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Formal Total Synthesis of (−)-Jiadifenolide and Synthetic Studies toward *seco*-Prezizaane-Type Sesquiterpenes

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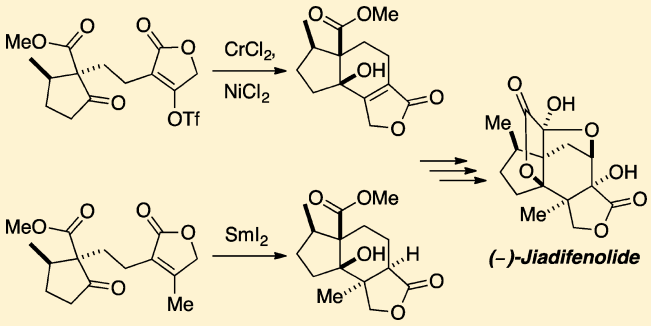
Supporting Information

ABSTRACT: Synthetic studies toward highly oxygenated *seco*-prezizaane sesquiterpenes are reported, which culminated in a formal total synthesis of the neurotrophic agent (−)-jiadifenolide. For the construction of the tricyclic core structure, an unusual intramolecular and diastereoselective Nozaki−Hiyama−Kishi reaction involving a ketone as electrophilic coupling partner was developed. In addition, synthetic approaches toward the related natural product (2*R*)-hydroxy-norneomajucin, featuring a Mn-mediated radical cyclization for the tricycle assembly and a regioselective OH-directed C−H activation are presented.



INTRODUCTION

Natural products that induce or stimulate neuron differentiation and neurite outgrowth have been identified as promising small molecule alternatives to the nerve growth factor (NGF), a key protein mediating neuritogenesis in humans.[1] Since the early studies of Schreiber, Corey, and Danishefsky, many groups, including ours, have investigated small molecule neurotrophins.[2] The large variety of chemotypes that are able to stimulate neurite outgrowth suggests chemical interference with different pathways beyond NGF-mediated differentiation and outgrowth. While many pathways remain to be discovered, chemical synthesis might provide a leading role in mapping out these molecular mechanisms of a process central to memory and learning. An interesting class of compounds featuring strong activity as small molecule neurotrophins is represented by the *seco*-prezizaane-sesquiterpenes, in particular those of the majucin-type (Figure 1).[3] Several such compounds have been shown to be neurotrophically active,[4] such as jiadifenin (**1**),[5] (−)-jiadifenolide (**2**), (2*S*)-hydroxy-3,4-dehydroneomajucin (**3**),[5] jiadifenoxolane A (**4**)[6] and the norsesquiterpenoid (2*R*)-hydroxy-norneomajucin (**5**).[7] Furthermore, also the synthetic carboxylic acid derivative of jiadifenin (**6**) showed potent neurite outgrowth promoting activity in primary cultured rat cortical neurons.[3b] Biological studies on (−)-jiadifenolide (**2**) suggested that the observed neuronal dendritic outgrowth might involve MAP2 and PSD95 proteins,[8] and Shenvi raised the possibility that (−)-jiadifenolide might interact with the Cys-loop family of ion channels based on structural similarity to picrotoxinin.[9]

The structurally complex framework of these terpenoids combined with their potent biological activity renders these compounds interesting targets for synthetic studies. A number of successful total syntheses have been reported for both jiadifenin (**1**)[10] and (−)-jiadifenolide (**2**),[11] culminating in the impressive eight-step, gram-scale synthesis of the latter compound by Shenvi and co-workers.[12] Our research group has been working toward this family of compounds over the past few years,[13] and in this publication, we report synthetic studies toward *seco*-prezizaane type sesquiterpenes, and a formal total synthesis of (−)-jiadifenolide (**2**), in full detail.

RESULTS AND DISCUSSION

(−)-Jiadifenolide (**2**) is a highly oxygenated sesquiterpene featuring a unique *seco*-prezizaane-type skeleton. Reported strategies for the assembly of the ABC-ring system[10a−d,11a,b] involve formation of the rings in the order B → AB → ABC, A → AB → ABC, and C → BC → ABC. So far B-ring cyclization from an AC-ring system is known to proceed via samarium-mediated cross-coupling[11c,d] or via tandem Tsuji−Trost/lactonization reaction.[10e] We envisioned a novel strategy by building up the B-ring via cyclization of the AC-ring system, where the A-ring is originally derived from readily available (*R*)-pulegone via methylester **7**[14] and the C-ring from tetronic acid (Scheme 1). For the connection of the A- and C-ring we envisioned a Knoevenagel condensation in order to form the AC-ring fragment **10**.[2f] The key step, viz. the aforementioned formation of the B-ring, was supposed to be performed by a Nozaki−Hiyama−Kishi (NHK) coupling.[15] The remaining methyl group at the quaternary stereogenic center C-5 was planned to be installed via 1,4-addition to the unsaturated γ-lactone, or a two-step procedure including Corey−Chaykovsky

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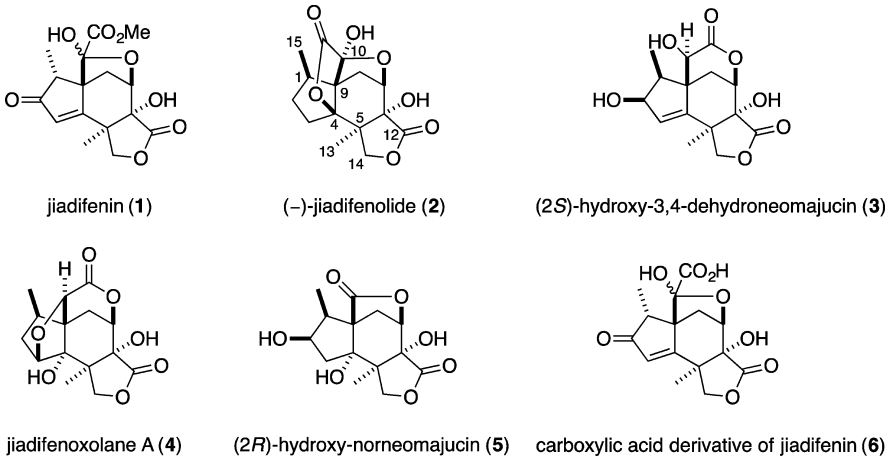
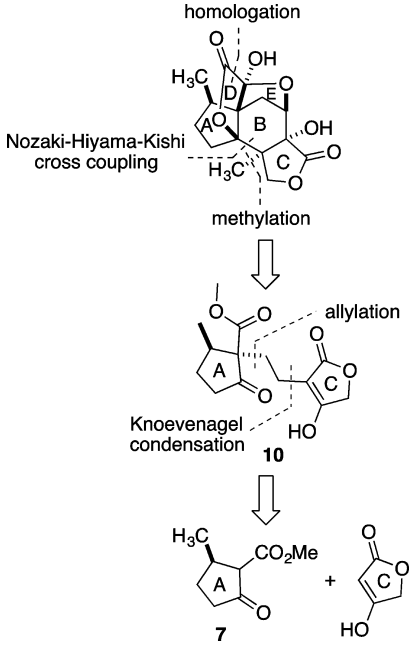
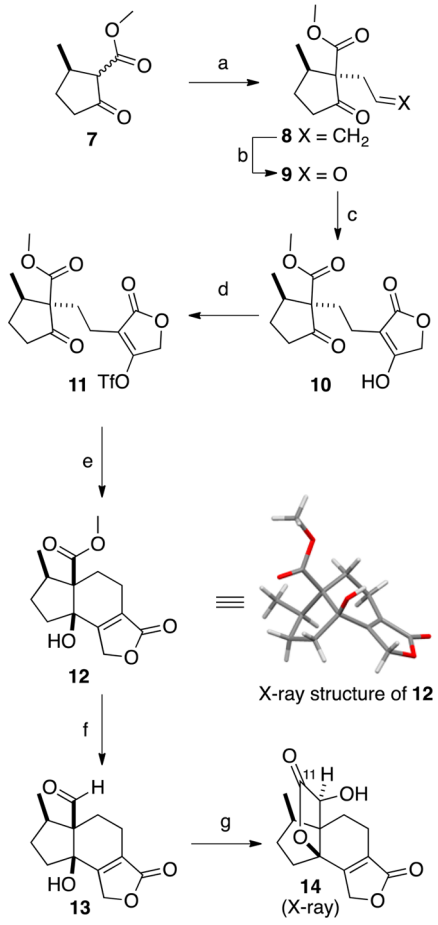


Figure 1. Neurotrophic *seco*-prezizaane-sesquiterpenes natural products.

Scheme 1. Retrosynthetic Analysis of (−)-Jiadifenolide



Scheme 2. Synthesis of the Tetracyclic Precursor[a]



[a]Reagents and conditions: (a) NaH, THF/DMPU (4:1), rt, 1 h, then allyl bromide, 0 °C, 13 h, 92%, dr = 11:1; (b) O_3, CH_2Cl_2/MeOH (5:1), −78 °C; Zn, AcOH, −78 °C to rt, quant.; (c) Tetronic acid, Hantzsch ester, L-proline (10 mol %), MeOH, 24 h, rt, 81%; (d) 2,6-Lutidine, Tf_2O, CH_2Cl_2, −78 °C to rt, 7 h, quant.; (e) $CrCl_2$, $NiCl_2$ (10 mol %), 3 Å MS, DMF, 50 °C, 24 h, 69%; (f) BH_3·DMS, THF, 2.5 h, 0 to 45 °C, 76%; (g) KCN, THF/H_2O (1:1), rt, 2 d, 65%.

cyclopropanation and subsequent Birch reduction.[16] The bridged D- and E-ring was planned to be constructed by ester reduction and C1-homologation.[17]

Methylester **7** was synthesized according to a literature procedure[14] in two steps starting from inexpensive (*R*)-pulegone. Subsequent allylation of **7** yielded compound **8** in good yield (92%) and diastereomeric ratio (11:1 in favor of the desired isomer, Scheme 2). Ozonolysis furnished the aldehyde **9**, which was coupled to tetronic acid with Hantzsch ester as reducing agent,[18] yielding the AC-ring fragment **10** in 81% yield. Triflation of the enol **10** led to vinyltriflate **11**, which was treated under NHK reaction conditions.[15] Pleasingly, diastereoisomer **12** was exclusively formed in 69% yield, and its constitution and configuration was subsequently confirmed by X-ray crystal structure analysis.

The next challenge was to find an appropriate reducing agent for the transformation of the methylester **12** to the corresponding aldehyde, and to install the D-ring later. The use of $LiAlH_4$ proved to be too harsh as several products were detected by NMR analysis of the reaction mixture after workup, whereas reaction with $NaBH_4$ in ethanol at 60 °C and superhydride ($LiEt_3BH$) in THF at 0 °C selectively reduced the lactone moiety, while the methylester remained intact. However, we were very pleased that reduction with borane

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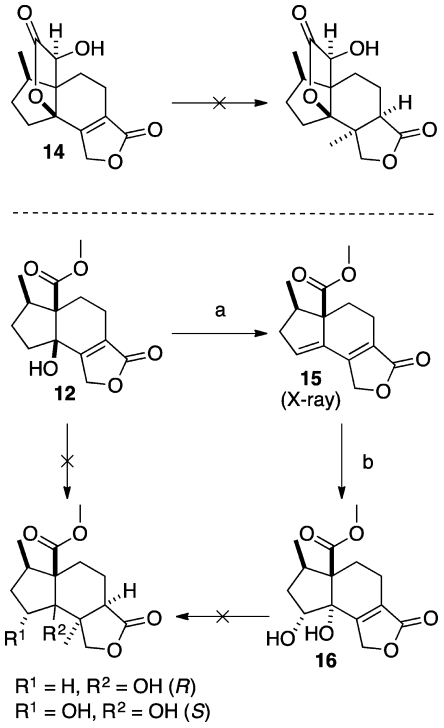
dimethyl sulfide was found to give aldehyde **13** in 76% yield, and initially expected over reduction to the corresponding diol did not take place. For the introduction of the second γ-lactone, we planned to install the C-11 carbon by cyanide addition followed by hydrolysis and lactonization. Cyanidation with TMSCN and Et_3N did not lead to the desired product.[19] Potassium cyanide in aqueous THF solution transformed the aldehyde **13** to the tetracyclic dilactone **14** as a single diasteroisomer (65% yield) and the expected cyanohydrin was not observed. The close juxtaposition of the neighboring C-4 hydroxy group to the putative cyanhydrin intermediate could facilitate formation of the corresponding imidate. As the reaction is conducted in aqueous organic solvent, the imine is prone to undergo hydrolysis to form the α-hydroxy lactone **14**. However, the exact mechanism for this observation remains unclear, as multiple other factors might be involved. Regarding the stereoselectivity, diastereoselective nucleophilic attack of the cyanide to the aldehyde would explain the configuration observed. However, also here a mechanism involving both epimeric cyanohydrins can be reasoned, which would be in equilibrium with the aldehyde **13**, and subsequently, only one diastereoisomer would react to the thermodynamic product **14**. Isomerization of the hydroxyl group due to steric effects with the proximate methyl group at C-1 would also be possible, but rather improbable due to the poor acidity at the C-10 position. To the best of our knowledge, this is the first kind of reaction sequence featuring a cyanohydration followed by hydrolysis and γ-lactonization. While this route proved to be effective in installing the ABCD ring system of these natural products, installation of the missing quaternary methyl function on the tetracyclic structure **14** was challenging. 1,4-Addition[20] using various conditions and Corey−Chaykovsky cyclopropanation appeared to be completely unreactive. We assumed that the D-ring lactone in butenolide **14** might be too sterically demanding or influenced the shape of the molecule, rendering a nucleophilic attack at the appropriate position not feasible. In order to test this hypothesis, we applied the conditions evaluated above on the simpler ABC-ring fragment (Scheme 3). Tertiary alcohol **12** was treated with Burgess reagent and the obtained trisubstituted olefin **15** was dihydroxylated to diol **16**. Once again, no reactivity toward cuprate addition[21] as well as Corey−Chaykovsky conditions[16] was observed for both substrates **12** and **16**. Additionally, Simmons-Smith conditions[22] were tested on the diol **16**, but even with the allylic hydroxy group serving as a directing group,[23] we were not able to cyclopropanate the butenolide moiety.

Sampson and co-workers described a similar scenario and attributed the lack of reactivity to a competitive γ-deprotonation pathway, which affords an aromatic furan oxide rather than the conjugate addition.[16] In order to avoid the reactivity issues for the C-5 methylation we focused on a temporary opening of the A-ring to overcome reactivity issues in this critical methyl group insertion (Scheme 4).

Olefin hydrogenation on the diol **16** was carried out successfully in quantitative yield in a diastereoselective fashion and the configuration of the hydrogenated product **17** was confirmed by X-ray crystal structure analysis.[24] The A-ring was then cleaved by oxidation to the unstable ketoaldehyde **18** using sodium periodate[25] and protected to obtain the corresponding acetal **19** in quantitative yield. Since methylation of compound **19** did not yield the desired product due to decomposition under basic (MeI with DBU or LDA) and acetal deprotection under acidic conditions, we performed a

Scheme 3. Methylation Attempts on Various Substrates[a]



[a]Reagents and conditions: (a) Burgess reagent, THF, rt, 3.5 h, 93%; (b) OsO_4 (5 mol %), NMO, *t*-BuOH/H_2O (3:1), 0 °C to rt, 3 d, 84%, dr = 10:1.

hydroxymethylation under neutral conditions to install the additional C-5 carbon on substrate **19**. The stereochemical outcome of the reaction was verified by 2D-NMR studies. Hydroxymethylation was expected to be stereospecific due to the formation of the thermodynamically favorable *cis*-fused bicyclic ring system.[26] A Garegg−Samuelsson iodination of the OH group in compound **20**, followed by radical dehalogenation of the resulting iodide **21** using tributyltin hydride gave the methylated intermediate **22**. The acetal was hydrolyzed under acidic conditions to form the aldehyde **23**. Reduction of **23** using $NaBH_4$ was not reproducible, but sodium tris-(hexafluoroisoproopoxy)borohydride, reported as a very mild reducing reagent,[27] was found to be efficient (85%). Primary alcohol **24** was subsequently iodinated applying Garegg−Samuelsson conditions and the structure of the resulting iodide **25** was confirmed by X-ray crystal structure analysis. First attempts to close the A-ring using organolithium reagents resulted in complex mixtures (*n*-BuLi)[28] or formation of minor amounts of **26** (*t*-BuLi).[2e] Finally, SmI_2 mediated ring closing using HMPA as an additive, which was found to be crucial, gave the desired tricycle **26** as a single diastereomer in a remarkable yield of 76%.[29] We were pleased that the borane dimethyl sulfide mediated reduction applied earlier on ester **12**, was reproducible for intermediate **26** to yield the desired aldehyde **27** in 66%.

