JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Synthesis of (±)-4,5-*dia*-Parthenolide, an Unnatural Parthenolide Stereoisomer

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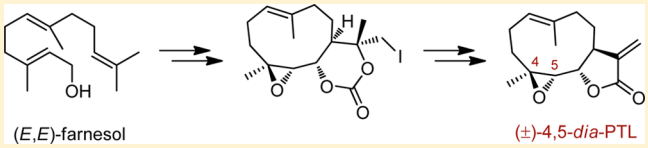
Supporting Information

ABSTRACT: A short total synthesis of the novel unnatural parthenolide diastereomer (±)-4,5-*dia*-parthenolide was accomplished in 13 steps and an overall yield of 1.75% starting from commercially available (*E*,*E*)-farnesol. The challenging isopropenyl side chain oxidation was regioselectively achieved via a newly developed stepwise dihydroxylation procedure, employing a Bartlett−Smith iodocarbonate cyclization followed by iodide substitution and catalytic transesterification.



INTRODUCTION

The sesquiterpene lactone (−)-parthenolide [PTL, (−)-**1**, Figure 1] from the medicinal herb feverfew (*Tanacetum parthenium*) features interesting anti-inflammatory and anticancer activity, including the induction of apoptosis of cancer stem cells, while regular stem cells seem not to be affected.[1,2] (−)-Parthenolide binds biological targets covalently, either by Michael-addition to the α-methylene-γ-butyrolactone moiety or by nucleophilic attack at the epoxide.[1,2] Its pharmacological activity is mainly attributed to the modulation of four out of seven major signaling pathways that ensure survival and self-renewal of cancer stem cells (NF-κB, PI3K/Akt/mTor, JAK/STAT3, and MAPK).[1−3] Furthermore, parthenolide was reported to indirectly activate p21 and p53 which are down-regulated in most cancers.[4] Moreover it stimulates the mitochondrial apoptotic pathway by activating caspase 8 and thus inducing the release of cytochrome c.[1,5,6] Further activities on cellular redox chemistry and on DNA methylation have also been reported.[7,8] The parthenolide prodrug dimethylamino-parthenolide (DMAPT, **2**, Figure 1)[9,10] is investigated in clinical trials for the treatment of different leukemias (AML, ALL) and lung cancer prevention.[1,11]

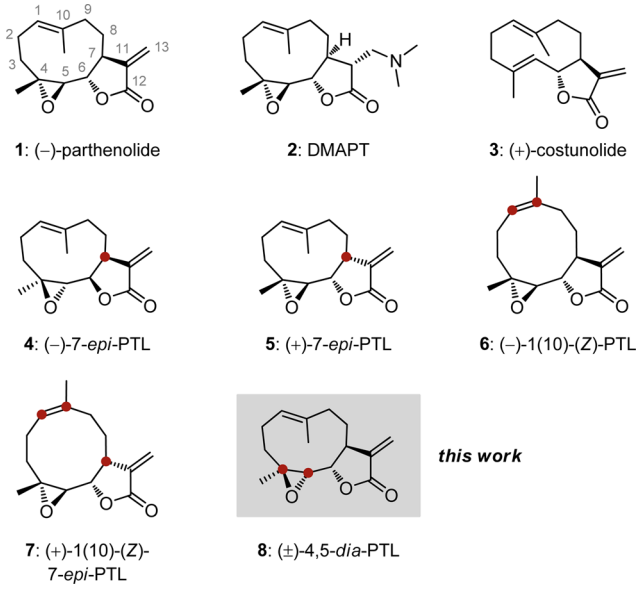


Figure 1. Known stereoisomers of (−)-parthenolide (**1**) and selected derivatives. References for respective total or semisyntheses are given in the text. Red dots highlight changed stereochemistry with respect to (−)-parthenolide.

However, targets and mechanism of action remain poorly understood. For systematic investigations a synthesis of (−)-parthenolide (**1**) as well as of derivatives and analogues would be highly valuable. Notable synthetic work includes the total synthesis of (±)-costunolide (**3**)—the nonepoxidized biosynthetic parthenolide precursor (Figure 1).[12−14] A total synthesis of the C7 epimer (**4**) of the (+)-parthenolide enantiomer has been reported by Baran's group.[15] Long et al. reported on a semisynthesis of (−)-parthenolide in 2013 and a total synthesis in 2014, albeit not stereoselectively, hence stereoisomers like (+)-7-*epi*-PTL (**5**), (−)-1(10)-(*Z*)-PTL (**6**), and (+)-1(10)-(*Z*)-7-*epi*-PTL (**7**) were accessed as well (Figure 1).[16,17] All of them had the same *all-trans* configuration pattern and showed similar or reduced cytotoxicity on the tested cancer cell lines compared to (−)-parthenolide.[16,17] The same group also described a second generation parthenolide synthesis in 2015[18] and the synthesis of further analogs in 2016.[19] In addition, a total synthesis of racemic (±)-parthenolide was reported recently.[20] Herein we report the total synthesis of the novel unnatural parthenolide diastereomer (±)-**8** which displays a hitherto unknown C4−C5-*trans* C5−C6-*cis* configuration (Figure 1).

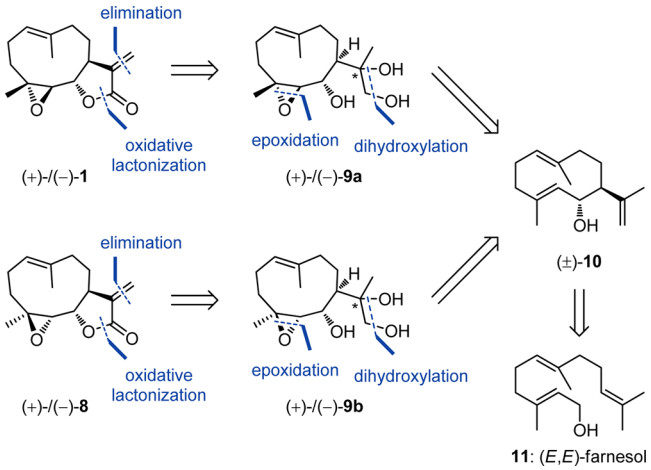
In a favorable synthesis concept both enantiomers of parthenolide (**1**) and of its C4−C5 diastereomer **8** could be prepared from a single racemic key intermediate. In our

Received: August 19, 2016
Published: October 11, 2016

DOI: 10.1021/acs.joc.6b01985
J. Org. Chem. 2016, 81, 11009−11016

retrosynthetic analysis (Scheme 1) the α-methylene-γ-butyrolactone of (±)-parthenolide (**1**) as well as of (±)-4,5-*dia*-

Scheme 1. Initial Retrosynthetic Analysis of the Desired Parthenolide Stereoisomers



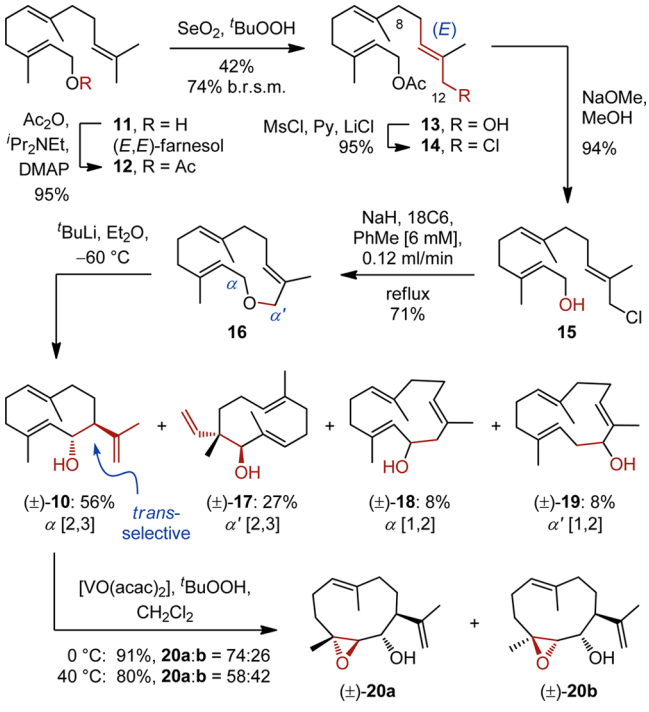
parthenolide (**8**) is formed by oxidative lactonization[21] of the epoxy triol **9a** or **9b**, respectively, and subsequent *exo*-selective dehydration of its 3° alcohol by *syn* or *anti* elimination. These triols could arise from the allylic alcohol (±)-**10** as a common intermediate,[12−14] by employing established hydroxyl-directed epoxidation and dihydroxylation chemistry. For both reaction types asymmetric variants should allow the preparation of selected parthenolide isomers. In our initial plan the vicinal diol motif would be installed after epoxidation by stereoselective dihydroxylation of the allylic alcohol's [(±)-**10**] isopropenyl group. The known *trans*-configured diallylic alcohol (±)-**10** can be prepared starting from (*E*,*E*)-farnesol (**11**),[12,13] the biosynthetic progenitor of germacrane sesquiterpenes.[22]

RESULTS AND DISCUSSION

An earlier reported sequence[12,13] for the synthesis of alcohol (±)-**10** was adopted and optimized to our purpose. Therefore, commercially available (*E*,*E*)-farnesol (**11**) was acetylated (**12**) and (*E*)-selectively oxidized[13] at the terminal allylic position using SeO_2 and *tert*-butyl hydroperoxide. The C12 alcohol **13** was formed along with the C8 alcohol (15%) as the major byproduct. The allylic alcohol **13** was converted into the allylic chloride **14** and chemoselectively deprotected by Zemplén-type de-*O*-acetylation[23,24] to obtain the ω-chloro farnesol **15** as precursor for the Williamson type macrocyclization. The latter was achieved using NaH/18-crown-6 at moderate dilution (6 mM) in refluxing toluene. Slow addition of the substrate gave rise to the 13-membered cyclic diallylic ether **16** in good yield (71%, Scheme 2).

