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Lipase-catalyzed resolution of *anti*-6-substituted 1,3-dioxepan-5-ols

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Abstract—Several *anti*-6-substituted 1,3-dioxepan-5-ols were kinetically resolved using an immobilized lipase (Amano PS–C II) in toluene in the presence of vinyl acetate at 30 °C. This approach provided, in some cases, the alcohol and the acetate in high enantiomeric purity, depending on the nature of the substituent (R = N_3, SePh, I, OBn) and the acetal group (unsubstituted or dimethyl). The role of the size of substituents is also discussed. Enantiopure *anti*-6-substituted 1,3-dioxepan-5-ols are useful building blocks.

1. Introduction

The importance of chiral 1,2-amino alcohols is evident since they are often present in many biologically active compounds. Enantiomerically pure *syn*- and *anti*-2-amino-1,3,4-trihydroxy-butane **1** and *syn*- and *anti*-2-azido-1,3,4-trihydroxy-butane **2** (Fig. 1) would be interesting chiral building blocks in the synthesis of several important compounds such as sphingosines,[1] FR900482 an antitumour antibiotic,[2] kainic acid,[3] liposidomycins[4] and glycomimetics.[5] Particularly, such compounds can be used for the synthesis of C4 unit of Nelfinavir, one of the most potent HIV-protease inhibitors (Fig. 2).[6]

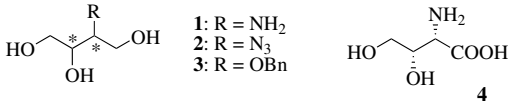

Figure 1.

Furthermore, (2*S*,3*S*)-2-amino-3,4-dihydroxybutyric acid **4** has been used as a synthetic intermediate in the synthesis of β-lactam antibiotics and phytosiderophores.[7]

These compounds can be obtained from the chiral pool. Enantiomerically enriched derivatives of **1** have already been obtained from transformations of isoascorbic acid,[1d,4c] ascorbic acid,[4b,5b] erythrulose[8] and from D- or L-diethyl tartrate.[1a]

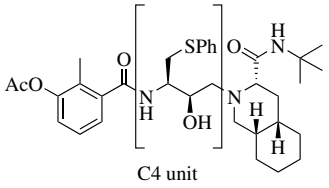

Figure 2. Structure of Nelfinavir.

Compounds **1** can also be prepared from chiral aziridino alcohols obtained by enzymatic method,[9] from separation of a diastereomeric mixture of *trans*-amino alcohol obtained by *meso*-epoxide ring opening with chiral amine,[6] from asymmetric aminolysis of *meso*-epoxide using Ti-(*S*)-1,1′-bi-2-naphthoxide complex as chiral catalyst,[10] from monoprotected optically active *cis*-1,4-dihydroxy-2,3-butene oxide.[11] The latter could be generated through Sharpless asymmetric epoxidation.[11] Sharpless asymmetric aminohydroxylation has also been used employing 2-butene-1,4-diol derivatives as substrates.[12]

In addition to compounds **1** and **2**, compound **3** is a very interesting building block too. It can be prepared starting from the chiral pool using L- or D-tartrate for (*S*,*S*)-[13] or (*R*,*R*)-enantiomers[14] or from D-erythronolactone[15] both for (*R*,*S*)- and (*S*,*R*)-enantiomers.

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In connection with our interest in stereoselective synthesis using lipase resolution of secondary alcohols, organocatalysis and organoselenium compounds,[16] we were interested in the stereoselective preparation of compounds **1**–**3** through enzymatic resolution. Enzymatic resolution of *syn*-2-azido-1,3,4-trihydroxy-butane catalyzed by lipases, both in the transesterification mode[17] and in the hydrolysis mode,[18] have been reported.

Enzymatic resolution in the transesterification mode gave compound **5** in 33% yield (>99% ee) and compound **6** in 19% yield (94% ee), whereas enzymatic resolution in the hydrolysis mode gave compound **7** in 30% yield (>99% ee). These approaches gave high ee values, but low isolated yields (Fig. 3).

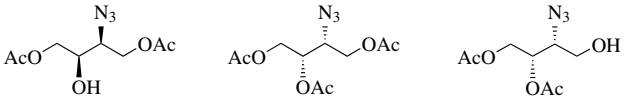


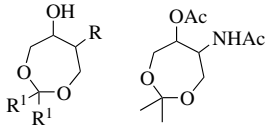
Figure 3.

Herein, we report our results on investigations about kinetic resolution, mediated by an immobilized lipase (Amano PS–C II), of several racemic *anti*-6-substituted 1,3-dioxepan-5-ols as useful precursors of compounds **1**–**3**.

2. Results and discussion

Compounds (±)-*anti*-**8a**–**i** (Table 1) were easily prepared starting from the proper cyclic epoxide by ring opening with NaN_3, NaSePh, NaI or BnOH.

