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Co(III)(salen)-catalyzed phenolic kinetic resolution of two stereocentered benzyloxy and azido epoxides: its application in the synthesis of ICI-118,551, an anti-hypertensive agent†

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The salen Co(III)-catalyzed phenolic kinetic resolution of racemic *anti*- or *syn*-azido and benzyloxy epoxides provides a practical route to a range of enantioenriched *anti*- or *syn*-1-aryloxy-3-azido or benzyloxy-2-alcohols in excellent yields and ees. The synthetic potential of this protocol is illustrated with an enantioselective synthesis of ICI-118,551, a β-blocker, in a highly optically pure form (99% ee).

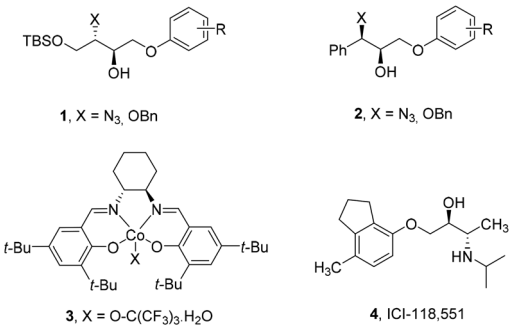
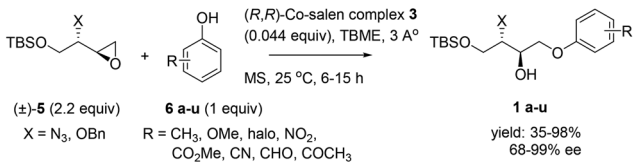


Fig. 1 Structures of *anti*- and *syn*-1-aryloxy-3-azido or benzyloxy-2 alcohols (**1** & **2**), Co(III)-salen complex (**3**) and ICI-118,551 (**4**).



Scheme 1 PKR of *anti*-azido- and benzyloxy epoxides.

Introduction

Enantiomerically pure *anti*- or *syn*-1-aryloxy-3-azido or benzyloxy-2-alcohols (**1** and **2**) are valuable 'building blocks' for asymmetric synthesis of bioactive pharmaceuticals.[1] These structural units are present in numerous bioactive compounds such as erythritol,[2] an antidiabetic C4 polyol, β-adrenolytic drugs,[3] and the broussonetine family of naturally occurring iminosugars,[4] which show potent glucosidase inhibitory activities with enormous therapeutic potential as anti-tumor and anti-HIV agents. In addition, these aryloxy azido or benzyloxy alcohols (**1a–o** and **2a–c**) are the direct precursors of amino alcohols and simple aziridines,[5] which are versatile intermediates in the synthesis of bioactive molecules[6] (Fig. 1).

Jacobsen's hydrolytic and phenolic kinetic resolutions (HKR & PKR) of terminal epoxides with one stereocenter catalyzed by Co(III)-salen complex **3** employ water and phenol as nucleophiles, respectively.[7] While HKR of epoxides has been comprehensively studied in recent years to understand its mechanistic and synthetic aspects that include a recent study[8] relating to HKR of functionalized epoxides with two stereocentres, its phenolic version (PKR) has been less explored.[7b] In the present work, we have extended the scope of the applicable substrates to cover multi-functionalized epoxides with two stereocenters and employing functionalized phenols (**6a–u**) as the nucleophiles. The aim of such an investigation was to obtain enantioenriched 1-aryloxy-3-azido or benzyloxy-2-alcohols (**1** and **2**) by a direct method from the respective racemic materials, thus complementing the other tedious routes.[9] In this note, we wish to report a flexible, novel method that employs PKR of racemic azido and benzyloxy epoxides **5** and **7** to generate azido- and benzyloxy alcohols **1** and **2** respectively, with two stereocenters of high optical purities in a single step (Schemes 1 and 2).

Results and discussion

We envisioned that the extension of PKR to the two stereocentered racemic epoxides would enable us to obtain both the

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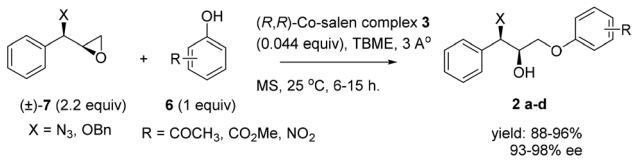


Scheme 2 PKR of *syn*-azido- and benzyloxy epoxides.

enantiomers of *anti*- or *syn*- aryloxy alcohols depending upon the chiral ligand chosen. Thus, the racemic *anti*- and *syn*-azido- and benzyloxy epoxides (**5** and **7**), the substrates for PKR, were efficiently prepared in a highly diastereoselective manner from the corresponding (*Z*)- and (*E*)-allylic alcohols, respectively, by following a reported procedure.[8] In this strategy, the relative stereochemistry between the benzyloxy or azido and epoxide groups is established prior to the PKR step itself and in this way a simple asymmetric reaction can be used to obtain the key enantiomerically pure 1-aryloxy-3-azido- or benzyloxy-2-alcohols (**1** and **2**).

Thus, when PKR of racemic *anti*-azido epoxide **5a** was performed with (*R*,*R*)-Co(III)-salen complex **3** (0.044 equiv.) and phenol (1 equiv.) in *tert*-butyl methyl ether (TBME), the corresponding *anti*-1-aryloxy-3-azido-2-alcohol **1a** was isolated in 65% yield and 92% ee (entry a, Table 1). The PKR can be conducted at low temperatures (−20 °C), although yields obtained were found to be low. Further, the stereoselectivities in the PKR displayed strong epoxide concentration dependence, requiring at least 2.2 equivalents of epoxides to realize excellent enantioselectivity (Scheme 1).

A variety of phenolic substrates were then screened for the PKR process that led to the isolated yields of **1a–u**, with complete regiocontrol (Table 1). In the case of azido epoxides, a wide range of substituted phenols bearing both electron-donating and electron-withdrawing groups reacted efficiently, delivering the corresponding benzyloxy alcohols (**1a–o**) in good to excellent yields and enantioselectivity (entries a–o), whereas benzyloxy epoxides underwent the reaction only with electron-deficient phenols (entries p–u). Additionally, *ortho* substituted phenol displayed poor reactivity (entry d), while 1-naphthol failed to undergo reaction.