Our initial established strategy for the C1-homologation on the aldehyde **27** was resumed to produce the tetracyclic structure **28** (Scheme 5). Selenoxide promoted elimination[30] then formed an α,β-unsaturated intermediate which under the applied reaction conditions cyclized to form the E-ring containing lactone **29**. Oxidation of lactone **29** in the presence of H_2O_2 led directly to pentacycle **33**. Unfortunately, the

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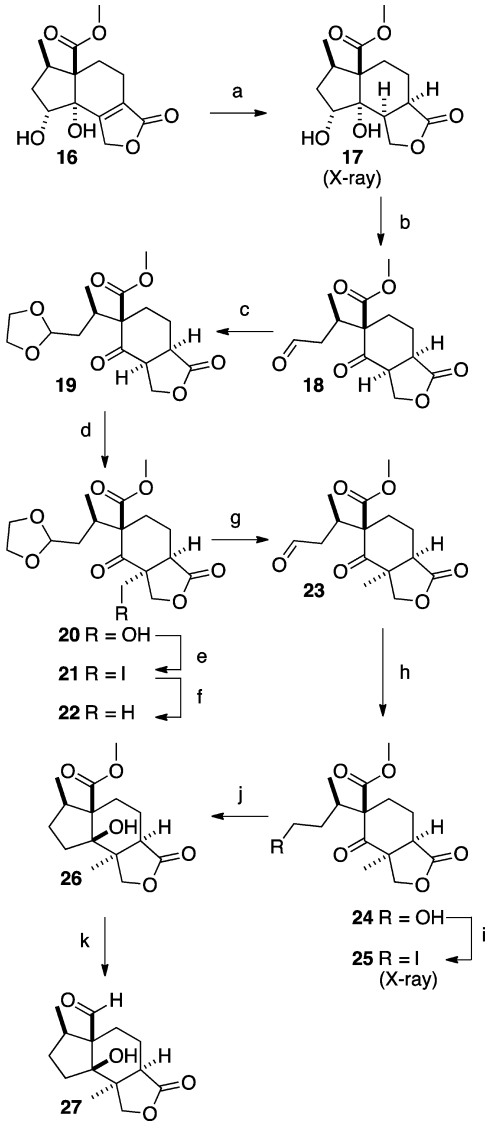
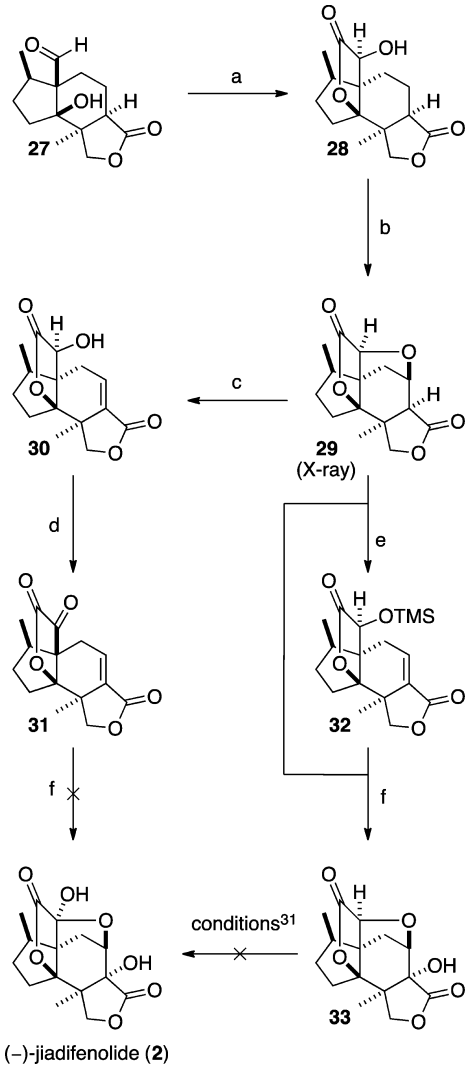
Scheme 4. Synthesis of the Aldehyde Fragment[a]



[a]Reagents and conditions: (a) $Rh/C/Al_2O_3$ (10 mol %), H_2 (60 bar), EtOAc, rt, 3 h, quant.; (b) $NaIO_4$, THF/H_2O (2:1), rt, 1.5 h, quant.; (c) ethylene glycol, *p*-TSA·H_2O, benzene, 90 °C, 2 h, quant.; (d) formaline, THF, pH 6, 40 °C, 14 h, 94%; (e) PPh_3, imidazole, I_2, benzene, rt, 12 h, 75%; (f) *n*-Bu_3SnH, AIBN, benzene, 85 °C, 3 h, 84%; (g) 1 M HCl, acetone, rt, 14 h, 99%; (h) $NaBH(OCH(CF_3)_2)_3$, hexafluoro-2-propanol, rt, 16 h, 85%; (i) PPh_3, imidazole, I_2, benzene, rt, 16 h, 95%; (j) SmI_2, HMPA, THF, rt, 1 h, 76%; (k) BH_3·DMS, THF, 2.5 h, 0 to 45 °C, 66%.

pentacycle **33** had shown to be completely unreactive toward the final installation of the hydroxyl-group at C-10 using various oxidation protocols[31] (Scheme 5). Aware of the difficulties accompanied by the introduction of this critical hydroxyl group, intermediate **29** was treated under different conditions using LiHMDS as base to obtain the α,β-unsaturated lactones **30** or **32**, which should act as stable precursors for the final E-ring formation. However, treating compound **32** under established epoxidation conditions yielded in desilylation and subsequent formation of the aforementioned α-hydroxy lactone **33**.[4b] Studies using the more stable TES protecting group led to formation of pentacycle **33** as well. It was thus decided to first oxidize the D-ring moiety at C-10 to overcome reactivity issues

Scheme 5. Synthetic Approaches toward (−)-Jiadifenolide[a]



[a]Reagents and conditions: (a) KCN, THF/H_2O, rt, 3 d (63% over two steps); (b) LDA, PhSeBr, H_2O_2, THF, −78 to 0 °C, 1.5 h, 48%; (c) LiHMDS, −78 °C to rt, 2 h, n.d; (d) DMP, CH_2Cl_2, rt, 16 h, n.d.; (e) LiHMDS, TMSCl, THF, −78 to 0 °C, 1 h, n.d.; (f) NaOH, H_2O_2, MeOH/THF (3:1), 0 °C to rt, 14 h.

of intermediate **33**. We oxidized compound **30** with DMP to the corresponding ketone **31**. To our disappointment, the same epoxidation conditions culminated in decomposition of the starting material. Presumably, the electrophilic properties of the ketone dominate over the Michael acceptor capability, which results in decomposition of the starting material.

As the introduction of the quaternary methyl group at C-5 proved cumbersome, and was only solved by a lengthy route, we directed our attention to alternative approaches toward the construction for the ABC-ring intermediate along with an earlier installation of this critical methyl group. At first, we aimed to construct the A- and B-ring via a diastereoselective inverse electron-demand Diels−Alder reaction or more likely to use a stepwise approach by the combination of either 1,4- or 1,6-addition and subsequent aldol addition (Scheme 6).

Different strategies involving aldol cyclization were evaluated. The 1,4-addition adduct **35** was synthesized by Michael addition of β-ketoester **7** to the literature known[32] benzyl protected hydroxy ketone **34** using potassium carbonate in

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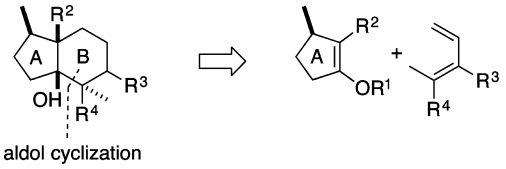
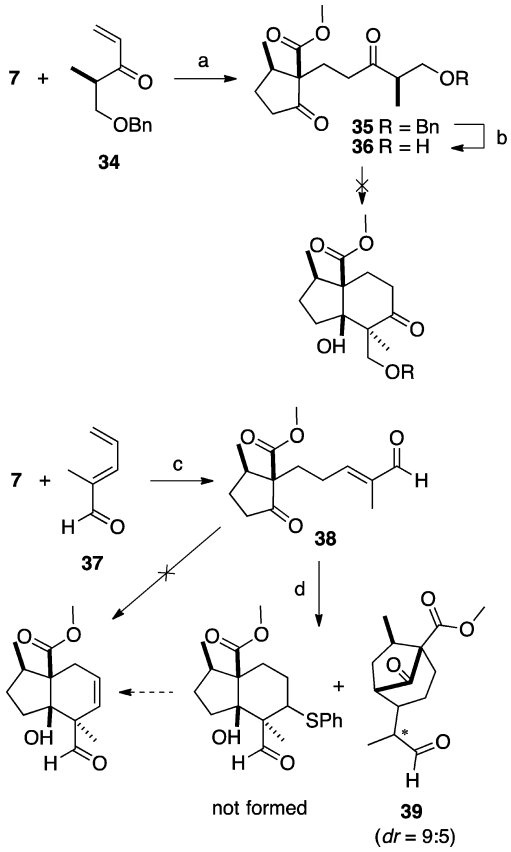
Scheme 6. Retrosynthetic Analysis of the AB-Ring System



acetone with 70% yield and a diastereoselectivity of 5:1 (Scheme 7). Neither for the benzyl protected alcohol **35** nor the deprotected alcohol **36** an aldol cyclization took place by using different bases (Cs_2CO_3, KOH, DBU, NaOMe, *t*-BuOK) or enamine catalysis (pyrrolidine/AcOH, proline). Attempts forming the thermodynamic silyl enol ether suitable for Mukaiyama aldol reaction from protected *β*-hydroxy ketone **35** (TMSCl, NaI, NEt_3 or TBSOTf, NEt_3) or trapping the formed enolate after reaction of ester **7** with benzyl protected alcohol **34** (LDA, then TBSOTf) were not successful either. The *α,β*-unsaturated aldehyde **38** was synthesized by 1,6-addition of ester **7** to the known dienal **37**[33] with K_2CO_3 in acetone at 30 °C in 66% yield.

Scheme 7. Synthetic Approaches toward the AB-Ring System[a]



[a]Reagents and conditions: (a) K_2CO_3, acetone, 40 °C, o.n., 70%, dr = 5:1; (b) 5% Pd/C, EtOH, rt, 2.5 h, quant.; (c) K_2CO_3, acetone, 30 °C, o.n., 66%; (d) Me_3Al, LiSPh, THF, 0 to 40 °C, 37%, dr = 9:5.

Cyclization of **38** via the enamine did not take place, most likely due to the challenges in the isomerization of the conjugated double bond. Nevertheless, the enamine derived from the condensation of the aldehyde moiety of **38** with piperidine (AcOH, 105 °C) was detected via ^{1}H NMR spectroscopy. In order to circumvent the problems accompanied by this double bond we considered using a temporary protecting group for this critical functional group. Aldol reaction of aluminum enolates generated by 1,4-addition of organoaluminum or organoselenium reagents to *α,β*-unsaturated carbonyl compounds was described by Nozaki.[34] Following the cyclization protocol applied for the oxahydrindene fragment from Danishefsky's synthesis of Avermectin A_{1a},[35] we treated aldehyde **38** with the species formed from the reaction of trimethylaluminum and lithium thiophenolate. Instead of the desired AB-ring product, Michael addition to form a diastereomeric mixture (dr = 9:5) of the bicyclo[3.2.1]-octanone **39** in 37% yield was observed.

Due to the failure of the cyclization of the B-ring using aldol addition protocols, we planned to use a diastereoselective intramolecular Hosomi–Sakurai reaction[36] instead (Scheme 8). Different strategies to efficiently prepare the allylsilane precursor were evaluated. Attempts to install the TMS group at C-7 using **7** and 2-(trimethylsilyl)acrylaldehyde or via introduction of the allylsilane part by Grubbs metathesis at the C-5 position proved to be unsuccessful. Finally, we were pleased to find a route to synthesize test substrates suitable for the Hosomi–Sakurai reaction but with a missing methyl group. The synthesis of these substrates started by Michael-addition of **7** to acrolein, followed by Grignard reaction of isopropenyl- or vinylmagnesium bromide to the formed aldehyde **40** to yield **41** and **42**, respectively. Cross metathesis using Grubbs second generation catalyst gave a moderate yield (51%) for the vinyl substrate **42** bearing the free alcohol. Higher yields (71%) were observed for the Dess–Martin periodinane oxidized substrate **45**, however for PMB protected substrate **43** no metathesis product was isolated. Neither the free alcohol **41**, nor the oxidized substrate **44**, derived from the reaction of **40** with isopropenyl Grignard reagent, were reactive in the metathesis reaction and only homocoupling of allyltrimethylsilane was observed using different reaction conditions. The Hosomi–Sakurai reaction was probed on the test substrates **46**, **47** and **48**, but even without bearing the sterically demanding methyl group at C-5 no reaction took place.

Zhang and co-workers recently published the protecting group free total synthesis of (−)-jiadifenolide (**2**).[11d] Their synthetic route lead through the same aldehyde intermediate **27**, which was constructed via a SmI_2 mediated closure of the B-ring and formed directly the critical methyl function bearing quaternary C-5 stereocenter. Radical cyclization of the B-ring of substrate **49** was investigated in our group as well, as the approaches to install the methyl group on the C-ring proved cumbersome. *β*-Methylated lactone **49** was synthesized by applying Fürstner's conditions to vinyltriflate **11** (Scheme 9). To our disappointment, initial evaluation of standard conditions did not facilitate the desired cyclization of **49**. Reaction with SmI_2 in THF without any further additives led mostly to the formation of an unidentified side-product at 0 °C as well as at reflux. Additives such as HMPA and NiI_2 or the addition of protic additives such as MeOH and *t*-BuOH did not lead to the formation of the desired product **26**. Given the encouraging results reported by Zhang and co-workers on the addition of excess water being crucial for the SmI_2-mediated radical cyclization, we tested these conditions on the substrate **49**. After small adaptions, we were able to isolate the desired cyclized product **26** in 50% yield as a 5:2 mixture of inseparable diastereoisomers with the lactone ring on C-5/C-6 either on the same (major product as shown for compound **26**) or on the

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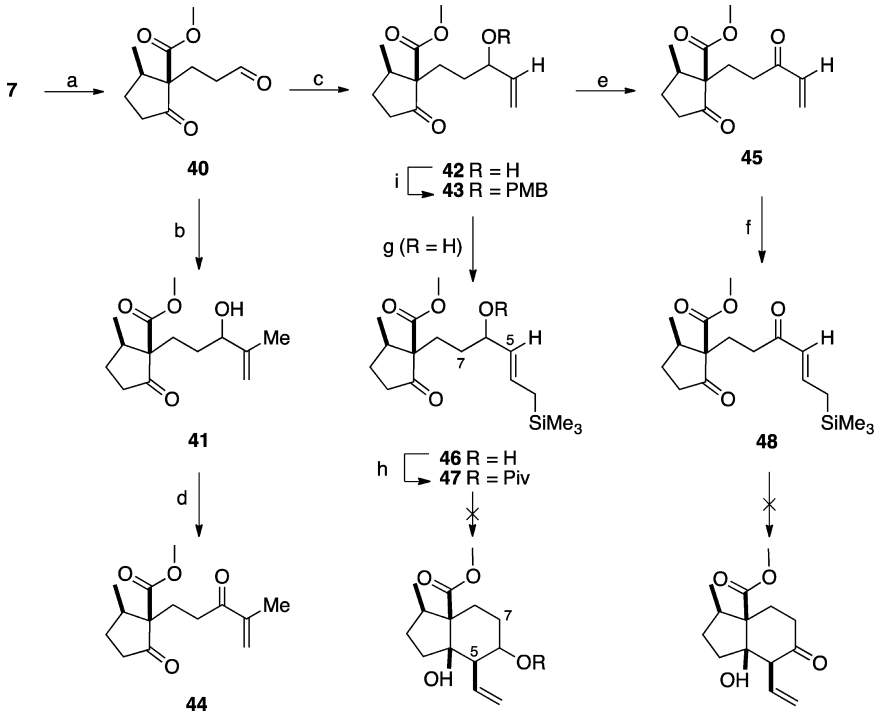
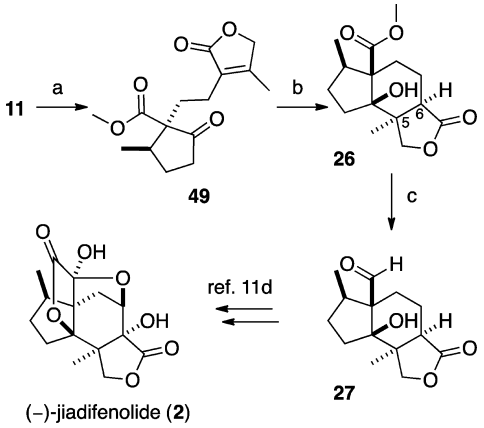
Scheme 8. Hosomi–Sakurai Approach[a]



[a]Reagents and conditions: (a) acrolein, NEt_3, CH_2Cl_2, rt, o.n., 71%; (b) isopropenylmagnesium bromide, THF, −78 °C, 3 h, 33%; (c) vinylmagnesium bromide, THF, −78 °C, 4 h, 42%; (d) DMP, CH_2Cl_2, rt, 1 h, quant.; (e) DMP, CH_2Cl_2, rt, 2 h, quant.; (f) allyltrimethylsilane, Grubb's II (5 mol %), CH_2Cl_2, 40 °C, 90 min, 71%; (g) allyltrimethylsilane, Grubb's II (5 mol %), CH_2Cl_2, 40 °C, 90 min, 51%; (h) PivCl, pyridine, DMAP, CH_2Cl_2, rt to 40 °C, o.n. crude; (i) $BnO(NH)CCl_3$, $Sc(OTf)_3$ (5 mol %), CH_2Cl_2, 0 °C, 90 min, 88%.

Scheme 9. Formal Synthesis of (−)-Jiadifenolide[a]



[a]Reagents and conditions: (a) MeMgBr, $Fe(acac)_3$, NMP, THF, −30 °C, 1 h, 96%; (b) SmI_2, THF/H_2O, rt, 13 h, 50%, dr = 5:2; (c) BH_3·DMS, THF, 6 h, 0 to 45 °C, 51%, dr = 5:1.

opposite (minor) face as the hydroxyl group on C-4, as confirmed by NOESY NMR spectroscopy. Additionally, a side-product where the keto group at C-4 was reduced to the OH function[37] could be isolated in 39% yield (dr = 13:1). Treating the diastereomeric mixture of **26** with BH_3·DMS furnished intermediate **27** in a diastereomeric ratio of 5:1 (51% isolated yield) along with recovered starting material (15%) in a diastereomeric ratio of 4:3. Concerning the increase of the diastereomeric ratio in the transformation from **26** to **27**, we suggest that in the minor diastereomer of **26** the methyl group at C-5 *syn* to the ester residue has a steric influence and slows down the reduction to the aldehyde. In contrast, a coordination of the butenolide moiety in the major diastereomer of **26** to the BH_3 might support the reduction to aldehyde **27**. In summary, aldehyde **27** was obtained from (*R*)-pulegone in a nine step procedure and an overall yield of 10%.

To gain access to a variety of majucin-type sesquiterpenes via derivatization, we targeted on a different synthetic approach with involving a similar precursor also represented by a common ABC-ring fragment. Manganese induced radical cyclization, already applied in our group and successfully utilized in the synthesis of endoperoxides,[38] might constitute a feasible approach for the construction of the B-ring. Functionalization of the geminal methyl functions is present in broad range of *seco*-prezizaane-type sesquiterpenes. The known tetrasubstitued olefin **50** would be an ideal substrate for a regiospecific sp^3 C–H oxidation of the geminal methyl group, which would be incorporated in the butenolide moiety.

Starting from enantiopure (*R*)-pulegone, the known intermediate **50** was readily accessible (Scheme 10).[14a] *α*-Alkylation attempts using LiHMDS or LDA without additives were found to only deprotonate one of the diastereomers, but addition of DMPU triggered the reaction to full conversion and the desired alkylated ester **51** was obtained as a single diastereomer. The TBS-protecting group was cleaved with TBAF/AcOH and the formed alcohol **52** was further oxidized with DMP to the desired aldehyde **53** in 89%. A Roskamp reaction[39] furnished the desired *β*-ketoester **54** in an excellent yield of 93%. Initial screening for the manganese induced radical cyclization showed formation of the desired B-ring. However, the cyclized product **55** was isolated in low yield and along with side-products. Raising the temperature to 50 °C could reduce the reaction time but byproduct formation was

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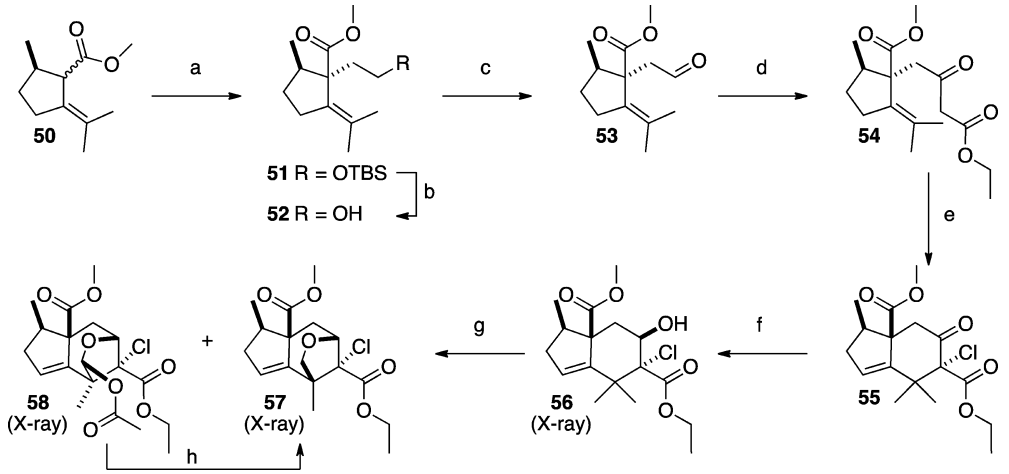
Scheme 10. Manganese-Mediated Cross-Reaction to Establish the AB-Core[a]



[a]Reagents and conditions: (a) LDA, DMPU, THF, *tert*-butyl(2-iodoethoxy)dimethylsilane,[43] −78 °C to rt, 77%; (b) TBAF, AcOH, CH_2Cl_2, rt, 16 h, 79%; (c) DMP, CH_2Cl_2, rt, 4 h, 89%; (d) ethyl 2-diazoacetate, $SnCl_2$ (cat.), CH_2Cl_2, 1 h, 93%; (e) $Mn(OAc)_3$, LiCl, AcOH, 50 °C, 5 h, 39%; (f) $NaBH_4$, MeOH, 0 °C to rt, 4 h, 86%; (g) $Pb(OAc)_4$, cyclohexane, I_2, $CaCO_3$, $h\nu$, 3 d, 81% (**57**), 15% (**58**); (h) $BF_3{\cdot}OEt_2$, Et_3SiH, CH_2Cl_2, −78 °C to rt, 15 h, 88%.

not eliminated. Slow addition of the $Mn(OAc)_3$ or of the substrate had no influence and an average yield of 25−30%, with 39% as the best result was obtained. The byproducts were only isolated as complex mixtures, suggesting that several intermolecular radical recombination reactions occurred. Instead of the excepted disubstituted compound, the trisubstituted olefin **55** was directly isolated, which might result from chloride elimination. Ketone **55** was reduced in the presence of $NaBH_4$ in a complete diastereoselective manner and alcohol **56** could be secured by X-ray crystallography analysis. With the desired hydroxy function in hand, a regioselective C−H functionalization to form the ether **57** was achieved in the presence of $Pb(OAc)_4$ in 81% yield.[40] The byproduct **58**, bearing an additional acetyl group at the carbon next to the ether,[41] was further isolated and successfully converted to the desired product **57** using $BF_3{\cdot}OEt_2$ and triethylsilane.[42] Both structures were confirmed by X-ray crystallographic analysis (Scheme 10).