Table 1. The target molecules

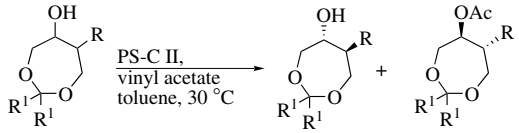


(±)-*anti*-**8a-i** (±)-*anti*-**9**

8	R	R^1
a	N_3	Me
b	NHCbz	Me
c	NHCOPh	Me
d	N_3	H
e	SePh	Me
f	SePh	H
g	I	H
h	OCH_2Ph	Me
i	OCH_2Ph	H

We started our investigation with compound (±)-**8a** using PS–C II lipase in toluene in the presence of vinyl acetate. The resolution of (±)-**8a** was slow. After 24 h, the conversion was 26% and the ee value of ester **11a** was 92% (Table 2, entry 1). After 48 h the conversion was 35% and the ee value of **11a** was 90% (entry 2). The reaction was stopped after 240 h and the conversion was 52%. Alcohol **10a** was obtained in 94% ee and ester **11a** in 87% ee (entry 3). We carried out the reaction again and stopped it when alcohol **10a** was enantiomerically pure (57% conversion, entry 4). Resolution in THF gave a lower conversion than in toluene after 24 h (entry 5). Resolution in THF gave similar results, about ee values, at higher conversion (entry 6). Using *Candida antarctica* lipase (Novozym 435), no selectivity was observed after 24 h (4% ee).

Table 2. Enantioselective lipase-catalyzed kinetic resolutions of compounds (±)-**8a**–**i**[a]



(±)-*anti*-**8a-i** **10a-i** **11a-i**

Entry	Compd	*t* (h)	*c* (%)	ee **10** (%)	ee **11** (%)	*E*[b]
1	(±)-**8a**	24	26	32	92	38
2		48	35	48	90	31
3		240	52	94	87	51
4		288	57	>99	76	37
5[c]		24	14	16	99	>200
6[c]		168	42	65	90	37
7	(±)-**8b**	—[d]	—	—	—	—
8	(±)-**8c**	—[e]	—	—	—	—
9	(±)-**8d**	3.5	51	>99	96	>200
10	(±)-**8e**	168	37	58	>99	>200
11		264	50	>99	>99	>200
12	(±)-**8f**	1	50	>99	>99	>200
13	(±)-**8g**	2	44	70	90	40
14	(±)-**8h**	0.5	50	14	14	1.5
15	(±)-**8i**	2	50	>99	>99	>200

[a] Conditions: (±)-**8** (0.4 mmol), lipase (50 mg), vinyl acetate (3 equiv), toluene (0.9 mL), 30 °C.
[b] $E = \ln[1 - c(1 + \text{ee}(\mathbf{11}))]/\ln[1 - c(1 - \text{ee}(\mathbf{11}))]$, $c = \text{ee}(\mathbf{10})/[\text{ee}(\mathbf{10}) + \text{ee}(\mathbf{11})]$.
[c] Solvent: THF.
[d] Decomposition.
[e] No reaction.

In order to improve the enantiopreference, we decided to follow two different strategies. The first was to study the enzymatic resolution of compounds (±)-**8b**,**c** having a larger R group than azido group and $R^1 = Me$. The second one was to keep the azido substituent ($R = N_3$) and to put a smaller acetal substituent [$R^1 = H$; (±)-**8d**]. We also prepared *N*,*O*-diacetyl compound **9** in order to study its alcoholysis.[19]

First we prepared the Cbz derivative (±)-**8b**, but no enzymatic resolution was carried out since this product gave, after 1 h, a complex and inseparable mixture.[6b] No resolution was observed with compound (±)-**8c**. Also the conversion of *N*,*O*-diacetyl compound (±)-**9** was very poor even after several days.

We then turned our attention to compound (±)-**8d**. The resolution of this molecule was very fast compared to (±)-**8a**. Indeed, after 3.5 h we obtained a 51% conversion. Moreover, the enantiopreference was high ($E > 200$) giving ester **11d** in 96% ee and alcohol **10d** in >99% ee (entry 9).

cis-1,2-Amino alcohols can be prepared starting from *anti*-β-hydroxy selenides through displacement of the phenylselenonyl group, following the procedure developed by Tiecco.[20] For this reason, we investigated the enzymatic resolution of compound (±)-**8e**.

Compound (±)-**8e** reacted slowly. The reaction was complete after 264 h. However, the resolution was excellent (>99%, entry 11). This result confirmed our hypothesis that with larger R groups better ee values could be reached. However, the reaction times are long.

