JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

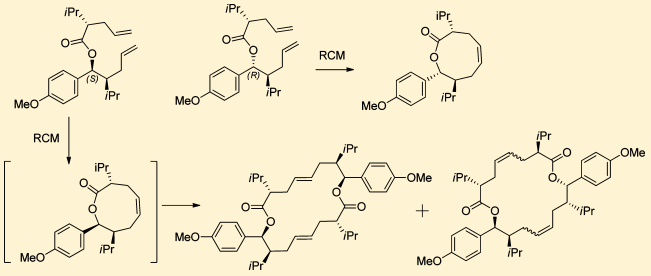
Conception and Evolution of Stereocontrolled Strategies toward Functionalized 8-Aryloctanoic Acids Related to the Total Synthesis of Aliskiren

Stephen Hanessian,* Etienne Chénard, Sébastien Guesné, and Jean-Philippe Cusson

Department of Chemistry, Université de Montréal, CP6128 Succursale A, Centre-ville, Montréal, Quebec H3C 3J7, Canada

Supporting Information

ABSTRACT: A detailed account is given describing the approaches used toward the total synthesis of aliskiren. In particular, ring-closing metathesis with the Hoveyda−Grubbs catalyst accelerates the formation of a 9-membered lactone from an (*R*)-ester. The diastereomeric (*S*)-ester leads to the formation of dimeric dilactones, which were characterized by X-ray analysis and chemical conversions.



INTRODUCTION

The regulation of arterial blood pressure is a complex physiological process with important implications in the pathogenesis of cardiovascular diseases.[1] Among these, hypertension is considered to be a high risk factor and associated with incidences of stroke and kidney failure. A natural substance produced by the kidney, named renin, was known to have a hypertensive effect in experimental animals as far back as 1898.[2] Since then, pioneering efforts in cardiovascular medicine have advanced the frontiers of antihypertensive research, culminating with the availability of drugs to control the disease.[3] The aspartyl protease renin is part of the renin angiotensin system (RAS), known to be a regulator of blood pressure and electrolyte balance.[4] Stimulation of the RAS leads to the release of renin from the kidney, whereupon a series of proteolytic events take place ultimately forming vasoconstricting peptides.[5] Thus, renin cleaves a Leu-Val peptide linkage in its endogenous substrate angiotensinogen, releasing the decapeptide angiotensin I (Figure 1A). A second enzyme in the RAS, angiotensin-converting enzyme (ACE), then cleaves two amino acids from angiotensin I to give the vasoconstricting octapeptide angiotensin II. On the basis of these observations, the inhibition of renin as the first and rate-limiting step in the RAS cycle was considered to be a viable and attractive strategy in the quest toward discovery of novel antihypertensives working by a unique mechanism.[6] Indeed, major advances toward this goal have been made during the past three decades.[7] Unfortunately, and in spite of achieving highly effective in vivo inhibition of renin with beneficial antihypertensive action, such activities had to be terminated in a number of pharmaceutical companies primarily due to issues dealing with cost of production and bioavailability. Nevertheless, the synthesis of minimally peptidic potent inhibitors, such as CGP-38960 (Figure 1B), was admirably guided by structure-based design relying on valuable information gleaned from cocrystal structures

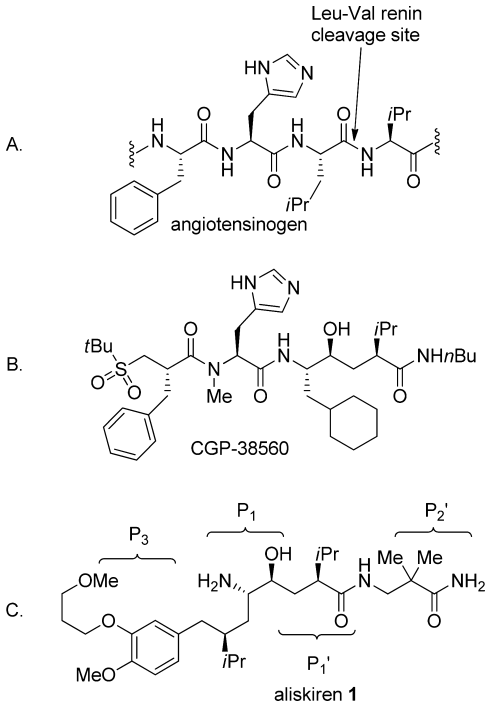


Figure 1. (A) Scissile Leu-Val bond in angiotensinogen by the enzyme renin. (B) First-generation peptidic inhibitor. (C) Structure of aliskiren.

with human recombinant renin.[8] Although active investigations toward the synthesis of new renin inhibitors had somewhat waned, a new class of nonpeptidic 8-aryloctanoic acid amides was

Received: July 11, 2014
Published: October 6, 2014

dx.doi.org/10.1021/jo5015195 | J. Org. Chem. 2014, 79, 9531−9545

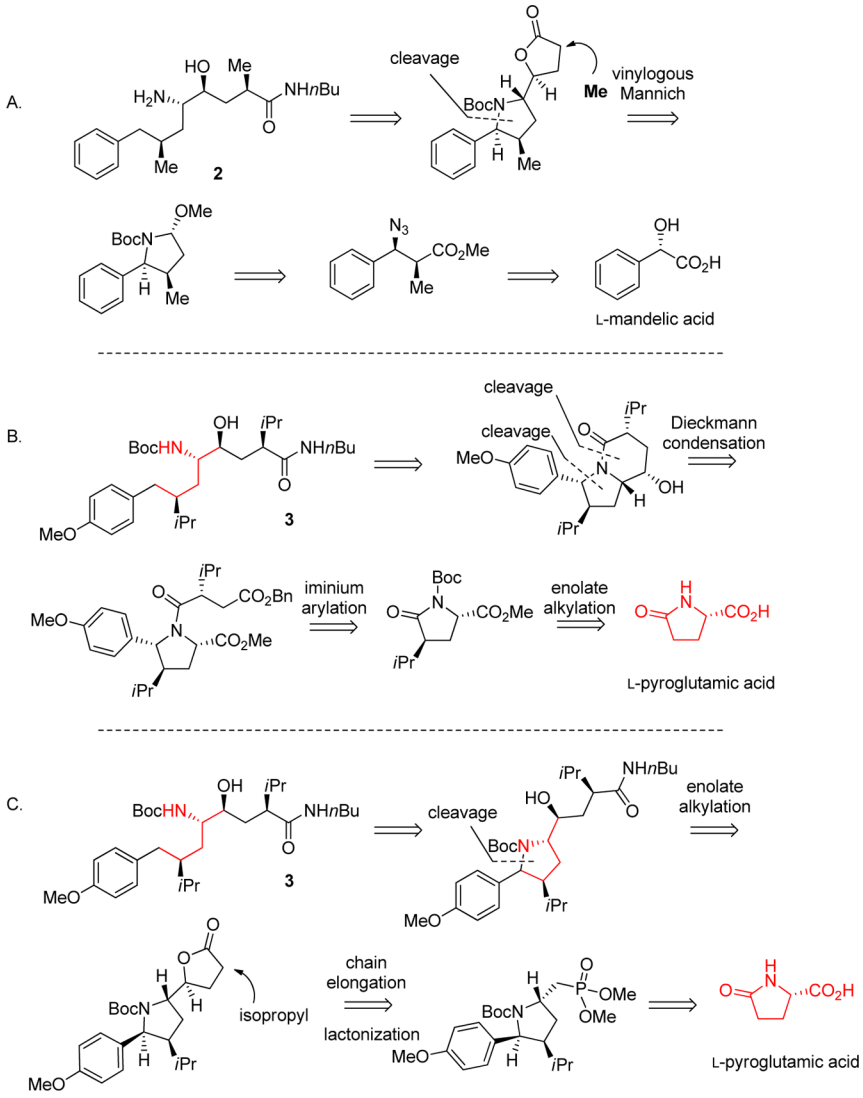


Figure 2. Early prototypes of renin inhibitors: (A) L-mandelic acid as starting chiron; (B and C) L-pyroglutamic acid as starting chiron and source of nitrogen (Dieckmann and phosphate extension routes).

found to have highly promising activity.[9] Further refinement in this series by scientists at Ciba-Geigy (Pharma) in Basel led to aliskiren (**1**), which is presently marketed by Novartis for the treatment of hypertension under the trade name Tekturna (Figure 1C).[10] The cocrystal structure analysis of aliskiren in complex with renin revealed the characteristic interactions of the hydroxyethylene segment with aspartic acid residue and unique binding interactions of the hydrophobic moieties.[11] Of particular significance in optimizing the inhibitory activity was the truncation of segments corresponding to the P_2 and P_4 site in the original inhibitors such as CGP-38560 by directly linking P_1 and P_3 (Figure 1). Compared to the previous generation of renin inhibitors, often possessing heterocyclic appendages near the hydroxyethylene subunit,[10] aliskiren represents a structurally simple ω-aryloctanoic acid amide harboring four stereogenic carbon atoms (Figure 1). Further SAR studies also demonstrated an improvement of the affinity at the P_2' site when the *n*-butylamide was exchanged for a 3-amino-2,2-dimethylpropionamide unit.[12] Already, considerable interest has been generated in the clinical aspects of aliskiren, a first-in-class, orally active antihypertensive.[13]

BACKGROUND

Among the many research collaborations with pharmaceutical companies, none are more challenging than when an academic is asked to contribute to an active project with the prospects of developing a viable synthesis of a molecule of interest.[14] Encouraged by such an opportunity, we first explored a stereocontrolled approach to a bioactive prototype of aliskiren, starting with L-mandelic acid (Figure 2A).[15] In the following years, we were motivated to devise strategies avoiding the use of azide as a source of the C-5 nitrogen atom (aliskiren numbering) for safety considerations in an eventual scale-up operation. Further consideration to our mandate was to avoid the use of chiral auxiliaries to create stereogenic carbon atoms with required substituents for cost and possibly IP reasons. Faced with these restrictions, we devised two stereocontrolled approaches to 2,7-dialkyl-4-hydroxy-5-amino-8-aryloctanoic acids exemplified by **3**, starting with the readily available L-pyroglutamic acid as a chiron[16] (Figure 2B and 2C). In addition to providing the source of the nitrogen atom, the inherent stereochemistry in the starting chiron served to control the sequential stereocontrolled introduction of appropriate functionality.

dx.doi.org/10.1021/jo5015195 | J. Org. Chem. 2014, 79, 9531−9545

Since our initial efforts toward the stereocontrolled synthesis of aliskiren,[15,16] there has been a plethora of reports particularly in the patent literature[17] describing a variety of approaches to intermediates and analogues. In a brief overview, we shall distinguish those involving approaches[18] or formal syntheses[19] from those pertaining to actual total syntheses[20] of aliskiren.[21] In the majority of these syntheses, extensive use was made of the Evans[22] and Schöllkopf[23] chiral auxiliaries to secure the C-2/C-7 isopropyl and C-4/C-5 amino alcohol groups, respectively, in high enantio- or diastereoselectivity. Alternative approaches are described in several patents.[17,24] For example, the key building blocks used in the Speedel process[25] for the synthesis of aliskiren are shown in Figure 3. Intermediate **A** was obtained by an

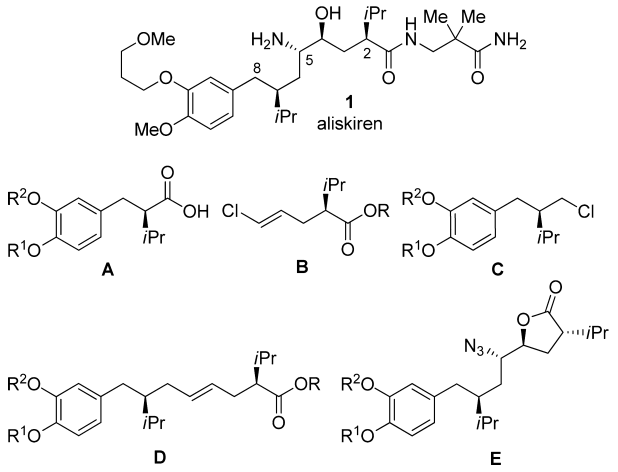


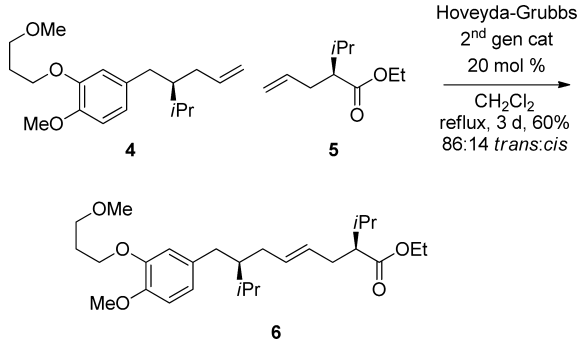
Figure 3. Key building blocks in the Speedel process toward aliskiren.

asymmetric catalytic hydrogenation of an α,β-unsaturated precursor in >95% ee starting from a racemic dialkoxyphenyl propionate precursor (total of seven steps). The enantiopure chlorovinyl intermediate **B** was prepared from the racemic ester via pig liver esterase resolution in 47% yield, after distillation. The undesired enantiomeric carboxylic acid was recycled by epimerization, esterification, and repeated enzyme treatment (total three steps to **B** from methyl isobutyrate in one pass). Intermediate **C** was prepared from acid **A** in three steps. Coupling of **C** and **B** was accomplished via the corresponding Grignard reagent derived from **B** in the presence of Fe^{III} acetylacetonate to give **D** in 75% yield. Subsequent steps involving hydrolysis to the acid, bromolactonization, epoxide formation, lactonization, mesylation, and azide displacement gave the azidolactone precursor **E**. Condensation with 3-amino-2,2-dimethylpropionamide, followed by hydrogenation and crystallization, gave aliskiren fumarate (total of 10 steps from **D**). Improvements in the bromolactonization step have also been reported.[24]

In the past, chiral auxiliaries were used to access intermediates such as **C** and **D** (Figure 3).[18−20,22] In spite of this invaluable method, all of the reported syntheses comprise numerous steps to access the building blocks individually and prior to engaging them in a stepwise assembly. Furthermore, except for some of the patented processes, none of the published papers provide experimental details leading to aliskiren.

Recently, we reported on an efficient synthesis of intermediate **4** adopting an extension of the Stoltz[26] catalytic asymmetric transposition of an allylic enolcarbonate derived from the corresponding aryl ketone precursor followed by reduction at the

Scheme 1. Shorter Route to an Advanced Intermediate in the Speedel Process



benzylic carbon (Scheme 1).[27] A cross-metathesis reaction with ester **5** led to the advanced Speedel intermediate **6** in five linear steps and 38% overall yield from 4-methoxy-3-(methoxypropoxy)-1-bromobenzene.

