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Total Synthesis of Racemic Laurenditerpenol, an HIF-1 Inhibitor

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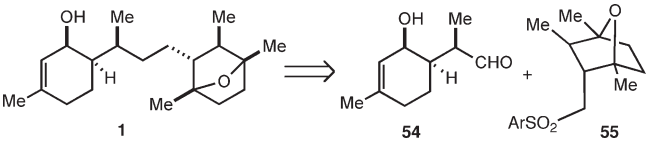

The convergent total synthesis of the HIF-1 inhibitor laurenditerpenol **1** and its diastereomer **1′** is reported. The key step involves the Julia−Kocienski olefination−reduction process between the sulfone **55** and the aldehyde **54**. The unusual trimethylated oxanorbornane sulfone **55** was 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 IC_{50} 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

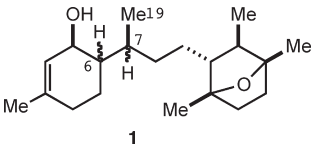

FIGURE 1. Laurenditerpenol.

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.[4−6] 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

(1) Brown, J. M. *Cancer Res.* **1999**, *59*, 5863–5870.
(2) Gray, L. H.; Conger, A. D.; Ebert, M.; Hornsey, S.; Scott, O. C. *Br. J. Radiol.* **1953**, *26*, 638–648.
(3) Patiar, S.; Harris, A. L. *Endocr. Relat. Cancer* **2006**, *13*, S61–S75.
(4) Mohammed, K. A.; Hossain, C. F.; Zhang, L.; Bruick, R. K.; Zhou, Y.-D.; Nagle, D. G. *J. Nat. Prod.* **2004**, *67*, 2002–2007.
(5) Wessels, M.; Konig, G. M.; Wright, A. D. *J. Nat. Prod.* **2000**, *63*, 920–928.
(6) Suzuki, M.; Daitoh, M.; Vairappan, C. S.; Abe, T.; Masuda, M. *J. Nat. Prod.* **2001**, *64*, 597–602.
(7) Chittiboyina, A. G.; Kumar, G. M.; Carvalho, P. B.; Liu, Y.; Zhou, Y.-D.; Nagle, D. G.; Avery, M. A. *J. Med. Chem.* **2007**, *50*, 6299–6302.
(8) A communication of this work was published recently: Jung, M. E.; Im, G.-Y. J. *Tetrahedron Lett.* **2008**, *49*, 4962–4964.

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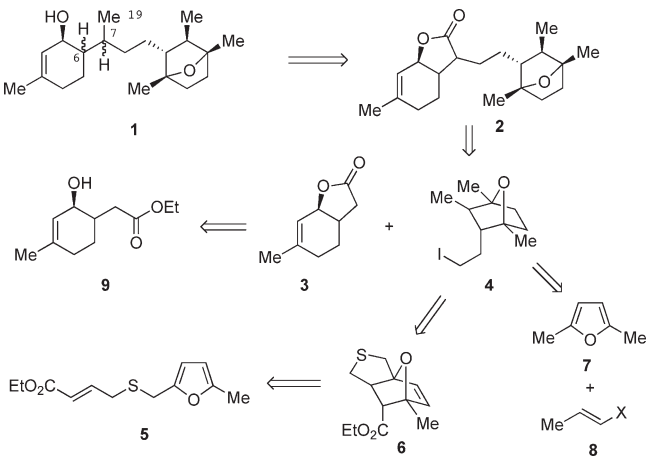
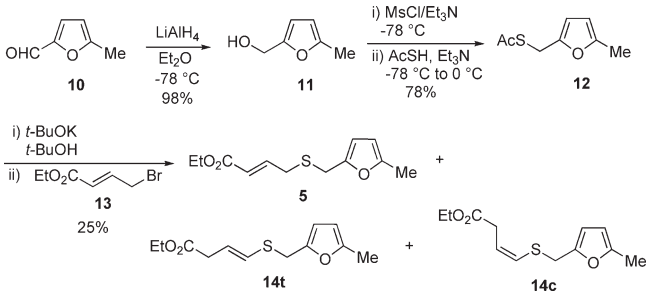
SCHEME 1. Retrosynthesis of 1



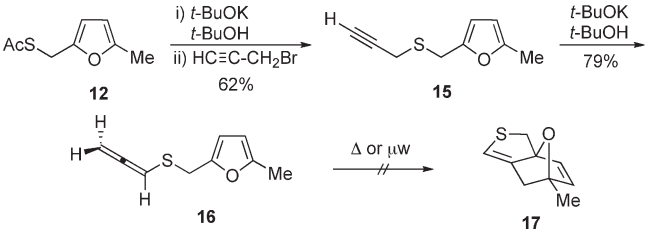
SCHEME 2. Synthesis of Sulfide 5



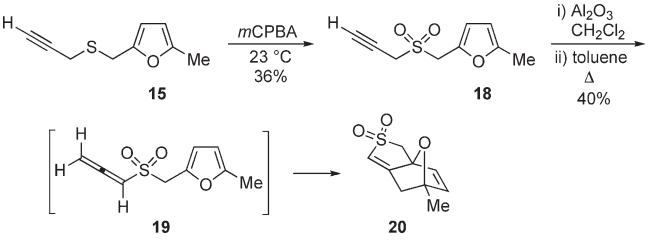
the iodide **4**. The oxanorbornane containing subunit **4** would be generated via a furan Diels–Alder reaction, using either an intramolecular version of the substrate **5** (via desulfurization and reduction of **6**) or an intermolecular version with 2,5-dimethylfuran **7** and a crotonate unit **8**.[9] 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.[10] 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 stereochemical 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–S_N2 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

SCHEME 3. Allene 16 Synthesis and Attempts at Cyclization



SCHEME 4. Successful Synthesis of the Tricyclic Sulfone 20



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 sp^1 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.[11] Since the direct oxidation of the allene **16** only yielded decomposition, the alkyne **15** was first converted to the sulfone **18** via *m*CPBA 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.[11]

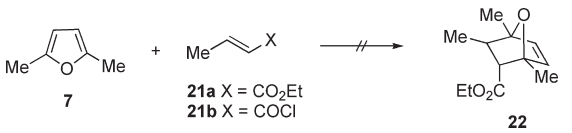
This result encouraged us to seek methods of elaborating the sulfone **18** with a terminal ester to allow a handle for elaboration to the target iodide **4**. Unfortunately, all attempts to convert the sulfone **18** to its corresponding terminal ester were unsuccessful. These difficulties, coupled 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**.

(9) (a) Klein, L. L. *J. Org. Chem.* **1985**, *50*, 1770–1773. (b) Klein, L. L. *J. Am. Chem. Soc.* **1995**, *107*, 2573–2574.

(10) Mineko, O.; Chiyoki, Y.; Takao, S. Jpn. Kokai Tokkyo Koho JP 2004269463 2A, September 30, **2004**.

(11) Kanematsu, K.; Kinoyama, I. *J. Chem. Soc., Chem. Commun.* **1992**, 735–736.

SCHEME 5. Attempts To Use an Intermolecular Diels–Alder Strategy

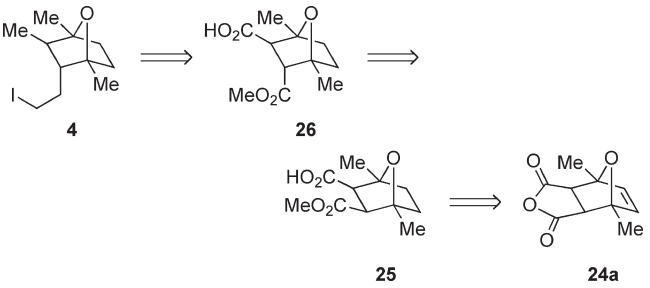


Synthesis of 4 via an Intermolecular Furan Diels–Alder Strategy. Concomitant with the intramolecular Diels–Alder approach, the intermolecular furan Diels–Alder route was also examined (Scheme 5). Although literature precedence existed for the reaction of 2,5-dimethylfuran **7** with simple α,β-unsaturated esters,[12] there was no corresponding description of reactions of 2,5-dimethylfuran with crotonates. The desired transformation was explored under various Lewis acidic conditions with both the ester **21a** and acid chloride **21b** but resulted in no cycloadduct. 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.

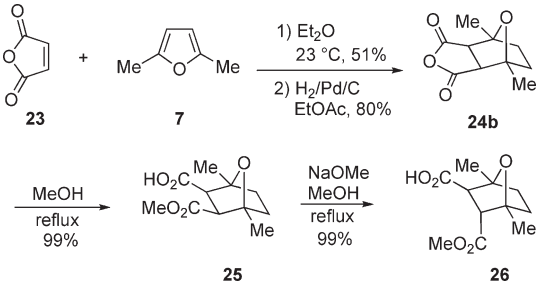
Synthesis of the Carboxylic Acid Ester 26. In our revised retrosynthesis of **4**, as shown in Scheme 6, we envisioned the use of the well-known *exo* Diels–Alder adduct **24a** of 2,5-dimethylfuran **7** and maleic anhydride **23**[13] as our starting point for the total synthesis. The use of this compound is advantageous since three out of the four stereocenters are set at the onset in a single step. In addition, the methanolysis 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

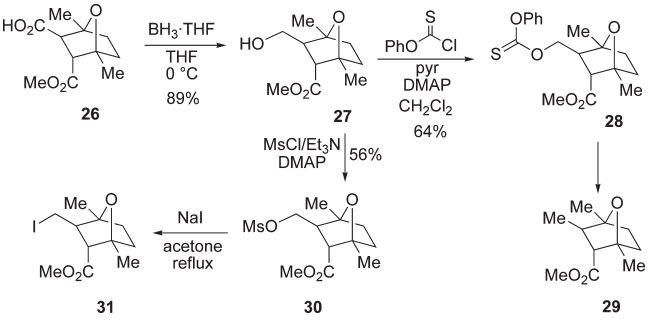
SCHEME 6. Revised Retrosynthesis of Subunit 4



SCHEME 7. Synthesis of the Carboxylic Acid Ester 26



SCHEME 8. Deoxygenation Strategies



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 α to an ester versus those α 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 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 $BH_3\cdot THF$ (Scheme 8). After conversion of the alcohol **27** to the thionoester **28**, we explored its deoxygenation under the

(12) (a) Hayashi, Y.; Nakamura, M.; Nakao, S.; Inoue, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4079–4082. (b) Lazlo, P.; Luccheti, J. *Tetrahedron Lett.* **1984**, *25*, 4387–4388. (c) Heiner, T.; Michalski, S.; Gerke, K.; Kutcha, G.; Buback, M.; de Meijere, A. *Synlett* **1995**, 355–357. (d) Kozikowski, A. P.; Floyd, W. C.; Kuniak, M. P. *J. Chem. Soc., Chem. Commun.* **1977**, 582–583. (e) Landscheidt, A. *Process for the Production of 7-Oxabicylo(2.2.1)hept-5-ene derivatives.* U.S. Patent 4,555,581, November 26, **1985**.