To our surprise, the ether bridge was found to be stable under several conditions.[44] Therefore, the chloride **57** was reduced by tributyltin hydride to form the ether **59** in 95% yield (Scheme 11). The bridged ether was then opened in the presence of Ac_2O and BF_3-etherate[45] to give the diacetate **60** along with the elimination byproduct **61**, and the acetyl groups of **60** were cleaved with K_2CO_3 in MeOH to form the corresponding diol **62**. The configuration of the OH group could not be assigned in compound **62**, and subsequent TPAP-mediated oxidation to the enolaldehyde **63** was carried out. Other oxidation conditions furnished enolaldehyde **63** as well, but were found to be not reproducible. Conditions using IBX showed traces of the overoxidized α-hydroxylated product **64**, which indicated a general accessibility of the missing OH function insertion at this stage. Nevertheless, the method of choice for the preparation of **64** turned out to be exposure of **63** to $CeCl_3$ and molecular oxygen to yield the α-hydroxylated product **64** in 43%.[46] A reductive cyclization of **64** formed the butenolide and also caused partially closure of the D-ring. This mixture was subjected to acid mediated lactonization involving *p*-TsOH to fully promote D-ring formation in compound **65**, however in a very low yield of 27% over the two steps. Final modifications of the A-ring are proposed in order to give access to the natural product (2*R*)-hydroxy-norneomajucin (**5**) from tetracyle **65**. This intermediate **65** might also serve as a common precursor to other *nor*-type *seco*-prezizaane sesquiterpenes.

CONCLUSION

In conclusion, we present a new strategy to access the tricyclic core structure of (−)-jiadifenolide via a Nozaki−Hiyama−Kishi coupling, which set the stage for a diastereoselective, formal total synthesis of the natural product. Due to the challenging introduction of the methyl group in order to construct this quaternary stereogenic center after the B-ring closure, we elaborated a more efficient route to the tricycle by using a SmI_2-mediated radical cyclization. Unfortunately, alternative strategies to close the B-ring using aldol-cyclization protocols or a Hosomi−Sakurai reaction were unsuccessful. Furthermore, a C1-homologation promoted by potassium cyanide successfully provided the D-ring formation in a remarkable one-step procedure to allow for the completion of the synthesis via successive oxidation protocols. Synthetic studies toward (2*R*)-hydroxy-norneomajucin were carried out, which involved a manganese mediated radical cyclization and a regiospecific C−H activation. Moreover, these studies potentially allow to access a variety of *nor*-derivative sesquiterpene natural products as potential neurotrophic modulators.

EXPERIMENTAL SECTION

General, Materials, and Equipment. All chemicals have been purchased from commercial sources and were used without further purification (except for Et_3N which was freshly distilled before use). All reactions have been carried out in heat gun-dried glassware (unless aqueous reagents were used) and reactions involving air sensitive compounds have been performed under an argon or nitrogen atmosphere. Solvents applied for chemical transformations were either puriss quality or HPLC grade solvents, which have been dried by filtration through activated aluminum oxide under nitrogen (H_2O content <10 ppm, Karl Fischer titration). For workup and purification solvents have been distilled from technical grade. All synthetic transformations have been monitored by either thin layer chromatography (TLC) or ^1H NMR spectroscopy. Yields refer to purified, dried

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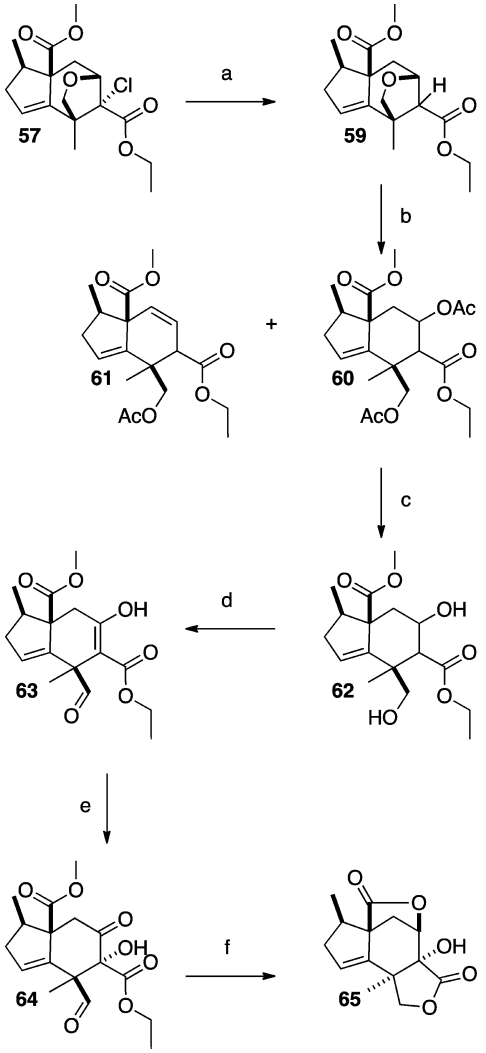
Scheme 11. Synthesis of the (2*R*)-Hydroxy-norneomajucin Precursor[a]



[a]Reagents and conditions: (a) Bu_3SnH, AIBN, benzene, reflux, 2 h, 95%; (b) $BF_3{\cdot}OEt_2$, AcOH, −20 °C to rt, 12 h, 60%; (c) K_2CO_3, MeOH, rt, 16 h, 98%; (d) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 16 h, 68%; (e) $CeCl_3{\cdot}7H_2O$, O_2, *i*-PrOH, rt, 24 h, 43%; (f) $NaBH_4$, MeOH, 0 °C to rt, 12 h, then *p*-TsOH, PhMe, 70 °C, μw, 2 h, 27% (2 steps).

and spectroscopically pure compounds. TLC was performed on silica gel 60 F_{254} plates (0.25 mm thickness) precoated with fluorescent indicator. Concentration under reduced pressure was performed by rotary evaporation at 40 °C. Flash chromatography was performed using silica gel 60 (230−400 mesh) with a forced flow eluent at 0.2−0.4 bar pressure. ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded using 250 MHz, 400 or 500 MHz (^{1}H) and 63 MHz, 101 or 126 MHz (^{13}C) and 376 MHz (^{19}F) spectrometers at room temperature. Chemical shifts (δ-values) are reported in ppm, spectra were calibrated related to solvents' residual proton chemical shifts ($CDCl_3$, δ = 7.26; MeOD-d_4, δ = 3.31) and solvents' residual carbon chemical shifts ($CDCl_3$, δ = 77.16; MeOD-d_4, δ = 49.00), multiplicity is reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved and coupling constant *J* in Hz. IR spectra were recorded on a Fourier transform spectrometer equipped with an ATR unit and the absorptions are reported in cm^{-1}. High resolution mass spectra (HRMS) were performed by electrospray (ESI) ionization on quadrupole time-of-flight (Q-TOF) or quadrupole orbitrap mass spectrometers. Melting points (mp) were determined in open capillaries and are uncorrected. Optical rotations $[\alpha]_D^T$ were measured in $CHCl_3$ at the sodium D line using a 1 mL cell with a 1 dm path length and the concentration *c* is given in g/100 mL.

*Methyl (2R)-2-methyl-5-oxocyclopentane-1-carboxylate (**7**).* Methyl (2*R*)-2-methyl-5-(propan-2-ylidene)cyclopentane-1-carboxylate[14a] (360 mg, 1.98 mmol, 1 equiv) was dissolved in MeOH (20 mL) and CH_2Cl_2 (100 mL) at −78 °C. Ozone was bubbled in the solution until the solution became light blue. Ozone addition was stopped and the solution was stirred under argon at −78 °C for 15 min and at rt for 10 min. Zinc powder (526 mg, 7.96 mmol, 4.0 equiv) and acetic acid (0.46 mL, 7.96 mmol, 4.0 equiv) were added to the solution. The resulting mixture was stirred at rt for 30 min and filtered over Celite. The filtrate was neutralized with saturated $NaHCO_3$ solution and the aqueous layer was extracted two times with CH_2Cl_2. The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure to afford ketone **7** (300.6 mg, 1.92 mmol, 97%) as colorless oil: R_f = 0.13 (pentane/Et_2O 9:1); $[\alpha]_D^{26}$ = +93.5 (*c* 0.46, $CHCl_3$). FTIR (neat); $\tilde{\nu}$ = 2959, 2875, 1754, 1724, 1436, 1335, 1289, 1260, 1202, 1128, 1006 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.76 (s, 3H), 2.77 (d, *J* = 11.4 Hz, 1H), 2.67−2.53 (m, 1H), 2.48−2.39 (m, 1H), 2.38−2.26 (m, 1H), 2.20 (dddd, *J* = 12.7, 8.3, 6.2, 2.0 Hz, 1H), 1.48 (dtd, *J* = 12.6, 11.2, 8.5 Hz, 1H), 1.18 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 212.0, 169.7, 63.1, 52.5, 38.9, 36.5, 29.5, 19.4; elemental analysis calcd for $C_8H_{12}O_3$ C = 61.52; H = 7.74; found C = 61.49; H = 7.60; HRMS (ESI) *m*/*z* calcd for $C_8H_{13}O_3$ $[M + H]^+$: 157.0859, found 157.0861.

*Methyl (1R,2R)-1-allyl-2-methyl-5-oxocyclopentane-1-carboxylate (**8**).* Ketone **7** (1.00 g, 6.4 mmol, 1.0 equiv) was dissolved in dry THF (14.0 mL) and freshly distilled DMPU (3.6 mL). Sodium hydride (60% dispersion in mineral oil, 307 mg, 7.7 mmol, 1.2 equiv) was added at rt and the gray suspension was stirred for 1 h after which it turned to a yellow solution. Allyl bromide (0.67 mL, 7.7 mmol, 1.2 equiv) was added at 0 °C and the milky mixture was stirred for 1 h at 0 °C before it was allowed to warm up to rt. After 12 h the mixture was diluted with Et_2O (20 mL) and washed three times with water. The aqueous layers were re-extracted twice with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. Both diastereoisomers were separated by chromatography (pentane/Et_2O 9:1) giving the desired allylated compound **8** (1.06 g, 5.4 mmol, 84%) as colorless oil; R_f = 0.48 (pentane/Et_2O 4:1); $[\alpha]_D^{25}$ = +38.4 (*c* 0.25, MeOH); FTIR (neat); $\tilde{\nu}$ = 3079, 2958, 2882, 1749, 1731, 1434, 1227, 1187, 1165, 998, 919 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.56−5.67 (m, 1H), 5.09−5.13 (m, 1H), 5.08 (s, 1H), 3.69 (s, 3H), 2.66 (dd, *J* = 14.2, 6.2 Hz, 1H), 2.47−2.58 (m, 2H), 2.27−2.38 (m, 1H), 2.00−2.18 (m, 2H), 1.72−1.84 (m, 1H), 1.02 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 216.2, 171.1, 133.2, 119.6, 63.1, 52.0, 39.1, 38.7, 35.8, 28.3, 15.6; elemental analysis calcd for $C_{11}H_{16}O_3$ C = 67.32; H = 8.22; found C = 67.29; H = 8.20; EI-MS 70 eV, *m*/*z* (%) = 196.1 (22, M^+), 168.1 (100), 136.1 (63), 109.1 (90), 81.1 (68).

*Methyl (1R,2R)-2-methyl-5-oxo-1-(2-oxoethyl)cyclopentane-1-carboxylate (**9**).* Alkene **8** (2.50 g, 12.8 mmol, 1.0 equiv) was dissolved in a CH_2Cl_2/MeOH mixture (30 mL, 5:1) and cooled down to −78 °C. Ozone was bubbled through the stirring mixture until it turned slightly blue. The addition of ozone was stopped and the solution was stirred for 15 min at −78 °C during which time the mixture turned colorless again. Zinc powder (3.36 g, 51.0 mmol, 4.0 equiv) and acetic acid (2.6 mL, 51.0 mmol, 4.0 equiv) were added. The resulting mixture was allowed to warm up to rt overnight. The mixture was filtered over Celite and washed with CH_2Cl_2. After evaporation of the solvent, the residue was suspended with CH_2Cl_2, filtered, and evaporated again to give aldehyde **9** (2.54 g, 12.8 mmol, quant.) as colorless oil; R_f = 0.68 (pentane/Et_2O 9:1); $[\alpha]_D^{25}$= +16.4 (*c* 0.51, MeOH); FTIR (neat) $\tilde{\nu}$ = 2959, 2881, 2857, 2746, 1749, 1717, 1629, 1599, 1456, 1435, 1401, 1397, 1350, 1326, 1233, 1217, 1197, 1167, 1126, 1059, 1038, 1006, 904, 759 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.66 (d, *J* = 0.5 Hz, 1H), 3.71 (s, 3H), 3.13 (d, *J* = 18.8 Hz, 1H), 2.91 (dd, *J* = 18.8, 1.2 Hz, 1H), 2.54−2.60 (m, 2H), 2.36−2.47 (m, 1H), 2.08−2.18 (m, 1H), 1.79−1.92 (m, 1H), 1.01 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 215.3, 199.3, 170.3, 60.5, 52.4,

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46.1, 40.1, 38.0, 28.6, 15.7; HRMS (ESI) m/z calcd for $C_{10}H_{15}O_4$ [M + H]$^+$: 199.0965, found 199.0963.

*Methyl (1R,2R)-1-(2-(4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)-ethyl)-2-methyl-5-oxocyclopentane-1-carboxylate (**10**).* A solution containing the aldehyde **9** (0.49 g, 2.47 mmol, 1.0 equiv), Hantzsch ester (1.38 g, 5.44 mmol, 2.2 equiv), tetronic acid (0.26 g, 2.47 mmol, 1.0 equiv) and L-proline (28.5 mg, 0.25 mmol, 0.1 equiv) in methanol (30 mL) was stirred for 24 h at rt. After evaporation under reduced pressure, the residue was purified by flash chromatography (CH_2Cl_2/MeOH 20:1) to give ketone **10** (0.56 g, 1.99 mmol, 81%) as a beige solid; mp 125.5−125.9 °C; R_f = 0.23 (CH_2Cl_2/MeOH 10:1); $[\alpha]_D^{25}$ = +12.8 (c 0.27, MeOH); FTIR (neat) $\tilde{\nu}$ = 2961, 2942, 2882, 2699, 1746, 1729, 1714, 1648, 1406, 1231, 1195, 1104, 1041, 988, 767 cm^{-1}; ^{1}H NMR (400 MHz, MeOD-d_4) δ = 4.57 (s, 2H), 3.67 (s, 3H), 2.41−2.52 (m, 2H), 2.23−2.34 (m, 2H), 2.05−2.16 (m, 2H), 1.85−2.17 (m, 2H), 1.77 (ddd, J = 23.8, 11.5, 8.5 Hz, 1H), 1.05 (d, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, MeOD-d_4) δ = 218.3, 178.4, 175.6, 172.6, 100.8, 68.3, 64.1, 52.2, 40.7, 39.7, 30.6, 29.3, 17.0, 16.1; elemental analysis calcd for $C_{14}H_{18}O_6$ C = 59.57; H = 6.43; found C = 59.27; H = 6.20; EI-MS 70 eV, m/z (%) = 282.1 (1, M$^+$), 251.1 (9), 157.2 (77), 141.1 (100), 109.1 (40).

*Methyl (1R,2R)-2-methyl-5-oxo-1-(2-(2-oxo-4-(((trifluoromethyl)-sulfonyl)oxy)-2,5-dihydrofuran-3-yl)ethyl)cyclopentane-1-carboxylate (**11**).* Enol **10** (228 mg, 0.81 mmol, 1.0 equiv) and 2,6-lutidine (95 μL, 0.81 mmol, 1.0 equiv) were dissolved in dry CH_2Cl_2 (10 mL) and cooled down to −78 °C. Trifluoromethanesulfonic anhydride (0.14 mL, 0.81 mmol, 1.0 equiv) was added dropwise in 20 min. The reaction mixture was allowed to warm up to rt over 7 h. The yellow solution was treated with pentane (10 mL), filtered and the filtrate was extracted with EtOAc, washed with saturated $NaHCO_3$ solution and brine. The organic layers were dried over Na_2SO_4, filtered and evaporated. Purification by flash chromatography (EtOAc/pentane 1:4) gave vinyltriflate **11** (334 mg, 0.81 mmol, quant.) as a slightly yellow solid; mp 43.6−44.4 °C; R_f = 0.33 (EtOAc/pentane 1:4); $[\alpha]_D^{26}$ = +7.2 (c 0.28, MeOH); FTIR (neat) $\tilde{\nu}$ = 2962, 2885, 2361, 2340, 1778, 1750, 1731, 1703, 1434, 1221, 1136, 1087, 1046, 816 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.90−4.92 (m, 2H), 3.71 (s, 3H), 2.72−2.52 (m, 2H), 2.41−2.20 (m, 3H), 2.01−2.14 (m, 2H), 1.73−1.95 (m, 2H), 1.07 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 215.7, 170.5, 169.8, 160.5, 120.3, 66.6, 62.2, 52.1, 41.2, 38.6, 29.4, 28.3, 17.8, 16.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −72.81; elemental analysis calcd for $C_{15}H_{17}F_3O_8S$ C = 43.48; H = 4.14; found C = 43.60; H = 3.95; EI-MS 70 eV, m/z (%) = 281.1 (16), 249.1 (52), 221.1 (57), 166.2 (62), 141.1 (100), 109.1 (68).

