JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

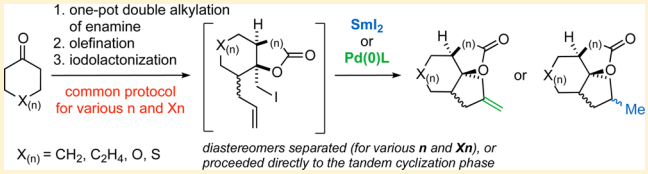
Synthesis of Tricyclic Spiranoid Lactones via I_2/Sm(II)- and I_2/Pd(0)-Mediated Cyclizations of a Common Cycloalkylmethylene Precursor

Yelena Mostinski,[‡] Viviana Valerio,[‡] David Lankri, and Dmitry Tsvelikhovsky*

The Institute for Drug Research, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem 91120, Israel

Supporting Information

ABSTRACT: A general synthesis of phylogenetically and structurally different tricyclic angularly fused spiranoid lactones, frequently observed as scaffold segments of various biochemical compounds and drugs of natural origin, is demonstrated via controlled cyclization of simple and easily accessible cycloalkylmethylene key precursors. The rapid composition of the key architecture yields an assembly of stable bicyclic iodolactones, which are converted to form a wide range of angularly fused tricyclic scaffolds.



INTRODUCTION

Tricyclic spirofuranone ring structures can frequently be observed as scaffold segments of various biochemical compounds and drugs of natural origin.[1] Examples of these structures have been identified among carbohydrates, terpenoids, alkaloids, glycosides, and antibiotics. Numerous studies have led to a wide variety of potential pharmaceutical candidates that share the compact tricyclic systems, as alliacanes,[2] arteannuins,[3] teucrolivins,[4] and many others.[5] Such a broad natural diversity and biological activity present in a wide spectrum of these systems make them attractive targets for synthetic chemists. Some distinct examples of families of natural products, all containing multiple tricyclic angularly fused spiranoid lactone frames despite having different biological origins, are shown in Figure 1.

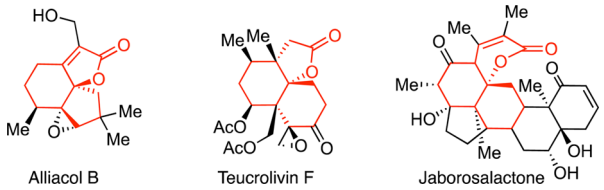
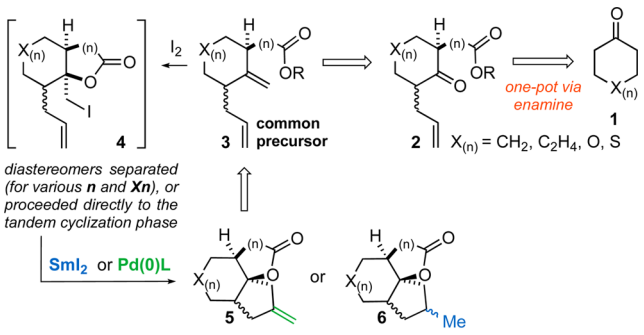


Figure 1. Natural products from diverse biological origins share tricyclic spiranoid ring systems.

Unfortunately, access to a large number of these target molecules and their structural analogues is either unknown or hindered by their multistep syntheses.[6] Thus, there is a need for an efficient, concise, and universal protocol to provide access to a diverse range of natural and artificial structural derivatives (potential therapeutic agents and drug candidates). To the best of our knowledge, a general approach toward the construction of quaternary carbon-centered tricyclic spiranoid lactones has yet to be reported. Here, our approach was to unite the families of described molecular frames under a common synthetic strategy and devise a simple means for building the tricyclic skeletons in a rapid and efficient manner.

There is remarkable overlap in the structures of the above-mentioned natural products. We realized that most of the tricyclic spiranoid lactones might be derived from a simple and common (or highly similar) collective precursor via a controlled intramolecular sequence of transformations.[7] We operated on the assumption that 1,3-disubstituted cycloalkylmethylene scaffold **3** (Scheme 1), which can be obtained in two steps from cyclic ketone **1**, could serve as an operationally acceptable collective key precursor for the construction of tricyclic spiranoid lactones. Our retrosynthetic analysis was cognizant of this framework and hypothesized that the desired

Scheme 1. General Strategy for Rapid Composition of Tricyclic Spiranoid Lactones



System functionality:
- Common methodology
- Early-step prediction and design of the ring system functionality
- Availability for post-synthetic modifications of the designed frames
- SmI_2 - mediated coupling of alkyl iodides with unactivated alkenes
- First time optimized for sequential alkylation of **1** with two different electrophiles

Received: June 7, 2015
Published: October 5, 2015

DOI: 10.1021/acs.joc.5b01278
J. Org. Chem. 2015, 80, 10464−10473

tricyclic systems might be successfully constructed through simple and straightforward cyclizations.

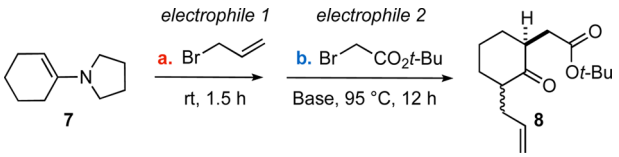
The virtues of the "rapid composition" concept can be clearly demonstrated in the following order: (1) α,α'-double enamine alkylation of cyclic ketone (first time optimized in this work in a one-pot mode for a variety of cyclic ketones),[8] (2) olefination (access to the key precursor), and (3) I_2/ML-mediated cyclization sequence to obtain the desired frames. The novel strategy is based on the notion that, in the presence of I_2 and a metal−ligand system (Pd^0L or SmI_2), designed key precursor **3** will generate lactone intermediate **4** and further undergo an intramolecular cyclization to form the corresponding tricyclic spiranoid lactones **5** or **6**.

RESULTS AND DISCUSSION

To illustrate the model, we prepared intermediate scaffolds of type-**2** (Scheme 1) through the double enamine α,α'-alkylation of cyclic ketones with *t*-Bu-bromoacetate and allyl bromide, followed by further methylenation to generate the key-precursors of type **3**.[9] The enamines of cyclohexanone, cycloheptanone, tetrahydro-pyranone, and tetrahydro-thiopyranone were selected as starting materials.[10]

Intriguingly, after reviewing the available literature, we did not find any reports of general protocols for tandem one-pot α,α'-dialkylation of cyclic ketones via enamine intermediate with two different electrophiles.[8] Our assumption was that base and solvent are the two factors having the most significant effect on the course of the reaction (Table 1). The assessment

Table 1. Sequential Alkylation of Cyclic Enamine with Two Different Electrophiles[a]



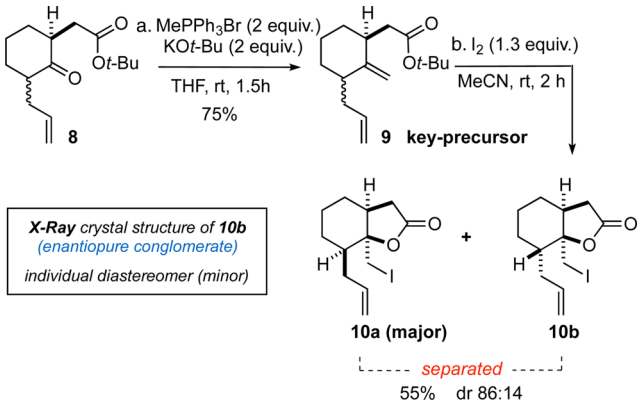
#	solvent	base	GC yield %
1	MeCN		<1
2	MeCN	TEA	6
3	MeCN	Py	<1
4	MeCN	pyrrolidine	<1
5	MeCN	Cs_2CO_3	<1
6	MeCN	DIEA	58 (55)[b]
7	dioxane	DIEA	48
8	toluene	DIEA	32

[a]Reagents and conditions: (a) allyl bromide (1.0 equiv), 1 M solution of enamine (1.0 equiv), rt, 1.5 h; (b) base (1.0 equiv) added in a single portion, *t*-Bu-2-bromo-acetate (1.0 equiv), 95 °C, 12 h. The mixture was quenched with water (stirred for 1.5 h at reflux). [b]Isolated yield, 5 g scale. Monoallylated and α,α'-diallylated ketone are the main byproducts.

of these variables led us to discover that the mode of sequential alkylation was mostly dependent on the base employed. We examined a variety of bases and found that DIEA was highly effective for such transformation to form the desired intermediate. To simplify, the first alkylation of an enamine was directly followed by addition of DIEA and alkyl-bromoacetate in one-pot to obtain the corresponding α,α'-dialkylated product as an inseparable mixture of diastereoisomers.[11]

Scheme 2 details the step-by-step synthetic protocol for the construction of stable and easily separable iodolactone scaffolds

Scheme 2. Synthesis of the Key Precursor and Corresponding Iodolactones[a]



[a]Reagents and conditions: (a) compound **8** (1.0 equiv) in THF, $MePh_3PBr$ (2.0 equiv), KO*t*-Bu (2.0 equiv), rt, 1.5 h; (b) precursor **9** (1.0 equiv) in MeCN, I_2 (1.25 equiv), rt, 2h. The diastereomeric ratios were determined by ^1H NMR and GCMS of the crude mixtures.

10a and **10b** in a rapid and efficient manner via iodolactonization of key precursor **9**.[12] The diastereomeric ratio, set by the enamine double alkylation reaction, was clearly disclosed at this stage.[13]

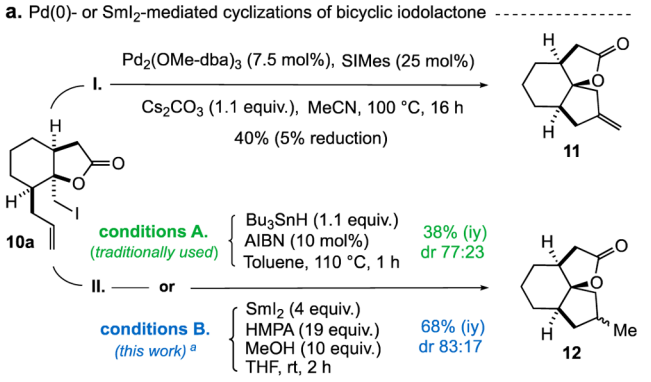
The proof-of-concept was tested through the use of single diastereomer **10a** (Scheme 3a). Following the Pd(0)/L-catalyzed C−C bond formation (Pathway **I**), **10a** yields the desired tricyclic angularly fused product **11** in 40%.[14] In comparison with the $Pd_2(OMe\text{-}dba)_3$/SIMes/Cs_2CO_3/MeCN system, which was optimal for the desired alkyl-Heck reaction, other combinations, such as $Pd_2(dba)_3$/SiMes, $Pd_2(dba)_3$/(*t*-Bu_3)P-HBF_4, $Pd_2(OMe\text{-}dba)_3$/(*t*-Bu_3)P-HBF_4, and $Pd_2(dba)_3$/XPhos with a variety of bases, were less effective. Alternatively, in the presence of Bu_3SnH or SmI_2 (Pathway **II**), the same compound **10a** underwent a radical 5-exo cyclization to yield the additional tricyclic target **12**.[15] Thus, an individual diastereomer can generate two conceptually different products by simple means of metal−ligand system substitution.