Resolution of the less hindered compound (±)-**8f** gave enantiopure alcohol **10f** and ester **11f** in a very short time (1 h, entry 12). In order to have a different leaving group, we decided to use an iodine atom instead of the phenylseleno group. Since an iodine atom is similar in size to the azido group, we investigated resolution of compound (±)-**8g**, which as compound (±)-**8d**, does not have the bulkier dimethyl acetal group. In this case a lower *E* value compared with compound (±)-**8d** was obtained. Indeed, after a 44% conversion ester **11g** was obtained in 90% ee (entry 13). The use of other lipases, such as *C. antarctica* lipase (Novozym 435) or *Candida rugosa* lipase, gave poor results. For instance, with the latter lipase, the ee value of **11g** was 30% after a 24% conversion.

Resolution of benzyloxy derivative (±)-**8h** gave an unexpected result (entry 14). Indeed, the reaction was very fast, being complete in 30 min and giving both alcohol **10h** and ester **11h** with very low ee value (14%). In order to improve the enantiopreference, we carried out the resolution of compound (±)-**8i**. In this case, as for (±)-**8d** and (±)-**8f**, the enantiopreference was excellent giving both enantiomeric pure alcohol **10i** and ester **11i** (entry 15).

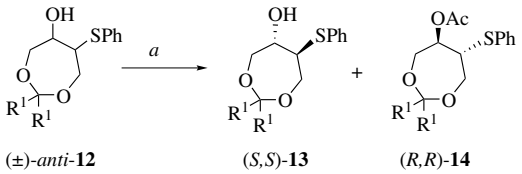
The enantiomeric excess values were determined by HPLC using a Chiracel OD-H chiral column and *n*-hexane/*i*-propanol as eluent (Table 3).

Table 3. HPLC retention times of compounds **10a–i** and **11a–i**

Compd	t_R (min)	Eluent[a,b]	Compd	t_R (min)	Eluent[a,b]
(5*S*,6*R*)-**10a**	17.24	98/2	(5*R*,6*R*)-**11f**	6.36[c]	90/10
(5*R*,6*S*)-**10a**	13.82[c]	98/2	(5*S*,6*S*)-**11f**	6.71	90/10
(5*S*,6*R*)-**11a**	5.42[c]	98/2	(5*R*,6*R*)-**10g**	[d]	—
(5*R*,6*S*)-**11a**	6.20	98/2	(5*S*,6*S*)-**10g**	[d]	—
(5*R*,6*S*)-**10d**	10.90[c]	95/5	(5*R*,6*R*)-**11g**	7.14[c]	98/2
(5*S*,6*R*)-**10d**	11.65	95/5	(5*S*,6*S*)-**11g**	8.67	98/2
(5*S*,6*R*)-**11d**	16.84[c]	98/2	(5*R*,6*R*)-**10h**	24.15	98/2
(5*R*,6*S*)-**11d**	17.53	98/2	(5*S*,6*S*)-**10h**	25.45[c]	98/2
(5*R*,6*R*)-**10e**	20.78	98/2	(5*R*,6*R*)-**11h**	10.29[c]	98/2
(5*S*,6*S*)-**10e**	27.61[c]	98/2	(5*S*,6*S*)-**11h**	10.95	98/2
(5*R*,6*R*)-**11e**	8.15[c]	98/2	(5*R*,6*R*)-**10i**	49.55	98/2[e]
(5*S*,6*S*)-**11e**	8.63	98/2	(5*S*,6*S*)-**10i**	53.46[c]	98/2[e]
(5*R*,6*R*)-**10f**	8.67	90/10	(5*R*,6*R*)-**11i**	23.51[c]	98/2[e]
(5*S*,6*S*)-**10f**	10.89[c]	90/10	(5*S*,6*S*)-**11i**	26.18	98/2[e]

[a] *n*-Hexane/*i*-propanol.
[b] Flow 1 mL/min.
[c] Major enantiomer.
[d] Determined as ester.
[e] Flow 0.6 mL/min.

The configuration of the products was assigned by analogy with resolution of compound (±)-**12**, which was resolved using the same lipase (lipase PS on Celite; Scheme 1).[21] In the cases of compounds **10h** and **11h**, which were poorly resolved, configuration was tentatively assigned since such compounds showed the same elution order and Cotton effect of compounds **10i** and **11i**.



Scheme 1. Reagents and conditions: (a) PS-on-Celite, *i*-Pr_2O, vinyl acetate, 30 °C.

When considering substrates having the dimethyl acetal group, the best resolution was obtained with R = SePh. With the less bulky azido group, the resolution was slightly less good. Despite the bulkiness of the benzyloxy substituent, compound (±)-**8h** showed very poor selectivity, probably because of the free rotation of such a group. The low enantiopreference observed is in agreement with the fact that the CH_2 group can also be fitted as a medium sized substituent into the stereoselective pocket of the enzyme, whereas the dimethyl acetal group acts as a large substituent (Fig. 4).