*Methyl (5aR,6R,8aR)-8a-hydroxy-6-methyl-3-oxo-1,3,4,5,6,7,8,8a-octahydro-5aH-indeno[4,5-c]furan-5a-carboxylate (**12**).* Nickel(II) chloride (106 mg, 0.82 mmol, 0.1 equiv), chromium(II) chloride (3.12 g, 7.72 mmol, 6.0 equiv) and some 3 Å molecular sieves were dried in a round-bottom flask under reduced pressure with a heat gun. Triflate **11** (1.70 g, 4.11 mmol, 1.0 equiv) dissolved in dry DMF (40 mL) was degassed and subsequently added to the dried chromium- and nickel-mixture. The green mixture was stirred at 50 °C for 24 h, then quenched by water (100 mL) and extracted with Et_2O until no more product could be detected in the aqueous layer by TLC. The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (EtOAc/pentane 1:4) to afford the cyclized product **12** (749.0 mg, 2.81 mmol, 69%) as a white solid; mp 129.5−129.7 °C; R_f = 0.30 (EtOAc/pentane 1:3); $[\alpha]_D^{25}$ = −37.0 (c 0.26, MeOH); FTIR (neat) $\tilde{\nu}$ = 3346, 2956, 2899, 2360, 1728, 1675, 1443, 1245, 1194, 1153, 1100, 1058, 1015, 653 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.06 (d, J = 1.9 Hz, 1H), 4.96−5.03 (m, 1H), 4.78 (dt, J = 17.5, 2.8 Hz, 1H), 3.77 (s, 3H), 2.25−2.36 (m, 2H), 2.01−2.24 (m, 4H), 1.85−1.95 (m, 2H), 1.73−1.83 (m, 1H), 1.11 (d, J = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 176.5, 173.4, 164.7, 124.8, 80.9, 64.9, 60.2, 52.4, 41.7, 38.5, 32.9, 31.2, 20.4, 18.7; elemental analysis calcd for $C_{14}H_{18}O_5$ C = 63.15; H = 6.81; found C = 63.02; H = 6.80; EI-MS 70 eV, m/z (%) = 266.1 (45, M$^+$), 238.1 (31), 206.1 (82), 178.1 (100), 133.1 (39), 91.1 (26); X-ray crystal structure is given in the Supporting Information.

*(5aR,6R,8aR)-8a-Hydroxy-6-methyl-3-oxo-1,3,4,5,6,7,8,8a-octahydro-5aH-indeno[4,5-c]furan-5a-carbaldehyde (**13**).* Borane dimethyl sulfide complex (2 M in THF, 0.83 mL, 1.65 mmol, 2.0 equiv) was added dropwise to a solution of the methylester **12** (220 mg, 0.83 mmol, 1.0 equiv) in dry THF (4 mL) at 0 °C. The colorless solution was stirred subsequently for 0.5 h and then warmed up to 45 °C for 2 h. After cooling down to rt, ethanol was added until the exothermic reaction and gas evolution ceased. After evaporation, the residue was purified by flash chromatography (Et_2O/pentane 3:1) giving aldehyde **13** (149 mg, 0.63 mmol, 76%) as a white solid; mp 158.1−158.5 °C; R_f = 0.21 (Et_2O/pentane 3:1); $[\alpha]_D^{26}$ = −49.3 (c 0.23, MeOH); FTIR (neat) $\tilde{\nu}$ = 3346, 2942, 2874, 2758, 1744, 1716, 1669, 1435, 1353, 1224, 1107, 1061, 1016, 929, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.70 (s, 1H), 5.01 (ddd, J = 17.4, 3.4, 1.7 Hz, 1H), 4.80 (dt, J = 17.4, 2.7 Hz, 1H), 4.07 (d, J = 1.7 Hz, 1H), 2.04−2.36 (m, 6H), 1.72−1.99 (m, 3H), 1.17 (d, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 206.8, 173.1, 163.5, 125.2, 80.1, 69.5, 61.9, 40.3, 37.7, 31.6, 28.6, 18.8, 17.7; elemental analysis calcd for $C_{13}H_{16}O_4$ C = 66.09; H = 6.83; found C = 65.90; H = 6.75; EI-MS 70 eV, m/z (%) = 236.1 (13, M$^+$), 190.1 (100), 175.1 (66), 145.1 (42), 91.1 (27).

*(5aS,6R,8aR,11S)-11-Hydroxy-6-methyl-4,5,7,8-tetrahydro-6H-8a,5a-(epoxyethano)indeno[4,5-c]furan-3,10(1H)-dione (**14**).* To the aldehyde **13** (43.0 mg, 0.18 mmol, 1.0 equiv), dissolved in THF/water (1:1, 5 mL), was added potassium cyanide (42.0 mg, 0.64 mmol, 3.5 equiv). The resulting mixture was stirred for 2 d at rt before the aqueous reaction mixture was extracted several times with EtOAc until no more product could be detected in the organic layer by TLC. The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The crude product was purified by flash chromatography (EtOAc/cyclohexane 1:1) giving tetracyclic compound **14** (31.0 mg, 0.12 mmol, 65%) as a white solid; mp 194.0−194.3 °C; R_f = 0.28 (EtOAc/cyclohexane 1:1); $[\alpha]_D^{25}$ = −32.6 (c 0.19, MeOH); FTIR (neat) $\tilde{\nu}$ = 3479, 2953, 2929, 2874, 2361, 1785, 1725, 1682, 1442, 1359, 1217, 1191, 1133, 1086, 1046, 1022, 967 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.82−4.99 (m, 2H), 4.57 (d, J = 2.8 Hz, 1H), 2.91 (d, J = 3.2 Hz, 1H), 2.45−2.54 (m, 2H), 2.21−2.30 (m, 1H), 2.00−2.10 (m, 3H), 1.83−1.98 (m, 2H), 1.62−1.70 (m, 1H), 1.42−1.53 (m, 1H), 1.16 (d, J = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.3, 172.5, 157.5, 127.8, 87.4, 69.6, 68.9, 56.2, 36.2, 35.9, 30.7, 21.3, 15.8, 14.0; HRMS (ESI) m/z calcd for $C_{14}H_{17}O_5$ [M + H]$^+$: 265.1071, found 265.1065; X-ray crystal structure is given in the Supporting Information.

*Methyl (5aR,6R)-6-methyl-3-oxo-1,3,4,5,6,7-hexahydro-5aH-indeno[4,5-c]furan-5a-carboxylate (**15**).* Ester **12** (301 mg, 1.13 mmol, 1.0 equiv) was dissolved in dry THF (16.0 mL) and Burgess reagent (417 mg, 1.70 mmol, 1.5 equiv) was added. The clear solution was stirred for 3.5 h at rt. Water (8.0 mL) was added and the aqueous layer extracted with Et_2O (3 × 25.0 mL). The combined organic layers were washed with brine (13.0 mL) and then dried over Na_2SO_4, filtered and evaporated to obtain a white solid. The residue was purified by flash chromatography (pentane/EtOAc 3:1) to obtain the desired olefin **15** (262 mg, 1.06 mmol, 93%) as a white solid; mp 124.9−125.6 °C; R_f = 0.24 (pentane/EtOAc 4:1); $[\alpha]_D^{25}$ = +193.5 (c 0.16, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 2952, 2936, 2846, 1740, 1715, 1644, 1439, 1346, 1239, 1172, 1042, 1014, 980, 761, 744 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.18 (s, 1H), 4.98−4.81 (m, 2H), 3.67 (s, 3H), 2.74−2.56 (m, 1H), 2.52−2.15 (m, 2H), 1.35 (ddd, J = 12.8, 11.7, 5.8 Hz, 1H), 1.07 (d, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.8, 173.1, 151.8, 136.2, 133.2, 126.5, 69.1, 59.9, 52.0, 45.8, 40.6, 30.8, 19.7, 14.9; HRMS (ESI) m/z calcd for $C_{14}H_{17}O_4$ [M + H]$^+$: 249.1121, found 249.1119; X-ray crystal structure is given in the Supporting Information.

*Methyl (5aR,6R,8R,8aS)-8,8a-dihydroxy-6-methyl-3-oxo-1,3,4,5,6,7,8,8a-octahydro-5aH-indeno[4,5-c]furan-5a-carboxylate (**16**).* Olefin **15** (80.0 mg, 0.32 mmol, 1.0 equiv) and NMO (49.7 mg, 0.48 mmol, 1.5 equiv) were dissolved in *tert*-butanol (3 mL) and water (1 mL). The clear solution was cooled to 0 °C and OsO_4 (4% solution in water, 0.13 mL, 16.1 μmol, 5 mol %) was added dropwise. The clear solution was then allowed to warm up to rt and then stirred for 3 days. To the yellow solution was added saturated Na_2SO_3 solution (15 mL)

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J. Org. Chem. 2016, 81, 11017−11034

and the orange to yellow emulsion was stirred for 30 min at rt. The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and evaporated to obtain a yellow oil. The crude was purified by flash chromatography (pentane/EtOAc 1:1) to obtain the desired diol **16** (76.7 mg, 0.27 mmol, 84%, dr = 10:1) as a white solid; mp 126.3−126.8 °C; R_f = 0.25 (pentane/EtOAc 1:1); $[\alpha]_D^{25}$ = +45.6 (*c* 0.16, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 3449, 2959, 2929, 2360, 1727, 1714, 1660, 1429, 1351, 1255, 1202, 1037, 1021, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 5.16 (dd, *J* = 12.2, 6.4 Hz, 1H), 5.03−4.70 (m, 2H), 3.69 (s, 1H), 3.62 (s, 3H), 2.72−2.53 (m, 1H), 2.50−2.40 (m, 1H), 2.40−2.22 (m, 3H), 2.22−2.09 (m, 1H), 1.90 (dd, *J* = 9.2, 7.0 Hz, 2H), 0.90 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.9, 173.5, 162.6, 128.0, 76.9, 71.5, 69.1, 63.3, 51.7, 41.4, 37.5, 22.4, 19.8, 15.7; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{19}O_6$ $[M + H]^+$: 283.1176, found 283.1178.

*Methyl (3aR,5aR,6R,8R,8aS,8bS)-8,8a-dihydroxy-6-methyl-3-oxo-decahydro-5aH-indeno[4,5-c]furan-5a-carboxylate (**17**).* Diol **16** (12.5 mg, 44.3 μmol, 1.0 equiv) and Rh/C/Al_2O_3 (5% Rh, 9.1 mg, 4.43 μmol, 0.1 equiv) were dissolved in dry EtOAc (0.3 mL) and hydrogenated at rt under a 60 bar H_2 pressure. After 3 h, the reaction was filtered over Celite and vigorously washed with EtOAc. The solvent was evaporated under reduced pressure to obtain a white solid. The residue was purified by flash chromatography (pentane/EtOAc 1:1) to obtain the desired hydrogenated lactone **17** (12.6 mg, 44.3 μmol, quant.) as a white solid; mp 197.7−198.5 °C; R_f = 0.31 (EtOAc/pentane 1:1); $[\alpha]_D^{25}$ = −110.8 (*c* 0.12, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 3498, 3425, 2955, 2871, 1743, 1708, 1366, 1202, 1038, 974, 716, 617 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 4.91 (dd, *J* = 9.2, 4.1 Hz, 1H), 4.24 (dd, *J* = 9.7, 8.3 Hz, 1H), 4.00 (dd, *J* = 11.5, 9.7 Hz, 1H), 3.69 (s, 3H), 3.43 (s, 1H), 2.93−2.84 (m, 2H), 2.63−2.55 (m, 1H), 2.22 (dt, *J* = 13.0, 3.6 Hz, 1H), 2.10 (brs, 1H), 2.06 (ddd, *J* = 10.6, 6.6, 3.5 Hz, 1H), 1.93−1.75 (m, 3H), 1.56−1.47 (m, 1H), 0.77 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 179.2, 174.3, 80.0, 72.5, 67.4, 59.6, 51.7, 44.1, 39.9, 39.3, 38.2, 24.9, 22.1, 14.7; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{21}O_6$ $[M + H]^+$: 285.1333, found 285.1334; X-ray crystal structure is given in the Supporting Information.

*Methyl (3aS,5R,7aR)-1,4-dioxo-5-((R)-4-oxobutan-2-yl)-octahydroisobenzofuran-5-carboxylate (**18**).* Diol **17** (11.3 mg, 39.7 μmol, 1.0 equiv) was dissolved in THF/water (2:1, 0.47 mL) and $NaIO_4$ (27.8 mg, 0.13 mmol, 3.2 equiv) was added at rt. After 1.5 h, the reaction mixture was diluted with EtOAc (2 mL) and filtered over Na_2SO_4. The filtrate was vigorously washed with EtOAc (4 × 2 mL). The solvent was evaporated to obtain a white solid. The residue was purified by flash chromatography (pentane/EtOAc 2:1) to obtain the desired ketoaldehyde **18** (12.5 mg, 43.6 μmol, quant.) as colorless oil; R_f = 0.38 (EtOAc/pentane 1:1); $[\alpha]_D^{25}$ = −137.3 (*c* 0.12, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 2955, 1770, 1712, 1452, 1167, 998, 732, 626 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 9.71 (s, 1H), 4.86 (dd, *J* = 9.4, 1.9 Hz, 1H), 4.19 (dd, *J* = 9.4, 6.6 Hz, 1H), 3.70 (s, 3H), 3.30−3.18 (m, 2H), 2.93−2.84 (m, 1H), 2.82−2.68 (m, 2H), 2.29−2.17 (m, 2H), 2.15−2.04 (m, 2H), 1.07 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 205.4, 201.3, 176.7, 170.7, 66.2, 63.0, 52.5, 47.5, 45.6, 40.2, 29.1, 28.8, 18.8, 15.8.

*Methyl (3aS,5R,7aR)-5-((R)-1-(1,3-dioxolan-2-yl)propan-2-yl)-1,4-dioxo-octahydroisobenzofuran-5-carboxylate (**19**).* To the diol **17** (130.0 mg, 0.45 mmol, 1.0 equiv) dissolved in a THF and water mixture (3:1, 5 mL) was added sodium periodate (332.0 mg, 1.60 mmol, 3.4 equiv). The mixture was stirred at rt for 2 h and subsequently dried by filtrating the mixture through a patch of Na_2SO_4 and washed with EtOAc. The solvent was evaporated, and the residue was obtained as colorless oil. The crude ketoaldehyde **18** was dissolved in dry benzene (4 mL), and ethylene glycol (27 μL, 0.48 mmol, 1.1 equiv) was added, followed by *p*-TSA·H_2O (9.2 mg, 0.05 mmol, 0.1 equiv). The resulting solution was heated to reflux (90 °C). After 1 h 45 min, the solution was allowed to cool to rt, and was then treated with saturated $NaHCO_3$ solution (3 mL) followed by extraction with EtOAc three times. The combined organic layers were washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was subjected to flash chromatography on silica (CH_2Cl_2/MeOH, 20:1) and concentrated to give protected aldehyde **19** (149.0 mg, 0.45 mmol, quant.) as a white solid; R_f = 0.63 (CH_2Cl_2/MeOH 20:1); $[\alpha]_D^{25}$ = −75.5 (*c* 0.77, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 2954, 2887, 1773, 1737, 1709, 1450, 1372, 1343, 1297, 1220, 1188, 1148, 1121, 1050, 1027, 998, 962, 734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 4.95 (dd, *J* = 9.3, 1.8 Hz, 1H), 4.86 (dd, *J* = 6.4, 2.6 Hz, 1H), 4.14 (dd, *J* = 9.3, 6.5 Hz, 1H), 3.97−3.90 (m, 2H), 3.87−3.79 (m, 2H), 3.70 (s, 3H), 3.47 (ddd, *J* = 10.0, 6.4, 1.7 Hz, 1H), 3.18 (ddd, *J* = 10.1, 6.4, 5.1 Hz, 1H), 2.42−2.35 (m, 1H), 2.22−2.07 (m, 4H), 2.03 (ddd, *J* = 14.9, 9.8, 2.6 Hz, 1H), 1.54 (ddd, *J* = 14.9, 6.4, 0.8 Hz, 1H), 1.09 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 205.2, 176.8, 170.9, 103.3, 66.0, 65.1, 64.9, 64.2, 52.2, 45.7, 40.9, 36.8, 30.3, 29.1, 18.6, 15.4; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{23}O_7$ $[M + H]^+$: 327.1438, found 327.1443.

*Methyl (3aR,5R,7aR)-5-((R)-1-(1,3-dioxolan-2-yl)propan-2-yl)-3a-(hydroxymethyl)-1,4-dioxooctahydroisobenzofuran-5-carboxylate (**20**).* Acetal **19** (161.0 mg, 0.49 mmol, 1.0 equiv) was dissolved in THF (2.8 mL), and formaline (37% aq. solution, 8.3 mL, 112 mmol, 226 equiv) was added, followed by aq. citrate buffer solution (8.3 mL, pH 6.0). The resulting solution was heated to 40 °C and stirred overnight. After cooling to rt, the reaction mixture was diluted with EtOAc and water. The aqueous layer was extracted three times with EtOAc, and the combined organic layers were washed with water, dried over Na_2SO_4, and evaporated under reduced pressure. The crude residue was dissolved in a CH_2Cl_2/MeOH mixture (20:1) and filtered through a pad of silica. Purification by flash chromatography (CH_2Cl_2/MeOH 20:1) gave alcohol **20** (164.3 mg, 0.46 mmol, 94%) as a white solid; R_f = 0.30 (CH_2Cl_2/MeOH 20:1); $[\alpha]_D^{25}$ = −23.5 (*c* 0.30, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 3467, 2957, 2923, 2854, 1766, 1728, 1702, 1465, 1437, 1382, 1300, 1223, 1174, 1137, 1096, 1017, 952, 881, 860, 826, 751, 713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 4.87 (dd, *J* = 5.8, 3.5 Hz, 1H), 4.34 (d, *J* = 9.8 Hz, 1H), 4.13 (d, *J* = 9.8 Hz, 1H), 4.00−3.91 (m, 3H), 3.88−3.79 (m, 2H), 3.71 (s, 3H), 3.60 (d, *J* = 10.8 Hz, 1H), 3.02−2.93 (m, 1H), 2.38−2.19 (m, 3H), 2.05 (ddd, *J* = 12.9, 11.5, 2.3 Hz, 1H), 1.98−1.84 (m, 1H), 1.79−1.64 (m, 2H), 1.12 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 208.5, 177.5, 171.4, 103.7, 70.9, 67.0, 65.0, 64.8, 63.3, 56.6, 42.8, 35.8, 33.8, 30.5, 28.9, 20.8, 17.0; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{25}O_8$ $[M + H]^+$: 357.1544, found 357.1552.