The presence of an exomethylene in the Heck products (in contrast to the fixed topology of the Sm products) makes these compounds suitable for further manipulations, such as oxidation, epoxidation, halogenations, cross-coupling, and many others, to achieve more complex compounds. The efficiency of the SmI_2-mediated cyclization (Scheme 3a, path **II**, conditions **B**) is particularly noteworthy considering that only a few examples involving reactions of alkyl radicals with alkenes have been reported. In the previously reported systems, alkyl halides are commonly reacted with activated π-acceptors,[16] whereas the coupling with unactivated alkenes occurs via sequential coupling/elimination or carbonyl addition reactions (for examples of traditional SmI_2-mediated reactions of alkyl iodides with alkenes, see Scheme 3b).[17]

Using other designed blocks and general conditions in hand, we tested the assumption that, collectively, the strategy allows for the preparation of variable tricyclic scaffolds of angularly fused spiranoid lactones. Thus, other precursors with diverse ring topologies (Schemes 4 and 5) were targeted using the optimized conditions. The diastereomeric ratio of each

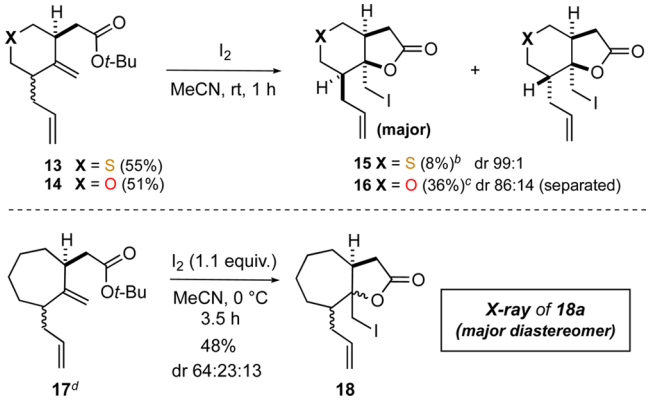
DOI: 10.1021/acs.joc.5b01278
J. Org. Chem. 2015, 80, 10464−10473

Scheme 3. Generation of Different Spiranoid Lactones by Metal−Ligand System Substitution[a]



[a]Optimized for SmI_2-mediated coupling of alkyl iodide with unactivated alkene. The diastereomeric ratio was determined by ^1H NMR and GCMS of the crude mixtures.

Scheme 4. Synthesis of Bicyclic γ-Iodolactones[a]



[a]All diastereomers were separated to obtain individual iodolactones. [b]Using 10 equiv of I_2. [c]Using 1.1 equiv of I_2. [d]Cycloheptanone was dialkylated in a stepwise fashion (see Experimental Section).

designed pair of iodolactones was calculated by GC and NMR of the crude reaction mixture and was dependent on the nature of the starting ketone ring and the functionalities installed.

It should be noted that all of the mixtures of bicyclic diastereomers were separated by column chromatography or crystallization to obtain individual diastereomeric iodolactones. Gratifyingly, single diastereomeric precursors carrying rings derived from hexa- or heptanones as well as rings integrated with heteroatoms were efficiently transformed into the corresponding angularly fused spiranoid lactones (compounds **23**−**25**, **29**, and **30**; Table 2). Similarly, *cis*- and *trans*-δ-lactones **22a**−**c**, generated by iodolactonization of key precursor **21** (Scheme 5), were converted to the stereodiverse sets of 6′6′5-ring systems (compounds **26**−**28** and **31**−**33**; Table 2).[18]

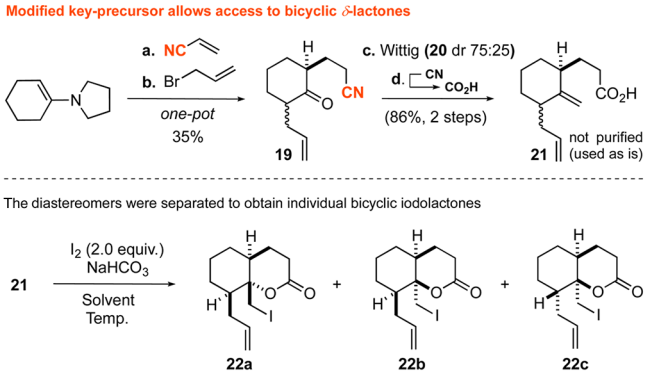
It should be mentioned that the stereochemical features of most prepared dialkylated ketones cannot be assigned because the individual isomers are not clearly identified by either GCMS or NMR analysis and are not separable by column chromatography under any set of conditions. However, the individual diastereomers of dialkylated ketone **19** (detected by GC and NMR) were clearly separated by column chromatography at a ratio of 80:20. Upon further Wittig olefination, performed on the above-mentioned mixture of diastereomeric ketones, GCMS and NMR analysis of the crude reaction mixture (compound **21**) revealed a diastereomeric ratio of 77:23. Assuming that such behavior might be equally addressed to other (structurally similar) reported dialkylated ketones, we can conclude that the basic conditions of the Wittig reaction only slightly influence the diastereomeric ratio already set by the enamine dialkylation reaction at the earlier stage. Further lactonization (under the optimized conditions) of precursor **21** delivered a stereodiverse mixture of bicyclic δ-lactones **22a**−**c** in 56% yield and 41:36:23 dr. Reasoning that major factors such as base, solvent, and temperature would have the most significant effect on the diastereoselective course of the iodolactonization reaction, we conducted a number of experiments identifying the most selective set of mentioned variables. Performing the lactonization reaction under kinetic control[19] at 0 °C in MeCN with no addition of base led us to discover that individual δ-lactone **22b** could be obtained, although with low yield and poor conversion of the starting precursor (Scheme 5, entry 8). The highest yield, conversion, and stereodiversity were obtained under the conditions outlined in entry 5 (finally adopted in our study).

A limitation of our strategy is encountered with S-containing bicyclic iodolactone **15**. The commercially available tetrahydro-4*H*-thiopyran-4-one generates the corresponding key precursor in acceptable yield over two steps, but further halolactonization toward **15** proved to be problematic. To overcome this limitation, we attempted oxidation of the key precursor to the corresponding sulfone. Unfortunately, low yields were also obtained in this case. The use of excess I_2 was not beneficial because of the prompt decomposition of the formed iodolactone under these conditions.

Having established a modular stepwise sequence for the assembly of tricyclic scaffolds from components of similar synthetic complexity, we next demonstrated the versatility of the methodology for the tandem synthesis of the desired motifs without isolation of the iodolactone intermediate. In this scenario, for illustration, easily accessible key precursor **9** was lactonized and immediately subjected to cyclization conditions without purification, thus generating the product frames **11** or **12** in a noninterrupted fashion (Scheme 6). Factors controlling yield, conversion, and selectivity were thoroughly examined. We were pleased to learn that the same set of conditions, previously developed to facilitate stepwise synthesis, can be applied to one-pot reactions and deliver equally successful outcomes. Indeed, compounds **12** and **11** were obtained in 31 and 30% yields, respectively, as compared with the corresponding 37 and 22% yields calculated from key precursor **9** in the stepwise protocol.

DOI: 10.1021/acs.joc.5b01278
J. Org. Chem. 2015, 80, 10464−10473

Scheme 5. Synthesis of Stereodiverse Bicyclic δ-Iodolactones[a]



#	Solvent	Temp. °C	Time	$NaHCO_3$ (equiv.)	dr 22a:22b:22c	Comments
1	DCM	0	2 h	5.2	-	reduction + **21**
2	DCM	r.t	2 h	5.2	-	reduction + **21**
3	MeCN	0	2 h	5.2	49:28:23	100% conv.
4	MeCN	r.t	2 h	5.2	46:34:20	100% conv.
5	MeCN	50	1.5 h	5.2	41:36:23	100% conv. (56% iy)
6	MeCN	50	2 h	-	-	reduction + **21**
7	MeCN	r.t	2 h	-	-	reduction + **21**
8	MeCN	0	2 h	-	1:98:1	20% conv.

[a]Reagents and conditions: (a) acrylonitrile (1.0 equiv), 1 M solution of enamine (1.0 equiv), reflux, 2 h; (b) DIPEA (1.0 equiv), allylbromide (1.0 equiv), 40 °C, 12 h; the mixture was quenched with water (stirred for 1 h at reflux); (c) $MePh_3PBr$ (2.0 equiv), KOt-Bu (2.0 equiv), THF, rt, 2 h; (d) 65% aq NaOH (20.0 equiv.), EtOH, 80 °C, 3 h.

CONCLUSIONS

As demonstrated above, we have successfully developed a versatile methodology for the construction of numerous combinations of angularly fused tricyclic lactones via (1) first time optimized one-pot double alkylation of enamines with two different electrophiles, (2) further methylenation to generate the cycloalkylmethylene core, and finally (3) I_2/Sm(II)- and I_2/Pd(0)-mediated cyclization of the key precursor. Our methodology allows rapid access (the shortest sequence reported to date) to a mixture of easily separable diastereomeric iodolactones, which are converted to form a wide range of angularly fused tricyclic scaffolds. These compounds closely resemble common natural scaffolds and carry potential for becoming valuable drugs/therapeutic agents.

