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Intramolecular tandem seleno-Michael/aldol reaction: a simple route to hydroxy cyclo-1-ene-1-carboxylate esters.

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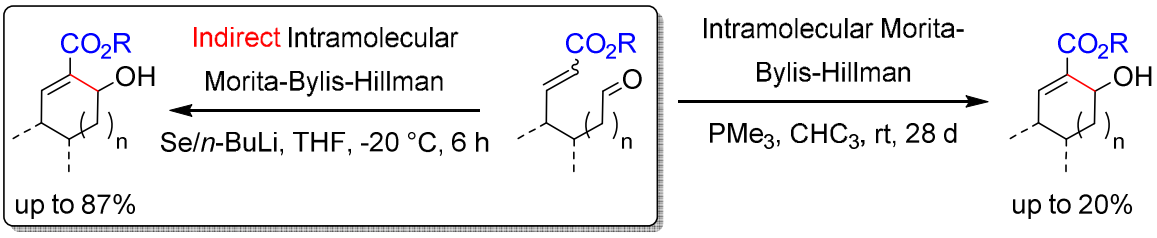
Supporting Information Placeholder



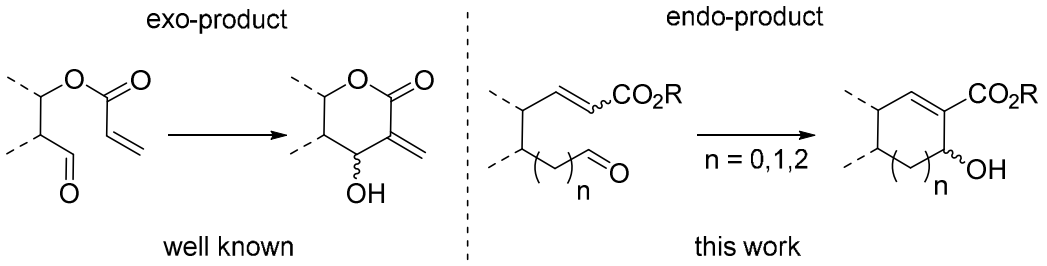
intramolecular, seleno-Michael/aldol,

ABSTRACT: Intramolecular tandem seleno-Michael/aldol reaction followed by oxidation-elimination process can be an efficient tool for the construction of hydroxy cyclo-1-ene-1-carboxylate esters from oxo-*α,β*-unsaturated esters. Generation of lithium selenolate from elemental selenium and *n*-BuLi provides a simple and efficient one-pot access to cyclic *endo*-Morita-Baylis–Hillman adducts.

Introduction

The tandem or domino reaction has been of interest for organic synthesis because it offers a convenient and economical way to prepare desired organic molecules.[1,2] The sequenced Michael/aldol tandem reaction is one of the most important processes for constructing carbon skeletons. Intramolecular Morita-Baylis-Hillman (IMBH) of *α,β*-unsaturated esters may lead to two types of products: a) "*exo*" when acrylate derivatives are cyclized; b) "*endo*" when the internal double bond is located in the substrate (Scheme 1).

Scheme 1. IMBH of *α,β*-unsaturated esters



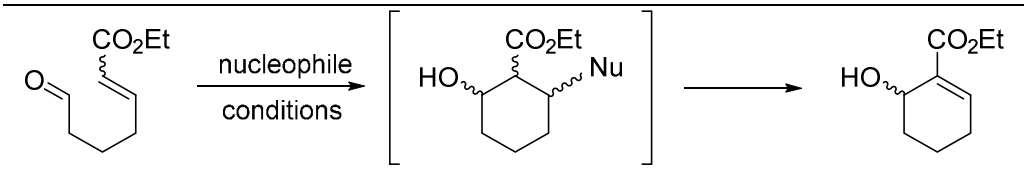
Results

It has been previously reported that simple phosphine and tertiary amines are efficient in promoting the MBH reaction of acrylates but are completely unreactive in the case of linear oxo-*α*,*β*-unsaturated esters. For this purpose, high nucleophilicity and very low basicity of chalcogenols and metallic chalcogenolates can be employed as initial nucleophiles in the intermolecular reaction leading to Morita-Baylis-Hillman products.[3–10]

Several examples of endo type products formed in IMBH reaction have been reported[11–17] and the most common procedures are based on intermolecular MBH followed by ring-closing metathesis (RCM).[18] This strategy fails in the presence of more than two double bonds in the molecule. Elegant work involving use of lithium benzylthiolate was presented by Ono.[19] They presented total synthesis of Neplanocin A and the key intermediate was obtained via thio-Michael/aldol cyclization.

A serious drawback of this methodology is the use of alkylchalcogenols as starting material, since these compound are volatile and have a foul odour. Comasseto *et. al*. recently described a sequence of intermolecular Michael-aldol reaction activated by lithium *n*-butylchalcogenate generated *in situ*.[6]

Table 1. Catalyst screening



1 **1a**

entry	[equiv] nuc.	conditions	yield [%]
1	0.2 DABCO	$CHCl_3$, rt, 7 d	0
2	1.0 DABCO	$CHCl_3$, rt, 7 d	0
3	0.2 DBU	$CHCl_3$, rt, 7 d	0

4	1.0 DBU	$CHCl_3$, rt, 7 d	0
5	0.2 PBu_3	$CDCl_3$, rt, 24 h	up to 70[15]
6	0.2 PBu_3	$CHCl_3$, rt, up to 7 d	<5
7	0.2 PMe_3	$CHCl_3$, rt, up to 7 d	<5
8	1.0 DABCO	THF, rt, 7 d	0
9	1.0 PBu_3	THF, rt, 7 d	0
10	1.0 PMe_3	THF, rt, 7 d	0
11	1.0 *n*-BuSeLi	THF, 0 °C (0.25 h) to rt (1 h)	38

Our initial attempts to induce cyclization simply by exposure of **1** to common catalysts in chloroform or THF at room temperature gave mostly no reaction (Table 1, Entries 1-10). Traces of product have been detected by crude NMR in phosphine catalyzed reactions (Table 1, Entries 6-7). Those results are opposite of previously reported yield.[15] Treatment of **1** with lithium benzenethiolate gave only acyclic sulpha-Michael adduct as previously reported.[17] Detailed NMR studies on the crude mixture containing lithium *n*-butylselenolates and oxo-*α*,*β*-unsaturated ester, clearly suggested the formation of seleno-Michael adduct and the consumption of aldehyde. We decided to stop the reaction with aqueous ammonium chloride and treated the crude mixture with excess of H_2O_2/pyridine at 50 °C. This protocol gave desired product with 38% isolable yield. The best experimental protocol for lithium *n*-butylselenolates generation was used to investigate the experimental conditions for the chalcogenation/condensation sequence. Several reaction conditions and sequences of addition of the components were tested (Table 2).

Table 2. Optimization of reaction conditions

entry	solvent (v/v)	*n*-BuSeLi equiv	conditions	yield [%][c]
1	**THF**	1.0	A	38
2	**THF**	1.0	A	49
3	**Et_2O**	1.0	A	0[a]
4	**THF/Et_2O** (1:6)	1.0	A	40

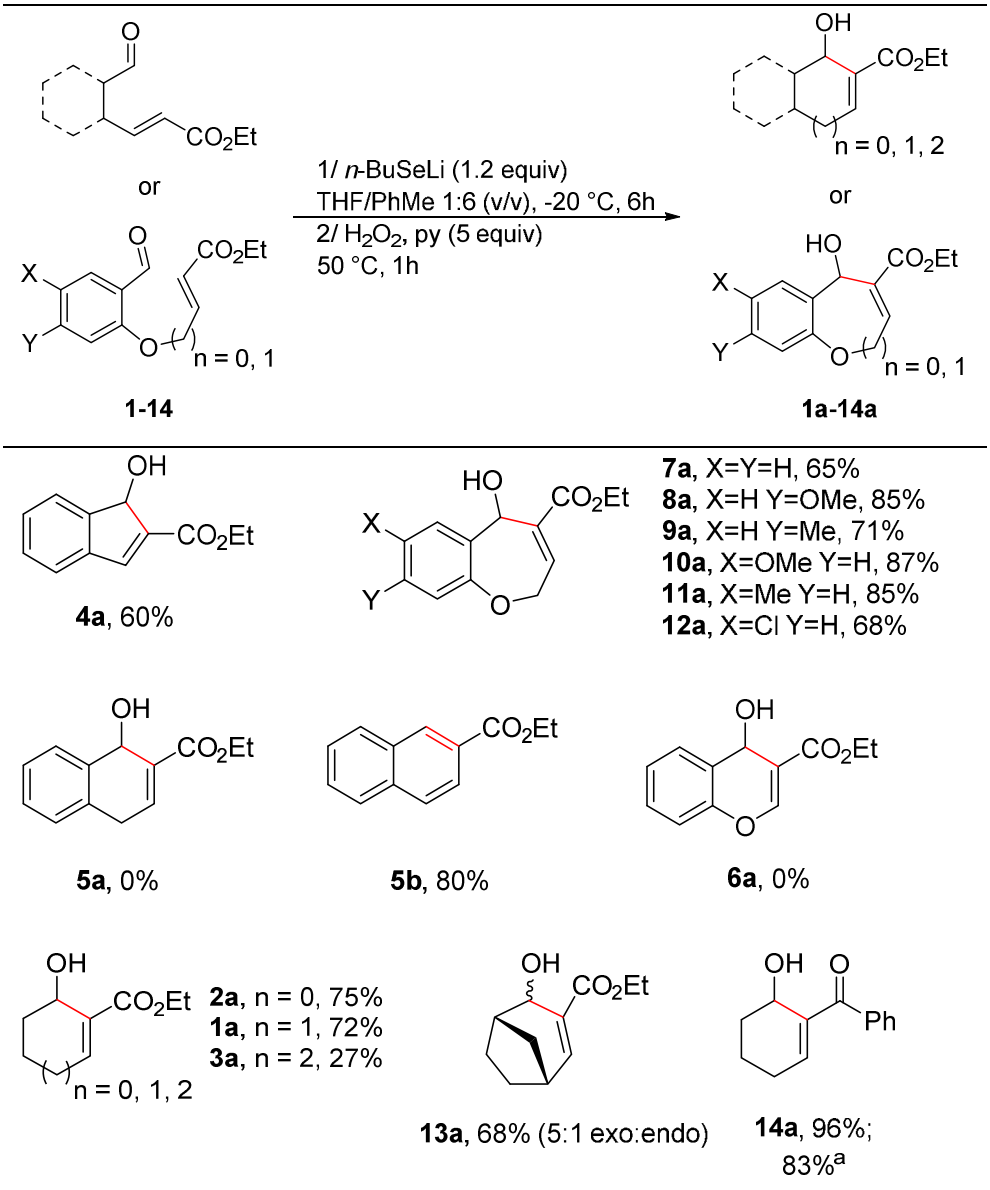
5	**THF/DMF** (1:6)	1.0	A	22
6	**THF/MeCN** (1:6)	1.0	A	48
7	**THF/1,4-dioxane** (1:6)	1.0	A	43
8	**THF/MeOH** (1:6)	1.0	A	0[b]
9	**THF/PhMe** (1:6)	1.0	A	53
10	**THF/PhMe** (1:6)	1.0	A	<10[d]
11	**THF/PhMe** (1:6)	1.0	B	65
12	**THF/PhMe** (1:6)	1.0	C	64
13	**THF/PhMe** (1:6)	1.0	D	0[b]
14	**THF/PhMe** (1:6)	1.0	D (6 h)	0[b]
15	**THF/PhMe** (1:6)	1.2	B	72

Reaction conditions: A: 0 °C (0.25 h) to rt (1 h); B: - 20 °C (6 h); C: - 40 °C (6 h); D: - 78 °C (1 h); [a] Nucleophile not soluble in Et_2O. [b] No conversion based on ^1H NMR. [c] The yields refer to the isolate product purified by column chromatography. [d] Opposite sequence of addition (*n*-BuSeLi in THF has been added to aldehyde solution in anhydrous THF).