Similarly, the racemic *syn*-azido- and benzyloxy epoxides (**7a–d**), prepared readily from the corresponding cinnamyl alcohols,[8] were subjected to PKR under identical reaction conditions that produced the corresponding enantiopure *syn*- products **2a–d** in high isolated yields and ees (Table 2).

Interestingly, only electron-deficient phenols reacted efficiently with the epoxides. Overall, phenols with a wide range of electronic properties participated in the ring-opening reaction with good yields and ees. The relative and absolute stereochemistry of the products **1** and **2** was confirmed by the asymmetric synthesis of ICI-118,551 from **1o** (Scheme 2).

Finally, an application of this methodology is demonstrated by the short synthesis of ICI-118,551 (**4**),[10] the most potent and selective β_2 AR antagonist, used in the treatment of a wide range of diseases including heart failure,[11] ischemic heart disease[12] and hypertension.[13] Its reported synthesis employs Sharpless asymmetric epoxidation as the key reaction.[10] Our synthesis commences from optically pure azido alcohol **1o** (entry o, Table 1). The acid-catalyzed silyl deprotection of **1o** followed by the resulting diol protection with 2,2-dimethoxypropane produced acetonide **9** in 89% yield over two steps. The catalytic hydrogenation of azide **9** gave crude amine, which was smoothly *N*-alkylated[14] with 2-bromopropane under basic conditions to give the *N*-isopropyl derivative **10**. The acid-catalyzed acetonide deprotection gave diol **11** in 65% yields. Selective monotosylation of diol **11** gave the crude tosylate, which on reduction with $LiAlH_4$ afforded **4** in 21% overall yield and 99% ee (Scheme 3).

Table 1 PKR of *anti*-azido- and benzyloxy epoxides[a]

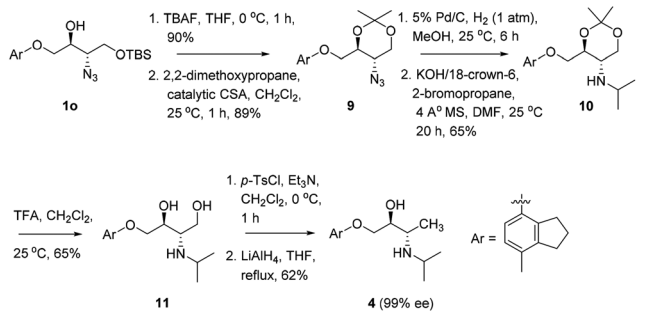
		anti-Azido- and benzyloxy alcohols (**1a–u**)		
Entry	Phenols (*R*) (**6a–u**)	X	Yield[b] (%)	ee[c] (%)
a	H	N_3	65	92
b	4-CH_3	N_3	72	99
c	3-CH_3	N_3	70	95
d	2-CH_3	N_3	35	94
e	4-*tert*-Bu	N_3	76	99
f	3-OMe	N_3	60	93
g	4-CN	N_3	87	98
h	4-F	N_3	72	68
i	4-Br	N_3	86	97
j	4-Cl	N_3	90	97
k	3,5-Cl_2	N_3	89	95
l	4-$COCH_3$	N_3	88	98
m	4-CO_2Me	N_3	81	94
n	4-NO_2	N_3	92	96
o	7-Me-4-indanol	N_3	75	99
p	4-CN	OBn	87	98
q	4-NO_2	OBn	89	97
r	4-$COCH_3$	OBn	98	86
s	4-CHO	OBn	75	99
t	4-CO_2Me	OBn	81	97
u	2,3,5-Cl_3	OBn	78	97

[a] Racemic azido or benzyloxy epoxide **5** (5 mmol), (*R*,*R*)-Co(III)-salen complex **3** (86 mg, 0.1 mmol), TBME, 3 Å MS, phenol (**6**) (2.25 mmol). [b] Isolated yield after column chromatographic purification with respect to nucleophiles. [c] ee determined by chiral HPLC analysis (see the Experimental section for details).

Table 2 PKR of *syn*-azido- and benzyloxy epoxides[a]

		syn-Azido- and benzyloxy alcohols (**2a–d**)		
Entry	Phenols (*R*) (**6l–n**)	X	Yield[b] (%)	ee[c] (%)
a	4-$COCH_3$	N_3	88	93
b	4-CO_2Me	N_3	96	93
c	4-NO_2	N_3	90	94
d	4-$COCH_3$	OBn	89	98

[a] For reaction conditions, see footnotes under Table 1.



Scheme 3 Asymmetric synthesis of ICI-118,551 (**4**).

Conclusion

In conclusion, the (salen) Co(III)-catalysed PKR of racemic azido- and benzyloxy epoxides provides a highly practical route to enantiopure *anti*- or *syn*-azido- and benzyloxy alcohols **1** and **2** in a single step. The reaction is convenient to carry out under mild conditions displaying a wide range of substrate scope. This methodology has been successfully demonstrated in the enantioselective synthesis of ICI-118,551, an anti-hypertensive agent. We believe that this PKR strategy will find applications in the field of asymmetric synthesis of bioactive molecules owing to the flexible nature of the synthesis of racemic azido and benzyloxy epoxides and the readily accessible catalyst in both enantiomeric forms.

Experimental section

General procedure for the phenolic kinetic resolutions of *anti*- and *syn*-aryloxy azido- and benzyloxy alcohols (see Schemes 1 and 2)

To a stirred solution of (*R*,*R*)-(salen) Co[OC(CF$_3$)$_3$](H$_2$O) (**3**) (86 mg, 0.1 mmol), molecular sieve (100 mg, 3 Å) and racemic *anti*- or *syn*-azido or benzyloxy epoxide (**5** or **7**) (5 mmol), in *tert*-butyl methyl ether (0.15 mL), phenol (2.25 mmol) (**6**) was added at 25 °C. The reaction was stirred for 6–15 h till all the phenol gets converted (as monitored by TLC). The solvent was removed under reduced pressure. The crude product was purified by column chromatography over silica gel (eluting with pet. ether–EtOAc) to give optically pure *anti*- or *syn*-1-aryloxy-3-azido or benzyloxy-2-alcohols in a pure form. The enantiomeric purity was determined by chiral HPLC analysis.