*Methyl (3aR,5R,7aR)-5-((R)-1-(1,3-dioxolan-2-yl)propan-2-yl)-3a (iodomethyl)-1,4-dioxooctahydroisobenzofuran-5-carboxylate (**21**).* Alcohol **20** (408 mg, 1.14 mmol, 1.0 equiv), triphenylphosphine (600 mg, 2.29 mmol, 2.0 equiv) and imidazole (311 mg, 4.57 mmol, 4.0 equiv) were dissolved in dry benzene (30 mL) under argon atmosphere. Iodine (580 mg, 2.29 mmol, 2.0 equiv) was added at rt and the resulting mixture was stirred for 12 h at that temperature. The reaction was quenched with a 1:1 mixture of saturated $NaHCO_3$ and $Na_2S_2O_3$ solution and extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica (pentane/EtOAc 5:2) giving iodide **21** (401.2 mg, 0.86 mmol, 75%) as colorless oil; R_f = 0.23 (pentane/EtOAc 3:1); $[\alpha]_D^{25}$ = +17.9 (*c* 0.48, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 2954, 2886, 2360, 1781, 1731, 1710, 1436, 1366, 1225, 1162, 1030, 947, 824, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 4.87 (dd, *J* = 5.8, 3.7 Hz, 1H), 4.39 (d, *J* = 10.2 Hz, 1H), 4.01 (d, *J* = 10.2 Hz, 1H), 3.98−3.87 (m, 3H), 3.86−3.78 (m, 2H), 3.72 (s, 3H), 3.15 (d, *J* = 10.3 Hz, 1H), 3.14−3.08 (m, 1H), 2.49−2.38 (m, 1H), 2.33−2.24 (m, 2H), 2.08−1.98 (m, 1H), 1.86 (tdd, *J* = 13.3, 8.3, 2.3 Hz, 1H), 1.72−1.55 (m, 2H), 1.11 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 203.7, 176.2, 171.1, 103.5, 72.9, 65.1, 64.8, 63.5, 55.3, 53.0, 46.9, 36.4, 35.6, 27.5, 20.8, 17.4, 11.3; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{24}IO_7$ $[M + H]^+$: 467.0561, found 467.0557.

*Methyl (3aS,5R,7aR)-5-((R)-1-(1,3-dioxolan-2-yl)propan-2-yl)-3a-methyl-1,4-dioxooctahydroisobenzofuran-5-carboxylate (**22**).* Iodide **21** (401.0 mg, 0.86 mmol, 1.0 equiv) was dissolved in dry and degassed benzene (30 mL) under argon atmosphere. Tri-*n*-butyltin hydride (348 μL, 1.29 mmol, 1.5 equiv) and AIBN (42.0 mg, 0.26 mmol, 0.3 equiv) were added and the mixture was stirred for 3 h at 85 °C. The solvent was removed in vacuo and the residue was purified by

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J. Org. Chem. 2016, 81, 11017−11034

flash column chromatography (pentane/EtOAc 2:1) to give the ketone **22** (242.0 mg, 0.72 mmol, 84%) as colorless oil. R_f = 0.18 (pentane/EtOAc 2:1); $[\alpha]_D^{25}$ = −68.5 (*c* 0.49, MeOH); FTIR (neat) $\tilde{\nu}$ = 2955, 2887, 1776, 1733, 1709, 1457, 1364, 1297, 1230, 1148, 1020, 963, 823, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 4.85 (t, *J* = 4.8 Hz, 1H), 4.47 (d, *J* = 9.3 Hz, 1H), 3.95−3.84 (m, 3H), 3.83−3.75 (m, 2H), 3.64 (s, 3H), 2.61 (dd, *J* = 10.3, 6.1 Hz, 1H), 2.43−2.32 (m, 1H), 2.26−2.11 (m, 2H), 2.03−1.86 (m, 2H), 1.59−1.53 (m, 2H), 1.33 (s, 3H), 1.03 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 207.7, 177.5, 171.1, 103.5, 74.6, 65.0, 64.7, 63.3, 52.6, 50.9, 46.3, 36.1, 34.8, 27.7, 24.3, 19.5, 16.8; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{25}O_7$ $[M + H]^+$: 341.1595, found 341.1591.

*Methyl (3aS,5R,7aR)-3a-methyl-1,4-dioxo-5-((R)-4-oxobutan-2-yl)octahydroisobenzofuran-5-carboxylate (**23**).* The ketone **22** (227.0 mg, 0.67 mmol, 1.0 equiv) was dissolved in acetone (10 mL) and 1 M aq. HCl solution (5 mL) was added. The resulting mixture was stirred at rt for 17 h. The reaction was quenched by addition of a saturated aq. $NaHCO_3$ solution and extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure to yield pure aldehyde **23** (195.8 mg, 0.66 mmol, 99%) as colorless oil; R_f = 0.56 (pentane/EtOAc 1:1); $[\alpha]_D^{25}$ = −87.8 (*c* 0.42, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 2956, 2360, 2339, 1776, 1717, 1457, 1385, 1295, 1234, 1155, 1022, 991, 787 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 9.72 (d, *J* = 1.7 Hz, 1H), 4.60 (d, *J* = 9.4 Hz, 1H), 3.90 (d, *J* = 9.4 Hz, 1H), 3.68 (s, 3H), 2.94 (dqd, *J* = 9.8, 6.8, 3.0 Hz, 1H), 2.69 (t, *J* = 7.4 Hz, 1H), 2.67−2.60 (m, 1H), 2.52−2.43 (m, 1H), 2.31−2.19 (m, 2H), 2.08−1.94 (m, 2H), 1.36 (s, 3H), 1.00 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 208.1, 200.7, 177.3, 170.8, 74.7, 62.3, 52.8, 51.2, 46.8, 46.2, 31.3, 27.2, 24.5, 18.9, 16.6; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{21}O_6$ $[M + H]^+$: 297.1333 found 297.1328.

*Methyl (3aS,5R,7aR)-5-((R)-4-hydroxybutan-2-yl)-3a-methyl-1,4-dioxooctahydroisobenzofuran-5-carboxylate (**24**).* Aldehyde **23** (78.1 mg, 0.26 mmol, 1.0 equiv) was dissolved in hexafluoroisopropanol (1 mL). Sodium tris(hexafluoroisoproopoxy)borohydride (1 M in THF, 791 μL, 0.79 mmol, 3.0 equiv) was added at rt under nitrogen atmosphere and stirred for 15 h. The reaction was quenched by addition of saturated NH_4Cl solution and extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (pentane/EtOAc 2:3) giving alcohol **24** (66.9 mg, 0.224 mmol, 85%) as colorless oil; R_f = 0.26 (EtOAc/pentane 3:2); $[\alpha]_D^{25}$ = −79.9 (*c* 0.18, MeOH); FTIR (neat) $\tilde{\nu}$ = 3529, 3407, 2955, 2884, 1775, 1731, 1708, 1456, 1385, 1364, 1293, 1231, 1187, 1154, 1055, 1021, 989, 916, 848, 732, 681 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 4.48 (d, *J* = 9.3 Hz, 1H), 3.94 (d, *J* = 9.3 Hz, 1H), 3.74 (ddd, *J* = 11.0, 8.8, 5.5 Hz, 1H), 3.69 (s, 3H), 3.67−3.58 (m, 1H), 2.64 (t, *J* = 8.4 Hz, 1H), 2.45−2.34 (m, 1H), 2.28 (dt, *J* = 9.3, 4.4 Hz, 1H), 2.25−2.17 (m, 1H), 2.07−1.92 (m, 2H), 1.69−1.52 (m, 2H), 1.39−1.33 (m, 1H), 1.37 (d, *J* = 2.9 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 208.1, 177.5, 171.3, 74.6, 63.2, 61.0, 52.8, 51.0, 46.5, 35.3, 34.8, 27.4, 24.4, 19.8, 16.1; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{22}NaO_6$ $[M + Na]^+$: 321.1309, found 321.1308.

*Methyl (3aS,5R,7aR)-5-((R)-4-iodobutan-2-yl)-3a-methyl-1,4-dioxooctahydroisobenzofuran-5-carboxylate (**25**).* Alcohol **24** (26.0 mg, 0.087 mmol, 1.0 equiv) was dissolved in dry benzene (5 mL) under nitrogen atmosphere. Triphenylphosphine (45.7 mg, 0.174 mmol, 2.0 equiv), imidazole (23.7 mg, 0.349 mmol, 4.0 equiv), and iodine (44.2 mg, 0.174 mmol, 2.0 equiv) were added at rt and the resulting mixture was stirred overnight. The crude mixture was filtered, washed with benzene and evaporated under reduced pressure. The resulting oil was purified by flash chromatography (pentane/EtOAc 2:1) to give iodide **25** (33.8 mg, 0.083 mmol, 95%) as a white solid; R_f = 0.44 (pentane/EtOAc 2:1); $[\alpha]_D^{25}$ = −9.8 (*c* 0.58, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 3245, 2971, 2927, 2860, 2171, 1762, 1728, 1700, 1591, 1532, 1489, 1439, 1385, 1368, 1287, 1230, 1207, 1173, 1119, 1069, 1012, 977, 961, 922, 905, 852, 773, 764, 722, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 4.48 (d, *J* = 9.3 Hz, 1H), 3.93 (d, *J* = 9.3 Hz, 1H), 3.71 (s, 3H), 3.33 (ddd, *J* = 9.8, 7.7, 4.3 Hz, 1H), 3.07 (td, *J* = 9.5, 7.1 Hz, 1H), 2.68−2.60 (m, 1H), 2.37−2.14 (m, 3H), 2.05−1.91 (m, 2H), 1.89−1.78 (m, 1H), 1.71−1.60 (m, 1H), 1.37 (s, 3H), 0.97 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 207.7, 177.4, 171.0, 74.6, 63.1, 52.9, 51.0, 46.4, 39.5, 35.6, 27.6, 24.5, 19.7, 15.1, 4.4; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{22}IO_5$ $[M + H]^+$: 409.0506, found 409.0508; X-ray crystal structure is given in the Supporting Information.

Samarium(II) Iodide. Following a literature procedure,[47] samarium (151 mg, 1.0 mmol, 1.0 equiv) was activated by hot stirring with a heat gun in vacuo. After cooling, 1,2-diiodoethane (prewashed by extraction with saturated aqueous $Na_2S_2O_3$ solution, 141 mg, 0.5 mmol, 1.0 equiv) was added under argon atmosphere. THF (dried over sodium, 2 mL) was added and the mixture was stirred for 5 min at room temperature. After that time, more THF (3 mL) was added and the solution was stirred until it turned dark blue and SmI_2 was obtained as a 0.1 M solution in THF and was used as such.

*Methyl (3aR,5aR,6R,8aR,8bS)-8a-hydroxy-6,8b-dimethyl-3-oxodecahydro-5aH-indeno[4,5-c]furan-5a-carboxylate (**26**).* Iodide **25** (118.0 mg, 0.289 mmol, 1.0 equiv) was dissolved in hexamethylphosphoramide (500 μL, 2.89 mmol, 10.0 equiv) under nitrogen atmosphere and cooled down to 0 °C. A freshly prepared SmI_2 solution (0.1 M in THF, 7.22 mL, 0.722 mmol, 2.5 equiv) was added and the resulting mixture was slowly heated up to rt and stirred for 1 h. The reaction was quenched by addition of a saturated aqueous Rochelle's salt solution and stirred at that temperature for 20 min. Extraction was performed three times with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica (pentane/EtOAc 4:1, CAM dip) giving the tricyclic product **26** (61.5 mg, 0.218 mmol, 76%) as a white solid; mp 97.8−98.6 °C; R_f = 0.41 (pentane/EtOAc 4:1); $[\alpha]_D^{25}$ = −17.6 (*c* 0.29, MeOH); FTIR (neat) $\tilde{\nu}$ = 3495, 2959, 2900, 2877, 1770, 1708, 1454, 1435, 1384, 1354, 1325, 1291, 1270, 1239, 1181, 1148, 1102, 1076, 1058, 1040, 1009, 988, 966, 920, 896, 845, 768, 739, 714, 681 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 5.17 (d, *J* = 2.1 Hz, 1H), 4.44 (d, *J* = 9.5 Hz, 1H), 3.97 (d, *J* = 9.5 Hz, 1H), 3.79 (s, 3H), 2.40−2.32 (m, 1H), 2.24−2.16 (m, 1H), 2.14−2.00 (m, 2H), 1.96−1.86 (m, 2H), 1.82−1.71 (m, 1H), 1.66−1.58 (m, 1H), 1.43 (td, *J* = 13.9, 2.6 Hz, 1H), 1.35−1.29 (m, 1H), 1.23 (s, 3H), 1.00 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 178.8, 178.5, 85.4, 74.6, 58.0, 52.6, 48.1, 46.8, 45.1, 36.9, 33.8, 29.4, 23.1, 22.4, 21.2; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{22}NaO_5$ $[M + Na]^+$: 305.1359, found 305.1359.

*(3aR,5aR,6R,8aR,8bS)-8a-Hydroxy-6,8b-dimethyl-3-oxodecahydro-5aH-indeno[4,5-c]furan-5a-carbaldehyde (**27**).*[11d] In a dry round bottomed flask under argon atmosphere, ester **26** (19.7 mg, 0.070 mmol, 1.0 equiv) was dissolved in dry THF (2 mL) and cooled to 0 °C. Borane-methyl sulfide complex (2 M in THF, 70 μL, 0.140 mmol, 2.0 equiv) was added, the resulting mixture was stirred for 15 min at 0 °C and subsequently at 45 °C for 5.5 h. The mixture was allowed to cool down to rt for 10 min before ethanol was added until bubbling (exothermic) ceased. The solution was evaporated giving a colorless oil. Purification was performed by flash chromatography (pentane/EtOAc 3:2) giving aldehyde **27** (11.6 mg, 0.0460 mmol, 66%) as a white solid; mp 51.4−51.9 °C; R_f = 0.32 (pentane/EtOAc 3:2, CAM dip); $[\alpha]_D^{25}$ = −13.7 (*c* 0.19, MeOH); FTIR (neat) $\tilde{\nu}$ = 3484, 2957, 2876, 1748, 1704, 1460, 1373, 1287, 1227, 1158, 1140, 1003, 973, 855, 793, 732, 690, 551 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 9.84 (s, 1H), 4.23 (d, *J* = 0.8 Hz, 1H), 3.95 (d, *J* = 9.6 Hz, 1H), 3.51 (s, 1H), 2.29−2.18 (m, 2H), 2.12 (dddd, *J* = 14.4, 10.4, 9.1, 2.2 Hz, 2H), 1.98−1.84 (m, 2H), 1.82−1.72 (m, 1H), 1.72−1.60 (m, 1H), 1.51−1.41 (m, 1H), 1.41−1.32 (m, 1H), 1.22 (d, *J* = 0.8 Hz, 3H), 1.08 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 210.1, 178.9, 86.4, 75.0, 59.8, 47.5, 46.4, 44.6, 37.8, 31.5, 30.5, 22.5, 22.3, 19.8; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{20}O_4Na$ $[M + Na]^+$: 275.1254, found 275.1253.

*(3aR,5aS,6R,8aR,8bS,11S)-11-Hydroxy-6,8b-dimethylhexahydro-6H-8a,5a-(epoxyethano)indeno[4,5-c]furan-3,10(1H)-dione (**28**).* In a dry round bottomed flask under argon atmosphere, ester **26** (31.8 mg, 0.113 mmol, 1.0 equiv) was dissolved in dry THF (3 mL) and cooled to 0 °C. Borane-methyl sulfide complex (2 M in THF, 113 μL, 0.225 mmol, 2.0 equiv) was added, the resulting mixture was stirred for 15 min at 0 °C and subsequently at 45 °C for 7 h. The mixture was

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J. Org. Chem. 2016, 81, 11017−11034

allowed to cool down to rt for 10 min before ethanol was added until bubbling (exothermic) ceased. The solution was evaporated giving a colorless oil. Crude aldehyde **27** was dissolved in THF/water (1:1, 4 mL) and potassium cyanide (25.8 mg, 0.396 mmol, 3.5 equiv) was added. The mixture was stirred for 2 d before EtOAc was added and the mixture was stirred for an additional day. The phases were separated and the aqueous layer was extracted with EtOAc for an additional day. Extractions were performed until no more product was observed in the separated organic layer. The combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc/pentane 3:2) giving lactone **28** (20.0 mg, 0.0713 mmol, 63%) as a white solid; R_f = 0.33 (EtOAc/pentane 1:1); $[\alpha]_D^{25}$ = −41.9 (*c* 0.16, MeOH); FTIR (neat) $\tilde{\nu}$ = 3421, 2965, 2888, 1774, 1758, 1678, 1462, 1379, 1254, 1196, 1159, 1132, 1091, 1026, 974, 944, 876, 820, 753, 716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 4.40 (d, *J* = 9.6 Hz, 1H), 4.35 (d, *J* = 2.8 Hz, 1H), 3.92 (d, *J* = 9.6 Hz, 1H), 2.69 (d, *J* = 2.9 Hz, 1H), 2.47 (dt, *J* = 8.3, 4.2 Hz, 1H), 2.29−2.19 (m, 1H), 2.12−2.00 (m, 3H), 1.90−1.78 (m, 2H), 1.75−1.65 (m, 1H), 1.35 (s, 3H), 1.08 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 179.7, 176.8, 98.1, 75.7, 68.7, 53.5, 44.7, 44.3, 43.0, 34.5, 30.2, 25.3, 22.3, 20.2, 14.5; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{21}O_5$ $[M + H]^+$: 281.1384, found 281.1380.

*(3aS,4R,6S,6aS,7R,9aR,9bS)-7,9b-Dimethylhexahydro-3H,6H,7H-9a,6-(epoxymethano)-4,6a-methanocyclopenta[c]furo[3,4-e]-oxepine-3,11-dione (**29**).* Alcohol **28** (2.5 mg, 8.9 μmol, 1.0 equiv) was dissolved in dry THF (1 mL) under nitrogen atmosphere and cooled down to −78 °C. LDA (0.28 M in THF, 96 μL, 26.8 μmol, 3.0 equiv) was added at −78 °C and the mixture was stirred for 1 h. A solution of phenylselenyl bromide (4.2 mg, 17.8 μmol, 2.0 equiv) in THF (0.15 mL) and was then added at −78 °C. The resulting mixture was stirred for 1 h at that temperature and subsequently heated up to 0 °C and stirred for additional 30 min. The reaction mixture was diluted with a saturated NH_4Cl solution and EtOAc. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was dissolved in THF (1 mL) and cooled down to 0 °C. One drop of AcOH and H_2O_2 (35% in water) were added and the mixture was stirred for 2 h before a saturated $NaHCO_3$ solution was added and stirred 1 h at rt. Extraction was performed three times with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. Purification was performed by flash chromatography to yield the desired product **29** (1.2 mg, 4.31 μmol, 48%) as a crystalline solid; R_f = 0.21 (pentane/EtOAc 1:4); $[\alpha]_D^{25}$ = −68.4 (*c* 0.29, MeOH); FTIR (neat) $\tilde{\nu}$ = 3357, 2923, 2853, 1762, 1662, 1467, 1378, 1263, 1208, 1159, 1095, 1022, 962, 930, 902, 795, 748 cm^{-1}; ^1H NMR (400 MHz, MeOD-d_4) δ = 4.75 (t, *J* = 5.7 Hz, 1H), 4.65 (d, *J* = 9.3 Hz, 1H), 4.01 (s, 1H), 3.87 (d, *J* = 9.3 Hz, 1H), 3.07 (d, *J* = 5.2 Hz, 1H), 2.31−2.21 (m, 2H), 2.09−1.94 (m, 4H), 1.36 (s, 3H), 1.27−1.15 (m, 1H), 1.08 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, MeOD-d_4) δ = 177.7, 174.9, 101.9, 78.7, 75.6, 75.5, 60.4, 55.4, 44.7, 39.0, 35.4, 34.0, 32.8, 27.3, 15.8; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{19}O_5$ $[M + H]^+$: 279.1227, found 279.1223; X-ray crystal structure is given in the Supporting Information.

