PAPER

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Synthesis of propellanes containing a bicyclo[2.2.2] octene unit *via* the Diels−Alder reaction and ring-closing metathesis as key steps†

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The synthesis of propellanes containing bicyclo[2.2.2]octene *via* olefin metathesis approach is less explored. Herein, we describe a simple and convenient method to synthesize propellane derivatives containing a bicyclo[2.2.2]octene unit which are structurally similar to 11β-HSD1 inhibitors by sequential usage of the Diels−Alder reaction, C-allylation and ring-closing metathesis (RCM) as the key steps. Additionally, we expanded this approach to an *endo*-tricyclo[4.2.2.0²,⁵]decene derivative which is a useful monomer for polymer synthesis and we have also synthesized basketene and anthracene-based propellanes using the same strategy.

Introduction

Propellanes are Y-shaped tricyclic molecules containing a bridgehead C–C bond. They can be classified as carbocyclic and heterocyclic frames and their physical or chemical properties vary with their ring size.[1] Heterocyclic propellanes are generally found in nature whereas carbocyclic propellanes are rare and found in secondary metabolites.[1c,d] Synthesis of the propellane motif is difficult using conventional methods because of their quaternary nature[2] and creation of vicinal quaternary carbons is not a trivial task. However, they can be assembled easily using a ring-closing metathesis (RCM) strategy.[2,3] The synthesis of propellanes containing a bicyclo[2.2.2]octene system and their metathetic behaviour is worthy of systematic investigation.[4]

Bicyclo[2.2.2]octene is a rigid and strain free system which is present in diverse and challenging targets varying from biomolecules to natural products.[5] Bicyclo[2.2.2]octene fused cyclic amides are potent bioactive molecules. 3,10-Dihydroxydielmentha-5,11-diene-4,9-dione 1[6a,7] is a diterpenoid isolated from *Callitris macleayana* heartwood and has a core of bicyclo[2.2.2]octene fused with a 6-membered carbocyclic ring (Fig. 1). Mitindomide 2 (Fig. 1) is a bicyclo[2.2.2]octene analogue which inhibits topoisomerase II and promotes DNA-interstrand cross-linking and thereby increases its antineoplastic activity.[6b] A water soluble derivative 3, which is structurally similar to mitindomide 2 but lacks the cyclobutane ring, exhibits antitumor activity.[5,6c]

A recent report explains that the norbornene amide derivative 4 and the bicyclic[2.2.2]octane fused cyclic amide derivatives 5–9 are potent 11β-hydroxysteroid dehydrogenase type-I (HSD1) inhibitors and this inhibition was determined in mixed sex, human liver microsomes (Fig. 1).[8] The introduction of lipophilic substituents has proven to be a successful strategy to enhance the inhibition of 11β-HSD1 activity. IC₅₀ values of compounds 4–8 against 11β-HSD1 activity range from 0.02 to 0.03 μM. Meanwhile, compound 9 has an IC₅₀ value of 1.49 μM which is little higher than the IC₅₀ values of compound 4–8 with 83% of the enzyme inhibition. These results suggest that the bicyclo[2.2.2]octane amide derivatives fit well into the hydrophobic pocket of 11β-HSD1.[8] In this regard, propellanes containing bicyclo[2.2.2]octene derivatives with enhanced hydrophobicity are worthy targets of investigation for human 11β-HSD1.

To the best of our knowledge, the synthesis of propellanes containing a bicyclo[2.2.2]octene system *via* olefin metathesis has been less explored. Ring-rearrangement metathesis (RRM) of the bicyclo[2.2.2]octene analogues 10 and 12 tethered to an *endo* olefin moiety is an excellent strategy for synthesizing hydrindanes 11 and 13 which are fused 7/6 and 6/6 decalines.[9] However, the *exo*-N-phenyl bicyclo[2.2.1] derivative 14 underwent RRM to synthesize triquinane 15 and the *endo*-N-phenyl bicyclo[2.2.1] derivative 17 underwent ROM–RCM to synthesize propellane 18.[3c] Our approach is that the *endo*-N-phenyl bicyclo[2.2.2] derivative 19 didn't go through ROM or RRM but underwent RCM to deliver bicyclo[2.2.2]octene propellane 20 (Scheme 1). Herein, we report a stereoselective synthesis of a new class of bicyclo[2.2.2]octene based propellane which is structurally similar to 11β-HSD1 inhibitors.

A bicyclic monomer unit, *endo*-tricyclo[4.2.2.0]deca-3,9-diene (TD) 21, is extensively used in copolymerization to synthesize block copolymer 22 *via* ring-opening metathesis polymerization

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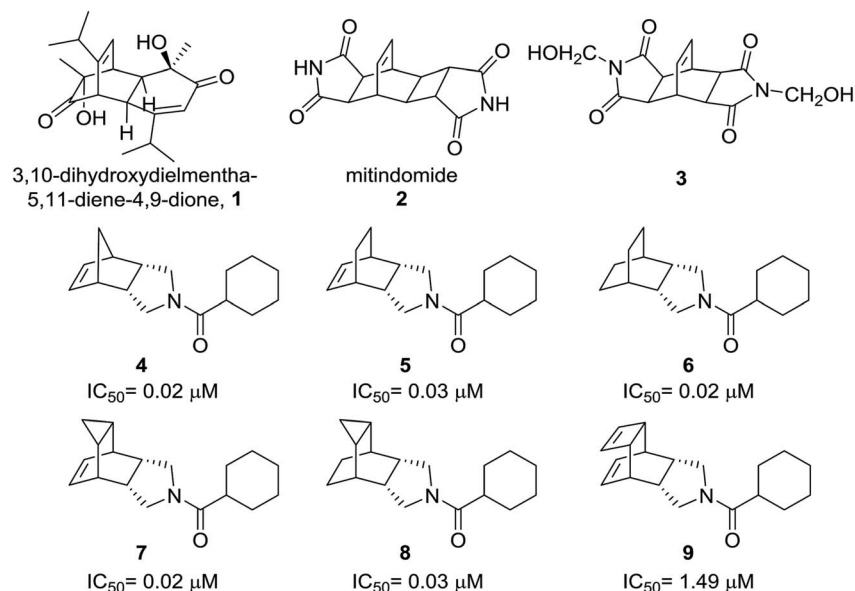
Fig. 1 List of bicyclo[2.2.2]octane containing bioactive molecules (1–3) and 11β-HSD1 inhibitors (4–9). IC_{50} values were determined in mixed sex, human liver microsomes.

