Synthesis S. Kotha, S. Pulletikurti Paper

A Metathetic Approach to [5/5/6] Aza-Tricyclic Core of Dendrobine, Kopsanone, and Lycopalhine A Type of Alkaloids

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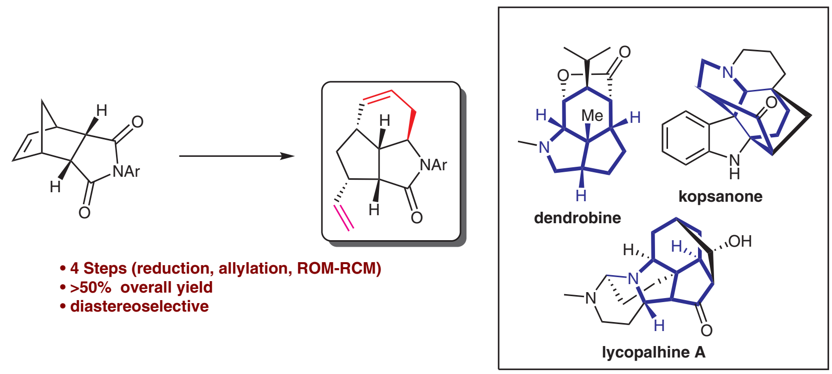

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Abstract A concise synthetic approach to [5/5/6] tricyclic pyrrolidine core of dendrobine is reported. This methodology relies on the construction of β-hydroxylactams by $NaBH_4$-I_2 reduction followed by reaction of allylsilane with the aid of Lewis acid to generate alkenyl lactams in good yields. Further, ring-opening metathesis (ROM) followed by ring-closing metathesis (RCM) were used to assemble the [5/5/6] aza-tricyclic skeleton of dendrobine. This short synthetic route has been expanded to assemble tricyclic [5/5/8] system with pentenylboronic acid.

Key words dendrobine, [5/5/6] aza-tricyclic, metathesis, allylation, NOE, BF_3·OEt_2

The total synthesis of alkaloids has been considered as a challenging task in organic synthesis.[1a] Alkaloids such as dendrobine (**1**), kopsanone (**2**), and lycopalhine A (**3**) contain the [5/5/6] aza-tricyclic core as a common structural element. Dendrobine (**1**), a tetracyclic pyrrolidine alkaloid isolated from the *Dendrobium nobile* plant, shows analgesic and antipyretic activity.[1] Dendrine (**4**) and mubironine C (**5**) are structurally related alkaloids to dendrobine (**1**), originated from similar orchid species.[2] Kopsinidines **6–8** and kopsanone (**2**) are monoterpenoid alkaloids isolated from *Kopsia officinalis* plant that exhibits anti-inflammatory, antirheumatic, and cholinergic effects.[3] Interestingly, lycopalhine A (**3**) is a hexacyclic *lycopodium* alkaloid isolated from *Palhinhaea cernua* plant, a family of *lycopodiaceae*.[4] Total synthesis of these pyrrolidine-based alkaloids have gained considerable interest in recent years due to their unique structural features and a wide range of biological activities (Figure 1).

Synthesis of tricyclic [5/5/6] pyrrolidine unit is not a trivial task. Previously, this pyrrolidine-based [5/5/6] tricyclic core has been assembled by a lengthy synthetic sequence in moderate yields. Recently, Chen and co-workers have disclosed the [5/5/6] aza-tricyclic Kende intermediate towards asymmetric synthesis of dendrobine in seven steps in 15% overall yield (Scheme 1a).[5] In 2018, Williams and Trauner have reported the synthesis of 5-deoxymubironine C in eight steps in 7% overall yield (Scheme 1b).[6]

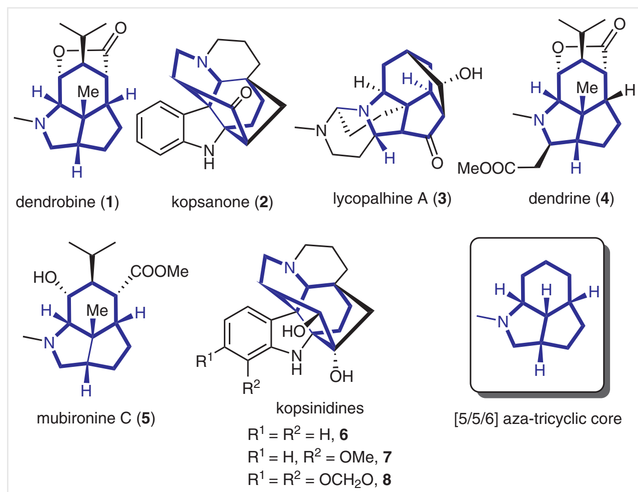
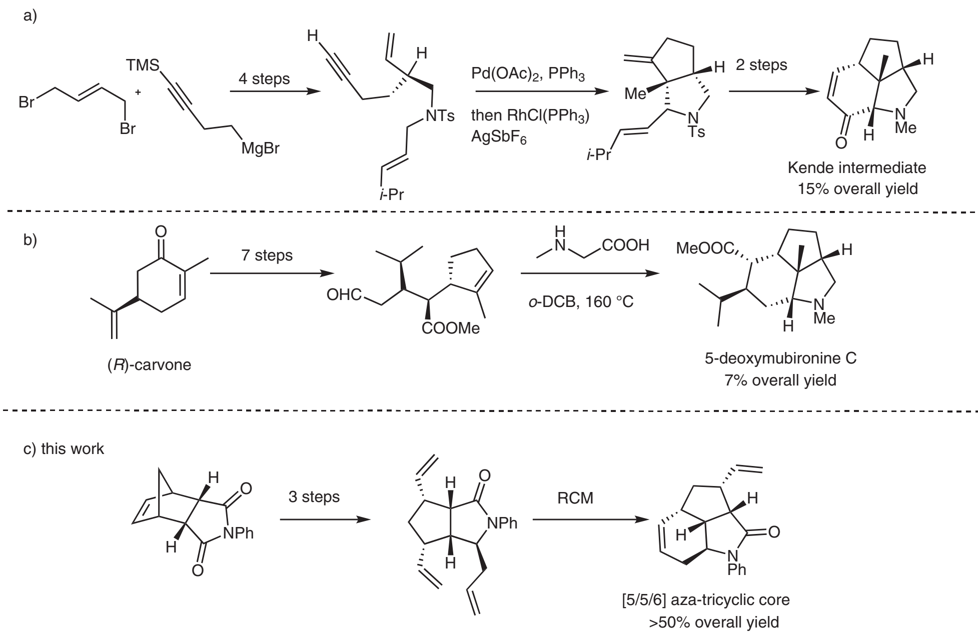


Figure 1 Alkaloids containing [5/5/6] aza-tricyclic core

Here, we have developed a simple and stereoselective metathesis strategy to synthesize [5/5/6] pyrrolidine aza-tricyclic core, which produced more than 50% overall yield in a stereoselective manner (Scheme 1c). Further, we expanded this strategy to assemble [5/5/8] aza-tricyclic core successfully. The methodology reported to pyrrolidine cores may be useful in generating compounds suitable for material science and bioactive targets.

