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<td>Author(s)</td>
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A Synthesis of Allahabadolactone A

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Abstract
A synthesis of Allahabadolactone A is described employing diastereoselective Diels-Alder and selenocyclisation reactions, starting from (R)-citronellal and propylene oxide. The Diels-Alder substrate is built up in an efficient manner by rhodium catalysed alkyne hydroboration and palladium catalysed coupling reactions of E-1,2-dichloroethene. It is observed that the Diels-Alder reaction only displays high diastereoselectivity when the diene bears an additional alkene substituent, but not an alkyne substituent.

Introduction
Allahabadolactone A 1 and its isomer allahabadolactone B were isolated from the fungus Aspergillus allahabadii and shown to have modest cytotoxic activity.1 The structure was solved by crystallographic means and this natural product was shown to have a trans-decalin structure, with a double bond in one ring, appended to a substituted lactone. The mono-unsaturated decalin moiety with the same methyl substituent is also found in the natural products oblongolide,2 equisetin,3-6 fusarisetin,6-9 paeciloseatin,10 phomasetin,11 cryptocin12 and aspermytin.13 The lactone moiety distinguishes the allahabadolactones. The authors proposed a biosynthetic pathway involving an intramolecular Diels-Alder reaction14 and a late stage lactone formation by means of a C-H bond oxidation.

Scheme 1. Allahabadolactone retrosynthesis

We proposed to employ an intramolecular Diels-Alder (IMDA) reaction2-9,15-17 for the construction of the decalin, and an electrophile-induced ring closure onto an alkene for lactone formation (Scheme 1).18-20 This latter transformation would have the effect of moving the double bond by one place and, hence, allows the use of readily available propylene oxide or an equivalent as the source of the side chain stereogenic centre. Citronellal is a well precedented source of the stereogenic centre bearing the methyl group.

Results and Discussion
The cyclic sulfate 2 derived from (S)-propylene glycol was subjected to ring opening, followed by desilylation to give the alkynol 3 (Scheme 2).21 Sonogashira coupling with an excess of trans-1,2-dichloroethene22 proceeded smoothly to
give the enynol 4. Reduction of enynol 4 to the corresponding $E,E$-dienol 5 using lithium aluminium hydride proved difficult and the reaction was plagued by hydrodechlorination. We eventually found that this transformation could be achieved with Red-Al to give the corresponding dienol 5 as, exclusively, the $E,E$-isomer. Both alcohols were converted into their TBS ethers, 6 and 7, routinely.

Following the procedure in our previous report, treatment of citronellal 8 with the Ohira-Bestmann reagent 25 or the Corey-Fuchs reagent 26 gave the anticipated alkyne 9 (scheme 3). Operationally, the use of the Ohira-Bestmann reagent was more convenient, although slightly lower yielding. Ozonolysis, followed by an in situ Wittig reaction yielded the unsaturated ester 10. Hydroboration of ester 10 with pinacolatoborane in the presence of (2-Fu3P)2Rh(CO)Cl delivered vinyl boronate 11 cleanly. Suzuki coupling could then be effected using a catalytic system derived from palladium(II) acetate and Sphos in the presence of sodium hydroxide to give trienyne 12. No product was obtained when catalysts employing PPh3 as a ligand were used. Gratifyingly, the ester was not hydrolysed under these conditions, provided that the reaction was not left longer than overnight. When weaker bases, potassium or cesium carbonate, were used, no product was obtained. Not unexpectedly, trienyne 12 failed to undergo the IMDA reaction upon treatment with a variety of Lewis acids, BF3•OEt2, AlCl3, and Me3Al, at up to 0 °C. The corresponding aldehyde 14, however, did so on treatment with BF3•OEt2 at 0 °C. To our disappointment, the product 15 was isolated as an inseparable 2:1 mixture of diastereoisomers. The major isomer was presumed to be the endo isomer; the stereochemistry of the minor isomer was not determined.
We anticipated that a system in which the dienophilic alkene carried two electron withdrawing groups would be more reactive, allowing the use of lower temperatures (scheme 4). To test this concept, alkyne 9 was subjected to ozonolysis followed by a reductive work up with sodium borohydride to give alcohol 17. Rhodium catalysed hydroboration, Suzuki coupling and Dess-Martin reoxidation of the alcohol gave aldehyde 19. The Knoevenagel reaction with dimethyl malonate gave an IMDA substrate 20 which underwent this reaction on treatment with AlCl$_3$ at -78° C, but gave a somewhat complex mixture that appeared to contain a 2:1 mixtures of diastereoisomers of cycloadduct 22, with loss of the TBS group. On the other hand, when aldehyde 19 was subjected to a Knoevenagel reaction with Meldrum’s acid, a tandem condensation-cycloaddition occurred and the Knoevenagel product 21 could neither be observed nor isolated. This is consistent with the known higher reactivity of Meldrum’s acid Knoevenagel products.$^{31,32}$ The Diels-Alder product 23 was once again obtained as a 2:1 mixture of diastereoisomers, though, in this case the TBS group was retained.
We suspected that the poor diastereoselectivity in this series of Diels-Alder reactions might be due to the alkyne moiety. Thus, the dienol TBS ether 7 was subjected to Suzuki coupling with boronic ester 11 to give tetraene 24, i.e. a dihydro version of trieneyne 12 (scheme 5). Conversion of the ester group by a reduction-oxidation sequence gave aldehyde 26. To our delight, aldehyde 26 underwent a Lewis acid catalysed IMDA reaction to give the decalin as a single stereoisomer 27, with concomitant loss of the silyl group. This reaction did not occur at -78°C, but proceeded slowly (overnight) at -40°C. At 0°C, the reaction was rapid (1 hour) and gave the same selectivity. Amongst the Lewis acids, studied (entries 7-10), AlCl₃ gave the best results. This cycloaddition product was assigned the stereochemistry shown based upon the assumption of an endo-transition state, and this was subsequently confirmed by conversion to the natural product. This result confirms the undesirability of the alkyne in the earlier studies (Table 1).