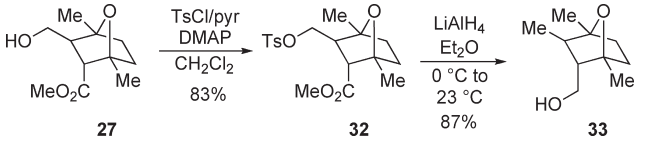
(13) (a) Diels, O.; Alder, K.; Naujoks, E. *Ber. Deutsch. Chem. Ges. B* **1929**, *62B*, 554–562. (b) Brickwood, D. J.; Ollis, W. D.; Stephanatou, J. S.; Stoddart, J. F. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1398–1414. (c) Imagawa, T.; Matsuura, K.; Murai, N.; Akiyama, T.; Kawanisi, M. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3020–3022. (d) Akiyama, T.; Fujii, T.; Ishiwari, H.; Imagawa, T.; Kawanisi, M. *Tetrahedron Lett.* **1978**, *19*, 2165–2166.

(14) (a) Seebach, D.; Jaeschke, G.; Wang, Y. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2395–2396. (b) Chen, Y.; Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2000**, *122*, 9542–9543. (c) Bolm, C.; Schiffers, I.; Dinter, C. L.; Gerlach, A. *J. Org. Chem.* **2000**, *65*, 6984–6991. (d) Bolm, C.; Shiffers, I.; Atodiresei, I.; Hackenberger, C. P. R. *Tetrahedron: Asymmetry* **2003**, *14*, 3455–3467.

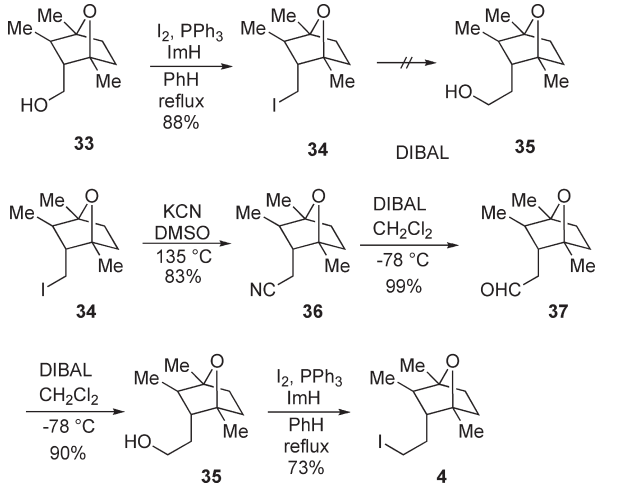
(15) Jung, M. E.; Sledeski, A. W. *J. Chem. Soc., Chem. Commun.* **1993**, 589–591.

(16) An epimerization and methanolysis of diacids on an oxanorbornane ring with excess sodium methoxide is described in the following publication: Ohtani, M.; Matsuura, T.; Watanabe, F.; Narisada, M. *J. Org. Chem.* **1991**, *56*, 4120–4123.

SCHEME 9. Tosylation−Reduction Sequence



SCHEME 10. Homologation and Synthesis of Subunit 4

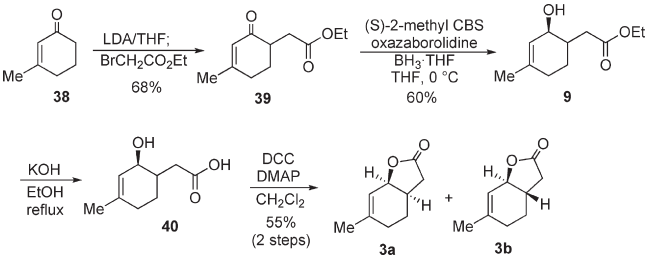


classic Barton conditions and Fu's modified conditions.[17] Unfortunately, extensive exploration of different reduction conditions did not achieve the necessary deoxygenation. Drawing inspiration from the successful deoxygenation of a similar primary alcohol in the total synthesis of (±)-Palasonin,[18] the alcohol **27** was converted to the mesylate **30** in 56% yield. 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**.

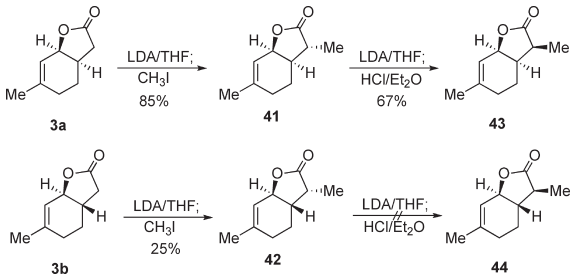
The low reactivity of the mesylate is presumably due to the highly sterically hindered nature of the substrate, and thus we sought to circumvent this issue by using a hydride reduction strategy. After much experimentation we found a two-step sequence involving the tosylation of alcohol **27** to generate **32** in 83% yield followed by concomitant reduction of both the tosylated alcohol and the ester via $LiAlH_4$ to give the alcohol **33** in 87% yield (Scheme 9). This successful deoxygenation generated the final methyl group of the oxanorbornane ring in excellent yield and was a marked improvement from our previous sequential deoxygenation−reduction strategy. Having now completed the most important motifs of the 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

SCHEME 11. Synthesis of Lactones 3a and 3b



SCHEME 12. Methylation Studies of the Lactones 3a and 3b



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 nitrile **36** in 83% yield. The nitrile 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 substrate by a few steps, each step (S_N2, double reduction, iodination) was easy in its operation and purification and more importantly allowed us access to useful quantities of the iodide **4** to test out the key alkylation step.

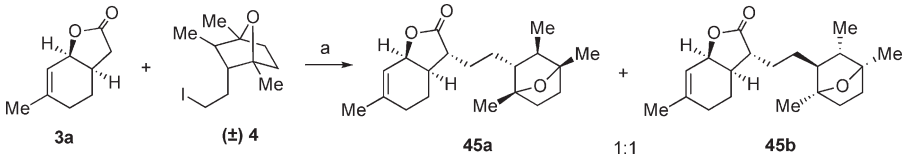
Construction of Lactone Partners 3a and 3b. The lactone fragment **3** was synthesized utilizing a modification of a known route (Scheme 11).[10] Optimization of the published route was necessary to ensure reproducible and scalable transformations. The Corey CBS-reduction of the ketoester **39**, prepared 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,[10] 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

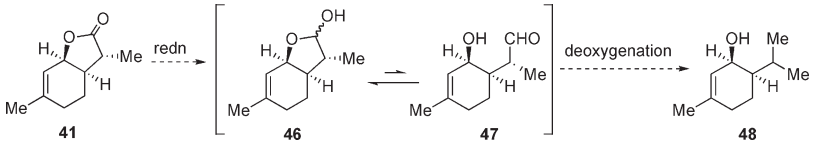
(17) (a) Barton, D. H. R.; Motherwell, W. B.; Stange, A. *Synthesis* **1981**, 743–745. (b) Barton, D. H. R.; Blundell, R.; Dorchak, J.; Jang, D. O.; Jaszberenyl, J .C. *Tetrahedron* **1991**, *47*, 8969–8984. (c) Lopez, R. M.; Hays, D. S.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 6949–6950. (d) Takao, K.; Yasui, H.; Yamamoto, S.; Sasaki, D.; Kawasaki, S.; Watanabe, G.; Tadano, K. *J. Org. Chem.* **2004**, *69*, 8789–8795.

(18) Rydberg, D. B.; Meinwald, J. *Tetrahedron Lett.* **1996**, *37*, 1129–1132.

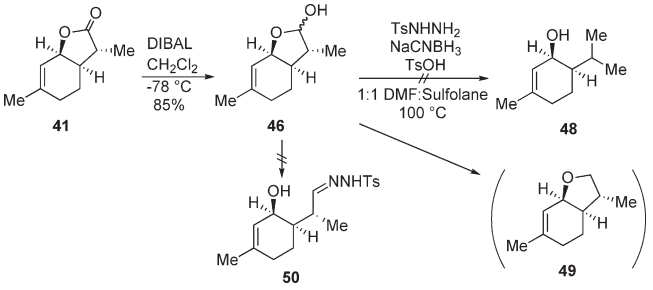
SCHEME 13. Alkylation of Lactone 3a with Racemic Iodide 4



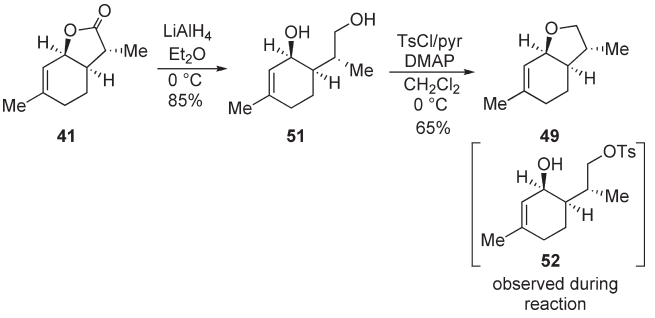
SCHEME 14. The Planned Deoxygenation Strategy



SCHEME 15. Deoxygenation of the Lactone via the Hutchins Method



SCHEME 16. Tosylation of the Primary Alcohol for Reduction

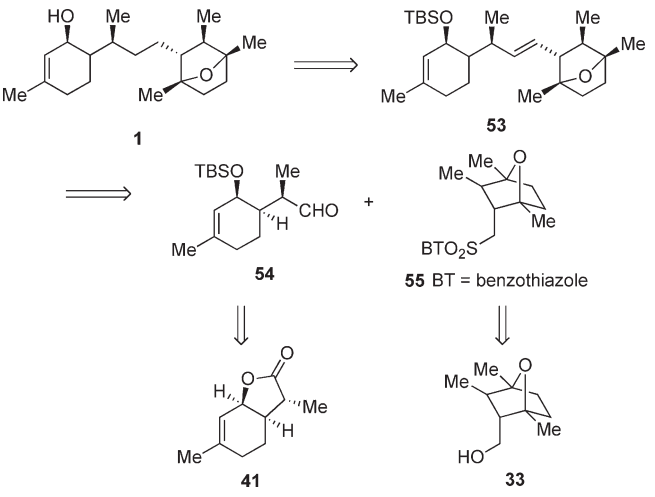


translated into the C7 carbon of laurenditerpenol. Thus the lactones **3a** and **3b** were each treated separately with LDA and quenched with methyl iodide (Scheme 12). To our delight, electrophile addition occurred from the *re* face for both lactones to yield methyl lactones **41** and **42**, respectively. 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 sp^2 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

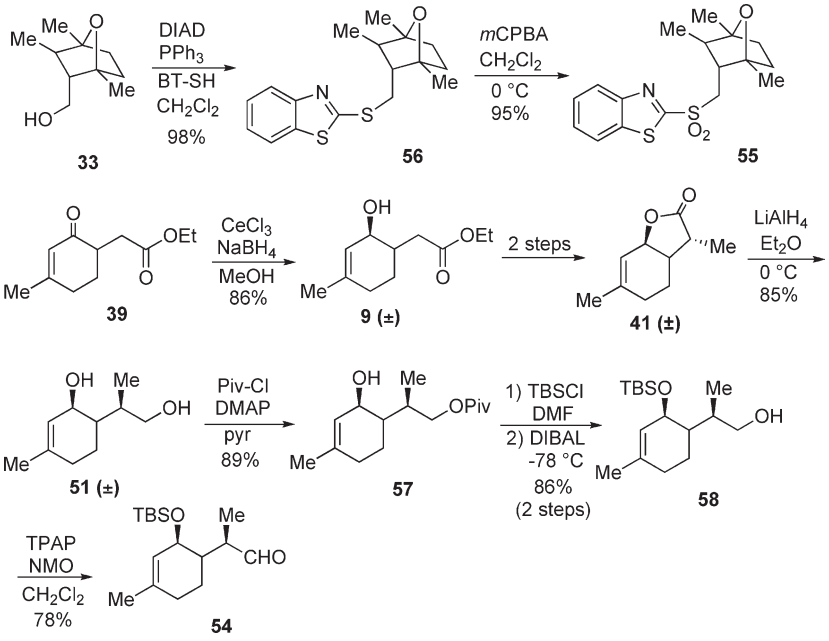
SCHEME 17. New Retrosynthesis Utilizing the Julia–Kocienski Olefination