(2*S*,3*S*)-3-Azido-4-(*tert*-butyldimethylsiloxy)-1-phenoxybutan-2-ol (1a)

Yield: 65%; gum; $[\alpha]_D^{25}$ +16 (*c* 1, CHCl$_3$); IR (CHCl$_3$, cm^{-1}): 690, 752, 837, 1042, 1108, 1243, 1497, 1599, 2099, 2857, 2929, 2953, 3460; ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.12 (s, 6H), 0.93 (s, 9H), 2.7 (d, *J* = 5.0 Hz, 1H), 3.88–4.17 (m, 5H), 6.89–7.00 (m, 3H), 7.29–7.33 (m, 2H); ^{13}C NMR (50 MHz, CDCl$_3$): −5.5, 18.2, 25.8, 63.4, 63.7, 69.0, 69.6, 114.5, 121.4, 129.5, 158.2; optical purity: 92% ee determined by HPLC analysis (chiral OD-H column, *n*-hexane–2-propanol (95 : 5), 0.5 mL min^{-1}, 254 nm); retention time: t_{major} = 14.36 and t_{minor} = 19.88 min; HRMS (ESI) *m*/*z* Calcd C$_{16}$H$_{27}$N$_3$O$_3$NaSi [M + Na]$^+$, 360.1714; found, 360.1713.

(2*S*,3*S*)-1-(*p*-Tolyloxy)-3-azido-4-(*tert*-butyldimethylsiloxy)-butan-2-ol (1b)

Yield: 72%; gum; $[\alpha]_D^{25}$ +28 (*c* 1, CHCl$_3$); IR (CHCl$_3$, cm^{-1}): 777, 838, 1047, 1109, 1172, 1258, 1289, 1462, 1490, 1586, 1603, 2098, 2857, 2284, 2929, 2953, 3451; ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.12 (s, 6H), 0.92 (s, 9H), 2.29 (s, 3H), 2.67 (d, *J* = 4.9 Hz, 1H) 3.55–3.60 (m, 1H), 3.86–4.08 (m, 5H), 6.8 (d, *J* = 8.5 Hz, 2H), 7.05–7.09 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (50 MHz, CDCl$_3$): −5.5, 18.2, 20.5, 25.8, 63.5, 63.8, 69.2, 69.6, 114.4, 130.0, 130.5, 156.2; optical purity: 99% ee determined by HPLC analysis (chiral OJ-H column, *n*-hexane–2-propanol (95 : 5), 0.5 mL min^{-1}, 210 nm); retention time: t_{minor} = 23.71 and t_{major} = 25.23 min; HRMS (ESI) *m*/*z* Calcd C$_{17}$H$_{29}$N$_3$O$_3$NaSi [M + Na]$^+$, 374.1870; found, 374.1874.

(2*S*,3*S*)-1-(*m*-Tolyloxy)-3-azido-4-(*tert*-butyl-dimethyl siloxy)-butan-2-ol (1c)

Yield: 70%; gum; $[\alpha]_D^{25}$ +16 (*c* 1.0, CHCl$_3$); IR (CHCl$_3$, cm^{-1}): 774, 838, 1109, 1172, 1258, 1289, 1462, 1500, 1603, 2098, 2857, 2884, 2929, 2953, 3451; ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.12 (s, 6H), 0.93 (s, 9H), 2.33 (s, 3H), 2.65–2.68 (d, *J* = 4.84 Hz, 1H), 3.56–3.62 (m, 1H), 3.67–4.15 (m, 5H), 6.69–6.80 (m, 3H), 7.12–7.20 (t, 1H); ^{13}C NMR (50 MHz, CDCl$_3$): −5.52, 18.25, 21.53, 25.85, 63.55, 63.80, 69.02, 69.63, 111.56, 115.43, 122.25, 129.30, 139.51, 158.30; optical purity: 95% ee determined by HPLC analysis (chiral OJ-H column, *n*-hexane–2-propanol (95 : 5), 0.5 mL min^{-1}, 210 nm); retention time: t_{minor} = 22.71 and t_{major} = 28.23 min; HRMS (ESI) *m*/*z* Calcd C$_{17}$H$_{29}$N$_3$O$_3$NaSi [M + Na]$^+$, 374.1870; found, 374.1868.

(2*S*,3*S*)-1-(*o*-Tolyloxy)-3-azido-4-(*tert*-butyl-dimethyl siloxy)-butan-2-ol (1d)

Yield: 35%; gum; $[\alpha]_D^{25}$ +15 (*c* 1.0, CHCl$_3$); IR (CHCl$_3$, cm^{-1}): 774, 838, 1109, 1172, 1258, 1289, 1462, 1500, 1603, 2098, 2857, 2884, 2929, 2953, 3451; ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.12 (s, 6H), 0.93 (s, 9H), 2.24 (s, 3H), 2.63–2.65 (d, *J* = 5.36 Hz, 1H), 3.57–3.65 (m, 1H), 3.88–4.15 (m, 5H), 6.81–6.91 (m, 2H), 7.11–7.15 (m, 2H); ^{13}C NMR (50 MHz, CDCl$_3$): −5.50, 16.38, 18.27, 25.85, 29.75, 63.65, 63.90, 69.07, 69.83, 111.33, 121.19, 126.61, 126.98, 130.87, 156.30 optical purity: 94% ee determined by HPLC analysis (chiral OJ-H column, *n*-hexane–2-propanol (95 : 5), 0.5 mL min^{-1}, 210 nm); retention time: t_{minor} = 20.71 and t_{major} = 24.23 min; HRMS (ESI) *m*/*z* Calcd C$_{17}$H$_{29}$N$_3$O$_3$NaSi [M + Na]$^+$, 374.1870; found, 374.1865.

(2*S*,3*S*)-1-(4-*tert*-Butylphenoxy)-3-azido-4-(*tert*-butyldimethyl-siloxy)butan-2-ol (1e)

Yield: 76%; gum; $[\alpha]_D^{25}$ +12 (*c* 1, CHCl$_3$); IR (CHCl$_3$, cm^{-1}): 777, 836, 1113, 1243, 1513, 2095, 2858, 2929, 2956, 3460; ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.12 (s, 6H), 0.92 (s, 9H), 1.30 (s, 9H), 2.64 (d, *J* = 5.2 Hz, 1H), 3.53–3.62 (m, 1H), 3.87–4.13 (m, 5H), 6.82–6.86 (m, 2H), 7.27–7.31 (m, 2H); ^{13}C NMR (50 MHz, CDCl$_3$): −5.4, 18.2, 25.8, 31.6, 34.1, 63.5, 63.8, 69.1, 69.6, 114.1,

126.3, 144.1, 156.0; optical purity: 99% ee determined by HPLC analysis (chiral OJ-H column, *n*-hexane–2-propanol (95 : 5), 0.5 mL min^{-1}, 210 nm); retention time: t_{major} = 21.61 and t_{minor} = 29.29 min; HRMS (ESI) *m*/*z* Calcd $C_{20}H_{35}N_3O_3SiNa$ $[M + Na]^+$, 416.2340; found, 416.2346.

