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Synthesis of spiro-annulated cyclobutane derivatives through ketene [2+2] cycloaddition and ring-rearrangement metathesis

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Herein is reported a concise synthesis of spiro-annulated cyclobutane tetracyclic and pentacyclic derivatives by ketene addition, and ring-rearrangement metathesis (RRM) as key steps, starting with commercially available norbornadiene and dicyclopentadiene. The tetracyclic spiro-derivative contains a [5/5/4] core unit, which is the key building block to angular triquinanes synthesis. Whereas, the pentacyclic spiro-derivative contains a basic core skeleton of presilphiperfolanes, and other sesquiterpenoids.

Keywords: Cyclobutane, spirocyclic, ketene addition, metathesis, dechlorination

Most of the natural products such as alkaloids, terpenoids, lactones, *etc*. contain spirocyclics as a core units. Due to their intrinsic rigidity and complexity, spirocycles draw increasing attention in modern drug design and also in medicinal chemistry[1,2]. Cyclobutane is a highly strained ring system, commonly present in natural products. However, cyclobutane containing spirocyclic compounds are present in limited number of natural products, for example phainanoids, phainanoid F **1**, licopodine derivative **2**. The cyclobutane compound **3** is a highly potent inhibitor of histone methyltransferase. Whereas, the hydroxyl derivatives **4** and **5** are BACE1 (β-site APP-cleaving enzyme 1) inhibitors that lower Aβ-levels in rat (Figure 1)[3].

Here, we described the synthesis of a rare class of spiro-annulated cyclobutane derivatives by in combination of ketene [2+2] cycloaddition[4] and ring-rearrangement metathesis (RRM)[5] in a concise manner. These derivatives can be useful building blocks to angular triquinanes[6], sesquiterpenoids, and presilphiperfolane type of compounds.

Results and Discussion

Our synthesis starts with ketene addition to norbornadiene **6** which involve the reaction of trichloroacetyl chloride in the presence of zinc metal in anhydrous ether at RT for overnight to deliver the [2+2] cycloaddition product **7** in 68% yield[7]. The dichloro compound **7** was exposed to allylation using NaHMDS and LiHMDS and we found that by using LiHMDS condition gave the allylation product to generate the compound **8** in 57% yield[8]. Subsequently, metathesis of the compound **8** using G-I catalyst in CH_2Cl_2 at RT gave ring-opening metathesis (ROM) conditions product **9** in 52% yield (Scheme I).

Thereafter, the ROM derivative **9** was subjected to ring-closing metathesis (RCM)[9] using various conditions by changing the catalysts (G-I, G-II, HG-I and HG-II), catalyst loading (5 mol% and 10 mol%), solvent (CH_2Cl_2, PhMe) and temperature (RT to reflux temperature). However, we failed to get the desired RCM product **10**[3a]. This may be because of steric factor associated with chlorine atoms present or unfavourable stereochemistry of the unsaturated double bonds present in the compound **9**.

Thereafter, the compound **11** was subjected to dechlorination using Zn/AcOH at 80°C, gave the cyclobutanone derivative **12** in good yield[10]. Using NaHMDS or LiHMDS as a base, the compound **12** was reacted with 4.0 equiv. of allyl bromide at −78°C, and obtained the triallyl derivative **13** in good yield. Finally, the triallyl compound **13** was subjected to metathesis with G-I catalyst (5 mol%) to deliver the spiro-tricylic derivative **14** *via* ring-rearrangment metathesis (RRM) and RCM in a moderate yields (Scheme II). Later, we have optimized the reaction conditions (Table I) to obtain better yields of metathesis product **14**[11]. The spiro compound **14** has a [5/5/4] tricyclic core. Compounds containing [5/5/4] tricyclic unit were synthetically transformed to angular triquinanes (*e.g*. ventricosene[12a]) by ring expansion of cyclobutane[12].

