Straightforward Construction of Fused 6,7,5-Tricarbocyclic Systems by Tandem [5 + 2]/[4 + 2] Cycloadditions

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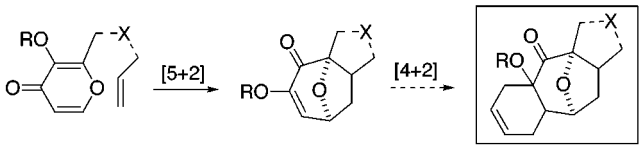
One-pot coupling of an intramolecular thermal [5C + 2C] pyrone−alkene cycloaddition to a [4C + 2C] Diels−Alder reaction provides immediate access to 6,7,5-tricarbocyclic systems bearing a 1,4-oxa-bridge in the seven-membered carbocycle. The transformation entails the net formation of four carbon−carbon bonds and creates three new cycles and a minimum of five new stereocenters. Preliminary attempts to open the oxa-bridge by reaction of the adducts with samarium diiodide and trimethylsilyl triflate led to relatively unexpected deoxygenated and aromatized products.

Introduction

Modern society with its increasing ecological concerns demands of synthetic chemists the development of processes that provide the desired targets not only rapidly and efficiently but also in an environmentally friendly manner.[1] One of the best ways to approach this challenge relies on the use of methods that achieve a maximum increase in molecular complexity per synthetic operation while generating minimal amounts of byproducts.[2] In this regard, cycloaddition reactions,[3] by allowing the direct construction of new rings by simple addition of two or more molecules, and tandem processes,[4] which integrate multistep sequences in a single operation, are particularly appealing. Herein, we report the successful coupling of [5 + 2] and [4 + 2] cycloadditions in a one-pot process to deliver relatively complex fused 6,7,5-tricarbocyclic systems from simple starting materials. The transformation leads to the net formation of four new carbon−carbon bonds and creates a minimum of five new stereocenters.

We have previously shown that the thermal intramolecular [5C + 2C] cycloaddition of β-alkoxy-γ-pyrones to temporarily tethered alkenes is a valuable strategy for rapidly assembling 8-oxabicyclo[3.2.1]octenone systems from readily available starting materials (Scheme 1).[5] The dense functionalization of the resulting oxabicycles has already allowed their stereoselective elaboration into a variety of products.[6] Recognition of a relatively low-field ^{1}H NMR chemical shift for the alkenyl hydrogen of these oxabicycles, suggestive of a substantial conjugation of the double bond with the carbonyl group, prompted us to examine the ability of these compounds to participate as dienophiles in a Diels−Alder type of reaction. This would provide a way to fuse a six-membered ring to the seven-membered carbocycle, which was of interest owing to the considerable amount of natural terpenoids that contain this type of ring system. Particularly relevant among them are a large number of diterpenes that contain 6,7,5-fused carbocyclic skeletons as basic structural core, such as those shown in Figure 1.[7] Most published approaches to this type of compounds involve relatively long, linear synthetic routes.[8]

Scheme 1



Results and Discussion

An appropriate precursor for the [5 + 2] cycloaddition reaction was readily prepared from maltol (**1**) by silylation, allylic bromination, and in situ trapping of the resulting unstable bromide with the sodium carbanion derivative of allylmalononitrile (45% for the two steps). Heating a solution of **2** in toluene at 160 °C for 12 h, in a sealed tube, afforded the expected [5C + 2C] adduct **3** in 90% yield (Scheme 2). The Diels−Alder reactivity on this substrate was examined using 2,3-dimethylbutadi-

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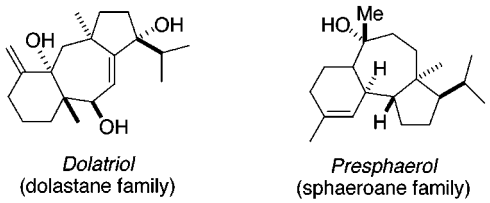
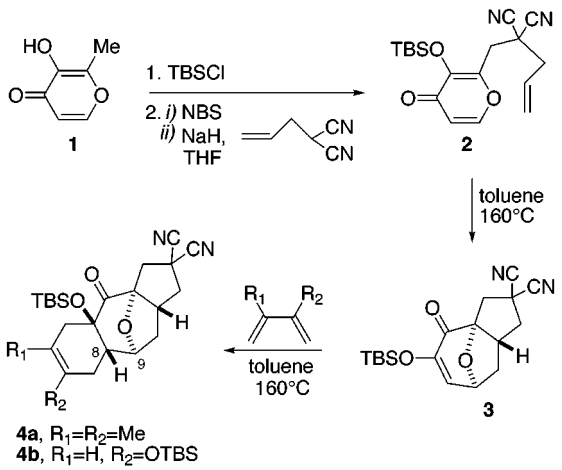


Figure 1.