*Methyl (1R,2R)-1-((R)-5-(benzyloxy)-4-methyl-3-oxopentyl)-2-methyl-5-oxocyclopentane-1-carboxylate (**35**).* To a solution of β-keto ester **7** (10 mg, 0.064 mmol, 1.0 equiv) and enone **34**[32] (19.6 mg, 0.096 mmol, 1.2 equiv) in acetone (0.25 mL) was added K_2CO_3 (4.4 mg, 0.032 mmol, 0.5 equiv) and the mixture was heated to 40 °C overnight. After cooling down to room temperature the mixture was filtered through a short pad of Celite. The solvent was removed and the residue was subjected to flash column chromatography (pentane/Et_2O 5:1 to 3:1) to give ester **35** (16.2 mg, 45 μmol, 70%) as colorless oil; R_f = 0.53 (pentane/Et_2O 6:1); $[\alpha]_D^{24}$ = +27.3 (*c* 0.44, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 2960, 2877, 2361, 1729, 1496, 1455, 1375, 1236, 1168, 1101, 1026, 997, 741, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.36−7.26 (m, 5H), 4.48 (d, *J* = 3.2 Hz, 2H), 3.68 (s, 3H), 3.62 (dd, *J* = 9.1, 7.7 Hz, 1H), 3.49−3.44 (m, 1H), 2.91−2.78 (m, 2H), 2.59−2.46 (m, 2H), 2.24−2.08 (m, 3H), 2.06−1.87 (m, 2H), 1.79−1.66 (m, 1H), 1.07 (d, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 216.5, 212.4, 171.0, 138.3, 128.5, 127.7, 127.7, 73.4, 72.5, 62.0, 51.9, 46.7, 41.6, 38.7, 37.2, 28.3, 26.1, 16.0, 13.7; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{28}NaO_5$ $[M + Na]^+$: 383.1829, found 383.1834.

*Methyl (1R,2R)-1-((R)-5-hydroxy-4-methyl-3-oxopentyl)-2-methyl-5-oxocyclopentane-1-carboxylate (**36**).* A mixture of ester **35** (50.0 mg, 0.139 mmol, 1.0 equiv) and 5% Pd/C (44.3 mg, 0.021 mmol, 15 mol %) in EtOH (3.0 mL) was stirred under a hydrogen atmosphere. After completion of the reaction (2.5 h), the mixture was filtered through a short pad of Celite and the solvent was removed under reduced pressure to give alcohol **36** (37.5 mg, 0.139 mmol, quant.) as colorless oil; R_f = 0.16 (pentane/Et_2O 1:2); $[\alpha]_D^{26}$ = +40.0 (*c* 0.98, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 3732, 3505, 2960, 2881, 2361, 2340, 1728, 1459, 1381, 1237, 1169, 1124, 1035, 678 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 3.69 (s, 3H), 3.75−3.63 (m, 2H), 2.87 (ddd, *J* = 18.1, 9.2, 5.7 Hz, 1H), 2.80−2.70 (m, 1H), 2.64−2.47 (m, 2H), 2.33−2.03 (m, 5H), 1.91 (ddd, *J* = 14.7, 9.3, 5.7 Hz, 1H), 1.80−1.66 (m, 1H), 1.10 (d, *J* = 7.2 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ = 216.8, 214.1, 170.9, 64.7, 61.9, 52.0, 48.3, 42.4, 38.7, 37.0, 28.3, 26.5, 16.0, 13.3; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{22}NaO_5$ $[M + Na]^+$: 293.1359, found 293.1361.

*Methyl (1R,2R)-2-methyl-1-((E)-4-methyl-5-oxopent-3-en-1-yl)-5-oxocyclopentane-1-carboxylate (**38**).* To a solution of β-keto ester **7** (284 mg, 1.82 mmol, 1.0 equiv) and α,β,γ,δ-unsaturated aldehyde **37**[33] (4.0 mL, 2.00 mmol, 1.1 equiv, 0.5 M solution in CH_2Cl_2) in acetone (10.0 mL) was added K_2CO_3 (503 mg, 3.64 mmol, 2.0 equiv) and the mixture was heated to 30 °C overnight. After cooling to room temperature, the mixture was filtered through a short pad of Celite. The solvent was removed and the residue was subjected to flash column chromatography (pentane/Et_2O 3:1 to 2:1) to give aldehyde **38** (319 mg, 1.26 mmol, 70%) as colorless oil; R_f = 0.47 (pentane/Et_2O 1:1); $[\alpha]_D^{24}$ = +55.2 (*c* 1.01, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 2958, 2361, 1730, 1685, 1645, 1436, 1406, 1356, 1232, 1168, 1124, 1042, 994, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 9.36 (s, 1H), 6.43 (td, *J* = 7.3, 1.4 Hz, 1H), 3.69 (s, 3H), 2.63−2.51 (m, 2H), 2.30−2.18 (m, 3H), 2.15−1.96 (m, 2H), 1.84−1.74 (m, 2H), 1.72 (d, *J* = 1.1 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 216.0, 195.1, 170.6, 153.4, 139.7, 62.4, 51.9, 40.6, 38.6, 30.7, 28.1, 23.9, 15.8, 9.2; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{20}NaO_4$ $[M + Na]^+$: 275.1254, found 275.1255.

*Methyl (1R,5S,7R)-7-methyl-8-oxo-4-(1-oxopropan-2-yl)bicyclo-[3.2.1]octane-1-carboxylate (**39**).* A 0.2 M stock solution of $Me_3AlSPhLi$ was prepared by adding Me_3Al (2.0 M in toluene, 0.5 mL, 1.0 mmol) to a solution of PhSH (111 mg, 1.0 mmol) and *n*-BuLi (1.6 M in hexane, 0.63 mL, 1.0 mmol) in THF (3.8 mL) at 0 °C. To a solution of α,β-unsaturated aldehyde **38** (50 mg, 0.198 mmol, 1.0 equiv) in THF was added the stock solution (1.28 mL, 0.257 mmol, 1.3 equiv) and the mixture was stirred at 40 °C for 3 h before it was poured into saturated NH_4Cl solution. The layers were separated and the aqueous was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with water, dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 1:1) to give **39** as colorless oil (18.4 mg, 0.073 mmol, 37%, dr = 2:1); R_f = 0.28 (pentane/Et_2O 1:1); FTIR (neat) $\tilde{\nu}$ = 3487, 2954, 2875, 1750, 1725, 1450, 1380, 1341, 1295, 1274, 1231, 1194, 1030, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 9.54 (d, *J* = 3.3 Hz, 1H), 9.49 (d, *J* = 3.3 Hz, 1H), 3.72 (s, 6H), 2.50−2.08 (m, 12H), 1.98−1.87 (m, 2H), 1.82−1.70 (m, 2H), 1.62−1.48 (m, 2H), 1.44−1.35 (m, 2H), 1.09 (d, *J* = 6.6 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 7.1 Hz, 3H), 0.97 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 213.9, 213.4, 203.4, 203.1, 171.0, 170.9, 60.9, 60.4, 51.9, 49.8, 49.5, 49.1, 48.1, 46.7, 46.5, 38.2, 38.0, 36.2, 36.1, 28.8, 28.5, 23.5, 21.7, 21.1, 21.1, 12.3, 12.2; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{20}NaO_4$ $[M + Na]^+$: 275.12538, found 275.12529.

*Methyl (1R,2R)-2-methyl-5-oxo-1-(3-oxopropyl)cyclopentane-1-carboxylate (**40**).* To a solution of β-keto ester 7 (95 mg, 0.608 mmol, 1.0 equiv) in CH_2Cl_2 (5.0 mL) was added NEt_3 (128 μL, 0.912 mmol, 1.5 equiv), followed by acrolein (41 μL, 0.730 mmol, 1.2 equiv). The mixture was stirred at room temperature for 4 h. The clear

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solution was filtered through a short pad of silica gel and washed with Et_2O. The solvent was evaporated and the residue subjected to flash column chromatography (pentane/Et_2O 2:1) to give **40** (92.0 mg, 0.433 mmol, 71%) as colorless oil; R_f = 0.36 (pentane/Et_2O 1:1); $[\alpha]_D^{26}$ = +64.7 (*c* 1.04, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 2958, 2839, 2727, 2361, 1722, 1437, 1386, 1236, 1166, 1126, 1062, 996, 836, 763, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 9.74 (s, 1H), 3.68 (s, 3H), 2.91−2.76 (m, 1H), 2.60−2.45 (m, 2H), 2.31−2.00 (m, 4H), 1.99−1.84 (m, 1H), 1.83−1.67 (m, 1H), 1.03 (d, *J* = 6.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 216.3, 201.5, 170.7, 61.7, 52.1, 41.9, 39.3, 38.6, 28.3, 24.8, 15.9; HRMS (ESI) *m*/*z* calcd for $C_{11}H_{16}NaO_4$ $[M + Na]^+$: 235.0941, found 235.0940.

*Methyl (1R,2R)-1-(3-hydroxy-4-methylpent-4-en-1-yl)-2-methyl-5-oxocyclopentane-1-carboxylate (**41**).* To a solution of aldehyde **40** (61.0 mg, 0.287 mmol, 1.0 equiv) in THF (0.8 mL) at −78 °C was added isopropylmagnesium bromide solution (0.5 M in THF, 0.69 mL, 0.345 mmol, 1.2 equiv). The mixture was allowed to stir at −78 °C for 3 h, and was then quenched by addition of sat. aq. NH_4Cl solution. Water and Et_2O were added after warming up to room temperature and the layers were separated. The aqueous layer was extracted with Et_2O (2×) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 1:1) to give **41** (24.0 mg, 0.094 mmol, 33%) as colorless oil; R_f = 0.57 (pentane/Et_2O 1:2); $[\alpha]_D^{25}$ = +54.2 (*c* 0.78, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 3481, 2958, 2879, 2361, 1730, 1451, 1382, 1329, 1234, 1165, 1125, 1061, 996, 900, 678 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 4.97−4.93 (m, 1H), 4.87−4.82 (m, 1H), 4.02 (t, *J* = 6.3 Hz, 1H), 3.67 (s, 3H), 2.60−2.49 (m, 1H), 2.31−2.12 (m, 2H), 2.12−2.00 (m, 1H), 1.85−1.62 (m, 5H), 1.70 (s, 3H), 1.48−1.35 (m, 1H), 1.04 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 216.5, 171.1, 147.0, 111.5, 76.0, 62.7, 51.8, 40.1, 38.8, 29.3, 28.2, 27.7, 17.5, 15.8; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{22}NaO_4$ $[M + Na]^+$: 277.1410, found 277.1412.

*Methyl (1R,2R)-1-(3-hydroxypent-4-en-1-yl)-2-methyl-5-oxocyclopentane-1-carboxylate (**42**).* To a solution of aldehyde **40** (50.0 mg, 0.236 mmol, 1.0 equiv) in THF (1.0 mL) at −78 °C was added vinylmagnesium bromide solution (0.7 M in THF, 0.42 mL, 0.294 mmol, 1.25 equiv). The mixture was allowed to stir at −78 °C for 4 h, and was then quenched by addition of sat. aq. NH_4Cl solution. Water and Et_2O were added after warming up to room temperature and the layers were separated. The aqueous layer was extracted with Et_2O (2×) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 1:1) to give **42** (12.0 mg, 0.050 mmol, 21%) as colorless oil: R_f = 0.44 (pentane/Et_2O 1:3); $[\alpha]_D^{25}$ = +62.6 (*c* 0.52, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 3443, 3081, 2957, 2879, 2361, 1729, 1435, 1404, 1328, 1234, 1165, 1121, 1061, 994, 924, 883, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 5.84 (ddd, *J* = 17.1, 10.4, 6.0 Hz, 1H), 5.23 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.11 (dt, *J* = 10.4, 1.3 Hz, 1H), 4.06 (q, *J* = 5.7 Hz, 1H), 3.67 (s, 3H), 2.54 (ddd, *J* = 18.9, 8.6, 1.1 Hz, 1H), 2.30−2.13 (m, 2H), 2.11−2.01 (m, 1H), 1.92−1.84 (m, 1H), 1.83−1.61 (m, 4H), 1.44−1.34 (m, 1H), 1.04 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 216.6, 171.3, 140.8, 115.1, 73.2, 62.9, 51.9, 40.2, 38.9, 31.6, 28.3, 27.7, 15.9; HRMS (ESI) *m*/*z* calcd for $C_{13}H_{20}NaO_4$ $[M + Na]^+$: 263.1254, found 263.1255.

*Methyl (1R,2R)-1-(3-((4-methoxybenzyl)oxy)pent-4-en-1-yl)-2-methyl-5-oxocyclopentane-1-carboxylate (**43**).* To a solution of **42** (10.4 mg, 0.043 mmol, 1.0 equiv) and 4-methoxybenzyl-2,2,2-trichloroacetimidate (24.5 mg, 0.087 mmol, 2.0 equiv) in CH_2Cl_2 (1.0 mL) at 0 °C was added $Sc(OTf)_3$ (1.1 mg, 4 μmol, 5 mol %). The mixture was stirred for 1.5 h at 0 °C and then quenched with sat. aq. $NaHCO_3$ solution and diluted with Et_2O. The layers were separated and the aqueous was extracted with Et_2O (3×). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 2:1) to give **43** (13.7 mg, 0.038 mmol, 88%) as colorless oil; R_f = 0.53 (pentane/Et_2O 1:1); $[\alpha]_D^{26}$ = +28.7 (*c* 0.36, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 3728, 3728, 3703, 3629, 3600, 2956, 2361, 2340, 1749, 1613, 1513, 1459, 1301, 1246, 1174, 1065, 1035, 995, 823, 679 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.26−7.22 (m, 2H), 6.86 (dd, *J* = 8.8, 2.4 Hz, 2H), 5.69 (ddd, *J* = 17.1, 10.6, 7.6 Hz, 1H), 5.24 (d, *J* = 2.1 Hz, 1H), 5.20 (d, *J* = 8.7 Hz, 1H), 4.50 (d, *J* = 11.3 Hz, 1H), 4.28 (d, *J* = 11.3 Hz, 1H), 3.80 (s, 3H), 3.72−3.67 (m, 1H), 3.66 (s, 3H), 2.52 (dd, *J* = 18.7, 8.2 Hz, 1H), 2.32−2.21 (m, 1H), 2.21−2.11 (m, 1H), 2.08−1.98 (m, 1H), 1.90−1.66 (m, 4H), 1.36−1.26 (m, 1H), 1.02 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 216.5, 171.3, 159.2, 138.8, 130.9, 129.5, 117.7, 113.9, 80.6, 69.9, 63.0, 55.4, 51.9, 39.6, 39.1, 30.2, 28.3, 27.6, 16.0; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{28}NaO_5$ $[M + Na]^+$: 383.1829, found 383.1831.

*Methyl (1R,2R)-2-methyl-1-(4-methyl-3-oxopent-4-en-1-yl)-5-oxocyclopentane-1-carboxylate (**44**).* Dess−Martin periodinane (25 mg, 0.059 mmol, 1.5 equiv) was added to a cold (0 °C) solution of allylic alcohol **41** (10.0 mg, 0.039 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL). The mixture was stirred at room temperature for 1.5 h and then quenched by addition of sat. aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 2:1) to give enone **44** (8.0 mg, 0.032 mmol, 81%) as colorless oil; R_f = 0.86 (pentane/Et_2O 1:2); $[\alpha]_D^{25}$ = +31.7 (*c* 0.40, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 2958, 2362, 2340, 1730, 1677, 1631, 1455, 1375, 1337, 1236, 1168, 1123, 1094, 1068, 1037, 939 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 5.99 (s, 1H), 5.76 (d, *J* = 1.6 Hz, 1H), 3.69 (s, 3H), 3.06 (ddd, *J* = 16.9, 10.8, 4.9 Hz, 1H), 2.74 (ddd, *J* = 16.9, 10.9, 5.0 Hz, 1H), 2.54 (ddd, *J* = 18.9, 8.5, 1.9 Hz, 1H), 2.32−2.13 (m, 3H), 2.14−2.00 (m, 1H), 1.92 (ddd, *J* = 14.4, 10.8, 4.9 Hz, 1H), 1.86 (s, 3H), 1.83−1.67 (m, 1H), 1.04 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 216.6, 171.3, 147.1, 111.7, 76.1, 62.8, 51.9, 40.2, 38.9, 29.5, 28.3, 27.9, 17.6, 16.0; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{20}NaO_4$ $[M + Na]^+$: 275.12538, found 275.12535.

*Methyl (1R,2R)-2-methyl-5-oxo-1-(3-oxopent-4-en-1-yl)-cyclopentane-1-carboxylate (**45**).* Dess−Martin periodinane (38.2 mg, 90 μmol, 1.5 equiv) was added to a cold (0 °C) solution of allylic alcohol **42** (14.4 mg, 0.06 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL). The mixture was stirred at room temperature for 4 h and then quenched by addition of sat. aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$ solution. The layers were separated and the aqueous was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 2:1) to give enone **45** (9.4 mg, 39 μmol, 65%) as colorless oil; R_f = 0.53 (pentane/Et_2O 1:1); $[\alpha]_D^{25}$ = +39.6 (*c* 0.47, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 2959, 2361, 1728, 1617, 1436, 1404, 1236, 1168, 1123, 1067, 992, 907 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 6.34 (dd, *J* = 17.7, 10.2 Hz, 1H), 6.24 (dd, *J* = 17.6, 1.5 Hz, 1H), 5.83 (dd, *J* = 10.2, 1.5 Hz, 1H), 3.70 (s, 3H), 3.00 (ddd, *J* = 17.3, 10.7, 4.9 Hz, 1H), 2.66 (ddd, *J* = 17.3, 10.7, 5.0 Hz, 1H), 2.54 (ddd, *J* = 19.0, 8.6, 1.8 Hz, 1H), 2.32−2.14 (m, 3H), 2.13−2.03 (m, 1H), 1.92 (ddd, *J* = 14.5, 10.8, 4.9 Hz, 1H), 1.84−1.68 (m, 1H), 1.05 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 216.5, 200.2, 170.9, 136.5, 128.4, 61.9, 52.0, 42.2, 38.7, 34.7, 28.4, 26.9, 16.0; HRMS (ESI) *m*/*z* calcd for $C_{13}H_{18}NaO_4$ $[M + Na]^+$: 261.1097, found 261.1099.

*Methyl (1R,2R)-1-((E)-3-hydroxy-6-(trimethylsilyl)hex-4-en-1-yl)-2-methyl-5-oxocyclopentane-1-carboxylate (**46**).* To a degassed solution of allylic alcohol **42** (27.9 mg, 0.120 mmol, 1.0 equiv) and allyltrimethyl silane (137 mg, 0.120 mmol, 10 equiv) in CH_2Cl_2 (1.5 mL) was added Grubbs second generation catalyst (5.00 mg, 6 μmol, 5.0 mol %). The mixture was heated for 4 h at 40 °C and then filtered through a short pad of silica (eluted with CH_2Cl_2). The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (pentane/Et_2O 2:1 to 1:1) to give **46** (20.1 mg, 0.062 mmol, 51%) as colorless oil; R_f = 0.54 (pentane/Et_2O 1:3); $[\alpha]_D^{26}$ = +30.5 (*c* 1.01, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 3444, 2955, 2361, 1731, 1457, 1405, 1245, 1162, 1122, 1059, 996, 966, 849, 755, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 5.63 (dt, *J* = 15.6, 8.2 Hz, 1H), 5.28 (dd, *J* = 15.2, 7.4 Hz, 1H), 3.98 (q, *J* = 6.7 Hz, 1H), 3.66 (s, 3H), 2.53 (dd, *J* = 18.8, 8.5 Hz, 1H), 2.31−2.13 (m, 2H), 2.09−2.01 (m, 1H), 1.88−1.61 (m, 5H), 1.45 (d, *J* = 8.2 Hz, 2H), 1.35−1.26 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 3H), −0.01 (s, 9H); ^{13}C NMR (101 MHz,

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$CDCl_3$) δ = 216.5, 171.3, 131.2, 129.6, 73.7, 62.9, 51.9, 40.0, 39.0, 32.0, 28.3, 27.9, 22.9, 15.9, −1.8; HRMS (ESI) m/z calcd for $C_{17}H_{30}NaO_4Si$ $[M + Na]^+$: 349.1806, found 349.1805.

