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Synthetic approach to oxa-triquinanes *via* olefin metathesis as a key step

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Earlier, a simple synthetic approach to *cis*, *syn*, *cis*-triquinanes and propellanes from *exo*-nadic anhydride through metathesis approach had been demonstrated. In the present work is discussed a distinct course of observations when this methodology has been extended to oxygenated *exo*-nadic anhydride derivatives and the importance of stereochemistry and the role of hetero atom in the outcome of olefin metathesis has been demonstrated.

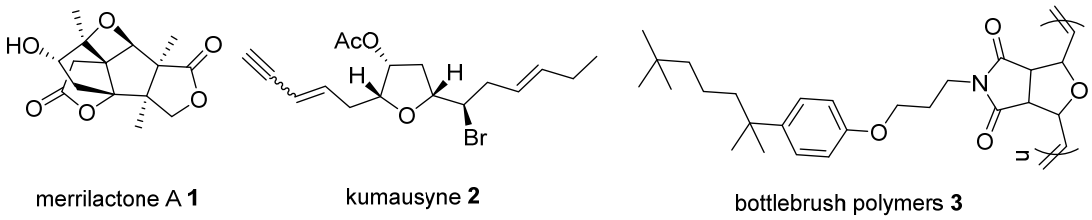
Keywords: Oxacycles, allylation, olefin metathesis, reduction, NOE

A large number of biologically active natural products[1,2] such as merrilactone A **1**[3], and kumausyne **2**[4] are composed of tetrahydrofuran (THF) as their structural unit (Figure 1). Recently, furan containing molecules are found to be useful in designing biopolymers, and bottlebrush polymers **3** (Figure 1)[5,6]. Synthesis of these complex structures involves a lengthy synthetic sequence by conventional routes. Interestingly, on several occasions, metathesis strategy was found to be a useful synthetic tool to assemble diverse heterocyclics in a concise manner[7].

Results and Discussion

In connection with our interest in polyquinane synthesis[8], we have reported a simple strategy to *cis*, *syn*, *cis*-triquinanes involving olefin metathesis as a key step[9]. In this regard, we identified *exo*-nadic anhydride as a useful starting material. To expand this strategy to hetero triquinane derivatives,we envisioned the *exo*-Diels-Alder (DA) adduct derived from furan is a useful synthon. Towards this goal, we prepared the *exo*-DA adduct **6** by [4+2] cyclocaddition reaction between furan **4**, and *N*-phenyl maleimide **5** in acetonitrile at 85°C[10]. The *exo* adduct **6** was subjected to allylation under basic conditions to produce the diallyl compound **7** (Scheme I). However, we did not get the desired compound **7**, and surprisingly, in the presence of lithium diisopropylamide (LDA), the adduct **6** gave *N*-phenyl phthalamide **9**, which might be formed through dehydration of the intermediate **8**. Whereas by using strong bases such as NaHMDS, LiHMDS, KO^{t}Bu, and KH the *C*-allylation reaction was not realized.

Further, ring-opening metathesis of the DA adduct **6** produced the divinyl derivative **10**, which was further subjected to allylation by using strong bases such as NaHMDS, LiHMDS, and NaH. Under the NaHMDS or LiHMDS conditions, we did not get the diallyl compound **13**. Interestingly, allylation by using NaH as a base in the presence of atmospheric moisture, the compound **6** undergo hydrolysis followed by *N*- and *O*-allylation in a one-pot manner to afford the compound **12** in 60% yield[11]. We found that moisture present in the reaction induce hydrolysis, and this observation was confirmed by carrying out the reaction using freshly dried THF, and