Our synthesis starts with the preparation of known *endo*-Diels–Alder (DA) adducts **9a–d**,[7] which on reduction with $NaBH_4$-I_2 system[8] at room temperature in CH_2Cl_2–MeOH gave the hydroxyl derivatives **10a–d** in good yields

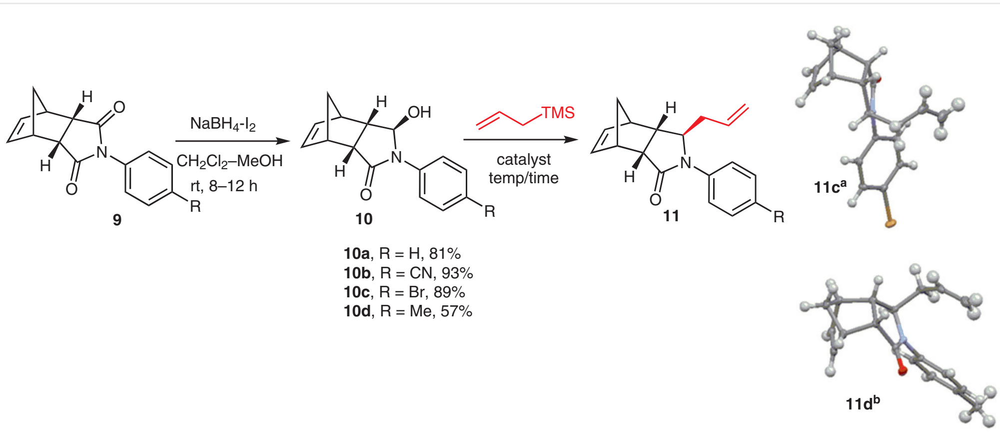


Scheme 1 (a) Earlier reported asymmetric pathway to dendrobine; (b) Previously reported azomethine ylide pathway to 5-deoxymubironine C; (c) Proposed metathetic approach to [5/5/6] aza-tricyclic core

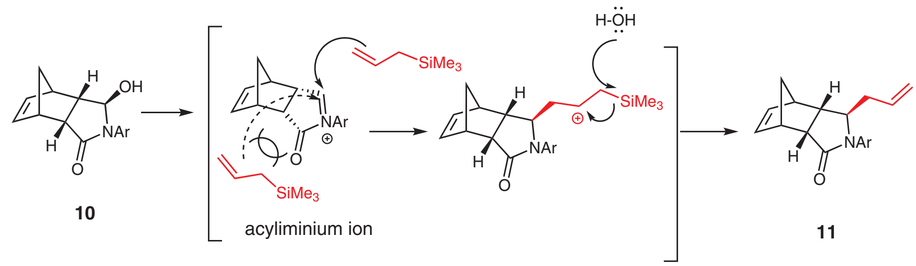
as a pure diastereomer (Scheme 2). We found that electron-withdrawing groups (CN, Br) at *para*-position produce excellent yields of **10b** and **10c**, whereas electron-donating group (Me) gave moderate yields. The stereochemistry of **10** was confirmed by NOE experiment. Recently, Bergens and co-workers have reported an enantioselective catalytic hydrogenation of amides and imides through base-catalyzed bifunctional addition. They assigned the stereochemistry of the hydroxyl group with the aid of single crystal X-ray analysis data of the corresponding carbamate derivative.[9] Further, addition of allylsilane via *N*-acyliminium ions is one of the mostly used methodology to synthesize functionalized lactams.[10] Thus, allylation of **10** with allyl TMS was accomplished in the presence of $BF_3{\cdot}OEt_2$ at –78 °C to deliver the allyl derivative **11** in good yield with a β-selectivity (Scheme 2).

The stereochemistry of allyl derivative **11** was derived by attack of allyl TMS on acyliminium ion from less hindered side as proposed in the mechanism (Scheme 3) and the stereochemistry was confirmed by NOE study and further supported by single-crystal X-ray diffraction studies.[11]

We have studied the allylation sequence at different temperatures (–78 °C to rt) to improve the yield and found that this reaction gave stereocontrolled product **11** even at



Scheme 2 Synthesis of α-allyl precursor **11**. [a] Crystal XRD of **11c** with thermal ellipsoids drawn at 50% probability level. [b] Crystal XRD of **11d** with thermal ellipsoids drawn at 50% probability level.



Scheme 3 Possible mechanism for allylation

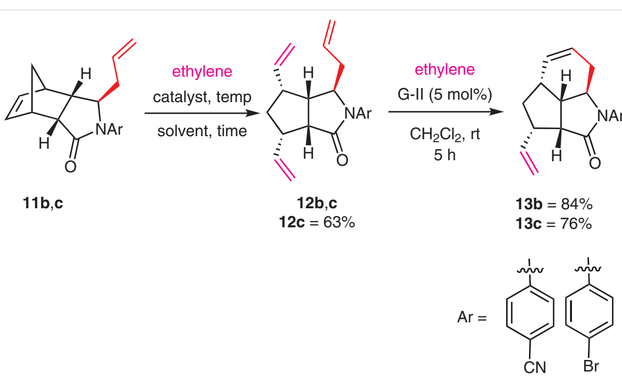
0 °C and also at room temperature in excellent yields (Table 1).

Table 1 Reaction Conditions of Allylation of **10**

Entry	Compound	R	Catalyst	Temp (°C)	Time (h)	Conversion (%)[a]
1	**10b**	CN	$BF_3{\cdot}OEt_2$	−78	15	73
2	**10d**	Me	$BF_3{\cdot}OEt_2$	−78	15	47
3	**10c**	Br	$BF_3{\cdot}OEt_2$	−78	15	65
4	**10c**	Br	$BF_3{\cdot}OEt_2$	−40	14	78
5	**10c**	Br	$BF_3{\cdot}OEt_2$	−20	15	97
6	**10c**	Br	$BF_3{\cdot}OEt_2$	0	8	98
7	**10c**	Br	$BF_3{\cdot}OEt_2$	rt	6	100
8	**10c**	Br	$TiCl_4$	0	8	40
9	**10c**	Br	CF_3CO_2H	0	8	45
10	**10c**	Br	$SiCl_4$	0	8	0

[a] Percentage of conversion of allylation is based on the ^{1}H NMR data.