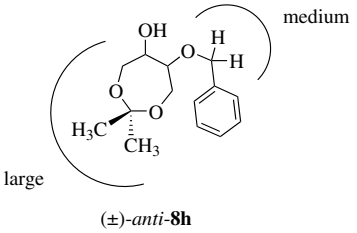


Figure 4. Size of substituents.

Following Ema's model,[22] the medium group should be fitted into the stereoselectivity pocket, whereas the large one is directed towards the external solvent (Fig. 5). On the grounds of simple computer molecular models, we can reasonably estimate that the size of the dimethyl group is able to produce an effective steric hindrance for the penetration

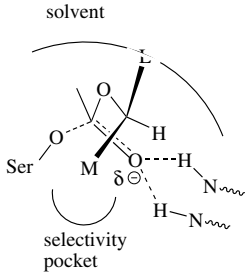


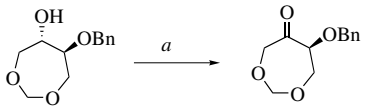
Figure 5. Ema's model.

of the species into the enzyme pocket, then acting as a large substituent too.[23]

In compounds **8a** and **8e**, the azido and the phenylseleno groups must act as large groups. Indeed, it is not possible to find a less hindered conformation. For these substrates, the portion of the molecule containing the dimethylacetal group was forced to be the medium one, causing a low reaction rate because of the steric repulsion.

Indeed, when the dimethyl acetal group was removed the reaction rates were high giving excellent enantiopreference for R = SePh, OCH_2Ph and N_3. The difference between N_3 and I could be ascribed to the higher polarizability of the iodine atom.

Finally, we carried out a simple manipulation. Compound **10i** was oxidized using stabilized 2-iodoxybenzoic acid[24] to give a protected form of (*S*)-erythrulose (Scheme 2).



10i **15**

Scheme 2. Reagents and conditions: (a) 2-iodoxybenzoic acid, ethyl acetate, 75 °C, 91%.

Compound **15** is a valuable building block that is currently used in our laboratory as a starting material for stereoselective transformations.

3. Conclusion

In conclusion, useful enantiopure building blocks have been obtained by enzymatic resolution of racemic *anti*-6-substituted 1,3-dioxepan-5-ols. Excellent resolutions were obtained with large R substituent (PhSe). With the smaller N_3 substituent, excellent resolution was observed with R^1 = H. When R^1 = Me the enantiopreference was lower because of the steric hindrance caused by the portion of the molecule containing the dimethyl acetal group. The iodine substituent (R = I) did not give excellent results even with the unsubstituted acetal. Finally, the benzyloxy substituent may also act as a medium substituent giving a low enantiopreference when the dimethylacetal group was present, whereas it acts as a large substituent when the dimethyl group was absent giving an excellent resolution. These compounds are precursors of compounds **1**–**3**, but other simple manipulations can be carried out. For example, oxidation of compound **10i** gave a protected form of (*S*)-erythrulose.

4. Experimental

4.1. General

The NMR spectra were recorded on a Bruker AC–E series 250 MHz or 300 MHz spectrometer using $CDCl_3$ as solvent. FT-IR spectra were registered with a Shimadzu FTIR 8300 infrared spectrophotometer. Carbon and hydrogen contents were determined by combustion analysis in a Fisons EA 1108 elemental analyzer. Optical rotations were measured in chloroform on a Jasco P1010 polarimeter. Chiral HPLC was performed using a Shimadzu LC-10AD pump with a SPD-M10A UV detector and Daicel column (OD-H). Compounds (±)-*anti*-**8a**–**i** were prepared starting from the proper cyclic epoxide. 2,2-Dimethyl-1,3-dioxepan-5,6-oxirane and 1,3-dioxepan-5,6-oxirane were obtained by epoxidation[6a] of 2,2-dimethyl-1,3-dioxep-5-en or dimethyl-1,3-dioxep-5-en. Epoxide ring opening was carried out with NaN_3, NaSePh, NaI or BnOH.[25] Compounds (±)-*anti*-**8b**–**c** and (±)-*anti*-**9** were prepared after reduction of the azido group with Ni–Raney and protection.

4.2. Enzymatic resolution procedure

To a solution of alcohol (±)-**8** (0.4 mmol) in toluene (0.9 mL) at 30 °C, vinyl acetate (1.2 mmol) and PS–C II lipase (50 mg) were added. The reaction was monitored by HPLC, then taken up with diethyl ether, filtered and the solvent removed under reduced pressure. The residue was checked by NMR, then purified by silica gel chromatography using light petroleum/ethyl acetate as eluent.

