Design and synthesis of $C_3$-symmetric molecules bearing propellane moieties via cyclotrimerization and a ring-closing metathesis sequence

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Full Research Paper

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Abstract

We have developed an efficient synthetic strategy to assemble $C_3$-symmetric molecules containing propellane moieties as end groups and a benzene ring as a central core. The synthesis of these $C_3$-symmetric molecules involves simple starting materials. Our approach to $C_3$-symmetric compounds relies on a Diels–Alder reaction, cyclotrimerization and ring-closing metathesis as key steps.

Introduction

In 1966 Ginsburg coined the word “propellane” [1,2] and Wiberg reviewed various aspects of medium and small ring propellanes [3,4]. Propellanes consist of tricyclic compounds where three rings are conjoined by a common C–C bond [1,5,6]. Heterocyclic systems contain a heteroatom (e.g., oxygen, nitrogen, and sulfur, etc.) along with carbon atoms. The name of a heterocyclic propellane may be organized by prefixing aza, oxa, etc.

Among various propellanes, nitrogen-containing compounds occupy a special place because they are present as core structural units in bioactive natural products and pharmaceuticals. Some of these propellanes exhibit interesting properties like antibacterial, antifungal, anticancer, platelet-activating factor antagonistic and antibacterial activities. The propellane skeleton is present in many alkaloids such as aknadidine (1), aknadilactam (2), and the known morphinan alkaloid sinococuline (3), which was identified as a bioactive component from $S. japonica$ [7]. In 1963 Brown et al. isolated 1-acetyl-aspidodialbidine (4) from $Vallesia dichotoma$ [8] and subsequently, Djerrassi proposed its structure [9]. Another alkaloid (−)-aspidophytine (5) differs from 1-acetylaspidoalbidine (4) only in the degree of unsaturation and the substitution pattern on the aromatic ring (Figure 1).
The design of propellanes demands unique synthetic methods and these include: manganese or palladium-catalyzed transformations [10], the Diels–Alder (DA) reaction [11,12], and rearrangement of spiro-ketones, nucleophilic substitutions of alkenes, and photochemical addition reactions. Multicomponent reactions (MCRs) are also used for the synthesis of hetero-propellanes [13,14]. Recently, heterocyclic propellanes have been reviewed [15,16]. Our group also developed simple synthetic approaches to propellanes via ring-closing metathesis (RCM) as a key step [17,18].

The development of new synthetic strategies to \( \text{C}_3 \)-symmetric molecules bearing propellane moieties from commercially available starting materials is worthy of systematic investigation. To this end, our efforts are directed to design star-shaped molecules that involve a wide range of structural variations. To the best of our knowledge there are no synthetic reports available for \( \text{C}_3 \)-symmetric molecules bearing propellane moieties.

As part of our major program aimed at designing star-shaped \( \text{C}_3 \)-symmetric molecules [19-30], here, we conceived new strategies to N-containing star-shaped molecules. Such star-shaped molecules are generally used in organic light-emitting diodes (OLEDs) [31-33], organic photovoltaics (OPVs) [34], organic field-effect transistors (OFETs) [35,36], and other optoelectronic devices. Our approach to \( \text{C}_3 \)-symmetric molecules containing propellane moieties involve DA reaction [37], cyclooctimerization [19] and RCM [38-41] as key steps.

**Results and Discussion**

The synthesis of propellane-bearing \( \text{C}_3 \)-symmetric derivatives starts with commercially available dicyclopentadiene and maleic anhydride (7). Here, we used a DA reaction of freshly cracked cyclopentadiene (6) and maleic anhydride (7) to obtain the *endo*-DA adduct 8 [42] in 98% yield. Next, the cycloadduct 8 was treated with commercially available 4-aminoacetophenone (9) in the presence of triethylamine in ethanol/silicon tetrachloride (EtOH/SiCl\(_4\)) conditions to deliver the trimerized product 11 (64%). Having the trimerized product 11, we attempted to open the norbornene system due to the fact that not all norbornene rings open up during RCM to generate propellane derivative. After allylation, RCM is not a clean reaction and it gave a mixture of the \( \text{C}_3 \)-symmetrical compounds. Therefore it is desirable to open the norbornene double bond before the trimerization sequence. To this end, the trimerized product 11 was treated with Grubbs first generation (G-I) catalyst in \( \text{CH}_2\text{Cl}_2 \) under ethylene atmosphere but, we were unable to get the ring-opened product 12 (Scheme 1).

