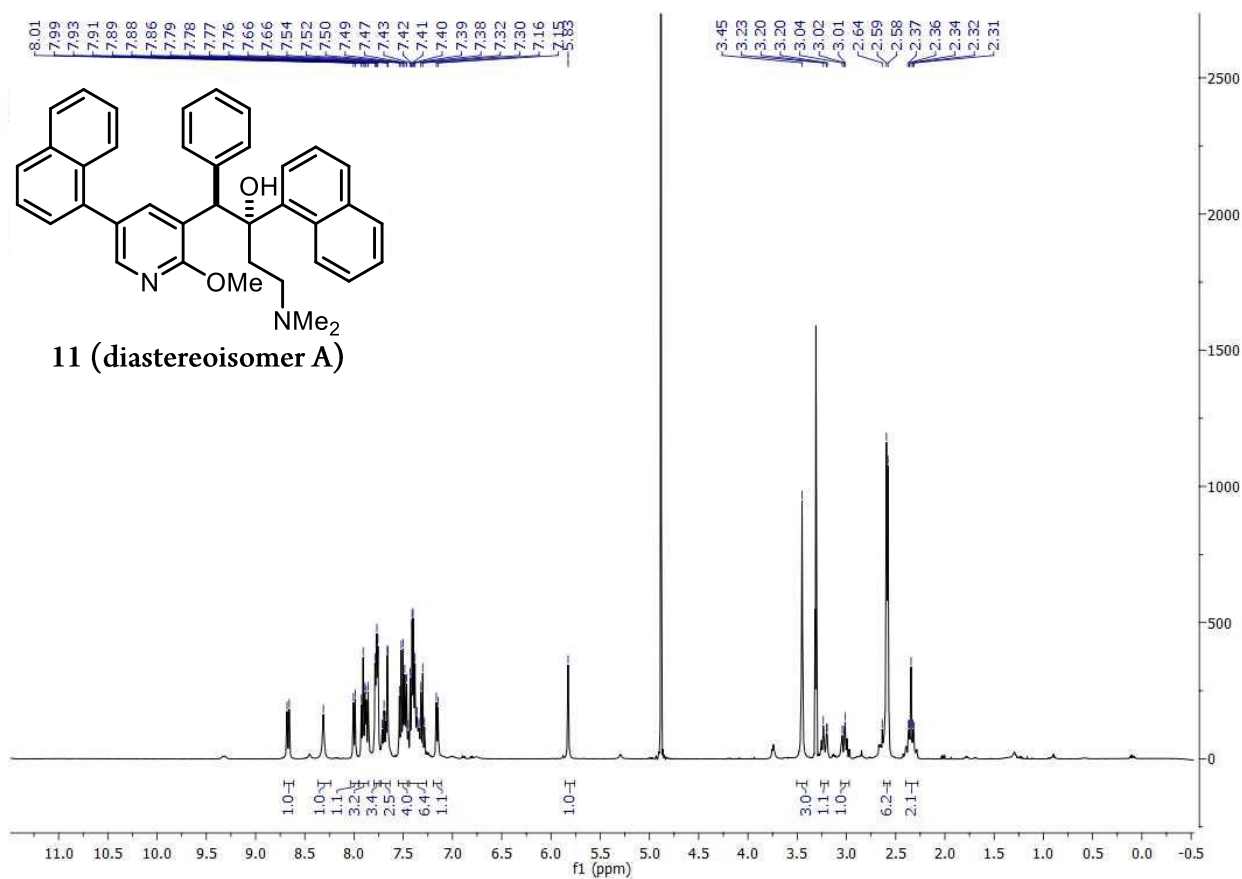
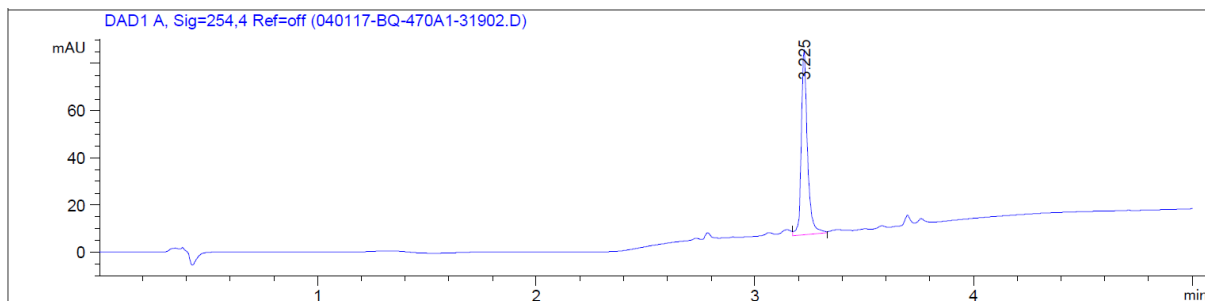


4-(dimethylamino)-1-(2-methoxy-5-(naphthalen-1-yl)pyridin-3-yl)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol
(11)

Diastereoisomer A:

LCMS (m/z): 553.0

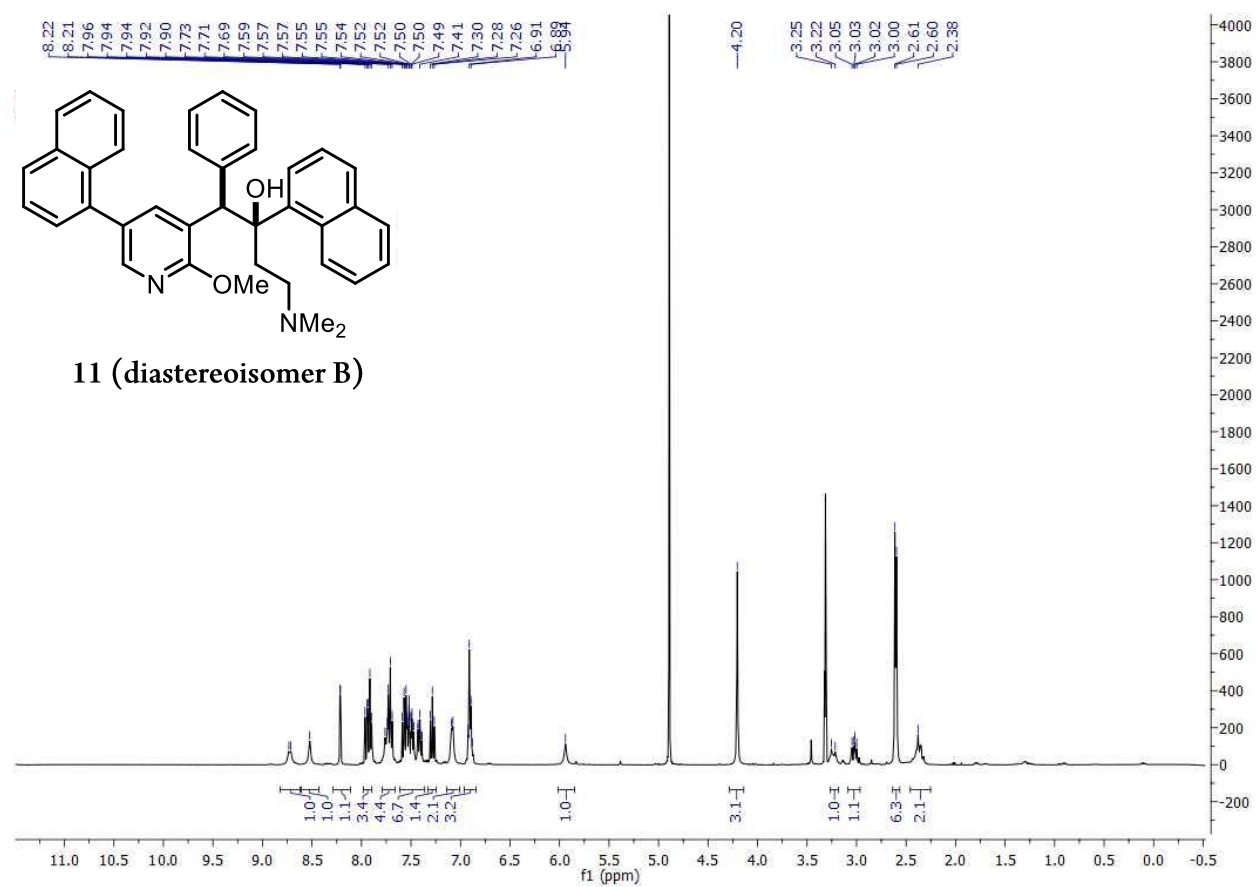
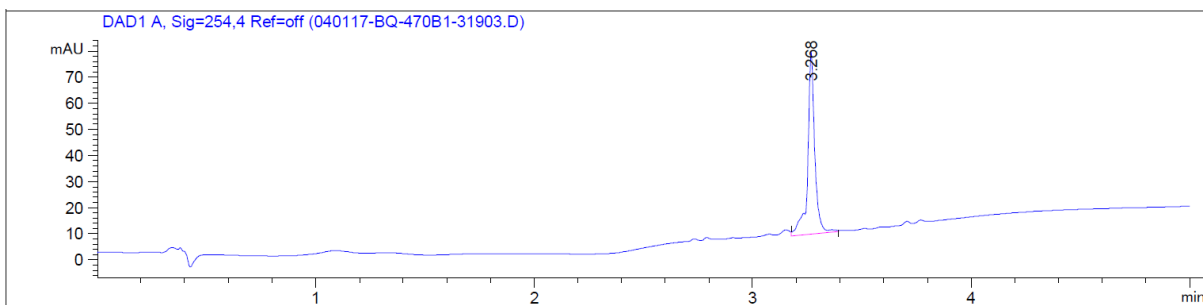
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Diastereoisomer B:

LCMS (m/z): 553.0

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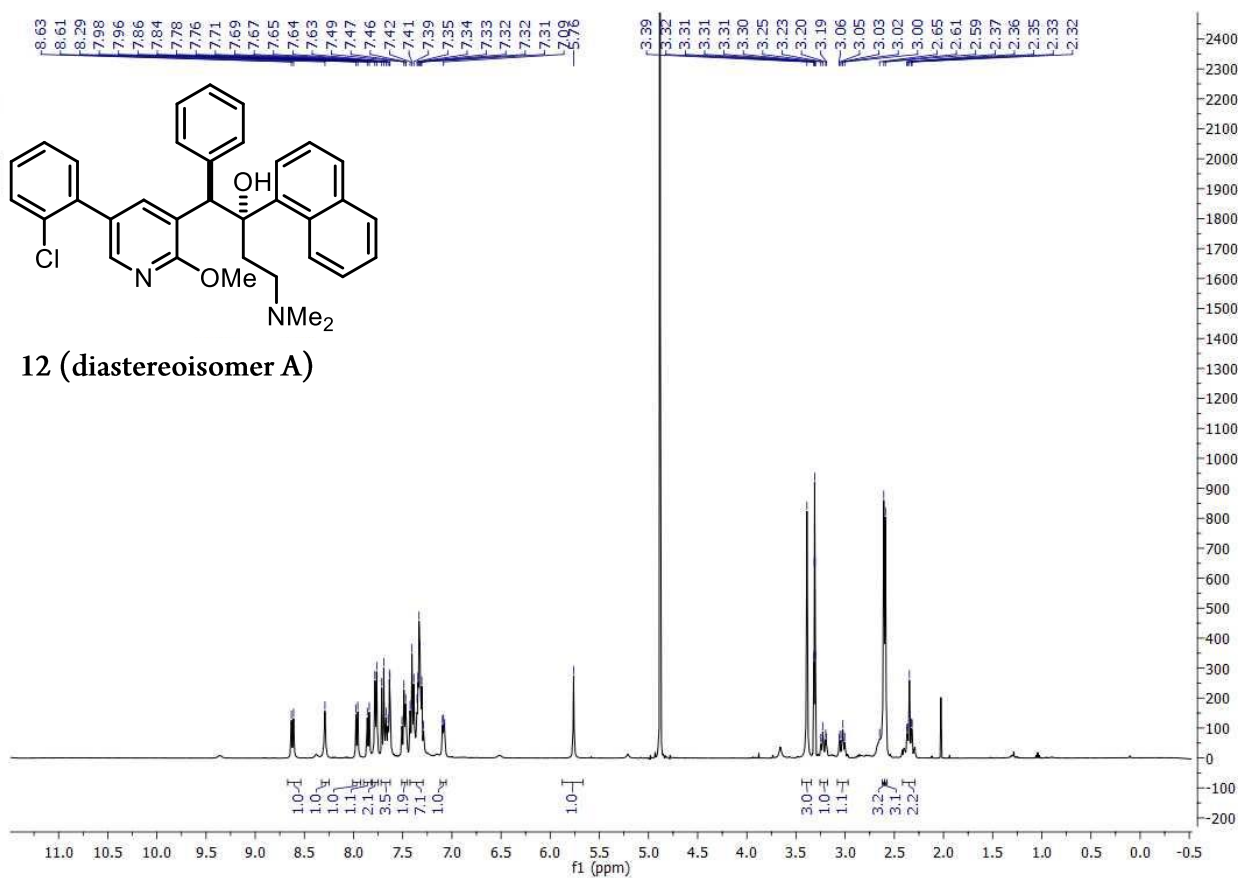
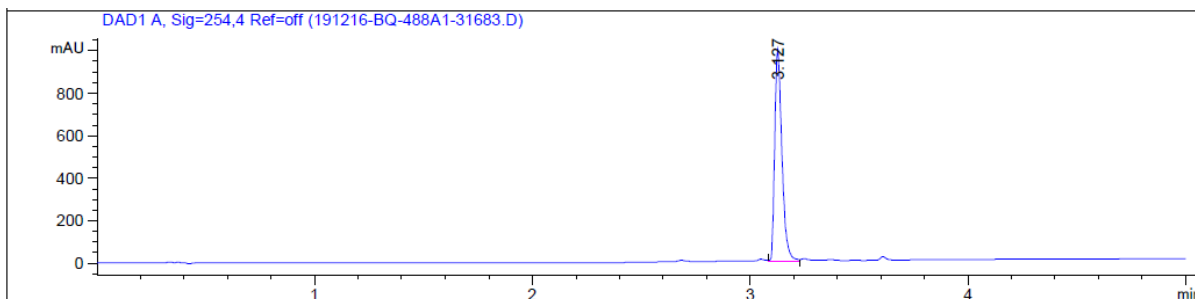


1-(5-(2-chlorophenyl)-2-methoxypyridin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol
(12)

Diastereoisomer A:

LCMS (m/z): 536.9

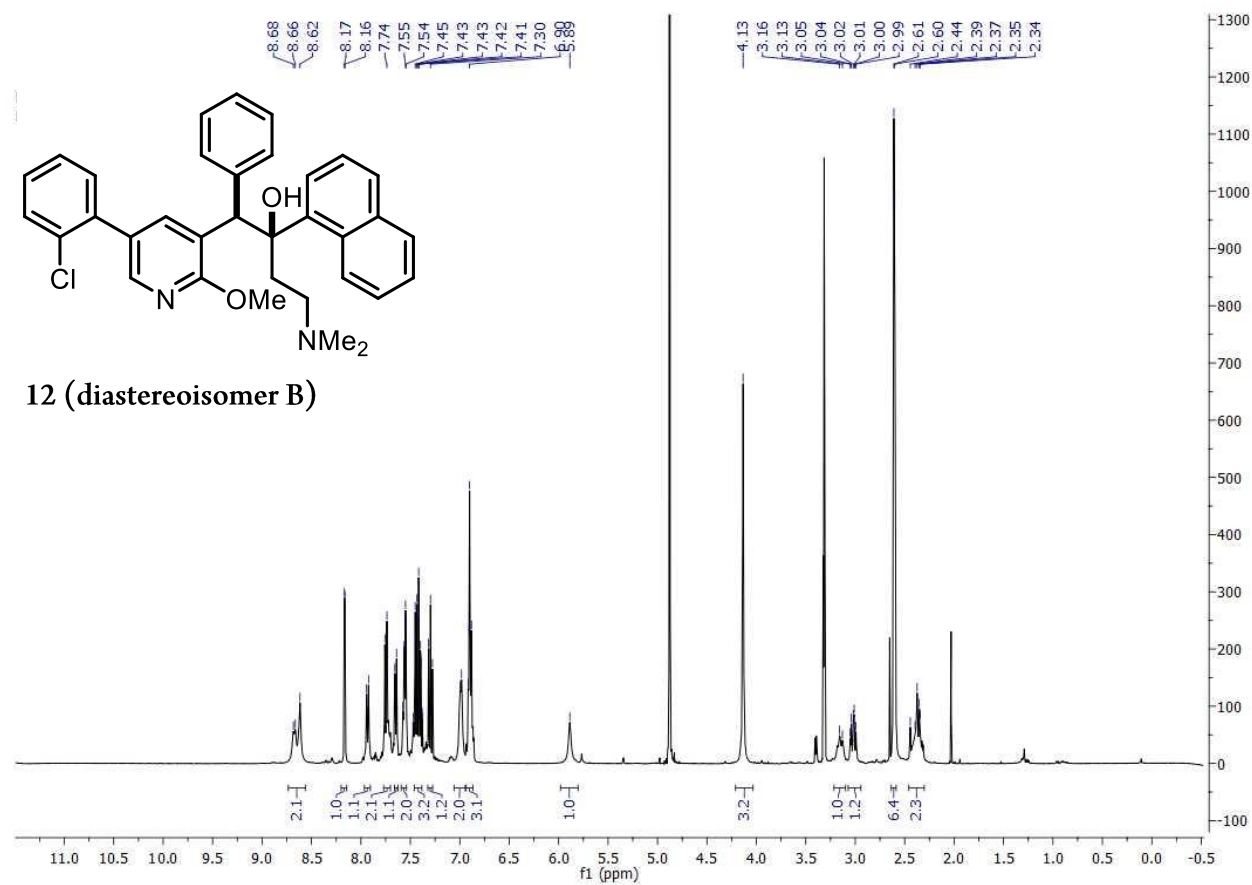
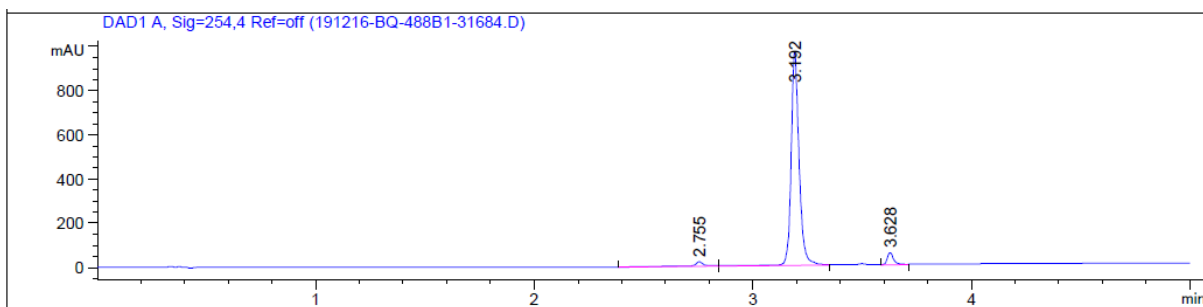
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Diastereoisomer B:

LCMS (m/z): 536.9

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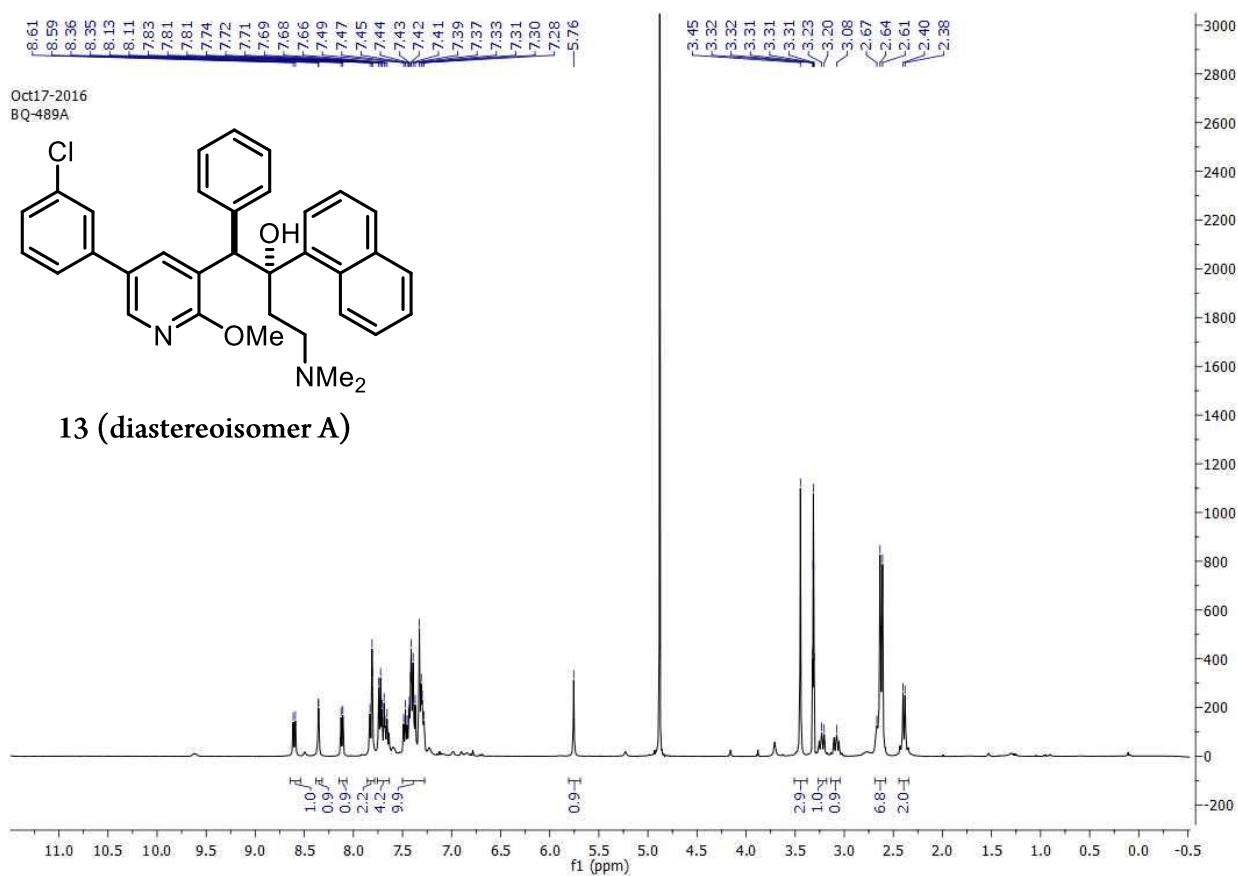
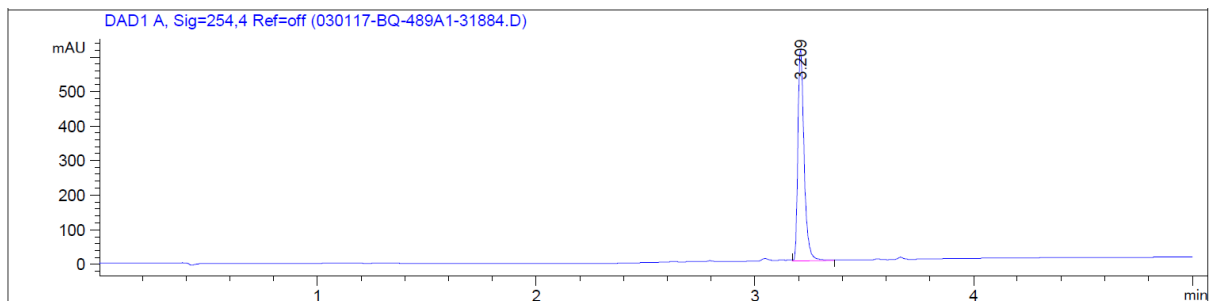


4-(dimethylamino)-1-(5-(3-chlorophenyl)-2-methoxypyridin-3-yl)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol
(13)

Diastereoisomer A:

LCMS (m/z): 536.9

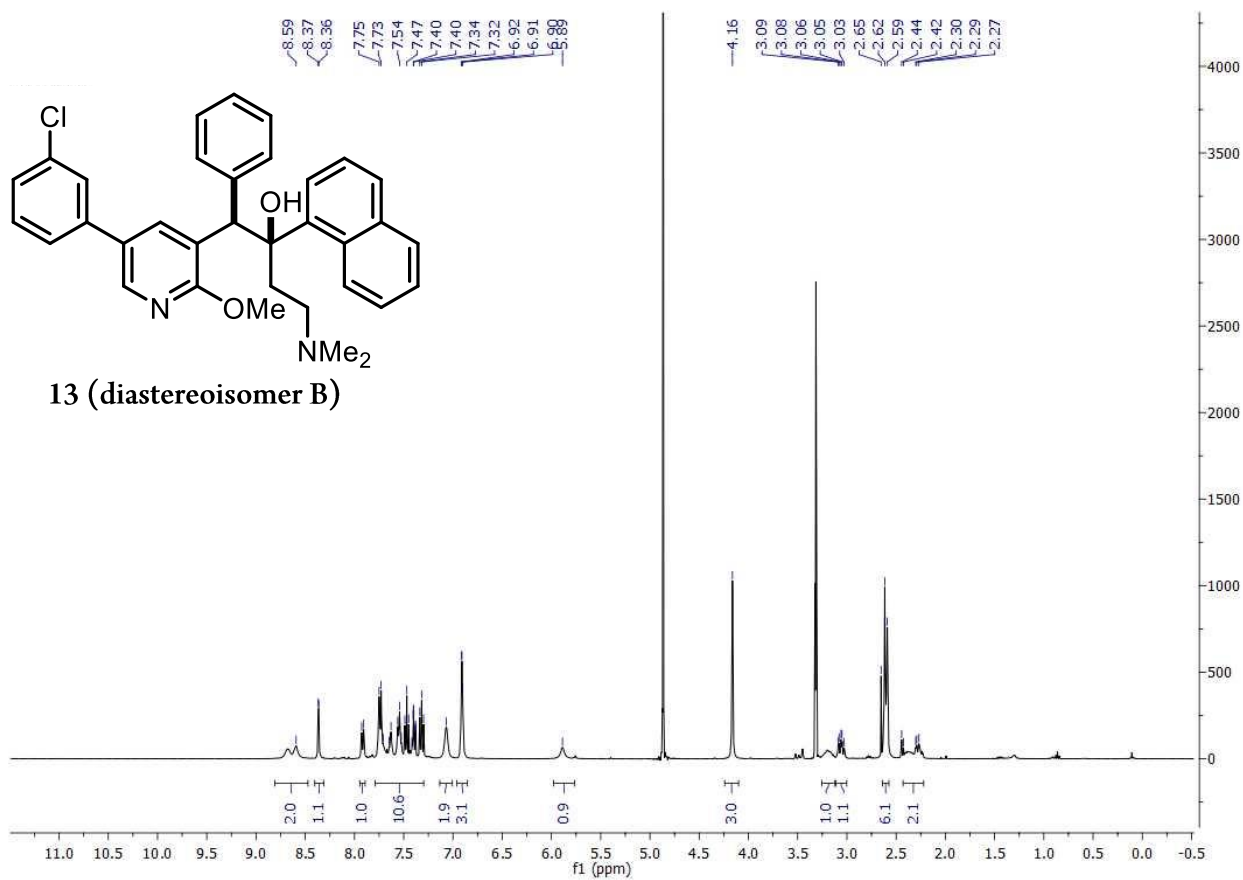
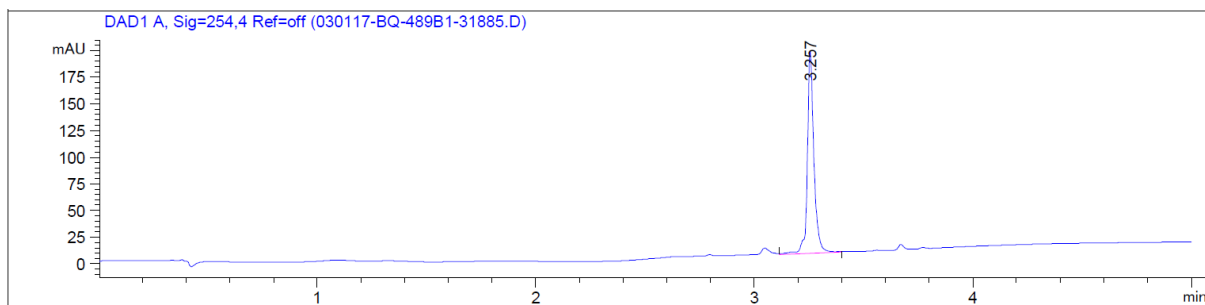
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Diastereoisomer B:

LCMS (m/z): 536.9

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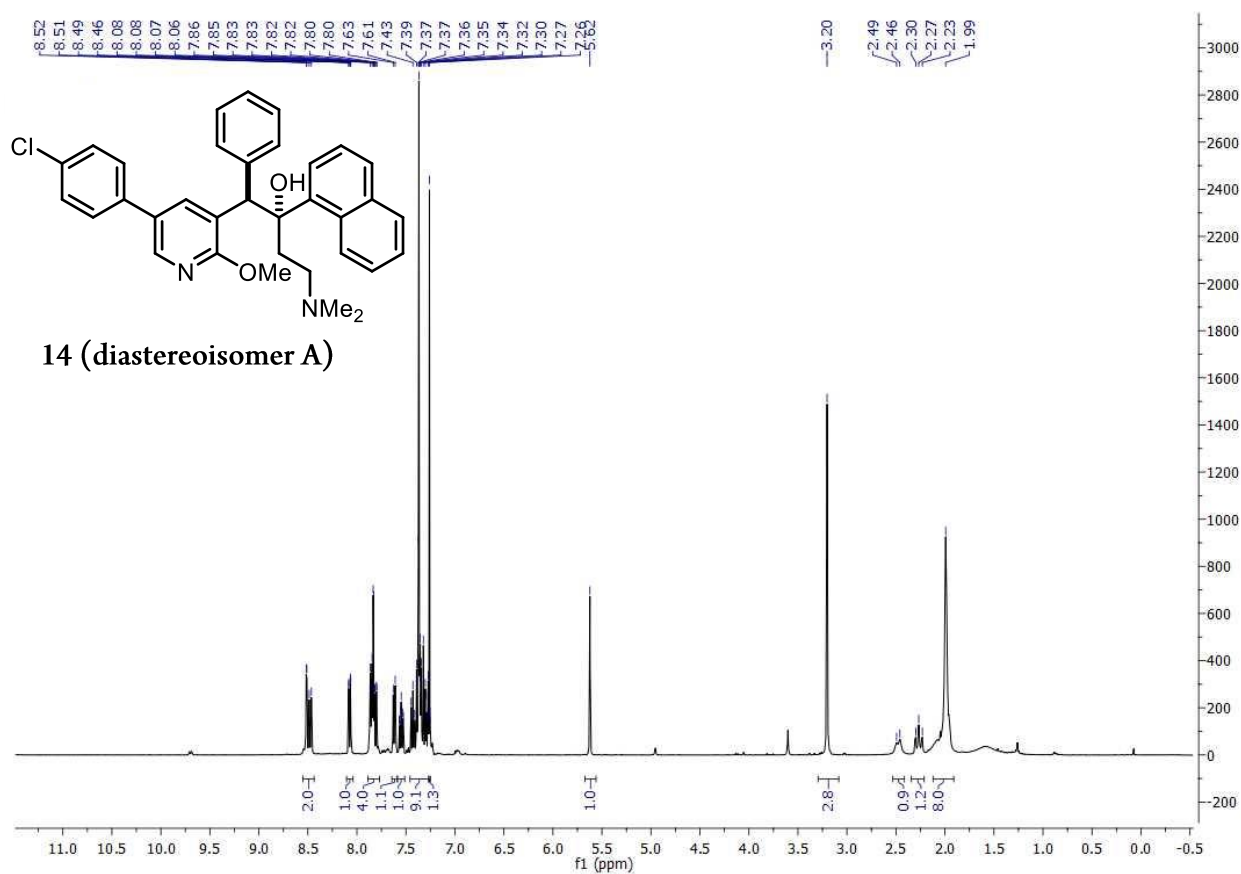
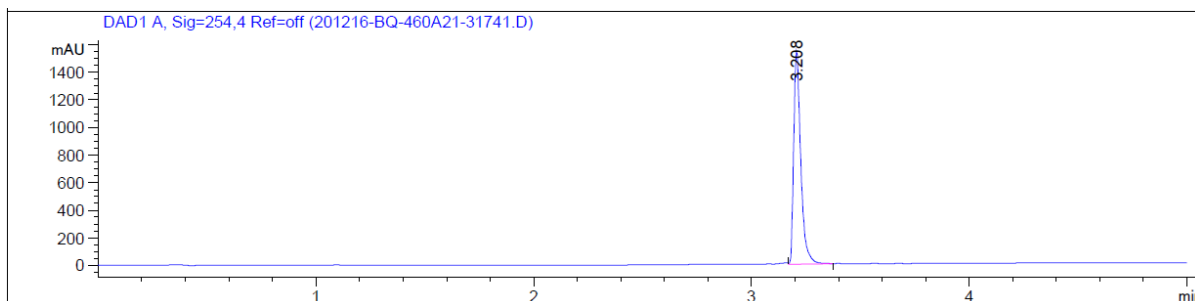


1-(5-(4-chlorophenyl)-2-methoxypyridin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol
(14)

Diastereoisomer A:

LCMS (m/z): 536.9

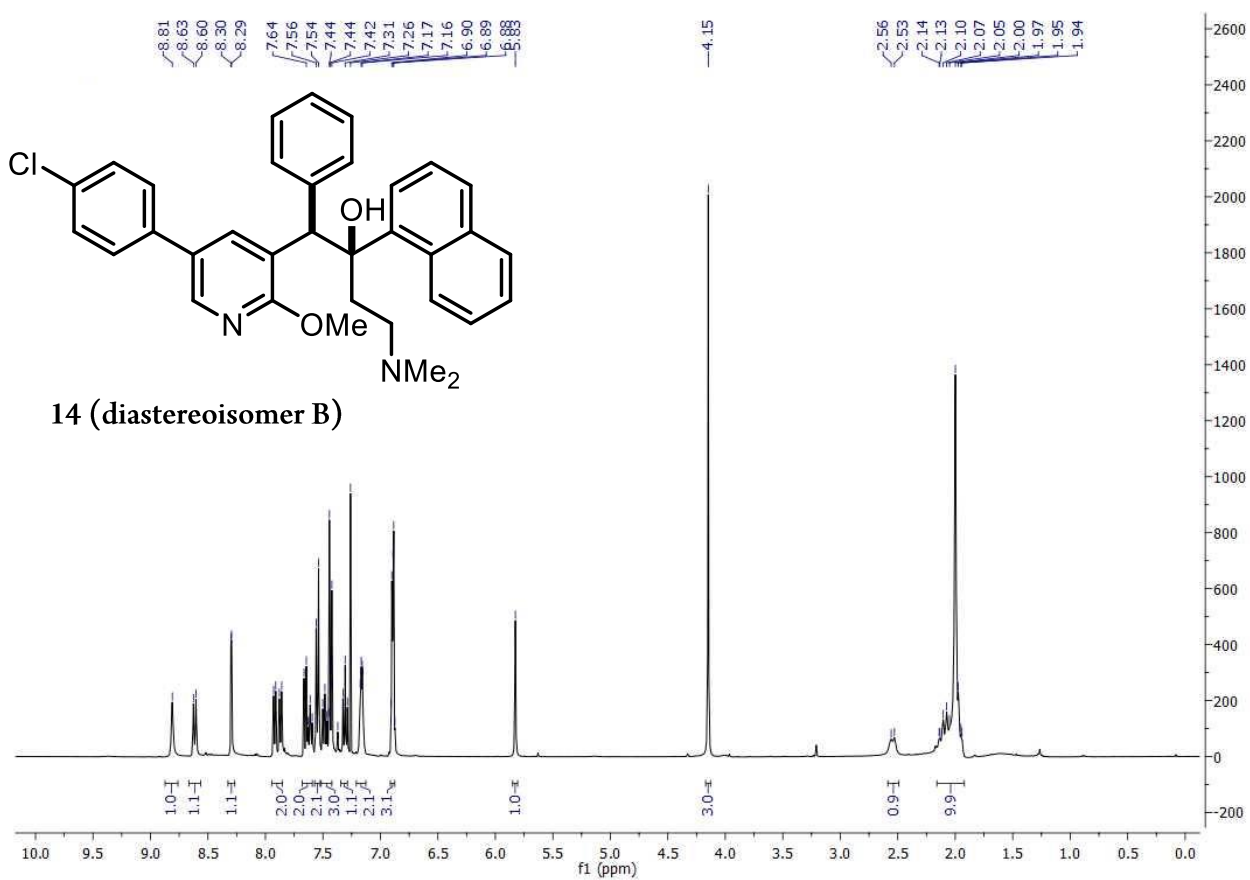
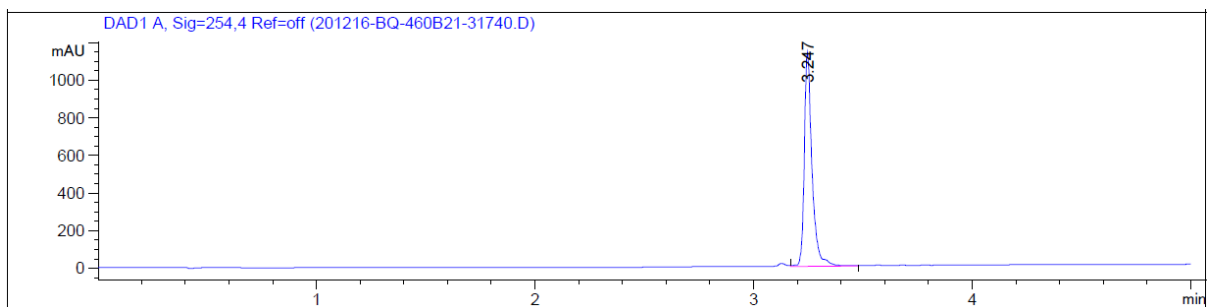
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Diastereoisomer B:

LCMS (m/z): 536.9

HPLC Trace:

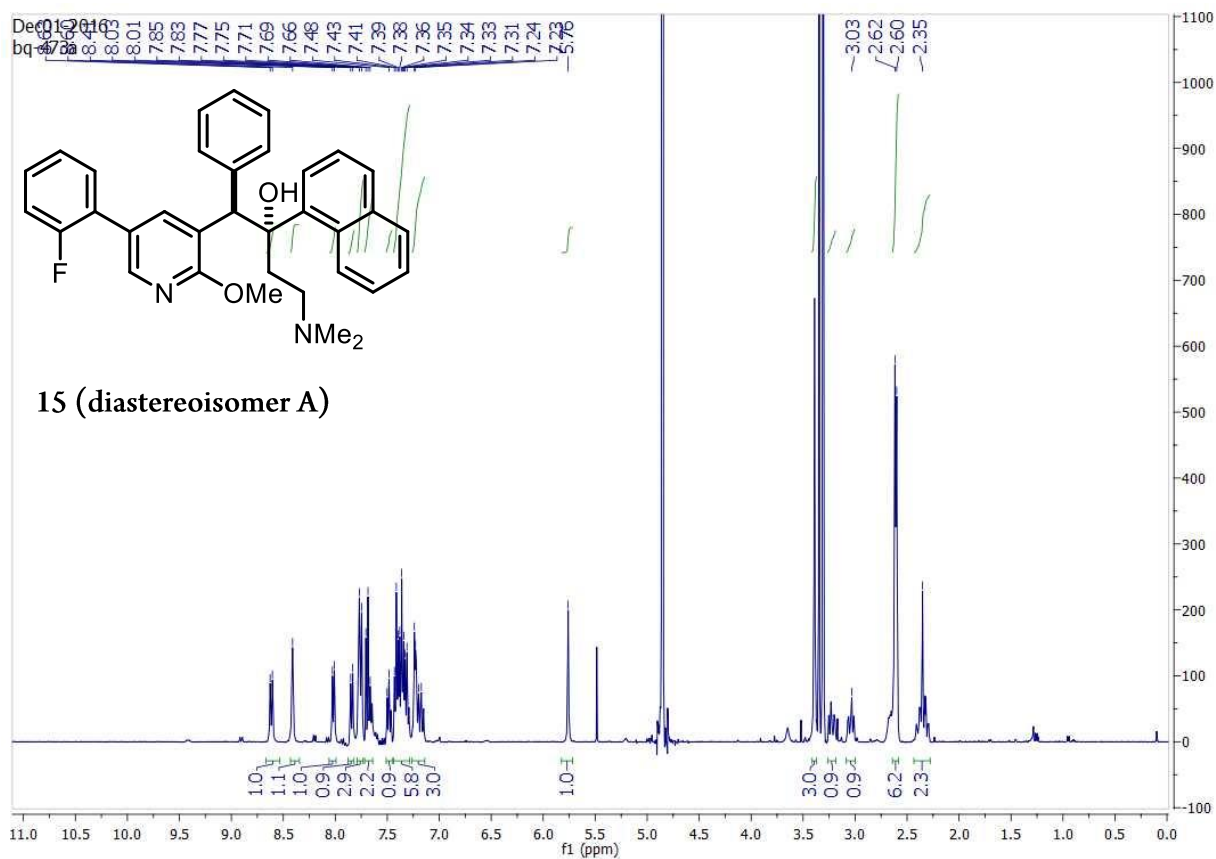
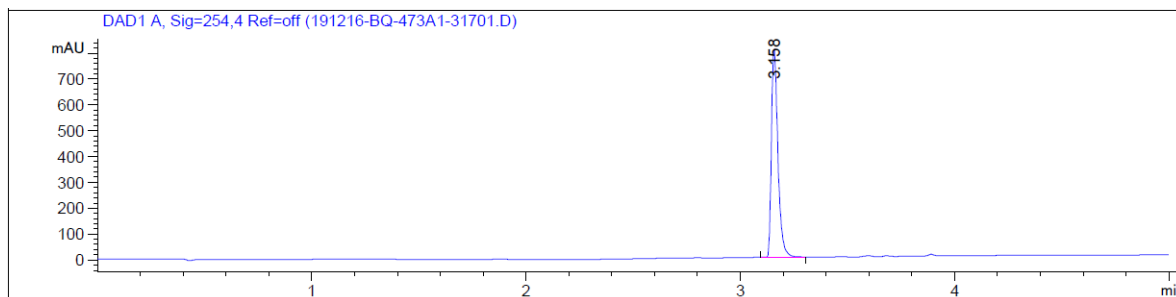


1-(5-(2-fluorophenyl)-2-methoxy-pyridin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol
(15)

Diastereoisomer A:

LCMS (m/z): 520.9

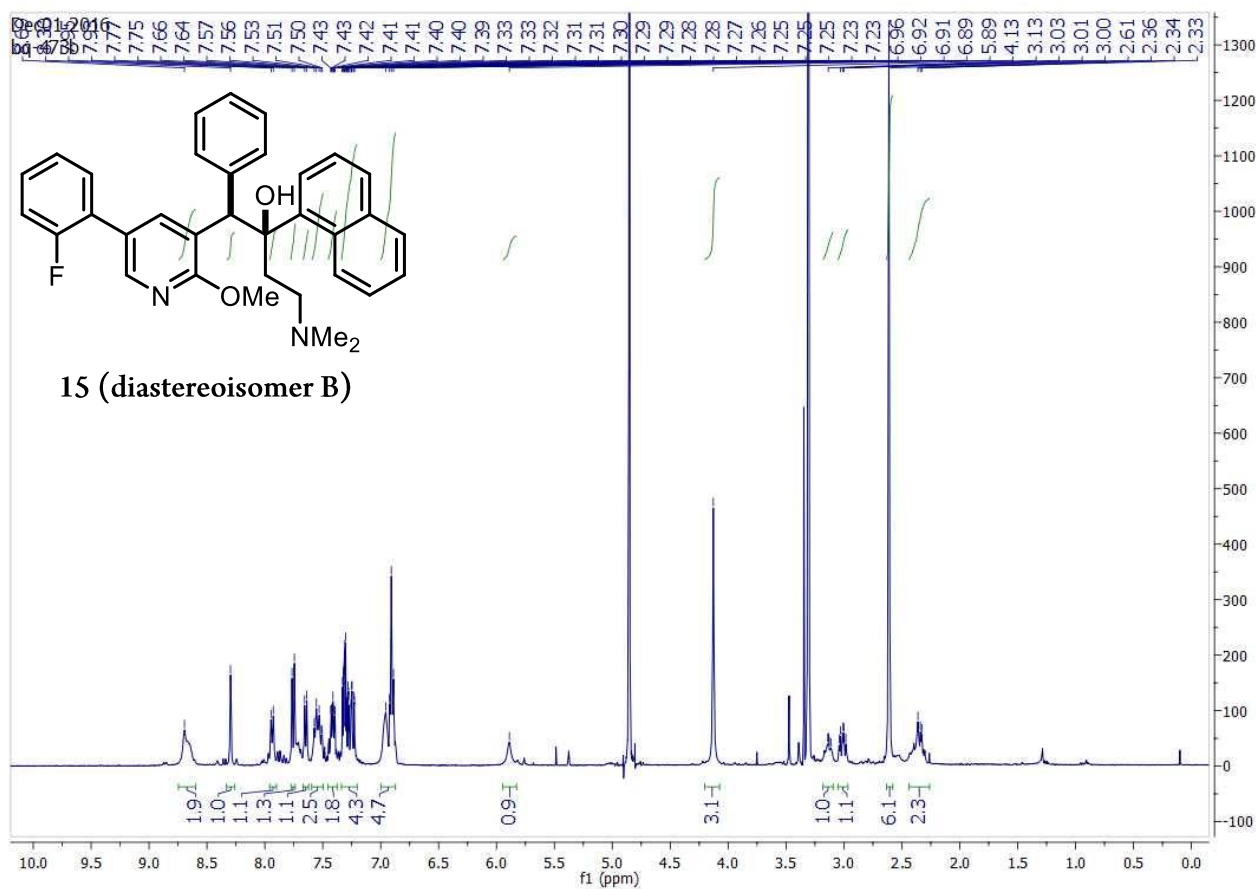
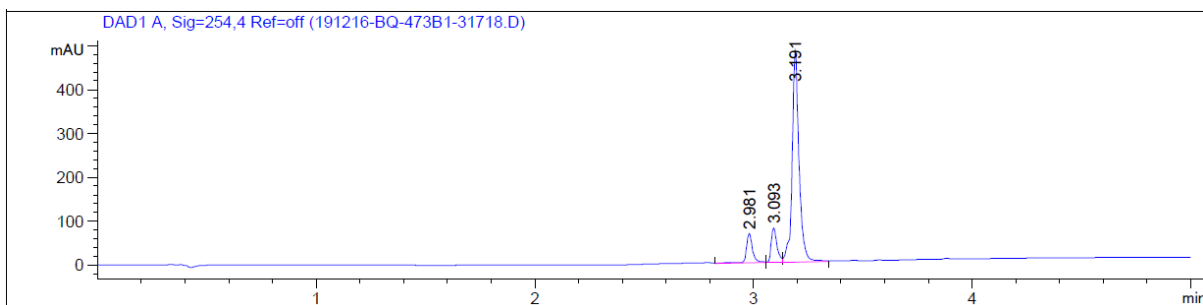
HPLC Trace:



Diastereoisomer B:

LCMS (m/z): 521.0

HPLC Trace:

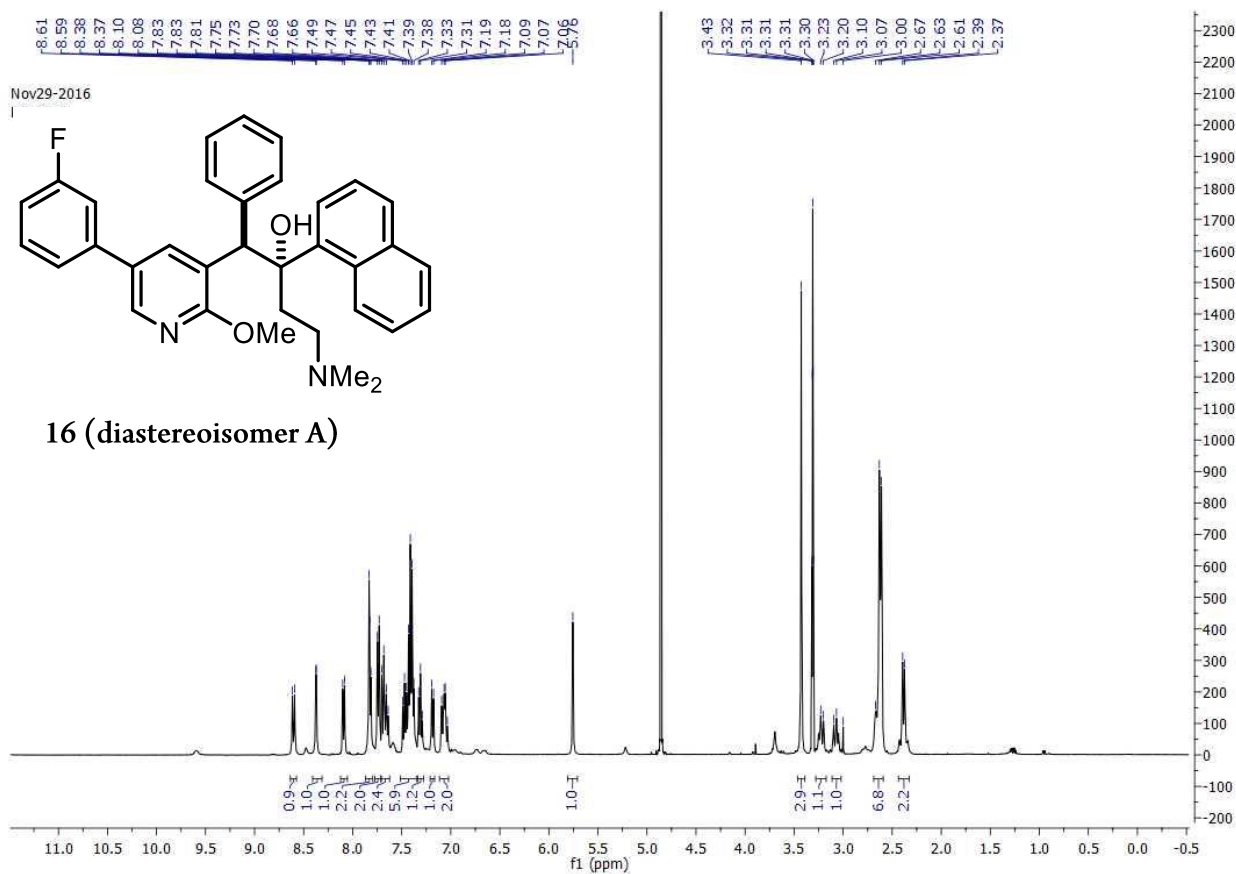
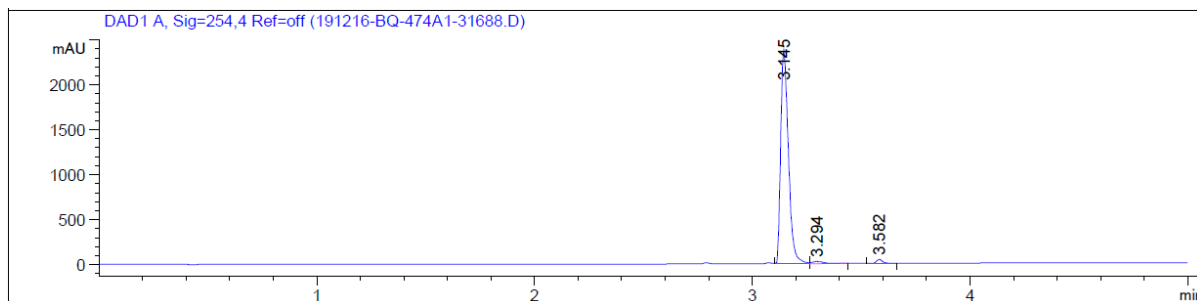


4-(dimethylamino)-1-(5-(3-fluorophenyl)-2-methoxypyridin-3-yl)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol
(16)

Diastereoisomer A:

LCMS (m/z): 520.9

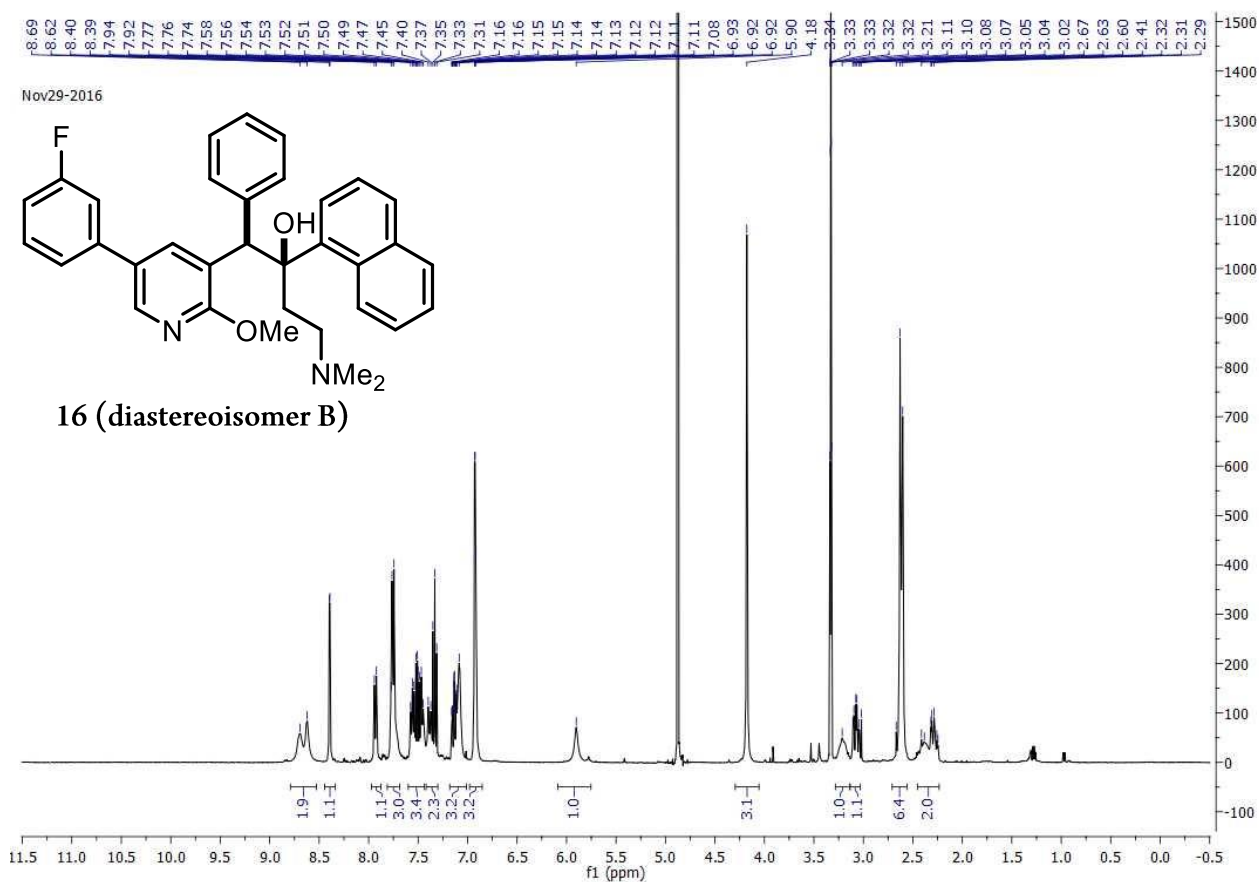
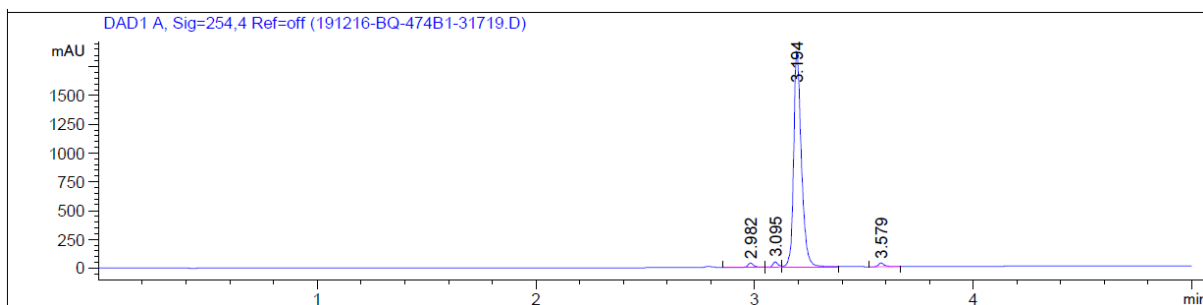
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Diastereoisomer B:

LCMS (m/z): 520.9

HPLC Trace:

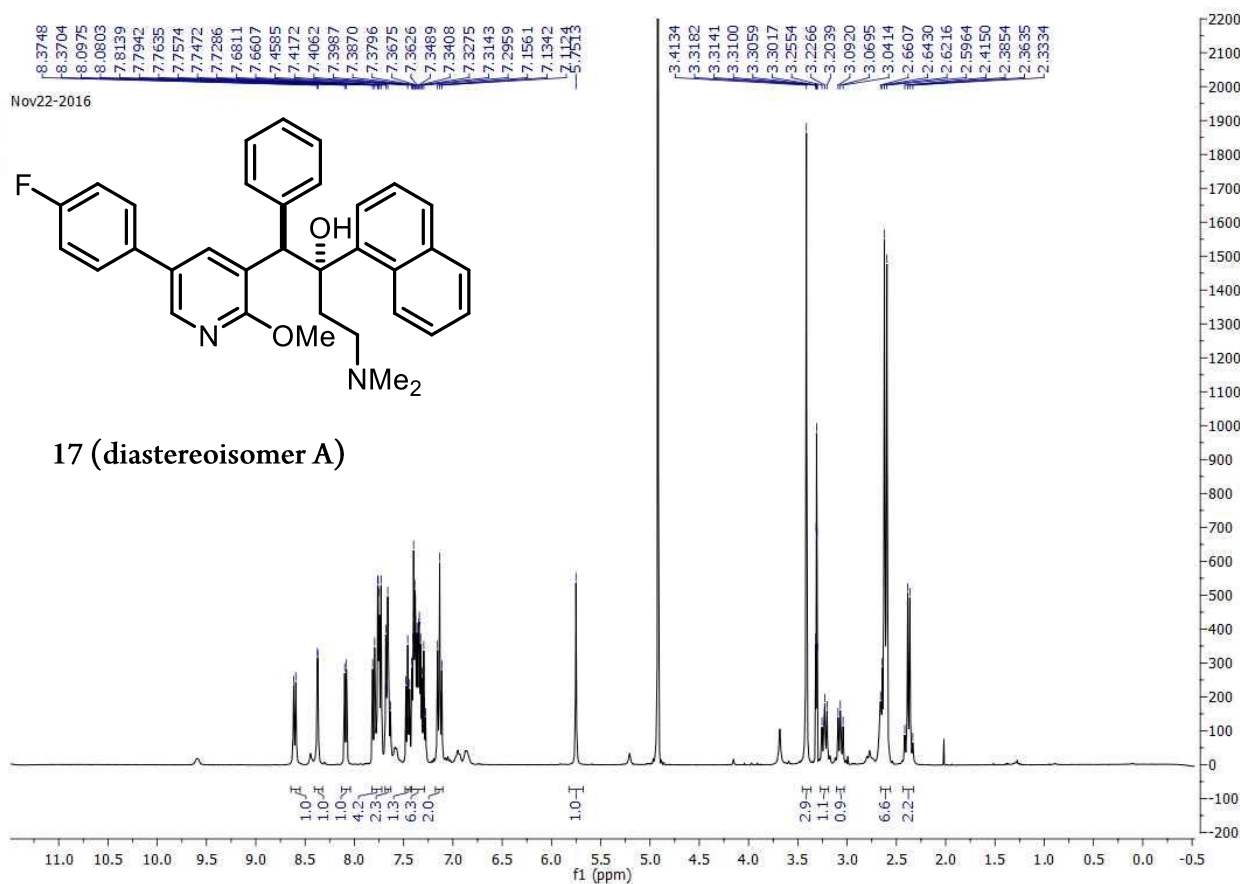
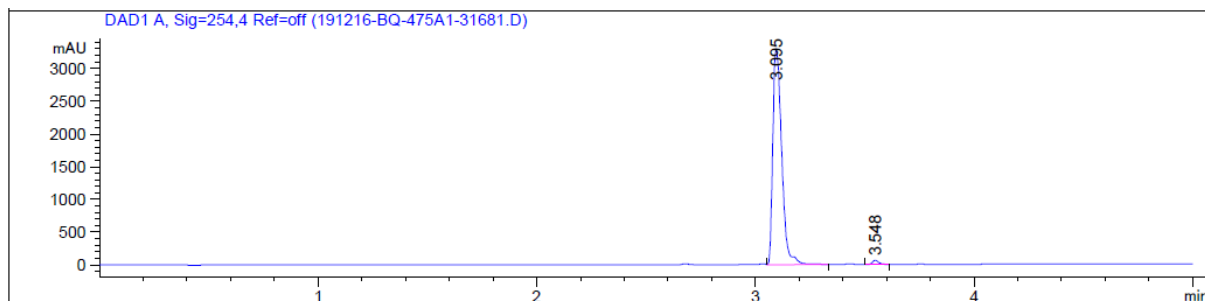


4-(dimethylamino)-1-(2-methoxy-5-(4-fluorophenyl)pyridin-3-yl)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol
(17)

Diastereoisomer A:

LCMS (m/z): 521.0 (M+H).

