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Total Synthesis of "Aliskiren": The First Renin Inhibitor in Clinical Practice for Hypertension

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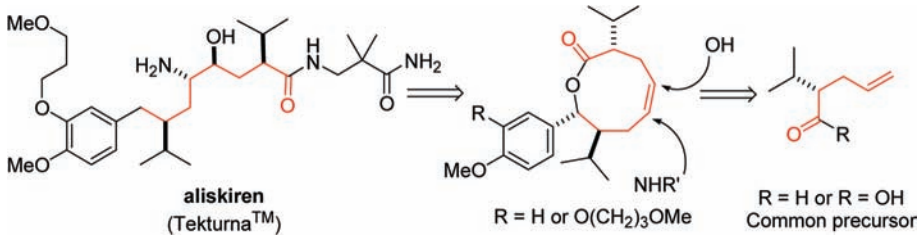
ABSTRACT



We report a "macrocycle route" toward aliskiren, a drug presently marketed for the treatment of hypertension, using a highly stereocontrolled approach starting from a common "isopropyl chiron". Highlights of the synthesis include a challenging RCM reaction to produce a nine-membered unsaturated lactone, a highly stereoselective catalytic Du Bois aziridination, and a regio- and diastereoselective aziridine ring-opening to a vicinal amino alcohol.

The renin-angiotensin system (RAS),[1] long known to be a key regulator of blood pressure, has been the target of seminal studies culminating with the discovery of ACE (angiotensin converting enzyme) inhibitors[2] and angiotensin II receptor blockers (ARBs).[3]

In view of its position in the enzymatic cascade leading to the eventual release of vasoconstricting peptides, the enzyme renin has been considered as a logical target to prevent hypertension.[4] Indeed, extensive studies relying on elegant structure-based design led to many potent inhibitors of renin.[5]

Unique among these is aliskiren, a first in a new class of drugs for the treatment of hypertension, which has been marketed under the trade name of Tekturna[6] (and Rasilez) since 2007.

Extensive synthetic efforts have been described in patented processes for producing aliskiren.[7,8] Formal syntheses have also been reported by other researchers.[9–11]

With the exception of an enzymatic desymmetrization step,[7a] and a catalytic asymmetric hydrogenation step,[7b] most other syntheses have relied on the use of one or more chiral auxiliaries[8–11] to produce early enantioenriched intermediates.

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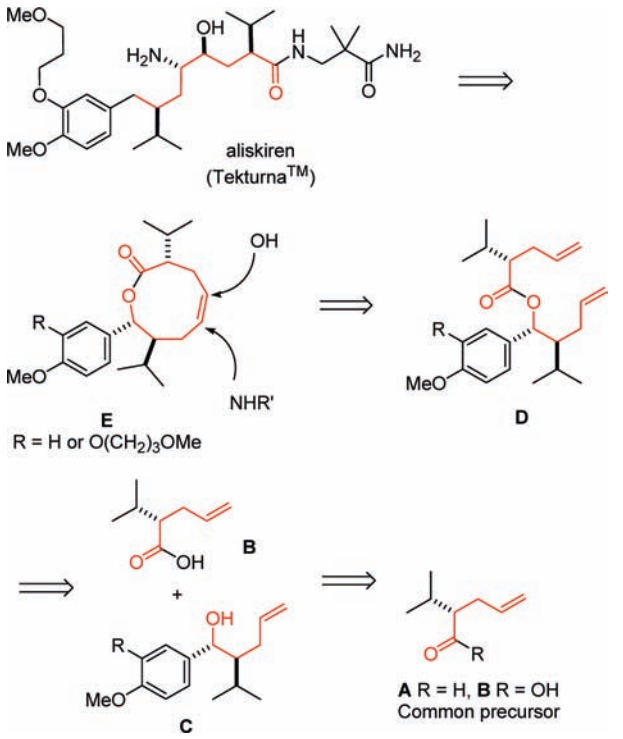

Figure 1. Retrosynthetic analysis of the "macrocycle route" toward aliskiren.

These were then used for convergent assemblies in a series of multiple operations en route to aliskiren.

We report herein a stereocontrolled and original synthesis of aliskiren, comprising 11 unoptimized linear steps in an overall yield of 7%. Our "macrocycle route" to aliskiren is shown in Figure 1, where a (2*S*)-2-isopropyl-4-pentenal **A**, obtained directly by application of MacMillan's iminium catalysis protocol[12,13] or from oxidation of the corresponding alcohol[14] is converted to intermediate **C**. Ester formation with carboxylic acid **B**, prepared by oxidation of **A**, or by an Evans allylation,[14] would afford **D**. Ring-closing metathesis[15] would lead to the nine-membered lactone **E**. Regioselective functionalization of the double bond, followed by amide formation and hydrogenolysis at the benzylic site, would produce aliskiren or its congeners[5a] depending on the nature of substituent R in the aromatic moiety. The feasibility of this highly stereocontrolled approach was put to the test, being cognizant of the challenges of effecting the seldom explored RCM reaction to produce a nine-membered lactone such as **E**[16] and developing strategies for the projected regio- and stereoselective introduction of the vicinal amino alcohol moiety in the target molecule.