(ROMP) (Scheme 2).[10] It seems that ROMP of an *endo*-tricyclo [4.2.2.0]deca-3,9-diene system is much faster than that of a norbornene system because of the high reactivity of the cyclobutene moiety present in the *endo*-tricyclo[4.2.2.0]deca-3,9-diene unit.[11] Recently, Choi and co-workers have proposed a controlled ROMP of terminal alkyne monomer 23 to alkyne copolymer 24 by taking advantage of the strain in the cyclobutene ring of TD (Scheme 2).[11c]
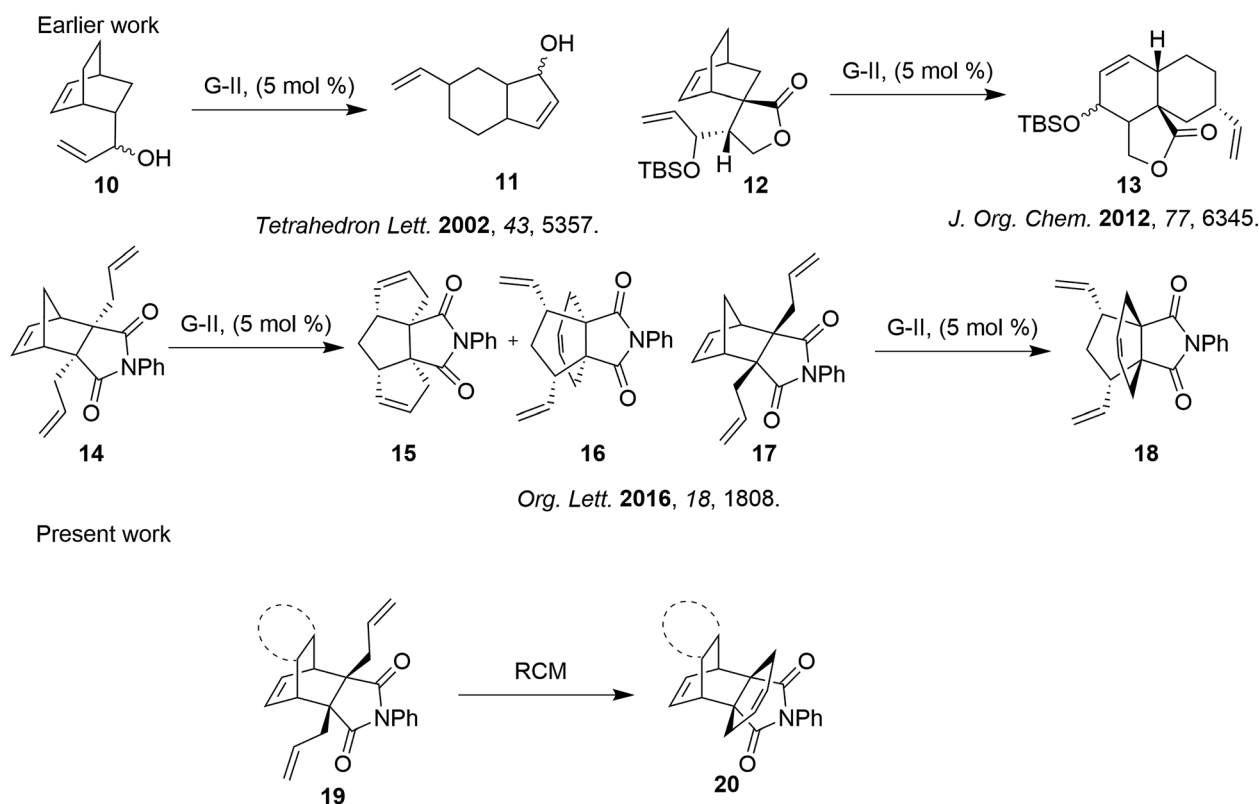
Scheme 1 Metathesis of bicyclo[2.2.2]octene analogues.
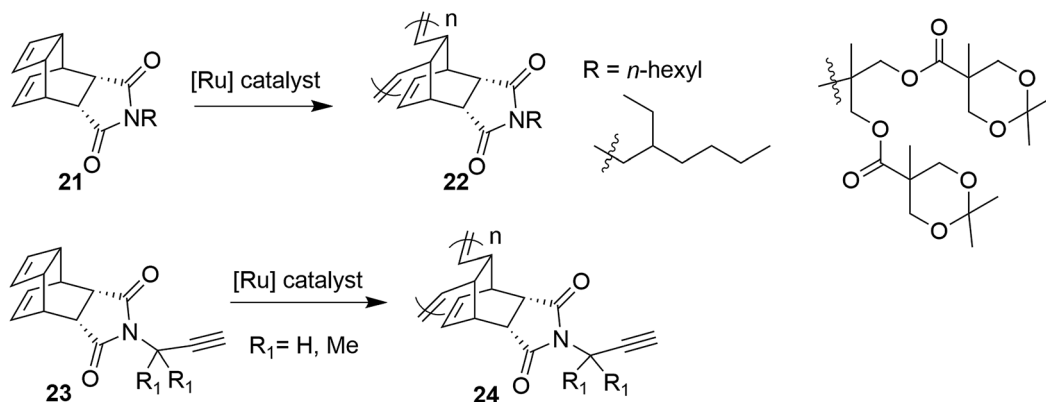
Scheme 2 Polymerization of *endo*-tricyclo[4.2.2.0]deca-3,9-diene (TD).

Results and discussion

Our synthetic approach to propellane derivatives relies on understanding the metathetic behaviour of the *endo*-tricyclo [4.2.2.0]deca-3,9-diene derivative **29**. Its synthesis starts with the preparation of the Diels–Alder (DA) adduct **27**, which is easily assembled from commercially available cyclooctatetraene **25** and maleic anhydride **26** using a [4 + 2] cycloaddition reaction.[11d,12] Next, anhydride **27** was treated with aniline in the presence of triethylamine in toluene at 120 °C to give compound **28** in 98% yield.[3c] Later, the *endo* adduct **28** was treated with an excess amount of allyl bromide in the presence of 1 M NaHMDS at −78 °C to deliver the diallyl compound **29** in 45% yield (Scheme 3).[3c] Compound **29**, which contains three distinct types of olefinic moiety, is an interesting substrate for studying metathetic behaviour.