Further, α-allyl derivatives **11b** and **11c** were subjected to metathesis using Grubbs 1st, 2nd generation and Hoveyda–Grubbs 1st and 2nd catalysts under different conditions.[12] Unfortunately, we did not observe the ring-rearrangement metathesis (RRM) product **13** under these conditions (Table 2); however, we found the ring-opening metathesis (ROM) products **12b** and **12c**. Later, these were again subjected to the ring-closing metathesis (RCM) using G-II catalyst at room temperature to deliver the desired aza-tricyclic derivatives **13b** and **13c** in 84% and 76% yield, respectively (Scheme 4).[12]



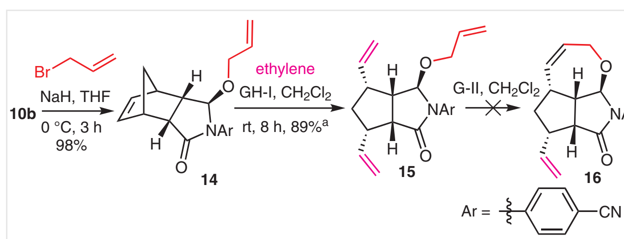
Scheme 4 Synthesis of aza-tricyclic core **13** using metathesis strategy

Table 2 Reaction Optimization of ROM of **11b**

Entry	Catalyst (mol%)	Solvent/temp/time	Yield of **12b** (%)[a]
1	G-I (5 mol%)	CH_2Cl_2/rt/12 h	34
2	G-I (10 mol%)	CH_2Cl_2/rt/12 h	26
3	G-I (10 mol%)	toluene/reflux/8 h	28
4	G-II (5 mol%)	CH_2Cl_2/rt/12 h	25
5	GH-I (5 mol%)	CH_2Cl_2/rt/12 h	72
6	GH-I (5 mol%)	toluene/reflux/8 h	70
7	GH-II (5 mol%)	CH_2Cl_2/rt/12 h	36

[a] Isolated yield.

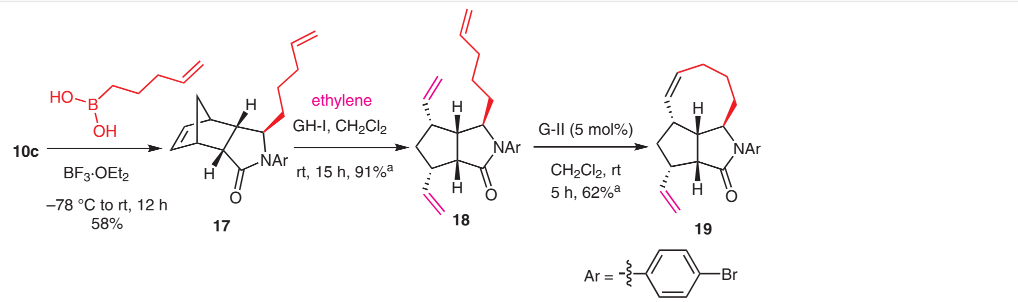
Along similar lines, the hydroxy derivative **10b** was treated with allyl bromide in the presence of NaH to furnish the *O*-allyl derivative **14** in 98% yield.[13] Further, this *O*-allyl derivative **14** was subjected to ROM to yield the compound **15**, which on treatment with G-I and G-II catalysts did not produce the expected ring-closure product **16** (Scheme 5).



Scheme 5 Synthesis of the compound **15** (70% of conversion from **14** to **15** by ^{1}H NMR analysis). [a] Yield is based on the recovery of 30% starting material.

NOE Study

We have performed the NOE studies of compounds **10**, **11**, **12**, and **14** to establish the relative stereochemistry of alkyl and vinyl side chains. For example, H_d proton of cyclic CH_d=CH moiety shows strong NOE correlation with H_a of



Scheme 6 Synthesis of compound **19** (65% of conversion from **17** to **18** by ^{1}H NMR analysis). ^{a} Yields are based on recovery of 35% starting material.

CH$_a$–NPh of compounds **10**, **11**, and **14**. Additionally, methylene protons (H$_j$, H$_k$) of CH$_2$=CH exhibit NOE correlation with the H$_g$ of bridged CH$_2$ in compound **14**. These results indicated that the stereochemistry of hydroxyl group of **10** is assigned as β-orientation. Similarly, methylene protons (H$_h$ and H$_i$) of allyl group exhibit strong NOE with the bridge protons (H$_b$ and H$_c$) in compound **11** and H$_a$ of CH$_a$–NPh of the compound **12** shows NOE correlation with H$_d$ of vinylic CH$_d$=CH$_2$ group of **12**. These observations support the stereochemistry of allyl group of **11** as β (Figure 2).

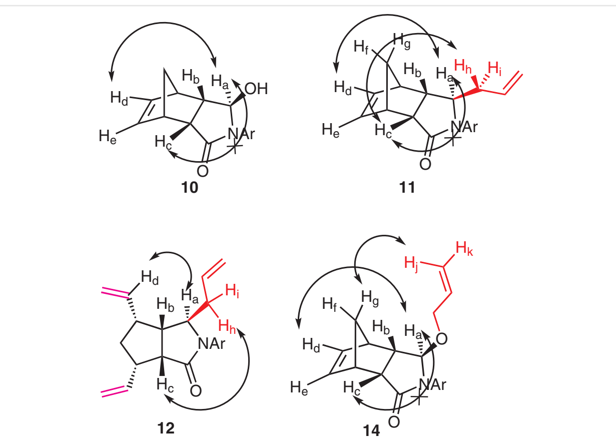


Figure 2 NOE correlation of the compounds **10**, **11**, **12**, and **14**

We have expanded this methodology to synthesize [5/5/8] tricyclic derivative **19**, which is difficult to assemble by conventional methods. Addition of unsaturated boronic acid such as pentenylboronic acid to *N*-acyliminium ions in the presence of Lewis acid, for example, BF$_3$·OEt$_2$, copper triflate, and Ca(II) catalysts, is not reported.[14–17]

Thus, the hydroxy derivative **10** was treated with pentenylboronic acid in the presence of BF$_3$·OEt$_2$ at –78 °C to deliver the pentenyl derivative **17** in 58% yield. This derivative **17** was further subjected to ROM using GH-I catalyst followed by RCM using G-II catalyst to obtain the corresponding aza-tricyclic analogue **19** in good yield (Scheme 6).[12]

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 N$_2$ atmosphere. Analytical TLC was performed on glass plates (7.5 × 2.5 cm) coated with Acme's silica gel GF 254 (containing 13% CaSO$_4$ as a binder) by using a suitable mixture of EtOAc and PE for development. Column chromatography was performed by using Acme's silica gel (100–200 mesh) with an appropriate mixture of EtOAc and PE. The coupling constants (*J*) are given in hertz (Hz) and chemical shifts are denoted in parts per million (ppm) downfield from internal standard TMS. Standard abbreviations are used to denote spin multiplicities. IR spectra were recorded on Nicolet Impact-400 FT-IR spectrometer. 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.

endo-Imides 9a–d;[7] General Procedure

The known *endo*-imides **9a–d** were prepared following the literature procedure.[7]

Compound 9a

Off-white solid; mp 143.9–144.9 °C[18a]; R_f = 0.35 (20% EtOAc/hexane).