(2*S*,3*S*)-1-(3-Methoxyphenoxy)-3-azido-4-(*tert*-butyldimethylsiloxy)butan-2-ol (1f)

Yield: 60%; gum; $[\alpha]_D^{25}$ +18 (*c* 1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 771, 839, 1112, 1170, 1254, 1283, 1436, 1511, 1606, 1716, 2099, 2857, 2930, 3471; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.12 (s, 6H), 0.93 (s, 9H), 2.7 (d, *J* = 3.1 Hz, 1H), 3.56–3.59 (m, 1H), 3.78 (s, 3H), 3.90–3.93 (m, 1H), 4.03 (br s, 1H), 4.02–4.12 (m, 3H), 6.46–6.53 (m, 3H), 7.19 (t, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): −5.4, 18.3, 25.8, 55.2, 63.5, 63.8, 69.2, 69.7, 101.2, 106.7, 107.1, 130.0, 159.5, 160.9; optical purity: 93% ee determined by HPLC analysis (chiral OJ-H column, *n*-hexane–2-propanol (95 : 5), 0.5 mL min^{-1}, 210 nm); retention time: t_{major} = 14.45 and t_{minor} = 20.25 min; HRMS (ESI) *m*/*z* Calcd $C_{17}H_{29}N_3O_4NaSi$ $[M + Na]^+$, 390.1820; found 390.1815.

4-(2*S*,3*S*)-[3-Azido-4-(*tert*-butyldimethylsiloxy)-2-hydroxybutoxy]-benzonitrile (1g)

Yield: 87%; gum; $[\alpha]_D^{25}$ +70 (*c* 1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 778, 836, 1031, 1111, 1172, 1257, 1463, 1471, 1509, 1609, 2099, 2226, 2857, 2929, 2953, 2445; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.13 (s, 6H), 0.93 (s, 9H), 2.71 (d, *J* = 4.9 Hz, 1H), 3.54–3.62 (m, 1H), 3.94–4.23 (m, 5H), 6.9 (d, *J* = 9.1 Hz, 2H), 7.6 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): −5.5, 18.1, 25.7, 63.1, 63.6, 69.5, 69.6, 104.7, 115.3, 133.9, 161.6; optical purity: 98% ee determined by HPLC analysis (chiral OD-H column, *n*-hexane–2-propanol (80 : 20), 0.5 mL min^{-1}, 210 nm); retention time: t_{major} = 10.35 and t_{minor} = 11.80 min; HRMS (ESI) *m*/*z* Calcd $C_{17}H_{26}N_4O_3NaSi$ $[M + Na]^+$, 385.1666; found 385.1656.

(2*S*,3*S*)-1-(4-Fluorophenoxy)-3-azido-4-(*tert*-butyldimethylsiloxy)butan-2-ol (1h)

Yield: 72%; gum; $[\alpha]_D^{25}$ +26 (*c* 1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 778, 836, 1098, 1220, 1252, 1507, 2100, 2858, 2930, 2953, 3440; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.12 (s, 6H), 0.93 (s, 9H), 2.68 (d, *J* = 5.0 Hz, 1H), 3.53–3.62 (m, 1H), 3.88–4.14 (m, 5H), 6.82–6.89 (m, 2H), 6.94–7.03 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): −5.5, 18.2, 25.8, 63.3, 63.7, 69.6, 69.8, 115.5, 115.7, 116.2, 154.3, 154.4, 155.2, 155.9; optical purity: 68% ee determined by HPLC analysis (chiral OD-H column, *n*-hexane–2-propanol (95 : 5), 0.5 mL min^{-1}, 210 nm); retention time: t_{major} = 15.53 and t_{minor} = 17.74 min; HRMS (ESI) *m*/*z* Calcd for $C_{16}H_{26}FN_3O_3NaSi$ $[M + Na]^+$, 378.1620; found, 378.1624.

(2*S*,3*S*)-1-(4-Bromophenoxy)-3-azido-4-(*tert*-butyldimethylsiloxy)butan-2-ol (1i)

Yield: 86%; gum; $[\alpha]_D^{25}$ +20 (*c* 1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 778, 837, 1003, 1072, 1103, 1242, 1488, 2099, 2857, 2929, 2953, 3461; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.12 (s, 6H), 0.93 (s, 9H), 2.68 (d, *J* = 4.7 Hz, 1H), 3.53–3.61 (m, 1H), 3.87–4.12 (m, 5H), 6.78–6.82 (m, 2H), 7.36–7.41 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): −5.5, 18.2, 25.8, 63.2, 63.7, 69.4, 69.6, 113.6, 116.3, 132.4, 157.3; optical purity: 97% ee determined by HPLC analysis (OD-H column, *n*-hexane–2-propanol (10 : 90), 0.5 mL min^{-1}, 254 nm); retention time: t_{major} = 10.99 and t_{minor} = 12.08 min. HRMS (ESI) *m*/*z* Calcd for $C_{16}H_{26}BrN_3O_3NaSi$ $[M + Na]^+$, 438.0819; found, 438.0821.

(2*S*,3*S*)-1-(4-Chlorophenoxy)-3-azido-4-(*tert*-butyldimethylsiloxy)butan-2-ol (1j)

Yield: 90%; gum; $[\alpha]_D^{25}$ −6.5 (*c* 1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 778, 837, 1095, 1243, 1492, 2100, 2858, 2929, 2953, 3446; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.12 (s, 6H), 0.93 (s, 9H), 2.66 (d, *J* = 4.6 Hz, 1H), 3.57–3.62 (m, 1H), 3.91–4.12 (m, 5H), 6.85 (d, *J* = 8.9 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): −5.5, 18.2, 25.8, 63.3, 63.7, 69.5, 69.6, 115.8, 126.4, 129.4, 156.9; optical purity: 97% ee determined by HPLC analysis (OD-H column, *n*-hexane–2-propanol (10 : 90), 0.5 mL min^{-1}, 254 nm); retention time: t_{major} = 12.33 and t_{minor} = 13.14 min. HRMS (ESI) *m*/*z* Calcd for $C_{16}H_{26}ClN_3O_3NaSi$ $[M + Na]^+$, 394.1324; found, 394.1320.