4.2.1. (5*R*,6*S*)-6-Azido-2,2-dimethyl-1,3-dioxepan-5-ol 10a. $[\alpha]_D^{27} = +91.9$ (*c* 0.40, $CHCl_3$); >99% ee. ^1H NMR (250 MHz): δ 1.34 (s, 6H), 2.87 (br s, 1H, OH), 3.36–3.43 (m, 1H), 3.55–3.74 (m, 3H), 3.80–3.90 (m, 2H); ^{13}C NMR (62.5 MHz): δ 24.2, 24.6, 58.9, 61.4, 64.3, 71.2, 101.9. IR (liquid film) 3423, 2108, 1452, 1375 cm^{-1}. Anal. Calcd for $C_7H_{13}N_3O_3$: C, 44.91; H, 7.00. Found: C, 44.78; H, 7.13.

4.2.2. (5*S*,6*R*)-6-Azido-2,2-dimethyl-1,3-dioxepan-5-yl acetate 11a. $[\alpha]_D^{22} = -43.3$ (*c* 0.49, $CHCl_3$); 93% ee. ^1H NMR (250 MHz): δ 1.34 (s, 6H), 2.10 (s, 3H), 3.49–3.54 (m, 1H), 3.63–3.85 (m, 4H), 4.76–4.82 (m, 1H); ^{13}C NMR (62.5 MHz): δ 20.9, 24.1, 24.3, 59.6, 59.7, 62.4, 73.6, 101.7, 169.7. IR (liquid film) 2112, 1745, 1454, 1372 cm^{-1}. Anal. Calcd for $C_9H_{15}N_3O_4$: C, 47.16; H, 6.60. Found: C, 47.32; H, 6.71.

4.2.3. (±)-*anti*-Benzyl 6-hydroxy-2,2-dimethyl-1,3-dioxepan-5-yl carbamate 8b. To a solution of (±)-*anti*-6-amino-2,2-dimethyl-1,3-dioxepan-5-ol (98 mg, 0.608 mmol) in methanol (1.2 mL), Na_2CO_3 (0.73 mmol) was added. The mixture was cooled at 0 °C, then benzyl chloroformate (85 μL, 0.73 mmol) was slowly added. The mixture was stirred for 2 h at room temperature, then filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography using light petroleum/ethyl acetate 2/1 as eluent. Yield 65%. ^1H NMR (250 MHz): δ 1.33 (s, 3H), 1.36 (s, 3H), 3.28 (s, 1H, OH), 3.49 (ddd, J = 12.7, 2.2 and 2.2 Hz, 1H), 3.51–3.81 (m, 4H), 4.03 (d, J = 12.7 Hz, 1H), 5.11–5.17 (m, 2H), 5.55 (d, J = 7.4 Hz, 1H), 7.33–7.40 (m, 5H).

4.2.4. (±)-*anti*-*N*-(6-Hydroxy-2,2-dimethyl-1,3-dioxepan-5-yl)-benzamide 8c. A solution of benzoyl chloride (109 μL, 0.943 mmol) in dichloromethane (1 mL) was

slowly added to a solution of (±)-*anti*-6-amino-2,2-dimethyl-1,3-dioxepan-5-ol (152 mg, 0.943 mmol) and $NaHCO_3$ (1.13 mmol) in water (1.6 mL). The mixture was stirred for 2 h at room temperature, then water was added (15 mL) and the solution extracted with dichloromethane (3 × 15 mL) and brine (1 × 15 mL). The organic solvent was removed under reduced pressure to give pure compound **8c** (80%). Mp 146 °C. ^{1}H NMR (300 MHz): δ 1.35 (s, 3H), 1.36 (s, 3H), 3.54 (dd, $J = 12.4$ and 3.9 Hz, 1H), 3.64 (dd, $J = 13.1$ and 3.9 Hz, 1H), 3.76–3.81 (m, 2H), 4.11–4.16 (m, 2H), 4.19 (br s, 1H, OH), 6.98 (d, $J = 7.7$ Hz, 1H), 7.35–7.51 (m, 3H), 7.74–7.77 (m, 2H); ^{13}C NMR (75 MHz): δ 24.8, 25.2, 54.8, 59.7, 62.3, 70.6, 102.3, 127.4, 128.9, 132.1, 134.5, 167.7. IR (nujol) 3382, 3289, 1638, 1626, 1554 cm^{-1}. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22. Found: C, 63.51; H, 7.33.

4.2.5. (5*R*,6*S*)-6-Azido-1,3-dioxepan-5-ol 10d. Mp 44–46 °C; $[\alpha]_D^{23} = +50.8$ (*c* 0.48, $CHCl_3$); >99% ee. ^{1}H NMR (250 MHz): δ 2.98 (br s, 1H, OH), 3.48–3.54 (m, 1H), 3.67–3.90 (m, 5H), 4.71 (d, $J = 4.5$ Hz, 1H), 4.74 (d, $J = 4.5$ Hz, 1H); ^{13}C NMR (62.5 MHz): δ 63.7, 64.8, 65.7, 71.8, 94.1. IR (liquid film) 3432, 2104, 1457 cm^{-1}. Anal. Calcd for $C_5H_9N_3O_3$: C, 37.74; H, 5.70. Found: C, 37.99; H, 5.60.