^{1}H and ^{13}C NMR spectra of compound **9a** matched with the literature reported values.[7]

Compound 9b

White solid; mp 169–172 °C[18b]; R_f = 0.39 (20% EtOAc/hexane).

^{1}H and ^{13}C NMR spectra of compound **9b** matched with the literature reported values.[7]

Compound 9c

White solid; mp 153.4–154.6 °C[18a]; R_f = 0.38 (20% EtOAc/hexane).

^{1}H and ^{13}C NMR spectra of compound **9c** matched with the literature reported values.[7]

Compound 9d

Off-white solid; mp 158.2–158.6 °C[18a]; R_f = 0.36 (20% EtOAc/hexane).

^{1}H and ^{13}C NMR spectra of compound **9d** matched with the literature reported values.[7]

β-Hydroxyl Lactams 10; General Procedure

The respective imide **9** (1 mmol, 1 equiv) was dissolved in CH_2Cl_2–MeOH (1:1, 20 mL) and I_2 (catalytic amount) was added at rt under N_2 atmosphere. Later, the resultant solution was stirred for 15 min at rt; $NaBH_4$ (5 mmol, 5 equiv) was added and the mixture was allowed to stir for 8–12 h at rt. 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 diastereomer.

Compound 10a

Pale yellow liquid yield: 820 mg (81%) starting from 1.0 g of **9a**; R_f = 0.32 (30% EtOAc/hexane).

IR (neat): 2946, 2931, 1687, 1551, 1392, 822, 771 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.45–7.33 (m, 4 H), 7.26–7.19 (m, 1 H), 6.25 (dd, *J* = 5.40, 2.60 Hz, 1 H), 6.16 (dd, *J* = 5.45, 2.55 Hz, 1 H), 4.97 (d, *J* = 7.20 Hz, 1 H), 3.38–3.31 (m, 2 H), 3.26 (br s, 1 H), 2.88 (d, *J* = 7.35 Hz, 1 H), 2.75 (dd, *J* = 8.25, 4.25 Hz, 1 H), 1.62 (dd, *J* = 8.55, 1.30 Hz, 1 H), 1.44 (dd, *J* = 8.50 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 175.2 (C), 137.1 (C), 136.7 (CH), 133.4 (CH), 129.3 (CH), 126.8 (CH), 124.6 (CH), 87.1 (CH), 51.4 (CH_2), 49.6 (CH), 46.5 (CH), 45.9 (CH), 45.30 (CH).

HRMS (ESI, Q-ToF): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{15}NO_2Na$: 264.0996; found: 264.0993.

Compound 10b

White solid; yield: 744 mg (93%) starting from 800 mg of **9b**; mp 161.1–165.7 °C; R_f = 0.30 (30% EtOAc/hexane).

IR (neat): 2925, 2228, 1683, 1510, 1392, 1304, 842, 760 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.70 (d, *J* = 8.76 Hz, 2 H), 7.60 (d, *J* = 8.72 Hz, 2 H), 6.17 (dd, *J* = 5.64, 2.80 Hz, 1 H), 6.09 (dd, *J* = 5.60, 2.92 Hz, 2 H), 5.00 (s, 1 H), 3.38–3.30 (m, 2 H), 3.28 (br s, 1 H), 2.76 (dd, *J* = 8.28, 4.24 Hz, 1 H), 1.62 (d, *J* = 8.60 Hz, 1 H), 1.42 (d, *J* = 8.68 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 175.5 (C), 141.5 (C), 136.5 (CH), 133.5 (CH), 133.1 (CH), 122.4 (CH), 118.7 (C), 108.8 (C), 86.5 (CH), 51.4 (CH_2), 49.9 (CH), 46.7 (CH), 46.4 (CH), 45.4 (CH).

HRMS (ESI, Q-ToF): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{14}N_2O_2Na$: 289.0947; found: 289.0946.

Compound 10c

White solid; yield: 890 mg (89%) starting from 1.0 g of **9c**; mp 186.1–188.3 °C; R_f = 0.29 (30% EtOAc/hexane).

IR (neat): 2922, 1689, 1516, 1429, 989, 770 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.43 (dt, *J* = 8.84, 2.04 Hz, 2 H), 7.30 (dt, *J* = 8.88, 2.04 Hz, 2 H), 6.17 (dd, *J* = 5.64, 2.96 Hz, 1 H), 6.09 (dd, *J* = 5.56, 2.88 Hz, 1 H), 4.85 (d, *J* = 6.32 Hz, 1 H), 3.61 (d, *J* = 8.08 Hz, 1 H), 3.31 (br t, *J* = 1.26 Hz, 1 H), 3.27–3.20 (m, 2 H), 2.70 (ddd, *J* = 8.52, 4.24, 0.76 Hz, 1 H), 1.60 (dt, *J* = 8.55, 1.52 Hz, 1 H), 1.38 (d, *J* = 8.52 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 175.7 (C), 136.4 (CH), 133.5 (CH), 132.1 (CH), 125.4 (CH), 119.7 (C), 87.2 (CH), 51.4 (CH_2), 49.6 (CH), 46.6 (CH), 46.1 (CH), 45.3 (CH).

HRMS (ESI, Q-ToF): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{14}BrNO_2Na$: 342.0099; found: 342.0100.

Compound 10d

White solid; yield: 455 mg (57%) starting from 800 mg of **9d**; mp 104.8–106.5 °C; R_f = 0.30 (30% EtOAc/hexane).

IR (neat): 2933, 1684, 1515, 1405, 1321, 842, 761 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.23 (d, *J* = 8.40 Hz, 2 H), 7.14 (d, *J* = 8.24 Hz, 2 H), 6.22 (dd, *J* = 5.52, 2.78 Hz, 1 H), 6.13 (dd, *J* = 5.56, 2.78 Hz, 1 H), 4.88 (s, 1 H), 3.37–3.17 (m, 4 H), 2.71 (dd, *J* = 8.40, 4.14 Hz, 1 H), 2.32 (s, 3 H), 1.59 (d, *J* = 8.48 Hz, 1 H), 1.40 (d, *J* = 8.48 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 175.1 (C), 136.7 (C), 136.6 (CH), 134.5 (C), 133.4 (CH), 129.8 (CH), 124.7 (CH), 87.3 (CH), 51.4 (CH_2), 49.5 (CH), 46.5 (CH), 45.8 (CH), 45.2 (CH), 21.1 (CH).

