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Study towards diversity oriented synthesis of optically active substituted cyclopentane fused carbocyclic and oxacyclic medium-sized rings: Competition between Grubbs-II catalyzed ring closing olefin metathesis and ring closing carbonyl-olefin metathesis

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Abstract. A study towards diversity-oriented synthesis of optically active cyclopentane fused bicyclic frameworks has been accomplished. The common intermediate was prepared from commercially available starting material (*S*)-carvone. The observations on competition between Grubbs-II catalyzed ring closing metathesis (RCM) and ring closing carbonyl-olefin metathesis (RCCOM) were the key features of the study.

Keywords. Diversity-oriented synthesis; bicyclic frameworks; ring closing metathesis; Grubbs-II catalyst; carbonyl-olefin metathesis.

1. Introduction

The synchronous evolution of synthetic chemistry and biology-led clinical trials over the last decade have intensified the significance of small molecule synthesis.[1] Small molecules are currently often treated as new drugs and drug candidates for their ability to unite to a pre-selected protein or other biological macromolecules in a specific manner with minimal chances of side effects. Thus, there is a constant switch over from cytotoxic chemotherapy to the consumption of small molecule cancer drugs that targets cancer cells at molecular level in a more efficient dose-dependent approach.[2] Incessant research has been going on to create and enrich the library of small molecules by means of carbocycles with bicyclic motif of different ring sizes.[3] Syntheses of these medium-sized bicyclic frameworks consequently have gained enormous attention as they form the structural core of a large number of biologically important natural products.[4] When there are several reports for the synthetic approaches to five- and six-membered ring systems *via* common cyclization and cycloaddition reactions, seven- and eight-membered ring formations are not too much familiar due to considerable entropy loss in the transition state and large enthalpy loss due to *trans*-annular interactions.[5]

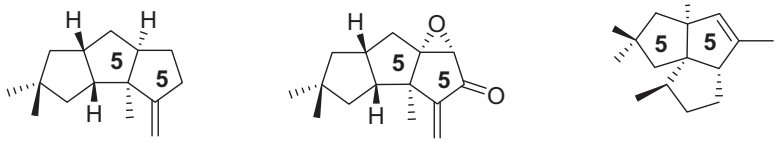
Diversity-oriented synthetic strategies for designing such a category of biologically relevant bicyclic skeletons have been frequently exercised in active scientific discussions. Diversity-oriented synthesis (DOS)[6] works with powerful planning algorithm which has numerous benefits over target-oriented synthesis (TOS) and has been successfully applied for constructing libraries of small molecules. In general, DOS is a protocol of synthesizing an array of compounds with structural diversity from a common synthetic intermediate. Though there are considerable amount of documentations of constructing nitrogen and oxygen containing heterocycles *via* DOS in the literature,[7] synthesis of carbocycles with densely functionalized bicyclic moieties have been persued in limited ways.[8] So, development of a practical and constructive diversity-oriented approach to improve the documentation of carbocycles with medium sized rings will cover synthetic as well as biological utility.

The literature survey of various natural products synthesis revealed that the core structures of a large number of naturally occurring biologically important molecules contains certain kind of bicyclic frameworks such as, for example, five-five, five-six, five-seven, or a five-eight fused bicyclic carbocycles (Scheme 1).[9] Inclination towards the substituted cyclopentane-fused carbocycles in natural products attracted chemists for synthesis of such molecules for years.

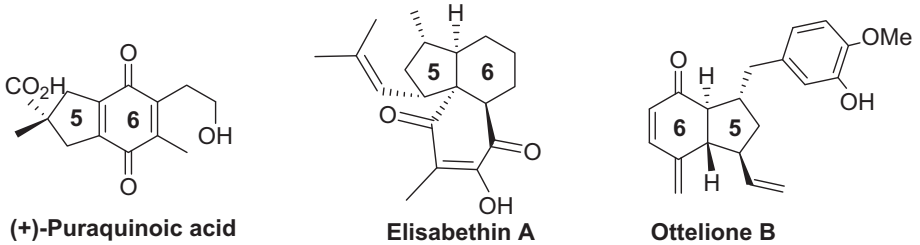
Herein, we depict a diversity-oriented study on the synthesis of optically active, highly functionalized

*For correspondence

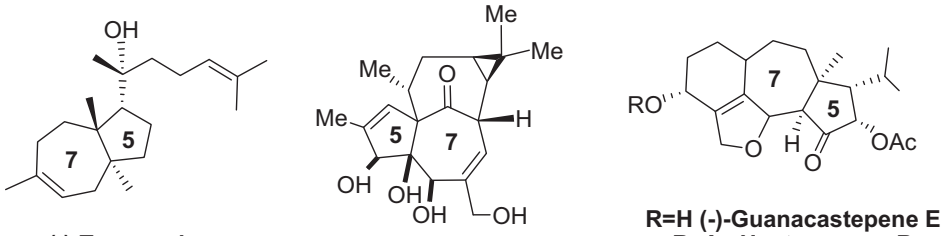
a) core structure with five-five fused bicyclic skeleton



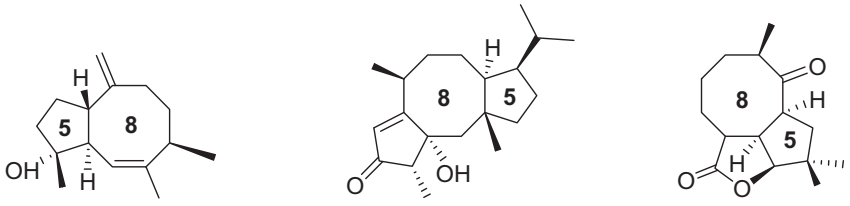
b) core structure with five-six fused bicyclic skeleton



c) core structure with five-seven fused bicyclic skeleton



d) core structure with five-eight fused bicyclic skeleton



Scheme 1. Natural products with different bicyclic framework as the core structure.

cyclopentane fused medium sized carbocyclic and oxacyclic frameworks using Grubbs-II catalyzed ring closing metathesis (RCM).[10] A competition between RCM and ring closing carbonyl-olefin metathesis (RCCOM)[11] was observed depending on the size of the ring formation. The common intermediate for DOS was prepared from commercially available starting material (*S*)-carvone.