4.2.6. (5*S*,6*R*)-6-Azido-1,3-dioxepan-5-yl acetate 11d. $[\alpha]_D^{23} = -40.35$ (*c* 0.49, $CHCl_3$); 96% ee. ^{1}H NMR (250 MHz): δ 2.11 (s, 3H), 3.63 (ddd, $J = 6.1$, 6.1 and 2.9 Hz, 1H), 3.71–3.82 (m, 2H), 3.84 (dd, $J = 13.7$ and 3.0 Hz, 1H), 3.93 (dd, $J = 12.5$ and 3.0 Hz, 1H), 4.73 (d, $J = 4.7$ Hz, 1H), 4.76 (d, $J = 4.7$ Hz, 1H), 4.87 (ddd, $J = 6.0$, 6.0 and 3.1 Hz, 1H); ^{13}C NMR (62.5 MHz): δ 20.8, 62.8, 64.0, 64.5, 73.9, 94.4, 169.7. IR (liquid film) 2107, 1735, 1374 cm^{-1}. Anal. Calcd for $C_7H_{11}N_3O_4$: C, 41.79; H, 5.51. Found: C, 41.98; H, 5.62.

4.2.7. (5*S*,6*S*)-2,2-Dimethyl-6-(phenylseleno)-1,3-dioxepan-5-ol 10e. $[\alpha]_D^{26} = +17.4$ (*c* 1.02, $CHCl_3$); >99% ee. ^{1}H NMR (300 MHz): δ 1.36 (s, 6H), 2.81 (d, $J = 5.4$ Hz, 1H, OH), 3.19–3.23 (m, 1H), 3.61–3.71 (m, 2H), 3.83 (dd, $J = 12.8$ and 6.1 Hz, 1H), 4.08–4.16 (m, 2H), 7.27–7.31 (m, 3H), 7.56–7.60 (m, 2H); ^{13}C NMR (75 MHz): δ 24.5, 24.7, 51.7, 61.2, 62.8, 71.6, 101.6, 127.7, 128.3, 129.2, 134.3. IR (liquid film) 3420, 1580, 1477, 1437, 1373 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_3Se$: C, 51.83; H, 6.02. Found: C, 51.70; H, 6.20.

4.2.8. (5*R*,6*R*)-2,2-Dimethyl-6-(phenylseleno)-1,3-dioxepan-5-yl acetate 11e. $[\alpha]_D^{26} = -29.8$ (*c* 1.47, $CHCl_3$); >99% ee. ^{1}H NMR (250 MHz): δ; ^{13}C NMR (62.5 MHz): δ 1.35 (s, 6H), 2.07 (s, 3H), 3.25–3.35 (m, 1H), 3.69–3.84 (m, 2H), 4.07–4.17 (m, 2H), 4.90–4.96 (m, 1H), 7.26–7.31 (m, 3H), 7.57–7.63 (m, 2H). IR (liquid film) 1738, 1580, 1480, 1437, 1371 cm^{-1}. Anal. Calcd for $C_{15}H_{20}O_4Se$: C, 52.48; H, 5.87. Found: C, 52.60; H, 5.99.

4.2.9. (5*S*,6*S*)-6-(Phenylseleno)-1,3-dioxepan-5-ol 10f. Mp 54–55 °C. $[\alpha]_D^{26} = +4.0$ (*c* 0.95, $CHCl_3$); >99% ee. ^{1}H NMR (300 MHz): δ 3.10 (br s, 1H, OH), 3.42–3.52 (m, 1H), 3.97–4.03 (m, 2H), 4.14 (dd, $J = 12.5$ and 6.3 Hz, 1H), 4.33–4.41 (m, 2H), 4.97 (d, $J = 4.5$ Hz, 1H), 5.00 (d, $J = 4.5$ Hz, 1H), 7.50–7.55 (m, 3H), 7.78–7.81 (m, 2H); ^{13}C NMR (75 MHz): δ 51.6, 65.8, 66.7, 72.0, 94.1, 127.6, 128.0, 129.3, 134.6. IR (nujol) 3345 cm^{-1}. Anal. Calcd for $C_{11}H_{14}O_3Se$: C, 48.36; H, 5.17. Found: C, 48.52; H, 5.30.