HRMS (ESI, Q-ToF): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{17}NO_2Na$: 278.1153; found: 278.1151.

β-Allyl Lactams 11b–d and Lactam 17; General Procedure

$BF_3{\cdot}OEt_2$ (4 mmol for 1 mmol of **10**, 4 equiv) was added to a solution of the respective β-hydroxyl lactam derivative **10b–d** (1 mmol, 1 equiv) at the given temperature (Table 1) and the mixture was stirred for 15 min under N_2 atmosphere. Next, allyl TMS or pentenylboronic acid (4 mmol for 1 mmol of **10**, 4 equiv) was added to the solution and allowed to stir for 1 h at the same temperature. The mixture was brought to rt over 4–8 h and the stirring was continued for 2 h at rt. After completion of reaction, the mixture was quenched and washed with H_2O (2 × 25 mL). The organic layer was dried (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.

Compound 11b

White solid; yield: 140 mg (73%) starting from 250 mg of **10b** (yield based on 30% recovered starting material); mp 105.8–108.2 °C; R_f = 0.55 (20% EtOAc/hexane).

IR (neat): 2935, 2222, 1692, 1508, 1385, 1295, 915, 763 cm$^{-1.}$

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.62 (d, *J* = 8.56 Hz, 2 H), 7.55–7.51 (m, 2 H), 6.19 (s, 2 H), 5.74–5.62 (m, 1 H), 5.18–5.02 (m, 2 H), 3.79 (dt, *J* = 7.72, 5.30 Hz, 1 H), 3.34 (br s, 1 H), 3.29 (dd, *J* = 9.16, 9.14 Hz, 1 H), 3.14 (br s, 1 H), 2.65 (ddd, *J* = 9.16, 2.52 Hz, 1 H), 2.38–2.30 (m, 1 H), 2.25–2.16 (m, 1 H), 1.61 (d, *J* = 8.50 Hz, 1 H), 1.43 (d, *J* = 8.50 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 175.1 (C), 141.7 (C), 137.6 (CH), 133.6 (CH), 133.1 (CH), 132.2 (CH), 123.0 (CH), 119.6 (CH_2), 118.8 (C), 108.3 (C), 61.1 (CH), 51.1 (CH_2), 51.0 (CH), 46.8 (CH), 46.0 (CH), 40.7 (CH), 38.2 (CH_2).

HRMS (ESI, Q-ToF): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{18}N_2ONa$: 313.1312; found: 313.1311.

Compound 11c

White solid; yields starting from 300 mg (0.874 mmol) of **10c** are mentioned in Table 1; mp 106.1–110.6 °C; R_f = 0.57 (20% EtOAc/hexane).

IR (neat): 2930, 1689, 1491, 1387, 1290, 826 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.44 (d, *J* = 8.76 Hz, 2 H), 7.17 (d, *J* = 8.76 Hz, 2 H), 6.21 (s, 2 H), 5.74–5.60 (m, 1 H), 5.12 (d, *J* = 10.12 Hz, 1 H), 5.06 (dd, *J* = 17.08, 1.38 Hz, 1 H), 3.68–3.61 (m, 1 H), 3.31 (s, 1 H), 3.23 (dd, *J* = 9.24, 9.14 Hz, 1 H), 3.10 (d, *J* = 3.10 Hz, 1 H), 2.61 (qt, *J* = 10.56, 2.22 Hz, 1 H), 2.33–2.24 (m, 1 H), 2.20–2.10 (m, 1 H), 1.59 (d, *J* = 8.38 Hz, 1 H), 1.41 (d, *J* = 8.44 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 174.6 (C), 137.5 (CH), 136.6 (C), 133.6 (CH), 132.5 (CH), 132.1 (CH), 125.8 (CH), 119.2 (CH_2), 61.9 (CH), 51.0 (CH_2), 50.6 (CH), 46.6 (CH), 45.6 (CH), 40.8 (CH), 38.3 (CH_2).

HRMS (ESI, Q-ToF): m/z [M + Na]$^+$ calcd for $C_{18}H_{18}BrNONa$: 366.0464; found: 366.0461.

Compound 11d

Colorless liquid; yield: 107 mg (47%) starting from 300 mg of **10d** (yield based on 30% recovered starting material); R_f = 0.55 (20% EtOAc/hexane).

IR (neat): 2927, 1688, 1395, 915, 816 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.17–7.10 (m, 4 H), 6.28–6.21 (m, 2 H), 5.77–5.65 (m, 1 H), 5.16–5.04 (m, 2H), 3.60 (dt, J = 7.88, 2.74 Hz, 1 H), 3.36–3.30 (m, 1 H), 3.23 (dd, J = 9.33, 9.16 Hz, 1 H), 3.12–3.07 (m, 1 H), 2.61 (qd, J = 10.56, 2.24 Hz, 1 H), 2.31 (s, 3 H), 2.30–2.25 (m, 1 H), 2.21–2.05 (m, 1 H), 1.60 (dt, J = 8.44, 1.56 Hz, 1 H), 1.42 (d, J = 8.44 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 174.7 (C), 137.5 (CH), 136.1 (C), 134.9 (C), 133.6 (CH), 133.0 (CH), 129.7 (CH), 124.8 (CH), 118.8 (CH_2), 62.4 (CH), 51.0 (CH_2), 50.5 (CH), 46.7 (CH), 45.6 (CH), 40.9 (CH), 38.5 (CH_2), 21.1 (CH).

HRMS (ESI, Q-ToF): m/z [M + Na]$^+$ calcd for $C_{19}H_{21}NONa$: 302.1515; found: 302.1515.

Compound 17

Colorless liquid; yield: 100 mg (58%) starting from 150 mg of **10c**; R_f = 0.50 (20% EtOAc/hexane).

IR (neat): 2926, 2857, 1691, 1484, 1384, 914 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.44 (d, J = 8.16 Hz, 2 H), 7.31 (d, J = 8.3 Hz, 2 H), 6.21 (s, 1 H), 6.12 (s, 1 H), 5.80–5.66 (m, 1 H), 5.03–4.90 (m, 2 H), 4.72 (s, 1 H), 3.43–3.27 (m, 4 H), 3.19 (s, 1 H), 2.76 (br s, 1 H), 2.06 (q, J = 6.90 Hz, 1 H), 1.70–1.53 (m, 4 H), 1.46 (d, J = 8.60 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 175.4 (C), 137.9 (CH), 136.9 (C), 136.8 (CH), 136.7 (CH), 133.2 (CH), 132.1 (CH), 125.6 (C), 125.2 (CH), 119.5 (C), 115.3 (CH_2), 92.7 (CH), 64.7 (CH_2), 51.5 (CH_2), 49.8 (CH), 46.1 (CH), 45.6 (CH), 43.3 (CH), 30.3 (CH_2), 28.9 (CH_2).