(2*S*,3*S*)-1-(3,5-Dichlorophenoxy)-3-azido-4-*tert*-butyl-dimethylsiloxy)-butan-2-ol (1k)

Yield: 89%; gum; $[\alpha]_D^{25}$ +12 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 771, 839, 1112, 1170, 1254, 1283, 1436, 1511, 1606, 1716, 2099, 2857, 2930, 3471; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.12 (s, 6H), 0.93 (s, 9H), 2.73–2.76 (d, *J* = 5.56 Hz, 1H), 3.58–3.67 (m, 1H), 3.88–4.21 (m, 5H), 6.86–6.91 (d, *J* = 8.82 Hz, 1H), 7.17–7.22 (dd, *J* = 2.53, 8.80 Hz, 1H), 7.37–7.38 (d, *J* = 2.53, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): −5.48, 18.27, 25.87, 63.40, 63.83, 69.44, 70.82, 114.65, 124.07, 126.76, 127.72 130.12, 152.72; optical purity: 95% ee determined by HPLC analysis (OD-H column, *n*-hexane–2-propanol (90 : 10), 0.5 mL min^{-1}, 254 nm); retention time: t_{minor} = 10.20 and t_{major} = 11.50 min. HRMS (ESI) *m*/*z* Calcd for $C_{16}H_{25}Cl_2N_3O_3NaSi$ $[M + Na]^+$, 428.0934; found, 428.0936.

(2*S*,3*S*)-1-(4-(3-Azido-4-(*tert*-butyldimethylsiloxy)-2-hydroxybutoxy)-phenyl)-ethanone (1l)

Yield: 88%; gum; $[\alpha]_D^{25}$ +6 (*c* 1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 777, 836, 1033, 1114, 1173, 1256, 1307, 1600, 2098, 2857, 2929, 2953, 3440; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.13 (s, 6H), 0.93 (s, 9H), 2.56 (s, 3H), 2.74 (d, *J* = 4.9 Hz, 1H), 3.55–3.67 (m, 1H), 3.89–4.25 (m, 5H), 6.95 (d, *J* = 8.8 Hz, 2H), 7.93 (d, *J* = 8.9 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): −5.5, 18.1, 25.7, 26.2, 63.4, 63.6, 69.4, 114.2, 130.6, 162.2, 196.6; optical purity: 98% ee determined by HPLC analysis (Chiral OD-H column, *n*-hexane–2-propanol (70 : 30), 0.5 mL min^{-1}, 254 nm); retention time: t_{major} = 10.15 and t_{minor} = 11.35 min; HRMS (ESI) *m*/*z* Calcd for $C_{18}H_{29}N_3O_4NaSi$ $[M + Na]^+$, 402.1820; found, 402.1823.

(2*S*,3*S*)-(Methyl-4-(3-azido-4-(*tert*-butyldimethylsiloxy)-2-hydroxybutoxy)benzoate (1m)

Yield: 81%; gum; $[\alpha]_D^{25}$ +14 (*c* 1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 771, 839, 1112, 1170, 1254, 1283, 1436, 1511, 1606, 1716, 2099, 2857, 2930, 3471; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.13 (s, 6H),

0.93 (s, 9H), 2.73 (d, J = 5.1 Hz, 1H), 3.55–3.64 (m, 1H), 3.89 (s, 3H), 3.94–4.23 (m, 5H), 6.94 (d, J = 9.0 Hz, 2H), 7.99 (d, J = 9.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): −5.5, 18.2, 25.7, 51.8, 63.2, 63.7, 69.3, 69.6, 114.1, 123.1, 131.6, 162.0, 166.6; optical purity: 94% ee determined by HPLC analysis (OD-H column, n-hexane–2-propanol (30 : 70), 0.5 mL min^{-1}, 254 nm); retention time: t_{minor} = 12.56 and t_{major} = 13.31 min; HRMS (ESI) m/z Calcd for $C_{18}H_{29}N_3O_5NaSi$ $[M + Na]^+$, 418.1769; found, 418.1765.

(2*S*,3*S*)-1-(4-Nitrophenoxy)-3-azido-4-(*tert*-butyldimethylsiloxy)-butan-2-ol (1n)

Yield: 92%; gum; $[\alpha]_D^{25}$ +18 (c 1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 779, 840, 862, 1111, 1260, 1298, 1343, 1498, 1514, 1593, 1608, 2100, 2857, 2929, 2954, 3461; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.13 (s, 6H), 0.93 (s, 9H), 2.74 (d, J = 4.8 Hz, 1H), 3.59–3.65 (m, 1H), 3.91–4.28 (m, 5H), 7.1 (d, J = 9.3 Hz, 2H), 8.22 (d, J = 9.3 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): −5.6, 18.1, 25.7, 63.0, 63.5, 69.6, 70.0, 114.5, 125.8, 141.8, 163.2; optical purity: 96% ee determined by HPLC analysis (OJ-H column, n-hexane–2-propanol 40 : 60), 0.5 mL min^{-1}, 254 nm); retention time: t_{major} = 10.51 and t_{minor} = 13.84 min; HRMS (ESI) m/z Calcd for $C_{16}H_{26}N_4O_5NaSi$ $[M + Na]^+$, 405.1565; found, 405.1558.