Omission of the extraction after reaction quenching increased yield to 49% (Table 2, Entry 2). An attempt to improve reaction by employing Et_2O was unsuccessful (Table 2, Entry 3). Reductive cleavage of elemental selenium under these conditions produced an insoluble mixture which when treated with substrate **1** did not provide desire product. Much better results were obtained using mixtures of solvents (Table 2, Entries 4-9). Protic solvents such as methanol stopped the reaction completely (Table 2, Entry 8). The greatest yield was observed in THF/toluene mixture at 0 °C. Alternative sequence of substrate addition gave a complex mixture and produced the desired product with a low yield (Table 2, Entry 10). Optimization of the reaction temperature improved the yield slightly to 65%. A small excess of nucleophile lead to the formation of product with 72% yield. Having identified conditions under which the desired reaction was high yielding, several other potential substrates for this reaction were prepared and tested. As presented in Table 3, our methodology provides a route to both single and fused cyclic systems. Synthesis of the six-membered carbocycles were very high yielding. Furthermore, the syntheses of five and seven-membered rings gave products with moderate (**2a** and **10a**) to very high isolated yields.

Interestingly, formation of bridged bicyclic system (**13a**) gave a desired product with 68% yield and good diastereomeric ratio (5:1). The simple seven-membered ring (**3a**) was obtained with 27% yield only. Interestingly, compound **5** did not yield the expected product **5a**. Rather, further aromatization was observed to give ethyl 2-naphthoate (**5b**). Surprisingly, compound **6** also did not give desired product and a complex mixture of degradation products were obtained. For detailed descriptions of substrate syntheses (**1-14**) please see supporting information.

Table 3. Substrate scope



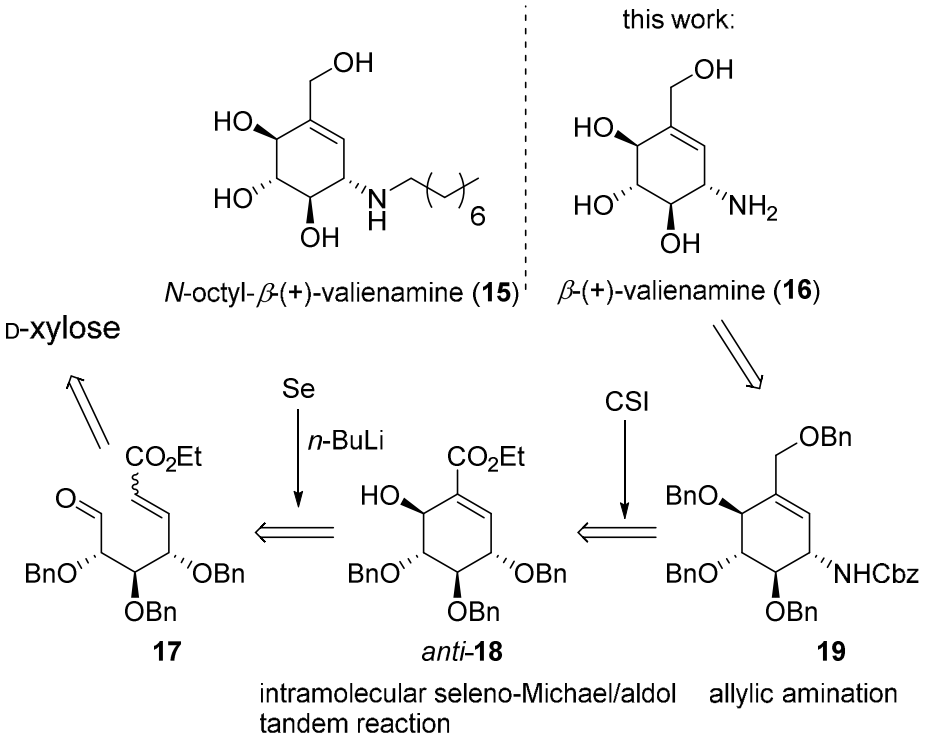
[a] Cyclization in the presence of 0.2 equiv PBu_3, $CHCl_3$, rt, 3h.

At this point we turned our attention to common IMBH substrates such as oxo-α,β-unsaturated ketones. (5*E*)-7-oxo-7-phenylhept-5-enal (**14**) was chosen as a model substrate. Treatment of **14** with 0.2 equiv

of PBu_3 in chloroform for 3 h at room temperature gave **14a** in 83% yield in comparison to 96% obtained under our conditions.

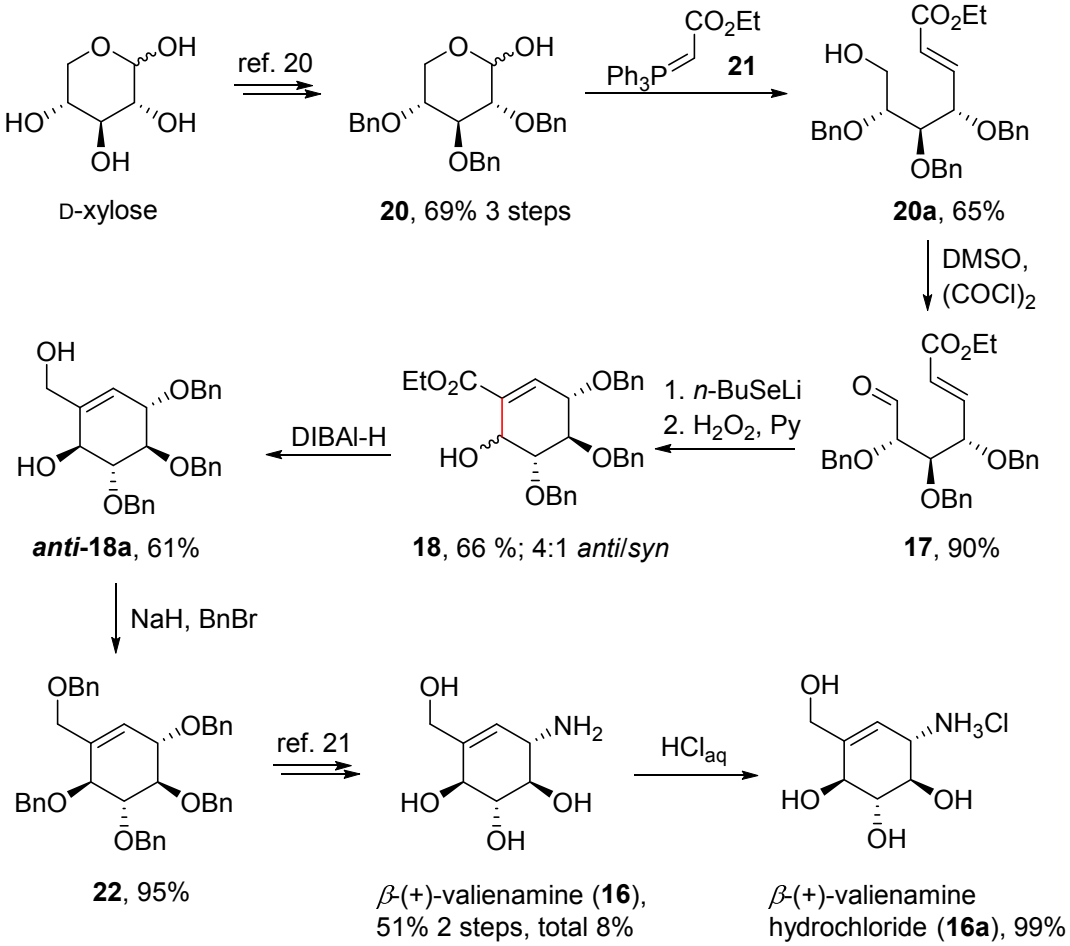
In addition, this method has been successfully applied to the synthesis of C-7 aminocyclitol with pharmacological properties. For example, *N*-octyl-*β*-(+)-valienamine (NOV, **15**) has been found as a potential chemical chaperone for Gaucher disease.[20] Fully protected *β*-(+)-valienamine (**19**) can be accessed from the key intermediate cyclohex-1-ene-1-carboxylate via seleno induced Michael/aldol tandem reaction (Scheme 2). Compound **18** can be obtained by the one-pot intramolecular lithium selenolate-induced Michael-aldol tandem reaction with furthered oxidation-elimination from simple oxo-*α*,*β*-unsaturated ester **17**.

Scheme 2. Retrosynthetic analysis of *β*-(+)-valienamine



The synthesis of compound **20** was completed in 5 steps from commercially available D-xylose in 69% overall yield.[21] Wittig reaction of the partially protected D-xylose **20** and ylide **21** gave a primary alcohol as mixture of isomers (*E*/*Z* = 1:0.2) in 65% yield. Oxidation of the remaining primary hydroxyl group gave compound **17** after flash chromatography as a mixture of isomers (*E*/*Z* =90:10) in 90% yield. Both isomers of compound **17** have been isolated and fully characterized (see supporting information).