Nine-Membered Lactone Route toward Aliskiren. As is clear from the preceding section, a major challenge in devising synthetic approaches to aliskiren is the introduction of the C-2/C-7 isopropyl groups and the C-4/C-5 amino alcohol subunit in the 8-aryloctanoic acid framework with high stereocontrol (Figure 1C). Added to this is the desire to devise a relatively shorter route compared to existing reports, including those in the patent literature. We recently reported an 11-step total synthesis of aliskiren starting with a single chiral progenitor (Figure 4).[28]

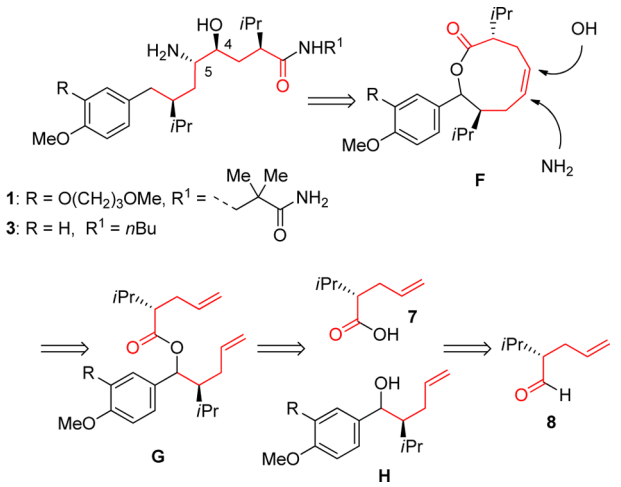
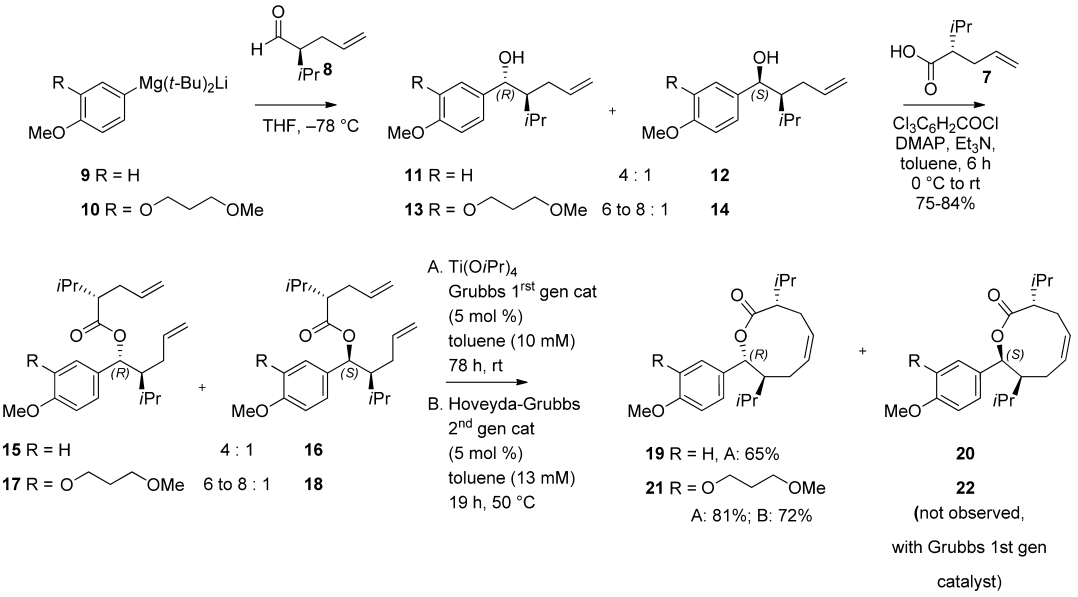


Figure 4. Nine-membered lactone route to aliskiren from a common chiron.

Thus, (2*S*)-2-isopropyl-4-pentenal **8**, easily prepared from the acid **7**,[28] was converted to a 6:1 mixture of diastereomeric benzylic alcohols **H**, which was used to assemble the ester **G**. Ring-closing metathesis in the presence of the Grubbs I catalyst[29,30] gave the 9-membered lactone **F** (Figure 4). Regio- and stereoselective introduction of an amino and an alcohol group provided the entirely functionalized 8-aryloctanoic acid framework of aliskiren and of selected amide variants. In this paper, we elaborate on various aspects of this synthesis, particularly with regard to the preparation and functionalization of the 9-membered lactones using a ring-closing metathesis en route toward aliskiren.

dx.doi.org/10.1021/jo5015195 | J. Org. Chem. 2014, 79, 9531−9545

Scheme 2. Synthesis of the 9-Membered Lactones



RESULTS AND DISCUSSION

Synthesis of the 9-Membered Lactone. Initially, we focused on the 4-methoxy analogue (**3**, Figure 4) in order to explore aspects of stereoselectivity and conditions for the ring-closing metathesis. As will become evident, it was important to attempt the ring-closing metathesis reaction with a higher proportion of the (*R*)-ester derived from alcohol diastereomer **11** (Scheme 2).[31]

Attempts to add various organometallic derivatives of **9** (X = Br; M = Mg-*n*-Bu; TMEDA; Mg-*n*-Bu inverse addition; Mg-*n*-Bu, $CeCl_3$; Li, $CeCl_3$; Et_2ZnLi; $Mg(n\text{-}Bu)_2Li$) to the aldehyde **8** resulted in modest to low yields and unsatisfactory ratios. After extensive trials, the best ratio of inseparable diastereomers **11** and **12** favoring the (*R*)-lactone was obtained with a mixed Mg/Li Grignard reagent described by Inoue[32] in 68% yield. Application of the same protocol to the aliskiren aryl moiety **10** led to a better ratio of **13** and **14** (5−8:1) of diastereomers. Esterification by the Yamaguchi method[33] afforded the diastereomeric mixture of esters **15**:**16** and **17**:**18**, maintaining the same ratios, respectively. In our original report, we had utilized the Grubbs first-generation catalyst due to its availability at time. A 5 mol % loading in a 10 mM solution of the esters **15**:**16** or **17**:**18** in toluene led, after 78 h at room temperature, to the intended lactones **19** and **21**, in 65% and 81% yield, respectively. In this process, the mixture of esters was first stirred with $Ti(O\text{-}i\text{-}Pr)_4$ for 24 h before adding the catalyst. Then, to ensure complete conversion of the (*R*)-esters **15** and **17**, an additional 5−10 mol % of the first generation Grubbs catalyst was added every 24 h. In the absence of $Ti(O\text{-}i\text{-}Pr)_4$, the low yield of the cyclization was attributed to the coordination of the Ru catalyst to the proximal ester carbonyl group.[34] The results of the cyclization of different batches of diastereomeric esters under different conditions and catalysts are shown in Table 1. Starting with an ester mixture enriched in the (*R*)-isomer, we obtained the (*R*)-lactone in 71% yield in the presence of the first-generation Grubbs catalyst (**G1**) at room temperature (Table 1, entry 9). Using a 4:1 mixture of esters **15** and **16** in the presence of the second-generation Hoveyda−Grubbs catalyst (**H−G2**)[35] at reflux resulted in the formation of **19** within 20 min in 64% yield (Table 1, entry 8). Ultimately, utilizing the second-generation Hoveyda−Grubbs catalyst and a 6:1 mixture of **17** and **18**, the cyclization was completed within 19 h at 50 °C to give **21** in 72% yield (Table 1, entry 13). We were at first intrigued by the observation that only the (*R*)-esters **15** and **17** were transformed to the corresponding lactones **19** and **21**, respectively. At the time of execution, reports of the formation of 9-membered functionalized lactones by ring-closing metathesis were sparse.[36,37]

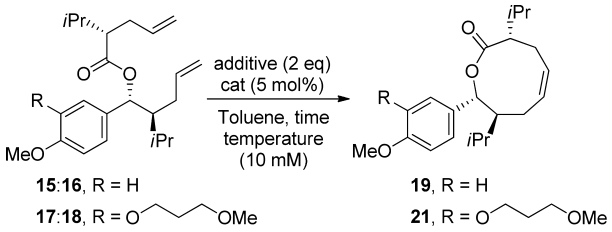
Functionalization of the 9-Membered Lactone. Our next task was to explore methods for the regio- and stereoselective introduction of an amino alcohol unit on the double bond of lactones **19** and **21**. We surmised that in the presence of NBS, CuI, and $TsNH_2$[38] a bromonium ion (**27**) would be attacked to give the corresponding vicinally substituted 9-membered lactone **23** (arbitrary regio- and stereochemistry, Scheme 3). Instead, the products formed with a good conversion were found to be the bromolactones **24** and **25** in a ratio of 3.9:1 arising from an intramolecular attack of the carboxylate released by concomitant formation of quinonoid intermediates followed by an *anti* attack of $TsNH_2$ relative to the bulky isopropyl group. The structures of **24** and **25** were assigned by detailed NMR studies. The bromolactone structure (**25**) was also confirmed by X-ray crystallography. Reductive cleavage of the benzylic sulfonamide group in the mixture of **24** and **25** with Et_3SiH and trifluoroacetic acid gave the bromolactone **26** in a good overall yield from **19**.

Next, we converted the 9-membered lactone **19** into the corresponding epoxide **28** (Scheme 4). The major product with the designated stereochemistry as shown was formed in excellent yield at 0 °C or room temperature. Surprisingly, treatment with NaN_3−NH_4Cl in methoxyethanol or Bu_4NN_3 in refluxing toluene gave back starting epoxide. Upon treatment with Et_3SiH and trifluoroacetic acid, it was expected that the benzylic carbon oxygen bond would be cleaved. Instead, a mixture of the three products **29**, **30**, and **31** (6:1:1 ratio) was obtained whose structures are proposed on the basis of detailed NOE studies.[31] A plausible mechanism is shown in Scheme 4.

Dihydroxylation of **19** under standard conditions led to the dihydroxy lactone **32** and the dibenzoate **33** after benzoylation,[28] whose structures and stereochemistry was confirmed by X-ray analysis,[31] validating a trajectory of approach that would be opposed

dx.doi.org/10.1021/jo5015195 | J. Org. Chem. 2014, 79, 9531−9545

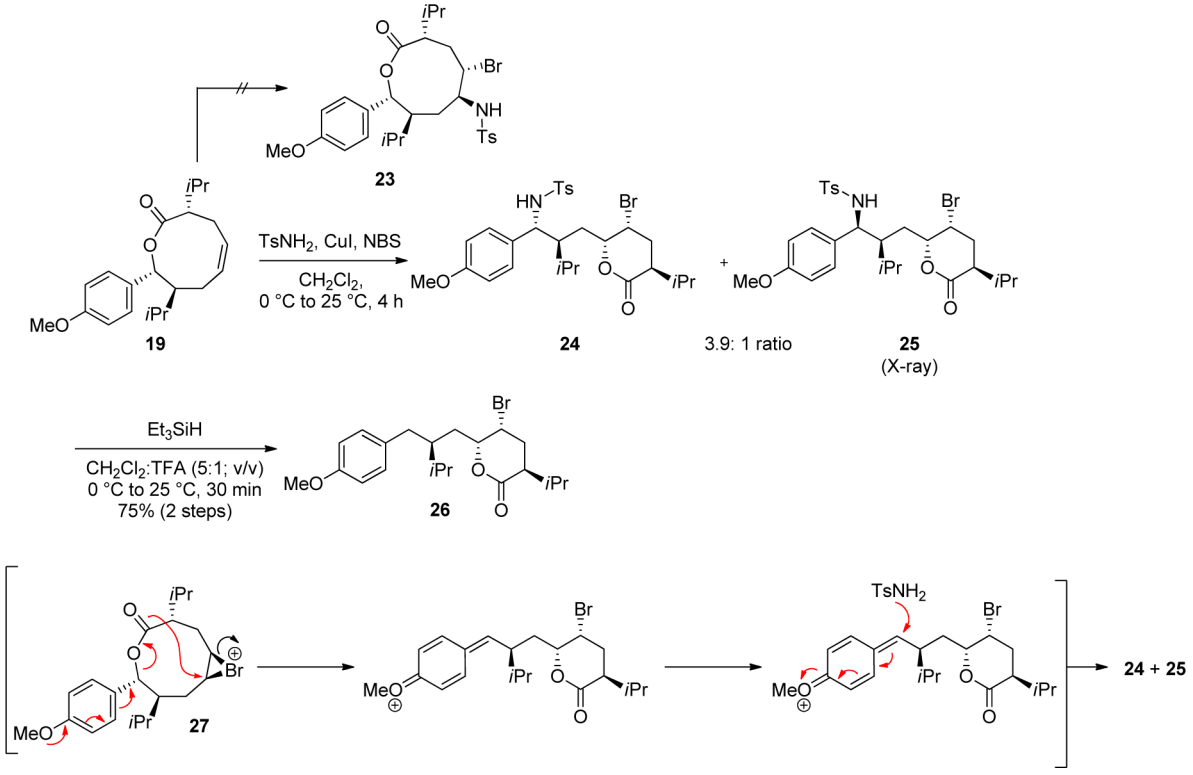
Table 1. Formation of the 9-Membered Lactones 19 and 21



entry	ester dr	R	cat.	add.	time	temp (°C)	yield[a] (%)
1	3:1	H	**G2**		1 d	rt	0
2	3:1	H	**G2**	$Ti(O\text{-}i\text{-}Pr)_4$	2 d	rt	43
3	3:1	H	**G1**	$Ti(O\text{-}i\text{-}Pr)_4$	2 d	rt	57
4	3:1	H	**G1**	$Ti(O\text{-}i\text{-}Pr)_4$	3 d	rt	58
5	2:1	H	**G1**	$Ti(O\text{-}i\text{-}Pr)_4$	3 d	rt	49
6	4:1	H	**G1**	$Ti(O\text{-}i\text{-}Pr)_4$	3 d	rt	65
7	4:1	H	**G2**		40 min	reflux	67
8	4:1	H	**H−G2**		20 min	reflux	64
9	7:1	H	**G1**	$Ti(O\text{-}i\text{-}Pr)_4$	3 d	rt	71
10	2:1	H	**H−G2**		20 h[b]	reflux	44
11	8:1	$O(CH_2)_3OCH_3$	**G1**	$Ti(O\text{-}i\text{-}Pr)_4$	3 d	rt	65
12	8:1	$O(CH_2)_3OCH_3$	**G1**	$Ti(O\text{-}i\text{-}Pr)_4$	3−4 d	rt	81[c]
13	5:1	$O(CH_2)_3OCH_3$	**H−G2**		16 h	50	72

[a]Isolated yield. [b]Conversion was completed within 20 h. [c]An extra 5 mol % of the catalyst was added if no further progress was noticed by TLC. **G1**, **G2**, and **H−G2** refer to Grubbs first generation, Grubbs second generation, and Hoveyda−Grubbs 2nd generation catalyst.