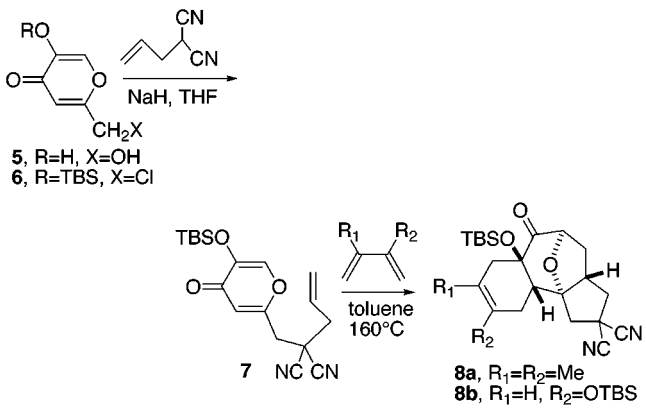
Scheme 2



ene as its diene partner. Heating a toluene solution of **3** at 160 °C in a sealed tube for 16 h, in the presence of 5 equiv of 2,3-dimethylbutadiene, afforded the adduct **4a** as a single diastereoisomer in 84% yield. The stereochemistry of the product was deduced from the negligible coupling between H-8 and H-9[9] and later confirmed by X-ray analysis of **9** (see below). The feasibility of carrying out the Diels−Alder cycloaddition upon simple thermal activation prompted us to test if both cycloadditions could be carried out in a single tandem process, which would require an appropriate orchestration of the reactivity so that the intramolecular [5 + 2] cycloaddition precedes the intermolecular [4 + 2] reaction.[10] Gratifyingly, heating a 1:5 mixture of compound **2** and 2,3-dimethylbutadiene at 160 °C in toluene for 30 h, in a sealed tube, led to the same adduct **4a** in 81% yield. Other dienes, such as 2-[(*tert*-butyldimethylsilyl)oxy]butadiene, do also participate in the reaction to give the expected regioisomer **4b** (83% yield). The regiochemistry of **4b** was confirmed by HMBC NMR experiments, being particularly enlightening the HMBC correlation between the alkenyl hydrogen and the tertiary carbon that brings the OTBS group. Therefore, relatively complex tetracycles embodying a fused 6,7,5-tricarbocyclic system that keeps a noticeable relationship to the basic policyclic skeleton of dolastane diterpenes can be assembled in a single step from readily available precursors by simple thermal activation.

The commercial availability of kojic acid (**5**) next prompted us to investigate whether the same strategy could lead to the regioisomeric adducts. This was of interest since these adducts would have a carbocyclic

Scheme 3



skeleton related to that of sphaeroanes (see Figure 1). Coupling of the sodium carbanion of allylmalononitrile with chloropyrone **6**, easily prepared from **5**,[5a] provided the required cycloaddition precursor **7** although in a modest 35% yield (Scheme 3). Adding sodium iodide to the reaction medium accelerated the transformation but did not substantially improve the yield (up to 43%). In any case, we did not consider prioritaire to pursue an optimization of the coupling at this stage and directly proceeded to study the cycloaddition capabilities of the substrate. Satisfyingly, heating a toluene solution of **7** in the presence of the formerly mentioned dienes under the conditions defined above afforded the expected cycloadducts **8a** and **8b** in 82% and 80% yield, respectively. In these cases, completion of the reaction required heating for approximately 3 days for **8a** and 2 days for **8b**. Overall, the sequence constitutes an inexpensive, extremely succinct route to stereochemically rich tetracycles bearing a 6,7,5-fused tricarbocyclic ring system related to the tricarbocyclic skeleton of sphaeroanes. It might be also noted that the tandem processes described above can be considered thoroughly atom economical, as they take place without the need of adding any external reagents, and the products result from simple summation of the reactant atoms.[11]

Refining these strategies for the synthesis of the natural diterpenes and their analogues requires appropriate processing of the tetracyclic adducts, the opening of the oxa-bridge being particularly challenging.[12] As a first step to address this goal we carried out a preliminary survey of the chemical response of the cycloadducts toward some electron-transfer reducing agents and Lewis acids. Precedents on the use of SmI_2 to induce the reductive opening of oxabicyclo[2.2.1]-heptanone units,[13] advised us to assay these conditions in our system. Treatment of **4a** with 2 equiv of SmI_2 in THF led to no reaction, even after refluxing for several hours. Remarkably, running the experiment in the presence of MeOH led to the immediate disappearance of the starting material to exclusively give the deoxy-

(9) The facial stereochemistry of the cycloadducts is in keeping with that obtained in other additions to homologous bicyclic systems; see: Blake, A. J.; Forsyth, A. C.; Paton, R. M. *J. Chem. Soc., Chem. Commun.* **1988**, 440.