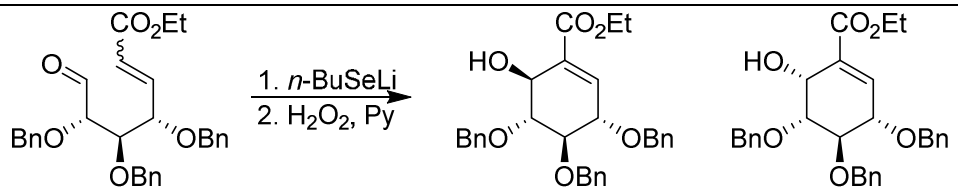
Scheme 3. Total synthesis of *β*-(+)-valienamine



With the enoate **17** in hand, the key intramolecular tandem reaction was attempted. Elemental selenium was suspended in dry THF, cooled and equimolar amount of *n*-BuLi in THF was added to generate lithium *n*-butylselenolate. Then, compound **17** was subjected to the Michael reaction with lithium *n*-butylselenolate followed by trapping of the produced enolate containing an aldehyde group to give a cyclic product as an inseparable mixture of isomers. The crude mixture of *n*-butylselenol adducts were treated with H_2O_2/pyridine system in THF at 50 °C to give mixture of cyclic Morita-Baylis-Hillman type products (**18** *anti*/*syn* = 65:35) in 38% total yield after 3 steps at first attempt. Short optimization gave compound **18** with 66% yield (Table 4). For further investigation we chose THF as the best solvent (Table 4, Entries 7 - 9). Treatment of **17** with excess of *n*-BuSeLi (1.2 equiv) at -20 °C gave **18** as mixture of *anti*/*syn* diastereomers (3:1) in 66% total. Diastereomeric ratio was determined by ^{1}H NMR analysis and pure isomers have been isolated by column chromatography. On the basis of above-described results, we decided to examine pure *Z*-**17** and *E*-**17** isomers in cyclization reactions under best reaction conditions. As presented in Table 4 (Entries 8 and 9), both isomers reacted to produce the same diastereomeric ratio, but *E*-isomer gave much better yield than *Z*-isomer. Simple phosphines gave better

selectivity (*dr* = 8:1) but unfortunately yields were very poor even after 14 or 28 days (Table 4, Entries 10 and 11).

Table 4. Reaction conditions and isolated yields of **18**.



17 *anti*-**18** *syn*-**18**

entry	[equiv] nuc.	solvent	*anti*/*syn*	yield [%]
1	1.0	THF, 0 °C (0.25 h) to rt (1 h)	65:35	38
2	1.0	THF/PhMe, 0 °C (0.25 h) to rt (1 h)	67:33	39
3	1.0	THF/DMF, 0 °C (0.25 h) to rt (1 h)	nd	traces
4	1.0	THF/MeCN, 0 °C (0.25 h) to rt (1 h)	54:46	32
5	1.0	THF/1,4-dioxane, 0 °C (0.25 h) to rt (1 h)	66:34	42
6	1.0	THF/Et_2O, 0 °C (0.25 h) to rt (1 h)	67:33	34
7	1.2	THF, - 20 °C (6 h)	74:26	66
8[a]	1.2	THF, - 20 °C (6 h)	75:25	42
9[b]	1.2	THF, - 20 °C (6 h)	74:26	69
10[c]	1.0 PBu3	$CHCl_3$, rt, 14 d	87:13	10
11[c]	1.0 PMe3	$CHCl_3$, rt, 28 d	81:19	20

[a] Pure *Z*-isomer of **17**. [b] Pure *E*-isomer of **17**. [c] PBu_3 or PMe_3 was used instead of *n*-BuSeLi.

With the *anti*-isomer of compound **18** in hand, the reduction of *α*,*β*-unsaturated ester reaction was attempted. As presented on Scheme 3, compound **18** was treated with 3.5 equivalents of DIBAL-H in DCM at -10 °C to give corresponding diol and protected with benzyl ethers under standard reaction conditions. Cyclic product (**22**) was treated with 3 equivalents of chlorosulfonyl isocyanate (CSI) under optimal reaction conditions (anhydrous toluene, 0 °C, 15 h) to afford the corresponding 1,2-*anti*-amino alcohol **19** in good yield (74%).[22] Only one single diastereomer was isolated. Protection groups were removed using BCl_3 to provide *β*-(+)-valienamine (**16**).

Conclusions

In conclusion, the tandem Michael/aldol reaction with lithium selenolates and subsequent oxidation-elimination of the seleno group is a highly efficient method for the construction of six-membered rings.

The presented methodology shows some interesting advantages in comparison to the classic IMBH reaction, such as the short reaction times and the substrate scope. We have developed a fast and high yielding route to multi-functionalized IMBH adducts employing in situ generated metallic chalcogenolates. This protocol can be a valuable alternative route to obtain IMBH adducts and derivatives. In this context, the asymmetric version of this reaction is under development in our laboratory.

Experimental section

General information

All starting materials and reagents were purchased from commercial sources and used without purification. Reactions were controlled using TLC on silica [alu-plates (0.2 mm)]. Plates were visualized with UV light (254 nm) and by treatment with: aqueous cerium(IV) sulfate solution with molybdic and sulfuric acid followed by heating. All organic solutions were dried over anhydrous magnesium sulfate. Reaction products were purified by flash chromatography using silica gel 60 (240-400 mesh). Optical rotations were measured at room temperature with a digital polarimeter. $CDCl_3$, D_2O were used as NMR solvents. ^1H spectra were recorded with 600, 400 and 300 MHz and referenced relative to: $CDCl_3$ - tetramethylsilane (δ = 0 ppm). Data are reported as follows: chemical shift in parts per million (ppm) , multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, m = multiplet), coupling constants (in hertz) and integration. ^{13}C NMR spectra were measured at 150, 100 and 75 MHz with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard: $CDCl_3$ (δ = 77.16 ppm). High-resolution mass spectra were acquired using ESI-TOF method.

General procedure for ozonolysis/Wittig reaction (Procedure A).[15] Cycloalkene (10 mmol) was dissolved in anhydrous methylene chloride (50 ml) and cooled to -78 °C whereupon ozone was bubbled in the flask until the solution became blue in color and at this point, the reaction was flushed with argon and triphenylphosphine (1 equiv. to the amount of alkene) was added in one portion. Reaction mixture was allowed to slowly warm to 0 °C and phosphorane (0.1-2 equiv., substrate dependent) was added and the reaction mixture was stirred for 12 h in room temperature. Products were purified by column chromatography in Hx/EA gradient.

Ethyl (E)-6-oxohex-2-enoate **(2)**[15] Procedure A: 1,5-Cyclooktadiene (1.40 g, 12.94 mmol), **21** (9.00 g, 25.88 mmol) gave product as a colorless oil (1.15 g, 7.36 mmol), 28 %. **^1H NMR** (600 MHz, $CDCl_3$) δ 9.80 (s, 1H), 6.94 (dt, *J* = 15.6, 6.7 Hz, 1H), 5.85 (dt, *J* = 15.7, 1.5 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H),

2.64 (t, *J* = 7.2 Hz, 2H), 2.57 – 2.50 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 200.3, 166.2, 146.2, 122.4, 60.3, 41.8, 24.4, 14.2.

Ethyl (E)-8-oxooct-2-enoate **(3)**[15] Procedure A: Cyclohexene (2.0 g, 24.35 mmol), **21** (4.24 g, 12.17 mmol) gave product as a colorless oil (1.43 g, 6.53 mmol), 54 %. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.77 (t, *J* = 1.6 Hz, 1H), 6.94 (dt, *J* = 15.6, 6.9 Hz, 1H), 5.83 (dt, *J* = 15.6, 1.6 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.46 (td, *J* = 7.3, 1.6 Hz, 2H), 2.23 (ddd, *J* = 14.6, 7.3, 1.6 Hz, 2H), 1.71 – 1.62 (m, 2H), 1.51 (dt, *J* = 15.2, 7.7 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 202.1, 166.6, 148.2, 121.8, 60.2, 43.6, 31.8, 27.4, 21.5, 14.2.

Ethyl (E)-4-(2-formylphenyl)but-2-enoate **(5)** Procedure A: Indene (2.00 g, 17.22 mmol), **21** (1.80 g, 5.17 mmol) gave product as a colorless oil (0.42 g, 1.90 mmol), 37%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 10.16 (s, 1H), 7.85 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.56 (td, *J* = 7.5, 1.5 Hz, 1H), 7.47 (td, *J* = 7.5, 1.1 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.14 (dt, *J* = 15.6, 6.4 Hz, 1H), 5.72 (dt, *J* = 15.6, 1.7 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.99 (dd, *J* = 6.4, 1.6 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 192.5, 166.3, 146.6, 139.7, 134.0, 133.8, 133.6, 131.4, 127.5, 122.6, 60.3, 35.2, 14.2.

Ethyl (E)-3-((1R,3S)-3-formylcyclopentyl)acrylate **(13)** Procedure A: Norbornene (2.16 g, 22.94 mmol), **21** (4.00 g, 11.47 mmol) gave product as a colorless oil (1.61 g, 8.21 mmol), 72%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.64 (d, *J* = 2.3 Hz, 1H), 6.91 (dd, *J* = 15.6, 7.7 Hz, 1H), 5.83 (dd, *J* = 15.6, 1.2 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.91 – 2.84 (m, 1H), 2.77 – 2.68 (m, 1H), 2.11 – 2.00 (m, 2H), 1.96 – 1.85 (m, 2H), 1.72 (ddd, *J* = 13.1, 9.9, 8.7 Hz, 1H), 1.49 – 1.42 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 202.6, 166.6, 150.8, 120.6, 60.3, 51.2, 42.9, 32.2, 31.8, 25.9, 14.2; **HRMS** (ESI): calcd. for $C_{11}H_{16}O_3Na$ $[M+Na]^+$ 219.0991, found 219.0991.

(E)-7-oxo-7-phenylhept-5-enal **(14)**[15] Procedure A: Cyclopentene (7.16 g, 105.15 mmol), **23** (4.00 g, 10.51 mmol) gave product as colorless oil (1.00 g, 4.94 mmol), 47%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.81 (t, *J* = 1.4 Hz, 1H), 7.94 (dt, *J* = 8.4, 1.6 Hz, 2H), 7.59 – 7.55 (m, 1H), 7.51 – 7.46 (m, 2H), 7.03 (dt, *J* = 15.4, 6.8 Hz, 1H), 6.92 (dt, *J* = 15.4, 1.4 Hz, 1H), 2.54 (td, *J* = 7.2, 1.4 Hz, 2H), 2.42 – 2.35 (m, 2H), 1.89 (p, *J* = 7.3 Hz, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 201.6, 190.5, 148.0, 137.7, 132.7, 128.5, 128.5, 126.6, 43.0, 31.8, 20.5.