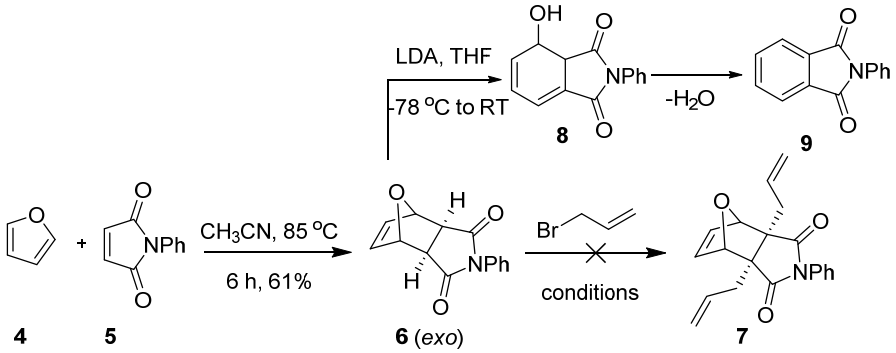


merrilactone A **1** kumausyne **2** bottlebrush polymers **3**

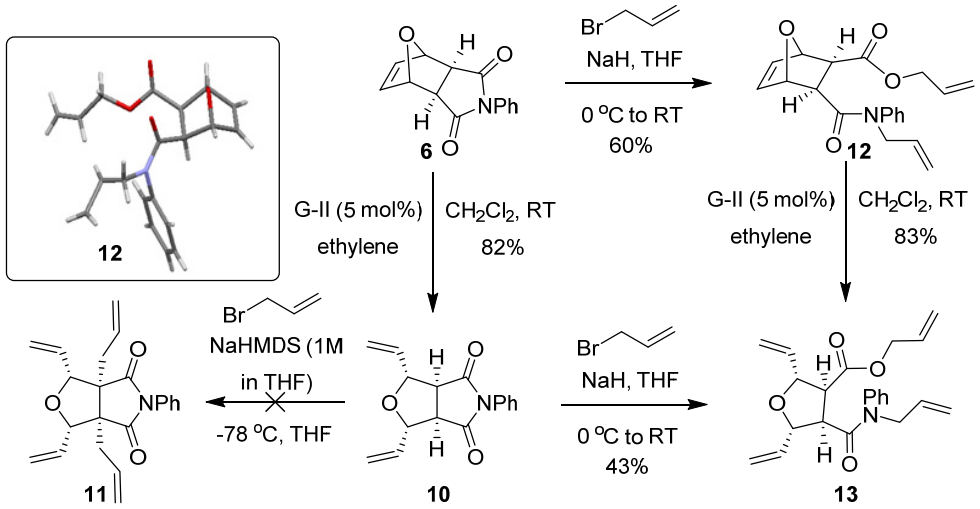
Figure 1 — Furan containing oxa-cycles

undried THF. The hydrolysis did not occur when freshly dried THF was used. The stereochemistry, and structure of compound **12** was confirmed by single-crystal XRD studies[12]. Under similar reaction conditions, the divinyl derivative **10** gave the diallyl compound **13** in 43% yield. This compound **13** was also obtained from compound **12** by ring-opening metathesis (ROM) sequence (Scheme II).

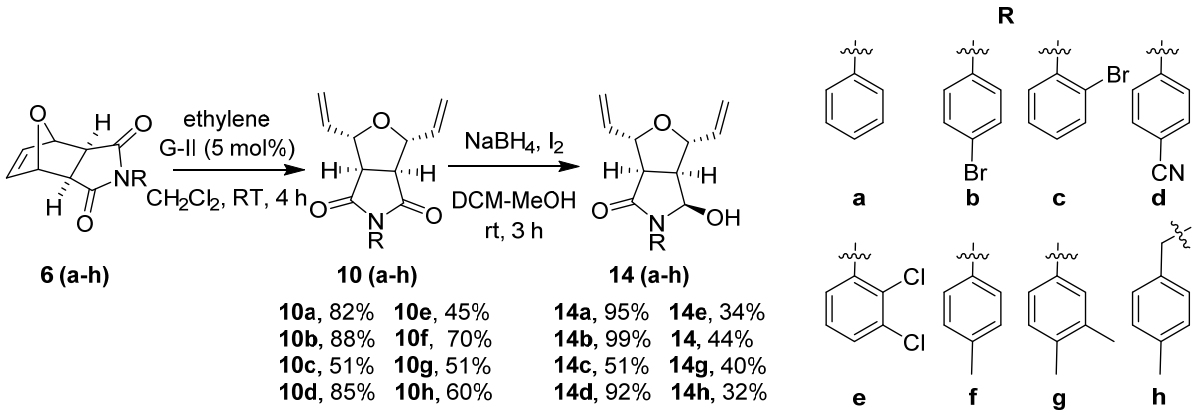
Further, ROM derivatives **10** (**a**-**h**) were treated with $NaBH_4$-I_2 in 1:1 mixture of CH_2Cl_2:MeOH to deliver the diastereoselective β-hydroxyl amide derivatives **14** (**a**-**h**) in good yields (Scheme III)[13].



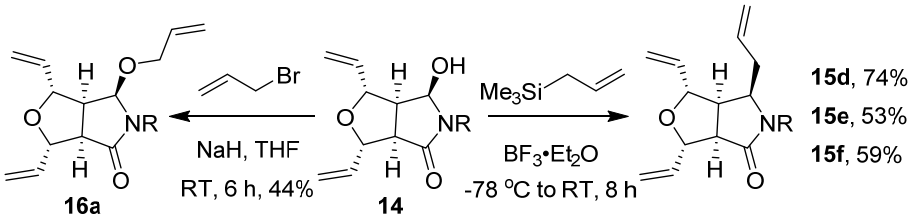
Scheme I — Attempted synthesis of diallyl derivative 7



Scheme II — Synthesis of the diallyl compound **13**



Scheme III — Synthesis of β-hydroxyl amide derivative **14**



Scheme IV — Synthesis of compounds **15** and **16**

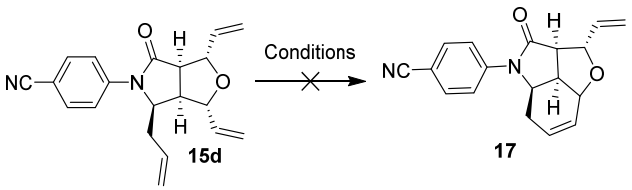
Stereochemistry of hydroxyl group present in the compound **14** was confirmed by NOE experiment. We found that substituents present in the benzene ring has influence on the yields of **14**. A higher yield of **14** was observed when electron-withdrawing groups (Br, CN) were present at the *para*-position, whereas the electron-donating group such as methyl group at the *para*-position diminishes the yield. Also, substitution at the *ortho*-position has decreases the yield of the hydroxyl derivative **14**.