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

SCHEME 18. Synthesis of the Sulfone 55 and the Aldehyde 54

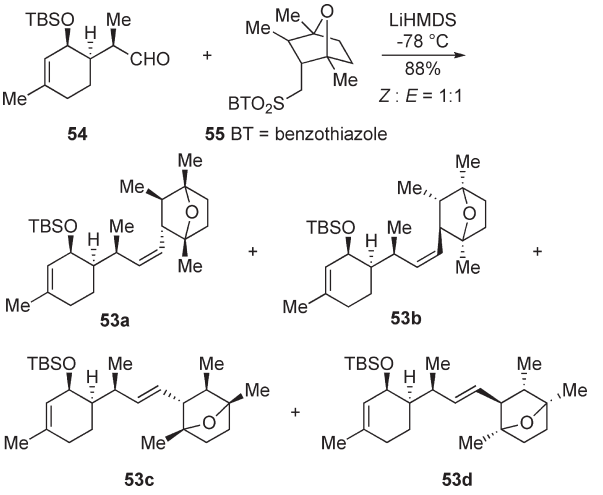


of **41** to the lactol **46** followed by deoxygenation of the isomeric hydroxyaldehyde **47** to give **48** (Scheme 14). Literature precedence involving the reduction of lactols to the hydroxyalkane via Wolff−Kishner conditions[19] suggested the use of a similar strategy would be possible in our synthesis.

We investigated the use of a mild carbonyl deoxygenation reaction pioneered by Hutchins[20] 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 to 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

SCHEME 19. Julia−Kocienski Olefination

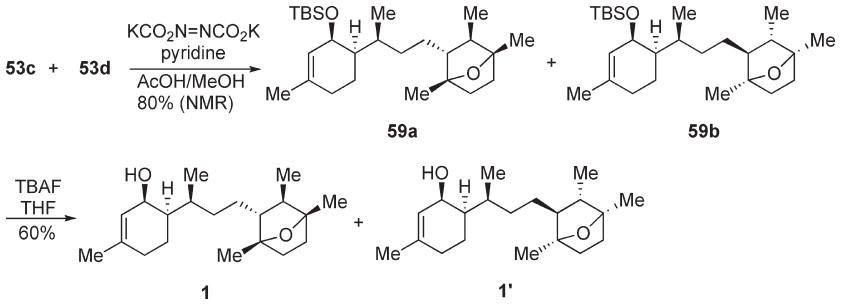


on the preferential formation of the lactol was probably accurate.

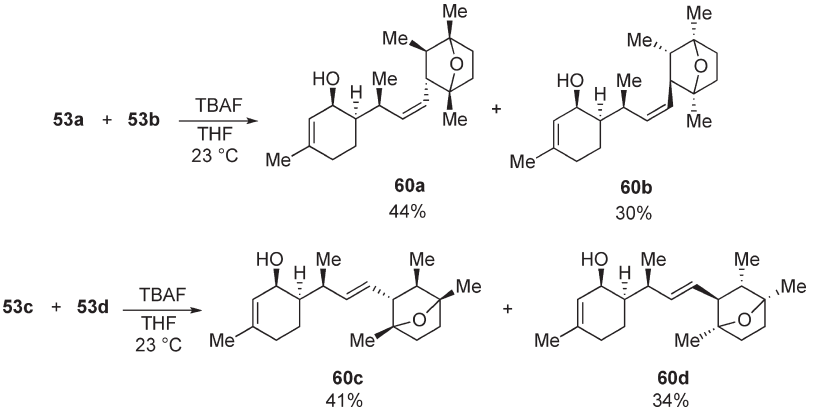
Instead of relying on an unfavorable equilibrium to effect the desired deoxygenation, we decided to reduce the lactone **41** to the diol **51** with the plan of converting the primary alcohol to the tosylate **52** for lithium aluminum hydride reduction (Scheme 16). However, during the tosylation of 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**.

(19) Cardona, L.; Garcia, B.; Gimenez, J. E.; Pedro, J. R. *Tetrahedron* **1992**, *48*, 851–860.
(20) Hutchins, R. O.; Maryanoff, B. E.; Milewski, C. A. *J. Am. Chem. Soc.* **1971**, *93*, 1793–1794.

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



SCHEME 21. Synthesis of Analogues of Laurenditerpenol



Julia−Kocienski Olefination Strategy. We turned to an alternate strategy that would involve the use of the dependable Julia−Kocienski olefination reaction[21] 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 **55**. Thus, the revised retrosynthesis envisioned the use of the protected aldehyde **54** (preparable from **41**) and sulfone **55** (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 *m*CPBA to generate the sulfone subunit **55** (Scheme 18). To synthesize the protected aldehyde **54**, we started from the racemic methyl lactone **41**,[22] 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 $LiAlH_4$, protecting group manipulation to give the silylated alcohol **58**, followed by a final oxidation of the primary alcohol with TPAP/NMO.[23] 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[24] (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).[25] The hindered *Z* isomers, **53a** and **53b**,

(21) (a) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, *14*, 4833–4836. (b) Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 829. (c) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26–28.

(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.

(23) (a) Tanner, D.; Tedenborg, L.; Somfai, P. *Acta Chem. Scand.* **1997**, *51*, 1217–1223. (b) Nielsen, T. E.; Le Quement, S.; Juhl, M.; Tanner, D. *Tetrahedron* **2005**, *61*, 8013–8024.

(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[21c] were hampered by severe difficulties in preparing the necessary substrate from **33**.

(25) (a) Pasto, D. J.; Taylor, R. T. *Org. React.* **1991**, *40*, 91–155. (b) Jung, M. E.; Min, S.-J. *J. Am. Chem. Soc.* **2005**, *127*, 10834–10835. (c) Jung, M. E.; Min, S.-J. *Tetrahedron* **2007**, *63*, 3682–3701.

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 **1** and **1′** 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 **1** in 12 longest linear steps and 2.5% overall yield from 2,5-dimethylfuran **7**. In addition, the diastereomer of laurenditerpenol **1′** 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 **1** 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.

(±)-(**1*S*,2*R*,6*S*,7*R*)-1,7-Dimethyl-4,10-dioxatricyclo[5.2.1.0^{2,6}]decane-3,5-dione** (**24b**). To an oven-dried and argon-purged 100 mL round-bottomed flask were added recrystallized maleic anhydride **23** (7.46 g, 76.0 mmol, 1 equiv) and diethyl ether (20 mL). Distilled 2,5-dimethylfuran **7** (7.31 g, 76.0 mmol, 1 equiv) was added slowly to the reaction via syringe, and the reaction was vigorously stirred at 23 °C overnight. The reaction was cooled to 0 °C for 1 h, and the crystals were filtered through a Büchner funnel. The crystals were washed with 20 mL of cold diethyl ether and dried in the funnel to yield 7.46 g (51%) of the Diels−Alder cycloadduct as pale-yellow crystals. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.35 (2H, s), 3.16 (2H, s), 1.77 (6H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.3, 141.0, 88.7, 53.9, 15.5. IR (thin film) 2990 (m), 2940 (w), 1854 (m), 1831 (m), 1777 (s), 1392 (m), 1242 (s), 1214 (m), 1098 (s), 1084 (s), 923 (s), 864 (s), 834 (m), 746 (m).

To an oven-dried and argon-purged 100 mL round-bottomed flask were added the Diels−Alder cycloadduct (1 g, 5.15 mmol, 1 equiv) and ethyl acetate (50 mL). Palladium on carbon (10%, 0.1 g, 10% of substrate by weight) was added to the flask. Hydrogen was delivered into the reaction via a balloon equipped with a syringe needle, and the reaction was stirred under hydrogen for 4 h. The mixture was filtered and concentrated via rotary evaporation. Flash column chromatography of the residue on silica gel (200 mL, hexane:ethyl acetate, 6:4) afforded 803 mg (80%) of the anhydride **24b** as white crystals.[13c] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.14 (2H, s), 1.80 (2H, dd, J = 9.5, 1.8 Hz), 1.78 (2H, dd, J = 9.5, 1.8 Hz), 1.63 (6H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.8, 85.9, 54.2, 37.5, 17.7. IR (thin film) 2998 (w), 2983 (m), 2957 (m), 2880 (w), 1867 (m), 1834 (m), 1771 (s), 1389 (m), 1259 (m), 1225 (s), 1191 (m), 1112 (m), 1089 (m), 931 (s), 872 (s), 856 (m). MS (MALDI) calcd for $C_{10}H_{12}NaO_4$ $[M + Na]^+$ 219.0633, found 219.0685.

(±)-(**1*S*,2*R*,3*S*,4*R*)-3-(Methoxycarbonyl)-1,4-dimethyl-7-oxabicyclo[2.2.1]heptane-2-carboxylic Acid** (**25**). To an oven-dried and argon-purged 25 mL round-bottomed flask were added the anhydride **24b** (100 mg, 0.51 mmol, 1 equiv) and methanol (5 mL). The reaction was heated to reflux and stirred for 16 h. The mixture was then cooled to 23 °C and concentrated via rotary evaporation. Flash column chromatography of the residue on silica gel (11 mL, dichloromethane:methanol, 9:1) afforded 115 mg (99%) of the carboxylic acid ester **25** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.63 (3H, s), 3.15 (2H, s), 1.69−1.76 (4H, m), 1.63 (3H, s), 1.62 (3H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.3, 170.7, 84.9, 84.7, 56.5, 55.6, 51.6, 39.4, 38.7, 18.3, 18.2. IR (thin film) 3400−2800 (br, m), 2953 (m), 1748 (s), 1437 (w), 1385 (w), 1355 (w), 1230 (m), 1194 (s), 1109 (m), 1088 (m), 1042 (m), 932 (m), 860 (m). MS (MALDI) calcd for $C_{11}H_{16}NaO_5$ $[M + Na]^+$ 251.0890, found 251.0883.

(±)-(**1*S*,2*R*,3*R*,4*R*)-3-(Methoxycarbonyl)-1,4-dimethyl-7-oxabicyclo[2.2.1]heptane-2-carboxylic Acid** (**26**). To an oven-dried and argon-purged 10 mL round-bottomed flask were added methanol (5 mL) and sodium metal (20 mg, 0.7 mmol, 4 equiv). After the sodium dissolved completely, the solution was heated to reflux. The carboxylic acid ester **25** (80 mg, 0.35 mmol, 1 equiv) in methanol (1 mL) was added dropwise into the reaction via syringe, and the reaction was stirred at reflux for 16 h. The mixture was cooled to 23 °C and quenched with 1 M HCl solution. The layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine and dried over $MgSO_4$. The mixture was filtered and concentrated via rotary evaporation. Flash column chromatography of the residue on silica gel (25 mL, dichloromethane:methanol, 95:5) afforded 80 mg (99%) of the epimeric carboxylic acid ester **26** as a clear solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.72 (3H, s), 3.27 (1H, dd, J = 5.5, 2.2 Hz), 3.24 (1H, d, J = 5.5 Hz) 1.86−1.68 (3H, m), 1.64 (3H, s), 1.59 (1H, dddd, J = 11.8, 11.8, 4.5, 2.3 Hz), 1.50 (3H, s); ^{13}C NMR

(26) Nicolaou, K. C.; Namoto, K.; Ritzen, A.; Ulven, T.; Shoji, M.; Li, J.; D'Amico, G.; Liotta, D.; French, C. T.; Wartmann, M.; Altmann, K.-H.; Giannakakou, P. *J. Am. Chem. Soc.* **2001**, *123*, 9313–9323.

