Total Synthesis of Racemic Laurenditerpenol, an HIF-1 Inhibitor

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The convergent total synthesis of the HIF-1 inhibitor laurenditerpenol 1 and its diastereomer 1’ is reported. The key step involves the Julia–Kocienski olefination–reduction process between the sulfone 55 and the aldehyde 54. The unusual trimethylated oxanorbornane sulfone 55 was successfully synthesized from the known exo Diels–Alder adduct 24 of 2,5-dimethylfuran 7 and maleic anhydride 23 in 8 steps. The aldehyde 54 was prepared by ring-opening and elaboration of lactone 41. In addition, four analogues of 1 were also successfully synthesized for biological testing.

Introduction

Hypoxia, or the shortage of oxygen, is a frequent hallmark of solid tumors when uncontrolled proliferation of cells outgrows the rate of blood vessel growth.1 Hypoxia confers resistance to tumors toward irradiation and chemical therapy commonly used in solid tumor treatment.1,2 In addition, the hypoxic condition in tumor cells promotes the formation of the hypoxia inducible factor-1 (HIF-1), a master transcription factor responsible for the activation of several oxygen-sensitive genes crucial for tumor survival.3

Laurenditerpenol (1) (Figure 1) is a secondary metabolite isolated by Zhou and Nagel from the Jamaican red alga Laurencia Intricata in 2004 that was shown in a T47D-based assay to inhibit activation of HIF-1 under hypoxia with an IC₅₀ of 0.4 μM.4 Small animal models have shown inhibition of HIF-1 generation or function significantly reduces tumor growth.4 Thus small molecule HIF-1 inhibitors such as laurenditerpenol represent exciting potential leads for anticancer drugs.4

In addition to its biological activity, the HIF-1 inhibitor 1 possesses a number of structural features that make it a challenging target for synthesis. First, the installation of seven stereocenters, four centers in an oxanorbornane system attached to a cyclohexanol with three contiguous centers via an alkane bridge, is a significant challenge. Second, the molecule contains a trimethyl oxanorbornane bicycle motif previously unencountered in the context of total synthesis, since this motif is found in only three natural products.5-6 Lastly, the configuration of C6 and C7 and the relative stereochemistry of the cyclohexanol and oxanorbornane units were unknown,7 making structural elucidation via synthesis crucial for the future development of 1 as an HIF-1 inhibitor. We report herein a convergent total synthesis of laurenditerpenol.8

Results and Discussion

Retrosynthesis of Laurenditerpenol. Our retrosynthetic analysis identified the intermediate 2, leaving the deoxygenative reduction of C19 as the last step in the synthesis (Scheme 1). The carbon skeleton of 2 was expected to be accessed via enolization and alkylation of the lactone 3 with

FIGURE 1. Laurenditerpenol.

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the iodide 4. The oxanorbornane containing subunit 4 would be generated via a furan Diels–Alder reaction, using either an intramolecular version of the substrate 5 (via desulfurization and reduction of 6) or an intermolecular version with 2,5-dimethylfuran 7 and a crotonate unit 8. The lactone fragment 3 was envisioned to arise from lactonization of 9, which would in turn be accessed by alkylation of 3-methyl-2-cyclohexenone with ethyl bromoacetate followed by reduction. Significantly, since the stereocenters at C6 and C7 could be easily epimerized, our convergent approach would enable access to all four possible isomers of 1 and allow for the stereochemoval assignment of 1 at C6 and C7.

**Synthesis of the Cycloadduct 6 via an Intramolecular Furan Diels–Alder Strategy.** Our synthesis began with the reduction of 5-methylfurfural 10 (98% yield) followed by a 1-pot mesylation–displacement reaction of the resulting alcohol 11 to generate the desired thioester 12 in 78% yield (Scheme 2). Initially we envisioned accessing the sulfide 5 via a base-catalyzed deprotection of the thioester 12 followed by reaction with the 4-bromocrotonate 13. Despite considerable experimentation, however, this deprotection–Sn2 displacement sequence yielded an inseparable mixture of the desired sulfide 5 along with isomeric vinyl sulfides 14t and 14c in low overall yield. The generation of the vinyl sulfides was unexpected since we had reasoned that the olefin would be stable to isomerization under the reaction conditions since it was in conjugation with the ester. Since the two vinyl sulfides should not undergo cyclization as they would yield very strained cyclobutanes, the mixture of compounds was subjected to thermal and microwave-promoted Diels–Alder reaction conditions to access the desired cycloadduct 6. However, extensive decomposition was observed with no detectable trace of cyclization products.

We sought to overcome this problem by using an alternate dienophile of higher reactivity. The allene 16 was deemed a suitable substrate for synthesis, as the allene side chain was expected to display heightened reactivity versus an olefin due to the electrophilic central sp² carbon to facilitate cyclization to the sulfide 17 (Scheme 3). Although readily accessible from the thioester 12 via deprotection and reaction with propargyl bromide to generate 15, followed by potassium tert-butoxide mediated isomerization, the allene 16 did not produce the desired adduct 17 under various thermal and microwave reaction conditions.

To circumvent the difficulties associated with utilization of sulfides, we turned our attention to the use of allene sulfones as tethers, since these compounds have been shown to exhibit greater stability compared to sulfides. Since the direct oxidation of the allene 16 only yielded decomposition, the alkyne 15 was first converted to the sulfone 18 via mCPBA oxidation in 36% yield (Scheme 4). Initial attempts to achieve isomerization of 18 to 19 via potassium tert-butoxide were met with little success, but the treatment of the sulfone 18 with alumina and heat allowed us to prepare the cycloadduct 20 in 40% yield.

This result encouraged us to seek methods of elaborating the sulfone 18 with a terminal ester to allow for elaboration to the target iodide 4. Unfortunately, all attempts to convert the sulfone 18 to its corresponding terminal ester were unsuccessful. These difficulties, coupled with the hurdles anticipated with the complete reduction of the aliphatic sulfones via the sulfides to the hydrocarbons suggested that the use of an intramolecular furan Diels–Alder strategy was not amenable for the assembly of our target intermediate 4.

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Synthesis of 4 via an Intermolecular Furan Diels–Alder Strategy. Concomitant with the intramolecular Diels–Alder approach, the intermolecular furan Diels–Alder route was also examined (Scheme 5). Although literature precedence existed for the reaction of 2,5-dimethylfuran 7 with simple \( \alpha,\beta \)-unsaturated esters,\(^{12}\) there was no corresponding description of reactions of 2,5-dimethylfuran with maleonitriles. The desired transformation was explored under various Lewis acidic conditions with both the ester 21a and acid chloride 21b but resulted in no cycloaduct. The increased steric hindrance imposed by the methyl of the crotonate was sufficient to retard its reactivity relative to literature examples with acrylate. These difficulties encouraged us to explore alternate strategies for assembly of the desired oxanorbornane moiety.