Scheme 3. Attempted Bromoamination of the Macrocyclic Lactone 19

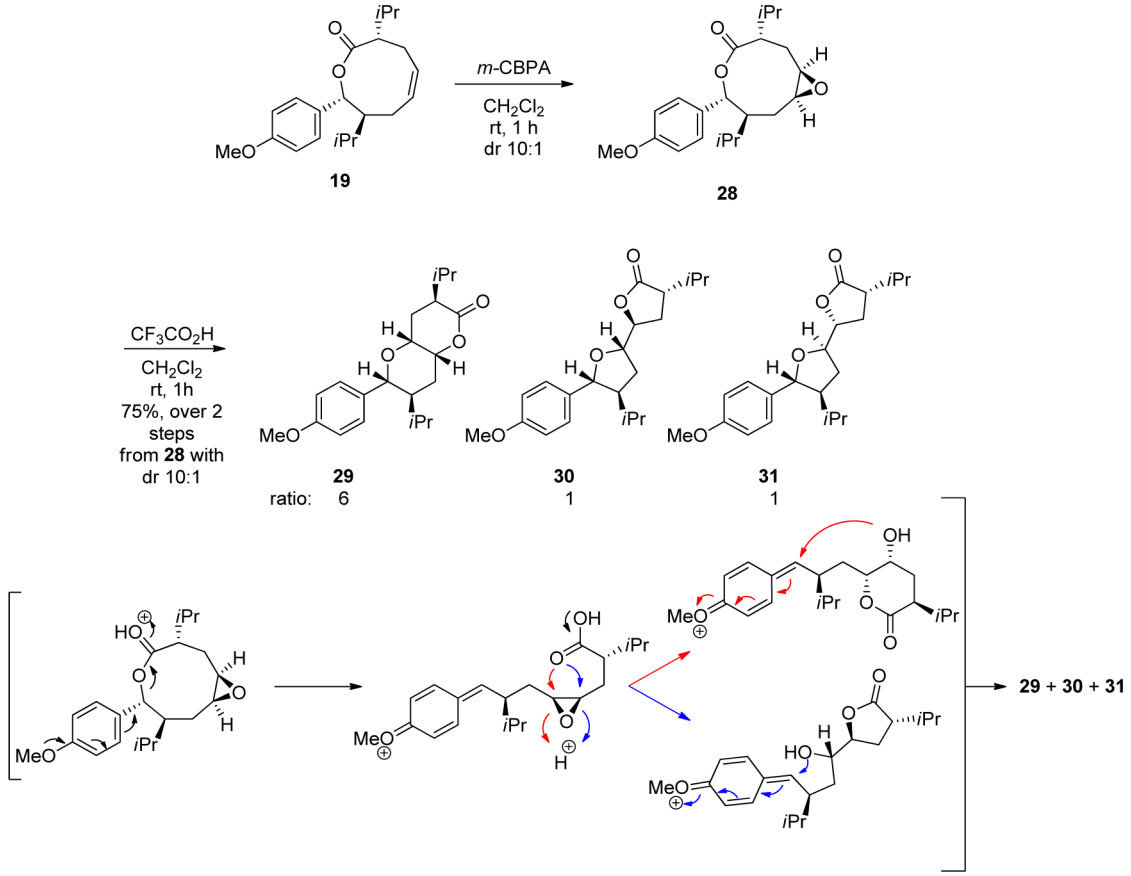


to the orientation of the resident C-8 4-methoxyphenyl group (Scheme 5).[28] Although this stereochemical outcome could not be predicted a priori in a quasi C_2-symmetrical 9-membered lactone with respect to the orientation of the isopropyl groups at C-2 and C-7 such as in **19**, it became clear that C-8 aryl group may have exerted a steric influence in the dihydroxylation step.

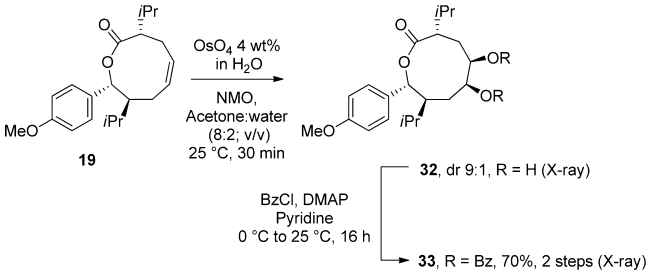
Encouraged by this result, we attempted a Du Bois aziridination reaction,[39] expecting to obtain the aziridine with the "up" orientation. We would then attempt a solvolysis with an appropriate carboxylic acid, hoping for a regioselective opening at the C-4 position, thereby generating the vicinal *trans*-amino alcohol (Scheme 6).

dx.doi.org/10.1021/jo5015195 | J. Org. Chem. 2014, 79, 9531−9545

Scheme 4. Epoxidation of the Lactone 19 and Further Transformations



Scheme 5. Diastereoselective Dihydroxylation of Lactone 19[28]



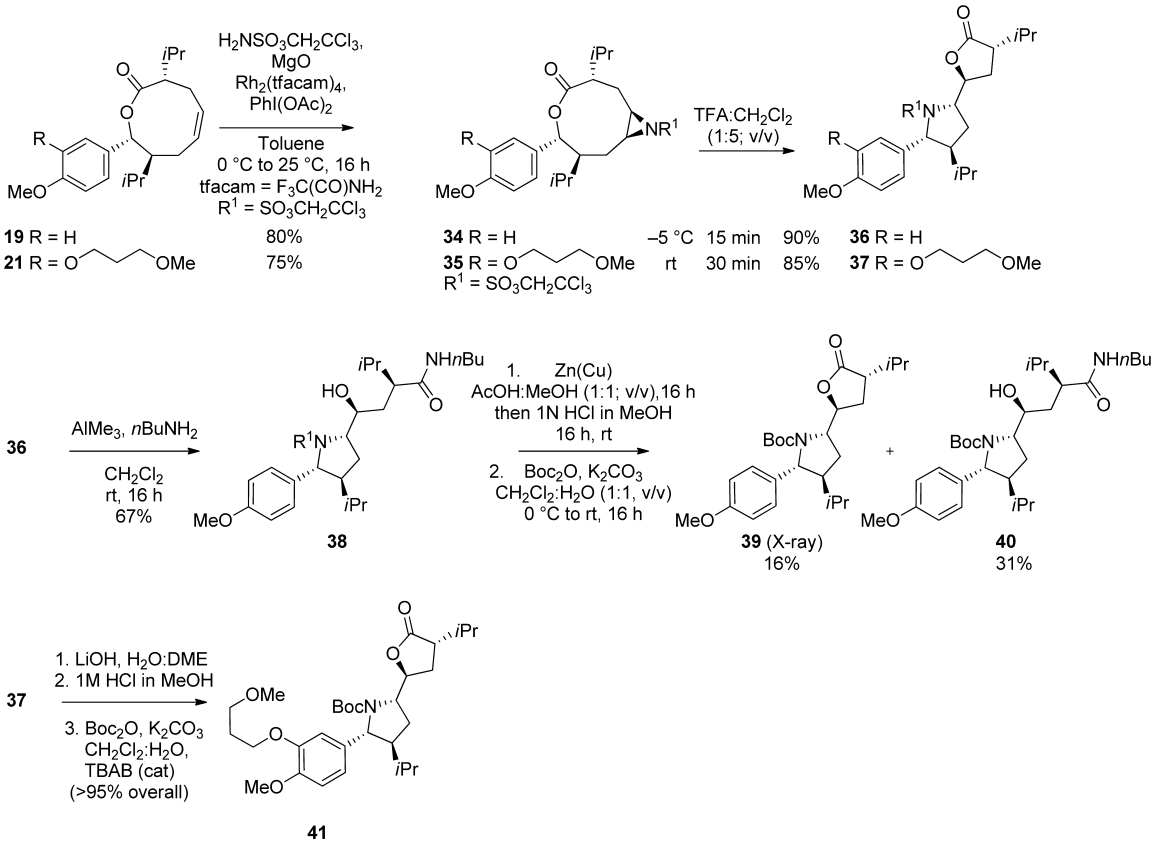
In the event, treatment of **19** and **21** individually with trichloroethylsulfamate in the presence of $Rh_2(tfacam)_4$ and $PhI(OAc)_2$ according to Du Bois[39] led to the desired aziridines **34** and **35** in excellent yields (Scheme 6). Suspecting the need for a strong acid to activate the *N*-(trichloroethyl)sulfamoyl group in the solvolysis, aziridines **34** and **35** were treated with a dilute solution of trifluoroacetic acid in CH_2Cl_2. Remarkably, in both cases, a double-ring contraction occurred to give the pyrrolidine lactones **36** and **37**, respectively, in excellent yields (Scheme 6).[28] It should be noted that this simple solvolytic reaction produced the desired (4*S*,5*S*) amino alcohol with exquisite regio- and stereocontrol. Confirmation of the structure and stereochemistry of **36** (hence **37**) was obtained from the X-ray crystal structure of the amide **38**. Treatment of **36** with $AlMe_3$ and *n*-butylamine gave the amide **38** which was converted to the *N*-Boc analogue **40**, accompanied by the lactone **39**, the structure of which was ascertained by X-ray crystallography.[31] Alternatively, alkaline hydrolysis of the sulfamate group in **37** followed by acidification and *N*-protection led to the known *N*-Boc lactone **41** (Scheme 6).[16b,40]

Completion of the Total Synthesis of Aliskiren. To test the compatibility of the sulfamate group under amide forming conditions from the lactone **37**, we were pleased that treatment with *n*-butylamine in the presence of $AlMe_3$ gave an excellent yield of the *n*-butylamine derivative **42** (Scheme 7). However, the same conditions to form an amide failed with the sterically demanding neopentylic 3-amino-2,2-dimethylpropionamide (ADPA). The utility of 2-hydroxypyridine as an activator in amide formation is well documented.[41] In fact, this method is claimed to work in high yield in a number of patents describing aliskiren.[25,42] In our hands, the methods described for the *N*-Boc derivative corresponding to the lactone **37** resulted in low yields. Prolonged heating of **37** with ADPA in neat Et_3N at 85 °C led to a 61% yield of the desired amide **43**, with recovery of starting lactone. We then decided to convert the *N*-sulfamoyl group in **43** into an *N*-Boc group to give **44** in good overall yield. There remained to cleave the benzylic amine bond and the *N*-Boc group to complete the total synthesis of aliskiren. Thus, treatment of **44** with Na in liquid ammonia in the presence of *t*-BuOH followed by acid cleavage of the *N*-Boc group gave aliskiren (**1**). Overall, our linear synthesis comprised 11 steps and a 7% unoptimized yield starting from aldehyde **8**.[28] After completion of this work, Foley and Jamieson described a conceptually innovative method for an acid-promoted aminolysis of lactones that has since been applied toward the synthesis of aliskiren.[43,44]

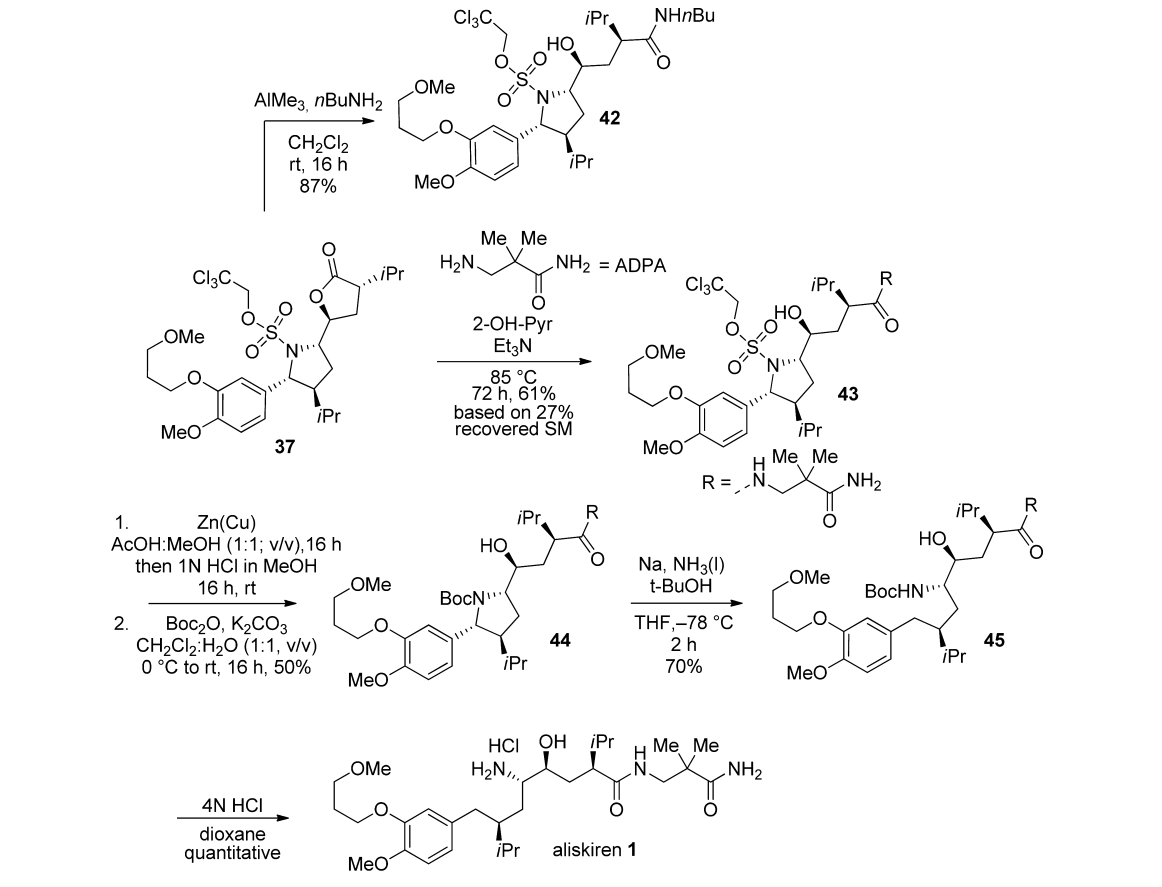
What about the (*S*)-Lactones 20 and 22? We previously commented on the exquisite selectivity of the Grubbs metathesis reaction with the first-generation catalyst. In fact, using an

dx.doi.org/10.1021/jo5015195 | J. Org. Chem. 2014, 79, 9531−9545

Scheme 6. Elaboration of 9-Membered Lactones via Aziridination and Ring Contraction



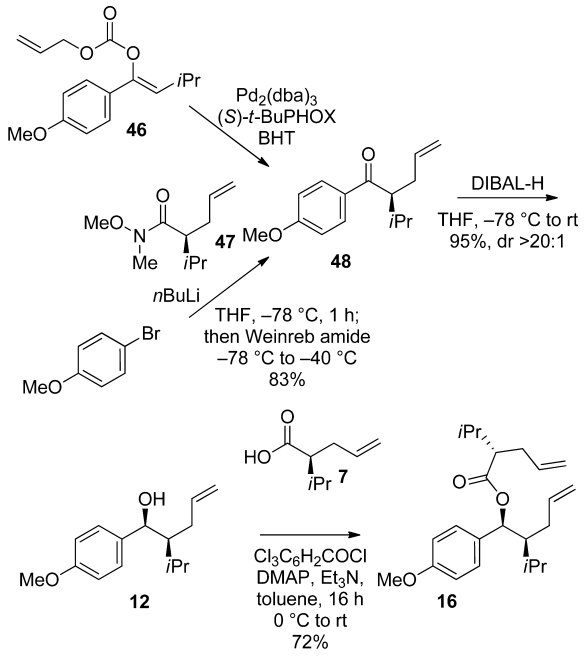
Scheme 7. Completion of the Synthesis of Aliskiren (1)



dx.doi.org/10.1021/jo5015195 | J. Org. Chem. 2014, 79, 9531–9545

inseparable mixture of the diastereomeric esters **15** and **16** (as well as **17** and **18**) led to a single diastereomer in each case involving the cyclization of the (*R*)-esters to give the 9-membered lactones **19** and **21**, respectively (Scheme 2). The other diastereomeric esters **16** (and **18**) were recovered in poor yield and contaminated with some other metathesis side products. To further study the fate of the (*S*)-ester **16**, we prepared it in a stereoselective manner (Scheme 8). Thus, allylic transposition of allyl enolcarbonate **46** in the presence of $Pd_2(dba)_3$ catalyst, (*S*)-*t*-BuPHOX ligand,[26,45] and BHT as additive[27] led to the ketone **48** in good yield and acceptable enantiomeric excess (average of 90% yield and 88 to 91% ee).