To study the metathesis behaviour of compound **29**, we screened various catalysts (Fig. 2) under different reaction conditions (Table 1).[13] Among the various catalysts, only the G-I and G-II catalysts (Table 1, entries 1 and 2) gave a significant yield of the propellane derivative **30**. The stereochemistry of compound **30** was further confirmed by single crystal X-ray diffraction studies (Fig. 3).[14]

We were able to suppress the polymerization mode by carrying out the reaction under an ethylene atmosphere in the presence of the G-I and G-II catalysts. However, with the Hoveyda–Grubbs catalysts (Table 1, entries 3 and 4), the diallyl compound **29** was polymerized along with trace amounts of the propellane derivative **30**. We didn't observe any RRM product under these conditions. The crystal data of compound **30** indicate that due to their orientation, the vinyl groups are not favourably disposed to interact with the allyl groups to deliver the RRM product (Fig. 3).[14]

To understand the metathetic behaviour of the different olefinic moieties present in the bicyclo[2.2.2]octene derivative **29**, we are interested in preparing compound **31** with the double bond present in the cyclobutene ring absent. In this regard, compound **28** was subjected to selective hydrogenation with the aid of 10% Pd/C–H$_2$ to afford the partially saturated compound **31** in 96% yield.[15] Later, it was subjected to allylation under 1 M NaHMDS conditions to generate the diallyl derivative **32** in 53% yield.[3c] Then, the diallyl compound **32** was subjected to a metathesis sequence with the G-II catalyst to obtain the propellane derivative **33** in 64% yield (Scheme 4).

We have also studied the metathetic behaviour of the DA adduct **28** using various catalysts under different reaction conditions (Table 2). Among these, the G-I and G-II (Table 2, entries 1 and 2) catalysts gave the cyclobutene ring-opened product **34** in excellent yields. However, we didn't observe the formation of the completely ring-opened product **35** under these conditions.

To understand the role of the cyclobutane ring in the metathetic behaviour of compound **29**, we synthesized the DA adduct **37** from maleic anhydride **26** with 1,3-cyclohexadiene **36** and subsequently **37** was reacted with aniline in the presence of Et$_3$N to deliver compound **38**.[3c,16] The metathetic behaviour of the *endo* adduct **38** was studied with various catalysts under different reaction conditions. Unfortunately, we didn't obtain the expected ROM product **39**. Later, the *N*-phenyl derivative **38** was treated with allyl bromide in the presence 1 M NaHMDS at −78 °C to afford the diallyl compound **40** in 45% yield. Subsequently, the diallyl derivative **40** was subjected to a metathesis
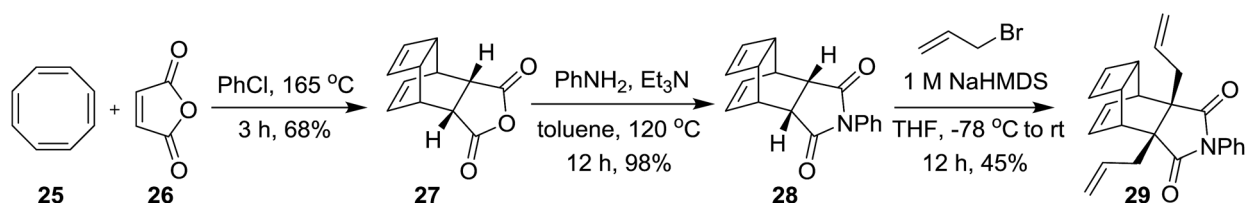
Scheme 3 Synthesis of diallyl *endo*-tricyclo[4.2.2.0]deca-3,9-diene **29**.
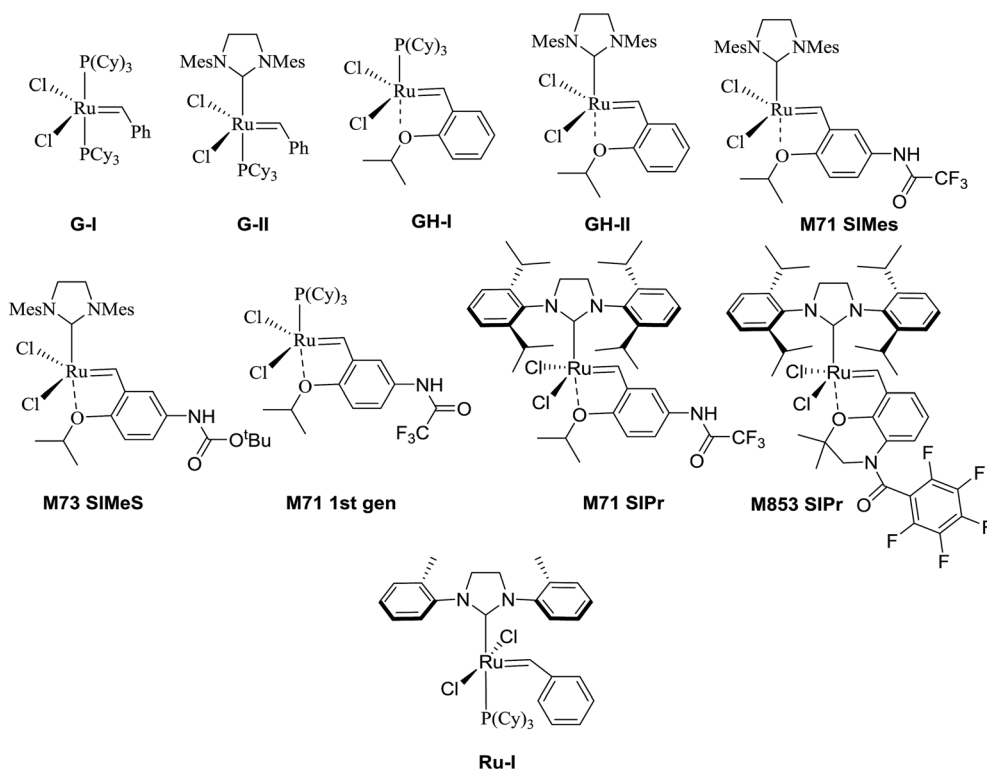
Fig. 2 The various metathesis catalysts used in the present study.

Table 1 Metathetic behaviour of compound **29** with different catalysts

Entry	Catalyst (mol%)	Solvent	Temp (°C)/time (h)	Yield (%)
1	G-I (5 mol%)	CH$_2$Cl$_2$	rt/6 h	65
2	G-II (5 mol%)	CH$_2$Cl$_2$	rt/6 h	58
3	GH-I (5 mol%)	CH$_2$Cl$_2$	rt/5 h	Trace
4	GH-II (5 mol%)	CH$_2$Cl$_2$	rt/3 h	Trace
5	G-I (10 mol%)	Toluene	Reflux/3 h	10
6	G-II (10 mol%)	CH$_2$Cl$_2$	rt/5 h	35
7	G-I (5 mol%) + Ti(OPr^i)$_4$ (catalytic)	CH$_2$Cl$_2$	rt/4 h	32
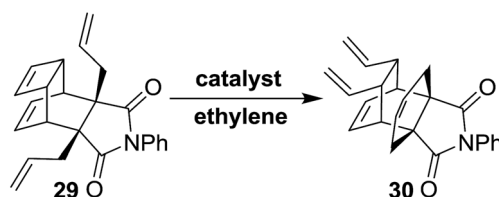
sequence using the G-II catalyst (5 mol%) under ethylene to produce the propellane derivative **41** in 92% yield (Scheme 5). These results suggest that the double bond present in the cyclobutene of the *endo*-tricyclo[4.2.2.0]deca-3,9-diene system is highly reactive and the double bond present in the bicyclo[2.2.2] octene system is inert under these conditions. Our attempt to synthesize the *exo* derivative of **37** and **38** was not successful.