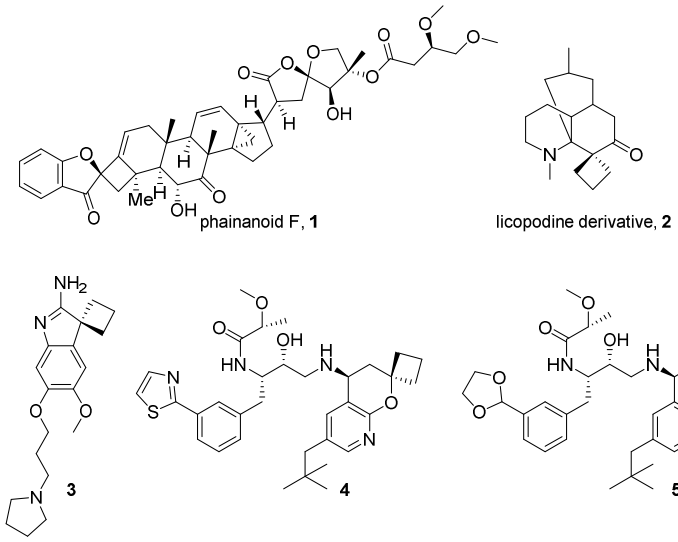
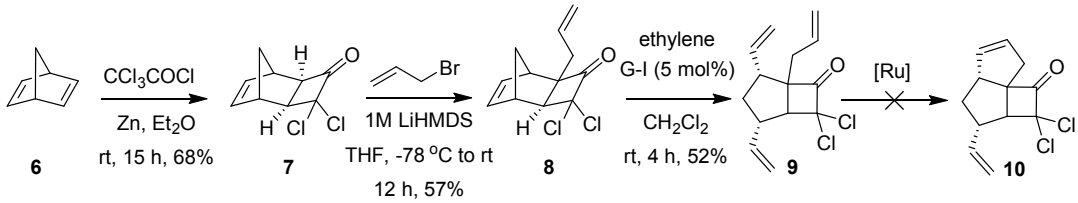
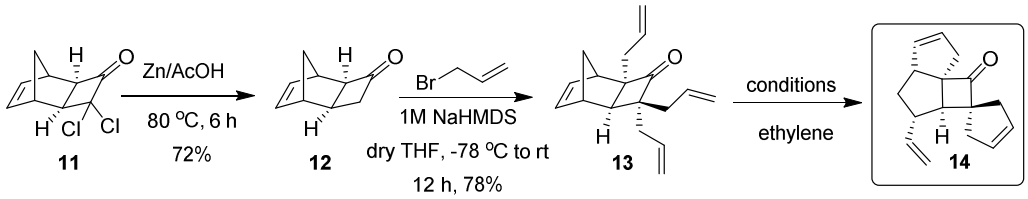


Figure 1 — Cyclobutane containing spirocyclic natural products



Scheme I — Synthesis of the allyl compound **9**



Scheme II — Synthesis of the spirocyclic compound **14**

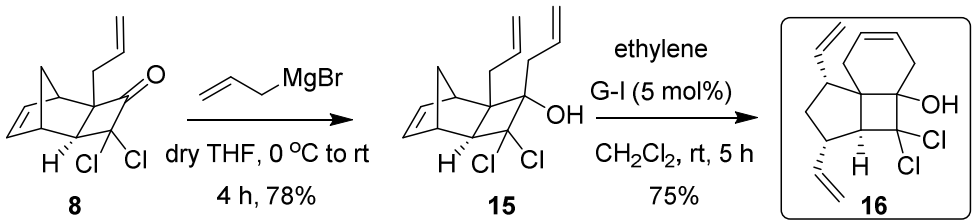
Table I — Reaction optimization of RRM of **13** under ethylene gas conditions