(2*S*,3*S*)-3-Azido-4-((*tert*-butyldimethylsilyl)oxy)-1-[(7-methyl-2,3-dihydro-1*H*-inden-4-yl)oxy]butan-2-ol (1o)

Yield: 75%; gum; $[\alpha]_D^{25}$ −6.7 (c 1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 770, 1170, 1112, 1253, 1284, 1510, 1605, 1715, 2104, 3550; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.12 (s, 6H), 0.93 (s, 9H), 2.08 (app. quintet, J = 7.4 Hz, 2H), 2.20 (s, 3H), 2.66 (d, J = 5.4 Hz, 1H), 2.86 (q, J = 7.7 Hz, 4H), 3.54–3.63 (m, 1H), 3.80–4.11 (m, 5H), 6.59 (d, J = 8.2 Hz, 1H), 6.9 (d, J = 7.9 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): −5.5, 18.2, 18.4, 24.4, 25.8, 29.7, 31.8, 63.7, 63.8, 69.1, 69.6, 109.6, 126.6, 127.9, 131.4, 144.9, 152.7; optical purity: 99% ee determined by HPLC analysis (Chiral OD-H column, n-hexane–2-propanol (95 : 5), 0.5 mL min^{-1}, 254 nm); retention time: t_{major} = 9.94 and t_{minor} = 11.41 min; HRMS (ESI) m/z Calcd for $C_{20}H_{33}N_3O_3NaSi$ $[M + Na]^+$, 414.2183; found, 414.2188.

(2*R*,3*S*)-4-(4-(*tert*-Butyldimethylsiloxy)-3-(benzyloxy)-2-hydroxybutoxy)benzo-nitrile (1p)

Yield: 87%; colorless solid, mp: 62–63 °C; $[\alpha]_D^{25}$ −7.74 (c 1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 778, 835, 1096, 1172, 1258, 1302, 1454, 1508, 1605, 2224, 2856, 2883, 2929, 2953, 3474; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.09 (s, 6H), 0.91 (s, 9H), 2.90–2.92 (m, 1H), 3.64 (q, J = 5.4 Hz, 1H), 3.86–3.89 (m, 2H), 4.10–4.18 (m, 3H), 4.51–4.73 (dd, J = 11.5 and 11.7 Hz, 2H), 6.90–6.96 (m, 2H), 7.27 (m, 5H), 7.53–7.61 (m, 2H); ^{13}C NMR (50 Hz, $CDCl_3$): −5.5, 18.1, 25.7, 62.9, 69.3, 70.6, 72.5, 78.2, 104.0, 115.1, 118.8, 127.7, 127.8, 128.2, 133.7, 137.7, 161.9; optical purity: 98% ee determined by HPLC analysis (Chiral OD-H column, n-hexane–2-propanol (80 : 20), 0.5 mL min^{-1}, 210 nm); retention time: t_{major} = 10.15 and t_{minor} = 11.35 min; HRMS (ESI) m/z Calcd for $C_{24}H_{33}NO_4NaSi$ $[M + Na]^+$, 450.2071; found, 450.2070.

(2*R*,3*S*)-4-(*tert*-Butyldimethylsiloxy)-1-(4-nitrophenoxy)-3-(benzyloxy)butan-2-ol (1q)

Yield: 89%; colorless liquid; $[\alpha]_D^{25}$ −16.52 (c 1, $CHCl_3$); IR (neat, cm^{-1}): 752, 778, 1111, 1263, 1340, 1517, 1593, 2856, 2928, 3472; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.10 (s, 6H), 0.92 (s, 9H), 2.97 (br s, 1H), 3.58–3.67 (m, 1H), 3.87–3.90 (m, 2H), 4.10–4.21 (m, 3H), 4.51–4.73 (dd, J = 11.6 and 11.8 Hz, 2H), 6.89–6.97 (m, 2H), 7.24–7.32 (m, 5H), 8.14–8.22 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.4, 18.2, 25.8, 63.0, 69.8, 71.0, 72.6, 78.1, 114.4, 125.7, 127.9, 128.4, 137.7, 141.6, 163.7; optical purity: 97% ee determined by HPLC analysis (Chiral OJ-H column, n-hexane–2-propanol (80 : 20), 0.5 mL min^{-1}, 210 nm); retention time: t_{major} = 12.53 and t_{minor} = 15.12 min; HRMS (ESI) m/z Calcd for $C_{23}H_{33}NO_6NaSi$ $[M + Na]^+$, 470.1969; found, 470.1975.

1-(4-((2*R*,3*S*)-4-(*tert*-Butyl dimethylsiloxy)-3-(benzyloxy)-2-hydroxybutoxy)phenyl)ethanone (1r)

Yield: 98%, white solid; mp: 91–92 °C; $[\alpha]_D^{25}$ −19.89 (c 1.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 699.28, 775.75, 957.19, 1093.07, 1258.78, 1359.27, 1470.93, 1575.75, 1600.40, 1671.94, 2856.59, 2928.76, 3473.28; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.09 (s, 6H), 0.92 (s, 9H), 2.56 (s, 3H), 2.90 (br s 1H), 3.61–3.69 (m, 1H), 3.87–3.90 (dd, J = 3.01, 5.44 Hz, 2H), 4.09–4.19 (m, 3H), 4.53–4.74 (dd, J = 11.62 Hz, 2H), 6.85–6.95 (m, 2H), 7.27 (s, 5H), 7.89–7.95 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): −5.43, 18.29, 25.91, 26.29, 63.25, 69.19, 71.02, 72.79, 78.40, 114.25, 127.88, 127.99, 128.43, 130.56, 137.96, 162.62, 196.44; optical purity: 86% ee determined by HPLC analysis (OJ-H column, n-hexane–2-propanol (80 : 20), 0.5 mL min^{-1}, 254 nm); retention time: t_{minor} = 14.38 and t_{major} = 15.07 min. HRMS (ESI) m/z Calcd for $C_{25}H_{36}O_5NaSi$ $[M + Na]^+$, 467.2224; found, 467.2220.

(2*R*,3*S*)-4-(4-(*tert*-Butyldimethylsiloxy)-3-(benzyloxy)-2-hydroxybutoxy)benzaldehyde (1s)

Yield: 75%; gum; $[\alpha]_D^{25}$ +14.02 (c 1, $CHCl_3$); IR (neat, cm^{-1}): 755, 834, 1097, 1256, 1462, 1509, 1600, 1693, 2928, 3454; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.09 (s, 6H), 0.92 (s, 9H), 2.95 (br s, 1H), 3.63–3.69 (m, 1H) 3.87–3.91 (m, 2H), 4.11–4.21 (m, 3H), 4.62 (dd, J = 11.6 and 11.8 Hz, 2H), 6.96–7.00 (m, 2H), 7.24–7.35 (m, 5H), 7.80–7.85 (m, 2H), 9.88 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.4, 18.2, 25.9, 63.2, 69.3, 71.0, 72.7, 78.3, 114.8, 128, 128.4, 130.1, 131.9, 137.9, 163.7, 190.4; optical purity: 99% ee determined by HPLC analysis (OJ-H column, n-hexane–2-propanol (80 : 20), 0.5 mL min^{-1}, 254 nm); retention time: t_{minor} = 14.38 and t_{major} = 15.07 min; HRMS (ESI) m/z Calcd for $C_{24}H_{34}O_5NaSi$ $[M + Na]^+$, 453.2068; found, 453.2062.