2. Experimental

The ^{1}H NMR spectra were recorded in $CDCl_3$ on 300, 400 and 500 MHz and ^{13}C NMR spectra were recorded on 75, 100 and 125 MHz spectrometer, respectively, using TMS as an internal standard. High-resolution mass spectra (HRMS) were obtained using a Qtof Micro YA263 instrument. Ethyl acetate was dried over anhydrous calcium chloride. Petroleum ether of boiling range 60–80°C and diethyl ether were dried over sodium. Silica gel of 60–120 mesh was used for column chromatography. THF and toluene were super dried by distillation over sodium. DCM solvent was used after freshly distilled over P_2O_5. Except 2-iodoxybenzoic acid (IBX) oxidation and 30% H_2O_2 mediated peroxidation procedures, all the reactions were carried out either in argon or nitrogen atmosphere with oven-dried

glass apparatus. A number of the compounds described are already reported in the literature and are characterized by NMR, IR and MASS spectral studies and compared them with authentic samples.[12]

2.1 *Preparation of (R)-1-((1S,2R,3S,5S)-3-(2,2-dimethyl-1,1-diphenylpropoxy)-2-methyl-5-(prop-1-en-2-yl)cyclopentyl)prop-2-en-1-ol (**9a**)*

2.44 mL of 1.0 M solution of vinyl magnesium bromide (2.44 mmol) in THF was added dropwise to a solution of the aldehyde **8**[12] (500 mg, 1.22 mmol) in THF (15 mL) at −78°C under Argon atmosphere. Stirring was continued for 3 h at that temperature. The reaction was monitored by checking TLC. It was then quenched with saturated aqueous ammonium chloride solution (2 mL). THF was removed under reduced pressure and the residue was extracted with diethyl ether (3 × 20 mL). The combined organic extract was washed with brine and finally dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue obtained was purified by column chromatography over silica gel (3% ethyl acetate in light petroleum) to furnish **9a** (430 mg, 81%) as a viscous liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.00 (d, J = 7.5 Hz, 3H), 1.08 (s, 9H), 1.52 (q, J = 6.0 Hz, 1H), 1.70–1.77 (m, 1H), 1.89 (s, 3H), 1.93–1.97 (m, 1H), 2.17–2.21 (m, 1H), 3.11-3.17 (m, 1H), 4.29–4.33 (m, 2H), 4.72 (s, 1H), 4.89 (s, 1H), 5.05 (doublet with further splitting, J = 9.0 Hz, 1H), 5.19 (doublet with further splitting, J = 13.5 Hz, 1H), 5.75–5.82 (m, 1H), 7.33–7.42 (m, 6H), 7.64–7.68 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.1, 19.6, 24.5, 27.2, 27.3, 37.9, 39.6, 45.8, 51.1, 71.8, 76.4, 110.1, 113.3, 127.5, 129.5, 134.4, 135.0, 135.9, 136.0, 136.1, 139.8, 148.1; HRMS: calcd for $C_{28}H_{38}O_2Si$ $[M+Na]^+$ 457.2539; found: 457.2541.

2.2 *Preparation of (R)-1-((1S,2R,3S,5S)-3-(2,2-dimethyl-1,1-diphenylpropoxy)-2-methyl-5-(prop-1-en-2-yl)cyclopentyl)but-3-en-1-ol (**9b**)*

Compound **9b** (77%) was prepared from **8** and freshly prepared allyl Grignard reagent, using the same procedure used for synthesizing **9a**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.01–1.11 (m, 12H), 1.48–1.55 (m, 1H), 1.64–1.74 (m, 1H), 1.83 (s, 3H), 1.88 (t, J = 7.0 Hz, 1H), 2.07–2.19 (m, 2H), 2.28 (q, J = 6.0 Hz, 1H), 3.08–3.10 (m, 1H), 3.70 (m, 1H), 4.34 (t, J = 4.0 Hz, 1H), 4.67 (s, 1H), 4.84 (s, 1H), 5.04–5.08 (m, 2H), 5.76–5.81 (m, 1H), 7.25–7.43 (m, 6H), 7.63–7.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.2, 19.6, 24.5, 27.3, 38.0, 39.6, 39.8, 46.2, 50.5, 71.4, 76.5, 110.0, 117.1, 127.5, 127.6, 129.5, 134.5, 135.0, 136.0, 136.1, 148.0; HRMS: calcd for $C_{29}H_{40}O_2Si$ $[M+Na]^+$ 471.2695; found: 471.2695.

2.3 *Preparation of (R)-1-((1S,2R,3S,5S)-3-(2,2-dimethyl-1,1-diphenylpropoxy)-2-methyl-5-(prop-1-en-2-yl)cyclopentyl)pent-4-en-1-ol (**9c**)*

Compound **9c** (67%) was prepared from **8** and freshly prepared homoallyl Grignard reagent, using the same procedure used for synthesizing **9a**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.06–1.09 (m, 12H), 1.36–1.42 (m, 1H), 1.50–1.73 (m, 4H), 1.86 (s, 3H), 2.03–2.07 (m, 1H), 2.16–2.20 (m, 1H), 2.25–2.29 (m, 1H), 3.10–3.15 (m, 1H), 3.70–3.71 (m, 1H), 4.34–4.35 (m, 1H), 4.69 (s, 1H), 4.86 (s, 1H), 4.94–5.04 (m, 2H), 5.79–5.84 (m, 1H), 7.34–7.44 (m, 6H), 7.65–7.69 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.3, 19.7, 24.6, 27.2, 27.3, 27.6, 30.8, 34.1, 38.0, 39.6, 46.2, 50.6, 71.3, 76.7, 109.7, 114.6, 127.5, 127.6, 127.9, 129.5, 129.6, 134.5, 135.0, 135.8, 136.0, 136.1, 138.8, 148.6; HRMS: calcd for $C_{30}H_{42}O_2Si$ $[M+Na]^+$ 485.2852; found: 485.2853.