Scheme 8. Catalytic Asymmetric Synthesis of (*S*)-Ester 16

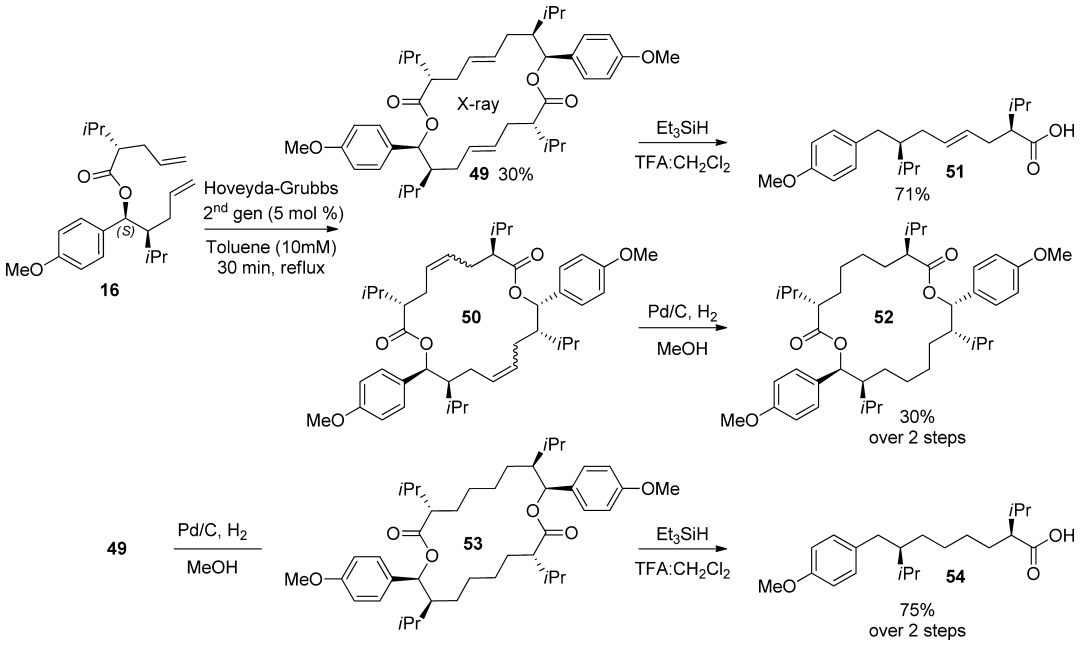


The same ketone was also prepared by arylation of the Weinreb amide derivative **47** of (2*S*)-isopropylbuta-4-enoic acid **7** independently prepared via an Evans[22] or MacMillan[28,46] asymmetric allylation. Reduction with a slow addition of DIBAL-H, keeping the temperature at −78 °C, led quantitatively to the (*S*)-alcohol **12** with a diastereomeric ratio of >20:1. Esterification with the acid **7** using the Yamaguchi method[33] led to **16**.

In the presence of 5 mol % of the second-generation Hoveyda−Grubbs catalyst (**H-G2**) at 10 mM in refluxing toluene, the (*S*)-ester **16** yielded 30% of the C_2-symmetrical *trans*−*trans* bis-unsaturated dilactone **49** and a mixture of non-symmetric dilactones as double-bond isomers **50** (Scheme 9). The structure of **49** was also confirmed by single-crystal X-ray analysis. Reductive cleavage of the benzylic ester bonds in **49** led to the acid **51**, which is a known intermediate in the Speedel process for the synthesis of aliskiren.[24,25] Controlled catalytic hydrogenation of the double bonds in **49** led to the saturated dilactone **53**, which upon reductive cleavage in acidic media yielded acid **54**. Alternatively, hydrogenation of the mixture of isomers corresponding to dilactones **50** afforded the head-to-head dilactone **52** (Scheme 9).

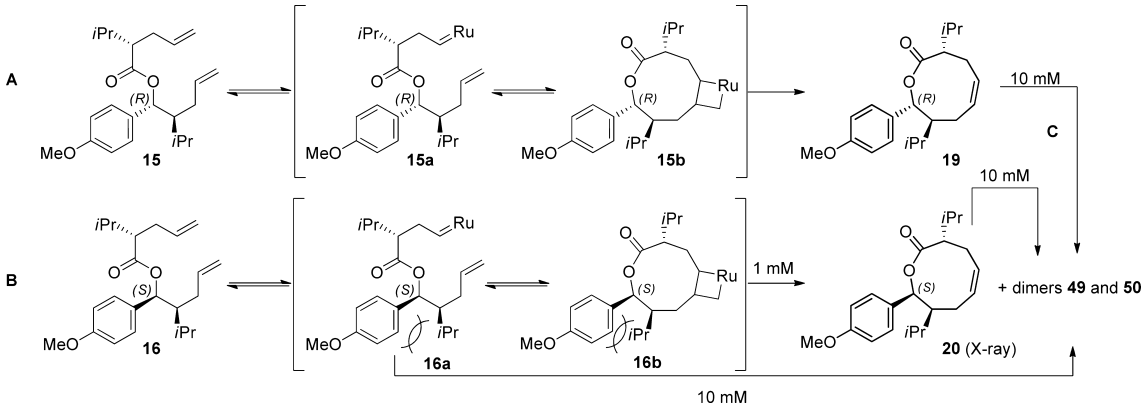
Judging from the results using the Grubbs first-generation catalyst (**G1**) with the (*R*)-esters **15** and **17** (10 mol % catalyst, 72 h, rt, toluene at 10 mM concentration), we speculate that the formation of the corresponding 9-membered lactones **19** (and **21**) can be attributed to the contribution of cooperative stereochemical, stereoelectronic, and conformational effects leading first to alkylidene Ru complexes (exemplified by the structure **15a** as one of the two possible intermediates). Presumably, the olefinic termini are favorably aligned with minimal steric interaction to lead to the Ru-metallacycle **15b**, which eventually collapses to the intended lactone **19** (Scheme 10A). In contrast, the transition state starting with the (*S*)-ester **16** will be subject to a significant steric clash between the isopropyl and aromatic moieties, thereby slowing

Scheme 9. Cross-Metathesis Reaction of the (*S*)-Ester 16 and Reductive Cleavage of Macrocylic Dilactones



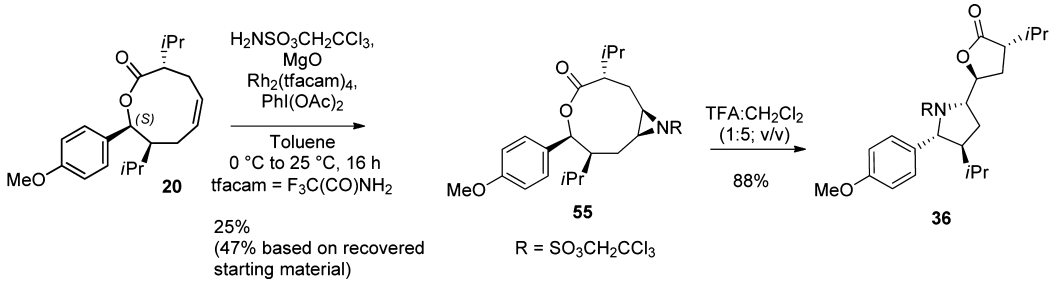
dx.doi.org/10.1021/jo5015195 | J. Org. Chem. 2014, 79, 9531−9545

Scheme 10. Possible Ru-Metallacyclic Intermediates[a]



[a](A) First-generation Grubbs (**G1**) and second-generation Hoveyda−Grubbs (**H−G2**) catalysts at 10 mM (72 h at rt and 20 min, toluene reflux, respectively). (B) **H−G2** catalyst at 1 mM (6 h, toluene reflux) and 10 mM (24 h, toluene reflux). (C) **H−G2** catalyst at 10 mM (24 h, toluene reflux). Only one alkylidene Ru-intermediate is shown.

Scheme 11. Aziridination and Double-Ring Contraction of the (*S*)-Lactone 20



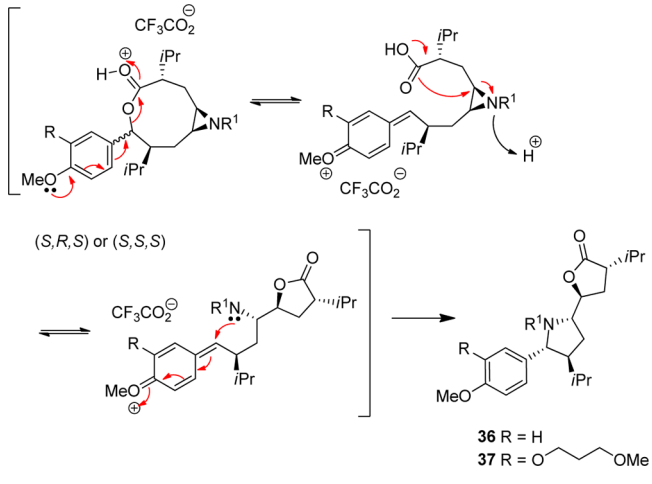
down the reaction (Scheme 10B). The same conclusion would also apply in the case of ester **18**.

In the presence of the more robust second-generation Hoveyda−Grubbs catalyst (**H−G2** 5 mol %, at a concentration of 10 mM in toluene at 110 °C for 20 min), the (*R*)-ester **15** in a mixture containing the (*S*)-ester **16** as the minor isomer is converted to lactone **19** in 64% yield. Under the same conditions, the minor (*S*)-ester **16** undergoes direct dimerization to the macrocyclic dilactones **49** and **50**, which were not reverted to starting material under these conditions (Scheme 10B). This was corroborated with the enantioenriched (*S*)-ester **16** (Scheme 9). Surprisingly, when the reaction was performed at a concentration of 1 mM instead of 10 mM, in refluxing toluene for 6 h, the (*S*)-ester **16** led to the elusive (*S*)-lactone **20** in 53% yield, accompanied by the usual dimers **49** and **50** (∼24%) (Scheme 10B). The structure of **20** was confirmed by X-ray crystallography.[31] When heated at reflux temperature in 10 mM in toluene for 24 h in the presence of the second-generation Hoveyda−Grubbs catalyst (**H−G2**), the (*S*)-lactone **20** was rapidly converted to the lactones **49** and **50**. At a concentration of 1 mM, a diastereomeric mixture of **15** and **16** led to the corresponding lactones **19** and **20** respectively, accompanied by the dimers **49** and **50**.

Intrigued by this observation, we subjected the (*R*)-lactone **19** to the same reaction conditions, only to find that dimerization to **49** and **50** had also taken place (Scheme 10A). We can conclude that, depending on the concentration, the catalyst, and temperature, the (*R*)-lactone **19** and (*S*)-lactone **20** are the kinetic products. Dimerization during ring-closing metathesis has been previously reported.[47]

Finally, we subjected the (*S*)-lactone **20** to an aziridination reaction to give **55** in 25% yield with recovery of starting material (Scheme 11). TFA-induced double-ring contraction as for the (*R*)-lactone **19** (Scheme 6) gave the known lactone **36** in 88% yield. Presumably, the activation of the *N*-sulfamoyl aziridine lactone in either 9-membered lactones engendered participation by the electron-rich aryl moiety to give a quinonoid oxocarbenium ion which underwent regioselective intramolecular attack liberating the sulfamate group (Scheme 12). The latter would attack the quinonoid benzylic carbon atom with high antiselectivity with regard to

Scheme 12. Proposed Double-Ring Contraction Mechanism[28]



dx.doi.org/10.1021/jo5015195 | J. Org. Chem. 2014, 79, 9531−9545

the C-7 isopropyl substituent leading to the observed pyrrolidine lactone **36**.[28]

CONCLUSION

In conclusion, we have provided a detailed account of various approaches leading to the total synthesis of the antihypertensive marketed drug aliskiren. Ring-closing metathesis using the Grubbs (**G1** and **G2**) and Hoveyda−Grubbs (**H−G2**) catalysts with stereochemically distinct esters carrying terminal allyl moieties led to 9-membered lactones which were further elaborated to aliskiren and its *p*-methoxyphenyl congener. The formation of 9-membered lactones from diastereomeric (*R*)- and (*S*)-esters **15** and **16** were found to be concentration dependent and favored at a concentration of 1 mM in toluene using the Hoveyda−Grubbs second-generation catalyst (**H−G2**). At higher concentrations, the (*R*)-ester **15** afforded the expected 9-membered lactone, while the (*S*)-ester **16** led to a mixture of macrocyclic dilactones. Further studies focusing on the nature and stereochemistry of substituents in related cyclizations by ring-closing metathesis are in progress and will be reported in due course.

EXPERIMENTAL SECTION

General Procedure. All reactions were performed in oven-dried glassware under an argon atmosphere using dry, deoxygenated solvents. Dichloromethane and toluene were dried by passage through an activated alumina column under argon (solvent drying system (SDS)). Reagents were purchased and used without further purification. Reactions were monitored by analytical thin-layer chromatography (TLC) carried out on 0.25 mm silica plates that were visualized under a UV lamp (254 nm) and developed by staining with ceric ammonium molybdate, *p*-anisaldehyde, and/or potassium permanganate solution. Flash column chromatography was performed using silica (particle size 40−63 μm, 230−400 mesh) at increased pressure. FTIR are reported in reciprocal centimeters (cm^{-1}). NMR spectra (^1H, ^{13}C, DEPT 135, COSY, HMQC, NOESY) were recorded at either 300, 400, 500, or 700 MHz. Chemical shifts for ^1H NMR spectra are recorded in parts per million relative to trimethylsilane (TMS, δ = 0.00 ppm) with the solvent resonance as the internal standard (CH_3Cl, δ = 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = hextet, m = multiplet, and br = broad), coupling constants in hertz (Hz), integration (*x*H). Chemical shifts for ^{13}C NMR spectra are recorded in parts per million using the central peak of $CDCl_3$ (δ = 77.16 ppm) as the internal standard. Optical rotations were determined with a polarimeter at 589 nm using a 1 dm cell at ambient temperature and are reported in units of $deg{\cdot}cm^3{\cdot}g^{-1}{\cdot}dm^{-1}$. Melting points are given as ranges and are reported in °C.

(1*S*,2*S*)-2-Isopropyl-1-(4-methoxyphenyl)pent-4-en-1-ol (12). A solution of 1.5 M of DIBAL-H in toluene (1.8 mL, 2.7 mmol, 1.5 equiv) was added in a slow dropwise manner to a solution of ketone **48** (0.42 g, 1.8 mmol, 1.0 equiv) in THF (10 mL) at −78 °C. The solution was kept at −78 °C for at least 3 h and then allowed to slowly warm to room temperature. Silica gel was added until the reaction mixture stopped to generate bubbles. The mixture was filtered on a silica pad (silica gel, 2.5 cm diameter ×4.0 cm height; 5 V diethyl ether, then 2 V ethyl acetate) to yield alcohol **12** (0.40 g, 95%, dr >20:1) as a colorless oil: R_f = 0.11 (1:9, diethyl ether:hexanes); $[\alpha]_D^{20}$ −12 (*c* 3.0, $CDCl_3$) (from ketone **48** with 83% ee, prepared with the PdAAA protocol[27]); ^1H NMR (400 MHz, $CDCl_3$) δ 7.28−7.23 (m, 2H), 6.89−6.85 (m, 2H), 5.53 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1H), 4.88−4.79 (m, 2H), 4.58 (dd, *J* = 7.7, 3.3 Hz, 1H), 3.81 (s, 3H), 2.16−2.04 (m, 1H), 2.04−1.95 (m, 1H), 1.92−1.83 (m, 1H), 1.74−1.68 (m, 1H), 1.67 (dd, *J* = 3.4, 0.4 Hz, 1H), 0.98−0.93 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 138.9, 136.5, 128.1, 115.1, 113.9, 75.9, 55.4, 50.6, 31.3, 27.2, 21.5, 18.4; IR (neat) 3454, 3005, 2962, 2940, 2880, 2845, 1615, 1515, 1468, 1248, 1177, 1038 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{15}H_{22}NaO_2$ $[M + Na]^+$ 257.1512, found $[M + Na]^+$ 257.1516.