*Methyl (1R,2R)-2-methyl-5-oxo-1-((E)-3-oxo-6-(trimethylsilyl)hex-4-en-1-yl)cyclopentane-1-carboxylate (**48**).* To a degassed solution of enone **45** (9.4 mg, 0.039 mmol, 1.0 equiv) and allyltrimethyl silane (45 mg, 0.39 mmol, 10 equiv) in CH_2Cl_2 (0.5 mL) was added Grubbs second generation catalyst (1.65 mg, 2 μmol, 5.0 mol %) The mixture was heated for 1 h at 40 °C and then filtered through a short pad of silica (eluted with CH_2Cl_2). The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (pentane/Et_2O 3:1) to give **48** (9.2 mg, 0.028 mmol, 73%) as colorless oil; R_f = 0.58 (pentane/Et_2O 1:1); $[\alpha]_D^{25}$ = +21.6 (c 0.46, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 2956, 2921, 2361, 1730, 1660, 1613, 1436, 1408, 1380, 1328, 1292, 1246, 1196, 1167, 1125, 1040, 979, 847, 756, 698, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 6.97 (dt, J = 15.5, 8.8 Hz, 1H), 5.94 (dt, J = 15.7, 1.2 Hz, 1H), 3.69 (s, 3H), 2.84 (ddd, J = 16.1, 10.9, 4.9 Hz, 1H), 2.59−2.49 (m, 2H), 2.30−2.02 (m, 4H), 1.98−1.88 (m, 1H), 1.80−1.71 (m, 3H), 1.04 (d, J = 6.8 Hz, 3H), 0.05 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 216.5, 199.3, 171.0, 147.0, 128.6, 62.1, 52.0, 41.8, 38.7, 35.0, 28.3, 27.3, 25.4, 16.0, −1.6; HRMS (ESI) m/z calcd for $C_{17}H_{28}NaO_4Si$ $[M + Na]^+$: 347.1649, found 347.1650.

*Methyl (1R,2R)-2-methyl-1-(2-(4-methyl-2-oxo-2,5-dihydrofuran-3-yl)ethyl)-5-oxocyclopentane-1-carboxylate (**49**).* Ester **11** (516.0 mg, 1.25 mmol, 1.0 equiv) and $Fe(acac)_3$ (22.0 mg, 62.3 μmol, 5 mol %) were added to a dry and degassed solution of THF (12.0 mL) and NMP (0.6 mL) and the reaction mixture was cooled to −30 °C. The mixture was stirred for 10 min at this temperature and MeMgBr (3.2 M in THF, 545 μL, 1.74 mmol, 1.4 equiv) was rapidly added to the orange solution. The color of the mixture turned into a brown to green mixture, which finally resulted in a colorless solution with a brown precipitate. The reaction was quenched after 1 h with saturated NH_4Cl solution at −30 °C. The mixture was allowed to warm up to rt, water was added and the organic layer was separated. The aqueous layer was extracted with EtOAc (4 × 20 mL) and the combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (pentane/EtOAc 2:1 then 1:1) to obtain the desired β-methyl lactone **49** (333.9 mg, 1.19 mmol, 96%) as colorless oil; R_f = 0.24 (EtOAc/pentane 1:2); $[\alpha]_D^{25}$ = +61.0 (c 0.29, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 2985, 1743, 1678, 1451, 1228, 1166, 1032, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 4.61 (s, 2H), 3.69 (s, 3H), 2.59−2.45 (m, 2H), 2.42−2.32 (m, 1H), 2.29−2.08 (m, 3H), 2.05 (brs, 3H), 1.92−1.87 (m, 2H), 1.85−1.73 (m, 1H), 1.07 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 216.4, 174.9, 171.0, 157.7, 127.0, 72.7, 62.7, 52.0, 40.3, 38.9, 30.6, 28.4, 18.4, 16.1, 12.3; HRMS (ESI) m/z calcd for $C_{15}H_{21}O_5$ $[M + H]^+$: 281.1384, found 281.1383.

*Methyl (3aR,5aR,6R,8aR,8bS)-8a-hydroxy-6,8b-dimethyl-3-oxo-decahydro-5aH-indeno[4,5-c]furan-5a-carboxylate (**26**) and Methyl (1R,5R)-2-hydroxy-5-methyl-1-(2-(4-methyl-2-oxo-2,5-dihydrofuran-3-yl)ethyl)cyclopentane-1-carboxylate (**66**).* The methylester **49** (40.4 mg, 144 mmol, 1.0 equiv) was dissolved in dry THF (0.59 mL) and water (17.6 mL) (both solvents were separately freeze−thawed, three cycles). SmI_2 (3.60 mL, 360 mmol, 2.5 equiv, 0.1 M solution in THF) was added over 1 h at room temperature by syringe-pump and stirred for 12 h at room temperature. The colorless solution was quenched with Rochelle's salt (saturated, 1.3 mL) and stirred for 30 min at rt. The mixture was extracted with EtOAc (4 × 10 mL) and the combined organic layers were washed with brine (1 × 5 mL), dried over $MgSO_4$, filtered and evaporated to obtain a yellow oil. The mixture was purified by flash column chromatography Pentane/EtOAc (5:1, 4:1 then 2:1) to obtain the desired cyclized product **26** as white solid (20.5 mg, 50.4 mmol, 50%, dr 5:2) and reduced alcohol **66** (see Supporting Information) as colorless oil (15.8 mg, 38.9 mmol, 39%, dr = 10:1); the analytical data for the tricyclic product **26** matched those reported above. Analytical data for the alcohol byproduct **66**: colorless oil (39%); R_f = 0.17 (pentane/EtOAc 2:1); $[\alpha]_D^{26}$ = −47.4 (c 1.53, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 3468, 2956, 2869, 1721, 1676, 1448, 1261, 1191, 1091, 1036, 802 cm-1; ^1H NMR (600 MHz, $CDCl_3$) δ = 4.63 (bs, 2H), 4.58 (dd, J = 6.6, 2.9 Hz, 1H), 3.70 (s, 3H), 2.38−2.31 (m, 2H), 2.19 (t, J = 11.8 Hz, 1H) 2.09−2.04 (m, 1H), 2.04 (s, 3H), 1.99−1.92 (m, 2H), 1.66−1.60 (m, 2H), 1.25−1.18 (m, 1H), 0.89 (d, J = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 176.1, 174.7, 156.6, 127.4, 75.3, 73.0, 61.5, 51.3, 41.6, 32.7, 30.8, 29.7, 19.8, 15.8, 12.3; HRMS (ESI) m/z calcd for $C_{15}H_{22}O_5Na$ $[M + Na]^+$: 305.1359, found 305.1359.

*Methyl (1R,2R)-1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2-methyl-5-(propan-2-ylidene)-cyclopentane-1-carboxylate (**51**).* Freshly distilled diisopropylamine (20.0 mL, 135 mmol, 1.4 equiv) was added to dry THF (50 mL) and cooled to −78 °C. n-BuLi (1.6 M in hexane, 79.0 mL, 126 mmol, 1.3 equiv) was slowly added to the solution and stirred for 15 min at this temperature. The reaction mixture was allowed to warm up to 0 °C and was stirred for 1 h at this temperature. The solution was cooled to −78 °C, methyl (2R)-2-methyl-5-(propan-2-ylidene)cyclopentane-1-carboxylate (17.6 g, 97.0 mmol, 1.0 equiv) and dry DMPU (62.0 g, 59.0 mL, 483 mmol, 5.0 equiv) were added slowly to the solution and stirred for 15 min at this temperature and then for 1 h at 0 °C. The yellow solution was cooled to −78 °C and a solution of *tert*-butyl(2-iodoethoxy)dimethylsilane[43] (33.2 g, 116 mmol, 1.2 equiv) in dry THF (50 mL) was added to the reaction mixture. The mixture was stirred for 1 h at this temperature and then was allowed to warm up to rt over 1 h. The reaction was quenched with aq. HCl soln. (1 M, 200 mL). The aqueous layer was extracted with Et_2O (4 × 150 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (pentane/Et_2O 40:1, then 20:1 and 8:1) to afford the alkylated ester **51** (25.3 g, 74.4 mmol, 77%) as yellow oil; R_f = 0.24 (pentane/Et_2O 40:1); $[\alpha]_D^{26}$ = +37.8 (c 0.79, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 2953, 2933, 2858, 1727, 1462, 1434, 1253, 1218, 1186, 1155, 1095, 1004, 837, 775, 631 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 3.63 (s, 3H), 3.62−3.53 (m, 2H), 2.49 (dd, J = 15.4, 7.3 Hz, 1H), 2.29−2.17 (m, 2H), 2.17−2.04 (m, 1H), 1.96 (ddd, J = 14.2, 9.0, 6.4 Hz, 1H), 1.77−1.69 (m, 1H), 1.64 (d, J = 1.7 Hz, 3H), 1.62−1.53 (m, 1H), 1.50 (d, J = 1.7 Hz, 3H), 0.90−0.89 (m, 3H), 0.88 (s, 9H), 0.03 (d, J = 1.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.6, 137.7, 125.0, 60.4, 57.2, 51.4, 44.6, 36.9, 32.6, 32.2, 26.1, 22.4, 20.6, 18.4, 14.9, −5.1, −5.1; HRMS (ESI) m/z calcd for $C_{19}H_{37}O_3Si$ $[M + H]^+$ 341.2506, found 341.2507.

*Methyl (1R,2R)-1-(2-hydroxyethyl)-2-methyl-5-(propan-2-ylidene)cyclopentane-1-carboxylate (**52**).* The protected alcohol **51** (2.32 g, 6.81 mmol, 1.0 equiv) was dissolved in dry THF (50 mL) and cooled to 0 °C. Acetic acid (1.0 mL) and TBAF (1.0 M in THF, 6.81 mL, 6.81 mmol, 1.0 equiv) were slowly added. The solution was allowed to warm up to rt and stirred for 18 h. The solution was cooled to 0 °C and quenched with aq. sat. $NaHCO_3$ solution (80 mL). The aqueous layer was extracted with Et_2O (3 × 100 mL) and the combined organic layers were washed with brine (50 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude was purified by flash column chromatography (pentane/Et_2O 1:1) to obtain the alcohol **52** (1.22 g, 5.39 mmol, 79%) as a slightly yellow oil; R_f = 0.27 (pentane/Et_2O 1:1); $[\alpha]_D^{26}$ = +35.4 (c 0.43, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 3428, 2952, 2334, 1725, 1457, 1226, 1032, 891, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 3.75−3.62 (m, 2H), 3.66 (s, 3H), 2.52 (dd, J = 15.6, 7.1 Hz, 1H), 2.29−1.99 (m, 5H), 1.83−1.74 (m, 1H), 1.65 (d, J = 1.9 Hz, 3H), 1.54 (dd, J = 2.8, 1.0 Hz, 3H), 1.53−1.46 (m, 1H), 0.92 (d, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 177.3, 138.7, 125.5, 59.9, 57.4, 51.7, 44.6, 37.8, 32.8, 32.0, 22.5, 20.7, 15.3; HRMS (ESI) m/z calcd for $C_{13}H_{23}O_3$ $[M + H]^+$: 227.1642, found 227.1642.

*Methyl (1R,2R)-2-methyl-1-(2-oxoethyl)-5-(propan-2-ylidene)-cyclopentane-1-carboxylate (**53**).* Alcohol **52** (3.35 g, 14.8 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (150 mL), DMP (7.05 g, 16.3 mmol, 1.1 equiv) was added and the reaction mixture was stirred for 2 h at rt. Sat. aq. $NaHCO_3$ solution (50 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (5 × 50 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (pentane/Et_2O 4:1) to

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J. Org. Chem. 2016, 81, 11017−11034

obtain the aldehyde **53** (2.95 g, 13.2 mmol, 89%) as colorless oil; R_f = 0.38 (pentane/Et_2O 5:1); $[\alpha]_D^{25}$ = +23.6 (*c* 0.59, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 2952, 2735, 2361, 1722, 1457, 1222, 1058, 892, 767 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 9.66 (t, *J* = 2.9 Hz, 1H), 3.68 (s, 3H), 2.93 (dd, *J* = 16.1, 2.8 Hz, 1H), 2.74 (dd, *J* = 16.1, 3.1 Hz, 1H), 2.56 (dd, *J* = 15.8, 7.5 Hz, 1H), 2.31−2.13 (m, 2H), 1.89−1.79 (m, 1H), 1.66 (d, *J* = 1.7 Hz, 3H), 1.61 (m, 1H), 1.56 (dd, *J* = 2.6, 1.1 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 202.5, 175.3, 137.4, 126.6, 56.2, 51.9, 48.3, 45.9, 32.6, 32.0, 22.6, 20.7, 14.6; HRMS (ESI) *m*/*z* calcd for $C_{13}H_{21}O_3$ $[M + H]^+$: 225.1485, found 225.1485.

*Methyl (1R,2R)-1-(4-ethoxy-2,4-dioxobutyl)-2-methyl-5-(propan-2-ylidene)cyclopentane-1-carboxylate (**54**).* Ethyl diazoacetate (3.08 g, 26.4 mmol, 2.0 equiv) was dissolved in dry CH_2Cl_2 (25 mL), $SnCl_2$ (255 mg, 1.32 mmol, 0.1 equiv) was added and the reaction mixture was stirred at rt. A solution of the aldehyde **53** (2.95 g, 13.2 mmol, 1.0 equiv) in dry CH_2Cl_2 (30 mL) was added dropwise to the mixture. The color changed to yellow and formation of N_2 was observed. The reaction mixture was stirred for 12 h at rt, then it was diluted with CH_2Cl_2 (50 mL), filtered over Celite and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (pentane/Et_2O 7:1 to 2:1) to obtain the β-keto ester **54** (3.82 g, 12 mmol, 93%) as slightly orange oil; R_f = 0.24 (pentane/Et_2O 5:1); $[\alpha]_D^{25}$ = +49.6 (*c* 0.75, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 2950, 1717, 1644, 1454, 1306, 1224, 1183, 1155, 1033 cm^{-1}; (ratio keto ester/enol ester 10:1, only the data for the keto ester **54** is reported for the NMR set) ^1H NMR (400 MHz, $CDCl_3$) δ = 4.17 (q, *J* = 7.1 Hz, 2H), 3.65 (d, *J* = 1.8 Hz, 3H), 3.41 (d, *J* = 5.5 Hz, 2H), 3.23 (d, *J* = 16.7 Hz, 1H), 2.95 (d, *J* = 16.7 Hz, 1H), 2.57−2.41 (m, 2H), 2.41−2.25 (m, 1H), 1.85−1.73 (m, 1H), 1.66−1.61 (m, 3H), 1.55−1.46 (m, 1H), 1.52 (d, *J* = 1.5 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.85 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 201.2, 175.8, 167.3, 138.5, 124.6, 61.4, 56.9, 51.7, 50.8, 46.6, 43.6, 32.8, 31.9, 22.5, 20.5, 14.7, 14.2; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{27}O_5$ $[M + H]^+$: 311.1853, found 311.1855.

*6-Ethyl 3a-methyl (3R,3aR,6R)-6-chloro-3,7,7-trimethyl-5-oxo-2,3,4,5,6,7-hexahydro-3aH-indene-3a,6-dicarboxylate (**55**).* β-Keto ester **54** (40.0 mg, 129 μmol, 1.0 equiv) was dissolved in degassed Ac_2O (3.0 mL, freeze−thaw method, 3 cycles). Flame-dried LiCl (54.7 mg, 1.29 mmol, 10 equiv) was added and the reaction mixture was heated to 50 °C. $Mn(OAc)_3{\cdot}2H_2O$ (141 mg, 516 μmol, 4.0 equiv) was added and the reaction mixture was stirred for 5 h at this temperature. Dist. water (5 mL) was added and the mixture was extracted with EtOAc (5 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography (pentane/Et_2O 6:1 to 3:1) to obtain the oxo-dicarboxylate **55** (17.1 mg, 50 μmol, 39%) as white solid; mp 66.2−67.8 °C; R_f = 0.26 (pentane/Et_2O 6:1); $[\alpha]_D^{25}$ = −53.2 (*c* 0.73, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 2982, 2931, 1728, 1459, 1408, 1385, 1366, 1346, 1246, 1225, 1105, 1034, 979, 894, 833, 757, 708, 606 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 5.91−5.90 (m, 1H), 4.36−4.21 (m, 2H), 3.68 (s, 3H), 3.49 (d, *J* = 15.3 Hz, 1H), 2.99 (d, *J* = 15.5 Hz, 1H), 2.55−2.42 (m, 2H), 2.35−2.23 (m, 1H), 1.38 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.21 (s, 3H), 0.97 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 199.7, 173.9, 165.8, 146.1, 129.9, 79.0, 62.7, 60.2, 52.1, 50.8, 45.2, 43.6, 39.2, 24.1, 22.1, 14.2, 14.1; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{24}O_5Cl$ $[M + H]^+$: 343.1307, found 343.1308.

*6-Ethyl 3a-methyl (3R,3aR,5R,6R)-6-chloro-5-hydroxy-3,7,7-trimethyl-2,3,4,5,6,7-hexa-hydro-3aH-indene-3a,6-dicarboxylate (**56**).* The oxo-dicarboxylate **55** (1.05 g, 3.05 mmol, 1.0 equiv) was dissolved in dry MeOH (50 mL). The solution was cooled to 0 °C and $NaBH_4$ (294 mg, 7.63 mmol, 2.5 equiv) was added in small portions. The reaction mixture was stirred at 0 °C for 1 h, then the cooling bath was removed and the reaction mixture was allowed to stir for 3 h at rt. The reaction mixture was cooled to 0 °C and quenched with brine (50 mL). The aqueous layer was extracted with EtOAc (5 × 50 mL) and the combined organic layers were washed with brine (30 mL). The organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography (pentane/Et_2O 6:1 to 3:1) to afford the hydroxy-dicarboxylate **56** (904 mg, 2.6 mmol, 86%) as white solid; mp 82.1−83.0 °C; R_f = 0.14 (pentane/Et_2O 6:1); $[\alpha]_D^{26}$ = +42.4 (*c* 0.28, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 3457, 2967, 2929, 2338, 1734, 1692, 1450, 1409, 1384, 1363, 1284, 1239, 1193, 1105, 1088, 1032, 995, 912, 887, 853, 819, 757, 702, 627 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 5.87 (dd, *J* = 3.2, 1.7 Hz, 1H), 4.50 (s, 1H), 4.36−4.21 (m, 3H), 3.69 (s, 3H), 2.88 (dd, *J* = 14.7, 2.8 Hz, 1H), 2.42 (ddd, *J* = 14.9, 7.4, 3.1 Hz, 1H), 2.32−2.20 (m, 1H), 2.17 (ddd, *J* = 14.9, 10.3, 1.7 Hz, 1H), 2.03 (dd, *J* = 14.8, 3.7 Hz, 1H), 1.53 (s, 3H), 1.38−1.31 (m, 6H), 0.97 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.6, 170.7, 147.6, 129.6, 75.0, 74.2, 62.2, 56.4, 51.7, 49.9, 42.3, 38.9, 35.8, 26.5, 26.1, 14.7, 14.1; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{26}O_5Cl$ $[M + H]^+$: 345.1463, found 345.1462; X-ray crystal structure is given in the Supporting Information.