2.4 *Preparation of (R)-1-((1S,2R,3S,5S)-3-(2,2-dimethyl-1,1-diphenylpropoxy)-2-methyl-5-(prop-1-en-2-yl)cyclopentyl)hex-5-en-1-ol (**9d**)*

Compound **9d** (64%) was prepared from **8** and freshly prepared corresponding Grignard reagent, using the same procedure used for synthesizing **9a**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.02–1.08 (m, 12H), 1.25–1.68 (m, 7H), 1.85 (s, 3H), 2.02–2.05 (m, 2H), 2.23–2.25 (m, 1H), 3.10 (m, 1H), 3.66 (m, 1H), 4.31–4.32 (m, 1H), 4.68 (s, 1H), 4.85 (s, 1H), 4.92–5.00 (m, 1H), 5.76–5.80 (m, 1H), 7.33–7.41 (m, 6H), 7.62–7.68 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.3, 19.7, 24.6, 25.9, 27.1, 27.2, 27.3, 33.8, 34.4, 38.0, 39.6, 46.2, 50.6, 71.8, 76.7, 109.7, 110.1, 114.6, 127.5, 127.6, 127.8, 129.6, 129.8, 130.0, 134.5, 135.1, 136.0, 136.1, 138.9, 139.0, 148.6; HRMS: calcd for $C_{31}H_{44}O_2Si$ $[M+Na]^+$ 499.3008; found: 499.3009.

2.5 *Preparation of (R)-1-((1S,2R,3S,5S)-3-(2,2-dimethyl-1,1-diphenylpropoxy)-2-methyl-5-(prop-1-en-2-yl)cyclopentyl)hept-6-en-1-ol (**9e**)*

Compound **9e** (63%) was prepared from **8** and freshly prepared corresponding Grignard reagent, using the same procedure used for synthesizing **9a**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.04–1.12 (m, 12H), 1.26–1.72 (m, 9H), 1.85 (s, 3H), 2.02–2.09 (m, 2H), 2.23–2.27 (m, 1H), 3.11 (m, 1H), 3.66 (m, 1H), 4.32 (t, J = 4.0 Hz, 1H), 4.68 (s, 1H), 4.85 (s, 1H), 4.93 (dd, J = 1.0, 10.5 Hz, 1H), 4.99 (dd, J = 1.5, 17.0 Hz,

1H), 5.77–5.83 (m, 1H), 7.33–7.43 (m, 6H), 7.63–7.70 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.3, 20.4, 24.6, 26.2, 27.1, 27.2, 27.3, 29.1, 33.9, 34.9, 38.0, 39.6, 46.1, 50.6, 71.99, 109.7, 114.4, 127.5, 127.7, 127.8, 129.5, 129.8, 129.9, 134.5, 135.1, 136.0, 136.1, 139.1, 148.6; HRMS: calcd for $C_{32}H_{46}O_2Si$ $[M+Na]^+$ 513.3165; found: 513.3169.

2.6 *Preparation of 1-((1S,2R,3S,5S)-3-(2,2-dimethyl-1,1-diphenylpropoxy)-2-methyl-5-(prop-1-en-2-yl) cyclopentyl)prop-2-en-1-one (**10a**)*

Solid Dess-Martin periodinate (730 mg, 1.72 mmol) and $NaHCO_3$ (150 mg, 1.8 mmol) were added to a stirring solution of alcohol **9a** (300 mg, 0.70 mmol) dissolved in 20 mL of DCM at room temperature and the reaction was continued for 3 h. The completion of the reaction was monitored by TLC before it was quenched by a mixture of saturated aqueous solution of $Na_2S_2O_3$ and $NaHCO_3$. The mixture was then extracted with diethyl ether (3×20 mL). The combined organic extract was washed with brine and finally dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue obtained was purified by column chromatography over silica gel (3% ethyl acetate in light petroleum) to furnish **10a** (280 mg, 92%) as a viscous liquid. $[\alpha]_D^{25}$ = 26.07 (c = 2.03, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.01 (d, J = 6.5 Hz, 3H), 1.11 (s, 9H), 1.51 (s, 3H), 1.72–1.73 (m. 2H), 2.40 (t, J = 3.5 Hz, 1H), 3.35–3.37 (m, 2H), 4.36–4.37 (m, 1H), 4.63 (s, 1H), 4.68 (s, 1H), 5.71 (d, J = 11 Hz, 1H), 6.18 (d, J = 17.5 Hz, 1H), 6.36–6.42 (m, 1H), 7.37–7.45 (m, 6H), 7.68–7.69 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.5, 19.6, 21.3, 27.2, 40.2, 42.8, 47.7, 57.4, 76.9, 113.1, 127.0, 127.6, 129.7, 134.1, 134.8, 135.9, 136.0, 137.6, 145.3, 201.9; HRMS: calcd for $C_{28}H_{36}O_2Si$ $[M+H]^+$ 433.2557; found: 433.2558.

2.7 *Preparation of 1-((1S,2R,3S,5S)-3-(2,2-dimethyl-1,1-diphenylpropoxy)-2-methyl-5-(prop-1-en-2-yl) cyclopentyl)but-3-en-1-one (**10b**)*

Compound **10b** (90%) was prepared from **9b** using the same procedure used for synthesizing **10a**. $[\alpha]_D^{25}$ = 27.78 (c = 0.977, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (d, J = 6.5 Hz, 3H), 1.09 (s, 9H), 1.53 (s, 3H), 1.66–1.70 (m, 2H), 2.32–2.37 (m, 1H), 3.08–3.16 (m, 2H), 3.22–3.27 (m, 1H), 3.32–3.38 (m, 1H), 4.31 (appeared as singlet, 1H), 4.71–4.72 (overlapping of two singlets of olefinic protons, 2H), 5.09 (d, J = 17 Hz, 1H), 5.15 (d, J = 10.5 Hz, 1H), 5.86–5.91 (m, 1H), 7.35–7.44 (m, 6H), 7.65 (d, J = 7.5 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 19.6, 20.8, 27.2, 27.6, 40.0, 42.2, 47.2, 49.0, 60.1, 113.4, 118.4, 127.6, 127.9, 129.7, 131.1, 134.1, 134.9, 135.8, 135.9, 136.0, 145.8, 210.0; HRMS: calcd for $C_{29}H_{38}O_2Si$ $[M+H]^+$ 447.2714; found: 447.2711.