(*S*)-(1*S*,2*S*)-2-Isopropyl-1-(4-methoxyphenyl)pent-4-en-1-yl-2-isopropylpent-4-enoate (Ester 16). Triethylamine (70 μL, 0.51 mmol, 1.2 equiv), 2,4,6-trichlorobenzoyl chloride (80 μL, 0.51 mmol, 1.2 equiv), and 4-(dimethylamino)pyridine (62 mg, 0.51 mmol, 1.2 equiv) were successively added to a solution of acid **7** (64 mg, 0.45 mmol, 1.05 equiv) in dry toluene (3 mL) at 0 °C. The resulting white slurry was stirred at 0 °C for 10 min during which the white slurry turned yellow. A solution of alcohol **12** (0.10 g, 0.43 mmol, 1.0 equiv) in dry toluene (1 mL) was added to the reaction vessel containing the yellow slurry in a dropwise manner at 0 °C. The flask that contained alcohol **12** was rinsed three times with dry toluene (1 mL), and the reaction mixture was allowed to warm to room temperature and monitored by TLC analysis until no more starting material was observed (Around 4 h at room temperature). The solvent was removed, and the resulting yellow solid was taken up in ethyl acetate (10 mL) and H_2O (10 mL). The aqueous layer was separated and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were successively washed with a 10% aqueous solution of acid citric (10 mL) and a saturated aqueous solution of sodium bicarbonate (10 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 2.5 cm × 14.0 cm; 1:19 diethyl ether/hexanes) to yield ester **16** (110 mg, 72%) as an oil: R_f = 0.53 (1:9 diethyl ether/hexanes); $[\alpha]_D^{20}$ − 58 (*c* 2.0, $CDCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.26−7.21 (m, 2H), 6.87−6.77 (m, 2H), 5.79−5.58 (m, 2H), 5.57−5.37 (m, 1H), 5.05−4.91 (m, 2H), 4.87−4.73 (m, 2H), 3.79 (s, 3H), 2.39−2.14 (m, 3H), 2.12−1.71 (m, 5H), 0.96−0.89 (m, 6H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.74 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 159.1, 138.3, 136.2, 132.4, 129.1, 116.6, 115.4, 113.5, 77.1, 55.3, 52.8, 48.7, 34.0, 30.9, 30.7, 27.2, 21.2, 20.5, 20.3, 18.0; IR (neat) 3075, 2957, 2931, 2873, 2837, 1728, 1612, 1513, 1249, 1169, 1035 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{23}H_{34}NaO_3$ $[M + Na]^+$ 381.2400, found $[M + Na]^+$381.2400.

Lactone 20. Hoveyda−Grubbs second-generation catalyst (3 mg, 0.048 mmol, 0.06 equiv) was added to a solution of **16** (30 mg, 0.084 mmol, 1.0 equiv, dr 20:1) in dry toluene (84 mL), and the mixture was stirred at reflux for 6 h. The reaction mixture was cooled to room temperature, then an excess of ethyl vinyl ether was added and gently evaporated. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter ×20.0 cm height, 1:50 ethyl acetate/hexanes) to yield **20** (16 mg, 53%) as pure white crystals: mp 89−91 °C; R_f = 0.55 (1:9 diethyl ether/hexanes); $[\alpha]^{20}{}_D$ −119 (*c* 0.5, $CDCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.7 Hz, 1H), 6.88 (d, *J* = 8.6 Hz, 1H), 5.74−5.64 (m, 1H), 5.55 (ddd, *J* = 11.0, 10.9, 6.1 Hz, 1H), 3.80 (s, 2H), 3.10−3.00 (m, 1H), 2.87−2.77 (m, 1H), 2.48 (ddd, *J* = 8.4, 7.0, 1.5 Hz, 1H), 2.23−2.10 (m, 1H), 2.00 (dq, *J* = 13.5, 6.7 Hz, 1H), 1.90−1.81 (m, 1H), 1.48 (dq, *J* = 13.2, 6.6 Hz, 1H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.84−0.79 (m, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.9, 159.1, 133.5, 131.0, 128.4 (2H), 126.2, 113.9 (2H), 78.2, 55.4, 50.7, 49.5, 28.8, 26.9, 26.5, 23.4, 22.4, 21.9, 20.3, 19.0; IR (neat) 3008, 2956, 2871, 2836, 1735, 1612, 1513, 1463, 1386, 1367, 1247, 1158, 1112, 1030 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd $C_{21}H_{31}O_3$ $[M + H]^+$ 331.2268, found $[M + H]^+$ 331.2259.

Lactone 21. See ref 28. Also prepared from addition of Hoveyda−Grubbs second-generation catalyst (4 mg, 0.0064 mmol, 0.06 equiv) to a solution of esters **17**:**18** (52 mg, 0.11 mmol, 1.0 equiv, dr 5:1) in dry toluene (9 mL) with stirring at 50 °C for 2 h. The reaction mixture was cooled to room temperature, filtered on silica and a Fluorisil pad, and then rinsed using 50% ethyl acetate/hexanes. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20.0 cm height, 1:9 ethyl acetate/hexanes) to yield **21** (33 mg, 72%).

Lactones 24 and 25. A solution of NBS (29 mg, 0.16 mmol, 1.1 equiv) was added in a dropwise manner to a mixture of lactone **19** (47 mg, 0.14 mmol, 1 equiv), copper(I) iodide (3 mg, 0.015, 0.11 equiv), and *p*-toluenesulfonamide (26 mg, 0.15 mmol, 1.1 equiv) in dichloromethane (3 mL). The mixture was stirred at room temperature for 4 h, and then H_2O (4 mL) was added in a round-bottom flask covered with aluminum foil. The mixture was diluted with ethyl acetate (15 mL) and stirred for a few minutes, and then layers were separated.

dx.doi.org/10.1021/jo5015195 | J. Org. Chem. 2014, 79, 9531−9545

The aqueous layer was back-extracted with ethyl acetate (5 mL), and the organic layers were combined, washed with brine (10 mL), dried over sodium sulfate, and concentrated. A diastereomeric ratio of 3.9:1 was observed by ^{1}H NMR of the crude mixture. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter ×21 cm height, 1:9 to 1:4 ethyl acetate/hexanes) to yield the lactone **24** (42 mg, 52%) as a white solid along with impure fractions of **25**, which could be obtained as a pure white solid by recrystallization in methanol. Also, starting from 63 mg (0.19 mmol, 1 equiv) of lactone **19**, 14 mg (13%) of lactone **25** could be obtained pure by flash chromatography (silica gel, 2.5 cm × 20 cm, 0 to 1:19 ethyl acetate/hexanes) and 64 mg of impure lactone **24** which was repurified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height, 1:4 ethyl acetate/hexanes) to yield the pure lactone **24** (40 mg, 36%).

Lactone 24: R_f = 0.29 (1:4 ethyl acetate/hexanes); (recrystallized from 2-propanol) mp 113−115 °C; $[\alpha]_D^{20}$ +49 (*c* 0.5, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.42−7.39 (m, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.91−6.88 (m, 2H), 6.63−6.60 (m, 2H), 5.34 (d, *J* = 7.7 Hz, 1H), 4.45−4.43 (m, 1H), 4.20 (dd, *J* = 9.2, 8.1 Hz, 1H), 4.16 (ddd, *J* = 9.0, 4.4, 1.5 Hz, 1H), 3.73 (s, 3H), 2.96 (ddd, *J* = 11.3, 7.6, 3.8 Hz, 1H), 2.58−2.51 (m, 1H), 2.31 (s, 3H), 2.31−2.27 (m, 1H), 2.11 (ddd, *J* = 14.4, 11.2, 3.1 Hz, 1H), 2.03 (ddd, *J* = 14.7, 9.2, 5.4 Hz, 1H), 1.81−1.77 (m, 1H), 1.69 (ddd, *J* = 14.9, 4.4 Hz, 1H), 1.47−1.42 (m, 1H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.82 (d, *J* = 7.0 Hz, 3H), 0.71 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 170.9, 158.8, 142.6, 138.2, 132.5, 129.2 (2C), 128.1 (2C), 127.1 (2C), 113.8 (2C), 81.1, 60.5, 55.4, 50.0, 45.7, 42.9, 32.0, 30.2, 29.2, 28.1, 21.7, 21.6, 19.7, 18.5, 16.2; IR (neat) 3252, 2958, 2923, 2852, 1732, 1704, 1612, 1514, 1463, 1443, 1325, 1248, 1218, 1179, 1160, 1093, 1046 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{28}H_{38}{}^{79}BrNNaO_5S$ $[M + Na]^+$ 602.1546, found $[M + Na]^+$ 602.1517.

Lactone 25: R_f = 0.21 (1:4 ethyl acetate/hexanes); (gradual dec) (recrystallized from ethanol) mp 151−167 °C; $[\alpha]_D^{20}$ −56 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48−7.44 (m, 2H), 7.07−7.03 (m, 2H), 6.92−6.86 (m, 2H), 6.65−6.59 (m, 2H), 5.30 (d, *J* = 8.5 Hz, 1H), 4.19−4.16 (m, 1H), 4.12−4.07 (m, 1H), 3.69 (s, 3H), 2.76−2.66 (m, 2H), 2.40−2.29 (m, 4H), 2.29−2.21 (m, 1H), 2.07 (ddd, *J* = 14.6, 8.2, 3.4 Hz, 1H), 1.66 (ddd, *J* = 14.4, 9.4, 1.5 Hz, 1H), 1.63−1.55 (m, 1H), 1.50−1.43 (m, 1H), 1.40 (ddd, *J* = 14.4, 9.3, 5.0 Hz, 1H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.81 (d, *J* = 7.0 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H), 0.69 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 171.3, 159.3, 143.1, 137.5, 132.3, 129.3 (2C), 128.3 (2C), 127.3 (2C), 114.0 (2C), 78.8, 60.4, 55.3, 49.0, 45.7, 42.9, 31.7, 30.3, 29.5, 28.1, 22.0, 21.6, 19.5, 18.1, 16.0; IR (neat) 3273, 2966, 2930, 2860, 2880, 1740, 1727, 1667, 1615, 1518, 1467, 1449 1329, 1256, 1183, 1161, 1052, 1041 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{28}H_{38}{}^{79}BrNNaO_5S$ $[M + Na]^+$ 602.1546, found $[M + Na]^+$ 602.1535.

Lactone 26. Starting from the lactone **19** (66 mg, 0.20 mmol, 1.0 equiv), the bromosulfonamidation protocol was followed and the crude mixture of the bromosulfonamides **24**:**25** (dr 3.9:1) was dissolved in dichloromethane and cooled to 0 °C. Triethylsilane (0.16 mL, 1.0 mmol, 5.0 equiv) was added to the solution followed by TFA (0.1 mL). The solution was allowed to slowly reach room temperature, and the progress of the reaction was monitored by TLC. Volatiles were removed under vacuum with a rotary evaporator, and the residue was purified by flash chromatography (silica gel, 2.0 cm diameter ×20 cm height, 1:9 ethyl acetate/hexanes) to yield bromolactone **26** (62 mg, 75%, 2 steps) as an oil: R_f = 0.43 (1:4, ethyl acetate/hexanes); $[\alpha]_D^{20}$ +11 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15−7.01 (m, 2H), 6.89−6.75 (m, 2H), 4.26−4.20 (m, 1H), 3.77 (s, 3H), 3.70 (ddd, *J* = 6.8, 5.2, 1.0 Hz, 1H), 2.79 (ddd, *J* = 11.3, 7.8, 3.9 Hz, 1H), 2.71 (dd, *J* = 13.8, 5.2 Hz, 1H), 2.54−2.33 (m, 2H), 2.13 (ddd, *J* = 14.6, 7.8, 3.4 Hz, 1H), 1.85−1.53 (m, 5H), 0.96−0.91 (m, 6H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 158.2, 133.4, 129.9 (2C), 114.1 (2C), 79.3, 55.4, 49.9, 42.8, 41.7, 37.8, 36.2, 31.21, 30.23, 29.3, 19.7, 19.6, 18.4, 18.3; IR (neat) 2966, 2940, 2879, 1736, 1615, 1515, 1468, 1249, 1226, 1209, 1180, 1069, 1041 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{21}H_{31}{}^{79}BrNaO_3$ $[M + Na]^+$ 433.1349, found $[M + Na]^+$ 433.1340.

Epoxide 28. *m*-CPBA (77%) (65 mg, 0.29 mmol, 1.9 equiv) was added to a solution of lactone **19** (51 mg, 0.15 mmol, 1.0 equiv) in dichloromethane (1 mL), and the reaction mixture was stirred for 1 h at room temperature. The solution was diluted with diethyl ether (5 mL) and washed with a saturated aqueous solution of sodium bicarbonate (2 × 10 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to yield 47 mg of the crude epoxide **28** (dr 10:1) as a gel: R_f = 0.52 (1:4, ethyl acetate/hexanes). Only the major diastereomer is reported: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.27 (m, 2H), 6.92−6.85 (m, 2H), 5.75 (d, *J* = 11.1 Hz, 1H), 3.81 (s, 3H), 3.29−3.20 (m, 1H), 3.04 (ddd, *J* = 10.7, 3.7, 1.8 Hz, 1H), 2.60−2.50 (m, 1H), 2.25 (ddd, *J* = 11.4, 5.2, 1.9 Hz, 1H), 2.21−2.07 (m, 1H), 2.07−1.93 (m, 2H), 1.58−1.38 (m, 2H), 1.03 (d, *J* = 6.5 Hz, 3H), 0.99−0.92 (m, 1H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 6.9 Hz, 3H), 0.79 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 159.6, 131.7, 128.9 (2C), 114.0 (2C), 78.0, 61.0, 55.4, 55.4, 52.7, 48.6, 28.5, 27.0, 26.5, 25.0, 22.0, 21.8, 19.7, 15.9; IR (neat) 3004, 2967, 2947, 2936, 2929, 2880, 1733, 1519, 1466, 1393, 1375, 1277, 1252, 1204, 1179, 1122, 1117, 1038 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{21}H_{31}O_4$ $[M + H]^+$ 347.2217, found $[M + H]^+$ 347.2204 and calcd for $C_{21}H_{30}NaO_4$ $[M + Na]^+$ 369.2036, found $[M + Na]^+$ 369.2029.

Lactones 29, 30, and 31. To a solution of the crude epoxide **28** (47 mg) in dichloromethane (1 mL) was added trifluoroacetic acid (60 μL). The solution was stirred 10 min,a nd then the reaction was stopped by adding a saturated aqueous solution of sodium bicarbonate (5 mL) followed by ethyl acetate (10 mL). The organic layer was washed with a saturated aqueous solution of sodium bicarbonate (5 mL), dried over magnesium sulfate, filtered, and concentrated. A ratio of 6:1:1 was observed in the ^{1}H NMR spectrum of the crude mixture. The residue was purified by flash chromatography (silica gel, 2.0 cm diameter × 20.0 cm height, 1:19 ethyl acetate:hexanes) to yield lactones **29** (15 mg, 29%) + **30** (4 mg, 8%) + **31** (4 mg, 8%) + 7 mg of mixed fractions. All lactones produced from this reaction were clear oils.