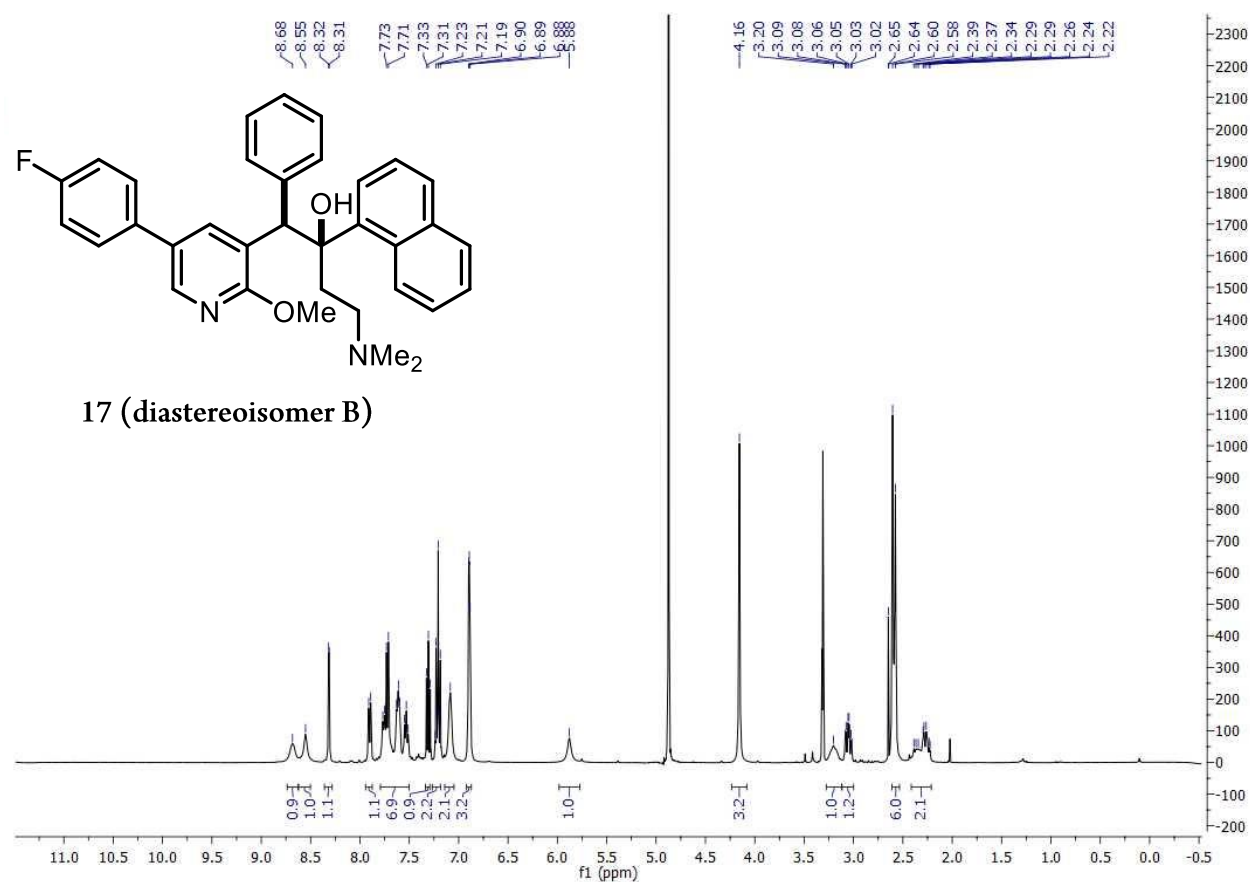
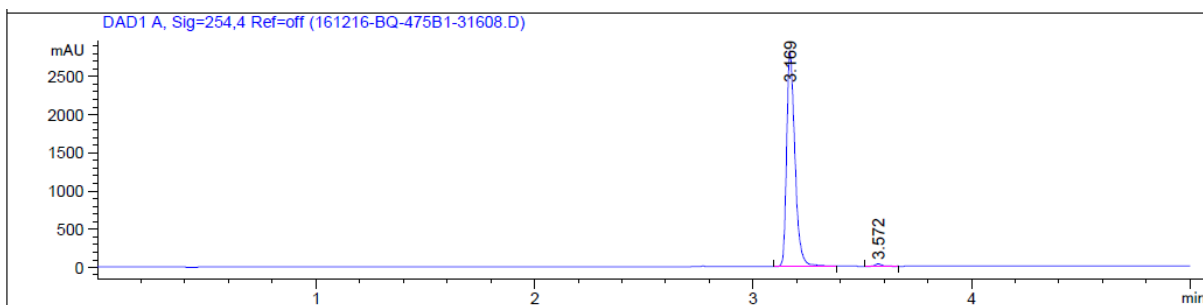
HPLC Trace:



Diastereoisomer B:

LCMS: m/z 521.0 (M+H).

HPLC Trace:

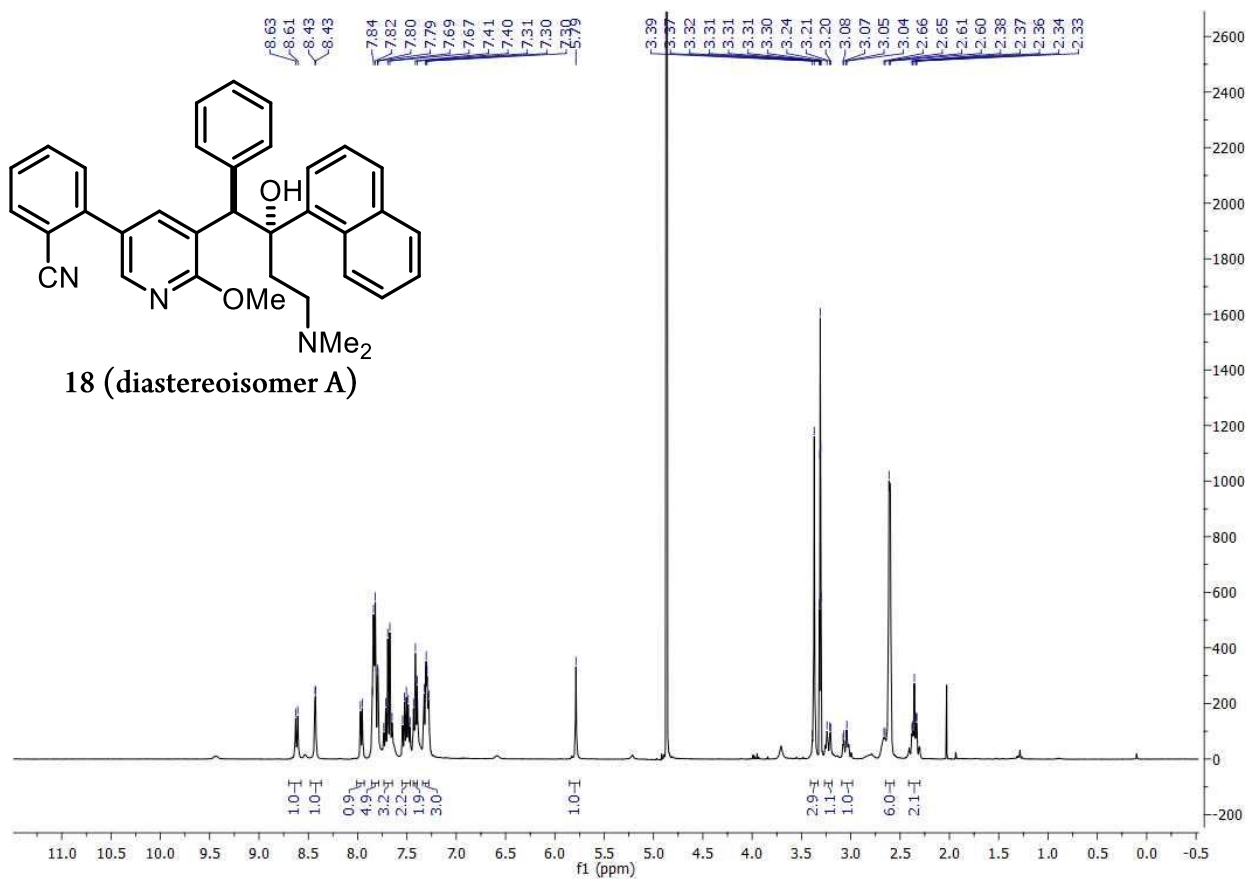
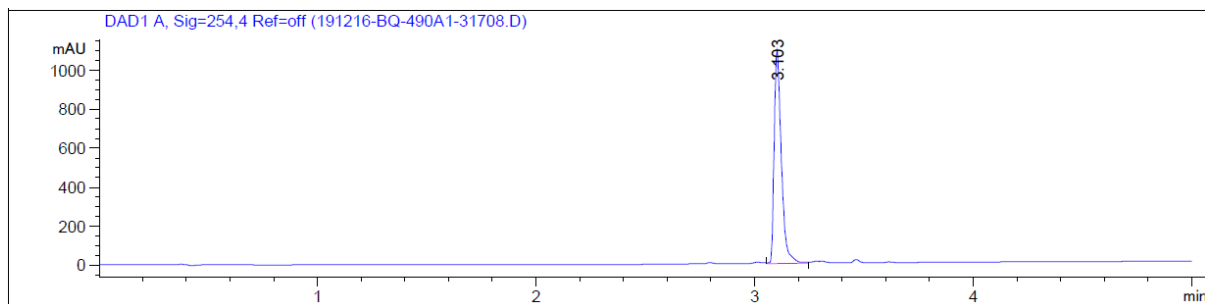


2-(5-(4-(dimethylamino)-2-hydroxy-2-(naphthalen-1-yl)-1-phenylbutyl)-6-methoxy-pyridin-3-yl)benzonitrile
(18)

Diastereoisomer A:

LCMS (m/z): 528.0

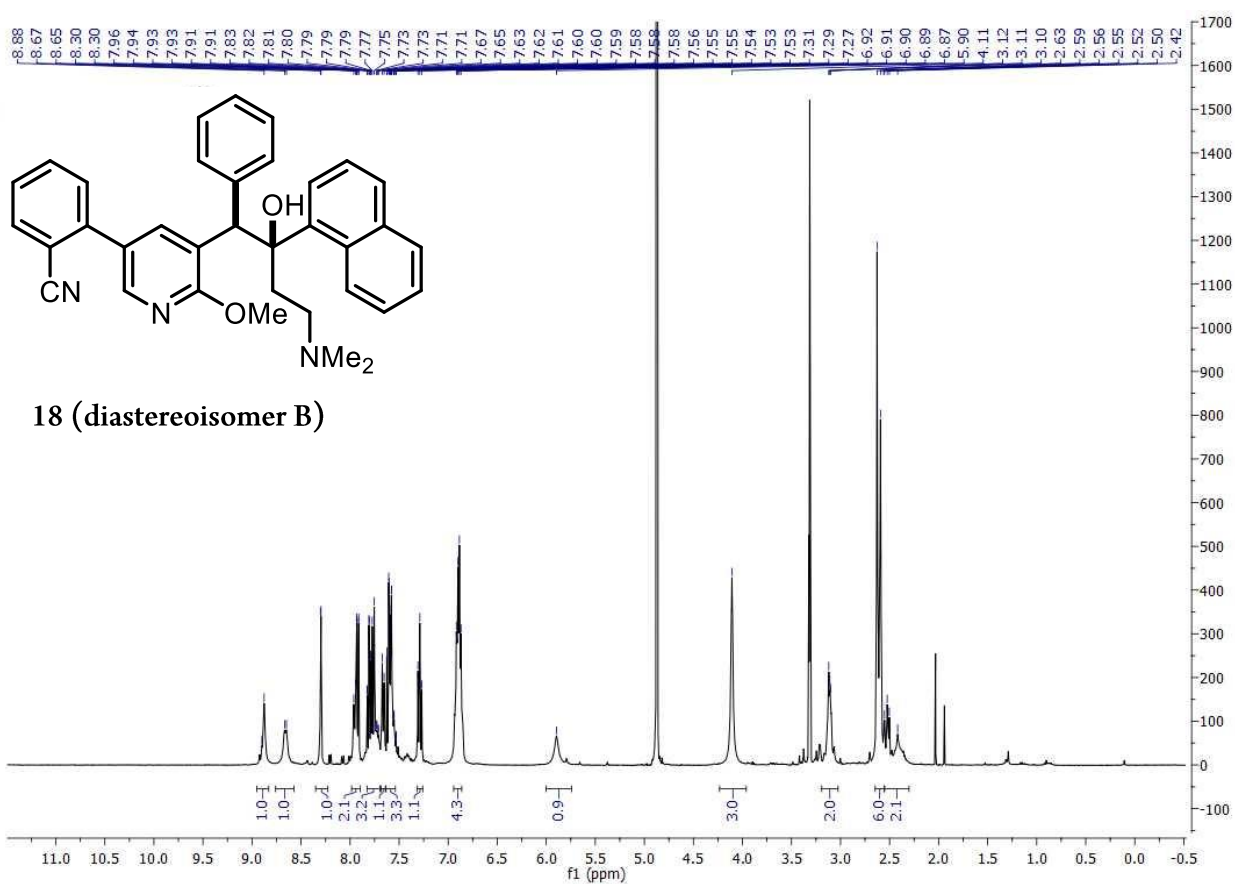
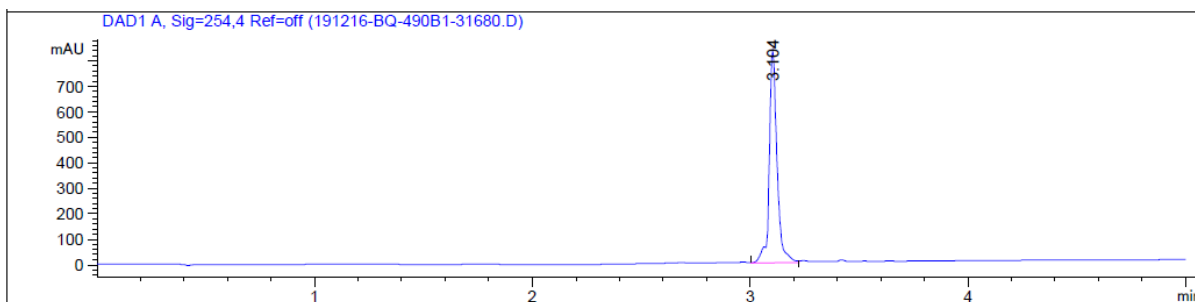
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Diastereoisomer B:

LCMS (m/z): 528.0

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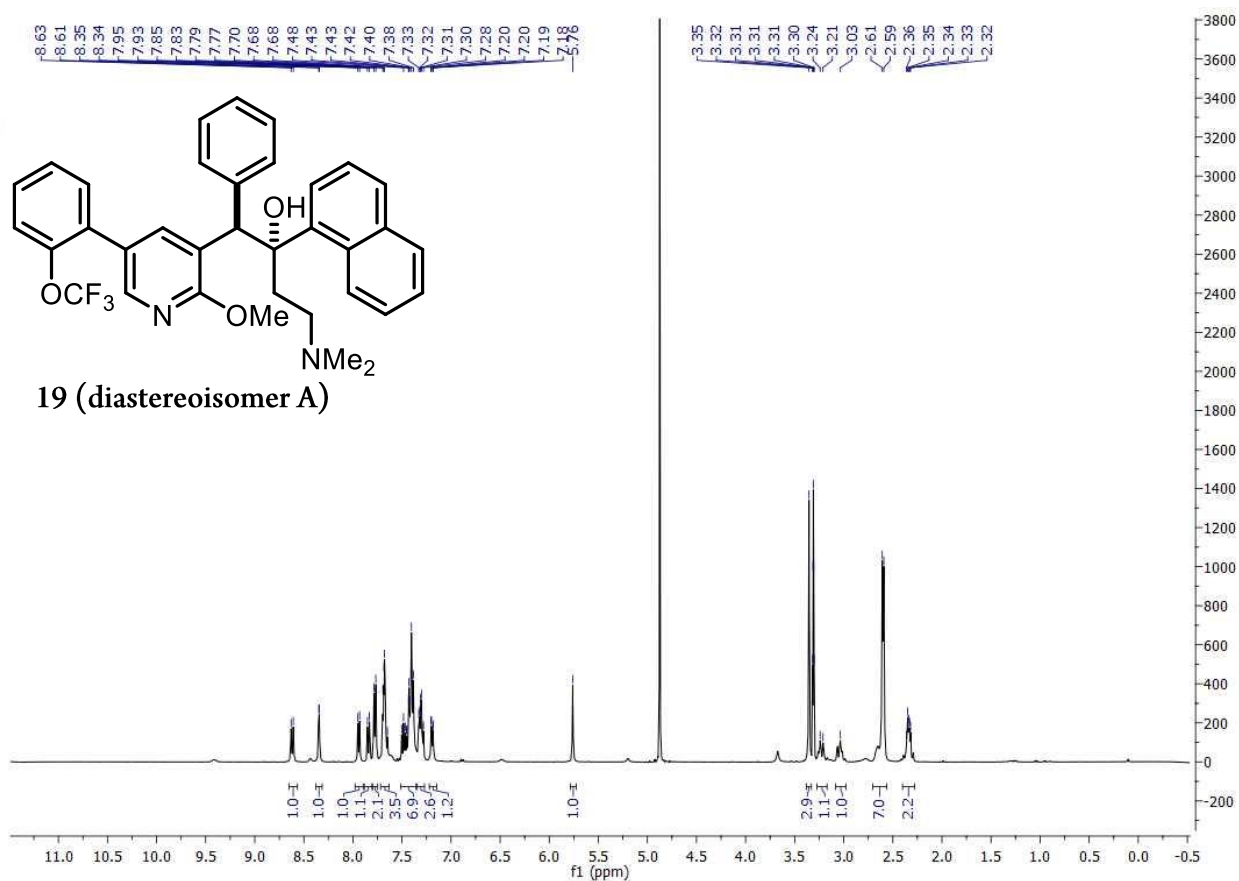
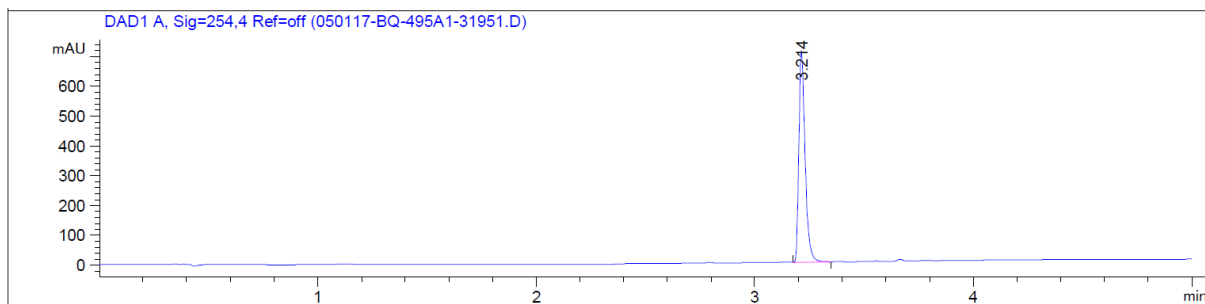


4-(dimethylamino)-1-(2-methoxy-5-(2-(trifluoromethoxy)phenyl)pyridin-3-yl)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (19)

Diastereoisomer A:

LCMS (m/z): 586.9

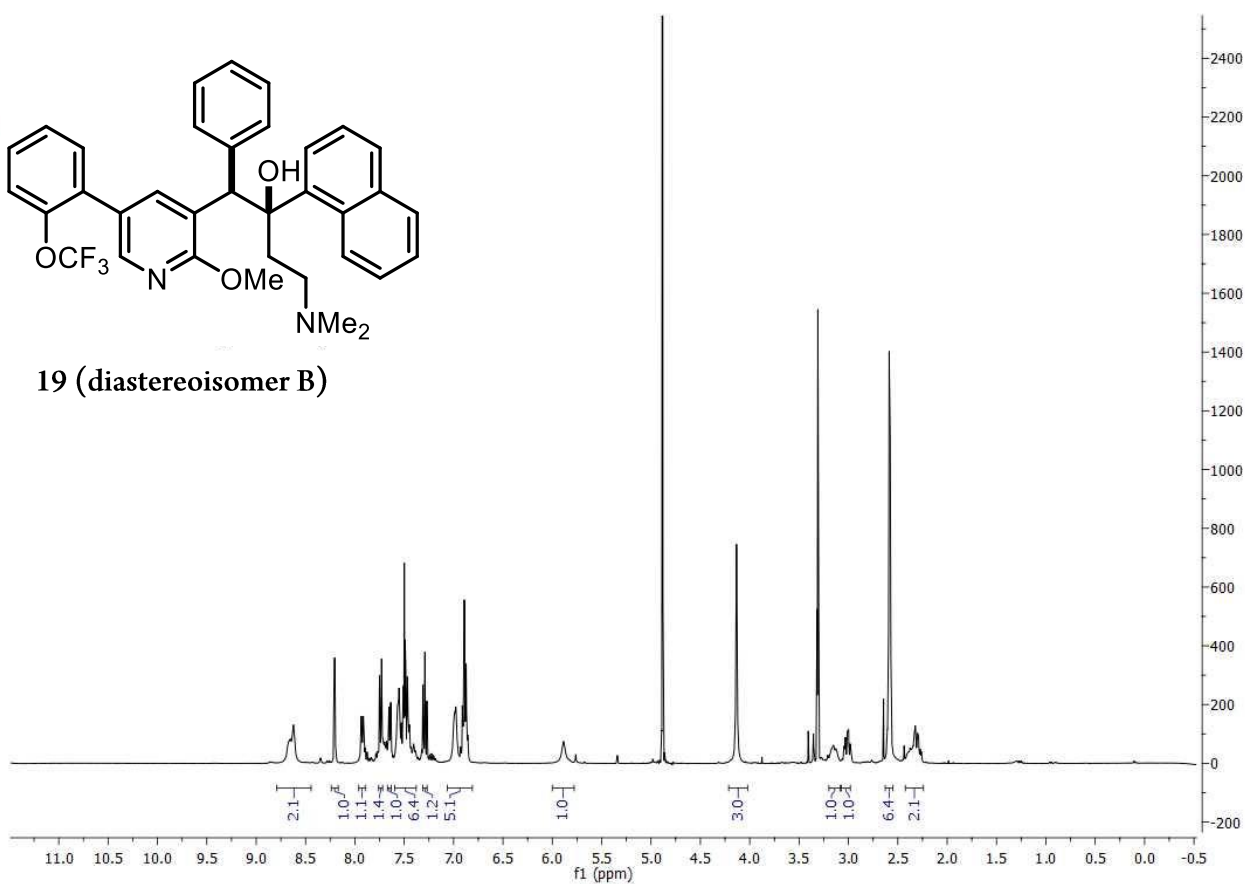
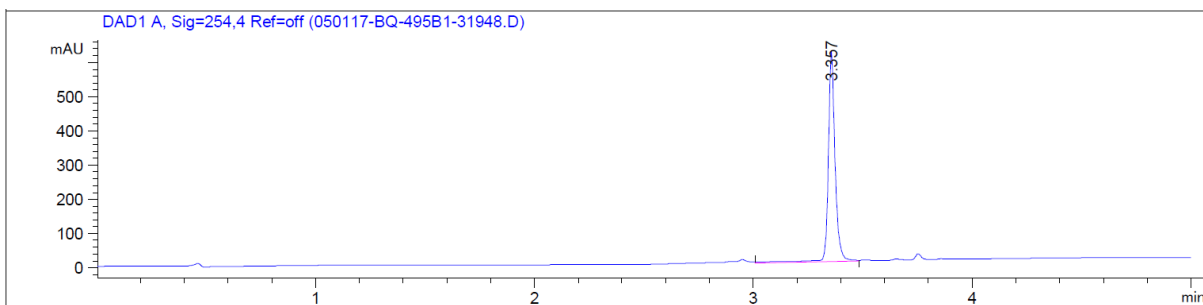
HPLC Trace:



Diastereoisomer B:

LCMS (m/z): 586.9

HPLC Trace:

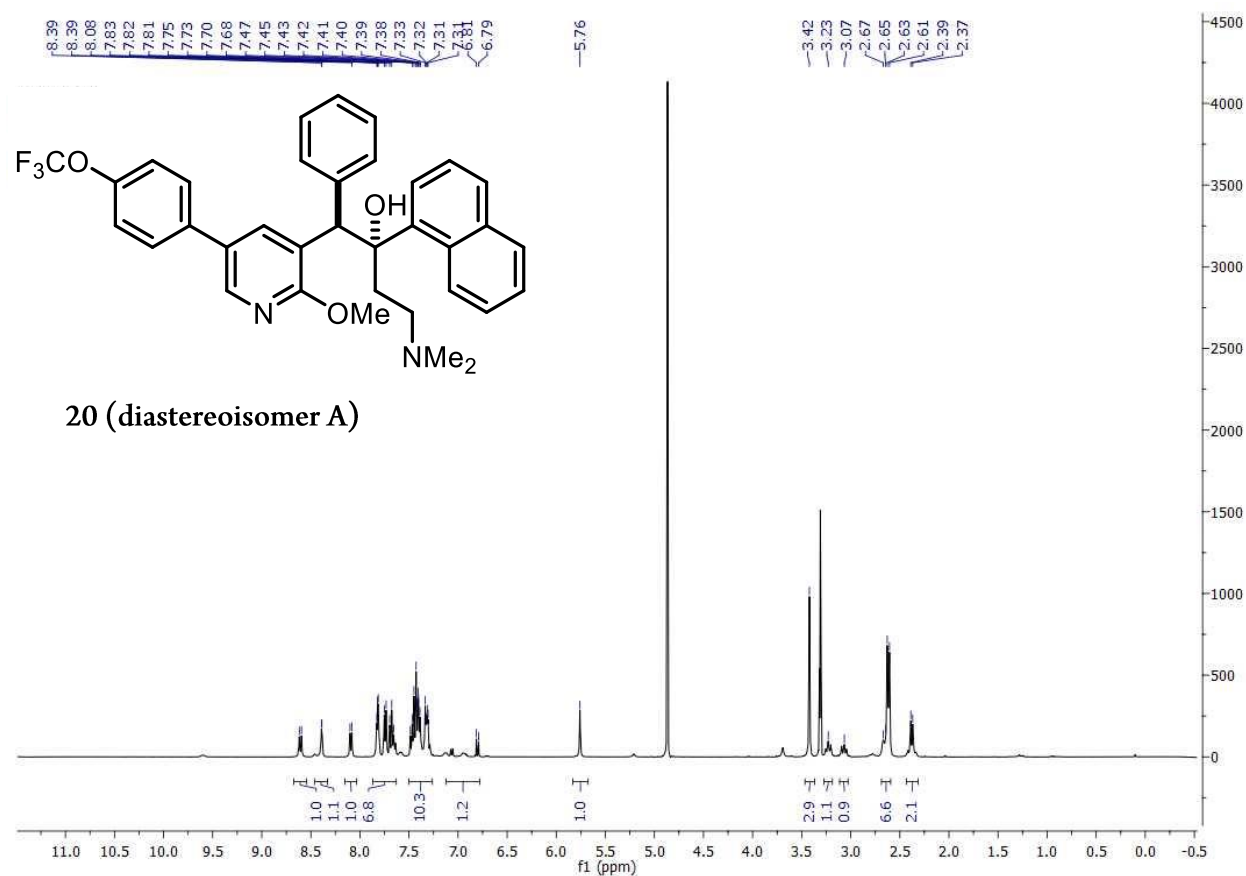
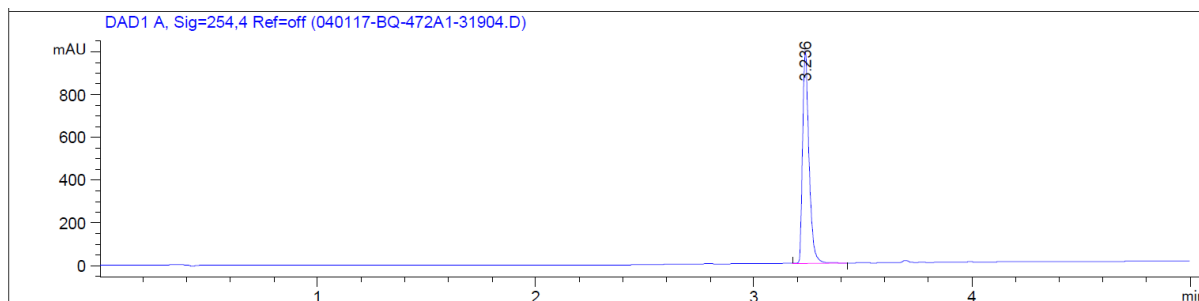


4-(dimethylamino)-1-(2-methoxy-5-(4-(trifluoromethoxy)phenyl)pyridin-3-yl)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (20)

Diastereoisomer A:

LCMS (m/z): 586.9

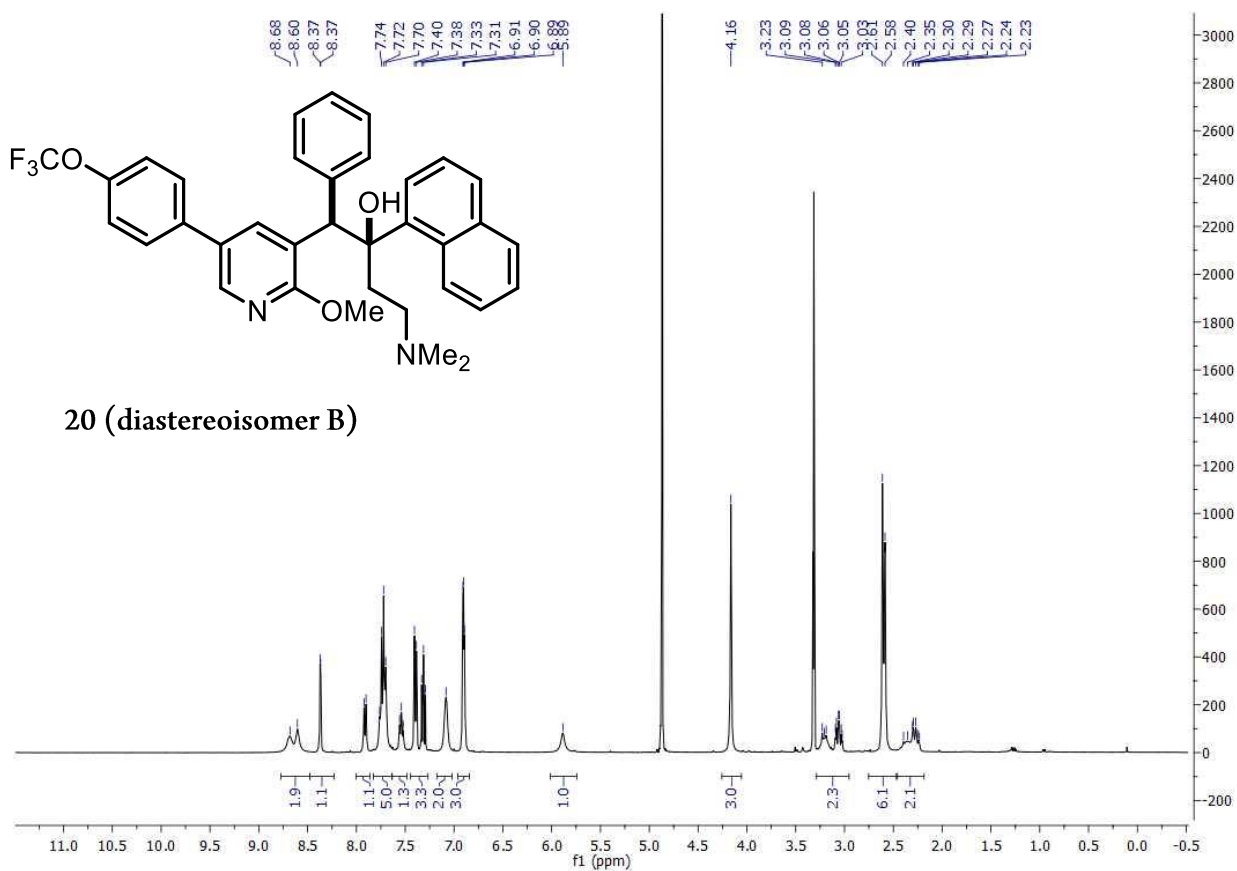
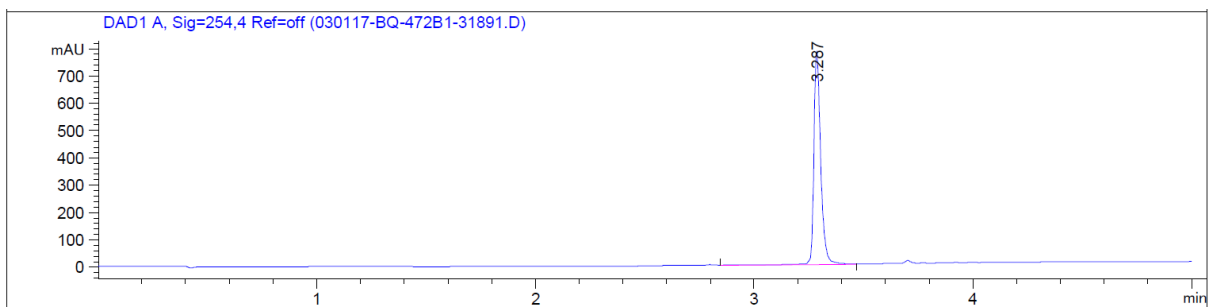
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Diastereoisomer B:

LCMS (m/z): 586.9

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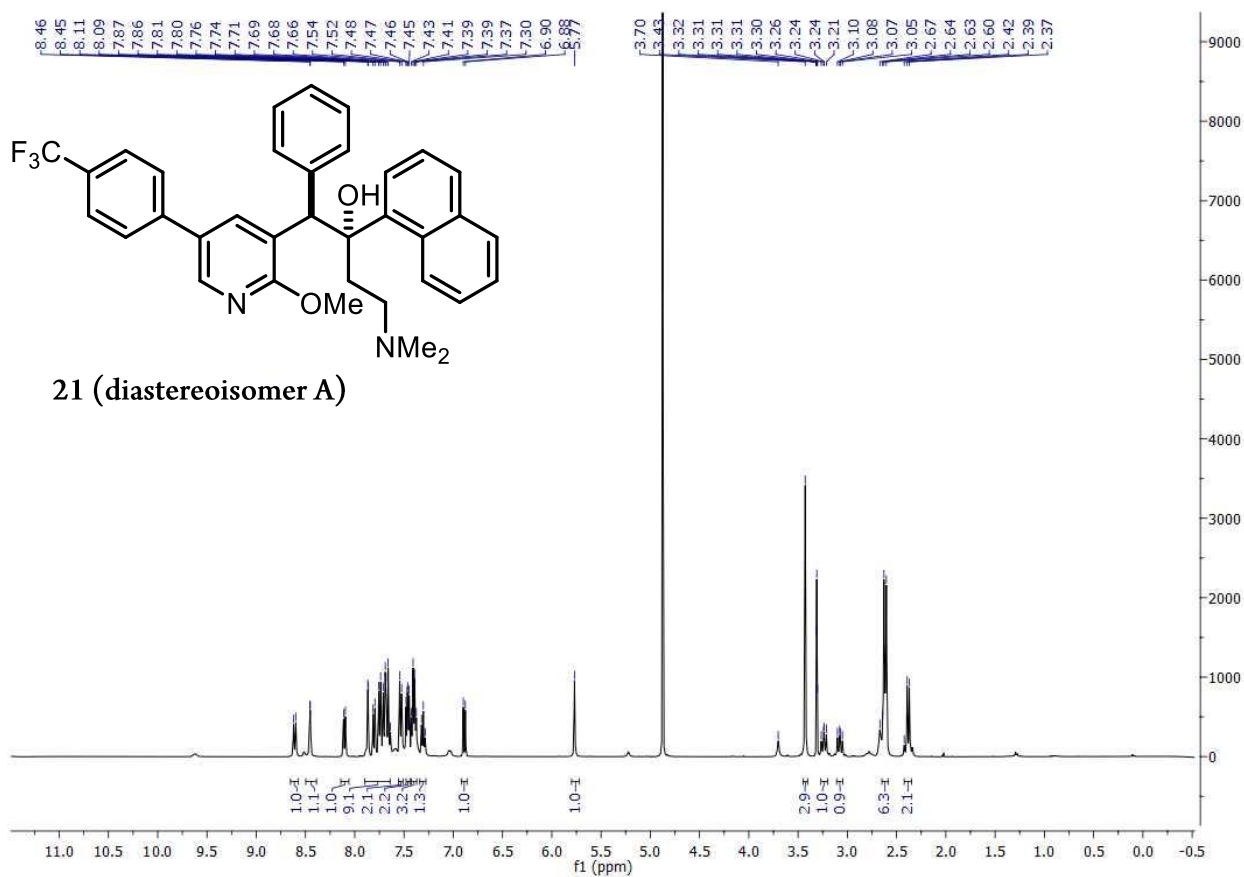
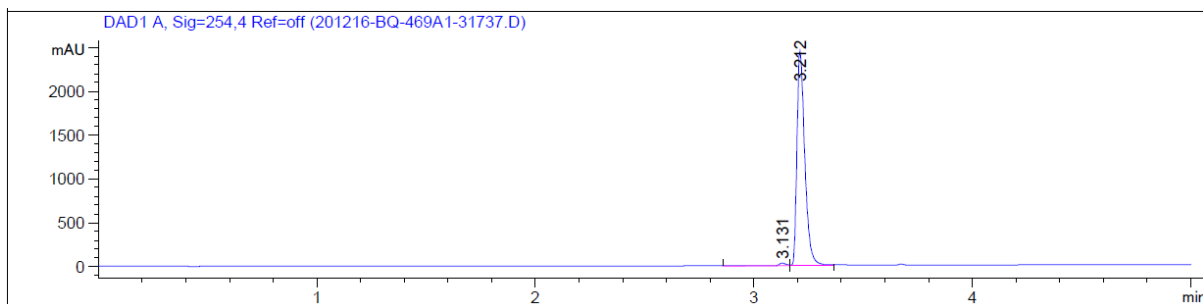


4-(dimethylamino)-1-(2-methoxy-5-(4-(trifluoromethyl)phenyl)pyridin-3-yl)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (21)

Diastereoisomer A:

LCMS (m/z): 570.9

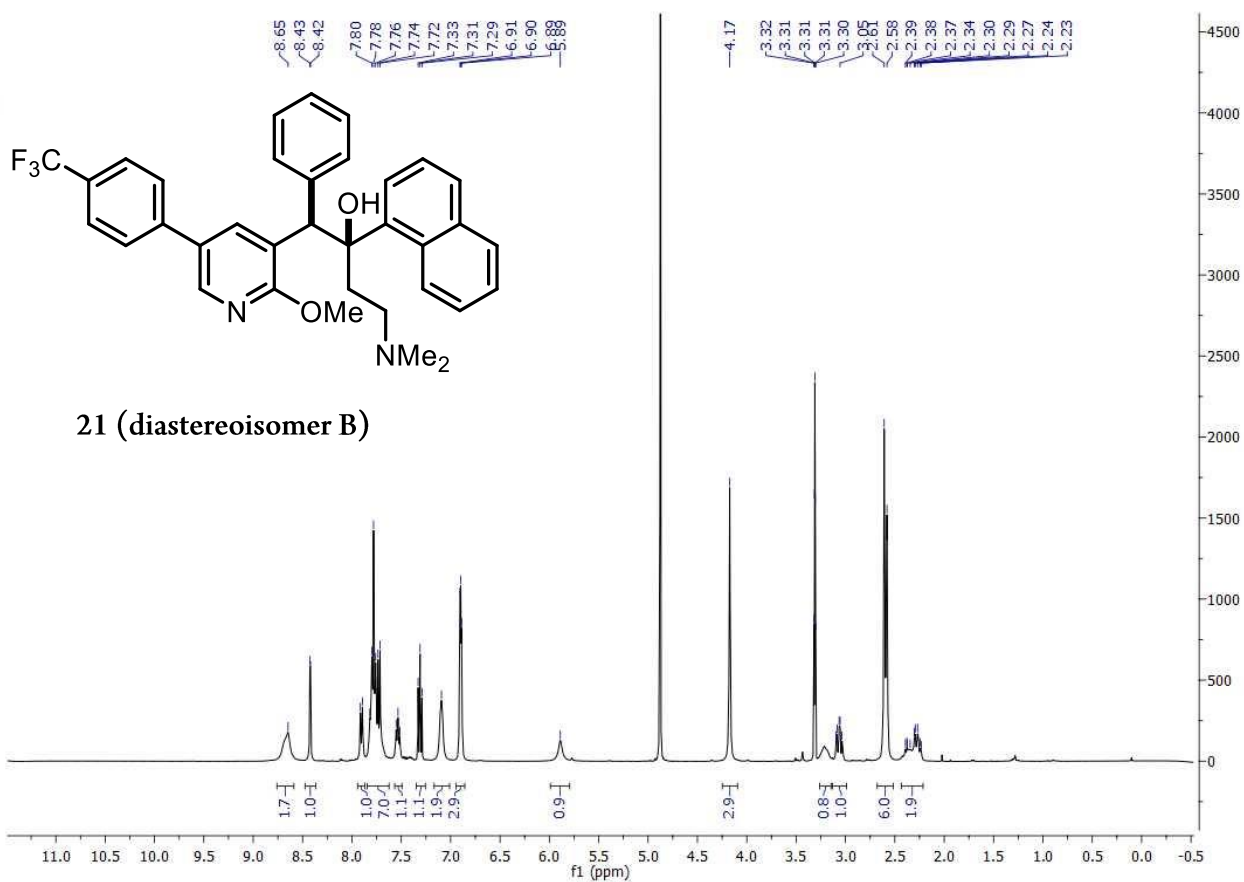
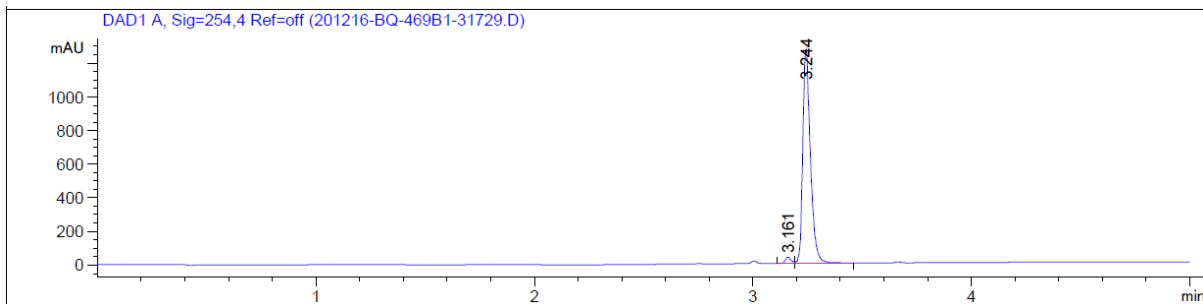
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Diastereoisomer B:

LCMS (m/z): 570.9

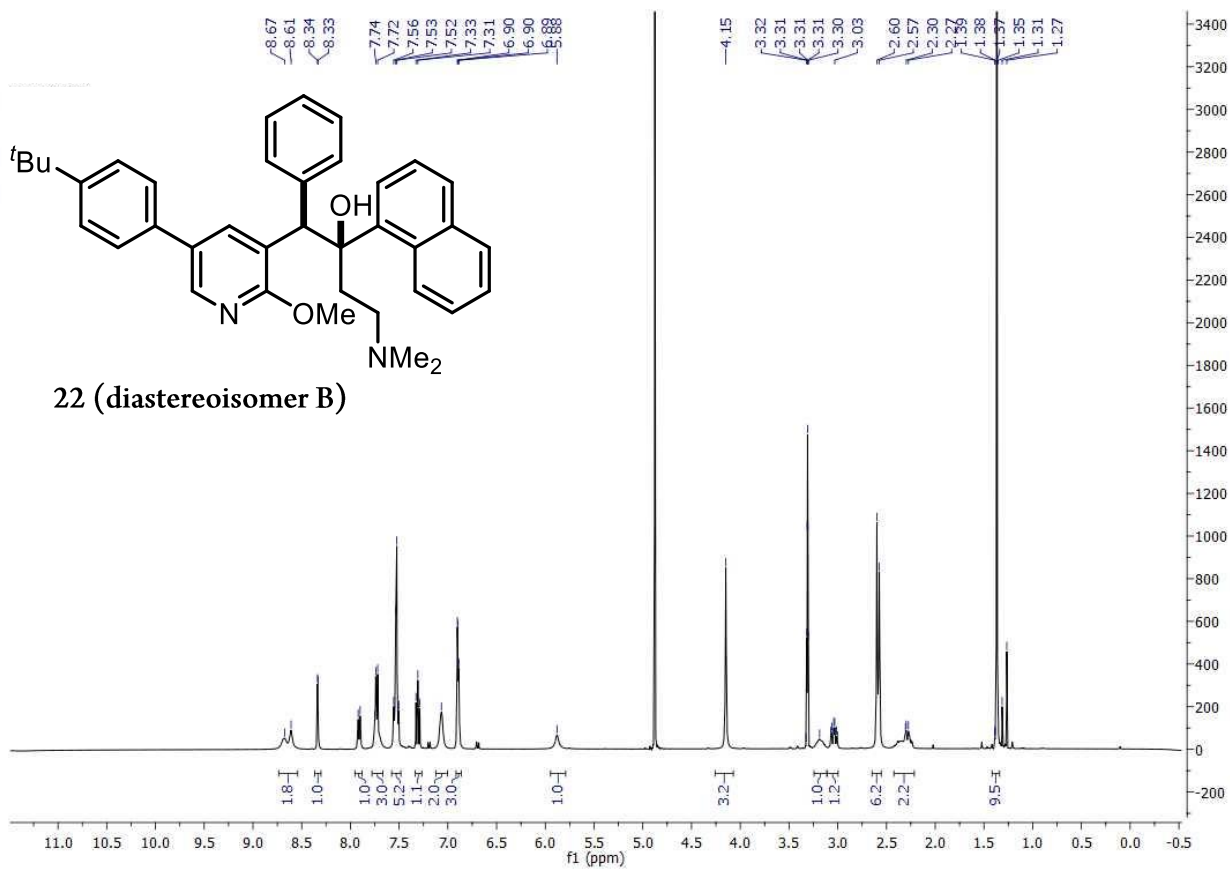
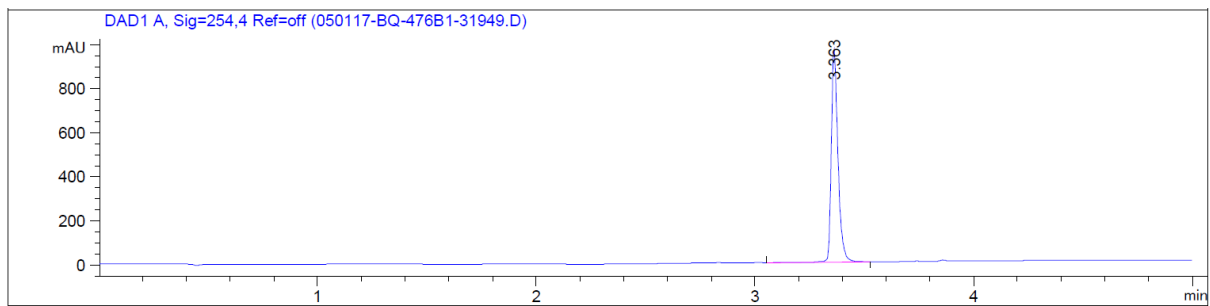
HPLC Trace:



1-(5-(4-*tert*-butyl)phenyl)-2-methoxy-pyridin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (22)

Diastereoisomer B:

LCMS (m/z): 559.0

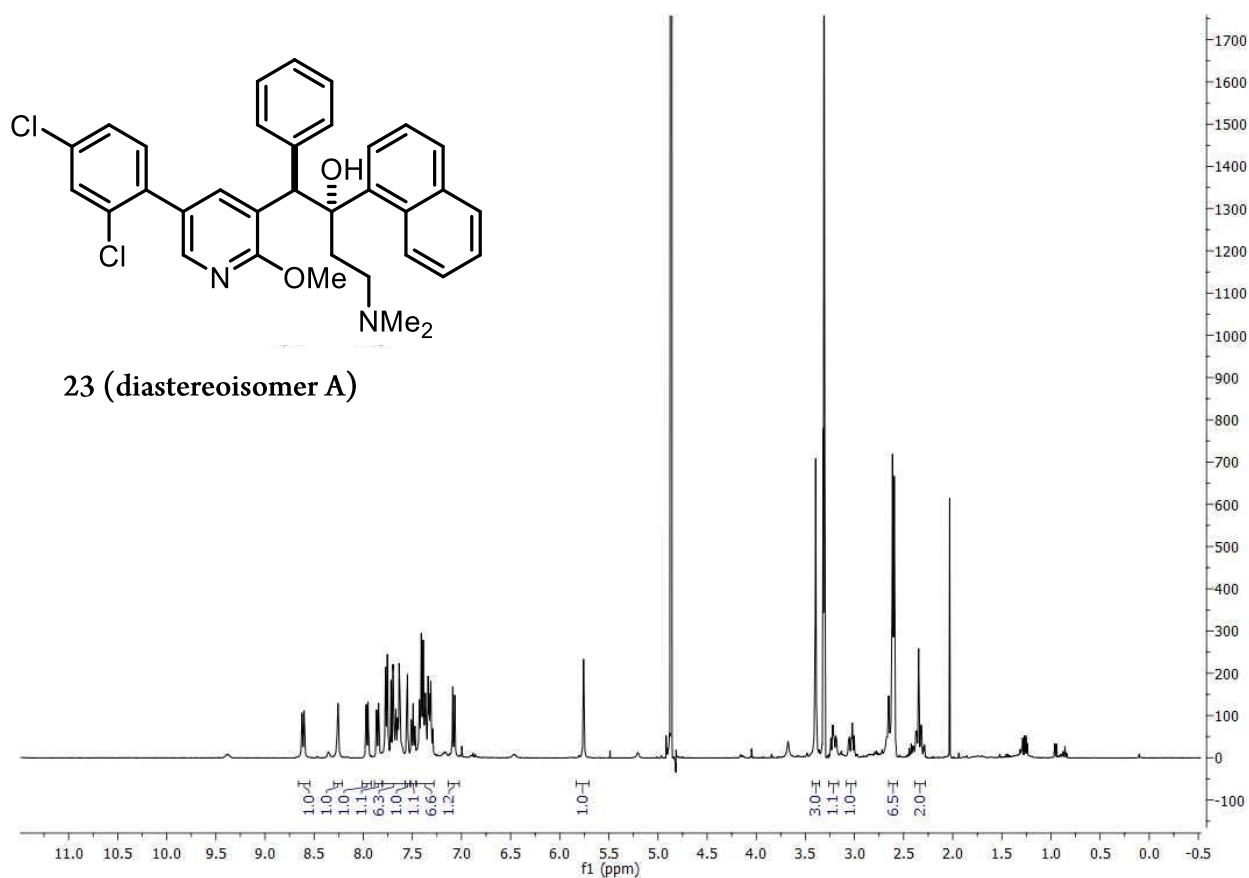
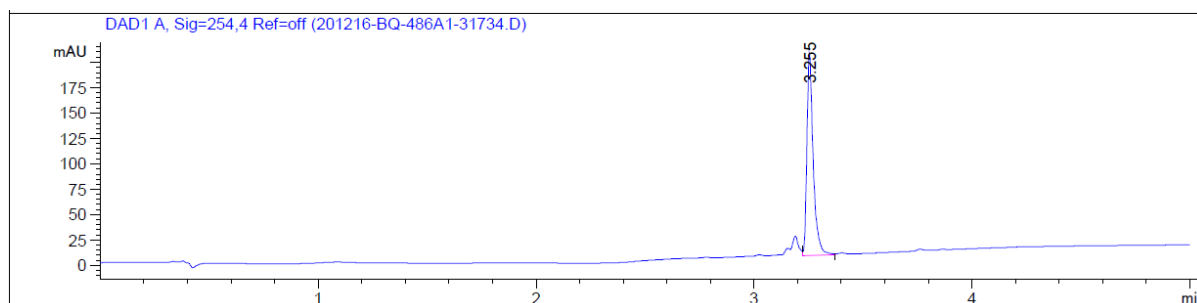


4-(dimethylamino)-1-(5-(2,4-dichlorophenyl)-2-methoxy-pyridin-3-yl)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (23)

Diastereoisomer A:

LCMS (m/z): 570.9

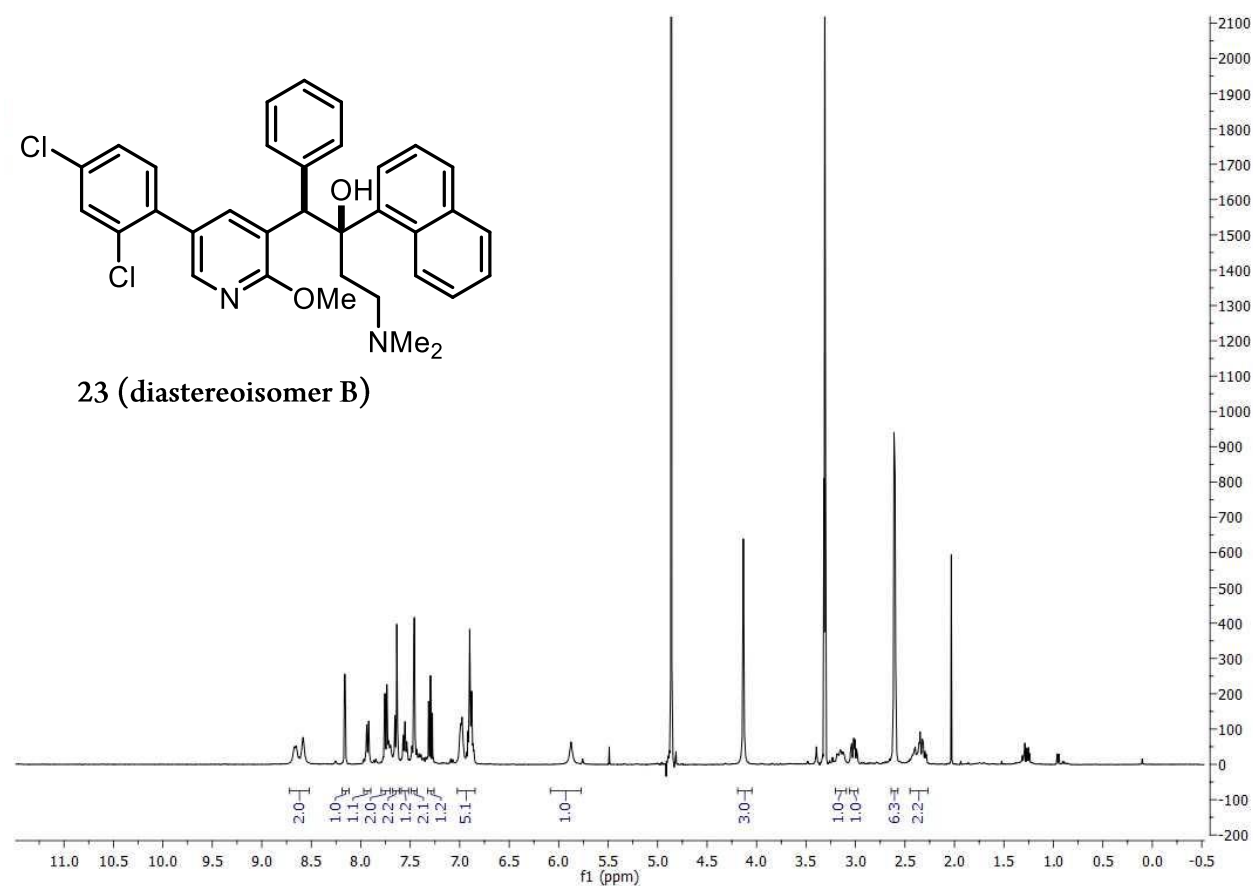
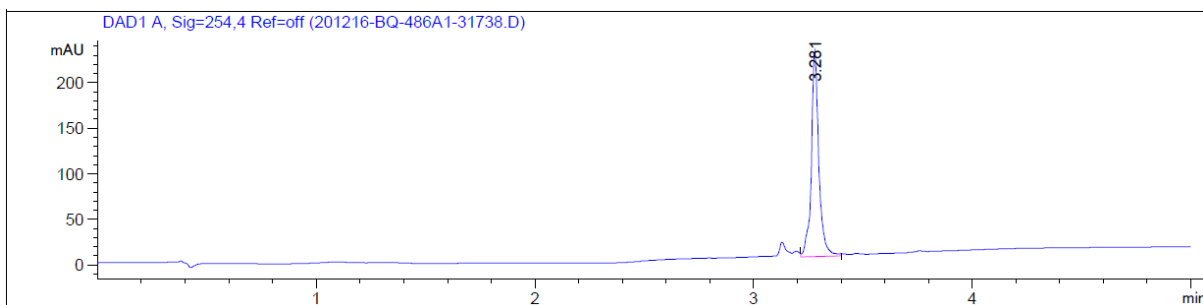
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Diastereoisomer B:

LCMS (m/z): 570.8

HPLC Trace:

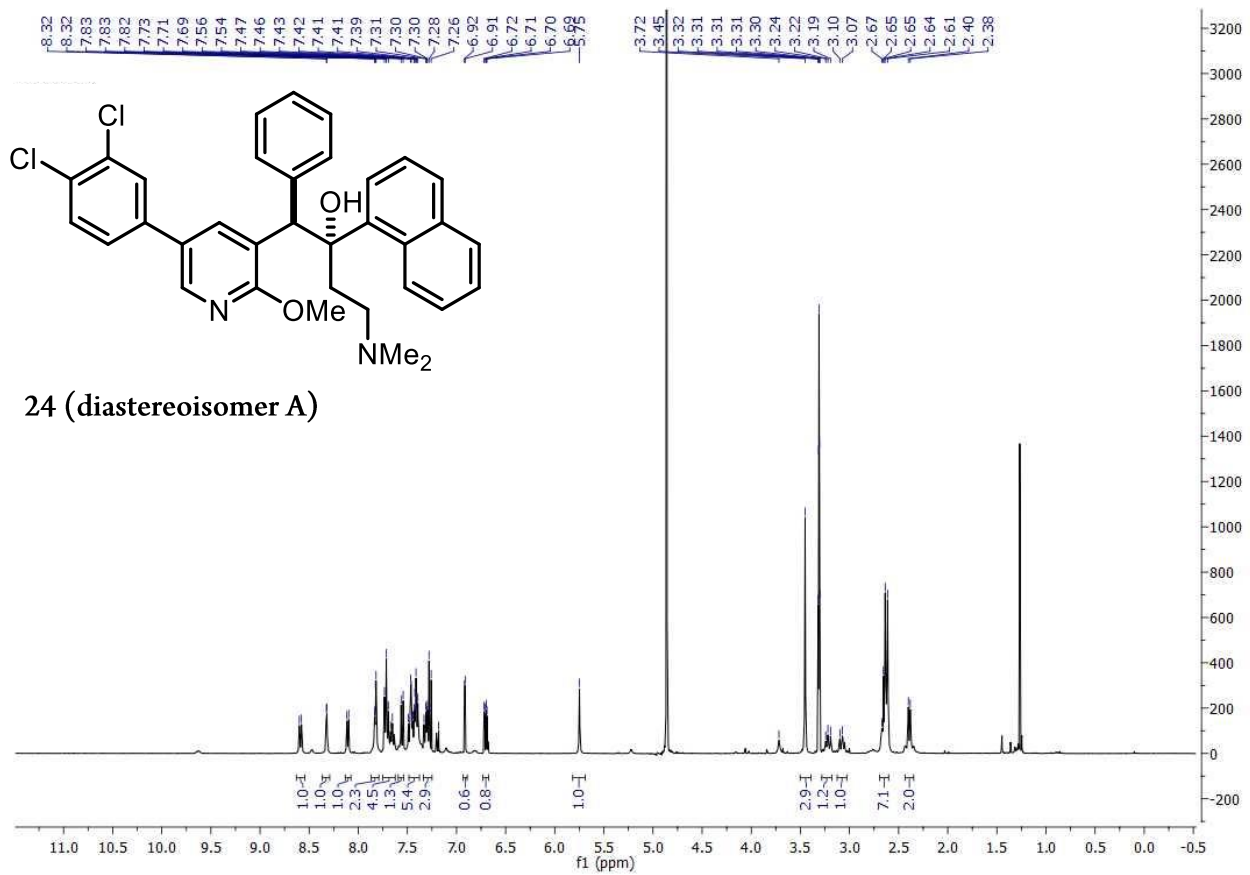
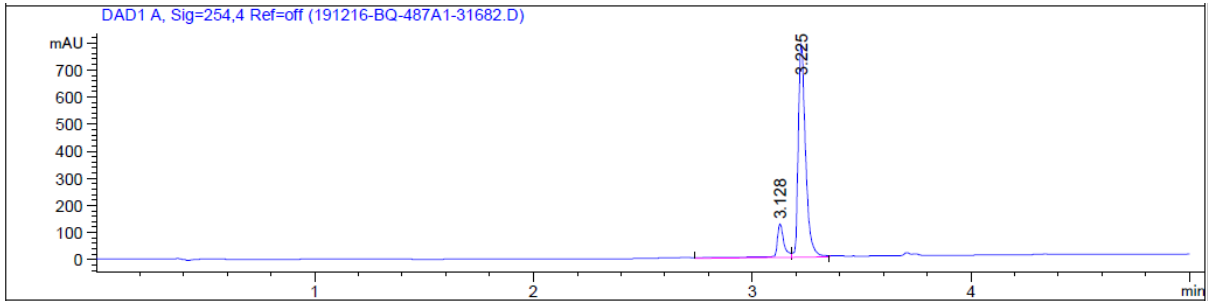


4-(dimethylamino)-1-(5-(3,4-dichlorophenyl)-2-methoxypyridin-3-yl)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (24)

Diastereoisomer A:

LCMS (m/z): 570.9

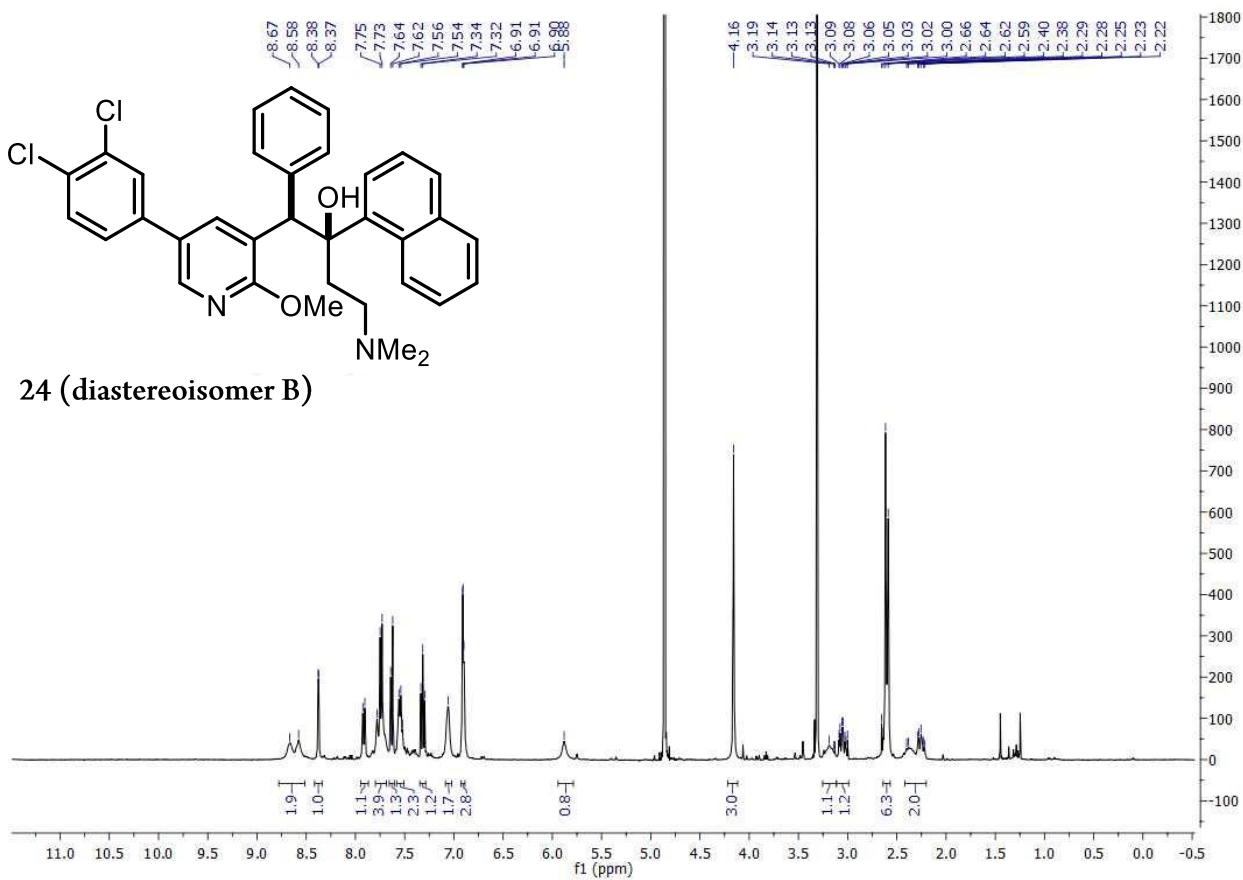
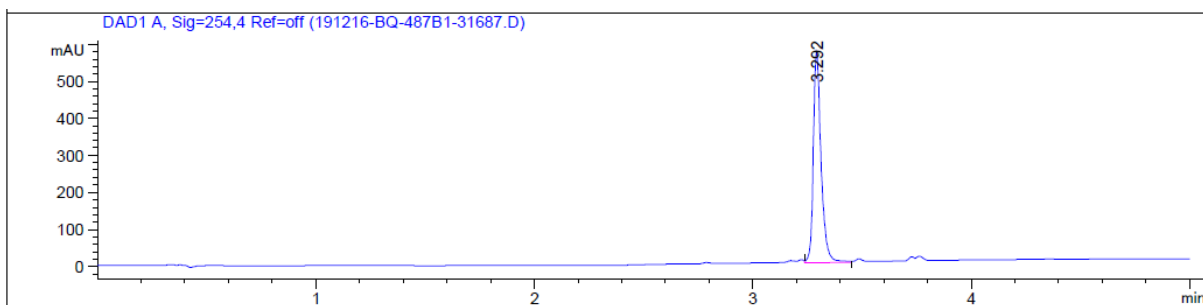
HPLC Trace:



Diastereoisomer B:

LCMS (m/z): 570.9

HPLC Trace:

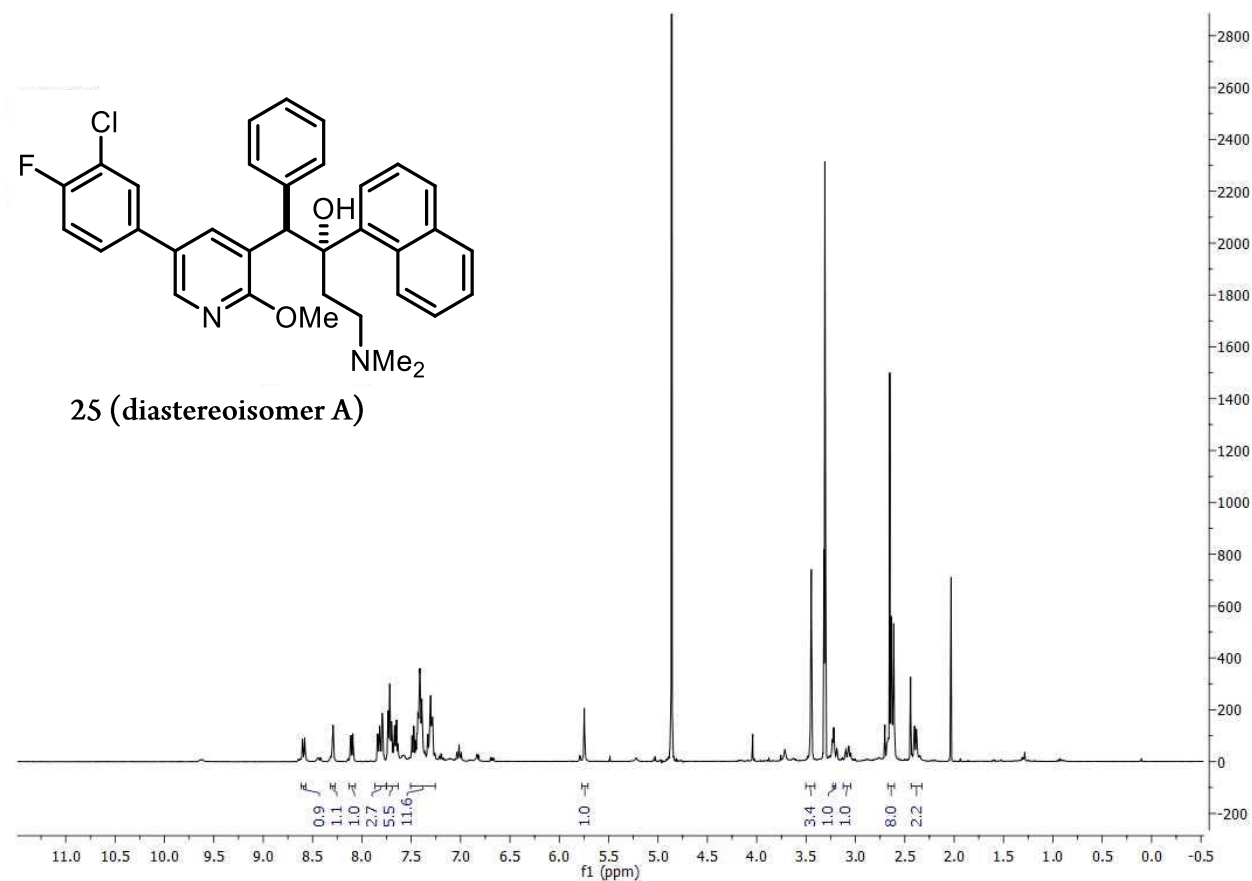
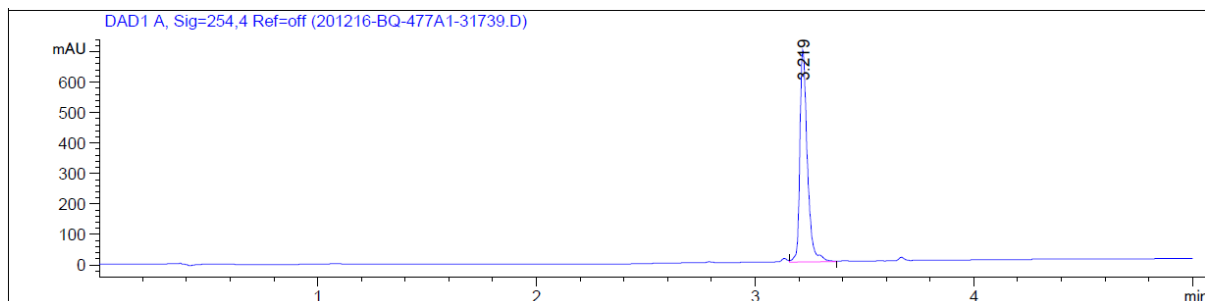


1-(5-(3-chloro-4-fluorophenyl)-2-methoxypyridin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (25)

Diastereoisomer A:

LCMS (m/z): 554.9

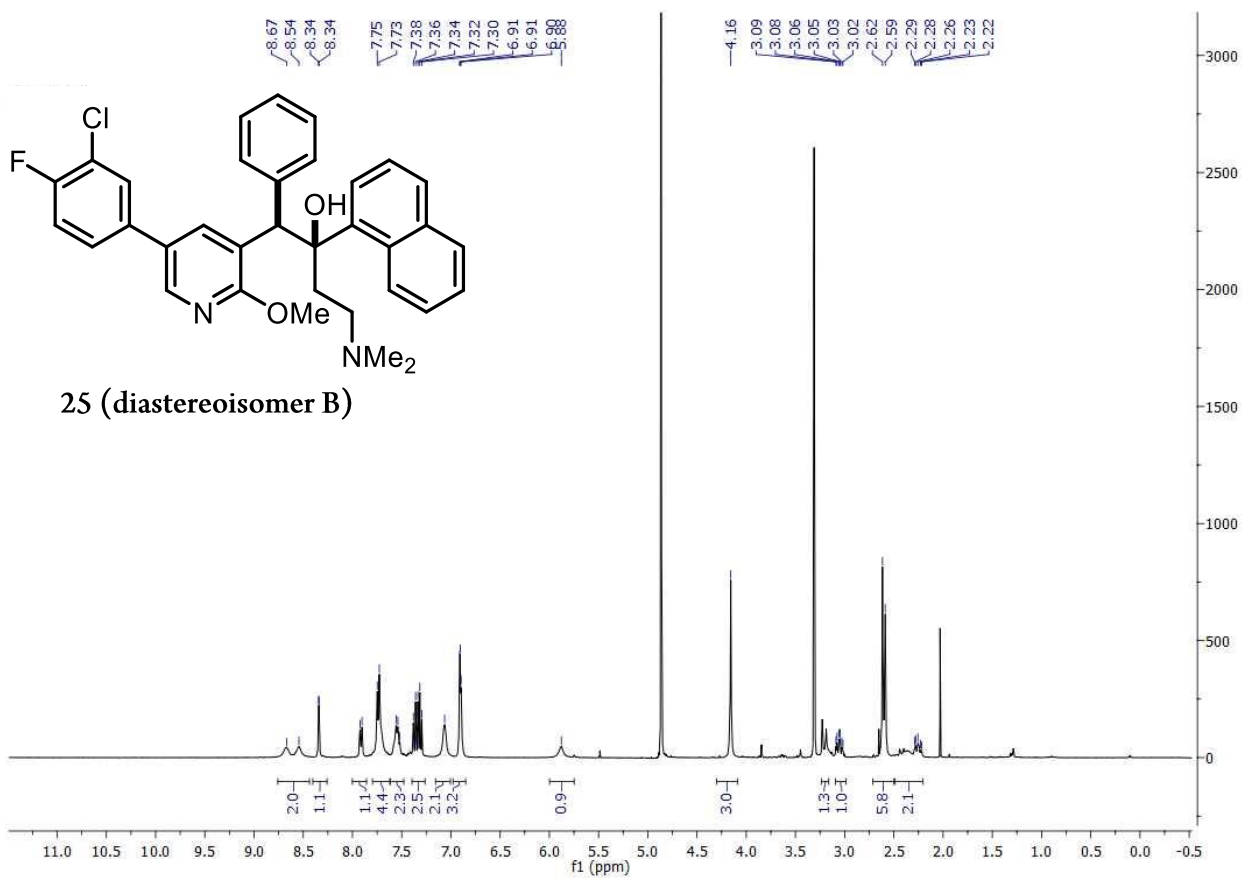
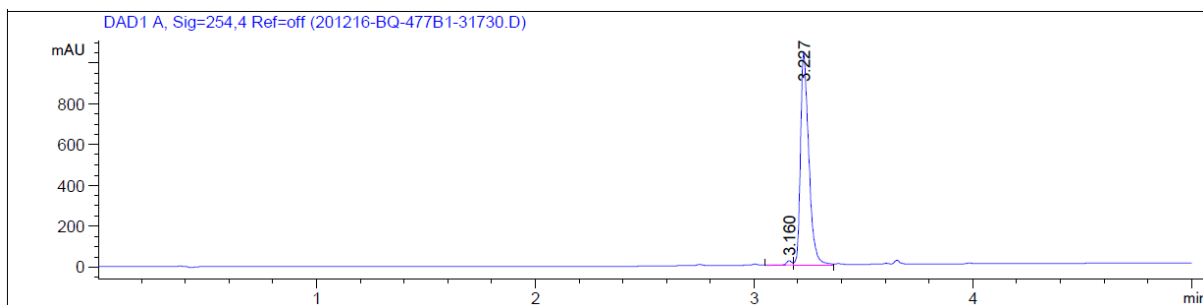
HPLC Trace:



Diastereoisomer B:

LCMS (m/z): 554.9

HPLC Trace:

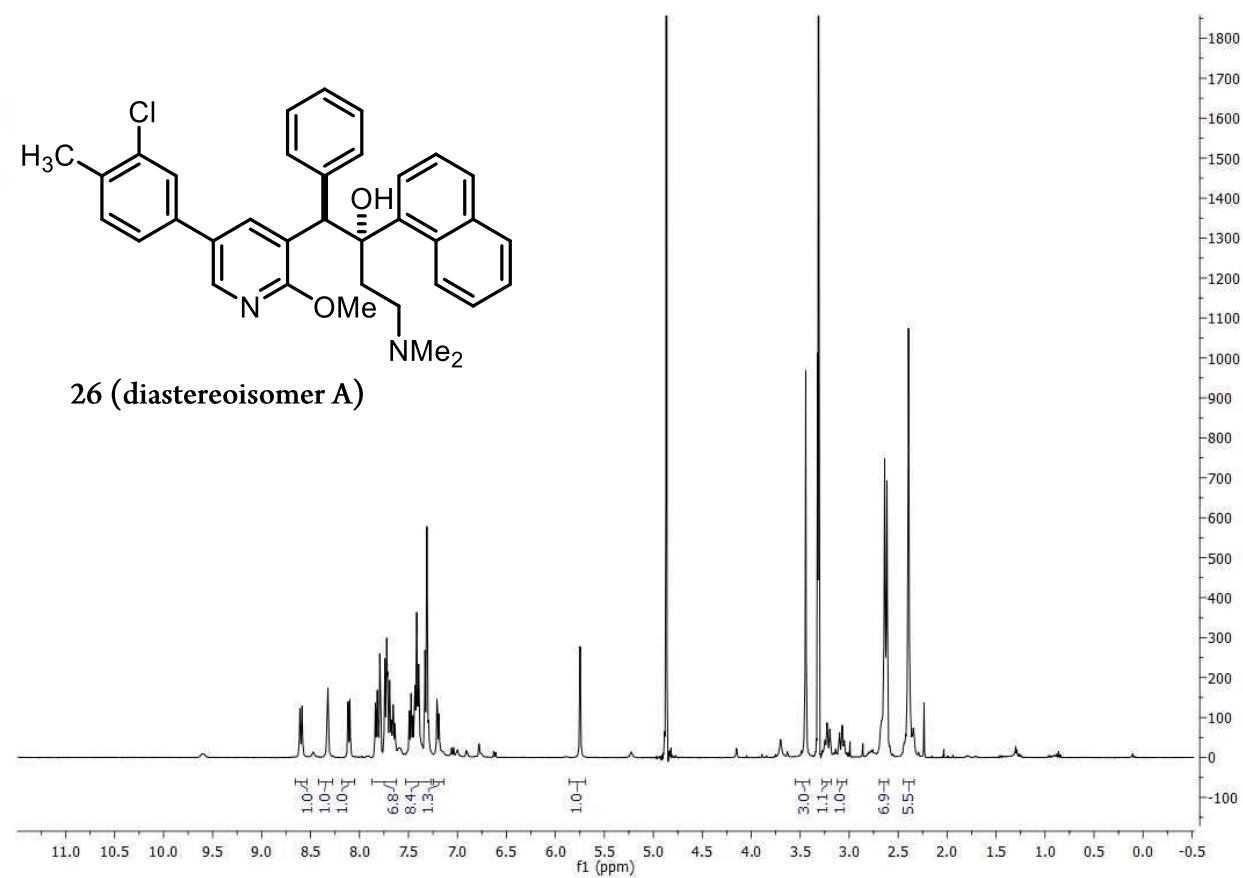
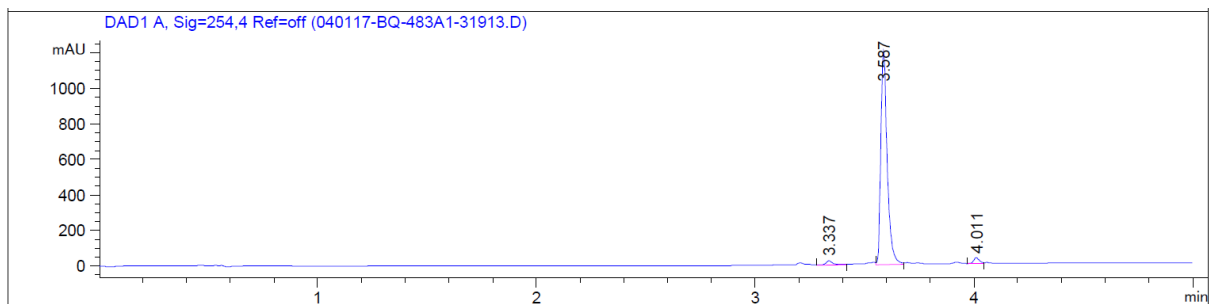


1-(5-(3-chloro-4-methylphenyl)-2-methoxypyridin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (26)

Diastereoisomer A:

LCMS (m/z): 550.9

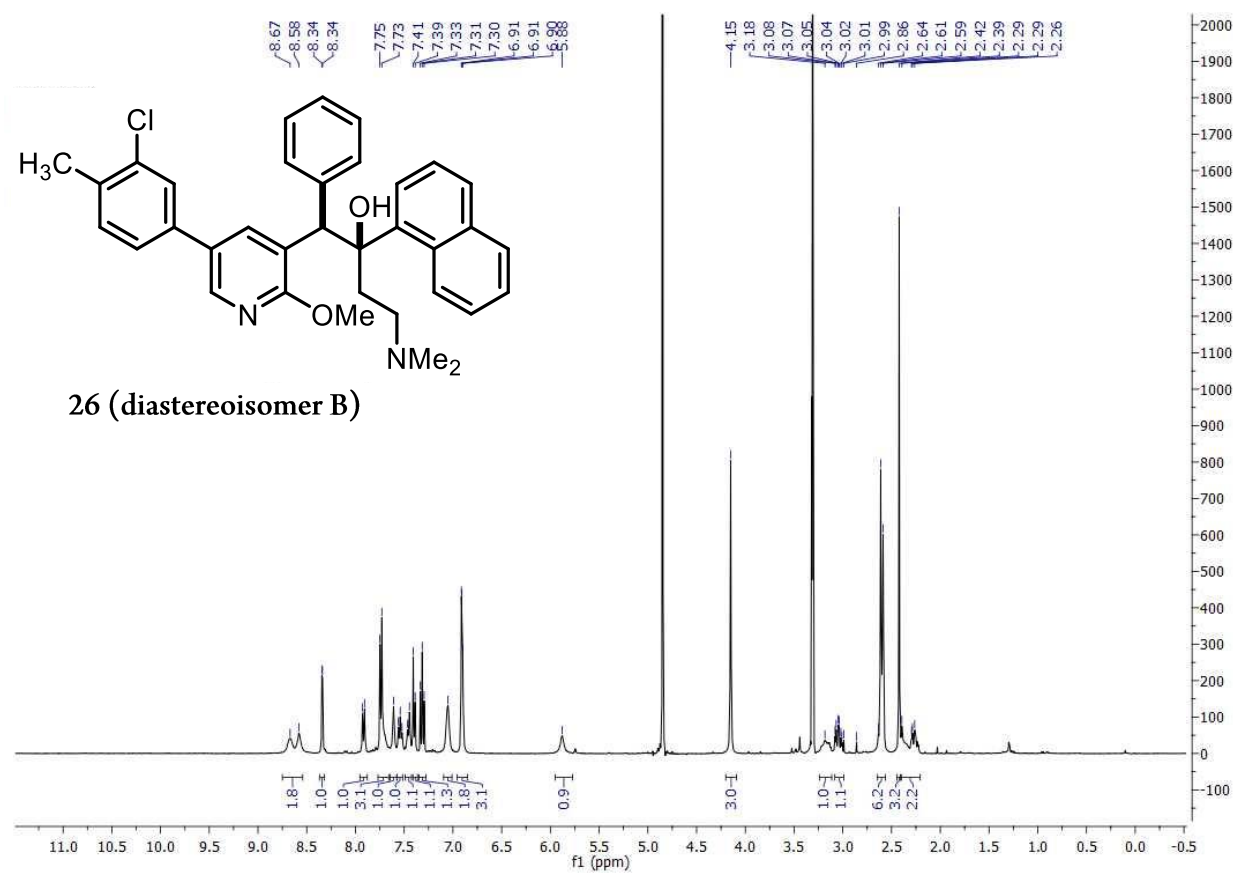
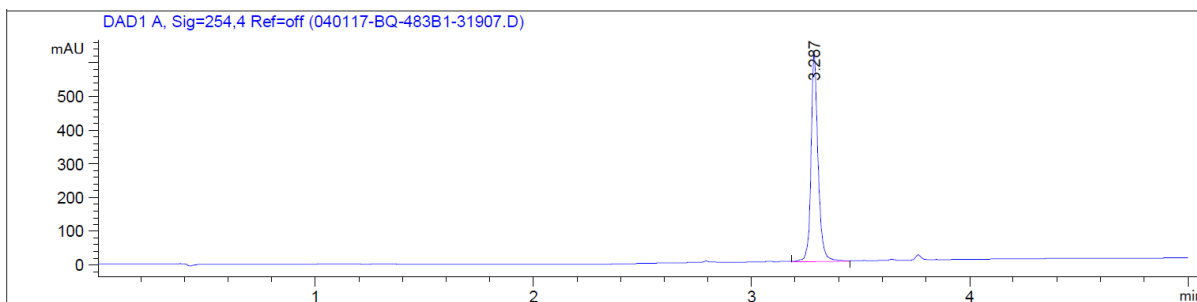
HPLC Trace:



Diastereoisomer B:

LCMS (m/z): 550.9

HPLC Trace:

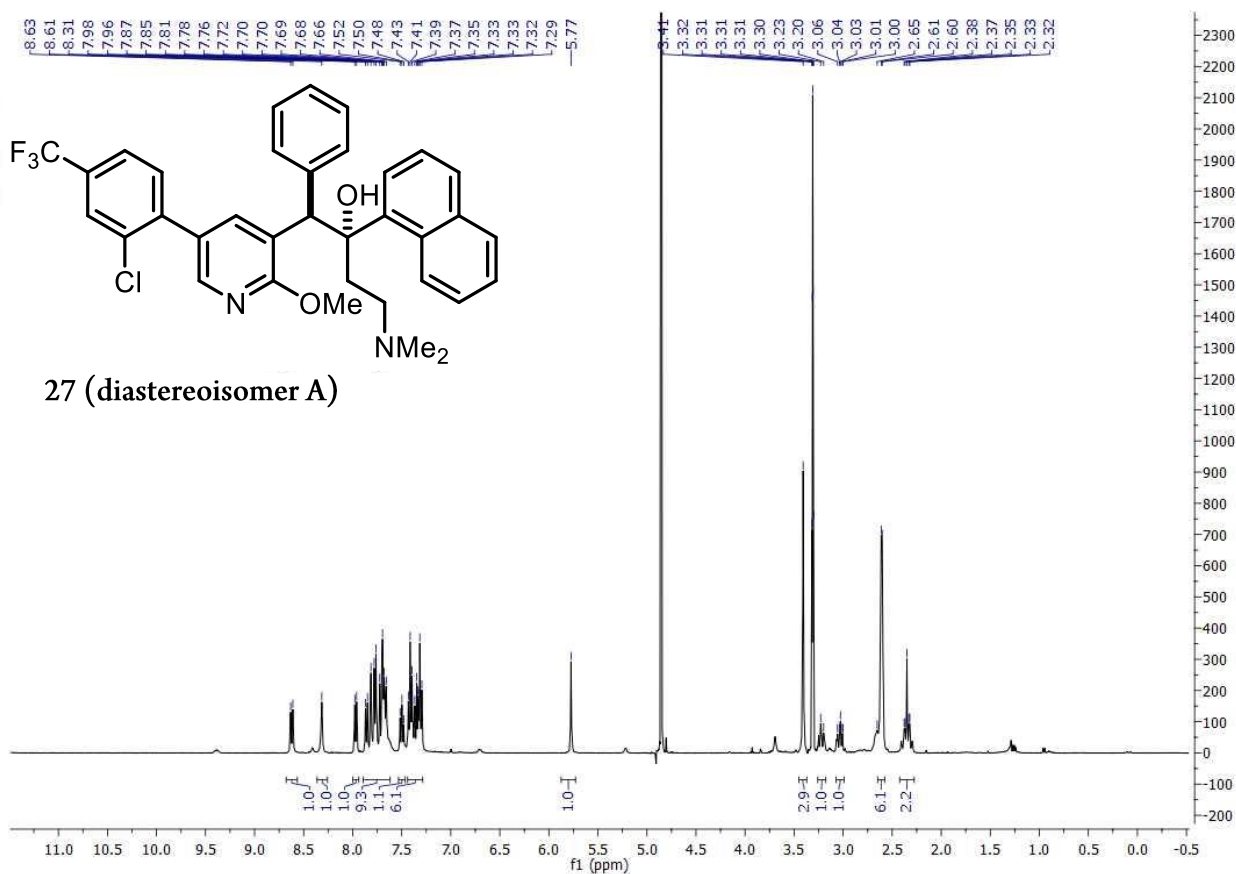
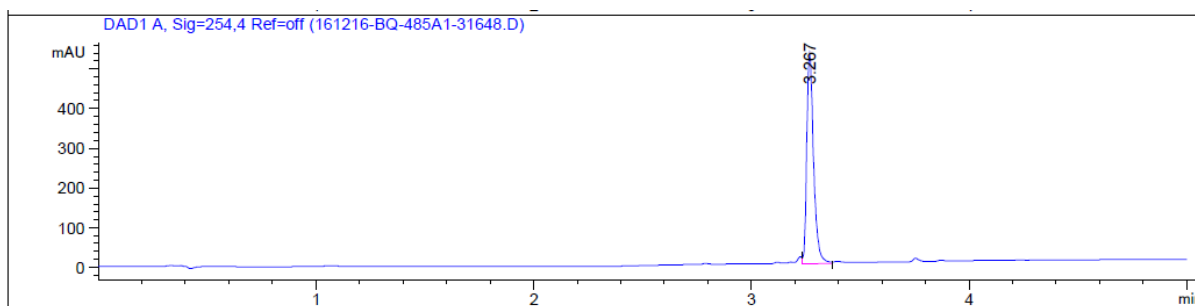


