Tetrahedron: *Asymmetry* xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

anti-Selective aldol reactions of chiral alcohol substituted γ-benzyloxyl vinylogous urethanes and the synthesis of 3-benzyloxyl-4-hydroxylalkan-2-ones

Yu-Jang Li [a,*], Chuan-Chung Chung [b], Pin-Zu Chen [b]

[a] Department of Applied Chemistry, National Chiayi University, 300 University Road, Chiayi City 60004, Taiwan
[b] Department of Applied Chemistry, Chaoyang University of Technology, 168 Gifeng E. Road, Wufeng, Taichung County 41349, Taiwan

ARTICLE INFO

Article history:
Received 6 July 2017
Revised 22 September 2017
Accepted 1 October 2017
Available online xxxx

ABSTRACT

The *anti*-selective aldol reaction of chiral alcohol-substituted γ-benzyloxy vinylogous urethanes is described. The use of (1*S*,2*R*,4*R*)-1-(hydroxydiphenylmethyl)-7,7-dimethylbicyclo[2,2,1]-heptan-2-ol as a chiral auxiliary in the aldol reaction of a vinylogous urethane enolate was found to provide *anti*-products in good yields with moderate to excellent enantioselectivities. The major *anti*-vinylogous urethane lactones were transformed into 3-benzyloxyl-4-hydroxylalkan-2-ones in good yields.

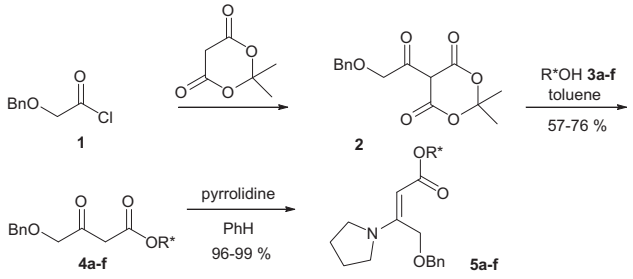
1. Introduction

The *syn*-selective aldol reaction of chiral vinylogous urethane enolate anions with various aldehydes have been successfully developed to generate *syn*-chiral vinylogous urethane lactones with high enantioselectivities. These *syn*-vinylogous urethane lactones were then used as important intermediates for the synthesis of natural products, such as virginiamycin M_2, zaragizic acid A, (+)-KDO, okadaic acid, (+)-asperlin and their derivatives.[1,2] In comparison to the many studies on the *syn*-selective aldol reaction of chiral vinylogous urethane enolate anions, *anti*-selective aldol reactions of chiral vinylogous urethane enolate anions have been less studied. In previous studies we have shown that chiral alcohol-substituted vinylogous urethanes, with γ-methyl substitution, can react with various aldehydes to give *anti*-selective aldol products in good yields and with moderate to good enantioselectivities. This was applied to the synthesis of pre-lactone B.[3] Herein, we report investigations on the chiral *anti*-selective aldol reactions and their product transformations, involving the use of chiral alcohol-substituted vinylogous urethanes with γ-benzyloxyl substitution.

2. Results and discussion

We began with the synthesis of various chiral alcohol substituted vinylogous urethanes. 2-(2-Benzyloxyacetyl)-Meldrum acid **2** was obtained by the acylation of 2-benzyloxyacetyl chloride **1** with Meldrum's acid in 85% yield.[4] Chiral alcohols **3a-f** were then reacted respectively with **2** in toluene at reflux to provide chiral ketoesters **4a-f** in 57–76% yields.[5] Condensation of **4a-f** with pyrrolidine furnished chiral γ-benzyloxy vinylogous urethanes **5a-f** in 96–99% yields (Schemes 1 and 2).[6]

Chiral alcohol-substituted vinylogous urethanes **5a-f** were subjected to aldol reaction studies. A typical procedure for the aldol reaction of chiral alcohol-substituted vinylogous urethanes was conducted using 2.5 (Entries 1–5) or 3.5 (Entry 6) equivalents of LDA as a base. Kinetic deprotonation of **5a-f** at −78 °C for 30 min was followed by warming to room temperature for 20 min. After re-cooling to −78 °C and stirring for 30 min, 2.5 equiv.of isobutyraldehyde (1 mol/L in THF, 2.5 mL) were added to the reaction mixture. Warming to room temperature over two hours followed by quenching with aqueous ammonium chloride (1 mol/L) pro-



Scheme 1. Synthesis of vinylogous urethane lactone **5**.

* Corresponding author.
E-mail address: yjli@mail.ncyu.edu.tw (Y.-J. Li).

https://doi.org/10.1016/j.tetasy.2017.10.003
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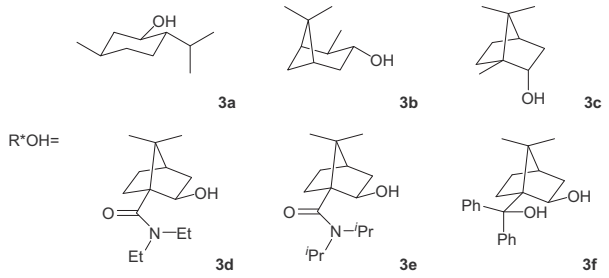


Scheme 2. Chiral alcohol **3a–f**.

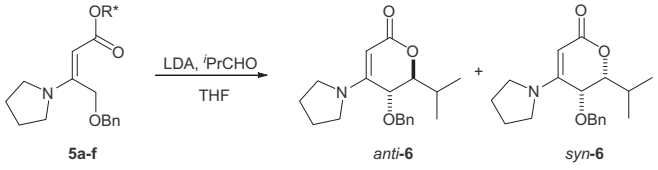
vided vinylogous urethane lactones *anti*-**6** and *syn*-**6** in moderate to good yields. The diastereoselectivity (*anti*-**6** vs. *syn*-**6**) and enantioselectivity of *anti*-**6** obtained from the individual reaction were determined respectively by regular and chiral HPLC analysis (Chiralcel® OD). Studies showed that the reaction of **5f** with isobutyraldehyde provided the best diastereoselectivity (92%) and enantioselectivity (98%) (Table 1).

When the aldol reaction of vinylogous urethane **5f** was performed in a different solvent system, it showed that the reaction gave comparable results (with slightly lower ee) when ether was used as the solvent (Entry 2). Solvent systems involving toluene provided less satisfactory yields and stereoselectivities, mainly due to it being less efficient in solvating the enolate aggregation (Entries 3–5) (Table 2).

When vinylogous urethane **5f** was reacted with various aldehydes, the reaction provided compounds **7a-i** in reasonable 60–81% yields. The reactions of straight chain aliphatic aldehydes showed excellent diastereoselectivities (93–97%) and moderate to good enantioselectivities (86–94%) (Entries 1–4). Reactions of 2-(benzyloxy)acetaldehyde and (*E*)-but-2-enal showed good diastereoselectivities (91%), but moderate enantioselectivities (77–85%) (Entries 5, 6). Although reactions of simple benzaldehydes showed moderate 74% diastereoselectivity and 86% enantioselectivity (Entry 7), reactions of bulkier aryl aldehydes showed significantly lower diastereoselectivity (57–64%) and enantioselectivity (63–68%) (Entries 8, 9). In addition to the bulkiness of the aldehyde used in entry 9, the oxygen atoms on the aryl substituents may disrupt the regular vinylogous urethane enolate aggregation, therefore lower both diastereoselectivity and enantioselectivity (Table 3). The X-ray crystallographic structure of *anti*-**6** was analyzed to confirm the structural assignments as shown in Fig. 1.[7]

Acid hydrolysis of vinylogous urethane lactone *anti*-**6** under 4 M HCl condition did not provide the expected enamine hydrolyzed β-keto lactone **8** as in the previous γ-methyl substituted case.[3] Instead, a decarboxylated product **11** was obtained in 90% yield. Presumably, the further decarboxylation process from β-ketol δ-lactone **8** to ketone **11** may be assisted by the existence of the

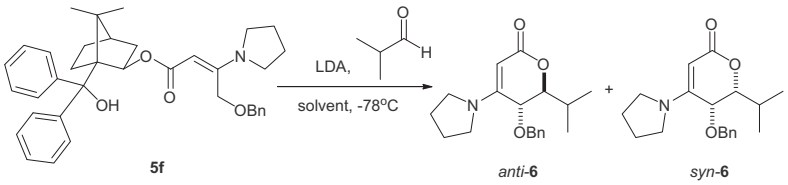
Table 1
Results of the *anti*-aldol reaction studies of **5a–f**



Entry	Vinylogous urethane	% Yield[a]	% de	% ee[b]
1	**5a**	78	47	8
2	**5b**	83	47	31
3	**5c**	80	36	41
4	**5d**	73	56	53
5	**5e**	70	18	14
6	**5f**	81	92	98

[a] Combined isolated yields of *anti*- and *syn*-products.
[b] The ee values and de values were determined by HPLC analysis on a Chiralcel OJ column [detected at 290 nm; eluent, *n*-hexane/ethanol, 94/6 (v/v)].