EXPERIMENTAL SECTION

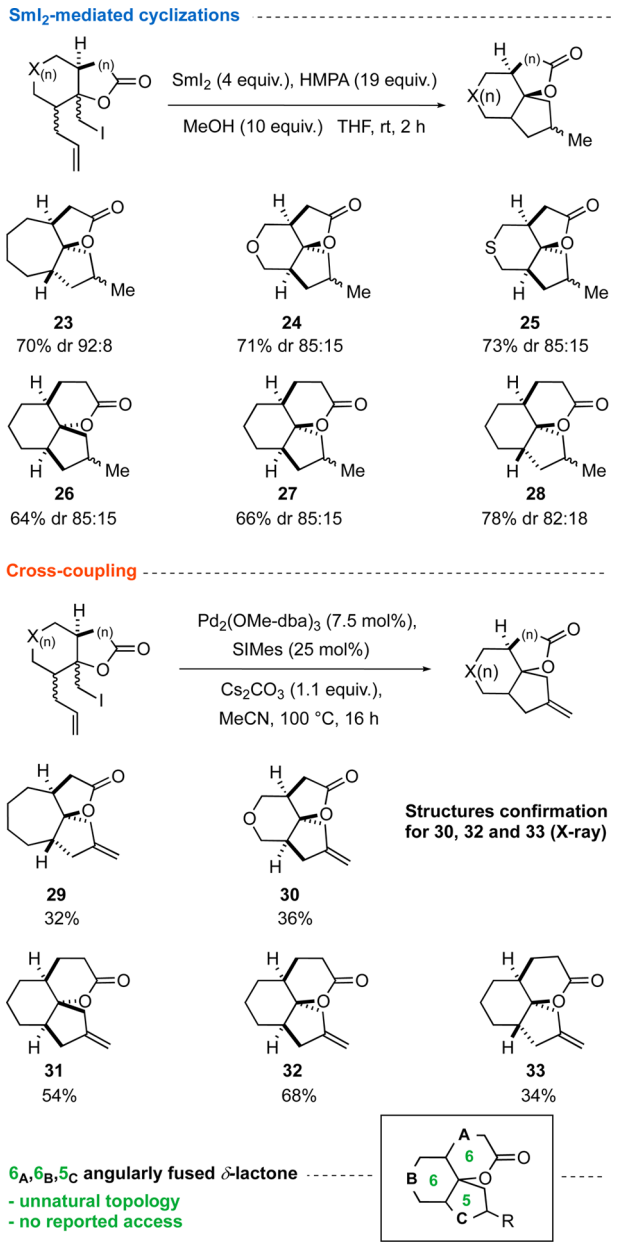
General Information. Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Solvents used in the reactions were distilled from appropriate drying agents prior to use. Reactions were monitored by thin-layer chromatography (TLC) on silica gel 60 F254 aluminum plates (Merck) and/or gas chromatography–mass spectrometry (GCMS). Visualization of compounds on TLC was accomplished by irradiation with UV light at 254 nm and/or vanillin stain. Unless otherwise noted, the diastereomeric ratios were calculated from GCMS analysis of the crude reaction mixture. Column chromatography was performed using silica gel 60 (particle size: 0.040–0.063 mm). Proton and carbon NMR spectra were recorded on a 300 or 500 MHz spectrometer in deuterated solvent. Proton chemical shifts are reported in ppm (δ) relative to tetramethylsilane with the solvent resonance employed as the internal standard ($CDCl_3$, δ 7.26 ppm). ^{13}C chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, δ 77.0 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, and coupling constants (Hz). High resolution mass spectra were determined using the electron spray ionization (ESI) LTQ Orbitrap XL (FTMS) method. Abbreviations: *p*TSA (p-toluenesulfonic acid), THF (tetrahydrofuran), DIEA (*N*,*N*-diisopropylethylamine), dr (diastereomeric ratio), dba (dibenzylideneacetone), SIMes-HBF_4 (1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydro-imidazolium tetrafluoroborate), and HMPA (hexamethylphosphoramide).

General Procedure A: Synthesis of Precursors and One-Pot α,α′-Dialkylation of Enamines of Cyclic Ketones. Unsaturated alkyl halide or methyl-2-bromoacetate was added dropwise to a 1 M solution of enamine of corresponding ketone in dry MeCN. The reaction mixture was stirred for 1 h at room temperature; DIEA was added as one portion, followed by slow addition of *tert*-butyl 2-bromoacetate. The mixture was refluxed for 12 h, then quenched with water and refluxed for another 1 h. After cooling to room temperature, the solution was diluted with diethyl ether, and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The product was purified by flash chromatography (silica gel, hexane/ethyl acetate) to yield the α,α′-dialkylated cyclic ketone.

General Procedure B: Olefination of α,α′-Dialkylated Cyclic Ketones (Wittig Reaction). Methyltriphenylphosphonium bromide (2.0 equiv) and potassium *tert*-butoxide (2.0 equiv) were stirred at 50 °C in dry THF (0.4 M) for 2 h. A 3 M solution of α,α′-dialkylated cyclic ketone (1.0 equiv) in dry THF was added dropwise at 0 °C, and the mixture was stirred for 1.5 h at room temperature. Water was added, and the aqueous layer was extracted twice with diethyl ether.

DOI: 10.1021/acs.joc.5b01278
J. Org. Chem. 2015, 80, 10464–10473

Table 2. Synthesis of Tricyclic Angularly Fused γ- and δ-Lactones[a]



[a]Reagents and conditions: For the synthesis of compounds **23**–**25**, **29**, and **30**, individual major diastereomers of **14**, **17**, and **18** were used. SmI_2-mediated cyclization: iodolactone (1 equiv), HMPA (19 equiv), MeOH (10 equiv), SmI_2 (0.1 M in THF, 4 equiv), THF, rt, 2 h. Pd-catalyzed cyclization: iodolactone (1 equiv), Pd_2(MeO-dba)$_3$ (7.5 mol %), SIMes-HBF_4 (25 mol %), Cs_2CO_3 (1.1 equiv), MeCN, rt, 5 min, then 100 °C, 16 h. Reduction byproducts were detected by GCMS (in the range 0–15%) for compound **29** (20%). The diastereomeric ratios were determined by ^{1}H NMR and GCMS of the crude mixtures.

The combined organic layers were dried (Na_2SO_4) and filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to yield the dialkylated cycloalkyl methylene.

General Procedure C: Iodolactonization. To a 0.1 M solution of cycloalkyl methylene (1.0 equiv) in MeCN was added I_2 (1.0–1.25 equiv). After being stirring for 1–2 h at room temperature, the reaction mixture was quenched with aqueous saturated sodium thiosulfate. The aqueous layer was extracted with dichloromethane (3×). The combined organic layers were dried (Na_2SO_4) and filtered, and the solvent was removed under reduced pressure. Purification of the residue by column chromatography (silica gel, hexane/diethyl ether or ethyl acetate) allows isolation of the two pure diastereoisomers of iodolactone. The reaction was monitored by GCMS. Decomposition of the desired iodolactones is observed when the reaction is not quenched immediately upon completion.

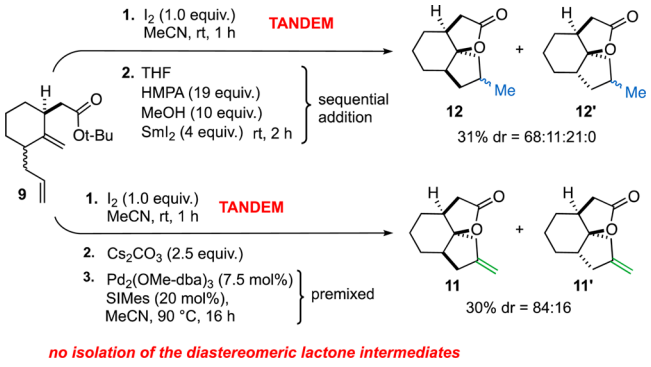
General Procedure D: Pd-Catalyzed Cyclization. Iodolactone (1.0 equiv, 0.5 mmol), Pd_2(MeO-dba)$_3$ (0.075 equiv, 0.04 mmol, 41 mg), SIMes-HBF_4 (0.25 equiv, 0.12 mmol, 49 mg), and Cs_2CO_3 (1.1 equiv, 0.55 mmol, 179 mg) were weighed into an oven-dried sealed flask. The flask was then evacuated and backfilled with nitrogen. After addition of dry MeCN (0.1 M, 5 mL), the reaction mixture was stirred at room temperature for 5 min, placed in a preheated oil bath at 100 °C, and stirred for 16 h. At the end of this time, the flask was allowed to cool to room temperature; the contents were diluted with EtOAc, and the mixture was filtered through a plug of silica. The solution was then concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel, hexane/diethyl ether) to afford the desired tricyclic product.

General Procedure E: SmI_2-Mediated Cyclization with Olefins. To a solution of iodolactone (1.0 equiv, 0.5 mmol) in dry THF (0.04 M, 12 mL), HMPA (19.0 equiv, 9.5 mmol, 1.6 mL), and MeOH (10.0 equiv, 5.0 mmol, 0.2 mL) at room temperature was added dropwise a solution of SmI_2 in THF (0.1 M, 4.0 equiv, 2.0 mmol, 20 mL). The reaction mixture was stirred under inert atmosphere for 1 h and quenched with aqueous saturated NH_4Cl. The mixture was diluted with diethyl ether; the phases were separated, and the aqueous layer was re-extracted with diethyl ether. The combined organic phases were washed with saturated aqueous solutions of $CuSO_4$, $Na_2S_2O_3$, and brine, dried (Na_2SO_4), and filtered, and the solvent was removed under reduced pressure. Purification of the residue by column chromatography (silica gel, hexane/dichloromethane) yields the desired tricyclic product.

One-Pot Tandem I_2/SmI_2-Mediated Radical Cyclization. To a 0.1 M solution of *tert*-butyl 2-(3-allyl-2-methylenecyclohexyl)acetate **9** (1.0 equiv, 0.4 mmol) in dry MeCN was added I_2 (1.0 equiv). After stirring for 1 h at room temperature, dry THF (6 mL), HMPA (19 equiv, 7.6 mmol), MeOH (10 equiv, 4 mmol), and a solution of SmI_2 in THF (0.1 M, 4 equiv, 16 mL) were added. The solution was stirred for 2 h and quenched with aqueous saturated NH_4Cl. The mixture was diluted with diethyl ether; the phases were separated, and the aqueous layer was re-extracted with diethyl ether. The combined organic phases were dried (Na_2SO_4) and filtered, and the solvent was removed under reduced pressure. Purification of the residue by column chromatography (50% dichloromethane in hexane) affords pure **12** and **12′** in 31% yield as a mixture of diastereomers (dr 68:11:21:0).