Tsuji's 13→10 ring contraction methodology that employs a [2,3]-Wittig rearrangement was then used to create the germacrane skeleton:[13] After α lithiation of the diallyic ether a diastereoselective [2,3]-Wittig rearrangement provided access to the racemic allylic alcohol (±)-**10**. In our experiments ^{t}BuLi was found essential for good and reproducible results (56% yield). Other metalation reagents [e.g., ^{n}BuLi, ^{s}BuLi, LiTMP,[25] $(TMP)_2Mg$[25]] gave lower yields or did not lead to rearranged products at all. The *trans* configuration of the homoallylic alcohol (±)-**10** was confirmed by the ^{1}H NMR coupling constants of H6−H7 (*dd*, $^3J_{H,H}$ = 9.4, 9.4 Hz), in perfect

Scheme 2. Synthesis of the Epoxide Diastereomers (±)-20a and (±)-20b



accordance with the published data.[13] Concomitant α' lithiation led to the regioisomer (±)-**17** (27% yield), also via a [2,3]-Wittig pathway. In addition, the α and α' [1,2] rearrangement products (±)-**18** and (±)-**19** were isolated as minor byproducts (both ∼8% yield) and fully characterized. Attempts aiming at an asymmetric [2,3]-Wittig rearrangement using chiral BOX ligands[26−29] together with various organolithium bases remained unsuccessful (see Table S1).

The 10-membered germacrane ring was then exposed to hydroxyl-directed epoxidation conditions. The α [2,3] product (±)-**10** gave the diastereomeric epoxy alcohols (±)-**20a** and (±)-**20b**. Compound (±)-**20a** displays the same relative configuration as (−)-parthenolide (**1**), whereas compound (±)-**20b** is a parthenolide diastereomer with regard to the C4−C5 epoxide configuration (Scheme 2). The stereochemistry of both epoxides was assigned by NOE correlations combined with DFT-based geometry modeling (B3LYP/6-31G*) of selected stereoisomers (Figure 2 and SI, backbone methyl group orientation:[30] U = up, D = down). Interestingly, the product ratio of the epoxidation was temperature dependent so that the amount of the kinetically unfavored diastereomer (±)-**20b** could be increased at higher temperature. Unfortunately, enantioselective epoxidation methods by Sharpless[31] or Yamamoto[32] were unproductive, apparently due to the poor differentiation of both diastereotopic faces of the alcohol and the flexibility of the germacrane ring.[30] Similar findings were reported by Li et al.[20]

With both epoxides (±)-**20a** and (±)-**20b** in hand, the oxidative functionalization of the isopropenyl side chain was studied. Unexpectedly, attempts for direct oxidation using conditions for dihydroxylation (Sharpless' AD-Mix α or β, OsO_4/NMO, OsO_4/TMEDA[33]), hydroboration−oxidation (9-BBN/NaOOH, $[(Ph_3P)_3RhCl]$/catBH/NaOOH), or allylic chlorination $[Ca(OCl)_2/CO_2$, NaOCl/$CeCl_3]$,[34,35] all of which are typically sensitive to sterics, either led exclusively

DOI: 10.1021/acs.joc.6b01985
J. Org. Chem. 2016, 81, 11009−11016

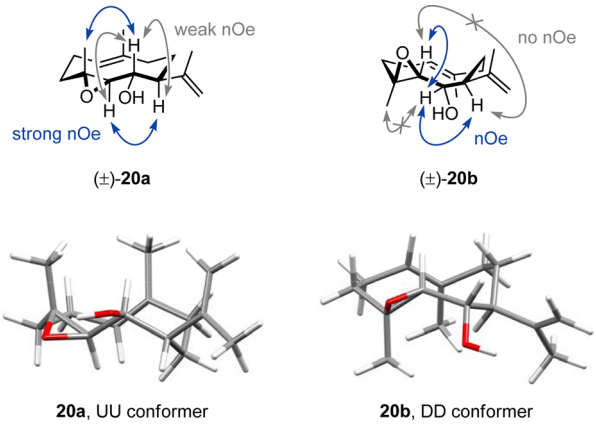


Figure 2. Structure elucidation employing NOESY and optimized equilibrium geometries (DFT B3LYP/6-31G*) of the epoxides (±)-21a and (±)-20b.

to the functionalization of the trisubstituted endocyclic double bond or to decomposition of the starting material. Apparently, electronics or strain render the endocyclic olefin particularly reactive toward electrophiles.

Finally, we were able to address the exocyclic double bond by using a Bartlett–Smith iodocarbonate cyclization.[36] Hence, the epoxy alcohols were converted into the *tert*-butyl carbonates (±)-**22a** and (±)-**22b** which were treated with IBr at low temperature.[36] In case of compound (±)-**22b** the iodocarbonate (±)-**23b** was produced as a single diastereomer (Scheme 3). The stereochemistry of iodocarbonate (±)-**23b** was assigned by SELNOESY experiments (see SI). Surprisingly, diastereomer (±)-**22a** remained unreactive under these conditions and decomposed when the reaction temperature was increased. Other iodine electrophiles (IBr, ICl, I_2, $[Py_2I][BF_4]$) did not lead to an improvement. Conformational restrictions in the polycyclic transition state or a facilitated (Lewis) acid-induced transannular cyclization[15] in case of compound (±)-**22a** probably account for the different reactivity. For diastereomer (±)-**22b** the latter could be prevented by the low reaction temperature and an optimized work up procedure.

After successful functionalization of the side chain the iodocarbonate had to be transformed into the triol (±)-**9b**. We developed a two step sequence including exchange of the hindered neopentyl iodide in (±)-**23b** for an acetate [(±)-**24b**], followed by hydrolysis to release the triol (±)-**9b**. The first transformation was accomplished using CsOAc and 18-crown-6 at elevated temperature.[37] We were pleased to find that the low observed reaction rate could be increased by using microwave heating. The acetate and the carbonate of compound (±)-**24b** were then cleaved by catalytic transesterification, leading to triol (±)-**9b** (Scheme 3).

For the oxidative lactonization two chemoselectivity issues had to be addressed: (1) the preferential oxidation of the 1° alcohol in the initial step and (2) suppression of glycol cleavage,[38] leading to the undesired ketone (±)-**25b** (Table 1).

The ketone (±)-**25b** was the major product in the presence of $PhI(OAc)_2$ and catalytic TEMPO (Entry 1).[39] When the co-oxidant was exchanged for $NaClO_2$ or NaOCl/HOBr the reaction rate dropped drastically and traces of the desired lactone were produced (Entry 2,3). Noteworthy, no detectable amount of ketone (±)-**25b** was formed in these reactions. The use of preformed[40] $TEMPO^+Cl^-$ as oxidant led to rapid decomposition of the triol (Entry 4). Also Fétizon's reagent[41,42] proved to be ineffective (Entry 5). Finally employing catalytic TPAP (Ley–Griffith oxidation)[21] led to formation of the α-

Scheme 3. Synthesis of the Parthenolide Isomer (±)-8 Starting From Epoxide (±)-20b

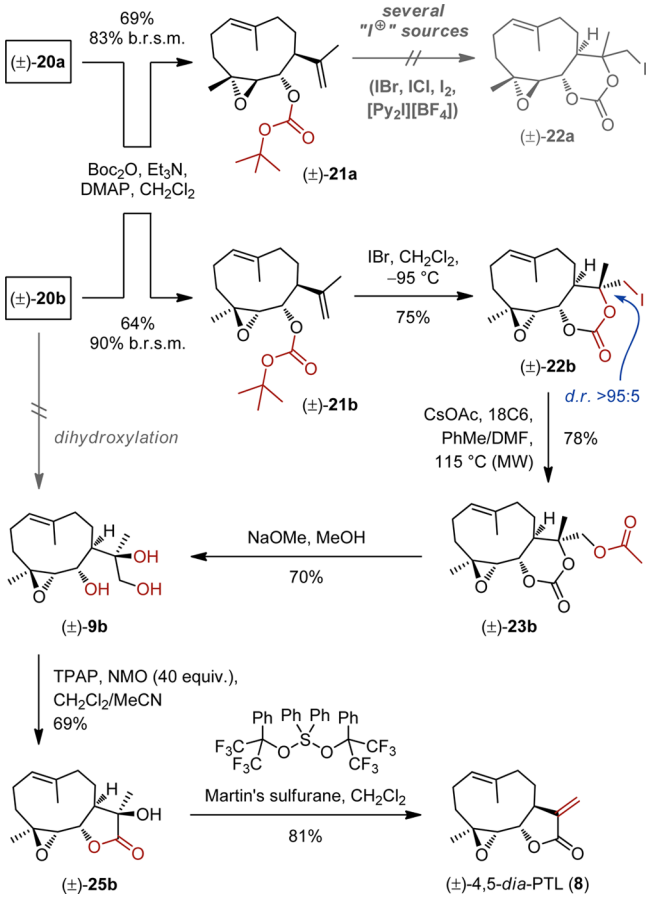
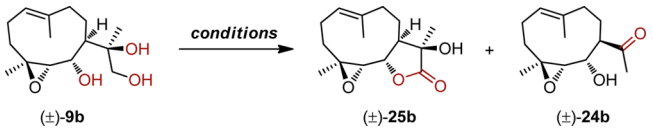