Table 2
Results of the *anti*-aldol reaction studies of **5f** under different solvent systems

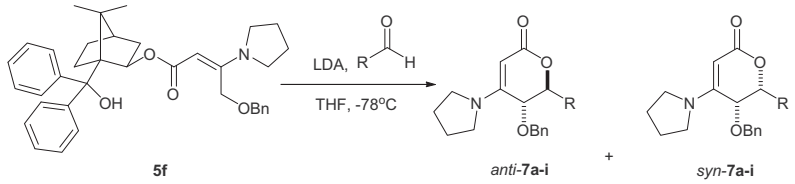


Entry	Solvent	% Yield[a]	% de	% ee[b]
1	THF	81	92	98
2	Et_2O	77	90	85
3	Toluene/THF (1:1)	68	77	85
4	Tolene/Ether (1:1)	66	77	86
5	Toluene	43	27	64

[a] Combined isolated yields of *anti*- and *syn*-products.
[b] The ee values were determined by HPLC analysis on a Chiralcel OD column; flow rate 0.5 mL/min [detected at 290 nm; eluent, hexane/^{i}PrOH = 3/1].

Please cite this article in press as: Li, Y.-J.; et al. *Tetrahedron: Asymmetry* (2017), https://doi.org/10.1016/j.tetasy.2017.10.003

Table 3
Aldol reaction of **5f** with various aldehydes



Entry	R	Product	% Yield[a]	% de	% ee[b]
1	Me	**7a**	60	93	86
2	Et	**7b**	69	94	94
3	Pr	**7c**	75	95	94
4	Bu	**7d**	77	97	93
5	CH_2OBn	**7e**	70	91	85
6	CH=CHMe(*E*)	**7f**	75	91	77
7	Ph	**7g**	81	74	86
8	1-napth	**7h**	81	64	68
9	2,3,4-$(OMe)_3$-6-(CH_2OMe)-Ph	**7i**	72	57	63

[a] Combined isolated yields of *anti*- and *syn*-products.
[b] The ee values of *anti*-products were determined by HPLC analysis on a Chiralcel OD or AD-H or AD column; flow rate 0.5 mL/min [detected at 290 nm; eluent, hexane/^{i}PrOH = 3/1].

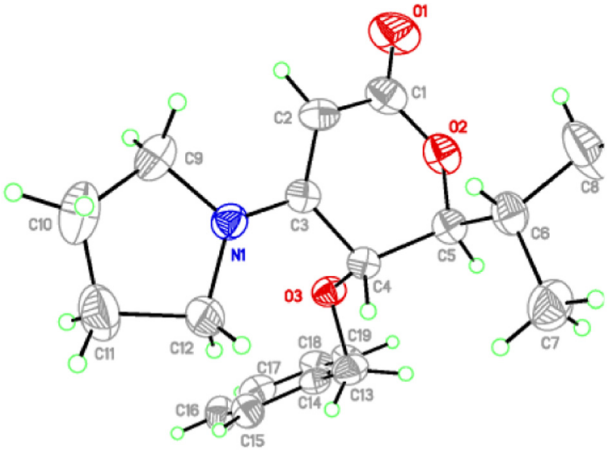
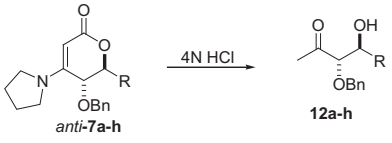


Figure 1. ORTEP view of the X-ray crystallographic structure of *anti*-**6** (thermal ellipsoids are shown at 30% probability).

hydrogen bonding between the carbonyl and OBn of the intermediate **9** (Scheme 3).

Since 1,2-diols are essential moieties in a variety of biologically active natural products, compounds such as **11** providing differentiated dihydroxyl groups would be highly desirable.[8,9] Therefore, *anti*-**7a-h** compounds were subsequently subjected to the hydrolysis to provide 3-benzyloxyl-4-hydroxyalkan-2-one compounds **12a-h** in good yields (83–91%) (Table 4).

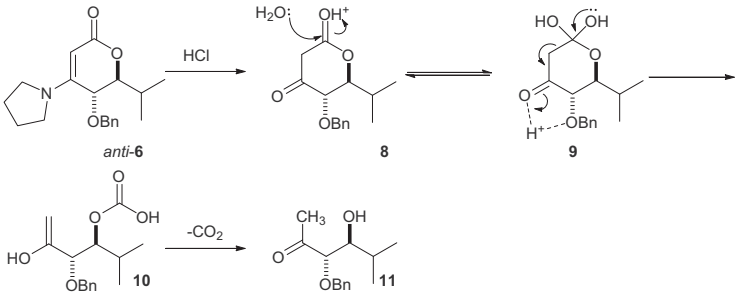
Table 4
Hydrolysis *anti*-**7a-h**



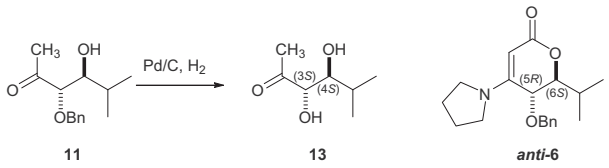
Entry	R	Products	% Yield[a]
1	Me	**12a**	90
2	Et	**12b**	88
3	Pr	**12c**	91
4	Bu	**12d**	88
5	CH_2OBn	**12e**	83
6	CH=CHMe(*E*)	**12f**	83
7	Ph	**12g**	85
8	1-napth	**12h**	88

[a] Isolated yield.

For the purpose of confirming the absolute configuration of *anti*-**7a-i**, hydrogenolysis of **11** under a hydrogen atmosphere using palladium on carbon afforded dihydroxy compound **13** in 78% yield. Compound **13** has the same rotation $[\alpha]_D^{26}$ = +64.7 (*c* 0.1, $CHCl_3$), as an authentic compound; [lit. $[\alpha]_D$ = +73.0 (*c* 1.0, $CHCl_3$)],[8e] which indicates that the absolute stereochemistry of the *anti*-**6** product generated from the aldol reaction is (5*R*,6*S*) (Scheme 4).



Scheme 3. Plausible mechanism for the hydrolysis of **6**-*anti*.



Scheme 4. Hydrogenolysis of **11**.

To account for the absolute configuration of *anti*-**6**, resulting from the reaction of **5f** with an aldehyde, a plausible mechanism is shown in Scheme 5. The 6-membered ring enolate moiety in the transition state **A** is *anti* to the *gem*-dimethyl group of the chiral auxiliary, which will encounter less steric hindrance than in transition state **A**′, whereas the 6-membered ring enolate moiety is *syn* to the *gem*-dimethyl group of the chiral auxiliary. Therefore, the reaction was expected to occur preferentially from the more stable transition state **A** in a *Si*-*Re* fashion to generate aldolate **B**, which would then cyclize to give vinylogous urethane lactone *anti*-**6** (5*R*,6*S*) as the major enantiomer.

3. Conclusion

In conclusion, aldol reactions of a series of alcohol-substituted vinylogous urethanes with γ-benzyloxyl substitution were studied. The resulting aldol products from the reaction of vinylogous urethane **5** provide moderate to good diastereoselectivities and enantioselectivities. Compounds *anti*-**7a-h** were hydrolyzed with 4 M HCl to provide 3-benzyloxyl-4-hydroxyalkan-2-one compounds with differentiated 1,2-dihydroxy moieties in good yields. Finally, a plausible mechanism was proposed to account for the generation of the major enantiomer. Further studies on synthetic applications as well as mechanistic studies of the reaction are currently in progress in our laboratory.

4. Experimental

4.1. General

NMR spectra were taken with a Varian Mercury-200 nuclear magnetic resonance spectrometer (200 MHz for ^{1}H NMR, 50 MHz for ^{13}C NMR) in $CDCl_3$. Chemical shifts were reported in parts per million (ppm) relative to internal standard $CDCl_3$ (7.24 ppm), and coupling constant was reported in hertz (Hz). Optical rotation was measured at ambient temperature on a Jasco P-1010 polarimeter using a NaD (586 nm) lamp quartz cell with a path length of 0.1 dm; abs values were corrected for the rotation of cell with solvent. Mass spectra were recorded on a VG-7035 mass spectrometer at an ionizing voltage of either 70 or 20 eV; alternatively, samples were analyzed by the Instrument Center of The National Science Counsel at National Chung Hsing University.

