(*S*)-Garner aldehyde derived Baylis-Hillman adduct: a substrate for the synthesis of a lactone ceramide analogue via a sequential Heck reaction

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Abstract

The first, general and efficient route has been developed for the synthesis of *N*-((*E*,3*S*,4*R*)-5-benzylidene-tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-3-yl) palmitamide, a lactone ceramide analogue from (*S*)-Garner aldehyde-methyl acrylate derived Baylis-Hillman adduct with *anti* configuration. Reaction conditions have been optimized for the Heck reaction of iodobenzene on Baylis-Hillman adduct with *anti* configuration to obtain the protected aromatic ceramide analogue intermediate which subsequently on deprotection and *N*-acylation provided the lactone ceramide analogue. Further, various substituted phenyl iodides have also been employed in the Heck reaction under the optimized conditions for the synthesis of few protected aromatic ceramide analogues intermediates to the test efficacy of the developed methodology.

Keywords: Lactone ceramide analogue, Baylis-Hillman reaction, Heck reaction, (*S*)-Garner aldehyde

Introduction

The Baylis–Hillman[1] and Heck reactions[2] are important carbon-carbon bond formation reactions utilized extensively in the synthesis of natural products[3,4] and their analogues, including α-alkylidene-β-lactams, α-methylene-γ-butyrolactones, frontalin, sarkaomycin, ilmofosine nuciferol, syributins, terpenoids and alkaloids. In the Baylis–Hillman reaction[5,6] the aldehydes are important substrates and among them the chiral α-amino aldehydes[7] are of special interest as the resulting adducts generate a new stereocenter which can be fine tuned to obtain multifunctional α-methylene-β-hydroxy-γ-amino acid intermediates to be exploited in asymmetric synthesis. The Heck reaction for arylation of unsubstituted alkenes is controlled by the nature of the substrate, solvent, base, nature of catalyst and its concentration used resulting in variable conditions for obtaining the desired intermediates.[8]

Recently, the work on Pd-catalyzed chemical transformations of Baylis-Hillman adducts has been reviewed in literature.[9] In particular the intermolecular Heck type arylation of achiral Baylis-Hillman adducts has led to α-benzyl-substituted β-keto ester as the major product instead of β-aryl substituted Baylis-Hillman adducts.[10] Recently Kim *et al.*[11] have successfully optimized condition for intermolecular Heck reaction of achiral aldehyde derived Baylis-Hillman adducts to yield the β-aryl substituted intermediates as major products.

Sphingolipids, e.g. sphingosine, ceramides, sphingomylein, cerbrosides and gangliosides are important structural and functional components of plasma membrane of essentially all eukaryotic cells and are implicated in the regulation of diverse cellular and physiological processes.[12] Ceramide [*N*-acylsphingosine **1a** (Figure 1)], a long-chain aliphatic 2-amido-1,3-diol with a C(4), C(5)-*trans* double bond, is known to induce apoptotis,[13] growth arrest[14] and senescence[15] in many human cancers, besides regulating many biochemical and cellular responses to stress, such as radiation, oxidative condition, exposure to heat and chemotherapeutic agents.[16] In addition to the natural ceramides, their analogues have also been evaluated for various biological activities.[17] In particular, Wascholowski and Giannis[18] have reported sphingolactones as potent inhibitors of the neutral sphingomyelinase (*N*-SMase).

Due to the wide spectrum of biological and pharmacological significance of ceramide and its analogues considerable effort has been devoted towards developing efficient methods for their synthesis.[19,20] Few reports in literature illustrate the use of Baylis-Hillman[21] and Heck reaction[22] for the synthesis of sphingolipids and their analogues.