HRMS (ESI, Q-ToF): m/z [M + Na]$^+$ calcd for $C_{21}H_{22}N_2ONa$: 341.1625; found: 341.1624.

Compound 14

NaH (60% dispersed in paraffin, 115 mg, 4.7 mmol, 5 equiv) was washed with anhyd PE (2 × 20 mL) and dried under N_2 before being suspended in anhyd THF (20 mL). To this suspension, was added compound **10b** (300 mg, 0.94 mmol) and stirred for 10 min at rt. After the reaction mixture was cooled to 0 °C, allyl bromide (0.45 mL, 2.82 mmol, 3 equiv) was added and allowed to stir for overnight at rt. After the completion of reaction, THF was removed and the residue was suspended in EtOAc (30 mL). The suspension was washed with H_2O (2 × 20 mL), the organic layer was separated, and dried (Na_2SO_4). Solvents were removed under reduced pressure to obtain the compound **14** as a pure product; yield: 330 mg (98%); colorless liquid; R_f = 0.35 (30% EtOAc/hexane).

IR (neat): 2972, 2223, 1708, 1508, 1385, 1064, 841, 748 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.65–7.60 (m, 2 H), 7.59–7.54 (m, 2 H), 6.15 (s, 1 H), 6.06 (d, J = 2.89 Hz, 1 H), 5.88–5.76 (m, 1 H), 5.23 (d, J = 17.16 Hz, 1 H), 5.15 (d, J = 10.40 Hz, 1 H), 4.87 (s, 1 H), 3.95 (d, J = 5.52 Hz, 2 H), 3.37–3.30 (m, 2 H), 3.18 (s, 1 H), 2.84–2.77 (m, 1 H), 1.52 (dd, J = 61.50, 8.48 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 175.6 (C), 141.7 (C), 136.5 (CH), 133.3 (CH), 133.2 (CH), 132.8 (CH), 122.4 (CH), 118.6 (C), 117.8 (CH_2), 108.6 (C), 91.4 (CH), 66.2 (CH_2), 51.4 (CH_2), 49.9 (CH), 46.2 (CH), 45.5 (CH), 42.8 (CH).

HRMS (ESI, Q-ToF): m/z [M + Na]$^+$ calcd for $C_{19}H_{18}N_2O_2Na$: 329.1259; found: 329.1260.

Ring-Opening Metathesis; General Procedure

The respective compound **11**, **17**, or **14** was dissolved in an anhyd solvent (7 mM, CH_2Cl_2, or toluene) and degassed with N_2 followed by ethylene for about 20 min. To this, was added Grubbs catalyst (5 mol% or 10 mol%) and stirred (as described in Table 2 conditions) under ethylene atmosphere. Solvent was removed and the crude product was purified by column chromatography to obtain the desired product.

Compound 12b

Colorless liquid; yields starting from 70 mg of **11b** (0.22 mmol) are given in Table 2; R_f = 0.6 (20% EtOAc/hexane).

IR (neat): 2925, 2227, 1703, 1509, 1386, 1295, 920, 760 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.63 (s, 4 H), 6.10–5.98 (m, 1 H), 5.94–5.82 (m, 1 H), 5.63–5.49 (m, 1 H), 5.26–4.93 (m, 6 H), 4.24 (pent, J= 3.04 Hz, 1 H), 3.22 (t, J = 8.68 Hz, 1 H), 2.96–2.82 (m, 2 H), 2.75 (td, J = 11.20, 2.64 Hz, 1 H), 2.34–2.15 (m, 2 H), 1.96–1.87 (m, 1 H), 1.45 (q, J = 12.45 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 173.7 (C), 141.7 (C), 137.5 (CH), 133.1 (CH), 131.7 (CH), 122.8 (CH), 120.0 (CH_2), 117.1 (CH_2), 115.1 (CH_2), 108.3 (C) 58.5 (CH), 51.6 (CH), 47.3 (CH), 46.4 (CH), 42.7 (CH), 37.7 (CH_2), 35.2 (CH_2).

HRMS (ESI, Q-ToF): m/z [M + H]$^+$ calcd for $C_{21}H_{22}N_2O$: 319.1804; found: 319.1805.

Compound 12c

Colorless liquid; yield: 48 mg (63%) from 70 mg of **11c** (0.19 mmol); R_f = 0.6 (20% EtOAc/hexane).

IR (neat): 2923, 1702, 1641, 1490, 1291, 916, 757 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.47 (dt, J = 8.84, 2.04 Hz, 2 H), 7.31 (dt, J = 8.78, 2.07 Hz, 2 H), 6.13–6.04 (m, 1 H), 5.97–5.86 (m, 1 H), 5.64–5.51 (m, 1 H), 5.65–5.51 (m, 6 H), 4.14 (dt, J = 6.52, 3.24 Hz, 1 H), 3.19 (t, J = 8.74 Hz, 1 H), 2.94–2.83 (m, 2 H), 2.74 (td, J = 8.48, 3.16 Hz, 1 H), 2.30–2.13 (m, 2 H), 1.92 (dt, J = 12.36, 5.89 Hz, 1 H), 1.50 (q, J = 12.45 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 173.2 (C), 137.9 (CH), 137.7 (CH), 136.6 (C), 132.2 (CH), 132.1 (CH), 125.4 (CH), 119.6 (CH_2), 118.9 (C), 116.8 (CH), 114.8 (CH), 59.1 (CH), 51.4 (CH), 47.2 (CH), 46.4 (CH), 42.9 (CH), 37.7 (CH_2), 35.3 (CH_2).

HRMS (ESI, Q-ToF): m/z [M + H]$^+$ calcd for $C_{20}H_{22}BrNO$: 394.0777; found: 394.0775.

Compound 18

Colorless liquid; yield: 45 mg (91%) from 70 mg of **17** (0.22 mmol) (yield based on 35% recovered starting material); R_f = 0.6 (20% EtOAc/hexane).

