Synthesis of Eight- and Nine-Membered Carbocycles through a Ring-Closing Metathesis/Ring Fragmentation Strategy: A Rapid and Versatile Approach to Bicyclo[6.4.0]- and Bicyclo[7.4.0]alkene Ring Systems

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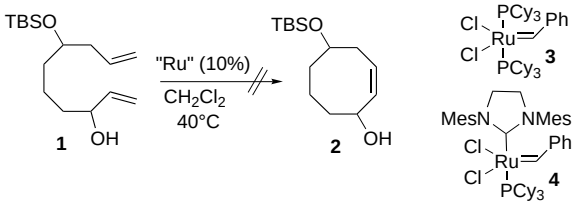
Abstract: Ring-closing metathesis (RCM) of *cis*-2,6-dialkenyl-2-hydroxy-1-cyclohexanones affords bicyclo[3.-*n*.1]alkenones that are easily converted into eight- or nine-membered carbocycles by oxidative cleavage of the keto-bridging tether. Since the starting cyclohexanones are readily assembled from commercially available 1,2-cyclohexanedione, the overall process constitutes a rapid and versatile route to medium-sized carbocycles, which are otherwise difficult compounds to assemble using currently available procedures. If one of the alkenes of the cyclohexanone chains is replaced by an alkyne, the subsequent RCM produces 1,3-diene systems capable of undergoing stereoselective Diels–Alder reaction with activated dienophiles. Oxidative cleavage of the keto bridge of the resulting tricycles leads to 8–6 and 9–6 fused bicarbocycles with up to four stereocenters.

Keywords: bicyclo[*n*.4.0]alkenes · carbocycles · cyclization · metathesis · ring cleavage

Introduction

The increasing economical and ecological concerns of modern society demand that synthetic chemists develop processes that provide desired target molecules in a rapid and practical way while minimizing by-products.[1] As a general rule, synthesis should start from readily available materials and convert them into target-relevant complex systems in as few steps as possible.[2]

Among targets of special interest for synthetic chemists, medium-sized carbocycles, particularly eight- and nine-membered rings, continue to occupy a prominent position. Rings of this size, which form the structural core of numerous bioactive natural products,[3] are difficult to construct by conventional cyclization procedures due to both enthalpic and entropic reasons.[4] It has recently been shown that ring-closing metathesis (RCM) is a particularly powerful method for the assembly of such rings;[5] however, its success is restricted to substrates bearing some sort of conformational constraint, such as a pre-existing ring, which bias the intra- versus the intermolecular process.[6] This is why we were unable to transform diene **1** into cyclooctane **2** by RCM, regardless of the catalyst used (Scheme 1). With ruthenium complex **3** the starting diene was mostly recovered, and with the newer Grubbs's catalyst **4**[7] the reaction gave a complex mixture of products.



Scheme 1. Unsuccessful attempts at RCM of **1**.

We have recently reported that cyclooctenes such as **2** can be prepared by an alternative method consisting of endowing the diene precursor with a one-atom internal tether that can be cleaved after the cyclization.[8] In this case, the cyclization takes place under mild conditions because of less demanding enthalpic and entropic requirements. As the tethered precursor we used compound **6**, which is easily prepared from cyclohexenone **5** by an addition–alkylation reaction (Scheme 2). Oxidative cleavage of the keto bridge after the RCM reaction afforded the desired cyclooctanoid ring.

A major difficulty in implementing the above protocol as a truly practical route to medium-sized rings is ensuring that the cyclohexanone alkenyl chains have a *cis* stereochemistry. In

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Supporting information for this article is available on the WWW under http://www.chemeurj.org or from the author: procedures for the synthesis of **6a**,**c**,**d** and **7a**,**c**,**d** by Claisen rearrangements, X-ray data for **20**, and relevant NMR spectra for **22**.

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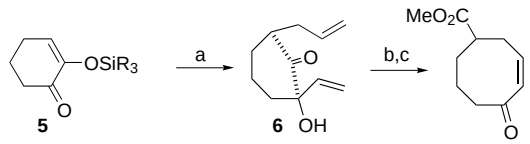
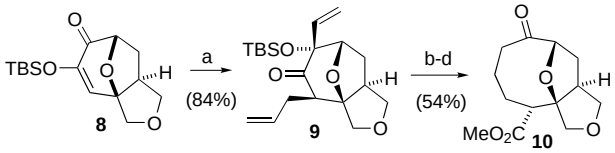


Scheme 2. Strategy for constructing the required cyclooctanoid ring: a) 1) CH_2CHLi, THF, −78 °C, then allyl bromide; 2) TBAF, THF; b) **3**, CH_2Cl_2, 20 °C; c) $Pb(OAc)_4$, MeOH, 20 °C.

this paper, in addition to giving more details of the approach, we demonstrate that such stereochemistry can be achieved by taking advantage of a dynamic kinetic isomerization process that occurs during desilylation of the initially obtained *cis*/*trans* mixture of *α-tert*-butyldimethylsilyloxycyclohexanones. We also describe a variant of the approach that uses an enyne instead of a diene for ring-closing metathesis; this allows construction of 8–6 and 9–6 fused carbobicyclic systems with up to four stereocenters.

Results and Discussion

The decision to use silylated cyclohexenones such as **5** as key starting materials in our route was based on previous studies of the transformation of [5+2] pyrone–alkene oxabicyclic cycloadducts into 1,4-oxygen-bridged cyclonona- and cyclodecanoid rings.[9] We knew that addition of vinyllithium to the *α*-silyloxyketone adduct **8** generates an enolate that can be stereoselectively trapped in situ with an alkylating agent such as allyl bromide (Scheme 3). The favorable *cis* arrangement of

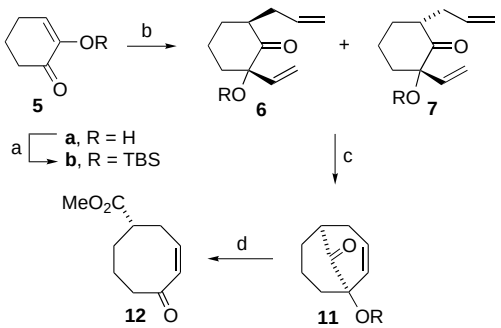


Scheme 3. Strategy for ring enlargement of the oxabicyclic pyrone-alkene cycloadducts: a) CH_2CHLi, THF, −78 °C, then allyl bromide; b) **3** (5 mol %), CH_2Cl_2, 40 °C; c) H_2, Pd/C; d) 1) TBAF, THF; 2) $Pb(OAc)_4$, MeOH, sealed tube, 100 °C, 1 h.

Abstract in Spanish: *La ciclación mediante metátesis de cis-2,6-dialquenil-2-hidroxi-1-ciclohexanonas conduce a biciclo[3.n.1]alquenonas que pueden convertirse fácilmente en carbociclos de ocho o nueve miembros mediante rotura oxidativa de la cadena del puente. Dado que las ciclohexanonas de partida pueden sintetizarse a partir de 1,2-ciclohexanodiona, sustancia asequible comercialmente, el proceso global permite obtener carbociclos de tamaño medio de forma práctica, rápida y versátil. Si uno de los alquenos de las cadenas sustituyentes de la ciclohexanona se reemplaza por un alquino, la ciclación da lugar a sistemas 1,3-diénicos que pueden participar en reacciones de Diels–Alder con dienófilos activados. La rotura oxidativa de la cadena puente de los triciclos que se obtienen produce bicarbociclos con anillos fusionados de 8 y 6, y de 9 y 6 miembros, y con la estereoquímica relativa de cuatro estereocentros completamente controlada.*

the alkenyl chains of the resulting product **9** facilitates a subsequent RCM reaction, which can be carried out by simply heating in refluxing CH_2Cl_2 in presence of 5 mol % of catalyst **3**. The *α*-silyloxyketo bridge provides a suitable site for oxidative cleavage of the tetracycle to obtain the ring-enlarged oxabicycle **10**.