Table 1. Optimization of the Oxidative Lactonization of Triol (±)-9b.[a]



			isol. yield/%	
entry	catalyst (equiv)	(co)oxidant (equiv)	(±)-25b	(±)-24b
1	TEMPO (0.3)	$PhI(OAc)_2$ (1.5)	0	71
2	TEMPO (0.5) NaOCl (0.3)	$NaClO_2$ (4)	traces	0
3	TEMPO (0.5)	NaOCl (4) KBr (1)	traces	0
4		$TEMPO^+Cl^-$ (4)	decomp.	
5		Ag_2CO_3/Celite (7)	traces	0
6[b]	TPAP (0.2)	NMO (4)	39	28
7[b]	**TPAP (0.2)**	**NMO (40)**	**69**	7

[a]Entry—solvent(s)—temperature: 1—CH_2Cl_2—r.t., 2—MeCN/pH 7 buffer—r.t. to 55 °C, 3—CH_2Cl_2/aq. $NaHCO_3$—0 °C, 4—CH_2Cl_2—0 °C to r.t., 5—PhMe—90 °C, 6,7—CH_2Cl_2/MeCN—r.t. NMO = *N*-methylmorpholine *N*-oxide, TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl, TPAP = tetrapropylammonium perruthenate. [b]Additive: 3 Å molecular sieves.

DOI: 10.1021/acs.joc.6b01985
J. Org. Chem. 2016, 81, 11009–11016

hydroxy lactone (±)-**26b** in good yield (69%, entry 7). A large excess of the co-oxidant NMO[43] (40 equiv) minimized the glycol cleavage side reaction (~10:1). Apparently, a swift reoxidation of the TPAP catalyst helps to suppress the glycol cleavage.

A *syn* elimination of the tertiary alcohol in lactone (±)-**26b** using Martin's sulfurane[44] then proceeded as expected and delivered the parthenolide diastereomer (±)-**8** in good yield (81%, Scheme 3).

In summary, the total synthesis of the novel C4C5 parthenolide diastereomer (±)-**8**, showing a hitherto unknown C4−C5-*trans* C5−C6-*cis* configuration, was accomplished in 13 steps and an overall yield of 1.75% starting from commercially available (*E*,*E*)-farnesol (**11**). All side products of the 13→10 ring contraction by a [2,3]-Wittig rearrangement were characterized. The challenging isopropenyl side chain oxidation was successfully achieved by utilizing a newly developed stepwise dihydroxylation, employing a Bartlett−Smith iodocarbonate cyclization followed by I→OAc exchange and hydrolysis. These results should be instrumental for other studies on α-methylene-γ-butyrolactone-containing terpenes and make unnatural isomers of parthenolide accessible to biological study.

EXPERIMENTAL SECTION

Instrumentation. NMR spectra (^{1}H/^{13}C{^{1}H}) were recorded at 250/63 MHz, 300/75 MHz or 400/101 MHz (*Z*-gradient broad band observe or inverse probe). Chemical shifts (δ) are expressed in parts per million (ppm) with respect to the solvent signal (^{13}C{^{1}H} NMR, δ_C: C_6D_6 128.06, $CDCl_3$ 77.16) or the residual nondeuterated solvent signal (^{1}H NMR, δ_H: C_6D_5H 7.16, $CHCl_3$ 7.26), respectively. Broad signals (*br*) are the result of the known slow conformational isomerism[15,30,45] which was confirmed by NOESY experiments in selected cases. Structural assignments were done employing HSQC/DEPT135, HMBC, and NOESY experiments. Microwave reactions were performed in capped vials under nitrogen atmosphere in a single-mode microwave synthesizer, equipped with a noninvasive IR sensor for temperature measurement (accuracy: ± 2%). Preparative HPLC (achiral stationary phase: VP 250/21 Nucleodur C_{18} Gravity 5 μm) purification of compounds was performed using MeCN/H_2O gradients at 20 mL/min flow rate.

General Methods and Materials. Unless otherwise stated all reactions of air/water sensitive substances were carried out using standard Schlenk techniques under a positive pressure of nitrogen. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F_{254} supported on aluminum sheets. Substances were detected by UV quenching (254 nm) or using a staining solution (acidic ethanolic *p*-anisaldehyde). Silica gel 60 (40−63 μm) was used for flash column chromatography (approximately 0.3 bar positive pressure).[46]

Reagents available from commercial sources were used without further purification with the following exceptions: Acetic anhydride was treated with P_2O_5, filtered, followed by treatment with K_2CO_3 and distilled afterward. Anhydrous amines (Et_3N, DIPEA, pyridine) were obtained by distillation from CaH_2. Anhydrous DMF, THF, and PhMe were obtained from a solvent purification system (HPLC grade solvents), prior to use. Anhydrous CH_2Cl_2 was obtained by distillation from CaH_2 or by storing HPLC grade CH_2Cl_2 over 3 Å molecular sieves for 24 h.[47] Anhydrous Et_2O was obtained by distilling predried ($CaCl_2$) and peroxide free (aq. Na_2SO_3) material from Na/benzophenone. Methanol (HPLC grade) was dehydrated by storing over 3 Å molecular sieves (min. 48 h)[47] and *N*-methylmorpholine *N*-oxide (NMO) by heating the commercial material at 40 °C in a fine vacuum (10^{-2}−10^{-3} mbar) for 4 h. $CDCl_3$ was passed through a short column of activated basic Al_2O_3 (63−200 μm, activity I) directly before use. Deionized water was used for all experiments. pH 7 phosphate buffer (0.5 m) was prepared by dissolving 58.8 g $Na_3PO_4 \times 12H_2O$ (144 mmol), 42.7 g NaH_2PO_4 (356 mmol) and 113 mg NaN_3 (1.74 mmol) in 900 mL water and filling up to a total volume of 1 L. The concentration of ^{t}BuLi solutions was determined by 3-fold titration using 4-biphenyl acetic acid in THF. Abbreviations: MTBE = methyl *tert*-butyl ether, PE = light petroleum (bp. 35−70 °C). (*E*,*E*)-farnesyl acetate (**12**) was prepared according to a literature procedure.[48]

*(2E,6E,10E)-12-Chloro-3,7,11-trimethyldodeca-2,6,10-trienyl Acetate (**14**).* Following a modified procedure anhydrous LiCl (305 mg, 7.20 mmol, 1.3 equiv) was dissolved in anhydrous DMF (45 mL) and cooled to 0 °C. To this mixture a solution of the allylic alcohol **13**[49] (1.58 g, 5.63 mmol, 1.0 equiv) in DMF (7 mL) was added followed by anhydrous pyridine (0.60 mL, 0.59 g, 7.49 mmol, 1.3 equiv). After 10 min at 0 °C methanesulfonyl chloride (0.54 mL, 0.80 g, 7.32 mmol, 1.2 equiv) was added dropwise. After 3 h at that temperature another equivalent of methanesulfonyl chloride (0.44 mL, 0.64 g, 5.63 mmol) was added and the solution was stirred for additional 2 h (TLC control: heptanes/acetone, 7:3). Then saturated $NaHCO_3$ solution (50 mL) was added and the mixture was stirred for 15 min. MTBE (50 mL) was added and the layers were separated. The aq. layer was extracted with MTBE (3 × 30 mL). The combined organic extracts were washed with saturated $CuSO_4$ solution (40 mL), water (2 × 20 mL), and brine (40 mL); dried with $MgSO_4$; filtered; and the solvent was removed *in vacuo*. The allylic chloride **14** (495 mg, 1.66 mmol, 95%) was obtained as slightly yellow oil and used without further purification. The NMR data were in accordance with published data.[50]

*(2E,6E,10E)-12-Chloro-3,7,11-trimethyldodeca-2,6,10-trien-1-ol (**15**).* Following a modified procedure a NaOMe solution (20 mL, 1.50 mmol, 0.5 equiv., 75 mM in MeOH) was cooled to 0 °C and added dropwise (cannula transfer) to a 0 °C cooled solution of the acetate **14** (910 mg, 3.05 mmol, 1.0 equiv) in anhydrous MeOH (10 mL). After the addition was completed the reaction mixture was warmed to 10 °C and kept at this temperature for 4 h (TLC control: heptanes/acetone, 3:1). The solution was neutralized using aq. HCl (1 M). Brine (20 mL) and CH_2Cl_2 (30 mL) were added and the organic layer was separated afterward. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried with $MgSO_4$, filtered and the solvent was removed *in vacuo*. The allylic alcohol **15** (740 mg, 2.90 mmol, 94%) was obtained as slightly yellow oil and used without further purification. The NMR data were in accordance with published data.[50]