Later, we considered an alternate route to synthesize compound 12. In this regard, we employed different ruthenium-based catalysts (Figure 2) and reaction conditions to obtain the ring-opening metathesis (ROM) product 13 from norbornene derivate 10. Under these conditions the starting material was not consumed completely. After some experimentation, we found that G-I catalyst (5 mol %) in \( \text{CH}_2\text{Cl}_2 \) is suitable to generate the ROM product 13 in 56% yield (Table 1).

Having the ROM product 13 in hand, it was subjected to trimerization in the presence of EtOH/SiCl\(_4\) at 0 °C to room temperature to afford the trimerized product 12 in 54% yield. Next, the \( \text{C}_3 \)-symmetric product 12 was reacted with allyl bromide in the presence of sodium bis(trimethylsilyl)amide (NaHMDS, 1 M solution in THF) at −75 °C to deliver the RCM precursor 14 in good yield (78%). The hexaallyl derivative 14 was subjected to RCM in the presence of Grubbs second generation (G-II) catalyst in \( \text{CH}_2\text{Cl}_2 \) under nitrogen to give the propellane moiety bearing \( \text{C}_3 \)-symmetric product 15 in good yield (87%). Its structure was established on the basis of NMR spectral data, and its molecular formula was confirmed by HRMS data (Scheme 2).

Along similar lines, we expanded the scope of this strategy. To this end, commercially available anthracene (16) was reacted with maleic anhydride (7) in a screw-capped tube at 150 °C in o-xylene to obtain the DA adduct 17 in 94% yield [44,45].
Scheme 1: Synthesis of the star-shaped norbornene derivative 11 via trimerization.

Figure 2: Selected list of ruthenium-based catalysts used for ROM.

Table 1: Different conditions attempted to obtain the ROM product 13.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>mol %</th>
<th>solvent</th>
<th>temp</th>
<th>time (h)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>G-I</td>
<td>5 or 10</td>
<td>CH₂Cl₂</td>
<td>rt</td>
<td>48</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>G-I</td>
<td>5 or 10</td>
<td>CH₂Cl₂</td>
<td>reflux</td>
<td>32</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>G-II</td>
<td>5 or 10</td>
<td>toluene</td>
<td>rt</td>
<td>46</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>G-II</td>
<td>5</td>
<td>toluene</td>
<td>reflux</td>
<td>43</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>Ru-II</td>
<td>5 or 10</td>
<td>CH₂Cl₂</td>
<td>rt</td>
<td>48</td>
<td>52</td>
</tr>
<tr>
<td>7</td>
<td>GH-I</td>
<td>5 or 10</td>
<td>CH₂Cl₂</td>
<td>rt</td>
<td>40</td>
<td>53</td>
</tr>
<tr>
<td>8</td>
<td>GH-I</td>
<td>5 or 10</td>
<td>CH₂Cl₂</td>
<td>reflux</td>
<td>40</td>
<td>50</td>
</tr>
</tbody>
</table>
Later, the DA adduct 17 was treated with 4-aminoacetophenone (9) in the presence of Et$_3$N in toluene at 140 °C to deliver the acetophenone derivative 18 (91% yield) and it was subjected to trimerization in the presence of EtOH/SiCl$_4$ at 0 °C to rt to obtain the trimerized product 19 in 64% yield. Afterwards, the trimerized product 19 was treated with allyl bromide to accomplish C-allylation in the presence of NaHMDS (1 M solution in THF) at −75 °C to deliver the hexaallyl derivative 20 in 84% yield. Then, RCM in the presence of G-II catalyst in CH$_2$Cl$_2$ under nitrogen atmosphere gave the propellane moieties bearing C$_3$-symmetric product 21 in good yield (91%). Its structure was established with the help of $^1$H NMR, $^{13}$C NMR spectral data and was further supported by HRMS details (Scheme 3).

**Conclusion**

We have demonstrated a simple synthetic methodology to C$_3$-symmetric star-shaped molecules containing propellane moieties at the periphery which may be useful for material science applications. Here, we have prepared DA adducts 8 and 17 from commercially available maleic anhydride (7), which was further utilized for trimerization and RCM sequence. We have successfully synthesized C$_3$-symmetric molecules 15 and 21 bearing propellane moieties by employing RCM in the presence of 2nd generation (G-II) catalyst.