(27) Since the completion of this research, a publication has appeared on the synthesis of analogues of laurenditerpenol: Athinaios, N.; Kazantzis, A.; Putzker, K.; Lewis, J.; Pitsinos, E. N. *Lett. Org. Chem.* **2009**, *6*, 269–271.

($CDCl_3$, 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), 1314 (w), 1252 (m), 1209 (m), 1174 (m), 1129 (w), 1066 (w), 869 (w); HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{11}H_{16}O_5Na$, 251.0895, found 251.0894.

(±)-(1*R*,2*R*,3*S*,4*S*)-Methyl 3-(Hydroxymethyl)-1,4-dimethyl-7-oxabicyclo[2.2.1]heptane-2-carboxylate (27). To an oven-dried and argon-purged 200 mL round-bottomed flask were added the carboxylic acid ester **26** (1.46 g, 6.40 mmol, 1 equiv) and tetrahydrofuran (64 mL). The reaction was cooled to 0 °C with an ice bath, and $BH_3 \cdot THF$ (1 M solution, 7.68 mL, 7.68 mmol, 1.2 equiv) was added dropwise via syringe. The mixture was stirred at 0 °C for 4 h, then quenched with methanol. The reaction was allowed to warm to 23 °C, and the solvent was removed via rotary evaporation. Flash column chromatography of the residue on silica gel (350 mL, hexane:ether, 2:8) afforded 1.22 g (89%) of the hydroxyester **27** as a clear oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.72 (3H, s), 3.67 (1H, dd, J = 10.6, 5.2 Hz), 3.59 (1H, dd, J = 10.6, 6.1 Hz), 2.71 (1H, dd, J = 4.8, 2.3 Hz), 2.44 (1H, ddd, J = 5.3, 5.3, 5.3 Hz), 1.88 (1H, br s), 1.78−1.85 (2H, m), 1.65−1.72 (1H, m), 1.58 (3H, s), 1.54−1.61 (1H, m), 1.43 (3H, s); ^{13}C NMR ($CDCl_3$, 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), 1736 (s), 1437 (m), 1381 (m), 1314 (m), 1222 (m), 1174 (m), 1066 (m), 1024 (m), 994 (w), 907 (m), 867 (m); HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{11}H_{18}O_4Na$ 237.1103, found 237.1096.

(±)-(1*R*,2*R*,3*S*,4*S*)-Methyl 1,4-Dimethyl-3-[(4-methylphenylsulfonyl)oxymethyl]-7-oxabicyclo[2.2.1]heptane-2-carboxylate (32). To an oven-dried and argon-purged 1 L round-bottomed flask were added the hydroxyester **27** (6.25 g, 29.2 mmol, 1 equiv) and dichloromethane (300 mL). The reaction was treated with pyridine (23.5 mL, 291.7 mmol, 10 equiv) and 4-(dimethylamino)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, 2 equiv) was added to the reaction. The mixture was stirred at 0 °C for 1 h, 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 $MgSO_4$. The mixture was filtered and concentrated via rotary evaporation. Flash column chromatography of the residue on silica gel (1 L, hexane:ether, 1:1) afforded 8.88 g (83%) of the ester tosylate **32** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.77 (2H, d, J = 8.3 Hz), 7.35 (2H, d, J = 8.0 Hz), 4.04 (1H, dd, J = 9.4, 7.5 Hz), 3.78 (1H, dd, J = 9.4, 7.5 Hz), 3.70 (3H, s), 2.65 (1H, ddd, J = 7.4, 7.4, 5.1 Hz), 2.45 (3H, s), 2.27 (1H, dd, J = 5.0, 2.2 Hz), 1.75 (2H, m), 1.59 (1H, m), 1.50 (1H, m), 1.49 (3H, s), 1.29 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.6, 144.8, 132.7, 129.8, 127.8, 84.9, 84.6, 70.5, 57.8, 52.0, 48.7, 38.3, 33.4, 21.6, 20.7, 17.8; IR (thin film) 2976 (m), 2954 (m), 1733 (s), 1598 (w), 1457 (m), 1437 (m), 1363 (s), 1309 (w), 1243 (m), 1190 (s), 1177 (s), 1134 (w), 1097 (m), 1020 (m), 966 (s), 910 (w), 869 (m), 816 (m), 779 (w); HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{18}H_{24}O_6SNa$ 391.1191, found 391.1198.

(±)-(1*R*,2*S*,3*R*,4*S*)-1,3,4-Trimethyl-7-oxabicyclo[2.2.1]heptane-2-methanol (33). To an oven-dried and argon-purged 25 mL round-bottomed flask were added lithium aluminum hydride (193 mg, 5.08 mmol, 5 equiv) and diethyl ether (12 mL). The reaction was cooled to 0 °C with an ice bath, and the ester **32** (360 mg, 1.02 mmol, 1 equiv) dissolved in 3 mL of diethyl ether was added dropwise to the reaction via syringe. The reaction was warmed to 23 °C, then stirred for 2 h. The mixture was then cooled to 0 °C, and 0.19 mL of distilled water (1 mL/1 g $LiAlH_4$) was added carefully via syringe. The reaction was allowed to stir for 10 min at 0 °C, then 0.19 mL of 15% aqueous sodium hydroxide (1 mL/1 g $LiAlH_4$) was added dropwise via syringe. The reaction was allowed to stir for another 10 min at 0 °C, then 0.57 mL of distilled water (3× initial volume of water) was added via syringe. The reaction was warmed to 23 °C over 20 min. $MgSO_4$ was added to the mixture to absorb excess water, then the solution was filtered through a glass frit. The solid residue was washed with diethyl ether (100 mL), and the filtrate was concentrated via rotary evaporation. Flash column chromatography of the residue on silica gel (40 mL, hexane:ether, 1:3) afforded 150 mg (87%) of the alcohol **33** as a clear oil.[7] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.73 (1H, dd, J = 10.7, 7.1 Hz), 3.63 (1H, dd, J = 10.7, 7.8 Hz), 1.80−1.87 (1H, m), 1.60−1.66 (1H, m), 1.48−1.58 (3H, m), 1.45 (3H, s), 1.38−1.43 (1H, m), 1.30 (3H, s), 0.96 (3H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 84.7, 84.5, 64.2, 60.0, 45.9, 38.9, 32.0, 21.5, 18.6, 17.8; IR (thin film) 3416 (br, s), 2968 (s), 2873 (s), 1653 (br, w), 1456 (s), 1378 (s), 1317 (m), 1262 (m), 1230 (m), 1214 (m), 1189 (m), 1175 (m), 1126 (s), 1064 (s), 1041 (m), 1016 (s), 937 (w), 910 (m), 863 (s), 830 (m).

(±)-(1*R*,2*R*,3*R*,4*S*)-2-(Iodomethyl)-1,3,4-trimethyl-7-oxabicyclo[2.2.1]heptane (34). To an oven-dried and argon-purged 500 mL round-bottomed flask were added the alcohol **33** (3.63 g, 21.3 mmol, 1 equiv) and benzene (200 mL). Imidazole (7.35 g, 113 mmol, 5.3 equiv) and iodine (26.8 g, 105.5 mmol, 4.95 equiv) were added to the reaction. Triphenylphosphine (28 g, 106.6 mmol, 5 equiv) was added to the mixture with vigorous stirring, and any solid deposits formed were broken up with a glass rod. The reaction was heated to reflux and allowed to stir for 16 h. After cooling to 23 °C, the reaction was diluted with ether and washed successively with saturated $NaHCO_3$ solution and 10% sodium sulfate solution. The aqueous layers were extracted with ether, then the combined organic layers were washed with brine and dried over $MgSO_4$. The mixture was filtered and concentrated via rotary evaporation. Flash column chromatography of the residue on silica gel (1 L, hexane:ether, 90:10) afforded 5.51 g (88%) of the iodide **34** as a white solid.[7] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.17 (1H, dd, J = 12.0, 7.5 Hz), 3.14 (1H, dd, J = 12.0, 12.0 Hz), 1.79−1.86 (2H, m), 1.66 (1H, ddd, 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 = 8.6 Hz); ^{13}C NMR ($CDCl_3$, 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).

(±)-(1*R*,2*R*,3*R*,4*S*)-1,3,4-Trimethyl-7-oxabicyclo[2.2.1]heptane-2-acetonitrile (36). To an oven-dried and argon-purged 10 mL round-bottomed flask were added the iodide **34** (100 mg, 0.34 mmol, 1 equiv) and dimethyl sulfoxide (3.5 mL). Potassium cyanide (133 mg, 2.04 mmol, 6 equiv) was added to the flask, and the reaction was heated at 135 °C for 5 h. The reaction was cooled 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 $MgSO_4$, filtered, and concentrated via rotary evaporation. Flash column chromatography of the residue on silica gel (12 mL, hexane:ether, 1:1) afforded 50.4 mg (83%) of the nitrile **36** as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.37 (2H, d, J = 7.7 Hz), 1.74−1.81 (1H, m), 1.65−1.71 (1H, m), 1.54−1.61 (3H, m), 1.47−1.53 (1H, m), 1.44 (3H, s), 1.31 (3H, s), 1.02 (3H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 118.6, 84.8, 84.6, 53.4, 48.1, 38.7, 31.4, 20.1, 18.4, 18.0, 17.6; IR (thin film) 2970 (s), 2932 (m), 2875 (m), 2246 (m), 1451 (m), 1423 (w), 1380 (m), 1229 (m), 1123 (m), 1137 (m), 1068 (w), 866 (m); HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{11}H_{17}NONa$ 202.1208, found 202.1208.

(±)-(1*R*,2*R*,3*R*,4*S*)-1,3,4-Trimethyl-7-oxabicyclo[2.2.1]heptane-2-acetaldehyde (37). To an oven-dried and argon-purged 10 mL round-bottomed flask were added the nitrile **36** (22 mg,

0.12 mmol, 1 equiv) and dichloromethane (1.2 mL). The reaction was cooled to −78 °C, and diisobutylaluminum hydride (1 M, 310 μL, 0.31 mmol, 2.5 equiv) was added to the reaction via syringe. The reaction was stirred at −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. The combined organic layers were washed with brine and dried over $MgSO_4$. The mixture was filtered and concentrated via rotary evaporation. Flash column chromatography of the residue on silica gel (10 mL, hexane:ether, 6:4) afforded 22 mg (99%) of the aldehyde **37** as a clear oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.77 (1H, t, J = 2.3 Hz), 2.48 (1H, ddd, J = 15.6, 4.8, 2.1 Hz), 2.40 (1H, ddd, J = 15.6, 9.9, 2.6 Hz), 1.73−1.79 (2H, m), 1.61−1.66 (1H, m), 1.53−1.56 (1H, m), 1.45−1.50 (1H, m), 1.38−1.43 (1H, m), 1.36 (3H, s), 1.29 (3H, s), 0.95 (3H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.4, 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), 1726 (s), 1453 (w), 1379 (m), 1226 (w), 1137 (w), 1076 (w), 1027 (m), 867 (m).