Entry	Catalyst (mol %)	Solvent	Temp. (°C)	Time (h)	Yield of **14**
1	G-I (5)	CH_2Cl_2	RT	8	79
2	G-I (10)	CH_2Cl_2	RT	6	83
3	G-II (5)	CH_2Cl_2	RT	6	80
4	G-II (10)	CH_2Cl_2	RT	4	82
5	G-I (5)	PhMe	80	4	68
6	G-II (5)	PhMe	80	4	70

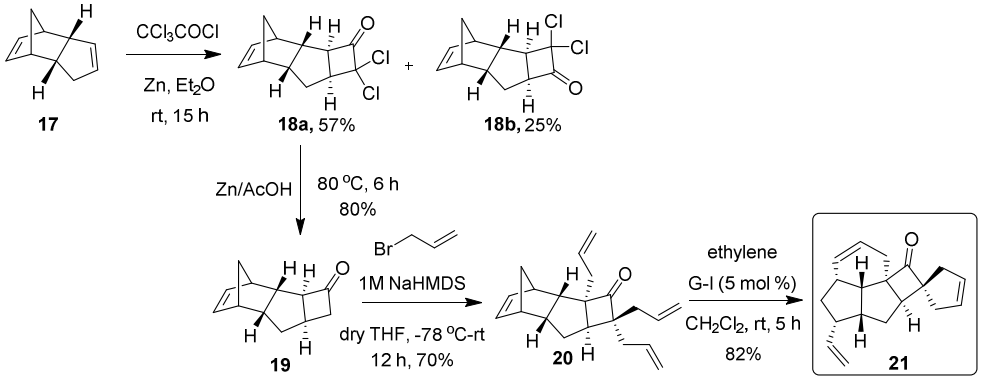
Additionally, the allyl derivative **8** was treated with allyl Grignard reagent at 0°C to synthesize the compound **15** in 78% yields[13]. Subsequent metathesis of **15** by using G-I catalyst, produced the [5/4/6] tricyclic derivative **16** in 75% yield (Scheme III).

Thereafter, we expanded this strategy to synthesize a new class of spiro-compound using dicyclopentadiene **17** as a starting material using ketene addition. First, the dicyclopentadiene **17** was treated with trichloroacetyl chloride in a suspension of Zn in AcOH to deliver a mixture of ketene addition products **18a** and **18b** in 57% and 25% respectively[7]. Upon dechlorination by using Zn/AcOH method the compound **18a**, delivered the dechlorinated compound **19** in 80% yield[9]. Further, this compound **19** was subjected to allylation by using 4.0 equiv. of allyl bromide in the presence of NaHMDS as a base at –78°C[8], to produce the triallyl derivative **20**, which was subjected to metathesis to yield the spiro-annulated pentacyclic compound **21** in 82% yields (Scheme IV).

This pentacyclic compound **21** containing spiro unit has a [5/5/4] tricyclic scaffold and [5/6/5] tricyclic scaffold. Interestingly, [5/5/4] tricyclic unit is a core structural element present in sesquiterpenoids[14]



Scheme III — Synthesis of the [5/4/6] tricyclic derivative **16**



Scheme IV — Synthesis of the pentacyclic compound **21**

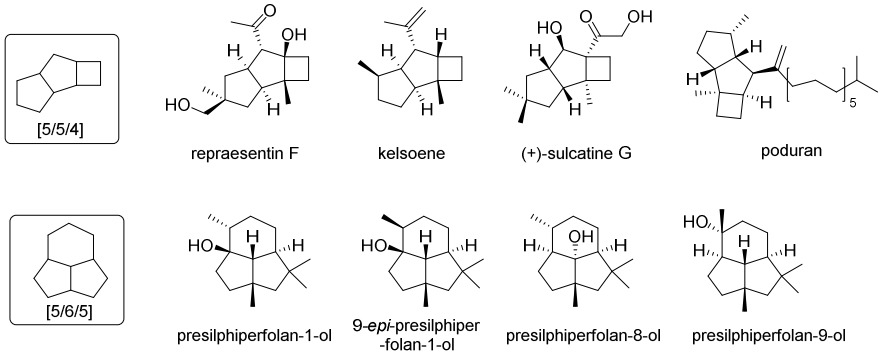


Figure 2 — Natural products containing [5/5/4] tricyclic core and [5/5/6] tricyclic core

such as repraesentin F, kelsoene, (+)-sulcatine G and poduran. While, the [5/6/5] tricyclic unit is a core structure of presilphiperfolanes (Figure 2)[15].