Although the above addition/silyl migration/alkylation sequence also worked when applied to cyclohexenone **5b**, the stereoselectivity was rather low and the *cis*/*trans* (**6b**/**7b**) ratio was only 58:42 (Scheme 4).[10] Since the diastereoisomers



Scheme 4. Synthesis of cyclooctenone **12**: a) TBSCl, imidazole, CH_2Cl_2; b) CH_2CHLi, THF, −78 °C, then allyl bromide; c) **3** (5 mol %), CH_2Cl_2, 40 °C; d) $Pb(OAc)_4$, MeOH, 20 °C.

could not be separated by conventional flash chromatography, the RCM was assayed on the mixture using standard conditions (0.05 M in CH_2Cl_2, 40 °C, 5 mol % of **3**). Although the reaction was more sluggish than in the case of **9**, after 12 h we could isolate a small amount of the desired bicycle **11b** (15 % yield from **5b**), which was easily separated from the uncyclized *trans* isomer (Scheme 4) after desilylation.

We later found that removal of the silyl protecting group from the mixture of **6b** and **7b** allowed separation of the diastereoisomers. Remarkably, alcohol **6a** smoothly cyclized at room temperature (0.005 M in CH_2Cl_2, 20 °C, 9 h) to give the bicycle **11a** in 95 % yield.[11] Furthermore, whereas oxidative cleavage of the keto bridge of the tetracycle obtained in the RCM of **9** required heating in MeOH in a sealed tube at 100 °C, transformation of **11a** into cyclooctenone **12** was instantaneous at room temperature, and occurred in 84 % yield.

We attributed the difference between the cyclization rates of **6a** and **6b** to the need of the substrate to adopt the reactive conformation ***B*** shown in Figure 1, since the population of this conformer must be considerably larger for the alcohol than for the silyloxy derivative, principally because of the feasibility of hydrogen bonding between the hydroxyl group and the ketone oxygen.[8]

For the above cyclization–fragmentation approach to be truly practical, the *cis*/*trans* (**6**/**7**) ratio had to be improved. Although epimerization of **7a** or **7b** is readily promoted by treatment with catalytic amounts of a relatively strong base such as KO*t*Bu in *t*BuOH/CH_2Cl_2,[12] the *trans* isomer predominates in the equilibrium in both the hydroxyl and silyloxy case (**6a**/**7a**, 26:74; **6b**/**7b**, 30:70; Table 1). Moreover, all attempts to couple the epimerization to the RCM

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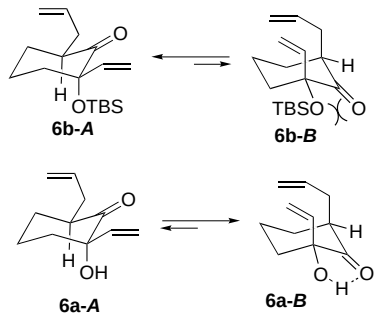
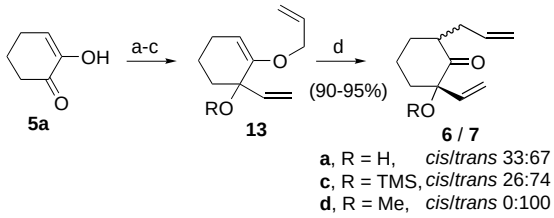


Figure 1. Proposed conformational equilibria, corroborated by simple MM2 calculations.[8]



Scheme 5. Synthesis of cyclohexanones **6** and **7** by Claisen rearrangement: a) Allyl alcohol, *p*-TsOH, benzene; b) $CH_2CHMgBr$, THF, $-78\,^{\circ}C$, then H_3O^+; c) for **13c**: TMS-imidazole, CH_2Cl_2, for **13d**: NaH, THF, $0\,^{\circ}C$, then MeI; d) toluene, sealed tube, $160\,^{\circ}C$.

failed. If the ruthenium catalyst was used in excess with respect to the base, RCM proceeded but epimerization was suppressed, and the use of excess base with respect to the catalyst seemed to prevent the metathesis. Catalytic amounts of acids (AcOH or TfOH in CH_2Cl_2/water) failed to induce the epimerization, and thereby the RCM was not evaluated in their presence.

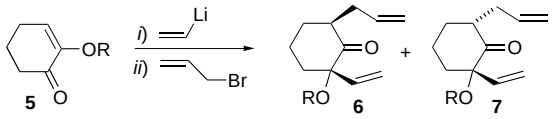
We also tried to obtain the α,α'-bisalkylated cyclohexanones by Claisen rearrangement of allylvinylethers **13** (Scheme 5);[13] however, this reaction gave mainly the undesired *trans* isomer.

The above failures to improve the *cis*/*trans* ratio led us to focus on the addition–alkylation step. We reasoned that increasing the bulk of the silyl group of the silyloxy cyclohexenone substituent might favor formation of the desired *cis* isomer **6** by hindering the approach of the allyl bromide to the face bearing this group. The use of triisopropylsilyl (TIPS) as a protecting-migrating group did not enhance the *cis*/*trans* ratio, whereas the introduction of a *tert*-butyldiphenylsilyl (TBDPS) allowed us to slightly improve the proportion of the desired *cis* isomer (**6f**:**7f**, 2:1, Table 1).

With these stereoselectivity results, and taking into account that the desilylation reaction could be achieved by adding excess tetrabutylammonium fluoride (TBAF) to the crude reaction mixture of the addition–alkylation process, the whole process for transforming **5f** into **12** (Scheme 4) involves three one-pot operations and leads to the product in approximately 39% overall yield.

In repeating this protocol, we realized that the **6a**/**7a** ratio obtained upon deprotection of the crude mixture of **6f** and **7f** was not entirely reproducible, according to ^{1}H NMR analysis, and it was sometimes even slightly better than the 2:1 proportion resulting from the alkylation step. These results, which appeared to be influenced by both the source of the

Table 1. The addition–alkylation step.

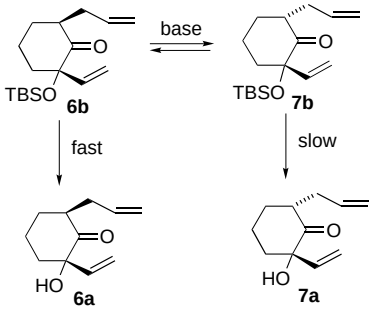


b, R = TBS
e, R = TIPS
f, R = TBDPS

Entry	Enone[a]	Yield[b] [%]	**6**:**7**[c]	Thermodynamic ratio **6**:**7**[d]
1	**5b**	83	**6b**:**7b** (58:42)	**6b**:**7b** (30:70)
2	**5e**	76	**6e**:**7e** (61:39)	**6e**:**7e** (44:56)
3	**5f**	78	**6f**:**7f** (67:33)	**6f**:**7f** (33:67)

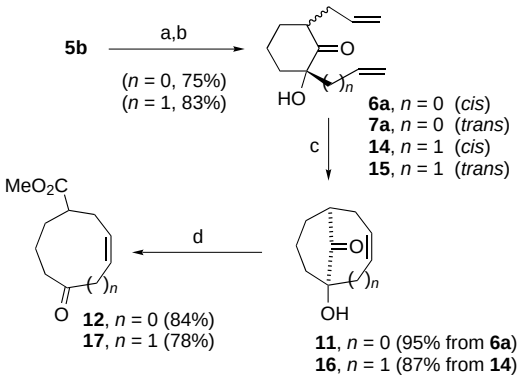
[a] Prepared by using standard silylation conditions. [b] Combined yield of isolated product after chromatography. [c] Ratio determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] Calculated after stirring the kinetic mixture with NaOMe in MeOH for 12 h.

organolithium and the amount of excess TBAF used, suggested that some kind of epimerization might be accompanying the desilylation reaction. Therefore, we decided to examine this reaction in more detail using a chromatographically pure thermodynamic (3:7) mixture of **6b** and **7b**. Remarkably, treatment of this mixture with just 1.2 equivalents of TBAF[14] for 30 min afforded a non-thermodynamic 80:20 proportion of *cis*/*trans* isomers **6a**/**7a**. Since the *cis*-OH derivative is produced faster than the *trans*-OH (TLC observation), and since an independent experiment showed that TBAF is unable to induce the epimerization between **6a** and **7a** this rapidly, the above result can be explained in terms of a kinetic, selective desilylation of the *cis* derivative with simultaneous re-equilibration of the protected isomers (Scheme 6).[15] This last epimerization is probably promoted by fluoride ion, since TBAF is able to induce the epimerization of the methoxy derivative **7d**.