General procedure for synthesis salicylic aldehyde derivatives (Procedure B).[23] Different substituent salicylic aldehyde (0.5 g), ethyl 4-bromocrotonate (1.2 equiv.) and K_2CO_3 (2 equiv.) were dissolved in DMF (15 ml) and heated to 40 °C or 70 °C under argon for 4 h. Reaction mixture was allowed to cool to room temperature and filtrated. After water addition (20 ml) the mixture was extracted with ethyl

acetate (3 x 20ml). The combined organic phases were washed with water (2 x 20 ml) and brine (30 ml) and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the residue was purified by column chromatography on silica gel in Hx/EA gradient to give the pure products.

Ethyl (E)-4-(2-formylphenoxy)but-2-enoate **(7)**[23] Procedure B: 70 °C, (0.34 g, 1.43 mmol), 35%, pale yellow solid mp: 68-70 (66-68 °C lit.).[23] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 10.56 (d, *J* = 0.7 Hz, 1H), 7.86 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.54 (ddd, *J* = 8.5, 7.3, 1.8 Hz, 1H), 7.13 – 7.05 (m, 2H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.22 (dt, *J* = 15.8, 2.1 Hz, 1H), 4.83 (dd, *J* = 4.1, 2.1 Hz, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 189.3, 165.8, 160.1, 141.1, 135.9, 128.8, 125.1, 122.5, 121.4, 112.5, 66.8, 60.7, 14.2.

Ethyl (E)-4-(2-formyl-5-methoxyphenoxy)but-2-enoate **(8)**[23] Procedure B: 40 °C, (0.72 g, 2.72 mmol) 83%, pale yellow solid, mp: 95-96 °C (91-93 °C lit.).[23] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 10.38 (d, *J* = 0.7 Hz, 1H), 7.84 (d, *J* = 8.7 Hz, 1H), 7.09 (dt, *J* = 15.8, 4.0 Hz, 1H), 6.59 (ddd, *J* = 8.7, 2.2, 0.6 Hz, 1H), 6.40 (d, *J* = 2.2 Hz, 1H), 6.22 (dt, *J* = 15.8, 2.1 Hz, 1H), 4.80 (dd, *J* = 4.0, 2.1 Hz, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 187.8, 166.0, 165.8, 161.8, 141.0, 130.9, 122.5, 119.2, 106.3, 99.0, 66.8, 60.7, 55.7, 14.2.

Ethyl (E)-4-(2-formyl-5-methylphenoxy)but-2-enoate **(9)** Procedure B: 40°C, (0.65 g, 2.63 mmol) 72%, pale yellow solid, mp: 63-65 °C. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 10.47 (d, *J* = 0.6 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.10 (dt, *J* = 15.8, 4.0 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 6.73 (s, 1H), 6.21 (dt, *J* = 15.8, 2.1 Hz, 1H), 4.81 (dd, *J* = 4.0, 2.1 Hz, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 2.39 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 188.9, 165.8, 160.2, 147.4, 141.3, 128.8, 122.9, 122.4, 122.3, 113.0, 66.7, 60.7, 22.3, 14.2. **HRMS** (ESI): calcd. for $C_{14}H_{16}O_4Na$ $[M+Na]^+$ 271.0941, found 271.0941.

Ethyl (E)-4-(2-formyl-4-methoxyphenoxy)but-2-enoate **(10)**[23] Procedure B: 70 °C, (0.61 g. 2.29 mmol) 70%, pale yellow solid, mp: 83-84 °C (83-85 °C lit.).[23] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 10.52 (s, 1H), 7.35 (d, *J* = 3.3 Hz, 1H), 7.13 – 7.06 (m, 2H), 6.90 (d, *J* = 9.1 Hz, 1H), 6.20 (dt, *J* = 15.8, 2.1 Hz, 1H), 4.78 (dd, *J* = 4.1, 2.1 Hz, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 189.0, 165.8, 155.0, 154.1, 141.4, 125.4, 123.4, 122.4, 114.4, 110.6, 67.5, 60.7, 55.8, 14.2.

Ethyl (E)-4-(2-formyl-4-methylphenoxy)but-2-enoate **(11)** Procedure B: 70 °C, (0.53 g, 2.11 mmol) 57%, pale yellow solid, mp: 64-65 °C. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 10.52 (s, 1H), 7.65 (d, *J* = 2.1 Hz, 1H), 7.34 (ddd, *J* = 8.5, 2.4, 0.6 Hz, 1H), 7.09 (dt, *J* = 15.8, 4.0 Hz, 1H), 6.84 (d, *J* = 8.5 Hz, 1H), 6.20 (dt, *J* = 15.8, 2.1 Hz, 1H), 4.80 (dd, *J* = 4.0, 2.1 Hz, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 2.32 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 189.4, 165.8, 158.3, 141.4, 136.5, 130.9, 128.8, 124.8,

122.4, 112.5, 66.9, 60.7, 20.2, 14.2. **HRMS** (ESI): calcd. for $C_{14}H_{16}O_4Na$ $[M+Na]^+$ 271.0941, found 271.0941.

Ethyl (E)-4-(4-chloro-2-formylphenoxy)but-2-enoate **(12)**[23] Procedure B: 70°C, (0.57 g, 2.12 mmol), 66%, pale yellow solid, mp: 66-67 (64-66 °C lit.).[23] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 10.48 (s, 1H), 7.82 (d, *J* = 2.7 Hz, 1H), 7.49 (dd, *J* = 8.9, 2.8 Hz, 1H), 7.09 (dt, *J* = 15.8, 4.1 Hz, 1H), 6.91 (d, *J* = 8.9 Hz, 1H), 6.19 (dt, *J* = 15.8, 2.0 Hz, 1H), 4.83 (dd, *J* = 4.1, 2.0 Hz, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 187.9, 165.6, 158.6, 140.6, 135.4, 128.3, 127.2, 125.9, 122.8, 114.2, 67.2, 60.8, 14.2.

Preparation of other substrates

Ethyl 7-oxohept-2-enoate **(1)**[15] To solution of tetrahydro-2*H*-pyran-2-ol (7.00 g, 68.54 mmol) in anhydrous 1,4-dioxane (100 ml) **21** (29.80 g, 85.68 mmol) was added. After 12 h of continuous stirring reaction mixture was heated up to 45 °C for 2 h. After solvent evaporation crude mixture was purified by flash chromatography Hx/EA (95:5 to 3:1) to give ethyl 7-hydroxyhept-2-enoate as a mixture of diastereoisomers *E/Z* >95/5. Ethyl-7-hydroxyhept-2-enoate was dissolved in anhydrous methylene chloride (60 ml) and was added to oxidative mixture prepared by addition of anhydrous dimethyl sulfoxide (19.6 ml, 275.93 mmol) to solution of oxalyl chloride (11.8 ml, 137.96 mmol) in anhydrous methylene chloride (100 ml) cooled to -78 °C. After 1 h of stirring in -78 °C triethylamine (58.2 ml, 413.89 mmol) was added and strirring was continued for next 30 min. After that time reaction mixture was allowed to slowly warm to room temperature. The reaction was quenched with addition of sat. NH_4Cl (100 ml), followed by addition of water (100 ml). The aqueous layer was extracted with methylene chloride (3 x 100 ml), and combined organic layers were washed with water (2 x 100 ml) and brine (100 ml). The organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure (below 35 °C). Crude product was purified by flash chromatography Hx/EA (95:5) to (4:1) to give **1** as an almost pure *E* diastereoisomer (traces of *Z*-product) as colorless oil (6.23 g, 37.01 mmol), 54% after 2 steps. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.78 (t, *J* = 1.4 Hz, 1H), 6.92 (dt, *J* = 15.6, 6.9 Hz, 1H), 5.84 (dt, *J* = 15.6, 1.6 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.49 (td, *J* = 7.3, 1.4 Hz, 2H), 2.26 (ddd, *J* = 14.7, 7.4, 1.6 Hz, 2H), 1.81 (p, *J* = 7.3 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 201.6, 166.4, 147.5, 122.3, 60.3, 42.9, 31.2, 20.3, 14.2.

Ethyl (E)-3-(2-formylphenyl)acrylate **(4)**[23] To the solution of phthaldialdehyde (1.0 g, 7.45 mmol) in anhydrous toluene **21** (2.6 g, 7.45 mmol) was added in one portion. The reaction mixture was heated to 50 °C under argon for 2 h. After solvent removal, semisolid residue was purified by column chromatography in Hx/EA gradient which results product as a clear, colorless oil (0.74 g, 3.62 mmol), 47%. **^{1}H**

NMR (600 MHz, $CDCl_3$) δ 10.24 (s, 1H), 8.45 (d, *J* = 15.9 Hz, 1H), 7.82 (d, *J* = 7.1 Hz, 1H), 7.59 – 7.52 (m, 2H), 7.49 (td, *J* = 7.4, 1.8 Hz, 1H), 6.31 (d, *J* = 15.9 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 191.7, 166.2, 140.9, 136.7, 133.9, 133.8, 132.1, 129.8, 128.0, 123.3, 60.8, 14.3.

Ethyl (E)-3-(2-formylphenoxy)acrylate **(6)** To the solution of salicylic aldehyde (1.00 g, 8.19 mmol) in anhydrous methylene chloride (10 ml) ethyl propiolate (0.99 ml, 9.83 mmol) was added in one portion. After addition catalytic amount of *N*-methylmorpholine (0.09 ml, 0.82 mmol) reaction mixture was stirred under argon for 12 h in room temperature. After that time solvent was removed under reduced pressure and crude product was purified by column chromatography in Hx/EA gradient (5:1 to 3:1) which gave pure product as a colorless oil (1.51 g, 6.86 mmol), 84 %. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 10.39 (d, *J* = 0.7 Hz, 1H), 7.95 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.86 (d, *J* = 12.2 Hz, 1H), 7.67 (ddd, *J* = 8.3, 7.4, 1.8 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 8.3 Hz, 1H), 5.66 (d, *J* = 12.2 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 188.1, 166.5, 158.0, 157.5, 136.0, 128.9, 126.5, 125.4, 118.3, 104.2, 60.4, 14.3.

General procedure for tandem seleno-Michael/aldol-oxidation/elimination reaction (Procedure C). A suspension of elemental selenium (0.50 g, 0.63 mmol) in anhydrous THF (0.8 ml) was cooled in ice bath and *n*-BuLi (1.6 M in hexanes, 0.394 ml, 0.63 mmol) was added dropwise (a clear, almost colorless, solution was produced) and the mixture was stirred 15 min in 0 °C. After that reaction mixture was cooled to -20 °C followed by addition anhydrous toluene (3 ml). Solution of substrate (0.53 mmol in 1.5 ml of anhydrous toluene) was added dropwise and stirring was continued through the next 6 hours. After that time, reaction was quenched by addition of aqueous, saturated solution of NH_4Cl (0.100 ml) following by addition of hydrogen peroxide solution (30 % v/v, 0.325 ml, 3.15 mmol) and pyridine (0.254 ml, 3.15 mmol). Reaction mixture was allowed to slowly back to room temperature and after that was heated to 50 °C for 1 hour (reaction mixture became almost colorless). The solvent was evaporated under reduced pressure and resign of pyridine was co-evaporated with toluene (2 x 15 ml). Crude products were purified by column chromatography Hx/EA gradient.