*9-Ethyl 5a-methyl (1R,4R,5aR,6R,9R)-9-chloro-1,6-dimethyl-1,2,4,5,6,7-hexahydro-5aH-1,4-methanocyclopenta[d]oxepine-5a,9-dicarboxylate (**57**) and 9-Ethyl 5a-methyl (1R,2R,4R,5aR,6R,9R)-2-acetoxy-9-chloro-1,6-dimethyl-1,2,4,5,6,7-hexahydro-5aH-1,4-methanocyclopenta[d]oxepine-5a,9-dicarboxylate (**58**).* Hydroxy-dicarboxylate **56** (3.48 g, 10.1 mmol, 1.0 equiv) was dissolved in degassed cyclohexane (200 mL, freeze−thaw method, 3 cycles). Pb(IV) acetate (11.5 g, 25.2 mmol, 2.5 equiv), iodine (6.54 g, 25.2 mmol, 2.5 equiv) and $CaCO_3$ (4.04 g, 40.4 mmol, 4.0 equiv) were added. The reaction mixture was stirred at rt under irradiation of Hg-light (low pressure lamp) for 3 days and Pb(IV) acetate (45.7 g, 101 mmol, 10 equiv), iodine (26.2 g, 101 mmol, 10 equiv) and $CaCO_3$ (10.3 g, 101 mmol, 10 equiv) were added in four equal portions (each 2.5 equiv) during this time. The violet reaction mixture was cooled to 0 °C and sat. aq. $Na_2S_2O_3$ (400 mL) was added until the mixture turned colorless. The mixture was extracted with EtOAc (4 × 200 mL), washed with brine (100 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude was purified by flash column chromatography (pentane/Et_2O 5:1 to 3:1) to afford the chloro-furan **57** (major product) (2.82 g, 8.2 mmol, 81%) as colorless solid and furan-acetate **58** (minor product) (600 mg, 1.5 mmol, 15%) as colorless solid; **57**: mp 96.5−97.1 °C; R_f = 0.16 (pentane/Et_2O 4:1); $[\alpha]_D^{25}$ = −50.5 (*c* 0.37, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 2961, 2945, 2906, 2360, 1736, 1721, 1453, 1383, 1228, 1081, 1031, 981, 936, 876, 772, 726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 5.83 (s, 1H), 4.71 (d, *J* = 4.8 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 1H), 3.85 (dd, *J* = 8.1, 0.8 Hz, 1H), 3.72−3.66 (m, 3H), 3.59 (d, *J* = 8.2 Hz, 1H), 3.07 (dd, *J* = 14.4, 4.9 Hz, 1H), 2.46−2.32 (m, 2H), 2.21−2.02 (m, 1H), 1.90 (d, *J* = 14.2 Hz, 1H), 1.35 (s, 3H), 1.29 (td, *J* = 7.1, 0.8 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.8, 168.5, 145.6, 129.8, 79.6, 73.7, 73.6, 62.4, 57.5, 51.8, 49.5, 48.7, 39.4, 37.0, 15.1, 14.1, 13.4; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{23}O_5ClNa$ $[M + Na]^+$: 365.1126, found 365.1125; X-ray crystal structure is given in the Supporting Information; **58**: mp 130.5−131.5 °C; R_f = 0.31 (pentane/Et_2O 2:1); $[\alpha]_D^{25}$ = +31.8 (*c* 0.57, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 2959, 1755, 1724, 1440, 1377, 1255, 1218, 1178, 1078, 1019, 991, 934, 882, 776, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 6.04−6.02 (m, 1H), 5.97 (s, 1H), 5.15 (d, *J* = 4.5 Hz, 1H), 4.33−4.18 (m, 2H), 3.73 (s, 3H), 3.12 (dd, *J* = 14.4, 5.2 Hz, 1H), 2.46−2.37 (m, 2H), 2.18−2.09 (m, 1H), 1.97 (s, 3H), 1.90 (dd, *J* = 14.5, 0.8 Hz, 1H), 1.43 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.4, 169.0, 168.0, 142.8, 132.9, 97.6, 80.1, 71.2, 62.4, 57.6, 54.0, 52.1, 48.5, 39.3, 36.0, 21.1, 15.2, 14.1, 12.5; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{25}O_7ClNa$ $[M + Na]^+$: 423.1181, found 423.1188; X-ray crystal structure is given in the Supporting Information.

Conversion of Acetyl-furan 58 to Chloro-furan 57. Acetyl-furan **58** (702 mg, 1.75 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (120 mL) and cooled to −78 °C. Triethylsilane (514 mg, 4.38 mmol, 2.5 equiv) and boron trifluoride etherate (621 mg, 4.38 mmol, 2.5 equiv) were added. The reaction mixture was stirred 1 h at −78 °C and then was allowed to warm up to rt over a period of 12 h. The reaction mixture was cooled to 0 °C and dist. water (80 mL) was slowly added. The mixture was extracted with Et_2O (3 × 80 mL), washed with brine (50 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude was purified by flash

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J. Org. Chem. 2016, 81, 11017−11034

column chromatography (pentane/Et_2O 4:1) to afford the chloro-furan **57** (525 mg, 1.53 mmol, 88%) as colorless solid.

*9-Ethyl 5a-methyl (1R,4R,5aR,6R,9S)-1,6-dimethyl-1,2,4,5,6,7-hexahydro-5aH-1,4-methanocyclopenta[d]oxepine-5a,9-dicarboxylate (**59**).* Chloro-furan **57** (483 mg, 1.41 mmol, 1.0 equiv) was dissolved in dry benzene (35 mL). $Sn(Bu)_3H$ (487 mg, 1.62 mmol, 1.15 equiv) and AIBN (23.9 mg, 0.14 mmol, 0.1 equiv) were added to the reaction mixture. The reaction mixture was heated to reflux and stirred for 2 h. The reaction was cooled to rt and then evaporated under reduced pressure. The residue was purified by flash column chromatography (pentane/Et_2O 3:1) to afford the hydro-furan **59** (411 mg, 1.34 mmol, 95%) as colorless oil; R_f = 0.16 (pentane/Et_2O 3:1); $[\alpha]_D^{25}$ = +9.0 (*c* 0.78, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 2955, 2880, 1725, 1450, 1378, 1337, 1196, 1155, 1049, 1023, 989, 925, 664, 627 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 5.72 (s, 1H), 4.56 (t, *J* = 5.2 Hz, 1H), 4.20−4.04 (m, 2H), 3.78 (d, *J* = 7.7 Hz, 1H), 3.69 (s, 3H), 3.46 (d, *J* = 7.7 Hz, 1H), 3.01 (dd, *J* = 14.2, 4.7 Hz, 1H), 2.83 (dd, *J* = 5.9, 1.1 Hz, 1H), 2.39−2.23 (m, 2H), 2.13−2.03 (m, 1H), 1.71 (d, *J* = 14.5 Hz, 1H), 1.35 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.3, 169.7, 145.8, 126.6, 77.4, 76.7, 60.3, 58.3, 55.7, 51.7, 48.9, 44.8, 39.0, 37.7, 17.4, 15.2, 14.4; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{25}O_5$ $[M + H]^+$: 309.1697, found 309.1698.

*6-Ethyl 3a-methyl (3R,3aR,6S,7R)-5-acetoxy-7-(acetoxymethyl)-3,7-dimethyl-2,3,4,5,6,7-hexahydro-3aH-indene-3a,6-dicarboxylate (**60**) and 6-Ethyl 3a-methyl (3R,3aS,7R)-7-(acetoxymethyl)-3,7-dimethyl-2,3,6,7-tetrahydro-3aH-indene-3a,6-dicarboxylate (**61**).* Hydro-furan **59** (44.7 mg, 145 μmol, 1.0 equiv) was dissolved in Ac_2O (0.9 mL). The solution was cooled to −20 °C and boron trifluoride etherate (56.2 μL, 435 μmol, 3.0 equiv) was added. The reaction was allowed to warm up to rt over 12 h. The reaction mixture was cooled to 0 °C and dist. water (1.0 mL) was added dropwise. The reaction mixture was stirred for 10 min and warmed up to rt. The mixture was extracted with Et_2O (3 × 1.5 mL), washed with brine (1.5 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography (pentane/Et_2O 2:1) to afford the diacetylated compound **60** (35.4 mg, 87 μmol, 60%) as a yellow oil and the monoacetylated compound **61** (31.7 mg, 46 μmol, 32%) as colorless oil; **60:** R_f = 0.17 (pentane/Et_2O 2:1); $[\alpha]_D^{25}$ = +8.9 (*c* 0.34, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 3480, 2956, 1727, 1440, 1367, 1224, 1028, 908, 790, 664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 5.83 (s, 1H), 5.30−5.23 (m, 1H), 4.19−4.03 (m, 2H), 3.77 (d, *J* = 11.3 Hz, 1H), 3.70 (d, *J* = 11.4 Hz, 1H), 3.65 (s, 3H), 3.13 (d, *J* = 5.4 Hz, 1H), 2.65 (dd, *J* = 12.3, 4.8 Hz, 1H), 2.51−2.36 (m, 2H), 2.26−2.14 (m, 1H), 2.07 (s, 3H), 2.03−1.97 (m, 1H), 1.99 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.15 (s, 3H), 0.94 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.3, 170.9, 170.8, 169.9, 143.3, 131.1, 68.8, 68.7, 60.3, 59.5, 51.8, 49.5, 49.1, 40.5, 39.1, 34.5, 21.5, 21.1, 21.0, 14.5; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{30}O_8Na$ $[M + Na]^+$: 433.1833, found 433.1835; **61:** R_f = 0.32 (pentane/Et_2O 2:1); $[\alpha]_D^{26}$ = +223.8 (*c* 0.14, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 2957, 1725, 1454, 1372, 1320, 1222, 1141, 1033, 793 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 6.22 (d, *J* = 10.0 Hz, 1H), 5.82 (s, 1H), 5.58 (dd, *J* = 10.0, 5.1 Hz, 1H), 4.14−4.01 (m, 2H), 3.92 (d, *J* = 10.9 Hz, 1H), 3.74 (d, *J* = 10.9 Hz, 1H), 3.65 (s, 3H), 3.15 (d, *J* = 5.1 Hz, 1H), 2.48−2.29 (m, 3H), 2.04 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.19 (s, 3H), 1.03 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.1, 171.3, 170.9, 143.3, 132.3, 129.8, 122.1, 68.3, 60.8, 59.3, 51.8, 50.2, 47.9, 39.7, 38.8, 21.0, 19.4, 14.4, 14.3. HRMS (ESI) *m*/*z* calcd for $C_{19}H_{27}O_6$ $[M + H]^+$: 351.1802, found 351.1800.

*6-Ethyl 3a-methyl (3R,3aR,6S,7R)-5-hydroxy-7-(hydroxymethyl)-3,7-dimethyl-2,3,4,5,6,7-hexahydro-3aH-indene-3a,6-dicarboxylate (**62**).* The diacetyled product **60** (38.7 mg, 94.3 μmol, 1.0 equiv) was dissolved in dry MeOH (1.5 mL), K_2CO_3 (53.2 mg, 0.38 mmol, 4.0 equiv) was added and the reaction mixture was stirred at rt for 16 h. The reaction mixture was diluted with EtOAc (5.0 mL), aq. HCl (1 M, 2.0 mL) was added and the mixture was extracted with EtOAc (3 × 2.0 mL). The combined organic layers were washed with brine (1.5 mL), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (pentane/EtOAc 1:1) to afford the diol **62** (30.1 mg, 92 μmol, 98%) as colorless sticky oil; R_f = 0.45 (pentane/EtOAc 1:1); $[\alpha]_D^{25}$ = −1.9 (*c* 0.25, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 3448, 2954, 1721, 1448, 1178, 1027, 885, 780, 710, 660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 5.86 (s, 1H), 4.20−4.04 (m, 3H), 3.70 (s, 3H), 3.20 (d, *J* = 11.3 Hz, 1H), 3.07 (d, *J* = 11.3 Hz, 1H), 2.70−2.60 (m, 2H), 2.51−2.40 (m, 2H), 2.22−1.88 (m, 4H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.17 (s, 3H), 0.96 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.4, 171.5, 142.5, 132.8, 66.6, 66.3, 60.4, 59.9, 54.3, 52.2, 48.6, 43.0, 39.0, 37.8, 21.4, 14.7, 14.4; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{26}O_6Na$ $[M + Na]^+$: 349.1622, found 349.1626.

*6-Ethyl 3a-methyl (3R,3aR,7S)-7-formyl-5-hydroxy-3,7-dimethyl-2,3,4,7-tetrahydro-3aH-indene-3a,6-dicarboxylate (**63**).* To a flask charged with flame-dried molecular sieves (4 Å, 120 mg) was added a solution of the diol **62** (58.1 mg, 178 μmol, 1.0 equiv) in dry CH_2Cl_2 (5.0 mL). NMO (56.0 mg, 0.46 mmol, 2.6 equiv) was added at rt and the reaction mixture was stirred for 20 min. TPAP (12.9 mg, 35 μmol, 0.2 equiv) was added and the solution was stirred at rt for 24 h, while the color turned from green to dark blue. The reaction mixture was filtered over Celite and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (pentane/Et_2O 3:1) to yield the enol **63** (39.0 mg, 0.12 mmol, 68%) as colorless oil; R_f = 0.39 (pentane/Et_2O 3:1); $[\alpha]_D^{25}$ = −124.9 (*c* 0.61, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 2960, 2934, 2848, 1728, 1642, 1607, 1458, 1402, 1297, 1228, 1076, 863, 732, 631 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 12.94 (s, 1H), 9.13 (s, 1H), 5.98 (s, 1H), 4.27−4.12 (m, 2H), 3.63 (s, 3H), 3.25 (d, *J* = 16.4 Hz, 1H), 2.54 (ddd, *J* = 15.3, 7.3, 3.1 Hz, 1H), 2.37−2.19 (m, 2H), 2.16 (d, *J* = 16.3 Hz, 1H), 1.47 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.3, 175.8, 172.8, 171.5, 141.3, 133.3, 99.0, 61.1, 60.2, 51.9, 50.8, 46.4, 39.8, 38.9, 22.7, 15.0, 14.1; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{23}O_6$ $[M + H]^+$: 323.1489, found 323.1490.

*6-Ethyl 3a-methyl (3R,3aR,7S)-7-formyl-6-hydroxy-3,7-dimethyl-5-oxo-2,3,4,5,6,7-hexa-hydro-3aH-indene-3a,6-dicarboxylate (**64**).* The enol **63** (89.0 mg, 276 μmol, 1.0 equiv) was dissolved in dry *i*-PrOH (5 mL), then degassed (freeze−thaw method, 2 cycles) and refilled with oxygen. $CeCl_3{\cdot}7H_2O$ (105 mg, 276 μmol, 1.0 equiv) was added at rt and oxygen was bubbled through the colorless solution for 15 min. The solution was stirred under oxygen atmosphere at rt for 20 h. Dist. water (5 mL) was added, the mixture was extracted with EtOAc (3 × 5 mL), the combined organic layers were washed with brine (3 mL), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography (pentane/Et_2O 2:1) to afford the α-hydroxylated product **64** (40 mg, 119 μmol, 43%) as colorless oil; R_f = 0.37 (pentane/Et_2O 1:1); $[\alpha]_D^{25}$ = −68.8 (*c* 0.53, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 3454, 2959, 1724, 1453, 1373, 1217, 1162, 1099, 1001, 916, 859, 732, 653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 9.40 (s, 1H), 6.11 (s, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.91 (s, 1H), 3.64 (s, 3H), 3.51 (d, *J* = 14.7 Hz, 1H), 2.84 (d, *J* = 14.7 Hz, 1H), 2.59−2.45 (m, 2H), 2.32−2.20 (m, 1H), 1.40 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 202.8, 197.3, 172.5, 170.4, 138.8, 135.1, 82.9, 63.8, 61.1, 58.7, 52.2, 50.6, 44.4, 39.3, 14.6, 14.5, 14.1; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{23}O_7$ $[M + H]^+$: 339.1438, found 339.1441.

*(3aR,4R,6aR,7R,9bR)-3a-Hydroxy-7,9b-dimethyl-1,3a,4,7,8,9b-hexahydro-3H,6H-4,6a-methanocyclopenta[c]furo[3,4-e]oxepine-3,6-dione (**65**).* The α-hydroxylated ketone **64** (21.3 mg, 63.0 μmol, 1.0 equiv) was dissolved in dry MeOH (1.0 mL) and cooled to 0 °C. $NaBH_4$ (11.9 mg, 315 μmol, 5.0 equiv) was added in small portions and the reaction mixture was allowed to warm up to rt over 11 h. The reaction mixture was cooled to 0 °C and dist. water (1.5 mL) was added. The aq. layer was extracted with EtOAc (4 × 1.5 mL), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to afford the crude diol as colorless solid. The crude diol (21 mg, 70.9 μmol, 1.0 equiv) was dissolved in dry toluene (1.0 mL) and *p*-toluensulfonic acid monohydrate (2.7 mg, 14.2 μmol, 0.2 equiv) was added. The reaction mixture was stirred at 77 °C for 2 h. The reaction mixture was diluted with EtOAc (3 mL) and washed with aq. sat. $NaHCO_3$ solution (2.0 mL). The aq. layer was extracted with EtOAc

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J. Org. Chem. 2016, 81, 11017−11034

(3 × 1.5 mL), the combined organic layers were washed with brine (1.5 mL), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (pentane/EtOAc 3:1) to afford the dilactone **65** (4.4 mg, 17 μmol, 27%, over two steps) as white solid; mp 129.5−130.2 °C; R_f = 0.53 (pentane/EtOAc 2:1); $[\alpha]_D^{25}$ = +75.0 (*c* 0.47, $CHCl_3$); FTIR (neat) $\tilde{\nu}$ = 3448, 2921, 2851, 1782, 1753, 1457, 1376, 1326, 1221, 1185, 1113, 1016, 1000, 938, 818, 732, 639 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 5.87 (s, 1H), 4.63 (d, *J* = 5.9 Hz, 1H), 3.98 (q, *J* = 9.5 Hz, 2H), 2.58 (ddd, *J* = 15.6, 8.1, 2.9 Hz, 1H), 2.48 (dd, *J* = 11.9, 5.9 Hz, 1H), 2.44−2.37 (m, 1H), 2.32 (ddd, *J* = 15.5, 9.7, 1.9 Hz, 1H), 2.21 (d, *J* = 12.1 Hz, 1H), 1.36 (s, 3H), 1.32 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 177.7, 174.9, 140.6, 129.8, 78.9, 78.0, 74.4, 56.6, 43.3, 39.2, 37.0, 35.0, 21.4, 13.3; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{16}O_5Na$ $[M + Na]^+$: 287.0890, found 287.0894.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02039.

Reaction conditions for the oxidation of compound **33**; ^1H and ^{13}C NMR spectra; X-ray crystal structure analysis data (PDF)

Crystal data (CIF)

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Notes

The authors declare no competing financial interest.

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