4.2.10. (5*R*,6*R*)-6-(Phenylseleno)-1,3-dioxepan-5-yl acetate 11f. $[\alpha]_D^{25} = -15.0$ (*c* 1.06, $CHCl_3$); >99% ee. ^{1}H NMR (300 MHz): δ 2.00 (s, 3H), 3.27–3.31 (m, 1H), 3.77–3.84 (m, 2H), 4.02 (dd, $J = 12.6$ and 2.3 Hz, 1H), 4.14 (dd, $J = 12.3$ and 2.4 Hz, 1H), 4.66 (d, $J = 4.5$ Hz, 1H), 4.72 (d, $J = 4.5$ Hz, 1H), 4.92–4.97 (m, 1H), 7.19–7.25 (m, 3H), 7.50–7.53 (m, 2H); ^{13}C NMR (75 MHz): δ 21.0, 48.0, 65.7, 65.8, 74.3, 94.3, 127.8, 127.9, 129.1, 134.5, 169.9. IR (liquid film) 1733, 1578 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O_4Se$: C, 49.53; H, 5.12. Found: C, 49.21; H, 5.01.

4.2.11. (5*S*,6*S*)-6-Iodo-1,3-dioxepan-5-ol 10g. $[\alpha]_D^{24} = +14.4$ (*c* 0.55, $CHCl_3$); 70% ee. ^{1}H NMR (250 MHz): δ 3.26 (br s, 1H, OH), 3.66–4.13 (m, 6H), 4.76–4.78 (m, 2H); ^{13}C NMR (62.5 MHz): δ 36.5, 66.0, 67.0, 75.5, 77.2, 94.0. IR (liquid film) 3425, 1452 cm^{-1}. Anal. Calcd for $C_7H_{13}IO_3$: C, 30.90; H, 4.82. Found: C, 30.99; H, 4.90.

4.2.12. (5*R*,6*R*)-6-Iodo-1,3-dioxepan-5-yl acetate 11g. $[\alpha]_D^{23} = -41.7$ (*c* 0.79, $CHCl_3$); 90% ee. ^{1}H NMR (250 MHz): δ 2.12 (s, 3H), 3.72 (dd, $J = 12.2$ and 7.0 Hz, 1H), 3.85 (dd, $J = 12.5$ and 8.0 Hz, 1H), 3.97 (dd, $J = 12.2$ and 3.1 Hz, 1H), 4.03–4.15 (m, 2H), 4.79 (d, $J = 4.5$ Hz, 1H), 4.82 (d, $J = 4.5$ Hz, 1H), 5.09–5.15 (m, 1H); ^{13}C NMR (62.5 MHz): δ 21.3, 30.6, 65.4, 67.7, 77.3, 94.6, 170.0. IR (liquid film) 1735, 1369 cm^{-1}. Anal. Calcd for $C_9H_{15}IO_4$: C, 34.41; H, 4.81. Found: C, 34.61; H, 4.99.

4.2.13. 6-(Benzyloxy)-2,2-dimethyl-1,3-dioxepan-5-ol 10h. $[\alpha]_D^{25} = +2.0$ (*c* 1.26, $CHCl_3$); 14% ee. ^{1}H NMR (300 MHz): δ 1.29 (s, 3H), 1.36 (s, 3H), 2.78 (br s, 1H, OH), 3.37–3.48 (m, 2H), 3.57 (dd, $J = 11.5$ and 4.3 Hz, 1H), 3.65 (dd, $J = 7.6$ and 7.6 Hz, 1H), 3.87 (dd, $J = 6.6$ Hz, 1H), 4.16 (ddd, $J = 6.6$, 6.6 and 6.6 Hz, 1H), 4.57 (d, $J = 11.9$ Hz, 1H), 4.63 (d, $J = 11.9$ Hz, 1H), 7.14–7.27 (m, 5H); ^{13}C NMR (75 MHz): δ 25.1, 26.1, 61.4, 65.3, 72.4, 76.3, 79.2, 109.0, 127.4, 127.6, 128.1, 138.0. IR (liquid film) 3457, 1454, 1380, 1370 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.80; H, 8.14.

4.2.14. 6-(Benzyloxy)-2,2-dimethyl-1,3-dioxepan-5-yl acetate 11h. $[\alpha]_D^{26} = -2.6$ (*c* 0.69, $CHCl_3$); 14% ee. ^{1}H NMR (300 MHz): δ 1.29 (s, 3H), 1.35 (s, 3H), 1.97 (s, 3H), 3.47–3.54 (m, 2H), 3.60–3.68 (m, 1H), 3.73 (dd, $J = 8.3$ and 7.1 Hz, 1H), 3.93 (dd, $J = 8.3$ and 6.6 Hz, 1H), 4.19–4.27 (m, 1H), 4.62 (d, $J = 11.8$ Hz, 1H), 4.69 (d, $J = 11.8$ Hz, 1H), 7.21–7.29 (m, 5H); ^{13}C NMR (75 MHz): δ 20.9, 25.3, 27.3, 63.6, 65.5, 72.9, 76.0, 76.8, 109.5, 127.8, 127.9, 128.4, 138.1, 170.8. IR (liquid film) 1742 cm^{-1}. Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.50; H, 7.67.