Ethyl 6-hydroxycyclohex-1-ene-1-carboxylate **(1a)**[15] Procedure C: colorless oil (0.065g, 0.38 mmol), 72%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.10 (t, *J* = 4.0 Hz, 1H), 4.54 (t, *J* = 4.4 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.15 (s, 1H), 2.33 – 2.23 (m, 1H), 2.18 – 2.10 (m, 1H), 1.87 – 1.72 (m, 3H), 1.65 – 1.55 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.3, 142.8, 132.4, 63.5, 60.6, 29.9, 26.1, 17.5, 14.2.

Ethyl 5-hydroxycyclopent-1-ene-1-carboxylate **(2a)**[15] Procedure C: colorless oil (0.063 g, 0.40 mmol), 75%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.91 (t, *J* = 2.5 Hz, 1H), 5.12 – 5.06 (m, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 2.65 (m, 1H), 2.45 – 2.38 (m, 1H), 2.38 – 2.32 (m, 1H), 1.88 (m, 1H), 1.32 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 165.0, 146.2, 138.0, 75.5, 60.4, 31.8, 30.8, 14.2.

Ethyl 7-hydroxycyclohept-1-ene-1-carboxylate **(3a)**[15] Procedure C: colorless oil (0.026 g, 0.14 mmol), 27%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.16 (t, *J* = 6.5 Hz, 1H), 4.81 (dd, *J* = 7.6, 2.2 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.20 (s, 1H), 2.48 – 2.38 (m, 1H), 2.33 – 2.22 (m, 1H), 2.01 – 1.92 (m, 2H), 1.82 – 1.76 (m, 1H), 1.76 – 1.63 (m, 2H), 1.62 – 1.55 (m, 1H), 1.30 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 168.4, 145.2, 136.8, 68.6, 60.8, 32.3, 27.3, 25.7, 23.5, 14.2.

Ethyl 1-hydroxy-1H-indene-2-carboxylate **(4a)** Procedure C: colorless oil (0.065 g, 0.32 mmol), 60%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.3 Hz, 1H), 7.56 (s, 1H), 7.41 (dd, *J* = 6.5, 1.0 Hz, 1H), 7.40 – 7.33 (m, 2H), 5.43 (s, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.19 (s, 1H), 1.38 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 164.8, 145.8, 141.3, 139.7, 139.3, 128.9, 128.9, 124.3, 123.8, 75.6, 60.7, 14.3.

Ethyl 2-naphthoate **(5b)** Procedure C: colorless oil (0.085 g, 0.42 mmol), 80%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.63 (d, *J* = 0.7 Hz, 1H), 8.08 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.97 (dd, *J* = 8.1, 0.6 Hz, 1H), 7.89 (d, *J* = 8.6 Hz, 2H), 7.60 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.55 (ddd, *J* = 8.0, 6.9, 1.3 Hz, 1H), 4.46 (q, *J* = 7.1 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 166.8, 135.5, 132.5, 130.9, 129.3, 128.1, 128.1, 127.7 (2C), 126.6, 125.2, 61.1, 14.4.

Ethyl 5-hydroxy-2,5-dihydrobenzo[b]oxepine-4-carboxylate **(7a)** Procedure C: white, amorphous solid (0.081 g, 0.34 mmol), 65%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.22 (d, *J* = 7.4 Hz, 2H), 7.08 – 7.03 (m, 2H), 6.82 (dd, *J* = 3.8, 2.2 Hz, 1H), 5.49 (d, *J* = 9.3 Hz, 1H), 4.93 (dd, *J* = 19.2, 3.9 Hz, 1H), 4.49 (dd, *J* = 19.2, 2.1 Hz, 1H), 4.24 – 4.17 (m, 2H), 3.14 (d, *J* = 9.6 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 166.2, 156.8, 140.3, 136.7, 133.9, 129.9, 128.6, 125.1, 121.7, 70.8, 69.1, 61.4, 14.2. **HRMS** (ESI): calcd. for $C_{13}H_{14}O_4Na$ $[M+Na]^+$ 257.0784, found 257.0784.

Ethyl 5-hydroxy-8-methoxy-2,5-dihydrobenzo[b]oxepine-4-carboxylate **(8a)** Procedure C: white, amorphous solid (0.118 g, 0.45 mmol), 85%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.3 Hz, 1H), 6.90 (dd, *J* = 4.0, 2.2 Hz, 1H), 6.68 (d, *J* = 2.5 Hz, 1H), 6.66 (dd, *J* = 8.3, 2.5 Hz, 1H), 5.51 (d, *J* = 8.5 Hz, 1H), 4.99 (dd, *J* = 19.1, 4.1 Hz, 1H), 4.57 (dd, *J* = 19.1, 2.2 Hz, 1H), 4.34 – 4.22 (m, 2H), 3.80 (s, 3H), 3.00 (d, *J* = 9.0 Hz, 1H), 1.34 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 166.3, 160.9, 157.9,

140.0, 134.1, 129.6, 128.7, 109.9, 107.8, 70.6, 68.8, 61.4, 55.5, 14.2; **HRMS** (ESI): calcd. for $C_{14}H_{16}O_5Na$ $[M+Na]^+$ 287.0890, found 287.0890.

Ethyl 5-hydroxy-8-methyl-2,5-dihydrobenzo[b]oxepine-4-carboxylate **(9a)** Procedure C: white, amorphous solid (0.093 g, 0.38 mmol), 71%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.0 Hz, 1H), 6.96 – 6.92 (m, 2H), 6.89 (dd, *J* = 3.9, 2.2 Hz, 1H), 5.53 (d, *J* = 9.3 Hz, 1H), 4.99 (dd, *J* = 19.2, 3.9 Hz, 1H), 4.55 (dd, *J* = 19.2, 2.2 Hz, 1H), 4.32 – 4.25 (m, 2H), 3.11 (d, *J* = 9.5 Hz, 1H), 2.34 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 166.3, 156.7, 140.3, 134.0, 133.6, 128.5, 125.6, 122.3, 70.7, 68.9, 61.4, 21.1, 14.2. **HRMS** (ESI): calcd. for $C_{14}H_{16}O_4Na$ $[M+Na]^+$ 271.0941, found 271.0941.

Ethyl 5-hydroxy-7-methoxy-2,5-dihydrobenzo[b]oxepine-4-carboxylate **(10a)** Procedure C: white, amorphous solid (0.122 g, 0.46 mmol), 87%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.03 (d, *J* = 8.7 Hz, 1H), 6.88 (dd, *J* = 3.7, 2.2 Hz, 1H), 6.83 (d, *J* = 3.0 Hz, 1H), 6.78 (dd, *J* = 8.7, 3.0 Hz, 1H), 5.51 (d, *J* = 9.3 Hz, 1H), 4.94 (dd, *J* = 19.3, 3.8 Hz, 1H), 4.52 (dd, *J* = 19.3, 2.1 Hz, 1H), 4.31 – 4.24 (m, 2H), 3.78 (s, 3H), 3.34 (d, *J* = 9.8 Hz, 1H), 1.33 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 166.2, 156.5, 150.2, 140.6, 137.7, 133.7, 122.3, 114.4, 113.6, 71.0, 69.1, 61.4, 55.6, 14.2; **HRMS** (ESI): calcd. for $C_{14}H_{16}O_5Na$ $[M+Na]^+$ 287.0890, found 287.0890.

Ethyl 5-hydroxy-7-methyl-2,5-dihydrobenzo[b]oxepine-4-carboxylate **(11a)** Procedure C: white, amorphous solid (0.111 g, 0.45 mmol), 85%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.12 – 7.08 (m, 2H), 7.01 (d, *J* = 7.9 Hz, 1H), 6.89 (dd, *J* = 3.8, 2.1 Hz, 1H), 5.52 (d, *J* = 9.1 Hz, 1H), 4.98 (dd, *J* = 19.3, 3.8 Hz, 1H), 4.54 (dd, *J* = 19.2, 2.1 Hz, 1H), 4.32 – 4.26 (m, 2H), 3.20 (d, *J* = 9.6 Hz, 1H), 2.32 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 166.3, 154.6, 140.5, 136.4, 134.8, 134.0, 130.2, 129.2, 121.4, 70.9, 69.2, 61.4, 20.8, 14.3. **HRMS** (ESI): calcd. for $C_{14}H_{16}O_4Na$ $[M+Na]^+$ 271.0941, found 271.0941.

Ethyl 7-chloro-5-hydroxy-2,5-dihydrobenzo[b]oxepine-4-carboxylate **(12a)** Procedure C: white, amorphous solid (0.097 g, 0.36 mmol), 68%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.30 (d, *J* = 2.6 Hz, 1H), 7.25 (dd, *J* = 8.5, 2.6 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.88 (dd, *J* = 3.7, 2.3 Hz, 1H), 5.55 (s, 1H), 4.97 (dd, *J* = 19.2, 3.8 Hz, 1H), 4.56 (dd, *J* = 19.2, 2.7 Hz, 1H), 4.32 – 4.25 (m, 2H), 3.35 (s, 1H), 1.34 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 166.1, 155.3, 140.1, 138.3, 133.4, 130.1, 129.6, 128.5, 123.1, 70.8, 68.5, 61.6, 14.2. **HRMS** (ESI): calcd. for $C_{13}H_{13}O_4ClNa$ $[M+Na]^+$ 291.0395, found 291.0395.