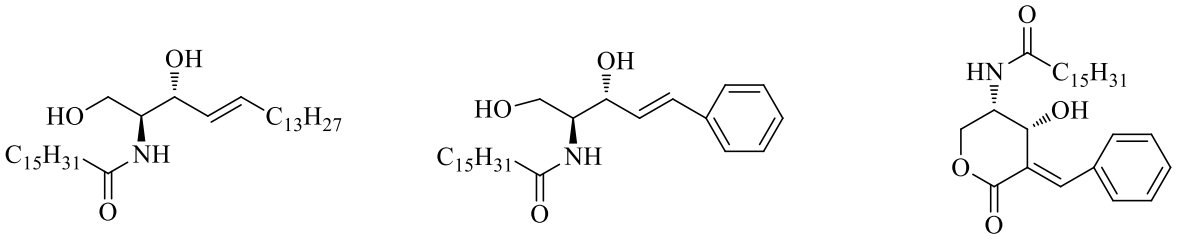
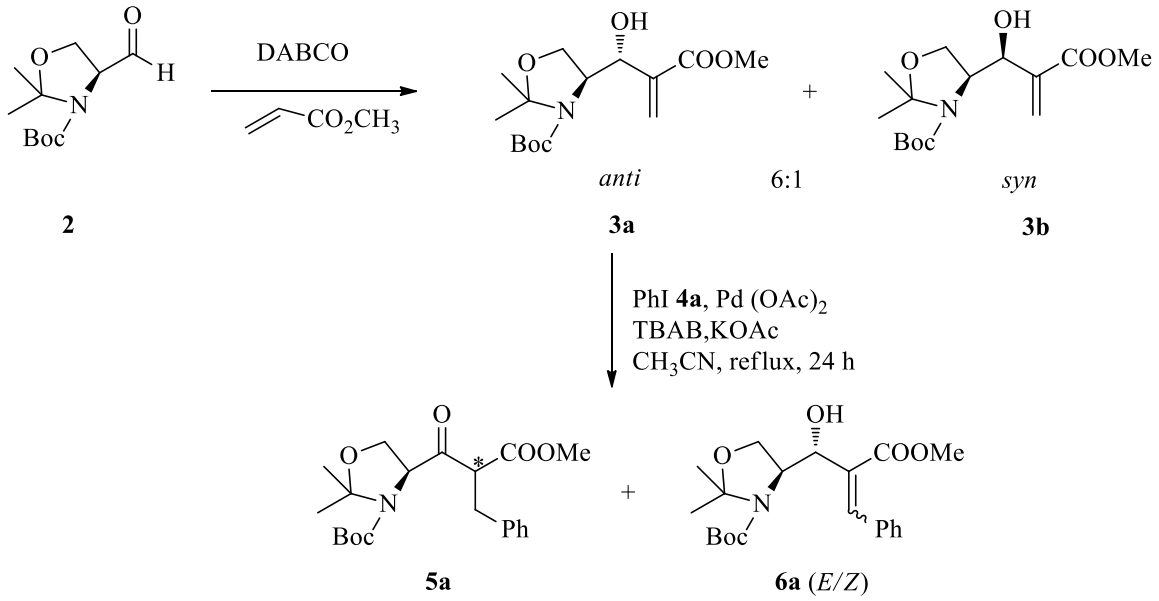


Figure 1. Ceramide and its analogues.

The configurationally stable Garner aldehyde[23,24] has received considerable attention as chiral synthon for the stereoselective synthesis of sphingolipids and their derivatives due to its inherent 2-amino-1,3-diol subunit which is the main backbone of sphingolipids. (*S*)-Garner aldehyde-methyl acrylate derived Baylis-Hillman adduct with *anti* configuration **3a** was reported by Drewes *et al.*[21] as a potential intermediate for the synthesis of sphingolipid analogue. However, no work has been reported in this direction in literature for further transformations to sphingolipids or their derivatives.

Results and Discussion

In continuation to our work[25] towards the synthesis of sphingolipid and its analogues, we have established the first, efficient and general methodology exploiting the multifunctional molecule **3a** for the synthesis of *N*-((*E*,3*S*,4*R*)-5-benzylidene-tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-3-yl) palmitamide, a lactone ceramide analogue **1c**. The key step involved was $Pd(OAc)_2$ mediated Heck reaction of iodobenzene **4a** on Baylis-Hillman adduct with *anti* configuration **3a** to obtain the protected ceramide analogue intermediate **6a**-*E* (Scheme 1).



Scheme 1. Baylis Hillman reaction of (*S*)-Garner aldehyde **2** and sequential Heck reaction with PhI **4a.**

The Baylis-Hillman reaction[7g] of (*S)*-Garner aldehyde **2** with methyl acrylate in the presence of DABCO and ultrasound sonication afforded 6:1 diastereomeric mixture of adducts **3a** and **3b** as observed by ^{1}H NMR spectral analysis of crude mixture**.** The major adduct **3a** was separated by column chromatography over silica gel in 73% yield as a colorless oil and the *anti* stereochemistry was assigned to **3a** by comparison with spectroscopic data and optical rotation value reported in literature.[21,7h] The *anti* stereochemistry of the major adduct may also be rationalized on the basis of the Felkin-Anh open-chain model.[26]

The pure adduct **3a** was utilized as a substrate for intermolecular Heck reaction. We first examined the reaction of the adduct **3a** with iodobenzene **4a** to determine the feasibility and optimum $Pd(OAc)_2$ concentration required for the complete consumption of starting adduct **3a** and its maximum conversion to the desired Heck product **6a**-*E/Z* (Table 1).