Later, this strategy was extended to design the basketene[17] and anthracene-based propellane derivatives **45** and **50** respectively. Recently, our group reported the synthesis of cage propellanes,[18] however, the basketene-based propellane synthesis is a worthy target for high energy systems. In this context, the DA adduct **27** was subjected to a [2 + 2] photo-cycloaddition reaction using a 450 W Hg lamp equipped with a Pyrex glass filter for 20 h to produce the cage compound **42**,[17d] which on treatment with aniline in the presence of trimethyl-amine in toluene gave the cage compound **43** in 68% yield. Additionally, allylation of the *N*-phenyl derivative **43** with allyl bromide under 1 M NaHMDS conditions afforded the diallyl compound **44** which underwent RCM with the G-II catalyst at
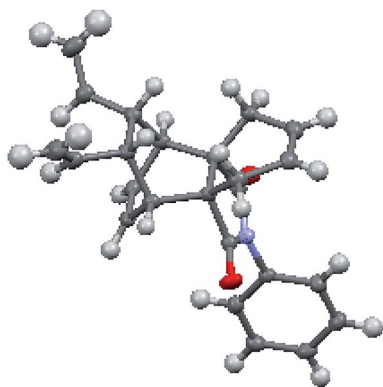
Fig. 3 Crystal XRD structure of **30** with thermal ellipsoids drawn at the 50% probability level.[14]

room temperature to produce the propellane derivative **45** in 65% yield (Scheme 6). The structure of **45** has been established on the basis of ^{1}H NMR and ^{13}C NMR spectral parameters and was further supported by the HRMS data. Along similar lines, anthracene derived propellane **50** was synthesized from the corresponding anhydride **47**[19] in three steps with a 31% overall yield (Scheme 6).

We have also carried out geometry optimization studies to illustrate the spatial demands and rigidity of these propellanes. Gas-phase calculations were carried out for **30**, **33**, **41**, and **45** at the M062X/6-31G** level of theory. All calculations were carried out using the Gaussian 09 program.[20] As shown by the optimized geometry study, ∠C1–C2–C7 and ∠C1–C2–C7 of the bicyclo[2.2.2]octene propellane derivatives **30**, **33**, and **41** are similar. However, the propellane derivative **45** was found to have larger bond angles compared to other derivatives due to distortion upon the [2 + 2] cyclo-addition reaction of **27**. ∠C2–C3–C10 of the basketene derivative **45** is 89.56° which is close to the cubane bond angle of 90° (Fig. 4). Because of the rigidity of the propellane containing bicyclo[2.2.2]octene derivatives **30**, **33**, **41** and **45** and their structural similarity to the reported compounds **5–9**, our methodology is useful for synthesizing biologically active derivatives such as these.

Experimental section

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 using the syringe-septum technique and the reactions were maintained under a nitrogen atmosphere. Analytical thin-layer chromatography (TLC) was performed on (7.5 × 2.5 cm) glass plates coated with the Acme silica gel GF 254 (containing 13% calcium sulfate as a binder) using a suitable mixture of EtOAc and petroleum ether for development. Column chromatography was performed using Acme silica gel (100–200 mesh) with an appropriate mixture of EtOAc and petroleum ether. Coupling constants (J) are given in hertz (Hz) and chemical shifts are denoted in parts per million (ppm) downfield from the 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 triplets and doublet of triplets, respectively. Infrared (IR) spectra were recorded on a 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.

The general procedure for the *endo*-anhydride synthesis

Compound 27. Off-white solid (190 mg starting from 150 mg of **26**, 68%), R_f = 0.56 (10% EtOAc/hexane). ^{1}H and ^{13}C NMR spectra of compound **27** were matched with those of the reported literature.[11d]

Compound 37. Off-white solid (242 mg starting from 150 mg of **36**, 74%), R_f = 0.48 (10% EtOAc/hexane). ^{1}H and ^{13}C NMR spectra of compound **37** were matched with those of the reported literature.[16]

Compound 42. White solid (180 mg starting from 345 mg of **27**, 52%), R_f = 0.56 (10% EtOAc/hexane). ^{1}H and ^{13}C NMR spectra of compound **42** were matched with those of the reported literature.[17d]

Compound 47. White solid (650 mg starting from 490 mg of **46**, 86%), R_f = 0.62 (10% EtOAc/hexane). ^{1}H and ^{13}C NMR spectra of compound **47** were matched with those of the reported literature.[19a]

The general procedure for the *endo-N*-phenyl adduct synthesis

Aniline (1 mmol, 1 equiv.) and trimethylamine (1 mL) were added to anhydride (1 mmol, 1 equiv.) in toluene in a sealed tube. The resulting mixture was heated at 120 °C for 12 h. After the depletion of anhydride, the extra solvent was distilled off.
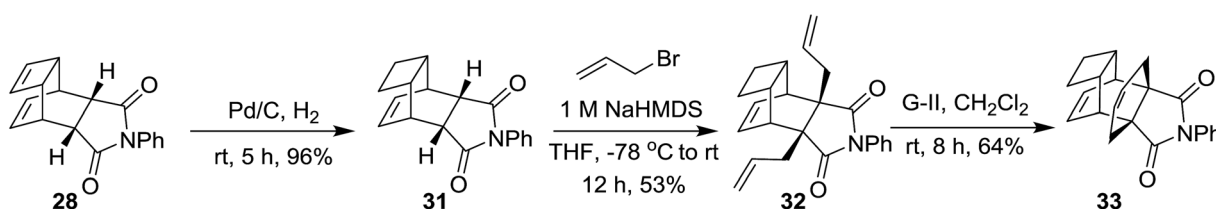
Scheme 4 Synthesis of the *endo*-tricyclo[4.2.2]deca-3-ene propellane **33**.

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Table 2 The metathetic behaviour of compound **28** with different catalysts

Entry	Catalyst	Time	Product **34**, yield (%)
1	G-I	6 h	83
2	G-II	6 h	85
3	GH-I	5 h	71
4	GH-II	12 h	68
5	M71 SIMes	12 h	65
6	M71 1st gen	12 h	69
7	M71 SIPr	12 h	58
8	M853 SIPr	12 h	60
9	M73 SIMes	12 h	63
10	Ru-I	5 h	75

The residue was washed with diethyl ether (2 × 30 mL) and dried under high vacuum to yield a pure *N*-phenyl adduct.