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<th>T/ °C</th>
<th>time</th>
<th>product, yield</th>
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Pinnick oxidation of aldehyde 27 gave carboxylic acid 28, the substrate for cyclofunctionalisation to form the lactone. While iodocyclisation (NaHCO₃, I₂)¹⁸⁻²⁰ proved to be completely stereoselective, attempts to eliminate the iodide under basic conditions gave an inseparable mixture of alkene regioisomers. A similar observation has been made by Bartlett.³³ Selenocyclisation using N-phenylselenylphthalimide³⁴ also proceeded smoothly and with complete stereoselectivity. Elimination of selenium from lactone 29 occurred cleanly and with complete regioselectivity after oxidation with hydrogen peroxide, to give allahabadolactone A 1. The melting point (116-117 °C; lit. 117.3-118.7 °C), ¹H and ¹³C NMR data for the synthetic material were in excellent agreement with those reported by Sadorn et al.¹ This indicates that the selenocyclisation occurred with the desired stereoselectivity. Presumably the conformation of intermediate 30 leading to the unobserved isomer is precluded due to unfavourable steric interactions, but this is not the case for the diastereoisomeric intermediate 31. The optical rotation recorded for our material (+25.9, c = 0.08, CHCl₃) is in excellent agreement with that reported¹ (+26.6, c = 0.13, CHCl₃), confirming the assigned absolute stereochemistry.
Conclusion
While the intramolecular Diels-Alder reaction route to molecules of this type has been extensively used, our results show that a small change in the diene substituent can have a profound effect. In particular, a dienyne and a triene give significantly different results in terms of the stereochemical outcome. Combining rapid triene construction by coupling of trans-1,2-dichloroethylene, the intramolecular Diels-Alder reaction and a highly efficient selenocyclisation-elimination procedure that is both stereo and regioselective, this work constitutes, to the best of our knowledge, the first synthesis of allahabadolactone A 1. The synthesis requires a total of 10 steps from citronellal and provides an overall yield of 13%.

Experimental
When appropriate, reactions were run under a nitrogen atmosphere in oven-dried glassware. THF and ether were distilled from sodium/ benzophenone, toluene was distilled from sodium and dichloromethane was distilled from calcium hydride. The other solvents and reagents were used as received. Column chromatography was carried out on silica gel 230-400 mesh, and analytical TLC on glass plates (silica gel 60, F254). NMR spectra were recorded in CDCl3 solutions at 400 MHz (1H) or 100 MHz (13C). Chemical shifts are recorded in ppm and
coupling constants are recorded in Hz. HRMS measurements were recorded using a TOF mass analyser.

\((S,E)-7\text{-Chlorohept-6-en-4-yn-2-ol (4)}\). A solution of trans-1,2-dichloroethene (276 µL, 3.66 mmol), alcohol 3 (200 mg, 2.38 mmol), Pd(PPh\(_3\))\(_4\) (69 mg, 2.5 mol%), Cul (23 mg, 5 mol%) and Et\(_3\)N (663 µL, 4.76 mmol) in anhydrous THF (10 mL) was stirred overnight under N\(_2\). The reaction was quenched with aq. NH\(_4\)Cl (10 mL) and the mixture was extracted with Et\(_2\)O (10 mL \(\times\) 3). The combined organic layers were washed with brine, dried (MgSO\(_4\)) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (20% EtOAc/Hexane) to give enynol 4 as a colorless oil (326 mg, 95%); \(\alpha \)\(_{D23}^\circ +12.5\) (c 3.00, CHCl\(_3\)); IR(neat) cm\(^{-1}\): 3372, 3073, 2907, 2220, 1718; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.49 (d, \(J=13.7\) Hz, 1H), 5.92 (dt, \(J=13.7, 2.3\) Hz, 1H), 3.97 (sex, \(J=6.4\) Hz, 1H), 2.52 (ddd, \(J=16.9, 6.0, 2.3\) Hz, 1H), 2.44 (ddd, \(J=16.9, 6.4, 2.3\) Hz, 1H), 1.27 (d, \(J=6.4\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 130.0, 114.0, 89.5, 78.1, 66.5, 30.1, 22.6; MS (ESI): \(m/z = 145.19 \ [C_7H_{19}O_{55}Cl+H]^+\); HRMS (EI): \(m/z \ [M + H]^+\) calcd for C\(_7\)H\(_{10}\)O\(_{55}\)Cl: 145.0420; found: 145.0414.

\((S,4E,6E)-7\text{-Chlorohepta-4,6-dien-2-ol (5)}\). Red-Al (3.36 mL, 11.19 mmol, 65% wt. in tol.) was slowly added to a solution of alcohol 4 (1.20 g, 8.30 mmol) in anhydrous THF (15 mL) at -78 ºC and then the reaction was heated at reflux for 3 h. The mixture was cooled to 0 ºC and quenched with H\(_2\)O. After adding HCl (5 ml, 2M), the mixture was extracted with Et\(_2\)O (10 mL \(\times\) 3). The combined organic layers were washed with brine and dried over Na\(_2\)SO\(_4\). After removal of the solvent under reduced pressure, the residue was purified by flash chromatography on silica gel (20% EtOAc/Hexane) to give dienol 5 as a colorless oil (1.12 g, 92%); \(\alpha \)\(_{D23}^\circ +12.9\) (c 1.00, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.44 (dd, \(J=13.3, 10.6\) Hz, 1H), 6.14 (d, \(J= 13.3\) Hz, 1H), 6.07 (dd, \(J= 15.6, 11.0\) Hz, 1H), 5.71 (dt, \(J= 15.6, 7.3\) Hz, 1H), 3.85 (sex, \(J=6.4\) Hz, 1H), 2.31-2.17 (m, 2H), 1.21 (d, \(J=6.0\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 133.6, 131.5, 129.5, 120.0, 120.0, 67.5, 42.7, 23.2; IR(neat) cm\(^{-1}\): 3372, 2970, 2928, 1653, 1583; MS (ESI): \(m/z = 147.27 \ [C_7H_{11}O_{35}Cl+H]^+\); HRMS (EI): \(m/z \ [M + H]^+\) calcd for C\(_7\)H\(_{12}\)O\(_{35}\)Cl: 147.0577; found: 147.0573.