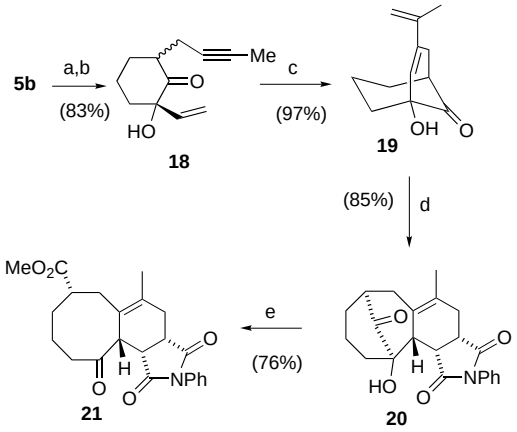


Scheme 6. Hypothesized isomerization–kinetic desilylation process.

In view of these results, the best experimental protocol for achieving the alkylation-cyclization-fragmentation process is as follows (Scheme 7): 1) addition of vinyllithium to **5b**, and trapping of the resulting enolate with allyl bromide (THF, $-78\,^{\circ}C$), 2) filtration of the crude residue through a pad of silica gel to remove salts and impurities, and deprotection by reaction with 1.2 equivalents of TBAF, 3) treatment of the resulting 80:20 mixture of **6a** and **7a** with the ruthenium catalyst **3** (5 mol%, CH_2Cl_2, $20\,^{\circ}C$, 9 h; 76% yield, 95% based on **6a**), 4) chromatographic purification of the bicycle **11** and treatment with $Pb(OAc)_4$ (MeOH, $20\,^{\circ}C$, 5 min). Overall, the



Scheme 7. Best protocol for the synthesis of cyclooctenone **12** and cyclononenone **17**: a) CH_2CHLi (for **12**) or CH_2CHCH_2Li (for **17**), THF, $-78\,^{\circ}C$, then allyl bromide; b) TBAF (1.2 equiv), THF, 30 min $20\,^{\circ}C$; c) **3** (5 mol%), CH_2Cl_2, $20\,^{\circ}C$; d) $Pb(OAc)_4$ (1.5 equiv), MeOH, $20\,^{\circ}C$, 5 min.



Scheme 8. Synthesis of the stereochemically-rich 8–6 bicarbocycle **21**: a) CH_2CHLi, THF, $-78\,^{\circ}C$, then 1-bromo-2-butyne; b) TBAF (1.2 equiv), THF, 30 min, $20\,^{\circ}C$; c) **3** (5 mol%), CH_2Cl_2, $40\,^{\circ}C$, 3 h; d) *N*-phenylmaleimide, toluene, sealed tube, $155\,^{\circ}C$, 5 h; e) $Pb(OAc)_4$, MeOH, $20\,^{\circ}C$, 5 min.

carbocycle **12** was obtained in 48% yield from commercially available 1,2-cyclohexanedione.

Importantly, the above approach is not limited to the construction of cyclooctanoid rings. A slight change in the synthetic sequence, the use of allyllithium instead of vinyllithium in the initial alkylation reaction, allowed preparation of the homologous nine-membered carbocycles (Scheme 7). The allylation reaction led to the expected 60:40 kinetic ratio of the *cis* and *trans* isomers, which were desilylated by treatment with 1.2 equivalents of TBAF to give an 80:20 mixture of **14** and **15** in 83% combined yield. Subjecting this mixture to the RCM conditions provided the expected bicyclo[4.3.1] product **16** in 70% yield (87% based on **14**), although in this case the reaction required 15 h at room temperature for completion. It should be noted that this type of bicyclo[4.3.1]decane system forms the basic carbocyclic skeleton of a wide variety of relevant natural products,[16] and hence compound **16** could be an interesting synthetic intermediate in approaching these targets. Finally, as expected, oxidative cleavage of the bridge proceeded efficiently upon treatment of **16** with $Pb(OAc)_4$ (MeOH, $20\,^{\circ}C$) to afford the expected cyclononene **17** in 78% yield (45% from **5b**).

In a number of natural products such as taxol,[17] medium-sized rings are fused to six-membered carbocycles. We were therefore led to investigate whether the above RCM could be extended to enynes, because the Diels–Alder reaction of the resulting dienes would open the way to this type of fused system.[18] Furthermore, the stereochemical bias posed by the bicyclic system might favor stereoselectivity in the Diels–Alder reaction.

Addition of vinyllithium to the cyclohexenone **5b** followed by alkylation of the resulting enolate with 1-bromo-2-butyne gave a 55:45 *cis*/*trans* mixture of dialkylated cyclohexanones in 88% yield. After rapid chromatographic filtration of the reaction residues, treatment of the isomeric mixture with 1.2 equivalents of TBAF led again to the expected *cis* isomer enrichment; *cis*/*trans*, 80:20 (94% yield). The ring-closing metathesis of the enyne **18** could be carried out at room temperature although it was slightly faster in refluxing CH_2Cl_2 and gave the desired diene **19** in 78% yield (97% based on the proportion of *cis* enyne; Scheme 8). The subsequent Diels–Alder reaction with *N*-phenylmaleimide took place by simply heating at $155\,^{\circ}C$ in toluene for 5 h. This gave only one of the four possible stereoisomeric adducts, thus fulfilling our expectations with respect to the exercise of stereocontrol by the rigid bicyclic skeleton (Scheme 8). This isomer was isolated in 85% yield and was unequivocally identified as the *endo* adduct **20** by X-ray crystallography (Figure 2).

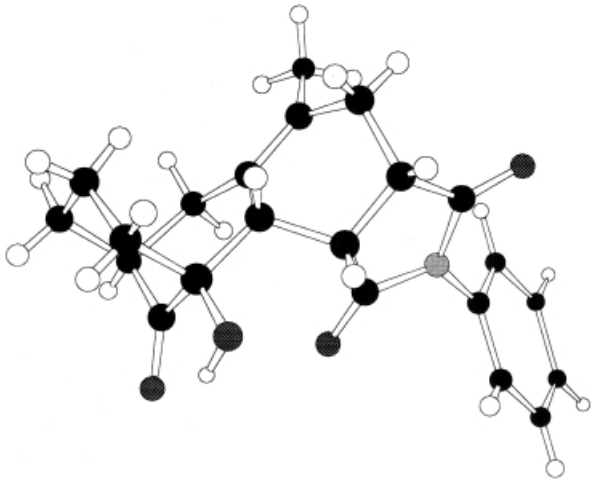


Figure 2. Representation of the structure of compound **20**, as determined by X-ray crystallography.

As in the case of the bicyclic systems, the one-carbon bridge can easily be fragmented by reaction with $Pb(OAc)_4$, which in this case afforded an 8–6 bicarbocyclic system with four stereocenters with controlled relative configuration (41% overall yield of **21** from **5b**).