*(3E,7E,11E)-3,7,11-Trimethyloxacyclotrideca-3,7,11-triene (**16**).* NaH (825 mg, 20.6 mmol, 60 *w*-% suspension in mineral oil, 4.0 equiv) was added to a stirred solution of 18-crown-6 (5.44 g, 13.6 mmol, 4.0 equiv) in anhydrous toluene (770 mL). The suspension was refluxed for 15 min and afterward a solution of the allylic alcohol **15** (1.26 g, 4.91 mmol, 1.0 equiv) in anhydrous toluene (50 mL) was added dropwise by using a syringe pump (0.12 mL/min). After complete addition (~7 h) the mixture was stirred for another hour (TLC control: heptanes/acetone, 3:1) and then cooled to 0 °C, neutralized by dropwise addition of saturated aq. NH_4Cl solution, and concentrated *in vacuo*. The residual oil was dissolved in MTBE (50 mL) and transferred to a separation funnel. Water (50 mL) was added and the layers were separated. The aqueous layer was extracted with MTBE (3 × 30 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried with $MgSO_4$, filtered, and the solvent was removed *in vacuo*. After column chromatography (PE/EtOAc, 30:1, 6 × 20 cm) the macrocyclic ether **16** (768 mg, 3.49 mmol, 71%) was obtained as colorless oil. The NMR data were in accordance with published data.[13]

(1R,2E,6E,10S*)-3,7-Dimethyl-10-(prop-1-en-2-yl)cyclodeca-2,6-dienol [(±)-**10**].* Following a modified procedure a stirred solution of the cyclic ether **16** (305 mg, 1.38 mmol, 1.0 equiv) in anhydrous Et_2O (9 mL) was cooled to −60 °C. After 10 min at this temperature a solution of ^{t}BuLi (2.44 mL, 4.15 mmol, 3.0 equiv., 1.7 M in hexane) was added dropwise and the reaction mixture was stirred for 14 h at −60 °C (TLC control: heptanes/MTBE, 4:1). The reaction was terminated by the addition of MeOH (1 mL) at −60 °C. The cooling bath was replaced by an ice bath and the mixture was neutralized with saturated aq. NH_4Cl solution. The organic layer was separated and the aqueous layer extracted with MTBE (3 × 20 mL). The combined

DOI: 10.1021/acs.joc.6b01985
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organic extracts were washed with brine (30 mL), dried with $MgSO_4$, filtered, and the solvent was removed *in vacuo* at 25 °C. After column chromatography (PE/MTBE, 6:1 + 1% $EtNMe_2$, 3 × 25 cm) the following products were obtained in order of elution as colorless oils: α' [2,3] product (±)-**17** (82.0 mg, 0.37 mmol, 27%), the desired α [2,3] product (±)-**10** (167 mg, 0.76 mmol, 56%), α' [1,2] product (±)-**19** (24.0 mg, 0.11 mmol, 8.0%), and α [1,2] product (±)-**18** (24.0 mg, 0.11 mmol, 8.0%). The NMR data for both products (±)-**10** and (±)-**17** were in accordance with published data.[13] α' [1,2] product (±)-**19**. TLC: R_f = 0.21 (heptanes/MTBE, 4:1); ^{1}H NMR (300 MHz, C_6D_6): δ = 4.90 (dd, 1H, $^3J_{H,H}$ = 10.0, 4.8 Hz, C=C(H)CH_2), 4.82 (dd, 1H, $^3J_{H,H}$ = 9.7, 5.6 Hz, C=C(H)CH_2), 4.72 (dd, 1H, $^3J_{H,H}$ = 9.3, 4.6 Hz, C=C(H)CH_2), 3.94 (dd, 1H, $^3J_{H,H}$ = 9.7, 4.1 Hz, C(H)OH), 2.40 (pseudo dt, 1H, $^{2/3}J_{H,H}$ = 13.4, 9.8 Hz, HOC(H)C(H)H′), 2.26–1.87 (m, 9H, 4 × CH_2 + HOC(H)C(H)H′), 1.46 (s, 3H, CH_3), 1.40 (s, 6H, 2 × CH_3), 1.20 (br s, 1H, OH); ^{13}C{^{1}H} NMR (75 MHz, C_6D_6): δ = 136.4 (C=C(CH_2)CH_3), 134.2 (C=C(CH_2)CH_3), 132.8 (C=C(CH_2)CH_3), 127.1 (C=C(H)CH_2), 126.8 (C=C(H)CH_2), 122.7 (C=C(H)CH_2), 78.4 (C(H)OH), 40.0 (CH_2), 39.9 (CH_2), 33.8 (HOC(H)C(H)H′), 25.7 (CH_2), 25.1 (CH_2), 15.4 (CH_3), 15.2 (CH_3), 10.8 (CH_3); IR (ATR): $\tilde{\nu}$ = 3773(w), 3657(w), 3341(m), 2947(s), 2909(s), 2847(s), 2646(w), 2168(w), 2029(w), 1975(w), 1674(w), 1443(m), 1383(w), 1358(w), 1319(w), 1227(w), 1150(w), 1018(s), 918(w), 833(m) cm^{-1}; HRMS (ESI–TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{15}H_{24}ONa$ 243.1719; Found 243.1717.

α [1,2] product (±)-**18**. TLC: R_f = 0.13 (heptanes/MTBE, 4:1); ^{1}H NMR (300 MHz, C_6D_6): δ = 4.85 (d, 1H, $^3J_{H,H}$ = 9.6 Hz, C=C(H)CH_2), 4.82–4.75 (m, 1H, C=C(H)CH_2), 4.75–4.67 (m, 1H, C=C(H)CH_2), 4.41 (ddd, 1H, $^3J_{H,H}$ = 10.8, 9.8, 4.1 Hz, C(H)OH), 2.52–2.45 (m, 1H, HOC(H)C(H)H′), 2.25–1.78, (m, 9H, 4 × CH_2 + HOC(H)C(H)H′), 1.39 (s, 3H, CH_3), 1.35 (s, 6H, 2 × CH_3), 1.23 (br s, 1H, OH); ^{13}C{^{1}H} NMR (75 MHz, C_6D_6): δ = 135.9 (C=C(CH_2)CH_3), 133.4 (C=C(CH_2)CH_3), 131.1 (C=C(CH_2)CH_3), 130.7 (C=C(H)CH_2), 128.7 (C=C(H)CH_2), 126.3 (C=C(H)CH_2), 66.7 (C(H)OH), 49.3 (HOC(H)C(H)H′), 40.3 (CH_2), 40.2 (CH_2), 25.5 (CH_2), 16.3 (CH_3), 15.4 (CH_3), 15.1 (CH_3); IR (ATR): $\tilde{\nu}$ = 3773(w), 3294(m), 3055(w), 2978(m), 2909(s), 2847(m), 2646(w), 2168(w), 2029(w), 1983(w), 1674(w), 1589(w), 1443(m), 1381(m), 1327(w), 1196(w), 1126(w), 1003(m), 825(w) cm^{-1}; HRMS (ESI–TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{15}H_{24}ONa$ 243.1719; Found 243.1718.

*Epoxy Alcohols (±)-**20a** and (±)-**20b**.* The allylic alcohol (±)-**10** (1.2 g, 5.4 mmol, 1.0 equiv) and [VO(acac)$_2$] (265 mg, 1.0 mmol, 0.2 equiv) were dissolved in anhydrous CH_2Cl_2 (65 mL). The turquoise-green solution was placed in a preheated oil bath (50 °C) and stirred for 5 min at reflux whereupon a *tert*-butyl hydroperoxide solution (1.14 mL, 5.7 mmol, 1.05 equiv., 5 M in decane) was added in 2 portions (second after 10 min). After 20 min (TLC control: heptanes/MTBE, 3:1) the solution was cooled to 0 °C. Aqueous saturated Na_2SO_3 solution (3 mL) was added and the mixture was stirred for 10 min. Water (30 mL) was added, the organic layer was separated, and the aqueous layer extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine (100 mL), dried with $MgSO_4$, filtered, and the solvent was removed *in vacuo* at 25 °C. After column chromatography (PE/MTBE, 3:1, 5 × 22 cm) the following products were obtained in order of elution: (1*S**,10*S**)-epoxide (±)-**20b** (436 mg, 1.84 mmol, 34%) as a colorless oil and the (1*R**,10*R**)-epoxide (±)-**20a** (581 mg, 2.46 mmol, 46%) as a colorless solid. (1*S**,10*S**)-epoxide (±)-**20b**. TLC: R_f = 0.42 (heptanes/MTBE, 3:1); ^{1}H NMR (400 MHz, C_6D_6): δ = 4.97 (br s, 1H, C=C(H)CH_2), 4.83 (s, 1H, C=C(H)H′), 4.80 (s, 1H, C=C(H)H′), 3.82 (d, 1H, $^3J_{H,H}$ = 11.0 Hz, C(H)OH), 2.54 (s, 1H, (H)C(O)C, epoxide), 2.11 (d, 1H, $^3J_{H,H}$ = 9.9 Hz, HOC(H)C(H)), 2.06–1.90 (m, 3H, C(H)H′ + CH_2), 1.86–1.67 (m, 5H, CH_2 + CH_3), 1.46 (br s, 3H, CH_3), 1.39–1.26 (m, 4H, C(H)H′ + CH_3), 1.20–1.02 (m, 2H, CH_2); ^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ = 148.0 (br, C=CH_2), 135.5 (br, C=C(CH_2)CH_3), 124.9 (br, C=C(H)CH_2), 111.5 (C=CH_2), 68.6 (br, C(H)OH), 65.5 ((H)C(O)C, epoxide), 61.1 ((H)C(O)C, epoxide), 50.0 (br, HOC(H)C(H)), 38.2 (br, 2C, 2 × CH_2), 30.0 (br, 2C, CH_2 + CH_3), 24.0 (br, CH_2), 18.4 (CH_3), 16.2 (CH_3); IR (ATR): $\tilde{\nu}$ = 3703(w), 3487(w), 3071(w), 2924(m), 2855(m), 2662(w), 2168(w), 2029(w), 1975(w), 775(w), 1643(w), 1450(m), 1381(m), 1296(w), 1219-(w),1026(w),972(w), 918(m),887(s), 694(m) cm^{-1}; HRMS (ESI–TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{15}H_{24}O_2Na$ 259.1669; Found 259.1671.