Synthesis of the Carboxylic Acid Ester 26. In our revised retrosynthesis of 4, as shown in Scheme 6, we envisioned the use of the well-known exo Diels–Alder adduct 24a of 2,5-dimethylfuran 7 and maleic anhydride 23\(^{13,17}\) as our starting point for the total synthesis. The use of this compound is advantageous since three out of the four stereocenters are set at the onset in a single step. In addition, the methanalysis of the anhydride functionality would yield two differentiated functional groups for elaboration. We also thought that methods described in the literature for asymmetric anhydride ring-opening might be taken advantage of at a later point for the enantioselective synthesis of iodide 4.\(^{14}\) Lastly, previous work done by our group on the total synthesis of Cyclobut A analogues had successfully demonstrated the selective epimerization of an ester versus an acid under basic conditions,\(^{15}\) which we believed would be amenable to our substrate to set the last stereocenter.

The new synthesis commenced with the aforementioned furan Diels–Alder reaction, and subsequent hydrogenation of the cycloadduct 24a allowed us quick access to the anhydride 24b\(^{13c}\) (Scheme 7). This compound was refluxed in methanol to give the desired carboxylic acid methyl ester 25 in quantitative yield. The direct application of the Cyclobut A epimerization conditions for selective epimerization of 25 gave no reaction, which we attributed to the lower reactivity of our system. After much experimentation we were able to take advantage of the \( pK_a \) differences of the protons \( \alpha \) to an ester versus those \( \alpha \) to a carboxylate via treatment of 25 with 5 equiv of sodium methoxide in refluxing methanol to synthesize the desired epimeric carboxylic acid ester 26 in quantitative yield.\(^{16}\) This set the relative stereochemistry of the four contiguous stereocenters around the oxanorbornane in just four steps, leaving us the tasks of exposing the last methyl group on the ring and elaboration of the side chain.

**Deoxygenation Strategies**

Deoxygenation of the Acid 26. We envisioned that the last methyl on the oxanorbornane ring could be formed by the selective reduction of the carboxylic acid followed by deoxygenation. The reduction of the acid 26 to the alcohol 27 in 89% yield was achieved via treatment with BH\(_3\)-THF (Scheme 8). After conversion of the alcohol 27 to the thionoester 28, we explored its deoxygenation under the


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The direct homologation of the alcohol 33 was a two-step sequence involving the tosylation of alcohol 27 followed by reduction strategy. After much experimentation, we found it was necessary to circumvent this issue by using a hydride reagent. The highly sterically hindered nature of the substrate, and thus the low reactivity of the mesylate is presumably due to the presence of both the tosylated alcohol and the ester via LiAlH₄ to give the alcohol 33 in 87% yield (Scheme 9). This successful homologation of the alkyl side chain was the key to the synthesis of the target iodide 4. The last challenge associated with the generation of the iodide 4 involved the synthesis of the mesylate 31. However, the conversion of the mesylate 30 to the iodide 31 with sodium iodide was unsuccessful, and attempts at mesylation and iodination in a one-pot sequence without purification also did not yield the desired iodide 31.

The low reactivity of the mesylate is presumably due to the low reactivity of the mesylate is presumably due to the highly sterically hindered nature of the substrate, and thus we sought to circumvent this issue by using a hydride reduction strategy. After much experimentation, we found a two-step sequence involving the tosylation of alcohol 27 to generate 32 in 83% yield followed by concomitant reduction of both the tosylated alcohol and the ester via LiAlH₄ to give the alcohol 33 in 87% yield (Scheme 9). This successful deoxygenation generated the final methyl group of the iodide 4. Thus the iodide 34 was reacted with potassium cyanide in a traditional S_N2 reaction to access the nitrile 35, which was easily converted to the alkyl iodide 4. Although this extended the synthesis of the desired iodide 4, we next sought to complete the synthesis of this subunit.

Homologation of the Side Chain and Synthesis of the Iodide 4. The last challenge associated with the generation of the target iodide 4 was the homologation of the alkyl side chain (Scheme 10). The direct homologation of the alcohol 33 was first attempted by halogenation of 33 to give 34 followed by lithiation and quenching with a one-carbon electrophile. This approach did not yield the desired homologation of the side chain, prompting us to explore an alternate route to the subunit 35. Thus the iodide 34 was reacted with potassium cyanide in a traditional S_N2 reaction to access the nitrite 36 in 83% yield. The nitrite functional group was subsequently reduced twice with DIBAL to yield, via the aldehyde 37, the alcohol 38, which was easily converted to the alkyl iodide 4. Although this extended the synthesis of the desired iodide 4, we next sought to complete the synthesis of this subunit.

Homologation and Synthesis of Subunit 4. The last challenge associated with the generation of the target iodide 4 was the homologation of the alkyl side chain (Scheme 10). The direct homologation of the alcohol 33 was first attempted by halogenation of 33 to give 34 followed by lithiation and quenching with a one-carbon electrophile. This approach did not yield the desired homologation of the side chain, prompting us to explore an alternate route to the subunit 35. Thus the iodide 34 was reacted with potassium cyanide in a traditional S_N2 reaction to access the nitrite 36 in 83% yield. The nitrite functional group was subsequently reduced twice with DIBAL to yield, via the aldehyde 37, the alcohol 38, which was easily converted to the alkyl iodide 4. Although this extended the synthesis of the desired iodide 4, we next sought to complete the synthesis of the desired iodide 4 to test out the key alklylation step.

Construction of Lactone Partners 3a and 3b. The lactone fragment 3 was synthesized utilizing a modified version of a known route (Scheme 11). Optimization of the published route was necessary to ensure reproducible and scalable transformations. The Corey CBS-reduction of the ketoester 39, prepared by alkylation of the kinetic anion of 3-methyl-2-cyclohexanone 38, required strict adherence to reaction times, with careful introduction of exactly 1 equiv of HCl in ether at the end of the reaction to avoid methanolysis. Saponification of the ester 9 also required similar care during workup to avoid loss of the allylic alcohol to yield the hydroxyacids 40. Finally, the lactonization via DCC coupling required the use of dichloromethane instead of benzene, plus a stoichiometric amount of DMAP, to generate the two separable lactones 3a and 3b in 55% overall yield in a 2:1 ratio. Although the formation of the trans lactone 3b has been described, its successful formation and isolation was still surprising since molecular models of this compound show a high degree of strain. Significantly, the synthesis of both lactone isomers provided us with a method of controlling the configuration at C6 of laurenditerpenol.

Our next focus was a study of the stereochemistry of alkylation of both lactones 3a and 3b, since this alkylation would generate a new stereocenter that would later be available for further elaboration.
translated into the C7 carbon of laurenditerpenol. Thus the lactones 3a and 3b were each treated separately with LDA and quenched with methyl iodide (Scheme 12). To our delight, electrophile addition occurred from the re face for both lactones to yield methyl lactones 41 and 42, respectively. This was an encouraging result since it provided a method to generate lactones with specific stereochemistries at C6 and C7. However, the alkylation of the trans lactone 3b proved to be a lot more difficult to effect as observed in the low yield, presumably due to the difficulty accommodating an extra sp² carbon within the bicycle during enolization of the already strained trans-fused bicyclic lactone.