2.8 *Preparation of 1-((1S,2R,3S,5S)-3-(2,2-dimethyl-1,1-diphenylpropoxy)-2-methyl-5-(prop-1-en-2-yl) cyclopentyl)pent-4-en-1-one (**10c**)*

Compound **10c** (89%) was prepared from **9c** using the same procedure used for synthesizing **10a**. $[\alpha]_D^{25}$ = 25.64 (c = 3.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (d, J = 6.5 Hz, 3H), 1.09 (s, 9H), 1.52–1.67 (m, 5H), 2.22–2.43 (m, 4H), 2.54–2.60 (m, 1H), 3.06–3.10(m, 1H), 3.34 (t, J = 8.0 Hz, 1H), 4.30 (appeared as singlet, 1H), 4.67–4.70 (overlapping of two singlets of olefinic protons, 2H), 4.93–5.02 (m, 2H), 5.77–5.80 (m, 1H), 7.36–7.41 (m, 6H), 7.65 (appeared as singlet, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.5, 19.6, 21.0, 27.0, 27.2, 27.8, 39.9, 42.3, 43.6, 47.2, 60.5, 113.2, 115.0, 127.6, 129.7, 134.2, 134.9, 136.0, 137.6, 145.8, 211.4; HRMS: calcd for $C_{30}H_{40}O_2Si$ $[M+Na]^+$ 483.2695; found: 483.2694.

2.9 *Preparation of 1-((1S,2R,3S,5S)-3-(2,2-dimethyl-1,1-diphenylpropoxy)-2-methyl-5-(prop-1-en-2-yl) cyclopentyl)hex-5-en-1-one (**10d**)*

Compound **10d** (88%) was prepared from **9d** using the same procedure used for synthesizing **10a**. $[\alpha]_D^{25}$ = 25.87 (c = 2.43, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (d, J = 7.0 Hz, 3H), 1.08 (s, 9H), 1.50–1.71 (m, 7H), 2.00–2.04 (m, 2H), 2.28–2.35 (m, 2H), 2.45–2.52 (m, 1H), 3.07 (t, J = 10.0 Hz, 1H), 3.32 (q, J = 9.0 Hz, 1H), 4.30-4.31 (m, 1H), 4.67 (s, 1H), 4. .69 (s, 1H), 4.95–5.03 (m, 2H), 5.72–5.79 (m, 1H), 7.35–7.43 (m, 6H), 7.64–7.66 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.2, 14.5, 19.6, 21.0, 22.7, 27.2, 29.8, 31.7, 33.2, 39.9, 42.3, 43.7,47.2, 60.5, 113.7, 115.0, 127.6, 129.7, 134.2, 134.9, 135.9, 136.0, 138.4, 145.9, 212.1; HRMS: calcd for $C_{31}H_{42}O_2Si$ $[M+Na]^+$ 497.2852; found: 497.2854.

2.10 *Preparation of 1-((1S,2R,3S,5S)-3-(2,2-dimethyl-1, 1-diphenylpropoxy)-2-methyl-5-(prop-1-en-2-yl) cyclopentyl)hept-6-en-1-one (**10e**)*

Compound **10e** (89%) was prepared from **9e** using the same procedure used for synthesizing **10a**. $[\alpha]_D^{25}$ = 27.52 (c = 2.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.93–1.68 (m, 21H), 2.03 (q, J = 7.5 Hz, 2H), 2.29–2.34 (m, 2H), 2.44–2.48 (m, 1H), 3.07 (t, J =

10.0 Hz, 1H), 3.32 (q, J = 10.0 Hz, 1H), 4.30 (m, 1H), 4.67–4.69 (overlapping of two singlets of olefinic protons, 2H), 4.92-5.00 (m, 2H), 5.74–5.82 (m, 1H), 7.34–7.43 (m, 6H), 7.63–7.65 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.2, 14.5, 19.6, 21.0, 22.7, 23.1, 25.4, 27.0, 27.2, 28.6, 29.8, 31.7, 33.7, 39.9, 42.3, 44.3, 47.2, 60.4, 113.1, 114.6, 127.6, 129.7, 134.2, 134.9, 136.0, 138.8, 145.9, 212.2; HRMS: calcd for $C_{32}H_{44}O_2Si$ $[M+Na]^+$ 511.3008; found: 511.3007.

2.11 *Preparation of (3aS,5S,6R,6aS)-5-(2,2-dimethyl-1,1-diphenylpropoxy)-4,5,6,6a-tetrahydro-3,6-dimethylpentalen-1(3aH)-one (**11a**)*

To a stirred solution of **10a** (100 mg, 0.23 mmol) in dry toluene at room temperature under argon atmosphere was added Grubbs second generation catalyst (20 mg, 10 mol%). The reaction mixture was then refluxed for 3 h and the reaction was monitored by TLC. The solvent was concentrated under vacuum and the resulting residue was purified by column chromatography over silica gel (10% ethyl acetate in light petroleum) to furnish the cyclized product **11a** (86 mg, 92%). ^{1}H NMR (500 MHz, $CDCl_3$): $[\alpha]_D^{25}$ = −17.18 (c = 4.08, $CHCl_3$); δ 1.07 (s, 9H), 1.18 (d, J = 6.5 Hz, 3H), 1.26–1.31 (m, 1H), 1.81–1.85 (m, 1H), 1.88 (s, 3H), 2.00 (q, J = 6.0 Hz, 1H), 2.58 (t, J = 6.0 Hz, 1H), 3.19 (dd, J = 15, 6.5 Hz, 1H), 4.10 (q, J = 5.0 Hz, 1H), 5.66 (s, 1H), 7.35–7.38 (m, 4H), 7.41–7.43 (m, 2H), 7.62 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.5, 17.6, 19.5, 27.1, 35.2, 41.7, 47.7, 56.7, 76.9, 127.6, 127.7, 129.2, 129.8, 133.8, 134.6, 135.8, 180.2; HRMS: calcd for $C_{26}H_{32}O_2Si$ $[M+Na]^+$ 427.2069; found: 427.2068.