\((S,E)-t\text{-Butyl((7-chlorohept-6-en-4-yn-2-yl)oxy)dimethylsilane (6)}\). A solution of alcohol 4 (237 mg, 1.64 mmol), TBSCl (299 mg, 1.99 mmol) and imidazole (226 mg, 3.32 mmol) in CH\(_2\)Cl\(_2\) (10 mL) was stirred at room temperature for 2 h. After quenching with aq. NH\(_4\)Cl, the mixture was extracted with Et\(_2\)O (10 mL \(\times\) 3). The combined organic solution was washed with brine, dried (Na\(_2\)SO\(_4\)) and filtered through celite. The volatiles were removed under reduced pressure and the residue was purified by flash chromatography (25% EtOAc/Hexane) to give enyne 6 as a colorless oil (399 mg, 94%); \(\alpha \)\(_{D23}^\circ +12.2\) (c 0.30, CHCl\(_3\)); IR(neat) cm\(^{-1}\): 2955, 2856, 2220, 1699, 1585; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.44 (d, \(J=14\), 1H), 5.91 (dt, \(J=14.0, 2.3\) Hz, 1H), 3.5 (sex, \(J=6.4\) Hz, 1H), 2.45 (ddd, \(J=16.5, 6.0, 2.3\) Hz, 1H), 2.34 (ddd, \(J=16.5, 6.8, 1.8\) Hz, 1H), 1.21 (d, \(J=5.9\) Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 129.2, 114.4, 91.1, 67.7, 30.5, 26.0, 23.8, -4.7; MS (ESI): \(m/z = 259.50 \ [M + H]^+\); HRMS (EI): \(m/z \ [M + H]^+\) calcd for C\(_{13}\)H\(_{24}\)OSi\(_{35}\)Cl: 259.1285; found: 259.1294.
t-Butyl(((S,4E,6E)-7-chlorohepta-4,6-dien-2-yl)oxy)dimethylsilane (7). A solution of alcohol 5 (240 mg, 1.64 mmol), TBSCl (299 mg, 1.99 mmol) and imidazole (226 mg, 3.32 mmol) in CH₂Cl₂ (10 mL) was stirred at room temperature for 2 h. The reaction was quenched with aq. NH₄Cl (10 mL) and the mixture was extracted with Et₂O (10 mL × 3). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc/Hexane) to give diene 7 as a colorless oil (397 mg, 93%); [α]₀²³ +12.0 (c 0.20, CHCl₃); IR(neat) cm⁻¹: 3422, 2955, 2857, 2100, 1653, 1638; ¹H NMR(400 MHz, CDCl₃) δ 6.42 (dd, J=13.3, 11.0 Hz, 1H), 6.09 (d, J=13.3 Hz, 1H), 5.99 (dd, J=15.6, 11.0 Hz, 1H), 5.70 (dt, J=15.1, 7.3 Hz, 1H), 3.87-3.80 (sex, J=6.4, 1H), 2.25-2.13 (m, 2H), 1.12 (d, J=6.0 Hz, 3H), 0.88 (s, 9H), 0.04-0.03 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 134.0, 132.8, 128.3, 119.0, 68.6, 43.2, 26.1, 23.8, 18.4, -4.3, -4.5; MS (ESI): m/z = 261.41 [C₁₃H₂₅O₃S⁺Cl + H]⁺; HRMS (EI): m/z [M + Na⁺] calcld for C₁₃H₂₅O₃S₅ClSiNa: 283.1261; found: 283.1275.

(R)-4,8-Dimethylnon-7-en-1-yne (9). Method A: (R)-Citronellal 8 (1.00 g, 6.48 mmol) was added to a mixture of diethyl (1-diazo-2-oxopropyl)phosphonate (1.87 g, 9.72 mmol) and K₂CO₃ (1.79 g, 13.0 mmol) in methanol (15 mL). The mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and H₂O (20 mL) was added. The mixture was extracted with Et₂O (20 mL × 3). The combined organic layers were washed with brine, dried (MgSO₄) and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc/Hexane) to afford alkyne 9 as a colorless oil (0.71 g, 73%); ¹H NMR(400 MHz, CDCl₃) δ 5.12-5.08 (m, 1H), 2.17 (ddd, J=16.5, 5.5, 2.8 Hz, 1H), 2.07 (ddd, J=16.5, 6.9, 2.8 Hz, 1H), 2.02-1.94 (m, 3H), 1.70-1.66 (m, 4H), 1.61 (s, 3H), 1.49-1.41 (m, 1H), 1.29-1.19 (m, 1H), 1.00 (d, J=6.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 131.7, 124.7, 83.6, 69.3, 36.2, 32.2, 26.0, 25.9, 25.8, 19.5, 17.9.

Methyl (R,E)-2,6-dimethylnon-2-en-8-ynoate (10). Alkyne 10 was prepared according to our procedure reported previously for the racemic compound;²³ [α]₀²³ +4.1 (c 0.68, CHCl₃).
Methyl (R,2E,8E)-2,6-dimethyl-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) nona-2,8-dienoate (11). Boronate 11 was prepared according to our procedure reported previously for the racemic compound;23 [α]D23 -1.8 (c 3.50, CHCl3).