(±)-(1*R*,2*R*,3*R*,4*S*)-1,3,4-Trimethyl-7-oxabicyclo[2.2.1]heptane-2-ethanol (35). To an oven-dried and argon-purged 10 mL round-bottomed flask were added the aldehyde **37** (22 mg, 0.12 mmol, 1 equiv) and dichloromethane (1.2 mL). The reaction was cooled to −78 °C, then diisobutylaluminum hydride (1 M, 180 μL, 0.18 mmol, 1.5 equiv) was added to the reaction via syringe. The reaction was stirred at −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. The combined organic layers were washed with brine and dried over $MgSO_4$. The mixture was filtered and concentrated via rotary evaporation. Flash column chromatography of the residue on silica gel (10 mL, hexane:ether, 1:3) afforded 20 mg (90%) of the alcohol **35** as a clear oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.73 (1H, ddd, J = 10.2, 8.6, 5.4 Hz), 3.66 (1H, ddd, J = 10.2, 7.6, 7.3 Hz), 1.85 (1H, ddd, J = 12.1, 9.1, 4.1 Hz), 1.63−1.70 (1H, m), 1.48−1.62 (4H, m), 1.45 (1H, ddd, J = 12.3, 5.2, 2.0 Hz), 1.40 (1H, ddd, J = 13.3, 6.9, 1.9 Hz), 1.36 (3H, s), 1.28 (3H, s), 0.91 (3H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 85.4, 84.7, 62.2, 54.4, 48.4, 38.9, 35.0, 32.0, 20.3, 18.9, 17.9; IR (thin film) 3416 (br, s), 2967 (s), 2930 (s), 2874 (m), 1453 (m), 1378 (m), 1074 (m), 1036 (m), 866 (m), 668 (m); HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{11}H_{20}O_2Na$ 207.1361, found 207.1354.

(±)-(1*R*,2*R*,3*R*,4*S*)-2-(2-Iodoethyl)-1,3,4-trimethyl-7-oxabicyclo[2.2.1]heptane (4). To an oven-dried and argon-purged 250 mL round-bottomed flask were added the alcohol **35** (510 mg, 2.77 mmol, 1 equiv) and benzene (30 mL). The reaction was treated successively with iodine (3.48 g, 13.7 mmol, 4.95 equiv) and imidazole (999 mg, 14.67 mmol, 5.3 equiv). Triphenylphosphine (3.63 g, 13.83 mmol, 5 equiv) in 20 mL of benzene was added to the mixture dropwise via syringe with vigorous stirring. Any solid deposits formed were broken up with a glass rod. The reaction was heated to reflux and allowed to stir for 16 h. After cooling to 23 °C, the reaction was diluted with ether and washed successively with saturated $NaHCO_3$ solution and 10% sodium sulfate solution. The aqueous layers were extracted with ether, and then the combined organic layers were washed with brine and dried over $MgSO_4$. The mixture was filtered and concentrated via rotary evaporation. Flash column chromatography of the residue on silica gel (150 mL, hexane:ether, 90:10) afforded 590 mL (73%) of the iodide **4** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.27 (1H, ddd, J = 9.6, 9.6, 5.1 Hz), 3.12 (1H, ddd, J = 9.3, 7.2, 7.2 Hz), 1.92−1.99 (1H, m), 1.76−1.87 (2H, m), 1.59−1.66 (1H, m), 1.51−1.55 (1H, m), 1.42−1.50 (1H, m), 1.37 (3H, s), 1.36−1.40 (1H, m), 1.30−1.35 (1H, m), 1.28 (3H, s), 0.95 (3H, d, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 84.9, 84.8, 58.7, 48.0, 38.8, 36.9, 32.2, 20.3, 19.1, 17.8, 4.5; IR (thin film) 2967 (s), 2930 (m), 2872 (m), 1452 (m), 1386 (w), 1377 (m), 1231 (m), 1186 (m), 1170 (m), 1149 (m), 1117 (m), 1071 (m), 1057 (w), 905 (m), 867 (m); HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{11}H_{20}IO$ 295.0559, found 295.0559.

(±)-Ethyl 2-(4-Methyl-2-oxocyclohex-3-enyl)acetate (39). To an oven-dried and argon-purged 1 L round-bottomed flask were added tetrahydrofuran (450 mL) and diisopropylamine (7.0 mL, 50.0 mmol, 1.1 equiv). The reaction was cooled to −78 °C, and 1.21 M *n*-butyllithium (41.3 mL, 50.0 mmol, 1.1 equiv) was added to the reaction dropwise via syringe. The reaction was stirred for 30 min at −78 °C, and 3-methyl-2-cyclohexen-1-one **38** (5.15 mL, 45.4 mmol, 1 equiv) in 15 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 NH_4Cl solution. The mixture was allowed to warm 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 $MgSO_4$. The mixture was filtered and concentrated via rotary evaporation. Flash column chromatography of the residue on silica gel (1 L, hexane:ether, 3:2) afforded 6.04 g (68%) of the ester **39** as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 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 (dddd, 1H, J = 13.3, 7.6, 5.0, 5.0 Hz), 2.45 (m, 1H), 2.27 (ddd, 1H, J = 18.6, 4.8, 2.7 Hz), 2.25 (dd, 1H, J = 16.3, 7.6 Hz), 2.11 (dddd, 1H, J = 13.1, 4.8, 2.7, 2.7 Hz), 1.95 (s, 3H), 1.78 (dddd, 1H, J = 13.2, 13.2, 11.8, 4.9 Hz), 1.26 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.2, 172.7, 162.0, 126.0, 60.5, 42.6, 34.6, 31.1, 28.5, 24.2, 14.2; IR (thin film) 2980 (m), 2920 (m), 2872 (w), 1735 (s), 1670 (s), 1634 (m), 1427 (w), 1379 (m), 1346 (w), 1320 (w), 1275 (m), 1217 (m), 1175 (s), 1153 (m), 1029 (m), 866 (w); HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{11}H_{16}O_3Na$ 219.0997, found 219.0998.

Ethyl 2-[(1*RS*,2*S*)-2-Hydroxy-4-methylcyclohex-3-enyl]acetate (9). To an oven-dried and argon-purged 500 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, 4.8 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 and a 1 M solution of borane−tetrahydrofuran (19.2 mL, 19.2 mmol, 0.88 equiv) were added dropwise via syringe simultaneously. The reaction was stirred for 15 min at 0 °C and then quenched with methanol (3.5 mL, 86.4 mmol, 3.96 equiv). 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:ether, 1:1) afforded 2.59 g (60%) of the hydroxyester **9** as a mixture of diastereomers, as a clear oil. ^{1}H NMR ($CDCl_3$, 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 5.58 (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),

1.70 (3H, s), 1.53 (1H, m), 1.40 (1H, m), 1.24 (3H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ major isomer 173.6, 137.3, 124.3, 71.5, 60.3, 39.1, 36.0, 29.2, 26.4, 23.0, 14.1, minor isomer 180.5, 139.0, 122.9, 65.9, 60.4, 38.1, 36.4, 30.0, 26.4, 23.3, 14.1; IR (thin film, mix of diastereomers) 3423 (br, s), 2967 (s), 2916 (s), 1732 (s), 1673 (m), 1448 (s), 1377 (s), 1344 (m), 1263 (s), 1183 (s), 1150 (s), 1096 (m), 1069 (m), 1032 (s), 960 (m), 926 (m), 895 (m); HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{11}H_{18}O_3Na$ 221.1154, found 221.1156.

(3a*R*,7a*S*)-6-Methyl-3,3a,4,5-tetrahydrobenzofuran-2(7a*H*)-one (3a) and (3a*S*,7a*S*)-6-Methyl-3,3a,4,5-tetrahydrobenzofuran-2(7a*H*)-one (3b). To an oven-dried and argon-purged 100 mL round-bottomed flask were added ethanol (38 mL) and the hydroxyester **9** (755 mg, 3.81 mmol, 1 equiv). Powdered potassium hydroxide (427 mg, 7.62 mmol, 2 equiv) was added, and the reaction was refluxed for 4 h. The reaction was cooled to 23 °C and solvent was removed via rotary evaporation. The residue was cooled to 0 °C and dissolved carefully with distilled water. A 1 M HCl solution was added dropwise to the reaction to bring it to pH 2 (with careful TLC monitoring to ensure no loss of the allylic alcohol). The aqueous layer was then extracted once with ether and three times with dichloromethane. The combined organic layers were washed with brine and dried over $MgSO_4$. The mixture was filtered and concentrated via rotary evaporation. The crude hydroxyacid **40** was taken on to the next step without further purification.

To an oven-dried and argon-purged 100 mL round-bottomed flask were added the hydroxyacid **40** (490 mg, 2.88 mmol, 1 equiv) and dichloromethane (30 mL). 4-(Dimethylamino)-pyridine (352 mg, 2.88 mmol, 1 equiv) was added to the reaction, followed closely by 1,3-dicyclohexylcarbodiimide (DCC, 594 mg, 2.88 mmol, 1 equiv). 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 (150 mL, hexane:ether, 1:1) afforded 150 mg (34%) of the lactone **3a** and 90 mg (21%) of the lactone **3b**, both as white solids. ^{1}H NMR ($CDCl_3$, 500 MHz) δ **3a** 5.62 (1H, m), 4.80 (1H, m), 2.71 (1H, dd, J = 17.3, 8.1 Hz), 2.46−2.52 (1H, m), 2.32 (1H, dd, J = 17.3, 3.6 Hz), 1.96−2.05 (2H, m), 1.78 (3H, s), 1.75 (1H, dddd, J = 13.9, 4.7, 4.7, 4.7 Hz), 1.50 (1H, dddd, J = 13.9, 10.8, 8.8, 5.9 Hz), **3b** 5.82 (1H, s), 4.42 (1H, br d, J = 9.3 Hz), 2.56 (1H, dd, J = 15.9, 6.0 Hz), 2.28 (1H, dd, J = 15.9, 13.6 Hz), 2.10−2.22 (3H, m), 2.03−2.07 (1H, m), 1.70 (3H, s), 1.62 (1H, dddd, J = 12.9, 12.9, 10.4, 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ **3a** 176.6, 142.8, 117.5, 76.7, 35.2, 32.9, 27.8, 23.9, 23.7, **3b** 176.8, 137.8, 120.0, 82.4, 42.1, 35.7, 30.7, 23.6, 22.8; IR (thin film) **3a** 2917 (m), 2855 (w), 1176 (s), 1672 (w), 1446 (w), 1382 (w), 1332 (w), 1293 (w), 1229 (w), 1215 (w), 1169 (m), 1032 (w), 949 (m), 925 (m), 879 (w), **3b** 2931 (m), 1779 (m), 1712 (m), 1659 (m), 1426 (w), 1381 (m), 1275 (m), 1219 (m), 1174 (m), 999 (w); HRMS-ESI (m/z) **3a** $[M + Na]^+$ calcd for $C_9H_{12}O_2Na$ 175.0735, found 175.0737, **3b** $[M + Na]^+$ calcd for $C_9H_{12}O_3Na$ 175.0735, found 175.0741.