2.12 *Preparation of (2S,3R,3aS,7aS)-2-(2,2-dimethyl-1,1-diphenylpropoxy)-1,2,3,3a-tetrahydro-3,7-dimethyl-5H-inden-4(7aH)-one (**11b**)*

Compound **11b** (93%) was prepared from **10b** using the same procedure used for synthesizing **11a**. $[\alpha]_D^{25}$ = −5.94 (c = 2.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (appeared as singlet, 12H), 1.24–1.33 (m, 1H), 1.54 (s, 3H), 1.91 (dd, J = 8.0, 12.8 Hz, 1H), 2.16–2.21 (m, 1H), 2.67 (t, J = 9.6 Hz, 1H), 2.75-2.89 (m, 2H), 3.17 (q, J = 8.8 Hz, 1H), 4.23 (appeared as singlet, 1H), 5.22 (appeared as singlet, 1H), 7.38–7.44 (m, 6H), 7.66–7.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 19.6, 21.4, 27.2, 38.2, 41.4, 43.5, 45.2, 55.3, 116.0, 127.6, 127.7, 129.7, 133.9, 134.9, 135.9, 136.0, 137.6, 212.0; HRMS: calcd for $C_{27}H_{34}O_2Si$ $[M+H]^+$ 441.2226; found: 441.2228.

2.13 *Preparation of (Z,2S,3R,3aS,8aS)-2-(2,2-dimethyl-1,1-diphenylpropoxy)-1,2,3,3a,5,6-hexahydro-3,8-dimethylazulen-4(8aH)-one (**11c**)*

Compound **11c** (89%) was prepared from **10c** using the same procedure used for synthesizing **11a**. $[\alpha]_D^{25}$ = 26.96 (c = 1.49, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ0.96 (d, J = 7.0 Hz, 3H), 1.09 (s, 9H), 1.25–1.42 (m, 2H), 1.49 (s, 3H), 1.71 (dd, J = 7.0, 13.0 Hz, 1H), 2.14–2.17 (m, 1H), 2.42–2.54 (m, 3H), 3.14 (dd, J = 9.0, 11.5 Hz, 1H), 3.46–3.52 (m, 1H), 4.26 (t, J = 3.5 Hz,1H), 5.53 (appeared as singlet, 1H), 7.35–7.44 (m, 6H), 7.66–7.68 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.0, 19.6, 22.1, 23.5, 27.3, 39.6, 40.5, 42.9, 44.7, 58.8, 76.2, 124.0, 127.6, 127.7, 129.7, 135.0, 136.0, 136.1, 140.5, 211.5; HRMS: calcd for $C_{28}H_{36}O_2Si$ $[M+Na]^+$ 455.2382; found: 455.2385.

2.14 *Preparation of (Z,2S,3R,3aS,9aS)-2-(2,2-dimethyl-1,1-diphenylpropoxy)-1,2,3,3a,6,7-hexahydro-3,9-dimethyl-5H-cyclopenta[8]annulen-4(9aH)-one (**11d**) and 1-((1R,2S,3R,5S)-2-methyl-3-(2,2,3,3-tetramethylbutyl)-5-(prop-1-en-2-yl)cyclopentyl)cyclopent-1-ene (**11e**)*

To a stirred solution of **10d** (200 mg, 0.42 mmol) in dry toluene at room temperature under argon atmosphere was added Grubbs second generation catalyst (36 mg, 10 mol%). The reaction mixture was then refluxed for 3 h and the reaction was monitored by TLC. The solvent was concentrated under vacuum. The resulting residue containing the mixture of **11d** and **11e** was separated by column chromatography over silica gel (5% ethyl acetate in light petroleum) to furnish **11d** (56 mg, 30%) and **11e** (13 mg, 7%). Spectral data of **11d**: $[\alpha]_D^{25}$ = 23.08 (c = 0.77, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (d, J = 5.0 Hz, 3H), 1.09 (s, 9H), 1.50–1.72 (m, 7H), 1.83–1.89 (m, 1H), 2.02–2.08 (m, 1H), 2.26–2.32 (m, 2H), 2.55–2.61 (m, 1H), 3.31-3.36 (m, 1H), 3.73–3.77 (m, 1H), 4.37–4.44 (m, 1H), 5.32 (t, J = 10.0 Hz, 1H), 7.36–7.44 (m, 6H), 7.65–7.68 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.2, 14.3, 19.6, 20.8, 22.1, 22.8, 22.9, 23.8, 25.4, 27.0, 27.2, 27.4, 29.1, 29.2, 29.5, 29.6, 29.8, 30.3, 31.7, 32.0, 33.9, 34.6, 34.8, 38.5, 39.1, 39.7, 40.4, 44.4, 58.9, 65.9, 126.6, 127.6, 127.7, 129.7, 136.0, 136.0, 136.1, 213.2; HRMS: calcd for $C_{29}H_{38}O_2Si[M+Na]^+$ 469.2539; found: 469.2537. Spectral data of **11e**: $[\alpha]_D^{25}$ = 19.00 (c = 0.71, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (t, J = 5.0 Hz, 3H), 1.09 (s, 9H), 1.52–1.71 (m, 7H), 1.89-1.99 (m, 2H), 2.25–2.37 (m, 2H), 2.43–2.51 (m, 1H), 3.07 (t, J = 10.0 Hz, 1H), 3.30–3.35 (m, 1H), 4.31 (appeared as singlet, 1H), 4.67 (S, 1H), 4.69 (s, 1H), 5.34–5.38 (m, 1H), 7.35-7.44 (m, 6H), 7.64–7.66 (m, 4H); ^{13}C NMR

(100 MHz, $CDCl_3$): δ 14.6, 19.6, 21.1, 23.5, 26.8, 27.3, 32.1, 40.0, 42.3, 43.8, 47.2, 60.5, 113.1, 127.7, 129.7, 130.4, 134.2, 134.9, 136.0, 136.1, 145.9; HRMS: calcd for $C_{30}H_{40}OSi$ $[M+Na]^+$ 467.2746; found: 467.2747.

2.15 *Preparation of 1-((1S,2R,3S,4S)-3-cyclohexenyl-2-methyl-4-(prop-1-en-2-yl)cyclopentyloxy)-2,2-dimethyl-1,1-diphenylpropane (**11f**)*

Compound **11f** 10%) was prepared from **10e** using the same procedure used for synthesizing **11a**. $[\alpha]_D^{25}$ = 15.85 (c = 0.955, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (d, J = 7.0 Hz, 3H), 1.08 (s, 9H), 1.25–1.31 (m, 4H), 1.52 (s, 3H), 1.65–1.68 (m, 2H), 1.94–1.98 (m, 2H), 2.25–2.35 (m, 2H), 2.43–2.50 (m, 1H), 3.06 (t, J = 10.0 Hz, 1H), 3.29–3.53 (m, 1H), 4.30–4.31 (m, 1H), 4.66 (s, 1H), 4.69 (s, 1H), 5.36 (m, 1H), 7.35–7.43 (m, 6H), 7.64–7.66 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6, 19.6, 21.0, 22.8, 23.2, 23.4, 27.3,29.1, 29.3, 29.5, 29.8, 32.5, 40.0, 42.4, 44.4, 47.2, 60.5, 113.1, 114.2, 127.6, 127.7, 129.7, 130.3, 134.2, 134.9, 136.0, 136.1, 145.9; HRMS: calcd for $C_{31}H_{42}OSi$ $[M+Na]^+$ 481.2903; found: 481.2905.