Methyl (2E,8E,10E,15S)-15-((t-Butyldimethylsilyl)oxy)-2,6-dimethylhexadeca-2,8,10-trien-12-ynoate (12). Trienyne 12 was prepared in 88% yield from alkenyl boronate 11 and enyne 6 according to the procedure described for tetraene 24; IR(neat) cm⁻¹: 2955, 2929, 2737, 2253, 2214, 1715, 1653; ¹H NMR (400 MHz, CDCl3) δ 6.73 (t, J=7.2 Hz, 1H), 6.45 (dd, J=15.6, 10.8 Hz, 1H), 6.04 (dd=15.6, 10.8 Hz, 1H), 5.70 (dt, J=15.6, 7.2 Hz, 1H), 5.48 (d, J=15.6 Hz, 1H), 3.97-3.93 (m, 3H), 3.73 (s, 3H), 2.52-2.33 (m, 3H), 2.19-1.92 (m, 4H), 1.83 (s, 3H), 1.62-1.39 (m, 2H), 1.29-1.22 (m, 3H), 0.89-0.78 (m, 12H), 0.08 (s, 6H); ¹³C NMR (100 MHz, CDCl3) δ 168.9, 142.8, 141.1, 135.3, 131.5, 127.7, 109.9, 90.0, 81.5, 68.2, 51.9, 40.3, 35.5, 33.1, 30.8, 26.5, 26.1, 23.7, 19.6, 18.4, 12.6, -4.5; MS (ESI): m/z = 419.34 [M + H]+; HRMS (EI): m/z [M + H]+ calcd for C25H43O3Si: 419.2981; found: 419.2998.

(2E,8E,10E,15S)-15-((t-Butyldimethylsilyl)oxy)-2,6-dimethylhexadeca-2,8,10-trien-12-yn-1-ol (13). Trienyne 13 was prepared in 72% yield from trienyne 12 according to the procedure described for alcohol 25; IR(neat) cm⁻¹: 3412, 2955, 2929, 2258, 1654; ¹H NMR (400 MHz, CDCl3) δ 6.48 (dd, J=15.6, 11.0 Hz, 1H), 6.04 (dd=15.1, 11.0 Hz, 1H), 5.70 (dt, J=15.1, 7.2 Hz, 1H), 5.47 (d, J=15.6 Hz, 1H), 5.38 (t, J=7.4 Hz, 1H), 3.99-3.91 (m, 3H), 2.52-2.32 (m, 2H), 2.13-1.89 (m, 4H), 1.66 (s, 3H), 1.59-1.28 (m, 3H), 1.23-1.08 (m, 6H), 0.87 (s, 9H), 0.07 (s, 6H); ¹³C NMR (100 MHz, CDCl3) δ 141.2, 135.7, 134.9, 131.3, 126.6, 109.6, 89.9, 81.4, 69.2, 68.2, 40.4, 36.5, 33.0, 30.8, 26.1, 25.4, 23.7, 19.7, 18.4, 13.9, -4.4; MS (ESI): m/z = 391.73 [M + H]+; HRMS (EI): m/z[M + H]+ calcd for C24H43O2Si: 391.3032; found: 391.3070.

(2E,8E,10E,15S)-15-((t-Butyldimethylsilyl)oxy)-2,6-dimethylhexadeca-2,8,10-trien-12-yn-1-ol (13). Trienyne 13 was prepared in 72% yield from trienyne 12 according to the procedure described for alcohol 25; IR(neat) cm⁻¹: 3412, 2955, 2929, 2258, 1654; ¹H NMR (400 MHz, CDCl3) δ 6.48 (dd, J=15.6, 11.0 Hz, 1H), 6.04 (dd=15.1, 11.0 Hz, 1H), 5.70 (dt, J=15.1, 7.2 Hz, 1H), 5.47 (d, J=15.6 Hz, 1H), 5.38 (t, J=7.4 Hz, 1H), 3.99-3.91 (m, 3H), 2.52-2.32 (m, 2H), 2.13-1.89 (m, 4H), 1.66 (s, 3H), 1.59-1.28 (m, 3H), 1.23-1.08 (m, 6H), 0.87 (s, 9H), 0.07 (s, 6H); ¹³C NMR (100 MHz, CDCl3) δ 141.2, 135.7, 134.9, 131.3, 126.6, 109.6, 89.9, 81.4, 69.2, 68.2, 40.4, 36.5, 33.0, 30.8, 26.1, 25.4, 23.7, 19.7, 18.4, 13.9, -4.4; MS (ESI): m/z = 391.73 [M + H]+; HRMS (EI): m/z[M + H]+ calcd for C24H43O2Si: 391.3032; found: 391.3070.

(2E,8E,10E,15S)-15-((t-Butyldimethylsilyl)oxy)-2,6-dimethylhexadeca-2,8,10-trien-12-ynal (14). Aldehyde 14 was prepared in 90% yield from alcohol 13 according to the procedure described for aldehyde 26; IR(neat) cm⁻¹: 2953, 2723, 2216, 1732, 1695, 1568; ¹H NMR (400 MHz, CDCl3) δ 9.39 (s, 1H), 6.51-6.45 (m, 2H), 6.05 (dd, J=15.1, 11.0 Hz, 1H), 5.72 (dt, J=15.1, 7.2 Hz, 1H), 5.49 (d, J=15.6 Hz, 1H), 3.98-3.91 (m, 1H), 2.52-2.33 (m, 4H), 2.18-1.93 (m, 2H), 1.74 (s, 3H), 1.67-1.48 (m, 3H), 1.28-1.18 (m, 6H), 0.89 (s, 9H), 0.08 (s, 6H); ¹³C NMR (100 MHz, CDCl3) δ 195.4, 154.9, 140.9, 134.9, 134.8, 131.6, 110.0, 90.0, 81.3, 68.1, 40.2, 35.1, 33.1, 26.8, 26.0, 23.6, 19.5, 18.3, 9.3, -4.5; MS (ESI): m/z = 389.62 [M + H]+; HRMS (EI): m/z[M + H]+ calcd for C24H41O2Si: 389.2876; found: 389.2879.