(10) There are precedents on the relative reluctance of γ-pyrones to participate as dienophiles in Diels−Alder processes, see; Hsung, R. P. *J. Org. Chem.* **1997**, *62*, 7904.

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(12) Opening of bridging ethers in oxabicyclic systems has always been a challenging problem; see, for instance: (a) Lautens, M. *Synlett* **1993**, 177. (b) Williams, D. R.; Benbow, J. W.; McNutt, J. G.; Allen, E. E. *J. Org. Chem.* **1995**, *60*, 833. (c) Molander, G. A.; Eastwood, P. R. *J. Org. Chem.* **1995**, *60*, 4559.

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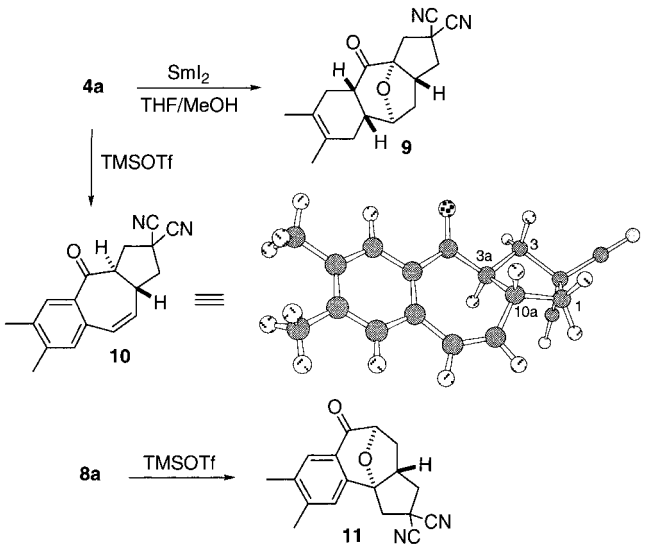
Scheme 4



genated derivative **9** in 96% yield.[14] The stereochemistry of this compound was deduced by crystallographic analysis (see the Supporting Information). Other electron-transfer reducing agents, such as Na/Bu_2O, gave uncertain results as a consequence of concurrent reactions with the nitriles. The supposition that homologating the carbonyl to an *exo*-methylene group might provide a more reactive substrate for the reductive opening,[12b] could not been ascertained because **4a** was completely reluctant to the Wittig reaction.

Reaction of **4a** with BBr_3 or $BF_3{\cdot}Et_2O$ led to complex reaction mixtures, but curiously, its treatment with 5 equiv of TMSOTf in refluxing benzene gave as the major product the aromatic derivative **10** (52% yield). The trans stereochemistry of the rings junction was deduced from the ^1H NMR coupling pattern observed for H-10a,[15] which is in keeping with the lowest energy conformation obtained for **10** (Scheme 4),[16] but cannot be accommodated by reasonable low energy conformations calculated for the alternative cis fusion. Although we have not yet determined the mechanistic path of the whole process, we did find that the transformation involves the initial desilylation of the tertiary hydroxy group, which is most probably caused by the presence of a small quantity of HOTf in the medium, since the reaction is inhibited by the presence of Et_3N. We have also confirmed that although HOTf induces the desilylation step it does not promote the subsequent transformations. Posterior formation of the observed product might then be explained in terms of an initial elimination of the hydroxy group followed by γ-enolization of the ketone, aromatization-driven opening of the oxa-bridge, and final dehydration of the resulting benzylic alcohol.[17] Remarkably, subjecting **8a** to a similar treatment gave as major product the aromatic derivative **11** (46% yield), in which the oxygen bridge persists. We are currently further exploring these processes in order to gain insights that might help to discover appropriate conditions for controlling the opening of the oxa-bridge.

(14) It is known that SmI_2 is able to promote α-ketone deoxygenations; see: Molander, G. A. In *Organic Reactions*; Paquette, L. A., Ed.; J. Wiley & Sons: New York, 1994; Vol. 46, p 211.