Compound 28. Yield 98% (310 mg, starting from 240 mg of **27**), white solid. ^{1}H and ^{13}C NMR spectra of compound **28** were matched with those of the reported literature.[10a]

Compound 38. White solid (465 mg starting from 480 mg of **37**, 68%), R_f = 0.52 (10% EtOAc/hexane). ^{1}H and ^{13}C NMR spectra of compound **38** were matched with those of the reported literature.

Compound 43. White solid (65 mg starting from 100 mg of **42**, 48%), R_f = 0.5 (10% EtOAc/hexane), mp: 165–167 °C. IR (neat): ν_{max} C=O stretch at 1705 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.49–7.43 (m, 2H), 7.41–7.35 (m, 1H), 7.25–7.21 (m, 2H), 3.38–3.32 (m, 4H), 3.29–3.25 (m, 2H), 3.13–3.09 (m, 2H), 2.99 (t, 2H, J = 1.9 Hz). ^{13}C NMR (CDCl$_3$, 100 MHz): δ = 178.50, 132.19, 129.28, 128.68, 126.65, 43.90, 38.95, 36.75, 32.79.

HRMS (ESI, Q-ToF) m/z: found [M + H]$^+$ = 278.1189, calculated = 278.1181 for C$_{18}$H$_{15}$NO$_2$.

Compound 48. Pale yellow solid (295 mg starting from 300 mg of **47**, 78%), R_f = 0.55 (10% EtOAc/hexane). ^{1}H and ^{13}C NMR spectra of compound **48** were matched with those of the reported literature.[19b]

Synthesis of compound 31

To compound **28** (320 mg, 1.15 mmol) in EtOAc, 10% Pd/C was added at room temperature the reaction mixture was allowed to stir for 5 h at room temperature until completion. The reaction mixture was passed through a celite column and washed with EtOAc several times to yield pure compound **31**. White solid (310 mg, 96%), mp: 195–197 °C, R_f = 0.68 (5% EtOAc/hexane). IR (neat): ν_{max} C=O stretch at 1704 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.44 (t, 2H, J = 7.5 Hz), 7.36 (t, 1H, J = 7.5 Hz), 7.18 (d, 2H, J = 8.6 Hz), 6.43 (t, 2H, J = 3.5 Hz), 3.23 (brs, 2H), 2.83 (br. s, 2H), 2.62–2.57 (m, 2H) 2.10–2.02 (m, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz): δ = 178.1, 132.2, 132.1, 129.1, 128.7, 126.6, 45.0, 37.0, 36.5, 22.3.
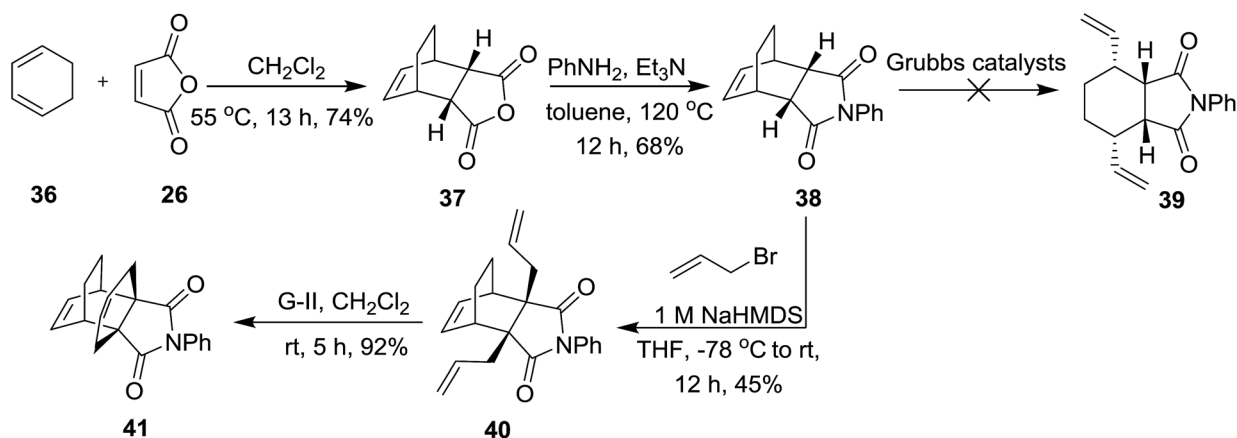
Scheme 5 Synthesis of the bicyclo[2.2.2]octene propellane **41**.
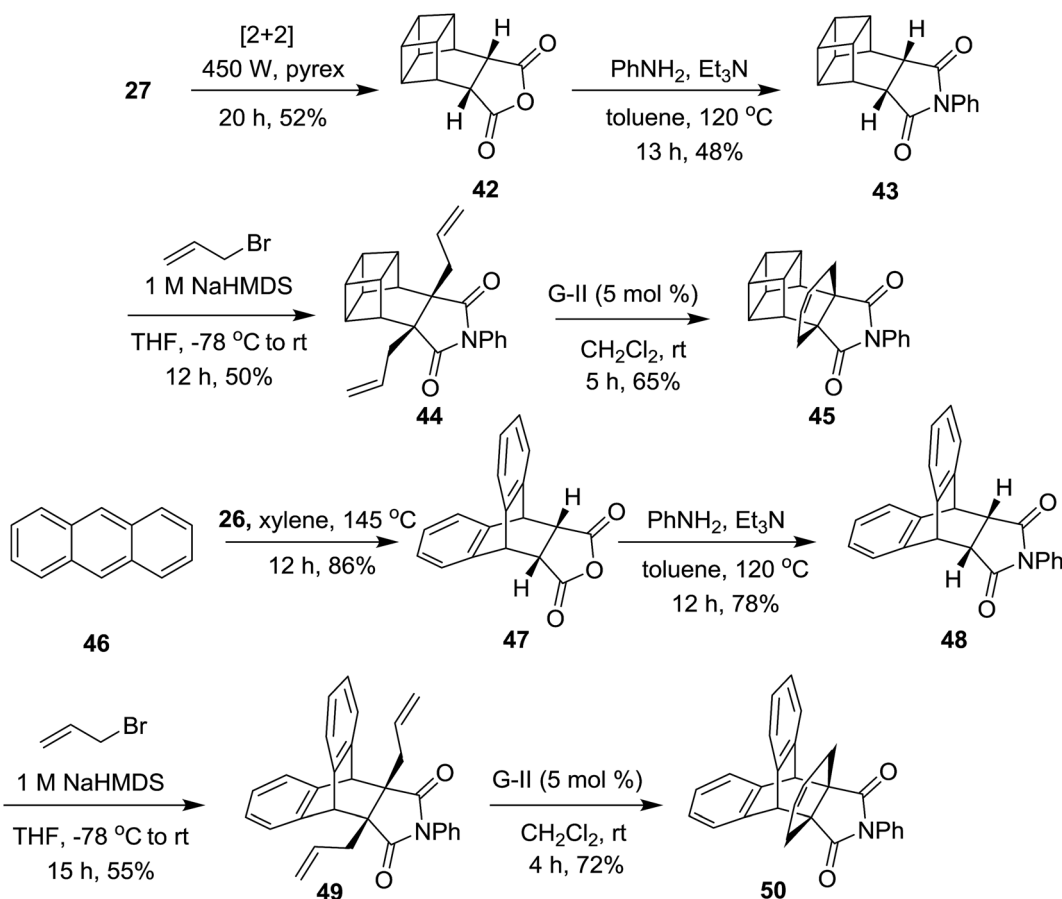
Scheme 6 Synthesis of the basketene-based and anthracene derived propellane derivatives **45** and **50**, respectively.