The Diels–Alder reaction is not limited to symmetric dienophiles. Use of methyl acrylate afforded the lactone **22**, which was isolated in a 55% yield (Scheme 9). We assigned the *endo* configuration on the basis of an NOE observed between the hydrogen α to the carboxyl group and the bridgehead hydrogen.

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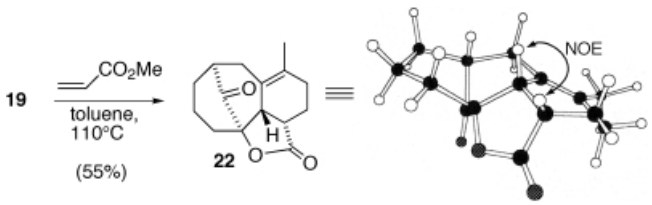
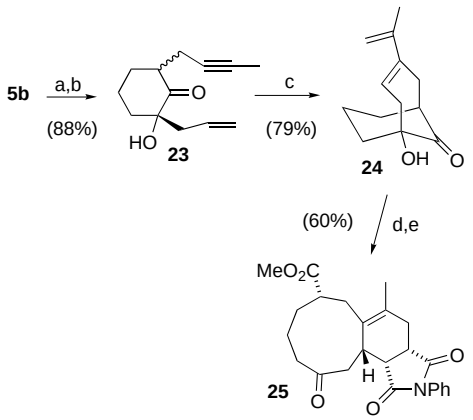


Scheme 9. Diels–Alder reaction of **19** with methyl acrylate.

As in the case of the medium-sized monocycles discussed above, the use of allylithium in the alkylation step instead of vinyllithium, followed by desilylation, led to enyne **23** as a 80:20 mixture of *cis* and *trans* isomers (88% yield for both steps). RCM of the mixture afforded the expected bicyclo[4.3.1] product **24** in a 79% yield (based on the proportion of the *cis* starting enyne). Again the Diels–Alder reaction with *N*-phenylmaleimide gave one major isomer that was isolated in 67% yield (Scheme 10). Subsequent oxidative



Scheme 10. Synthetic approach to the stereochemically rich fused 9–6 bicarbocycle **25**: a) CH_2CHCH_2Li, THF, −78 °C, then 1-bromo-2-butyne; b) TBAF (1.2 equiv), THF, 20 °C, 30 min; c) **3** (5 mol%), CH_2Cl_2, 40 °C, 5 h; d) *N*-phenylmaleimide, toluene, sealed-tube, 160 °C, 4 h; e) $Pb(OAc)_4$, MeOH, 20 °C, 5 min.

cleavage provided the desired fused carbobicycle **25** in 89% yield (33% overall yield from **5b**). The stereochemistry of the final product **25** was tentatively assigned by assuming that in the Diels–Alder reaction the dienophile approaches the same face of the diene as in the case of **19**.

Conclusion

In summary, commercially available 1,2-cyclohexanedione can be converted in four operational simple steps into bicyclo[3.3.1]nonenones or bicyclo[4.3.1]decenones by combining a dialkylation and a RCM reaction. Oxidative cleavage of the keto bridge in these bicycles produces eight- and nine-membered carbocycles, which are otherwise difficult to assemble. By using an enyne instead of a diene, RCM allows construction of a bicycle with a conjugated diene capable of undergoing a Diels–Alder reaction with activated olefins (Table 2). Importantly, the rigid bicyclic framework provides an excellent stereocontrolling element for this cycloaddition that takes place with almost complete stereoselectivity. Cleavage of the one-carbon bridging tether of the resulting systems affords 8–6 and 9–6 fused carbobicyclic systems with up to four stereocenters.

Table 2. The structure of the final product is determined by the organolithium/alkylbromide pair.

RX \ RLi	CH_2=CHLi	CH_2=$CHCH_2Li$
Allyl bromide	eight-membered carbocycle	nine-membered carbocycle
1-bromo-2-butyne	bicyclo[6.4.0]dodecane	bicyclo[7.4.0]tridecane

Experimental Section

General: All dry solvents were freshly distilled before use under argon over the appropriate drying agent. Toluene and THF were distilled from sodium/benzophenone. CH_2Cl_2 was distilled from P_2O_5. MeOH was distilled from Mg/I_2. All reactions were conducted in dry solvents under argon atmosphere unless otherwise stated. Thin-layer chromatography (TLC) was performed on aluminum silica gel plates, and components were visualized by observation under UV light, or by treating the plates with a phosphomolybdic reagent followed by heating. Flash chromatography was performed on silica gel. Dryings were performed with anhydrous Na_2SO_4. Concentrations were carried out in a rotary evaporator. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, at 250 MHz and 62.9 MHz, respectively, and in some cases at 300 or 500 MHz (75.4 or 125.7 MHz for ^{13}C NMR). Carbon multiplicities were determined from DEPT ^{13}C NMR experiments. The following abbreviations are used to indicate signal multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Vinyllithium (0.45 M in Et_2O/pentane) was freshly prepared from vinylbromide by treatment with *t*BuLi (1.5 M in pentane). Allyllithium (0.35 M in THF) was freshly prepared from allyltriphenyltin and phenyllithium. The TBAF used was 1 M in THF.

2-*tert*-Butyldimethylsilyloxy-2-cyclohexen-1-one (5b): Imidazole (204 mg, 3.0 mmol) and TBSCl (345 mg, 2.3 mmol) were added to a solution of 1,2-cyclohexanedione (225 mg, 2.0 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 30 min and then poured into brine. Extraction with CH_2Cl_2, drying, filtering, and concentration gave a residue that was purified by flash chromatography (3% EtOAc/hexanes) to afford compound **5b** (450 mg, 99% yield) as a colorless oil. R_f = 0.66 (20% EtOAc/hexanes); ^1H NMR: δ = 6.11 (t, J = 4.6 Hz, 1H), 2.43–2.19 (m, 4H), 1.9 (m, 2H), 0.88 (s, 9H), 0.08 (s, 6H); ^{13}C NMR: δ = 195.4 (C), 147.9 (C), 127.5 (CH), 38.6 (CH_2), 25.6 (CH_3), 24.7 (CH_2), 23.1 (CH_2), 18.3 (C), −4.8 (CH_3); MS (70 eV): *m/z* (%): 169 (100) [$M^+ - C(CH_3)_3$], 139 (11), 111 (6), 95 (4); HRMS-FAB: *m/z* [M^++1] calcd for $C_{12}H_{22}O_2Si$: 227.1467; found: 227.1467.

Addition–allylation–desilylation process: Synthesis of 6a/7a and 14/15

Compounds 6a/7a: Vinyllithium (4.9 mL, 2.2 mmol) was added to a −78 °C cooled solution of **5b** (454 mg, 2 mmol) in THF (20 mL). The reaction was allowed to reach room temperature and was stirred for 1 h. After re-cooling to −78 °C, allyl bromide (0.26 mL, 3 mmol) was added and the mixture stirred overnight at that temperature and then poured into brine. Extraction with Et_2O, drying, filtering, and concentration gave a crude that was filtered through a short pad of silica gel (1–2% EtOAc/hexanes) to afford the addition–alkylation product (490 mg, 83% yield) as an inseparable *cis*/*trans* mixture of isomers (58:42 ratio). R_f = 0.66 (6% EtOAc/hexanes); ^1H NMR: δ = 6.31–6.00 (m, 1H), 5.85–5.63 (m, 2H), 5.37–5.14 (m, 2H), 5.05–4.9 (m, 2H), 3.11 (m, 0.58H), 2.64–2.28 (m, 1.42H), 2.26–1.54 (m, 6H), 1.20 (m, 1H), 0.87, 0.85 (2s, 9H), 0.14 to −0.05(m, 6H); ^{13}C NMR: δ = 211.5 (C), 209.5 (C), 139.1 (CH), 138.8 (CH), 136.5 (CH), 136.2 (CH), 116.7 (CH_2), 116.5 (CH_2), 116.2 (CH_2), 115.9 (CH_2), 82.9 (C), 79.0 (C), 48.0 (CH), 45.4 (CH), 42.9 (CH_2), 38.1 (CH_2), 34.4 (CH_2), 33.63 (CH_2), 33.61 (CH_2), 33.43 (CH_2), 33.40 (CH_2), 25.95 (CH_3), 25.87 (CH_3), 22.2 (CH_2), 20.3 (CH_2), 18.5 (C), 18.3 (C), −2.2 (CH_3), −2.4 (CH_3), −2.5 (CH_3), −2.7 (CH_3).