Encouraged by the results, we attempted the epimerization of the newly generated stereocenter to see if we could access the two additional stereoisomeric methyl lactones 43 and 44. The lactone 42 was thus enolized and quenched with 1 equiv of HCl in ether to affect epimerization to generate the epi-lactone 43 in 67% yield. It is of note that a simple aqueous acidic quench of the enolate delivers the proton to the oxygen of the enolate to regenerate, after tautomerization, the thermodynamically more favorable lactone 41 with no epimerization. The same reaction conditions were employed for 42, but this yielded only very small amounts of the desired lactone 44. This result was a reconfirmation of the large amount of strain present in the trans lactones 3b and 42 that previously thwarted efforts to optimize yields of 42. We were still satisfied with the results at hand, since we had a method to gain access to three of the four possible stereoisomers of laurenditerpenol.

**Coupling of Lactone 3a and Iodide 4.** With the two subunits in hand, we turned our attention to the coupling of the enantiopure lactone 3a and the racemic iodide 4 (Scheme 13). To our delight, the treatment of the lactone 3a with LDA followed by addition of 4 resulted in the generation of 45a and 45b as an inseparable 1:1 mixture of diastereomers in 20% yield. The alkylation also showed similar re-face selective addition seen in previous alkylation studies, to generate only two diastereomers out of the possible four. Although the yields were low, we were confident that higher yields would be achievable with further optimization of the reaction conditions.

**Deoxygenation of the Lactone 41.** With the carbon framework complete, the only task left at hand was the deoxygenation of C19 to generate a methyl group. We envisioned this could be achieved via reduction of the lactone moiety.
of 41 to the lactol 46 followed by deoxygenation of the isomeric hydroxyaldehyde 47 to give 48 (Scheme 14). Literature precedence involving the reduction of lactols to the hydroxyalkane via Wolff–Kishner conditions suggested the use of a similar strategy would be possible in our synthesis.

We investigated the use of a mild carbonyl deoxygenation reaction pioneered by Hutchins on our system to avoid the loss of the allylic alcohol stereocenter that may be possible under the harsher Wolff–Kishner conditions. Although there were no direct literature examples utilizing the Hutchins modification on lactols, the first step of the reaction still involved the formation of a hydrazone for reduction much like the traditional Wolff–Kishner reaction. Thus we deemed it worthwhile to investigate the use of this modification in the context of deoxygenation of lactols to the hydroxyalkane.

As a test substrate, the lactone 41 was converted to the lactol 46 in 85% yield (Scheme 15). However, accessing the desired alcohol 48 via the Hutchins modification was elusive. Increasing reagent concentrations and reaction times only generated the tetrahydrofuran 49 in low yields (∼10%). Significantly, we discovered that we were unable to preform the hydrazone 50 for a stepwise reduction strategy. Our experience led us to hypothesize that the equilibrium lies heavily toward the formation of the lactol versus the hydroxyaldehyde. To test our hypothesis, we devised reactions to probe the possibility of isolating the previously mentioned hydroxyaldehyde 47 from either the lactol 46 via Lewis acid-catalyzed ring-opening or from the lactone 41 via a one-pot DIBAL reduction–Lewis acid-catalyzed ring-opening sequence. We were unable to observe any products that corresponded to the targeted aldehyde 47 in all instances, indicating that our hypothesis on the preferential formation of the lactol was probably accurate.

Instead of relying on an unfavorable equilibrium to effect the desired deoxygenation, we decided to reduce the lactone 41 to the diol 51 with the plan of converting the primary alcohol to the tosylate 52 for lithium aluminum hydride reduction (Scheme 16). However, during the tosylation of the diol 51, the aforementioned tetrahydrofuran 49 as well as the desired product 52 were observed. Upon workup and purification, we found that the isolation of 52 was not possible since it was fully converted to the tetrahydrofuran 49. This result suggested that the activation of the primary alcohol carbon promotes the formation of the thermodynamically stable 5-membered bicyclic product. More significantly, this result provided additional evidence corroborating our previous hypothesis that cyclization to the 5-membered bicyclic lactol 46 was favored over that of the ring-opened hydroxyaldehyde 47.

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SCHEME 20. The Successful Synthesis of Laurenditerpenol 1 and Its Diastereomer 1'

J. Kocienski Olefination Strategy. We turned to an alternate strategy that would involve the use of the dependable Julia–Kocienski olefination reaction to construct the bridge between the cyclohexanol and the oxanorbornane subunits of laurenditerpenol (Scheme 17). We recognized that we could take advantage of our methylation studies for installation of the C19 methyl group without the need for deoxygenation. This had the added benefit of bypassing the multistep homologation of the oxanorbornane subunit for synthesis of the sulfone. Thus, the revised retrosynthesis envisioned the use of the protected aldehyde (preparable from 33) as substrates for the Julia–Kocienski olefination key step to yield the key intermediate 53.

The alcohol 33 was thus converted to the sulfide 56 via a Mitsunobu reaction, followed by oxidation with mCPBA to generate the sulfone subunit (Scheme 18). To synthesize the protected aldehyde 54, we started from the racemic methyl lactone 41, which was formed via the cerium chloride-mediated reduction of ketoester 39 followed by the two-step elaboration sequence described earlier. We decided to target aldehyde 54 as the Julia–Kocienski olefination substrate since we were well aware from our previous experiences of the difficulties of utilizing lactol 46 to access the aldehyde functionality. Thus, the lactone 41 was converted to the desired TBS-protected aldehyde 54 via a 5-step sequence, involving reduction of the lactone to the diol 51 with LiAlH₄, protecting group manipulation to give the silylated alcohol 58, followed by a final oxidation of the primary alcohol with TPAP/NMO. Even though this sequence was somewhat long, each step was high yielding and could be performed on multigram quantities, providing the aldehyde 54 in 51% overall yield from methyl lactone 41.

Gratifyingly, the key modified Julia–Kocienski olefination of the aldehyde 54 and sulfone 55 proceeded smoothly to yield the desired set of racemic cis olefins 53a and 53b along with the racemic trans olefins 53c and 53d in 88% yield as a 1:1 mixture of Z and E isomers (Scheme 19). We obtained a 1:1:1:1 mixture of four diastereomers due to the racemic nature of the substrates used. However, the planned end game sequence involved the reduction of the disubstituted olefin to generate the alkyl bridge, which would lead to only two diastereomers of the TBS-protected derivative of 1.

Completion of the Total Synthesis of Laurenditerpenol 1 and Its Diastereomer 1'. The Z and E isomers were separated via careful flash column chromatography, and each isomer was separately treated with diimide, prepared by reaction of dipotassium azodicarboxylate and acetic acid, for selective reduction of the disubstituted olefin versus the trisubstituted olefin (Scheme 20). The hindered Z isomers, 53a and 53b,

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(22) We decided to utilize the racemic lactone to complete the total synthesis due to the ease of scale-up with the cerium chloride/sodium borohydride reduction conditions.