4.2.15. (5*S*,6*S*)-6-(Benzyloxy)-1,3-dioxepan-5-ol 10i. $[\alpha]_D^{30} = +29.0$ (*c* 0.82, $CHCl_3$); >99% ee. ^{1}H NMR (300 MHz): δ 2.70 (br s, 1H, OH), 3.26–3.29 (m, 1H),

3.48–3.61 (m, 4H), 3.76 (dd, $J = 11.6$ and 1.1 Hz, 1H), 4.38 (d, $J = 12.0$ Hz, 1H), 4.45 (d, $J = 12.0$ Hz, 1H), 4.52–4.56 (m, 2H), 7.06–7.15 (m, 5H); ^{13}C NMR (75 MHz): δ 64.4, 65.6, 71.4, 71.5, 80.3, 94.5, 127.7, 127.8, 128.4, 137.9. IR (liquid film) 3445, 1454 cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.42; H, 7.27.

4.2.16. (5*R*,6*R*)-6-(Benzyloxy)-1,3-dioxepan-5-yl acetate 11i. $[\alpha]_D^{31} = -11.7$ (*c* 0.88, $CHCl_3$); >99% ee. ^{1}H NMR (300 MHz): δ 2.00 (s, 3H), 3.42–3.47 (m, 1H), 3.74–3.80 (m, 3H), 3.89 (dd, $J = 12.9$ and 2.2 Hz, 1H), 4.60 (s, 2H), 4.69 (d, $J = 4.6$ Hz, 1H), 4.72 (d, $J = 4.6$ Hz, 1H), 4.90–4.94 (m, 1H), 7.21–7.28 (m, 5H); ^{13}C NMR (75 MHz): δ 20.11, 63.6, 63.7, 70.5, 72.1, 76.8, 93.7, 126.9, 127.4, 136.9, 169.1. IR (liquid film) 1739, 1454, 1371, 1238 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81. Found: C, 63.25; H, 6.98.

4.2.17. (±)-*anti*-6-Acetamido-2,2-dimethyl-1,3-dioxepan-5-yl acetate 9. To a solution of (±)-*anti*-6-amino-2,2-dimethyl-1,3-dioxepan-5-ol (125 mg, 0.775 mmol) in *N*,*N*-dimethylformamide (0.5 mL), Na_2CO_3 (1.55 mmol) and acetic anhydride (1 mL) were added. The mixture was stirred for 2 h at room temperature, then water (20 mL) was added and the mixture extracted with ethyl acetate (3×15 mL) and brine (1×15 mL). The solvent was removed under reduced pressure and the residue purified by washing with diethyl ether. Yield 90%. Mp 123 °C. ^{1}H NMR (300 MHz): δ 1.36 (s, 3H), 1.38 (s, 3H), 2.03 (s, 3H), 2.11 (s, 3H), 3.49 (dd, $J = 12.6$ and 4.2 Hz, 1H), 3.72 (d, $J = 13.5$ Hz, 1H), 3.84 (dd, $J = 13.5$ and 3.9 Hz, 1H), 4.00–4.08 (m, 2H), 4.72–4.76 (m, 1H), 6.04 (d, $J = 6.9$ Hz, 1H); ^{13}C NMR (75 MHz): δ 21.5, 23.7, 24.6, 25.2, 51.9, 59.8, 60.4, 72.8, 102.3, 162.7, 169.8. IR (nujol) 3231, 3068, 1736, 1644 cm^{-1}. Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81. Found: C, 53.60; H, 7.98.

4.2.18. (*S*)-6-Benzyloxy-1,3-dioxepan-5-one 15. To a solution of compound **10i** (300 mg, 1.34 mmol) in ethyl acetate (9.5 mL) was added 2-iodoxybenzoic acid (1.2 equiv, 1.0 g) and the mixture heated at 75 °C for 4.5 h. After cooling at room temperature, the mixture was filtered and the solid washed with ethyl acetate. The filtrate was evaporated under reduced pressure, then purified by column chromatography using light petroleum ether/ethyl acetate 5/1 as eluent to give compound **15**. Yield 91%. $[\alpha]_D^{26} = -28.10$ (*c* 0.33, $CHCl_3$). Mp 67–68 °C. ^{1}H NMR (250 MHz): δ 3.81 (dd, $J = 12.3$ and 6.6 Hz, 1H), 3.94 (d, $J = 17.8$ Hz, 1H), 4.04 (dd, $J = 12.3$ and 7.4 Hz, 1H), 4.28 (d, $J = 17.8$ Hz, 1H), 4.41 (d, $J = 11.7$ Hz, 1H), 4.70–4.81 (m, 3H), 4.93 (d, $J = 5.6$ Hz, 1H), 7.30–7.37 (m, 5H); ^{13}C NMR (62.5 MHz): δ 68.7, 72.3, 72.8, 82.5, 96.2, 127.9, 128.0, 128.5, 137.3, 208.4. IR (nujol) 1734, cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.90; H, 6.41.

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