1-(5-(2-chloro-4-(trifluoromethyl)phenyl)-2-methoxypyridin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (27)

Diastereoisomer A:

LCMS (m/z): 604.9

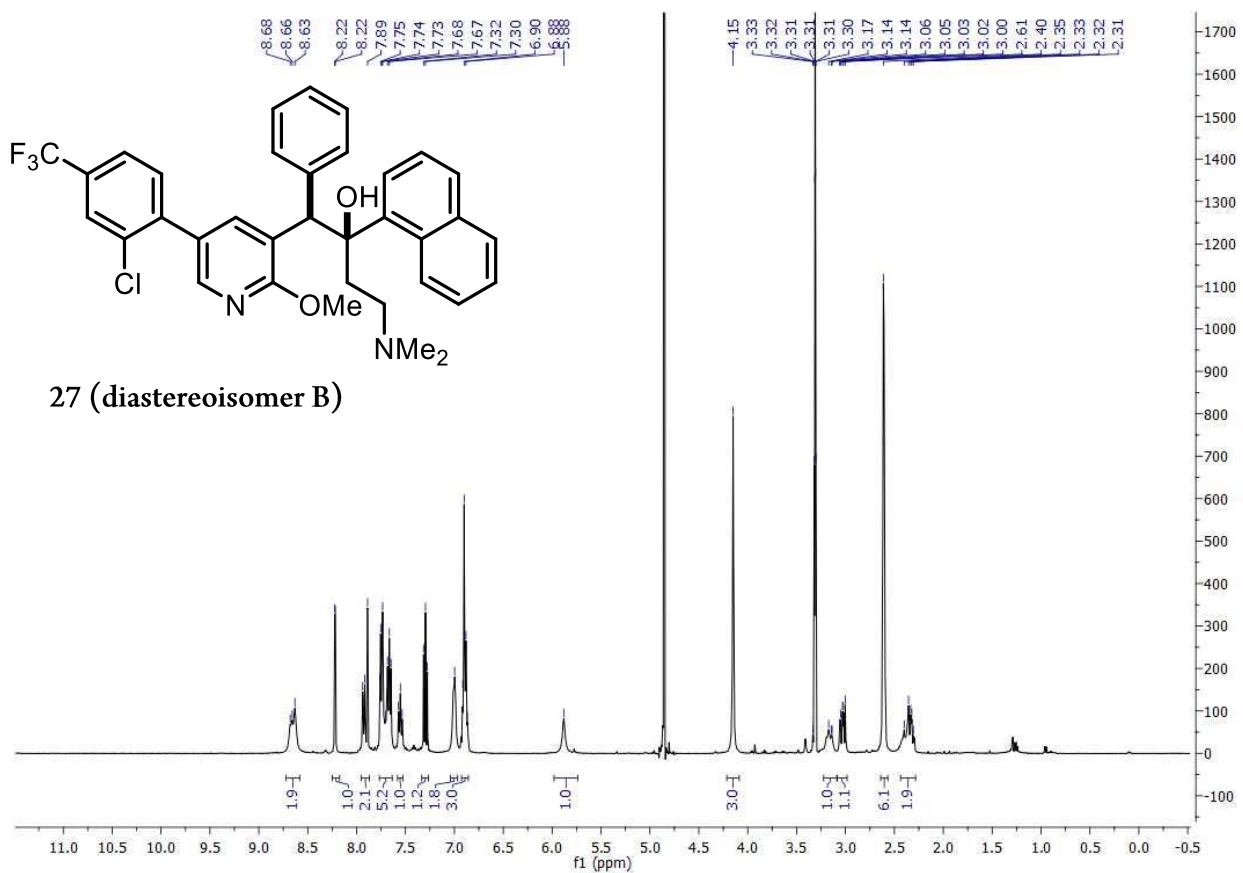
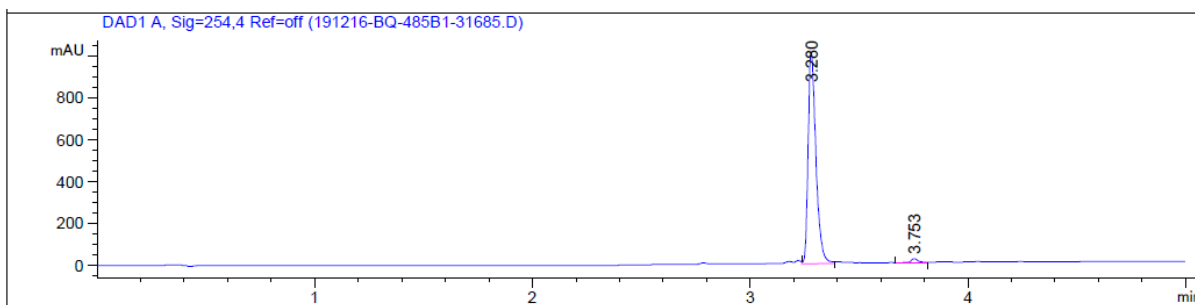
HPLC Trace:



Diastereoisomer B:

LCMS (m/z): 604.9

HPLC Trace:

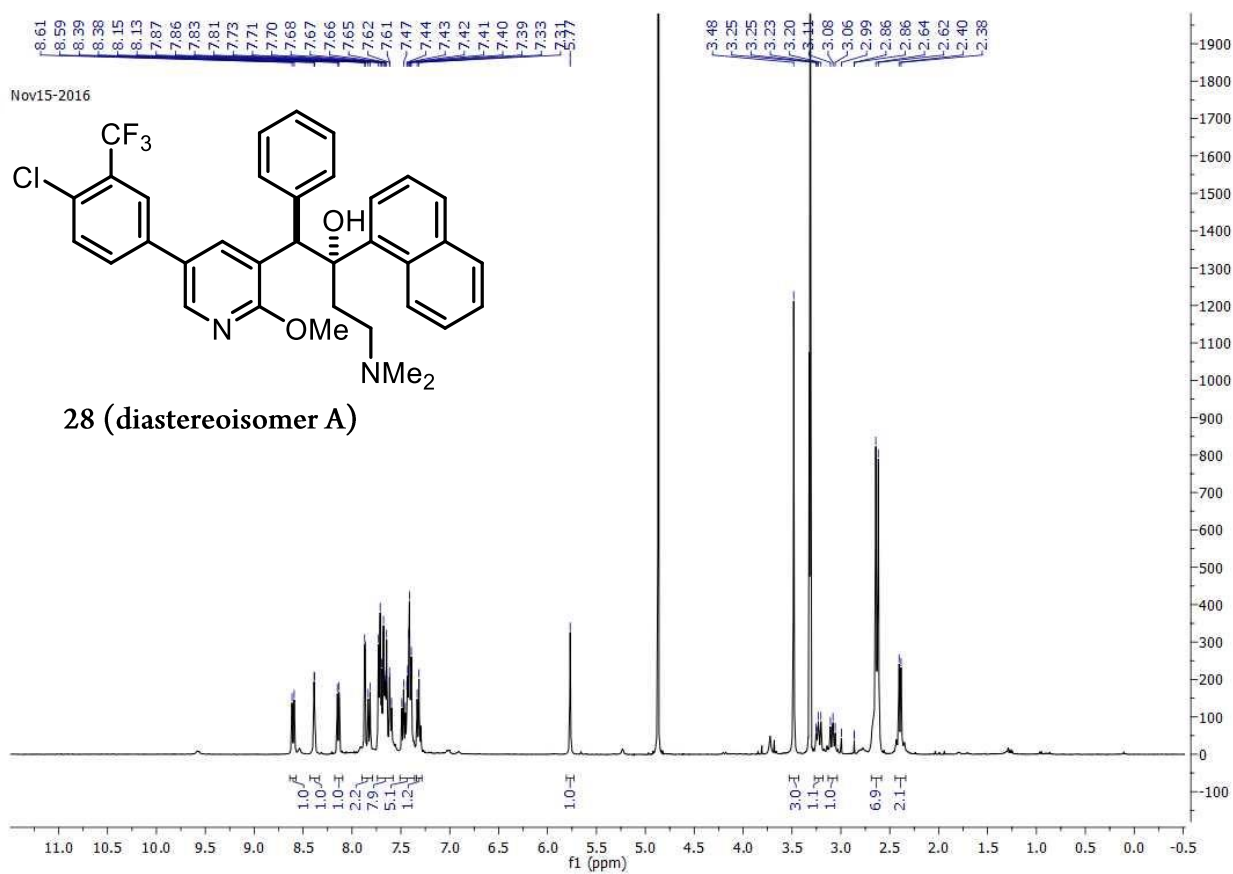
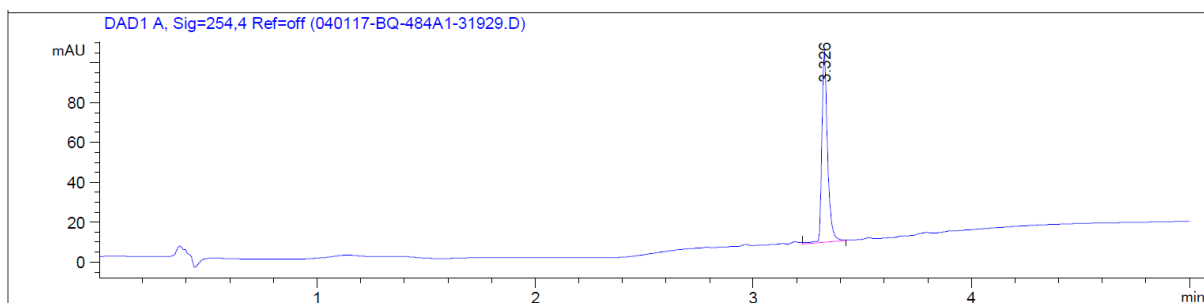


1-(5-(4-chloro-3-(trifluoromethyl)phenyl)-2-methoxypyridin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (28)

Diastereoisomer A:

LCMS (m/z): 604.9

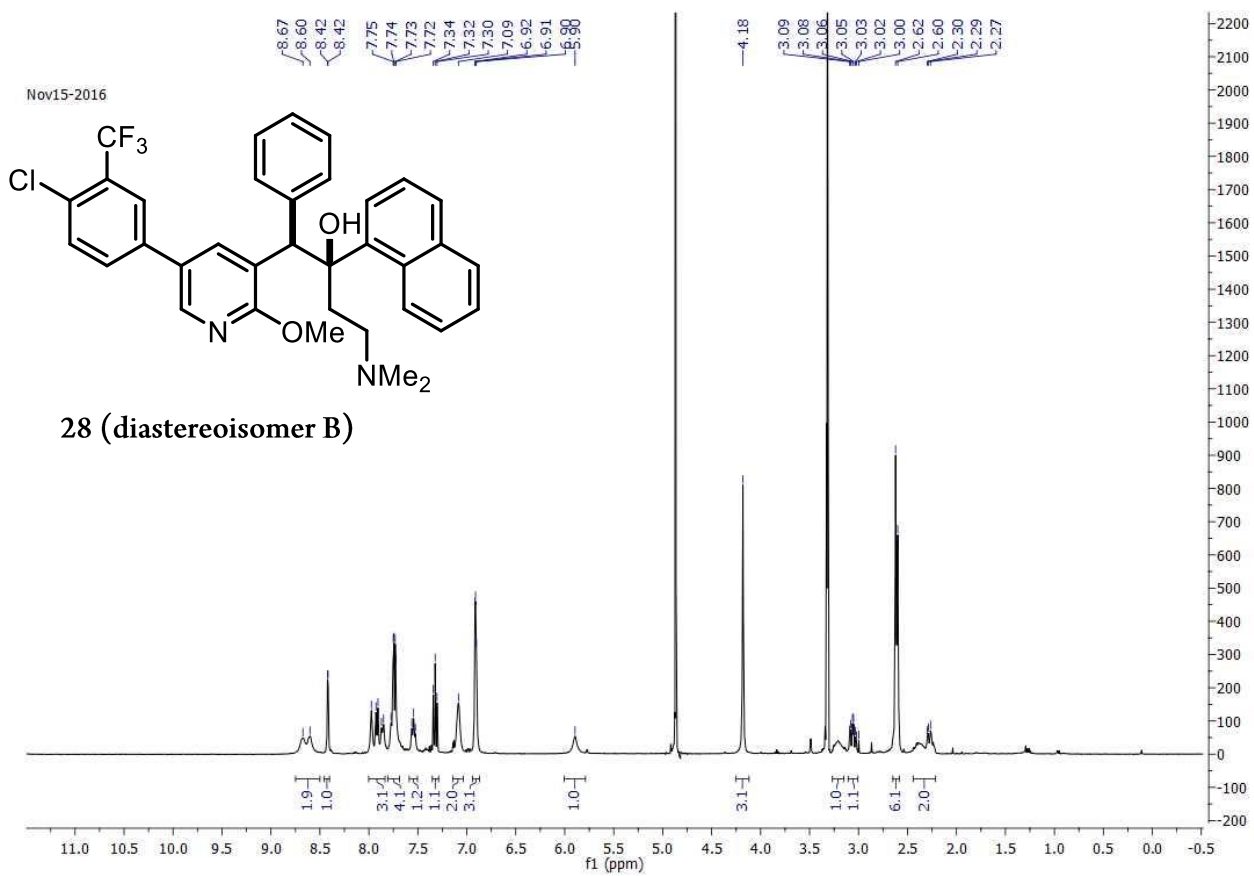
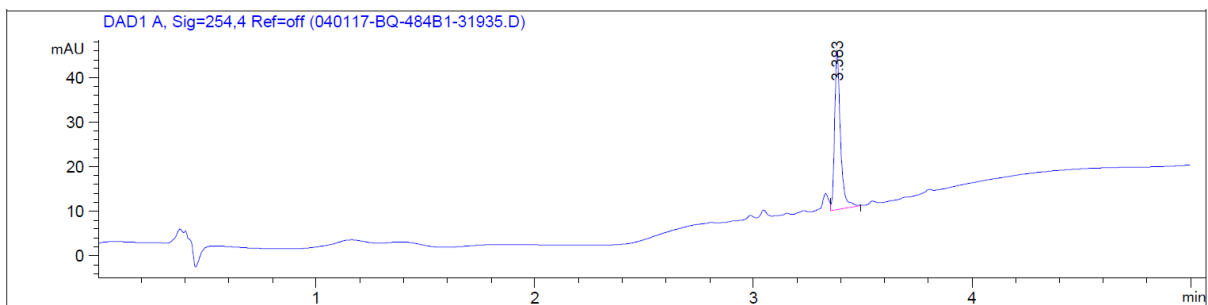
HPLC Trace:



Diastereoisomer B:

LCMS (m/z): 604.9

HPLC Trace:

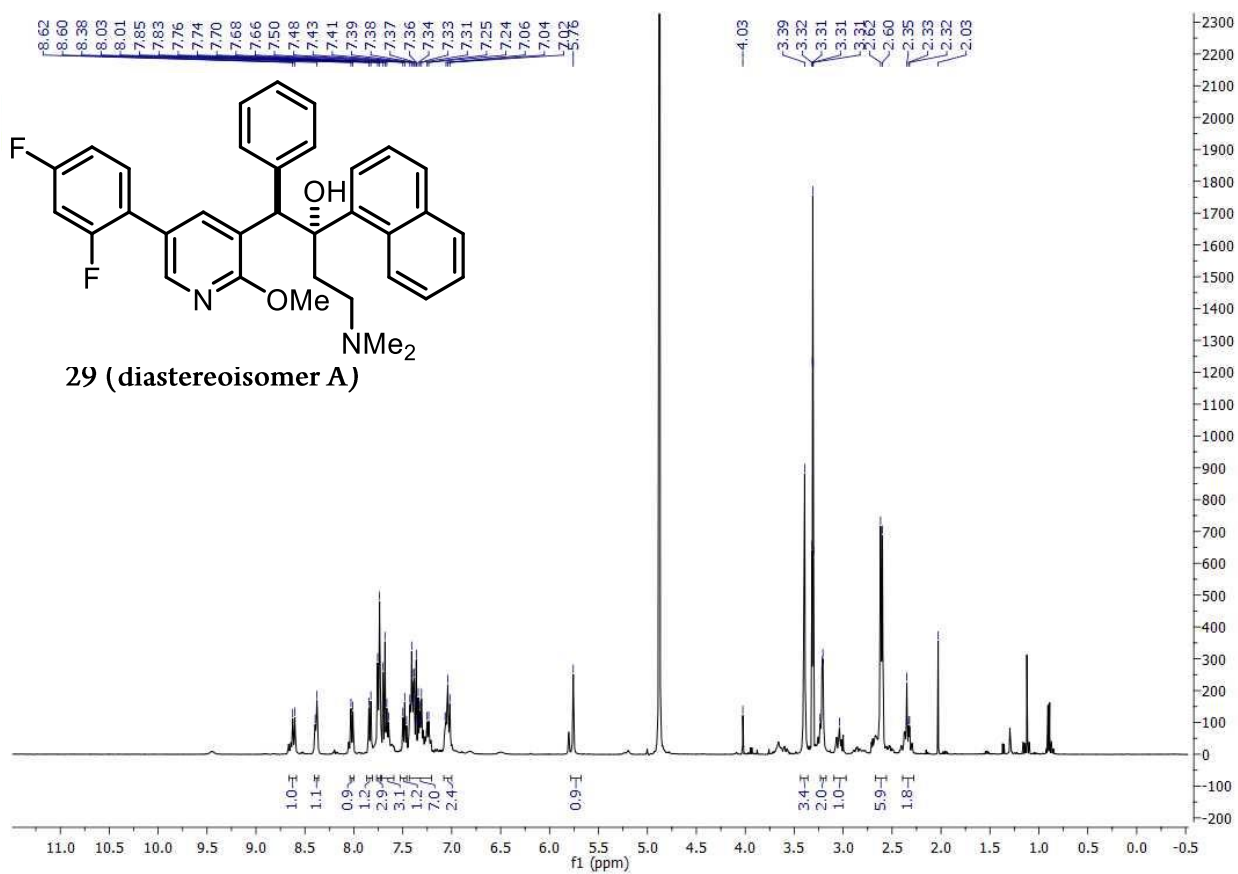
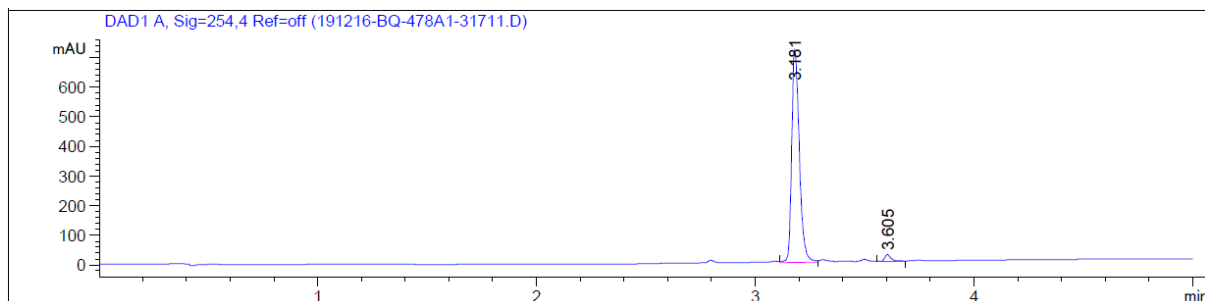


1-(5-(2,4-difluorophenyl)-2-methoxypyridin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (29)

Diastereoisomer A:

LCMS (m/z): 538.9

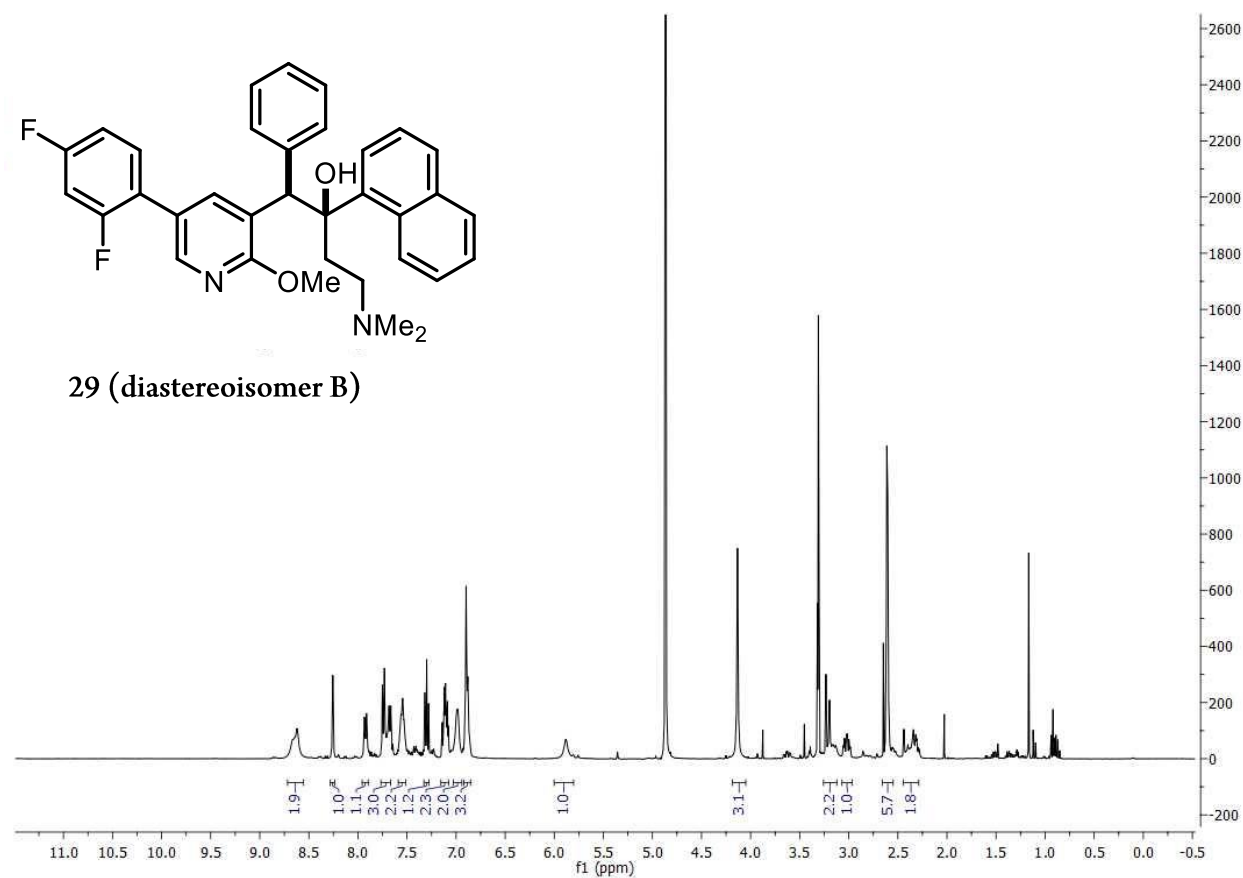
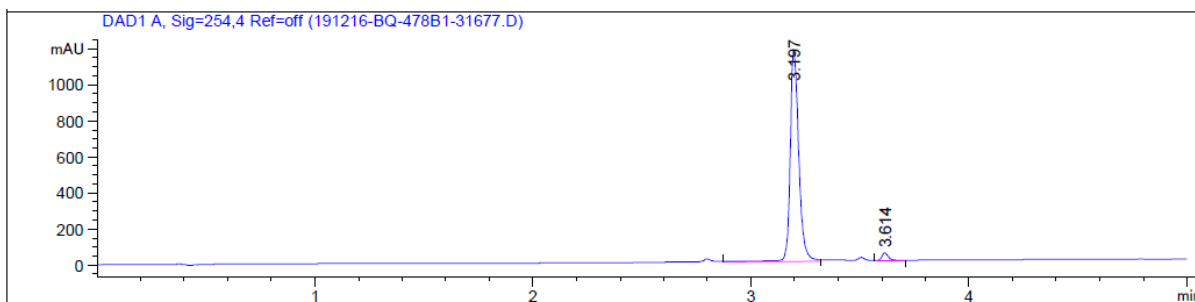
HPLC Trace:



Diastereoisomer B:

LCMS (m/z): 538.9 (M+H)⁺

HPLC Trace:

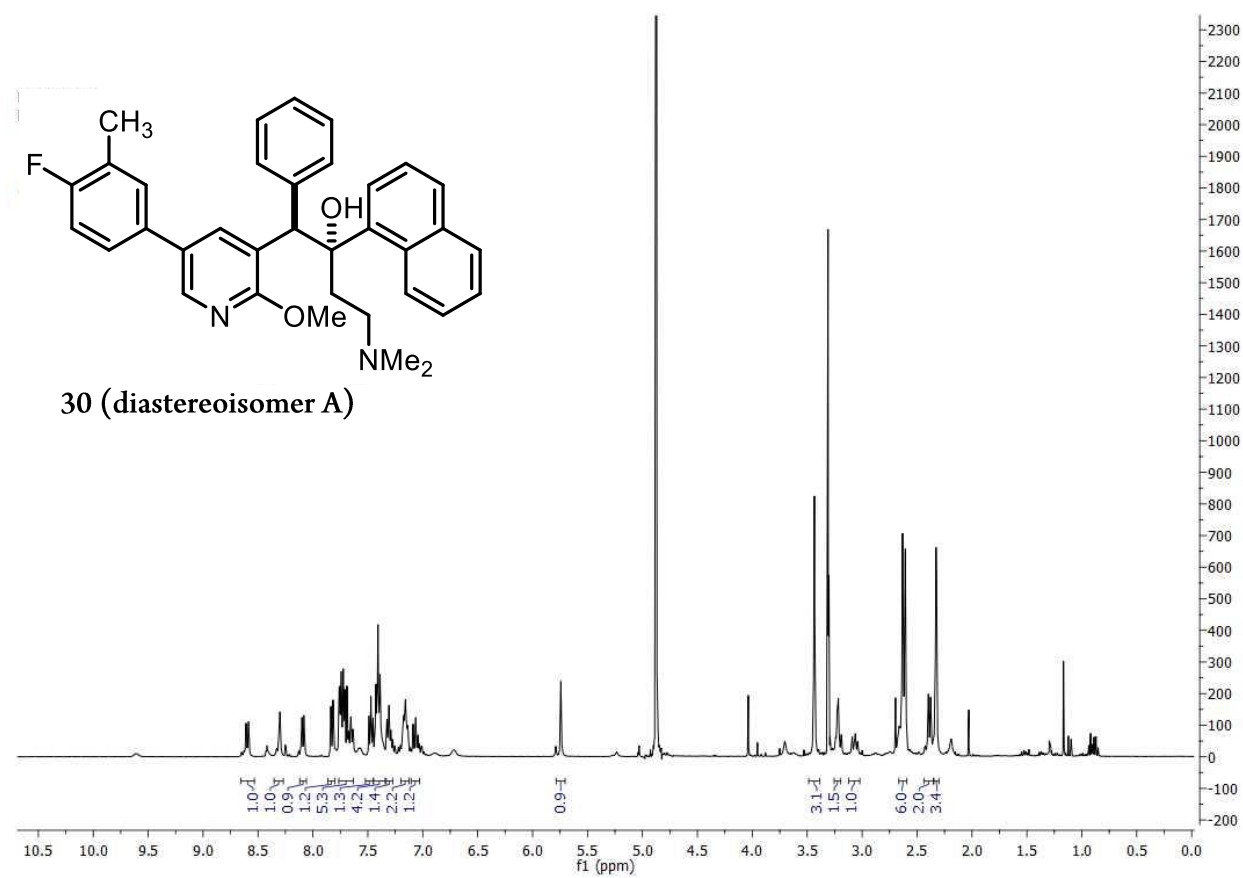
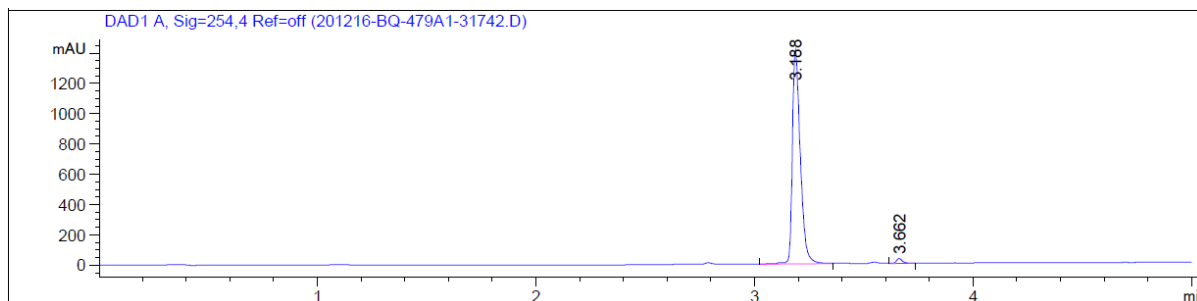


4-(dimethylamino)-1-(5-(4-fluoro-3-methylphenyl)-2-methoxypyridin-3-yl)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (30)