(±)-4-Methylhept-6-yn-1-ol (16). O₃ in O₂ was bubbled through a solution of alkyne 9 (1.00 g, 6.65 mmol) in MeOH (40 mL) at room temperature. When all the starting material was consumed, O₂ was flushed through the solution for 10 min. The mixture was cooled to 0 °C and NaBH₄ was added portionwise. The reaction was stirred for 30 min before aq. NH₄Cl (5 mL) was added. The mixture was concentrated in vacuo and the mixture was extracted with CH₂Cl₂ (10 mL x 3). The combined organic layers were washed with brine and dried (MgSO₄). The volatiles were removed under reduced pressure and the residue was purified by flash chromatography on silica gel (25% EtOAc/Hexane) to give alcohol 16.
(705 mg, 84%) as a colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 3.65 (t, J=6.4 Hz, 2H), 2.21-2.07 (m, 2H), 1.96 (t, J=2.3 Hz, 1H), 1.75-1.48 (m, 4H), 1.38-1.23 (m, 1H), 1.00 (d, J=6.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 83.3, 69.5, 63.4, 32.5, 32.1, 30.5, 26.0, 19.6; all data are consistent with that reported.

(±)- (E)-4-Methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-6-en-1-ol (17). Tri(2-furyl)phosphine (18.4 mg, 0.08 mmol) and [Rh(CO)₂Cl]₂ (15.4 mg, 0.04 mmol) were mixed in toluene (40 mL) at room temperature under N₂. A solution of alcohol 16 (500 mg, 3.96 mmol) in toluene (2 mL) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.69 mL, 4.80 mmol) was added. The mixture was stirred for 2 h at room temperature. The reaction was quenched with H₂O and the mixture was extracted with Et₂O (10 mL x 3). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash chromatography (25% EtOAc/Hexane) to give alkenyl boronate 17 as a colorless oil (886 mg, 88%); IR(neat) cm⁻¹: 3397, 2976, 2870, 2247, 1734, 1636; ¹H NMR (400 MHz, CDCl₃) δ 6.59 (dt, J=18.0, 6.9 Hz, 1H), 5.42 (d, J=18.0 Hz, 1H), 3.64-3.60 (m, 2H), 2.21-2.14 (m, 1H), 2.05-1.97 (m, 1H), 1.64-1.48 (m, 1H), 1.43-1.34 (m, 1H), 1.26 (s, 12H), 0.90 (d, J=6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 153.4, 83.3, 63.5, 43.8, 32.8, 30.6, 25.0, 19.8; MS (ESI): m/z = 255.32 [M + H]⁺; HRMS (EI): m/z [M + Na]⁺ calcd for C₁₄H₂₇BO₃Na: 277.1951; found: 277.1933.

(6E,8E,13S)-13-((t-Butyldimethylsilyl)oxy)-4-methyltetradeca-6,8-dien-10-yn-1-ol (18). A solution of alcohol 17 (500 mg, 1.76 mmol), vinyl chloride 6 (455 mg, 1.76 mmol), Pd(OAc)₂ (8 mg, 0.035 mmol), Sphos (29 mg, 0.070 mmol) and NaOH (142 mg, 3.52 mmol) in THF/H₂O (20 mL, 1:1) was stirred at 70 °C for 2 h. The mixture was cooled to room temperature and extracted with Et₂O (10 mL x 3). The combined organic layers were washed with brine, dried (Na₂SO₄), filtered through celite and concentrated in vacuo. The residue was purified by flash chromatography (25% EtOAc/Hexane) to give dienyne 18 as a colorless oil (842 mg, 94%) as a colorless oil; IR(neat) cm⁻¹: 3421, 3053, 2929, 2919, 2856, 2304, 2123, 1637; ¹H NMR (400 MHz, CDCl₃) δ 6.48 (dd, J=15.6, 11.0 Hz, 1H), 6.05 (dd, J=18.0, 6.9 Hz, 1H), 5.72 (dt, J=15.1, 7.3 Hz, 1H), 5.47 (d, J=15.6 Hz, 1H), 3.98-3.93 (m, 1H), 3.62 (t, J=6.4 Hz, 2H), 2.49 (ddd, J=16.9, 5.9, 2.3 Hz, 1H), 2.36 (ddd, J=16.5, 6.9, 2.3 Hz, 1H), 2.14-2.08 (m, 1H), 1.99-1.92 (m, 1H), 1.64-1.48 (m, 4H), 1.42-1.20 (m, 7H), 0.89 (s, 9H), 0.07 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 141.2, 135.6, 131.4, 109.7, 89.9, 81.5, 68.2, 63.5, 40.5, 33.3, 32.8, 30.8, 30.6, 26.1, 23.7, 19.7, 18.4, -4.4; MS (ESI): m/z = 351.59 [M + H]⁺; HRMS (EI): m/z [M + H]⁺ calcd for C₂₁H₃₉O₂Si: 351.2719; found: 351.2715.

(6E,8E,13S)-13-((t-Butyldimethylsilyl)oxy)-4-methyltetradeca-6,8-dien-10-ynal (19). A solution of alcohol 18 (900 mg, 2.58 mmol) and DMP (1.63 g, 3.87 mmol) in CH₂Cl₂ (20 mL) was stirred at room temperature for 30 min. After quenching with aq. NaHCO₃ (20 mL), the mixture was extracted with CH₂Cl₂ (10 mL x 3). The combined organic layers were washed with brine, dried (MgSO₄), filtered through celite and concentrated in vacuo. The residue was purified by flash chromatography (25% EtOAc/Hexane) to give aldehyde 19 (842 mg, 94%) as a colorless oil; IR(neat) cm⁻¹: 2957, 2928, 2904, 2856, 2719, 2150, 1724, 1638; ¹H NMR (400 MHz, CDCl₃) δ 9.76 (t, J=1.8 Hz, 1H), 6.48 (dd, J=15.6, 11.0 Hz, 1H),
6.06 (dd, J=15.1, 11.0 Hz, 1H), 5.70 (dt, J=15.1 Hz, 7.3 Hz, 1H), 5.49 (d, J= 15.6 Hz, 1H), 3.98-3.92 (m, 1H), 2.52- 2.33 (m, 4H), 2.14 - 2.07 (m, 1H), 2.01- 1.94 (m, 1H), 1.72- 1.39 (m, 3H), 1.22 (d, J=6.0 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H); ^13C NMR (100 MHz, CDCl3) δ 202.8, 141.0, 134.8, 131.7, 110.1, 90.1, 81.4, 68.2, 41.9, 40.2, 33.0, 30.8, 28.7, 26.1, 23.7, 19.5, 18.4, -4.5; MS (ESI): m/z = 349.67 [M + H]+; HRMS (EI): m/z [M + H]+ calcd for C21H37O2Si: 349.2563; found: 349.2594.

Dimethyl 2-((6E,8E,13S)-13-((t-butyldimethylsilyl)oxy)-4-methyltetradeca-6,8-dien-10-yn-1-ylidene)malonate (20). A solution of aldehyde 19 (500 mg, 1.50 mmol), dimethyl malonate (165 μL, 1.50 mmol), piperidine (30 μL, 0.30 mmol) and AcOH (17 μL, 0.30 mmol) in CH2Cl2 (10 mL) was stirred for 4 h at room temperature. The solvent was removed under reduced pressure. H2O (5 mL) was added and the mixture was extracted with Et2O (5 mL x 3). The combined layers were washed with aq. NaHCO3, brine and dried over MgSO4. The combined layers were removed in vacuo and the residue was purified by flash chromatography (25% EtOAc/Hexane) to give alkylidene malonate 20 as a colorless oil (500 mg, 75%); IR(neat) cm⁻¹: 3022, 2953, 2928, 2857, 2081, 1732, 1688, 1643; ^1H NMR (400 MHz, CDCl3) δ 7.01 (t, J=8.2 Hz, 1H), 6.47 (dd, J=15.6, 11.0 Hz, 1H), 6.05 (dd, J=15.1, 11.0 Hz, 1H), 5.69 (dt, J=15.1 Hz, 7.3 Hz, 1H), 5.48 (d, J=15.6 Hz, 1H), 3.97-3.93 (m, 1H), 3.78 (s, 3H), 3.78 (s, 3H), 2.51 -2.27 (m, 4H), 2.11-2.04 (m, 1H), 1.97-1.93 (m, 1H), 1.57-1.43 (m, 2H), 1.32-1.22 (m, 7H), 0.89 (s, 9H), 0.07 (s, 6H); ^13C NMR (100 MHz, CDCl3) δ 166.3, 164.6, 150.7, 141.0, 135.0, 131.7, 127.9, 110.0, 89.8, 81.2, 68.2, 52.6, 52.5, 40.2, 35.1, 33.0, 30.8, 27.7, 26.1, 23.7, 19.5, 18.4, -4.5; MS (ESI): m/z = 463.68 [M + H]+; HRMS (EI): m/z [M + H]+ calcd for C26H43O5Si: 463.2880; found: 463.2866.

2-((S)-4-((t-Butyldimethylsilyl)oxy)pent-1-yn-1-yl)-2',2',6-trimethyl-4a,5,6,7,8,8a-hexahydro-2H-spiro[naphthalene-1,5'-[1,3]dioxane]-4',6'-dione (23). A solution of Meldrum's acid (365 mg, 2.53 mmol), aldehyde 19 (840 mg, 2.41 mmol), piperidine (48 μL, 0.48 mmol) and AcOH (28 μL, 0.48 mmol) in CH2Cl2 (10 mL) was stirred for 2h at room temperature. The solvent was removed under reduced pressure. H2O (10 mL) was added and the mixture was extracted with Et2O (5 mL x 3). The combined organic layers were washed with aq. NaHCO3, brine and dried (MgSO4). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (25% EtOAc/Hexane) to give tricycle 23 as a colorless oil (655 mg, 82%, 2:1 mixture of diastereoisomers); ^1H NMR (major isomer) (400 MHz, CDCl3) δ 5.68 (d, J=10.1 Hz, 1H), 5.64-5.50 (m, 1H), 3.93-3.88 (m, 1H), 3.58 (s, 1H), 2.25-2.17 (m, 2H), 2.00-1.86 (m, 2H), 1.64-1.54 (m, 3H), 1.73 (s, 3H), 1.72 (s, 3H), 1.27-1.16 (m, 7H), 0.89-0.82 (m, 2H), 0.05 (s, 6H).

Methyl (2E,6R,8E,10E,12E,15S)-15-((t-butyldimethylsilyl)oxy)-2,6-dimethylhexadeca-2,8,10,12-tetraenoate (24). A solution of vinyl chloride 7 (500 mg, 1.92 mmol), boronate 11 (620 mg, 1.92 mmol), NaOH (155 mg, 3.84 mmol), Pd(OAc)2 (8.8 mg, 0.038 mmol) and Sphos (30 mg, 0.076 mmol) in THF/H2O (20 mL, 1:1) was heated at 70 °C for 2 h under N2. Aq. NH4Cl (5 mL) was added and the mixture was extracted with Et2O (10 mL x 3). The combined organic layers were washed with brine, dried (MgSO4) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (10% EtOAc/Hexane) to give
tetraene 24 as a colorless oil (704 mg, 87%); [α]D23 +7.9 (c 1.80, CHCl3); IR(neat) cm⁻¹: 3419, 2953, 2857, 2360, 1717, 1647; 1H NMR (400 MHz, CDCl3) δ 6.74 (t, J=7.8 Hz, 1H), 6.11-5.98 (m, 4H), 5.68-5.59 (m, 2H), 3.86-3.80 (m, 1H), 3.73 (s, 3H), 2.28-2.07 (m, 4H), 2.00-1.93 (m, 1H), 1.83 (s, 3H), 1.55-1.43 (m, 2H), 1.30-1.19 (m, 2H), 1.12 (d, J=6.0 Hz, 3H), 0.94-0.83 (m, 12H), 0.04-0.03 (m, 6H); 13C NMR (100 MHz, CDCl3) δ 168.9, 142.9, 132.8, 132.7, 132.2, 131.3, 131,1, 127.7, 69.0, 51.9, 43.5, 35.4, 33.2, 26.5, 26.1, 23.8, 19.6, 18.4, 12.6, -4.3, -4.4; MS (ESI): m/z = 443.61 [M + Na]+; HRMS (EI): m/z [M + H]+ calcd for C25H45O3Si: 421.3138; found: 421.3140.