Later, the β-hydroxyl amide derivatives **14** (**d-f**) were subjected to allylation with Lewis acid such as BF_3•Et_2O to give the corresponding *C*-allyl derivatives **15** (**d-f**) with moderate to good yields[14]. Additionally, the hydroxy derivative **14a** was reacted with allyl bromide in the presence of NaH to furnish the *O*-allyl derivative **16a** in 44% yield (Scheme IV).

We have performed the NOE studies of compounds **14b**, **14c**, and **16a** to establish the relative stereochemistry of the hydroxyl group. The details are included in supporting information. Finally, these allyl derivatives **15d** were subjected to metathesis under a variety of conditions which involve variation in catalyst, solvent or temperature (Table I)[15]. However, we failed to obtain the desired ring-closure product **19**.

Further, the *O*-allyl derivative **16a** was treated with the G-II catalyst under different conditions by changing the solvent, and temperature to obtain the tricyclic compound **19**. Unfortunately, we failed to deliver the desired tricyclic derivative **19**. These results can be explained from our previous observations on RCM which indicates that an unfavourable orientation of the olefinic moieties prevents the ring-closure[16].

Table I — Attempted reaction conditions for the metathesis of **15d**



S.No	Catalyst	Solvent	Temp (°C)/Time (h)
1	G-I	CH_2Cl_2	RT/8
2	G-I	PhMe	80/5
3	G-II	CH_2Cl_2	RT/8 h
4	G-II	PhMe	80/8
5	GH-I	PhMe	80/8

Experimental Section

Materials and Methods

All commercially available reagents were used without further purification and the reactions involving air-sensitive catalysts or reagents were performed in degassed solvents. Moisture-sensitive materials were transferred by using syringe-septum technique and the reactions were maintained under nitrogen atmosphere. Analytical thin-layer chromatography (TLC) was performed on (7.5 × 2.5 cm) glass plates coated with Acme's silica gel GF 254 (containing 13% calcium sulfate as a binder) by using a suitable mixture of EtOAc and petroleum ether for development. Column chromatography was performed by using Acme's silica gel (100-200 mesh) with an appropriate mixture of EtOAc and petroleum ether. The coupling constants (*J*) are given in hertz (Hz) and chemical shifts are denoted in parts per million (ppm) downfield from internal standard, tetramethylsilane (TMS). The abbreviations, s, d, t, q, m, dd, brs, td, tt and dt refer to singlet, doublet, triplet, quartet, multiplet, doublet of doublets, broad singlet, triplet of doublet, triplet of triplet and doublet of triplets, respectively. Infrared (IR) spectra were recorded on Nicolet Impact-400 FT-IR spectrometer. Nuclear Magnetic Resonance (NMR) spectra were generally recorded on a Bruker (AvanceTM 400 or AvanceTM III 500) spectrometer operating at 400 or 500 MHz for ^{1}H and 100.6 or 125.7 MHz for ^{13}C nuclei. The high-resolution mass spectrometric (HRMS) measurements were carried out using a Bruker (Maxis Impact) or Micromass Q-ToF spectrometer.

General procedure for metathesis

The compound (**6** or **12**) was dissolved in dry CH_2Cl_2 (7 mM) and degassed with N_2 gas followed by ethylene for about 20 min. To this, the G-II (5 mol%) catalyst was added and stirred at RT under ethylene atmosphere. The solvent was removed and the crude product was purified by column chromatography to obtain the pure product (**10** or **13**).

10a: Colourless liquid. Yield 82% (64 mg, starting from 70 mg of **6a**). R_f = 0.6 (silica gel, 10% EtOAc-Hexane); IR (neat): 1776, 1712, 1495, 1390, 1197 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.53–7.44 (m, 2H), 7.44–7.37 (m, 1H), 7.33–7.28 (m, 2H), 6.06 (ddd, 2H, *J* = 6.0 Hz, 10.7 Hz, 16.9 Hz), 5.50 (td, 2H, *J* = 1.2 Hz, 17.2 Hz), 5.33 (td, 2H, *J* = 1.0 Hz, 10.5 Hz), 4.63–4.53 (m, 2H), 3.47–3.37 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 174.9 (C), 136.0 (CH), 131.6 (CH), 129.4 (CH), 128.9 (CH), 126.5 (C), 118.3 (CH_2), 82.7 (CH), 52.5 (CH); HRMS (ESI, Q-ToF) *m/z* for $[M+Na]^+$ Found $[M+H]^+$: 272.1281. Calcd: 272.1279 for $C_{16}H_{15}NO_3$.