One-Pot Tandem I_2/Pd-Catalyzed Cyclizations. To a 0.1 M solution of *tert*-butyl 2-(3-allyl-2-methylenecyclohexyl)acetate **9** (1.0 equiv, 0.5 mmol) in dry MeCN was added I_2 (1.0 equiv). After stirring

Scheme 6. Tandem Cyclization of the Key Precursor[a]



[a]Reduction byproducts were detected by GCMS (for a mixture of **12** and **12′**: product/reduction = 49:51; for a mixture of **11** and **11′**: product/reduction = 51:49).

DOI: 10.1021/acs.joc.5b01278
J. Org. Chem. 2015, 80, 10464–10473

for 1 h at room temperature, Cs_2CO_3 (2.5 equiv, 1.25 mmol) was added, and the mixture was stirred for further 10 min. To the resulting solution was added in one portion a premixed and nitrogen-flushed solution of $Pd_2(MeO\text{-}dba)_3$ (0.075 equiv, 0.038 mmol) and SIMes-HBF_4 (0.25 equiv, 0.125 mmol) in 4 mL of dry MeCN. The mixture was stirred at 100 °C. After 16 h, the mixture was filtered through a plug of silica and evaporated. Purification of the crude product by flash column chromatography (10% ethyl acetate in pentane) afforded pure **11** and **11′** in 30% yield and 84:16 dr.

***tert*-Butyl 2-(5-Allyl-4-oxotetrahydro-2*H*-pyran-3-yl)acetate (2, n_1, $X_{(n)}$ = O).** 1-(3,6-Dihydro-2*H*-pyran-4-yl)pyrrolidine was prepared performing the reaction at room temperature for 1 h. After removal of toluene and traces of pyrrolidine by vacuum evaporation, the crude compound was used directly. General procedure A was applied using freshly prepared 1-(3,6-dihydro-2*H*-pyran-4-yl)-pyrrolidine (1.0 equiv, 20.0 mmol), allyl bromide (1.0 equiv, 20.0 mmol, 1.8 mL), DIEA (1.0 equiv, 20.0 mmol, 3.5 mL), and *tert*-butyl 2-bromoacetate (1.0 equiv, 20.0 mmol, 2.4 mL). Purification of the crude product by flash column chromatography (15% ethyl acetate in hexane) yielded pure *tert*-butyl 2-(5-allyl-4-oxotetrahydro-2*H*-pyran-3-yl)acetate (1.96 g, 39% yield, light yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.84−5.62 (m, 1H), 5.07−4.97 (m, 2H), 4.31−4.22 (m, 2H), 3.40−3.21 (m, 2H), 3.18−3.01 (m, 1H), 2.79−2.50 (m, 3H), 2.06−1.83 (m, 2H), 1.44 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.1, 170.9, 135.1, 116.8, 80.8, 73.3, 73.0, 50.0, 47.6, 30.9, 29.0, 28.0. IR (neat): 2976, 1713, 1641, 1366, 1252, 1149, 916 cm^{-1}. HRMS (m/z): calcd for $C_{14}H_{22}O_4Na$ ([M + Na]$^+$), 277.1403; found, 277.14127.

***tert*-Butyl 2-(5-Allyl-4-oxotetrahydro-2*H*-thiopyran-3-yl)-acetate (2, n_1, $X_{(n)}$ = S).** General procedure A was applied using freshly prepared 1-(3,6-dihydro-2*H*-thiopyran-4-yl)pyrrolidine (1.0 equiv, 31.0 mmol), allyl bromide (1.0 equiv, 31.0 mmol, 2.7 mL), DIEA (1.0 equiv, 31.0 mmol, 5.4 mL), and *tert*-butyl 2-bromoacetate (1.0 equiv, 31.0 mmol, 3.7 mL). Purification of the crude product by flash column chromatography (5% ethyl acetate in hexane) yielded *tert*-butyl 2-(5-allyl-4-oxotetrahydro-2*H*-thiopyran-3-yl)acetate in a mixture with monoalkylated products (1.4 g). The impure compound **2** (n_1, $X_{(n)}$ = S) was used directly for the next step without further purification.

***tert*-Butyl 2-(3-Allyl-2-oxocycloheptyl)acetate (2, n_1, $X_{(n)}$ = C_2H_4).** 1-(Cyclohept-1-en-1-yl)pyrrolidine was freshly prepared by refluxing the corresponding cyclic ketone (1.0 equiv) and pyrrolidine (3.0 equiv) in dry toluene (1 M) in the presence of a catalytic amount of *p*TSA until all water was distilled by a Dean−Stark apparatus. To a 1 M solution of freshly prepared 1-(cyclohept-1-en-1-yl)pyrrolidine (1.0 equiv, 42.4 mmol) in MeCN was dropwise added allyl bromide (1.0 equiv, 42.4 mmol, 3.66 mL). The solution was stirred for 12 h at room temperature, quenched with H_2O, and refluxed for 2 h. After cooling to room temperature, the aqueous layer was extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of the crude product by flash column chromatography (10% diethyl ether in hexane) afforded pure 2-allylcycloheptanone (3.7 g, 57% yield, colorless oil). 2-Allylcycloheptanone (1.0 equiv, 14.0 mmol, 2.3 g) was added to in situ prepared LDA (1.1 equiv) at −78 °C, and the mixture was stirred for 90 min at −78 °C. *tert*-Butyl 2-bromoacetate (2.0 equiv, 28.0 mmol, 4.2 mL) was added slowly. The reaction mixture was allowed to reach room temperature over 12 h and was then quenched with water. The aqueous layer was extracted with diethyl ether; the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of the crude compound by flash column chromatography (15% diethyl ether in hexane) yielded *tert*-butyl 2-(3-allyl-2-oxocycloheptyl)acetate (1.79 g, 49% yield, colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.76−5.61 (m, 1H), 5.09−4.93 (m, 2H), 3.08−2.95 (m, 1 H), 2.63 (dd, J = 16.4, 8.3 Hz, 1H), 2.49−2.28 (m, 2H), 2.28−2.08 (m, 2H), 1.98−1.79 (m, 3H), 1.79−1.66 (m, 1H), 1.44−1.42 (m, 1H), 1.40 (s, 9H), 1.37−1.12 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.0, 171.5, 135.9, 116.6, 80.4, 52.9, 46.1, 38.2, 37.7, 32.0, 29.9, 29.6, 28.0, 27.9. IR (neat): 2926, 1725, 1701, 1639, 1365, 1152, 912 cm^{-1}. HRMS (m/z): calcd for $C_{16}H_{26}O_3Na$ ([M + Na]$^+$), 289.1774; found, 289.1779.

*tert-Butyl 2-(3-Allyl-2-oxocyclohexyl)acetate (**8**).* General procedure A was applied using 1-(1-cyclohexen-1-yl)pyrrolidine (1.0 equiv, 22.0 mmol, 3.5 mL), allyl bromide (1.0 equiv, 22.0 mmol, 1.9 mL), DIEA (1.0 equiv, 22.0 mmol, 4.0 mL), and *tert*-butyl 2-bromoacetate (0.85 equiv, 18.7 mmol, 2.8 mL). Purification of the crude product by flash column chromatography (5% ethyl acetate in hexane) yielded pure *tert*-butyl 2-(3-allyl-2-oxocyclopentyl)acetate (2.7 g, 55% yield, colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.85−5.63 (m, 1H), 5.10−4.90 (m, 2H), 2.95−2.75 (m, 1H), 2.68 (dd, J = 16.3, 7.4 Hz, 1H), 2.6−2.46 (m, 1H), 2.46−2.32 (m, 1H), 2.23−1.67 (m, 6H), 1.43 (s, 9H), 1.42−1.17 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.4, 171.9, 136.5, 116.2, 80.3, 50.2, 47.4, 35.6, 35.1, 34.4, 33.5, 28.0, 25.2. IR (neat): 2931, 1709, 1640, 1392, 1366, 1276, 1152, 910 cm^{-1}. HRMS (m/z): calcd for $C_{15}H_{24}O_3Na$ ([M + Na]$^+$), 275.1618; found, 275.1624.

*tert-Butyl 2-(3-Allyl-2-methylenecyclohexyl)acetate (**9**).* General procedure B was applied using *tert*-butyl 2-(3-allyl-2-oxocyclohexyl)-acetate **8** (10.8 mmol, 2.7 g), methyltriphenylphosphonium bromide (21.6 mmol, 7.7 g), and potassium *tert*-butoxide (21.6 mmol, 2.6 g). Purification of the residue by flash column chromatography (20% diethyl ether in hexane) yielded pure *tert*-butyl 2-(3-allyl-2-methylenecyclohexyl)acetate as an inseparable mixture of diastereoisomers (2.0 g, 75%, colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.88−5.71 (m, 1H), 5.08−4.92 (m, 2H), 4.66−4.61 (m, 1H), 4.61−4.55 (m, 1H), 2.56−2.45 (m, 1H), 2.45−2.32 (m, 2H), 2.24−2.13 (m, 1H), 2.07−1.71 (m, 5H), 1.47−1.40 (m, 10H), 1.12−0.89 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5, 154.9, 137.7, 115.7, 101.8, 80.1, 43.6, 40.9, 39.2, 37.1, 35.2, 34.8, 28.1, 25.9. IR (neat): 2976, 2924, 2853, 1730, 1640, 1445, 1367, 1340, 1293, 1256, 1140, 993, 949, 909, 886, 850, 760 cm^{-1}. HRMS (m/z): calcd for $C_{16}H_{26}O_2Na$ ([M + Na]$^+$), 273.1852; found 273.1829.