IR (neat): 2937, 1691, 1491, 1385, 1292, 827, 757 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.49–7.44 (m, 2 H), 7.40–7.36 (m, 2 H), 6.19–6.10 (m, 1 H), 5.97–5.89 (m, 1 H), 5.75–5.66 (m, 1 H), 5.24–5.04 (m, 6 H), 3.34–3.23 (m, 3 H), 2.94–2.84 (m, 2 H), 2.80 (t, J = 8.60 Hz, 1 H), 2.00 (q, J = 7.15 Hz, 2 H), 1.95–1.87 (m, 1 H), 1.70–1.64 (m, 1 H), 1.59–1.53 (m, 2 H), 1.39 (q, J = 12.52 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 173.5 (C), 137.9 (CH), 137.5 (CH), 137.3 (CH), 136.8 (C), 132.3 (CH), 132.1 (CH), 125.3 (CH), 125.1 (CH), 119.4 (C), 117.1 (CH_2), 115.2 (CH_2), 115.1 (CH_2), 91.1 (CH), 65.3 (CH_2), 50.5 (CH), 47.0 (CH), 45.8 (CH), 45.2 (CH), 35.0 (CH_2), 30.2 (CH_2), 28.8 (CH_2).

HRMS (ESI, Q-ToF): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{26}N_2ONa$: 369.1935; found: 369.1937.

Compound 15

Colorless liquid; yield: 68 mg (89%) from 100 mg of **14** (yield based on 30% recovered starting material); R_f = 0.45 (30% EtOAc/hexane).

IR (neat): 2863, 2227, 1713, 1499, 1400, 1058, 932, 761 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.74–7.69 (m, 2 H), 7.66–7.60 (m, 2 H), 6.20–6.09 (m, 1 H), 5.96–5.86 (m, 1 H), 5.84–5.73 (m, 1 H), 5.36 (d, *J* = 1.00 Hz, 1 H), 5.25–5.07 (m, 6 H), 3.90 (dt, *J* = 5.52, 1.32 Hz, 2 H), 3.31 (t, *J* = 8.10 Hz, 1 H), 3.00–2.84 (m, 3 H), 1.98–1.86 (m, 1 H), 1.37 (q, *J* = 12.46 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 173.8, 141.7, 137.0, 133.3, 133.0, 122.5, 118.7, 117.9, 117.5, 115.4, 108.8, 90.0, 66.7, 50.5, 47.1, 45.1, 34.9, 29.8.

HRMS (ESI, Q-ToF): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{22}N_2O_2$: 357.4083; found: 357.4085.

Ring-Closing Metathesis; General Procedure

The respective compound **12** or **18** was dissolved in an anhyd solvent (7 mM, CH_2Cl_2 or toluene) and degassed with N_2 followed by ethylene for about 20 min. To this, Grubbs 2nd generation catalyst (G-II, 5 mol%) was added and stirred for 5 h at rt under ethylene atmosphere. Solvents were removed and purified by column chromatography to obtain the desired product.

Compound 13b

Colorless liquid; yield: 30 mg (84%) starting from 40 mg of **12b**; R_f = 0.48 (20% EtOAc/hexane).

IR (neat): 2876, 2219, 1717, 1476, 990, 755 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.69–7.63 (m, 2 H), 7.39–7.34 (m, 2 H), 6.01–5.93 (m, 1 H), 5.83–5.66 (m, 2 H), 5.08 (dt, *J* = 16.92, 1.30 Hz, 1 H), 4.97 (dt, *J* = 10.20, 2.48 Hz, 1 H), 3.87 (td, *J* = 10.44, 3.80 Hz, 1 H), 3.36–3.23 (m, 1 H), 3.15 (dd, *J* = 11.76, 6.92 Hz, 1 H), 2.86–2.75 (m, 1 H), 2.61–2.50 (m, 2 H), 2.44–2.34 (m, 1 H), 2.09–2.00 (m, 1 H), 1.80–1.69 (m, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 176.7 (C), 141.9 (C), 139.0 (CH), 132.9 (CH), 131.5 (CH), 125.9 (CH), 123.5 (CH), 118.9 (C), 115.2 (CH_2), 108.5 (C), 57.3 (CH), 51.4 (CH), 50.7 (CH), 45.0 (CH), 40.2 (CH), 38.2 (CH_2), 30.2 (CH_2).

HRMS (ESI, Q-ToF): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{18}N_2ONa$: 313.1316; found: 313.1318.

Compound 13c

Colorless liquid; yield: 28 mg (76%) starting from 40 mg of **12c**; R_f = 0.50 (20% EtOAc/hexane).

IR (neat): 2925, 2853, 1714, 1490, 992, 762 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.49 (d, *J* = 8.68 Hz, 2 H), 7.11 (d, *J* = 8.72 Hz, 2 H), 5.99–5.92 (m, 1 H), 5.85–5.73 (m, 2 H), 5.08 (dt, *J* = 16.96, 1.25 Hz, 1 H), 4.99 (dt, *J* = 10.28, 1.16 Hz, 1 H), 3.81 (td, *J* = 14.52, 3.38 Hz, 1 H), 3.33–3.23 (m, 1 H), 3.11 (dd, *J* = 11.88, 6.96 Hz, 1 H), 2.83–2.73 (m, 1 H), 2.55–2.48 (m, 1 H), 2.47–2.34 (m, 2 H), 2.08–2.02 (m, 1 H), 1.79–1.72 (m, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 176.9 (C), 139.3 (CH), 136.8 (C), 132.1 (CH), 131.5 (CH), 126.1 (CH), 125.7 (CH), 114.9 (CH_2), 57.8 (CH), 51.6 (CH), 50.7 (CH), 44.9 (CH), 40.1 (CH), 38.3 (CH), 30.2 (CH_2).

HRMS (ESI, Q-ToF): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{18}BrNONa$: 366.0461; found: 366.0464.

Compound 19

Colorless liquid; yield: 13 mg (62%) starting from 25 mg of **18**; R_f = 0.46 (20% EtOAc/hexane).

IR (neat): 2923, 2857, 1710, 1491, 1384, 1286, 1074, 915 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.53–7.47 (m, 2 H), 7.41–7.34 (m, 2 H), 5.26–5.19 (m, 1 H), 5.18–5.06 (m, 2 H), 4.39–4.09 (m, 1 H), 3.84–3.37 (m, 2 H), 3.26–3.24 (m, 1 H), 3.01–2.84 (m, 2 H), 2.77 (t, *J* = 8.91 Hz, 1 H), 2.08–1.89 (m, 2 H), 1.54–1.28 (m, 6 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 173.1, 137.3, 136.9, 136.0, 132.3, 125.3, 125.2, 119.7, 118.1, 117.1, 115.3, 114.2, 85.1, 50.2, 50.0, 49.4, 46.7, 45.1, 34.9.

HRMS (ESI, Q-ToF): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{22}BrNO$: 394.0775; found: 394.0776.