(3*R*,3a*R*,7a*S*)-3,6-Dimethyl-3,3a,4,5-tetrahydrobenzofuran-2(7a*H*)-one (41). To an oven-dried and argon-purged 50 mL round-bottomed flask were added diisopropylamine (343 μL, 2.44 mmol, 1.1 equiv) and tetrahydrofuran (22 mL). The reaction was cooled to −78 °C, and a 1.33 M solution of *n*-butyllithium in hexane (1.84 mL, 2.44 mmol, 1.1 equiv) was added dropwise via syringe. The reaction was stirred for 30 min at −78 °C, and a solution of the cis-lactone **3a** (340 mg, 2.22 mmol, 1 equiv) in 2 mL of tetrahydrofuran was added dropwise via syringe. The reaction was stirred for 30 min at −78 °C, and iodomethane (277 μL, 4.45 mmol, 2 equiv) was added dropwise via syringe. The reaction was stirred for 2 h at −78 °C. The reaction was quenched with saturated NH_4Cl solution 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 $MgSO_4$. The mixture was then filtered, and concentrated via rotary evaporation. Flash column chromatography of the residue on silica gel (70 mL, hexane:ether, 6:4) afforded 305 mg (82%) of the methylated cis-lactone **41** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.51 (1H, br q, J = 1.5 Hz), 4.89 (1H, m), 2.42 (1H, dq, J = 8.5, 7.3 Hz), 2.23−2.28 (1H, m), 1.19−2.06 (1H, m), 1.94 (1H, ddd, J = 18.0, 5.0, 5.0 Hz), 1.82 (1H, dddd, J = 14.0, 8.9, 5.4, 4.3 Hz), 1.74 (1H, m), 1.73 (3H, br s), 1.26 (3H, d, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.6, 140.6, 118.7, 75.3, 40.2, 37.5, 25.8, 23.6, 22.2, 13.9; IR (thin film) 2969 (w), 2931 (m), 1767 (s), 1449 (w), 1383 (w), 1323 (w), 1211 (w), 1173 (m), 1149 (w), 1086 (w), 1056 (w), 973 (m), 951 (m), 899 (w), 712 (w); HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{10}H_{14}O_2Na$ 189.0892, found 189.0889; NOESY correlations δ 4.89 ↔ δ 1.26, δ 4.89 ↔ δ 2.23, δ 4.89 ↔ δ 1.74, δ 1.26 ↔ δ 2.23.

(3*R*,3a*S*,7a*S*)-3,6-Dimethyl-3,3a,4,5-tetrahydrobenzofuran-2(7a*H*)-one (42). To an oven-dried and argon-purged 25 mL round-bottomed flask were added diisopropylamine (101 μL, 0.72 mmol, 1.1 equiv) and tetrahydrofuran (7 mL). The reaction was cooled to −78 °C, and a 1.01 M solution of *n*-butyllithium in hexane (675 μL, 0.72 mmol, 1.1 equiv) was added dropwise via syringe. The reaction was stirred for 30 min at −78 °C, and a solution of the trans-lactone **3b** (100 mg, 0.65 mmol, 1 equiv) in 1 mL of tetrahydrofuran was added dropwise via syringe. The reaction was stirred for 30 min at −78 °C, and iodomethane (82 μL, 1.31 mmol, 2 equiv) was added dropwise via syringe. The reaction was stirred for 2 h at −78 °C. The reaction was quenched with saturated NH_4Cl solution, then 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 $MgSO_4$. The mixture was then filtered and concentrated 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) $[M + Na]^+$ calcd for $C_{10}H_{14}O_2Na$ 189.0892, found 189.0892; NOESY correlations δ 4.61 ↔ δ 1.26, δ 1.62 ↔ δ 1.26, δ 2.11 ↔ δ 2.68.

(3*S*,3a*R*,7a*S*)-3,6-Dimethyl-3,3a,4,5-tetrahydrobenzofuran-2(7a*H*)-one (43). To an oven-dried and argon-purged 10 mL round-bottomed flask were added tetrahydrofuran (1 mL) and diisopropylamine (24 μL, 0.17 mmol, 1.2 equiv). The reaction was cooled to −78 °C, and *n*-butyllithium (1.3 M in hexanes, 133 μL, 0.17 mmol, 1.2 equiv) was added to the reaction dropwise via syringe. The mixture was stirred for 30 min at −78 °C, and the lactone **41** (24 mg, 0.14 mmol, 1 equiv) in 0.5 mL of tetrahydrofuran was added dropwise via syringe. The reaction was stirred for 1 h, then quenched with ammonium chloride solution at −78 °C. 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 $MgSO_4$. The mixture was filtered and concentrated via rotary evaporation. Flash column chromatography of the residue on silica gel (10 mL, hexane:ether, 1:1) afforded 16 mg of the epimeric lactone **43** (67%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.66 (1H, br s), 4.62 (1H, m), 2.89 (1H, dq, J = 7.3, 7.3 Hz), 2.34 (1H, dddd, J = 13.7, 7.3, 4.7, 4.7 Hz), 1.94−2.04 (2H, m), 1.77 (3H, s), 1.66−1.70 (1H, m), 1.18 (3H, d, J = 7.3 Hz), 1.12−1.21 (1H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.7, 143.9, 116.9, 74.6, 40.1, 37.7, 28.8, 23.6, 19.6, 9.2; IR (thin film) 2976 (m), 2940 (m), 2915 (m), 1763 (s), 1672 (m), 1449 (m),

1382 (m), 1351 (m), 1324 (w), 1309 (w), 1282 (w), 1200 (m), 1169 (s), 1124 (m), 1095 (w), 1065 (w), 1003 (w), 973 (m), 946 (s), 890 (m), 823 (w), 708 (w), 616 (w); HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{10}H_{14}O_2Na$ 189.0892, found 189.0895; NOESY correlations δ 4.62 ↔ δ 2.34, δ 4.62 ↔ δ 2.89, δ 2.34 ↔ δ 2.89, δ 1.18 ↔ δ 1.94.

(1*S*,6*R*)-6-((*R*)-1-Hydroxypropan-2-yl)-3-methylcyclohex-2-enol (51). To an oven-dried and argon-purged 100 mL round-bottomed flask were added lithium aluminum hydride (360 mg, 9.48 mmol, 2.5 equiv) and ether (30 mL). The reaction was cooled to 0 °C, and the lactone **41** (630 mg, 3.79 mmol, 1 equiv) in 4 mL of ether was added dropwise via syringe. The reaction was stirred at 0 °C for 30 min, then it was carefully quenched with 0.36 mL of distilled water (1 mL/ 1 g $LiAlH_4$). After 10 min of stirring at 0 °C, 0.36 mL of 15% NaOH solution was added to the mixture (1 mL/1 g $LiAlH_4$). The reaction was stirred for 10 min at 0 °C, and 1.08 mL of distilled water (3× initial volume used) was added to the mixture. The mixture was warmed to 23 °C and stirred for 20 min. $MgSO_4$ was added to the reaction to absorb excess water, then the mixture was filtered through a glass frit and rinsed with ether. The filtrate was concentrated via rotary evaporation. Flash column chromatography of the residue on silica gel (130 mL, hexane:ether, 10:90) afforded 550 mg (85%) of the diol **51** as a white solid. ^1H NMR ($CDCl_3$, 500 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, dddd, J = 12.8, 12.8, 11.0, 6.3 Hz), 1.28 (1H, dddd, J = 12.4, 8.5, 3.2, 3.2 Hz), 1.01 (3H, d, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 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) 3319 (br, s), 2960 (m), 2911 (s), 2828 (m), 1450 (m), 1429 (m), 1378 (w), 1042 (m), 1017 (m), 957 (m), 901 (w); HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{10}H_{18}O_2Na$ 193.1205, found 193.1200.

(±)-2-((1*R*,3*R*,4*S*-Trimethyl-7-oxabicyclo[2.2.1]heptan-2*R*-yl)methylthio)benzo[*d*]thiazole (56). To an oven-dried and argon-purged 250 mL round-bottomed flask were added the alcohol **33** (2 g, 11.75 mmol, 1 equiv), tetrahydrofuran (60 mL), 2-mercaptobenzothiazole (2.26 g, 13.50 mmol, 1.15 equiv), and triphenylphosphine (3.39 g, 12.92 mmol, 1.1 equiv). The flask was cooled to 0 °C and diisopropyl azodicarboxylate (DIAD, 2.31 mL, 11.75 mmol, 1 equiv) was added dropwise via syringe. The mixture was stirred at 0 °C for 30 min, then warmed to 23 °C. The mixture was diluted with ether and quenched with saturated sodium bicarbonate solution. 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. Flash column chromatography of the residue on silica gel (800 mL, hexane:ether, 80:20) afforded 3.69 g (98%) of the sulfide **56** as a white solid. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.87 (1H, br d, J = 8.0 Hz), 7.76 (1H, br d, J = 8.0 Hz), 7.42 (1H, ddd, J = 8.1, 7.3, 1.2 Hz), 7.30 (1H, ddd, J = 8.0, 7.0, 1.1 Hz), 3.49 (1H, dd, J = 12.3, 5.5 Hz), 3.34 (1H, dd, J = 12.3, 10.0 Hz), 1.98 (1H, ddd, J = 12.4, 8.7, 4.1 Hz), 1.71 (1H, dddd, J = 5.2, 5.2, 5.2, 1.8 Hz), 1.57−1.69 (3H, m), 1.54 (1H, ddd, J = 12.3, 5.2, 1.9 Hz), 1.49 (3H, s), 1.30 (3H, s), 1.00 (3H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.5, 153.1, 135.0, 126.0, 124.1, 121.4, 120.9, 85.3, 84.9, 56.4, 48.8, 38.8, 35.2, 32.0, 20.6, 18.7, 17.8; IR (thin film) 2967 (m), 2923 (w), 2870 (w), 1460 (m), 1428 (s), 1378 (w), 1308 (w), 1237 (w), 1125 (w), 1078 (w), 1018 (w), 995 (m), 866 (w), 755 (m), 726 (m); HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{17}H_{22}NOS_2$ 320.1143, found 320.1139.

(±)-2-((1*R*,3*R*,4*S*-trimethyl-7-oxabicyclo[2.2.1]heptan-2*R*-yl)-methylsulfonyl)benzo[*d*]thiazole (55). To an oven-dried and argon-purged 100 mL round-bottomed flask were added the sulfide **56** (1.09 g) and dichloromethane (35 mL). The reaction was cooled to 0 °C, and *m*-chloroperbenzoic acid (*m*CPBA, 70% w/w, 2.10 g, 8.53 mmol, 2.5 equiv) was added to the flask with vigorous stirring. The reaction was stirred at 0 °C for 1.5 h, then quenched with distilled water. The reaction was warmed to 23 °C, and the layers were separated. The aqueous layer was extracted with dichloromethane (1×) and ether (3×). The combined organic layers were washed with brine and dried over $MgSO_4$. The mixture was filtered and concentrated via rotary evaporation. Flash column chromatography of the residue on silica gel (170 mL, hexane:ether, 80:20) afforded 1.14 g of the sulfone **55** (95%) as a white solid. ^1H NMR ($CDCl_3$, 500 MHz) δ 8.21 (1H, br d, J = 8.3, 0.5 Hz), 8.03 (1H, br d, J = 8.4, 0.8 Hz), 7.65 (1H, ddd, J = 8.2, 7.2, 1.3 Hz), 7.60 (1H, ddd, J = 8.2, 7.1, 1.0 Hz), 3.60 (1H, dd, J = 13.9, 2.8 Hz), 3.47 (1H, dd, J = 13.9, 10.9 Hz), 1.92 (1H, dddd, J = 10.7, 4.5, 2.5, 2.1 Hz), 1.79 (1H, qd, J = 6.8, 4.5 Hz), 1.69−1.74 (1H, m), 1.66 (1H, dd, J = 12.1, 3.8 Hz), 1.57−1.62 (1H, m), 1.49−1.55 (1H, m), 1.38 (3H, s), 1.31 (3H, s), 1.04 (3H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.1, 152.5, 136.5, 128.0, 127.7, 125.3, 122.3, 85.6, 85.0, 56.9, 49.9, 48.1, 38.3, 32.5, 19.7, 17.9, 17.8; IR (thin film) 2969 (m), 2876 (w), 1472 (m), 1380 (m), 1331 (s), 1319 (s), 1266 (w), 1224 (w), 1193 (w), 1148 (s), 1085 (w), 1064 (w), 1026 (w), 880 (w), 867 (w), 763 (m), 730 (m); HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{17}H_{21}NO_3S_2Na$ 374.0861, found 374.0854.