4.2. Synthesis of ketoesters 4a-f

4.2.1. (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 4-(benzyloxy)-3-oxobutanoate 4a

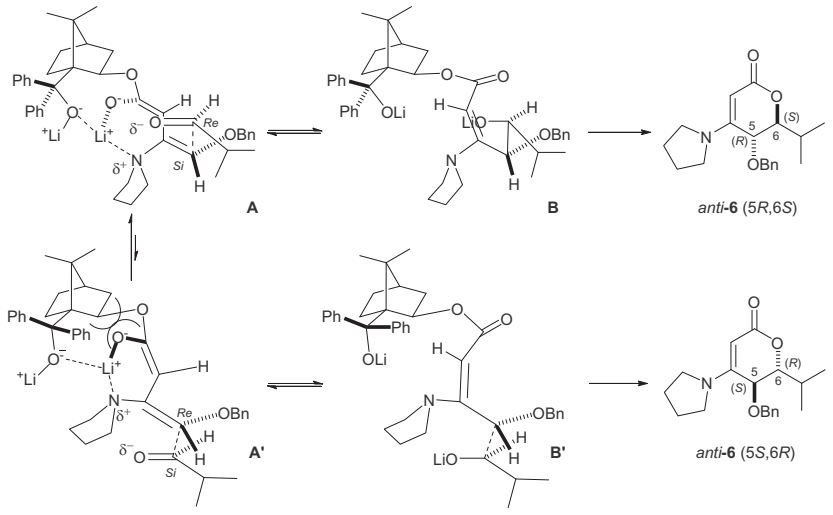
To (−)-menthol **3a** (1.25 g, 8 mmol) in a 100 mL round-bottom flask was added 5-(2-benzyloxy-acetyl)-2,2-dimethyl-1,3-dioxane-4,6-dione **2** (2.34 g, 8 mmol) and xylene (40 mL) as solvent. The mixtures were heated to reflux for 6 h, then concentrated in vacuo to remove solvent. The crude material was purified by flash chromatography (*n*-hexane/EtOAc = 4:1) to give 2.13 g of ketoesters **4a** in 77% yield. Colorless oil. R_f = 0.80 (*n*-hexane/EtOAc = 4:1); $[\alpha]_D^{26}$ = −53.1 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41–7.29 (m, 5H), 4.80–4.62 (m, 1H), 4.60 (s, 2H), 4.14 (s, 2H), 3.53 (s, 2H), 2.03–0.80 (m, 9H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 7.1 Hz, 3H), 0.74 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.4, 166.4, 136.8, 128.3(2C), 127.9, 127.6(2C), 75.3, 74.6, 73.2, 46.7, 46.1, 40.5, 34.0, 31.2, 25.9, 23.1, 21.8, 20.6, 16.0; HRMS-EI calcd for $C_{21}H_{30}O_4$, 346.2144 found 347.2214.

4.2.2. (1*R*,2*R*,3*R*,5*S*)-2,6,6-Trimethylbicyclo[3.1.1]heptan-3-yl 4-(benzyloxy)-3-oxobutanoate 4b

This was synthesized according to the general procedure, on an 8 mmol scale in 76% yield. Colorless oil. R_f = 0.70 (*n*-hexane/EtOAc = 4:1); $[\alpha]_D^{26}$ = −32.7 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39–7.30 (m, 5H), 5.13–5.01 (m, 1H), 4.60 (s, 2H), 4.15 (s, 2H), 3.54 (s, 2H), 2.64–1.61 (m, 7H), 1.21 (s, 3H), 1.08 (d, *J* = 7.5 Hz, 3H), 0.94 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.1, 166.4, 136.6, 128.0(2C), 127.5, 127.3(2C), 74.7, 74.3, 72.8, 46.9, 45.8, 43.1, 40.6, 37.7, 35.1, 32.9, 26.9, 23.2, 20.0; HRMS-EI calcd for $C_{21}H_{28}O_4$, 344.1988 found 344.1902.

4.2.3. (1*R*,2*S*,4*R*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 4-(benzyloxy)-3-oxobutanoate 4c

This was synthesized according to the general procedure, on an 8 mmol scale in 79% yield. Colorless oil. R_f = 0.70 (*n*-hexane/EtOAc



Scheme 5. Plausible mechanism for the generation of *anti*-**6** (5*R*,6*S*) from the reaction of enolate of **5f** with aldehydes.

= 4:1); $[\alpha]_D^{26}$ = −20.8 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41–7.29 (m, 5H), 4.98–4.88 (m, 1H), 4.60 (s, 2H), 4.15 (s, 2H), 3.56 (s, 2H), 2.42–0.83 (m, 7H), 0.89 (s, 3H), 0.86 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.6, 167.2, 136.8, 128.5(2C), 128.0, 127.8(2C), 81.1, 74.8, 73.4, 48.7, 47.7, 46.2, 44.7, 36.4, 27.8, 26.9, 19.6, 18.7, 13.3; HRMS-EI calcd for $C_{21}H_{28}O_4$, 344.1988 found 344.1994.

4.2.4. (1*S*,2*R*,4*R*)-1-(Diethylcarbamoyl)-7,7-dimethylbicyc[2.2.1] heptan-2-yl 4-(benzyloxy)-3-oxobutanoate 4d

This was synthesized according to the general procedure, on an 8 mmol scale in 65% yield. Colorless oil. R_f = 0.36 (*n*-hexane/EtOAc = 4:1); $[\alpha]_D^{26}$ = −22.6 (*c* 0.3, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25 (m, 5H), 5.10 (dd, *J* = 6.0, 5.1 Hz, 1H), 4.48 (s, 2H), 4.01 (s, 2H), 3.54–3.43 (br, 2H), 3.40 (s, 2H), 3.14–2.96 (br, 2H), 2.03–1.14 (m, 7H), 1.25 (s, 3H), 1.07 (s, 3H), 1.05–0.91 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.0, 169.7, 165.9, 136.6, 128.2(2C), 127.7, 127.5(2C), 79.3, 74.5, 73.1, 58.5, 50.9, 45.4, 44.4, 40.0, 40.1, 39.3, 29.8, 26.6, 21.4, 21.3, 13.8, 12.3; HRMS-EI calcd for $C_{25}H_{35}NO_5$, 429.2515 found 429.2506.

4.2.5. (1*S*,2*R*,4*R*)-1-(Diisopropylcarbamoyl)-7,7-dimethylbicyc [2.2.1]heptan-2-yl 4-(benzyloxy)-3-oxobutanoate 4e

This was synthesized according to the general procedure, on an 8 mmol scale in 57% yield. Colorless oil. R_f = 0.55 (*n*-hexane/EtOAc = 4:1); $[\alpha]_D^{26}$ = −27.7 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39–7.20 (m, 5H), 5.05 (dd, *J* = 7.3, 3.7 Hz, 1H), 4.53 (s, 2H), 4.15 (hep, *J* = 6.8 Hz, 1H), 4.07 (s, 2H), 3.48 (s, 2H), 3.23 (hep, *J* = 6.8 Hz, 1H), 2.31–1.20 (m, 7H), 1.36 (d, *J* = 4.9 Hz, 6H), 1.28 (s, 3H), 1.24 (s, 3H), 1.08 (d, *J* = 6.6 Hz, 3H), 1.03 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.3, 169.4, 166.2, 136.7, 128.4(2C), 127.9, 127.7(2C), 80.3, 74.7, 73.3, 59.2, 51.4, 47.1, 46.2, 45.5, 44.6, 39.9, 29.7, 26.7, 21.8, 21.5, 21.0, 20.5, 20.4, 20.4; HRMS-EI calcd for $C_{27}H_{39}NO_5$, 457.2828 found 457.2836.

4.2.6. (1*S*,2*R*,4*R*)-1-(Hydroxydiphenylmethyl)-7,7-dimethylbicyclo [2.2.1]heptan-2-yl 4-(benzyloxy)-3-oxobutanoate 4f

This was synthesized according to the general procedure, on an 8 mmol scale in 62% yield. Colorless oil. R_f = 0.57 (*n*-hexane/EtOAc = 4:1); $[\alpha]_D^{26}$ = +72.1 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.78–7.59 (m, 4H), 7.41–7.29 (m, 5H), 7.31–7.12 (m, 6H), 5.22 (dd, *J* = 7.8, 3.9 Hz, 1H), 4.55 (s, 2H), 3.96 (s, 2H), 3.15 (s, 2H), 2.39–1.12 (m, 7H), 1.45 (s, 3H), 0.64 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 200.9, 164.1, 149.1, 143.2, 136.6, 128.4(2C), 128.3(2C), 127.9, 127.8(2C), 127.7(2C), 126.6(2C), 126.4, 126.0, 125.8(2C), 82.4, 80.9, 74.5, 73.2, 58.9, 51.2, 47.5, 44.9, 38.1, 31.1, 26.8, 24.3, 22.4; HRMS-EI calcd for $C_{33}H_{36}O_5$, 512.2563 found 512.2569.

4.3. Synthesis of 5a-f

4.3.1. (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (*E*)-4-(benzyloxy)-3-(pyrrolidin-1-yl)but-2-enoate 5a

To **4a** (1.73 g, 5 mmol) in a 50 mL round-bottom flask was added benzene (20 mL) as the solvent, followed by the addition of pyrrolidine (0.5 ml, 6.0 mmol) and *tert*-butyl alcohol (0.5 mL, 5.23 mmol). The mixtures were heated to reflux under Dean–Stark apparatus to remove water. After 10 h, the reaction mixtures were concentrated in vacuo to remove the solvent to give 1.96 g of **5a** in 98% yield. The material was used directly in the next reaction without further purification. Pale-yellow oil. $[\alpha]_D^{26}$ = −45.4 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42–7.18 (m, 5H), 4.94 (s, 2H), 4.74–4.58 (m, 1H), 4.60 (s, 2H), 4.51 (s, 1H), 3.75–2.91 (br, 4H), 2.09–0.80 (m, 9H), 1.95–1.79 (m, 4H), 0.88 (d, *J* = 6.0 Hz, 3H), 0.87 (d, *J* = 6.0 Hz, 3H), 0.77 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.1, 156.4, 138.3, 128.2(2C), 127.9(2C), 127.5, 86.4, 72.4, 71.6, 64.5, 47.8(2C), 47.3, 41.5, 34.4, 31.4, 26.2, 25.1(2C), 23.6, 22.0, 20.7, 16.5; HRMS-EI calcd for $C_{25}H_{37}NO_3$, 399.2773 found 399.2781.