*4-Allyl-3a-(iodomethyl)hexahydro-1H-inden-2(3H)-one (**10**).* General procedure C was applied using *tert*-butyl 2-(3-allyl-2-methylenecyclohexyl)acetate **9** (1.0 equiv, 1.6 mmol, 0.40 g) and I_2 (1.25 equiv, 2.0 mmol, 0.5 g). Purification of the crude product by flash column chromatography (20% diethyl ether in hexane) yielded the two diastereoisomers (0.28 g, 55% total yield, dr 86:14). Major diastereoisomer **10a** (white solid); mp 31−33 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.93−5.69 (m, 1H), 5.22−5.01 (m, 2H), 3.60 (d, J = 10.8 Hz, 1H), 3.33 (d, J = 10.9 Hz, 1H), 2.83 (dd, J = 17.7, 7.6 Hz, 1H), 2.80−2.67 (m, 1H), 2.48−2.34 (m, 1H), 2.30−2.14 (m, 2H), 2.12−1.96 (m, 1H), 1.94−1.83 (m, 1H), 1.83−1.73 (m, 1H), 1.74−1.60 (m, 1H), 1.38−1.27 (m, 1H), 1.26−1.09 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.9, 136.6, 116.8, 86.9, 38.8, 37.4, 36.7, 34.1, 29.0, 25.5, 21.6, 9.8. IR (neat): 2936, 2857, 1772, 1703, 1639, 1443, 1361, 1215, 1187, 1147, 1089, 999, 949, 917, 884, 762, 694 cm^{-1}. HRMS (m/z): calcd for $C_{12}H_{18}IO_2$ ([M + H]$^+$), 321.0346; found, 321.0350. Minor diastereoisomer **10b**: see Supporting Information (SI) for X-ray crystal data.

*8-Methyleneoctahydroindeno[3a,4-b]furan-2(3H)-one (**11**).* General procedure D was applied using iodolactone **10a** (major isomer, 160 mg). Purification of the residue by flash column chromatography (30% diethyl ether in hexane) yielded 8-methyleneoctahydroindeno[4-b]furan-2(3*H*)-one (37 mg, 40% yield, yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.04−4.81 (m, 2H), 2.78−2.04 (m, 7H), 2.01−1.57 (m, 4H), 1.58−0.97 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.8, 145.8, 108.6, 93.7, 45.5, 43.9, 38.5, 37.9, 35.7, 28.8, 24.0, 23.2. IR (neat): 2930, 1768, 1446, 1175, 942, 912 cm^{-1}. HRMS (m/z): calcd for $C_{12}H_{17}O_2$ ([M + H]$^+$), 193.1223; found, 193.1225.

*8-Methyloctahydroindeno[3a,4-b]furan-2(3H)-one (**12**).* General procedure E was applied using iodolactone **10a** (major isomer, 160 mg). Purification of the residue by flash column chromatography (50% dichloromethane in hexane) yielded 8-methyloctahydroindeno[3a,4-b]furan-2(3*H*)-one as a mixture of diastereoisomers (66 mg, 68% yield, dr 83:17, colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$, mixture of diastereoisomers): δ 2.70 (dd, J = 16.6, 6.0 Hz, 2H), 2.24−2.04 (m, 6H), 2.01−1.45 (m, 14H), 1.40−1.18 (m, 6H), 1.13−1.00 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$), major diastereoisomer: δ 177.0, 94.9, 46.5, 44.2, 38.7, 38.5, 37.6, 29.4, 28.9, 24.1, 23.4, 22.6; minor diastereoisomer, characteristic signals: δ 45.2, 43.7, 38.5, 38.0, 36.1,

DOI: 10.1021/acs.joc.5b01278
J. Org. Chem. 2015, 80, 10464−10473

28.9, 28.2, 24.2, 23.5, 22.8. IR (neat): 2928, 1765, 1445, 1427, 1353, 1279, 1221, 1179, 1168, 1054, 940 cm^{-1}. HRMS (m/z): calcd for $C_{12}H_{19}O_2$ ($[M + H]^+$), 195.1380; found, 195.1379.

*tert-Butyl 2-(5-Allyl-4-methylenetetrahydro-2H-thiopyran-3-yl)-acetate (**13**).* General procedure B was applied using *tert*-butyl 2-(5-allyl-4-oxotetrahydro-2*H*-thiopyran-3-yl)acetate **2**(n_1, $X_{(n)}$ = S) (5.0 mmol, 1.35 g), methyltriphenylphosphonium bromide (10.0 mmol, 3.6 g), and potassium *tert*-butoxide (10.0 mmol, 1.1 g). Purification of the residue by flash column chromatography (30% ethyl acetate in hexane) yielded *tert*-butyl 2-(5-allyl-4-methylenetetrahydro-2*H*-thiopyran-3-yl)acetate as an inseparable mixture of diastereoisomers (0.74 g, 55% yield, pale yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.81–5.68 (m, 1H), 5.11–5.01 (m, 2H), 4.77–4.72 (m, 2H), 2.89–2.68 (m, 3H), 2.53–2.32 (m, 6H), 2.23–2.10 (m, 1H), 1.43 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 152.1, 136.5, 116.8, 106.6, 80.6, 45.4, 42.7, 39.4, 37.4, 36.1, 35.6, 28.1. IR (neat): 2976, 1727, 1640, 1367, 1150, 1131, 899 cm^{-1}. HRMS (m/z): calcd for $C_{15}H_{24}O_2SNa$ ($[M + Na]^+$), 291.1389; found, 291.1392.

*tert-Butyl 2-(5-Allyl-4-methylenetetrahydro-2H-pyran-3-yl)-acetate (**14**).* General procedure B was applied using *tert*-butyl 2-(5-allyl-4-oxotetrahydro-2*H*-pyran-3-yl)acetate **2** (n_1, $X_{(n)}$ = O) (7.7 mmol, 1.96 g), methyltriphenylphosphonium bromide (15.4 mmol, 5.5 g), and potassium *tert*-butoxide (15.4 mmol, 1.73 g). Purification of the residue by flash column chromatography (10% ethyl acetate in hexane) yielded *tert*-butyl 2-(5-allyl-4-methylenetetrahydro-2*H*-pyran-3-yl)acetate as an inseparable mixture of diastereoisomers (1.0 g, 51% yield, pale yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.92–5.66 (m, 1H), 5.10–4.97 (m, 2H), 4.81–4.67 (m, 2H), 4.03–3.87 (m, 2H), 3.18–2.98 (m, 2H), 2.82–2.66 (m, 1H), 2.50–2.41 (m, 1H), 2.39–2.06 (m, 2H), 2.17 (dd, J = 15.4, 7.8 Hz, 1H), 2.10–1.93 (m, 1H), 1.44 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 150.2, 136.2, 116.5, 104.5, 80.6, 73.8, 73.7, 42.5, 40.2, 35.3, 33.1, 28.0. IR (neat): 2976, 1728, 1643, 1367, 1147, 1108, 912, 982, 848 cm^{-1}. HRMS (m/z): calcd for $C_{15}H_{24}O_3Na$ ($[M + Na]^+$), 275.16177; found, 275.16199.

*7-Allyl-7a-(iodomethyl)tetrahydro-4H-thiopyrano[4,3-b]furan-2(3H)-one (**15**).* General procedure C was adapted using *tert*-butyl 2-(5-allyl-4-methylenetetrahydro-2*H*-thiopyran-3-yl)acetate **13** (1.0 equiv, 1.1 mmol, 300 mg) and a larger amount of I_2 (10.0 equiv, 11.2 mmol, 2.8 g). Purification of the crude product by flash column chromatography (30% diethyl ether in hexane) yielded a mixture of the desired compound **15** and hydrolyzed starting material (2-(5-allyl-4-methylenetetrahydro-2*H*-thiopyran-3-yl)acetic acid) in a 2:1 ratio. The mixture was submitted to further iodolactonization using I_2 (2.0 equiv) and $NaHCO_3$ (5.20 equiv) in MeCN (0.1 M) at room temperature for 1 h. Purification by flash column chromatography (30% diethyl ether in hexane) yielded a single pure diastereoisomer (30 mg, 8% yield).

*Major Diastereoisomer **15a** (yellow oil).* ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.73 (dtd, J = 17.9, 9.0, 5.5 Hz, 1H), 5.16–5.02 (m, 2H), 3.50 (d, J = 10.8 Hz, 1H), 3.38 (d, J = 10.8 Hz, 1H), 3.10–2.97 (m, 2H), 2.89–2.78 (m, 2H), 2.71 (dd, J = 12.4, 3.6 Hz, 1H), 2.53–2.27 (m, 4H), 2.09–1.94 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.9, 135.0, 118.1, 84.8, 39.6, 38.5, 33.6 (2C), 27.1, 24.2, 12.5. IR (neat): 2925, 1770, 1639, 1437, 1154, 921 cm^{-1}. HRMS (m/z): calcd for $C_{11}H_{15}IO_2SNa$ ($[M + Na]^+$), 360.9730; found, 360.9732.

*7-Allyl-7a-(iodomethyl)hexahydro-2H-furo[3,2-c]pyran-2-one (**16**).* General procedure C was applied using *tert*-butyl 2-(5-allyl-4-methylenetetrahydro-2*H*-pyran-3-yl)acetate **14** (1.0 equiv, 2.4 mmol, 600 mg) and I_2 (1.1 equiv, 2.6 mmol, 659 mg). Purification of the crude product by flash column chromatography (30% diethyl ether in hexane) yielded the two diastereoisomers (278 mg, 36% total yield, dr 86:14).

*Major Diastereoisomer **16a** (white solid).* Mp 48–49 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.84–5.64 (m, 1H), 5.15–5.00 (m, 2H), 4.01–3.87 (m, 1H), 3.87–3.75 (m, 1H), 3.62–3.51 (m, 1H), 3.35–3.06 (m, 3H), 2.90–2.70 (m, 2H), 2.61–2.45 (m, 1H), 2.41–2.26 (m, 1H), 2.21–2.05 (m, 1H), 2.03–1.85 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.8, 135.1, 117.5, 84.4, 67.7, 66.9, 37.2, 36.6, 32.6, 30.1, 8.9. IR (neat): 2969, 1767, 1639, 1145, 1107, 915 cm^{-1}. HRMS (m/z): calcd for $C_{11}H_{15}IO_3Na$ ($[M + Na]^+$), 344.99581; found, 344.99603.