(1*R**,10*R**)-epoxide (±)-**20a**. TLC: R_f = 0.27 (heptanes/MTBE, 3:1); Mp. 51–53 °C (PE/MTBE); ^{1}H NMR (400 MHz, C_6D_6): δ = 4.93–4.77 (m, 3H, C=C(H)CH_2 + C=CH_2), 3.23 (dd, 1H, $^3J_{H,H}$ = 8.5, 8.3 Hz, C(H)OH), 2.59 (d, 1H, $^3J_{H,H}$ = 8.3 Hz, (H)C(O)C, epoxide), 2.22 (ddd, 1H, $^3J_{H,H}$ = 8.5, 7.6, 0.9 Hz, HOC(H)C(H)), 2.13–1.91 (m, 3H, CH_2 + C(H)H′), 1.90–1.80 (m, 2H, CH_2), 1.78 (s, 3H, CH_3), 1.58 (ddt, 1H, $^3J_{H,H}$ = 14.9, 7.6, 1.6 Hz, C(H)H′), 1.40–1.27 (m, 4H, C(H)H′ + CH_3), 1.13–1.03 (m, 1H, C(H)H′), 1.01 (s, 3H, CH_3); ^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ = 149.5 (C=CH_2), 135.6 (br, C=C(CH_2)CH_3), 124.8 (C=C(H)CH_2), 110.9 (C=CH_2), 70.9 (C(H)OH), 70.7 ((H)C(O)C, epoxide), 63.6 ((H)C(O)C, epoxide), 56.0 (HOC(H)C(H)), 40.4 (br, C(H)H′), 37.8 (br, C(H)H′), 33.1 (br, C(H)H′), 23.9 (br, C(H)H′), 19.3 (CH_3), 17.4 (2 × CH_3); IR (ATR): $\tilde{\nu}$ = 3703(w), 3472(w), 3071(w), 2970(m), 2924(s), 2862(m), 2167(w), 2021(w), 1983(w), 1643(w), 1443(m), 1381(m), 1288(w), 1204(w),1065(m), 1026(m), 880(m), 833(m), 671(w) cm^{-1}; HRMS (ESI–TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{15}H_{24}O_2Na$ 259.1669; Found 259.1673.

tert-Butyl [(1S,2S*,3S*,10S*,E)-6,10-Dimethyl-3-(prop-1-en-2-yl)-11-oxabicyclo[8.1.0] undec-6-en-2-yl] Carbonate [(±)-**22b**].* To a solution of the epoxy alcohol (±)-**20b** (460 mg, 1.95 mmol, 1.0 equiv), DMAP (123 mg, 1.01 mmol, 0.52 equiv) and anhydrous Et_3N (281 μL, 205 mg, 2.03 mmol, 1.05 equiv) in anhydrous CH_2Cl_2 (8 mL) was added a solution of Boc_2O (1.1 g, 5.08 mmol, 2.60 equiv) in anhydrous CH_2Cl_2 (3 mL) dropwise at 25 °C and the solution was allowed to stir for 17 h (TLC control: heptanes/MTBE, 3:1). The reaction mixture was directly filtered through a short silica pad (CH_2Cl_2/PE, 10:1) and the orange filtrate was concentrated *in vacuo* at 25 °C. The residual oil was purified by column chromatography (PE/MTBE, 5:1 → 2:1, 1 × 25 cm) to isolate in order of elution the carbonate (±)-**22b** (412 mg, 1.22 mmol, 64%, 90% b.r.s.m.) as a colorless solid and recovered starting material (±)-**20b** (141 mg, 0.60 mmol, 31%) as a colorless oil. TLC: R_f = 0.54 (heptanes/MTBE, 3:1); Mp. 86–88 °C (PE/MTBE); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.39–5.20 (br s, 1H, C=C(H)CH_2), 5.02 (dd, 1H, $^3J_{H,H}$ = 11.8, 3.1 Hz, C(H)OBoc), 4.77–4.66 (m, 2H, C=CH_2), 2.79 (br s, 1H, (H)C(O)C, epoxide), 2.37–2.16 (m, 4H, CH_2 + C(H)H′ + C(H)C_{quart}), 2.11–1.99 (m, 1H, C(H)H′), 1.97–1.80 (m, 1H, C(H)H′), 1.71 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 1.64–1.55 (m, 2H, CH_2), 1.44 (s, 9H, 3 × CH_3, Boc), 1.39 (s, 3H, CH_3), 1.27–1.13 (m, 1H, C(H)H′); ^{13}C{^{1}H} NMR (75 MHz, C_6D_6): δ = 153.2 (OCO_2), 146.3 (C=C(H)H′), 135.8 (br, C=C(CH_2)CH_3), 125.0 (br, C=C(H)CH_2), 112.1 (C=CH_2), 81.8 ($CO_2C(CH_3)_3$), 72.1 (C(H)OCO_2), 63.4 ((H)C(O)C, epoxide), 60.3 ((H)C(O)C, epoxide), 47.8 (br, C(H)C_{quart}), 38.2 (br, CH_2), 30.3 (2C, br, 2 × CH_2), 27.9 ($CO_2C(CH_3)_3$), 23.8 (br, CH_2), 18.3 (2C, 2 × CH_3), 16.0 (CH_3); IR (ATR): $\tilde{\nu}$ = 3657(w), 3078(w), 2970(w), 2924(w), 2870(w), 1736(s), 1651(w), 1450(w), 1389(m), 1366(m), 1281(s), 1250(s), 1165(s), 1103(s), 864(s), 795(m), 694(w) cm^{-1}; HRMS (ESI–TOF) *m/z*: [M +Na]$^+$ Calcd for $C_{20}H_{32}O_4Na$ 359.2193; Found 359.2200.

tert-Butyl [(1R,2S*,3S*,10R*,E)-6,10-Dimethyl-3-(prop-1-en-2-yl)-11-oxabicyclo[8.1.0] undec-6-en-2-yl] Carbonate [(±)-**22a**].* To a solution of the epoxy alcohol (±)-**20a** (365 mg, 1.54 mmol, 1.00 equiv), DMAP (94 mg, 0.77 mmol, 0.50 equiv), and anhydrous Et_3N (280 μL, 202 mg, 2.00 mmol, 1.30 equiv) in anhydrous CH_2Cl_2 (5.5 mL) was added a solution of Boc_2O (840 mg, 3.85 mmol, 2.50 equiv) in anhydrous CH_2Cl_2 (2.5 mL) dropwise at 25 °C and the solution was allowed to stir for 13 h (TLC control: heptanes/MTBE, 3:1). The reaction mixture was directly filtered through a short silica pad (CH_2Cl_2/PE, 10:1) and the orange filtrate was concentrated *in vacuo* at 25 °C. The residual oil was purified by column chromatography (PE/MTBE, 7:1 → 2:1, 2 × 20 cm) to isolate in order of elution the carbonate (±)-**22a** (254 mg, 1.07 mmol, 69%, 84% b.r.s.m.) and recovered starting material (±)-**20a** (65.2 mg, 0.28 mmol, 18%), both as colorless solids. TLC: R_f = 0.49 (heptanes/MTBE, 3:1); Mp. 109–