(±)-Ethyl 2-[(1*RS*,2*S*)-2-Hydroxy-4-methylcyclohex-3-enyl]-acetate ((±)-9). To an oven-dried and argon-purged 25 mL round-bottomed flask were added the ester **39** (196 mg, 1 mmol, 1 equiv), methanol (6 mL), and cerium chloride heptahydrate (391 mg, 1.05 mmol, 1.05 equiv). The flask was cooled to 0 °C, and sodium borohydride (39 mg, 1.04 mmol, 1.04 equiv) was added to the flask. The reaction was stirred at 0 °C for 30 min, 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 NH_4Cl 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 $MgSO_4$. 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 (±)-**9** as a clear oil. ^1H NMR ($CDCl_3$, 500 MHz) δ major diastereomer 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 diastereomer 5.58 (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), 1.70 (3H, s), 1.53 (1H, m), 1.40 (1H, m), 1.24 (3H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ major diastereomer 173.6, 137.3, 124.3, 71.5, 60.3, 39.1, 36.0, 29.2, 26.4, 23.0, 14.1, minor diastereomer 180.5, 139.0, 122.9, 65.9, 60.4, 38.1, 36.4, 30.0, 26.4, 23.3, 14.1; IR (thin film) 3423 (br, s), 2967 (s), 2916 (s), 1732 (s), 1673 (m), 1448 (s), 1377 (s), 1344 (m), 1263 (s), 1183 (s), 1150 (s), 1096 (m), 1069 (m), 1032 (s), 960 (m), 926 (m), 895 (m); HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{11}H_{18}O_3Na$ 221.1154, found 221.1146.

(±)-(*R*) 2-((1*R*,2*S*)-2-Hydroxy-4-methylcyclohex-3-enyl)propyl 2,2-dimethyl Propanoate (57). To an oven-dried and argon-purged 100 mL round-bottomed flask were added the racemic diol **51** (550 mg, 3.23 mmol, 1 equiv) and pyridine (32.3 mL). 4-(Dimethylamino)pyridine (39 mg, 0.32 mmol, 0.1 equiv) was added, and the reaction was stirred at 23 °C for 10 min. The reaction was cooled to 0 °C, then pivaloyl chloride (676 μL, 5.49 mmol, 1.7 equiv) was added dropwise via syringe. The reaction was then warmed to 23 °C and stirred for 1 h, during which time the contents of the reaction went from clear to cloudy white. The reaction was diluted with ether, and the organic layer was repeatedly washed with saturated $CuSO_4$ solution until no

color changes were observed in the aqueous layer. The organic layer was washed with brine and dried over $MgSO_4$. 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. ^{1}H NMR ($CDCl_3$, 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, dddd, J = 13.0, 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); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.7, 139.6, 123.2, 67.8, 64.8, 41.7, 38.8, 33.4, 31.2, 27.1, 23.3, 20.3, 15.5; IR (thin film) 3441 (br, s), 2969 (m), 2932 (m), 2910 (m), 2875.9 (m), 1728 (s), 1713 (m), 1480 (m), 1458 (w), 1398 (m), 1286 (m), 1163 (s), 955 (w); HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{15}H_{26}O_3Na$ 277.1780, found 277.1786.

(±)-(*R*)-2-[(1*R*,2*S*)-2-[(1,1-Dimethylethyl)dimethylsilyloxy]-4-methylcyclohex-3-enyl]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), dimethylformamide (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 dimethylformamide). 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 $MgSO_4$. 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. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.48 (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); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.6, 137.9, 123.9, 67.6, 65.8, 41.7, 38.8, 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 $C_{21}H_{40}O_3SiNa$ 391.2644, found 391.2639.

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, 2.85 mmol, 2.5 equiv) was added dropwise via syringe. The reaction was stirred at −78 °C for 1 h, then quenched with saturated potassium tartrate 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 $MgSO_4$, filtered, and concentrated via rotary evaporation. Flash column chromatography of the residue on silica gel (60 mL, hexane:ether, 7:3) afforded 280 mg of the alcohol **58** (86% over 2 steps) as a clear oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.49 (1H, m), 4.28 (1H, m), 3.62 (1H, ddd, J = 10.7, 5.3, 5.3 Hz), 3.57 (1H, ddd, J = 10.7, 6.3, 5.2 Hz), 2.37 (1H, dd, J = 6.2, 5.2 Hz), 1.86−2.01 (2H, m), 1.70−1.79 (1H, m), 1.66 (3H, s), 1.56−1.63 (2H, m), 1.31 (1H, dddd, J = 12.0, 8.2, 3.7, 3.7 Hz), 0.99 (3H, d, J = 7.0 Hz), 0.88 (9H, s), 0.08 (3H, s), 0.06 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.2, 123.9, 67.3, 66.6, 42.8, 36.2, 30.8, 25.8, 23.2, 21.0, 18.2, 15.4, −3.4, −4.3; IR (thin film) 3345 (br, s), 2956 (s), 2928 (s), 2884 (s), 2857 (s), 1472 (m), 1462 (m), 1378 (w), 1360 (w), 1252 (m), 1127 (w), 1057 (s), 994 (s), 919 (w), 884 (w), 831 (s), 773 (s); HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{16}H_{32}O_2SiNa$ 307.2069, found 307.2072.

(±)-(*R*)-2-[(1*R*,2*S*)-2-[(1,1-Dimethylethyl)dimethylsilyloxy]-4-methylcyclohex-3-enyl]propanal (54). To an oven-dried and argon-purged 10 mL round-bottomed flask were added the alcohol **58** (280 mg, 0.98 mmol, 1 equiv), dichloromethane (2 mL, 2 mL/1 mmol substrate), and powdered 4 Å molecular sieves (500 mg, 500 mg/1 mmol substrate). 4-Methylmorpholine *N*-oxide (173 mg, 1.48 mmol, 1.5 equiv) was added, and the reaction was stirred at 23 °C for 10 min. Tetrapropylammonium perruthenate (TPAP, 35 mg, 0.10 mmol, 0.1 equiv) was added in one portion, and the reaction was stirred for 30 min. The mixture was filtered through a short plug of silica gel and rinsed with dichloromethane. The filtrate was concentrated via rotary evaporation, and flash column chromatography of the residue on silica gel (55 mL, hexane:ether, 97:3) afforded 213 mg of the aldehyde **54** (78%) as a clear oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.75 (1H, d, J = 2.2 Hz), 5.41 (1H, m), 4.24 (1H, m), 2.49 (1H, dqd, J = 7.2, 7.2, 2.2 Hz), 1.89−2.00 (2H, m), 1.76−1.87 (2H, m), 1.67 (3H, s), 1.60 (1H, m), 1.09 (3H, d, J = 7.1 Hz), 0.86 (9H, s), 0.04 (3H, s), 0.02 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 204.9, 137.4, 124.0, 66.8, 46.3, 41.9, 29.7, 25.9, 23.1, 21.4, 18.1, 12.1, −3.9, −4.5; IR (thin film) 2955 (s), 2929 (s), 2883 (m), 2857 (s), 1724 (s), 1472 (w), 1462 (w), 1252 (m), 1051 (m), 1030 (m), 988 (m), 918 (w), 884 (w), 834 (m), 812 (w), 775 (m).

(±)-3*RS*-[1*RS*,2*SR*-{2-([(1,1-Dimethylethyl)dimethylsilyloxy]-4-methylcyclohex-3-enyl)-3*RS*-methyl-1*EZ*-propenyl}]-1*RS*,3*RS*,4*SR*-1,3,4-trimethyl-7-oxabicylo[2.2.1]hex-ane (53a/53b and 53c/53d). To an oven-dried and argon-purged 100 mL round-bottomed flask were added the *racemic* aldehyde **54** (226 mg, 0.8 mmol, 1 equiv), the *racemic* sulfone **55** (337 mg, 0.96 mmol, 1.2 equiv), and tetrahydrofuran (10 mL). The mixture was cooled to −78 °C, and LiHMDS (1 M solution in hexane, 1.04 mL, 1.04 mmol, 1.3 equiv) was added dropwise via syringe. The reaction was allowed to stir for 2 h at −78 °C, and then it was warmed to 23 °C and stirred for 1 h. The mixture was diluted with ether and the layers were separated. The aqueous layer was extracted with ether and the combined organic layers were washed with brine and dried over $MgSO_4$. The mixture was filtered and concentrated via rotary evaporation. Flash column chromatography of the residue on silica gel (70 mL, hexane:ether, 97:3) afforded 290 mg of the Julia−Kocienski products **53a**/**53b** and **53c**/**53d** (87%) as a clear oil. The *E* and *Z* isomers were separated via careful gradient flash column chromatography on silica gel (55 mL, hexane 100% → hexane:ether 97:3 via 0.5% increase of ether at each step) to afford 140 mg of **53c/53d** and 135 mg of **53a/53b** as clear oils. ^{1}H NMR ($CDCl_3$, 500 MHz) δ **53a**/**53b**, isomer 1 5.68 (1H, dd, J = 10.5, 10.5 Hz), 5.43 (1H, br s), 5.12 (1H, dd, J = 10.8, 10.8 Hz), 4.16 (1H, m), 2.70 (1H, m), 2.27 (1H, m), 1.84−2.00 (3H, m), 1.65 (3H, s), 1.53−1.72 (3H, m), 1.35−1.46 (4H, m), 1.32 (3H, s), 1.31 (3H, s), 1.008 (3H, d, J = 6.9 Hz), 0.912 (3H, d, J = 6.9 Hz), 0.89 (9H, s), 0.09 (3H, s), 0.052 (3H, s), isomer 2 5.64 (1H, dd, J = 10.8, 10.8 Hz), 5.46 (1H, br s), 5.12 (1H, dd, J = 10.8, 10.8 Hz), 4.17 (1H, m), 2.70 (1H, m), 2.27 (1H, m), 1.84−2.00 (3H, m), 1.65 (3H, s), 1.53−1.72 (3H, m), 1.35−1.46 (4H, m), 1.32 (3H, s), 1.31 (3H, s), 1.013 (3H, d, J = 6.9 Hz), 0.907 (3H, d, J = 6.9 Hz), 0.89 (9H, s), 0.09 (3H, s), 0.046 (3H, s); ^{1}H NMR ($CDCl_3$, 500 MHz) δ **53c/53d** 5.51 (1H, br s), 5.43 (1H, dd, J = 15.3, 8.2 Hz), 5.32 (1H, dd, J = 15.3, 8.6 Hz), 4.08 (1H, m), 2.28 (1H, m), 1.82−2.07 (3H, m), 1.75−1.78 (1H, m), 1.65 (3H, s), 1.48−1.63 (6H, m), 1.36−1.43 (1H, m), 1.30 (3H, d, J = 6.3 Hz), 0.99 (3H, d, J = 6.9 Hz), 0.87 (9H, s), 0.03 (3H, s), 0.009 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ **53a/53b**, major isomer 138.82, 137.2, 126.2, 124.8, 86.0, 84.8, 68.6, 56.4, 49.0, 44.1, 39.3, 33.0, 31.9, 31.0, 25.98, 23.27, 20.4, 19.8, 18.16, 17.8, 17.4, −3.8, −4.2, minor isomer 138.77, 137.5, 126.7, 124.7, 86.1, 84.9, 68.0, 56.4, 49.2, 44.7, 39.2, 33.1, 32.0, 31.2, 26.01, 23.30, 20.3, 19.9, 18.6, 18.20,

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, −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), 988 (m), 877 (w), 830 (m), 773 (m); HRMS-ESI (*m*/*z*) **53a/53b** [M + Na]$^+$ calcd for $C_{26}H_{46}O_2SiNa$ 441.3165, found 441.3161, **53c/53d** [M + Na]$^+$ calcd for $C_{26}H_{46}O_2Na$ 441.3165, found 441.3165.