*tert-Butyl 2-(3-Allyl-2-methylenecycloheptyl)acetate (**17**).* General procedure B was applied using *tert*-butyl 2-(3-allyl-2-oxocycloheptyl)acetate **2** (n_1, $X_{(n)}$ = C_2H_4) (6.5 mmol, 1.74 g), methyltriphenylphosphonium bromide (17.2 mmol, 6.14 g), and potassium *tert*-butoxide (17.2 mmol, 2.08 g). The reaction required 18 h to go to completion. Purification of the residue by flash column chromatography (5% diethyl ether in hexane) yielded pure *tert*-butyl 2-(3-allyl-2-methylenecycloheptyl)acetate as an inseparable mixture of diastereoisomers (0.69 g, 40% yield, colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.86–5.64 (m, 1H), 5.05–4.88 (m, 2H), 4.88–4.70 (m, 2H), 2.69–2.03 (m, 6H), 1.97–1.44 (m, 5H), 1.42 (s, 9H), 1.31–1.03 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), major diastereoisomer: δ 172.2, 155.2, 138.0, 115.2, 106.5, 79.9, 45.7, 42.4, 41.2, 39.2, 35.2, 35.1, 28.1, 28.0, 25.7; minor diastereoisomer, characteristic signals: δ 156.2, 110.4, 44.2, 41.9, 40.5, 39.9, 35.8. IR (neat): 2923, 1728, 1639, 1452, 1130, 908 cm^{-1}. HRMS (m/z): calcd for $C_{17}H_{28}O_2Na$ ($[M + Na]^+$), 287.1981; found 287.1989.

*7a-(Iodomethyl)-7-(2-oxopropyl)hexahydrobenzofuran-2(3H)-one (**18**).* General procedure C was applied using *tert*-butyl 2-(3-allyl-2-methylenecycloheptyl)acetate **17** (1.0 equiv, 1.5 mmol, 0.40 g) and I_2 (1.1 equiv, 4.5 mmol, 0.48 g). The mixture was stirred in the ice/salt bath for 3.5 h, slowly raising the temperature from −5 to 0 °C. Quenching and workup were performed in the standard way. Purification of the crude product by flash column chromatography (15% diethyl ether in hexane) yielded 7a-(iodomethyl)-7-(2-oxopropyl)hexahydrobenzofuran-2(3*H*)-one as one pure diastereomer and an inseparable mixture of two other diastereoisomers (243 mg, 48% total yield, dr 64:23:13). Major diastereomer **14a** (white solid): mp 48–49 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.81–5.63 (m, 1H), 5.12–4.98 (m, 2H), 3.64 (d, J = 11.1 Hz, 1H), 3.53 (d, J = 11.2 Hz, 1H), 3.29 (dd, J = 18.8, 10.5 Hz, 1H), 2.64–2.46 (m, 2H), 2.16 (dd, J = 18.7, 4.3 Hz, 1H), 2.05–1.94 (m, 1H), 1.92–1.59 (m, 6H), 1.36–1.15 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.4, 136.6, 117.1, 89.9, 45.2, 45.1, 39.2, 36.3, 33.1, 29.3, 29.2, 28.4, 14.4. IR (neat): 2925, 1767, 1639, 1159, 973 cm^{-1}. HRMS (m/z): calcd for $C_{13}H_{20}IO_2$ ($[M + H]^+$), 335.0502; found, 335.0509. See SI for X-ray crystal data.

*3-(3-Allyl-2-oxocyclohexyl)propanenitrile (**19**).* General procedure A was adapted: acrylonitrile (1.0 equiv, 35.2 mmol, 2.3 mL) was added to a 1 M solution of 1-(1-cyclohexen-1-yl)pyrrolidine (1.0 equiv, 35.2 mmol, 5 mL) in MeCN and refluxed for 2 h. DIEA (1.0 equiv, 35.2 mmol, 6.1 mL) was added as one portion, followed by slow addition of allyl bromide (1.0 equiv, 35.2 mmol, 3.0 mL). The mixture was stirred for 12 h at 40 °C, then quenched with water and refluxed for 1 h. Purification of the crude product by flash column chromatography (10% ethyl acetate in hexane) yielded pure 3-(3-allyl-2-oxocyclohexyl)-propanenitrile (2.24 g, 35% yield, light orange oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.82–5.68 (m, 1H), 5.04–4.97 (m, 2H), 2.55–2.33 (m, 5H), 2.22–1.68 (m, 6H), 1.56–1.21 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.0, 136.2, 136.2, 116.3, 50.5, 49.1, 35.2, 34.6, 33.4, 25.4, 25.1, 15.2. IR (neat): 2933, 2245, 1706, 1640, 1447, 912 cm^{-1}. HRMS (m/z): calcd for $C_{12}H_{17}NONa$ ($[M + Na]^+$), 214.1202; found, 214.1203.

*3-(3-Allyl-2-methylenecyclohexyl)propanenitrile (**20**).* General procedure B was applied using 3-(3-allyl-2-oxocyclohexyl)-propanenitrile **19** (12.2 mmol, 2.3 g), methyltriphenylphosphonium bromide (24.3 mmol, 8.7 g), and potassium *tert*-butoxide (24.3 mmol, 2.7 g). Purification of the residue by flash column chromatography (10% ethyl acetate in hexane) yielded pure 3-(3-allyl-2-methylenecyclohexyl)propanenitrile as a mixture of diastereoisomers (1.9 g, 86% yield, yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.87–5.73 (m, 1H), 5.06–4.99 (m, 2H), 4.74–4.58 (m, 2H), 2.44–2.32 (m, 3H), 2.07–1.42 (m, 9H), 1.10–0.87 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$), major diastereoisomer: δ 154.3, 137.5, 137.4, 115.8, 107.6, 102.6, 43.8, 43.1, 37.5, 34.9, 28.2, 25.7, 15.2; minor diastereoisomer, characteristic signals: δ 152.1, 120.0, 41.9, 39.7, 36.7, 33.4, 33.1, 27.5, 21.3, 15.3. IR (neat): 2923, 2245, 1640, 1444, 1392, 1333, 994, 891 cm^{-1}. HRMS (m/z): calcd for $C_{13}H_{19}NNa$ ($[M + Na]^+$), 212.14097; found, 212.14099.

*3-(3-Allyl-2-methylenecyclohexyl)propanoic Acid (**21**).* A mixture of 3-(3-allyl-2-methylenecyclohexyl)propanenitrile **20** (1.0 equiv, 10.6

DOI: 10.1021/acs.joc.5b01278
J. Org. Chem. 2015, 80, 10464–10473

mmol, 2.0 g), ethanol (70 mL), and 65% aq NaOH (212.0 mmol, 8.5 g) was stirred at 80 °C for 3 h. The mixture was concentrated under vacuum, and the residue was quenched with water. The aqueous solution was extracted with ether, acidified with concd HCl to pH 1, and then extracted again with ethyl acetate. The mixture was dried over Na_2SO_4, filtered, and evaporated to yield 3-(3-allyl-2-methylenecyclohexyl)propanoic acid as a mixture of diastereoisomers (2.3 g, orange oil). The compound was used directly for the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.35 (bs, 1H), 5.88−5.75 (m, 1H), 5.07−4.98 (m, 2H), 4.70−4.66 (m, 2H), 2.46−2.29 (m, 3H), 2.07−1.39 (m, 9H), 1.20−0.89 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$), major diastereoisomer: δ 180.8, 155.1, 137.7, 115.6, 102.3, 43.9, 43.6, 37.2, 35.3, 35.0, 32.1, 27.3, 25.9; minor diastereoisomer, characteristic signals: δ 153.4, 137.5, 115.5, 106.6, 42.2, 39.8, 36.8, 33.5, 33.4, 32.3, 26.7, 21.3. IR (neat): 2924, 1705, 1640, 1414, 1280, 890 cm^{-1}.

*8-Allyl-8a-(iodomethyl)octahydro-2H-chromen-2-one (**22**).* A solution of 3-(3-allyl-2-methylenecyclohexyl)propanoic acid **21** (1.0 equiv, 10.5 mmol, 2.2 g) in acetonitrile (110 mL) at 50 °C was treated with sodium bicarbonate (5.2 equiv, 54.6 mmol, 4.6 g), and the resulting mixture was stirred at 50 °C for 10 min. Iodine (2.0 equiv, 21.2 mmol, 5.4 g) was added to the reaction at 50 °C, and the resulting mixture was stirred at room temperature for 1.5 h. The reaction was quenched with aq saturated sodium thiosulfate, and the resulting aq solution was extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of the crude product by flash column chromatography (2% acetic acid and 28% diethyl ether in hexane) yielded three pure diastereoisomers (55% total yield, dr 41:36:23).

First diastereoisomer **22a** (pale yellow solid): mp 79−80 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.84−5.70 (m, 1H), 5.09−5.00 (m, 2H), 3.63 (d, J = 10.8 Hz, 1H), 3.30 (d, J = 10.9 Hz, 1H), 2.62−2.55 (m, 2H), 2.34−2.22 (m, 2H), 2.15−1.98 (m, 3H), 1.75 (t, J = 10.5 Hz, 2H), 1.60−1.22 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 136.9, 116.5, 41.2, 33.3, 32.6, 26.9, 26.3, 25.1, 24.6, 21.1, 8.1. IR (neat): 2926, 1724, 1640, 1482, 1224, 906 cm^{-1}. HRMS (m/z): calcd for $C_{13}H_{19}IO_2Na$ ([M + Na]$^+$), 357.0322; found, 357.0327. Second diastereoisomer **22b** (pale yellow oil): ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.77−5.59 (m, 1H), 5.03−4.95 (m, 2H), 3.47 (d, J = 18.0 Hz, 1H), 3.44 (d, J = 15.0 Hz, 1H), 2.85−2.50 (m, 3H), 2.03−1.55 (m, 9H), 1.40−1.18 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8, 136.9, 116.7, 81.3, 49.0, 43.3, 33.5, 30.3, 29.5, 27.8, 24.9, 22.9, 1.6. IR (neat): 2926, 1731, 1639, 1439, 1225, 909 cm^{-1}. HRMS (m/z): calcd for $C_{13}H_{19}IO_2Na$ ([M + Na]$^+$), 357.0322; found, 357.0330. Third diastereoisomer **22c** (yellow oil): ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.76−5.62 (m, 1H), 5.06−4.99 (m, 2H), 3.64 (d, J = 18.0 Hz, 1H), 3.59 (d, J = 18.0 Hz, 1H), 2.68−2.41 (m, 4H), 2.20−1.19 (m, 10H), ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 136.4, 170.0, 84.8, 41.7, 37.5, 33.3, 29.9, 28.8, 27.8, 21.7, 19.8, 14.3. IR (neat): 2932, 1729, 1639, 1451, 1219, 912 cm^{-1}. HRMS (m/z): calcd for $C_{13}H_{19}IO_2Na$ ([M + Na]$^+$), 357.0322; found, 357.0326.