TBAF (2.1 mL, 2.1 mmol) was added to a solution of the above mixture (515 mg, 1.75 mmol) in THF (15 mL). After stirring for 30 min at room temperature, the reaction was poured into brine and extracted with Et_2O. Drying, filtering, and concentration gave a crude residue that was purified by flash chromatography (2–3% EtOAc/hexanes) to afford of an 80:20 mixture of isomers **6a** and **7a** (284 mg, 90% combined yield) as a colorless oil.

***(2R*,6R*)*-6-Allyl-2-hydroxy-2-vinyl-1-cyclohexanone (6a)**: $R_f = 0.18$ (6% EtOAc/hexanes); ^{1}H NMR: $\delta = 6.19$ (dd, $J = 10.8$, 17.4 Hz, 1H), 5.78–5.44 (m, 1H), 5.40 (dd, $J = 17.6$, 0.9 Hz, 1H), 5.30 (dd, $J = 10.6$, 0.7 Hz, 1H), 5.00 (m, 2H), 2.97 (m, 1H), 2.54–2.36 (m, 1H), 2.12–1.83 (m, 5H), 1.80–1.65 (m, 1H), 1.55–1.41 (m, 1H); ^{13}C NMR: $\delta = 212.4$ (C), 138.9 (CH), 135.9 (CH), 116.6 (CH_2), 114.7 (CH_2), 78.4 (C), 46.6 (CH), 40.0 (CH_2), 34.2 (CH_2), 32.7 (CH_2), 19.6 (CH_2); MS (70 eV): *m/z* (%): 180 (2) [M^+], 169 (18), 149 (31), 96 (19), 95 (17), 83 (33), 79 (22); HRMS: *m/z* calcd for $C_{11}H_{16}O_2$ 180.1150; found: 180.1150.

***(2S*,6R*)*-6-Allyl-2-hydroxy-2-vinyl-1-cyclohexanone (7a):** $R_f = 0.25$ (6% EtOAc/hexanes); ^{1}H NMR: $\delta = 6.16$ (dd, $J = 17.1$, 10.5 Hz, 1H), 5.74 (m, 1H), 5.45 (d, $J = 17.1$ Hz, 1H), 5.26 (d, $J = 10.5$ Hz, 1H), 5.02 (m, 2H), 4.23 (s, 1H), 2.68–2.53 (m, 2H), 2.32–2.16 (m, 2H), 2.03 (m, 1H), 1.86–1.68 (m, 3H), 1.38–1.32 (m, 1H); ^{13}C NMR: $\delta = 211.9$ (C), 137.2 (CH), 135.7 (CH), 116.7 (CH_2), 116.65 (CH_2), 79.4 (C), 46.7 (CH), 41.8 (CH_2), 34.1 (CH_2), 33.3 (CH_2), 21.8 (CH_2); MS (70 eV): *m/z* (%): 180 (14), 169 (100), 149 (23), 111 (16), 96 (22), 83 (36); HRMS: *m/z* calcd for $C_{11}H_{16}O_2$: 180.1150; found: 180.1153.

***cis*- and *trans*-2,6-Diallyl-2-hydroxy-1-cyclohexanone (14 and 15)**: Using the same protocol, but with allyllithium (6.30 mL, 2.2 mmol, 0.35 M in THF) instead of vinyllithium, afforded of a chromatographically inseparable mixture of compounds **14** and **15** (323 mg, 83% yield) as a colorless oil. $R_f = 0.44$ (15% EtOAc/hexanes); ^{1}H NMR: $\delta = 5.94–5.59$ (m, 2H), 5.19–4.87 (m, 4H), 3.00 (m, 0.8H), 2.68–2.31 (m, 3.2H), 2.25–1.84 (m, 5H), 1.76–1.42 (m, 2H), 1.37–1.12 (m, 1H); ^{13}C NMR: $\delta = 213.6$ (C), 213.2 (C), 136.3 (CH), 135.7 (CH), 133.1 (CH), 131.5 (CH), 119.8 (CH_2), 118.6 (CH_2), 116.5 (CH_2), 116.2 (CH_2), 78.9 (C), 77.1 (C), 46.6 (CH), 45.8 (CH), 41.8 (CH_2), 41.4 (CH_2), 40.9 (CH_2), 40.0 (CH_2), 34.2 (CH_2), 33.9 (CH_2), 33.5 (CH_2), 33.3 (CH_2), 21.9 (CH_2), 20.1 (CH_2); HRMS-FAB: *m/z* [M^++1] calcd for $C_{12}H_{19}O_2$: 195.1385; found: 195.1385. The ratios of isomers were determined by ^{1}H NMR integration of characteristic alkenyl hydrogens.

Diene metatheses and oxidative fragmentation: Synthesis of 12 and 17

1-Hydroxybicyclo[3.3.1]non-2-en-9-one (11): Catalyst **3** (30 mg, 0.036 mmol) was added to the 80:20 mixture of **6a** and **7a** (145 mg, 0.805 mmol) in CH_2Cl_2 (160 mL). The reaction mixture was stirred at room temperature for 9 h, the solvent was evaporated, and the residue was purified by flash chromatography (5–10% EtOAc/hexanes) to afford unreacted **7a** (26 mg) and **11** (93 mg, 76% yield, 95% based on **6a**) as a white solid. $R_f = 0.32$ (25% EtOAc/hexanes); m.p. 82 °C; ^{1}H NMR: $\delta =$ 5.85 (m, 1H), 5.52 (m, 1H), 3.79 (br s, 1H), 2.87–2.67 (m, 2H), 2.45–2.37 (m, 1H), 2.05 (m, 1H), 1.99–1.60 (m, 5H); ^{13}C NMR: $\delta = 213.9$ (C), 131.7 (CH), 129.0 (CH), 76.0 (C), 44.7 (CH), 41.2 (CH_2), 36.7 (CH_2), 36.1 (CH_2), 19.4 (CH_2); MS (70 eV): *m/z* (%): 152 (3) [M^+], 149 (100), 95 (27), 85 (15), 69 (23); HRMS: *m/z* calcd for $C_9H_{12}O_2$: 152.0837; found: 152.0831.

1-Hydroxybicyclo[4.3.1]dec-3-en-10-one (16): Catalyst **3** (20 mg, 0.024 mmol) was added to the 80:20 mixture of **14** and **15** (115 mg, 0.593 mmol) in CH_2Cl_2 (120 mL). The reaction mixture was stirred at room temperature for 15 h, the solvent was evaporated, and the residue was purified by flash chromatography (5–10% EtOAc/hexanes) to afford unreacted **15** (18 mg) and **16** (69 mg, 76% yield, 87% based on **14**) as a white solid. $R_f = 0.38$ (15% EtOAc/hexanes); m.p. 89 °C; ^{1}H NMR: $\delta =$ 5.86–5.78 (m, 2H), 4.21 (br s, 1H), 2.95 (m, 1H), 2.69 (m, 1H), 2.41–2.14 (m, 5H), 1.97–1.74 (m, 3H), 1.56 (m, 1H); ^{13}C NMR: $\delta = 216.3$ (C), 129.8 (CH), 127.4 (CH), 78.7 (C), 46.6 (CH), 42.3 (CH_2), 39.5 (CH_2), 33.6 (CH_2), 30.1 (CH_2), 20.9 (CH_2); MS (FAB): *m/z* (%): 167 (27) [M^++1], 149 (100) [$M^+ - 17$], 112 (39), 104 (24), 84 (35), 83 (30); HRMS-FAB [$M^+ + 1$] calcd for $C_{10}H_{15}O_2$: 167.1072, found: 167.1070.