Diastereoisomer A:

LCMS (m/z): 534.9

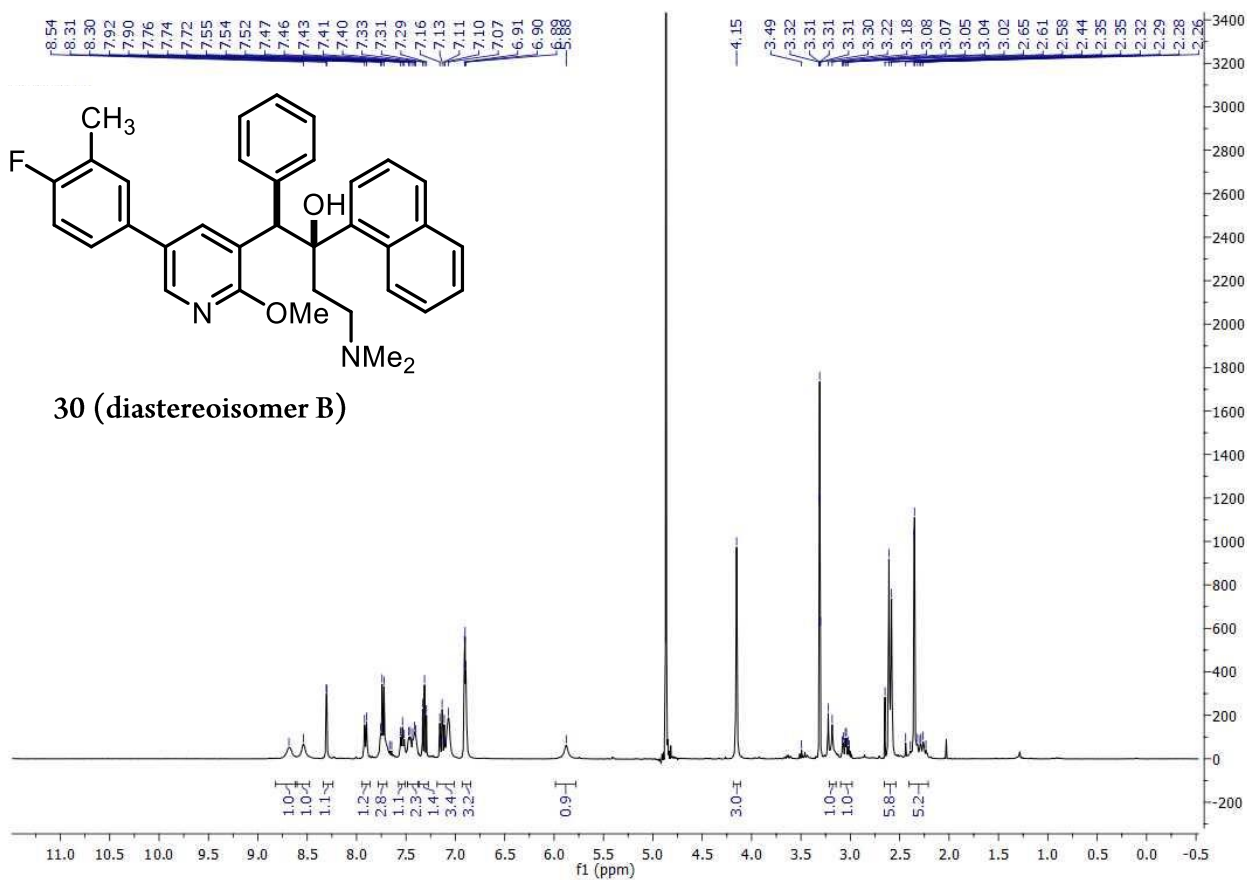
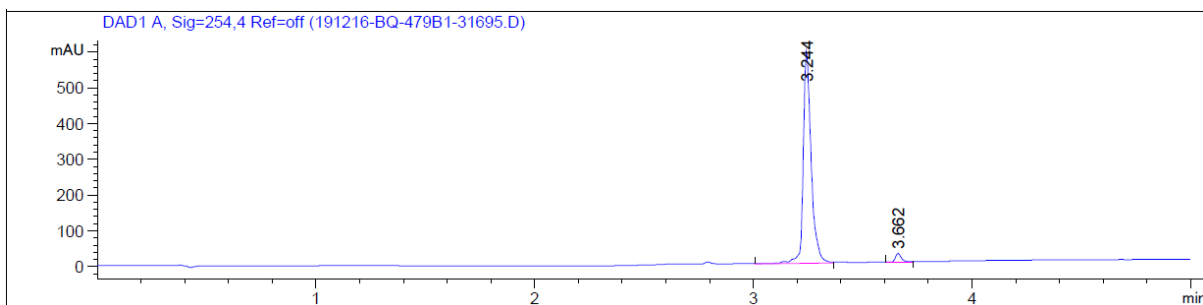
HPLC Trace:



Diastereoisomer B:

LCMS (m/z): 535.0

HPLC Trace:

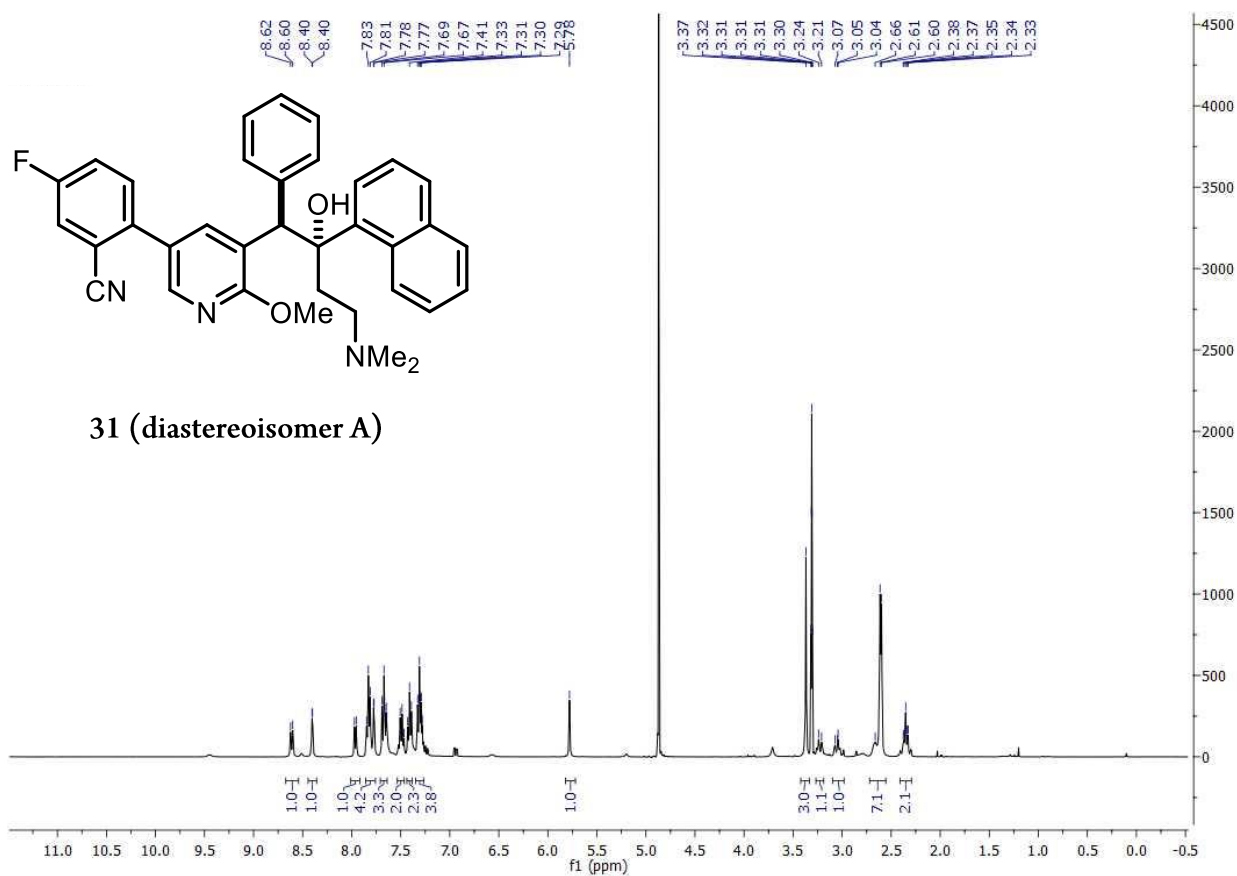
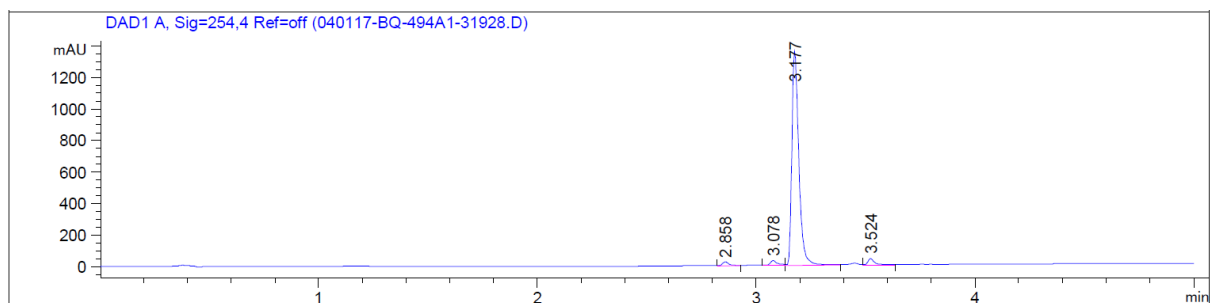


2-(5-(4-(dimethylamino)-2-hydroxy-2-(naphthalen-1-yl)-1-phenylbutyl)-6-methoxy-pyridin-3-yl)-5-fluorobenzonitrile (31)

Diastereoisomer A:

LCMS (m/z): 545.9

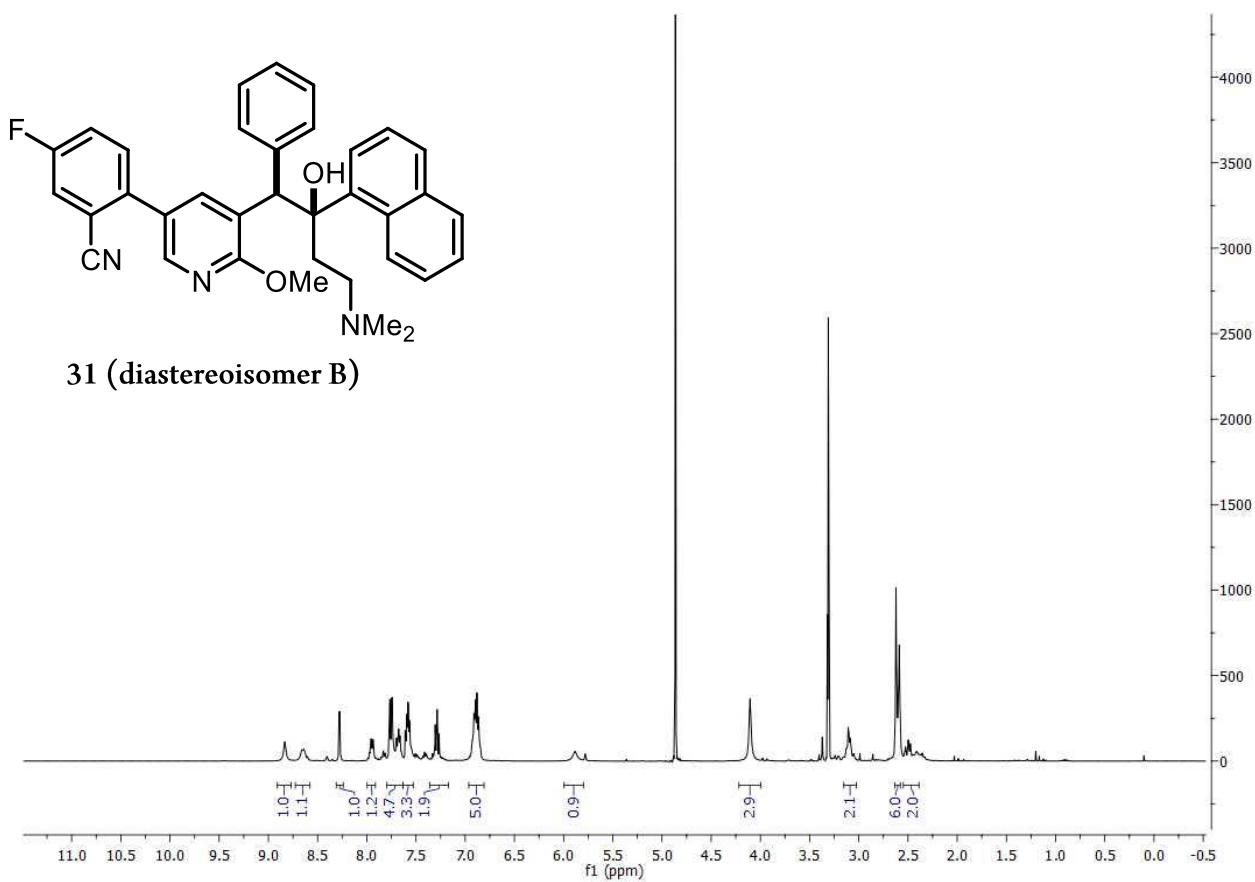
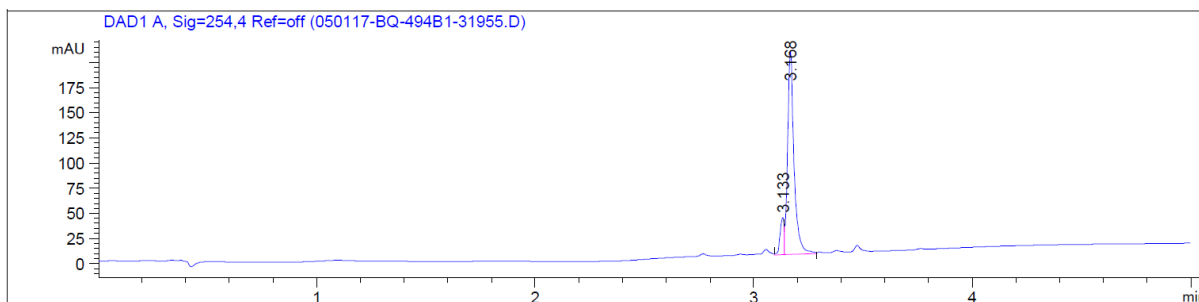
HPLC Trace:



Diastereoisomer B:

LCMS (m/z): 545.9

HPLC Trace:

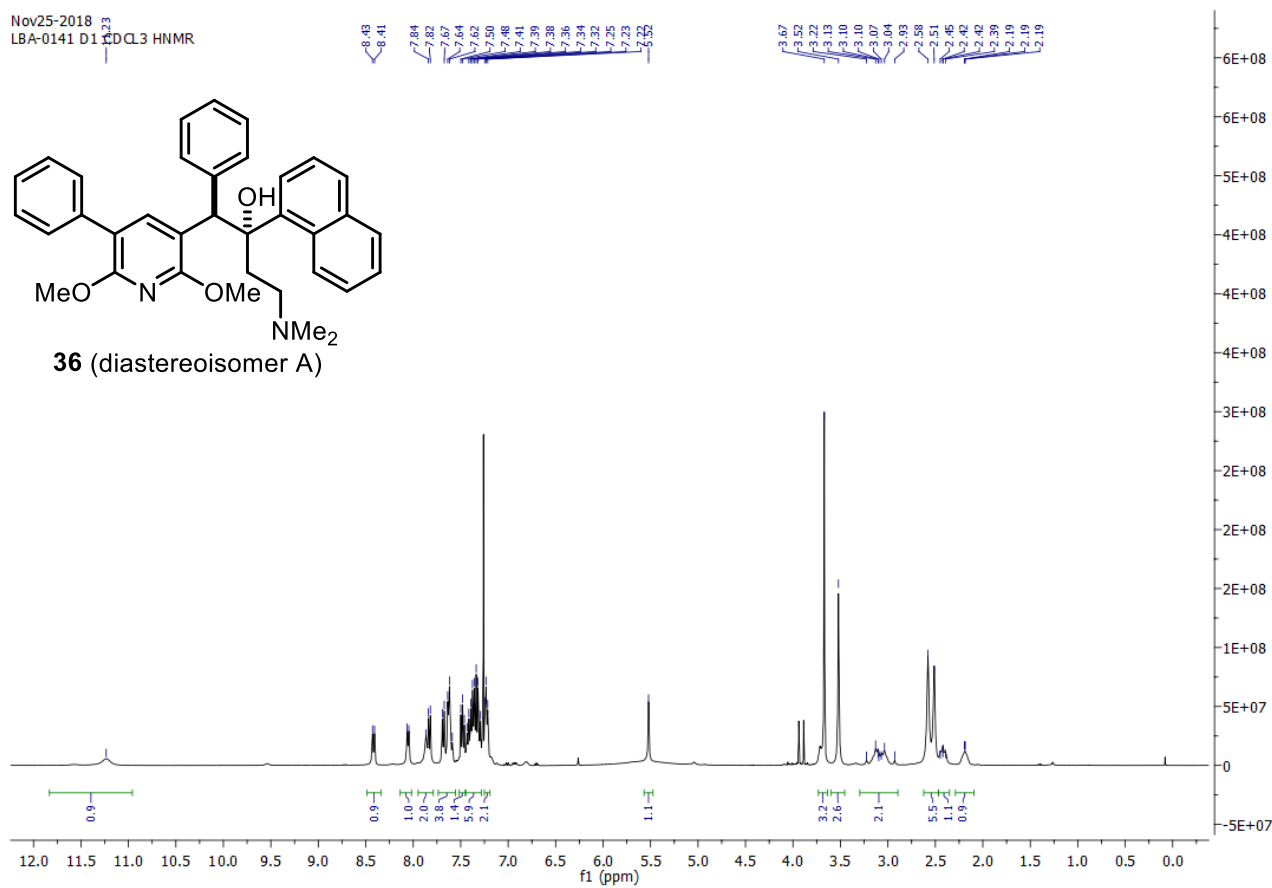
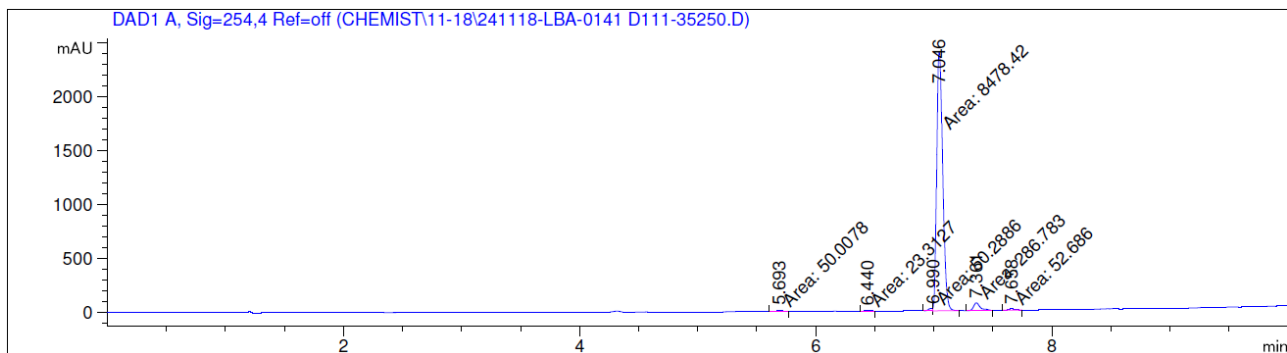


1-(2,6-dimethoxy-5-phenylpyridin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (36)

Diastereoisomer A:

LCMS (m/z): 533.1

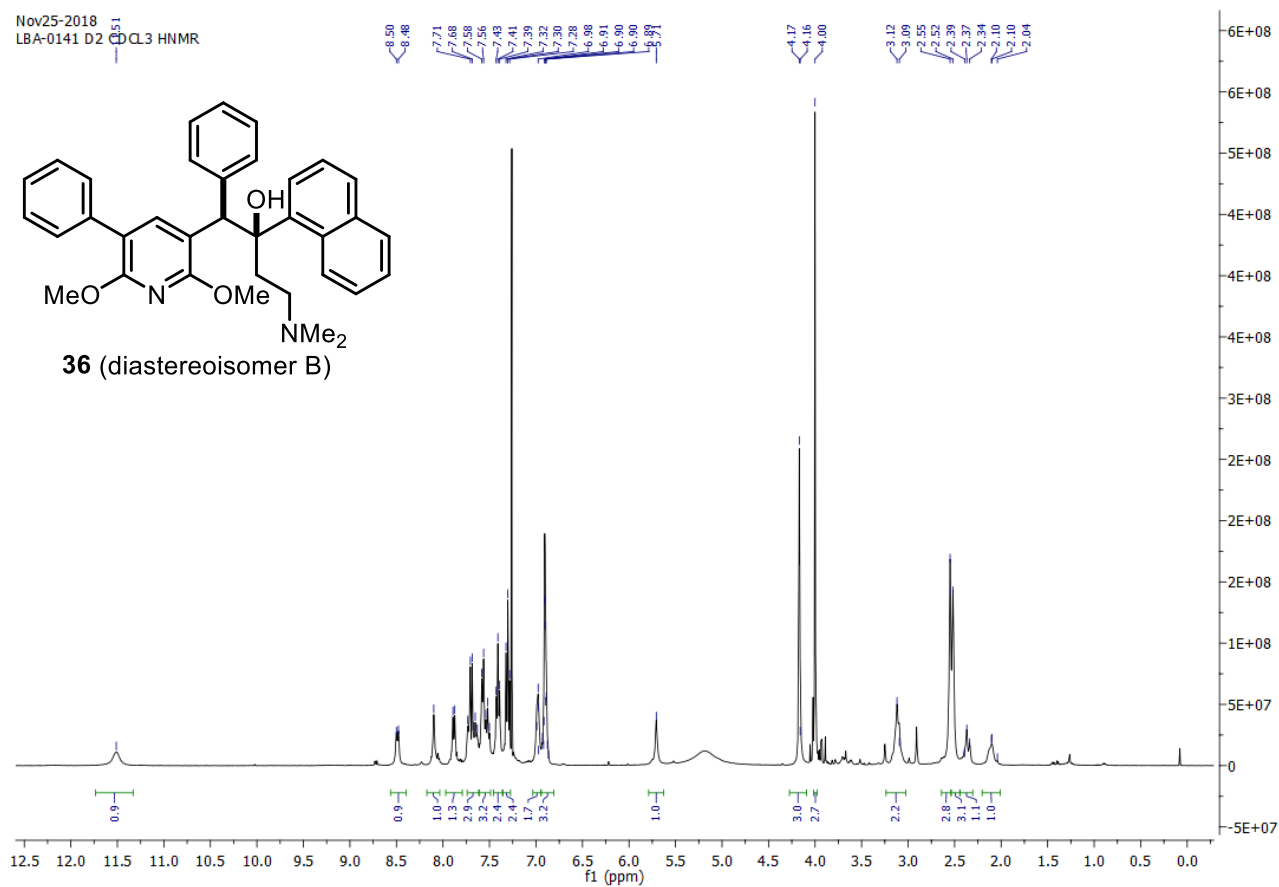
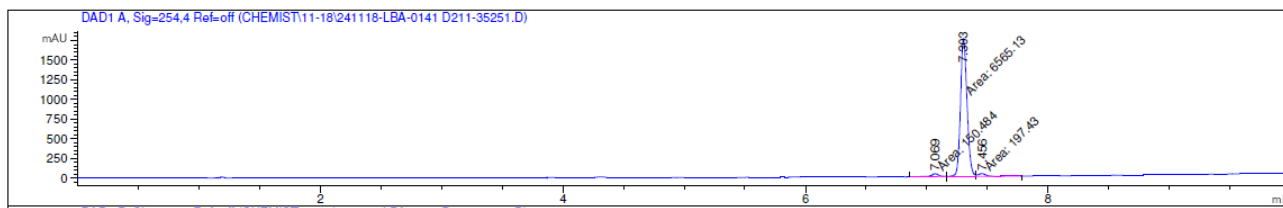
HPLC Trace:



Diastereoisomer B:

LCMS (m/z): 533.1

HPLC Trace:

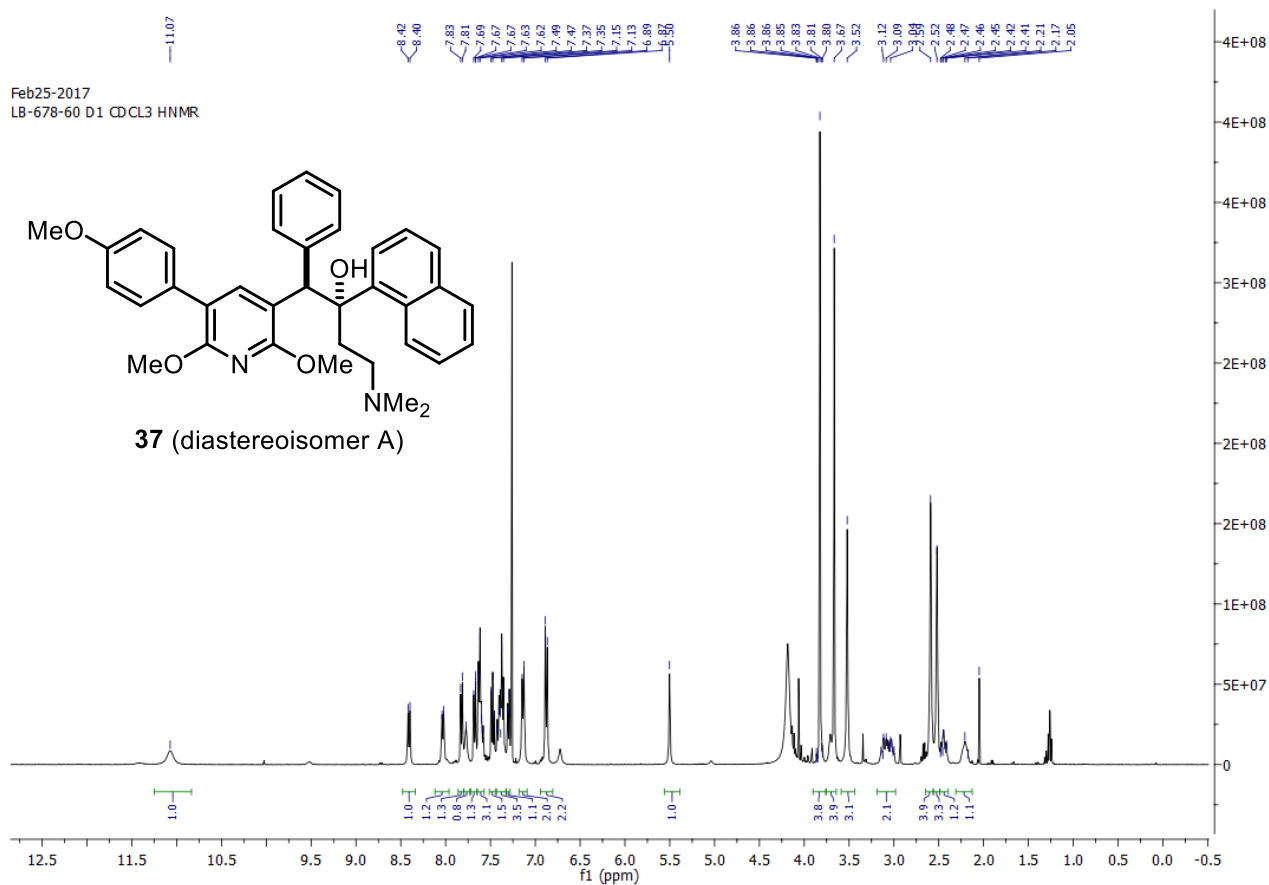
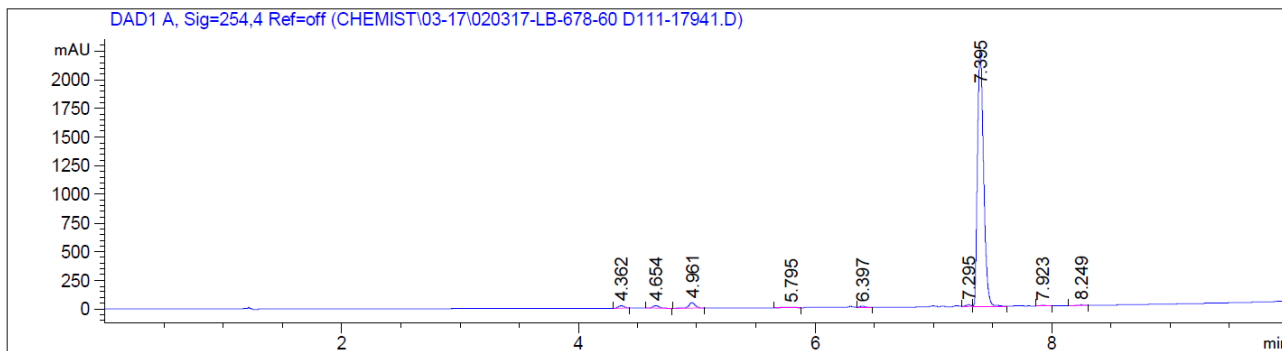


1-(2,6-dimethoxy-5-(4-methoxyphenyl)pyridin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (37)

Diastereoisomer A:

LCMS (m/z): 562.9

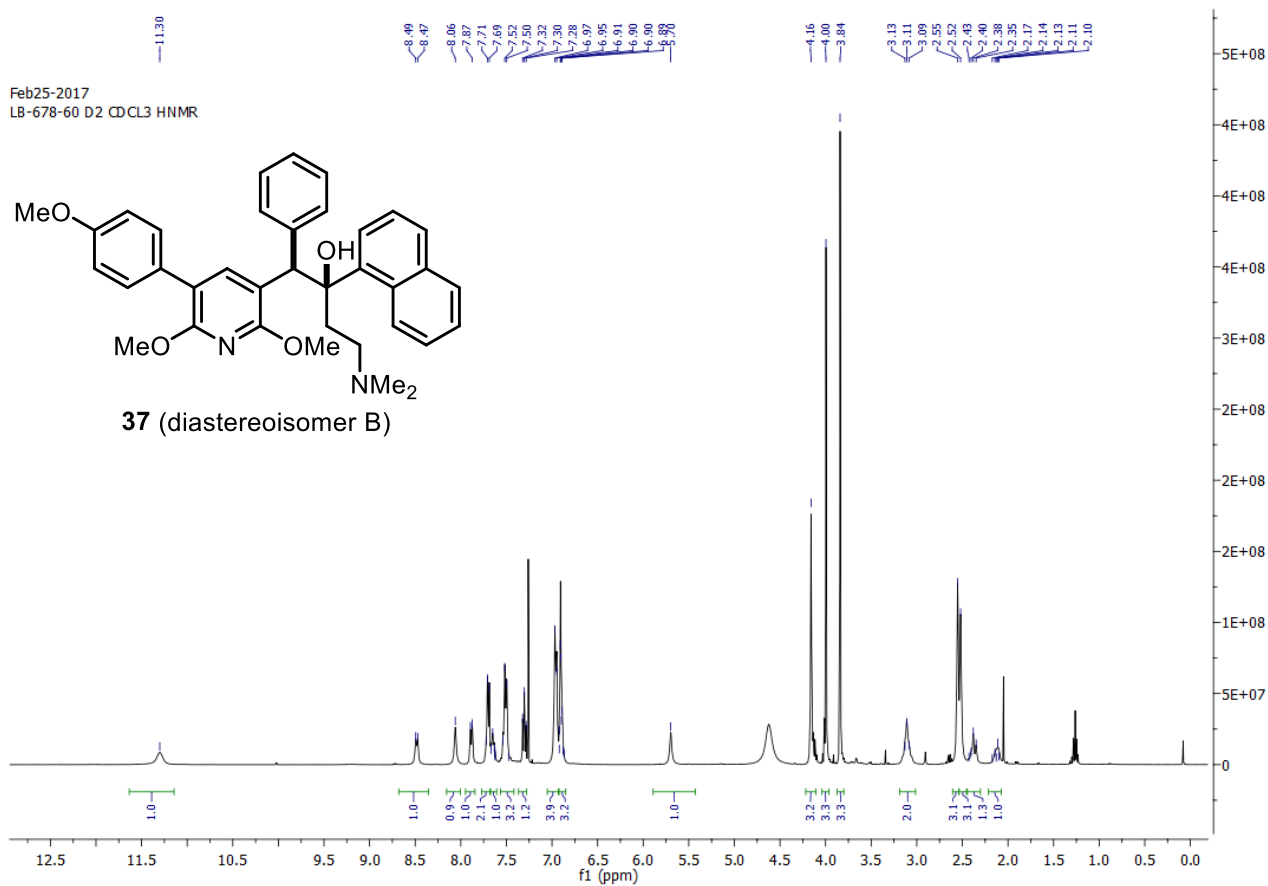
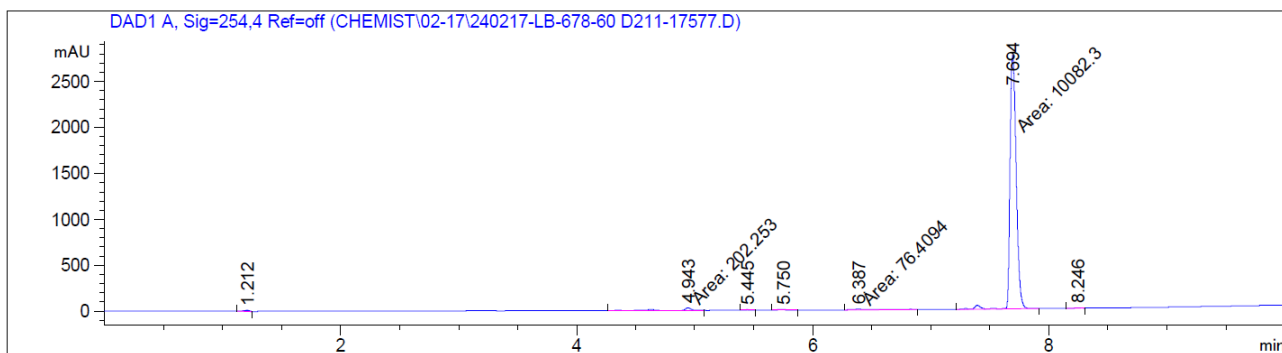
HPLC Trace:



Diastereoisomer B:

LCMS (m/z): 562.9

HPLC Trace:

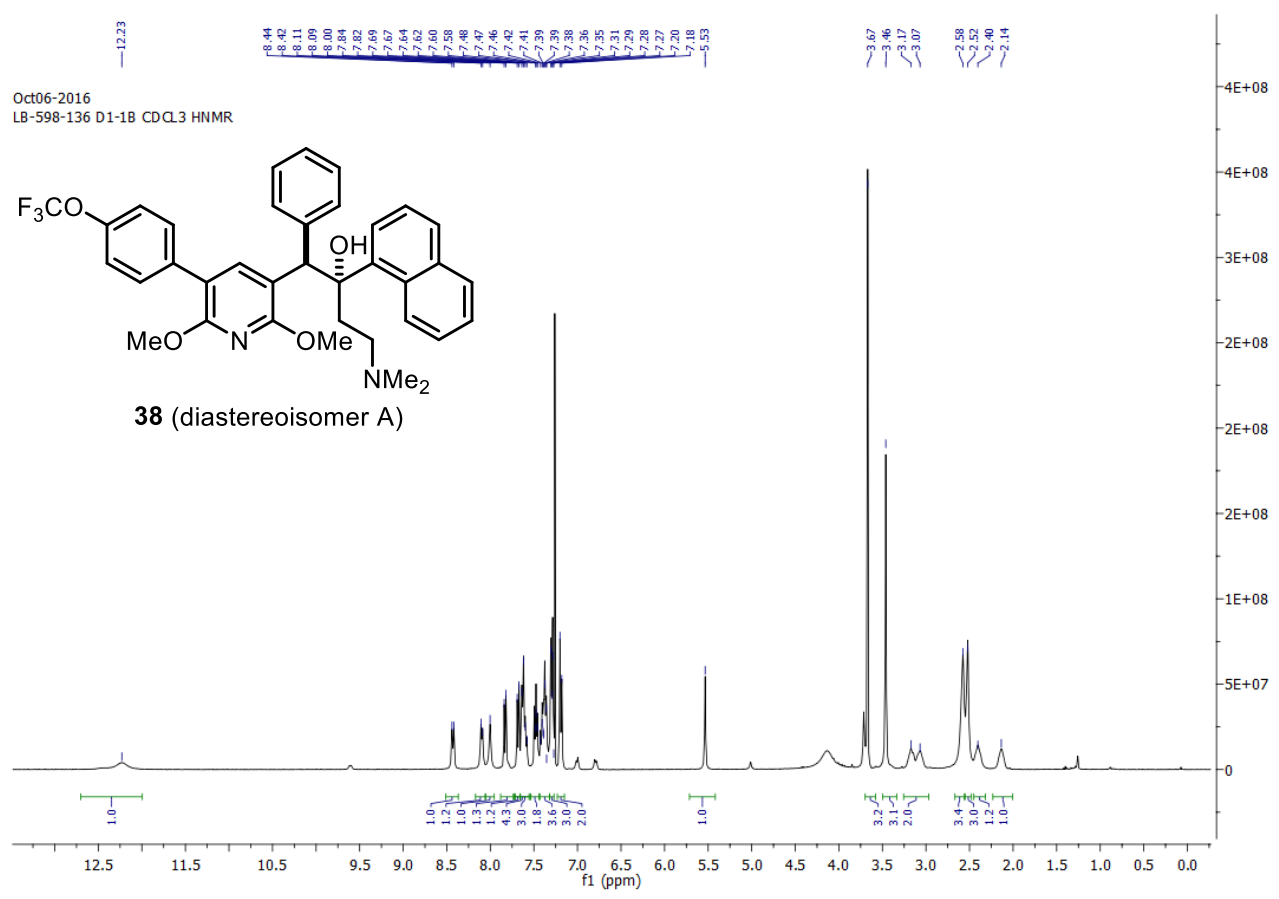
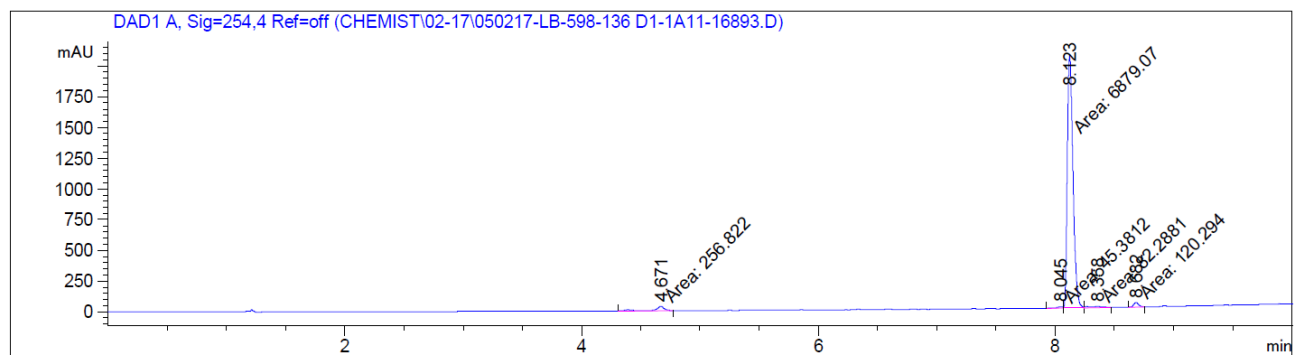


1-(2,6-dimethoxy-5-(4-(trifluoromethoxy)phenyl)pyridin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (38)

Diastereoisomer A:

LCMS (*m/z*): 616.9

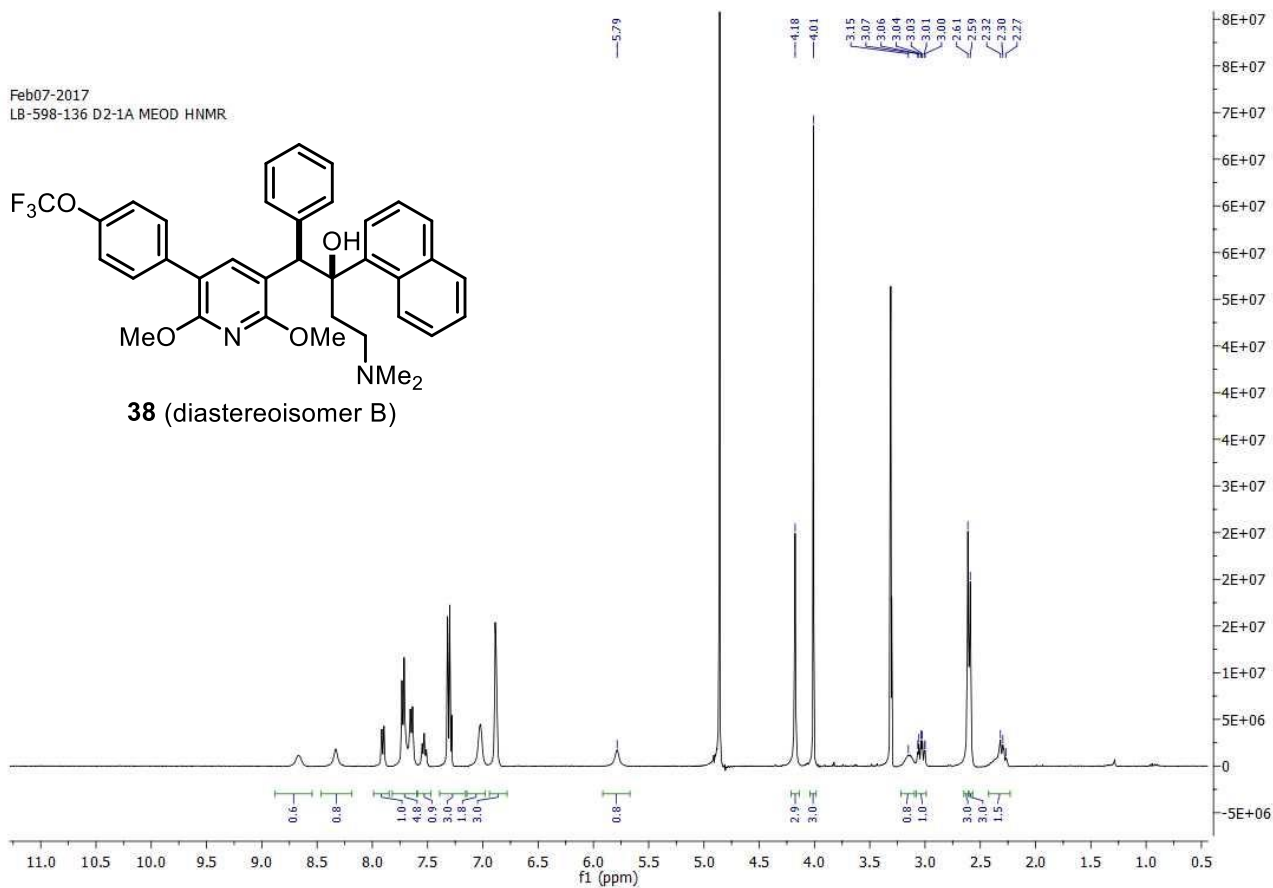
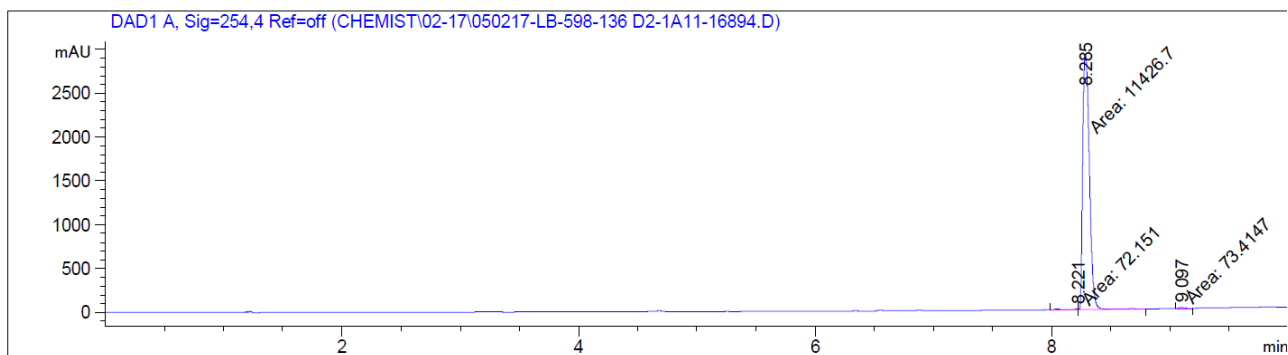
HPLC Trace:



Diastereoisomer B:

LCMS (m/z): 616.9

HPLC Trace:

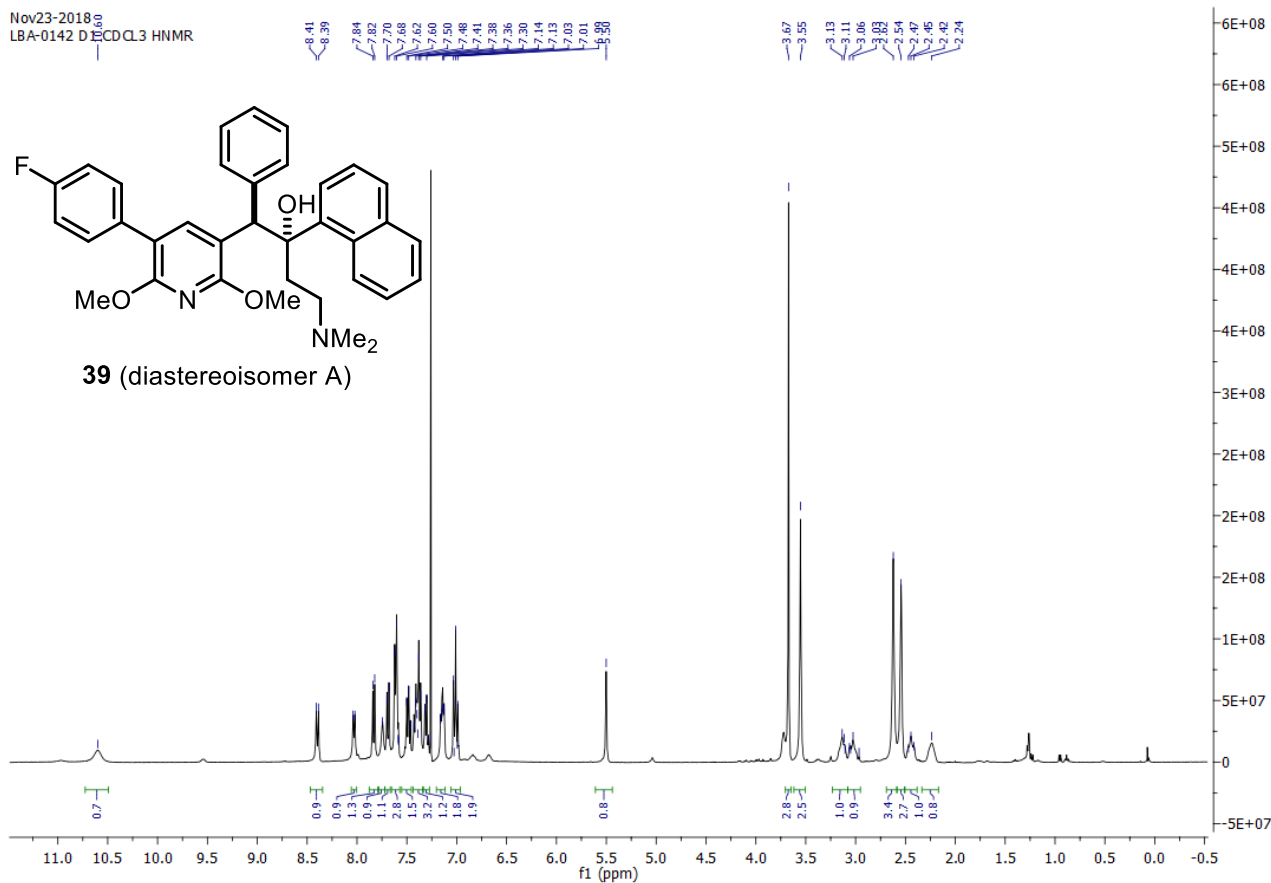
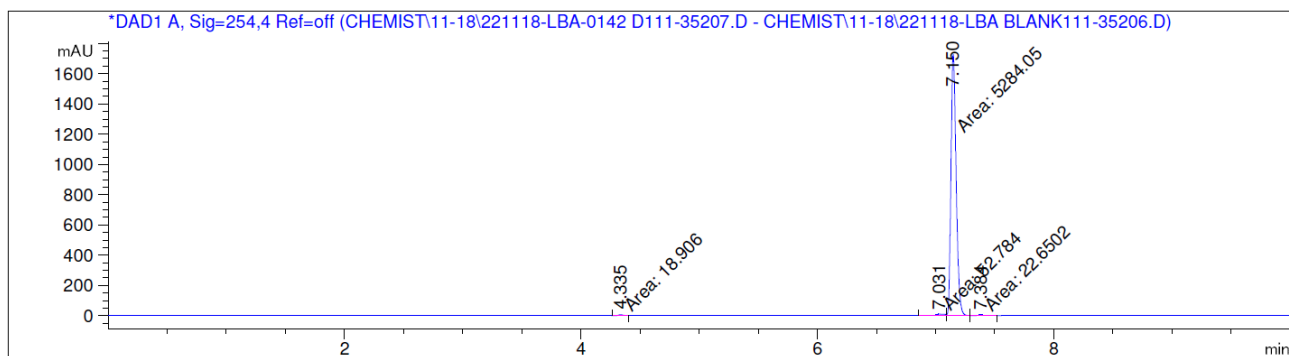


4-(dimethylamino)-1-(5-(4-fluorophenyl)-2,6-dimethoxypyridin-3-yl)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (39)

Diastereoisomer A:

LCMS (m/z): 551.0

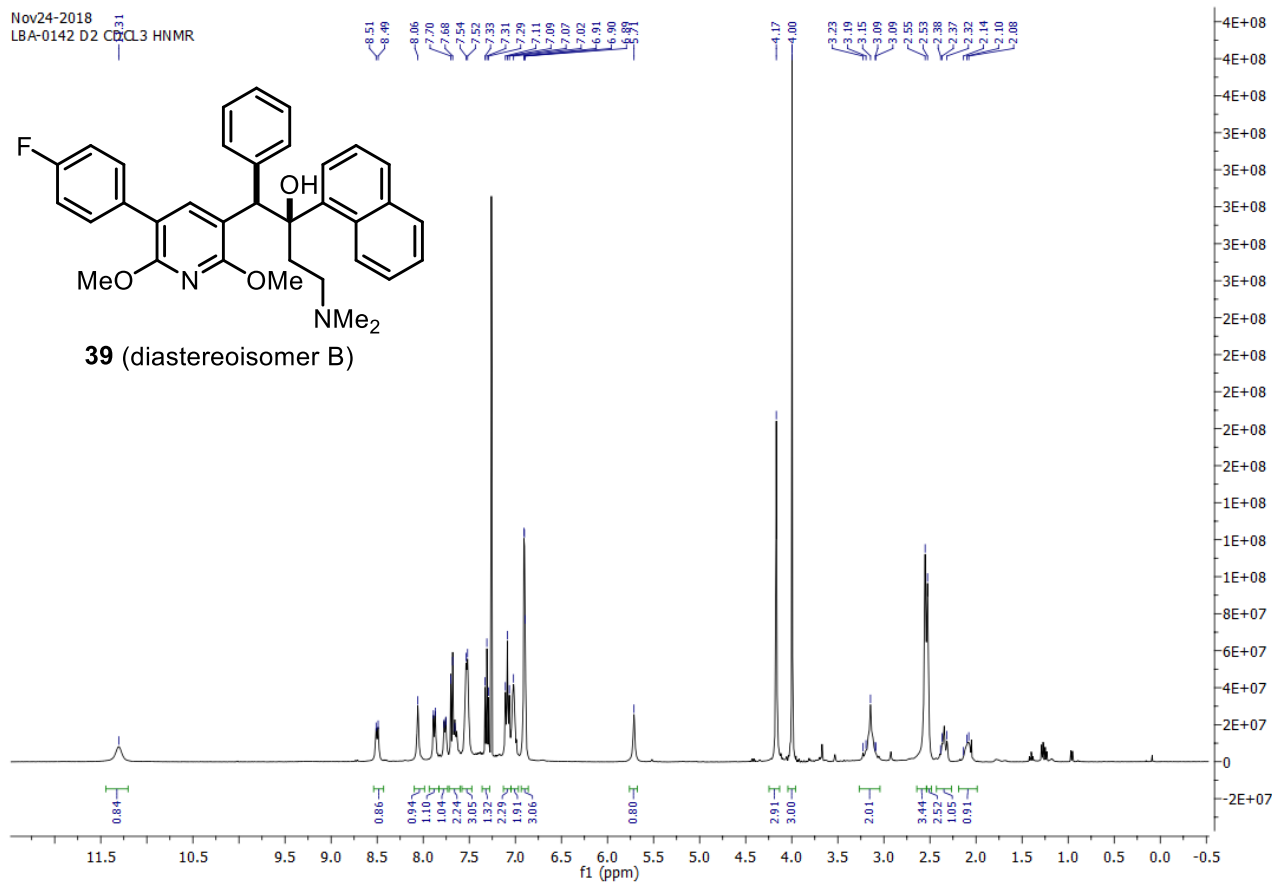
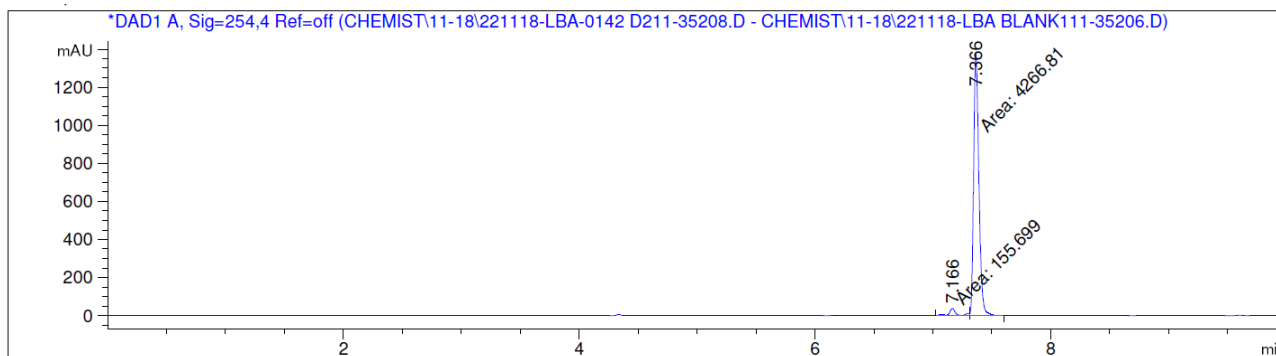
HPLC Trace:



Diastereoisomer B:

LCMS (m/z): 551.0

HPLC Trace:

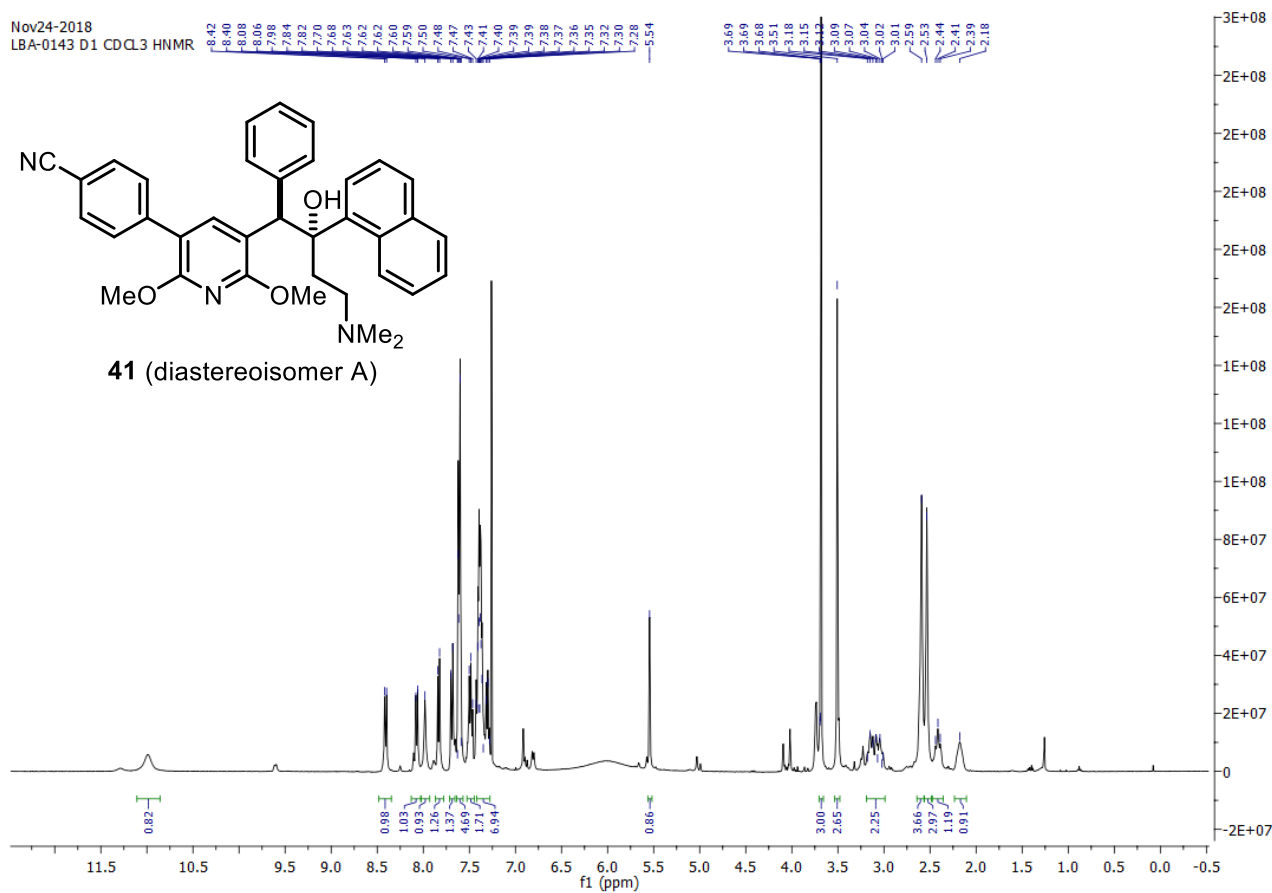
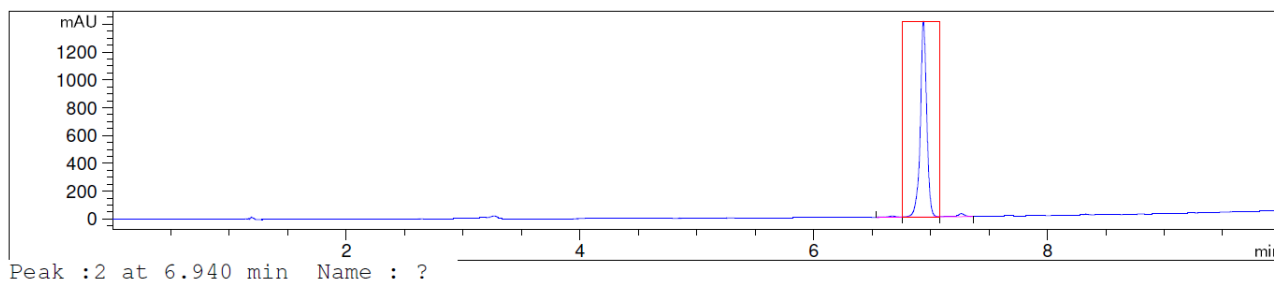


4-(5-(4-(dimethylamino)-2-hydroxy-2-(naphthalen-1-yl)-1-phenylbutyl)-2,6-dimethoxy-3-pyridinyl)benzonitrile (41)

Diastereoisomer A:

LCMS (m/z): 558.0

HPLC Trace:



Diastereoisomer B:

LCMS (m/z): 558.0

HPLC Trace:

