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A stereoselective approach for the total synthesis of [2(*S*)-phenyl-propionyl]-2-piperidinone-3-(*R*)-yl-ester and its diastereomer

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ABSTRACT

Stereoselective total synthesis of isomers of [2-phenyl-propionyl]-2-piperidinone-3(*R*)-yl-ester has been achieved using commercially available starting materials like *trans* cinnamaldehyde and 4-pentene-1-ol. The key steps are Steglich conditions for the esterification of the two crucial intermediates; reduction of the azide to amine under Staudinger reaction conditions with concomitant intramolecular amidation reaction in one pot afforded the target compound(s). However, the total syntheses revealed that the structural revision is necessary for the reported natural product.

1. Introduction

A new [2-phenyl-propionyl]-2-piperidinone-3(*R*)-yl-ester was first isolated by Wang et al.[1] from the *Fusarium oxysporum* in 2011 and showed cytotoxicity against three human cancer cell lines PC-3, PANC-1, and A549. As part of our interest in the synthesis of bioactive natural products,[2] herein we report the synthesis of **1** and its diastereomer **1a** (Fig. 1) by a convergent strategy so that the absolute configuration at C8 position could be determined. This was necessitated since the authors Wang et al.,[1] though assigned the absolute stereochemistry at C3 position as '*R*', did not assign the absolute configuration of the methyl center at C8 position. Our synthetic strategy was conceived to address the same issue. Accordingly, the strategy involves the esterification of the respective acid components (**3** and **3a**) with alcohol **4** under Steglich condition; Staudinger reaction was used to reduce the azide (**2** and **2a**) to amine with concomitant intramolecular amidation reaction in one pot to furnish the target compound (**1** and **1a**). Toward this endeavor, synthesis of compound **1**, assigned as [2(*S*)-phenyl-propionyl]-2-piperidinone-3(*R*)-yl-ester was taken up first.

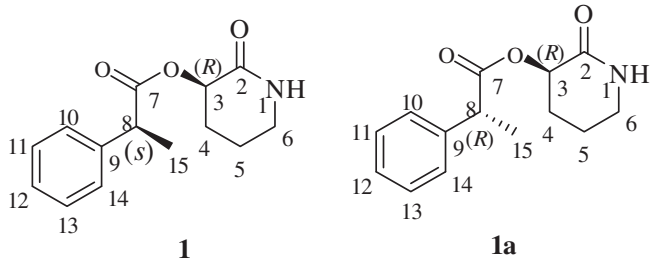

Fig. 1. Structures of both isomers of [2-phenyl-propionyl]-2-piperidinone-3(*R*)-yl-ester.

Interesting structural features coupled with the biological activity (cytotoxicity) of [2-phenyl-propionyl]-2-piperidinone-3(*R*)-yl-ester have attracted us to embark on its first total synthesis. Herein, we report our synthetic efforts en route to **1** and **1a** achieved through the key intermediates **3**, **3a**, and **4**, respectively.

Retrosynthetic analysis of compound **1** as depicted in Scheme 1, could be derived from **2** via oxidation of terminal double bond into acid and its conversion into methyl ester followed by reduction of azide to amine under Staudinger's conditions and subsequent intramolecular amidation in one pot. While **2** in turn could be achieved by the coupling of **3** and **4** under Steglich conditions, followed by the deprotection of silyl ether group and conversion of the ensuing hydroxyl group into its azide. Furthermore, compounds

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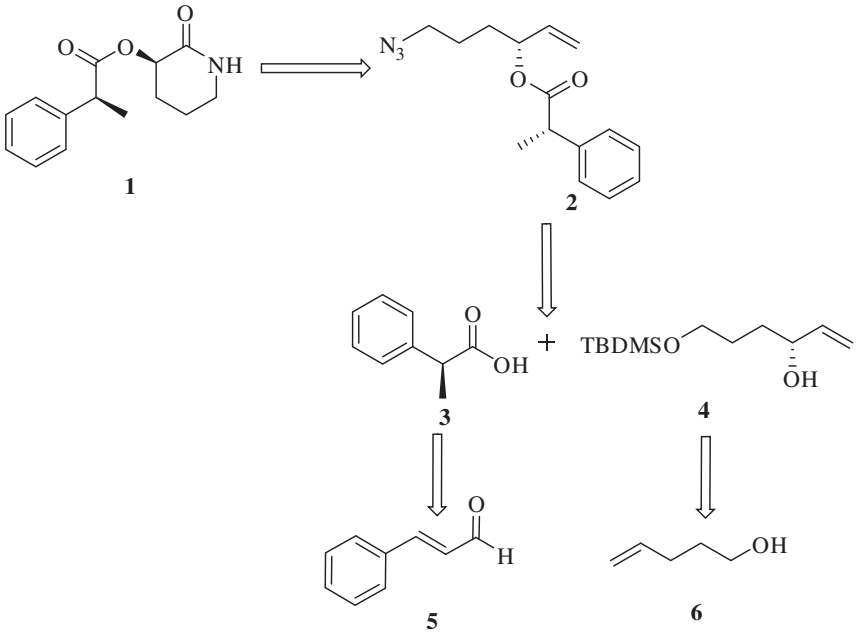


Scheme 1. Retrosynthetic analysis of **1**.

3 and **4** could be synthesized from commercially available inexpensive starting materials **5** and **6**, respectively.

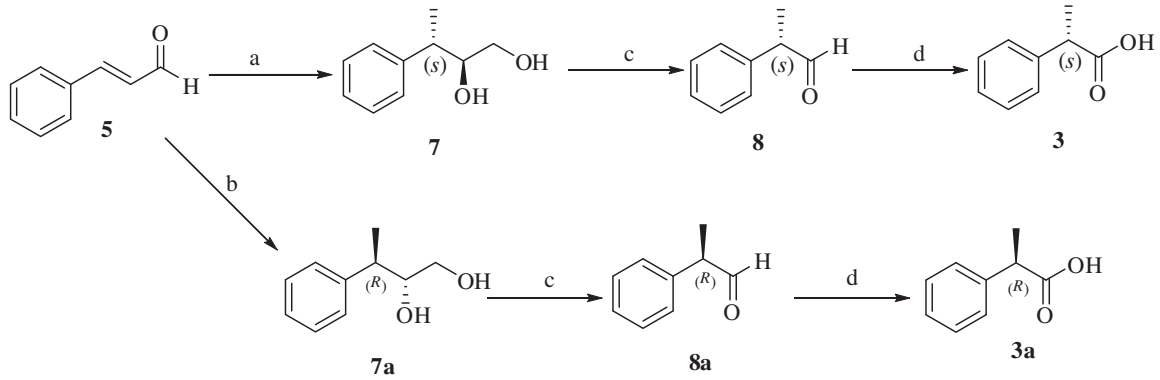
2. Results and discussions

As depicted in Scheme 2, synthesis of acid fragments **3** and **3a** was initiated from respective diols.[3] Oxidative cleavage of diols **7** and **7a** ($NaIO_4$/satd $NaHCO_3$/CH_2Cl_2/0 °C to rt/4 h) afforded corresponding aldehydes **8** (77%) and **8a** (74%), which on further oxidation ($NaClO_2$/$NaH_2PO_4\cdot 2H_2O$/2-methyl-2-butene/*t*-BuOH/0 °C to rt/2 h) gave acid components **3** (79%) and **3a** (76%), respectively.

Next, alcohol **4** (Scheme 3) was generated from 4-pentene-1-ol (**6**) by a reported procedure.[4] Compound **9** (72%) was accessed by coupling between **3** and **4** under Steglich[5] conditions (DCC/DMAP/CH_2Cl_2/0 °C to rt) followed by deprotection of the TBDMS ether (HF–Py/THF/0 °C to rt) to afford compound **10** (84%). Mesylation of alcohol **10** (MsCl/Et_3N/CH_2Cl_2/0 °C to rt) followed by its conversion led to azide **2** (68%, over two steps) under conventional conditions (NaN_3/DMF/60 °C). The functional group conversion of terminal double bond into its acid ($RuCl_3$/$NaIO_4$/1.5:1:1 CCl_4/H_2O/CH_3CN)[6] followed by esterification (CH_2N_2/ether/0 °C) gave **11** (75% over two steps). Compound **1** (66%) was obtained from **11** via the reduction of azide to amine under Staudinger[7] reaction conditions (TPP/methanol) followed by its intramolecular amidation reaction in one pot.

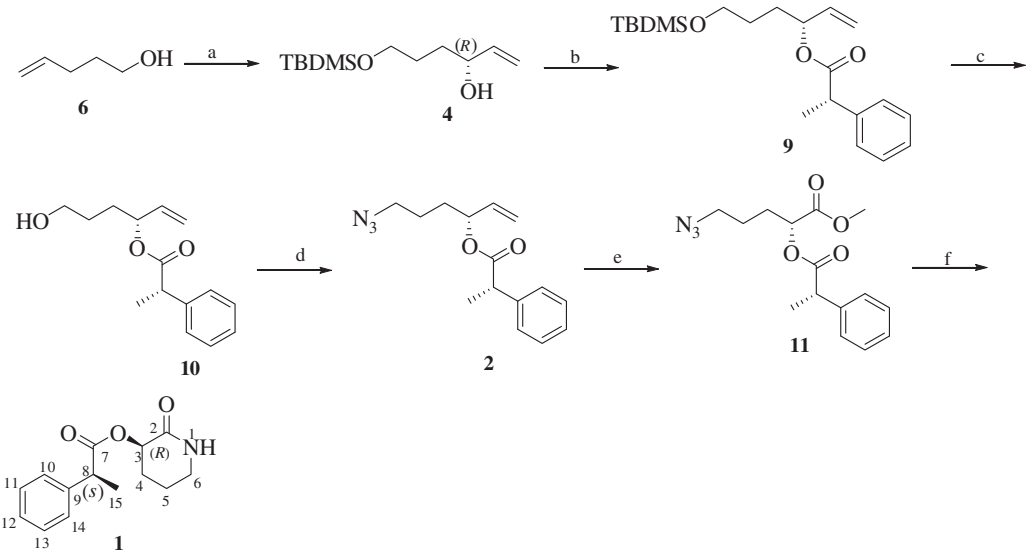
The data of **1** did not match with the reported values[1] (see Table 1). For instance, the ^1H NMR spectrum of **1** revealed the characteristic H3 proton resonating at δ 5.16 ppm as a doublet of doublet (J=6.5, 9.0 Hz) instead of at δ 4.56 ppm as a doublet of doublet (J=3.3, 8.0 Hz). The ^{13}C spectrum revealed differences too. The C3 carbon appeared at δ 69.1 ppm while the same carbon in natural product showed at δ 60.2 ppm. The rest of the spectra (1H and 13C) displayed slight variations than the reported values

Synthesis of acid fragments **3** and **3a**



Scheme 2. Reagents and conditions: (a) i. $NaBH_4$,MeOH, 0 °C to rt, 0.5 h, 83%; ii. (−)-DIPT, CHP, $Ti(O^iPr)_4$, 4 Å MS, CH_2Cl_2, −20 °C, 8 h, 87%; iii. MeLi, CuI, ether, −20 °C to rt, 10 h, 68%; (b) i. $NaBH_4$, MeOH, 0 °C to rt, 0.5 h, 83%; ii. (+)-DIPT, CHP, $Ti(O^iPr)_4$, 4 Å MS, CH_2Cl_2, −20 °C, 8 h, 81%; iii. MeLi, CuI, ether, −20 °C to rt, 10 h, 62%; (c) $NaIO_4$, satd $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 4 h; (d) $NaClO_2$, $NaH_2PO_4\cdot 2H_2O$, 2-methyl-2-butene, *t*-BuOH, 0 °C to rt, 2 h.

Synthesis of target compound **1**



Scheme 3. Reagents and conditions: (a) Ref .4; (b) **3**, DCC, DMAP, CH_2Cl_2, 0 °C to rt, 2 h, 72%; (c) HF–Py, THF, 0 °C to rt, 3 h, 84%; (d) i. mesyl chloride, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 0.5 h; ii. NaN_3, DMF, 60 °C, 2h, 68% over two steps; (e) $NaIO_4$, $RuCl_3$, 1.5:1:1 $CCl_4/H_2O/CH_3CN$, 0 °C, 5 min; ii. CH_2N_2, ether, 0 °C, 75% over two steps; (f) TPP, MeOH, 0 °C to rt, 2 h, 66%.

Table 1
Detailed account of data

Position	Natural product		**1** (Synthetic)		**1a** (Synthetic)	
	δ ^{13}C	δ ^{1}H, *J* in Hz	δ ^{13}C	δ ^{1}H, *J* in Hz	δ ^{13}C	δ ^{1}H, *J* in Hz
2	173.2	—	168.7	—	168.9	—
3	60.2	4.56 (dd, 3.3, 8.0)	69.1	5.16 (dd, 6.5, 9.0)	68.7	5.24 (dd, 6.5, 8.9)
4	27.6	1.90–1.93 (m); 2.23–2.29 (m)	26.8	1.87–1.97 (m); 2.06–2.15(m)	26.7	1.88–1.96 (m); 2.05–2.14(m)
5	24.7	1.82–1.85 (m); 1.98–2.02 (m)	20.5	1.74–1.86 (m); 1.98–2.05 (m)	19.9	1.74–1.83 (m); 1.98–2.04 (m)
6	47.5	3.18–3.22 (m); 3.62–3.64 (m)	45.4	3.25–3.31 (m);	45.2	3.24–3.32 (m);
7	175.5		173.6		173.7	
8	45.1	3.82 (q, 7.0)	42.1	3.82 (q, 7.0)	42.1	3.82 (q, 6.9)
9	140.3		140.1		140.5	
10/14	129.0	7.32–7.35 (m)	128.5	7.30–7.35 (m)	128.6	7.30–7.36 (m)
11/13	127.5	7.26–7.29 (m)	127.6	7.22–7.27 (m)	127.4	7.22–7.27 (m)
12	127.2	7.26–7.29 (m)	127.1	7.22–7.27 (m)	127.1	7.22–7.27 (m)
15	20.1	1.48 (d, 7.0)	18.6	1.54 (d, 7.0)	18.5	1.52 (d, 6.9)
–NH		—		5.73 (br s)		6.06 (br s)

^{1}H and ^{13}C assignments of natural product and synthetic compounds **1** and **1a** ($CDCl_3$, 500 MHz).

(Table 1). Interestingly, the optical rotation value of the synthetic sample was measured as $[\alpha]_D^{25}=-96.4$ (*c* 0.3, MeOH) while the literature value was $[\alpha]_D^{25}=-100.0$ (*c* 0.5, MeOH).[1]

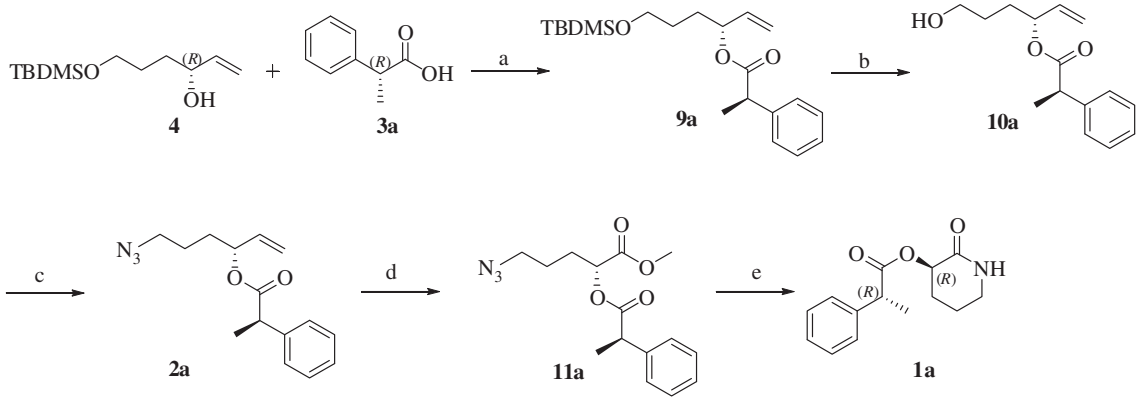
Next, the synthesis of compound **1a** (Scheme 4), which is a C8 epimer of **1**, was accomplished from the fragments **3a** and **4** by adopting the same procedure as utilized for the preparation of compound **1**. Compound **1a** was obtained as a semi solid. Even herein, the data of **1a** did not match with the reported values[1] (see Table 1). The optical rotation value of the synthetic sample was measured as $[\alpha]_D^{25}=+23.5$ (*c* 0.3, MeOH) while the literature value noted was $[\alpha]_D^{25}=-100.0$ (*c* 0.5, MeOH).[1]

Since the spectral data showed difference at C3 in both **1** and **1a**, it was felt necessary to synthesize hydroxy piperidinone independently and ascertain if it was rightly assigned and characterized. Accordingly, initially it was decided to access the hydroxy piperidinone from compound **1** (or **1a**) by a hydrolytic protocol. Consequently, ester hydrolysis of **1** and **1a** gave a hydroxy lactam (*R*)-3-hydroxy-piperidinone (**17**) along with their respective acid components **3** and **3a**. However, it was not possible to isolate both alcohol and acid components in pure form. Alternatively, we accomplished the synthesis of both the isomers **1**and **1a** firstly by synthesizing alkaloid, (*R*)-3-hydroxy-piperidinone (**17**) as described below followed by its Steglich esterification with respective acid components **3** and **3a**.

Accordingly, allylic alcohol **4** (Scheme 5) was protected as its methoxymethyl ether (MOM–Cl/DIPEA/CH_2Cl_2/0 °C) to give compound **12** (82%) followed by the deprotection of silyl ether (HF–Py/THF/0 °C) led to compound **13** (70%). Next, mesylation (MsCl/Et_3N/CH_2Cl_2/0 °C to rt) of alcohol **13** followed by its immediate conversion (NaN_3/DMF/60 °C, 71% over two steps) furnished the azide **14**. Terminal double bond in **14** on exhaustive oxidation ($RuCl_3$/$NaIO_4$/1.5:1:1 $CCl_4/H_2O/CH_3CN$)[6] afforded the corresponding acid, which on esterification (CH_2N_2/ether/0 °C) furnished **15** (72% over two steps). Later, reduction of azide to amine under Staudinger[7] reaction conditions (TPP/MeOH) followed by intramolecular amidation gave compound **16** (82%) in one pot. MOM-deprotection (Dowex-H/MeOH/reflux) of compound **16** gave (*R*)-3-hydroxy-piperidinone (**17**, 86%) as a white solid whose spectral and analytical data matched with the reported values.[8] Interestingly, (*R*)-3-hydroxy-piperidinone (**17**) is an alkaloid and has been independently synthesized earlier.[8]

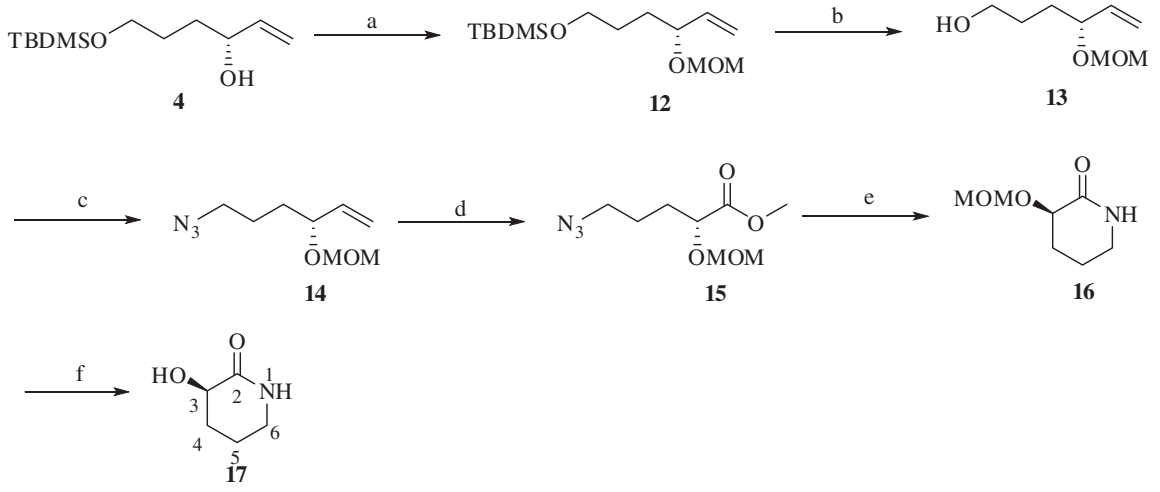
Next, coupling of **3** and **17**; **3a** and **17** (Scheme 6) under Steglich esterification conditions (DCC/DMAP/CH_2Cl_2/0 °C-rt) gave the compounds **1** (59%) and **1a** (55%), respectively, in lower yields.

Synthesis of target compound **1a**



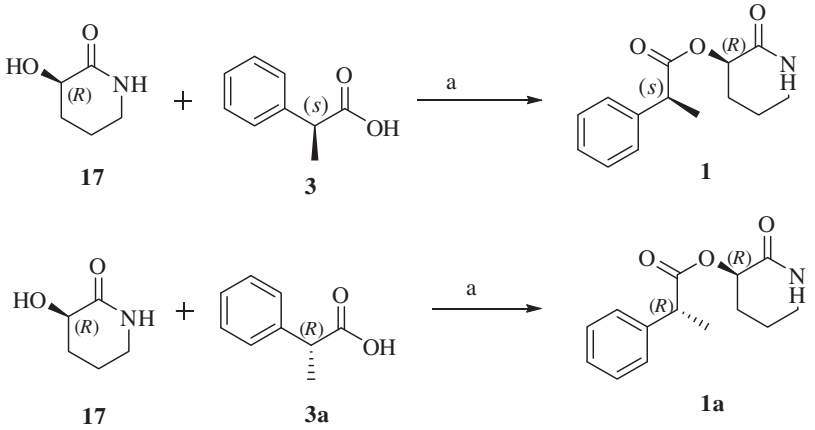
Scheme 4. Reagents and conditions: (a) DCC, DMAP, CH_2Cl_2, 0 °C to rt, 2 h, 68%; (b) HF–Py, THF, 0 °C to rt, 3 h, 80%; (c) i. mesyl chloride, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 0.5 h; ii. NaN_3, DMF, 60 °C, 2 h, 66% over two steps; (d) $NaIO_4$, $RuCl_3$, 1.5:1:1 $CCl_4/H_2O/CH_3CN$, 0 °C, 5 min; ii. CH_2N_2, ether, 0 °C, 78% over two steps; (e) TPP, MeOH, 0 °C to rt, 2 h, 64%.

Synthesis of (*R*)-3-hydroxy-piperidinone **17**



Scheme 5. Reagents and conditions: (a) MOMCl, DIPEA, DMAP, CH_2Cl_2, 0 °C, 2 h, 82%; (b) HF–pyridine, THF, 0 °C, 4 h, 70%; (c) i. mesyl chloride, TEA, DMAP, CH_2Cl_2, 0 °C, 30 min; ii. NaN_3, DMF, at 60 °C, 2 h, 71% over two steps; (d) i. $RuCl_3$, $NaIO_4$, 1.5:1:1 $CCl_4/H_2O/CH_3CN$, at 0 °C, 5 min; ii. CH_2N_2, ether, 0 °C, 5 min, 72% over two steps; (e) TPP, MeOH 2 h, 82%; (f) Dowex, MeOH reflux, 2 h, 86%.

Synthesis of target compounds **1** and **1a**



Scheme 6. Reagents and conditions: (a) DCC, DMAP, $CHCl_2$, 0 °C to rt, 2 h.

However, the data of these new set of compounds matched with the earlier obtained synthetic compounds.

In addition to ^{1}H NMR, CD spectra could differentiate both isomers as shown in Fig. 2.

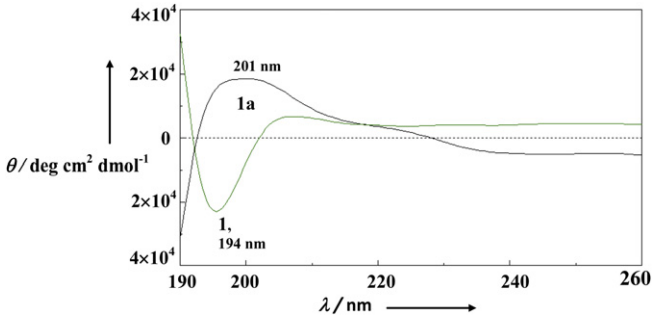


Fig. 2. CD spectra of **1** and **1a**.

Compound **1** showed a negative cotton effect at 194 nm while **1a** showed a positive cotton effect at 201 nm. The CD spectrum of the natural product showed a negative Cotton effect at 224 nm.[1]

3. Conclusion

Thus in summary, the stereoselective total synthesis of both isomers [2(*S*)-phenyl-propionyl]-2-piperidinone-3(*R*)-yl-ester (**1**) and its diastereomer [2(*R*)-phenyl-propionyl]-2-piperidinone-3(*R*)-yl-ester (**1a**), were accomplished by a convergent strategy wherein, Steglich esterification and reduction of azide to amine under Staudinger conditions with concomitant intramolecular amidation reaction in one pot are the key steps invoked herein. However, out of four possible isomers, the experimental (^{1}H NMR and ^{13}C NMR) data of the synthetic **1** and **1a** (other two isomers being enantiomeric to **1** and **1a**, respectively) did not match with the reported one. Hence, it is concluded that the structural revision of the natural product is necessary.

4. Experimental section

4.1. General methods

Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40 °C in vacuo. All column chromatographic separations were performed using silica gel (Acme's, 60–120, 100–200 mesh). ^{1}H NMR was measured on Varian Gemini 200 MHz, Bruker Avance 300 MHz, and Inova 500 MHz. ^{13}C NMR was measured (75 MHz and 150 MHz) on a Bruker Avance 300 MHz and 600 MHz spectrometers with 7–10 mM solutions in deuteriochloroform, tetramethylsilane as internal standard. *J* values are given in Hertz (Hz). IR spectra were recorded on Perkin–Elmer IR-683 spectrophotometer with NaCl optics. Optical rotations were measured with a JASCO P-1020 instrument and $[\alpha]_D$ values were in units of 10^{-1} deg cm^2 g^{-1} at 25 °C. Mass spectra were recorded on Finnigan Mat 1210 double focusing mass spectrometers operating at a direct inlet system and ESI-MS were measured using ion-trap mass spectrometer. Elemental analysis was carried on a Vario Micro Cube Elementar at Analytical Chemistry Division, CSIR-IICT, Hyderabad. Unless otherwise stated, all the reactions were performed under inert atmosphere. The CD spectra were obtained with a spectropolarimeter using rectangular fused quartz cells of 0.2 cm path length in 200 μM methanol solutions. The binomial method was used to smooth the spectra. The values are expressed in terms of $[\theta]$, the total molar ellipticity (deg cm^2 dmol^{-1}) per residue.

4.2. (*S*)-2-Phenylpropanal 8

To a stirred solution of diol[3] **7** (2.2 g, 13.2 mmol) in CH_2Cl_2 (25 mL), $NaIO_4$ (8.5 g, 39.7 mmol) was added at 0 °C. To it satd $NaHCO_3$ (1.0 mL) was added slowly at same temperature and reaction mixture was allowed to stir for 4 h. Reaction mixture was filtered with funnel through Na_2SO_4 using the CH_2Cl_2 (20.0 mL) and then the solvent was removed under reduced pressure, purified by column chromatography (silica gel, 60–120 mesh, R_f 0.75, 3% EtOAc/hexane) to furnish **8** (1.37 g, 77%) as a colorless oil. Found: C, 80.38; H, 7.26. $C_9H_{10}O$ requires C, 80.56; H, 7.51%; $[\alpha]_D^{25}$ −94.7 (*c* 0.4, $CHCl_3$); IR (neat) $\bar{\nu}$: 3026, 2968, 2809, 1595, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): 9.69 (1H, s, −CHO), 7.36–7.16 (5H, m, Ar–H), 3.62 (1H, q, *J*=6.9 Hz, −CHCHO), 1.44 (3H, d, *J*=6.9 Hz, −CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 201.2, 133.1, 129.0, 128.3, 127.5, 52.9, 14.5; MS (ESI) *m*/*z* 157 $[M+Na]^+$.

4.3. (*R*)-2-Phenylpropanal 8a

Adopted the same procedure as described for the synthesis of compound **8** and purified by column chromatography (silica gel, 60–120 mesh, R_f 0.75, 3% EtOAc/hexane). Compound **7a** (2.0 g, 12.0 mmol) gave **8a** (1.20 g, 74%) as a colorless liquid.

4.4. (*S*)-2-Phenylpropanoic acid 3

Aldehyde **8** (1.35 g, 10.1 mmol) was dissolved in mixture of *t*-BuOH and 2-methyl-2-butene (6 mL in 2:1 ratio). To it $NaClO_2$ (1.81 g, 20.1 mmol) and $NaH_2PO_4{\cdot}2H_2O$ (3.12 g, 20.1 mmol) dissolved in minimum amount of water were added to reaction mixture at 0 °C and allowed to stir for 2 h at room temperature. Solvent was removed under reduced pressure and extracted with EtOAc (2×10.0 mL), washed with water (10.0 mL) and brine (10.0 mL). The combined organic layers were dried (Na_2SO_4), concentrated in vacuo, and purified by column chromatography (silica gel, 60–120 mesh, R_f 0.30, 10% EtOAc/hexane) to afford **3** (1.20 g, 79%) as a yellow oil. Found: C, 71.72; H, 6.45. $C_9H_{10}O_2$ requires C, 71.98; H, 6.71%; $[\alpha]_D^{25}$ +72.7 (*c* 0.4, $CHCl_3$); IR (neat) $\bar{\nu}$: 3443, 3012, 2977, 1745, 746 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): 7.33–7.18 (5H, m, Ar–H), 3.70 (1H, q, *J*=7.2 Hz, −CHCOOH), 1.52 (3H, d, *J*=7.2 Hz, −CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 176.0, 132.2, 129.8, 129.0, 128.8, 49.7, 17.5; MS (ESI) *m*/*z* 173 $[M+Na]^+$.

4.5. (*R*)-2-Phenylpropanoic acid 3a

Adopted the same procedure as described for the synthesis of compound **3** and purified by column chromatography (silica gel, 60–120 mesh, R_f 0.30, 10% EtOAc/hexane). Compound **8a** (1.0 g, 7.46 mmol) gave **3a** (0.86 g, 76%) as a yellow oil.

4.6. (*S*)-((*R*)-6-(*tert*-Butyl dimethyl silyloxy)hex-1-en-3-yl)-2-phenyl propanoate 9

To a stirred solution of alcohol **4** (0.6 g, 2.60 mmol) in CH_2Cl_2 (8 mL), DCC (0.591 g, 2.87 mmol), DMAP (0.03 g, 0.26 mmol) followed by a solution of acid **3** (0.47 g, 3.13 mmol) in CH_2Cl_2 (6 mL) were added at 0 °C. After 2 h, it was diluted with water (8.0 mL) and extracted with CH_2Cl_2 (2×8.0 mL). The combined organic layers were washed with brine (10.0 mL), dried (Na_2SO_4), evaporated, and the residue purified by column chromatography (silica gel, 60–120 mesh, R_f 0.60, 5% EtOAc/hexane) to furnish **9** (0.68 g, 72%) as a colorless oil. Found: C, 69.38; H, 9.26; Si, 7.58.$C_{21}H_{34}O_3Si$ requires C, 69.56; H, 9.45; Si, 7.75%; $[\alpha]_D^{25}$ −23.4 (*c* 0.2, $CHCl_3$); IR (neat) $\bar{\nu}$: 3059, 2986, 2934, 1734, 1608, 1586, 1391, 1372, 1062, 744 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): 7.36–7.28 (3H, m, Ar–H), 7.26–7.22 (2H, m, Ar–H), 5.71–5.58 (1H, m, olefinic-H), 5.28–5.16 (2H, m, olefinic-H),

5.06–4.98 (m, 1H, –CHOCOR), 3.72 (1H, q, J=7.2 Hz, –CHCOOR), 3.59 (1H, t, J=6.4 Hz, $-CH_aH_bOTBS$), 3.48 (1H, t, J=6.4 Hz, $-CH_aH_bOTBS$), 1.71–1.55 (4H, m, $-CH_2$), 1.50 (3H, d, J=7.2 Hz, $-CH_3$), 0.89 (9H, br s, *t*-BuSi), 0.04 (6H, s, MeSi (2)); ^{13}C NMR ($CDCl_3$, 75 MHz): 173.7, 140.5, 136.2, 133.6, 128.5, 127.5, 116.2, 74.4, 62.6, 45.7, 30.6, 28.2, 25.9, 18.3, −5.33; MS (ESI) m/z 385 $[M+Na]^+$.

4.7. (*S*)-((*R*)-6-Hydroxy hex-1-en-3-yl)-2-phenylpropanoate 10

To a stirred solution of compound **9** (0.66 g, 1.82 mmol) in dry THF, HF–Py (1.1 mL, 1.09 mmol) was added and stirred for 3 h at room temperature. The reaction mixture was quenched with $CuSO_4$ solution (8.0 mL), extracted with EtOAc (2×8.0 mL), washed with water (8.0 mL), and brine (8.0 mL). The combined organic layers were dried (Na_2SO_4), concentrated in vacuo, and purified by column chromatography (silica gel, 60–120 mesh, R_f 0.40, 12% EtOAc/hexane) to afford **10** (0.383 g, 84%) as a sticky oil. Found: C, 72.27; H, 7.92. $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.12%; $[\alpha]_D^{25}$ −41.7 (*c* 0.2, $CHCl_3$); IR (neat) $\bar{\nu}$: 3414, 3054, 2986, 2921, 1726, 1634, 1597, 981, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): 7.36–7.28 (3H, m, Ar–H), 7.26–7.22 (2H, m, Ar–H), 5.71–5.62 (1H, m, olefinic-H), 5.29–5.16 (2H, m, olefinic-H), 5.06–5.00 (1H, m, –CHOCOR), 3.72 (1H, q, J=7.2 Hz, –CHCOOR), 3.62 (1H, t, J=6.4 Hz, $-CH_aH_bOH$), 3.47 (1H, t, J=6.4 Hz, $-CH_aH_bOH$), 1.72–1.54 (4H, m, $-CH_2$), 1.51 (3H, d, J=7.2 Hz, $-CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): 173.7, 140.4, 135.9, 128.5, 127.5, 127.1, 116.4, 74.4, 62.4, 45.7, 30.4, 28.1, 18.3; MS (ESI) m/z 271 $[M+Na]^+$.

4.8. (*S*)-((*R*)-6-Azidohex-1-en-3-yl)-2-phenylpropanoate 2

To a stirred solution of alcohol **10** (0.35 g, 1.41 mmol) in CH_2Cl_2 (5.0 mL), Et_3N (0.4 mL, 2.82 mmol) and methanesulfonyl chloride (0.13 mL, 1.70 mmol) were added at 0 °C and allowed to stir at 0 °C for 0.5 h. After completion of reaction, the compound was diluted with CH_2Cl_2 (6.0 mL), washed with satd $NaHCO_3$ (1×4.0 mL), 1 N HCl (1×4.0 mL), and water (2×4.0 mL), and brine solution (1×4.0 mL). The CH_2Cl_2 layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude mesylate used as such without further purification.

To a stirred solution of above mesylate in dry DMF (4.0 mL), NaN_3 (0.18 g, 2.8 mmol) was added and heated to 60 °C and stirring continued for 2 h. After completion of the reaction, reaction mixture was extracted with EtOAc/*n*-hexane (6:4) (2×10.0 mL), organic phase was washed with brine (2×6.0 mL), dried (Na_2SO_4), the solvent was evaporated, and the residue purified by column chromatography (silica gel, 60–120 mesh, R_f 0.80, 3% EtOAc/hexane) afforded **2** (0.262 g, 68% over two steps) as a yellow liquid. Found: C, 65.75; H, 6.84; N, 15.21. $C_{15}H_{19}N_3O_2$ requires C, 65.91; H, 7.01; N, 15.37%; $[\alpha]_D^{25}$ +68.3 (*c* 0.3, $CHCl_3$); IR (neat) $\bar{\nu}$: 3022, 2955, 2158, 1737, 1644, 1546, 744 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.39–7.23 (5H, m, Ar–H), 5.73–5.58 (1H, m, olefinic-H), 5.29–5.16 (2H, m, olefinic-H), 5.08–5.01 (1H, m, –CHOCOR), 3.72 (1H, q, J=7.2 Hz, –CHCOOR), 3.24 (1H, t, J=6.4 Hz, $-CH_aH_bN_3$), 3.09 (1H, t, J=6.8 Hz, $-CH_aH_bN_3$), 1.72–1.54 (4H, m, $-CH_2$), 1.53 (3H, d, J=7.2 Hz, $-CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): 173.6, 140.3, 135.6, 128.5, 127.4, 127.1, 116.6, 73.9, 51.0, 45.6, 31.2, 24.4, 18.3; MS (ESI) m/z 296 $[M+Na]^+$.

4.9. (*R*)-Methyl-5-azido-2-((*S*)-2-phenylpropanoyloxy)pentanoate 11

Azide **2** (0.24 g, 0.88 mmol) was dissolved in mixture of CH_3CN, H_2O, and CCl_4 (3.5 mL in 1:1:1.5). To it $NaIO_4$ (0.76 g, 3.52 mmol) was added at 0 °C, followed by the addition of $RuCl_3$ (0.004 g, 0.02 mmol) and allowed to stir for 5 min at the same temperature to afford acid. Solvent was removed under reduced pressure, filtered through Na_2SO_4 with EtOAc (2×3 mL), concentrated in vacuo and was ready for the next reaction without purification.

Acid was dissolved in ether and to it diazomethane was added slowly at 0 °C until the acid completely converted into methyl ester. Afterward, the solvent was removed under reduced pressure and purified by column chromatography (silica gel, 60–120 mesh, R_f 0.50, 7% EtOAc/hexane) to afford **11** (0.20 g, 75% over two steps) a colorless oil. Found: C, 58.89; H, 6.14; N, 13.63. $C_{15}H_{19}N_3O_4$ requires C, 59.01; H, 6.27; N, 13.76%; $[\alpha]_D^{25}$ +19.1 (*c* 0.3, $CHCl_3$); IR (neat) $\bar{\nu}$: 3028, 2954, 2097, 1738, 1717, 1584, 747, 584 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.36–7.28 (3H, m, Ar–H), 7.26–7.22 (2H, m, Ar–H), 5.09–4.99 (1H, m, –CHOCOR), 3.81 (1H, q, J=6.9 Hz, –CHCOOR), 3.64 (3H, s, –OMe), 3.24 (1H, t, J=6.4 Hz, $-CH_aH_bN_3$), 3.13 (1H, t, J=6.4 Hz, $-CH_aH_bN_3$), 1.95–1.79 (4H, m, $-CH_2$), 1.55 (3H, d, J=7.2 Hz, $-CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): 173.7, 169.9, 139.7, 128.5, 127.6, 127.2, 71.8, 52.2, 50.6, 45.3, 28.1, 24.5, 18.2; MS (ESI) m/z 328 $[M+Na]^+$.

4.10. (*S*)-((*R*)-2-Oxopiperidin-3-yl)-2-phenylpropanoate 1

To a solution of compound **11** (0.16, 0.52 mmol) in MeOH, TPP was added and allowed to stir for 2 h. Solvent was removed under reduced pressure and purified by column chromatography (silica gel, 60–120 mesh, R_f 0.7, 2% MeOH/$CHCl_3$) to afford **1** (0.085 g, 66%) as a sticky oil. Found: C, 67.91; H, 6.85; N, 5.59. $C_{14}H_{17}NO_3$ requires C, 68.00; H, 6.93; N, 5.66%; $[\alpha]_D^{25}$ −96.4 (*c* 0.3, MeOH) (lit.[1] $[\alpha]_D^{25}$ −100.5 (*c* 0.5, MeOH)); IR (neat) $\bar{\nu}$: 3205, 3059, 2952, 2846, 1732, 1654, 1576, 1319, 1095, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): 7.35–7.30 (2H, m, Ar–H), 7.27–7.22 (3H, m, Ar–H), 5.73 (1H, br s, –NH), 5.16 (1H, dd, J=9.0 Hz, 6.5 Hz, –CHCONH), 3.82 (1H, q, J=7.0 Hz, –CHCOOR), 3.31–3.25 (2H, m, $-CH_2NH$), 2.15–2.06 (1H, m, $-CH_aH_bCH_2NH$), 2.05–1.98 (1H, m, $-CH_aH_bCH(OCO)CONH$), 1.97–1.87 (1H, m, $-CH_aH_bCH_2NH$), 1.86–1.74 (1H, m, CH_aH_b-$CH(OCO)CONH$), 1.54 (3H, d, J=7.0 Hz, $-CH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz): 173.6, 168.7, 140.1, 128.5, 127.6, 127.1, 69.1, 45.4, 42.1, 26.8, 20.5, 18.6; MS (ESI) m/z 270 $[M+Na]^+$.

4.11. (*R*)-((*R*)-6-(*tert*-Butyldimethylsilyloxy)-hex-1-en-3-yl)-2-phenyl propanoate 9a

Adopted the same procedure to compounds **4** (0.7 g, 3.03 mmol) and **3a** (0.55 g, 3.66 mmol), as described for the synthesis compound **9**, and purified by column chromatography (silica gel, 60–120 mesh, R_f 0.60, 5% EtOAc/hexane). Compound **9a** afforded (0.75 g, 68%) as a colorless liquid. Found: C, 69.42; H, 9.28; Si, 7.64. $C_{21}H_{34}O_3Si$ requires C, 69.56; H, 9.45; Si, 7.75%; $[\alpha]_D^{25}$ +11.5 (*c* 0.2, $CHCl_3$); IR (neat) $\bar{\nu}$: 3047, 2989, 1732, 1612, 1592, 1389, 1368, 1057, 704 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): 7.35–7.30 (3H, m, Ar–H), 7.26–7.23 (2H, m, Ar–H), 5.80–5.72 (1H, m, olefinic-H), 5.28–5.19 (m, 2H, olefinic-H), 5.04–4.99 (1H, m, –CHOCOR), 3.72 (1H, q, J=6.9 Hz, –CHCOOR), 3.59 (1H, t, J=6.5 Hz, $-CH_aH_bOTBS$), 3.48 (1H, t, J=6.5 Hz, $-CH_aH_bOTBS$), 1.69–1.61 (1H, m, $-CH_aH_b$), 1.61–1.53 (3H m, $-CH_aH_b$, $-CH_2$), 1.51 (3H, d, J=7.4 Hz, $-CH_3$), 0.87 (9H, br s, *t*-BuSi), 0.04 (6H, br s, MeSi (2)); ^{13}C NMR ($CDCl_3$, 75 MHz): 173.8, 140.6, 136.4, 133.8, 128.5, 127.0, 116.6, 74.7, 62.5, 45.7, 30.4, 27.9, 25.9, 18.3, −5.35; MS (ESI) m/z 385 $[M+Na]^+$.

4.12. (*R*)-((*R*)-6-Hydroxy hex-1-en-3-yl)-2-phenylpropanoate 10a

Adopted the same procedure as described for the synthesis compound **10** and purified by column chromatography (silica gel, 60–120 mesh, R_f 0.40, 12% EtOAc/hexane). Compound **9a** (0.72 g, 1.99 mmol) gave **10a** (0.397 g, 80%) as a yellow oil. Found: C, 72.34; H, 7.88. $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.12%; $[\alpha]_D^{25}$ +58.2 (*c* 0.3, $CHCl_3$); IR (neat) $\bar{\nu}$: 3421, 2982, 2935, 1737, 1608, 1584, 982, 704 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): 7.36–7.28 (3H, m, Ar–H), 7.26–7.22 (2H, m, Ar–H), 5.81–5.72 (1H, m, olefinic-H), 5.29–5.18 (2H, m, olefinic-H), 5.06–5.02 (1H, m, –CHOCOR), 3.72 (1H, q,

J=6.9 Hz, −CHCOOR), 3.61 (1H, t, J=6.5 Hz, $-CH_aH_bOH$), 3.47 (1H, t, J=6.5 Hz, $-CH_aH_bOH$), 1.71–1.65 (1H, m, $-CH_aH_b$), 1.64–1.53 (3H, m, $-CH_aH_b$, $-CH_2$), 1.51 (3H, d, J=6.9 Hz, $-CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): 173.8, 140.6, 136.2, 128.5, 127.5, 127.1, 116.7, 74.5, 62.2, 45.7, 30.2, 27.8, 18.2; MS (ESI) m/z 271 $[M+Na]^+$.

4.13. (*R*)-((*R*)-6-Azidohex-1-en-3-yl)-2-phenylpropanoate 2a

Adopted the same procedure as described for the synthesis compound **2** and purified by column chromatography (silica gel, 60–120 mesh, R_f 0.80, 3% EtOAc/hexane). Compound **10a** (0.37 g, 1.49 mmol) gave **2a** (0.27 g, 66% over two steps) as a colorless syrup. Found: C, 65.72; H, 6.89; N, 15.16. $C_{15}H_{19}N_3O_2$ requires C, 65.91; H, 7.01; N, 15.37%; $[\alpha]_D^{25}$ −88.5 (c 0.3, $CHCl_3$); IR (neat) $\bar{\nu}$: 3029, 2982, 2174, 1745, 1638, 1584, 704 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.39–7.23 (5H, m, Ar–H), 5.84–5.75 (1H, m, olefinic-H), 5.32–5.21 (2H, m, olefinic-H), 5.00–4.99 (1H, m, −CHOCOR), 3.72 (1H, q, J=6.9 Hz, −CHCOOR), 3.25 (1H, t, J=6.2 Hz, $-CH_aH_bN_3$), 3.09 (1H, t, J=6.6 Hz, $-CH_aH_bN_3$), 1.78–1.54 (4H, m, $-CH_2$), 1.50 (3H, d, J=6.9 Hz, $-CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): 173.6, 140.5, 135.9, 128.5, 127.4, 127.3, 116.6, 74.1, 50.9, 45.5, 31.0, 24.2, 18.3; MS (ESI) m/z 296 $[M+Na]^+$.

4.14. (*R*)-Methyl-5-azido-2-((*R*)-2-phenylpropanoyloxy)pentanoate 11a

Adopted the same procedure as described for the synthesis compound **11** and purified by column chromatography (silica gel, 60–120 mesh, R_f 0.50, 7% EtOAc/hexane). Compound **2a** (0.24 g, 0.88 mmol) gave **11a** (0.21 g, 78% over two steps) as a colorless liquid. Found: C, 58.94; H, 6.18; N, 13.56. $C_{15}H_{19}N_3O_4$ requires C, 59.01; H, 6.27; N, 13.76%; $[\alpha]_D^{25}$ +74.6 (c 0.2, $CHCl_3$); IR (neat) $\bar{\nu}$: 3068, 2994, 2185, 1725, 1589, 784 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.36–7.28 (3H, m, Ar–H), 7.27–7.23 (2H, m, Ar–H), 5.00 (1H, dd, J=7.5 Hz, 4.5 Hz, −CHOCOR), 3.83 (1H, q, J=6.9 Hz, −CHCOOR), 3.74 (3H, s, −OMe), 3.24 (1H, t, J=6.5 Hz, $-CH_aH_bNH$), 3.16–3.10 (1H, m, $-CH_aH_bNH$), 1.95–1.79 (4H, m, $-CH_2$), 1.54 (3H, d, J=7.9 Hz, $-CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): 173.9, 170.2, 140.0, 128.6, 127.5, 127.3, 71.6, 52.4, 50.5, 45.1, 28.1, 24.4, 18.2; MS (ESI) m/z 328 $[M+Na]^+$.

4.15. (*R*)-((*R*)-2-Oxopiperidin-3-yl)-2-phenylpropanoate 1a

Adopted the same procedure as described for the synthesis compound **1** and purified by column chromatography (silica gel, 60–120 mesh, R_f 0.7, 2% MeOH/$CHCl_3$). Compound **11a** (0.18 g, 0.59 mmol) gave **1a** (0.094 g, 64%) as a semi solid. Found: C, 67.93; H, 6.82; N, 5.61. $C_{14}H_{17}NO_3$ requires C, 68.00; H, 6.93; N, 5.66%; $[\alpha]_D^{25}$ +23.5 (c 0.3, MeOH) (lit.[1] $[\alpha]_D^{25}$ −100.5 (c 0.5, MeOH)); IR (neat) $\bar{\nu}$: 3209, 3065, 2946, 2853, 1737, 1662, 1571, 1312, 1089, 707 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): 7.36–7.30 (2H, m, Ar–H), 7.27–7.22 (3H, m, Ar–H), 6.06 (1H, br s, −NH), 5.24 (1H, dd, J=8.9, 6.5 Hz, −CH(OCO)CONH), 3.82 (1H, q, J=6.9 Hz, −CHCOOR), 3.32–3.24 (2H, m, $-CH_2NH$), 2.14–2.05 (1H, m, $-CH_aH_bCH_2NH$), 2.04–1.98 (1H, m, $-CH_aH_bCH(OCO)CONH$), 1.96–1.88 (1H, m, $-CH_aH_bCH_2NH$), 1.83–1.74 (1H, m, $-CH_aH_bCH(OCO)CONH$), 1.52 (3H, d, J=6.9 Hz, $-CH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz): 173.7, 168.9, 140.5, 128.6, 127.4, 127.1, 68.7, 45.2, 42.1, 26.7, 19.9, 18.5; MS (ESI) m/z 270 $[M+Na]^+$.

4.16. (*R*)-10,10,11,11-Tetramethyl-5-vinyl-2,4,9-trioxa-10-siladodecane 12

To a stirred solution of **4** (0.80 g, 3.48 mmol) in CH_2Cl_2 (8 mL), DIPEA (1.38 mL, 10.44 mmol), methoxymethyl chloride (0.45 mL, 5.22 mmol), and DMAP (cat.), were added at 0 °C and stirred at room temperature for 6 h. Reaction mixture was extracted with CH_2Cl_2 (2×15 mL), and combined organic layers were washed with water (12 mL), brine (12 mL) and dried (Na_2SO_4). Solvent was evaporated and the residue purified by column chromatography (silica gel, 60–120 mesh, R_f 0.50, 10% EtOAc/hexane) to furnish **12** (0.78 g, 82%) as a colorless oil. Found: C, 61.09; H, 10.92; Si, 10.07. $C_{14}H_{30}O_3Si$ requires C, 61.26; H, 11.02; Si, 10.23%; $[\alpha]_D^{25}$ +139.7 (c 0.3, $CHCl_3$); IR (neat) $\bar{\nu}$: 3047, 2986, 2934, 1794, 1745, 1645, 1454, 1373, 1217, 1159, 1059 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): 5.72–5.62 (1H, m, olefinic-H), 5.23–5.14 (2H, m, olefinic-H), 4.70 (1H, d, J=6.1 Hz, $-CH_aH_bOMe$), 4.54 (1H, d, J=5.5 Hz, $-CH_aH_bOMe$), 4.03–3.96 (1H, m, −CHOMOM), 3.67–3.59 (2H, m, $-CH_2OTBS$), 3.37 (3H, s, −OMe), 1.68–1.52 (m, 4H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): 138.1, 117.0, 93.5, 76.4, 62.8, 55.2, 31.5, 28.5, 25.8, 18.1, −5.5; MS (ESI) m/z 297 $[M+Na]^+$.