Methyl 5-oxo-3-cyclooctene-1-carboxylate (12): $Pb(OAc)_4$ (300 mg, 0.676 mmol) was added to a solution of **11** (63 mg, 0.414 mmol) in MeOH (12 mL). The reaction was stirred at room temperature for 5 min, poured into brine and extracted with Et_2O. Drying, filtering, and concentration gave a crude that was purified by flash chromatography (7% EtOAc/hexanes) to afford of cyclooctenone **12** (63 mg, 84% yield) as a colorless oil. $R_f = 0.34$ (15% EtOAc/hexanes); ^{1}H NMR: $\delta = 6.42$ (dt, $J = 12.3$, 7.9 Hz, 1H), 6.14 (d, $J = 12.3$ Hz, 1H), 3.67 (s, 3H), 2.89–2.63 (m, 5H), 1.94–1.70 (m, 4H); ^{13}C NMR: $\delta = 203.3$ (C), 175.0 (C), 139.9 (CH), 135.1 (CH), 51.9 (CH_3), 41.9 (CH_2), 40.3 (CH), 29.2 (CH_2), 26.6 (CH_2), 20.9 (CH_2); MS (70 eV): *m/z* (%): 182 (3) [M^+], 150 (20), 149 (29), 123 (41) [$M^+ - CO_2CH_3$], 97 (26), 95 (100), 81 (72), 79 (53); HRMS-FAB: *m/z* [M^++1] calcd for $C_{10}H_{15}O_3$: 183.1017; found: 183.1021.

Methyl 6-oxo-3-cyclononene-1-carboxylate (17): Applying a similar procedure used for the oxidative cleavage of **11** to **16** (0.40 mmol) gave cyclononene **17** (61 mg, 78% yield) as a colorless oil. $R_f = 0.34$ (15% EtOAc/hexanes); ^{1}H NMR: $\delta = 5.71–5.50$ (m, 2H), 3.65 (s, 3H, s), 3.26 (m, 1H), 3.01 (m, 1H), 2.59–2.31 (m, 5H), 1.83–1.55 (m, 4H); ^{13}C NMR: $\delta =$ 211.9 (C), 175.6 (C), 130.4 (CH), 124.7 (CH), 52.1 (CH_3), 44.7 (CH_2), 42.4 (CH), 41.6 (CH_2), 27.1 (CH_2), 26.9 (CH_2), 20.4 (CH_2); MS (70 eV): *m/z* (%): 149 (8), 114 (20), 85 (12), 71 (26), 58 (100); HRMS-FAB: *m/z* [M^++1] calcd for $C_{11}H_{17}O_3$: 197.1177; found: 197.1168.

Addition–propargylation process and enyne metatheses: Synthesis of 19 and 24

***cis*- and *trans*-6-(2-Butynyl)-2-hydroxy-2-vinyl-1-cyclohexanone (18)**: Vinyllithium (9.8 mL, 4.41 mmol) was added to a −78 °C cooled solution of **5b** (900 mg, 3.98 mmol) in THF (20 mL). The mixture was warmed to room temperature and stirred for 10 min. After cooling to −78 °C, 1-bromo-2-butyne (0.49 mL, 5.6 mmol) was added. The reaction was stirred at room temperature for 30 min and then poured into brine. Extraction with Et_2O, drying, filtering, and concentration gave a crude residue that was purified by flash chromatography (1–2% EtOAc/hexanes) to afford an inseparable *cis*/*trans* (55:45) mixture of isomers of the addition-alkylation product (1.07 g, 88% yield) as colorless oil. $R_f = 0.66$ (5% EtOAc/hexanes); ^{1}H NMR: $\delta = 6.39–6.00$ (m, 1H), 5.40–5.14 (m, 2H), 3.18 (m, 0.55H), 2.71–1.90 (m, 5.45H), 1.86–1.75 (m, 1H), 1.74, 1.72 (2s, 3H), 1.71–1.58 (m, 1H), 1.3–1.11 (m, 1H), 0.92, 0.86 (s, 9H), 0.14 to −0.02 (m, 6H); ^{13}C NMR: $\delta = 210.6$ (C), 208.9 (C), 138.9 (CH), 138.7 (CH), 116.9 (CH_2), 116.3 (CH_2), 82.3 (C), 80.1 (C), 78.8 (C), 77.1 (C), 76.9 (C), 76.4 (C), 47.8 (CH), 45.5 (CH), 42.9 (CH_2), 38.1 (CH_2), 34.1 (CH_2), 33.2 (CH_2), 25.92 (CH_3), 25.91 (CH_3), 21.9 (CH_2), 20.2 (CH_2), 19.1 (CH_2), 18.9 (CH_2), 18.5 (C), 18.3 (C), 3.5 (CH_3), 3.4 (CH_3), −2.2 (CH_3), −2.4 (CH_3), −2.5 (CH_3), −2.7 (CH_3).

TBAF (2 mL, 2 mmol) was added to a solution of the mixture prepared above (500 mg, 1.63 mmol) in THF (15 mL). After stirring for 30 min at room temperature, the reaction mixture was poured into brine and then extracted with Et_2O. Drying, filtering, and concentration gave a crude residue that was purified by flash chromatography (5–10% EtOAc/hexanes) to afford a *cis*/*trans* (80:20) mixture of isomers **18** (295 mg, 94% yield) as a colorless oil. $R_f = 0.43$ (20% EtOAc/hexanes); ^{1}H NMR: $\delta =$ 6.33–6.05 (m, 1H), 5.50–5.17 (m, 2H), 3.11 (m, 0.8H), 2.81–2.37 (m, 2.2H), 2.35–2.09 (m, 2H), 2.08–1.78 (m, 3H), 1.76 (s, 3H), 1.55–1.32 (m, 1H); ^{13}C NMR: $\delta = 211.3$ (C), 211.2 (C), 139.2 (CH), 137.3 (CH), 116.9 (CH_2), 114.5 (CH_2), 79.4 (C), 79.3 (C), 78.3 (C), 77.2 (C), 76.7 (C), 76.4 (C), 46.2 (CH), 46.1 (CH), 41.7 (CH_2), 40.2 (CH_2), 33.9 (CH_2), 33.0 (CH_2), 21.6 (CH_2), 19.8 (CH_2), 19.4 (CH_2), 19.0 (CH_2), 3.5 (CH_3), 3.4 (CH_3).