2.16 *Preparation of 1-(1-((1R,2S,3R,4S)-3-((allyloxy) methyl)-2-methyl-4-(prop-1-en-2-yl)cyclopentyl)-3,3-dimethyl-2-phenylbutan-2-yl)benzene (**12**)*

LiHMDS (0.5 mL, 0.50 mmol, 1M solution in THF) was added to a stirred solution of alcohol **7** (100 mg, 0.24 mmol) in dry DMF (3 mL) at −40°C under Argon. After 1 h of stirring, allyl bromide (0.05 mL, 0.50 mmol) was added dropwise. The reaction mixture was stirred for 3 h and then carefully quenched with saturated aqueous ammonium chloride solution (2 mL). After removal of most of the solvent under reduced pressure, the resulting residue was extracted with diethyl ether (4 × 25 mL). The combined ether extract was successively washed with water (2 × 10 mL) and brine (1 × 10 mL) and finally dried (Na_2SO_4). Solvent was removed under reduced pressure and the crude mass obtained was purified by column chromatography over silica gel (2% ethyl acetate in light petroleum) to furnish **12** (75 mg, 69%) as a viscous liquid. $[\alpha]_D^{25}$ = 7.64 (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03–1.06 (m, 12H), 1.57–1.61 (m, 1H), 1.72 (s, 3H), 1.77–1.80 (m, 1H), 2.02-2.04 (m, 1H), 2.11–2.15 (m, 1H), 3.02–3.11 (m, 2H), 3.22 (dd, J = 6.4, 9.2 Hz, 1H), 3.84 (t, J = 6.0 Hz, 2H), 4.24–4.27 (m, 1H), 4.51 (s, 1H), 4.73 (s, 1H), 5.09 (dd, J = 0.8, 10.4 Hz, 1H), 5.20 (dd, J = 1.6, 17.6 Hz, 1H), 5.61–8.85 (m, 1H), 7.32–7.41 (m, 6H), 7.63–7.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 15.5, 19.6, 24.0, 27.2, 29.1, 29.3, 29.5, 29.6, 29.7, 39.2, 43.6, 44.8, 46.4, 71.8, 71.9, 76.3, 76.8, 110.2, 114.2, 116.3, 127.5, 127.6, 129.5, 134.5, 135.1, 135.3, 136.0, 136.1, 146.2; HRMS: calcd for $C_{29}H_{40}O_2Si$ $[M+Na]^+$ 471.2695; found: 471.2692.

2.17 *Preparation of (Z,5aS,7R,8S,8aR)-3,5a,6,7,8,8a-hexahydro-5,8-dimethyl-7-(3,3-dimethyl-2-phenylbutyl)-1H-cyclopenta[c]oxepine (**13**)*

To a stirred solution of **12** (70 mg, 0.15 mmol) in dry toluene at room temperature under argon atmosphere was added Grubbs second generation catalyst (12 mg, 10 mol%). The reaction mixture was then refluxed for 3 h and the reaction was monitored by TLC. The solvent was concentrated under vacuum and the resulting residue was purified by column chromatography over silica gel (10% ethyl acetate in light petroleum) to furnish the cyclized product **13** (52 mg, 78%). $[\alpha]_D^{25}$ = 14.12 (c = 0.42, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (d, J = 6.8 Hz, 3H), 1.06 (s, 9H), 1.55–1.61 (m, 4H), 1.81 (q, J = 6.8 Hz, 1H), 1.89–1.94 (m, 1H), 2.00–2.04 (m, 1H), 2.96–3.04 (m, 1H), 3.62–3.68 (m, 2H), 4.12 (appeared as singlet, 2H), 4.20 (appeared as singlet, 1H), 5.04 (appeared as singlet, 1H), 7.32–7.42 (m, 6H), 7.66 (d, J = 6.8 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 19.6, 26.9, 27.2, 30.3, 31.5, 42.9, 43.3, 43.5, 48.6, 70.0, 70.2, 76.6, 76.7, 120.4, 127.4, 127.5, 129.6, 134.3. 135.3, 136.0, 136.1, 138.4; HRMS: calcd for $C_{27}H_{36}O_2Si$ $[M+Na]^+$ 443.2382; found: 443.2385.

3. Results and Discussion

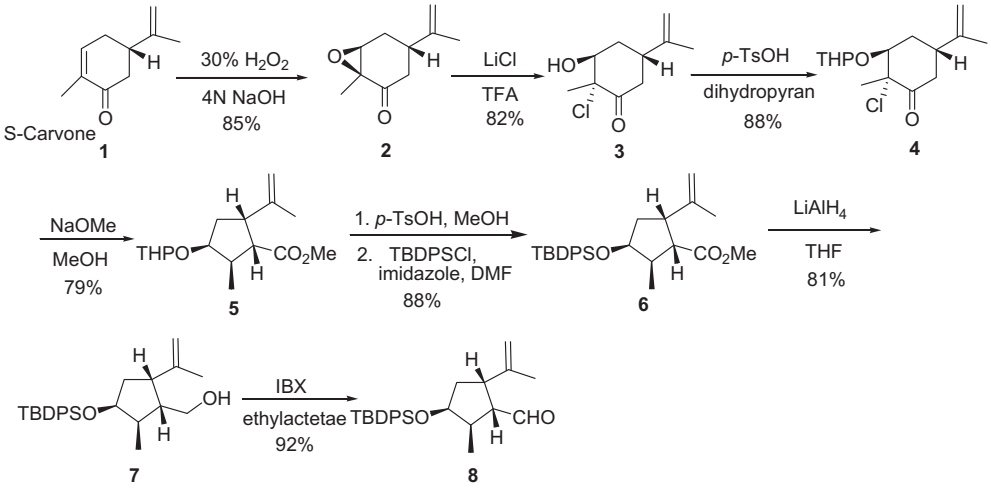
Thus, the common chiral cyclopentyl aldehyde **8** was prepared following the procedure reported[12] by Ley and co-workers from commercially available S-carvone. The synthesis was initiated by reacting 30% H_2O_2 with (*S*)-carvone **1** to synthesize the epoxide **2** which on trifluoroacetic acid catalyzed the ring opening reaction in the presence lithium chloride furnished the chlorohydrin **3** as the only product. The hydroxyl group of **3** was then protected as tetrahydropyranyl (THP) ether **4** which on treatment with an ice-cold solution of NaOMe in methanol afforded the chiral methyl ester **5** in good yield (Scheme 2).