Ethyl (1R,4R,5S)-4-hydroxybicyclo[3.2.1]oct-2-ene-3-carboxylate (exo-13a) and Ethyl (1R,4S,5S)-4-hydroxybicyclo[3.2.1]oct-2-ene-3-carboxylate **(*endo*-13a)** Procedure C: colorless oil (0.071 g, 0.36 mmol), 68% (5:1 *exo*/*endo*); *exo*-**13a**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.24 (dd, *J* = 7.0, 1.1 Hz, 1H),

4.23 – 4.17 (m, 2H), 4.11 (d, *J* = 2.8 Hz, 1H), 2.71 (s, 1H), 2.67 (dd, *J* = 9.8, 6.3 Hz, 1H), 2.55 – 2.49 (m, 1H), 1.93 – 1.87 (m, 1H), 1.85 (d, *J* = 11.3 Hz, 1H), 1.71-1.64 (m, 1H), 1.63 – 1.58 (m, 1H), 1.35-1.31 (m, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.24 – 1.19 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.7, 148.6, 129.1, 70.9, 60.5, 38.7, 35.6, 30.3, 30.2, 24.7, 14.2; **HRMS** (ESI): calcd. for $C_{11}H_{16}O_3Na$ $[M+Na]^+$ 219.0991, found 219.0992. *endo*-**13a**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.19 (d, *J* = 6.7 Hz, 1H), 4.77 (d, *J* = 4.8 Hz, 1H), 4.24 – 4.17 (m, 2H), 3.71 (s, 1H), 2.62 – 2.56 (m, 2H), 2.21 – 2.14 (m, 1H), 1.78 – 1.72 (m, 3H), 1.72 – 1.62 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.6, 148.2, 129.6, 71.7, 60.6, 39.6, 36.5, 36.3, 32.0, 21.2, 14.2; **HRMS** (ESI): calcd. for $C_{11}H_{16}O_3Na$ $[M+Na]^+$ 219.0991, found 219.0992.

(6-hydroxycyclohex-1-en-1-yl)(phenyl)methanone **(14a)**[15] Procedure C: colorless oil (0.103 g, 0.51 mmol), 96%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.69 – 7.63 (m, 2H), 7.57 – 7.52 (m, 1H), 7.44 (dd, *J* = 10.7, 4.7 Hz, 2H), 6.77 – 6.71 (m, 1H), 4.74 (dd, *J* = 6.0, 2.8 Hz, 1H), 3.54 (s, 1H), 2.40 – 2.32 (m, 1H), 2.30 – 2.20 (m, 1H), 1.98 – 1.90 (m, 1H), 1.90 – 1.81 (m, 1H), 1.66 (qd, *J* = 7.1, 3.8 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 199.4, 147.2, 139.9, 137.7, 132.0, 129.3, 128.2, 64.0, 29.7, 26.4, 17.4.

Total Synthesis of *β*-(+)-valienamine.

2,3,4-Tri-O-benzyl-D-xylopyranose **(20)**[24,25] To methanolic solution of 1.2 % HCl (100 ml) (prepared by dissolved 2.4 ml $SOCl_2$ in anhydrous methanol) D-xylose (10 g, 66.6 mmol) was added in one portion and resulting mixture was refluxed for 4.5 h under argon (reaction was monitored by TLC CH_2Cl_2/MeOH 2:1). The reaction mixture was allowed to cool to rt, neutralized by addition of solid $NaHCO_3$ and concentrated under reduced pressure. The residue was dissolved in EtOH (80 ml) and concentrated to the half of the original volume, toluene (2 x 50 ml) was added and the mixture was two times concentrated to dryness. The residue crude mixture oil was used without further purification in the next step. The viscous oil from the previous step was dissolved in anhydrous DMF (100 ml) and anhydrous THF (100 ml) and in 5 portion was added to 60% NaH suspension in mineral oil (13.6 g, 340 mmol) cooled to 0 °C. After hydrogen evolution was complete the mixture was treated with BnBr (29.6 ml, 244 mmol) and stirred for 30 min in 0 °C and then overnight in rt. The reaction mixture was carefully quenched with 10 % cold, aqueous solution of NH_4Cl (60 ml) followed by addition of water (150 ml). The aqueous layer was extracted with ethyl acetate (3 x 100 ml) and combined organic layers were washed with water (2 x 120 ml) and brine (100 ml), then dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Flash column chromatography Hx/EA (8:1) to (6:1) allows to remove mayor impurities before next step. The partially purified mixture of xylosides from previous step was heated under reflux for 15 h with 1M H_2SO_4 (90 ml), AcOH (90 ml) and 1,4-dioxane (80 ml). Mixture was

cooled to rt, hexane (40 ml) and water (200 ml) were added with intense stirring. The precipitate was collected by filtration, washed with hexane (2 x 50 ml) and dried under *vacuo*. Recrystallization from methanol gave product as a white solid (19.48 g, 69 %), mp 137-139 °C (137-138 °C lit.), ^{1}H NMR and ^{13}C NMR spectra were compared with lit.[25]

Ethyl (4S,5R,6R)-4,5,6-tri-O-benzyl-7-hydroxyhept-2-enoate **(20a)** To solution of **21** (3.65 g, 10.46 mmol) in anhydrous toluene (10 ml), **20** (2.00 g, 4.76 mmol) was added in one portion and mixture was heated to 95 °C for 8 h (reaction was monitored by TLC $CHCl_3$/Acetone 20:1). The reaction mixture was concentrated under reduced pressure and pass through thin pad of silica to remove part of triphenylphosphine oxide (product was eluted with ca. 200 ml Et_2O). After concentration under reduced pressure crude product was purified by chromatography $CHCl_3$/Acetone (1:0) to (93:7). Product as a mixture of diastereoisomers (*E*/*Z*, 1:0.25) was obtained as a colorless oil (1.52 g, 65%). *E*-**20a**: $[\alpha]_D^{26}$= -5.2 (c 1.0, CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 15H), 6.96 (dd, *J* = 15.8, 5.9 Hz, 1H), 6.07 (dd, *J* = 15.8, 1.4 Hz, 1H), 4.72 – 4.67 (m, 2H), 4.65 – 4.56 (m, 3H), 4.40 (d, *J* = 11.7 Hz, 1H), 4.28 – 4.24 (m, 1H), 4.24 – 4.18 (m, 2H), 3.75 – 3.64 (m, 2H), 3.62 (dd, *J* = 10.1, 4.5 Hz, 1H), 3.54 (dt, *J* = 10.0, 4.8 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 165.9, 144.6, 138.1, 137.7, 137.3, 128.5, 128.5, 128.4, 128.0, 127.9, 127.8, 123.3, 80.7, 79.3, 78.2, 74.7, 72.9, 71.8, 61.3, 60.5, 14.2; **HRMS** (ESI): calcd. for $C_{30}H_{34}O_6Na$ $[M+Na]^+$ 513.2248, found 513.2238. *Z*-**20a**: $[\alpha]_D^{24}$= +58.5 (c 0.65, CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.39 – 7.24 (m, 15H), 6.37 (dd, J = 11.7, 8.2 Hz, 1H), 5.80 (dd, J = 11.7, 1.3 Hz, 1H), 5.17 (d, J = 11.6 Hz, 1H), 4.76 (d, J = 11.4 Hz, 2H), 4.65 – 4.57 (m, 3H), 4.35 (d, J = 11.8 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.85 – 3.80 (m, 2H), 3.69 – 3.64 (m, 1H), 3.50 – 3.45 (m, 1H), 1.25 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, CDCl3) δ 165.8, 148.9, 138.5, 138.1, 137.5, 128.5, 128.4, 128.2, 127.9, 127.9, 127.7, 127.6, 81.3, 80.3, 75.1, 73.8, 73.2, 71.5, 61.6, 60.4, 14.2; **HRMS** (ESI): calcd. for $C_{30}H_{34}O_6Na$ $[M+Na]^+$ 513.2248, found 513.2248.

Ethyl (4S,5R,6R)-4,5,6-tri-O-benzyl-7-oxohept-2-enoate **(17)** A solution of oxalyl chloride (0.629 ml, 7.34 mmol) in anhydrous methylene chloride (30 ml) was cooled to -78 °C, after that DMSO (1.042 ml, 14.68 mmol) was dropwise added and stirred for 30 min. The **20a** (1.20 g, 2.45 mmol) was dissolved in dry CH_2Cl_2 (15 ml) and slowly added to oxidative mixture and kept in -78 °C for 30 min. The triethylamine (3.094 ml, 22.01 mmol) was added, and continued stirring for next 30 min, after that reaction mixture was allowed slowly warm to 0 °C. The reaction was quenched with addition of sat. NH_4Cl (20 ml), followed by addition of water (20 ml). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 ml), and combined organic layers were washed with water (2 x 20 ml) and brine (20 ml). The organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure (below 35 °C). Crude product was purified by flash chromatography Hx/EA (1:0) to (85:15) to give the title compound as a mix-

ture of diastereoisomers (*E*/*Z* 1:0.1) as colorless oil (1.080 g, 90 %); *E*-**17:** $[\alpha]_D^{26}$= -5.4 (c 1.0, CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.65 (d, *J* = 0.5 Hz, 1H), 7.38 – 7.27 (m, 13H), 7.22 (dd, *J* = 7.4, 1.8 Hz, 2H), 6.88 (dd, *J* = 15.8, 6.2 Hz, 1H), 6.01 (dd, *J* = 15.8, 1.3 Hz, 1H), 4.72 (d, *J* = 11.8 Hz, 1H), 4.62 (d, *J* = 11.8 Hz, 1H), 4.57 (d, *J* = 11.8 Hz, 1H), 4.50 (d, *J* = 11.7 Hz, 2H), 4.39 (d, *J* = 11.4 Hz, 1H), 4.28 (ddd, *J* = 6.0, 4.6, 1.3 Hz, 1H), 4.23 – 4.17 (m, 2H), 3.88 (dd, *J* = 4.4, 0.4 Hz, 1H), 3.82 (t, *J* = 4.5 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 201.2, 165.8, 144.2, 137.1, 137.1, 136.9, 128.5, 128.4, 128.4, 128.3, 128.2, 128.2, 128.1, 127.9, 123.6, 81.7, 80.7, 77.4, 74.3, 73.3, 72.0, 60.5, 14.2. **HRMS** (ESI): calcd. for $C_{30}H_{32}O_6Na$ $[M+Na]^+$ 511.2091, found 511.2072. *Z*-**17:** $[\alpha]_D^{24}$= +27.1 (c 0.85, CH_2Cl_2); **^{1}H NMR** (400 MHz, CDCl3) δ 9.74 (d, J = 0.7 Hz, 1H), 7.42 – 7.21 (m, 15H), 6.35 (dd, J = 11.8, 8.3 Hz, 1H), 5.84 (dd, J = 11.8, 1.3 Hz, 1H), 5.37 (ddd, J = 8.3, 3.0, 1.3 Hz, 1H), 4.77 (d, J = 12.0 Hz, 1H), 4.66 (d, J = 12.0 Hz, 1H), 4.64 – 4.55 (m, 2H), 4.51 – 4.43 (m, 2H), 4.14 (q, J = 7.1 Hz, 2H), 4.05 (dd, J = 5.6, 3.0 Hz, 1H), 3.98 (dd, J = 5.6, 0.7 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 200.3, 165.5, 147.5, 137.4, 137.3, 128.4, 128.4, 128.3, 128.2, 128.0, 128.0, 127.9, 127.7, 122.2, 81.4, 81.1, 74.1, 73.7, 72.9, 72.0, 60.3, 14.1; **HRMS** (ESI): calcd. for $C_{30}H_{32}O_6Na$ $[M+Na]^+$ 511.2091, found 511.2090.