***cis* and *trans*-2-Allyl-6-(2-butynyl)-2-hydroxy-1-cyclohexanone (23)**: Allyllithium (11.2 mL, 3.92 mmol) was added to a −78 °C cooled solution of **5b** (800 mg, 3.54 mmol) in THF (20 mL). The reaction was warmed to room temperature, stirred for 5 min and then cooled to −78 °C. 1-Bromo-2-butyne (0.45 mL, 5.14 mmol) was added, and the reaction was stirred at room temperature for 30 min, poured into brine, and then extracted with Et_2O. After drying, concentration, and filtration, the crude residue was purified by flash chromatography (1–2% EtOAc/hexanes) to afford an inseparable *cis*/*trans* (45:55) mixture of isomers of the addition-alkylation product (1.05 g, 93% yield) as colorless oil. $R_f = 0.64$ (4% EtOAc/hexanes); ^{1}H NMR: $\delta = 5.85–5.57$ (m, 1H), 5.06–4.89 (m, 2H), 2.99 (m, 0.45H), 2.63–2.12 (m, 4.55H), 2.12–1.80 (m, 3H), 1.67 (s, 3H), 1.63–1.06 (m, 3H), 0.89, 0.73 (2s, 9H), 0.17 to −0.14 (m, 6H); ^{13}C NMR: $\delta = 210.7$ (C), 210.2 (C), 133.8 (CH), 132.3 (CH), 117.7 (CH_2), 117.6 (CH_2), 82.5 (C), 79.6 (C), 76.8 (C), 76.6 (C), 76.2 (C), 47.3 (CH), 45.9 (CH), 43.1 (CH_2), 41.6 (CH_2), 41.2 (CH_2), 39.9 (CH_2), 33.9 (CH_2), 33.0 (CH_2), 25.81 (CH_3), 25.80 (CH_3), 22.0 (CH_2), 20.2 (CH_2), 19.1 (CH_2), 18.8 (CH_2), 18.4 (C), 18.3 (C), 3.30 (CH_3), 3.29 (CH_3), −2.1 (CH_3), −2.68 (CH_3), −2.69 (CH_3), −3.8 (CH_3).

TBAF (2.8 mL, 2.8 mmol) was added to a solution of the above enynes (750 mg, 2.34 mmol) in THF (20 mL) and stirred at room temperature for

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30 min. The reaction mixture was poured into brine and extracted with Et_2O. Drying, filtering, and concentration gave a crude residue that was purified by flash chromatography (5–10% EtOAc/hexanes) to afford an inseparable mixture of isomers (*cis*/*trans* ratio 80:20) of **23** (459 mg, 95% yield) as a colorless oil. $R_f = 0.54$ (20% EtOAc/hexanes); ^{1}H NMR: $\delta =$ 5.97–5.44 (m, 1H), 5.20–4.87 (m, 2H), 3.06 (m, 0.8H), 2.64–1.85 (m, 7.2H), 1.65 (s, 3H), 1.62–1.36 (m, 2H), 1.16 (m, 1H); ^{13}C NMR: $\delta = 212.9$ (C), 211.9 (C), 133.0 (CH), 131.3 (CH), 119.5 (CH_2), 118.5 (CH_2), 78.8 (C), 76.9 (C), 76.8 (C), 76.7 (C), 76.5 (C), 76.4 (C), 46.3 (CH), 45.5 (CH), 41.1 (CH_2), 40.7 (CH_2), 40.0 (CH_2), 39.8 (CH_2), 33.8 (CH_2), 33.7 (CH_2), 21.6 (CH_2), 21.4 (CH_2), 20.0 (CH_2), 18.8 (CH_2), 3.26 (CH_3), 3.25 (CH_3).

1-Hydroxy-3-isopropenylbicyclo[3.3.1]non-2-en-9-one (19): Catalyst **3** (60 mg, 0.07 mmol) was added to a solution of **18** (80:20 *cis*/*trans* mixture, 250 mg, 1.30 mmol) in CH_2Cl_2 (200 mL). The mixture was heated at reflux for 3 h, and the solvent was then evaporated. The crude residue was purified by flash chromatography (5–10% EtOAc/hexanes) to afford unreacted *trans*-**18** (45 mg) and **19** (193 mg, 97% yield) as a colorless oil. $R_f = 0.38$ (20% EtOAc/hexanes); ^{1}H NMR: $\delta = 5.66$ (s, 1H), 5.10 (s, 1H), 5.01 (s, 1H), 4.82 (br s, 1H), 2.78 (m, 2H), 2.63 (m, 1H), 2.09 (m, 1H), 1.98–1.73 (m, 8H); ^{13}C NMR: $\delta = 214.3$ (C), 141.0 (C), 138.4 (C), 129.1 (CH), 113.3 (CH_2), 75.6 (C), 44.0 (CH), 41.8 (CH_2), 36.7 (CH_2), 36.2 (CH_2), 20.7 (CH_3), 19.5 (CH_2); MS (70 eV): *m/z* (%): 192 (39) [M^+], 147 (61), 135 (100), 121 (29), 107 (28), 91 (52); HRMS: *m/z* calcd for $C_{12}H_{16}O_2$: 192.1150; found: 192.1141.

1-Hydroxy-3-isopropenylbicyclo[4.3.1]dec-3-en-10-one (24): Catalyst **3** (17 mg, 0.02 mmol) was added to a solution of **23** (80:20 mixture of *cis*/*trans* isomers, 76 mg, 0.37 mmol) in CH_2Cl_2 (75 mL), and the reaction mixture was heated at reflux for 5 h. The solvent was evaporated and the residue was purified by flash chromatography (5–12% EtOAc/hexanes) to afford **24** (48 mg, 79% yield) as a colorless oil. $R_f = 0.4$ (20% EtOAc/hexanes); ^{1}H NMR: $\delta = 5.90$ (t, $J = 7.2$ Hz, 1H), 5.04 (s, 1H), 4.90 (s, 1H), 4.21 (br s, 1H), 2.96 (m, 2H), 2.87–2.56 (m, 2H), 2.48–2.19 (m, 3H), 2.05–1.86 (m, 2H), 1.83 (s, 3H), 1.80–1.67 (m, 2H); ^{13}C NMR: $\delta = 211.9$ (C), 143.3 (C), 143.2 (C), 124.8 (CH), 112.8 (CH_2), 80.1 (C), 47.6 (CH), 42.9 (CH_2), 36.9 (CH_2), 33.0 (CH_2), 28.1 (CH_2), 21.0 (CH_3), 19.4 (CH_2); MS (70 eV): *m/z* (%): 206 (6) [M^+], 188 (88), 144(14), 131(18), 95(20), 85(35), 79(100); HRMS: *m/z* calcd for $C_{13}H_{18}O_2$: 206.1307; found: 206.1311.

Diels–Alder reactions and oxidative fragmentations. Synthesis of 21, 22 and 25

(1*S,2*S**,3*R**,7*S**,12*S**)-1-Hydroxy-9-methyl-5-phenyl-5-azatetracyclo-[10.3.1.0^{2,10}0^{3,7}]hexadec-9-ene-4,6,16-trione (20)**: A solution of **19** (65 mg, 0.34 mmol) and *N*-phenylmaleimide (100 mg, 0.58 mmol) in toluene (14 mL) was heated at 155 °C in a sealed-tube for 5 h. The solvent was evaporated and the residue was purified by flash chromatography (20–60% EtOAc/hexanes) to afford **20** (105 mg, 85% yield) as a white solid. $R_f = 0.42$ (75% EtOAc/hexanes); m.p. 98 °C; ^{1}H NMR: $\delta = 7.38–7.17$ (m, 3H), 6.97 (m, 2H), 4.38 (br s, 1H), 3.80 (dd, $J = 8.4$, 4 Hz, 1H), 3.13 (t, $J =$ 7.5 Hz, 1H), 2.97 (s, 1H), 2.78–2.56 (m, 4H), 2.39 (m, 1H), 2.13 (d, $J =$ 8.4 Hz, 1H), 1.96–1.81 (m, 5H), 1.67 (s, 3H), 1.59 (m, 1H); ^{13}C NMR: $\delta =$ 212.5 (C), 178.6 (C), 178.0 (C), 131.4 (C), 128.9 (CH), 128.5 (CH), 128.3 (C), 128.2 (C), 126.2 (CH), 77.2 (C), 53.1 (CH), 47.4 (CH_2), 44.3 (CH), 42.3 (CH), 40.1 (CH), 36.8 (CH_2), 34.6 (CH_2), 32.6 (CH_2), 19.2 (CH_3). MS (70 eV): *m/z* (%): 365 (6) [M^+], 337 (32), 254 (89), 174 (12), 91 (100), 77 (61); HRMS: *m/z* calcd for $C_{22}H_{23}NO_4$: 365.1627; found: 365.1620.