4.3.2. (1*R*,2*R*,3*R*,5*S*)-2,6,6-Trimethylbicyclo[3.1.1] heptan-3-yl (*E*)-4-(benzyloxy)-3-(pyrrolidin-1-yl)but-2-enoate 5b

This was synthesized according to the general procedure on a 5 mmol scale in 98% yield. Pale-yellow oil. $[\alpha]_D^{26}$ = −26.9 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39–7.23 (m, 5H), 5.10–5.00 (m, 1H), 4.99 (d, *J* = 11.4 Hz, 1H, *A*Bq), 4.93 (d, *J* = 11.4 Hz, 1H, A*B*q), 4.62 (s, 2H), 4.56 (s, 1H), 3.62–3.02 (br, 4H), 2.68–1.50 (m, 7H), 2.00–1.79 (m, 4H), 1.21 (s, 3H), 1.10 (d, *J* = 7.5 Hz, 3H), 0.98 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.5, 156.3, 138.2, 128.1(2C), 127.8(2C), 127.4, 86.6, 72.4, 71.6, 67.8, 64.4, 47.7, 47.5, 43.7, 41.3, 38.2, 36.3, 33.5, 27.4, 25.5, 24.9, 23.6, 20.5; HRMS-EI calcd for $C_{25}H_{35}NO_3$, 397.2617 found 397.2617.

4.3.3. (1*R*,2*S*,4*R*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl (*E*)-4-(benzyloxy)-3-(pyrrolidin-1-yl)but-2-enoate 5c

This was synthesized according to the general procedure on a 5 mmol scale in **99**% yield. Pale-yellow oil. $[\alpha]_D^{26}$ = −25.1 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–7.22 (m, 5H), 5.00 (d, *J* = 11.4 Hz, 1H, *A*Bq), 4.91(d, *J* = 11.4 Hz, 1H, A*B*q), 4.92–4.84 (m, 1H), 4.62 (s, 2H), 4.59 (s, 1H), 3.61–3.05 (br, 4H), 2.43–0.90 (m, 7H), 1.92–1.83 (m, 4H), 0.92 (s, 3H), 0.87(s, 3H), 0.85(s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$)δ 168.8, 156.0, 138.0, 127.9(3C), 127.6(2C), 127.3, 86.3, 77.2, 72.2, 64.2, 48.4, 47.6, 47.4, 44.7, 36.8, 27.8, 27.0, 24.8(2C), 19.5, 18.6, 13.4; HRMS-EI calcd for $C_{25}H_{35}NO_3$, 397.2617 found 397.2610.

4.3.4. (1*S*,2*R*,4*R*)-1-(Diethylcarbamoyl)-7,7-dimethylbicyc[2.2.1] heptan-2-yl(*E*)-4-(benzyloxy)-3-(pyrrolidin-1-yl)but-2-enoate 5d

This was synthesized according to the general procedure on a 5 mmol scale in 97% yield. Pale-yellow oil. $[\alpha]_D^{26}$ = −54.3 (*c* 0.1, CH_2Cl_2); 1H NMR (200 MHz, $CDCl_3$) δ 7.41–7.22 (m, 5H), 5.12 (dd, *J* = 7.1, 4.0 Hz, 1H), 4.96 (d, *J* = 11.4 Hz, 1H, *A*Bq), 4.79 (d, *J* = 11.4 Hz, 1H, A*B*q), 4.59 (s, 2H), 4.45 (s, 1H), 3.70–3.41 (m, 4H), 3.37–2.89 (br, 4H), 2.09–0.99 (m, 7H), 2.00–1.79 (br, 4H), 1.37 (s, 3H),1.36–0.99 (m, 6H), 1.16 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.9, 167.7, 156.7, 138.2, 128.1(2C), 127.8(2C), 127.5, 85.9, 76.4, 72.4, 64.4, 58.8, 50.9, 47.8(2C), 44.9, 40.2, 39.8(2C), 30.3, 26.9, 24.9 (2C), 21.8, 21.7, 13.9, 12.6; HRMS-EI calcd for $C_{29}H_{42}N_2O_4$, 482.3145 found 482.3145.

4.3.5. (1*S*,2*R*,4*R*)-1-(Diisopropylcarbamoyl)-7,7-dimethylbicyc [2.2.1]heptan-2-yl (*E*)-4-(benzyloxy)-3-(pyrrolidin-1-yl)but-2-enoate 5e

This was synthesized according to the general procedure on a 5 mmol scale in **96**% yield. Pale-yellow oil. $[\alpha]_D^{26}$ = −30.4 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H), 5.09 (d, *J* = 11.5 Hz, 1H, *A*Bq), 5.02 (dd, *J* = 7.5, 3.7 Hz, 1H), 4.72 (d, *J* = 11.5 Hz, 1H, A*B*q), 4.58 (s, 2H), 4.50 (s, 1H), 4.27 (hep, *J* = 6.6 Hz, 1H), 3.62–2.96 (br, 4H), 3.24 (hep, *J* = 6.6 Hz, 1H), 2.29–1.12 (m, 7H), 1.99–1.78 (m, 4H), 1.40 (d, *J* = 6.8 Hz, 6H), 1.36 (s, 3H), 1.17 (s, 3H), 1.20–1.01 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.5, 167.9, 156.8, 138.3, 128.2(2C), 127.9(2C), 127.6, 86.0, 77.7, 72.4, 64.5, 59.5, 51.2, 47.9, 47.1, 46.1, 45.0, 40.5, 30.0, 27.0, 22.1, 21.8, 21.1, 20.8, 20.5, 20.4; HRMS-EI calcd for $C_{31}H_{46}N_2O_4$, 510.3458 found 510.3466.

4.3.6. (1*S*,2*R*,4*R*)-1-(Hydroxydiphenylmethyl)-7,7-dimethylbicyclo [2.2.1]heptan-2-yl (*E*)-4-(benzyloxy)-3-(pyrrolidin-1-yl)but-2-enoate 5f

This was synthesized according to the general procedure on a 5 mmol scale in 96% yield. Pale-yellow oil. $[\alpha]_D^{26}$ = −49.9 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.80–7.63 (m. 4H), 7.38–6.90 (m,

11H), 5.11 (dd, J = 7.5, 4.2 Hz, 1H), 4.87 (d, J = 11.9 Hz, 1H, *A*Bq), 4.57 (d, J = 11.4 Hz, 1H, A*B*q), 4.57 (s, 1H), 4.40 (d, J = 11.5 Hz, 1H, *A*Bq), 4.32 (d, J = 11.5 Hz, 1H, A*B*q), 4.23 (s, 1H), 3.63–3.31 (br, 2H), 3.30–2.99 (br, 2H), 2.41–1.03 (m, 7H), 1.99–1.78 (br, 4H), 1.54 (s, 3H), 0.56 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$)δ 165.7, 157.0, 149.0, 143.8, 138.2, 128.2, 128.1, 128.0, 127.8, 127.4, 127.3, 126.6, 126.2, 125.9, 84.9, 81.2, 79.3, 71.9, 63.9, 58.8, 50.9, 47.7, 38.8, 30.7, 27.0, 24.5, 22.6; HRMS-EI calcd for $C_{37}H_{45}NO_4$, 565.3192 found 565.3191.

4.4. General procedure for the reaction of 5a-f with isobutyraldehyde

4.4.1. 5-Benzyloxy-6-isopropyl-4-pyrrolidin-1-yl-5,6-dihydro-pyran-2-one *anti*-6 and *syn*-6