10b: Yield 88% (237 mg starting from 250 mg of **6b)**; White solid. R_f = 0.55 (silica gel, 10% EtOAc-Hexane); IR (neat): 1791, 1813, 1717, 1397, 1196, 676 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.61 (d, 2H, *J* = 8.72 Hz), 7.22 (d, 2H, *J* = 8.72 Hz), 6.12–5.96 (m, 2H), 5.50 (d, 2H, *J* = 17.16 Hz), 5.33 (d, 2H, *J* = 10.48 Hz), 4.64–4.52 (m, 2H), 3.42 (dd, 2H, *J* = 4.12 Hz, 1.84 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.6 (C), 135.8 (CH), 132.5 (CH), 127.9 (CH), 118.5 (CH_2), 82.6 (CH), 52.4 (CH_2); HRMS (ESI, Q-ToF) *m/z* for $[M+Na]^+$ Found: 370.0062. Calcd: 370.0049 for $C_{16}H_{14}NO_3Br$.

10c: Yield 51% (66 mg starting from 120 mg of **6c**); Colourless liquid. R_f = 0.55 (silica gel, 10% EtOAc-Hexane); IR (neat): 1791, 1716, 1397, 1196, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.71 (dd, 1H, *J* = 8.04 Hz, 1.32 Hz), 7.45 (dt, 1H, *J* = 7.64 Hz, 1.36 Hz), 7.34 (dt, 1H, *J* = 7.96 Hz, 1.68 Hz), 7.24 (dd, 1H, *J* = 7.80 Hz, 1.64 Hz), 6.12–6.01 (m, 2H), 5.52 (td, 2H, *J* = 17.20 Hz, 1.18 Hz), 5.33 (td, 2H, *J* = 10.48 Hz, 1.12 Hz), 4.73–4.68 (m, 2H), 3.42 (dd, 2H, *J* = 4.52 Hz, 1.96 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.9, 135.9, 135.6, 133.8, 133.7, 131.3, 131.0, 130.3, 128.8, 128.6, 122.4, 118.4, 118.3, 82.5, 82.3, 52.9, 52.6; HRMS (ESI, Q-ToF) *m/z* for $[M+Na]^+$ Found: 370.0066. Calcd: 370.0049 for $C_{16}H_{14}NO_3Br$.

10d: Yield 85% (230 mg starting from 250 mg of **6d**); Colourless liquid. R_f = 0.60 (silica gel, 10% EtOAc-Hexane); IR (neat): 2989, 2221, 1718, 1514, 1397, 1205 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.77 (td, 2H, *J* = 8.72 Hz, 2.10 Hz), 7.53 (td, 2H, *J* = 8.72 Hz, 1.91 Hz), 6.10–5.99 (m, 2H), 5.50 (td, 2H, *J* = 17.20 Hz, 1.10 Hz), 5.34 (td, 2H, *J* = 10.48 Hz, 0.95 Hz), 4.61–5.34 (m, 2H), 3.45 (dd, 2H, *J* = 4.16Hz, 1.86 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.2, 135.6, 135.5, 133.1, 126.9, 118.6, 118.0, 112.5, 82.6, 52.4; HRMS (ESI, Q-ToF) *m/z* for found $[M+Na]^+$ = 317.0884. Calcd: 317.0897 for $C_{17}H_{14}N_2O_3$.

10e: Yield 60% (324 mg starting from 500 mg of **6e**); Colourless liquid. R_f = 0.30 (silica gel, 20% EtOAc-Hexane); IR (neat): 2986, 2217, 1785, 1715, 1495, 1390, 1197, 767 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.58 (dd, 1H, *J* = 8.15 Hz, 1.42 Hz), 7.36–7.31 (m, 1H), 7.18–7.14 (m, 1H), 6.10–5.99 (m, 1H), 5.54–5.47 (m, 2H), 5.36–5.31 (m, 2H), 4.65–4.59 (m, 2H), 3.53–3.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.9, 173.7, 135.7, 135.4, 131.9, 131.8, 131.4, 131.0, 128.5, 128.1, 128.0, 127.9, 118.6, 118.4, 82.5, 82.4, 52.9, 52.6; HRMS (ESI, Q-ToF) *m/z* Found: $[M+Na]^+$ = 360.0174. Calcd: 360.0170 for $C_{16}H_{13}Cl_2NO_3$.

10h: Yield 60% (65 mg starting from 100 mg of 6h); colourless liquid. R_f = 0.35 (silica gel, 20% EtOAc-Hexane); IR (neat): 3084, 1718, 1495, 1390, 1210 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40–7.23 (m, 5H), 6.06–5.92 (m, 2H), 5.44 (d, 2H, *J* =17.20 Hz), 5.28 (d, 2H, *J* = 10.50 Hz), 4.6 (s, 2H), 4.36 (brs, 2H), 3.4 (d, 2H, *J* = 2.20 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.5, 135.8, 135.5, 128.7, 128.6, 128.0, 117.9, 82.0, 52.3, 42.4; HRMS (ESI, Q-ToF) *m/z* for found $[M+Na]^+$ = 306.1108. Calcd: 306.1105 for $C_{17}H_{17}NO_3$.