*9-Methyldecahydro-2H-azuleno[4-b]furan-2-one (**23**).* General procedure E was applied using **18a** (major isomer, 167 mg). Purification of the residue by flash column chromatography (20% ethyl acetate in hexane) yielded 9-methyldecahydro-2*H*-azuleno[4-b]furan-2-one as a mixture of diastereoisomers (73 mg, 70% yield, dr 92:8, pale yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.87 (dd, J = 17.5, 8.4 Hz, 1H), 2.35−2.06 (m, 5H), 1.96−1.18 (m, 11H), 1.02 (d, J = 6.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.6, 101.6, 50.2, 46.4, 45.9, 43.2, 39.2, 32.9, 32.4, 30.7, 30.6, 30.4, 21.7. IR (neat): 2923, 1767, 1448, 1163, 973 cm^{-1}. HRMS (m/z): calcd for $C_{13}H_{20}O_2Na$ ([M + Na]$^+$), 231.13555; found, 231.13596.

*8-Methyloctahydro-2H-cyclopenta[c]furo[2,3-d]pyran-2-one (**24**).* General procedure E was applied using **16a** (major isomer, 129 mg). Purification of the residue by flash column chromatography (60% ethyl acetate in hexane) yielded 8-methyloctahydro-2*H*-cyclopenta[c]furo[2,3-*d*]pyran-2-one as a mixture of diastereoisomers (56 mg, 71% yield, dr 85:15, pale yellow solid). Mp 51 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.02−3.80 (m, 2H), 3.50 (t, J = 10.7 Hz, 1H), 3.15−2.97 (m, 1H), 2.73 (dd, J = 17.2, 6.4 Hz, 1H), 2.50−2.37 (m, 1H), 2.37−2.17 (m, 1H), 2.12−1.85 (m, 4H), 1.68−1.55 (m, 1H), 1.27−1.18 (m, 1H), 1.11 (d, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.9, 92.5, 67.1, 66.1, 44.6, 43.6, 38.5, 34.3, 33.4, 29.5, 22.5. IR (neat): 2957, 1760, 1456, 1186, 918 cm^{-1}. HRMS (m/z): calcd for $C_{11}H_{16}O_3Na$ ([M + Na]$^+$), 219.09917; found, 219.09918.

*8-Methylhexahydro-6H-cyclopenta[4,5]thiopyrano[4,3-b]furan-2(3H)-one (**25**).* General procedure E was applied using **15a** (major isomer, 30 mg). Purification of the residue by flash column chromatography (30% ethyl acetate in hexane) yielded 8-methylhexahydro-6*H*-cyclopenta[4,5]thiopyrano[4,3-*b*]furan-2(3*H*)-one as a mixture of diastereoisomers (14 mg, 73% yield, dr 85:15, pale yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$), mixture of diastereoisomers: δ 2.93−2.80 (m, 2H), 2.72−2.54 (m, 3H), 2.39−2.27 (m, 2H), 2.24−1.94 (m, 4H), 1.70−1.60 (m, 1H), 1.32−1.21 (m, 1H), 1.08 (d, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), major diastereoisomer: δ 176.0, 93.0, 46.0, 43.9, 39.2, 38.5, 36.7, 29.2, 28.8, 24.7, 22.3; minor diastereoisomer, characteristic signals: 46.7, 41.4, 38.6, 36.9, 27.8, 25.1. IR (neat): 2951, 1760, 1427, 1173, 910 cm^{-1}. HRMS (m/z): calcd for $C_{11}H_{16}O_2SNa$ ([M + Na]$^+$), 235.0763; found, 235.0764.

*9-Methyldecahydro-2H-cyclopenta[i]chromen-2-one (**26**).* General procedure E was applied using iodolactone **22a** (first isomer, 167 mg). Purification of the residue by flash column chromatography (15% ethyl acetate in hexane) yielded 9-methyldecahydro-2*H*-cyclopenta[i]chromen-2-one as an 85:15 mixture of diastereoisomers (67 mg, 64% isolated yield, pale yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$), mixture of diastereoisomers: δ 2.63−2.58 (m, 4H), 2.28−2.18 (m, 4H), 1.94−1.88 (m, 2H), 1.83−1.46 (m, 18H), 1.31−1.10 (m, 6H); major diastereoisomer: δ 1.05 (d, J = 6.21 Hz, 3H); minor diastereoisomer: δ 0.99 (d, J = 3.98 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), major diastereoisomer: δ 172.1, 95.3, 47.3, 38.8, 38.5, 37.9, 29.8, 29.5, 29.2, 29.1, 24.7, 23.8, 23.1; minor diastereoisomer, characteristic signals: δ 45.7, 38.7, 38.2, 37.7, 32.9, 29.3, 29.1, 25.1, 24.0, 23.2. IR (neat): 2929, 1722, 1464, 1351, 1184, 1005 cm^{-1}. HRMS (m/z): calcd for $C_{13}H_{20}O_2Na$ ([M + Na]$^+$), 231.1355; found, 231.1359.

*9-Methyldecahydro-2H-cyclopenta[i]chromen-2-one (**27**).* General procedure E was applied using iodolactone **22b** (second isomer, 167 mg). Purification of the residue by flash column chromatography (15% ethyl acetate in hexane) yielded 9-methyldecahydro-2*H*-cyclopenta[i]chromen-2-one as a mixture of diastereoisomers (69 mg, 66% isolated yield, dr 85:15, pale yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$), mixture of diastereoisomers: δ 2.54−2.48 (m, 4H), 2.17−2.01 (m, 4H), 1.90−1.82 (m, 4H), 1.67−1.22 (m, 22H); major diastereoisomer: δ 1.05 (d, J = 7.0 Hz, 3H); minor diastereoisomer: δ 0.99 (d, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), major diastereoisomer: δ 172.3, 91.6, 49.1, 45.0, 37.0 (2C), 29.5, 25.9, 25.9, 25.2, 24.1, 22.8, 22.5; minor diastereoisomer, characteristic signals: δ 92.3, 46.3, 46.1, 36.7, 36.8, 31.5, 28.2, 25.8, 25.7, 25.3, 24.2, 22.9. IR (neat): 2929, 1720, 1460, 1352, 1281, 1173, 977 cm^{-1}. HRMS (m/z): calcd for $C_{13}H_{20}O_2Na$ ([M + Na]$^+$), 231.1355; found, 231.1358.

*9-Methyldecahydro-2H-cyclopenta[i]chromen-2-one (**28**).* General procedure E was applied using iodolactone **22c** (third isomer, 167 mg). Purification of the residue by flash column chromatography (15% ethyl acetate in hexane) yielded 9-methyldecahydro-2*H*-cyclopenta[i]chromen-2-one as a mixture of diastereoisomers (81 mg, 78% isolated yield, dr 82:18, pale yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$), mixture of diastereoisomers: δ 2.57−1.66 (m, 16H), 1.62−1.09 (m, 18H); major diastereoisomer: δ 1.04 (d, J = 6.8 Hz, 3H); minor diastereoisomer: δ 0.99 (d, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), major diastereoisomer: δ 171.3, 93.2, 44.6, 43.0, 35.6, 32.5, 28.5, 27.6, 27.6, 26.0, 22.8, 22.7, 19.6; minor diastereoisomer, characteristic signals: δ 171.5, 93.94, 45.2, 44.6, 37.4, 33.4, 29.6, 27.6, 27.3, 22.4, 22.2, 20.1. IR (neat): 2930, 1727, 1455, 1284, 1116, 995 cm^{-1}. HRMS (m/z): calcd for $C_{13}H_{20}O_2Na$ ([M + Na]$^+$), 231.1355; found, 231.1359.

*9-Methylenedecahydro-2H-azuleno[4-b]furan-2-one (**29**).* General procedure D was applied using 7a-(iodomethyl)-7-(2-oxopropyl)-hexahydrobenzofuran-2(3*H*)-one **18a** (major isomer, 167 mg). Purification of the residue by flash column chromatography (10% ethyl acetate in hexane) yielded 9-methylenedecahydro-2*H*-azuleno[4-

DOI: 10.1021/acs.joc.5b01278
J. Org. Chem. 2015, 80, 10464−10473

b]furan-2-one (33 mg, 32% yield, yellow solid). Mp 34−35 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.95−4.82 (m, 2H), 2.99−2.86 (m, 2H), 2.70−2.59 (m, 2H), 2.38−2.05 (m, 4H), 2.03−1.81 (m, 2H), 1.78−1.61 (m, 1H), 1.55−1.21 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.2, 147.1, 107.4, 99.8, 48.2, 44.8, 44.4, 41.3, 38.9, 33.1, 32.8, 30.4, 30.4. IR (neat): 2919, 1747, 1651, 1460, 1163, 938 cm^{-1}. HRMS (m/z): calcd for $C_{13}H_{18}O_2Na$ ([M + Na]$^+$), 229.1199; found, 229.1200.

8-Methyleneoctahydro-2H-cyclopenta[c]furo[2,3-d]pyran-2-one (30). General procedure D was applied using 7-allyl-7a-(iodomethyl)-hexahydro-2*H*-furo[3,2-*c*]pyran-2-one **16a** (major isomer, 161 mg). Purification of the residue by flash column chromatography (40% ethyl acetate in hexane) yielded 8-methyleneoctahydroindeno[4-b]furan-2(3*H*)-one (35 mg, 36% yield, white solid). Mp 76−77 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.12−4.99 (m, 2H), 4.04−3.91 (m, 2H), 3.56 (t, J = 10.8 Hz, 1H), 3.21−3.07 (m, 1H), 2.82−2.07 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.5, 144.4, 109.8, 91.3, 67.3, 65.7, 43.5, 43.4, 37.9, 34.2, 31.8. IR (neat): 2845, 1768, 1661, 1424, 1194, 907 cm^{-1}. HRMS (m/z): calcd for $C_{11}H_{14}O_3Na$ ([M + Na]$^+$), 217.0835; found, 217.0836. See SI section for X-ray crystal data.