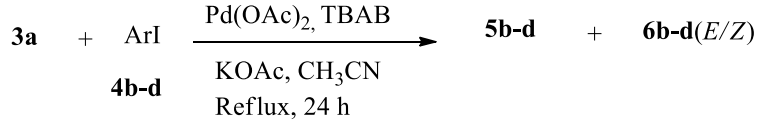
Table 1. The reaction[a] of adduct **3a** with Iodobenzene **4a** under various $Pd(OAc)_2$ concentration

S.No.	Catalyst (mol%)	Relative composition(%)[b]			
		3a	**5a**	**6a-*E***	**6a-*Z***
1	$Pd(OAc)_2$ (10)	33	30	16	13
2	$Pd(OAc)_2$ (15)	21	34	20	18
3	$Pd(OAc)_2$ (20)	-	43	27	24
4	$Pd(OAc)_2$ (25)	-	42	28	24

[a]**3a** (1.0 equiv), **4a** (2.0 equiv), TBAB (1.0 equiv), KOAc (3.0 equiv), mixture in CH_3CN was refluxed for 24 h. [b]Determined by the ^{1}HNMR spectral analysis of the crude mixture.

The reaction was screened with different concentration of $Pd(OAc)_2$ starting from 10 mol% and increasing upto 25 mol%. It was observed that in the conversion of adduct **3a** to **6a**-*E/Z*, the desired Heck product increases moderately on enhancing the $Pd(OAc)_2$ concentration upto 20 mol% and beyond which there was no significant effect of increased $Pd(OAc)_2$ concentration on the relative composition (Table 1). The best result was obtained (Table 1, entry 3) when a mixture of **3a** (1.0 equiv**), 4a** (2.0 equiv), $Pd(OAc)_2$ (20 mol%), TBAB (1.0 equiv.), KOAc (3.0 equiv) in CH_3CN was refluxed for 24 h. The adduct **3a** was consumed completely to give **5a** (43%), **6a**-*E* (27%) and **6a**-*Z* in 24% relative composition as determined by ^{1}H NMR spectral analysis of the crude reaction mixture, wherein the characteristic chemical shift of vinylic proton of **6a**-*E* was observed as a singlet at 7.79 ppm and for **6b**-*Z* isomer at 7.01 ppm, while the benzylic $-CH_2$ of α-benzyl-β-keto ester **5a** appeared at 3.17 ppm as a multiplet. Purification by column chromatography over silica gel, eluting with hexane:EtOAc/89:11, yielded β-keto ester **5a** (36%) as a white solid. Further elution with hexane:EtOAc/86:14 afforded **6a**-*E* (21%) and **6b**-*Z* (18%) as colorless oils.

Under these optimized conditions the Heck reaction was carried out with adduct **3a** and various aryl iodides **4b-d** to obtain the desired Heck products **6b-d** and corresponding β-keto esters **5b-d** as shown in Scheme 2 and results are summarized in Table 2.



4b: Ar = 4-MeC_6H_4
4c: Ar = 4-$MeOC_6H_4$
4d: Ar = 4-$MeCOC_6H_4$

Scheme 2. Heck reaction of adduct **3a** with selected aryl halides **4b-d.**

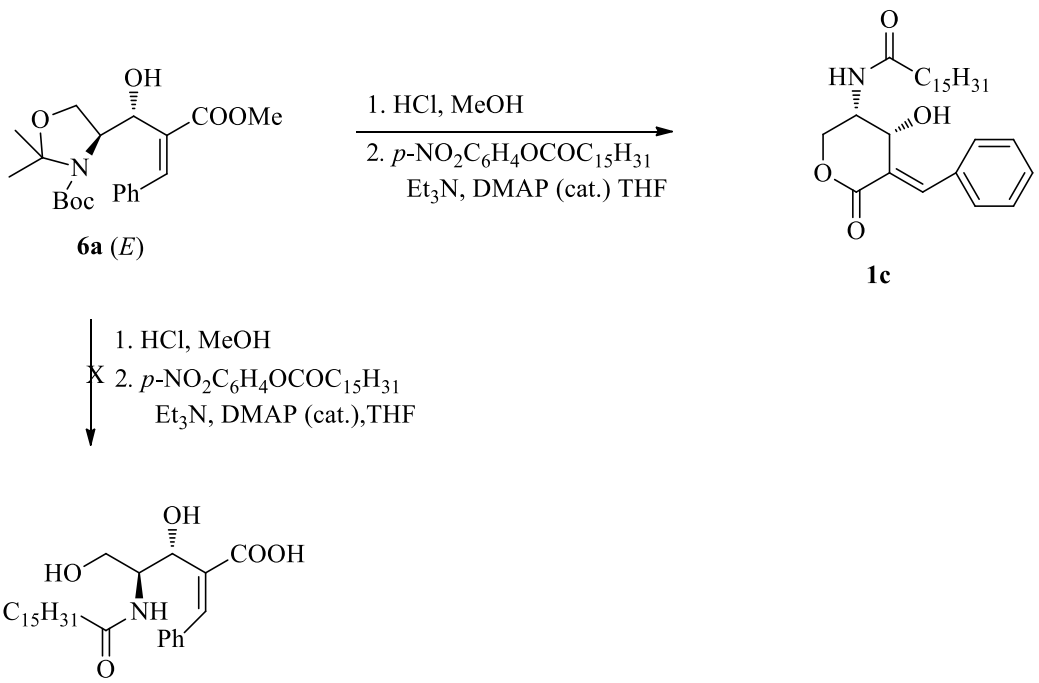
Table 2. Heck reaction of adduct **3a** with selected aryl iodides **4b-d**[a]

S.No.	Substrates	Relative composition(%)[b]	Yield (%)[c,d]
1	**3a** + **4b**	**3a** (0)/**5b** (49)/**6b**-*E* (24)/**6b**-*Z* (22)	**5b** (41)/**6b** (37)
2	**3a** + **4c**	**3a** (0)/**5c** (48)/**6c**-*E* (25)/**6c**-*Z* (23)	**5c** (43)/**6c** (41)
3	**3a** + **4d**	**3a** (40)/**5d** (30)/ **6d**-*E* (14)/**6d**-*Z* (12)	**3a** (36)/**5d** (26)/**6d** (21)

[a] Conditions: compound **3a** (1.0 equiv), aryl Iodides **4a-d** (2.0 equiv), $Pd(OAc)_2$ (20 mol%), TBAB(1.0 equiv), KOAc (3.0 equiv), CH_3CN, reflux, 24 h. [b] Determined by the ^1H NMR spectral analysis of the crude mixture. [c] Isolated yield. [d] E/Z mixture not separated.

It has been observed that the adduct **3a** was completely consumed except when *p*-iodoacetophenone **4d** (Table 2, entry 3) was used as the aryl halide, under the optimized conditions. The relative composition of products was again determined by ^1H NMR spectral analysis of respective crude mixtures. It has been observed from ^1H NMR spectra that the isomer *E* and *Z* for compounds **6a-d** are obtained in approximately 1:1 ratio as explained by Kumareswaran and Vankar.[10a] The *β*-keto esters **5b-d** were isolated in 26-43% yield and the desired Heck products were isolated in 21-41% yield. The *E* and *Z* isomers of **6b-d** were not separated. All compounds were characterized by NMR, IR, and mass spectroscopy.

The *N*-Boc and oxazolidine groups of pure **6a**-*E* were removed under acidic condition using 1M HCl/MeOH followed by *N*-acylation[27] using *p*-nitrophenyl palmitate, Et_3N, DMAP (cat.) in dry THF to afford crude lactone ceramide analogue **1c** as the major product instead of the expected open chain ceramide analogue**.** The lactonisation may have occurred due to the intramolecular condensation of primary hydroxyl group of the sphingoid backbone with –COOH group generated during the deprotection step of intermediate **6a**-*E* or by the direct attack of the primary hydroxyl group to the ester group, before its hydrolysis, with subsequent elimination of methanol. The mixture was purified by column chromatography over silica gel to obtain the product **1c** in 54% yield (Scheme 3). The title compound **1c** was characterized by NMR, IR and mass spectroscopy. The characteristic peaks for **1c** were observed for the carbonyl of lactone at 1732 cm^{-1} in the IR spectrum and at δ 4.30-4.31 (d, J = 6.2 Hz, 1H, HCHOH) and 4.40-4.45 (m, 2H, HCHOH, -CH-N) in the ^1H NMR spectrum, which showed downfield shift of these protons as compared to that expected in the corresponding acyclic ceramide analogue. In the ^{13}C NMR spectrum, the peaks at δ 45.6 and 164.9 were observed for –C–N and for lactone group respectively, which further confirmed the formation of lactone ceramide analogue **1c.**



Scheme 3. Synthesis of lactone ceramide analogue **1c.**

Conclusions

In summary: we have developed a methodology for the efficient synthesis of lactone ceramide analogues from chiral precursors, accessible via Heck reaction on adduct **3a**. To the best of our knowledge this is the first approach for the Heck reaction on chiral aldehyde derived Baylis-Hillman adduct and its use as a chiral synthon for synthesis of *N*-((*E*,3*S*,4*R*)-5-benzylidene-tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-3-yl)palmitamide, a lactone ceramide analogue **1c**. This general methodology could be utilized for synthesis of lactone ceramide substituted aromatic analogues which could be evaluated for biological activities.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance II 400 MHz spectrometer at 400 and 100 MHz respectively using TMS as internal standard in CDCl3. IR spectra were recorded using a Perkin-Elmer model RX 1 FT-IR spectrometer. Mass spectra were recorded on Waters Micromass q-Tof Micro spectrometer. Elemental analyses were performed using automatic Perkin Elmer 2400 CHN elemental analyzer. Optical rotations (in degrees) were recorded on Autopol-III polarimeter. The Baylis–Hillman reaction was sonicated in an ultrasonic cleaner (40 ±5 kHz). Column chromatography was conducted on Silica gel 100-200 mesh (E-

Merck) using ethyl acetate and hexane as eluant. All reactions were carried out using oven dried glassware. All solvents were dried as reported in literature prior to use.

(*S*)-*tert*-Butyl 4-((*R*)-2-(methoxycarbonyl)-1-hydroxyallyl)-2,2-dimethyloxazolidine-3-carboxylate (3a). A mixture of Garner aldehyde **2** (1.2 g, 5.24 mmol), methyl acrylate (0.677 g, 7.86 mmol), and DABCO (0.588 g, 5.24 mmol) was sonicated for 40 h till there was no further change in reaction mixture composition as monitored by TLC. The ultrasound bath temperature was constantly monitored and maintained at 30-40 ºC during the reaction, through ice addition. After 40 h, the mixture was evaporated under reduced pressure in order to remove excess of methyl acrylate. The residue was diluted with dichloromethane (30 ml), washed successively with cold 5 % aqueous HCl (2 X 15 ml), saturated $NaHCO_3$ (20 ml), brine (20 ml) and dried over Na_2SO_4. After filtration the solvent was removed under reduced pressure. The ^{1}H NMR analysis of crude mixture indicated the formation of Baylis-Hillman adducts **3a**:**3b** in 6:1 diastereomeric ratio. The residue was purified by column chromatography over silica gel, eluting with hexane:EtOAc (85:15) to afford pure major adduct **3a** (1.20 g, 73%) as a colorless oil. $[\alpha]_D^{25}$ -1.8 (*c* 1, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}) 3464, 1715, 1696, 1389, 1261, 1165, 1096; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45-1.55 (m, 15H), 3.79 (s, 3H), 3.92 (br s, 1H), 4.14-4.25 (m, 2H), 4.48-4.62 (m, 2H), 5.79 (br s, 1H), 6.25 (br s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.2, 27.0, 28.3, 51.8, 61.7, 65.0, 74.3, 80.6, 94.1, 126.9, 140.2, 153.8, 166.9 ppm. The spectroscopic data of the major adduct **3a** were consistent with those reported in literature.[20]

General procedure for the Heck coupling of (*S*)-Garner aldehyde-methyl acrylate derived Baylis-Hillman adducts 3a with various aryl halides (4a-d)

A stirred solution of (*S*)-Garner aldehyde-methyl acrylate derived Baylis-Hillman adduct **3a** (1.0 equiv), aryl halides **4a-d** (2.0 equiv), $Pd(OAc)_2$ (20 mol%), KOAc (3.0 equiv), TBAB (1.0 equiv) in dry CH_3CN (8-10 ml) was heated to reflux for 24 h under nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature followed by solvent removal under reduced pressure. The residue was diluted with water and extracted with diethyl ether (5 x 10 ml). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the crude product was passed through a small pad of celite. The solvent was evaporated under reduced pressure and ^{1}H NMR spectra was recorded to determine conversion ratio of the products. The column chromatographic separation over silica gel, eluting with hexane/EtOAc (89:11-72:28) yielded the *β*-keto esters **5a-d** in 26-43% as a white solids and desired Heck products **6a-d** *(E/Z*) in 21-41% as colorless oils.

Compound (5a) (diastereomeric mixture). White solid; 36 % yield; mp 120-122 ºC; $[\alpha]_D^{25}$ + 2.6 (*c* 1, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}) 3012, 2931, 1741, 1687, 1617, 1365, 1262, 1160, 1081; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40-1.62 (m, 15H), 3.16-3.18 (m, 2H), 3.66 (s, 3H), 3.72-3.76 (m, 1H), 3.91-4.07 (m, 2H), 4.56-4.63 (m, 1H), 7.16-7.26 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.7, 25.2, 28.2, 29.7, 34.2, 52.5, 52.6, 57.1, 57.3, 64.3, 64.5, 65.0, 65.2, 80.7, 81.1, 94.7, 95.4, 126.7, 126.9, 128.5, 128.6, 128.9, 137.9, 138.2, 151.4, 152.4, 168.5, 168.7, 200.0,

201.7 ppm. MS, *m/z* (%) = 392.1 (M + 1, 8)$^+$, 414.1 (M + Na, 100)$^+$; Anal. Calcd. for $C_{21}H_{29}NO_6$: C, 64.43; H, 7.46; N, 3.57%. Found: C, 64.36; H, 7.40; N, 3.52%.

(*S*)-*tert*-Butyl 4-((*R*,*E*)-2-(methoxycarbonyl)-1-hydroxy-3-phenylallyl)-2,2-dimethyloxazolidine-3-carboxylate (**6a-*E***). Colorless oil; 21% yield; $[\alpha]_D^{25}$ -7.5 (*c* 1, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}) 3460, 1712, 1672, 1389, 1261, 1165, 1096; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44-1.60 (m, 15H), 3.79-3.87 (m, 1H), 3.88 (s, 3H), 4.07 (br s, 1H), 4.17 (d, *J* = 9.2 Hz, 1H), 4.29-4.32 (m, 1H), 4.59 (d, *J* = 9.7 Hz, 1H), 7.26-7.39 (m, 5H), 7.76 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 24.0, 26.5, 28.3, 51.0, 60.1, 65.0, 69.4, 79.9, 93.6, 128.3, 128.6, 128.8, 131.3, 134.8, 141.6, 152.8, 168.7 ppm. MS, *m/z* (%) = 414.4 (M + Na, 76)$^+$, 415.4 (M + 1 + Na, 20)$^+$, 374.4 (M - OH, 11)$^+$, 314.4 (M^+ - C_6H_5, 6)$^+$; Anal. Calcd for $C_{21}H_{29}NO_6$: C, 64.43; H, 7.46; N, 3.57%. Found: C, 64.37; H, 7.39; N, 3.54%.

(*S*)-*tert*-Butyl 4-((*R*,*Z*)-2-(methoxycarbonyl)-1-hydroxy-3-phenylallyl)-2,2-dimethyloxazolidine-3-carboxylate (6a-*Z*). colorless oil; 18% yield; $[\alpha]_D^{25}$ -8.1 (*c* 1, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}) 3464, 1715, 1685, 1391, 1265, 1156, 1085; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42-1.61 (m, 15H), 3.64 (s, 3H), 3.79-3.85 (m, 1H), 3.97 (br s, 1H), 4.18 (dd, *J* = 1.2, 9.5 Hz, 1H), 431-4.32 (m, 1H), 4.59 (d, *J* = 9.7 Hz, 1H), 7.05 (s, 1H), 7.24-7.37 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 25.2, 27.2, 29.2, 51.0, 61.5, 65.0, 69.1, 78.9, 92.6, 127.1, 127.9, 129.5, 132.0, 134.8, 140.6, 151.8, 168.3 ppm. MS, *m/z* (%) = 414.4 (M + Na, 78)$^+$, 374.4 (M - OH, 12)$^+$, 314.4 (M - C_6H_5, 5)$^+$; Anal. Calcd for $C_{21}H_{29}NO_6$: C, 64.43; H, 7.46; N, 3.57%. Found: C, 64.38; H, 7.39; N, 3.55%.

Compound (5b) (diastereomeric mixture). white solid; 41% yield; mp 151-153 ºC; $[\alpha]_D^{25}$ +2.9 (*c* 1.1, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}) 3032, 2935, 1745, 1625, 1695, 1610, 1384, 1254, 1168, 1067; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.43-1.62 (m, 15H), 2.29 (s, 3H), 3.13-3.18 (m, 2H), 3.66 (s, 3H), 3.71-3.79 (m, 1H), 3.89-4.10 (m, 2H), 4.56-4.63 (m, 1H), 7.04-7.07 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 23.6, 24.8, 25.7, 26.0, 28.3, 29.3, 29.7, 33.8, 52.4, 57.2, 57.4, 64.6, 64.8, 65.0, 65.2, 80.8, 81.1, 94.9, 95.4, 128.7, 129.2, 129.3, 136.4, 151.8, 168.8, 200.2 ppm. MS, *m/z* (%) = 428.5 (M + Na, 100)$^+$; Anal. Calcd for $C_{22}H_{31}NO_6$: C, 65.16; H, 7.70; N, 3.45%. Found: C, 65.10; H, 7.65; N, 3.41%.

(*S*)-*tert*-Butyl 4-((*R*)-2-(methoxycarbonyl)-1-hydroxy-3-*p*-tolylallyl)-2,2-dimethyl-oxazolidine-3-carboxylate (**6b-*E*/*Z***). colorless oil; 37 yield%; $[\alpha]_D^{25}$ -7.3 (*c* 1, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}) 3470, 2903, 1705, 1370, 1261, 1177, 1076; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.43-1.62 (m, 15H), 2.34 (s, 3H), 3.66 (s, 1.44H), 3.78-3.84 (m, 1H), 3.88 (s, 1.56 H), 3.97 (br s, 1H), 4.17 (dd, *J* = 1.6, 7.9 Hz, 1H), 428-4.32 (m, 1H), 4.62 (d, *J* = 9.7 Hz, 1H), 7.0 (s, 0.48 H), 7.10-7.25 (m, 4H), 7.72 (s, 0.52 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 23.3, 25.5, 27.2, 29.9, 50.8, 51.0, 59.0, 64.0, 68.4, 78.9, 92.5, 127.3, 127.9, 128.7, 130.8, 131.1, 137.6, 140.8, 151.8, 167.8 ppm; MS, *m/z* (%) = 428.5 (M + Na, 100)$^+$, 388.5 (M^+ – OH, 20)$^+$; Anal. Calcd for $C_{22}H_{31}N\,O_6$: C, 65.12; H, 7.70; N, 3.45%. Found: C, 65.09; H, 7.66; N, 3.42%.

Compound (5c) (diastereomeric mixture). White solid; 43% yield; mp 171-174 ºC; $[\alpha]_D^{25}$ +2.7 (*c* 1, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}) 3030, 2955, 1748, 1675, 1620, 1364, 1275, 1162, 1045; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.42-1.63 (m, 15H), 3.11-3.17 (m, 2H), 3.66 (s, 3H), 3.71-3.80

(m, 4H), 3.89-4.08 (m, 2H), 4.54-4.61 (m, 1H), 6.79-6.81 (m, 2H), 7.07-7.13 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.6, 24.7, 26.0, 28.2, 29.7, 33.1, 33.6, 52.4, 52.5, 55.2, 57.6, 57.9, 64.4, 64.6, 65.0, 65.2, 80.7, 81.1, 94.7, 95.4, 113.9, 114.0, 129.8, 130.0, 130.3, 151.2, 151.4, 158.4, 168.6, 168.9, 200.2, 201.8 ppm. MS, *m/z* (%) = 444.4 (M + Na, 100)$^+$; Anal. Calcd for $C_{22}H_{31}NO_7$: C, 62.69; H, 7.41; N, 3.32%. Found: C, 62.62; H, 7.36; N, 3.29%.

(*S*)-*tert*-Butyl 4-((*R*)-2-(methoxycarbonyl)-1-hydroxy-3-(4-methoxyphenylallyl)-2,2-dimethyloxazolidine-3-carboxylate (6c-*E*/*Z*). Viscous oil; 41% yield; $[\alpha]_D^{25}$-7.1 (*c* 1, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}) 3460, 2931, 1720, 1375, 1261, 1154, 1093; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42-1.61 (m, 15H), 3.68 (s, 1.44H), 3.80-3.84 (m, 4H), 3.88 (s, 1.56 H), 3.97 (br s, 1H), 4.18 (dd, *J* = 1.3, 9.4 Hz, 1H), 429-4.33 (m, 1H), 4.65 (d, *J* = 9.7 Hz, 1H), 6.82-6.90 (m, 2H), 6.96 (s, 0.48H), 7.22-7.30 (m, 2H), 7.70 (s, 0.52 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.1, 26.6, 28.4, 29.7, 51.8, 55.2, 55.3, 60.1, 65.1, 69.5, 80.0, 80.1, 93.6, 114.1, 116.1, 127.1, 129.6, 130.5, 141.6, 152.8, 159.6, 159.9, 168.9 ppm. MS, *m/z* (%) = 444.4 (M + Na, 100)$^+$; Anal. Calcd for $C_{22}H_{31}NO_7$: C, 62.69; H, 7.41; N, 3.32%. Found: C, 62.61; H, 7.37; N, 3.28%.