Ethyl (3S,4R,5R,6S)-3,4,5-tri-O-benzyl-6-hydroxycyclohex-1-enecarboxylate **(*anti*-18)** *and Ethyl (3S,4R,5R,6R)-3,4,5-tri-O-benzyl-6-hydroxycyclohex-1-enecarboxylate* **(*syn*-18)** A suspension of elemental selenium (0.116 g, 1.47 mmol) in anhydrous THF (20 ml) was cooled in ice bath and *n*-BuLi (1.6 M in hexanes, 0.918 ml, 1.47 mmol) was added dropwise (a clear solution was produced) and the mixture was stirred 15 min in 0 °C. After that reaction mixture was cooled to -20 °C, solution of substrate **17** (0.60 g, 1.23 mmol in 3 ml of anhydrous THF) was added dropwise and stirring was continued through the next 6 hours. After that time, reaction was quenched by addition of aqueous, saturated solution of NH_4Cl (0.500 ml) following by addition of hydrogen peroxide solution (30 % v/v, 0.633 ml, 6.15 mmol) and pyridine (0.495 ml, 6.15 mmol). Reaction mixture was allowed to slowly back to rt and after that was heated to 50 °C for 1 hour (reaction mixture became almost colorless). The solvent was evaporated under reduced pressure and resign of pyridine was co-evaporated with toluene (2 x 30 ml). Crude products (mixture of diastereoisomers *anti*/*syn* 74:26) were purified by column chromatography Hx/EA (6:1) to (5:1). Pure *syn*-***18*** (0.101 g, 17%) and *anti*-**18** (0.289 g, 48%) diastereoisomers were obtained as a colorless syrups. *Syn*-**18:** $[\alpha]_D^{26}$= +3.4 (c 1.0, CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 15H), 6.92 (d, J = 2.4 Hz, 1H), 4.96 (d, J = 10.9 Hz, 1H), 4.85 (d, J = 10.9 Hz, 1H), 4.82 (d, J = 11.6 Hz, 1H), 4.79 (d, J = 11.6 Hz, 1H), 4.76 (d, J = 3.8 Hz, 1H), 4.74 (s, 2H), 4.29 – 4.22 (m, 2H), 4.19 (dd, J = 7.8, 2.4 Hz, 1H), 4.12 (dd, J = 10.3, 7.8 Hz, 1H), 3.52 (dd, J = 10.3, 3.8 Hz, 1H), 2.75 (s, 1H), 1.31 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 165.5, 140.1, 138.6, 137.9, 137.8, 130.6, 128.5, 128.4,

128.3, 128.0, 127.9, 127.8, 127.6, (2C)79.1, 78.9, 75.4, 72.8, 72.4, 64.4, 61.2, 14.2; **HRMS** (ESI): calcd. for $C_{30}H_{32}O_6Na$ $[M+Na]^+$ 511.2091, found 511.2086. *Anti*-**18:** $[\alpha]_D^{26}$= +23.5 (c 1.0, CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.39 – 7.25 (m, 15H), 6.78 (dd, J = 2.1, 1.2 Hz, 1H), 4.92 (d, J = 11.2 Hz, 1H), 4.89 (d, J = 11.0 Hz, 1H), 4.86 (d, J = 11.2 Hz, 1H), 4.79 (d, J = 11.0 Hz, 1H), 4.76 – 4.70 (m, 2H), 4.69 – 4.65 (m, J = 5.3 Hz, 1H), 4.28 – 4.25 (m, 1H), 4.24 (q, J = 7.1 Hz, 2H), 3.74 – 3.68 (m, 2H), 3.51 (d, J = 1.6 Hz, 1H), 1.30 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 166.0, 138.6, 138.3, 137.8, 131.3, 128.5, 128.4, 128.3, 128.0, 127.9, 127.9, 127.7, 127.6, 82.9, 81.7, 78.4, 75.4, 75.3, 73.1, 71.9, 61.3, 14.2. **HRMS** (ESI): calcd. for $C_{30}H_{32}O_6Na$ $[M+Na]^+$ 511.2091, found 511.2096.

(3S,4R,5R,6S)-3,4,5-tri-O-benzyl-6-hydroxy-1-hydroxymethyl-cyclohexene **(*anti-18a*)** A solution of compound *anti-**18*** (0.250 g, 0.51 mmol) in anhydrous methylene chloride (5 ml) was cooled to -10 °C and solution of DIBAL-H (1 M in hexane, 1.790 ml, 1.79 mmol) was added dropwise. When the addition was complete, the mixture was stirred at -10 °C for 3 h. After that time, H_2O (0.200 ml) was added to quench the reaction, and mixture was stirred at -10 °C for 30 min. Evaporation of the solvent under reduced pressure gave a crude solid residue. Then, methanol (10 ml) and celite (~1 g) were added and the mixture was vigorously stirred at room temperature for 30 min and then filtered by suction through thin pad of celite. Crude product was eluted with methanol (20-30 ml, TLC-check) and filtrate was concentrated under vacuo to give oily residue. Crude product was purified by column chromatography Hx/EA (2:1) to (1:1). Pure *anti-**18a*** was obtained as a colorless syrup (0.139 g, 61%). $[\alpha]_D^{24}$= +77.1 (c 0.8, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 15H), 5.69 (s, 1H), 5.00 (d, J = 11.5 Hz, 1H), 4.88 (s, 2H), 4.72 – 4.66 (m, 3H), 4.38 (d, J = 7.7 Hz, 1H), 4.27 – 4.09 (m, 3H), 3.75 (dd, J = 10.1, 7.4 Hz, 1H), 3.59 (dd, J = 10.1, 7.8 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.4, 138.3, 138.2, 138.1, 128.6, 128.4, 128.4, 127.9, 127.9, 127.8, 127.8, 127.7, 123.7, 83.6, 82.9, 79.7, 75.2, 75.1, 73.0, 72.3, 64.2; **HRMS** (ESI): calcd. for $C_{28}H_{30}O_5Na$ $[M+Na]^+$ 469.1985, found 469.1985.

(3S,4R,5R,6S)-3,4,5,6-penta-O-benzyl-1-O-benzylmethyl-cyclohexene **(22)** To stirred suspension of NaH (0.035 g, 0.87 mmol, 60% in mineral oil) in anhydrous DMF (3 ml) was added a solution of *anti*-**18a** (0.130 g, 0.29 mmol) and BnBr (0.104 ml, 0.87 mmol) at 0 °C under argon. After 30 min stirring, ice bath was removed and stirring was continued overnight in room temperature. The reaction mixture was carefully quenched with a cold, 10% aqueous solution of NH_4Cl (3 ml). The aqueous layer was extracted with ethyl acetate (3 x 5 ml). The organic layer was washed with H_2O (7 ml) and brine (7 ml), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography Hx/EA (9:1) to (8:1). Pure **22** was obtained as an amorphous white solid (0.174 g, 95%). $[\alpha]_D^{24}$= +59.2 (c 0.36, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.26 (m, 25H), 5.82 (s, 1H), 5.02 (d, J = 10.9 Hz, 1H), 4.94 (s, 2H), 4.89 – 4.81 (m, 2H), 4.73 (d, J = 9.2 Hz, 3H), 4.58 – 4.47 (m,

2H), 4.34 (d, J = 7.0 Hz, 1H), 4.29 – 4.21 (m, 2H), 3.96 (d, J = 12.3 Hz, 1H), 3.90 – 3.77 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.6, 138.6, 138.4, 138.3, 138.1, 136.4, 128.4, 128.4, 128.3, 128.3, 127.9, 127.9, 127.8, 127.8, 127.6, 127.6, 127.60, 125.17, 84.4, 83.7, 80.0, 79.8, 75.5, 75.5, 74.9, 72.4, 72.2, 69.8; **HRMS** (ESI): calcd. for $C_{42}H_{42}O_5Na$ $[M+Na]^+$ 649.2924, found 649.2924.

Benzyl ((3S,4R,5R,6S)-4,5,6-tri-O-benzyl-3-((benzyloxy)methyl)cyclohex-2-en-1-yl)carbamate (**19**) To stirred solution of **22** (0.170 g, 0.27 mmol) in anhydrous toluene (1.8 ml) was added Na_2CO_3 (0.316 g, 2.98 mmol) and chlorosulfonyl isocyanate (0.189 ml, 2.17 mmol) at 0 °C under argon. The reaction mixture was stirred 15 h at 0 °C and quenched with carefully addition H_2O (2 ml). The aqueous layer was extracted with ethyl acetate (3 x 4 ml). The organic layer was added to solution of aqueous 25% Na_2SO_3 (12 ml). The reaction mixture was stirred for 24 h at room temperature. The organic layer was washed with H_2O (~6 ml) and brine (~6 ml), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The solid residue was purified by column chromatography DCM/Acetone (1:0) to (99:1) to afford **19** (0.135 g, 74%) as a white solid, mp. 117-118 °C (116-119 °C for enantiomer lit.).[22] $[\alpha]_D^{24}$= +83.2 (c 0.64, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 7.19 (m, 25H), 5.68 (s, 1H), 5.19 – 5.06 (m, 2H), 4.88 – 4.64 (m, 7H), 4.54 – 4.39 (m, 3H), 4.24 (d, J = 8.6 Hz, 2H), 3.95 – 3.86 (m, 2H), 3.61 – 3.52 (t, J = 7.8 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.9, 138.4, 138.2, 138.2, 136.6, 136.4, 128.6, 128.5, 128.5, 128.3, 128.2, 128.0, 128.0, 127.9, 127.9, 127.8, 127.7, 126.1, 82.3, 79.7, 77.9, 74.7, 74.3, 74.2, 72.6, 70.4, 66.8, 52.1; **HRMS** (ESI): calcd. for $C_{43}H_{43}NO_6Na$ $[M+Na]^+$ 692.2983, found 692.2983. ^{1}H NMR and ^{13}C NMR spectra were compared with enantiomeric form published in lit.[22]

β-(+)-valienamine **(16)** To stirred solution of **19** (0.050 g, 0.07 mmol) in anhydrous methylene chloride (1.5 ml) was added BCl_3 (7 ml, 7 mmol, 1M in DCM) at -78 °C. The reaction mixture was stirred for 24 h in -78 °C and after that time quenched with methanol (1.5 ml) was added and kept in -78 °C for next 1 h. The resulting mixture was warmed to room temperature and methylene chloride was distilled. The resulting mixture of hydrogen chloride in methanol was refluxed for 3 h and then evaporated under reduced pressure. The residue was purified by ion-exchange resin DOWEX 50WX8-100 using 0.5 M NH_4OH as eluent to afford free amine **16** (0.009 g, 69%) as a nearly colorless syrup.[1]H NMR and ^{13}C NMR spectra were compared with lit.[26] $[\alpha]_D^{24}$= +83.5 (c 0.45, D_2O); **^{1}H NMR** (600 MHz, D_2O) δ 5.48 – 5.45 (m, 1H), 4.13 – 4.08 (m, 2H), 3.99 (d, J = 14.1 Hz, 1H), 3.46 (dd, J = 10.4, 8.1 Hz, 1H), 3.41 (d, J = 8.8 Hz, 1H), 3.31 (dd, J = 10.2, 8.9 Hz, 1H); **^{13}C NMR** (151 MHz, D_2O) δ 139.0, 123.4, 75.9, 74.5, 71.9, 61.0, 53.0; **HRMS** (ESI): calcd. for $C_7H_{13}NO_4Na$ $[M+Na]^+$ 198.0736, found 198.0738, calcd. for $C_{14}H_{26}N_2O_8Na$ $[2M+Na]^+$ 373.1581, found 373.1587.