(2E,6R,8E,10E,12E,15S)-15-((t-Butyldimethylsilyl)oxy)-2,6-dimethylhexadeca-2,8,10,12-tetraen-1-ol (25). DIBAL-H (2.15 mL, 2.15 mmol, 1 M in cyclohexane) was added slowly to a solution of the ester 24 (600 mg, 1.43 mmol) in CH2Cl2 (20 mL) at -78 °C. After stirring overnight at -78 °C, aqueous potassium sodium tartrate solution (1.21 g, 5 mL) was added to the mixture. The solution was allowed to warm to room temperature and stirred for 2 h further, then extracted with CH2Cl2 (10 mL × 3). The combined organic layers were washed with brine, dried (MgSO4) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (50% EtOAc/Hexane) to give alcohol 25 as a colorless oil (432 mg, 77%); [α]D23 +9.0 (c 0.80, CHCl3); IR(neat) cm⁻¹: 3356, 3013, 2955, 2928, 1689, 1644, 1641; 1H NMR (400 MHz, CDCl3) δ 6.11-6.00 (m, 4H), 5.68-5.60 (m, 2H), 5.39 (t, J=7.3 Hz, 1H), 3.99 (d, J=5.0 Hz, 2H), 3.84-3.79 (m, 1H), 2.24-1.93 (m, 6H), 1.66 (s, 3H), 1.57-1.24 (m, 3H), 1.12 (d, J=6.0 Hz, 3H), 0.89-0.84 (m, 12H), 0.04-0.03 (m, 6H); 13C NMR (100 MHz, CDCl3) δ 134.8, 133.2, 132.7, 132.0, 131.4, 131.1, 131.0, 126.8, 69.3, 69.0, 43.5, 40.5, 36.5, 33.2, 26.1, 25.4, 23.8, 19.7, 18.4, 13.9, -4.3, -4.4; MS (ESI): m/z = 393.35 [M + H]+; HRMS (EI): m/z [M + H]+ calcd for C24H45O2Si: 393.3189; found: 393.3182.

(2E,6R,8E,10E,12E,15S)-15-((t-Butyldimethylsilyl)oxy)-2,6-dimethylhexadeca-2,8,10,12-tetraenal (26). DMP (1.86 g, 4.38 mmol) was added to a solution of alcohol 25 (860 mg, 2.19 mmol) in CH2Cl2 (20 mL) and the mixture was stirred for 30 min at room temperature. The reaction was quenched with aq. NaHCO3 (20 mL) and the mixture was extracted with CH2Cl2 (10 mL × 3). The combined organic layers were washed with brine, dried (MgSO4) and filtered through celite. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (20% EtOAc/Hexane) to give aldehyde 26 as a colorless oil (780 mg, 91%); [α]D23 +14.0 (c 0.80, CHCl3); IR(neat) cm⁻¹: 3422, 2957, 2928, 2857, 1726, 1690, 1639, 1462, 1375; 1H NMR (400 MHz, CDCl3) δ 9.39 (s, 1H), 6.47 (t, J=7.3 Hz, 1H), 6.12-6.02 (m, 4H), 5.69-5.61 (m, 2H), 3.86-3.80 (m, 1H), 2.38-1.98 (m, 5H), 1.75 (s, 3H), 1.60-1.49 (m, 2H), 1.32-1.23 (m, 2H), 1.12 (d, J=5.9 Hz, 3H), 0.95-0.87 (m, 12H), 0.07-0.03 (m, 6H); 13C NMR (100 MHz, CDCl3) δ 195.6, 155.2, 139.4, 132.6, 132.5, 132.4, 131.4, 131.3, 131.2, 68.9, 43.5, 40.4, 35.2, 33.3, 26.9, 26.1, 23.8, 19.6, 18.4, 9.4,-4.3, -4.4; MS (ESI): m/z = 413.62 [M + Na]+; HRMS (EI): m/z [M + H]+ calcd for C24H43O2Si: 391.3032; found: 391.3037.

(1S,2R,4aS,6R,8aR)-2-((S,E)-4-Hydroxypent-1-en-1-yl)-1,6-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carbaldehyde (27). AlCl3 (136 mg, 1.02 mmol) was added to a solution of aldehyde 26 (200 mg, 0.51 mmol) in CH2Cl2
(10 mL) at 0 ºC. After stirring for 1 h, the reaction was quenched with aq. NaHCO₃ (10 mL). The mixture was extracted with Et₂O (5 mL x 3). The combined organic layers were washed with brine and dried (MgSO₄). The solvent was removed in vacuo and the residue was purified by flash chromatography on silica gel (30% EtOAc/Hexane) to give bicycle 27 as a colorless oil (88 mg, 62%); [α]D²³ +21.1 (c 0.50, CHCl₃); IR(neat) cm⁻¹: 3410, 2955, 2928, 2857, 1719; ¹H NMR (400 MHz, CDCl₃) δ 9.49 (s, 1H), 5.54-5.36 (m, 4H), 3.82-3.76 (m, 3H), 2.61-2.58 (m, 1H), 2.23-2.08 (m, 2H), 1.85-1.39 (m, 9H), 1.17 (d, J=5.9 Hz, 3H), 1.04 (s, 3H), 0.92 (d, J=6.9 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 209.1, 132.6, 131.6, 129.8, 126.5, 67.4, 50.7, 49.2, 42.7, 41.8, 39.1, 37.6, 35.6, 33.4, 27.2, 23.0, 22.7, 14.3; MS (ESI): m/z = 299.48 [M + Na]⁺; HRMS (EI): m/z [M + H]⁺ calcd for C₁₈H₂₉O₂: 277.2168; found: 277.2173.