Compound (5d) (diastereomeric mixture). White solid; 26 yield%; mp 195-197 ^{o}C; $[\alpha]_D^{25}$ +3.1 (*c* 1, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}) 3052, 2934, 1751, 1681, 1607, 1387, 1269, 1096; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41-1.60 (m, 15H), 2.57 (s, 3H), 3.22-3.24 (m, 2H), 3.66 (s, 3H), 3.71-3.87 (m, 1H), 3.89-4.06 (m, 2H), 4.49-4.63 (m, 1H), 7.28-7.31 (m, 2H), 7.85-7.87 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.2, 25.5, 27.9, 28.6, 30.9, 33.0, 51.5, 57.6, 57.9, 64.7, 64.8, 65.1, 65.3, 80.7, 81.1, 94.7, 95.4, 127.7, 128.1, 129.2, 136.4, 144.5, 152.1, 168.3, 196.7, 200.1 ppm; MS, *m/z* (%) = 456.4 (M + Na, 95)$^+$; Anal. Calcd for $C_{23}H_{31}NO_7$: C, 63.72; H, 7.20; N, 3.23%. Found: C, 63.67; H, 7.16; N, 3.18%.

(*S*)-*tert*-Butyl 4-((*R*)-2-(methoxycarbonyl)-3-(4-acetylphenyl)-1-hydroxyallyl)-2,2-dimethyloxazolidine-3-carboxylate (6d-E/*Z*). Colorless viscous oil; 21% yield; $[\alpha]_D^{25}$ - 6.8 (*c* 1, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}) 3467, 2954, 1715, 1690, 1389, 1272, 1165, 1059; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41-1.60 (m, 15H), 2.60 (s, 3H), 3.62 (s, 1.44H), 3.85 (dd, *J* = 5.4, 9.0 Hz, 1H), 3.90 (s, 1.56 H), 4.01 (br s, 1H), 4.16 (dd, *J* = 2.9, 9.2 Hz, 1H), 431-4.33 (m, 1H), 4.51 (d, *J* = 9.6 Hz, 1H), 7.07 (s, 0.48H), 7.31-7.44 (m, 2H), 7.74 (s, 0.52H), 7.89-7.97 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 26.6, 28.4, 29.3, 29.5, 29.7, 52.0, 60.1, 64.9, 69.5, 80.1, 93.6, 128.6, 129.0, 133.0 136.6, 139.6, 140.0, 152.9, 168.3, 197.4 ppm. MS, *m/z* (%) = 456.6 (M + Na, 100)$^+$; Anal. Calcd for $C_{23}H_{31}NO_7$: C, 63.72; H, 7.20; N, 3.23%. Found: C, 63.65; H, 7.17; N, 3.19%.

N*-((*E*,3*S*,4*R*)-5-Benzylidene-tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-3-yl)palmitamide (1c).** To a solution of **5a-*E (130 mg, 0.332 mmol) in MeOH (2.5 ml) was added 4N HCl-EtOAc (2 ml). The mixture was refluxed for 1 h, cooled to room temperature and concentrated under reduced pressure to afford the crude product. To this flask was added dry THF (5.0 ml), Et_3N (67.2 mg, 0.664 mmol), *p*-nitrophenyl palmitate (250.7 mg, 0.664 mmol) and DMAP (cat.) successively. The reaction mixture was stirred at room temperature for 10 h till no further change in reaction mixture composition as monitored by TLC. The reaction was quenched by adding saturated aqueous $NaHCO_3$ and 1N NaOH solutions. The mixture was extracted with EtOAc (3 x

10 ml), washed with brine and dried over Na_2SO_4. The solvent was evaporated and residue was purified by column chromatography on silica gel, eluting with hexane/EtOAc (68:32) to yield pure **1c** (82.1 mg , 54%) as a white solid; mp 95-97 ºC; $[\alpha]_D^{25}$ -3.6 (*c* 1, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}) 3460, 3305, 2964,1732, 1670, 1652, 1380; ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.25-1.33 (m, 24H), 1.60-1.61 (m, 2H), 2.20 (t, *J* = 6.8 Hz, 2H), 4.31 (d, *J* = 6.2 Hz, 1H), 4.40-4.45 (m, 2H), 4.83 (s, 1H), 5.93 (d, *J* = 7.3 Hz, 1H), 7.44-7.45 (m, 3H), 7.51-7.56 (m, 2H), 8.08 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.7, 25.5, 29.3, 29.6, 31.9, 36.6, 46.5, 64.3, 64.9, 125.1, 129.0, 130.2, 133.6, 148.8, 164.9, 173.2 ppm. MS, *m/z* (%) = 458.6 (M + 1, 18)$^+$, 480.6 (M + Na, 55)$^+$; Anal. Calcd for $C_{28}H_{43}NO_4$: C, 73.48; H, 9.47; N, 3.06%. Found: C, 73.39; H, 9.44; N, 3.04%.

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