(24) Although the Julia–Kocienski reaction generally gives E alkenes selectively, we were unable to improve the 1:1 isomeric ratio. Attempts at using the generally more E-selective tetrazole sulfone were hampered by severe difficulties in preparing the necessary substrate from 33.
did not react with diimide and the starting alkenes were recovered unchanged. Although the literature indicates a general preference for the reduction of E olefins over Z olefins in diimide reductions,\(^{25}\) there are successful examples of the reduction of linear Z olefins in the literature\(^ {26}\) and thus this result was somewhat of a surprise. Nonetheless, the mixture of the E isomers, \(53c\) and \(53d\), was successfully reduced with diimide to afford, in addition to 15% starting material, a 1:1 mixture of the desired reduced products \(59a\) and \(59b\) in 80% yield, as observed by NMR. TBAF deprotection of the TBS ethers of this mixture gave both laurenditerpenol diastereomers I and I’ as a 1:1 mixture of products in 60% yield. An analytically pure sample of Laurenditerpenol and its isomer were obtained via flash column chromatography. The proton, and especially the carbon, NMR spectra of these isolated diastereomers matched the published values of laurenditerpenol.\(^ {4,7}\)

Synthesis of Analogues of Laurenditerpenol. We also prepared several analogues of laurenditerpenol\(^ {27}\) and have submitted them for biological evaluation as potential HIF-1 inhibitors (Scheme 21). Thus deprotection of the silyl ethers of the four alkene stereoisomers, \(53a/53b\) and \(53c/53d\), with TBAF in THF afforded the dienols \(60a/60b\) and \(60c/60d\), which were all isolated as pure compounds via flash column chromatography. The results of the biological assays of these compounds will be reported in due course.

Conclusion

In summary, we have described a convergent total synthesis of racemic laurenditerpenol I in 12 longest linear steps and 2.5% overall yield from 2,5-dimethylfuran 7. In addition, the diastereomer of laurenditerpenol I’ was also produced in the same overall yield. The unusual trimethylated oxanorbornane sulfone \(55\) was successfully synthesized from the known exo Diels–Alder adduct \(24\) of 2,5-dimethylfuran 7 and maleic anhydride \(23\) in 8 steps, utilizing the selective base-promoted epimerization of an ester versus a carboxylate followed by a tosylation–reduction sequence to install the non-bridgehead methyl group. The lactone fragment \(41\), which was further elaborated to the protected aldehyde \(54\) for the key coupling step, was prepared via an alkylation–reduction strategy that would be amenable to an enantioselective synthesis. The highly selective alkylation of the lactone \(3a\) enabled the diastereoselective installation of the methyl group at \(C7\) and provided access to three of the four possible stereoisomers at \(C6\) and \(C7\). Finally, the protected aldehyde \(54\) and sulfone \(55\) were successfully coupled via a high-yielding modified Julia–Kocienski olefination procedure. We were also successful in generating analogues of I and details on the biological assays of these analogues will be forthcoming in the near future.

Experimental Section

The experimental details for compounds 5, 11, 12, 15, 16, 18, 20, 21b, 28, 30, 45a, 45b, 46, 49, and 51, are given in the Supporting Information.


(CDCl₃, 125 MHz) δ 177.6, 171.5, 86.1, 85.4, 56.9, 55.2, 52.0, 38.8, 33.4, 20.5, 18.8; IR (thin film) 3400~2800 (br, m), 2978 (m), 2955 (m), 1731 (s), 1438 (w), 1383 (w), 1252 (m), 1209 (m), 1174 (m), 1129 (w), 1066 (w), 869 (w); HRMS-ESI (m/z) [M + Na]⁺ cored for C₁₁H₁₇ONa₂ 202.1208, found 202.1208.

(±)-(1R,2R,3S,4S)-Methyl 2-(Hydroxymethyl)-1,4-dimethyl-7-oxabicyclo[2.2.1]heptane-2-carboxylate (32). To an oven-dried and argon-purged 500 mL round-bottomed flask were added the nitrile (3.85 g, 21.3 mmol, 1 equiv) and benzene (200 mL). Imidazole (7.35 g, 112.9 mmol, 1 equiv) and benzene (200 mL). Potassium cyanide (133 mg, 2.04 mmol, 6 equiv) was added to the reaction via syringe. The reaction was warmed to 23 °C and the solvent was removed via rotary evaporation. Flash column chromatography of the residue on silica gel (360 mL, heptane-2-acetonitrile) afforded 5.51 g (88%) of the isodide 34 as a white solid. ¹H NMR (CDCl₃, 400 MHz) δ 3.17 (1H, dd, J = 12.0, 7.5 Hz), 3.14 (1H, dd, J = 12.0, 7.5 Hz), 1.79~1.86 (2H, m), 1.66 (1H, dd, J = 10.0, 10.0, 4.9 Hz), 1.54~1.59 (1H, m), 1.46~1.52 (1H, m), 1.43 (3H, s), 1.40~1.44 (1H, m), 1.29 (3H, s), 1.04 (3H, d, J = 6.8 Hz); ¹⁳C NMR (CDCl₃, 100 MHz) δ 85.7, 84.9, 60.0, 50.4, 38.6, 31.6, 20.8, 18.5, 18.1, 6.0; IR (thin film) 2967 (s), 2871 (m), 1461 (m), 1454 (m), 1378 (s), 1334 (m), 1220 (m), 1208 (m), 1191 (s), 1148 (w), 1132 (m) 1077 (m), 1025 (w), 918 (m), 877 (m), 865 (m).

(±)-(1R,2R,3R,4S)-1,3,4-Trimethyl-7-oxabicyclo[2.2.1]heptane-2-carboxylate (34). To an oven-dried and argon-purged 500 mL round-bottomed flask were added the isodide 33 (3.63 g, 21.3 mmol, 1 equiv) and benzene (200 mL). The residue was washed with ether and dried over MgSO₄. The mixture was filtered and concentrated via rotary evaporation. Flash column chromatography of the residue on silica gel (120 mL, hexane-2-acetonitrile) afforded 3.51 g (91%) of the isodide 34 (3.63 g, 21.3 mmol, 1 equiv) as a yellow solid. ¹H NMR (CDCl₃, 400 MHz) δ 3.17 (1H, dd, J = 12.0, 7.5 Hz), 3.14 (1H, dd, J = 12.0, 7.5 Hz), 1.79~1.86 (2H, m), 1.66 (1H, dd, J = 10.0, 10.0, 4.9 Hz), 1.54~1.59 (1H, m), 1.46~1.52 (1H, m), 1.43 (3H, s), 1.40~1.44 (1H, m), 1.29 (3H, s), 1.04 (3H, d, J = 6.8 Hz); ¹⁳C NMR (CDCl₃, 100 MHz) δ 85.7, 84.9, 60.0, 50.4, 38.6, 31.6, 20.8, 18.5, 18.1, 6.0; IR (thin film) 2967 (s), 2871 (m), 1461 (m), 1454 (m), 1378 (s), 1334 (m), 1220 (m), 1208 (m), 1191 (s), 1148 (w), 1132 (m) 1077 (m), 1025 (w), 918 (m), 877 (m), 865 (m).