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. Grubbs (G-I, G-II) and Grubbs-Hoveyda (GH-I, GH-II) catalysts were purchased from Aldrich Chemical Company. All metathesis reactions were carried out under ethylene atmosphere. The ^{1}H NMR (400 and 500 MHz) chemical shifts were reported in parts per million (δ) relative to internal solvent signal (δ 7.26 in $CDCl_3$) and the coupling constants *J* are reported in Hertz (Hz). The ^{13}C NMR (100 and 125 MHz) chemical shifts were referenced to the internal solvent signals (central peak is δ 77.16 in $CDCl_3$). The high-resolution mass spectrometric (HRMS) measurements were carried out using a Bruker (Maxis Impact) or Micromass Q-ToF spectrometer. Infrared (IR) spectra were recorded on Nicolet Impact-400 FT-IR spectrometer and absorption bands are given in wavenumbers (cm^{-1}).

Synthesis of the allyl derivative 13

To the solution of the compound **12** (200mg, 1 mmol) in dry THF, 1M solution of LiHMDS (4.0 eq) in THF was added and stirred for 15 min at −78°C. Later, allyl bromide (0.22 mL, 2.5 eq.) was added

drop-wise at −78°C, and the reaction mixture was stirred at the same temperature for 1 h. Further, the reaction mixture brought back to RT slowly in 8 h. After completion of reaction, it was quenched with H_2O and extracted with ethylacetate (3 × 30 mL). The combined organic layer was washed with H_2O, dried over Na_2SO_4 and concentrated to get the crude compound **13** which was purified by column chromatography. Yield 57% (136 mg), colourless liquid, R_f = 0.75 (2% EtOAc/hexane). IR (neat): 2931, 2389, 1735, 1627, 1216, 1108, 994, 770 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.50 (dd, 1H), 6.33 (dd, 1H), 5.92–5.80 (m, 1H), 5.28–5.18 (m, 2H), 3.19 (s, 1H), 2.90–2.73 (m, 2H), 2.48 (t, 1.46 Hz, 1H), 1.95 (d, *J* = 10.68 Hz, 1H), 1.65 (qd, *J* = 14.36 Hz, 1.84 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 200.4, 140.6, 137.1, 130.3, 120.8, 82.4, 71.4, 56.2, 49.6, 46.3, 44.44, 44.41.

General procedure for dechlorination

The chloro compound (**11** or **18a**, 0.5 mmol, 1 equiv) was dissolved in glac. AcOH (0.2 mL) and added to the suspension of Zn in AcOH (1.0 mL) and the resulting mixture was heated to 80°C for 5 h. After completion of reaction, the reaction mixture was brought to RT and quenched with H_2O. Compound was extracted with Et_2O (3 × 40 mL) from the aqueous reaction mixture. The combined ether layer was washed with H_2O (2 × 30 mL), dried over Na_2SO_4 and evaporated to dry. The crude product was purified by column chromatography to get the desired dechloro compound as a colourless liquid.