(1*S,4*S**,10*S**,15*S**)-7-Methyl-2-oxatetracyclo[6.6.1.1^{1,10}0^{4,15}]hexadec-7-ene-3,16-dione (22)**: A solution of **19** (82 mg, 0.43 mmol) and methyl acrylate (0.25 mL, 4.30 mmol) in toluene (9 mL) was heated at reflux for 50 h. The reaction mixture was concentrated, and the residue was purified by flash chromatography to afford of an inseparable mixture of adducts (18 mg) and **22** (58 mg, 55% yield) as a white solid. $R_f = 0.3$ (40% EtOAc/hexanes); m.p. 141 °C; ^{1}H NMR: $\delta = 3.36$ (d, $J = 11$ Hz, 1H), 3.15 (dd, $J =$ 11, 14.6 Hz, 1H), 2.95 (m, 1H), 2.82 (m, 1H), 2.25 (d, $J = 11$ Hz, 1H), 2.20–1.96 (m, 3H), 1.88–1.77 (m, 6H), 1.63 (s, 3H), 1.59 (m, 1H); ^{13}C NMR: $\delta =$ 210.0 (C), 176.9 (C), 131.9 (C), 120.2 (C), 88.7 (C), 45.5 (CH), 45.0 (CH), 39.8 (CH), 33.3 (CH_2), 31.5 (CH_2), 28.7 (CH_2), 22.9 (CH_2), 19.6 (CH_3), 17.6 (CH_2). MS (70 eV): *m/z* (%): 246 (64) [M^+], 218 (44), 173 (37), 131 (43), 113 (100); HRMS *m/z* calcd for $C_{15}H_{18}O_3$: 246.1256; found: 246.1258.

Methyl (3a*S,7*S**,11a*S**,11b*R**)-5-methyl-1,3,11-trioxo-2-phenyl-2,3,3a,4,6,7,8,9,10,11,11a,11b-dodecahydro-1*H*-cyclooct[*e*]isoindole-7-carboxylate (21)**: $Pb(OAc)_4$ (175 mg, 0.395 mmol) was added to a solution of **20** (95 mg, 0.26 mmol) in MeOH (8 mL). After stirring for 5 min at room temperature, the reaction mixture was poured into brine and then extracted with Et_2O. Drying, filtering, and concentration gave a crude residue that was purified by flash chromatography (10–25% EtOAc/hexanes) to give **21** (78 mg, 76% yield) as a colorless oil. $R_f = 0.60$ (60% EtOAc/hexanes); ^{1}H NMR: $\delta = 7.51–7.30$ (m, 5H), 4.19 (d, $J = 5.7$ Hz, 1H), 3.72 (s, 3H), 3.17–2.85 (m, 4H), 2.60–2.39 (m, 4H), 2.32–2.17 (m, 1H), 1.98 (m, 1H), 1.83 (s, 3H), 1.71 (m, 3H); ^{13}C NMR: $\delta = 207.1$ (C), 178.6 (C), 178.1 (C), 175.8 (C), 134.8 (C), 132.3 (C), 129.0 (CH), 128.4 (CH), 126.7 (CH), 125.7 (C), 52.0 (CH_3), 51.3 (CH), 41.9 (CH), 41.3 (CH_2), 41.0 (CH), 39.2 (CH), 33.8 (CH_2), 30.6 (CH_2), 29.8 (CH_2), 22.4 (CH_2), 20.2 (CH_3); MS (70 eV): *m/z* (%): 395 (27) [M^+], 317 (23), 159 (25), 105 (100); HRMS: *m/z* calcd for $C_{23}H_{25}NO_5$: 395.1733; found: 395.1725.

(1*S,2*S**,3*R**,7*S**,12*S**)-1-Hydroxy-9-methyl-5-phenyl-5-azatetracyclo-[10.4.1.0^{2,10}0^{3,7}]heptadec-9-ene-4,6,17-trione**: A mixture of **24** (70 mg, 0.34 mmol) and *N*-phenylmaleimide (117 mg, 0.68 mmol) in toluene (14 mL) was heated at 160 °C in a sealed tube for 4 h. The solvent was evaporated and the residue was purified by flash chromatography (20–60% EtOAc/hexanes) to afford the Diels–Alder adduct (86 mg, 67% yield) as a viscous oil. $R_f = 0.44$ (60% EtOAc/hexanes); ^{1}H NMR: $\delta =$ 7.48–7.34 (m, 3H), 7.12 (m, 2H), 4.18 (s, 1H), 3.30–3.02 (m, 3H), 2.81 (m, 1H), 2.79–2.43 (m, 3H), 2.37–2.11 (m, 4H), 1.93–1.81 (m, 2H), 1.76 (s, 3H), 1.75–1.42 (m, 3H); ^{13}C NM: $\delta = 212.4$ (C), 178.5 (C), 177.2 (C), 131.7 (C), 130.9 (C), 130.5 (C), 128.9 (CH), 128.4 (CH), 126.2 (CH), 79.0 (C), 47.8 (CH), 45.3 (CH), 42.8 (CH_2), 40.4 (CH), 36.0 (CH_2), 35.6 (CH), 32.5 (CH_2), 31.5 (CH_2), 27.5 (CH_2), 19.4 (CH_3), 18.8 (CH_2); MS (70 eV): *m/z* (%): 379 (22) [M^+], 361 (57), 333 (100), 185 (49), 175 (72), 159 (24), 105 (56); HRMS: *m/z* calcd for $C_{23}H_{25}NO_4$: 379.1784; found: 379.1779.

Methyl (3a*S,7*S**,12a*S**,12b*R**)-5-methyl-1,3,11-trioxo-2-phenyl-1,2,3,3a,4,6,7,8,9,10,11,12,12a,12b-tetradecahydrocyclonona[*e*]isoindole-7-carboxylate (25)**: $Pb(OAc)_4$ (140 mg, 0.32 mmol) was added to a solution of the above tetracycle (80 mg, 0.21 mmol) in MeOH (10 mL) and the resulting solution stirred at room temperature for 5 min. The reaction mixture was poured into brine and extracted with Et_2O, dried, filtered, and concentrated. The crude residue was purified by flash chromatography (30–50% EtOAc/hexanes) to afford **25** (77 mg, 89% yield) as a white solid. $R_f = 0.52$ (60% EtOAc/hexanes); ^{1}H NMR: $\delta = 7.46–7.38$ (m, 3H), 7.24–7.20 (m, 2H), 3.58 (s, 3H), 3.49 (m, 1H), 3.26–3.18 (m, 3H), 3.02 (dd, $J = 6.1$, 15.7 Hz, 1H), 2.60–2.44 (m, 6H), 2.08–1.98 (m, 3H), 1.76 (s, 3H), 1.60 (m, 1H); ^{13}C NMR: $\delta = 212.8$ (C), 178.5 (C), 177.4 (C), 176.2 (C), 132.4 (C), 131.6 (C), 130.9 (C), 128.9 (CH), 128.5 (CH), 126.2 (CH), 79.3 (C), 51.7 (CH_3), 45.2 (CH), 43.2 (CH), 43.0 (CH_2), 40.3 (CH_2), 39.9 (CH), 39.5 (CH), 35.4 (CH_2), 30.5 (CH_2), 23.6 (CH_2), 19.6 (CH_3); MS (70 eV): *m/z* (%): 409 (71) [M^+], 332 (54), 183 (42), 159 (36), 119 (100), 105 (88); HRMS: *m/z* calcd for $C_{24}H_{27}NO_5$: 409.1889; found: 409.1877.

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