(±)-(1R,2R,3R,4S)-3-Methyl-3-(4-methylphenylsulfonyl)oxo(3-methyl-7-oxabicyclo[2.2.1]heptane-2-carboxylate (35). To an oven-dried and argon-purged 5 mL round-bottomed flask were added the isodide 34 (0.34 mmol, 1 equiv) and dimethyl sulfoxide (3.5 mL). ¹H NMR (CDCl₃, 400 MHz) δ 2.06 (3H, s), 1.93 (3H, s), 1.91~2.01 (2H, m), 1.67 (1H, dd, J = 10.0, 10.0, 4.9 Hz), 1.54~1.59 (1H, m), 1.46~1.52 (1H, m), 1.43 (3H, s), 1.40~1.44 (1H, m), 1.29 (3H, s), 1.04 (3H, d, J = 6.8 Hz); ¹⁳C NMR (CDCl₃, 100 MHz) δ 85.7, 84.9, 60.0, 50.4, 38.6, 31.6, 20.8, 18.5, 18.1, 6.0; IR (thin film) 2967 (s), 2871 (m), 1461 (m), 1454 (m), 1378 (s), 1334 (m), 1220 (m), 1208 (m), 1191 (s), 1148 (w), 1132 (m) 1077 (m), 1025 (w), 918 (m), 877 (m), 865 (m).

(±)-(1R,2R,3R,4S)-3-Methyl-3-(4-methylphenylsulfonyl)oxo(3-methyl-7-oxabicyclo[2.2.1]heptane-2-thiolate (36). To an oven-dried and argon-purged 5 mL round-bottomed flask were added the isodide 34 (0.34 mmol, 1 equiv) and dimethyl sulfoxide (3.5 mL). Sodium cyanide (133 mg, 2.04 mmol, 6 equiv) was added to the reaction via syringe. The reaction was warmed to 23 °C and poured into a 1:1 distilled water and ether mixture (~3× volume of dimethyl sulfoxide). The resulting layers were separated, and the aqueous layer was diluted with distilled water. The aqueous layer was then extracted with ether (3× 10 mL), and the combined organic layers were washed with brine. The organic layer was dried over MgSO₄, filtered, and concentrated via rotary evaporation. Flash column chromatography of the residue on silica gel (12 mL, hexane:ether, 1:1) afforded 0.54 mg (83%) of the nitrile 36 as a yellow solid. ¹H NMR (CDCl₃, 500 MHz) δ 7.77 (2H, d, J = 8.6 Hz), 3.45 (2H, s), 1.92 (3H, s), 1.60 (1H, hept-1-en-3-yl) and 4-(3-methylbenzyl)pyridine (36 mg, 0.29 mmol, 0.01 equiv), and the mixture was stirred at 23 °C for 10 min. The flask was cooled to 0 °C with an ice bath, and recrystallized tosyl chloride (11.10 g, 58.3 mmol, 5.3 equiv) and diethyl ether (12 mL). The reaction was cooled to 0 °C, then kept at −10 °C for 16 h. The reaction was quenched with distilled water at 0 °C and warmed to 23 °C. The layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine and dried over MgSO₄. The mixture was filtered and concentrated via rotary evaporation. Flash column chromatography of the residue on silica gel (12 mL, hexane:ether, 1:1) afforded 0.54 mg (83%) of the ester 32 as a white solid. The residue on silica gel (125 MHz) δ 172.9, 85.2, 84.9, 63.6, 57.2, 51.9, 51.2, 38.4, 33.7, 20.8, 17.8; IR (thin film) 3447 (s, br), 2953.2 (s), 2876 (m), 1731 (s), 1437 (m), 1381 (m), 1314 (m), 1224 (m), 1174 (m), 1066 (m), 1024 (m), 994 (w), 907 (m), 867 (m); HRMS-ESI (m/z) [M + Na]⁺ cored for C₁₁H₁₇NO₃Na 237.1103, found 237.1096.
The reaction was cooled to −78 °C for 1 h, and then quenched with saturated potassium tartrate solution. The reaction was warmed to 23 °C, then stirred until the mixture became clear. The layers were separated, and the aqueous layer was extracted with ether, and the combined organic layers were washed with brine and dried over MgSO4. The mixture was filtered and concentrated via rotary evaporation. Flash column chromatography of the residue on silica gel (10 mL, hexane, ethyl acetate) afforded 20 mg (90%) of the alcohol 78. 1H NMR (CDCl3, 500 MHz) δ 7.77 (1H, d, J = 6.6 Hz); 13C NMR (CDCl3, 125 MHz) δ 201.4, 149.3, 124.0, 84.9, 84.8, 51.5, 48.1, 46.3, 38.7, 32.1, 20.6, 18.0, 17.8; IR (thin film) 2969 (s), 2874 (m), 2724 (s), 1453 (w), 1379 (m), 1226 (w), 1137 (w), 1076 (w), 967 (m). HRMS-ESI ([M + Na]+ calcd for C176H20IO295.0559, found 295.0559.

Ethyl 2-(4-Methyl-2-oxocyclohex-3-enyl)acetate (9). To an oven-dried and argon-purged 1 mL round-bottomed flask were added tetrahydrofuran (12 mL, 120 mmol, 2 equiv) in 10 mL of tetrahydrofuran was added dropwise via syringe. The reaction was stirred for 30 min at −78 °C, and ethyl bromoacetate (8.6 mL, 90.8 mmol, 2 equiv) in 10 mL of tetrahydrofuran was added dropwise via syringe. The reaction was stirred for another 30 min at −78 °C, and ethyl bromoacetate (8.6 mL, 90.8 mmol, 2 equiv) in 10 mL of tetrahydrofuran was added dropwise via syringe. The reaction was stirred for 2 h at −78 °C, then it was diluted with ether and quenched with saturated NH4Cl solution. The mixture was warmed to 23 °C and the layers were separated. The aqueous layer was extracted with ether, and the combined organic layers were washed with brine, and dried over MgSO4. The mixture was filtered and concentrated via rotary evaporation. Flash column chromatography of the residue on silica gel (1 L, hexane:ethyl acetate) afforded 2075 mg (90%) of the ester 90. 1H NMR (CDCl3, 500 MHz) δ 5.88 (s, 1H), 4.155 (q, 1H, J = 7.1 Hz), 4.150 (q, 1H, J = 7.1 Hz), 2.87 (dd, 1H, J = 16.3, 5.3 Hz), 2.71 (dd, 1H, J = 13.3, 5.0, 5.0 Hz, 2.45 (m, 1H), 2.27 (dd, 1H, J = 16.8, 4.6, 2.7 Hz), 2.25 (dd, 1H, J = 16.3, 7.6 Hz), 2.11 (dd, 1H, J = 13.1, 4.8, 2.7 Hz), 1.95 (s, 3H), 1.78 (s, 3H), 1.42 (1H, 2.1 Hz), 1.37 (m, 1H), 1.21 (m, 1H), 0.95 (s, 3H). IR (thin film) 2967 (s), 2930 (m), 2872 (m), 1453 (m), 1377 (m), 1231 (m). HRMS-ESI ([M + Na]+ calcd for C176H20C13IO295.0559, found 295.0559.