12: Yield 72% (240 mg), from 500 mg of **11**, Colorless liquid. R_f = 0.85 (2% EtOAc/hexane). ^1H NMR ($CDCl_3$, 400 MHz): δ 6.23 (dd, *J* = 5.63 Hz, 1H), 6.06 (dd, *J* = 6.62 Hz, 3.32 Hz, 1H), 2.98 (brs, 1H), 2.94 (brs, 1H), 2.83–2.72 (m, 1H), 2.29–2.19 (m, 2H), 1.48 (d, *J* = 1.48 Hz, 2H), 1.34–1.32 (m, 1H), 1.14 (t, *J* = 7.02 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 211.5, 139.7, 136.0, 66.1, 45.5, 44.0, 43.0, 40.9, 30.1.

19: Yield 80% (265 mg), from 500 mg of **18a**, Colorless liquid. R_f = 0.85 (2% EtOAc/hexane). IR (neat): 2932, 1734, 1439, 1227, 848, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.17 (s, 2H), 2.91 (d, 1H, *J* = 3.46 Hz), 2.66 (s, 1H), 2.62 (d, 1H, *J* = 16.56 Hz), 2.48 (d, 1H, *J* = 3.47 Hz) 2.17 (s, 2H), 1.54 (ABq, 1H, *J* = 39.18 Hz, 9.45 Hz), 1.44 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 211.5, 139.7, 136.0, 66.1, 45.5, 44.0, 43.0, 40.9, 30.1; HRMS (ESI, Q-ToF): *m/z* [M + H]$^+$ Calcd for $C_{12}H_{15}O$: 175.1123. Found: 175.1120.

General procedure of triallylation

To the solution of the keto compound **12** or **19** (1 eq) in dry THF, 1M solution of NaHMDS (4.0 eq) in THF was added and stirred for 15 min at −78°C. Later, allyl bromide (4.0 eq.) was added drop-wise at −78°C and the reaction mixture was stirred at the same temperature for 1 h. Further, the reaction mixture brought back to RT slowly in 8 h. After completion of reaction, it was quenched with H_2O and extracted with ethylacetate (3 × 30 mL). The combined organic layer was washed with H_2O, dried over Na_2SO_4 and concentrated to get the crude triallyl compound (**13** or **20**) which was purified by column chromatography using 2% EtOAc/ hexane.

13: Yield 78% (220 mg from 150 mg of **12**) as a colorless liquid. R_f = 0.85 (2% EtOAc/hexane). IR (neat): 2936, 2412, 1765, 1455, 1412, 1117, 915, 761 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.95–5.72 (m, 3H), 5.30–4.98 (m, 6H), 3.23–2.78 (m, 5H), 2.26–2.17 (m, 1H), 2.03–1.98 (m, 1H). 14.36 Hz, 1.84 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 200.1, 139.8, 135.3, 130.3, 120.9, 118.1, 115.4, 60.7, 51.2, 45.8, 43.8, 40.4; HRMS (ESI, Q-ToF): *m/z* [M + Na]$^+$ Calcd for $C_{18}H_{22}ONa$: 277.1563. Found: 277.1567.

20: Yield 70% (200 mg from 150 mg of **19**) as a colorless liquid. R_f = 0.85 (2% EtOAc/hexane). IR (neat): 2936, 2405, 1770, 1458, 1117, 759 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 6.22 (s, 2H), 5.93-5.81 (m, 2H), 5.74-5.63 (m, 1H), 5.17-5.08 (m, 6H), 2.99 (s, 1H), 2.89 (dd, 1H, *J* = 9.70 Hz, 3.60 Hz), 2.80 (s, 1H), 2.66 (t, 2H, *J* = 6.64 Hz), 2.50 (d, 1H, *J* = 8.88 Hz), 2.33-2.25 (m, 3H), 2.20 (dd, 1H, *J* = 14.36 Hz, 2.21 Hz), 1.78 (dd, 1H, *J* = 14.53 Hz, 9.22 Hz), 1.72-1.67 (m, 2H), 1.63 (d, 1H, *J* = 8.09 Hz), 1.48-1.43 (m, 1H), 1.38 (td, 1H, *J* = 14.44 Hz, 7.28 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 220.7 (C), 142.6 (CH), 136.4 (CH), 135.7 (CH), 128.5 (CH), 128.3 (CH), 125.7 (CH), 118.4 (CH_2), 117.8 (CH_2), 117.5 (CH_2), 71.9 (C), 62.5 (C), 55.5 (CH), 54.2 (CH_2), 51.2 (CH), 51.0 (CH), 46.5 (CH), 46.1 (CH), 35.9 (CH_2), 34.4 (CH_2), 31.2 (CH_2), 29.4 (CH_2); HRMS (ESI, Q-ToF): *m/z* [M + Na]$^+$ Calcd for $C_{21}H_{26}ONa$: 317.1876. Found: 317.1873.