DOI: 10.1021/acs.joc.6b01985
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111 °C (PE/MTBE); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.27−5.15 (m, 1H, C=C(H)CH_2), 4.73 (s, 1H, C=C(H)H′), 4.67 (s, 1H, C=C(H)H′), 4.43 (dd, 1H, $^3J_{H,H}$ = 8.8, 8.6 Hz, C(H)OBoc), 2.80 (d, 1H, $^3J_{H,H}$ = 8.8 Hz, (H)C(O)C, epoxide), 2.49 (t, 1H, $^3J_{H,H}$ = 8.5 Hz, C(H)C_{quart}), 2.37−2.15 (m, 3H, CH_2 + C(H)H′), 2.10 (dd, 1H, $^{2,3}J_{H,H}$ = 13.8, 4.7 Hz, C(H)H′), 1.99 (t, 1H, $^2J_{H,H}$ = 12.4 Hz, C(H)H′), 1.80 (dd, 1H, $^{2,3}J_{H,H}$ = 15.1, 7.4 Hz, C(H)H′), 1.70 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.63−1.54 (m, 1H, C(H)H′), 1.44 (s, 9H, 3 × CH_3, Boc), 1.35 (s, 3H, CH_3), 1.30−1.14 (m, 1H, C(H)H′); ^{13}C{^{1}H} NMR (75 MHz, C_6D_6): δ = 153.2 (OCO_2), 147.5 (C=C(H)H′), 136.3 (br, C=C(CH_2)CH_3), 124.6 (C=C(H)CH_2), 111.5 (C=CH_2), 81.8 ($CO_2C(CH_3)_3$), 76.6 (C(H)OCO_2), 67.7 ((H)C(O)C, epoxide), 63.2 ((H)C(O)C, epoxide), 53.7 (br, C(H)C_{quart}), 40.0 (br, CH_2), 37.3 (br, CH_2), 33.1 (br, CH_2), 27.9 (CH_3, Boc), 23.5 (br, CH_2), 19.1 (CH_3), 18.0 (br, CH_3), 17.2 (CH_3); IR (ATR): $\tilde{\nu}$ = 3657(w), 2970(w), 2932(w), 2870(w), 2180(w), 2029(w), 1975(w), 1728(s), 1458(w), 1389(w), 1366(w), 1327(m), 1281(s), 1258(s), 1157(s), 1088(w), 949(w), 856(s), 787(m), 710(w) cm^{-1}; HRMS (ESI−TOF) m/z: [M+Na]+ Calcd for $C_{20}H_{32}O_4Na$ 359.2193; Found 359.2196.

*Iodocarbonate (±)-**23b**.* A stirred solution of the carbonate (±)-**22b** (148 mg, 0.44 mmol, 1.00 equiv) in "anhydrous" (see note) CH_2Cl_2 (8 mL) was cooled to −95 °C. Then a solution of IBr (93.1 mg, 0.45 mmol, 1.02 equiv) in "anhydrous" CH_2Cl_2 (3 mL) was added dropwise over 5 min and the solution was stirred for 2.5 h at −95 °C (TLC control: CH_2Cl_2/MTBE, 30:1). (NOTE: The reaction rate strongly depended on the water content of CH_2Cl_2. Best results were obtained when the solvent was dried by refluxing for 1 h over CaH_2 and distilled afterward. Prolonged drying or storing over 3 Å molecular sieves (min. 24 h) resulted in reaction times >5 h without full conversion and increased formation of side products.) The reaction was terminated at −95 °C by the addition of a 1:1 mixture of aq. Na_2SO_3 (1.5 mL, 10%) and aq. $NaHCO_3$ (1.5 mL, 5%) and mechanically stirred until disappearance of the orange red color. Then the mixture was warmed to 0 °C, the organic layer was separated and the aqueous was extracted with CH_2Cl_2 (3 × 5 mL).The combined organic extracts were washed with brine (10 mL), dried with $MgSO_4$, filtered and the solvent was removed *in vacuo* at 25 °C. After column chromatography (CH_2Cl_2/MTBE, 30:1, 2 × 16 cm) the iodocarbonate (±)-**23b** (134 mg, 0.33 mmol, 75%) was obtained as a colorless solid. TLC: R_f = 0.30 (CH_2Cl_2/MTBE, 30:1); Mp. 96−98 °C (decomp.); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.67−5.55 (m, 1H, C=C(H)CH_2), 4.71 (dd, 1H, $^3J_{H,H}$ = 11.7, 2.5 Hz, C(H)OBoc), 3.52 (d, 1H, $^2J_{H,H}$ = 11.6 Hz, C(H)H′I), 3.45 (d, 1H, $^2J_{H,H}$ = 11.6 Hz, C(H)H′I), 2.65 (d, 1H, $^3J_{H,H}$ = 1.8 Hz, (H)C(O)C, epoxide), 2.49−2.31 (m, 3H, 2 × C(H)H′ + C(H)C_{quart}), 2.24−2.12 (m, 2H, 2 × C(H)H′), 2.11−2.01 (m, 1H, C(H)H′), 1.66 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.49−1.41 (m, 5H, CH_3 + CH_2), 1.36−1.25 (m, 1H, C(H)H′); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 146.7 (OCO_2), 136.1 (br, C=C(CH_2)CH_3), 124.2 (br, C=C(H)CH_2), 82.7 (CCH_2I), 75.7 (C(H)OCO_2), 62.3 ((H)C(O)C, epoxide), 60.5 ((H)C(O)C, epoxide), 39.9 (C(H)C_{quart}), 37.9 (br, CH_2), 37.3 (CH_2), 25.1 (CH_2), 22.7 (CH_2), 20.2 (CH_3), 17.7 (br, CH_3), 16.0 (CH_3), 13.2 (CH_2I); IR (ATR): $\tilde{\nu}$ = 3418(w), 2924(w), 2862(w), 2330(w), 1728(s), 1450(w), 1389(m), 1366(m), 1288(m), 1250(m), 1227(m), 1173(m), 1119(m), 1057(m), 1003(w), 980(w), 949(w), 878(m), 833(w), 756(m), 733(w), 633(m) cm^{-1}; HRMS (ESI−TOF) m/z: [M+Na]$^+$ Calcd for $C_{16}H_{23}IO_4Na$ 429.0533; Found 429.0529.

*Acetoxy Carbonate (±)-**24b**.* The iodocarbonate (±)-**23b** (109 mg, 0.27 mmol, 1.0 equiv), CsOAc (518 mg, 2.70 mmol, 10.0 equiv), and 18-crown-6 (214 mg, 0.81 mmol, 3.0 equiv) were weighed in a microwave vial opened to air which was sealed afterward and the atmosphere was exchanged for nitrogen by 3 evacuate/refill cycles. The solids were suspended in anhydrous PhMe and DMF (2:1, 13.5 mL) and the mixture was then heated to 115 °C for 9 h in a microwave reactor (TLC control: CH_2Cl_2/MTBE, 12:1) followed by the addition of pH 7 phosphate buffer solution (15 mL, 0.5 m). The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts where then washed with brine (30 mL), dried with $MgSO_4$, filtered, and the solvent was removed *in vacuo*. After column chromatography (CH_2Cl_2/MTBE, 15:1, 2 × 17 cm) the acetoxy carbonate (±)-**24b** (70.0 mg, 0.21 mmol, 78%) was obtained as a slightly yellow solid. TLC: R_f = 0.31 (CH_2Cl_2/MTBE, 12:1); Mp. 151−153 °C (CH_2Cl_2/MTBE); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.43−5.30 (m, 1H, C=C(H)CH_2), 4.79 (dd, 1H, $^3J_{H,H}$ = 11.9, 2.0 Hz, C(H)OCO_2), 4.24 (d, 1H, $^3J_{H,H}$ = 12.5 Hz, C(H)H′OAc), 4.08 (d, 1H, $^3J_{H,H}$ = 12.5 Hz, C(H)H′OAc), 2.67 (br s, 1H, (H)C(O)C, epoxide), 2.47−2.36 (m, 1H, C(H)H′), 2.30−2.19 (m, 2H, C(H)H′ + C(H)C_{quart}), 2.14 (s, 3H, CH_3), 2.11−2.02 (m, 1H, C(H)H′), 1.94−1.79 (m, 1H, C(H)H′), 1.67 (s, 3H, CH_3), 1.60−1.36 (m, 8H, 2 × CH_3 + CH_2), 1.35−1.19 (m, 2H, 2 × C(H)H′); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 170.2 ($OCOCH_3$), 147.1 (OCO_2), 136.1 (br, C=C(CH_2)CH_3), 124.3 (br, C=C(H)CH_2), 83.6 (CCH_2OAc), 74.9 (C(H)OCO_2), 66.3 (CH_2OAc), 62.4 ((H)C(O)C, epoxide), 60.4 ((H)C(O)C, epoxide), 37.5 (br, 2C, C(H)C_{quart} + CH_2), 29.8 (br, CH_2), 24.5 (br, CH_2), 23.1 (br, CH_2), 21.0 (CH_3), 17.8 (2C, 2 × CH_3), 15.9 (CH_3); IR (ATR): $\tilde{\nu}$ = 3441(w), 2940(w), 2862(w), 2531(w), 2160(w), 2029(w), 1975(w), 1728(s), 1535(w), 1458(w), 1389(m), 1296(m), 1242(s), 1188(m), 1126(s), 1088(m), 1049(s), 1011(w), 864(m), 772(m) cm^{-1}; HRMS (ESI−TOF) m/z: [M+Na]$^+$ Calcd for $C_{18}H_{26}O_6Na$ 361.1622; Found 361.1625.