9-Methylenedecahydro-2H-cyclopenta[i]chromen-2-one (31). General procedure D was adapted using iodolactone **22a** (first isomer, 167 mg) and a larger amount of Pd_2(MeO-dba)$_3$ (0.1 equiv, 0.05 mmol, 55 mg). The reaction required 24 h to go to completion. Purification of the residue by flash column chromatography (40% diethyl ether in pentane) yielded 9-methylenedecahydro-2*H*-cyclopenta[*i*]chromen-2-one (56 mg, 54% isolated yield, light brown oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.97 (d, J = 15.0 Hz, 2H), 2.96−2.86 (m, 1H), 2.73−2.63 (m, 3H), 2.32−2.26 (m, 1H), 2.03−1.96 (m, 2H), 1.87−1.66 (m, 5H), 1.61−1.49 (m, 1H), 1.41−1.23 (m, 1H), 1.23−0.93 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.7, 146.9, 109.3, 93.6, 45.1, 38.6, 37.5, 36.8, 29.9, 29.4, 29.0, 24.4, 23.7. IR (neat): 3071, 1723, 1661, 1464, 1448, 1350, 999, 876 cm^{-1}. HRMS (m/z): calcd for $C_{13}H_{18}O_2Na$ ([M + Na]$^+$), 229.1199; found, 229.1200.

9-Methylenedecahydro-2H-cyclopenta[i]chromen-2-one (32). General procedure D was applied using iodolactone **22b** (second isomer, 167 mg). The reaction required 24 h to go to completion. Purification of the residue by flash column chromatography (30% diethyl ether in pentane) yielded 9-methylenedecahydro-2*H*-cyclopenta[i]chromen-2-one (70 mg, 68% isolated yield, white crystalline solid). Mp 97−98 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.92 (d, J = 14.7 Hz, 2H), 2.61−2.52 (m, 3H), 2.42−2.34 (m, 3H), 2.10−2.06 (m, 1H), 1.82−1.35 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0, 146.3, 108.2, 90.5, 47.9, 44.6, 36.4, 35.1, 25.9, 25.8, 25.1, 23.9, 22.5. IR (neat): 3071, 2938, 2843, 1719, 1659, 1465, 1259, 1178, 1054, 983, 856 cm^{-1}. HRMS (m/z): calcd for $C_{13}H_{18}O_2Na$ ([M + Na]$^+$), 229.1199; found, 229.1205. See SI section for X-ray crystal data.

9-Methylenedecahydro-2H-cyclopenta[i]chromen-2-one (33). General procedure D was applied using iodolactone **22c** (third isomer, 167 mg). The reaction required 24 h to go to completion. Purification of the residue by flash column chromatography (30% diethyl ether in pentane) yielded 9-methylenedecahydro-2*H*-cyclopenta[i]chromen-2-one (35 mg, 34% isolated yield, white powder). Mp 106−107 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.92 (bs, 2H), 2.69−2.40 (m, 4H), 2.33−2.12 (m, 2H), 1.97−1.44 (m, 9H), 1.35−1.26 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 146.4, 108.6, 91.8, 43.8, 42.9, 35.1, 32.3, 20.8, 27.5, 26.3, 22.7, 19.4. IR (neat): 3064, 2978, 1717, 1661, 1456, 1337, 1290, 1167, 980 cm^{-1}. HRMS (m/z): calcd for $C_{13}H_{18}O_2Na$ ([M + Na]$^+$), 229.1199; found, 229.1202. See SI section for X-ray crystal data.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01278.

^{1}H NMR and ^{13}C NMR spectra for new compounds (PDF)

CIF file for compound **22** (CIF)

CIF file for compound **11** (CIF)

CIF file for compound **30** (CIF)

CIF file for compound **32** (CIF)

CIF file for compound **33** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dmitryt@ekmd.huji.ac.il.

Author Contributions

‡Y.M. and V.V. contributed equally to this study.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge Marie Curie Integration Grant (CIG 321746) and German-Israeli-Foundation Grant (GIF I-2330-1145.5/2012) for financial support. We also thank Yissum-HUJI for Technology Transfer Start-up Grant. V.V. thanks Minerva-Stiftung for a postdoctoral fellowship.

■ REFERENCES

(1) (a) Dewick, P. M. *Medicinal Natural Products: A Biosynthetic Approach*, 2nd ed.; Wiley, 2002. (b) Osbourn, A. E.; Lanzotti, V. *Plant-Derived Natural Products*; Springer: New York, 2009.

(2) Anke, T.; Watson, W. H.; Giannetti, B. M.; Steglich, W. J. *J. Antibiot.* **1981**, *34*, 1271−1277.

(3) (a) Tan, W.; Lu, J.; Huang, M.; Li, Y.; Chen, M.; Wu, G.; Gong, J.; Zhong, Z.; Xu, Z.; Dang, Y.; Guo, J.; Chen, X.; Wang, Y. *Chin. Med.* **2011**, *6*, 27. (b) White, N. J. *Science* **2008**, *320*, 330−334.

(4) De la Torre, M. C.; Bruno, M.; Piozzi, F.; Savona, G.; Rodriguez, B.; Omar, A. A. *Phytochemistry* **1991**, *30*, 1603−1606.

(5) (a) Liu, Y.-W.; Cheng, Y.-B.; Liaw, C.-C.; Chen, C.-H.; Guh, J.-H.; Hwang, T.-S.; Tsai, J.-S.; Wang, W.-B.; Shen, Y.-C. *J. Nat. Prod.* **2012**, *75*, 689−693. (b) Nicotra, V. E.; Ramacciotti, N. S.; Gil, R. R.; Oberti, J. C.; Feresin, G. E.; Guerrero, C. A.; Baggio, R. F.; Garland, M. T.; Burton, G. *J. Nat. Prod.* **2006**, *69*, 783−789.

(6) (a) Schwaebe, M.; Little, R. D. *J. Org. Chem.* **1996**, *61*, 3240. (b) Wu, H.; Moeller, K. D. *Org. Lett.* **2007**, *9*, 4599−4602. (c) Lansbury, P. T.; Zhi, B. X. *Tetrahedron Lett.* **1988**, *29*, 5735−5738. (d) Trost, B. M.; Balkovec, J. M.; Mao, M. K.-T. *J. Am. Chem. Soc.* **1986**, *108*, 4974−4983.

(7) (a) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. *Nature* **2011**, *475*, 183−188. (b) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46−58. (c) Tsvelikhovsky, D.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14048−14051. (d) Tsvelikhovsky, D.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**, *133*, 14228−14231.

(8) Posner, G. H.; Oh, C. H.; Gerena, L.; Milhous, W. K. *J. Med. Chem.* **1992**, *35*, 2459−2467.

(9) (a) Bestmann, H. J.; Vostrowsky, O. Selected topics of the Wittig reaction in the synthesis of natural products. In *Wittig Chemistry*; Springer: Berlin Heidelberg, 1983; pp 85−163. (b) Nicolaou, K. C.; Härter, M. W.; Gunzner, J. L.; Nadin, A. *Liebigs Annalen* **1997**, *1997*, 1283−1301.

(10) *The Chemistry of Enamines*; Rappoport, Z., Ed.; John Wiley & Sons: NY, 1994; part 1.

(11) The second alkylation reaction requires high temperatures; performing the reaction at room temperature decreased the yield of the dialkylated product.

(12) (a) Holland, J. M.; Lewis, M.; Nelson, A. *J. Org. Chem.* **2003**, *68*, 747−753. (b) Paruch, E.; Ciunik, Z.; Nawrot, J.; Wawrzenczyk, C. *J. Agric. Food Chem.* **2000**, *48*, 4973−4977.

(13) GCMS analysis showed that the basic conditions of the Wittig olefination do not have a significant effect on the diastereomeric ratio.

(14) Firmansjah, L.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 11340−11341.

(15) (a) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307−338. (b) Szostak, M.; Fazakerley, N. J.; Parmar, D.; Procter, D. J. *Chem.*

DOI: 10.1021/acs.joc.5b01278
J. Org. Chem. 2015, 80, 10464−10473

Rev. **2014**, *114*, 5959−6039. (c) Procter, D. J.; Flowers, R. A., II; Skrydstrup, T. *Organic Synthesis Using Samarium Diiodide: A Practical Guide*; RSC Publishing, 2009. (d) Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworth: London, 1987. (e) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237−1286. (f) Just-Baringo, X.; Procter, D. J. *Acc. Chem. Res.* **2015**, *48*, 1263−1275. (g) It has proven difficult to completely remove Sn byproducts from the crude reaction mixture (Pathway **II**, conditions **A**); the low yield of **12** is a direct outcome of this limitation.

(16) (a) Reutrakul, V.; Thongpaisanwong, T.; Tuchinda, P.; Kuhakarn, C.; Pohmakotr, M. *J. Org. Chem.* **2004**, *69*, 6913−6915. (b) Molander, G. A.; Harris, C. R. *J. Org. Chem.* **1997**, *62*, 7418−7429. (c) Molander, G. A.; St. Jean, D. J., Jr. *J. Org. Chem.* **2002**, *67*, 3861−3865. (d) Cyclization of oxygen-containing alkyl halides onto alkenes: Fukuzawa, S.; Tsuchimoto, T. *Synlett* **1993**, *1993*, 803−804.

(17) (a) Curran, D. P.; Totleben, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 6050−6058. (b) Hasegawa, E.; Curran, D. P. *Tetrahedron Lett.* **1993**, *34*, 1717−1720. (c) Ferjani, M. B. S.; Zhou, Z.; Bennett, S. M. *Tetrahedron* **2004**, *60*, 8113−8130.

(18) The structures of iodolactones **22b** and **22c** are deduced from the X-ray analysis of the corresponding products **32** and **33**, respectively. The diastereomeric ratio of compound **20** (Scheme 5) was detected as 75:25. Following mass and dr balance calculations, iodolactone **22a** (derived from ***syn*-20**) was found to consist of a *trans*-*δ*-lactone.

(19) Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc.* **1978**, *100*, 3950−3952.

DOI: 10.1021/acs.joc.5b01278
J. Org. Chem. 2015, 80, 10464−10473