HRMS (ESI, Q-ToF) m/z: found $[M + Na]^+ = 302.1151$, calculated $= 302.1146$ for $C_{18}H_{17}NO_2$.

The general procedure for allylation using NaHMDS

NaHMDS (4.33 mmol, 8 eq.) and allyl bromide (4.3 mmol, 8 eq.) were added to the N-phenyl adduct compound (0.55 mmol, 1 eq.) in dry THF at -78 °C under a nitrogen atmosphere. The resulting mixture was brought to room temperature in 12 h and stirred at rt for 1 h. After the completion of the reaction, THF was removed under reduced pressure and the residue was partitioned between ethylacetate and water. The organic layer was concentrated and purified by column chromatography to yield the allylated compound.

Compound 29. Off-white solid (41 mg starting from 70 mg of **28**, 45%), $R_f = 0.75$ (5% EtOAc/hexane), mp: 156.5–157.2 °C. IR (neat): ν_{max} C=O stretch at 1764, 1701 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): $\delta = 7.47$–7.40 (m, 3H), 7.40–7.32 (m, 1H), 7.22–7.12 (m, 2H), 6.25–6.13 (m, 2H), 6.03 (dd, $J = 2.5$ Hz, 4.5 Hz, 2H), 5.82 (s, 2H), 5.27–5.17 (m, 4H), 3.13–3.03 (m, 4H), 2.71–2.50 (m, 5H). ^{13}C NMR (CDCl$_3$, 100 MHz): $\delta = 180.2$, 137.6, 133.9, 132.1, 130.2, 129.2, 128.7, 126.7, 118.8, 51.8, 42.2, 38.9, 35.5. HRMS (ESI, Q-ToF) m/z: found $[M + Na]^+ = 380.1621$, calculated $= 380.1619$ for $C_{24}H_{23}NO_2$.

Compound 32. White solid (101 mg starting from 150 mg of **31**, 53%), $R_f = 0.56$ (5% EtOAc/hexane), mp: 129.3–133.5 °C. IR (neat): ν_{max} C=O stretch at 1742, 1705 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): $\delta = 7.48$–7.40 (m, 2H), 7.38–7.33 (m, 1H), 7.20–7.16 (m, 2H), 6.47 (dd, 2H, $J = 3.32$, 1.2), 6.20–6.07 (m, 2H), 5.19 (q, 1H, $J = 1.44$ Hz), 5.16–5.14 (m, 2H), 5.13 (brs, 1H), 3.01–2.97 (m, 2H), 2.82–2.75 (m, 2H), 2.57 (td, 1H, $J = 4.36$, 1.45 Hz), 2.53 (td, 1H, $J = 5.81$ Hz, 1.33 Hz), 2.42 (dd, 2H, $J = 14.6$ Hz, 8.3 Hz), 2.06–2.02 (m, 2H), 1.48–1.43 (m, 2H) ppm. ^{13}C NMR (CDCl$_3$, 125 MHz): $\delta = 180.3$, 134.0, 133.7, 129.1, 128.6, 126.7, 50.9, 41.7, 35.6, 31.0, 22.0 ppm. HRMS (ESI, Q-ToF) m/z: found $[M + H]^+ = 360.1958$, calculated $= 360.1953$ for $C_{24}H_{26}NO_2$.

Compound 40. White solid (60 mg starting from 100 mg of **38**, 45%), $R_f = 0.8$ (5% EtOAc/hexane), mp: 116.1–118.4 °C. IR (neat): ν_{max} C=O stretch at 1705 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): $\delta = 7.47$–7.40 (m, 2H), 7.40–7.32 (m, 1H), 7.22–7.09 (m, 2H), 6.36–6.27 (m, 2H), 6.23–6.07 (m, 2H), 5.27–5.10 (m, 4H), 2.97 (brs, 2H), 2.72–2.46 (m, 4H), 1.88–1.76 (m, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz): $\delta = 180.5$, 134.2, 132.2, 129.2, 128.7, 126.7, 118.7, 51.5, 37.5, 35.9, 18.4. HRMS (ESI, Q-ToF) m/z: found $[M + Na]^+ = 356.1624$, calculated $= 356.1626$ for $C_{22}H_{23}NO_2$.