(R)-2-[(1S*,2S*,3R*,10S*,E)-2-Hydroxy-6,10-dimethyl-11-oxabicyclo[8.1.0]undec-6-en-3-yl]propane-1,2-diol [(±)-**9b**].* A methanolic NaOMe solution (17.2 μL, 75.0 μmol, 0.2 equiv., 4.35 M) was added dropwise to a stirred solution of the carbonate (±)-**24b** (127 mg, 0.37 mmol, 1.0 equiv) in anhydrous MeOH (13 mL) at 25 °C. After 20 h (TLC control: CH_2Cl_2/MTBE, 15:1), dry ice (ca. 100 mg) was added in several portions and the solution was stirred for 15 min. Toluene (5 mL) was added and the suspension was concentrated *in vacuo* at 25 °C. After column chromatography (CH_2Cl_2/acetone, 7:1, 2 × 12 cm) the triol (±)-**9b** (70.0 mg, 0.26 mmol, 70%) was obtained as a colorless solid. TLC: R_f = 0.21 (CH_2Cl_2/acetone, 7:1); Mp. 135−137 °C (CH_2Cl_2/MTBE); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.37−5.13 (m, 1H, C=C(H)CH_2), 5.03 (s, 1H, OH), 4.21 (dd, 1H, $^3J_{H,H}$ = 11.2, 2.4 Hz, C(H)OH), 3.54 (dd, 1H, $^{2,3}J_{H,H}$ = 10.2, 10.2 Hz, C(H)H′OH), 3.40 (dd, 1H, $^{2,3}J_{H,H}$ = 11.0, 1.5 Hz, C(H)H′OH), 2.89 (br s, 2H, (H)C(O)C, epoxide + OH), 2.50 (d, 1H, $^3J_{H,H}$ = 8.8, 2.4 Hz, OH), 2.41−2.14 (m, 3H, C(H)H′ + CH_2), 2.13−2.01 (m, 2H, 2 × C(H)H′), 1.93 (d, 1H, $^3J_{H,H}$ = 9.4 Hz, C(H)C_{quart}), 1.75 (s, 3H, CH_3), 1.49−1.35 (m, 4H, C(H)H′ + CH_3), 1.33−1.21 (m, 2H, 2 × C(H)H′), 1.18 (s, 3H, CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 136.4 (br, C=C(CH_2)CH_3), 124.2 (br, C=C(H)CH_2), 76.7 (C(H)C_{quart}), 70.2 (br, C(H)OH), 68.2 (CH_2OH), 65.5 ((H)C(O)C, epoxide), 62.3 ((H)C(O)C, epoxide), 42.8 (br, C(H)C_{quart}), 37.8 (br, CH_2), 27.7 (br, CH_2), 27.2 (br, CH_2), 24.0 (br, CH_2), 23.8 (br, CH_3), 19.2 (CH_3), 16.0 (CH_3); IR (ATR): $\tilde{\nu}$ = 3318(w), 2970(w), 2924(w), 2870(w), 2546(w), 2245(w), 2168(w), 1798(w), 1867(w), 1458(w), 1443(w), 1404(m), 1373(w), 1227(w), 1165(w), 1049(m), 1026(m), 910(m), 872(m), 787(w), 764(w), 733(m), 640(m) cm^{-1}; HRMS (ESI−TOF) m/z: [M+Na]$^+$ Calcd for $C_{15}H_{26}O_4Na$ 293.1723; Found 293.1728.

*α-Hydroxy Lactone (±)-**26b**.* Anhydrous *N*-methylmorpholine *N*-oxide (221 mg, 1.89 mmol, 40.0 equiv) and activated powdered 3 Å molecular sieves (50 mg) were suspended in anhydrous MeCN (0.22 mL) and CH_2Cl_2 (0.38 mL) and stirred for 1 h at 25 °C followed by the addition of TPAP (3.30 mg, 9.50 μmol, 0.2 equiv). After 10 min a solution of the triol (±)-**9b** (12.8 mg, 47.3 μmol, 1.0 equiv) in anhydrous CH_2Cl_2 (0.4 mL) was added dropwise and the reaction mixture was stirred for 3 h [HPLC and TLC control: CH_2Cl_2/acetone, 7:1]. Then the mixture was filtered through a silica pad (CH_2Cl_2/acetone, 7:1) and the filtrate was concentrated *in vacuo* at 25 °C. After column chromatography (CH_2Cl_2/acetone, 15:1, 2 × 20 cm) the α-hydroxy lactone (±)-**26b** (8.50 mg, 35.5 μmol, 75%) was obtained as a colorless solid. TLC: R_f = 0.64 (CH_2Cl_2/acetone, 7:1); Mp. 171−173 °C (CH_2Cl_2/acetone); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.40−5.25 (m, 1H, C=C(H)CH_2), 4.74 (dd, 1H, $^3J_{H,H}$ = 10.4, 3.6 Hz, C(H)OCO), 2.67 (s, 1H, (H)C(O)C, epoxide), 2.48−2.36 (m, 1H, C(H)H′), 2.32 (s, 1H, C(H)H′), 2.20−2.00 (m, 3H, 2 × C(H)H′ + C(H)H′), 1.95−1.82 (m, 2H, C(H)C_{quart}(CH_3)OH + C(H)H′), 1.63 (s, 3H, CH_3), 1.52−1.40 (m, 4H, CH_3 + C(H)H′), 1.39−1.28 (m, 4H, CH_3 + C(H)H′); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 176.3

DOI: 10.1021/acs.joc.6b01985
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(OCO), 137.0 (br, C=C(CH$_2$)CH$_3$), 124.1 (br, C=C(H)CH$_2$), 78.2 (C(H)OCO), 74.6 (C(H)C$_{quart}$(CH$_3$)OH), 62.4 ((H)C(O)C, epoxide), 60.5 ((H)C(O)C, epoxide), 50.2 (C(H)C(CH$_3$)OH), 39.9 (br, CH$_2$), 36.7 (CH$_2$), 22.6 (br, CH$_2$), 21.6 (CH$_3$), 20.8 (CH$_2$), 17.2 (br, CH$_3$), 16.2 (CH$_3$); IR (ATR): $\tilde{\nu}$ = 3433(w), 2916(w), 2862(w), 2322(w), 1759(s), 1651(w), 1458(m), 1381(m), 1258(s), 1204(s), 1180(s), 1165(s), 1103(s), 1072(s), 1018(s), 941(s), 878(s), 810(s), 764(m), 679(m), 633(m) cm^{-1}; HRMS (ESI−TOF) *m*/*z*: [M+Na]$^+$ Calcd for C$_{15}$H$_{22}$O$_4$Na 289.1410; Found 289.1413.

*(±)-4,5-dia-Parthenolide [(±)-**8**].* To a stirred solution of Martin's sulfurane (93.0 mg, 138 μmol, 2.0 equiv) in anhydrous CH$_2$Cl$_2$ (0.4 mL) was added a solution of the hydroxy lactone (±)-**26b** (18.4 mg, 69.0 μmol, 1.0 equiv) in anhydrous CH$_2$Cl$_2$ (1 mL) at 25 °C. After 2.5 h (TLC control: CH$_2$Cl$_2$/PhMe/MTBE, 10:3:1) the reaction mixture was directly purified by column chromatography (CH$_2$Cl$_2$/PhMe/MTBE, 10:5:1, 2 × 22 cm) whereupon 4,5-*dia*-PTL [(±)-**8**] (14.0 mg, 56.0 μmol, 81%) was isolated as a colorless solid. Analytically pure material was obtained by preparative HPLC purification. TLC: R_f = 0.34 (CH$_2$Cl$_2$/PhMe/MTBE, 10:5:1); Mp. 147−149 °C (MeCN/H$_2$O); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.23 (d, 1H, $^2J_{H,H}$ = 3.4 Hz, C=C(H)H′), 5.56 (d, 1H, $^2J_{H,H}$ = 3.4 Hz, C=C(H)H′), 5.44−5.30 (m, 1H, C=C(H)CH$_2$), 4.37 (dd, 1H, $^3J_{H,H}$ = 10.2, 3.5 Hz, C(H)OCO), 2.90−2.79 (m, 1H, C(H)C=CH$_2$), 2.75 (br s, 1H, (H)C(O)C, epoxide), 2.48−2.36 (m, 1H, C(H)H′), 2.34−2.25 (m, 1H, C(H)H′), 2.23−2.01 (m, 4H, 2 × C(H)H′ + 2 × C(H)H′), 1.70−1.55 (m, 4H, C=C(CH$_2$)CH$_3$ + C(H)H′), 1.43−1.24 (m, 4H, CH$_3$ + C(H)H′); ^{13}C{^{1}H} NMR (75 MHz, CDCl$_3$): δ = 169.1 (CO$_2$), 139.5 (C=CH$_2$), 136.7 (br, C=C(CH$_2$)CH$_3$), 125.0 (br, C=C(H)CH$_2$), 119.1 (C=CH$_2$), 79.6 (C(H)OCO), 62.4 ((H)C(O)C, epoxide), 60.4 ((H)C(O)C, epoxide), 44.2 (C(H)C=CH$_2$), 39.4 (br, CH$_2$), 36.5 (br, CH$_2$), 25.7 (br, CH$_2$), 22.5 (br, CH$_2$), 17.0 (C=C(CH$_2$)CH$_3$), 16.6 (CH$_3$); IR (ATR): $\tilde{\nu}$ = 3288(w), 2940(w), 2847(w), 2398(m), 2337(m), 2083(w), 1767(m), 1643(m), 1450(w), 1258(m), 1096(m), 1018(m), 795(s), 656(s) cm^{-1}; HRMS (ESI−TOF) *m*/*z*: [M+Na]$^+$ Calcd for C$_{15}$H$_{20}$O$_3$Na 271.1305; Found 271.1307.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01985.

Computational details, structure elucidation, and NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Support by the FCI (PhD fellowship to R.R.A.F.) is gratefully acknowledged.