General procedure for allylation using NaH

NaH (60% dispersed in oil, 0.8-1.2 mmol) was washed with dry hexane (2 × 20 mL), and dry THF (10 mL) was added. After cooled to 0 °C, the compound (**6** or **10** or **14**, 0.15 mmol) followed by allyl bromide (1.33 mmol) was added over the period of 5 min. The mixture was brought to RT, and stirred for 90 min. After complete consumption of the starting material, the solvent was removed under reduced pressure and the residue was partitioned between EtOAc, and water. The organic layer was concentrated and the crude mixture was purified by column chromatography to yield the compound **12** or **13** or **16a**.

12: Yield 60% (380 mg, starting from 450 mg of 6); white solid. R_f = 0.25 (silica gel, 8% EtOAc-Hexane); IR (neat): 1727, 1662, 1390, 1296, 1166, 758 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.46–7.36 (m, 2H), 7.36–7.29 (m, 1H), 7.29–7.18 (m, 2H), 6.33–6.15 (m, 2H), 6.05–5.77 (m, 2H), 5.42–5.30 (m, 2H), 5.26 (d, 1H, *J* = 10.5 Hz), 5.12–5.04 (m, 2H), 5.01 (s, 1H), 4.65 (ddq, 2H, *J* = 1.1 Hz, 6.0 Hz, 12.9 Hz), 4.37–4.1 9 (m, 2H), 2.67 (d, 1H, *J* = 8.8 Hz), 2.40 (d, 1H, *J* = 8.8 Hz), 2.44–2.33 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.3 (C), 170.6 (C), 142.7 (C), 137.3 (CH), 136.5 (CH), 133.4(CH), 132.6 (CH), 129.9 (CH), 128.5 (CH), 128.1 (CH), 118.6 (CH_2), 118.2 (CH_2), 81.7 (CH), 79.7 (CH), 66.1 (CH_2), 52.8 (CH_2), 47.5 (CH), 44.8 (CH); HRMS (ESI, Q-ToF) *m/z*: $[M+H]^+$ Found: 339.1501 calculated= 339.1480 for $C_{20}H_{21}NO_4$.

13: Yield 43% (56 mg, starting from 120 mg of 10); colorless liquid. R_f = 0.25 (silica gel, 8% EtOAc-Hexane); IR (neat): 2983, 1740, 1374, 1242, 1047 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.44–7.30 (m, 7H), 7.19 (d, 4H, *J* = 7.3 Hz), 6.03–5.88 (m, 2H), 5.87–5.70 (m, 4H), 5.57–5.45 (m, 2H), 5.41–5.31 (m, 4H), 5.31–5.16 (m, 4H), 5.16–5.01(m,8H), 4.97–4.90 (m, 2H), 4.69–4.53 (m, 6H), 4.30–4.18 (m, 4H), 3.05 (dd, 2H, *J* = 6.8 Hz, 10.0 Hz), 2.72 (dd, 2H, *J* =8.4 Hz, 9.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.4 (C), 170.3 (C), 142.0 (C), 136.8 (CH), 136.4 (CH), 132.9 (CH), 132.3 (CH), 129.8 (CH), 128.7 (CH), 128.4 (CH), 118.9 (CH_2), 118.3 (CH_2), 117.5 (CH_2), 117.3 (CH_2), 83.6 (CH),81.3 (CH), 66.0 (CH_2), 53.0 (CH), 52.6 (CH_2), 50.7 (CH);HRMS (ESI, Q-ToF) *m/z* for $[M+Na]^+$ Found: 367.1792. Calcd: 367.1784 for $C_{22}H_{25}NO_4$.

16a: Yield 44% (61 mg, starting from 120 mg of **14**); colourless liquid. R_f = 0.35 (silica gel, 20% EtOAc-Hexane); IR (neat): 2983, 1733, 1451, 1374, 1242, 1042, 998 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.55–7.50 (m, 2H), 7.43–7.37 (m, 2H), 7.29–7.23 (m, 1H), 6.05–5.94 (m, 2H), 5.87–5.76 (m, 1H), 5.42 (tt, 2H, *J* = 17.08 Hz, 1.10 Hz), 5.30 (d, 1H, *J* = 10.28 Hz), 5.71–5.10 (m, 4H), 4.68–4.63 (m, 1H), 4.04 (t, 1H, *J* =8.04 Hz), 3.97–3.91 (m, 2H), 3.29 (dd, 2H, *J* =8.76 Hz, 4.32 Hz), 2.71 (t, 2H, *J* =8.80 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.9, 137.6, 137.5, 136.1, 133.3, 129.2, 126.7, 123.7, 118.6, 118.1, 116.7, 90.9, 84.0, 82.6, 67.9, 53.2, 49.6; HRMS (ESI, Q-ToF) *m/z* for $[M+Na]^+$ Found: 412.0504. Calcd: 412.0519 for $C_{19}H_{20}NO_3Br$.

General procedure of β-hydroxyl lactam synthesis

Imide (**10,** 1 mmol, 1 equiv.) was dissolved in CH_2Cl_2-MeOH(1:1, 20mL) and I_2(catalytic amount) was added under N_2 atmosphere. After stirred for 15 min at RT, $NaBH_4$ (4 equiv.) was added and the mixture was allowed to stir at RT for 8 h- 12 h. After completion of the reaction, solvents were removed under reduced pressure. The residue was diluted with CH_2Cl_2, washed with H_2O (2 × 30 mL), and concentrated to obtain the desired compound as a pure diastereomeric isomer.