To a THF solution (4 mL) of **5f** (565 mg, 1 mmol) was added a THF solution of LDA (1 mol/L, 2.5 mL) at −78 °C. (2.5 eqiv. LDA for **5a-e**, 3.5 equiv. LDA for **5f**). The temperature of the reaction mixture was allowed to rise to 20 °C during a period of 40 min. After re-cooled to −78 °C and stirred for 30 min, a solution of isobutyraldehyde (1N in THF, 4 mL) was added to the reaction mixture. This mixture was then allowed to warm to room temperature slowly over a period of 2 h. The reaction was quenched by the addition of aqueous ammonium chloride (1N, 5 mL), extracted with ethyl acetate (5 mL × 2) then dried over anhydrous sodium sulfate, followed by concentration to afford the crude material. The crude was purified by flash chromatography (*n*-hexane:acetone, 1:1) to give *anti*-**6** and *syn*-**6** in 81% yield. 92% de, [HPLC Hypersil Silica, hexane/^{i}PrOH = 3/1; flow rate 0.5 mL/min; t_R = 13.0 min (major), t_R = 14.1 min (minor)]. *anti*-**6**: 78% yield, colorless solid, mp 118–119 °C; 98% ee, [HPLC Chiralcel OD, hexane/^{i}PrOH = 3/1; flow rate 0.5 mL/min; t_R = 18.6 min (major), t_R = 22.5 min (minor)]. R_f = 0.36 (*n*-hexane/acetone = 2:1); $[\alpha]_D^{26}$ = −25.6 (*c* 0.2, CH_2Cl_2), 98% ee; 1H NMR (200 MHz, $CDCl_3$) δ 7.39–7.20 (m, 5H), 4.64 (s, 1H), 4.62 (d, J = 11.4 Hz, 1H, *A*Bq), 4.52 (d, J = 11.4 Hz, 1H, A*B*q), 4.22 (d, J = 9.2 Hz, 1H), 4.19 (s, 1H), 3.49–2.98 (br, 4H), 2.00–1.81 (m, 1H), 1.98–1.77 (br, 4H), 1.02 (d, J = 6.6 Hz, 3H), 0.91(d, J = 6.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.9, 152.9, 136.9, 128.3(2C), 127.9(3C), 85.2, 82.3, 69.5, 69.2, 47.4, 46.8, 30.4, 25.1, 24.4, 19.5, 19.2; HRMS-EI calcd for $C_{19}H_{25}NO_3$, 315.1834 found 315.1826. *syn*-**6**: 3% yield, pale-yellow oil. R_f = 0.39 (*n*-hexane/acetone, 2:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39–7.20 (m, 5H), 4.84 (s, 1H), 4.66 (d, J = 11.4 Hz, 1H, *A*Bq), 4.44 (d, J = 11.4 Hz, 1H, A*B*q), 4.39 (d, J = 3.0 Hz, 1H), 3.82 (dd, J = 10.0, 3.0 Hz, 1H), 3.81–3.01 (m, 4H), 2.40–2.13 (m, 1H), 2.03–1.70 (br, 4H), 1.20 (d, J = 6.5 Hz, 3H), 1.07 (d, J = 6.5 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.9, 153.9, 137.8, 128.0(2C), 127.4, 127.2(2C), 86.4, 84.2, 67.9, 67.7, 47.4, 46.9, 28.5, 25.1, 24.3, 19.3, 18.5; HRMS-EI calcd for $C_{19}H_{25}NO_3$, 315.1834 found 315.1830.

4.5. Reactions of 5f with aldehydes

4.5.1. 5-Benzyloxy-6-methyl-4-pyrrolidin-1-yl-5,6-dihydro-pyran-2-one *anti*-7a and *syn*-7a

This was synthesized according to the general procedure on a 1 mmol scale in 60% yield, 93% de. [HPLC Hypersil Silica, hexane/^{i}-PrOH = 3/1; flow rate 0.5 mL/min; t_R = 20.5 min (major), t_R = 22.0 min (minor)]. *anti*-**7a**: 58% yield, pale-yellow oil. 86% ee, [HPLC Chiralcel OD, hexane/^{i}PrOH = 3/1; flow rate 0.5 mL/min; t_R = 24.0 min (major), t_R = 27.6 min (minor)]. R_f = 0.23 (*n*-hexane/acetone = 2:1); $[\alpha]_D^{26}$ = −7.2 (*c* 0.2, CH_2Cl_2), 86% ee; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–7.23 (m, 5H), 4.90–4.79 (m, 1H), 4.69 (s,1H), 4.67 (d, J = 11.1 Hz, 1H, ABq), 4.57 (d, J = 11.1 Hz, 1H, A*B*q), 4.00 (s,1H), 3.60–3.03 (br, 4H), 2.02–1.80 (br, 4H), 1.37 (d, J = 6.8 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$)δ 165.9, 152.8, 137.0, 128.4(2C), 128.0, 127.9(2C), 84.9, 73.2, 72.7, 69.5, 47.6, 47.0, 25.3, 24.5, 18.7; HRMS-EI calcd for $C_{17}H_{21}NO_3$, 287.1521 found 287.1512. *syn*-***7a***: 2% yield, pale-yellow oil. R_f = 0.27 (*n*-hexane/acetone = 2:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–7.21 (m, 5H), 4.84 (s, 1H), 4.68 (d, J = 11.2 Hz, 1H, *A*Bq), 4.47 (d, J = 11.2 Hz, 1H, A*B*q), 4.57–4.45 (m, 1H), 4.18 (d, J = 3.0 Hz, 1H), 3.72–3.05 (br, 4H), 2.02–1.78 (br, 4H), 1.56 (d, J = 6.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.1, 154.2, 137.7, 128.4(2C), 127.8, 127.6(2C), 86.4, 75.2, 70.5, 68.4, 47.7, 47.3, 25.4, 24.5, 16.1; HRMS-EI calcd for $C_{17}H_{21}NO_3$, 287.1521 found 287.1519.

4.5.2. 5-Benzyloxy-6-ethyl-4-pyrrolidin-1-yl-5,6-dihydro-pyran-2-one *anti*-7b and *syn*-7b

This was synthesized according to the general procedure on a 1 mmol scale in 69% yield, 94% de. [HPLC Hypersil Silica, hexane/^{i}-PrOH = 3/1; flow rate 0.5 mL/min; t_R = 14.4 min (major), t_R = 15.7 min (minor)]. *anti*-**7b**: 66% yield, pale-yellow oil. 94% ee, [HPLC Chiralcel OD, hexane/^{i}PrOH = 3/1; flow rate 0.5 mL/min; t_R = 20.6 min (major), t_R = 24.0 min (minor)]. R_f = 0.25 (*n*-hexane/acetone = 2:1); $[\alpha]_D^{26}$ = −22.5 (*c* 0.1, CH_2Cl_2), 94% ee; 1H NMR (200 MHz, $CDCl_3$) δ 7.39–7.18 (m, 5H), 4.66 (d, J = 11.3 Hz, 1H, *A*Bq), 4.56 (d, J = 11.3 Hz, 1H, A*B*q), 4.63 (s, 1H), 4.57–4.50 (m, 1H), 4.05(s, 1H), 3.53–3.00 (br, 4H), 2.02–1.78 (br, 4H), 1.64–1.38 (m, 2H), 1.03 (t, J = 7.4 Hz, 3H); 13C NMR (50 MHz, $CDCl_3$) δ 165.8, 152.9, 137.0, 128.4(2C), 127.9(3C), 85.1, 78.6, 71.3, 69.4, 47.5, 46.9, 25.9, 25.2, 24.5, 10.5; HRMS-EI calcd for $C_{18}H_{23}NO_3$, 301.1678 found 301.1688. *syn*-***7b***: 3% yield, pale-yellow oil. R_f = 0.29 (*n*-hexane/acetone = 2:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–7.21 (m, 5H), 4.82 (s, 1H), 4.64 (d, J = 11.4 Hz, 1H, *A*Bq), 4.45 (d, J = 11.4 Hz, 1H, A*B*q), 4.26 (d, J = 3.1 Hz, 1H), 4.27–4.15 (m, 1H), 3.73–3.00 (m, 4H), 2.16–1.69 (m, 6H), 1.11 (t, J = 7.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.9, 154.0, 137.8, 128.3(2C), 127.7, 127.5(2C), 86.7, 80.5, 69.2, 68.3, 47.6, 47.2, 25.3, 24.5, 23.6, 10.0; HRMS-EI calcd for $C_{18}H_{23}NO_3$, 301.1678 found 301.1681.

4.5.3. 5-Benzyloxy-6-propyl-4-pyrrolidin-1-yl-5,6-dihydro-pyran-2-one *anti*-7c and *syn*-7c

This was synthesized according to the general procedure on a 1 mmol scale in 75% yield, 95% de. [HPLC Hypersil Silica, hexane/^{i}-PrOH = 3/1; 0.5 mL/min; t_R = 12.8 min (major), t_R = 15.3 min (minor)]. *anti*-**7c**: 73% yield, 94% ee, [HPLC Chiralcel OD, hexane/^{i}-PrOH = 3/1; flow rate 0.5 mL/min; t_R = 19.0 min (major), t_R = 22.3 min (minor)]. Pale yellow solid, mp 124–125 °C; R_f = 0.33 (*n*-hexane/acetone = 2:1); $[\alpha]_D^{26}$ = −22.7 (*c* 0.1, CH_2Cl_2), 94% ee; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H), 4.70 (s, 1H), 4.69–4.60 (m, 1H), 4.66 (d, J = 11.3 Hz, 1H, *A*Bq), 4.57 (d, J = 11.3 Hz, 1H, A*B*q), 4.05 (s, 1H), 3.59–3.08 (br, 4H), 2.02–1.80 (br, 4H), 1.89–1.36 (m, 4H), 0.94 (t, J = 6.8 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.8, 153.0, 137.0, 128.4(2C), 127.9(3C), 85.1, 76.9, 71.1, 69.4, 47.5, 46.9, 34.7, 29.5, 25.2, 24.4, 19.1, 13.6; IR (CH_2Cl_2) 2926, 1671, 1593, 1451, 1220 cm^{-1}; HRMS-EI calcd for $C_{19}H_{25}NO_3$, 315.1834 found 315.1837. *syn*-**7c**: 2% yield, pale-yellow oil. R_f = 0.36 (*n*-hexane/acetone = 2:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38–7.20 (m, 5H), 4.81 (s, 1H), 4.65 (d, J = 11.3 Hz, 1H, *A*Bq), 4.45 (d, J = 11.3 Hz, 1H, A*B*q), 4.30–4.21 (m, 1H), 4.22 (d, J = 3.0 Hz, 1H), 3.68–3.01 (br, 4H), 2.02–1.70 (br, 4H), 1.90–1.39 (m, 4H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.9, 154.1, 137.8, 128.3(2C), 127.6, 127.4(2C), 86.7, 78.7, 69.6, 68.3, 47.6, 47.2, 32.3, 25.3, 24.5, 18.6, 13.8; HRMS-EI calcd for $C_{19}H_{25}NO_3$, 315.1834 found 315.1834.