■ REFERENCES

(1) Ghantous, A.; Sinjab, A.; Herceg, Z.; Darwiche, N. *Drug Discovery Today* **2013**, *18*, 894−905.

(2) Mathema, V. B.; Koh, Y.-S.; Thakuri, B. C.; Sillanpää, M. *Inflammation* **2012**, *35*, 560−565.

(3) Siedle, B.; García-Piñeres, A. J.; Murillo, R.; Schulte-Mönting, J.; Castro, V.; Rüngeler, P.; Klaas, C. A.; Da Costa, F. B.; Kisiel, W.; Merfort, I. *J. Med. Chem.* **2004**, *47*, 6042−6054.

(4) Gopal, Y. N. V.; Chanchorn, E.; Van Dyke, M. W. *Mol. Cancer Ther.* **2009**, *8*, 552−562.

(5) Zhang, S.; Ong, C.-N.; Shen, H.-M. *Cancer Lett.* **2004**, *211*, 175−188.

(6) Li, H.; Zhu, H.; Xu, C.-j.; Yuan, J. *Cell* **1998**, *94*, 491−501.

(7) D'Anneo, A.; Carlisi, D.; Lauricella, M.; Puleio, R.; Martinez, R.; Di Bella, S.; Di Marco, P.; Emanuele, S.; Di Fiore, R.; Guercio, A.; Vento, R.; Tesoriere, G. *Cell Death Dis.* **2013**, *4*, e891.

(8) Liu, Z.; Liu, S.; Xie, Z.; Pavlovicz, R. E.; Wu, J. W.; Chen, P.; Aimiuwu, J.; Pang, J.; Bhasin, D.; Neviani, P.; Fuchs, J. R.; Plass, C.; Li, P.-K.; Li, C.; Huang, T. H.-M.; Wu, L.-C.; Rush, L.; Wang, H.; Perrotti, D.; Marcucci, G.; Chan, K. K. *J. Pharmacol. Exp. Ther.* **2009**, *329*, 505−514.

(9) Neelakantan, S.; Nasim, S.; Guzman, M. L.; Jordan, C. T.; Crooks, P. A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4346−4349.

(10) Hwang, D.-R.; Wu, Y.-S.; Chang, C.-W.; Lien, T.-W.; Chen, W.-C.; Tan, U.-K.; Hsu, J. T. A.; Hsieh, H.-P. *Bioorg. Med. Chem.* **2006**, *14*, 83−91.

(11) Song, J. M.; Qian, X.; Upadhyayya, P.; Hong, K. H.; Kassie, F. *Curr. Cancer Drug Targets* **2014**, *14*, 59−69.

(12) Shibuya, H.; Ohashi, K.; Kawashima, K.; Hori, K.; Murakami, N.; Kitagawa, I. *Chem. Lett.* **1986**, *15*, 85−86.

(13) Takahashi, T.; Nemoto, H.; Kanda, Y.; Tsuji, J.; Fukazawa, Y.; Okajima, T.; Fujise, Y. *Tetrahedron* **1987**, *43*, 5499−5520.

(14) Takahashi, T.; Nemoto, H.; Kanda, Y.; Tsuji, J.; Fujise, Y. *J. Org. Chem.* **1986**, *51*, 4315−4316.

(15) Foo, K.; Usui, I.; Götz, D. C. G.; Werner, E. W.; Holte, D.; Baran, P. S. *Angew. Chem.* **2012**, *124*, 11659−11663; *Angew. Chem., Int. Ed.* **2012**, *51*, 11491−11495.

(16) Long, J.; Zhang, S.-F.; Wang, P.-P.; Zhang, X.-M.; Yang, Z.-J.; Zhang, Q.; Chen, Y. *J. Med. Chem.* **2014**, *57*, 7098−7112.

(17) Long, J.; Ding, Y.-H.; Wang, P.-P.; Zhang, Q.; Chen, Y. *J. Org. Chem.* **2013**, *78*, 10512−10518.

(18) Yang, Z.-J.; Ge, W.-Z.; Li, Q.-Y.; Lu, Y.; Gong, J.-M.; Kuang, B.-J.; Xi, X.; Wu, H.; Zhang, Q.; Chen, Y. *J. Med. Chem.* **2015**, *58*, 7007−7020.

(19) Long, J.; Ding, Y.-H.; Wang, P.-P.; Zhang, Q.; Chen, Y. *Tetrahedron Lett.* **2016**, *57*, 874−877.

(20) Li, L.; Pan, X.; Guan, B.; Liu, Z. *Tetrahedron* **2016**, *72*, 4346−4354.

(21) García-Granados, A.; Gutiérrez, M. C.; Parra, A.; Rivas, F. *J. Nat. Prod.* **2002**, *65*, 1011−1015.

(22) Majdi, M.; Liu, Q.; Karimzadeh, G.; Malboobi, M. A.; Beekwilder, J.; Cankar, K.; de Vos, R.; Todorović, S.; Simonović, A.; Bouwmeester, H. *Phytochemistry* **2011**, *72*, 1739−1750.

(23) Zemplén, G.; Kunz, A. *Ber. Dtsch. Chem. Ges. B* **1924**, *57*, 1357−1359.

(24) Wang, Z. in *Comprehensive Organic Name Reactions and Reagents*; John Wiley & Sons, Inc., 2010.

(25) Unsinn, A.; Rohbogner, C. J.; Knochel, P. *Adv. Synth. Catal.* **2013**, *355*, 1553−1560.

(26) Kitamura, M.; Hirokawa, Y.; Yoshioka, Y.; Maezaki, N. *Tetrahedron* **2012**, *68*, 4280−4285.

(27) Hirokawa, Y.; Kitamura, M.; Kato, C.; Kurata, Y.; Maezaki, N. *Tetrahedron Lett.* **2011**, *52*, 581−583.

(28) Barrett, I. M.; Breeden, S. W. *Tetrahedron: Asymmetry* **2004**, *15*, 3015−3017.

(29) Tsubuki, M.; Takahashi, K.; Honda, T. *J. Org. Chem.* **2003**, *68*, 10183−10186.

(30) Faraldos, J. A.; Wu, S.; Chappell, J.; Coates, R. M. *Tetrahedron* **2007**, *63*, 7733−7742.

(31) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974−5976.

(32) Zhang, W.; Basak, A.; Kosugi, Y.; Hoshino, Y.; Yamamoto, H. *Angew. Chem.* **2005**, *117*, 4463−4465; *Angew. Chem., Int. Ed.* **2005**, *44*, 4389−4391.

(33) Donohoe, T. J. *Synlett* **2002**, *8*, 1223−1232.

(34) Hegde, S. G.; Vogel, M. K.; Saddler, J.; Hrinyo, T.; Rockwell, N.; Haynes, R.; Oliver, M.; Wolinsky, J. *Tetrahedron Lett.* **1980**, *21*, 441−444.

(35) Moreno-Dorado, F. J.; Guerra, F. M.; Manzano, F. L.; Aladro, F. J.; Jorge, Z. D.; Massanet, G. M. *Tetrahedron Lett.* **2003**, *44*, 6691−6693.

DOI: 10.1021/acs.joc.6b01985
J. Org. Chem. 2016, 81, 11009−11016

(36) Duan, J. J.-W.; Smith, A. B., III *J. Org. Chem.* **1993**, *58*, 3703−3711.
(37) Vitale, J. P.; Wolckenhauer, S. A.; Do, N. M.; Rychnovsky, S. D. *Org. Lett.* **2005**, *7*, 3255−3258.
(38) Schmidt, A.-K. C.; Stark, C. B. W. *Synthesis* **2014**, *46*, 3283−3308.
(39) Shibuya, M.; Shibuta, T.; Fukuda, H.; Iwabuchi, Y. *Org. Lett.* **2012**, *14*, 5010−5013.
(40) Hunter, D. H.; Racok, J. S.; Rey, A. W.; Zea-Ponce, Y. *J. Org. Chem.* **1988**, *53*, 1278−1281.
(41) Fétizon, M.; Golfier, M.; Balogh, V. *J. Org. Chem.* **1971**, *36*, 1339−1341.
(42) Chandrasekhar, M.; Chandra, K. L.; Singh, V. K. *J. Org. Chem.* **2003**, *68*, 4039−4045.
(43) Andrews, S. P.; Ball, M.; Wierschem, F.; Cleator, E.; Oliver, S.; Högenauer, K.; Simic, O.; Antonello, A.; Hünger, U.; Smith, M. D.; Ley, S. L. *Chem. - Eur. J.* **2007**, *13*, 5688−5712.
(44) Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003−5010.
(45) Adio, A. M. *Tetrahedron* **2009**, *65*, 1533−1552.
(46) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.
(47) Williams, D. B. G.; Lawton, M. *J. Org. Chem.* **2010**, *75*, 8351−8354.
(48) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *J. Am. Chem. Soc.* **2010**, *132*, 14303−14314.
(49) Li, Y.; Li, W.; Li, Y. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2953−2956.
(50) Takahashi, T.; Yokoyama, H.; Haino, T.; Yamada, H. *J. Org. Chem.* **1992**, *57*, 3521−3523.

DOI: 10.1021/acs.joc.6b01985
J. Org. Chem. 2016, 81, 11009−11016