Four-directional synthesis of adamantane derivatives

Tao Qu, Andrew J. P. White, and Anthony G. M. Barrett*

Department of Chemistry, Imperial College, Molecular Sciences Research Hub, White City Campus, Wood Lane, London, W12 0BZ, England
Email: agmb@ic.ac.uk

Dedicated to Professor Horst Kunz on the occasion of his 80th Birthday

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Abstract

1-Adamantanemethanol, 1,3-adamantanedimethanol and 1,3,5,7-adamantanetetramethanol were converted into adamantanes functionalized with one or four (2R,1S)-2-formyl-1-cyclopropyl residues using Charette enantioselective cyclopropanation reactions and with one, two or four 4-ethoxy- (or 4-t-butoxy)-3-diazo-2,4-dioxobutyl residues from aldehyde and diazo-acetate ester condensation reactions by 1-directional, 2-directional or 4-directional syntheses. The synthesis of adamantane fused to cyclopentadiene is also reported.

Keywords: Adamantane, 4-directional synthesis, enantioselective cyclopropanation, α-diazo-β-keto-esters
Introduction

Fuchs introduced the concept of the Intricacy Quotient (IQ) as a measure of the efficiency of natural product total synthesis.\(^1\) One of the natural product examples highlighted in this study, was the total synthesis of the CETP inhibitor U-106305 (5) independently by Barrett and Charette.\(^2,3\) This synthesis was scored at an IQ of 1.83 by Fuchs and the reason for this high value was due to the use of an iterative two-directional synthesis with late stage desymmetrization (Scheme 1) which, for example in the conversion of tercyclopropane 3 into quinquecyclopropane 4 generated two rings and controlled four stereocenters in an absolute sense. There is an added benefit with two-directional introduction of stereocenters by enantioselective synthesis and that is Horeau amplification of enantioselectivities.\(^4\) It is clear, based on the Fuchs’ analysis, that a total synthesis that depends on a four-directional synthesis is likely to score highly on the Fuchs IQ scale.

**Scheme 1.** Barrett and Charette two directional homologation in the total synthesis of U-106305 (5)

Four-directional transformations of adamantanes bearing identical tertiary substituents at C\(_1\), C\(_3\), C\(_5\) and C\(_7\) are well precedented. In a general sense, reaction of the adamantane derivative 6 with various reagents have been used to synthesize other adamantanes 7 bearing four identical substituents Y thereby conserving the symmetry. Most of these known transformations involve the construction of four carbon–heteroatom bonds or the quadruple derivatization of adamantanes functionalized by four identical tertiary aromatic rings. These are illustrated in Table 1 and the paragraph thereafter.

Tetra-aryl adamantanes 6 (X = Ph, 4-AcC\(_6\)H\(_4\), 4-O\(_2\)NC\(_6\)H\(_4\), 4-IC\(_6\)H\(_4\) and 4-ethynylC\(_6\)H\(_4\)) have been converted into higher molecular weight adamantanes 7 by four-directional electrophilic aromatic substitution reactions, enantioselective reductions, aryl iodide to aryl nitrile conversions, nitroarene to aniline reductions, aniline to aryl azide conversions, Suzuki and Sonogashira coupling reactions and 3-component allene, aryl iodide and amine coupling reactions.\(^{19-26}\) Of particular note in this chemistry are the application of four-directional syntheses to construct more complex adamantanes bearing nucleoside and nucleotide side chains\(^{21}\) and the Naemura four-directional synthesis of the (+)-[1,3,5,7-tetrakis-trishomocubanylbuta-1,3-diynyl]adamantane derivative 10 (Scheme 2).\(^{18}\)
Table 1. General four-directional synthesis of adamantane derivatives

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Substituent X</th>
<th>Reagent</th>
<th>Substituent Y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amide Synthesis$^{5-8}$</td>
<td>CO$_2$H or COCl</td>
<td>R’R’“NH</td>
<td>CONR’R’</td>
</tr>
<tr>
<td>Dendrimer Amide Synthesis$^9$</td>
<td>CO$_2$H or COCl</td>
<td>R’R’“NH</td>
<td>CONR’R’</td>
</tr>
<tr>
<td>Ester Synthesis$^{10-13}$</td>
<td>COCl</td>
<td>R’OH or ArOH</td>
<td>CO$_2$R’ or CO$_2$Ar</td>
</tr>
<tr>
<td>Ester Saponification$^{13,14}$</td>
<td>CO$_2$Me</td>
<td>KOH, MeOH, H$_2$O, MeCN</td>
<td>CO$_2$H (90%)</td>
</tr>
<tr>
<td>Nitrile Alcoholsysis$^6$</td>
<td>CN</td>
<td>HCl, MeOH</td>
<td>CO$_2$Me (72%)</td>
</tr>
<tr>
<td>Nitrile Reduction$^{15}$</td>
<td>CN</td>
<td>Me$_2$S.BH$_3$</td>
<td>CH$_2$NH$_2$ (98%)</td>
</tr>
<tr>
<td>Tetrazole Synthesis$^{16}$</td>
<td>CN</td>
<td>NaN$_3$, ZnCl$_2$, DMF, Δ</td>
<td>5-Tetrazolyl (54%)</td>
</tr>
<tr>
<td>Arene Oxidative Degradation$^{13}$</td>
<td>Ph</td>
<td>RuCl$_3$, NaIO$_4$, CCl$_4$, H$_2$O, SOCl$_2$, MeOH</td>
<td>CO$_2$Me (35%)</td>
</tr>
<tr>
<td>Alcohol Swern Oxidation$^{17}$</td>
<td>CH$_2$OH</td>
<td>(COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$</td>
<td>CHO (55%)</td>
</tr>
<tr>
<td>4-Toluenesulfonylation$^{18}$</td>
<td>CH$_2$OH</td>
<td>TsCl, pyridine</td>
<td>CH$_2$OTs</td>
</tr>
<tr>
<td>Cyanide Displacement$^{18}$</td>
<td>CH$_2$OTs</td>
<td>NaCN, DMF, Δ</td>
<td>CH$_2$CN (77% from tetraol)</td>
</tr>
<tr>
<td>Cyanide Hydrolysis$^{18}$</td>
<td>CH$_2$CN</td>
<td>H$_2$SO$_4$, H$_2$O, 120-130 °C</td>
<td>CH$_2$CO$_2$H (88%)</td>
</tr>
<tr>
<td>Amide Synthesis$^{18}$</td>
<td>CH$_2$CO$_2$H</td>
<td>SOCl$_2$, Δ; PhH, Me$_2$N</td>
<td>CH$_2$CONMe$_2$ (93%)</td>
</tr>
<tr>
<td>Amide Reduction$^{18}$</td>
<td>CH$_2$CONMe$_2$</td>
<td>LiAlH$_4$, THF, Δ</td>
<td>CH$_2$CH$_2$NMe$_2$ (84%)</td>
</tr>
<tr>
<td>Tertiary Amine Oxidation$^{18}$</td>
<td>CH$_2$CH$_2$NMe$_2$</td>
<td>H$_2$O$_2$, MeOH, H$_2$O</td>
<td>CH$_2$CH$_2$N(O)Me$_2$</td>
</tr>
<tr>
<td>Cope Elimination$^{18}$</td>
<td>CH$_2$CH$_2$N(O)Me$_2$</td>
<td>160-170 °C</td>
<td>CH=CH$_2$ (79% from tetraamine)</td>
</tr>
<tr>
<td>Alkene Bromination$^{18}$</td>
<td>CH=CH$_2$</td>
<td>Br$_2$, CCl$_4$</td>
<td>CH(Br)CH$_2$Br (80%)</td>
</tr>
<tr>
<td>Acetylene Synthesis$^{18}$</td>
<td>CH(Br)CH$_2$Br</td>
<td>KOH, triglyme, 160 °C, 30 mm</td>
<td>C=CH = 9 (18%)</td>
</tr>
</tbody>
</table>
Scheme 2. Naemura four-directional synthesis of the adamantane derivative 10.

There are fewer examples known for four-directional conversion of adamantanes 6 into adamantanes 7 by carbon-carbon bond construction at sp$^3$ centers. These are illustrated in Table 2. The de Meijere conversion of tetra-alkene 11 to tetracyclopropyl-adamantane 12 (91%) using diazomethane with a palladium catalyst (Scheme 3) is particularly relevant to this work.$^{17}$

Table 2. Four-directional synthesis by carbon–carbon construction or change at sp$^3$ centers

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Substituent X</th>
<th>Reagent</th>
<th>Substituent Y (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromide Photosubstitution$^6$</td>
<td>Br</td>
<td>hν, NaCN, DMSO</td>
<td>CN (73%)</td>
</tr>
<tr>
<td>Wittig Reaction$^{17}$</td>
<td>CHO</td>
<td>Ph$_3$P=CH$_2$</td>
<td>CH=CH$_2$ (82%)</td>
</tr>
<tr>
<td>Friedel Crafts Acylation$^5$</td>
<td>COCl</td>
<td>PhH, AlBr$_3$</td>
<td>COPh (42%),</td>
</tr>
<tr>
<td>Friedel Crafts Alkylation$^5$</td>
<td>Br</td>
<td>PhH, AlBr$_3$</td>
<td>Ph (77%),</td>
</tr>
<tr>
<td>Friedel Crafts Alkylation$^{27}$</td>
<td>OH</td>
<td>MeOC$_6$H$_5$, TsOH</td>
<td>4-MeOC$_6$H$_5$ (68%)</td>
</tr>
<tr>
<td>Arene Oxidative Degradation$^{27}$</td>
<td>4-MeOC$_6$H$_5$</td>
<td>RuCl$_3$, H$_3$IO$_6$, SOCl$_2$, MeOH</td>
<td>CO$_2$Me (42%)</td>
</tr>
<tr>
<td>Tertiary Alcohol Synthesis$^{28}$</td>
<td>CO$_2$Me</td>
<td>PhLi, Et$_2$O, 0 °C</td>
<td>C(OH)Ph$_2$ (78%)</td>
</tr>
</tbody>
</table>
In this paper, four directional syntheses of the chiral tetracyclopropyl-tetra-aldehyde 14 and the tetra-β-keto-esters 15 from 1,3,5,7-tetra-hydroxymethyl-adamantane (13) are described (Scheme 4). In addition, the conversion of tetra-aldehyde 14 into the derived tetra-4-toluenesulfonylhydrazone and tetra-β-keto-esters 15 into the derived tetra-α-diazo-β-keto-esters as potential carbene precursors are outlined. Related transformations of adamantanes bearing one cyclopropane-carboxaldehyde residue and one and two α-diazo-β-keto-ester residues are described. Such studies may be relevant to the synthesis of diamondoid hydrocarbons.29

**Scheme 3.** de Meijere four-directional synthesis of tetracyclopropyl-adamantane 12.

**Scheme 4.** Conversion of tetraol 13 into tetra-aldehyde 14 and tetra-β-keto-ester 15 (this work).

### Results and Discussion

**Four-directional homologation of 1,3,5,7-adamantanetetracarboxylic acid derivatives**

Tetramethyl 1,3,5,7-adamantanetetracarboxylate (18) was synthesized from 1,3-adamantanedicarboxylic acid (16) by a modification of Bashir-Hashemi and Li’s method.30 Since dicarboxylic acid 16 is of low solubility in oxalyl chloride, the dicarboxylic acid 16 was first converted into the more soluble dichloride 17 with thionyl chloride. This was dissolved in oxalyl chloride and irradiated at 20 °C using a medium pressure mercury-vapor lamp (450 Watts) in a quartz vessel to provide, on methanolysis, the tetra-ester 18 in variable yield (25% on a 10 g scale to 43% on a 2 g scale) depending on the efficiency of irradiation decreasing with scale. Reduction of tetra-ester 18 using lithium aluminum hydride gave the corresponding tetraol 13 (91%). Attempted oxidation of the tetraol 13 to the corresponding tetra-aldehyde 19 was complicated due to its poor solubility in non-
polar solvents. Nonetheless it was soluble in solvents such as MeOH, THF or DMSO. Dess-Martin oxidation of tetraol 13 (50 mg scale) in a mixed-solvent system (dichloromethane/DMSO, 2:1), which was necessary to dissolve the substrate, gave tetra-aldehyde 19 (45%, 40 mg scale) but this yield was not reproducible on a larger scale (32%, 80 mg scale). Swern oxidation of tetraol 13 in the same mixed-solvent system (dichloromethane/DMSO)\textsuperscript{17} gave tetra-aldehyde 19 in a significantly better yield (70%, 1 g scale).

\(\text{(Z)-Selective Horner-Emmons reaction of tetra-aldehyde 19 under Still-Gennari conditions}^{32} \text{ at } \) -78 °C \(\text{ provided an inseparable mixture of the desired product 20 and the incomplete olefination products, however reaction at } -20 \degree \text{C gave the tetra-alkene 20 as the sole product in 64% yield. From } 3^\text{H} \text{ NMR spectroscopy, the coupling constant between two olefinic protons was } J 13.1 \text{ Hz, which is consistent with all four alkenes possessing the } \text{cis} \text{ geometry}.^{33} \text{ Finally, DIBAI-H reduction of tetra-ester 20 gave the tetra-(Z)-allylic alcohol 21 in excellent yield (98%) (Scheme 5). The } \text{cis}-\text{geometry and constitution were unambiguously confirmed by a single crystal X-ray structure determination (see Supplementary Material: Appendix-1).}

\[\text{Scheme 5. Synthesis of tetraol 21 using photochemical substitution and (Z)-selective Horner-Emmons reaction}\]

The tetra-(Z)-allylic alcohol 21 was of low solubility and this caused significant problems in attempted tetra-cyclopropanation reactions. Prolonged reactions using samarium amalgam or samarium(II) iodide with diiodomethane or chloroiodomethane\textsuperscript{34} failed to provide any identifiable cyclopropanated products. Additionally, the tetra-(Z)-allylic alcohol 21 was recovered unchanged on attempted tetra-cyclopropanation using the Charette’s procedure.\textsuperscript{35} Although, in this reaction, the tetra-(Z)-allylic alcohol 21 has very low solubility in the solvent CH\textsubscript{2}Cl\textsubscript{2}, it was anticipated that the intermediate zinc-alkoxide species formed from Zn(CH\textsubscript{2}I\textsubscript{2})\textsubscript{2} and tetraol 21 would result in desymmetrization and enhanced solubility. This proved incorrect and the Charette reaction gave only unreacted starting material. Attempted transient desymmetrization of tetra-(Z)-allylic alcohol 21 by alkoxide exchange using trimethyl borate and subsequent Charette reaction also gave unreacted tetraol 21.
Since direct cyclopropanation of tetra-cis-alkene 21 had failed to produce any desired tetra-cyclopropane, the corresponding reactions with allylic alcohol 25 were examined to underscore that the failure in the tetracyclopropanation reaction was solely due to poor solubility. Thus, Swern oxidation of commercially available 1-adamantanemethanol (22) gave rise to aldehyde 23 (82%). This product 23 was subject to the (Z)-selective Horner-Emmons olefination of aldehyde 23 under Still-Gennari conditions, which provided the desired cis-olefin 24 in low but unoptimized yield (30%), owing to the low solubility of 23 in THF. DIBAI-H reduction of ester 24 gave allylic alcohol 25 (90%), which smoothly underwent Charette cyclopropanation to produce the cyclopropyl alcohol 27 (87%). Oxidation of alcohol 27 by Dess-Martin periodinane gave the corresponding aldehyde 28 (Scheme 6). These results clearly indicated that the failure in our attempted tetracyclopropanation of tetra-cis-alkene 21 under Charette conditions was only the result of low solubility.

**Scheme 6.** Synthesis of cyclopropane 28 using (Z)-selective Horner-Emmons and Charette Cyclopropanation.

In order to overcome the reactivity issues with the four-directional approach, desymmetrization and a three-directional strategy was examined. Mono-protection of tetraol 21 with t-butyldiphenylsilyl chloride in pyridine at room temperature gave the mono-silyl derivative 29 (44%, 66% allowing for 33% recovered starting material). To our delight, triol 29 was soluble in dichloromethane and smoothly underwent triple Charette cyclopropanation to produce tricyclopropane 30 (90%) and this was desilylated using tetra-n-butylammonium fluoride in THF to give the tetraol 31 (94%) (Scheme 7). Unfortunately, this tetraol 31 being insoluble in dichloromethane was inert to the Charette reagent.
Scheme 7. Synthesis and three directional Charette enantioselective cyclopropanation of triol 29.

This solubility problem associated with tetraol 31 was circumvented by triple pivaloylation. Thus, acylation of triol 30 with pivaloyl chloride in pyridine gave the triester 32 (95%), which was desilylated to give the allylic alcohol 33 (95%). Charette cyclopropanation of the dichloromethane soluble allylic alcohol 33 gave the tetra-cyclopropane 34 (63%). Finally, the key intermediate tetra-syn-cyclopropyl alcohol 35 (90%) was obtained by DIBAL-H reductive deacylation of the tri-pivaloate 34 (Scheme 8). The constitution of the tetra-syn-cyclopropyl alcohol 35 was confirmed by a single crystal X-ray structure determination (see Supplementary Material: Appendix-2). We were unable to define the absolute stereochemistry due to the lack of heavy atoms in the molecule. Perhaps unsurprisingly, the structure is disordered and actually shows an inversion of chirality in one of the four cyclopropyl arms. The figures in Appendix-2 show both diastereoisomers individually and overlapped, with the major diastereoisomer 35A being ca. 64% occupancy, and the minor diastereoisomer 35B ca. 36% occupancy and with each diastereoisomer possessing greater than 95% optical purity. Presumably, the final cyclopropanation reaction showed significantly lower diastereoselectivity than expected with the Charette chiral boronate 26 additive and/or recrystallization enhanced the percentage of the minor diastereoisomer. The $^{13}$C NMR spectrum of the tetraol 35 did not show any duplication of any peaks.
Scheme 8. Completion of the synthesis of target tetra-syn-cyclopropyl alcohol 35.

Swern oxidation of tetraol 35 was carried out in DMSO and dichloromethane solution due to poor solubility in dichloromethane alone. This gave the tetra-aldehyde 14 and subsequent condensation with p-toluenesulfonylhydrazine gave the derived tetra-tosylhydrazone 36 (82%) (Scheme 9). Attempts to generate tetra-carbene C–H insertion or fragmentation products from the tetra-tosylhydrazone 36 by conversion to the derived tetra-potassium salt, generated with either potassium tert-butoxide or potassium hexamethyldisilazide, and aprotic Bamford Stevens thermolysis at 138 °C or reaction with dirhodium tetraacetate in the presence of the phase transfer catalysts benzyltriethylammonium chloride or 18-crown-6\(^{36}\) in dioxane or dichloromethane gave only intractable materials. Evidence for the formation of potassium salt from tetra-tosylhydrazone 36 was seen in the IR spectum with shifts of the sulfone stretches from 1332 and 1162 cm\(^{-1}\) to 1228 and 1126 cm\(^{-1}\) on reaction with the two bases.

Four-directional homologation of 1,3,5,7-adamantanetetraacetic acid derivatives

In the light of the difficulties with the four-directional reactions to synthesize the adamantane derivatives 35 and 14, studies on four-directional rhodium catalyzed C–H insertion reactions of adamantanes functionalized with four tertiary α-diazo-β-keto-ester units were carried out. Three model adamantane systems with one α-diazo-β-keto-ester unit and two α-diazo-β-keto-ester units were also synthesized. The known aldehyde 38 was synthesized from the commercially available alcohol 37 by Swern oxidation. Interestingly, upon standing overnight at room temperature, the aldehyde 38 underwent hydration to give the corresponding geminal diol very easily. Therefore aldehyde 38 was used in the next step immediately following its purification. Treatment of freshly prepared aldehyde 38 with ethyl diazoacetate in the presence of a catalytic amount of tin(II) chloride smoothly gave β-keto-ester 39a as a 4:1 mixture of enol and keto tautomers. Finally, diazo transfer reaction of β-keto ester 39a with 4-acetamidobenzenesulfonyl azide (40) gave the α-diazo-β-keto-ester 41a (99%). The aldehyde 38 was converted by the same method via β-keto-ester 39b (61%) into the α-diazo-β-keto-ester 41b (90%) (Scheme 10).

Scheme 10. Syntheses of α-diazo-β-keto-esters 41.

The commercially available di-carboxylic acid 42 was reduced to the corresponding diol 43 (74%) using lithium aluminum hydride. Swern oxidation of diol 43 gave dialdehyde 44, which was allowed to react with tert-butyl diazoacetate in the presence of tin(II) chloride to give the di-β-keto ester 45 (75%). The diazo transfer reaction was used again to convert di-β-keto ester 45 to the desired di-α-diazo-β-keto-ester 46 (Scheme 11).

Dirhodium tetraacetate catalyzed carbene insertion of α-diazo-β-keto-esters 41a and 41b proceeded smoothly at room temperature to generate the cyclized products 47a (90%) and 47b (91%) both as single undetermined racemic stereoisomers. Respective Krapcho deethoxycarbonylation$^{41}$ and TFA catalyzed t-butyl ester cleavage and decarboxylation in chlorobenzene at 120 °C gave the same fused cyclopentanone 49$^{42}$ (90 and 99% respectively). Alternatively, TFA catalyzed t-butyl ester cleavage in dichloromethane at room temperature gave the β-keto-carboxylic acid 48 (99%) and this smoothly gave the fused cyclopentanone 49 (82%) on reflux in 1,4-dioxane (Scheme 12).

Scheme 12. Rhodium catalyzed C−H insertion reactions of α-diazo-β-keto-esters 41 and synthesis of ketone 49.

Double dirhodium tetraacetate catalyzed carbene insertion of di-α-diazo-β-keto-ester 46 gave the doubly cyclized product 50 (52%) along with minor unidentified by-products. Subsequent de-t-butylation and decarboxylation catalyzed by TFA in chlorobenzene at 115 °C proceeded smoothly and gave the di-cyclopentanone 51 (97%) as an unidentified racemic stereoisomer (Scheme 13). It should be noted that
there are many possible stereo- and regio-isomers arising from the double carbene insertion reaction of di-α-diazo-β-keto-ester 46. For example, the final diketone 51 could either have the syn-51 and/or the anti-51 constitution and each of these could have the meso- and/or (±)-stereochemistry (Figure 1).

![Scheme 13. Rhodium catalyzed C–H insertion reactions of α-diazo-β-keto-ester 46 and synthesis of dione 51.](image)

**Scheme 13.** Rhodium catalyzed C–H insertion reactions of α-diazo-β-keto-ester 46 and synthesis of dione 51.

**Figure 1.** Possible isomers of ketone 51.

Wittig reaction\textsuperscript{17} of tetra-aldehyde 19 with excess of methoxymethyl-triphenylphosphonium chloride and sodium hexamethyldisilazane gave tetra-enol ether 52 (79%) as a mixture of (E)- and (Z)-olefins. Hydrolysis using triflic acid in aqueous dichloromethane and iso-propanol gave the tetra-aldehyde 53 (60%). The yield of tetra-aldehyde 53 was inferior if the intermediate enol ether 52 was not isolated due to greater difficulty in purification. Pinnick oxidation\textsuperscript{43} of tetra-aldehyde 53 smoothly gave the desired tetra-acid 54a (83%), which was converted \textit{via} the tetra-acyl chloride (IR 1802 cm\textsuperscript{-1}) into the tetramethyl ester 54b (42%). Attempts to convert the tetra-acid 54a \textit{via} its derived tetra-acyl chloride or via its tetra-mixed anhydride with ethyl chloroformate to the derived tetra-diazo-ketone by reaction with diazomethane gave only intractable mixtures of products. In contrast tetra-aldehyde 53 was smoothly converted into the tetra-β-keto-ester 15a (82%), which was obtained as a mixture of enol and keto-tautomers (ca 3 : 1), by reaction with ethyl diazoacetate in the presence of tin(II) chloride\textsuperscript{38} and subsequently into the tetra-α-diazo-β-keto-ester 55a (97%) by diazo transfer from 4-acetamidobenzenesulfonyl azide (40).\textsuperscript{39} In the same way, the tetra-aldehyde 53 was readily converted into the tetra-β-keto-ester 15b (81%), which was obtained as a mixture of enol and keto-tautomers (ca 4 : 1), and thence into the tetra-α-diazo-β-keto-ester 55b (99%) (Scheme 14).

A range of catalysts were examined for the attempted quadruple C−H insertion reaction of tetra-α-diazo-β-keto-ester 55a. Reactions using dirhodium tetraacetate in dilute solution (0.01 M) in dichloromethane at room temperature, copper sulfate or copper iodide in toluene at room temperature or reflux all were unsuccessful. In contrast, catalysis using dirhodium tetra-carboxylate (acetate, trifluoroacetate, perfluorobutyrate, octanoate) salts at reflux in toluene or trifluoromethylbenzene gave an isolable fraction by chromatography that may have contained carbene insertion products. For example, catalysis with dirhodium tetra-octanoate in toluene at reflux with slow addition of the tetra-α-diazo-β-keto-ester 55a gave a complex product mixture that may have contained the tetra-β-keto-ester 56a. The $^1$H and $^{13}$C NMR spectra of the product was complex presumably due to the presence of multiple isomers and the molecular ion could not be detected in the mass spectrum, although the IR spectrum was consistent with the presence of ester and keto-carbonyl groups (keto-ester 47a at 1755 and 1724 cm$^{-1}$ and tetra-β-keto-ester 56a at 1753 and 1725 cm$^{-1}$). Attempted Krapcho deethoxycarbonylation$^{41}$ of the product mixture failed to produce identifiable products.
Reaction of the tetra-α-diazo-β-keto-ester 55b with dirhodium tetra-octanoate in toluene (0.01M) at reflux with slow addition of the substrate gave a complex product mixture that may have contained the tetra-β-keto-ester 56b. Again, this structural assignment was tentative since the \(^1\)H and \(^13\)C NMR spectra of the product was complex presumably due to the presence of multiple isomers and the molecular ion could not be detected in the mass spectrum, although the IR spectrum was consistent with the presence of an ester and keto-carbonyl groups (1747 and 1722 cm\(^{-1}\)) (Scheme 15). Attempted global de-t-butylation and decarboxylation catalyzed by TFA using the one step or two step methods in Scheme 12, failed to provide any isolable material although the t-butyl esters were cleaved.

\[
\begin{align*}
55a \quad (R = \text{Et}) \\
55b \quad (R = \text{t-Bu})
\end{align*}
\]

**Scheme 15.** Attempted syntheses of tetra-β-keto-esters 56.

**Synthesis of and Dimerization of Adamantanocyclopentadiene 59**

Ketone 49 was synthesized by the methods in Scheme 12 and additionally by sequential reaction of 1-adamantanecacetic acid with thionyl chloride, diazomethane in diethyl ether and copper sulfate in toluene at reflux.\(^{42}\) Conversion to the cyclopentenone 57 was carried out in modest yield (23\% with 32\% recovery of starting material) by enol silane formation with lithium 2,2,6,6-tetramethylpiperidine (LiTMP), trimethylsilyl chloride and triethylamine and Saegusa oxidation with palladium acetate. DIBAl-H reduction of the cyclopentenone 57 at \(-78 \, ^\circ\)C gave the allylic alcohol 58 (90\%) and this delicate compound underwent complete dehydration, presumably DCI catalyzed, in deuterated chloroform over 2 hours during the recording of NMR spectra to produce diene 59 (82\% isolated yield) (Scheme 16).

\[
\begin{align*}
\text{1. LiTMP, THF, Et}_3\text{N, Me}_3\text{SiCl, -78 to 25 } ^\circ\text{C} \\
\text{2. Pd(OAc)}_2, \text{MeCN 23\%}
\end{align*}
\]

\[
\begin{align*}
57 \xrightarrow{\text{DIBAI-H, THF, -78 } ^\circ\text{C}} 58 \xrightarrow{\text{CDCl}_3, 2 \text{ h}} 59
\end{align*}
\]

**Scheme 16.** Synthesis and reactions of cyclopentadiene derivative 59.
Diene 59 underwent a Diels-Alder reaction with maleic anhydride (60) to produce the adduct 61 (23% unoptimized). Whilst diene 59 did not undergo dimerization by a self-Diels-Alder reaction on standing for 23 days, it did undergo an alternative dimerization reaction in the presence of tris(p-bromophenyl)aminium hexachloroantimonate (62), a known SET acceptor for mediating Diels-Alder reactions via diene cation radicals. Of particular interest in this context is the known Diels-Alder rapid dimerization of 1,3-cyclohexadiene mediated by an SET pathway with aminium cation radical modulators, although 1,3-cyclohexadiene is known not to be normally reactive towards such self-Diels-Alder reactions below 200 °C. Attempted SET-Diels-Alder reaction of diene 59 gave an adduct that was assigned as dimer 63 (40%). Clearly a product this unexpected requires some further discussion with regard to its assignment.

The proposed structure 63 was elucidated based on the following key facts and explanations: (1) the dimer 63 has the molecular formula of C26H32 as confirmed by MS and high resolution MS; (2) there are three vinyl protons (δ 6.30, 5.93, 5.21 ppm) in the 1H NMR spectrum; (3) there are three quaternary olefinic carbons (δ 162.2, 157.9 and 153.0 ppm) and three tertiary olefinic carbons (δ 123.9, 117.4, 114.6 ppm) in 13C NMR and 13C DEPT spectra (see Supplementary Material: Appendix-3); (4) there are two adjacent vinyl protons (δ 6.30 and 5.93 ppm), which are correlated to each other have the coupling constant of 1.9 Hz in the 1H NMR and 1H COSY spectra and this coupling constant is consistent with bonding B and not bonding A below (Figure 2); (5) there are three relatively low-field proton signals (δ 3.74 ppm, 2.98 ppm and 2.75 ppm) and these protons must be positioned next to a carbon-carbon double bond (H_D, H_E and H_F in the structure 63 in Scheme 16); (6) there is one proton (δ 3.72 ppm) next to a carbon-carbon double bond has the correlation with one vinyl proton and two protons in a CH2 unit from the 1H COSY and 1H/13C correlation spectra (see Appendix-3) (H_E in the structure 63 in Scheme 16); (7) the λ_max in the UV spectrum is at 262 nm (log ε) 262 (3.76) is inconsistent with the alkene and cyclopentadiene units being in conjugation since 1,4,5,5-tetramethylcyclopentadiene shows a λ_max of 258 nm and if the third double bond was conjugated with the cyclopentadiene unit, the absorption maximum should be significantly red shifted. In spite of these considerations, the structural assignment for the dimer 63 must, in the absence of an X-ray crystallographic structure determination, be considered tentative.

Conclusions

It is clear that not all transformations are readily amenable to four-directional synthesis of adamantane derivatives either for issues of low solubilities and/or the formation of multiple products. Nonetheless, (Z)-selective Horner-Emmons reaction of tetra-aldehyde 19 under Still-Gennari conditions, DIBAI-H reduction of tetra-ester 20, Wittig reaction of tetra-aldehyde 19 with methoxymethyleneetriphenylphosphorane and
subsequent Pinnick oxidation of the derived tetra-aldehyde 53, Roskamp coupling of condensation of tetra-aldehyde 53 with both ethyl and t-butyl diazoacetate and conversions of the derived β-keto-esters 15a and 15b with 4-acetamidobenzesulfonyl azide (40) to produce the α-diazo-β-keto-esters 55a and 55b all worked well in a four-directional sense. Although, three-directional Charette enantioselective cyclopropanation of triol 29 was successful, the equivalent four-directional reaction on tetraol 21 failed due to low solubility. Whilst one-directional rhodium catalyzed C–H insertion of the carbene derived from α-diazo-β-keto-esters 41a and 41b and two-directional rhodium catalyzed C–H insertion of the carbenes derived from the di-α-diazo-β-ketoester 46 all gave adamantane-cyclopentanone annulation products 47a, 47b and 50 and thence 48, 49, 50 and 51, related four-directional carbene reactions gave only intractable mixtures. The adamantane cyclopentadiene 59 underwent dimerization to the adduct 63 and not to the Diels-Alder product.

**Experimental Section**

**General.** Melting points were obtained on a hot stage melting point apparatus and are uncorrected. Infrared spectra were recorded as thin films on sodium chloride plates with absorptions reported in wavenumbers (cm⁻¹). ¹H NMR spectra were recorded at 300 MHz, 400 MHz and 500 MHz with chemical shifts (δ) quoted in parts per million (ppm) and referenced to the residual solvent peak, 7.27 for CDCl₃, 7.15 for C₆D₆, 3.34 for methanol-d₄, 2.52 for DMSO-d₆. ¹³C NMR spectra were recorded at 75 MHz, 100 MHz and 125 MHz with chemical shifts (δ) quoted in parts per million (ppm) and referenced to the residual solvent peak, 77.0 for CDCl₃, 128.6 for C₆D₆, 49.9 for methanol-d₄, 39.7 for DMSO-d₆. Coupling constants (J) are quoted in Hertz (Hz) for both ¹H and ¹³C NMR spectra.

All reactions were carried out in oven or flame-dried glassware under an inert atmosphere of nitrogen or argon. Reaction temperatures other than room temperature were recorded as bath temperatures unless otherwise stated. CH₂Cl₂, MeOH, pyridine and Et₃N were distilled from calcium hydride under a nitrogen atmosphere. Et₂O and THF were distilled from sodium benzophenone ketyl under a nitrogen atmosphere. PhMe was distilled from sodium under a nitrogen atmosphere. Column chromatography was performed on silica gel 60, particle size 20-63 μm or particle size 33-70 μm. TLC was performed on silica gel 60 F₂₅₄ glass-backed plates with visualization under ultraviolet light 254 nm and/or by chemical staining using a potassium permanganate dip and drying with a heat gun.

**Tetramethyl 1,3,5,7-Adamantanetetracarboxylate (18).** 1,3-Adamantanedicarboxylic acid 16 (10.0 g, 44.6 mmol) and freshly distilled thionyl chloride (60 mL) were heated at reflux with vigorous stirring for 2 h and the excess thionyl chloride was removed in vacuo. The mixture was cooled to room temperature and dry PhH (50 mL) was added which was further removed in vacuo to give an off-white solid, which was stored under vacuum for 12 h to leave crude 1,3adamantanedicarbonyl chloride 17 (11.7 g) as an off-white solid. This material showed spectroscopic data consistent with the reported values.³¹ 1,3-Adamantanedicarbonyl chloride 17 (11.7 g, 44.6 mmol) in oxalyl chloride (130 mL) was irradiated at 20 °C by a medium pressure mercury-vapor lamp (450 Watts) immersed into a double-walled quartz well with inlet and outlet tubes for cooling. The reaction vessel constructed of glass was placed outside the immersion well with one vertical joint for the condenser. After 16 h of irradiation, the excess oxalyl chloride was removed on a rotary evaporator and the residue was stirred with dry MeOH (80 mL) at room temperature overnight. The mixture was concentrated in vacuo, the oily residue was dissolved in EtOAc (100 mL), washed with 5% aqueous Na₂CO₃ (30 mL) and brine (30 mL) and the organic layer was dried (MgSO₄), and concentrated in vacuo. The residue was
triturated with the minimal amount of MeOH and the solid filtered off and dried under vacuum to give tetraester 18 (4.2 g; 25%, over 2 steps) as colorless crystals: mp 167 - 168 °C (hexanes : EtOAc, 5 : 1) (lit. mp 168 - 170 °C); Rf 0.36 (hexanes : EtOAc, 2 : 1); IR (film) 1725, 1429, 1306 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 3.69 (s, 12H, OCH₃), 1.99 (s, 12H, CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 175.5, 52.1, 41.7, 38.5; MS (ES) m/z 369 (M + H⁺); HRMS (ES) m/z calc for C₁₈H₂₅O₈ 369.1549, found: 369.1559.

1,3,5,7-Tetrakis(hydroxymethyl)adamantane (13).¹⁸ Tetra-ester 18 (3.0 g, 8.15 mmol) in THF (40 mL) was added dropwise with stirring to a suspension of LiAlH₄ (1.24 g, 32.6 mmol) in THF (32 mL) at 0 °C under argon. The mixture was heated at reflux for 3 h, cooled and saturated aqueous Na₂SO₄ (2.43 mL) was added carefully to quench the reaction. After 30 min, THF (40 mL), MeOH (40 mL) and silica gel (2.0 g) were added, and the mixture was filtered through a short pad of Celite. Rotary evaporation and flash chromatography (CH₂Cl₂ : MeOH, 10:1 to 8:1) to give tetaol 13 (1.90 g, 91%) as a white solid: mp 226 - 228 °C (MeOH) (lit. mp 231 - 232 °C); Rf 0.36 (CH₂Cl₂ : MeOH, 4 : 1); IR (film) 3323 broad, 2919, 2851, 1576 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.34 (s, 4H, CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 75.1, 52.1, 41.7, 38.5; MS (ES) m/z 182 (M + H⁺); HRMS (ES) m/z calc for C₁₃H₂₂O₄ 182.1651, found: 182.1646.

1,3,5,7-Adamantanetetracarboxaldehyde (19).¹⁷ Anhydrous DMSO (4.66 mL, 65.7 mmol) in CH₂Cl₂ (12 mL) was added over 10 min with vigorous stirring to oxalyl chloride (2.82 mL, 32.9 mmol) in CH₂Cl₂ (18 mL) at −78 °C. After 15 min, tetraol 13 (990 mg, 3.87 mmol) in anhydrous DMSO (15 mL) and CH₂Cl₂ (30 mL) was added dropwise over 10 min, and the reaction mixture was stirred at −78 °C for 1 h. Et₃N (22 mL) was added dropwise with stirring, the mixture was allowed to warm up to room temperature, H₂O (60 mL) was added and the two phases were separated. The organic layer was washed with 5% aqueous HCl (20 mL), H₂O (20 mL), 5% aqueous NaHCO₃ solution (40 mL) and brine (20 mL), dried (MgSO₄), concentrated in vacuo and the residue chromatographed (hexanes : EtOAc : MeOH, 1 : 1) to afford the tetra-aldehyde 19 (670 mg, 70%) as a white solid: Rf 0.26 (hexanes : EtOAc : MeOH, 1 : 1 : 0.2); mp 142 - 144 °C (EtOAc) (lit. mp 143 - 145 °C); IR (film) 2935, 2856, 1719, 1449 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.51 (s, 4H, CHO), 1.79 (s, 12H, CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 201.8, 44.8, 33.7; MS (EI) m/z 248 (M⁺); HRMS (EI) m/z calc for C₁₄H₁₆O₄ 248.1049, found: 248.1054.

Tetramethyl 3,3',3'',3'''-(Adamantane-1,3,5,7-tetrayl)(2Z,2'Z,2''Z,2'''Z)-tetraacrylate (20). KN(TMS)₂ in PhMe (0.5 M; 4.26 mL, 2.13 mmol) was added dropwise with stirring to 18-crown-6 (2.80 g, 10.6 mmol) and bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphonate (762 mg, 2.40 mmol) in THF (3 mL) at −78 °C. After 30 min, tetra-aldehyde 19 (66 mg, 0.266 mmol) in THF (4 mL) was added and the mixture was allowed to warm up to −20 °C over 2.5 h, when reaction was quenched with saturated aqueous NH₄Cl (5 mL). The separated aqueous layer was extracted with EtOAc (3 x 8 mL) and the combined organic layers were washed with brine, dried (MgSO₄), concentrated in vacuo and the residue chromatographed (hexanes : EtOAc : MeOH, 8 : 1) to give the tetra-ester 20 (80 mg, 64%) as a thick oil: Rf 0.57 (hexanes : EtOAc, 2 : 1); IR (film) 2951, 2920, 1726 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.85 (d, J 13.1 Hz, 4H, CH=CHO₂Me), 5.70 (d, J 13.1 Hz, 4H, CH=CHO₂Me), 3.72 (s, 12H, OCH₃), 1.97 (s, 12H, CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 168.8, 153.6, 119.3, 51.4, 42.0, 37.8; MS (EI) m/z 472 (M⁺); HRMS (EI) m/z calc for C₂₅H₃₂O₈ 472.2097, found: 472.2101.

1,3,5,7-Tetra-(3-hydroxy-(1Z)-propenyl)adamantane (21). DIBAL-H in hexanes (1.0 M; 1.67 mL, 1.67 mmol) was added dropwise with stirring over 5 min to tetra-ester 20 (79 mg, 0.167 mmol) in CH₂Cl₂ (3 mL) at −78 °C. After 1 h, reaction was carefully quenched by the dropwise addition of saturated aqueous NH₄Cl (0.30 mL), i-
PrOH (5 mL), silica gel (0.2 g) and Celite (0.2 g). The mixture was allowed to warm to room temperature and filtered and the solids were washed with CH₂Cl₂/i-ProH (2:1). Rotary evaporation of the combined filtrates and chromatography (CH₂Cl₂ : MeOH, 16 : 1 to 12 : 1) to give the tetra-allylic alcohol 21 (78 mg, 98%) as a solid. Colorless crystals of tetraol 21 were obtained by crystallization from MeOH/PhMe (1:1) at 4 °C: Rf 0.25 (CH₂Cl₂ : MeOH, 8 : 1); mp 114 - 116 °C (MeOH : toluene, 1 : 1); IR (film) 3556, 2922, 2851 cm⁻¹; ¹H NMR (300 MHz, MeOH-d₄) δ 5.41 (dt, J 12.4, 6.2 Hz, 4H, CH=CH₂OH), 5.22 (d, J 12.4 Hz, 4H, CH=CH₂OH), 4.30 (dd, J 6.2, 1.5 Hz, 8H, CH₂OH), 1.65 (s, 12H, CH₂). ¹³C NMR (75 MHz, MeOH-d₄) δ 141.0, 131.2, 60.5, 48.2, 39.8; MS (Cl, NH₃) m/z 378 (M + NH₄⁺). Anal. calc for C₂₂H₃₃O₄: C, 76.44; H, 7.90. Found: C, 76.37; H, 8.03.

**Methyl (Z)-3-(Adamantan-1-yl)acrylate (24).** KN(TMS)₂ in PhMe (0.5 M; 7.32 mL, 3.66 mmol) was added dropwise with stirring to 18-crown-6 (4.83 g, 18.3 mmol) and bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl) phosphate (1.28 g, 4.02 mmol) in THF (4 mL) at −78 °C. After 30 min, aldehyde 23 (300 mg, 1.83 mmol) in THF (10 mL) was added with stirring and, after further stirring at −78 °C for 1 h, 0 °C for 2 h and room temperature for 2 h, reaction was quenched with saturated aqueous NH₄Cl (20 mL). The separated aqueous layer was extracted with EtoAc (3 x 25 mL) and the combined organic layers were washed with brine (30 mL), dried (MgSO₄), concentrated in vacuo and the residue chromatographed (hexanes : EtOAc, 50 : 1) to give the methyl ester 24 ⁴⁶ (116 mg, 30%) as a colorless oil: Rf 0.46 (hexanes : EtoAc, 15 : 1); IR (film) 2904, 2849, 1729, 1194 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.78 (d, J 13.2 Hz, 1H, CH=CHCO₂Me), 5.65 (d, J 13.2 Hz, 1H, CH=CHCO₂Me), 3.72 (s, 3H, OCH₃), 1.98 (s, 3H, adamantane methine), 1.86 (d, J 2.1 Hz, 6H, CH₂), 1.71 (s, 6H, CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 167.4, 155.1, 117.9, 51.3, 40.9, 36.6, 36.2, 28.5; MS (El) m/z 220 (M⁺); HRMS (El) m/z calc for C₁₄H₂₀O₂ 220.1463, found: 220.1462.

**[(Z)-3-(Adamantan-1-yl)prop-2-en-1-ol (25).** DIBAL-H in hexanes (1.0 M; 1.16 mL, 1.16 mmol) was added dropwise with stirring to acrylate 24 (102 mg, 0.464 mmol) in CH₂Cl₂ (5 mL) at −78 °C. After 40 min, reaction was quenched with saturated aqueous NH₄Cl (2 mL) and 4 M aqueous HCl (1 mL). The separated aqueous layer was extracted with EtoAc (3 x 10 mL) and the combined organic layers were washed with saturated aqueous NaHCO₃ (20 mL) and brine (20 mL), dried (MgSO₄), concentrated in vacuo and the residue chromatographed (hexanes : EtoAc, 4 : 1) to give the allylic alcohol 25 (79 mg, 90%) as a colorless oil, which was used directly in the next step: Rf 0.58 (hexanes : EtoAc, 2 : 1); IR (film) 3560, 2920, 2854 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.35 (dt, J 12.3, 6.2 Hz, 1H, CH=CH₂), 5.17 (d, J 12.3 Hz, 1H, CH=CHCH₂OH), 4.33 (d, J 6.2 Hz, 2H, CH₂OH), 1.95 (s, 3H, adamantane methine), 1.84 (s, 1H, CH₂OH), 1.72 (s, 6H, CH₂), 1.68 (s, 6H, CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 142.0, 127.4, 59.5, 42.8, 36.6, 35.9, 28.5.

**((1R,2S)-2-(Adamantan-1-yl)cyclopropyl)methanol (27).** CH₂Cl₂ (3 mL) and 1,2-dimethoxyethane (0.182 mL, 1.75 mmol) in a flame-dried flask were cooled to −15 °C and neat Et₂Zn (0.179 mL, 1.75 mmol) was added with stirring. CH₂I₂ (0.282 mL, 3.50 mmol) was added slowly with stirring keeping the internal temperature below −10 °C. After 10 min at −10 °C, dioxaborolane 26 (189 mg, 0.70 mmol) in CH₂Cl₂ (2 mL) was added slowly with stirring while maintaining the internal temperature below −5 °C. Allylic alcohol 25 (112 mg, 0.583 mmol) in CH₂Cl₂ (2 mL) was immediately added to the solution and the mixture allowed to reach and react further at room temperature. After 5 h, reaction was quenched with saturated aqueous NH₄Cl (10 mL), the separated aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL), and the combined organic layers were washed with brine (20 mL), dried (MgSO₄), concentrated in vacuo and the residue chromatographed (hexanes : EtoAc, 7 : 1 → 6 : 1) to give the cyclopropane 27 (104 mg, 87%) as colorless needle crystals: mp 88 - 90 °C (hexanes : EtoAc, 2 : 1); Rf 0.57 (hexanes : EtoAc, 2 : 1); IR (film) 3271 broad, 2891, 2847, 1447 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ
(1R,2S)-2-(Adamantan-1-yl)cyclopropane-1-carboxaldehyde (28). Dess-Martin periodinane (268 mg, 0.631 mmol) was added with stirring to alcohol 27 (100 mg, 0.485 mmol) in CH₂Cl₂ (5 mL). After 1.2 h at room temperature, reaction was quenched with saturated aqueous NaHCO₃ (3 mL) and saturated aqueous Na₂S₂O₃ (3 mL). The mixture was extracted with CH₂Cl₂ (3 x 10 mL) and the combined organic extracts were washed with brine (20 mL), dried (MgSO₄), concentrated in vacuo and chromatographed (hexanes : EtOAc, 14 : 1) to afford the aldehyde 28 (71 mg, 72%) as a colorless oil: Rₓ 0.68 (hexanes : EtOAc, 4 : 1); IR (film) 2902, 2847, 1698 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.29 (d, J = 7.2 Hz, 1H, CHO), 1.97 (s, 3H, adamantane methine), 1.59-1.76 (m, 6H, adamantane methylene), 1.53 (s, 6H, adamantane methylene), 1.16-1.35 (m, 4H, cyclopropane); ¹³C NMR (75 MHz, CDCl₃) δ 200.9, 43.2, 38.0, 36.6, 32.4, 30.2, 28.5, 9.9; MS (EI) m/z 224 (M⁺); HRMS (EI) m/z calc for C₁₄H₂₆NO (M⁺) 224.1514, found: 224.1522.

(2Z,2',Z,2''-Z)-3,3',3''-7-(Z)-3-(( tert-Butyldiphenylsilyl)oxy)prop-1-en-1-yl)adamantane-1,3,5-triyl)tris(prop-2-en-1-ol) (29). DMAP (30 mg, 0.241 mmol) and tBuPh₂SiCl (0.173 mL, 0.663 mmol) were added with stirring to tetra-allylic alcohol 21 (217 mg, 0.603 mmol) in dry pyridine (5 mL). After 41 h at room temperature, reaction was quenched with saturated aqueous NH₄Cl (3 mL) and the aqueous layer was extracted with CH₂Cl₂/i-PrOH (4:1) (4 x 10 mL). The combined organic layers were dried (MgSO₄), concentrated in vacuo, and chromatographed (CH₂Cl₂ : MeOH, 16 : 1 to 12 : 1) to give recovered tetra-allylic alcohol 21 (71 mg, 33%) and the mono-silylated product 29 (160 mg, 44%) as a thick oil: Rₓ 0.48 (CH₂Cl₂ : MeOH, 8 : 1); IR (film) 3350, 2928, 2855 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.69 (d, J = 7.2 Hz, 4H, ArH), 7.42 (m, 6H, ArH), 5.50 (dt, J = 12.3, 5.8 Hz, 1H, CH=CH₂Osii), 5.39 (dt, J = 12.2, 6.0 Hz, 3H, CH=CH₂Osii), 5.15 (dt, J = 12.2 Hz, 3H, CH=CH₂Osii), 5.10 (d, J = 12.3 Hz, 1H, CH=CH₂Osii), 4.37 (d, J = 6.0 Hz, 6H, CH=CH₂Osii), 4.20 (d, J = 5.8 Hz, 2H, CH=CH₂Osii), 4.20 (d, J = 5.8 Hz, 2H, CH=CH₂Osii), 1.73 (s, 3H, CH=CH₂Osii), 1.52 (m, 6H, adamantane methylene), 1.44 (s, 6H, adamantane methylene), 1.05 (s, 9H, tert-butyl); ¹³C NMR (75 MHz, CDCl₃) δ 140.0, 137.9, 135.6, 133.7, 129.7, 129.4, 128.4, 127.7, 60.9, 59.3, 46.0, 45.9, 37.6, 29.7, 26.7, 19.1; the product did not exhibit a molecular ion in the MS.

(Z)- tert-Butyldiphenyl(3-(3,5,7-tri-(1R,2S)-2-hydroxymethyl-1-cyclopropyl)-adamantan-1-yl)allyloxy)silane (30). CH₂Cl₂ (8 mL) and 1,2-dimethoxyethane (0.64 mL, 6.17 mmol) in a flame-dried flask were cooled to −15 °C and neat Et₂Zn (0.63 mL, 6.17 mmol) was added with stirring. CH₂I₂ (0.99 mL, 12.3 mmol) was added slowly with stirring keeping the internal temperature below −10 °C. After 10 min at −10 °C, dioxaborolane 26 (500 mg, 1.85 mmol) in CH₂Cl₂ (3 mL) was added slowly with stirring while maintaining the internal temperature below −5 °C. Allylic alcohol 29 (308 mg, 0.514 mmol) in CH₂Cl₂ (4 mL) was immediately added to the solution and the mixture allowed to reach and react further at room temperature. After 4 h, reaction was quenched with saturated aqueous NH₄Cl (8 mL) and the aqueous layer was extracted with CH₂Cl₂/MeOH (7:1) (4 x 10 mL). The combined organic layers were washed with brine (20 mL), dried (MgSO₄), concentrated in vacuo, and the residue chromatographed (hexanes : EtOAc : MeOH, 1 : 1 : 0.03 to 1 : 1 : 0.05) to give the tricyclop propane 30 (295 mg, 90%) as a colorless oil: Rₓ 0.40 (hexanes : EtOAc : MeOH, 1 : 1 : 0.2); [α]D²² -15.3 (c 0.96, CHCl₃); IR (film) 3366 (br), 2928, 2895, 2855, 1427 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.70 (d, J = 7.3 Hz, 4H, ArH), 7.41 (m, 6H, ArH), 5.48 (dt, J = 12.4, 5.5 Hz, 1H, CH=CH₂Osii), 5.12 (d, J = 12.4 Hz, 1H, CH=CH₂Osii), 4.37 (d, J = 5.5 Hz, 2H, CH=CH₂Osii), 3.78 (dd, J = 11.0, 7.5 Hz, 3H, CH₂OH), 3.50 (dd, J = 11.0, 8.6 Hz, 3H, CH₂OH), 2.03
(s, 3H, CH2OH), 1.24 (s, 6H, adamantane methylene), 1.17 (s, 6H, adamantane methylene), 1.05 (s, 9H, tert-butyl), 1.00 (m, 3H, cyclopropane methine), 0.55 (m, 6H, cyclopropane methylene), 0.16 (m, 3H, cyclopropane methine); 13C NMR (75 MHz, CDCl3) δ 138.8, 135.6, 133.8, 129.6, 128.8, 127.6, 63.3, 61.1, 46.9, 46.7, 37.8, 34.2, 28.9, 26.7, 19.2, 19.1, 4.6; MS (Cl, NH3) m/z 658 (M + NH4+). Anal. calc for C41H56O4Si: C, 76.83; H, 8.81. Found: C, 76.77; H, 8.90.

1-((1Z)-3-Hydroxy-1-propenyl)-((3-(3,5,7-tri-(1R,2S)-2-hydroxymethyl-1-cyclopropyl)adamantane (31).

Bu4NF in THF (1.0 M; 0.233 mL, 0.233 mmol) was added with stirring to allylic alcohol 30 (136 mg, 0.212 mmol) in THF (3 mL) at room temperature. After 24 h, reaction was quenched with H2O (2 mL) and the separated aqueous layer was extracted with CH2Cl2/i-PrOH (4:1) (4 x 5 mL). The combined organic layers were washed with brine (10 mL), dried (MgSO4), and the residue chromatographed (hexanes : EtOAc : MeOH, 1 : 1 : 0.2) to give the free allylic alcohol 31 (79 mg, 94%) as a colorless oil: Rf 0.32 (CH2Cl2 : MeOH, 8 : 1); [α]D22 16.2 (c 1.03, MeOH); IR (film) 3345 (br), 2995, 2895 cm−1; 1H NMR (300 MHz, CDCl3) δ 5.33 (dt, J 12.4, 6.0 Hz, 1H, CH=CHCH2OH), 5.17 (d, J 12.4 Hz, 1H, CH=CHCH2OH), 4.26 (dd, J 6.0, 1.4 Hz, 2H, CH=CHCH2OH), 3.75-3.62 (m, 6H, cyclopropyl CH2OH), 1.41 (s, 6H, adamantane methylene), 1.27 (s, 6H, adamantane methylene), 1.03 (m, 3H, cyclopropane), 0.67-0.60 (m, 6H, cyclopropane), 0.26 (m, 3H, cyclopropane); 13C NMR (75 MHz, CDCl3) δ 141.9, 130.6, 64.6, 60.7, 46.9, 46.7, 37.8, 34.2, 28.9, 26.7, 19.2, 19.1, 4.6; the product did not exhibit a molecular ion in the MS.

(Z)-tert-Butyldiphenyl((3-(3,5,7-tri-(1R,2S)-2-(pivaloyloxymethyl)-1-cyclopropyl)-adamantan-1-yl)allyloxy)silane (32). Me3CCOCl (0.233 mL, 1.89 mmol) was added with stirring to triol 30 (121 mg, 0.189 mmol) in dry pyridine (4 mL) at room temperature. After 2h, reaction was quenched with saturated aqueous NH4Cl (4 mL) and the separated aqueous layer was extracted with CH2Cl2 (3 x 10 mL). The combined organic layers were washed with brine (15 mL), dried (MgSO4), and the residue chromatographed (hexanes : EtOAc, 25 : 1 to 20 : 1) to give the tri-pivaloate 32 (160 mg, 95%) as a colorless thick oil: Rf 0.32 (hexanes : EtOAc, 10 : 1); [α]D22 24.5 (c 1.02, CHCl3); IR (film) 3069, 2967, 2932, 1726 cm−1; 1H NMR (300 MHz, CDCl3) δ 7.68 (d, J 7.1 Hz, 4H, ArH), 7.39 (m, 6H, ArH), 5.45 (dt, J 12.4, 5.6 Hz, 1H, CH=CHCH2OSi), 5.05 (d, J 12.4 Hz, 1H, CH=CHCH2OSi), 4.42-4.36 (m, 5H, CH=CHCH2OSi and CH2OPiv), 3.83 (dd, J 11.1, 9.0 Hz, 3H, CH2OPiv), 1.24 (m, 12H, adamantane methylene), 1.21-1.16 (m, 30H, COC(CH3)3 and cyclopropane methine), 1.05 (s, 9H, Si(CH3)3), 0.57 (m, 6H, cyclopropane methylene), 0.19 (m, 3H, cyclopropane methine); 13C NMR (75 MHz, CDCl3) δ 178.5, 138.4, 135.5, 133.7, 129.6, 128.8, 127.6, 65.6, 61.0, 46.9, 46.4, 38.6, 38.0, 34.2, 28.8, 27.3, 26.8, 19.1, 15.5, 4.7; the product did not exhibit a molecular ion in the MS.

1-((1Z)-3-Hydroxy-1-propenyl)-((3-(3,5,7-tri-(1R,2S)-2-(pivaloyloxymethyl)-1-cyclopropyl)adamantane (33).

Bu4NF in THF (1.0 M; 0.086 mL, 0.086 mmol) was added dropwise with stirring to silyl ether 32 (70 mg, 0.078 mmol) in THF (2 mL) at room temperature. After 16 h, reaction was quenched with H2O (2 mL) and the separated aqueous layer was extracted with CH2Cl2 (3 x 6 mL). The combined organic layers were washed with brine, dried (MgSO4), and concentrated in vacuo, and the residue chromatographed (hexanes : EtOAc, 7 : 1 to 4 : 1) to give the allylic alcohol 33 (49 mg, 95%) as a colorless thick oil: Rf 0.15 (hexanes : EtOAc, 4 : 1); [α]D22 31.2 (c 1.60, CHCl3); IR (film) 3516 broad, 2971, 2906, 1726, 1480, 1283 cm−1; 1H NMR (300 MHz, CDCl3) δ 5.39 (dt, J 12.3, 6.5 Hz, 1H, CH=CHCH2OH), 5.17 (d, J 12.3 Hz, 1H, CH=CHCH2OH), 4.44 (dd, J 11.5, 7.5 Hz, 3H, CH2OPiv), 4.26 (d, J 6.5 Hz, 2H, CH=CHCH2OH), 3.92 (dd, J 11.5, 8.9 Hz, 3H, CH2OPiv), 1.35 (s, 6H, adamantane methylene), 1.31-1.29 (m, 6H, adamantane methylene), 1.22 (s, 27H, COC(CH3)3), 1.11 (m, 3H, cyclopropane
methylene), 0.64 (m, 6H, cyclopropane methylene), 0.27 (m, 3H, cyclopropane methine); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 178.7, 140.3, 128.2, 65.7, 59.2, 47.3, 46.3, 38.7, 37.8, 34.3, 28.9, 27.3, 15.5, 4.7; the product did not exhibit a molecular ion in the MS.

1-((1R,2S)-2-(Hydroxymethyl)-1-cyclopropyl)-3,5,7-tri-((1R,2S)-2-(pivaloyloxymethyl)-1-cyclopropyl)adamantane (34). CH$_2$Cl$_2$ (4 mL) and 1,2-dimethoxyethane (0.196 mL, 1.89 mmol) in a flame-dried flask were cooled to −15 °C and neat Et$_2$Zn (0.193 mL, 1.89 mmol) was added with stirring. CH$_2$Cl$_2$ (0.304 mL, 3.77 mmol) was added slowly with stirring keeping the internal temperature below −10 °C. After 10 min at −10 °C, dioxaborolane ligand 26 (153 mg, 0.566 mmol) in CH$_2$Cl$_2$ (1 mL) was added slowly with stirring while maintaining the internal temperature below −5 °C. An aliquot (2 mL) of this cold solution was immediately added with stirring to allylic alcohol 33 (103 mg, 0.157 mmol) in CH$_2$Cl$_2$ (1 mL) at −10 °C and the mixture allowed to warm up to room temperature. After 5h, reaction was quenched with saturated aqueous NH$_4$Cl (2 mL) and the separated aqueous layer was extracted with CH$_2$Cl$_2$/MeOH (6:1) (4 x 5 mL). The combined organic layers were washed with brine (10 mL), dried (MgSO$_4$), concentrated in vacuo, and the residue chromatographed (hexanes : EtOAc, 16:1 (formyl) and COC(CH$_3$)$_3$ and CHCH$_2$OPiv), 0.87 (m, 1H, CHCH$_2$OH), 0.64-0.60 (m, 8H, cyclopropane methylene), 0.27-0.21 (m, 4H, cyclopropane methine); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 178.6, 65.7, 63.3, 47.7, 46.6, 38.7, 34.3, 28.9, 27.3, 19.4, 15.5, 4.7; MS (Cl, NH$_3$) m/z 686 (M + NH$_4^+$); HRMS (Cl, NH$_3$) n/z calc for C$_{41}$H$_{68}$NO$_7$ (M + NH$_4^+$) 686.4996, found: 686.5004.

1,3,5,7-Tetra-((1R,2S)-2-(hydroxymethyl)-1-cyclopropyl)adamantane (35). DIBAl-H in hexanes (1.0 M; 0.706 mL, 0.706 mmol) was added dropwise with stirring over 5 min to tri-pivaloate 34 (63 mg, 0.094 mmol) in CH$_2$Cl$_2$ (3.5 mL) at −78 °C. After 1 h at −78 °C, saturated aqueous NH$_4$Cl (0.14 mL), i-PrOH (4 mL), silica gel (200 mg) and Celite (200 mg) were added. The mixture was allowed to warm to room temperature and filtered, and the solids were washed with CH$_2$Cl$_2$/MeOH (4:1). Rotary evaporation of the combined organic layers and chromatography (CH$_2$Cl$_2$ : MeOH, 16 : 1 to 12 : 1) gave the tetra-syn-cyclopropyl alcohol 35 (35 mg, 89%) as a viscous oil. Colorless crystals of tetra-syn-cyclopropyl crystals 35 were obtained by crystallization from MeOH/PhMe/THF (1:1:1): mp 168 - 170 °C (MeOH : PhMe : THF, 1 : 1 : 1); $R_f$ 0.32 (CH$_2$Cl$_2$ : MeOH, 8 : 1); $[\alpha]_D^{25}$ −17.6 (c 1.0, MeOH); IR (film) 3321 (br), 2894, 2360 cm$^{-1}$; $^1$H NMR (300 MHz, MeOH-d$_4$) δ 3.72 (m, 8H, adamantane methylene), 1.03 (m, 4H, cyclopropane methylene), 0.29 (d, J 3.4 Hz, 4H, cyclopropane methyl); $^{13}$C NMR (75 MHz, MeOH-d$_4$) δ 434 (M + NH$_4^+$).

1,3,5,7-Tetra-((1R,2S)-2-(formyl)-1-cyclopropyl)adamantane (14). DMSO (32 µL, 0.448 mmol) was added slowly with vigorous stirring to (COCl)$_2$ (19 µL, 0.224 mmol) in CH$_2$Cl$_2$ (1 mL) at −78 °C. After a further 15 min at −78 °C, tetra-alcohol 35 (11 mg, 0.0264 mmol) in DMSO (0.3 mL) and CH$_2$Cl$_2$ (0.6 mL) was added slowly, and the reaction mixture was stirred at −78 °C for an additional 1 h. Et$_3$N (0.15 mL) was added dropwise, and the mixture was allowed to warm up to room temperature. H$_2$O (5 mL) and CH$_2$Cl$_2$ (5 mL) were added and the two phases were separated. The organic phase was washed with 5% aqueous HCl (2 mL), H$_2$O (2 mL), 5% aqueous NaHCO$_3$ (4 mL) and brine (4 mL), dried (MgSO$_4$), concentrated in vacuo and the residue chromatographed (hexanes : EtOAc : MeOH, 1 : 1 : 0.04) to afford the tetra-aldehyde 14 (8 mg, 82%) as a white solid: mp 121 -
123 °C (hexanes : EtOAc, 1 : 2); \( R_f \) 0.35 (hexanes : EtOAc : MeOH, 1 : 1 : 0.2); \([\alpha]_D^{22} \) -73.1 (c 1.03, CHCl_3); IR (film) 2924, 2849, 1692 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl_3) \( \delta \) 9.33 (d, \( J \) 6.1 Hz, 4H, CHO), 1.87-1.77 (m, 4H, cyclopropane), 1.33-1.10 (m, 12H, cyclopropane), 1.20 (s, 12H, adamantane methylene); \(^{13}\)C NMR (75 MHz, CDCl_3) \( \delta \) 200.0, 46.9, 36.5, 34.9, 29.6, 9.9; the product did not exhibit a molecular ion in the MS. Anal. calc for C_{26}H_{32}O_{4}: C, 76.44; H, 7.90. Found: C, 76.37; H, 8.03.

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1,3,5,7-Tetra-((1R,2S)-2-(N-4-toluenesulfonylamino-iminomethyl)-1-cyclopropyl)adamante (36).

p-Toluenesulfonylhydrazine hydrochloride (42 mg, 0.225 mmol) was added with stirring to tetra-aldehyde 14 (23 mg, 0.056 mmol) in MeOH (3 mL) at room temperature. After 4.5 h, evaporation \textit{in vacuo} and chromatography of the residue (hexanes : EtOAc : MeOH, 1 : 1 : 0.02) gave tetra-tosylhydrazone 36 (50 mg, 82%) as a white solid: \( mp \) 149 - 151 °C (hexanes : EtOAc, 1 : 2); \( R_f \) 0.31 (hexanes : EtOAc : MeOH, 1 : 1 : 0.2); \([\alpha]_D^{22} \) -154.7 (c 1.02, CHCl_3); IR (film) 3204, 2923, 2852, 1334, 1164 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl_3) \( \delta \) 9.23-8.38 (m, 4H, CH=NNHTs), 7.97-7.89 (m, 8H, ArH), 7.35-7.28 (m, 8H, ArH), 7.08-6.98 (m, 2H, CH=NNHTs), 6.61-6.48 (m, 2H, CH=NNHTs), 2.40 (s, 12H, ArCH_3), 1.59 (br s, 4H, cyclopropane methine), 1.27 (s, 8H, cyclopropane methylene), 1.12-0.75 (m, 16H, cyclopropane methine and adamantane methylene); the product did not exhibit a molecular ion in the MS.

1-Adamantyl)acetalddehyde 38. DMSO (1.60 mL, 22.5 mmol) in CH_2Cl_2 (2 mL) was added with vigorous stirring over 2 min to (COCl)_2 (0.263 mL, 3.06 mmol) in CH_2Cl_2 (7 mL) at –78 °C. After 15 min, 1-adamantaneethanol (37) (500 mg, 2.78 mmol) in CH_2Cl_2 (4 mL) was added and the mixture was allowed to warm up to room temperature over 1 h. H_2O (15 mL) was added and the two phases were separated and the organic layer was washed with 5% aqueous HCl (10 mL), H_2O (10 mL), 5% aqueous NaHCO_3 (10 mL) and brine (10 mL), dried (MgSO_4), and concentrated \textit{in vacuo}. The residue was chromatographed (hexanes : EtOAc, 30 : 1) to afford the aldehyde 38 (444 mg, 90%) as a colorless oil: \( R_f \) 0.44 (hexanes : EtOAc, 10 : 1); IR (film) 2902, 2848, 1720 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl_3) \( \delta \) 9.87 (t, \( J \) 3.4 Hz, 1H, CHO), 2.12 (d, \( J \) 3.4 Hz, 2H, CH_2CHO), 1.98 (s, 3H, adamantane methine), 1.74-1.64 (m, 12H, adamantane methylene); \(^{13}\)C NMR (100 MHz, CDCl_3) \( \delta \) 203.8, 57.2, 42.7, 36.6, 33.3, 28.4; MS (EI) \( m/z \) 178 (M\(^+\)); HRMS (EI) \( m/z \) calcd for C_{12}H_{22}O, 178.1358, found: 178.1353. All spectroscopic data were consistent with the literature values.\(^{37}\)

Ethyl 4-(Adamantan-1-yl)-3-oxobutanoate (39a).\(^{47}\) Aldehyde 38 (89 mg, 0.50 mmol) in CH_2Cl_2 (2 mL) was added with stirring to anhydrous SnCl_2 (9.5 mg, 0.05 mmol) and ethyl diazoacetate (58 \( \mu l \), 0.55 mmol) in CH_2Cl_2 (2 mL) at room temperature. After 1 h, the mixture was washed with brine (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were dried (MgSO_4), concentrated \textit{in vacuo} and the residue was chromatographed (hexanes : EtOAc, 40 : 1) to afford the \( \beta \)-keto ester 39a (106 mg, 80%) (ca. 4 : 1 keto form and enol form) as a colorless oil: \( R_f \) 0.44 (hexanes : EtOAc, 10 : 1); IR (film) 2903, 2848, 1744, 1715, 1630 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl_3): (keto form) \( \delta \) 4.19 (q, \( J \) 7.1 Hz, 2H, CO_2CH_2CH_3), 3.41 (s, 2H, CH_2COEt), 2.28 (s, 2H, CH_2COCH_2COEt), 1.96 (s, 3H, adamantane methine), 1.65-1.64 (m, 12H, adamantane methylene), 1.29 (t, \( J \) 7.1 Hz, 3H, CO_2CH_2CH_3); (enol form) \( \delta \) 12.10 (s, 1H, HO-C=CH), 4.90 (s, 1H, HO-C=CH), 4.19 (q, \( J \) 7.2 Hz, 2H, CO_2CH_2CH_3), 1.93 (s, 2H, CH_2OH=CH), 1.72 (s, 3H, adamantane methine), 1.69-1.59 (m, 12H, adamantane methylene), 1.31 (t, \( J \) 7.2 Hz, 3H, CO_2CH_2CH_3); \(^{13}\)C NMR (100 MHz, CDCl_3): (keto form) \( \delta \) 202.4, 167.2, 61.3, 56.0, 51.9, 42.3, 36.8, 33.7, 28.5, 14.2; (enol form) \( \delta \) 176.8, 172.6, 91.3, 59.9, 50.0, 42.6, 36.7, 33.4, 28.7, 14.3; MS (EI) \( m/z \) 264 (M\(^+\)); HRMS (EI) \( m/z \) calcd for C_{16}H_{24}O_3 264.1725, found: 264.1717.
**Ethyl 4-(Adamant-1-yl)-2-diazo-3-oxobutanoate (41a).** Et₃N (0.126 mL, 0.898 mmol) was added dropwise with stirring to β-keto ester 39a (79 mg, 0.299 mmol) and 4-acetamidobenzenesulfonyl azide (40) (79 mg, 0.329 mmol) in dry MeCN (4 mL) at 0 °C. After stirring for 3 h at room temperature, the reaction mixture was concentrated in vacuo and the resultant solid was triturated with Et₂O and hexanes (1:1) (60 mL). The filtrate was concentrated in vacuo and the residue was chromatographed (hexanes : EtOAc, 30 : 1) to afford α-diazo-β-keto ester 41a (86 mg, 99%) as a viscous oil: \( R_f \) 0.46 (hexanes : EtOAc, 10 : 1); IR (film) 2903, 2849, 2131, 1719, 1650 cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃) δ 4.29 (q, \( J = 7.2 \) Hz, 2H, \( CH₂CO₂(CH₃)₃ \)), 2.71 (s, 2H, \( CH₂COC(N₂) \)), 1.95 (s, 3H, adamantane methine), 1.67-1.66 (m, 12H, adamantane methylene), 1.34 (t, \( J = 7.2 \) Hz, 3H, \( CO₂CH₂CH₃ \)); \(^1^3\)C NMR (100 MHz, CDCl₃) δ 191.9, 161.5, 77.3, 61.3, 51.5, 42.4, 36.8, 34.7, 28.7, 14.4; MS (EI) \( m/z \) 290 (M⁺); HRMS (EI) \( m/z \) calc for C₁₈H₂₂N₂O₃ 290.1630, found: 290.1626.

**tert-Butyl 4-(Adamant-1-yl)-3-oxobutanoate (39b).** Aldehyde 38 (390 mg, 2.19 mmol) in CH₂Cl₂ (6 mL) was added with stirring to anhydrous SnCl₂ (42 mg, 0.22 mmol) and tert-butyl diazoacetate (0.333 mL, 2.41 mmol) in CH₂Cl₂ (6 mL) at room temperature. After 1.5 h, the mixture was washed with brine (15 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The organic extracts were dried (MgSO₄), concentrated in vacuo and the residue was chromatographed (hexanes : EtOAc, 40 : 1) to afford the β-keto ester 39b (390 mg, 61%) (ca. 6 : 4 keto form and enol form) as a colorless oil: \( R_f \) 0.41 (hexanes : EtOAc, 10 : 1); IR (film) 2902, 2848, 1739, 1714, 1637 cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃) (keto form) δ 3.24 (s, 2H, \( CH₂CO₂(CH₃)₃ \)), 2.19 (s, 2H, \( CH₂COCH₂CO₂(CH₃)₃ \)), 1.89 (s, 3H, adamantane methine), 1.64-1.52 (m, 12H, adamantane methylene), 1.40 (s, 9H, \( CH₂CO₂(CH₃)₃ \)); (enol form) δ 12.15 (s, 1H, \( HOCH=CH \)), 4.73 (s, 1H, \( HOCH=CH \)), 1.89 (s, 3H, adamantane methine), 1.83 (s, 2H, \( CH₂(OH)=CH \)), 1.61-1.52 (m, 12H, adamantane methylene), 1.43 (t, \( CH₂CO₂(CH₃)₃ \)); \(^1^3\)C NMR (100 MHz, CDCl₃) (keto form) δ 202.9, 166.5, 81.7, 55.9, 53.1, 42.3, 36.7, 33.6, 28.5, 28.0; (enol form) δ 176.1, 172.6, 92.7, 80.6, 50.0, 42.6, 36.8, 33.3, 28.7, 28.3; MS (EI) \( m/z \) 292 (M⁺); HRMS (EI) \( m/z \) calc for C₁₈H₂₂O₃ 292.2038, found: 292.2034; Anal. Calc for C₁₈H₂₂O₃: C, 73.93; H, 9.65. Found: C, 73.01; H, 9.58.

**tert-Butyl 4-(Adamant-1-yl)-2-diazo-3-oxobutanoate (41b).** Et₃N (0.162 mL, 1.15 mmol) was added dropwise with stirring to β-keto ester 39b (112 mg, 0.384 mmol) and 4-acetamidobenzenesulfonyl azide (40) (101 mg, 0.422 mmol) in dry MeCN (5 mL) at 0 °C and the mixture was allowed to warm up to room temperature. After 4 h, the reaction mixture was concentrated in vacuo and the resultant solid was triturated with Et₂O and hexanes (1:1), the filtrate was concentrated in vacuo and the residue was chromatographed (hexanes : EtOAc, 40 : 1) to afford α-diazo-β-keto ester 41b (109 mg, 90%) as a viscous oil: \( R_f \) 0.41 (hexanes : EtOAc, 10 : 1); IR (film) 2904, 2848, 2129, 1712, 1689, 1648 cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃) δ 2.66 (s, 2H, \( CH₂CO₂(CH₃)₃ \)); \(^1^3\)C NMR (100 MHz, CDCl₃) δ 192.0, 160.6, 82.9, 78.2, 51.3, 42.3, 36.7, 34.5, 28.7, 28.2; MS (EI) \( m/z \) 318 (M⁺); HRMS (EI) \( m/z \) calc for C₁₈H₂₂N₂O₃ 318.1943, found: 318.1942; Anal. Calc for C₁₈H₂₂N₂O₃: C, 67.90; H, 8.23; N, 8.80. Found: C, 68.01; H, 8.27; N, 8.74.

**1,3-Di-(2-hydroxyethyl)adamantane (43).**LiAlH₄ (754 mg, 19.8 mmol) was added portionwise with stirring to di-acid 42 (1.0 g, 3.97 mmol) in THF (30 mL) at 0 °C and the mixture was allowed to warm up to room temperature. After 18 h, saturated aqueous Na₂SO₄ (1.50 mL) was added carefully to quench the reaction at 0 °C and the mixture was stirred for an additional 30 min, when THF (40 mL) and silica gel (2.0 g) were added. The mixture was filtered through a short pad of Celite, eluting with THF (60 mL). Rotary evaporation of the filtrate and chromatography of the residue (hexanes : EtOAc : MeOH, 1 : 1 : 0.02 to 1 : 1 : 0.05) gave diol 43 (658 mg, 74%) as colorless needles: mp 112 - 113 °C (MeOH : CH₂Cl₂, 1 : 2) (lit.⁴⁰ mp 113 - 115 °C); \( R_f \) 0.39
(hexanes : EtOAc : MeOH, 1 : 1 : 0.02); IR (film) 3389 (br), 2899, 2359, 1644 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 4.19 (t, \(J\ 5.0\ Hz, 2H, CH_2OH\), 3.45 (td, \(J\ 7.6, 5.0\ Hz, 4H, CH_2OH\)), 1.94 (m, 2H, adamantane methine), 1.55 (s, 2H, adamantane methylene), 1.46-1.36 (m, 8H, adamantane methylene and \(CH_2CH_2OH\)), 1.28-1.23 (m, 6H, adamantane methylene); \(^13\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) 56.4, 47.9, 46.8, 41.9, 36.3, 32.2, 28.6; MS (EI) \(m/z\) 224 (M\(^+\)); HRMS (EI) \(m/z\) calc for \(C_{14}H_{24}O_2\) 224.1776, found: 224.1773. All spectroscopic data were consistent with the literature values.\(^{40}\)

### 2,2’-(Adamantane-1,3-diyl)diacetaldehyde (44).
DMSO (0.47 mL, 6.61 mmol) in \(CH_2Cl_2\) (2 mL) was added dropwise over 2 min with vigorous stirring to (COCl)\(_2\) (0.284 mL, 3.30 mmol) in \(CH_2Cl_2\) (2 mL) at \(-78\) °C. After 10 min, diol 43 (500 mg, 2.78 mmol) in \(CH_2Cl_2\) (4 mL) and anhydrous DMSO (2 mL) was added slowly with stirring at \(-78\) °C. After 1 h, Et\(_3\)N (2.30 mL) was added dropwise with stirring, and the mixture was allowed to warm up to room temperature for 1 h. \(H_2O\) (15 mL) was added, the two phases were separated and the organic layer was washed with 5\% aqueous HCl (10 mL), \(H_2O\) (10 mL), 5\% aqueous NaHCO\(_3\) (10 mL) and brine (10 mL), dried (MgSO\(_4\)) and concentrated in \textit{vacuo}. The residue was chromatographed (hexanes : EtOAc, 8 : 1) to afford the di-aldehyde 44 (150 mg, 83\%) as a colorless oil: \(R_f\) 0.52 (hexanes : EtOAc, 2 : 1); IR (film) 2901, 2848, 1719 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.86 (t, \(J\ 3.1\ Hz, 2H, CH_2CHO\), 2.12 (d, \(J\ 3.1\ Hz, 4H, CH_2CHO\)), 2.10 (m, 2H, adamantane methine), 1.69-1.58 (m, 12H, adamantane methylene); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 202.9, 56.6, 47.7, 41.7, 35.7, 33.9, 28.6; MS (EI) \(m/z\) 220 (M\(^+\)); HRMS (EI) \(m/z\) calc for \(C_{14}H_{24}O_2\) 220.1463, found: 220.1462.

### Di-tert-butyl 4,4’-(Adamantane-1,3-diyl)bis(3-oxobutanoate) (45).
Di-aldehyde 44 (148 mg, 0.673 mmol) in \(CH_2Cl_2\) (2 mL) was added with stirring to anhydrous SnCl\(_2\) (38 mg, 0.202 mmol) and tert-butyl diazoacetate (0.24 mL, 1.68 mmol) in \(CH_2Cl_2\) (4 mL) at room temperature. After 1.5 h, the mixture was washed with brine (5 mL) and extracted with \(CH_2Cl_2\) (3 x 10 mL), the organic extracts were dried (MgSO\(_4\)) and concentrated in \textit{vacuo}. The resultant residue was chromatographed (hexanes : EtOAc, 12 : 1) to afford the di-\(\beta\)-keto ester 45 (225 mg, 75\%) (ca. 2.5 : 1 keto : enol forms) as a viscous colorless oil: \(R_f\) 0.51 (hexanes : EtOAc, 4 : 1); IR (film) 2903, 1739, 1713, 1638 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) (keto form) \(\delta\) 3.30 (s, 4H, \(CH_2COCH_2COC(CH_3)_3\)), 2.29 (s, 4H, \(CH_2COCH_2COC(CH_3)_3\)), 2.05 (s, 2H, adamantane methine), 1.64-1.54 (m, 12H, adamantane methylene), 1.47 (s, 18H, \(CH_2COCH_2C(CH_3)_3\)); (enol form) \(\delta\) 12.21 (s, 2H, HOC=CH), 4.80 (s, 2H, HOC=CH), 2.05 (s, 2H, adamantane methine), 1.92 (s, 4H, \(CH_2C(OH)=CH\)), 1.64-1.54 (m, 12H, adamantane methylene), 1.50 (s, 9H, \(CH_2COCH_2C(CH_3)_3\)); \(^13\)C NMR (100 MHz, CDCl\(_3\)) (keto form) \(\delta\) 202.6, 166.4, 81.8, 55.3, 53.0, 46.9, 41.3, 34.1, 28.7, 28.0; (enol form) \(\delta\) 175.7, 172.6, 92.9, 80.7, 49.5, 47.5, 41.7, 35.8, 28.9, 28.4; MS (ES) \(m/z\) 471 (M + Na\(^+\)); HRMS (ES) \(m/z\) calc for \(C_{26}H_{40}O_6Na\) 471.2723, found: 471.2715; Anal. Calc for \(C_{26}H_{40}O_6C\): C, 69.61; H, 8.99. Found: C, 69.56; H, 9.04.

### Di-tert-butyl 4,4’-(Adamantane-1,3-diyl)bis(2-diazo-3-oxobutanoate) (46).
Et\(_3\)N (0.395 mL, 2.81 mmol) was added dropwise with stirring to di-\(\beta\)-keto ester 45 (210 mg, 0.469 mmol) and 4-acetamidobenzenesulfonyl azide (40) (248 mg, 1.03 mmol) in dry MeCN (12 mL) at 0 °C and the mixture was allowed to warm up to room temperature. After 4 h, the mixture was concentrated in \textit{vacuo} and the resultant solid was triturated with Et\(_2\)O and hexanes (1:1) (80 mL). The mixture was filtered, the filtrate was concentrated in \textit{vacuo} and the residue chromatographed (hexanes : EtOAc, 20 : 1) to afford di-\(\alpha\)-diazo-\(\beta\)-keto ester 46 (184 mg, 79\%) as a viscous colorless oil: \(R_f\) 0.60 (hexanes : EtOAc, 4 : 1); IR (film) 2904, 2129, 1712, 1648 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.65 (s, 4H, \(CH_2COC(N_2)\)), 1.97 (m, 2H, adamantane methine), 1.61-1.54 (m, 12H, adamantane methylene), 1.49 (s, 18H, C(CH\(_3\))\(_3\)); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 191.8, 160.5, 83.0, 78.2, 51.0, 47.2, 41.4, 35.9, 35.1, 29.0, 28.3; MS (ES) \(m/z\) 471 (M + Na\(^+\)); HRMS (ES) \(m/z\) calc for \(C_{26}H_{40}O_6Na\) 471.2723, found: 471.2715.
Ethyl 2-Oxodecahydro-3a,7:5,9-dimethanocyclopenta[8]annulene-1-carboxylate (47a). Rh₂(OAc)₄ (1.8 mg, 4.1 μmol) was added with stirring to α-diazo-β-keto ester 41a (60 mg, 0.21 mmol) in CH₂Cl₂ (5 mL) at room temperature. After 1.5 h, the solvent was removed in vacuo and the residue was chromatographed (hexanes : EtOAc, 25 : 1) to afford β-keto ester 47a (49 mg, 90%) as a viscous oil containing a single diastereoisomer: Rf 0.27 (hexanes : EtOAc, 10 : 1); IR (film) 2905, 2852, 1755, 1724 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.19 (q, J 7.2 Hz, 2H, COCH), 1.45 (s, 9H, C(C₃H₆)₃); ¹³C NMR (100 MHz, CDCl₃) δ 211.1, 168.9, 81.5, 56.7, 53.1, 51.2, 42.9, 38.3, 37.9, 37.0, 35.6, 29.7, 29.1, 28.5, 28.0, 27.8; MS (EI) m/z 262 (M⁺); HRMS (EI) m/z calc for C₁₆H₂₂O₃ 262.1569, found: 262.1566.

tert-Butyl 2-Oxodecahydro-3a,7:5,9-dimethanocyclopenta[8]annulene-1-carboxylate (47b). Rh₂(OAc)₄ (14.5 mg, 0.033 mmol) was added with stirring to α-diazo-β-keto ester 41b (208 mg, 0.654 mmol) in CH₂Cl₂ (10 mL) at room temperature. After 1.5 h, the solvent was removed in vacuo and the residue chromatographed (hexanes : EtOAc, 30 : 1) to afford β-ketoester 47b (173 mg, 91%) as a colorless viscous oil: Rf 0.34 (hexanes : EtOAc, 10 : 1); IR (film) 2906, 2852, 1752, 1722 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.18 (d, J 12.9 Hz, 1H, COCH(C₃H₆)₃), 2.46 (d, J 12.8 Hz, 1H, COCH(CO₂C(CH₃)₃)CH), 2.06-1.67 (m, 13H, adamantane methylene and methine), 2.03 (s, 2H, CH₂COCH), 1.45 (s, 9H, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ 211.4, 168.9, 81.5, 56.7, 53.1, 51.2, 42.9, 38.3, 37.9, 37.0, 35.6, 29.7, 29.1, 28.5, 28.0, 27.8; MS (EI) m/z 290 (M⁺); HRMS (EI) m/z calc for C₁₈H₂₆O₃ 290.1881; Anal. Calc for C₁₈H₂₆O₃: C, 74.45; H, 9.02. Found: C, 74.55; H, 8.99.

2-Oxodecahydro-3a,7:5,9-dimethanocyclopenta[8]annulene-1-carboxylic Acid (48). CF₃CO₂H (0.3 mL) was added with stirring to tert-butyl ester 47b (20 mg, 0.069 mmol) in CH₂Cl₂ (3 mL) at room temperature. After 3 h, volatile materials were removed in vacuo and the residue was dried under vacuum for 4 h to leave the β-keto acid 48 (16 mg, 99%) as a white solid: mp 118 - 120 °C (CH₂Cl₂); Rf 0.39 (hexanes : EtOAc : MeOH, 1 : 1 : 0.2); IR (film) 2906, 2852, 1752, 1702 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.54 (br s, 1H, COOH), 7.29 (d, J 13.0 Hz, 1H, CH₂COCHCO₂H and adamantane), 1.98-1.68 (m, 9H, adamantane), 1.51 (s, 2H, adamantane); ¹³C NMR (100 MHz, CDCl₃) δ 211.4, 174.3, 55.3, 53.1, 51.1, 42.9, 38.2, 37.9, 37.0, 35.8, 29.6, 29.1, 28.5, 27.8; MS (EI) m/z 234 (M⁺); HRMS (EI) m/z calc for C₁₄H₁₈O₃ 234.1256; found: 234.1254.

Octahydro-3a,7:5,9-dimethanocyclopenta[8]annulen-2(3H)-one (49). From β–keto-ethyl ester 47a. β–Ketoester 47a (46 mg, 0.176 mmol) and NaCl (20 mg, 0.351 mmol) in DMSO (6 mL) and H₂O (0.095 mL, 5.27 mmol) was stirred at 130 - 140 °C for 1.5 h. The solution was cooled to room temperature, diluted with Et₂O (50 mL) and washed with H₂O (2 x 15 mL) and brine (15 mL). The organic extracts were dried (MgSO₄), concentrated in vacuo and the residue was chromatographed (hexanes : EtOAc, 25 : 1) to afford cyclopentanone 49 (30 mg, 90%). From β–keto-tert-butyl ester 47b. CF₃CO₂H (0.3 mL) was added with stirring to tert-butyl ester 47b (20 mg, 0.069 mmol) in dry PhCl (5 mL) at room temperature. The mixture was subsequently stirred at 120 °C for 3 h, after which the solvent was removed in vacuo. The crude material was dried under vacuum for 3 h to afford the cyclopentanone 49 (13 mg, 100%). From β–keto-acid 48. β–Keto-acid 48 (18 mg, 0.077 mmol) in 1,4-dioxane (5 mL) was heated under reflux for 3 h, and the solvent was removed in vacuo. The residue was chromatographed (hexanes : EtOAc, 20 : 1) to afford the cyclopentanone 49 (12 mg,
82%). The cyclopentanone 49 in these experiments was obtained as colorless crystals: mp 73 - 75 °C (EtOAc) (lit.48 mp 74 - 76 °C); Rf 0.22 (hexanes : EtOAc, 15 : 1); IR (film) 2903, 2851, 1744, 1452 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.31 (m, 1H, CH₂C=O), 2.16 (m, 2H, CH₂C=O), 2.07 (m, 1H, CH₂C=O), 1.99-1.40 (m, 14H, adamantane methine and methylene); ¹³C NMR (75 MHz, CDCl₃) δ 219.1, 53.8, 47.3, 43.1, 39.6, 38.6, 37.5, 37.1, 36.9, 29.5, 29.2, 29.1, 27.9; MS (EI) m/z 190 (M⁺); HRMS (EI) m/z calc for C₁₉H₁₈O (M⁺) 190.1358, found: 190.1358. Anal. Calc for C₁₉H₁₈O: C, 82.06; H, 9.53. Found: C, 82.14; H, 9.63.

**Di-tert-butyl 2,9-Dioxodecaydro-3a,7:5,10a-dimethanodicyclopenta[a,c][8]annulene-1,8-dicarboxylate (50).** Rh₂(OAc)₄ (17 mg, 0.038 mmol) was added with stirring to di-α-diazo-β-keto ester 46 (126 mg, 0.252 mmol) in CH₂Cl₂ (6 mL) at room temperature. After 1 h, the solvent was removed in vacuo and the residue chromatographed (hexanes : EtOAc, 10 : 1 to 8 : 1) to give diester 50 (57 mg, 52%) as a colorless viscous oil: Rf 0.25 (hexanes : EtOAc, 4 : 1); IR (film) 2913, 2859, 1753, 1720 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.34-3.13 (m, 2H, CHCO₂C(CH₃)₃), 2.77-2.45 (m, 2H, CHCHCO₂C(CH₃)₃), 2.31-1.61 (m, 14H, CH₂C=O and adamantane), 1.48-1.45 (m, 18H, CO₂C(CH₃)₃); MS (EI) m/z 444 (M⁺); HRMS (EI) m/z calc for C₂₆H₃₆O₆ 444.2512, found: 444.2514.

**Octahydro-3a,7:5,10a-dimethanodicyclopenta[a,c][8]annulene-2,9(3H,10H)-dione (51).** CF₃CO₂H (0.5 mL) was added with stirring to di-tert-butyl ester 50 (28 mg, 0.063 mmol) in dry PhCl (5 mL) at room temperature. The mixture was stirred at 115 °C for 3 h, cooled and the solvent was removed in vacuo. The residue was chromatographed (hexanes : EtOAc, 4 : 1) to afford the di-ketone 51 (15 mg, 97%) as a colorless oil: Rf 0.24 (hexanes : EtOAc, 2 : 1); IR (film) 2910, 2856, 1740 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.4-2.1 (m, CH₂C=O), 2.1-1.3 (m, adamantane methine and methylene); ¹³C NMR (75 MHz, CDCl₃) δ 217, 53.8, 53.3, 53.0, 51.5, 50.2, 48.8, 47.4, 47.2, 47.144, 44.4, 43.1, 39.7, 39.6, 39.4, 39.2, 39.1, 39.0, 38.9, 38.2, 37.3, 37.2, 36.9, 36.8, 36.535, 35.4, 30.5, 30.3, 29.8, 29.7, 29.4, 29.2; MS (EI) m/z 244 (M⁺); HRMS (EI) m/z calc for C₁₆H₁₀O₂ 244.1463, found: 244.1464; Anal. Calc for C₁₆H₁₀O₂: C, 78.65; H, 8.25. Found: C, 78.55; H, 8.37.

**1,3,5,7-Tetra-(2-methoxyethyl)adamantane (52).** NaN(SiMe₃)₂ in THF (1.0 M; 6.05 mL, 6.05 mmol) was added with stirring to Ph₃PCH₂OMeCl (2.21 g, 6.45 mmol) in THF (10 mL) at −78 °C. After 1 h, tetra-aldehyde 19 (200 mg, 0.806 mmol) in THF (10 mL) was added dropwise with stirring to the red solution and the mixture allowed to warm up to room temperature. After 16 h, saturated aqueous NH₄Cl (10 mL) was added and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried (MgSO₄), concentrated in vacuo and the residue chromatographed (hexanes : EtOAc, 30 : 1 to 15 : 1) to give the tetra-enol ether 53 (ca. 1 : 1 (E)-olefin : (Z)-olefin isomers) (230 mg, 80%) as a colorless oil: Rf 0.62 (hexanes : EtOAc, 4 : 1); IR (film) 3019, 2930, 2819, 1656, 1449 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.22 (d, J 12.9 Hz, 2H, (E)-isomer CH=CHOCH₃), 5.71-5.67 (m, 2H, (Z)-isomer CH=CHOCH₃), 4.72 (d, J 12.9 Hz, 2H, (E)-isomer CH=CHOCH₃), 4.05 (d, J 7.0 Hz, 2H, (Z)-isomer CH=CHOCH₃), 3.53 (s, 6H, (Z)-isomer CH=CHOCH₃), 3.49 (s, 6H, (E)-isomer CH=CHOCH₃), 1.72-1.69 (m, 6H, (Z)-isomer adamantane methylene), 1.52 (s, 6H, (E)-isomer adamantane methylene); ¹³C NMR (75 MHz, CDCl₃) δ complex due to mixtures of geometric isomers 145.6-144.7 (multiple peaks, CH=CH(OMe), 116.4-114.5 (multiple peaks, CH=CH(OMe), 59.7, 55.8, 47.8-46.0 (multiple peaks), 35.8, 34.4 (the peaks in the ¹H and ¹³C NMR spectra for the E- and Z- CH=CHOMe units were consistent with those in the spectra reported for the isolated E- and Z- isomers of 1-(2-methoxyethenyl)-1-methylcyclohexane⁴⁹); the product did not exhibit a molecular ion in the MS. Anal. Calc for C₂₂H₃₂O₄: C, 73.30; H, 8.95. Found: C, 73.34; H, 8.96.
2,2',2''',2'''-((Adamantane-1,3,5,7-tetrayl)tetraacetamide (53). CF₃CO₂H (41 mg, 0.275 mmol) in solvent CH₂Cl₂, f-PrOH and H₂O (60:20:1; 5 mL) was added dropwise with stirring to tetra-enol ether 52 (23 mg, 0.064 mmol) at room temperature. After 16 h, saturated aqueous NaHCO₃ (8 mL) was added and the mixture was extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were dried (MgSO₄), concentrated in vacuo and the residue chromatographed (hexanes : EtOAc : MeOH, 1 : 1 : 0.2) to afford tetra-aldehyde 53 (11.5 mg, 60%) as colorless crystals: mp 124 - 126 °C (EtOAc); Rf 0.24 (hexanes : EtOAc : MeOH, 1 : 1 : 0.2); IR (film) 2923, 2850, 1713 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.83 (s, J 2.6 Hz, 4H, CHO), 2.28 (d, J 2.6 Hz, 8H, CH₂CHO), 1.56 (s, 12H, adamantane methylene); ¹³C NMR (100 MHz, CDCl₃) δ 201.6, 55.4, 45.6, 34.8; MS (EI) m/z 304 (M⁺); HRMS (EI) m/z calc for C₁₈H₂₄O₄ (M⁺) 304.1675, found: 304.1683; Anal. Calc for C₁₈H₂₄O₄: C, 71.03; H, 7.95. Found: C, 70.98; H, 7.93.

2,2',2''',2'''-((Adamantane-1,3,5,7-tetrayl)tetraacetic Acid (54a). NaClO₂ (308 mg, 2.74 mmol) and NaH₂PO₄·H₂O (378 mg, 2.74 mmol) in H₂O (2.8 mL) were added slowly with stirring to t-BuOH (11.2 mL), 2-methyl-2-butene (2.8 mL) and tetra-aldehyde 53 (52 mg, 0.171 mmol) in the dark at room temperature. After overnight stirring, the mixture was acidified to pH 1-2 and extracted with EtOAc (5 x 15 mL). The combined organic layers were back extracted into saturated aqueous NaHCO₃ (70 mL). This solution was reacidified to pH 1-2 using 4 M HCl and extracted with EtOAc (4 x 40 mL). These combined organic extracts were dried (MgSO₄), concentrated in vacuo and the residue further dried under vacuum overnight to afford the tetra-acid 54a (52 mg, 83%) as a white solid, which was used directly in the subsequent step without further purification: ¹H NMR (400 MHz, DMSO-d₆) δ 11.96 (br s, 4H, CO₂H), 2.01 (s, 8H, CH₂CO₂H), 1.32 (s, 12H, adamantane methylene); ¹³C NMR (100 MHz, DMSO-d₆) δ 172.8, 47.7, 45.6, 34.2.

Tetramethyl 2,2',2''',2'''-((Adamantane-1,3,5,7-tetrayl)tetraacetate (54b). SOCl₂ (35 µL, 0.47 mmol) was added slowly with stirring to tetra-acid 54a (29 mg, 0.079 mmol) and DMF (1.2 µL, 0.016 mmol) in CH₂Cl₂ (3 mL) at 0 °C. After stirring overnight at room temperature, all volatile materials were removed in vacuo and the crude tetra-acid chloride was allowed to dry under vacuum for an additional 4 h and was used in the subsequent step without any further purification. MeOH (6 mL) was added with stirring to crude tetra-acid chloride at room temperature overnight, during which time the original cloudy mixture became a clear solution. The MeOH and HCl were removed in vacuo, the residue was dissolved in EtOAc (20 mL), washed with H₂O (5 mL), 5% aqueous Na₂CO₃ (5 mL) and brine (10 mL), dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed (hexanes : EtOAc, 4 : 1) to afford tetra-methyl ester 54b (14 mg, 42% over two steps) as colorless crystals: mp 80 - 82 °C (hexanes : EtOAc, 1 : 1); Rf 0.31 (hexanes : EtOAc, 2 : 1); IR (film) 2951, 2924, 2851, 1732, 1438 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.65 (s, 12H, CO₂CH₃), 2.17 (s, 8H, CH₂CO₂CH₃), 1.40 (s, 12H, adamantane methylene); ¹³C NMR (100 MHz, CDCl₃) δ 171.6, 51.2, 47.1, 45.2, 34.3; MS (EI) m/z 424 (M⁺); HRMS (EI) m/z calc for C₂₂H₃₂O₈ 424.2097, found: 424.2083.

Tetraethyl 4,4',4'',4'''-((adamantane-1,3,5,7-tetrayl)tetraakis(3-oxobutanoate) (15a). Tetra-aldehyde 53 (238 mg, 0.78 mmol) in CH₂Cl₂ (6 mL) was added with stirring to anhydrous SnCl₂ (60 mg, 0.31 mmol) and ethyl diazoacetate (0.362 mL, 3.44 mmol) in CH₂Cl₂ (10 mL) at 0 °C and the mixture allowed to warm up to room temperature. After 2 h, the mixture was washed with brine (15 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The organic extracts were dried (MgSO₄), concentrated in vacuo and the residue was chromatographed (hexanes : EtOAc, 2 : 1) to afford the tetra-β-keto ester 15a (417 mg, 82%) (3 : 1 keto : enol forms) as a colorless oil: Rf 0.46 (hexanes : EtOAc, 1 : 1); IR (film) 2983, 2905, 1744, 1714, 1633 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): (all keto form) δ 4.17 (q, J 7.2 Hz, 8H, CO₂CH₂CH₃), 3.36 (m, 8H, CH₂CO₂Et), 2.34 (m, 8H, CH₂COCH₂CO₂Et), 1.46-1.38 (m,
Tetraethyl 4,4',4'',4'''-(adamantane-1,3,5,7-tetrayl)tetrakis(2-diazo-3-oxobutanoate) (55a). Et₃N (1.04 mL, 7.44 mmol) was added dropwise with stirring to tetra-β-ketoester 15a (402 mg, 0.62 mmol) and 4-acetamidobenzenesulfonyl azide (40) (655 mg, 2.73 mmol) in dry MeCN (15 mL) at 0 °C and the mixture was allowed to warm up to room temperature. After 3 h, the reaction mixture was concentrated in vacuo and the resultant solid was triturated with Et₂O and hexanes (1:1) (100 mL). The mixture was filtered, the filtrate was concentrated in vacuo and the residue was chromatographed (hexanes : EtOAc, 2 : 1) to afford the tetra-diazoster 55a (450 mg, 97%) as a viscous oil: Rf 0.51 (hexanes : EtOAc, 1 : 1); IR (film) 2133, 1714, 1649, 1300 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.23 (q, J 7.2 Hz, 8H, CO₂CH₂CH₃), 2.68 (s, 8H, CH₂COC=N₂), 1.45 (s, 12H, adamantane methylene), 1.28 (t, J 7.2 Hz, 12H, CO₂CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 190.8, 161.2, 77.2, 61.2, 50.1, 45.2, 35.9, 14.2; MS (ES) m/z 775 (M + Na⁺); HRMS (ES) m/z calcd for C₃₄H₄₈N₄O₁₂Na 775.2663, found: 775.2654.

Tetra-tert-butyl 4,4',4'',4'''-(Adamantane-1,3,5,7-tetrayl)tetrakis(3-oxobutanoate) (15b.) Tetra-aldehyde 53 (30 mg, 0.099 mmol) in CH₂Cl₂ (3 mL) was added with stirring to anhydrous SnCl₂ (7.5 mg, 0.040 mmol) and tert-butyl diazoacetate (0.060 mL, 0.43 mmol) in CH₂Cl₂ (2 mL) at 0 °C and the mixture was allowed to warm up to room temperature. After 2 h, the reaction was quenched with brine (10 mL) and the mixture was extracted with CH₂Cl₂ (3 × 15 mL). The organic extracts were dried (MgSO₄), concentrated in vacuo and the residue was chromatographed (hexanes : EtOAc, 4 : 1) to afford the tetra-β-keto ester 15b (61 mg, 81%) (ca. 4 : 1 keto : enol forms) as a colorless oil: Rf 0.41 (hexanes : EtOAc, 2 : 1); IR (film) 2978, 2932, 2914, 2855, 2364, 1724, 1707, 1698, 1584, 1417, 1384, 1351, 1302, 1247, 1214, 1170, 1150, 1118, 1087, 1065, 1044, 968, 946, 905, 872, 842, 811, 761, 747, 728, 677, 648, 627, 605, 582, 559, 537, 515, 493, 470, 448, 426, 405, 383, 361, 340, 320, 300, 280, 260, 240, 220, 200, 180, 160, 140, 120, 100, 80, 60, 40, 20, 10 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) (all keto form) δ 3.26 (s, 8H, CH₂CO₂Bu), 2.33 (s, 8H, CH₂COCH₂CO₂Bu), 1.48 (s, 12H, adamantane methylene), 1.45 (s, 36H, C(CH₃)₃); (enol form) δ 12.19 (s, 4H, C(OH)=CHCO₂Bu), 4.77 (s, 4H, C(OH)=CHCO₂Bu), 1.94 (s, 8H, CH₂C(OH)=CHCO₂Bu); (all enol form) δ 175.6, 172.4, 91.7, 59.9, 48.5, 45.3, 34.7, 14.2; MS (EI) m/z 648 (M⁺); HRMS (EI) m/z calcd for C₃₄H₄₈N₄O₁₂ 648.3146, found: 648.3145; Anal. Calc for C₃₄H₄₈N₄O₁₂: C, 61.93; H, 6.95; N, 12.96.