14a: Yield 95% (57 mg, starting from 60 mg of **10a**); Colorless liquid. R_f = 0.32 (silica gel, 20% EtOAc-Hexane); IR (neat): 3146, 2983, 1733, 1411, 1374, 1242, 1047 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.56–7.51 (m, 2H), 7.41–7.36 (m, 2H), 7.28–7.24 (m, 1H), 6.06–5.92 (m, 1H), 5.89–5.82 (m, 1H), 5.39–5.33 (m, 2H), 5.28–5.24 (m, 2H), 5.18 (td, 1H, *J* =10.35 Hz, 1.17 Hz), 4.59–4.54 (m, 1H), 4.00 (t, 1H, *J* =7.87 Hz), 3.20 (dd, 1H, *J* =8.80 Hz, 4.40 Hz), 2.61 (t, 1H, *J* =8.75 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 174.4, 137.4, 137.0, 136.1, 129.4, 126.8, 123.5, 118.6, 116.8, 86.0, 84.1, 82.6, 53.0, 52.3; HRMS (ESI, Q-ToF) *m/z* for $[M+Na]^+$ Found: 394.1111. Calcd: 394.1106 for $C_{16}H_{17}NO_3$.

14c: Yield 51% (30 mg, starting from 60 mg of **10c**); Colourless liquid. R_f = 0.30 (silica gel, 20% EtOAc-Hexane); IR (neat): 3130, 2974, 1742, 1388, 1242, 1047 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.51–7.41 (m, 4H), 6.00–5.77 (m, 2H), 5.40–5.31 (m, 2H), 5.27 (d, 1H, *J* =10.32 Hz), 5.21–5.15 (m, 2H), 4.52 (t, 1H, *J* =5.02 Hz), 4.16 (brs, 1H), 3.95 (t, 1H, *J* =7.86 Hz), 3.14 (dd, 1H, *J* =8.76 Hz, 4.32 Hz), 2.60 (t, 1H, *J* =8.74 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.4, 137.2, 136.1, 135.9, 132.3, 124.6, 124.5, 119.9, 118.8, 117.0, 85.9, 84.1, 82.6, 53.1, 52.3; HRMS (ESI, Q-ToF) *m/z* for $[M+H]^+$ Found: 350.0384. Calcd: 350.0386 for $C_{16}H_{16}NO_3Br$.

14d: Yield 92% (184 mg, starting from 200 mg of **10d**); Colourless liquid. R_f = 0.30 (silica gel, 20% EtOAc-Hexane); IR (neat): 3144, 2983, 1739, 1411, 1374, 1242, 1187 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.71 (d, 2H, *J* =8.76 Hz), 7.57 (d, 2H, *J* = 8.72 Hz), 5.99–5.79 (m, 2H), 5.41–5.27 (m, 3H), 5.28–5.21 (m, 2H), 4.54 (t, 1H, *J* =5.04 Hz), 3.96 (t, 1H, *J* =7.86 Hz), 3.26 (dd, 1H, *J* =8.80 Hz, 4.96 Hz), 2.65 (t, 1H, *J* =8.76 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.5, 141.6, 137.0, 135.7, 133.0, 122.0, 118.8, 118.5, 117.0, 108.5, 85.0, 83.9, 82.5, 53.3, 52.0;HRMS (ESI, Q-ToF) *m/z* for $[M+Na]^+$ Found: 319.1059. Calcd: 319.1053 for $C_{17}H_{16}NO_3$.

14e: Yield 34% (34 mg, starting from 100 mg of **10e**); Colourless liquid. R_f = 0.35 (silica gel, 20% EtOAc-Hexane); IR (neat): 3146, 2983, 1733, 1411, 1374, 1248, 1047 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.44 (dd, 1H,*J* =8.70 Hz, 0.70 Hz), 7.18–7.06 (m, 2H), 5.96–5.78 (m, 2H), 5.33 (dd, 2H, *J* =17.15 Hz, 4.60 Hz), 5.21 (dd, 2H, *J* =29.15 Hz, 10.35 Hz), 4.95 (brs, 1H), 4.40 (t, 1H, *J* =5.50 Hz), 4.14 (t, 1H, *J* =7.90 Hz), 3.08 (dd, 1H, *J* =8.95 Hz, 4.90 Hz), 2.53 (t, 1H, *J* =8.90 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 174.5, 136.9, 135.7, 134.7, 133.7, 131.3, 130.6, 129.4, 127.6, 118.5, 117.0, 85.0, 83.8, 82.1, 53.2, 52.0; HRMS (ESI, Q-ToF) *m/z* for $[M+Na]^+$ Found: 340.0504. Calcd: 340.0502 for $C_{16}H_{16}NO_3Cl_2$.