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Supporting Information

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References

(1) (a) Nawrat, C. C.; Moody, C. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 2056. (b) Inubushi, Y.; Sasaki, Y.; Tsuda, Y.; Yasui, B.; Konita, T.; Matsumoto, J.; Katarao, E.; Nakano, J. *Tetrahedron* **1964**, *20*, 2007. (c) Chen, K. K.; Chen, A. L. *J. Biol. Chem.* **1935**, *111*, 653.

(2) (a) Inubushi, Y.; Nakano, J. *Tetrahedron Lett.* **1965**, 2723. (b) Morita, H.; Fujiwara, M.; Yoshida, N.; Kobayashi, J. I. *Tetrahedron* **2000**, *56*, 5801.

(3) (a) Zeng, T.; Wu, X.-Y.; Yang, S.-X.; Lai, W.-C.; Shi, S.-D.; Zou, Q.; Liu, Y.; Li, L.-M. *J. Nat. Prod.* **2017**, *80*, 864. (b) Yap, W.-S.; Gan, C.-Y.; Sim, K.-S.; Lim, S.-H.; Low, Y.-Y.; Kam, T.-S. *J. Nat. Prod.* **2016**, *79*, 230. (c) Leng, L.; Zhou, X.; Liao, Q.; Wang, F.; Song, H.; Zhang, D.; Liu, X.-Y.; Qin, Y. *Angew. Chem. Int. Ed.* **2017**, *56*, 3703.

(4) (a) Dong, L.-B.; Yang, J.; He, J.; Luo, H.-R.; Wu, X.-D.; Deng, X.; Peng, L.-Y.; Cheng, X.; Zhao, Q.-S. *Chem. Commun.* **2012**, *48*, 9038. (b) Ochi, Y.; Yokoshima, S.; Fukuyama, T. *Org. Lett.* **2016**, *18*, 1494.

(5) Lee, Y.; Rochette, E. M.; Kim, J.; Chen, D. Y. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 12250.

(6) Williams, B. M.; Trauner, D. *J. Org. Chem.* **2018**, *83*, 3061.

(7) Kotha, S.; Aswar, V. R. *Org. Lett.* **2016**, *18*, 1808.

(8) (a) Periasamy, M.; Thirumalaikumar, M. *J. Organomet. Chem.* **2000**, *609*, 137. (b) Haldar, P.; Ray, J. K. *Tetrahedron Lett.* **2003**, *44*, 8229.

(9) John, J. M.; Takebayashi, S.; Dabral, N.; Miskolzie, M.; Bergens, S. H. *J. Am. Chem. Soc.* **2013**, *135*, 8578.

(10) (a) Yazici, A.; Wille, U.; Pyne, S. G. *J. Org. Chem.* **2016**, *81*, 1434. (b) Burgess, K. L.; Lajkiewicz, N. J.; Sanyal, A.; Yan, W.; Snyder, J. K. *Org. Lett.* **2005**, *7*, 31. (c) Liu, X.; Snyder, J. K. *J. Org. Chem.* **2008**, *73*, 2935.

(11) (a) CCDC 1887403 (**11c**) and 1887402 (**11d**) contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures. (b) NOE data of compound **11c** and **11d** are provided in the Supporting Information.

(12) (a) Kotha, S.; Pulletikurti, S. *RSC Adv.* **2018**, *8*, 14906. (b) Ogba, O. M.; Warner, N. C.; O'Leary, D. J.; Grubbs, R. H. *Chem. Soc. Rev.* **2018**, *47*, 4510. (c) Connon, S. J.; Blechert, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 1900. (d) Grela, K. *Beilstein J. Org. Chem.* **2015**, *11*, 1639. (e) Randall, M. L.; Snapper, M. L. *J. Mol. Catal. A: Chem.* **1998**, *133*, 29. (f) Acharyya, R. K.; Rej, R. K.; Nanda, S. *J. Org. Chem.* **2018**, *83*, 2087. (g) Bose, S.; Ghosh, M.; Ghosh, S. *J. Org. Chem.* **2012**, *77*, 6345. For previous work of our research group in the field, see: (h) Kotha, S.; Rao, N. N.; Ravikumar, O.; Sreevani, G. *Tetrahedron Lett.* **2017**, *58*, 1283. (i) Kotha, S.; Chinnam, A. K.; Shirbhate, M. E. *J. Org. Chem.* **2015**, *80*, 9141. (j) Kotha, S.; Manivannan, E.; Ganesh, T.; Sreenivasachary, N.; Deb, A. *Synlett* **1999**, 1618. (k) Kotha, S.; Sreenivasachary, N. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 257. (l) Kotha, S.; Waghule, G. T. *J. Org. Chem.* **2012**, *77*, 6314. (m) Kotha, S.; Bansal, D.; Singh, K.; Banerjee, S. *J. Organomet. Chem.* **2011**, *1856*, 696. (n) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9203. (o) Kotha, S.; Shah, V. R.; Mandal, K. *Adv. Synth. Catal.* **2007**, *349*, 1159.

(13) (a) Kotha, S.; Gunta, R. *Beilstein J. Org. Chem.* **2016**, *12*, 1877. (b) Kotha, S.; Ravikumar, O.; Sreevani, G. *Tetrahedron* **2016**, *72*, 6611. For previous work of our research group in the field of allylation, see: (c) Kotha, S.; Behera, M.; Shah, V. R. *Synlett* **2005**, 1877.

(14) (a) Batey, R. A.; MacKay, D. B.; Santhakumar, V. *J. Am. Chem. Soc.* **1999**, *121*, 5075. (b) Wu, P.; Petersen, M. A.; Cohrt, A. E.; Petersen, R.; Clausen, M. H.; Nielsen, T. E. *Eur. J. Org. Chem.* **2015**, 2346. (c) Wu, P.; Nielsen, T. E. *Chem. Rev.* **2017**, *117*, 7811.

(15) Rao, H. S. P.; Rao, A. V. B. *J. Org. Chem.* **2015**, *80*, 1506.

(16) (a) Qi, C.; Gandon, V.; Leboeuf, D. *Adv. Synth. Catal.* **2017**, *359*, 2671. (b) Maury, J.; Force, G.; Darses, B.; Leboeuf, D. *Adv. Synth. Catal.* **2018**, *360*, 2752.

(17) Lansakara, A. I.; Mariappan, S. V. S.; Pigge, F. C. *J. Org. Chem.* **2016**, *81*, 10266.

(18) (a) Andrade, E. S.; Nunes, R. J.; Uieara, M. *Synth. Commun.* **2004**, *34*, 3073. (b) Mikroyannidis, J. A. *J. Appl. Polym. Sci.* **1993**, *47*, 1915.