4.17. (*R*)-4-(Methoxymethoxy)hex-5-en-1-ol 13

Adopted the same procedure as described for the synthesis compound **10** and purified by column chromatography (silica gel, 60–120 mesh, R_f 0.40, 20% EtOAc/hexane). Compound **12** (0.75 g, 2.74 mmol) gave **13** (0.306 g, 70%) as a thick syrup. Found: C, 59.82; H, 9.94. $C_8H_{16}O_3$ requires C, 59.97; H, 10.07%; $[\alpha]_D^{25}$ +227.6 (c 0.2, $CHCl_3$); IR (neat) $\bar{\nu}$: 3416, 2935, 1711, 1608, 1514, 1441, 1252, 1101, 1034, 916 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): 5.74–5.65 (1H, m, olefinic-H), 5.25–5.18 (2H, m, olefinic-H), 4.71 (1H, d, J=6.6 Hz, $-CH_aH_bOMe$), 4.55 (1H, d, J=6.6 Hz, $-CH_aH_bOMe$), 4.07–4.00 (1H, m, −CH−OMOM), 3.67 (2H, t, J=5.5 Hz, $-CH_2OH$), 3.38 (3H, s, −OMe), 1.73–1.55 (4H, m, $-CH_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): 138.1, 117.0, 93.5, 76.4, 63.2, 55.2, 31.5, 27.6; MS (ESI) m/z 183 $[M+Na]^+$.

4.18. (*R*)-6-Azido-3-(methoxymethoxy)hex-1-ene 14

Adopted the same procedure as described for the synthesis compound **2** and purified by column chromatography (silica gel, 60–120 mesh, R_f 0.60, 4% EtOAc/hexane). Compound **13** (0.28 g, 1.75 mmol) gave **14** (0.232 g, 71% over two steps) as a colorless liquid. Found C, 51.71; H, 8.01; N, 22.51. $C_8H_{15}N_3O_2$ requires C, 51.88; H, 8.16; N, 22.69%; $[\alpha]_D^{25}$ +256.8 (c 0.3, $CHCl_3$); IR (neat) $\bar{\nu}$: 3081, 2987, 2194, 2143, 1595, 1054 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): 5.74–5.60 (1H, m, Olefinic-H), 5.27–5.17 (2H, m, olefinic-H), 4.70 (1H, d, J=6.8 Hz, $-CH_aH_bOMe$), 4.54 (1H, d, J=6.7 Hz, $-CH_aH_bOMe$), 4.06–3.97 (1H, m, −CH−OMOM), 3.38 (3H, s, −OMe), 3.31 (2H, t, J=6.4 Hz, $-CH_2N_3$), 1.79–1.53 (4H, m, $-CH_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): 137.8, 117.5, 93.7, 76.7, 55.5, 51.3, 32.4, 24.8; MS (ESI) m/z 208 $[M+Na]^+$.

4.19. (*R*)-Methyl-5-azido-2-(methoxymethoxy)pentanoate 15

Adopted the same procedure as described for the synthesis compound **11** and purified by column chromatography (silica gel, 60–120 mesh, R_f 0.40, 12% EtOAc/hexane). Compound **14** (0.20 g, 1.08 mmol) gave **15** (0.17 g, 72% over two steps) as a thick syrup. Found: C, 44.14; H, 6.88; N, 19.29. $C_8H_{15}N_3O_4$ requires C, 44.23; H, 6.96; N, 19.34%; $[\alpha]_D^{25}$ −238.6 (c 0.4, $CHCl_3$); IR (neat) $\bar{\nu}$: 2982, 2194, 1725, 1595, 1145 cm^{-1}; ^{1}H NMR($CDCl_3$, 300 MHz): 4.69 (2H, 2×d, AB pattern, J=7.2 Hz, $-CH_2OMe$), 4.19–4.13 (1H, m, −CH(OMOM)COOMe), 3.76 (3H, s, −OMe), 3.40 (3H, s, −OMe), 3.33 (2H, t, J=6.8 Hz, $-CH_2N_3$), 1.91–1.80 (1H, m, $-CH_2$), 1.79–1.54 (3H, m, $-CH_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): 172.6, 96.1, 74.7, 55.9, 51.9, 50.9, 29.8, 24.6; MS (ESI) m/z 240 $[M+Na]^+$.

4.20. (*R*)-3-(Methoxymethoxy)piperidin-2-one 16

Adopted the same procedure as described for the synthesis compound **1** and purified by column chromatography (silica gel, 60–120 mesh, R_f 0.70, 2% MeOH/CH_2Cl_2). Compound **15** (0.14 g, 0.65 mmol) gave **16** (0.085 g, 82%) as a sticky oil. Found: C, 52.77; H, 8.17; N, 8.72. $C_7H_{13}NO_3$ requires C, 52.82; H, 8.23; N, 8.80%; $[\alpha]_D^{25}$

+270.3 (*c* 0.2, $CHCl_3$); IR (neat) $\bar{\nu}$: 3307, 3205, 2959, 2868, 1656, 1319, 1095 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): 6.30 (1H, br s, −NH), 5.01 (1H, d, *J*=6.6 Hz, $-CH_aH_bOMe$), 4.76 (1H, d, *J*=6.6 Hz, $-CH_aH_bOMe$), 4.09 (1H, dd, *J*=2.6, 5.4 Hz, −CHCONH), 3.43 (3H, s, −OMe), 3.36–3.23 (2H, m, $-CH_2NH$), 2.18–2.06 (1H, m, $-CH_aH_bCH_2NH$), 2.05–1.79 (3H, m, $-CH_aH_bCH_2NH$, $-CH_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): 171.7, 96.4, 71.6, 55.5, 41.9, 28.1, 19.8; MS (ESI) *m*/*z* 182 $[M+Na]^+$.

4.21. (*R*)-3-Hydroxypiperidin-2-one 17

To a solution of compound **16** (0.07 g, 0.44 mmol) in MeOH, Dowex was added and allowed to stir at reflux for 2 h. Reaction mixture was filtered with funnel through cotton, then solvent was removed under reduced pressure and purified by column chromatography (silica gel, 60–120 mesh, R_f 0.50, 5% MeOH/CH_2Cl_2) to afford **17** (0.044 g, 86%) as a solid, mp 135–137 °C. Found: C, 52.08; H, 7.80; N, 12.09. $C_5H_9NO_2$ requires C, 52.16; H, 7.88; N, 12.17%; $[\alpha]_D^{25}$ +6.0 (*c* 0.4, $CHCl_3$); IR (neat) $\bar{\nu}$: 3307, 3205, 2959, 2868, 1656, 1319, 1095 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): 5.83 (1H, br s, −NH), 4.05 (1H, dd, *J*=11.0 Hz, 6.0 Hz, −CHCONH), 3.60 (1H, br s, −OH), 3.38–3.29 (2H, m, $-CH_2NH$), 2.33–2.27 (1H, m, $-CH_aH_bCH_2NH$), 2.02–1.93 (1H, m, $-CH_aH_bCH(OH)CONH$), 1.92–1.82 (1H, m, $-CH_aH_bCH_2NH$), 1.78–1.69 (1H, m, $-CH_aH_bCH(OH)CONH$); ^{13}C NMR ($CDCl_3$, 75 MHz): 174.4, 67.7, 42.5, 28.3, 20.6; MS (ESI) *m*/*z* 138 $[M+Na]^+$.

4.22. (*S*)-((*R*)-2-Oxopiperidin-3-yl)-2-phenylpropanoate 1

Adopted the same procedure for the synthesis of compound **9** to the fragments **3** (0.034 g, 0.23 mmol) and **17** (0.022 g, 0.19 mmol), purified by column chromatography (silica gel, 60–120 mesh, R_f 0.70, 2% MeOH/$CHCl_3$) to afford **1** (0.028 g, 59%) as a sticky oil.

4.23. (*R*)-((*R*)-2-Oxopiperidin-3-yl)-2-phenylpropanoate 1a

Adopted the same procedure for the synthesis of compound **9** to the fragments **2a** (0.034 g, 0.23 mmol) and **17** (0.022 g, 0.19 mmol), purified by column chromatography (silica gel, 60–120 mesh, R_f 0.70, 2% MeOH/$CHCl_3$) to afford **1** (0.026 g, 55%) as a semi solid.

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