The sensitive THP protecting group in **5** was transformed to the relatively stable *t*-butyldiphenylsilyl (TBDPS) derivative **6** which on treatment with $LiAlH_4$ furnished the alcohol **7**. IBX mediated controlled oxidation of **7** afforded the desired chiral aldehyde **8** (Scheme 2) in excellent yield. The next target was to convert the aldehyde **8** for the required advanced intermediates for fused bicyclic frameworks through RCM reaction. Accordingly, **8** was treated with different

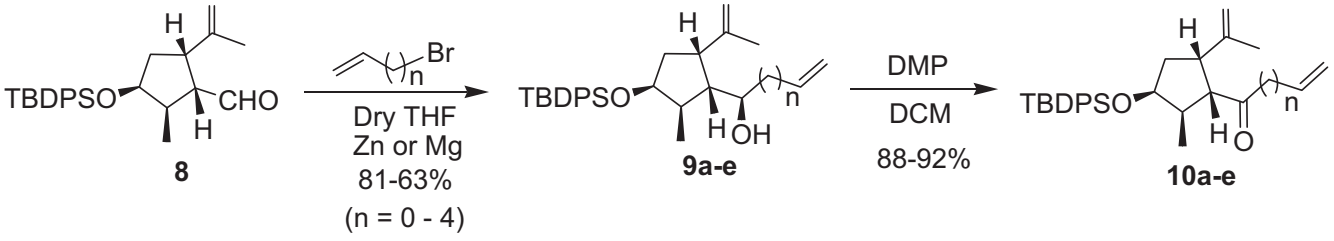
Grignard reagents made from unsaturated aliphatic bromides to furnish solely the alcohol **9a–e** as a single isomer which was already explained by Ley *et al.*[12] Since, the alcohol **9** was converted immediately to the ketone **10**, the detailed study for the stereochemistry of the −OH group in compound **9** was not necessary. Thus, alcohol **9a–e** on oxidation with DMP afforded the ketones **10a–e** as the sole product in satisfactory yields (Scheme 3).

Now the treatment of the ketones **10a–e** with Grubbs-II catalyst (10 mol%) were thoroughly investigated for the synthesis of bicyclic frameworks. Thus, when compound **10a** provided the 5-5 fused bicyclic skeleton, **10b** and **10c** efficiently furnished 5–6 and 5–7 fused bicyclic motifs, respectively, in good yields *via* ring closing metathesis (RCM) reaction (Scheme 4).

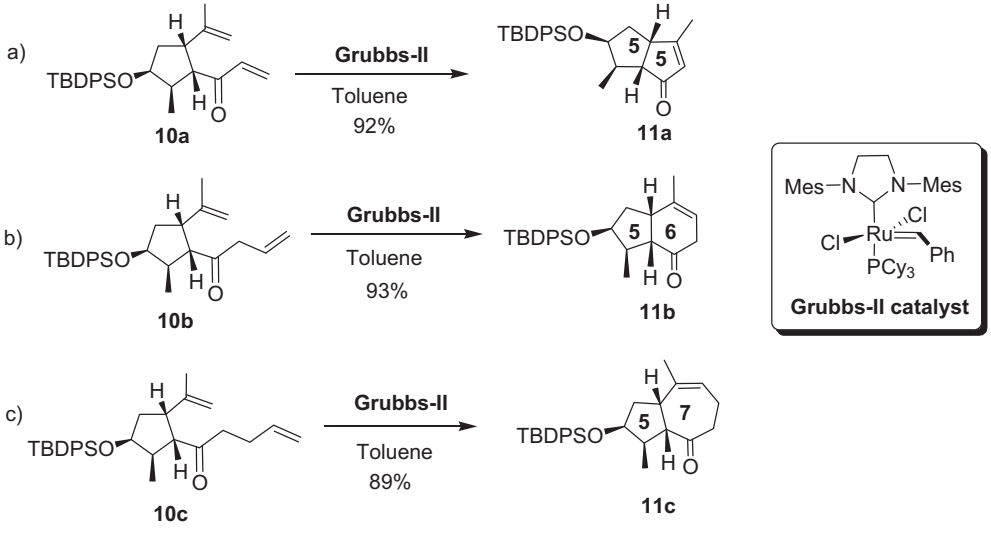
But when compound **10d** was subjected to RCM in the presence of Grubbs-II catalyst (10 mol%), it was



Scheme 2. Synthesis of the known intermediate for the diversity oriented approach.



Scheme 3. Synthesis of the precursors for RCM.

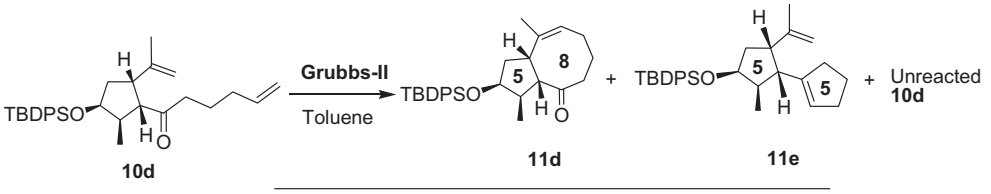


Scheme 4. Synthesis of 5-5, 5-6 and 5-7 bicyclic frameworks.

observed that 5–8 fused bicyclic compound **11d** (30%) along with a ring closing carbonyl-olefin metathesis (RCCOM) product **11e** (7%) were formed (Scheme 5). On the other hand, when 20 mol% of Grubbs II catalyst was used for RCM, the yield of both **11d** (40%) as well as **11e** (13%) increased which established the concept that ring closing metathesis and ring closing carbonyl-olefin metathesis are very much competitive in nature, so far as the higher-membered ring formation is concerned.