Ethyl 2-(1R,3S,5S)-2-Hydroxy-4-methylcyclohex-3-enylacetate (9). To an oven-dried and argon-purged 1 mL round-bottomed flask were added tetrahydrofuran (218 mL) and (S)-2-methyl-CBS-oxazaborolidine (302 mg, 1.09 mmol, 0.05 equiv). A 1 M solution of borane–tetrahydrofuran (4.8 mL, 48 mmol, 0.22 equiv) was added dropwise via syringe, and the reaction was stirred for 5 min at 23 °C. The reaction was cooled to 0 °C, and a solution of the ester 39 (4.28 g, 21.8 mmol, 1 equiv) in 10 mL of tetrahydrofuran was added dropwise via syringe. The reaction was stirred for 10 min at 0 °C, and a 1 M solution of HCl in ether (21.8 mL, 21.8 mmol, 1 equiv) was added dropwise via syringe. The reaction was stirred for 5 min at 0 °C and warmed to 23 °C. The reaction was stirred for 30 min at 23 °C and the solvent was removed via rotary evaporation. The residue was then dissolved in benzene and concentrated via rotary evaporation twice. The residue was then dissolved in ether and the resulting white solid was filtered. The filtrate was concentrated via rotary evaporation, and flash column chromatography of the residue on silica gel (1 L, hexane:ethyl acetate:1:1) afforded 2.59 g (60%) of the hydroxyster 9 as a mixture of diastereomers, as a clear oil. 1H NMR (CDCl3, 500 MHz) δ major isomer 5.39 (1H, s), 4.14 (2H, q, J = 7.1 Hz), 3.88 (1H, br d, J = 7.7 Hz), 2.60 (1H, dd, J = 15.3, 6.2 Hz), 2.28 (1H, dd, J = 15.3, 7.4 Hz), 1.97–2.06 (2H, m), 1.87–1.95 (1H, m), 1.83 (1H, m), 1.68 (3H, s), 1.53 (1H, m), 1.39 (1H, m), 1.26 (3H, t, J = 7.1 Hz), minor isomer 5.85 (1H, s), 4.14 (2H, q, J = 7.1 Hz), 4.07 (1H, m), 2.53 (1H, dd, J = 15.1, 8.1 Hz), 2.30 (1H, dd, J = 15.1, 6.7 Hz), 1.97–2.06 (2H, m), 1.87–1.95 (1H, m), 1.83 (1H, m),
To an oven-dried and argon-purged 100 mL round-bottomed flask were added diisopropylamine (101 mg, 0.72 mmol, 1 equiv) and tetrahydrofuran (7 mL). The reaction was stirred at 23 °C for 2 h, and the solvent was removed via rotary evaporation. Flash column chromatography of the residue on silica gel (25 mL, hexane-ether, 6:4) afforded 30 mg (28%) of the methylated trans-lactone 42 as a white solid. 1 H NMR (CDCl 3 , 500 MHz) δ 5.81 (1H, s), 4.61 (1H, br d, J = 10.0 Hz), 2.68 (1H, dq, J = 7.6, 7.6 Hz), 2.11–2.22 (3H, m), 1.86 (1H, m), 1.68 (3H, s), 1.62 (1H, dddd, J = 13.1, 13.1, 10.3, 7.4 Hz), 1.14 (3H, d, J = 7.7 Hz); 13 C NMR (CDCl 3 , 125 MHz) δ 180.4, 137.6, 120.5, 79.0, 44.5, 38.6, 30.7, 22.8, 20.3, 9.1; IR (thin film) 2927 (s), 1781 (m), 1454 (m), 1380 (w), 1211 (w), 1175 (w), 1153 (w), 1042 (w), 991 (m), 974 (w), 699 (m); HRMS-ESI (m/z): [M + Na] + found 343.2 [M + Na] + calculated for C 17 H 18 O 3 Na 2 343.2168.

To an oven-dried and argon-purged 25 mL round-bottomed flask were added diisopropylamine (101 mg, 0.72 mmol, 1 equiv) and tetrahydrofuran (7 mL). The reaction was stirred at 23 °C for 2 h, and the solvent was removed via rotary evaporation. Flash column chromatography of the residue on silica gel (25 mL, hexane-ether, 6:4) afforded 30 mg (28%) of the methylated trans-lactone 42 as a white solid. 1 H NMR (CDCl 3 , 500 MHz) δ 5.81 (1H, s), 4.61 (1H, br d, J = 10.0 Hz), 2.68 (1H, dq, J = 7.6, 7.6 Hz), 2.11–2.22 (3H, m), 1.86 (1H, m), 1.68 (3H, s), 1.62 (1H, dddd, J = 13.1, 13.1, 10.3, 7.4 Hz), 1.14 (3H, d, J = 7.7 Hz); 13 C NMR (CDCl 3 , 125 MHz) δ 180.4, 137.6, 120.5, 79.0, 44.5, 38.6, 30.7, 22.8, 20.3, 9.1; IR (thin film) 2927 (s), 1781 (m), 1454 (m), 1380 (w), 1211 (w), 1175 (w), 1153 (w), 1042 (w), 991 (m), 974 (w), 699 (m); HRMS-ESI (m/z): [M + Na] + found 343.2 [M + Na] + calculated for C 17 H 18 O 3 Na 2 343.2168.
To an oven-dried and argon-purged 100 mL round-bottomed flask were added lithium aluminium hydride (360 mg, 9.48 mmol, 2.5 equiv) and ether (30 mL). The reaction was cooled to 0 °C, and the lactone (41 mL, 0.37 mmol, 1 equiv) in 4 mL of ether was added dropwise via syringe. The reaction was stirred at 0 °C for 30 min, then cooled to 0 °C and quenched with saturated sodium bicarbonate solution. The reaction was carefully quenched with saturated NH₄Cl solution, and the layers were separated. The aqueous layer was washed with brine and dried over MgSO₄. The mixture was filtered and concentrated via rotary evaporation. Flash column chromatography of the residue on silica gel (100 mL, hexane:ether:20:80) afforded 1.14 g of the sulfone (95%) as a white solid.¹ H NMR (CDCl₃, 300 MHz) δ 5.62 (1H, m), 4.22 (1H, br s), 3.68 (1H, dd, J = 10.8, 3.2 Hz), 3.62 (1H, dd, J = 10.8, 6.5 Hz), 2.73 (1H, br s), 2.34 (1H, br s), 1.93–2.05 (2H, m), 1.76 (1H, m), 1.70 (3H, s), 1.59–1.63 (1H, m), 1.55 (1H, ddd, J = 12.8, 11.0, 6.3 Hz), 1.28 (1H, ddd, J = 12.4, 8.5, 3.2, 3.2 Hz), 1.01 (3H, d, J = 7.0 Hz).¹ C NMR (CDCl₃, 75 MHz) δ 139.7, 123.0, 66.0, 64.6, 44.0, 37.1, 31.4, 23.3, 21.5, 15.8; IR (thin film) 2967 (s), 2916 (s), 1732 (s), 1673 (m), 1448 (s), 1263 (s), 1183 (s), 1150 (s), 1096 (m), 1069 (m), 1032 (m), 995 (m), 871 (m), 714 (m), 616 (w), 570 (w), 472 (m), 362 (m), 342 (m), 322 (m), 286 (m), 259 (w), 251 (m), 219 (m), 187 (w), 158 (s), 143 (s), 124 (s), 105 (s), 100 (s), 80 (s), 61 (s), 57 (s), 48 (s), 39 (s), 32 (s), 28 (s). HRMS-ESI (m/z) [M + Na]+ calcd for C₃H₄O₂Na 139.0892, found 139.0895.