(15) The ^1H NMR spectrum shows for H-10a a signal width of roughly 30 Hz, two of the coupling constants being approximately 11 and 12 Hz. Absence of NOE for H-10a by irradiation of H-3a, which exclusively induces a NOE signal enhancement at its neighbor H-3, is in consonance with the stereochemical assignation.

(16) The minimization was carried out using molecular mechanics methods (MMX implemented in the program CS Chem3D pro).

(17) Several intermediates that corroborate the proposed mechanistic sequence were detected spectroscopically but could not be isolated due to their unstability.

Conclusion

In summary, relatively complex policyclic systems that embody the basic tricarbocyclic frame of several families of diterpenes can be assembled in just three steps from commercially available compounds. The approach relies on the one-step programmed coupling of an intramolecular [5 + 2] pyrone−alkene cycloaddition and a Diels−Alder reaction. Preliminary studies of the reactivity of the tetracyclic adducts revealed a relatively unexpected chemical behavior from which it is hoped to draw out valuable information allowing the strategy to be refined for synthesis of natural diterpenes and a variety of analogues.

Experimental Section

General Procedures. All dry solvents were freshly distilled under argon from an appropriate drying agent before use. Toluene and THF were distilled from sodium/benzophenone ketyl. CH_2Cl_2 and Et_3N were distilled from CaH_2. MeOH was distilled from Mg/I_2. Allyl bromide was distilled from CaH_2. All reactions were conducted in dry solvents under an argon atmosphere unless otherwise stated. External bath temperatures were used to record all reaction temperatures. Melting points (open capillary tubes) are uncorrected. Thin-layer chromatography (TLC) was performed on silica gel plates, and components were visualized by observation under UV light or by treating the plates with a phosphomolybdic reagent followed by heating. Dryings were performed with anhydrous Na_2SO_4. Concentration refers to the removal of volatile solvents via distillation using a Buchi rotary evaporator at water aspirator pressure, followed by residual solvent removal at high vacuum (~0.5 mmHg). TMSOTf was acquired from Aldrich and stored under nitrogen.

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, at 250 and 62.9 MHz, respectively, and in some cases at 300 or 500 MHz (75.4 or 125.7 for ^{13}C NMR). Carbon types 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. Mass spectra were measured at 70 eV, and relative intensities are given in parentheses.

Allylmalononitrile. Malononitrile (15 g, 227.3 mmol) was added to a cooled (approximately −10 °C) suspension of NaH (10 g, 60% mineral oil, 250 mmol) in THF (100 mL). After being stirred for 5 min, the reaction mixture was cooled at −78 °C, and allyl bromide (29.5 mL, 341 mmol) was slowly added. After being stirred for 20 min at that temperature, the reaction was allowed to reach rt and further stirred for 30 min. The mixture was poured into brine, extracted with Et_2O, dried, filtered, and concentrated. The crude was distilled under reduced pressure (~15 mmHg, 118 °C) to afford 18.07 g of allylmalononitrile [75%, R_f 0.82 (Et_2O), viscous oil]: ^1H NMR δ 5.87 (1H, m), 5.41 (2H, m), 3.84 (1H, t, J = 6.6 Hz), 2.72 (2H, m); ^{13}C NMR δ 128.9 (CH_2), 122.6 (CH), 112.9 (CN), 34.8 (CH), 23.3 (CH_2).

2-Allyl-2-[[3-[(*tert*-butyldimethylsilyl)oxy]-4-oxo-4*H*-2-pyranyl]methyl]malononitrile (2). NBS (3.71 g, 20.83 mmol) was added to a solution of 2-methyl-3-[(*tert*-butyldimethylsilyl)oxy]-4-pyrone (5 g, 20.83 mmol) in CCl_4 (100 mL). After the solution was refluxed for 10 h, most of the solvent was evaporated, and the crude was slowly added to an ice−water cooled mixture of allylmalononitrile (3.2 g, 30.18 mmol) and NaH (2.2 g, 33.2 mmol, 60% oil suspension) in THF (45 mL) that had been previously stirred for 15 min. After being stirred for 10 min at room temperature, the solvent was

evaporated and the residue diluted with Et_2O, washed with brine, dried, filtered, and concentrated. The crude was flash chromatographed on silica gel (10−20% EtOAc/hexanes) to afford 3.25 g of compound **2** as a white solid [45%, R_f 0.69 (Et_2O), mp 86−90 °C]: ^{1}H NMR δ 7.72 (1H, d, J = 5.6 Hz), 6.39 (1H, d, J = 5.6 Hz), 5.91 (1H, m), 5.45 (2H, m), 3.36 (2H, s), 2.78 (2H, d, J = 7.17 Hz), 0.96 (9H, s), 0.30 (6H, s); ^{13}C NMR δ 173.7 (C), 153.5 (CH), 147.5 (C), 145.1 (C), 127.9 (CH), 124.1 (CH_2), 115.9 (CH), 114.1 (C), 42 (CH_2), 35.4 (C), 34.6 (CH_2), 26.1 (CH_3), 18.8 (C), −3.5 (CH_3); LRMS m/z 329 ($M^+ - CH_3$, 1.6); HRMS calcd for $C_{18}H_{24}O_3N_2Si - CH_3$ 329.1321, found 329.1316.

(1*R,5*R**,7*S**)-9-[(*tert*-Butyldimethylsilyl)oxy]-10-oxo-11-oxatricyclo-[5.3.1.0^{1,5}]undec-8-ene-3,3-dicarbonitrile (3).** A solution of compound **2** (93 mg, 0.27 mmol) in toluene (25 mL) was heated at 160 °C in a sealed tube for 12 h. The solvent was evaporated and the crude purified by flash chromatography (10−15% EtOAc/hexanes) to afford 84 mg of the tricycle **3** as a white solid [90%, R_f 0.51 (25% EtOAc/hexanes), mp 138−140 °C]: ^{1}H NMR δ 6.12 (1H, d, J = 5 Hz), 4.9 (1H, t, J = 5.5 Hz), 3.06 (1H, d, J = 14.4 Hz), 2.61 (2H, m), 2.40 (2H, m), 1.98 (1H, m), 2.14 (1H, m), 0.78 (9H, s), 0.0 (6H, s); ^{13}C NMR δ 191.3 (C), 145.9 (C), 128.6 (CH), 115.6 (C), 96.6 (C), 76.7 (CH), 44.5 (CH), 44 (CH_2), 41.1 (CH_2), 37.9 (CH_2), 35.3 (C), 25.9 (CH_3), 18.7 (C), − 4.3 (CH_3); LRMS m/z 329 ($M^+ - CH_3$, 3.2); HRMS calcd for $C_{18}H_{24}O_3N_2Si - CH_3$ 329.1321, found 329.1319.

(1*R,3*R**,8*S**,9*S**,11*R**)-3-[(*tert*-Butyldimethylsilyl)-oxy]-5,6-dimethyl-2-oxo-15-oxatetracyclo[7.5.1.0.^{1,11}0^{3,8}]-pentadec-5-ene-13,13-dicarbonitrile (4a).** A solution of compound **3** (500 mg, 1.45 mmol) and 2,3-dimethylbutadiene (0.82 mL, 7.25 mmol) in toluene (10 mL) was heated at 160 °C in a sealed tube for 16 h. The solvent was evaporated and the crude purified by flash chromatography on silica gel (6% Et_2O /hexanes) to afford 520 mg of compound **4a** as a white solid [84%, R_f 0.7 (25% EtOAc/hexanes), mp 145−146 °C]: ^{1}H NMR δ 4.22 (1H, br s), 2.98 (2H, br d, J = 14 Hz), 2.66 (3H, m), 2.49 (2H, m), 2.30 (1H, m), 2.01 (1H, m), 1.87 (2H, m), 1.59 (3H, s), 1.53 (3H, s), 0.82 (9, s), 0.11 (3H, s), 0.09 (3H, s); ^{13}C NMR δ 209.4 (C), 123.6 (C), 123.2 (C), 116.6 (CN), 116.2 (CN), 95.6 (C), 83.3 (CH), 79.0 (C), 49.1 (CH), 44.9 (CH_2), 44.6 (CH), 43.0 (CH_2), 42.7 (CH_2), 40.3 (CH_2), 35.3 (C), 33.6 (CH_2), 26.7 (CH_3), 20.4 (CH_3), 19.7 (CH_3), 19.5 (C), −1.7 (CH_3), −1.8 (CH_3); LRMS m/z 426 (M^+, 0.5); HRMS calcd for $C_{24}H_{34}O_3N_2O_3$-Si − CH_3 411.2104, found 411.2102.

Tandem Cycloaddition of 2 with 2,3-Dimethylbutadiene. A solution of compound **2** (757 mg, 2.2 mmol) and 2,3-dimethylbutadiene (1.25 mL, 11 mmol) in toluene (10 mL) was heated at 160 °C in a sealed tube for 30 h. The solvent was evaporated and the crude purified by flash chromatography on silica gel (6% Et_2O/hexanes) to afford 760 mg of compound **4a** (81% yield).

Tandem Cycloaddition of 2 with 2-[(*tert*-Butyldimethylsilyl)oxy]butadiene. Synthesis of (1*R,3*R**,8*S**,9*S**,-11*R**)-3,6-Bis[(*tert*-butyldimethylsilyl)oxy]-2-oxo-15-oxatetracyclo[7.5.1.0^{1,11}.0^{3,8}]pentadec-5-ene-13,13-dicarbonitrile (4b).** A solution of pyrone **2** (490 mg, 1.424 mmol) and 2-[(*tert*-butyldimethylsilyl)oxy]butadiene (1320 mg, 7.13 mmol) in toluene (10 mL) was heated at 180 °C in a sealed tube for 30 h. The sovent was evaporated and the residue purified by flash chromatography on silica gel (10% EtOAc/hexanes) to afford 620 mg of the desired compound **4b** as a white solid [83%, R_f 0.71 (20% EtOAc/hexanes), mp 138−142 °C]: ^{1}H NMR δ 4.76 (1H, s), 4.34 (1H, s), 2.98 (2H, m), 2.78 (1H, m), 2.66 (2H, m), 2.49 (2H, m), 2.26 (1H, m), 2.05 (1H, d, J = 13.4 Hz), 1.98 (1H, m), 1.86 (2H, m), 0.91 (9H, s), 0.83 (9H, s), 0.15 (3H, s), 0.13 (3H, s), 0.11 (3H, s), 0.08 (3H, s); ^{13}C NMR δ 208.8 (C), 147.2 (C), 115.4 (CN), 115.1 (CN), 99.5 (CH), 94.6 (C), 82.1 (CH), 76.6 (C), 48.2 (CH), 44.5 (CH), 43.8 (CH_2), 42.0 (CH_2), 41.7 (CH_2), 34.3 (C), 33.7 (CH_2), 30.6 (CH_2), 25.8 (CH_3), 25.7 (CH_3), 18.5 (C), 17.9 (C), −2.73 (CH_3), −4.2 (CH_3), −4.4 (CH_3); LRMS m/z 528 (M^+, 0.1); HRMS calcd for $C_{28}H_{44}O_4N_2Si_2 - CH_3$ 513.2605, found 513.2608.

2-Allyl-2-[[5-[(*tert*-butyldimethylsilyl)oxy]-4-oxo-4*H*-2-pyranyl]methyl]malononitrile (7). A solution of compound **6**[5a] (4 g, 14.57 mmol) in THF (2 mL) was slowly added to an ice−water cooled suspension of allylmalononitrile (2.17 g, 20.40 mmol), NaI (500 mg, 3.3 mmol), and NaH (500 mg, 20.8 mmol) in THF (40 mL) that had been previously stirred for 15 min. After the solution was stirred at room temperature for 45 min, the reaction was quenched by adding 3 mL of water. The solvent was evaporated and the residue diluted with Et_2O, washed with brine, dried, filtered, and concentrated. The crude was flash chromatographed on silica gel (10−30% EtOAc/hexanes) to afford 1.72 g of **7** as a white solid [35%, R_f 0.56 (25% EtOAc/hexanes), mp 92−95 °C]: ^{1}H NMR δ 7.72 (1H, s), 6.40 (1H, s), 5.88 (1H, m), 5.46 (2H, m), 3.1 (2H, s), 2.76 (2H, d, J = 7.2 Hz), 0.95 (9H, s), 0.23 (6H, s); ^{13}C NMR δ 174.6 (C), 158 (C), 145.9 (C), 144.4 (CH), 127.5 (CH), 124.4 (CH_2), 117.3 (CH), 113.7 (C), 41.4 (CH_2), 39.8 (CH_2), 35.7 (C), 25.5 (CH_3), 18.4 (C), −4.4 (CH_3); LRMS m/z 329 ($M^+ - CH_3$, 2); HRMS calcd for $C_{18}H_{24}O_3N_2Si - CH_3$ 329,1321 found 329,1324.