(1S,2R,4aS,6R,8aR)-2-(((S,E)-4-Hydroxypent-1-en-1-yl)-1,6-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylic acid (28). NaH₂PO₄ (60 mg, 0.50 mmol), 2-methylbut-2-ene (172 μL, 1.62 mmol) was added to a solution of aldehyde 27 (100mg, 0.36 mmol) in t-BuOH/H₂O (8 mL, 3:1). NaClO₂ (82 mg, 0.90 mmol) was added to the mixture. The reaction was stirred for 4 h at room temperature. H₂O (10 mL) was added to the reaction, and the mixture was extracted with Et₂O (10 mL x 3). The combined organic layers were washed with brine, dried (MgSO₄) and the solvent was removed under reduced pressure. The acid 28 was obtained by flash chromatography on silica gel (50% EtOAc/Hexane) as a colorless oil (117 mg, 80%); [α]D²³ +114.1 (c 0.80, CHCl₃); IR(neat) cm⁻¹: 3422, 2953, 2924, 2855, 1667, 1608, 1585; ¹H NMR (400 MHz, CDCl₃) δ 5.50-5.35 (m, 4H), 5.09 (br, 1H), 3.82-3.72 (m, 1H), 2.61 (dd, J=8.7, 4.1 Hz, 1H), 2.24-2.17 (m, 2H), 2.02-1.97 (m, 1H), 1.81-1.72 (m, 4H), 1.63-1.47 (m, 4H), 1.19-1.16 (m, 6H), 0.91 (d, J=6.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 179.7, 135.7, 131.3, 127.6, 126.2, 67.3, 50.7, 49.6, 42.5, 42.0, 40.4, 38.3, 35.7, 33.6, 27.7, 22.7, 22.7, 16.8; MS (ESI): m/z = 315.48 [M + Na]⁺; HRMS (EI): m/z [M + Na]⁺ calcd for C₁₈H₂₈O₃Na: 315.1936; found: 315.1928.

(3R,3aR,5aS,7R,9aR,9bS)-3-(((1S,3S)-3-Hydroxy-1-(phenylselanyl)butyl)-7,9b-dimethyl-3a,5a,6,7,8,9,9a,9b-octahydronaphtho[1,2-c]furan-1(3H)-one (29). N-(Phenylseleno)phthalimide (123 mg, 0.42 mmol) was added to a solution of acid 28 (60 mL, 0.21 mmol) in CH₂Cl₂. After stirring for 2 h, the solvent was removed under reduced pressure and excess hexane was added. The mixture was filtered through celite and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (50% EtOAc/Hexane) to give selenide 29 as a colorless oil (157 mg, 83%); [α]D²³ +50.5 (c 0.20, CHCl₃); IR(neat) cm⁻¹: 3441, 2928, 2367, 2097, 1772, 1636, 1558; ¹H NMR (400 MHz, CDCl₃) δ 7.63-7.60 (m, 2H), 7.30-7.28 (m, 3H), 5.80-5.76 (m, 1H), 5.61 (d, J=10.1 Hz, 1H), 4.37 (dd, J=9.6, 5.0 Hz, 1H), 4.32-4.26 (m, 1H), 2.50 (dd, J=9.6, 4.6 Hz, 1H), 1.94-1.77 (m, 5H), 1.71-1.63 (m, 2H), 1.48-1.47 (m, 2H), 1.31-1.24 (m, 5H), 1.12 (s, 3H), 0.90 (d, J=6.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 179.0, 134.7, 134.6, 129.5, 129.3, 128.1, 122.7, 85.4, 65.7, 49.4, 46.7, 45.6, 41.8, 41.3, 40.5, 36.2, 35.3, 33.0, 25.7, 24.5, 22.6, 16.1; MS (ESI): m/z = 471.16 [M + Na]⁺; HRMS (EI): m/z [M + Na]⁺ calcd for C₂₄H₃₂O₃SeNa: 471.1414; found: 471.1427.
Allahabadolactone A (1). H$_2$O$_2$ (2 mL, 30% in H$_2$O) was added to a solution of selenide 29 (157 mg, 0.35 mmol) in THF (5 mL). The mixture was stirred for 1 h at room temperature. After adding H$_2$O (5 mL), the mixture was extracted with Et$_2$O (5 mL x 3). The combined organic layers were washed with brine, dried (MgSO$_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (25% EtOAc/Hexane) to give Allahabadolactone A 1 as a colorless solid (50 mg, 100%); m.p. 116 – 117 °C; [α]$_D^{23}$ +25.9 (c 0.08, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 5.91 (dd, J=15.6, 5.5 Hz, 1H), 5.72 (ddd, J=15.6, 7.3, 1.3 Hz, 1H), 5.66 (d, J=10.1 Hz, 1H), 5.55 - 5.49 (m, 1H), 4.47 (dd, J=10.2, 7.3 Hz, 1H), 4.39-4.35 (m, 1H), 2.35 -2.32 (m, 1H), 1.95- 1.78 (m, 4H), 1.53- 1.41 (m, 1H), 1.31- 1.20 (m, 1H), 1.30 (d, J=6.8 Hz, 3H), 1.14 (s, 3H), 0.97 - 0.76 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 179.5, 139.1, 135.2, 126.1, 121.0, 82.8, 68.0, 51.7, 44.9, 41.8, 40.3, 36.4, 35.3, 33.0, 25.7, 23.5, 22.6, 16.5.

Acknowledgements
We thank the Agency for Science Technology and Research (A-STAR) for financial support of this work (PSF grant number 1321202095).

Supporting Information Available
$^1$H and $^{13}$C NMR spectra for compounds 4 - 7, 9 - 20, 23 - 29, 1.

References
24. Racemic citronellal was used for early studies, hence compounds 12, 13, 14, 17, 18, 19, 22 and 23 were prepared as mixtures of diastereoisomers. (R)-Citronellal was employed for the ultimately selective route.


32. There are, to our knowledge, only a few examples of Diels-Alder reactions of alkylidene derivatives of Meldrum's acids. See, for example Zitsane, D. R.; Ravinya, I. T.; Riikure, I. A.; Teter, Z. F.; Gudrinieste, E. Yu.; Kalei, U. O. *Russ. J. Org. Chem.* 1999, 35, 1457. This is, to the best of our knowledge, the first example of an intramolecular example.