Lactone 29: R_f = 0.41 (1:4 ethyl acetate/hexanes); $[\alpha]_D^{20}$ +14 (*c* 1.5, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.24−7.21 (m, 2H), 6.89−6.86 (m, 2H), 4.53−4.43 (m, 1H), 4.25 (d, *J* = 10.5 Hz, 1H), 3.89−3.87 (m, 1H), 3.80 (s, 3H), 2.81 (ddd, *J* = 11.5, 7.3, 3.8 Hz, 1H), 2.59−2.52 (m, 1H), 2.17−2.11 (m, 1H), 2.08 (ddd, *J* = 14.0, 7.3, 3.9 Hz, 1H), 2.00−1.93 (m, 1H), 1.74 (ddd, *J* = 14.3, 12.5, 2.3 Hz, 1H), 1.64 (ddd, *J* = 14.4, 12.9, 2.8 Hz, 1H), 1.43−1.36 (m, 1H), 0.93−0.90 (m, 6H), 0.78 (d, *J* = 7.0 Hz, 3H), 0.74 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 173.9, 159.6, 132.7, 128.6 (2C), 114.1 (2C), 83.2, 76.1, 70.5, 55.4, 41.0, 39.7, 29.0, 28.3, 26.4, 25.8, 20.9, 19.8, 17.9, 15.9; IR (neat) 3018, 3003, 2965, 2954, 2941, 2935, 2923, 2913, 2905, 2881, 2844, 1724, 1617, 1590, 1518, 1469, 1446, 1391, 1373, 1367, 1350, 1248, 1226, 1175, 1157, 1129, 1082, 1056, 1030, 1007 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{21}H_{30}O_4$ $[M + H]^+$ 347.2217, found $[M + H]^+$ 347.2225 and calcd for $C_{21}H_{30}NaO_4$ $[M + Na]^+$ 369.2036, found $[M + Na]^+$ 369.2044.

Lactone 30: R_f = 0.46 (1:4 ethyl acetate/hexanes); $[\alpha]_D^{20}$ +39 (*c* 0.4, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.24−7.21 (m, 2H), 6.88−6.85 (m, 2H), 4.50 (ddd, *J* = 9.3, 3.2, 2.1 Hz, 1H), 4.41 (d, *J* = 9.3 Hz, 1H), 4.08 (ddd, *J* = 9.2, 5.0, 2.0 Hz, 1H), 3.79 (s, 3H), 2.70 (ddd, *J* = 9.8, 9.3, 5.0 Hz, 1H), 2.22 (ddd, *J* = 13.1, 10.0, 3.3 Hz, 1H), 2.20−2.13 (m, 2H), 2.13−2.06 (m, 2H), 1.92 (ddd, *J* = 12.4, 9.3 Hz, 1H), 1.60−1.53 (m, 1H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 6.1 Hz, 3H), 0.89 (d, *J* = 6.0 Hz, 3H), 0.71 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 179.8, 159.6, 133.2, 128.7 (2C), 114.0 (2C), 85.8, 79.6, 79.4, 55.4, 52.4, 45.4, 31.7, 29.0, 28.6, 26.3, 22.0, 20.6, 19.6, 18.1; IR (neat) 3000, 2967, 2931, 2907, 2899, 2889, 2878, 2859, 1771, 1619, 1519, 1471, 1374, 1251, 1178, 1110, 1093, 1036 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{21}H_{31}O_4$ $[M + H]^+$ 347.2217, found $[M + H]^+$ 347.2220 and calcd for $C_{21}H_{30}NaO_4$ $[M + Na]^+$ 369.2036, found $[M + Na]^+$ 369.2042.

Lactone 31: R_f = 0.31 (1:4 ethyl acetate/hexanes); $[\alpha]_D^{20}$ −2 (*c* 0.4, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.26−7.23 (m, 2H), 6.87−6.84 (m, 2H), 4.57 (d, *J* = 9.3 Hz, 1H), 4.36−4.32 (m, 1H), 4.25−4.20 (m, 1H), 3.79 (s, 3H), 2.61−2.56 (m, 1H), 2.21−2.15 (m, 2H), 2.15−2.12 (m, 1H), 2.12−2.07 (m, 1H), 2.05−1.95 (m, 1H), 1.84−1.77 (m, 1H), 1.71−1.64 (m, 1H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.75 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 178.0, 159.3, 134.3, 128.5 (2C), 113.9 (2C), 85.0, 79.9, 78.7,

dx.doi.org/10.1021/jo5015195 | J. Org. Chem. 2014, 79, 9531−9545

55.4, 54.1, 46.9, 31.8, 28.9, 27.9, 26.3, 22.4, 20.8, 19.6, 18.5; IR (neat) 3006, 2966, 2928, 2906, 2897, 2878, 2864, 2858, 2834, 2818, 1770, 1618, 1518, 1469, 1251, 1177, 1038, 1001, 981, 828, 763 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{21}H_{31}O_4$ $[M + H]^+$ 347.2217, found $[M + H]^+$ 347.2223 and calcd for $C_{21}H_{30}NaO_4$ $[M + Na]^+$ 369.2036 and $[M + Na]^+$ 369.2044.

Lactone Diol 32. *N*-Methylmorpholine *N*-oxide (53 mg, 0.45 mmol, 1.5 equiv) was added to a solution of lactone **15** (0.1 g, 0.3 mmol, 1 equiv) in acetone (2.4 mL) and distilled water (0.6 mL) at 0 °C, a 2.5 wt % solution of osmium tetra oxide in 2-methyl-2-propanol (0.2 mL, 0.02 mmol, 0.05 equiv) was added, and the reaction mixture was allowed to warm to room temperature. After 1 h of stirring, the reaction media was poured into a cold solution of ethyl acetate (2 mL) and a saturated aqueous solution of sodium thiosulfate (2 mL). The aqueous layer was separated and back-extracted with ethyl acetate (3 × 2 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated to leave 102 mg of a black oil which was purified by flash chromatography (silica gel, 1.5 cm × 20 cm; 2:3 ethyl acetate/hexanes) to yield diol **32** (89 mg, 81%, dr 9:1) as a colorless oil.

Diol **32** was also prepared using the same protocol, with 4 wt % solution of osmium tetraoxide in H_2O in 91% yield and an estimated dr of 6:1 by NMR. The oil was recrystallized from ethyl acetate:hexanes (1:4) to give white needles with an estimated dr of 7:1; mp 96 to 106 °C; R_f = 0.2 (2:3 ethyl acetate/hexanes): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.26 (m, 0.27H), 7.26−7.20 (m, estimated to ∼1.6H), 6.88−6.82 (m, 2H), 5.68 (d, J = 11.0 Hz, 1H), 4.50 (d, J = 6.5 Hz, 1H), 3.84−3.69 (m, 4H), 2.47 (s, 2H), 2.29 (ddd, J = 15.9, 6.8, 2.7 Hz, 1H), 2.24−2.01 (m, 2H), 1.92−1.58 (m, 3H), 1.55−1.45 (m, 0.21H), 1.45−1.30 (m, 1H), 1.24−1.08 (m, 1H), 0.98 (d, J = 6.1 Hz, 3H), 0.92−0.71 (m, 9H).Only the major diastereomer is reported for the ^{13}C NMR. ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 159.7, 131.0, 128.7, 114.1, 78.8, 77.9, 69.0, 55.4, 53.2, 48.4, 31.6, 30.1, 27.5, 26.9, 21.5, 21.3, 20.2, 15.3; IR (neat) 3394, 2867, 2945, 2881, 1730, 1617, 1519, 1467, 1253, 1179, 1052, 1036 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{21}H_{32}NaO_5$ $[M + Na]^+$ 387.2142, found $[M + Na]^+$ 387.2126.

Pyrrolidine Lactone 36. A dry round-bottomed flask was charged with 8 mg (0.014 mmol, 1.0 equiv) of **55**, a magnetic stirrer and 0.5 mL of dry dichloromethane ([**55**] = 0.028 M) were introduced via a glass syringe then added 5 drops of trifluoroacetic acid. The solution was stirred and monitored by TLC analysis (20:80 ethyl acetate−hexanes, CAM). After 10 min, when TLC analysis showed no more starting material, the trifluoroacetic acid and dichloromethane were first removed under reduced pressure at room temperature to leave yellow oil which was purified by flash column chromatography (silica gel, 1.5 cm × 20 cm; 1:19 ethyl acetate−hexanes) to yield 7 mg (0.0123 mmol, 88%) of the titled compound **36** as a yellow oil: R_f = 0.44 (1:9 ethyl acetate:hexanes); $[\alpha]_D^{20}$ +21 (c 0.7, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7−31 (m, 2H), 6.89−6.86 (m, 2H), 4.57−4.52 (m, 2H), 4.34 (d, J = 11.2 Hz, 2H), 4.23 (dd, 5.2 and 8.4 Hz, 1H), 3.78 (s, 3H), 2.64 (ddd, J = 5.6, 7.6, 10.0 Hz, 1H), 2.56−2.47 (m, 1H), 2.41−2.34 (m, 1H), 2.21−2.05 (m, 3H), 1.95 (dd, J = 6.4, 12.8 Hz, 1H), 1.71−1.62 (m, 1H), 1.04 (d, J = 6.4 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.4 Hz, 3H).

Lactone 39. Zn(Cu) (0.18 g, 2.8 mmol, 5.0 equiv) was added to a solution of amide **38** (0.36 g, 0.56 mmol, 1.0 equiv) in methanol/ethyl acetate (1 mL, 1:1 v/v) and stirred at room temperature. The reaction was monitored by MS. The mixture was filtered on Celite, rinsed with a minimal amount of MeOH, and concentrated. The resulting solid was dissolved in dry MeOH (5 mL) and cooled to 0 °C, and AcCl (0.36 mL) was added. The solution was allowed to reach room temperature and stirred 24 h. The solvent was removed under vacuum with a rotary evaporator, and the resulting white solid was dissolved in CH_2Cl_2 (2 mL). To this last were added H_2O (2 mL), Boc_2O (0.16 g, 0.73 mmol, 1.3 equiv), K_2CO_3 (0.39 g, 2.8 mmol, 5.0 equiv), and TBAB (43 mg, 0.11 mmol, 0.2 equiv). The mixture was stirred at room temperature and monitored by TLC. An excess of imidazole was added, and then the mixture was acidified to a pH = 3−4, with a 10% solution of citric acid. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, dried over sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 1:4 ethyl acetate/hexanes) to yield the known amide **40**[28] (90 mg, 31%) (R_f = 0.57, 2:3 ethyl acetate/hexanes) as a colorless oil and lactone **39** (40 mg, 16%) (R_f = 0.37, 2:3 ethyl acetate/hexanes) as a white solid, which was recrystallized from diffusing hexanes to a solution of lactone **39** in a minimal amount of ethyl acetate: mp 140 to 143 °C; $[\alpha]_D^{20}$ +14 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 4.60−4.25 (m, 2H), 4.20−4.05 (m, 1H), 3.79 (s, 1H), 4.70−4.55 (m, 1H), 2.40−2.10 (m, 4H), 2.00−1.80 (m, 1H), 1.73 (br s, 2H), 1.50−1.10 (br m, 9H), 1.04 (d, J = 6.8 Hz, 3H), 0.97−0.90 (m, 6H), 0.82 (d, J = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.1, 158.4, 136.0, 127.9, 113.7, 80.3, 65.7, 60.0, 55.3, 52.5, 45.1, 29.2, 28.3, 28.2, 27.8, 27.4, 22.2, 20.7, 18.6, 17.8; IR (neat) 2959, 2930, 2874, 2837, 1772, 1690, 1613, 1513, 1466, 1386, 1366, 1245, 1170, 1101, 1033 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{26}H_{40}NO_5$ $[M + H]^+$ 446.2901, found $[M + H]^+$ 446.2891 and calcd for $C_{26}H_{39}NNaO_5$ $[M + Na]^+$ 468.2720, found $[M + Na]^+$ 468.2729.

Lactone 41. An aqueous 1 M solution of LiOH (1.4 mL, 1.4 mmol, 10 equiv) was added to a solution of lactone **37** (88 mg, 0.14 mmol, 1.0 equiv) in DME (1.4 mL) at 0 °C. The reaction mixture was allowed to reach room temperature and monitored by TLC and MS. The mixture was then acidified with a 1 M HCl solution in MeOH to pH = 3−4, and volatiles were removed under vacuum with a rotary evaporator to give 312 mg of the crude mixture.

Boc_2O (0.10 g, 0.48 mmol, 2.4 equiv) was added to a mixture of the crude deprotected intermediate (0.18 g, estimated to 0.20 mmol, 1.0 equiv) in dichloromethane (1 mL) and H_2O (1 mL) at 0 °C. K_2CO_3 (0.26 g, 1.9 mmol, 10 equiv) and TBAB (24 mg, 74 μmol, 0.37 equiv) were added, and the mixture was allowed to reach room temperature. The mixture was stirred for 16 h at room temperature, and then the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL), and the organic layers were combined, dried over sodium sulfate, filtered, and concentrated. The residue was purified via flash chromatography (silica gel, 1:9 ethyl acetate:hexanes) to yield Boc-protected lactone **41** (105 mg, >95%) as a colorless oil: $[\alpha]_D^{20}$ −70 (c 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (s, 1H), 6.85−6.72 (m, 2H), 4.82 (s, 1H), 4.35−3.95 (m, 4H), 3.83 (s, 3H), 3.62−3.48 (m, 2H), 3.36−3.28 (m, 3H), 2.66−2.53 (m, 1H), 2.35−2.02 (m, 5H), 1.99−1.56 (m, 4H), 1.35−1.10 (m, 9H), 1.04 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.7 Hz, 3H), 0.80 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.64, 155.42, 148.26, 148.15, 119.86, 111.86, 111.19, 80.12, 79.22, 69.73, 66.32, 66.29, 61.11, 58.76, 56.14, 46.86, 29.60, 28.59, 28.31, 27.90, 27.66, 21.88, 20.72, 18.36, 18.28; IR (NaCl) 2961, 2874, 2835, 1770, 1682, 1515, 1469, 1391, 1260, 1143, 1028 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{47}NNaO_7$ $[M + Na]^+$ 556.3245, found $[M + Na]^+$ 556.3241.