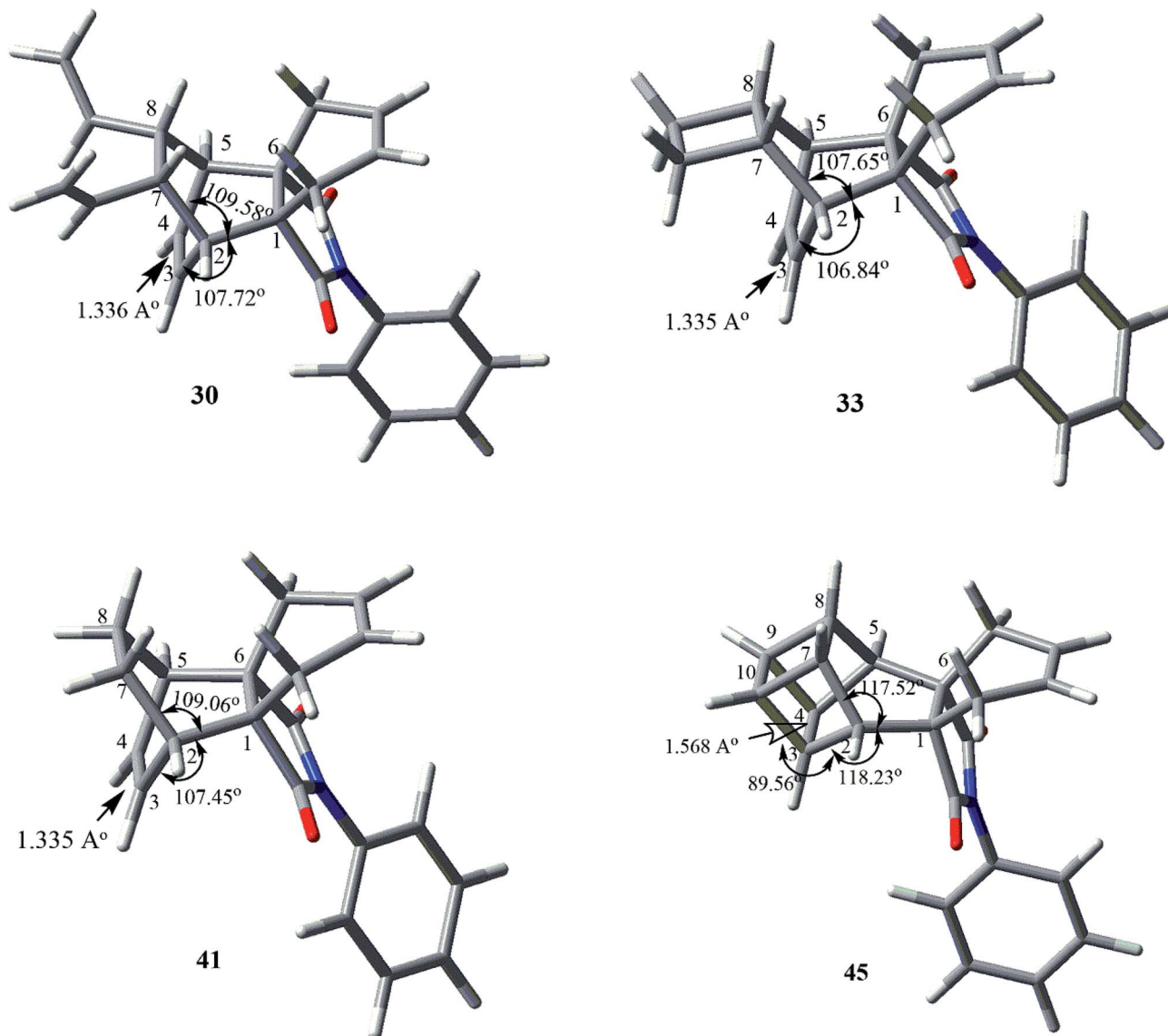**Compound 44.** Colourless liquid (25 mg starting from 40 mg of **43**, 50%), $R_f = 0.74$ (5% EtOAc/hexane). IR (neat): ν_{max} C=O

Fig. 4 The optimized geometries of 30, 33, 41 and 45 at the M06-2X/6-31G** level of theory. C = grey, H = white, N = blue and O = red.

stretch at 1708 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ = 7.47–7.43 (m, 2H), 7.39–7.37 (m, 1H), 7.20–7.18 (m, 2H), 6.17–6.06 (m, 2H), 5.18–5.12 (m, 4H), 3.28 (sex, 4H, J = 3.0 Hz), 3.27–3.23 (m, 2H), 3.15–3.12 (m, 4H), 2.65 (dd further split into triplet, 2H, J = 1.28 Hz, 6.24 Hz, 14.52 Hz), 2.43 (dd, 2H, J = 8.04 Hz, 14.52 Hz). ^{13}C NMR (CDCl$_3$, 125 MHz): δ = 180.0, 134.3, 129.2, 128.6, 126.7, 118.4, 46.5, 43.0, 39.2, 37.1, 37.0, 36.5. HRMS (ESI, Q-ToF) m/z: found [M + Na]$^+$ = 380.1621, calculated = 1619 for C$_{24}$H$_{23}$NO$_2$.

Compound 49. White solid (67 mg starting from 100 mg of **48**, 55%), R_f = 0.75 (5% EtOAc/hexane), mp: 182.8–186.1 °C. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.50–7.13 (m, 13H), 6.53–6.40 (m, 2H), 6.34–6.17 (m, 2H), 5.33–5.00 (m, 4H), 4.65 (s, 2H), 2.42 (dd, 2H, J = 5.6 Hz, 14.4 Hz), 2.14 (dd, 2H, J = 8.5 Hz, 14.6 Hz). ^{13}C NMR (CDCl$_3$, 100 MHz): δ = 178.5, 140.0, 139.4, 133.7, 131.6, 129.1, 128.8, 127.1, 126.8, 126.7, 126.5, 125.3, 119.4, 55.7, 51.6, 37.3. HRMS (ESI, Q-ToF) m/z: found [M + Na]$^+$ = 454.1777, calculated = 454.1783 for C$_{30}$H$_{25}$NO$_2$.

The general procedure for metathesis

The compound (0.12 mmol) was dissolved in dry dichloromethane or toluene and degassed with nitrogen gas followed by ethylene gas. The catalyst was added to the reaction under an ethylene atmosphere and the reaction was carried out under the conditions given above. After the removal of the solvent, the residue was purified using column chromatography to obtain the corresponding compound.

Compound 30. White solid (51 mg starting from 70 mg of **29**, 68%), R_f = 0.35 (5% EtOAc/hexane), mp: 177.6–181.5 °C. IR (neat): ν_{max} C=O stretch at 1755, 1705 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ = 7.49–7.40 (m, 2H), 7.40–7.33 (m, 1H), 7.20–7.11 (m, 2H), 6.46–6.35 (m, 2H), 6.10–6.00 (m, 2H), 5.66–5.51 (m, 2H), 5.12–4.97 (m, 4H), 3.09–2.99 (m, 2H), 2.88 (brs, 2H), 2.78–2.65 (m, 2H), 2.40 (d, 2H, J = 14.6 Hz). ^{13}C NMR (CDCl$_3$, 125 MHz): δ = 181.3, 139.5, 133.9, 132.3, 129.2, 128.7, 126.5,

115.6, 52.5, 43.0, 42.4, 28.3. HRMS (ESI, Q-ToF) m/z: found $[M + Na]^+ = 352.1317$, calculated $= 352.1312$ for $C_{22}H_{19}NO_2$.

Compound 33. White solid (42 mg starting from 70 mg of **32**, 64%), $R_f = 0.38$ (5% EtOAc/hexane), mp: 115.2–118.3 °C. IR (neat): ν_{max} C=O stretch at 1706 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): $\delta = 7.44$–7.38 (m. 2H), 7.37–7.31 (tt, 1H, $J = 7.5$ Hz, 1.4 Hz), 7.16–7.12 (m, 2H), 6.50–6.46 (dd, 2H, $J = 4.3$ Hz, 3.2 Hz), 5.97–5.94 (m, 2H), 2.86 (t, 4H, $J = 3.0$ Hz), 2.59 (dd, 1H, $J = 2.45$ Hz, 4.50 Hz), 2.56 (dd, 1H, $J = 2.45$ Hz, 4.50 Hz), 2.17 (d, 2H, $J = 14.6$ Hz), 2.10–2.03 (m, 2H), 1.54–1.49 (m, 2H). ^{13}C NMR (CDCl$_3$, 125 MHz): $\delta = 181.8$, 134.1, 132.3, 129.1, 128.9, 128.6, 126.5, 52.1, 40.7, 32.5, 29.84, 28.6, 21.4.

Compound 34. White solid (yields given in Table 2 from 0.27 mmol of **28**), $R_f = 0.55$ (5% EtOAc/hexane), mp: 150–152 °C. IR (neat): $\nu_{max} = 2896$, 2335, 1712, 1498, 1395, 1183, 913 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): $\delta = 7.43$ (tt, 2H, $J = 7.2$ Hz), 7.36 (tt, 1H, $J = 7.32$ Hz), 7.18 (td, 2H, $J = 1.4$ Hz), 6.33 (dd, 2H, $J = 3.2$ Hz, 1.0 Hz), 5.56–5.47 (m, 2H), 5.03 (dd, 2H, $J = 17.0$ Hz, 1.4 Hz), 4.98 (dd, 2H, $J = 10.2$ Hz, 1.6 Hz), 3.25 (brs, 2H), 3.10 (s, 2H), 2.75 (d, 2H, $J = 7.3$ Hz). ^{13}C NMR (CDCl$_3$, 100 MHz): $\delta = 177.5$, 139.3, 131.9, 131.8, 129.2, 128.7, 126.5, 115.5, 46.8, 44.2, 38.3. HRMS (ESI, Q-ToF) m/z: found $[M + H]^+ = 306.1489$, calculated $= 306.1482$ for $C_{20}H_{19}NO_2$.

Compound 41. White solid (36 mg starting from 36 mg of **40**, 92%), $R_f = 0.3$ (5% EtOAc/hexane), mp: 150.1–152.3 °C. IR (neat): ν_{max} C=O stretch at 1703 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): $\delta = 7.46$–7.29 (m, 3H), 7.17–7.07 (m, 2H), 6.39–6.29 (m, 2H), 6.06–5.92 (m, 2H), 2.86–2.75 (m, 2H), 2.68–2.55 (m, 2H), 2.25 (d, $J = 14.6$ Hz, 2H), 1.97–1.80 (m, 2H), 1.40–1.29 (m, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz): $\delta = 181.9$, 131.5, 129.1, 129.1, 128.6, 126.6, 52.2, 36.6, 28.2, 19.5. HRMS (ESI, Q-ToF) m/z: found $[M + Na]^+ = 328.1306$, calculated $= 328.1313$ for $C_{20}H_{19}NO_2$.

Compound 45. White solid (7.1 mg starting from 10 mg of **44**, 65%), $R_f = 0.58$ (5% EtOAc/hexane), mp: 150–152 °C. IR (neat): ν_{max} C=O stretch at 1725, 1712 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): $\delta = 7.43$ (tt, 2H, $J = 7.7$ Hz, $J = 1.5$ Hz), 7.35 (tt, 1H, $J = 7.40$ Hz, 1.32 Hz), 7.16 (td, 2H, $J = 7.05$ Hz, 1.44 Hz), 5.95–5.92 (m, 2H), 3.32 (dd, 2H, $J = 2.84$ Hz, 1.44 Hz), 3.12–3.10 (m, 2H) 3.09–3.03 (m, 2H), 2.67 (dd, 2H, $J = 2.6$ Hz, 2.0 Hz), 2.63 (dd, 2H, $J = 2.7$ Hz, 1.9 Hz), 1.92 (d, 2H, $J = 14.7$ Hz). ^{13}C NMR (CDCl$_3$, 125 MHz): $\delta = 181.1$, 132.4, 129.2, 128.6, 128.2, 126.6, 45.7, 42.2, 38.8, 37.5, 28.4. HRMS (ESI, Q-ToF) m/z: found $[M + H]^+ = 330.1489$, calculated $= 330.1488$ for $C_{22}H_{19}NO_2$.

Compound 50. White solid (35 mg starting from 46 mg of **49**, 72%), $R_f = 0.35$ (5% EtOAc/hexane), mp: 132.1–136.5 °C. ^{1}H NMR (CDCl$_3$, 400 MHz): $\delta = 7.45$–7.37 (m, 2H), 7.34–7.29 (m, 2H), 7.28–7.24 (m, 4H), 7.24–7.17 (m, 4H), 6.50–6.37 (m, 2H), 5.84–5.72 (m, 2H), 2.94–2.78 (m, 2H), 1.83–1.71 (m, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz): $\delta = 180.0$, 140.5, 140.2, 129.1, 128.8, 127.9, 127.2, 127.1, 127.0, 126.7, 126.6, 125.2, 57.3, 51.5, 30.2. HRMS (ESI, Q-ToF) m/z: found $[M + Na]^+ = 426.1461$, calculated $= 426.1470$ for $C_{28}H_{21}NO_2$.

Conclusion

We have developed a simple synthetic strategy to synthesize propellane containing bicyclo[2.2.2]octene derivatives which are structurally similar to 11β-HSD1 inhibitors. We have also designed interesting bicyclo[2.2.2]octene derivatives which contain a variety of unsaturated moieties to study their metathetic behaviour. The allylic groups present in compounds **40** and **49** undergo RCM to generate the corresponding propellane derivatives **41** and **50**, respectively. Surprisingly, compound **40** didn't undergo RRM due to the extra stability of the bicyclo [2.2.2]octene moiety towards metathesis. Similarly, the allyl groups present in compound **32** underwent RCM to generate the propellane derivative **33**. However, compound **29** underwent RCM and ROM to generate the propellane derivative **30**. We have extended this methodology to the cage compound **42** to produce the basketene-based propellane derivative **45**. As shown by the geometry optimization studies, these propellane derivatives are rigid and the bond angles of the propellane derivatives **30**, **33**, and **41** are similar, whereas the basketene derivative **45** has larger values for its bond angles. These propellane derivatives will find useful applications in medicinal and polymer chemistry. Since cage molecules and propellanes have various applications as high energy systems, our results may be of interest in designing high-density materials.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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