14f: Yield 44% (44 mg, starting from 100 mg of **10f**); Colourless liquid. R_f = 0.30 (silica gel, 20% EtOAc-Hexane); IR (neat): 3139, 2983, 1736, 1411, 1374, 1242, 1177 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.40 (d, 2H, *J* = 8.40 Hz), 7.21 (d, 2H, *J* =8.10 Hz), 6.05–5.91 (m, 2H), 5.40 (tt, 2H, *J* =17.15 Hz, 1.10 Hz), 5.29 (m, 2H), 5.21 (td, 1H, *J* =10.45 Hz, 1.25 Hz), 4.63 (m, 1H), 4.05 (t, 1H, *J* =7.90 Hz), 3.27 (dd, 1H, *J* =8.80 Hz, 4.35 Hz), 3.05 (d, 1H, *J* =6.45 Hz), 2.67 (t, 1H, *J* =8.75 Hz), 2.35 (s, 3H); HRMS (ESI, Q-ToF) *m/z* for $[M+Na]^+$ Found: 308.1246. Calcd: 308.1257 for $C_{17}H_{19}NO_3$.

14g: Yield 40% (24 mg, starting from 60 mg of **10g**); Colourless liquid. R_f = 0.39 (silica gel, 20% EtOAc-Hexane); IR (neat): 3136, 2983, 1738, 1411, 1374, 1233, 998 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.28 (d, 1H, *J* =2.00 Hz), 7.21 (dd, 1H, *J* =8.08 Hz, 2.08 Hz), 7.09 (d, 1H, *J* =8.04 Hz), 5.98–5.73 (m, 2H), 5.37–5.07 (m, 5H), 4.50 (dd, 1H, *J* =5.9 Hz, 4.40 Hz), 3.94 (t, 1H, *J* =7.82 Hz), 3.14 (dd, 1H, *J* =8.72 Hz, 4.36 Hz), 2.53 (t, 1H, *J* =8.74 Hz), 2.23 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.4, 137.5, 137.3, 136.0, 135.2, 134.6, 130.2, 124.8, 121.1, 118.3, 116.5, 86.2, 84.0, 82.4, 52.9, 52.3, 19.9, 19.4; HRMS (ESI, Q-ToF) *m/z* for $[M+Na]^+$ Found: 322.1407. Calcd: 322.1414 for $C_{18}H_{21}NO_3$.

14h: Yield 92% (55 mg, starting from 60 mg of **10h**); Colourless liquid. R_f = 0.39 (silica gel, 20% EtOAc-Hexane); IR (neat): 3144, 2983, 1739, 1377, 1242, 1187 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ7.48–7.42 (m, 4H), 5.97–5.88 (m, 1H), 5.88–5.77 (m, 1H), 5.38–5.31 (m, 2H), 5.25 (d, 1H), 5.21–5.17 (m, 2H), 4.52 (dd, 1H, *J* =5.90 Hz, 4.55 Hz), 3.95 (t, 1H, *J* =7.92 Hz), 3.16 (dd, 1H, *J* =8.80 Hz, 4.30 Hz), 2.60 (t, 1H, *J* =8.75 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 174.4, 137.2, 136.2, 135.9, 132.3, 124.6, 121.9, 119.8, 118.7, 116.9, 84.1, 82.5, 53.1, 52.3; HRMS (ESI, Q-ToF) *m/z* for $[M+Na]^+$ Found: 308.1268. Calcd: 308.1263 for $C_{17}H_{19}NO_3$.

General procedure of β-allyl lactam synthesis

BF_3•Et_2O (1M, 4 equiv.) was added to the solution of β-hydroxyl lactam derivative (**10d-f**, 1 mmol, 1 equiv.) at -78 °C and stirred for 15 min under N_2 atmosphere. At which, allyl TMS (4 equiv.) was added to the resulted solution and allow to stir at the same temperature for 1 h. The reaction mixture was brought to RT in 4 – 8 h and continued to stir at RT for 2 h. After completion of the reaction, the reaction mixture was quenched, washed with H_2O (2 × 25 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to obtain the desired compound as a pure isomer. The crude product was purified by column chromatography.

15d: Yield 74% (74 mg, starting from 100 mg of **14d**); Colourless liquid. R_f = 0.42 (silica gel, 20% EtOAc-Hexane); IR (neat): 2945, 2217, 1710, 1482, 1390, 915cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.78–7.63 (m, 4H), 6.05–5.88 (m, 2H), 5.71–5.55 (m, 1H), 5.41 (dd, 2H, *J* =17.08 Hz, 9.28 Hz), 5.30 (d, 1H, *J* =10.28 Hz), 5.20 (dd, 2H, *J* =19.20Hz, 10.16 Hz), 5.09 (d, 1H, *J* =17.04 Hz), 4.60 (t, 1H, *J* = 5.14 Hz), 4.12 (dd, 1H, *J* =7.40 Hz, 2.40 Hz), 4.01 (t, 1H, *J* =7.90 Hz), 3.21 (dd, 1H, *J* =9.28 Hz, 4.40 Hz), 2.54 (t, 1H, *J* =9.04 Hz), 2.47–2.24 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.8, 141.6, 137.4, 135.8, 133.3, 131.3, 122.0, 120.4, 118.9, 118.6, 116.7, 108.5, 85.2, 82.6, 59.5, 54.5, 46.8, 37.1; HRMS (ESI, Q-ToF) *m/z* for $[M+H]^+$ Found: 343.1422. Calcd: 343.1422 for $C_{20}H_{23}N_2O_2$.