(1*S,2*S**,7*R**,9*R**,11*S**)-7-[(*tert*-Butyldimethylsilyl)oxy]-4,5-dimethyl-8-oxo-5-oxatetracyclo[7.5.1.0.^{1,11}0^{2,7}]pentadec-4-ene-13,13-dicarbonitrile (8a).** A solution of compound **7** (325 mg, 0.95 mmol) and 2,3-dimethylbutadiene (0.53 mL, 4.73 mmol) in toluene (10 mL) was heated at 160 °C in a sealed tube for 92 h. The solvent was evaporated and the crude residue purified by flash chromatography to give 332 mg of **8a** as a white solid [82%, R_f 0.67 (25% EtOAc/hexanes), mp 134−136 °C]: ^{1}H NMR δ 4.47 (1H, d, J = 7.7 Hz), 3.07 (1H, m), 2.81 (1H, d, J = 14.1 Hz), 2.63 (1H, m), 2.39 (5H, m), 2.04 (4H, m), 1.68 (3H, s), 1.61 (3H, s), 0.81 (9H, s), 0.16 (3H, s), 0.02 (3H, s); ^{13}C NMR δ 208.2 (C), 125.4 (C), 123.4 (C), 115.8 (CN), 115.6 (CN), 94.3 (C), 82.4 (CH), 78.7 (C), 49.7 (CH), 46.4 (CH), 44.9 (CH_2), 44.4 (CH_2), 40.2 (CH_2), 38.8 (CH_2), 33.1 (C), 31.6 (CH_2), 25.7 (CH_3), 18.7 (C), 18.68 (CH_3), 18.3 (CH_3), −2.4 (CH_3), −3.2 (CH_3); LRMS m/z 426 (M^+, 0.1); HRMS calcd for $C_{24}H_{34}O_3N_2Si$ 426.2339, found 426.2349.

(1*S,2*S**,7*R**,9*R**,11*S**)-4,7-Bis[(*tert*-butyldimethylsilyl)oxy]-8-oxo-15-oxatetracyclo-[7.5.1.0.^{1,11}0^{2,7}]-pentadec-4-ene-13,13-dicarbonitrile (8b).** A solution of pyrone **7** (240 mg, 0.7 mmol) and 2-[(*tert*-butyldimethylsilyl)-oxy]butadiene (650 mg, 3.5 mmol) in toluene (10 mL) was heated at 160 °C in a sealed tube for 52 h. The solvent was evaporated and the crude residue purified by flash chromatography to give 295 mg of **8b** as a white solid [80%, R_f 0.73 (25% EtOAc/hexanes), mp 115−118 °C]: ^{1}H NMR δ 4.69 (1H, m), 4.55 (1H, d, J = 7.9 Hz), 3.17 (1H, m), 2.85 (1H, d, J = 14.1 Hz), 2.66 (2H, m), 2.44 (4H, m), 2.20 (1H, m), 2.12 (3H, m), 0.92 (9H, s), 0.84 (9H, s), 0.17 (3H, s), 0.13 (3H, s), 0.12 (3H, s), 0.06 (3H, s); ^{13}C NMR δ 207.6 (C), 149.5 (C), 115.8 (CN), 115.4 (CN), 98.3 (CH), 94.1 (C), 82.8 (CH), 77.6 (C), 50.1 (CH), 46.7 (CH), 44.9 (CH_2), 44.7 (CH_2), 38.6 (CH_2), 33.4 (C), 33.1 (CH_2), 30.1 (CH_2), 25.9 (CH_3), 25.6 (CH_3), 18.4 (C), 17.9 (C), −2.2 (CH_3), −3.0 (CH_3), −4.5 (CH_3); LRMS m/z 513 ($M^+ - CH_3$, 0.02); HRMS calcd for $C_{28}H_{44}O_4N_2Si_2$ 528.2839, found 528.2821.

(1*R,3*S**,8*S**,9*S**,11*R**)-5,6-Dimethyl-2-oxo-15-oxatetracyclo[7.5.1.0^{1,11}.0^{3,8}]pentadec-5-ene-13,13-dicarbonitrile (9).** A solution of **4a** (300 mg, 0.704 mmol) in THF (3 mL) and MeOH (1.5 mL) was added to a freshly prepared solution of SmI_2 (1.86 mmol)[18] in THF (4 mL). The reaction mixture was stirred at room temperature for 1 min, poured into a saturated aqueous solution of $NaHCO_3$, extracted with Et_2O, dried, filtered, and concentrated. The crude residue was flash chromatographed on silica gel (10−20% EtOAc/hexanes) to afford 201 mg of **9** as a white solid [96%, R_f 0.28 (25% EtOAc/hexanes), mp 145−148 °C]: ^{1}H NMR δ 4.49 (1H, d, J = 6.3 Hz), 3.24 (1H, d, J = 14.8 Hz), 2.97 (1H, m), 2.8 (2H, m), 2.6 (1H, d, J = 16.1 Hz), 2.45 (1H, d, J = 14.8 Hz), 2.38 (3H, m), 2.21 (1H, m), 1.96 (1H, m), 1.84 (1H, d, J = 11.6 Hz), 1.62 (3H, s), 1.57 (3H, s); ^{13}C NMR δ 202.5 (C), 123.6 (C), 122.4