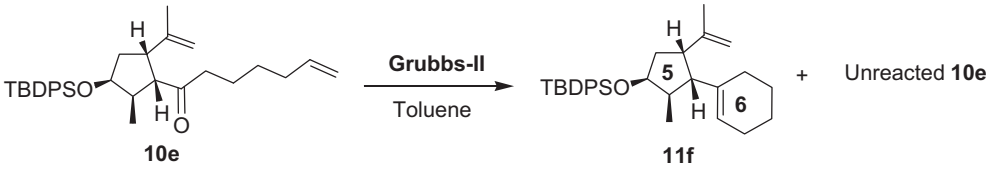
It is already reported[11] that unlike RCM, the RCCOM propagation requires a stoichiometric amount of Grubbs-II catalyst, as the formation of metal-oxo complex destroys the catalytic activity of Grubbs-II. To extend the protocol for synthesis of 5–9 fused bicyclic carbocycles, compound **10e** was treated under identical reaction conditions in the presence of 10 mol% Grubbs-II catalyst. It was observed that exclusively the RCCOM product **11f** (10%) could be isolated along with recovery of the starting material **10e** (Scheme 6). This result is in accordance with the fact that greater loss of entropy for a nine membered ring formation favored the formation of cyclohexene ring from thermodynamical point of view. The enhancement of the yield of **11f** (20%) with gradual increase of amount of Grubbs-II catalyst (20 mol%), only confirmed the stoichiometric relationship between the substrate and the catalyst.

In this context, it should be mentioned that compared to RCM, available examples of RCCOM are very rare.[11] Earlier works on RCCOM had involved photochemical reactions, stoichiometric use of metal alkylidene complexes (tungsten, molybdenum and titanium) and use of Tebbe reagents, Petasis reagents and Takai-utimoto



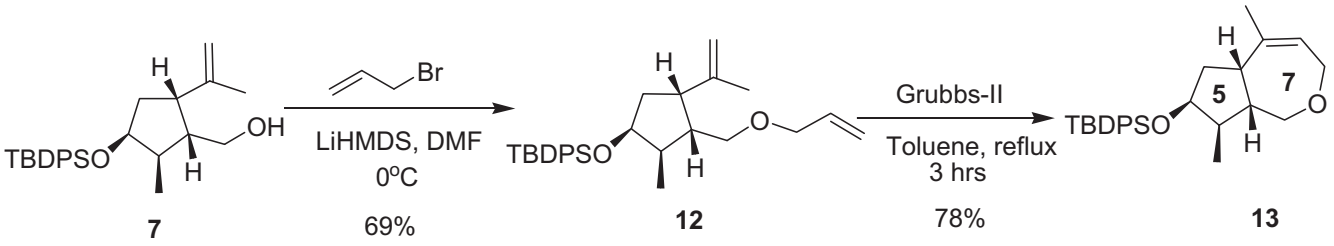
Grubbs-II	11d	11e
10 mol%	30%	7%
20 mol%	40%	13%

Scheme 5. Grubbs-II catalyzed RCM and RCCOM.

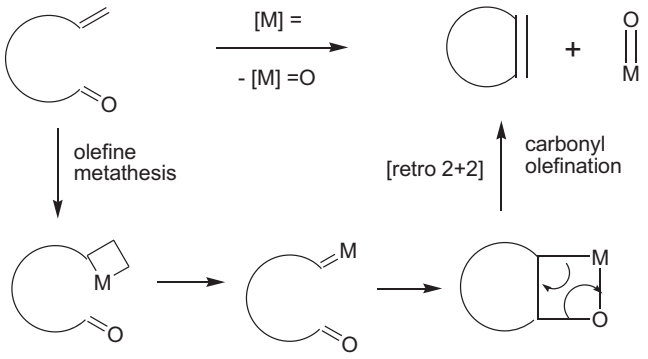


Grubbs-II	11f
10 mol%	10%
20 mol%	20%

Scheme 6. Grubbs-II catalyzed RCCOM.



Scheme 7. Synthesis of 5–7 fused oxygen containing heterocycle.



Scheme 8. Probable mechanism for the formation of RCCOM product.

reagents. Very recently, alternative strategies have been envisioned which implicated $FeCl_3$-catalyzed and organocatalytic carbonyl-olefin metathesis methods.[13] Moreover, there was no indication of E/Z isomerization in final product which is usually a drawback of RCM for the synthesis of larger rings.

After successful implementation of diversity-oriented approach towards the synthesis of a number of bicyclic carbocycles with different ring sizes, we turned our attention for the synthesis of medium-sized cyclopentane-fused oxacyclic skeletons. Such type of oxygen containing heterocycles are primarily found in various biologically important molecules and thus, the developments of new methodologies for synthesizing medium-sized oxacycles have always garnered the attention of scientific community.[14]

Thus, the alcohol **7** on treatment with allyl bromide and LiHMDS in DMF was converted to the allyl ether **12** in good yield (Scheme 7). Compound **12** on ring closing metathesis in the presence of Grubs-II catalyst (10 mol%) furnished the 5–7 fused oxygen heterocycle **13** in 78% yield. The study towards the formation of higher membered oxacylic rings through RCM and their applications for the synthesis of natural products is under progress.

The probable mechanism for the RCCOM reaction, as already indicated by Fu and Grubbs[11] with stoichiometric amount of molybdenum alkylidene complex, is depicted below (Scheme 8).

4. Conclusions

In summary, diversity-oriented approach for the synthesis of optically active, substituted cyclopentane-fused carbocyclic and oxacyclic frameworks through ring closing metathesis (RCM) from a common chiral aldehyde intermediate prepared from (*S*)-carvone has been demonstrated. As the size of the ring increases, a competition between RCM and ring closing carbonyl-olefin metathesis (RCCOM) was observed. The initial chiral centers have been retained throughout the reaction course. The final compounds have ample scope to be the core structures for biologically active natural products.

Supplementary Information (SI)

Copies of NMR spectra of new compounds are available in Supplementary Information at www.ias.ac.in/chemsci.

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