Synthesis of compound 15

The compound **8** (150 mg, 0.62 mmol) was dissolved in dry THF under N_2 atmosphere and cooled to 0°C. To this 1 M allyl Grignard solution (1.2 mL, 2 eq) in THF was added at 0°C and allowed to stir for 4 h at RT under N_2 atmosphere. After completion of reaction by TLC monitoring, the reaction mixture was quenched with Sat. NH_4Cl solution, extracted with EtOAc (3 × 30 mL). The combined organic layer was

washed with H_2O (2 × 20 mL), dried over Na_2SO_4 and concentrated to give the crude product **15** which was purified by column chromatography using 2% EtOAc/ hexane.

Yield 78% (137 mg), colourless liquid. R_f = 0.75 (2% EtOAc/hexane). IR (neat): 3331, 2936, 2410, 1170, 915, 759 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.33 (dd, 1H, *J* = 5.68 Hz, 3.12 Hz), 6.28 (dd, 1H, *J* = 5.60 Hz, 3.00 Hz), 6.19-6.04 (m, 2H), 5.38-5.00 (m, 4H), 3.22 (s, 1H), 2.97 (brs, 1H), 2.88-2.80 (m, 3H), 2.74 (d, 1H, *J* = 1.96 Hz), 1.79 (d, 1H, *J* = 9.84 Hz), 1.59 (qd, 1H, *J* = 9.84 Hz, 1.78 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.6 (CH), 136.6 (CH), 133.2 (CH), 132.0 (C), 122.0 (CH_2), 84.2 (C), 82.2 (C), 64.7 (CH), 51.8 (CH), 45.7 (CH_2), 44.3 (CH), 43.8 (CH_2); HRMS (ESI, Q-ToF): *m/z* $[M + Na]^+$ Calcd for $C_{15}H_{18}OCl_2Na$: 307.0632. Found: 307.0635.

General procedure for metathesis. The compound (**13**, or **15**, or **20**, 0.2 mmol) was dissolved in CH_2Cl_2 (7 mM) and degassed with N_2 gas followed by ethylene for about 20 min. To this, the Grubbs catalyst (as mentioned in Table I, 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.

14: Yield 83% (optimized yield (Table I), 44 mg from 60 mg of **13**) as a colorless liquid. R_f = 0.80 (2% EtOAc/hexane). IR (neat): 2936, 2435, 1773, 1455, 1117, 918, 761 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.90-5.78 (m, 1H), 5.70-5.58 (m, 2H), 5.55-5.49 (m, 2H), 4.98 (td, 1H, *J* = 17.08 Hz, 1.32 Hz), 4.89 (td, 1H, *J* = 10.23 Hz, 1.24 Hz), 3.46-3.38 (m, 1H), 2.92-2.78 (m, 2H), 2.73-2.47 (m, 5H), 2.32 (d, 1H, *J* = 3.88 Hz), 2.20 (td, 1H, *J* = 13.14 Hz, 6.60 Hz), 1.67 (td, 1H, *J* = 13.10 Hz, 1.65 Hz). 1.58 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 221.0 (C), 142.4 (CH), 133.9 (CH), 129.1 (CH), 128.2 (CH), 127.6 (C), 113.4 (CH_2), 66.3 (C), 58.4 (CH), 56.5 (CH), 47.7 (CH), 44.3 (CH_2), 40.7 (CH_2), 40.5 (CH_2), 35.5 (CH_2); HRMS (ESI, Q-ToF): *m/z* $[M + Na]^+$ Calcd for $C_{16}H_{18}ONa$: 249.1255. Found: 249.1258.