(18) The SmI_2 solution in THF was prepared according to the following procedure: To a suspension of powdered Sm (280 mg, 1.86 mmol) in THF (2 mL, further deoxygenated by bubling argon for 15 min) was added a solution of ICH_2CH_2I (520 mg, 1.84 mmol) in deoxygenated THF (2 mL). The mixture was stirred at room temperature for 30 min, observing the appearance of a dark blue color.

(C), 115.6 (CN), 115.2 (CN), 95.4 (C), 82.5 (CH), 46.7 (CH), 45.1 (CH_2), 42.9 (CH), 40.9 (CH), 40.0 (CH_2), 35.9 (CH_2), 34.3 (C), 31.6 (CH_2), 27.4 (CH_2), 19.0 (CH_3), 18.6 (CH_3); LRMS *m*/*z* 296 (M^+, 11); HRMS calcd for $C_{18}H_{20}O_2N_2$ 296.1525, found 296.1529.

Reactions with TMSOTf. TMSOTf (0.23 mL, 1.2 mmol) was added to a solution of **4a** (100 mg, 0.235 mmol) in benzene (10 mL). After being refluxed for 7 h, the mixture was poured into water, extracted with Et_2O, and washed with HCl (5%), saturated $NaHCO_3$, and brine. Drying, filtering, and concentration gave a residue that was flash chromatographed on silica gel (10% EtOAc/hexanes) to afford 38 mg of **10** as a white solid [53%, R_f 0.58 (25% EtOAc/hexanes, mp 46−48 °C]: ^{1}H NMR δ 7.79 (1H, s), 7.19 (1H, s), 6.4 (1H, dd, J = 2.7, 11.4 Hz), 5.94 (1H, dd, J = 2.7, 11.4 Hz), 3.44 (1H, dt, J = 8.8, 12.3 Hz), 3.2 (1H, dd, J = 9, 14.3 Hz), 3.0 (1H, m), 2.86 (1H, dd, J = 8.6, 12.3 Hz), 2.62 (1H, dd, J = 8.6, 14.3 Hz), 2.43 (1H, dd, J = 11.0, 13 Hz), 2.22 (6H, s); ^{13}C NMR δ 195.9 (C), 143.0 (C), 137.1 (C), 134.3 (CH), 133.4 (C), 132.2 (CH), 131.6 (CH), 131.2 (C), 130.8 (CH), 116.2 (CN), 116.0 (CN), 54.0 (CH), 44.6 (CH_2), 39.9 (CH), 38.9 (CH_2), 32.0 (C), 19.7 (CH_3), 19.3 (CH_3); LRMS *m*/*z* 276 (M^+, 100); HRMS calcd for $C_{18}H_{16}ON_2$ 276.1263, found 276.1262.

Application of the same procedure to **8a** gave **11** as a white solid [46% yield, R_f 0.38 (25% EtOAc/hexanes), mp 207−211 °C]: ^{1}H NMR δ 7.76 (1H, s), 7.02 (1H, s), 4.87 (1H, d, J = 7.5 Hz), 3.24 (1H, d, J = 14.8 Hz), 2.91 (1H, d, J = 14.8 Hz), 2.8 (2H, m), 2.44 (1H, m), 2.3 (3H, s), 2.25 (3H, s), 2.06 (2H, m); ^{13}C NMR δ 194.3 (C), 144.6 (C), 141.5 (C), 137.8 (C), 128.7 (CH), 126.7 (C), 122.8 (CH), 115.9 (CN), 115.1 (CN), 92.2 (C), 84.2 (CH), 49.6 (CH), 44.8 (CH_2), 44.1 (CH_2), 35.3 (C), 33.7 (CH_2), 29.7 (C), 20.6 (CH_3), 19.5 (CH_3); LRMS *m*/*z* 292 (M^+, 65); HRMS calcd for $C_{18}H_{16}O_2N_2$ 292.1212, found 292.1216.

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Supporting Information Available: Copies of ^{1}H, ^{13}C NMR, and HMBC, HMQC, decoupling and NOE spectra of selected products, X-ray data for **9**, and full lists of mass spectral data for all compounds (33 pages). See any current masthead page for ordering information and Internet access information.

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