[(+)-2-[(1R,3R,5S)-2-Hydroxy-4-methylcyclohex-3-enyl]-2,6-dimethylpropanoate (57)]. To an oven-dried and argon-purged 100 mL round-bottomed flask were added the ester (39 mg, 0.105 mmol, 1 equiv) in methanol (6 mL), and cerium chloride heptahydrate (391 mg, 1.05 mmol, 1.05 equiv). The reaction was cooled to 0 °C, then pivaloyl chloride (676 mg, 5.41 mmol, 1.05 equiv) was added. The reaction was stirred at 0 °C for 1 h, then warmed to 23 °C. The solvent was removed via rotary evaporation, and the residue was redissolved in ether. The reaction was carefully quenched with saturated NH₄Cl solution, and the layers were separated. The aqueous layer was extracted with ether, and the combined organic layers were washed with brine and dried over MgSO₄. The mixture was filtered and concentrated via rotary evaporation. Flash column chromatography of the residue on silica gel (200 mL, hexane:ether, 1:1) afforded 170 mg (86%) of the hydroxyester (85%) as a white solid.¹ H NMR (CDCl₃, 300 MHz) δ 5.61 (1H, m), 4.22 (1H, br s), 3.68 (1H, dd, J = 10.8, 3.2 Hz), 3.62 (1H, dd, J = 10.8, 6.5 Hz), 2.73 (1H, br s), 2.34 (1H, br s), 1.93–2.05 (2H, m), 1.76 (1H, m), 1.70 (3H, s), 1.59–1.63 (1H, m), 1.55 (1H, ddd, J = 12.8, 11.0, 6.3 Hz), 1.28 (1H, ddd, J = 12.4, 8.5, 3.2, 3.2 Hz), 1.01 (3H, d, J = 7.0 Hz).¹ C NMR (CDCl₃, 75 MHz) δ 139.7, 123.0, 66.0, 64.6, 44.0, 37.1, 31.4, 23.3, 21.5, 15.8; IR (thin film) 2967 (s), 2916 (s), 1732 (s), 1673 (m), 1448 (s), 1263 (s), 1183 (s), 1150 (s), 1096 (m), 1069 (m), 1032 (m), 995 (m), 871 (m), 714 (m), 616 (w), 570 (w), 472 (m), 362 (m), 342 (m), 322 (m), 286 (m), 259 (w), 251 (m), 219 (m), 187 (w), 158 (s), 143 (s), 124 (s), 105 (s), 100 (s), 80 (s), 61 (s), 57 (s), 48 (s), 39 (s), 32 (s), 28 (s). HRMS-ESI (m/z) [M + Na]+ calcd for C₃H₄O₂Na 139.0892, found 139.0895.
color changes were observed in the aqueous layer. The organic layer was washed with brine and dried over MgSO₄. The mixture was filtered and concentrated via rotary evaporation. Flash column chromatography of the residue on silica gel (170 mL, hexane:ether, 6:4) afforded 728 mg (89%) of the alcohol ester 57 as a clear oil. ¹H NMR (CDCl₃, 500 MHz) δ 5.61 (1H, br d, J = 4.5 Hz), 4.23 (1H, dd, J = 10.9, 4.0 Hz), 4.11 (1H, m), 3.99 (1H, dd, J = 10.9, 6.4 Hz), 1.88–2.04 (3H, m), 1.70 (3H, s), 1.68 (1H, m), 1.43 (1H, dd, J = 13.0, 11.5, 5.9 Hz), 1.28 (1H, m), 1.20 (9H, s), 1.23 (1H, br s), 1.03 (3H, d, J = 6.8 Hz). ¹³C NMR (CDCl₃, 125 MHz) δ 178.7, 137.6, 132.2, 67.8, 41.7, 38.8, 33.4, 31.2, 27.1, 23.3, 20.3, 15.5; IR (thin film) 3441 (br), 2969 (m), 2932 (m), 2910 (m), 2875.9 (m), 1728 (s), 1713 (s), 1480 (m), 1458 (w), 1398 (m), 1268 (s), 1073 (s), 955 (w); HRMS-ESI (m/z) [M + Na]⁺ calcd for C₁₂H₂₀O₂Na 277.1780, found 277.1786.

(±)-R-2-[(1R,2S)-2-[(1,1-Dimethylhydrazino)methyl]cyclohex-3-enyl]-4-methyloxacyclohex-3-ene]propan-1-ol (58). To an oven-dried and argon-purged 50 mL round-bottomed flask were added the alcohol 57 (290 mg, 1.14 mmol, 1 equiv), dichloromethane (10 mL), and imidazole (388 mg, 5.70 mmol, 5 equiv). tert-Butyldimethylsilyl chloride (753 mg, 2.85 mmol, 2.5 equiv) was added and the reaction was stirred at 23 °C for 16 h, during which time the contents changed color from clear to deep yellow. The reaction was poured into a 1:1 mixture of distilled water and ether (6× the volume of the dimethylamine). The layers were separated, and the aqueous layer was diluted with additional distilled water. The aqueous layer was extracted with ether, and the combined organic layers were washed with brine and dried over MgSO₄. The mixture was filtered and concentrated via rotary evaporation. Flash column chromatography of the residue on silica gel (90 mL, hexane:ether, 95:5) afforded a mixture of the protected diol along with minor amounts of TBSOH. The compound was taken onto the next step without calculation of yield. ¹H NMR (CDCl₃, 500 MHz) δ 4.98 (1H, m), 4.11 (1H, dd, J = 10.7, 3.7 Hz), 4.10 (1H, m), 3.98 (1H, dd, J = 10.7, 6.7 Hz), 1.84–2.00 (3H, m), 1.67 (3H, s), 1.61 (1H, m), 1.55 (1H, m), 1.24 (1H, m), 1.19 (9H, s), 1.00 (3H, d, J = 6.9 Hz), 0.86 (9H, s), 0.06 (3H, s), 0.03 (3H, s). ¹³C NMR (CDCl₃, 125 MHz) δ 178.6, 137.9, 123.9, 67.6, 65.8, 41.7, 33.2, 31.2, 27.1, 25.6, 23.3, 20.2, 18.1, 15.3, −3.3, −4.7; IR (thin film) 2957 (s), 2930 (s), 2884 (m), 2857 (m), 1731 (s), 1472 (m), 1462 (m), 1398 (w), 1361 (w), 1285 (m), 1253 (m), 1161 (s), 1059 (s), 1033 (m), 993 (m), 884 (w), 835 (m), 808 (w), 775 (m); HRMS-ESI (m/z) [M + Na]⁺ calcd for C₁₃H₂₄O₂Na 291.1644, found 291.1639.