Amide 42. A 2 M solution of $AlMe_3$ in toluene (0.1 mL, 0.2 mmol, 5 equiv) was added to a solution of *n*-butylamine (20 μL, 0.20 mmol, 5.0 equiv) in dichloromethane (1 mL), and the mixture was stirred at room temperature for 5 min. The resulting solution was transferred to a solution of lactone **37** (25 mg, 40 μmol, 1.0 equiv) in dichloromethane (1 mL), and the solution was stirred at room temperature overnight and then quenched with a saturated solution of ammonium chloride (10 mL). The organic phase was separated, and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 1:4 ethyl acetate/hexanes) to yield amide **42** (25 mg, 87%) as a colorless oil: R_f = (0.31, 2:3 ethyl acetate/hexanes); $[\alpha]_D^{20}$ + 11 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (d, J = 2.0 Hz, 1H), 6.86 (dd, J = 8.3, 2.0 Hz, 1H), 6.79 (d, J = 8.3 Hz, 1H), 5.94 (t, J = 5.7 Hz, 1H), 4.55 (d, J = 9.2 Hz, 1H), 4.44 (q, J = 10.8 Hz, 2H), 4.16−4.07 (m, 2H), 4.00−3.93 (m, 1H), 3.83 (s, 3H), 3.65−3.57 (m, 3H), 3.37 (s, 3H), 3.34−3.24 (m, 1H), 3.23−3.13 (m, 1H), 2.34−2.25 (m, 1H), 2.17−2.07 (m, 3H), 2.00−1.83 (m, 4H), 1.75−1.67 (m, 1H), 1.60 (ddd, J = 13.5, 10.4, 2.8 Hz, 1H), 1.51−1.44 (m, 2H), 1.38−1.28 (m, 3H), 0.97−0.86 (m, 12H), 0.83 (d, J = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4, 149.2, 148.7, 134.2, 120.1, 112.6, 111.6, 93.9, 77.6, 71.4, 69.9, 69.7, 67.7, 66.2, 58.8, 56.1, 53.4, 51.5, 39.3, 35.1, 32.0, 30.6, 30.4, 29.6, 28.7, 22.1, 21.3, 20.6, 20.3, 18.5, 13.9; IR (NaCl) 3330, 3012, 2960, 2931, 2874, 1634, 1516,

dx.doi.org/10.1021/jo5015195 | J. Org. Chem. 2014, 79, 9531−9545

1464, 1373, 1261, 1183, 1000 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{31}H_{52}Cl_3N_2O_8S$ $[M + H]^+$ 717.2505, found $[M + H]^+$ 717.2524 and calcd for $C_{31}H_{51}Cl_3N_2NaO_8S$ $[M + Na]^+$ 739.2324, found $[M + Na]^+$ 739.2341.

(*S*)-2-Isopropyl-*N*-methoxy-*N*-methylpent-4-enamide (47). EDC (0.71 g, 3.7 mmol, 1.1 equiv) was added to a solution of acid **7** (0.50 g, 3.5 mmol, 1 equiv) in dichloromethane (15 mL) at 0 °C, followed by triethylamine (0.59 mL, 4.2 mmol, 1.2 equiv), *N*,*O*-dimethylhydroxylamine hydrochloride, and a small chip of DMAP. The reaction mixture was allowed to slowly reach room temperature and stirred for 16 h. Volatiles were removed under vacuum with a rotary evaporator, and the resulting residue was partitioned between ethyl acetate (10 mL) and H_2O (10 mL). The aqueous layer was back-extracted twice with ethyl acetate (2 × 10 mL), and the organic layers were combined, washed with a saturated aqueous solution of sodium bicarbonate (3 × 10 mL), dried over sodium sulfate, and concentrated. The residue was purified by flash chromatography (silica gel, 2.5 cm diameter × 20 cm height, 1:4 ethyl acetate/hexanes) to yield **47** (0.46 g, 70%) as an oil: R_f = 0.7 (3:7, ethyl acetate/hexanes) $[\alpha]_D^{20}$ +8 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.74 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.05 (ddt, *J* = 17.0, 1.8, 1.2 Hz, 1H), 5.00−4.90 (m, 1H), 3.66 (s, 3H), 3.18 (s, 3H), 2.69 (br s, 1H), 2.43−2.23 (m, 2H), 1.96−1.82 (m, 1H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H); (residual chloroform signal was set at 77.9 ppm); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 137.3, 117.0, 62.1, 48.2, 35.1, 32.8, 31.4, 21.9, 21.8; IR (neat) 3077, 2961, 2873, 2820, 1661, 1464, 1440, 1416, 1385, 1337, 1321, 1177, 1116, 1085; HRMS (ESI-TOF) m/z calcd for $C_{10}H_{20}NO_2$ $[M + H]^+$ 186.1489, found $[M + H]^+$ 186.1482.

(*S*)-2-Isopropyl-1-(4-methoxyphenyl)pent-4-en-1-one (48).[27] A solution of 1.6 M *n*-BuLi in hexane (1.35 mL, 2.16 mmol, 1.03 equiv) was added to a solution of 4-bromoanisole (0.26 mL, 2.1 mmol, 1.0 equiv) in tetrahydrofuran (8 mL) at −78 °C. The solution was stirred at −78 °C for 40−60 min, and then a solution of **47** (0.46 g, 2.5 mmol, 1.2 equiv) in tetrahydrofuran (2−3 mL) was added in a dropwise manner. The reaction mixture was allowed to warm to room temperature, stirred for 1 h, and then quenched with water (10 mL). The organic layer was separated from the aqueous layer. The aqueous layer was extracted with diethyl ether (2 × 10 mL). Organic solutions were combined, washed with brine (2 × 10 mL), dried over magnesium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 2.5 cm diameter × 13 cm height; 1:9 diethyl ether/hexanes) to yield ketone **48** (0.40 g, 83%) as a clear oil: R_f = 0.47 (1:4 ethyl acetate/hexanes); $[\alpha]_D^{20}$ +38 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.69 (ddt, *J* = 17.0, 10.1, 7.0 Hz, 1H), 4.99 (d, *J* = 17.0 Hz, 1H), 4.89 (d, *J* = 10.1 Hz, 1H), 3.87 (s, 3H), 3.29 (ddd, *J* = 10.2, 6.8, 3.9 Hz, 1H), 2.64−2.45 (m, 1H), 2.38−2.21 (m, 1H), 2.16−1.91 (m, *J* = 6.7 Hz, 1H), 0.98−0.88 (m, 6H);^{13}C NMR (75 MHz, $CDCl_3$) δ 202.4, 163.4, 136.6, 131.5, 130.6 (2C), 116.3, 113.8 (2C), 55.6, 52.0, 33.4, 30.8, 21.4, 19.7; IR (neat) 3076, 2960, 2934, 2872, 2840, 1670, 1640, 1599, 1576, 1509, 1463, 1439, 1419, 1388, 1370, 1308, 1259, 1211, 1170, 1114, 1031 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{15}H_{21}O_2$ $[M + H]^+$ 233.1536, found $[M + H]^+$ 233.1530 and calcd for $C_{15}H_{20}NaO_2$ $[M + Na]^+$ 255.1356, found $[M + Na]^+$ 255.1345.

Dilactone 49. Hoveyda−Grubbs' second-generation catalyst (6 mg, 0.01 mmol, 0.05 equiv) was added to a solution of ester **16** (70 mg, 0.20, 1.0 equiv) in toluene (20 mL), and the mixture was heated to reflux for 24 h. The solution was concentrated by blowing air in the flask. The residue was purified by flash chromatography (silica gel, 2.0 cm diameter × 20 cm height, 0:100 to 3:97 ethyl acetate/hexanes) to yield the dilactone **49** (20 mg, 30%): R_f = 0.2 (1:9 ethyl acetate/hexanes); recrystallization from methanol gave white crystals; mp 191−198 °C; $[\alpha]_D^{20}$ −48 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.22−7.13 (m, 4H), 6.91−6.78 (m, 4H), 6.14 (d, *J* = 2.7 Hz, 2H), 5.75−5.60 (m, 2H), 5.54−5.35 (m, 2H), 3.80 (s, 6H), 2.54−2.27 (m, 4H), 2.21 (ddd, *J* = 11.2, 7.9, 3.6 Hz, 2H), 2.14−1.94 (m, 4H), 1.94−1.70 (m, 4H), 1.52−1.42 (m, 2H), 0.98 (d, *J* = 6.7 Hz, 6H), 0.94 (d, *J* = 6.9 Hz, 6H), 0.90 (d, *J* = 6.6 Hz, 6H), 0.78 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 158.6, 132.8, 131.4, 130.0, 127.3, 113.5, 75.3, 55.4, 54.4, 50.1, 34.5, 31.5, 28.2, 25.7, 23.3, 21.2, 20.6, 18.0; IR (neat) 2956, 2932, 2873, 1733, 1513, 1465, 1248, 1148, 1035 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{42}H_{64}NO_6$ $[M + NH_4]^+$ 678.4728, found $[M + NH_4]^+$ 678.4721.

Other fractions were combined to give 28 mg of mixture of head-to-head isomers **50**.

(2*S*,7*R*,*E*)-2-Isopropyl-7-(4-methoxybenzyl)-8-methylnon-4-enoic Acid (Acid 51). TFA (3 drops) was added to a solution of dilactone **49** (17 mg, 0.026 mmol, 1.0 equiv) and triethylsilane (0.10 mL, 0.63 mmol, 24 equiv) in dichloromethane (1 mL). The solution was stirred at room temperature for 10 min. Volatiles were removed under vacuum with a rotary evaporator, and the residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height, 100 mL of hexanes then 1:19 ethyl acetate/hexanes) to yield acid **51** (12 mg, 71%) as a clear oil: R_f = 0.14 (1:9 ethyl acetate/hexanes); $[\alpha]_D^{20}$ +27 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 10.74 (s, 1H), 7.07−7.02 (m, 2H), 6.83−6.78 (m, 2H), 5.47−5.29 (m, 2H), 3.78 (s, 3H), 2.50 (dd, *J* = 13.8, 6.6 Hz, 1H), 2.36 (dd, *J* = 13.8, 8.0 Hz, 1H), 2.31−2.12 (m, 3H), 2.00−1.80 (m, 3H), 1.76−1.62 (m, 1H), 1.53−1.40 (m, 1H), 1.00−0.92 (m, 6H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.6, 157.7, 134.2, 132.0, 130.1, 128.3, 113.7, 55.4, 52.7, 46.4, 35.7, 33.0, 32.7, 30.1, 28.3, 20.4, 20.3, 19.3, 19.0; IR (neat) 2956, 2925, 2871, 1703, 1511, 1244, 1176, 1038 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{21}H_{36}NO_3$ $[M + NH_4]^+$ 350.2690, found $[M + NH_4]^+$ 350.2688 and calcd for $C_{21}H_{32}NaO_3$ $[M + Na]^+$ 355.2244, found $[M + Na]^+$ 355.2248.

Dilactone 52. Pd/C (cat) was added to a solution of the mixture of isomers **50** (28 mg) in methanol/ethyl acetate (6 mL, 1:1). The suspension was purged with H_2 and stirred 24 h. The mixture was then filtered on Celite and concentrated to afford a residue which was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height, 1:9 ethyl acetate/hexanes) to yield dilactone **52** (20 mg, 30% over two steps) as a clear oil: R_f = 0.33 (1:9 ethyl acetate/hexanes); $[\alpha]_D^{20}$ −64 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.19−7.11 (m, 4H), 6.90−6.83 (m, 4H), 6.05 (d, *J* = 1.5 Hz, 2H), 3.79 (s, 6H), 2.22 (td, *J* = 8.7, 2.8 Hz, 2H), 2.00−1.82 (m, 2H), 1.82−1.27 (m, 20H), 0.96−0.84 (m, 18H), 0.81 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 158.7, 132.4, 127.5, 113.6, 76.2, 55.3, 52.7, 50.3, 30.3, 29.7, 29.5, 27.0, 26.9, 25.8, 23.0, 21.5, 20.0, 18.6; IR (neat) 2953, 2934, 2868, 1730, 1608, 1507, 1461, 1379, 1295, 1250, 1172, 1118, 1035 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{42}H_{64}NaO_6$ $[M + Na]^+$ 687.4595, found $[M + Na]^+$ 687.4580.

(2*S*,7*R*)-2-Isopropyl-7-(4-methoxybenzyl)-8-methylnonanoic Acid (Acid 54). Pd/C (cat) was added to a solution of dilactone **49** (4 mg, 0.006 mmol, 1 equiv) in methanol (0.5 mL) and ethyl acetate (0.05 mL). The suspension was purged with H_2, and the reaction was stirred under H_2 atmosphere (H_2 balloon). The reaction was monitored by TLC: R_f = 0.31 (1:9 ethyl acetate/hexanes). When completed, the mixture was filtered through Celite and concentrated to afford 4 mg of the crude dilactone **53**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.18−7.09 (m, 2H), 6.88−6.75 (m, 2H), 6.14 (d, *J* = 1.8 Hz, 1H), 3.77 (s, 3H), 2.15−2.03 (m, 1H), 1.91−1.10 (m, 11H), 0.92 (d, *J* = 6.7 Hz, 6H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.74 (d, *J* = 7.0 Hz, 3H); HRMS (ESI-TOF) m/z calcd for $C_{42}H_{64}NaO_6$ $[M + Na]^+$ 687.4595, found $[M + Na]^+$ 687.4576.

TFA (3 drops) was added to a solution of the crude dilactone **53** (4 mg, 0.006 mmol, 1 equiv) and triethylsilane (0.1 mL, 0.63 mmol, 100 equiv) in dichloromethane (1 mL). The solution was stirred at room temperature for 10 min. Volatiles were removed under vacuum with a rotary evaporator, and the residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height, 100 mL of hexanes then 1:19 ethyl acetate:hexanes) to yield acid **54** (3 mg, 75%): $[\alpha]_D^{20}$ +16 (*c* 0.3, $CDCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 9.45 (s, 1H), 7.10−7.02 (m, 2H), 6.84−6.76 (m, 2H), 3.78 (s, 3H), 2.51 (dd, *J* = 13.7, 6.7 Hz, 1H), 2.35 (dd, *J* = 13.7, 7.8 Hz, 1H), 2.17−2.03 (m, 1H), 1.94−1.79 (m, 1H), 1.75−1.62 (m, 1H), 1.62−1.49 (m, 2H), 1.49−1.36 (m, 2H), 1.36−1.08 (m, 5H), 0.96−0.92 (m, 6H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 179.6, 157.7, 134.5, 130.1, 113.7, 55.4, 52.4, 46.1, 36.3, 30.6, 29.6, 29.5, 28.6, 28.4, 27.7, 20.6, 20.3, 19.3, 16.9; ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.5, 157.7, 134.4, 130.1, 113.7, 55.4, 52.6, 46.1, 36.3, 30.6, 29.5, 29.4, 28.6, 28.2, 27.7, 20.6, 20.2, 19.3, 18.8; IR (neat) 2925, 2860, 1704, 1511, 1461, 1375, 1245,

dx.doi.org/10.1021/jo5015195 | J. Org. Chem. 2014, 79, 9531−9545

1178, 1038 cm^{-1}; HRMS (ESI_NEG) calcd for $C_{21}H_{33}O_3$ $[M - H]^-$ 333.2435, found $[M-H]^-$ 333.2440.

Lactone 55. 2,2,2-Trichloroethylsulfamate (14 mg, 0.061 mmol, 1.1 equiv) was added to a solution of lactone **20** (18 mg, 0.055 mmol, 1.0 equiv) in toluene (0.3 mL) followed by magnesium oxide (6 mg, 0.15 mmol, 2.7 equiv) and rhodium trifluoroacetamide dimer (2 mg, 0.003 mmol, 0.04 equiv). The resulting pale blue slurry was cooled to 0 °C, diacetoxyiodobenzene (27 mg 0.083 mmol, 1.5 equiv) was added, and the reaction was slowly warmed to room temperature. The progress of the reaction was monitored by TLC analysis (30:70 ethyl acetate−hexanes, CAM). After 20 h of stirring at room temperature, TLC analysis showed no more conversion. The reaction mixture was diluted with dichloromethane, filtered through a pad of Celite, and then washed with dichloromethane (3 × 10 mL). The solvent was removed under reduced pressure to leave a brown oil which was purified by flash column chromatography (silica gel, 1.5 cm diameter ×20.0 cm height, 1:19 ethyl acetate/hexanes) to yield compound **55** (8 mg, 0.014 mmol; 25%) and starting material **20** (8 mg, 0.024 mmol, yield based on recovered starting material: 47%): R_f = 0.27 (1:9 ethyl acetate/hexanes); $[\alpha]_D^{20}$ −19 (*c* 0.8, $CDCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.7 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 1H), 5.85 (d, *J* = 6.3 Hz, 1H), 4.80 (s, 1H), 3.81 (s, 1H), 2.94 (ddd, *J* = 12.2, 6.8, 2.6 Hz, 1H), 2.81 (ddd, *J* = 10.1, 6.8, 3.0 Hz, 1H), 2.48−2.39 (m, 1H), 2.32−2.25 (m, 1H), 2.21−1.99 (m, 1H), 1.97−1.87 (m, *J* = 14.6, 11.3, 6.2 Hz, 1H), 1.51−1.41 (m, 1H), 1.03 (t, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 2H), 0.77 (d, *J* = 6.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 159.8, 129.2, 128.9, 114.1, 93.1, 79.5, 77.1, 55.4, 49.1, 48.1, 44.1, 43.6, 29.6, 26.9, 26.0, 23.4, 22.6, 21.7, 20.2, 19.7; IR (neat) 2959, 2931, 2873, 2839, 1733, 1612, 1515, 1464, 1369, 1250, 1178, 1118 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{23}H_{33}NO_6SCl_3$ $[M + H]^+$ 556.1089, found $[M + H]^+$ 556.1075.