4.5.4. 5-Benzyloxy-6-butyl-4-pyrrolidin-1-yl-5,6-dihydro-pyran-2-one *anti*-7d and *syn*-7d

This was synthesized according to the general procedure on a 1 mmol scale in 77% yield, 97% de. [HPLC Hypersil Silica, hexane/^{i}-PrOH = 3/1; flow rate 0.5 mL/min; t_R = 11.1 min (major), t_R = 12.8 min (minor)]. *anti*-**7d**: 76% yield, Pale yellow solid, mp 128–129

°C; 93% ee, [HPLC Chiralcel OD, hexane/^{i}PrOH = 3/1; flow rate 0.5 mL/min; t_R = 18.4 min (major), t_R = 20.9 min (minor)]. R_f = 0.35 (*n*-hexane/acetone = 2:1); $[\alpha]_D^{26}$ = −32.0 (*c* 0.3, CH_2Cl_2), 93% ee; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39–7.22 (m, 5H), 4.68 (s, 1H), 4.65–4.59 (m, 1H), 4.66 (d, *J* = 11.1 Hz, 1H, ABq), 4.59 (d, *J* = 11.1 Hz, 1H, A*B*q), 3.54–3.03 (br, 4H), 2.01–1.78 (br, 4H), 1.61–1.22 (m, 6H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.8, 152.9, 137.1, 128.4 (2C), 127.9 (3C), 85.2, 77.2, 71.7, 69.4, 47.5, 47.0, 32.5, 27.9, 25.2, 24.5, 22.3, 13.8; HRMS-EI calcd for $C_{20}H_{27}NO_3$, 329.1991 found 329.1984. *syn*-**7d**: 1% yield, pale-yellow oil. R_f = 0.36 (*n*-hexane/acetone = 2:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41–7.20 (m, 5H), 4.84 (s, 1H), 4.67 (d, *J* = 11.5 Hz, 1H, *A*Bq), 4.47 (d, *J* = 11.5 Hz, 1H, A*B*q), 4.37–4.20 (m, 2H), 3.76–3.03 (br, 4H), 2.07–1.73 (br, 4H), 1.66–1.09 (m, 6H), 0.94 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.9, 154.1, 137.9, 128.3 (2C), 127.7, 127.5 (2C), 86.7, 79.0, 69.6, 68.3, 47.6, 47.2, 30.0, 27.5, 25.3, 24.5, 22.5, 13.9; HRMS-EI calcd for $C_{20}H_{27}NO_3$, 329.1991 found 329.1987.

4.5.5. 5-Benzyloxy-6-benzyloxymethyl-4-pyrrolidin-1-yl-5,6-dihydro-pyran-2-one *anti*-7e and *syn*-7e

This was synthesized according to the general procedure on a 1 mmol scale in 70% yield, 91% de. [HPLC Hypersil Silica, hexane/^{i}-PrOH = 3/1; flow rate 0.5 mL/min; t_R = 12.9 min (major), t_R = 17.1 min (minor)]. *anti*-**7e**: 67% yield, pale yellow solid, decomposed 253 °C; 85% ee, [HPLC Chiralcel AD-H, hexane/^{i}PrOH = 3/1; flow rate 0.5 mL/min; t_R = 19.8 min (minor), t_R = 21.7 min (major)]. R_f = 0.28 (*n*-hexane/acetone = 2:1); $[\alpha]_D^{26}$ = −24.5 (*c* 0.2, CH_2Cl_2), 85% ee; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.43–7.20 (m, 10H), 4.86 (dd, *J* = 9.1, 5.0 Hz, 1H), 4.64 (s, 2H), 4.65 (d, *J* = 12.0 Hz, 1H, *A*Bq), 4.50 (d, *J* = 12.0 Hz, 1H, A*B*q), 4.51 (s, 1H), 4.41 (s, 1H), 3.74 (dd, *J* = 9.6, 5.0 Hz, 1H), 3.56 (dd, *J* = 9.4, 9.4 Hz, 1H), 3.48–3.05 (br, 4H), 2.02–1.72 (br, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.5, 152.7, 137.5, 136.9, 128.4(4C), 128.2(2C), 128.1, 127.9, 127.7(2C), 84.6, 75.2, 73.3, 69.6, 68.8, 68.5, 47.6, 46.9, 25.3, 24.5; HRMS-EI calcd for $C_{24}H_{27}NO_4$, 393.1940 found 393.1934. *syn*-**7e**: 3% yield, pale-yellow oil. R_f = 0.29 (*n*-hexane/acetone = 2:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42–7.20 (m, 10H), 4.79 (s, 1H), 4.62 (s, 2H), 4.65 (d, *J* = 11.5 Hz, 1H, *A*Bq), 4.53 (d, *J* = 11.5 Hz, 1H, A*B*q), 4.57–4.43 (m, 2H), 4.00–3.81 (m, 2H), 3.62–3.03 (br, 4H), 2.01–1.77 (br, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.0, 154.4, 137.8, 137.6, 128.4(2C), 128.3(2C), 127.9(3C), 127.7, 127.5(2C), 86.3, 77.3, 73.7, 69.5, 68.2, 67.5, 47.7, 47.5, 25.3, 24.7; HRMS-EI calcd for $C_{24}H_{27}NO_4$, 393.1940 found 393.1936.

4.5.6. 5-Benzyloxy-6-propenyl-4-pyrrolidin-1-yl-5,6-dihydro-pyran-2-one *anti*-7f and *syn*-7f

This was synthesized according to the general procedure on a 1 mmol scale in 75% yield, 91% de. [HPLC Hypersil Silica, hexane/^{i}-PrOH = 3/1; flow rate 0.5 mL/min; t_R = 13.0 min (major), t_R = 18.8 min (minor)]. *anti*-**7f**: 72% yield, white solid, mp 109–110 °C; 77% ee, [HPLC Chiralcel OD, hexane/^{i}PrOH = 3/1; flow rate 0.5 mL/min; t_R = 23.0 min (major), t_R = 27.4 min (minor)]. R_f = 0.31 (*n*-hexane/acetone = 2:1); $[\alpha]_D^{26}$ = −49.5 (*c* 0.1, CH_2Cl_2), 77% ee; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39–7.20 (m, 5H), 5.90–5.39 (m, 2H), 5.06 (d, *J* = 6.7 Hz, 1H), 4.66 (s, 1H), 4.69 (d, *J* = 11.4 Hz, 1H, *A*Bq), 4.58 (d, *J* = 11.4 Hz, 1H, A*B*q), 4.05 (s, 1H), 3.49–2.99 (br, 4H), 1.99–1.75 (br, 4H), 1.65 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.9, 152.8, 136.9, 130.6, 128.3(2C), 127.9(3C), 126.5, 85.3, 77.4, 72.3, 69.9, 47.4, 46.9, 25.1, 24.4, 17.6; IR (CH_2Cl_2) 2926, 1666, 1590, 1447, 1219 cm^{-1}; HRMS-EI calcd for $C_{19}H_{23}NO_3$, 313.1678 found 313.1674. *syn*-**7f**: 3% yield, pale-yellow oil. R_f = 0.33 (*n*-hexane/acetone = 2:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41–7.18(m, 5H), 6.12–5.71 (m, 2H), 4.82 (s, 1H), 4.81–4.69 (m, 1H), 4.67 (d, *J* = 11.2 Hz, 1H, ABq), 4.53 (d, *J* = 11.2 Hz, 1H, A*B*q), 4.27 (d, *J* = 3.1 Hz, 1H), 3.65–3.06 (br, 4H), 2.03–1.75 (br, 4H), 1.79 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.5, 254.2, 137.8, 131.1, 128.4(2C), 127.8, 127.6(2C), 124.9, 86.5, 79.5, 70.8, 68.9, 47.7, 47.3, 25.4, 24.5, 17.9; HRMS-EI calcd for $C_{19}H_{23}NO_3$, 313.1678 found 313.1681.