(±)-Laurenditerpenol (1) and (±)-Laurenditerpenol Isomer (1′). Into an oven-dried and argon-purged 10 mL round-bottomed flask were added the trans olefin mixture **53c/53d** (100 mg, 0.24 mmol, 1 equiv), potassium azodicarboxylate (923 mg, 4.75 mmol, 20 equiv), and pyridine (2.4 mL). Acetic acid (547 μL, 9.50 mmol, 40 equiv) dissolved in 2.18 mL of methanol (4× volume of acetic acid) was added dropwise via syringe at 23 °C over 6 h, and the mixture was stirred for an additional 7 h afterward. The resulting white mixture was diluted with ether and quenched carefully with distilled water. The resulting layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with copious amounts of saturated $CuSO_4$ solution to remove all residual pyridine, and then washed with brine. The mixture was dried over $MgSO_4$, filtered, concentrated via rotary evaporation, and dried over reduced pressure for 2 h. The crude mixture was placed under the same reaction condition as outlined above one more time. NMR analysis showed about 80% yield of the alkane **59a** and **59b** and 15% of the unreacted alkene **53c/53d**.

To an oven-dried and argon-purged 10 mL round-bottomed flask was added the mixture of **53c/53d**, **59a**, and **59b** (35 mg, 0.08 mmol, 1 equiv) and tetrahydrofuran (1 mL). Oven-dried powdered 4 Å molecular sieves was added to the flask, and TBAF (1 M in THF, 330 μL, 0.33 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 to give 15 mg of Laurenditerpenol **1** and its diastereomer **1′** as a 1:1 mixture via NMR. Careful gradient column afforded 4 mg (16%) of Laurenditerpenol **1** as a clear oil, along with the mixture of **1** and **1′**. A second careful gradient flash column chromatography of the mixture of **1** and **1′** on silica gel (5 mL, hexane 100% → hexane:ether = 1:1, with 5% steps) yielded 3 mg (12%) of **1′** as a clear oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ **1** 5.64 (1H, m), 4.12 (1H, m), 1.92−2.04 (2H, m), 1.86 (1H, ddd, J = 11.9, 9.0, 4.0 Hz), 1.70 (3H, s), 1.50−1.63 (6H, m), 1.37−1.44 (2H, m), 1.36 (3H, s), 1.29−1.34 (3H, m), 1.28 (3H, s), 1.15−1.21 (2H, m), 1.02 (1H, d, J = 7.3 Hz), 0.95 (3H, d, J = 6.7 Hz), 0.92 (3H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.7, 123.7, 85.6, 84.6, 65.2, 58.2, 48.7, 44.1, 39.0, 33.3, 33.2, 32.1, 31.4, 28.9, 23.3, 20.5, 20.3, 19.1, 18.0, 17.1; IR (thin film) 3451 (br, m), 2965 (s), 2927 (s), 2871 (m), 1462 (m), 1451 (m), 1377 (m), 1263 (w), 1223 (w), 1132 (m), 1110 (m), 1064 (m), 1023 (m), 956 (w), 865 (w); HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{20}H_{34}O_2Na$, 329.2456, found 329.2449. ^{1}H NMR ($CDCl_3$, 500 MHz) δ **1′** 5.64 (1H, m), 4.10 (1H, m), 1.91−2.04 (2H, m), 1.84 (1H, ddd, J = 11.9, 9.0, 4.0 Hz), 1.70 (3H, s), 1.40−1.60 (7H, m), 1.36 (3H, s), 1.30−1.35 (2H, m), 1.27 (3H, s), 1.12−1.21 (4H, m), 1.04 (1H, d, J = 7.1 Hz), 0.96 (3H, d, J = 6.7 Hz), 0.92 (3H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.7, 123.6, 85.6, 84.5, 65.3, 58.5, 48.8, 43.9, 40.0, 33.50, 33.47, 32.0, 31.4, 29.0, 23.3, 20.7, 20.2, 19.2, 18.0, 17.2; IR (thin film) 3451 (br, m), 2965 (s), 2927 (s), 2871 (s), 1462 (m), 1451 (m), 1377 (m), 1225 (w), 1128 (w), 1067 (w), 1022 (w), 955 (m), 906 (w), 866 (m); HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{20}H_{34}O_2Na$ 329.2456, found 329.2450.

(±)-(1*S*,6*R*)-3-Methyl-6-[(2*S*,3*Z*)-4-((1*R*,2*R*,3*R*,4*S*)-1,3,4-trimethyl-7-oxabicyclo[2.2.1]-heptan-2-yl)but-3-en-2-yl]cyclohex-2-enol (60a) and (±)-(1*S*,6*R*)-3-Methyl-6-[(2*S*,3*Z*)-4-((1*S*,2*S*,3*S*,4*R*)-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 (2.5 mL). Oven-dried powdered 4 Å molecular sieves were added to the flask, and TBAF (1 M in THF, 960 μL, 0.96 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%. ^{1}H NMR ($CDCl_3$, 500 MHz) δ **60a** 5.57 (1H, m), 5.45 (1H, dd, J = 10.9, 10.9 Hz), 5.29 (1H, dd, J = 10.9, 10.9 Hz), 4.05 (1H, s), 2.51 (1H, m), 2.31 (1H, m), 1.85−2.04 (1H, m), 1.68 (3H, s), 1.68−1.71 (1H, m), 1.54−1.66 (2H, m), 1.38−1.51 (3H, m), 1.34 (3H, s), 1.29 (3H, s), 1.15−1.21 (1H, m), 1.01 (3H, d, J = 6.7 Hz), 1.92 (3H, d, J = 6.9 Hz), **60b** 5.57 (1H, m), 5.50 (1H, dd, J = 10.6, 10.5 Hz), 5.31 (1H, dd, J = 10.9, 10.9 Hz), 4.05 (1H, s), 2.50−2.57 (1H, m), 2.27−2.31 (1H, m), 1.90−2.03 (3H, m), 1.68 (3H, s), 1.60−1.70 (2H, m), 1.53−1.58 (1H, m), 1.39−1.47 (3H, m), 1.35 (3H, s), 1.30 (3H, s), 1.19−1.24 (2H, m), 1.02 (3H, d, J = 6.8 Hz), 0.93 (3H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ **60a** 139.5, 137.6, 129.1, 123.1, 86.2, 85.1, 65.0, 56.4, 49.3, 45.1, 39.0, 32.5, 32.2, 31.1, 23.3, 20.41, 20.36, 19.6, 17.8, 17.5, **60b** 139.4, 137.4, 128.6, 123.2, 85.9, 84.7, 65.2, 56.6, 49.3, 44.9, 39.2, 32.5, 31.9, 31.1, 23.3, 20.5, 20.26, 20.24, 17.8, 17.4; IR (thin film) **60a** 3472 (m, br), 2965 (s), 2928 (s), 2871 (s), 1452 (m), 1376 (m), 1223 (w), 1132 (w), 1115 (m), 1182 (w), 1060 (w), 1018 (w), 958 (m), 863 (m), 813 (w), 761 (w), **60b** 3442 (s, br), 2955 (s), 2904 (s), 2869 (s), 2842 (m), 1446 (m), 1394 (m), 1380 (m), 1370 (m), 1220 (m), 1131 (w), 1113 (m), 1085 (w), 1027 (w), 1020 (w), 962 (m), 860 (s), 746 (m); HRMS-ESI (*m*/*z*) **60a** [M + Na]$^+$ calcd for $C_{20}H_{32}O_2Na$ 327.2300, found 327.2293, **60b** [M + Na]$^+$ calcd for $C_{20}H_{32}O_2Na$ 327.2300, found 327.2296.

(±)-(1*S*,6*R*)-3-Methyl-6-[(2S,3*E*)-4-((1*R*,2*R*,3*R*,4*S*)-1,3,4-trimethyl-7-oxabicyclo[2.2.1]-heptan-2-yl)but-3-en-2-yl]cyclohex-2-enol (60c) and (±)-(1*S*,6*R*)-3-Methyl-6-[(2*S*,3*E*)-4-((1*S*,2*S*,3*S*,4*R*)-1,3,4-trimethyl-7-oxabicyclo[2.2.1]heptan-2-yl)but-3-en-2-yl]cyclohex-2-enol (60d). To an oven-dried and argon-purged 10 mL round-bottomed flask were added the mixture of **53c/53d** (80 mg, 0.19 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, 760 μL, 0.76 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 (12 mL, dichloromethane 100% → dichloromethane:ether = 90:10, with 2% steps) afforded 24 mg (41%) of **60c** and 20 mg (34%) of **60d**, both as clear oils, for a total yield of 75%. ^{1}H NMR ($CDCl_3$, 500 MHz) δ **60c** 5.58 (1H, m), 5.48 (1H, dd, J = 15.1, 8.6 Hz), 5.41 (1H, dd, J = 15.1, 8.2 Hz), 4.05 (1H, s), 2.16−2.24 (1H, m), 1.90−2.04 (2H, m), 1.78−1.86 (2H, m), 1.69 (3H, s), 1.63−1.66 (1H, m), 1.49−1.62 (3H, m), 1.37−1.46 (3H, m), 1.30 (3H, s), 1.29 (3H, s), 1.13−1.19 (1H, m), 1.04 (3H, d, J = 6.7 Hz), 0.88 (3H, d, J = 6.9 Hz), **60d** 5.59 (1H, m), 5.48 (1H, dd, J = 15.2, 8.5 Hz), 5.42

(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); ^{13}C NMR ($CDCl_3$, 125 MHz) δ **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, 20.3, 20.0, 19.0, 17.8, 17.3; IR (thin film) **60c** 3462 (br, m), 2967 (s), 2928 (s), 2870 (s), 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 $C_{20}H_{32}O_2Na$, 327.2300, found 327.2295, **60d** $[M + Na]^+$ calcd for $C_{20}H_{32}O_2Na$, 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.