(2*R*,3*S*)-Methyl 4-(4-(*tert*-butyldimethylsiloxy)-3-(benzyloxy)-2-hydroxybutoxy)-benzoate (1t)

Yield: 81%, colorless liquid; $[\alpha]_D^{25}$ −20.04 (c 1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 771, 837, 1169, 1255, 1435, 1511, 1605, 1718, 2928, 3478; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.09 (s, 6H), 0.91 (s, 9H), 2.94 (br s, 1H), 3.63–3.68 (m, 1H), 3.81–3.96 (m, 5H), 4.07–4.17 (m, 3H), 4.53–4.74 (dd, J = 11.6 and 11.8 Hz, 2H), 6.85–6.92 (m, 2H), 7.27 (m, 5H), 7.93–8.00 (m, 2H); ^{13}C NMR

(50 MHz, $CDCl_3$): −5.4, 18.2, 25.8, 51.7, 63.2, 69.0, 70.8, 72.7, 78.4, 114.1, 122.7, 127.8, 127.9, 128.3, 131.5, 137.9, 162.4, 166.6; optical purity: 97% ee determined by HPLC analysis (OJ-H column, *n*-hexane–2-propanol (80 : 20), 0.5 mL min^{-1}, 254 nm); retention time: t_{minor} = 14.38 and t_{major} = 15.07 min. HRMS (ESI) *m*/*z* Calcd for $C_{25}H_{36}O_6NaSi$ $[M + Na]^+$, 483.2173; found, 483.2169.

(2*R*,3*S*)-1-(2,4,5-Trichlorophenoxy)-4-(*tert*-butyldimethylsiloxy)-3-(benzyloxy)butan-2-ol (1u)

Yield: 78%; gum; $[\alpha]_D^{25}$ +5.9 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}): 701, 763, 1050, 1261, 1454, 1492, 2104, 2935, 3034, 3416; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.09 (s, 6H), 0.92 (s, 9H), 2.88–2.95 (m, 1H), 3.64–3.71 (m, 1H) 3.84–3.91 (m, 2H), 4.06–4.13 (m, 3H), 4.52–4.75 (dd, *J* = 11.76, 2H), 6.93 (s, 1H), 7.28–7.30 (m, 5H), 7.43 (s, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ −5.39, 18.32, 25.95, 63.43, 70.63, 70.90, 72.92, 78.24, 115.05, 122.11, 124.40, 127.92, 127.99, 128.11, 128.47, 130.82, 131.27, 137.99, 153.36; optical purity: 97% ee determined by HPLC analysis (OJ-H column, *n*-hexane–2-propanol (90 : 10), 0.5 mL min^{-1}, 254 nm); retention time: t_{minor} = 14.38 and t_{major} = 15.07 min; HRMS (ESI) *m*/*z* Calcd for $C_{23}H_{31}Cl_3O_4NaSi$ $[M + Na]^+$, 527.0949; found, 527.0953.

(2*S*,3*R*)-1-(4-(3-Azido-2-hydroxy-3-phenylpropoxy)phenyl)-ethanone (2a)

Yield: 88%; gum; $[\alpha]_D^{25}$ +16 (*c* 1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 775, 845, 1110, 1173, 1254, 1359, 1599, 1671, 2104, 3426; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.54 (s, 3H), 2.65–2.67 (d, *J* = 4.6 Hz, 1H), 3.77–3.84 (dd, *J* = 4.8 and 9.7 Hz, 1H), 3.96–4.15 (m, 2H), 4.81 (d, *J* = 7.3 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 7.32–7.41 (m, 5H), 7.89 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): 26.1, 67.7, 68.3, 73.1, 114.0, 127.4, 128.7, 128.8, 130.4, 136.0, 162.0, 196.6; optical purity: 93% ee determined by HPLC analysis (chiral OJ-H column, *n*-hexane–2-propanol (70 : 30), 0.5 mL min^{-1}, 214 nm); retention time: t_{minor} = 11.21 and t_{major} = 11.64 min; HRMS (ESI) *m*/*z* Calcd for $C_{17}H_{17}N_3O_3Na$ $[M + Na]^+$, 334.1162; found, 334.1169.

(2*S*,3*R*)-Methyl4-(3-azido-2-hydroxy-3-phenylpropoxy)benzoate (2b)

Yield: 96%; gum; $[\alpha]_D^{25}$ +18 (*c* 1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 770, 1170, 1112, 1253, 1284, 1510, 1605, 1715, 2104, 3550; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.76–2.69 (br s, 1H), 3.73–3.80 (dd, *J* = 4.9 and 9.7 Hz, 1H), 3.85 (s, 3H), 3.92–3.99 (dd, *J* = 3.6 and 9.7 Hz, 1H), 4.09–4.11 (m, 1H), 4.79 (d, *J* = 7.0 Hz, 1H), 6.82–6.84 (m, 2H), 7.35–7.37 (m, 5H), 7.94–7.96 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): 51.8, 67.9, 68.2, 73.4, 114.1, 123.2, 127.5, 129.0, 129.1, 131.6, 136.0, 161.9, 166.5; optical purity: 93% ee determined by HPLC analysis (chiral OJ-H column, *n*-hexane–2-propanol (70 : 30), 0.5 mL min^{-1}, 254 nm); retention time: t_{minor} = 13.35 and t_{major} = 14.48 min; HRMS (ESI) *m*/*z* Calcd for $C_{17}H_{17}N_3O_4Na$ $[M + Na]^+$, 350.1111; found, 350.1118.