4.5.7. 5-Benzyloxy-6-phenyl-4-pyrrolidin-1-yl-5,6-dihydro-pyran-2-one *anti*-7g and *syn*-7g

This was synthesized according to the general procedure on a 1 mmol scale in 81% yield, 74% de. [HPLC Hypersil Silica, hexane/^{i}-PrOH = 3/1; flow rate 0.5 ml/min; t_R = 12.1 min (major), t_R = 21.9 min (minor)]. *anti*-**7g**: 71% yield, white solid, mp 147–148 °C; 86% ee, [HPLC Chiralcel OD, hexane/^{i}PrOH = 3/1; flow rate 0.5 mL/min; t_R = 34.7 min (major), t_R = 48.7 min (minor)]. R_f = 0.33 (*n*-hexane/acetone = 2:1); $[\alpha]_D^{26}$ = −26.8 (*c* 0.2, CH_2Cl_2), 86% ee; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–7.15 (m, 10H), 5.73 (s,1H), 4.74 (d, *J* = 11.4 Hz, 1H, *A*Bq), 4.68 (d, *J* = 11.4 Hz, 1H, A*B*q), 4.67 (s, 1H), 4.41 (s, 1H), 3.43–2.89 (br, 4H), 1.83–1.65 (br, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.8, 152.4, 136.6, 128.2(2C), 128.1(2C), 127.8(2C), 127.5(2C), 125.4(2C), 85.2, 77.9, 73.5, 70.1, 47.2; IR (CH_2Cl_2) 2926, 1684, 1595, 1453, 1221 cm^{-1}; HRMS-EI calcd for $C_{22}H_{23}NO_3$, 349.1678 found 349.1674. *syn*-**7g**: 10% yield, white solid, mp 155–156 °C; R_f = 0.30 (*n*-hexane/acetone = 2:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.63–6.91 (m, 10H), 5.44 (d, *J* = 2.3 Hz, 1H), 4.79 (s, 1H), 4.41 (d, *J* = 2.3 Hz, 1H), 4.31 (d, *J* = 11.1 Hz, 1H, *A*Bq), 4.02 (d, *J* = 11.1 Hz, 1H, A*B*q), 3.51–3.00 (br, 4H), 2.02–1.69 (br, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.3, 155.1, 137.2, 135.9, 128.3(2C), 128.0(3C), 127.6, 127.5(2C), 126.3(2C), 85.3, 79.7, 72.2, 70.9, 47.7, 47.2, 25.2, 24.4; HRMS-EI calcd for $C_{22}H_{23}NO_3$, 349.1678 found 349.1677.

4.5.8. 5-Benzyloxy-6-naphthalen-1-yl-4-pyrrolidin-1-yl-5,6-dihydro-pyran-2-one *anti*-7h and *syn*-7h

This was synthesized according to the general procedure on a 1 mmol scale in 81% yield, 64% de. [HPLC Hypersil Silica, hexane/^{i}-PrOH = 3/1; flow rate 0.5 mL/min; t_R = 10.9 min (minor), t_R = 16.9 min (major)]. *anti*-**7h**: 66% yield, white solid, mp 135–136 °C; 68% ee, [HPLC Chiralcel AD, hexane/^{i}PrOH = 3/1; flow rate 0.5 mL/min; t_R = 40.4 min (major), t_R = 49.1 min (minor)]. R_f = 0.25 (*n*-hexane/acetone = 2:1); $[\alpha]_D^{26}$ = +30.0 (*c* 0.2, CH_2Cl_2), 68% ee; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.02–7.27 (m, 12H), 6.54 (s, 1H), 4.85 (s, 1H), 4.88 (d, *J* = 11.1 Hz, 1H, *A*Bq), 4.75 (d, *J* = 11.1 Hz, 1H, A*B*q), 4.75 (d, *J* = 1.2 Hz, 1H), 3.61–3.00 (br, 4H), 2.01–1.70 (br, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.6, 152.3, 137.3, 133.7, 132.5, 129.9, 129.3, 128.8, 128.5(2C), 128.1, 127.9 (2C), 126.8, 125.8, 125.3, 124.3, 122.2, 86.0, 78.1, 72.3, 69.1, 47.7, 47.3, 25.3, 24.4; HRMS-EI calcd for $C_{26}H_{25}NO_3$, 399.1834 found 399.1833. *syn*-**7h**: 15% yield, pale-yellow oil. R_f = 0.22 (*n*-hexane/acetone = 2:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.16–6.80 (m, 12H), 6.19 (d, *J* = 1.4 Hz, 1H), 4.84 (s, 1H), 4.56 (d, *J* = 1.4 Hz, 1H), 4.04 (d, *J* = 11.0 Hz, 1H, *A*Bq), 3.68 (d, *J* = 11.0 Hz, 1H, A*B*q), 3.45–3.06 (br, 4H), 2.02–1.70 (br, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.5, 155.5, 136.8, 133.3, 130.9, 129.4, 129.2, 128.6, 127.9(3C), 127.6(4C), 126.4, 125.7, 125.4(2C), 121.5, 84.9, 76.8, 71.6, 71.1, 47.8, 47.2, 25.1, 24.3; HRMS-EI calcd for $C_{26}H_{25}NO_3$, 399.1834 found 399.1837.

4.5.9. 5-Benzyloxy-4-pyrrolidin-1-yl-6-(2,3,4-trimethoxy-6-methoxymethyl-phenyl)-5, 6-dihydro-pyran-2-one 7

This was synthesized according to the general procedure on a 1 mmol scale in 72% yield, 57% de. [HPLC Hypersil Silica, hexane/^{i}-PrOH = 3/1; flow rate 0.5 mL/min; t_R = 23.2 min (major), t_R = 25.4 min (minor)] *anti*-**7i**: 57% yield, pale-yellow solid, mp 157–158 °C; 63% ee, [HPLC Chiralcel AD-H, hexane/^{i}PrOH = 3/1; flow rate 0.5 mL/min; t_R = 15.1 min (major), t_R = 20.0 min (minor)]. R_f = 0.21 (*n*-hexane/acetone = 2:1); $[\alpha]_D^{26}$ = −35.6 (*c* 0.3, CH_2Cl_2), 63% ee; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39–7.08 (m, 5H), 6.79 (s, 1H), 5.73 (d, *J* = 7.6 Hz, 1H), 5.01 (d, *J* = 7.6 Hz, 1H), 4.71 (s, 1H), 4.59

(d, J = 11.4 Hz, 1H, *A*Bq), 4.49 (d, J = 11.4 Hz, 1H, A*B*q), 4.36 (d, J = 10.5 Hz, 1H, *A*Bq), 4.12 (d, J = 10.5 Hz, 1H, A*B*q), 3.88 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.38 (s, 3H), 3.41–3.18 (br, 4H), 2.05–1.79 (br, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.9, 158.2, 153.8, 153.1, 141.9, 136.9, 133.5, 128.3(2C), 127.9, 127.8(2C), 121.9, 108.5, 83.6, 74.9, 74.0, 72.3, 71.9, 61.4, 60.7, 58.4, 55.9, 48.9(2C), 29.6 (2C); HRMS-EI calcd for $C_{27}H_{33}NO_7$, 483. 2257 found 483.2254. *syn*-**7i**: 15% yield, pale-yellow solid, mp 169–170 °C; R_f = 0.22 (*n*-hexane/acetone = 2:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.23–6.98(m, 6H), 5.67 (d, J = 2.3 Hz, 1H), 4.88 (d, J = 13.8 Hz, 1H, *A*Bq), 4.70 (d, J = 13.8 Hz, 1H, A*B*q), 4.65 (s, 1H), 4.20 (d, J = 2.3 Hz, 1H), 4.14 (d, J = 10.7 Hz, 1H, *A*Bq), 3.96 (d, J = 10.7 Hz, 1H, A*B*q), 3.86 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.29 (s, 3H), 3.23–3.08 (br, 4H), 1.99–1.70(br, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.8, 156.0, 152.8, 150.0, 139.9, 146.6, 135.2, 127.9(2C), 127.7(2C), 127.6, 117.9, 106.4, 84.3, 75.8, 73.9, 72.6, 71.5, 60.7, 60.4, 57.9, 55.5, 47.6, 47.2, 25.0, 24.1; HRMS-EI calcd for $C_{27}H_{33}NO_7$, 483. 2257 found 483.2254.

4.6. Synthesis of 11 and 12a-h

4.6.1. (3*S*,4*S*)-3-Benzyloxy-4-hydroxy-5-methyl-hexan-2-one 11

To *anti*-**6** (60 mg, 0.19 mmol) in 10 mL round bottom flask with THF (2 mL) was added 4 M HCl aqueous solution (0.95 mL, 3.8 mmol) and let to stir for 36 h. The reaction mixture was added 1 N NH_4Cl aqueous solution (5 mL) then extracted with CH_2Cl_2 (15 mL × 2), combined organic layers were dried over anhydrous sodium sulfate, followed by concentration to afford the crude material. The crude was purified by flash chromatography (*n*-hexane:acetone, 3:1) to give 40 mg of **11** in 90% yield. Pale-yellow oil. R_f = 0.58 (*n*-hexane/acetone = 2:1); $[\alpha]_D^{26}$ = −39.9 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42–7.28 (m, 5H), 4.61 (d, J = 11.4 Hz, 1H, *A*Bq), 4.46 (d, J = 11.4 Hz, 1H, A*B*q), 3.77 (d, J = 6.1 Hz, 1H), 3.62 (dd, J = 6.0, 5.9 Hz, 1H), 2.26 (s, 3H), 1.93–1.78 (m, 1H), 0.96 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 211.1, 136.9, 128.5(2C), 128.1, 127.9(2C), 85.7, 76.5, 72.7, 29.5, 27.1, 19.3, 16.7; HRMS-EI calcd for $C_{14}H_{20}O_3$, 236.1412 found 236.1410.