Tetra-tert-butyl 4,4',4'',4'''-(Adamantane-1,3,5,7-tetrayl)tetrakis(2-diazo-3-oxobutanoate) (55b). Et₃N (0.255 mL, 1.82 mmol) was added dropwise with stirring to tetra-β-keto ester 15b (115 mg, 0.151 mmol) and 4-acetamidobenzenesulfonyl azide (40) (160 mg, 0.666 mmol) in dry MeCN (10 mL) at 0 °C was added and the mixture was allowed to warm up to room temperature. After stirring overnight, the reaction mixture was concentrated in vacuo and the resultant solid was triturated with Et₂O and hexanes (1:1) (80 mL), the mixture was filtered, and the filtrate was concentrated in vacuo. The residue was chromatographed (hexanes : EtOAc, 4 : 1) to afford tetra-diazo-tert-butyl ester 55b (130 mg, 99%) as a viscous oil: Rf 0.57 (hexanes : EtOAc, 2 : 1); IR (film) 2979, 2930, 2130, 1712, 1645, 1310 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.67 (s, 8H, CH₂C(O)=N₂), 1.48 (s, 36H, tert-butyl), 1.46 (s, 12H, adamantane methylene); ¹³C NMR (100 MHz, CDCl₃) δ 191.2, 160.4, 82.9, 78.0, 50.2, 45.2, 35.9, 28.2; MS (ES) m/z 887 (M + Na⁺); HRMS (ES) m/z calcd for C₄₂H₅₆N₄O₁₂Na 887.3915, found: 887.3923; Anal. Calc for C₄₂H₅₆N₄O₁₂: C, 58.32; H, 6.53; N, 12.96. Found: C, 58.42; H, 6.47; N, 12.86.
2-(1-Adamantane)acetyl chloride. Freshly distilled SOCl₂ (12 mL) was added to 2-(1-adamantane)acetic acid (1.50 g, 7.33 mmol) in a flame-dried flask. The mixture was heated to reflux with vigorous stirring for 5 h, when the excess thionyl chloride was removed in vacuo. PhH (15 mL) was added and was subsequently removed in vacuo to leave a light yellow oil, which was stored under vacuum overnight to leave crude 2-(1-adamantane)acetyl chloride (1.65 g, 99%) as a light yellow oil: IR (film) 2904, 2850, 1797, 1451 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.70 (s, 2H, CH₂COCl), 1.99 (s, 3H, adamantane methine), 1.74-1.67 (m, 12H, adamantane methylene); ¹³C NMR (75 MHz, CDCl₃) δ 170.9, 60.7, 41.6, 36.4, 34.0, 28.3.

1-Diazo-3-(1-adamantyl)-2-propanone. N-Nitroso-N-methyl urea (3.0 g, 28.6 mmol) was added in small portions with stirring to aqueous KOH (50%; 8 mL) and Et₂O (20 mL) at 0 °C. After 15 min, the bright yellow ethereal solution of CH₂N₂ was carefully decanted and maintained at 0 °C. 2-(1-Adamantane)acetyl chloride (1.5 g, 7.04 mmol) in Et₂O (10 mL) was added dropwise with stirring to the ice-cold CH₂N₂ solution. After 2 h at 0 °C and room temperature overnight, removal of solvent in vacuo left the title diazo-ketone (1.54 g, quantitative yield) as a yellow oil: Rᵣ 0.42 (hexanes : EtOAc, 4 : 1); IR (film) 2902, 2847, 2099, 1631, 1354 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.19 (s, 1H, COCH₂), 2.05 (s, 2H, CH₂CO), 1.97 (s, 3H, adamantane methine), 1.63 (s, 12H, adamantane methylene); MS (Cl, NH₃) m/z 219 (M + H⁺); HRMS (Cl, NH₃) m/z calc for C₁₃H₁₉N₂O (M + H⁺) 219.1497, found: 219.1496.

Octahydro-3a,7:5,9-dimethanocyclopent[a][8]annulen-2(3H)-one (49). 1-Diazo-3-(1-adamantyl)-2-propanone 1-(3-Diazo-2-oxo-1-propyl)-adamantane (1.55 g, 7.11 mmol) in PhMe (40 mL) was added over 5 h via syringe pump to toluene (160 mL) containing CuSO₄ (320 mg, 2.0 mmol) at reflux. The mixture was subsequently heated under reflux for an additional 2 h, cooled down to room temperature and filtered. The filtrate was sequentially washed with H₂O (50 mL), 5 M aqueous NaOH (50 mL), H₂O (50 mL) and brine (50 mL), dried (MgSO₄) filtered and evaporation in vacuo. The residual thick light brown oil was chromatographed (hexanes : EtOAc, 50 : 1) to give the cyclopentanone 49 (632 mg, 47% over 3 steps), which was identical with the material previously prepared.

4,5,6,7,8,9-Hexahydro-3a,7:5,9-dimethanocyclopent[a][8]annulen-2(3H)-one (57). Me₃SiCl (3.74 mL, 29.2 mmol) and cyclopentanone 49 (554 mg, 2.92 mmol) in THF (6 mL) were added sequentially dropwise with stirring to lithium 2,2,6,6-tetramethylpiperidine (13.1 mmol), prepared from 2,2,6,6-tetramethylpiperidine (2.46 mL, 14.6 mmol) and n-BuLi (1.6 M in hexanes, 8.2 mL, 13.1 mmol) in THF (5 mL), at −78 °C. After a further 20 min at −78 °C, Et₃N (6.3 mL) was added, and the mixture was allowed to warm to room temperature during a period of 1 h. Et₂O (50 mL) was added, and the organic solution was washed with H₂O (20 mL) and brine (20 mL), dried (MgSO₄), concentrated in vacuo and the remaining tetramethylpiperidine removed under vacuum. Pd(OAc)₂ (643 mg, 2.86 mmol) was added to residue of silyl enol ethers in dry MeCN (10 mL) and the mixture stirred overnight at room temperature. The mixture was filtered through a short pad of Celite, eluting with Et₂O and the organic phase was washed with saturated aqueous NH₄Cl (10 mL), dried (MgSO₄), concentrated in vacuo and the residue chromatographed (hexanes : EtOAc, 15 : 1 to 10 : 1) to afford the cyclopentenone 57 (125 mg, 23%) and recovered starting material 49 (178 mg, 32%). The enone 57 was obtained as a colorless oil: Rᵣ 0.29 (hexanes : EtOAc, 4 : 1); IR (film) 2917, 2851, 1703, 1626 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.73 (s, 1H, COCH=C), 3.06 (s, 2H, CH₂CO), 2.10-2.01 (m, 7H, adamantane methine and methylene), 1.84-1.82 (m, 4H, adamantane methylene), 1.66 (m, 2H, adamantane methylene); ¹³C NMR (75 MHz, CDCl₃) δ 170.9, 60.7, 41.6, 36.4, 34.0, 28.3.
MHCl, CDCl3) δ 208.5, 192.3, 121.5, 49.4, 45.2, 43.3, 38.2, 35.7, 35.2, 28.7; MS (El) m/z 188 (M+); HRMS (El) m/z calc for C13H16O (M+) 188.1201, found: 188.1201.

2,3,4,5,6,7,8,9-Octahydro-3a,7:5,9-dimethanocyclopenta[8]annulen-2-ol (58). DIBAl-H in hexanes (1.0 M; 0.59 mL, 0.59 mmol) was added dropwise with stirring to cyclopentenone 57 (55 mg, 0.29 mmol) in dry THF (5 mL) at −78 °C. After a further 30 min at −78 °C, saturated aqueous NH4Cl (0.16 mL), Et2O (10 mL), and silica gel (200 mg) were added and the mixture was stirred vigorously and allowed to warm up to room temperature. The mixture was filtered through a short pad of anhydrous MgSO4 and the solids were leached with EtOAc. The combined organic phases were rotary evaporated and the residue chromatographed (hexanes : EtOAc, 8 : 1) to give the cyclopentenol 59 (50 mg, 90%) as a colorless oil: RF 0.28 (hexanes : EtOAc, 4 : 1); IR (film) 2933 broad, 2902, 2847, 1666 cm−1; 1H NMR (400 MHz, CDCl3) δ 5.25 (d, J 2.0 Hz, 1H, CH=C), 4.83 (ddd, J 7.8, 3.9, 2.0 Hz, 1H, CHO), 2.61 (m, 1H, CH2CHOH), 2.31 (m, 1H, CH2CHOH), 1.91 (dd, J 14.1, 7.8 Hz, 1H, CH=CHCH), 1.86-1.37 (m, 12H, adamantane); 13C NMR (100 MHz, CDCl3) δ 157.4, 118.0, 76.3, 48.4, 46.9, 46.3, 46.2, 38.7, 36.7, 33.9, 30.2, 30.0, 29.8; the product did not exhibit a molecular ion in the MS.

4,5,6,7,8,9-Hexahydro-3a,7:5,9-dimethanocyclopenta[8]annulene (59). Allylic alcohol 58 (48 mg, 0.25 mmol) was dissolved in CDCl3 (2 mL). After 2 h, CDCl3 was carefully removed in vacuo and the residue was chromatographed (hexanes only) to afford adamantanocyclopentadiene 60 (40 mg, 89%) as a colorless and volatile oil: RF 0.26 (hexanes : EtOAc, 15 : 1); IR (film) 2914, 2848 cm−1; 1H NMR (300 MHz, CDCl3) δ 6.41 (d, J 5.0 Hz, 1H, CH=CHCH=C), 6.30 (d, J 5.0 Hz, 1H, CH=CHCH=C), 5.82 (s, 1H, CH=CHCH=C), 3.06 (apparent s, 1H, CH=CHCH=C), 2.15 (apparent d, J 12.0 Hz, 2H, adamantane), 2.01 (apparent s, 2H, adamantane), 1.93 (apparent d, J 12.0 Hz, 2H, adamantane), 1.78 (apparent s, 2H, adamantane), 1.51 (apparent d, J 11.5 Hz, 2H, adamantane), 1.12 (apparent d, J 11.5 Hz, 2H, adamantane); 13C NMR (75 MHz, CDCl3) δ 160.6, 142.7, 130.0, 113.8, 53.0, 41.2, 39.3, 36.1, 33.8, 28.1; MS (El) m/z 172 (M+); HRMS (El) m/z calc for C13H16 (M+) 172.1252, found: 172.1253.

(±)-(3aR,3bR,4S,6R,8S,9aR,10S,10aR)-4,5,6,7,8,9,10,10a-Octahydro-1H-3b,10-etheno-4,8:6,9a-dimethanocycloocta[3,4]cyclopenta[1,2-c]furan-1,3(3aH)-dione (61). Diene 59 (15 mg, 0.087 mmol) and maleic anhydride (60) (11 mg, 0.13 mmol) in CH2Cl2 (0.5 mL) and CHCl3 (1 mL) were allowed to stand for 21 h at room temperature. CHCl3 and CH2Cl2 were removed in vacuo and the residue was chromatographed (hexanes : Et2O) to give the Diels-Alder adduct 61 (5 mg, 23%) as a light yellow oil; RF 0.40 (hexanes : EtOAc, 4:1); IR (film) 2912, 2854, 2359, 1856, 1776 cm−1; 1H NMR: (300 MHz, CDCl3) δ 6.25 (d, J 5.7 Hz, 1H), 6.15 (dd, J 5.7, 2.8 Hz, 1H), 3.91 (d, J 7.7 Hz, 1H), 3.70 (dd, J 7.6, 4.5 Hz, 1H), 3.10 (m, 1H), 2.55 (s, 1H), 2.21-2.17 (m, 1H), 2.06-2.02 (m, 2H), 1.90-1.62 (m, 6H), 1.34-1.26 (m, 3H); 13C NMR: (75 MHz, CDCl3) δ 172.3, 171.8, 138.8, 133.1, 63.1, 61.3, 53.5, 47.8, 46.4, 38.2, 35.1, 33.7, 31.9, 29.7, 28.4, 28.2, 27.8; MS (El) m/z 270 (M+); HRMS (El) m/z calc for C17H18O3 (M+) 270.1256, found 270.1256.

(2,3,4,5,6,7,8,9-Octahydro-3a,7:5,9-dimethanocyclopenta[8]annulen-2-yl) 3-(4,5,6,7,8,9-hexahydro-3a,7:5,9-dimethanocyclopenta[8]annulene) (63). Tris(p-bromophenyl)ammonium hexachloroantimonate (62) (57 mg, 0.070 mmol) was added with stirring to adamantanocyclopentadiene 59 (120 mg, 0.70 mmol) in CH2Cl2 (3.5 mL) at 0 °C. After 2.5 h, reaction was quenched with excess methanolic sodium methoxide and the mixture was diluted with excess CH2Cl2. The organic phase was washed with H2O (3 x 10 mL) and brine (10 mL), dried (MgSO4), concentrated in vacuo and the residue chromatographed (hexanes only) to give the substituted cyclopentadiene dimer 63 (48 mg, 40%) as a colorless oil: RF 0.78 (hexanes : EtOAc, 15 : 1); IR (film) 2904, 2846,
1445 cm\(^{-1}\); UV-Vis (hexanes) \(\lambda_{\text{max}} \log \varepsilon\) 262 (3.76) nm; \(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)) \(\delta\) 6.30 (m, 1H, H\(_A\)), 5.93 (d, \(J\) 1.9 Hz, 1H, H\(_B\)), 5.21 (d, \(J\) 2.0 Hz, 1H, H\(_C\)), 3.72 (m, 1H, H\(_E\)), 2.98 (m, 1H, H\(_F\)), 2.75 (m, 1H, H\(_D\)), 2.10-1.20 (m, 26H, adamantane and H\(_G\)); \(^{13}\)C NMR (125 MHz, C\(_6\)D\(_6\)) \(\delta\) 162.2, 157.9, 153.0, 123.9, 117.4, 114.6, 53.3, 47.3, 47.1, 46.4, 45.9, 41.9, 41.5, 41.4, 40.4, 39.8, 39.5, 38.7, 37.0, 36.5, 34.2, 34.1, 30.39, 30.36, 28.74, 28.70; MS (EI) \(m/z\) 344 (M\(^+\)); HRMS (EI) \(m/z\) calc for C\(_{26}\)H\(_{32}\) (M\(^+\)) 344.2504, found: 344.2503.

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**Supplementary Material**

Copies of the single crystal X-ray crystallographic structures of tetraol 21 and tetra-((hydroxymethyl)-cyclopropyl)-adamantane 35, their CIF files and NMR spectra for the dimer 63 are provided in the Supplementary Material.

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