(1*R*,2*S*)-3-(4-Nitrophenoxy)-1-azido-1-phenylpropan-2-ol (2c)

Yield: 90%; gum; $[\alpha]_D^{25}$ +21.56 (*c* 1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 702, 752, 845, 1111, 1167, 1260, 1342, 1510, 1592, 2105, 3481; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.64 (d, *J* = 4.2 Hz, 1H), 3.83–3.87 (dd, *J* = 4.8 and 9.8 Hz, 1H), 4.00–4.17 (m, 2H), 4.80 (d, *J* = 7.3 Hz, 1H), 6.88–6.92 (m, 2H), 7.32–7.40 (m, 5H), 8.16–8.21 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): 67.8, 68.8, 73.1, 114.4, 125.8, 127.4, 129.1, 135.8, 141.8, 163.1; optical purity: 94% ee determined by HPLC analysis (chiral OJ-H column, *n*-hexane–2-propanol (70 : 30), 0.5 mL min^{-1}, 254 nm); retention time: minor = 13.27 and t_{major} = 14.03 min; HRMS (ESI) *m*/*z* Calcd for $C_{15}H_{14}N_4O_4Na$ $[M + Na]^+$, 337.0907; found, 337.0898.

(2*R*,3*R*)-1-[4-(3-(Benzyloxy)-2-hydroxy-3-phenylpropoxy)phenyl]-ethanone (2d)

Yield: 89%; gum; $[\alpha]_D^{25}$ +21.56 (*c* 1, $CHCl_3$); IR (neat, cm^{-1}): 701, 755, 1065, 1255, 1358, 1454, 1599, 1673, 3453; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.54 (s, 3H), 3.04 (br s, 1H), 3.74–3.80 (m, 1H), 3.97–4.16 (m, 2H), 4.30–4.56 (dd, *J* = 11.2 and 11.3 Hz, 2H), 4.61 (d, *J* = 6.8 Hz, 1H), 6.79–6.86 (m, 2H), 7.30–7.42 (m, 10H), 7.86 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.2, 68.0, 70.8, 73.9, 81.4, 114.1, 127.4, 127.8, 127.9, 128.4, 128.5, 128.7, 130.4, 137.5, 137.8, 162.4, 196.2; optical purity: 98% ee determined by HPLC analysis (chiral OJ-H column, *n*-hexane–2-propanol (70 : 30), 0.5 mL min^{-1}, 254 nm); retention time: minor = 10.72 and t_{major} = 11.28 min; HRMS (ESI) *m*/*z* Calcd for $C_{24}H_{24}O_4Na$ $[M + Na]^+$, 399.1567; found, 399.1567.

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References

1 (*a*) J. L. Wright, T. F. Gregory, T. G. Heffner, R. G. MacKenzie, T. A. Pugsley, S. V. Meulen and L. D. Wise, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 1377; (*b*) N. R. Baker, N. G. Byrne, A. P. Economides and T. Javed, *Chem. Pharm. Bull.*, 1995, 1045; (*c*) M. P. Kirkup, R. Rizvi, B. B. Shankar, S. Dugar, J. Clader, S. W. McCombie, S. Lin, N. Yumibe, K. Huie, M. Heek, D. S. Compton, H. R. Davis and A. T. McPhail, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 2069; (*d*) M. C. Desai, S. L. Lefkowitz, P. F. Thadeio, K. P. Longo and R. M. Snider, *J. Med. Chem.*, 1992, **35**, 4911.

2 (*a*) T. Yokozawa, H. Y. Kim and E. J. Choj, *Agric. Food Chem.*, 2002, **50**, 5485; (*b*) K. Noda, K. Nakayama and T. Oku, *Eur. J. Clin. Nutr.*, 1994, **48**, 286; (*c*) W. O. Bernt, J. F. Borzelleca, G. Flamm and I. C. Munro, *Regul. Toxicol.*

Pharmacol., 1996, **24**, S191; (*d*) P. Cock, *World Rev. Nutr. Diabetics*, 1999, **85**, 110.

3 J. G. Baker, *Br. J. Pharmacol.*, 2005, **144**, 317.

4 (*a*) H. Zhao, A. Kato, K. Sato, Y. Jia and C. Yu, *J. Org. Chem.*, 2013, **78**, 7896; (*b*) M. Shibano, D. Tsukamoto and G. Kusano, *Heterocycles*, 2002, **57**, 1539; (*c*) R. Saul, J. P. Chambers, R. J. Molyneux and A. D. Elbein, *Arch. Biochem. Biophys.*, 1983, **221**, 593; (*d*) R. Saul, R. J. Molyneux and A. D. Elbein, *Arch. Biochem. Biophys.*, 1984, **230**, 668; (*e*) B. Winchester and G. W. Fleet, *J. Carbohydr. Chem.*, 2000, **19**, 471.

5 P. Besse, H. Veschambre, V. R. Chenevert and M. Dickman, *Tetrahedron: Asymmetry*, 1994, **5**, 1727.

6 (*a*) M. Tomasz, M. Jung, G. Verdine and K. Nakanishi, *J. Am. Chem. Soc.*, 1984, **106**, 7367; (*b*) S. Danishefsky and M. Ciufolini, *J. Am. Chem. Soc.*, 1984, **106**, 6424.

7 (*a*) S. E. Schaus, B. E. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 1307; (*b*) J. M. Ready and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1999, **121**, 6086.

8 (*a*) R. S. Reddy, P. V. Chouthaiwale, G. Suryavanshi, V. B. Chavan and A. Sudalai, *Chem. Commun.*, 2010, **46**, 5012; (*b*) M. Tokunaga, J. F. Larrow, F. Kakiuchi and E. N. Jacobsen, *Science*, 1997, **277**, 936.

9 (*a*) B. K. Pchelka, A. Loupy, J. Plenkiewiczb and L. Blancoc, *Tetrahedron: Asymmetry*, 2000, **11**, 2719; (*b*) A. M. Fernandez, J. M. Sanfrutos, F. H. Mateo and F. S. Gonzalez, *Curr. Org. Chem.*, 2010, **14**, 401.

10 J. R. Baker, J. D. Hothersall, R. J. Fitzmaurice, M. Tucknott, A. Vinter, A. Tinker and S. Caddick, *Chem. Commun.*, 2010, **46**, 3953.

11 R. Adorisio, D. L. Luca, J. Rossi and M. Gheorghiade, *Heart Fail. Rev.*, 2006, **11**, 109.

12 A. Hjalmarson and G. Olsson, *Circulation*, 1991, **84**, 101.

13 S. Goldstein, *Arch. Intern. Med.*, 1996, **156**, 1267.

14 R. N. Salvatore, A. S. Nagle and K. W. Jung, *J. Org. Chem.*, 2002, **67**, 674.