**Experimental**

**General information**

Some of these reactions were carried out in screw-capped tubes and other reactions under nitrogen or argon and ethylene atmosphere in oven-dried glassware. Air- and moisture-sensitive reactions were performed in degassed solvents. Transfer of moisture-sensitive materials were carried out using standard syringe–septum techniques. All the commercial grade reagents were used without any purification until otherwise specified.
Melting points were recorded on a Veego or Büchi melting point apparatus and are uncorrected. NMR Spectra were generally recorded on Bruker (Avance 400 or Avance III 500) spectrometers operated at 400 or 500 MHz for $^1H$ and 100 or 125.7 MHz for $^{13}C$ nuclei. NMR Samples were generally made in chloroform-$d$ solvent, and chemical shifts ($\delta$ values) are reported in parts per million (ppm). Coupling constants ($J$ values) were reported in hertz (Hz). HRMS measurements were carried out using a Bruker (Maxis Impact) spectrometer. IR spectra were recorded on a Nicolet Impact-400 or Cary 630 FTIR spectrometer.

**Synthesis of norbornene-based trimerized product 11**

To a solution of norbornene derivative 10 (500 mg, 1.77 mmol) in EtOH (8 mL), silicon tetrachloride (SiCl$_4$, 0.61 mL, 5.36 mmol) was added dropwise at 0 °C and the reaction mixture was stirred for 10–15 min at the same temperature. Later,
the reaction mixture was stirred at room temperature for 20 h. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with sat. aq NH₄Cl. Thereafter, the reaction mixture was diluted with EtOAc (10 mL) washed with water and brine (2 × 10 mL). Then, the aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (65% EtOAc/petroleum ether) to afford the trimerized product 11 (321 mg, 64%) as a colourless solid. Rₐ = 0.54 (6:4 EtOAc/petroleum ether); mp 203–206 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.68 (d, J = 5.2 Hz, 6H), 7.66 (s, 3H), 7.24 (d, J = 2.4 Hz, 6H), 6.28 (s, 6H), 3.51–3.44 (m, 12H), 1.79 (d, J = 8.8 Hz, 3H), 1.61 (d, J = 8.8 Hz, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 177.0, 141.8, 141.3, 134.8, 131.4, 128.2, 127.2, 125.7, 52.4, 46.0, 45.7 ppm; HRMS (ESI, Q-ToF) m/z: [M + H]⁺ calcd for C₅₁H₄₀N₂O₆ 790.2912; found, 790.2918; IR (neat) νₘₐₓ: 2918, 1706, 1512, 1371, 1173, 754 cm⁻¹.

Synthesis of ring open metathesis (ROM) product 13

The solution of compound 10 (500 mg, 1.76 mmol) in dry CH₂Cl₂ (25 mL) was degassed by ethylene and G-I (5 mol %) was added to the reaction mixture at rt. Further, the reaction mixture was stirred for 48 h under ethylene atmosphere at rt. After completion of the reaction (TLC monitoring), the solvent was removed under reduced pressure. Later, the crude product was purified by silica gel column chromatography (30% EtOAc/petroleum ether) to obtain the ROM product 13 as a colourless oil (310 mg, 56%); Rₐ = 0.68 (4:6 EtOAc/petroleum ether); mp 143–145 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.03 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 6.12–6.03 (m, 2H), 5.20–5.15 (m, 4H), 3.43 (q, J = 2.0 Hz, 2H), 3.08–3.00 (m, 6H), 2.04 (q, J = 6.8 Hz, 3H), 1.58 (q, J = 13.2 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 141.7, 141.1, 136.4, 131.4, 128.1, 126.9, 125.6, 116.1, 49.1, 46.3, 35.5 ppm; HRMS (ESI, Q-ToF) m/z: [M + Na]⁺ calcd for C₇₅H₇₅N₂O₆Na, 896.3670; found; 896.3678; IR (neat) νₘₐₓ: 2318, 1266, 745, 707 cm⁻¹.

Synthesis of trimerized product 19

Based on the earlier procedure of trimerization, compound 18 (500 mg, 1.27 mmol) was treated with SiCl₄ (0.43 mL, 3.83 mmol) in the presence of EtOH (8 mL) for 20 h to give the trimerized product 19 after silica gel (100–200 mesh) column chromatography (50% EtOAc/petroleum ether) as a colourless solid (324 mg, 64%); Rₐ = 0.61 (4:6 EtOAc/petroleum ether); mp 224–226 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.56 (s, 3H), 7.51 (d, J = 8.0 Hz, 6H), 7.43 (d, J = 3.0 Hz, 6H), 7.37 (d, J = 3.0 Hz, 6H), 7.24–7.22 (m, 12H), 6.62 (d, J = 8.5 Hz, 6H), 4.92 (s, 6H), 3.41 (s, 6H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 176.3, 141.5, 141.4, 138.9, 128.2, 127.4, 127.1, 127.0, 125.3, 124.5, 47.2, 46.1 ppm; HRMS (ESI, Q-ToF) m/z: [M + Na]⁺ calcd for C₇₅H₇₅N₂O₆Na, 1148.3670; found, 1148.3672; IR (neat) νₘₐₓ: 2318, 1266, 745, 707 cm⁻¹.