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra of new compounds as well as X-ray crystallography reports and CIF files for compounds **20**, **25**, **32**, **33**, **39**, and **49**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: stephen.hanessian@umontreal.ca.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from NSERC and FQRNT. We thank Robert D. Giacometti and Benoît Deschênes-Simard for X-ray crystallographic analyses.

■ REFERENCES

(1) (a) *Braunwald's Heart Disease: Review and Assessment*; Lilly, L. S., Ed.; Elsevier Health Sciences: New York, 2012. (b) *Pathophysiology of Heart Disease*; Lilly, L. S., Ed.; Lippincott Williams & Wilkins: New York, 2011. (c) Chilton, R. J. *J. Am. Osteopath. Assoc.* **2004**, *104* (9), S5.

(2) Tigerstedt, R.; Bergman, P. G. *Skand. Arch. Physiol.* **1898**, *8*, 223.

(3) White, W. B. *Am. J. Med.* **2005**, *118*, 695.

(4) (a) Skeggs, L. T.; Doven, F. E.; Levins, M.; Lentz, K.; Kahn, J. R. In *The Renin-Agiotensin System*; Johnson, J. A., Anderson, R. R., Eds.; Plenum Press: New York, 1980; p 1. (b) McGregor, G. A.; Markandu, N. D.; Roulston, J. E.; Jones, J. C.; Morton, J. J. *Nature* **1981**, *291*, 329. (c) Reid, I. A.; Morris, B. J.; Ganong, W. F. *Annu. Rev. Physiol.* **1978**, *40*, 377.

(5) Foundling, S. I.; Cooper, J.; Watson, F. E.; Cleasby, A.; Pearl, L. H.; Sibanda, B. L.; Hemmings, A.; Wood, S. P.; Blundell, T. L.; Valler, M. J.; Norey, C. G.; Kay, J.; Boger, J.; Dunn, B. M.; Leckie, B. J.; Jones, D. M.; Atrash, B.; Hallett, A.; Szelke, M. *Nature* **1987**, *327*, 349.

(6) (a) Kobori, H.; Nangaku, M.; Navar, L. G.; Nishiyama, A. *Pharmacol. Rev.* **2007**, *59*, 251. (b) Wood, J. M.; Stanton, J. L.; Hofbauer, K. G. *J. Enzym. Inhib.* **1981**, *1*, 169. (c) For a historical perspective, see: Peart, W. S. *Proc. R. Soc., B* **1969**, *173*, 317. (d) Skeggs, L. T., Jr.; Kahn, J. R.; Lentz, K.; Shumway, N. P. *J. Exp. Med.* **1957**, *106*, 439.

(7) See, for examples: (a) Kasani, A.; Subedi, R.; Stier, M.; Holsworth, D. D.; Maiti, S. N. *Heterocycles* **2007**, *73*, 47. (b) Tice, C. M. *Annu. Rep. Med. Chem.* **2006**, *41*, 155. (c) Rosenberg, S. H.; Kleinert, H. D. *Pharm. Biotechnol.* **1998**, *11*, 7. (d) Rosenberg, S. H. *Prog. Med. Chem.* **1995**, *32*, 37. (e) Greenlee, W. J. *Med. Res. Rev.* **1990**, *2*, 173.

(8) (a) Sielecki, A. R.; Hayakawa, K.; Fujinaga, M.; Murphy, M. E. P.; Fraser, M.; Muir, A. K.; Carilli, C. T.; Lewicki, J. A.; Baxter, J. D.; James, M. N. G. *Science* **1989**, *243*, 1346. (b) Dhanaraj, V.; Dealwis, C. G.; Frazao, C.; Badasso, M.; Sibanda, B. L.; Tickle, I. J.; Cooper, J. B.; Driessen, H. P.; Newman, M.; Aguilar, C.; Wood, S. P.; Blundell, T. L.; Hobart, P. M.; Geoghegan, K. F.; Ammirati, M. J.; Danley, D. E.; O'Connor, B. A.; Hoover, D. J. *Nature* **1992**, *357*, 466.

(9) For reviews, see: (a) Maibaum, J.; Feldman, D. L. *Annu. Rep. Med. Chem.* **2009**, *44*, 105. (b) Jensen, C.; Herold, P.; Brunner, H. R. *Nat. Rev. Drug Discovery* **2008**, *7*, 399. (c) Siragy, H. M.; Kar, S.; Kirkpatrick, P. *Nat. Rev. Drug Discovery* **2007**, *6*, 779.

(10) (a) Webb, R. L.; Schiering, N.; Sedrani, R.; Maibaum, J. *J. Med. Chem.* **2010**, *53*, 7490. (b) Rahuel, J.; Rasetti, V.; Maibaum, J.; Rueger, H.; Goschke, R.; Cohen, N. C.; Stutz, S.; Cumin, F.; Fuhrer, W.; Wood, J. M.; Gruetter, M. G. *Chem. Biol.* **2000**, *7*, 493.

(11) (a) Wood, J. M.; Maibaum, J.; Rahuel, J.; Grütter, M. G.; Cohen, N.-C.; Rasetti, V.; Rüger, H.; Göschke, R.; Stutz, S.; Fuhrer, W.; Schilling, W.; Rigollier, P.; Yamaguchi, Y.; Cumin, F.; Baum, H.-P.; Schnell, C. R.; Herold, P.; Mah, R.; Jensen, C.; O'Brien, E.; Stanton, A.; Bedigian, M. P. *Biochem. Biophys. Res. Commun.* **2003**, *308*, 698. (b) Rahuel, J.; Priestle, J. P.; Gruetter, M. G. *J. Struct. Biol.* **1991**, *107*, 227.

(12) Maibaum, J.; Stutz, S.; Göschke, R.; Rigollier, P.; Yamaguchi, Y.; Cumin, F.; Rahuel, J.; Baum, H.-P.; Cohen, N.-C.; Schnell, C. R.; Fuhrer, W.; Gruetter, M. G.; Schilling, W.; Wood, J. M. *J. Med. Chem.* **2007**, *50*, 4832.

(13) See, for example: (a) Morganti, A.; Lonati, C. *J. Nephrol.* **2011**, *24*, 541. (b) Wal, P.; Wal, A.; Rai, A. K.; Dixit, A. *J. Pharm. Bioallied Sci.* **2011**, *3*, 189. (c) Mohamed Saleem, T. S.; Jain, A.; Tarani, P.; Ravi, V.; Gauthaman, K. *Syst. Rev. Pharm.* **2010**, *1*, 93. (d) Price, L. *Drugs Context* **2008**, *4*, 105. (e) Allikmetz, K. *Vasc. Health Risk Manag.* **2007**, *3*, 809. (f) Fisher, N. D.; Hollenberg, N. K. *Exp. Opin. Investig. Drugs* **2001**, *10*, 417.

(14) See, for example: Hanessian, S. *Chem. Med. Chem.* **2006**, *1*, 1300.

(15) Hanessian, S.; Raghavan, S. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1697.

(16) (a) Hanessian, S.; Claridge, S.; Johnstone, S. *J. Org. Chem.* **2002**, *67*, 4261. (b) For related approaches, see: Acemoglu, M.; Grimler, D.; Sedelmeier, G. WO 045420 A3, 2007.

(17) For a summary, see: Yokokawa, F.; Maibaum, J. *Expert Opin. Ther. Patents* **2008**, *18*, 581 and references cited therein.

(18) See, for example: (a) Göschke, R.; Stutz, S.; Heinzelmann, W.; Maibaum, J. *Helv. Chim. Acta* **2003**, *86*, 2848. (b) Dondoni, A.; De Lathauwer, G.; Perrone, D. *Tetrahedron Lett.* **2001**, *42*, 4819. (c) Sandham, D. A.; Taylor, R. J.; Carey, J. S.; Fässler, A. *Tetrahedron Lett.* **2000**, *41*, 10091. (d) Rüeger, H.; Stutz, S.; Göschke, R.; Spindler, F.; Maibaum, J. *Tetrahedron Lett.* **2000**, *41*, 10085.

(19) (a) Neelam, U. K.; Gangula, S.; Reddy, V. P.; Bandichhor, R. *Chem. Biol. Interface* **2013**, *3*, 14. (b) Lindsay, K. B.; Skrydstrup, T. *J. Org. Chem.* **2006**, *71*, 4766.

(20) (a) Mascia, S.; Heider, P. L.; Zhang, H.; Lakerveld, R.; Benyahia, B.; Barton, P. I.; Braatz, R. D.; Cooney, C. L.; Evans, J. M.; Jamison, T. F.; Jensen, K. F.; Myerson, A. S.; Trout, B. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 12359. (b) Nam, G.; Ko, S. Y. *Helv. Chim. Acta* **2012**, *95*, 1937. (c) Slade, J.; Liu, H.; Prashad, M.; Prasad, K. *Tetrahedron Lett.* **2011**, *52*, 4349. (d) Dong, H.; Zhang, Z.-L.; Huang, J.-H.; Ma, R.; Chen, S.-H.; Li, G. *Tetrahedron Lett.* **2005**, *46*, 6337.

(21) Cee, V. J. In *Modern Drug Synthesis*; Li, J. J., Johnson, D. S., Eds.; J. Wiley & Sons: Hoboken, NJ, 2010; Chapter 11.

(22) (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737. (b) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (c) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233.
(23) (a) Sckhöllkopf, U.; Westphalen, K.-O.; Schröder, J.; Horn, K. *Liebigs Ann. Chem.* **1988**, 781. (b) Schöllkopf, U. *Pure Appl. Chem.* **1983**, *55*, 1799.
(24) See, for example: (a) Milan, S. US Patent 0296100A1, 2012. (b) Satyanarayna Reddy, M.; Thirumalai Rajan, S.; Eswaraiah, S.; Venkat Reddy, G.; Rama Subba Reddy, K.; Sahadeva Reddy, M. WO 148392 A1, 2011. (c) Kidemet, D.; Zupet, R.; Smodis, J.; Stefane, B.; Pozgan, F. EP 2189442A1, 2010. (d) Meier, V.; Reuter, K.; Stolz, F.; Wedel, T. WO 049837 A1, 2009.
(25) (a) Herold, P.; Stutz, S. EP 1303478B1, 2004. (b) Herold, P.; Stutz, S. WO 0202487 A1, 2002. (c) Herold, P.; Stutz, S. WO 02092828 A3, 2002. (d) Herold, P.; Stutz, S.; Spindler, F. WO 0202508 A1, 2002. (e) See also: Boogers, J. A. F.; Felfer, U.; Kotthaus, M.; Lefort, L.; Steinbauer, G.; de Vries, A. H. M.; de Vries, J. G. *Org. Process Res. Dev.* **2007**, *11*, 585. (f) Sturm, T.; Weissensteiner, W.; Spindler, F. *Adv. Synth. Catal.* **2003**, *345*, 160.
(26) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044.
(27) Hanessian, S.; Chénard, E. *Org. Lett.* **2012**, *14*, 3222.
(28) Hanessian, S.; Guesné, S.; Chénard, E. *Org. Lett.* **2010**, *12*, 1816.
(29) For a relevant review, see: (a) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003; Vols. *1*−*3*. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.
(30) (a) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592. (b) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.
(31) See the Supporting Information
(32) Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 4333.
(33) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(34) For examples of the use of $Ti(O\text{-}i\text{-}Pr)_4$ in metathesis reactions, see: (a) Baba, Y.; Saha, G.; Nakao, S.; Iwata, C.; Tanaka, T.; Ibuka, T.; Ohishi, H.; Takemoto, Y. J. *Org. Chem.* **2001**, *66*, 81. (b) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130.
(35) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791.
(36) For example, see: (a) Shiina, I. *Chem. Rev.* **2007**, *107*, 239. (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199.
(37) For recent studies on the influence of substituent in ring-closing metathesis to form 9-membered lactone, see: (a) Ramírez-Fernández, J.; Collado, I. G.; Hernández-Galán, R. *Synlett* **2008**, 339. (b) Takahashi, T.; Wataqnabe, H.; Kitahara, T. *Heterocycles* **2002**, *58*, 99. (c) Baba, Y.; Saha, G.; Nakao, S.; Iwata, C.; Tanaka, T.; Ibuka, T.; Ohishi, H.; Takemoto, Y. *J. Org. Chem.* **2001**, *66*, 81.
(38) Thakur, V. V.; Talluri, S. K.; Sudalai, A. *Org. Lett.* **2003**, *5*, 861.
(39) Guthikonda, K.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 13672.
(40) Ramarao, C.; Michel, P. T.; Navakoti, R.; Nandipati, R. D.; Rao, R.; WO 064790 A1, 2011.
(41) Openshaw, H. T.; Whittaker, N. *J. Chem. Soc. C* **1969**, 89.
(42) Mickel, S. J.; Sedelmeier, G.; Hirt, H.; Schäfer, F.; Foulkes, M. WO 131304, 2006.
(43) Foley, M. A.; Jamison, T. F. *Org. Process Res. Dev.* **2010**, *14*, 1177.
(44) (a) Arena, G.; Barreca, G.; Carcone, L.; Cini, E.; Marras, G.; Nedden, H. G.; Rasparini, M.; Roseblade, S.; Russo, A.; Taddei, M.; Zanotti-Geraso, A. *Adv. Synth. Catal.* **2013**, *355*, 1449. (b) Taddei, M.; Russo, A.; Cini, E.; Riva, R.; Rasparini, M.; Carcone, L.; Banfi, L.; Vitale, R.; Roseblade, S.; Zanotti-Gerosa, A. WO 151442 A2, 2011.
(45) For reviews, see: (a) Mohr, J. T.; Krout, M. R.; Stoltz, B. M. *Nature* **2008**, *455*, 323. (b) Mohr, J. T.; Stoltz, B. M. *Chem.—Asian J.* **2007**, *2*, 1476. (c) You, S.-L.; Dai, L.-X. *Angew. Chem., Int. Ed.* **2006**, *45*, 5246. For the design, synthesis, and reactivity of chiral phosphinooxazolines (PHOX) ligands, see: (d) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336 and references cited therein. (e) Williams, J. M. J. *Synlett* **1996**, 705.
(46) Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582.
(47) (a) Thiel, O. R.; Ackermann, L.; Fürstner, A. *Org. Lett.* **2001**, *3*, 449. (b) Kozmin, Sergey A.; Adams, C. M.; Paone, D. V.; Smith, A. B., III. *J. Am. Chem. Soc.* **2000**, *122*, 4984.