To an oven-dried and argon-purged 50 mL round-bottomed flask were added the protected diol (420 mg, 1.14 mmol, 1 equiv) and dichloromethane (11 mL). The reaction was cooled to −78 °C, and a 1 M solution of diisobutylaluminum hydride in dichloromethane (2.85 mL, 2.5 mmol, 2 equiv) was added dropwise via syringe. The reaction was stirred at −78 °C for 1 h, then quenched with saturated potassium tetaurate solution. The reaction was warmed to 23 °C and the layers were separated. The aqueous layer was extracted with ether and the combined organic layers were washed with brine. The reaction was then dried over MgSO₄, filtered, and concentrated via rotary evaporation. Flash column chromatography of the residue on silica gel (40 mL, hexane:ether, 97:3) afforded 280 mg of the Julia–Kocienski products 53a/53b and 53c/53d as a clear oil. ¹H NMR (CDCl₃, 500 MHz) δ 78.3 (78%) as a clear oil. ¹H NMR (CDCl₃, 500 MHz) δ 78.3 (78%) as a clear oil. ¹H NMR (CDCl₃, 500 MHz) δ 78.3 (78%) as a clear oil. ¹H NMR (CDCl₃, 500 MHz) δ 78.3 (78%) as a clear oil.
17.5, -3.6, -4.0. $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 53c/53d (138.5, 138.3), 137.9, 128.0, 124.5, 85.7, 84.7, 65.8, 62.6, 47.6, (45.8, 45.7), 39.3, 36.8, 32.0, 31.4, 26.0, 23.2, (19.9, 19.7), 18.8, 18.2, 17.9, 17.3, 3.2, -3.2, -4.4; IR (thin film) 53a/53b 2957 (s), 2929 (s), 2856 (m), 1462 (m), 1376 (m), 1252 (m), 1131 (w), 1086 (m), 1054 (m), 1029 (m), 987 (m), 919 (w), 874 (m), 865 (m), 831 (s), 811 (w), 773 (m), 53c/53d 2957 (s), 2928 (s), 2869 (m), 1462 (m), 1451 (m), 1377 (m), 1250 (m), 1108 (m), 1082 (w), 1042 (m), 985 (m), 877 (w), 830 (m), 773 (m); HRMS-ESI (m/z) 53a/53b [M + Na$^+$] calcd for C$_{24}$H$_{45}$O$_2$Na 441.3165, found 441.3166, 35c/35d [M + Na$^+$] calcd for C$_{20}$H$_{34}$O$_2$Na 329.2456, found 329.2450.

(±)-15,6-R-3-Methyl-6-[2S,3E]-4-{(1R,2R,3R,4S)-1,3,4-trimethyl-7-oxabicyclo[2.2.1]heptan-2-yl}-but-3-en-2-yl)cyclohex-2-enol (60a) and (±)-15,6-R-3-Methyl-6-[2S,3E]-4-{(1S,2S,3R,4R)-1,3,4-trimethyl-7-oxabicyclo[2.2.1]heptan-2-yl}-but-3-en-2-yl)cyclohex-2-enol (60b). To an oven-dried and argon-purged 10 mL round-bottomed flask were added the mixture of 53a/53b (100 mg, 0.24 mmol, 1 equiv) and tetrahydrofuran (2 mL). Oven-dried powdered 4 Å molecular sieves were added to the flask, and TBAF (1 M in THF, 0.96 mL, 0.46 mmol, 4 equiv) was added dropwise via syringe. The reaction was stirred at 23 °C for 16 h, then diluted with ether and quenched with distilled water. The layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine and dried over MgSO$_4$. The mixture was filtered and concentrated via rotary evaporation. Gradient flash column chromatography of the residue on silica gel (15 mL, hexane:ether, 55:45) afforded 32 mg (44%) of 60a and 22 mg (30%) of 60b, both as clear oils for a total yield of 74%.

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(1H, dd, J = 15.2, 8.1 Hz), 4.06 (1H, m), 2.17–2.27 (1H, m), 1.91–2.05 (2H, m), 1.81–1.86 (2H, m), 1.70 (3H, s), 1.63–1.68 (1H, m), 1.51–1.63 (4H, m), 1.39–1.47 (2H, m), 1.32 (3H, s), 1.30 (3H, s), 1.15–1.20 (1H, m), 1.06 (3H, d, J = 6.7 Hz), 0.89 (3H, d, J = 6.9 Hz); \(^1^C\)NMR (CDCl\(_3\), 125 MHz) \(\delta\) 60d 139.7, 138.1, 128.7, 123.0, 85.6, 84.7, 65.2, 62.4, 47.7, 44.9, 39.3, 38.1, 32.0, 31.2, 23.4, 20.3, 19.9, 19.1, 17.7, 17.4, 60d 139.8, 137.9, 128.8, 123.0, 85.7, 84.8, 65.1, 62.3, 47.6, 44.9, 39.3, 38.2, 32.1, 31.2, 23.3, 20.2, 20.0, 19.0, 17.8, 17.3; IR (thin film) 60c 3462 (br, m), 2967 (s), 2928 (s), 2870 (m), 2828 (w), 1451 (m), 1377 (m), 1229 (m), 1128 (w), 1107 (w), 1059 (w), 1018 (w), 955 (m), 908 (w), 863 (m), 846 (w), 60d 3452 (br, m), 2966 (s), 2927 (s) 2870 (m), 1450 (m) 1377 (m), 1228 (w), 1109 (m), 1019 (m), 955 (m), 863 (w); HRMS-ESI (m/z) 60c [M + Na]\(^+\) calcd for C\(_{20}\)H\(_{32}\)O\(_2\)Na, 327.2300, found 327.2295, 60d [M + Na]\(^+\) calcd for C\(_{20}\)H\(_{32}\)O\(_2\)Na, 327.2300, found 327.2304.

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**Supporting Information Available:** Proton and carbon NMR spectra of all pure compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.