Synthesis of hexaallyl derivative 14

To the solution of compound 12 (200 mg, 0.22 mmol) in anhydrous THF (15 mL) was added NaHMDS (2 mL of 1 M solution in THF, 1.93 mmol) at −75 °C and the reaction mixture was stirred for 30 min under nitrogen atmosphere. Then allyl bromide (0.11 mL, 1.60 mmol) was added to the reaction mixture and stirred for 2 h at −75 °C. Later, the reaction mixture was stirred to room temperature for 10 h. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with 1 M aq HCl solution, and the aqueous layer was extracted by EtOAc (3 × 10 mL). Then the organic fraction was washed with brine solution, dried over Na₂SO₄ and concentrated. The crude residue was purified by silica gel column chromatography (10% EtOAc/petroleum ether) to afford hexaallyl derivative 14 as a colourless solid (199 mg, 78%); Rₐ = 0.60 (3:7 EtOAc/petroleum ether); mp 204–206 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.71 (d, J = 5.5 Hz, 6H), 7.69 (s, 3H), 7.33 (d, J = 8.5 Hz, 6H), 6.08–5.96 (m, 12H), 5.28–5.13 (m, 24H), 2.77–2.66 (m, 18H), 2.04–2.00 (m, 3H), 1.65 (q, J = 12.5 Hz, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 178.2, 141.9, 141.3, 136.5, 132.8, 131.5, 128.1, 127.1, 127.0, 120.3, 117.1, 59.9, 51.2, 36.6, 35.1 ppm; HRMS (ESI, Q-ToF) m/z: [M + Na]⁺ calcd for C₇₅H₇₅N₂O₆Na, 1136.5548; found, 1136.5544; IR (neat) νₘₐₓ: 2345, 1671, 1263, 746 cm⁻¹.

Synthesis of hexaallyl product 20

Based on the earlier procedure of allylation, compound 19 (336 mg, 0.29 mmol) was treated with NaHMDS (2.3 mL of 1 M solution in THF, 2.36 mmol) to give the hexaallyl product 20 as a white solid (303 mg, 64%) after silica gel column chromatography (45% EtOAc/petroleum ether) to afford hexaallyl product 20 as a white solid (199 mg, 78%).
1 M solution in THF, 2.39 mmol) and allyl bromide (0.14 mL, 1.93 mmol) for 17 h to deliver hexaallyl product 20 after silica gel column chromatography (20% EtOAc/petroleum ether) as a colourless solid (345 mg, 84%); \( \delta \) 7.51 (s, 6H), 7.40 (q, \( J = 3.2 \) Hz, 6H), 7.32 (q, \( J = 3.2 \) Hz, 6H), 7.24–7.20 (m, 12H), 6.58 (d, \( J = 8.0 \) Hz, 6H), 6.33–6.23 (m, 6H), 5.20 (dd, \( J_1 = 11.6 \) Hz, \( J_2 = 17.2 \) Hz, 12H), 4.68 (s, 6H), 2.45 (dd, \( J_1 = 5.6 \) Hz, \( J_2 = 5.6 \) Hz, 6H), 2.16 (q, \( J = 8.8 \) Hz, 6H) ppm; \( ^{13} \)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) ppm: 178.2, 141.8, 141.2, 139.9, 139.4, 133.6, 131.0, 128.1, 127.2, 127.1, 126.7, 125.6, 125.3, 119.4, 55.7, 51.6, 37.3 ppm; HRMS (ESI, Q-ToF) [M + Na]\(^+\): 305.4363 calcld for \( \text{C}_{96}\text{H}_{72}\text{N}_{3}\text{O}_{6}\cdot\text{Na} \); found, 305.4364. IR (neat) \( \nu_{\text{max}} \): 2328, 1708, 1383, 837, 690 cm\(^{-1}\).

**Supporting Information**

**Supporting Information File 1**

Copies of \(^1\)H, \(^{13}\)C NMR and HRMS spectra of new compounds.

[https://www.beilstein-journals.org/bjoc/content SUPPLEMENTARY/1860-5397-14-230-S1.pdf]

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**References**