15e: Yield 53% (37 mg, starting from 70 mg of **14e**); Colourless liquid. R_f = 0.45 (silica gel, 20% EtOAc-Hexane); IR (neat): 3016, 2945, 1708, 1482, 1390, 921, 778 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.48 (dd, 1H, *J* =8.10 Hz, 1.50 Hz), 7.27 (t, 1H, *J* =8.00 Hz), 7.19 (dd, 1H, *J* =7.90 Hz, 1.50 Hz), 6.05–5.88 (m, 2H), 5.70–5.59 (m, 1H), 5.43 (tt, 2H, *J* =17.10 Hz, 1.30 Hz), 5.30–5.11 (m, 4H), 4.63 (t, 1H, *J* =3.60Hz), 4.33 (t, 1H, *J* =7.92 Hz), 3.91 (dd, 1H, *J* = 8.55 Hz, 3.10 Hz), 3.13 (dd, 1H, *J* =9.40 Hz, 4.85 Hz), 2.58 (t, 1H, *J* = 8.80 Hz), 2.36–2.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.6, 137.4, 135.8, 134.3, 131.9, 130.4, 127.7, 119.8, 118.4, 116.5, 85.3, 82.3, 52.7, 48.1, 37.9; HRMS (ESI, Q-ToF) *m/z* for $[M+Na]^+$ Found: 386.0688. Calcd: 386.0691 for $C_{19}H_{19}Cl_2NO_2$.

15f: Yield 59% (41 mg, starting from 70 mg of 14f); Colourless liquid. R_f = 0.48 (silica gel, 20% EtOAc-Hexane); IR (neat): 2957, 1712, 1482, 1515, 1390, 918 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.36–7.29 (m, 2H), 7.20 (d, 2H), 6.05–5.89 (m, 2H), 5.73–5.58 (m, 1H), 5.41 (tdd, 2H, *J* =17.12 Hz, 7.20 Hz, 1.36 Hz), 5.31–5.05 (m, 4H), 4.66–4.60 (m, 1H), 4.08 (t, 1H, *J* =7.94 Hz), 3.97 (dd, 1H, *J* =7.52 Hz, 3.08 Hz), 3.15 (dd, 1H, *J* = 9.24 Hz, 4.48 Hz), 2.50 (t, 1H, *J* =8.98 Hz), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.1, 137.9, 136.2, 136.1, 134.7, 132.1, 129.9, 123.7, 119.7, 118.4, 116.3, 85.9, 82.6, 60.8, 54.3, 47.0, 37.4, 21.1; HRMS (ESI, Q-ToF) *m/z* for $[M+H]^+$ Found: 309.1230. Calcd: 309.1729 for $C_{20}H_{23}NO_2$.

15g: Yield 57% (40 mg, starting from 70 mg of **14g**); Colourless liquid. R_f = 0.39 (silica gel, 20% EtOAc-Hexane); IR (neat): 2957, 1701, 1495, 1511, 1218 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.23 (d, 1H, *J* =1.65 Hz), 7.17– 7.10 (m, 2H), 6.03–5.90 (m, 2H), 5.72–5.62 (m, 1H), 5.42 (dd, 2H, *J* =17.15 Hz, 1.32 Hz), 5.31–5.07 (m, 4H), 4.63 (t, 1H, *J* =4.55 Hz), 4.08 (t, 1H, *J* =7.92 Hz), 3.95 (dd, 1H, *J* =7.65 Hz, 3.05 Hz), 3.15 (dd, 1H, *J* =9.25 Hz, 4.50 Hz), 2.50 (t, 1H, *J* =8.97 Hz), 2.40–2.32 (m, 1H), 2.27 (s, 3H), 2.25 (s, 3H), 2.24–2.20 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.1, 137.9, 137.7, 136.2, 134.9, 134.9, 132.2, 130.3, 125.2, 121.3, 119.7, 118.4, 116.3, 85.9, 82.6, 60.9, 54.3, 47.1, 37.4, 29.8, 20.1, 19.4; HRMS (ESI, Q-ToF) *m/z* for $[M+H]^+$ Found: 309.1226. Calcd: 309.1729 for $C_{20}H_{23}NO_2$.

Conclusion

We found that the imide derivatives **6** and **10** undergo hydrolysis followed by allylation by using NaH as a base in the presence wet THF. To design oxacylics and to synthesize β-hydroxyl amide derivatives **14** (**a-h**), we have developed a diastereoselective methodology using $NaBH_4$-I_2 mixture in good yields. Later, these hydroxyl derivatives were subjected to allylation by Lewis acid to produce β-allyl derivatives in a diastereoselective manner. However, metathesis of these β-allyl derivatives did not result in the formation of ring-closure products. This might be due to an unfavourable orientation of the olefinic residues which does not facilitate the RCM.

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