4.6.2. (3*S*,4*S*)-3-Benzyloxy-4-hydroxy-pentan-2-one 12a

Pale-yellow oil. R_f = 0.43 (*n*-hexane/acetone = 2:1); $[\alpha]_D^{26}$ = −16.9 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42–7.30 (m, 5H), 4.67 (d, J = 11.5 Hz, 1H, *A*Bq), 4.51 (d, J = 11.5 Hz, 1H, A*B*q), 4.17–4.01 (m, 1H), 3.72 (d, J = 4.9 Hz, 1H), 2.23 (s, 3H), 1.19 (d, J = 6.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 210.4, 136.9, 128.6(2C), 128.2, 127.9 (2C), 88.3, 73.3, 68.2, 27.4, 18.4; HRMS-EI calcd for $C_{12}H_{16}O_3$, 208.1099 found 208.1095.

4.6.3. (3*S*,4*S*)-3-Benzyloxy-4-hydroxy-hexan-2-one 12b

Pale-yellow oil. R_f = 0.48 (*n*-hexane/acetone = 2:1); $[\alpha]_D^{26}$ = −26.8 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41–7.26 (m, 5H), 4.65(d, J = 11.4 Hz, 1H, *A*Bq), 4.49 (d, J = 11.4 Hz, 1H, A*B*q), 3.82–3.71 (m, 2H), 2.24 (s, 3H), 1.60–1.41 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 210.6, 136.9, 128.6(2C), 128.2, 127.9(2C), 87.5, 73.5, 73.1, 27.4, 25.5, 9.9; HRMS-EI calcd for $C_{13}H_{18}O_3$, 222.1256 found 222.1258.

4.6.4. (3*S*,4*S*)-3-Benzyloxy-4-hydroxy-heptan-2-one 12c

Pale-yellow oil. R_f = 0.56 (*n*-hexane/acetone = 2:1); $[\alpha]_D^{26}$ = −56.4 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42–7.30 (m, 5H), 4.64 (d, J = 11.5 Hz, 1H, *A*Bq), 4.48 (d, J = 11.5 Hz, 1H, A*B*q), 3.99–3.82 (br, 1H), 3.73 (d, J = 4.9 Hz, 1H), 2.23 (s, 3H), 1.50–1.21 (m, 4H), 0.91 (t, J = 6.9 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 210.5, 136.9, 128.6(2C), 128.2, 127.9(2C), 87.8, 73.1, 71.8, 34.5, 27.5, 18.8, 13.9; HRMS-EI calcd for $C_{14}H_{20}O_3$, 236.1412 found 236.1409.

4.6.5. (3*S*,4*S*)-3-Benzyloxy-4-hydroxy-octan-2-one 12d

Pale-yellow oil. R_f = 0.35 (*n*-hexane/acetone = 2:1); $[\alpha]_D^{26}$ = −145.3 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42–7.27(m, 5H), 4.65 (d, J = 11.5 Hz, 1H, *A*Bq), 4.49 (d, J = 11.5 Hz, 1H, A*B*q), 3.92–3.79(m, 1H), 3.73(d, J = 4.9 Hz, 1H), 2.23(s, 3H), 1.58–1.19 (m, 6H), 0.89(t, J = 6.7 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 210.4, 137.0, 128.6(2C), 128.2, 127.9(2C), 87.8, 73.1, 72.1, 32.1, 27.7, 27.5, 22.5, 13; HRMS-EI calcd for $C_{15}H_{22}O_3$, 250.1569 found 250.1566.

4.6.6. (3*S*,4*S*)-3,5-Bis-benzyloxy-4-hydroxy-pentan-2-one 12e

Pale-yellow oil. R_f = 0.45 (*n*-hexane/acetone = 2:1); $[\alpha]_D^{26}$ = −30.5 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42–7.20 (m, 10H), 4.61 (d, J = 11.5 Hz, 1H, *A*Bq), 4.58–4.42 (m, 2H), 4.45 (d, J = 11.5 Hz, 1H, A*B*q), 4.11–4.00 (m, 1H), 3.87 (d, J = 6.4 Hz, 1H), 3.65–3.48 (m, 2H), 2.22 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.7, 137.6, 136.9, 128.5 (2C), 128.4 (2C), 128.1, 128.0 (2C), 127.8 (3C), 84.4, 73.4, 73.1, 70.9, 69.9, 27.2; HRMS-EI calcd for $C_{19}H_{22}O_4$, 314.1518 found 314.1521.

4.6.7. (3*S*,4*S*)-3-Benzyloxy-4-hydroxy-hept-5-en-2-one 12f

Pale-yellow oil. R_f = 0.51 (*n*-hexane/acetone = 2:1); $[\alpha]_D^{26}$ = −9.3 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42–7.26 (m, 5H), 5.83–5.40 (m, 2H), 4.68 (d, J = 11.6 Hz, 1H, *A*Bq), 4.53 (d, J = 11.6 Hz, 1H, A*B*q), 4.39–4.30 (m, 1H), 3.85 (d, J = 4.9 Hz, 1H), 2.19 (s, 3H), 1.70 (d, J = 6.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.7, 137.0, 129.9, 128.6(2C), 128.3, 128.2, 128.0(2C), 87.5, 73.4, 73.2, 27.5, 17.8; HRMS-EI calcd for $C_{14}H_{18}O_3$, 234.1256 found 234.1258.

4.6.8. (3*S*,4*S*)-3-Benzyloxy-4-hydroxy-4-phenyl-butan-2-one 12g

Pale-yellow oil. R_f = 0.51 (*n*-hexane/acetone = 2:1); $[\alpha]_D^{26}$ = −22.1 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.21–7.05 (m, 10H), 4.90 (d, J = 6.5 Hz, 1H), 4.46 (d, J = 11.5 Hz, 1H, *A*Bq), 4.29 (d, J = 11.5 Hz, 1H, A*B*q), 3.94 (d, J = 6.5 Hz, 1H), 3.42–3.29 (br, 1H), 2.09 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 210.1, 139.8, 136.7, 128.3(2C), 128.1(2C), 127.9, 127.8, 127.7(2C), 126.7(2C), 87.5, 74.1, 73.1, 27.2; HRMS-EI calcd for $C_{17}H_{18}O_3$, 270.1256 found 270.1255.

4.6.9. (3*S*,4*S*)-3-Benzyloxy-4-hydroxy-4-naphthalen-1-yl-butan-2-one 12h

Pale-yellow oil. R_f = 0.45 (*n*-hexane/acetone = 2:1); $[\alpha]_D^{26}$ = −9.0 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.99–7.00 (m, 12H), 5.73 (d, J = 5.8 Hz, 1H), 4.48 (d, J = 11.5 Hz, 1H, *A*Bq), 4.22 (d, J = 5.8 Hz, 1H), 4.17 (d, J = 11.5 Hz, 1H, A*B*q), 2.09 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.4, 136.6, 135.0, 133.6, 130.6, 128.9, 128.7, 128.4 (2C), 128.2 (2C), 128.1, 126.2, 125.6, 125.3, 124.4, 123.0, 86.6, 73.2, 71.5, 28.1; HRMS-EI calcd for $C_{21}H_{20}O_3$, 320.1412 found 320.1409.

4.7. Synthesis of 13

To Pd/C (100 mg) with MeOH (3 mL) in a 10 mL round bottom flask was added compound **11** (100 mg, 0.42 mmol) in 1 mL MeOH. The reaction misture was hydrogenated under hydrogen atmosphere (1 atm) for 3 h, the reaction was filtered, followed by concentration to afford the crude material. The crude was purified by flash chromatography (*n*-hexane:acetone, 3:1) to give 57 mg of **13** in 93% yield. Pale-yellow oil. R_f = 0.36 (*n*-hexane/acetone = 2:1); $[\alpha]_D^{26}$ = +64.7 (*c* 0.1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.18 (d, J = 5.5 Hz, 1H), 3.49 (t, J = 5.6 Hz, 1H), 2.29 (s, 3H), 2.02–1.85 (m, 1H), 0.96 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 210.1, 78.6, 77.9, 29.9, 27.7, 19.5, 16.9.

Please cite this article in press as: Li, Y.-J.; et al. *Tetrahedron: Asymmetry* (2017), https://doi.org/10.1016/j.tetasy.2017.10.003

Acknowledgments

We would like to thank the Ministry of Science and Technology of Taiwan (NSC-89-2113-M-324-003 & MOST-105-2113-M-415-005) for generous financial support. Partial support of the Mass spectrometer facility provided by National Chung-Hsing University is also acknowledged.

A. Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra for compounds **4a-f**, **5a-f**, ***anti*-6**, ***anti*-7a-i**, and **12a-h** are provided) associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetasy.2017.10.003.

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