21: Yield 82% (44 mg from 60 mg of **20**) as a colorless liquid. R_f = 0.80 (2% EtOAc/hexane). IR (neat): 2936, 2438, 1771, 1458, 1119, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 6.08-5.66 (m, 4H), 5.15-4.90 (m, 4H), 3.24-3.13 (m, 2H), 2.96 (s, 1H), 2.91 (dd, 1H, *J* = 15.53 Hz, 7.01 Hz), 2.59-2.56 (m, 1H), 2.43 (d, 1H, *J* = 4.25 Hz), 2.26-2.19 (m, 1H), 2.07-2.00 (m, 1H), 1.82-1.73 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 141.6 (CH), 140.6 (CH), 136.7 (CH), 129.0 (CH), 126.4 (CH), 116.5 (CH_2), 114.1 (CH_2), 78.9 (C), 60.1 (CH), 51.7 (CH), 45.0 (CH_2), 41.2 (C), 39.2 (CH_2), 38.1 (CH_2), 34.7 (CH_2); HRMS (ESI, Q-ToF): *m/z* $[M + Na]^+$ Calcd for $C_{15}H_{18}OCl_2Na$: 307.0632. Found: 307.0633.

16: Yield 75% (30 mg from 40 mg of **15**) as a colorless liquid. R_f = 0.80 (2% EtOAc/hexane). IR (neat): 3330, 2936, 2433, 1170, 915, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.86-5.72 (m, 2H), 5.71-5.65 (m, 1H), 5.64-5.53 (m, 2H), 5.03 (td, 1H, *J* = 17.16 Hz, 1.56 Hz), 4.97 (td, 1H, *J* = 10.33 Hz, 1.34 Hz), 2.84 (td, 1H, *J* = 16.86 Hz, 2.10 Hz), 2.68 (dd, 2H, *J* = 11.46 Hz, 6.64 Hz), 2.63-2.47 (m, 4H), 2.41 (td, 1H, *J* = 17.11 Hz, 2.04 Hz), 2.37-2.29 (m, 2H), 2.10-1.99 (m, 1H), 1.69 (dd, 1H, *J* = 14.16 Hz, 7.04 Hz), 1.39 (d, 1H, *J* = 10.56 Hz), 1.54-1.47 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 224.6 (C), 139.5 (CH), 133.2 (CH), 129.0 (CH), 128.0 (CH), 121.9 (CH), 114.6 (CH_2), 77.3 (CH), 70.2 (C), 65.7 (C), 53.2 (CH), 50.8 (CH), 48.1 (CH), 45.8 (CH), 45.4 (CH_2), 36.2 (CH_2), 35.7 (CH_2), 35.3 (CH), 29.4 (CH_2), 27.2 (CH_2); HRMS (ESI, Q-ToF): *m/z* $[M + Na]^+$ Calcd for $C_{19}H_{22}ONa$: 289.1563.

Conclusion

Cyclobutane containing spiro compounds are rare class of spiro compounds, and a limited number of natural products are present. Here, we have synthesized [5/5/4] spiro-compound **14** and [5/6/5/4] spiro compound **21** starting with commercially available norbornadiene and dicyclopentadiene respectively *via* ketene addition, dechlorination followed by triallylation and metathesis sequence in good yields. Additionally, we have also synthesized [5/4/6] tricyclic derivative **16** by Grignard addition followed by metathesis. The core structures of these derivatives are present in natural products and bioactive compounds. This methodology has a potential application in natural and non-natural products synthesis

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

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