β-(+)-valienamine hydrochloride **(16a) 16** (0.009 g, 0,05 mmol) was dissolved in water (1 ml). After addition 3 drops of 1M HCl, water was evaporated under high vacuum. Received syrup was dissolved in D_2O and ^1H and ^{13}C NMR spectra were collected. **^{1}H NMR** (300 MHz, D_2O) δ 5.61 – 5.56 (m, 1H), 4.22 – 4.11 (m, 3H), 3.87 (d, J = 7.4 Hz, 1H), 3.67 – 3.52 (m, 2H); **^{13}C NMR** (75 MHz, D_2O) δ 143.8, 117.2, 76.0, 72.2, 71.9, 61.3, 54.1.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. ^1H and ^{13}C NMR spectra for the synthesized compounds (PDF)

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NOTES

There are no conflicts to declare.

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REFERENCES

(1) Tietze, L. F. Domino Reactions in Organic Synthesis. *Chem. Rev.* **1996**, *96*, 115–136.

(2) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. Cascade Reactions in Total Synthesis. *Angew. Chemie - Int. Ed.* **2006**, *45*, 7134–7186.

(3) Kamimura, A.; Mitsudera, H.; Asano, S.; Kidera, S.; Kakehi, A. Stereoselective Thio-Michael/Aldol Tandem Reaction to α,β-Unsaturated Esters. *J. Org. Chem.* **1999**, *64*, 6353–6360.

(4) Ono, M.; Nishimura, K.; Nagaoka, Y.; Tomioka, K. The Conjugate Addition-Aldol Tandem Reaction of α,β-Unsaturated Esters Catalyzed By Lithium Benzenethiolate. *Tetrahedron Lett.* **1999**, *40*, 1509–1512.

(5) Nishimura, K.; Tsubouchi, H.; Ono, M.; Hayama, T.; Nagaoka, Y.; Tomioka, K. Asymmetric Michael–aldol Tandem Cyclization of ω-Oxo-α,β-Unsaturated Esters with 10-Mercaptoisoborneol Methyl Ether. **2003**, *44*, 2323–2326.

(6) Keppler, A. F.; Gariani, R. A.; Lopes, D. G.; Comasseto, J. V. Lithium Butylchalcogenolate Induced Michael-Aldol Tandem Sequence: Easy and Rapid Access to Highly Functionalized Organochalcogenides and Unsaturated Compounds. *Tetrahedron Lett.* **2009**, *50*, 2181–2184.

(7) Wang, X. F.; Hua, Q. L.; Cheng, Y.; An, X. L.; Yang, Q. Q.; Chen, J. R.; Xiao, W. J. Organocatalytic Asymmetric Sulfa-Michael/Michael Addition Reactions: A Strategy for the Synthesis of Highly Substituted Chromans with a Quaternary Stereocenter**. *Angew. Chemie - Int. Ed.* **2010**, *49*, 8379–8383.

(8) Selig, P. S.; Miller, S. J. Ortho-Acidic Aromatic Thiols as Efficient Catalysts of Intramolecular Morita-Baylis-Hillman and Rauhut-Currier Reactions. *Tetrahedron Lett.* **2011**, *52*, 2148–2151.

(9) Sousa, B. A.; Dos Santos, A. A. A Facile, Versatile, and Mild Morita-Baylis-Hillman-Type Reaction for the Modular One-Pot Synthesis of Highly Functionalized MBH Adducts. *European J. Org. Chem.* **2012**, 3431–3436.

(10) Tarsis, E.; Gromova, A.; Lim, D.; Zhou, G.; Coltart, D. M. Overcoming the Limitations of the Morita-Baylis-Hillman Reaction: A Rapid and General Synthesis of α-Alkenyl-β′-Hydroxy Thioesters. *Org. Lett.* **2008**, *10*, 4819–4822.

(11) Roth, F.; Gygax, P.; Frater, G. An Intramolecular Bayliss-Hillman Reaction. *Tetrahedron Lett.* **1992**, *33*, 1045–1048.

(12) Drewes, S. E.; Emslie, N. D. DABCO-Catalysed Dimerisation of Some α,β-Unsaturated Esters. *Synth. Commun.* **1990**, *20*, 1915–1921.

(13) Black, G. P.; Dinon, F.; Fratucello, S.; Murphy, P. J.; Nielsen, M.; Williams, H. L.; Walshe, N. D. A. An Intramolecular Baylis-Hillman Reaction Catalysed by Secondary Amines. *Tetrahedron*

Lett. **1997**, *38*, 8561–8564.

(14) Dinon, F.; Richards, E.; Murphy, P. J.; Hibbs, D. E.; Hursthouse, M. B.; Malik, K. M. A. Tandem Michael/Intramolecular Aldol Reactions Mediated by Secondary Amines, Thiols and Phosphines. *Tetrahedron Lett.* **1999**, *40*, 3279–3282.

(15) Richards, E. L.; Murphy, P. J.; Dinon, F.; Fratucello, S.; Brown, P. M.; Gelbrich, T.; Hursthouse, M. B. Assessing the Scope of the Tandem Michael/Intramolecular Aldol Reaction Mediated by Secondary Amines, Thiols and Phosphines. *Tetrahedron* **2001**, *57*, 7771–7784.

(16) Tan, Y. X.; Santhanakrishnan, S.; Yang, H. Y.; Chai, C. L. L.; Kwok, E.; Tam, W. Synthesis of Neplanocin A and Its 3′-Epimer via an Intramolecular Baylis−Hillman Reaction. *J. Org. Chem.* **2014**, *79*, 8059–8066.

(17) Ono, M.; Nishimura, K.; Nagaoka, Y.; Tomioka, K. Efficient Cyclization of ω-Oxo-α,β-Unsaturated Esters Using Lithium Thiolate-Initiated Michael-Aldol Tandem Reaction. *Tetrahedron Lett.* **1999**, *40*, 6979–6982.

(18) Krafft, M. E.; Song, E. H.; Davoile, R. J. Intramolecular Morita-Baylis-Hillman Adducts via Sequential MBH and Ring-Closing-Metathesis Reactions. *Tetrahedron Lett.* **2005**, *46*, 6359–6362.

(19) Ono, M.; Nishimura, K.; Tsubouchi, H.; Nagaoka, Y.; Tomioka, K. Total Synthesis of (-)-Neplanocin A by Using Lithium Thiolate-Initiated Michael-Aldol Tandem Cyclization Reaction. *J. Org. Chem.* **2001**, *66*, 8199–8203.

(20) Lin, H.; Sugimoto, Y.; Ohsaki, Y.; Ninomiya, H.; Oka, A.; Taniguchi, M.; Ida, H.; Eto, Y.; Ogawa, S.; Matsuzaki, Y.; Sawa, M.; Inoue, T.; Higaki, K.; Nanba, E.; Ohno, K.; Suzuki, Y. N-Octyl-β-Valienamine up-Regulates Activity of F213I Mutant β-Glucosidase in Cultured Cells: A Potential Chemical Chaperone Therapy for Gaucher Disease. *Biochim. Biophys. Acta - Mol. Basis Dis.* **2004**, *1689*, 219–228.

(21) Nadein, O. N.; Kornienko, A. An Approach to Pancratistatins via Ring-Closing Metathesis: Efficient Synthesis of Novel 1-Aryl-1-Deoxyconduritols F. *Org. Lett.* **2004**, *6*, 831–834.

(22) Li, Q. R.; Kim, S. I.; Park, S. J.; Yang, H. R.; Baek, A. R.; Kim, I. S.; Jung, Y. H. Total Synthesis of (+)-Valienamine and (-)-1-Epi-Valienamine via a Highly Diastereoselective Allylic Amination of Cyclic Polybenzyl Ether Using Chlorosulfonyl Isocyanate. *Tetrahedron* **2013**, *69*, 10384–

10390.

(23) Li, N.; Song, J.; Tu, X. F.; Liu, B.; Chen, X. H.; Gong, L. Z. Organocatalytic Asymmetric Intramolecular [3+2] Cycloaddition: A Straightforward Approach to Access Multiply Substituted Hexahydrochromeno[4,3-b] Pyrrolidine Derivatives in High Optical Purity. *Org. Biomol. Chem.* **2010**, *8*, 2016–2019.

(24) Kireev, A. S.; Nadein, O. N.; Agustin, V. J.; Bush, N. E.; Evidente, A.; Manpadi, M.; Ogasawara, M. A.; Rastogi, S. K.; Rogelj, S.; Shors, S. T.; Kornienko, A. Synthesis and Biological Evaluation of Aromatic Analogues of Conduritol F, L-Chiro-Inositol, and Dihydroconduritol F Structurally Related to the Amaryllidaceae Anticancer Constituents. *J. Org. Chem.* **2006**, *71*, 5694–5707.

(25) De Paz, M. V.; Aznar Moreno, J. A.; Galbis, J. A. Versatile Sugar Derivatives for the Synthesis of Potential Degradable Hydrophilic-Hydrophobic Polyurethanes and Polyureas. *J. Carbohydr. Chem.* **2008**, *27*, 120–140.

(26) Cui, L.; Zhu, Y.; Guan, X.; Deng, Z.; Bai, L.; Feng, Y. De Novo Biosynthesis of β-Valienamine in Engineered Streptomyces Hygroscopicus 5008. *ACS Synth. Biol.* **2016**, *5*, 15–20.