Extensive studies with various organometallic reagents prepared from **1** led to the mixed organomagnesiate reagent **2**[17] as the preferred reacting partner to enantioenriched aldehyde **A**,[13] furnishing the (*R*,*S*)-isomer **3** as the major product (Scheme 1). Ester formation with **B** produced an 8:1 mixture of esters in which the (*S*,*R*,*S*)-isomer **4** was predominant as determined by NMR. Treatment of this mixture with 5 mol % of Grubbs first-generation catalyst[15b] in the presence of $Ti(O\text{-}i\text{-}Pr)_4$[15c] in toluene at 10 mM concentration led to the lactone **5** as a single diastereoisomer in 81% yield.[18] Aziridination using Du Bois' elegant catalytic method[19] produced **6** in 75% yield. At this juncture, its relative stereochemistry was based on the results of a diastereoselective dihydroxylation reaction of the *p*-methoxyphenyl congener (Scheme 2). When lactone **6** was subjected to TFA in dichloromethane, a remarkably smooth one-step formation of a pyrrolidine lactone took place to afford **7** in 85% yield. A plausible pathway, shown for the *p*-methoxyphenyl congener in Scheme 3, most likely involves the formation of a benzylic cation stabilized by the *p*-methoxyphenyl group,[20] thereby releasing the carboxylic acid, which effects an intramolecular opening of the *N*-trichloroethylsulfamoyl aziridine ring with inversion of configuration. This is followed by a stereocontrolled attack of the sulfamate nitrogen on the benzylic cation (or its quinonoid equivalent) to give the lactone **14** (or **7** in the case of **6**).

In spite of documented precedents for analogous compounds,[7,8] amide formation with the highly hindered 3-amino-2,2-dimethylpropionamide (ADPA) from lactone **7** was problematic, affording the amide **8** in modest yield (61% based on 27% of recovered starting lactone). This was transformed to the known *N*-Boc-pyrrolidine amide **9**[8a] in 60% yield over two steps. After much experimentation, it

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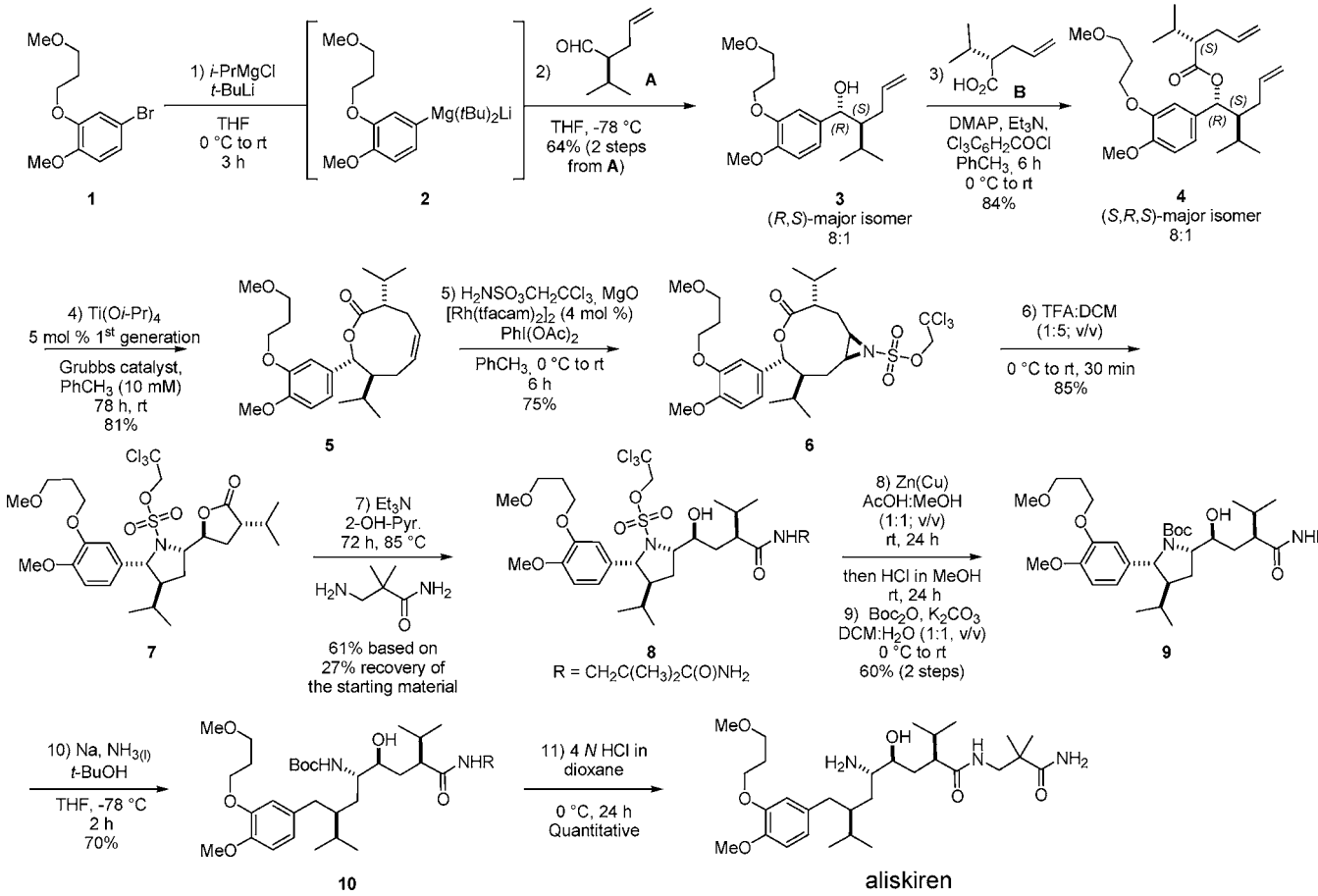
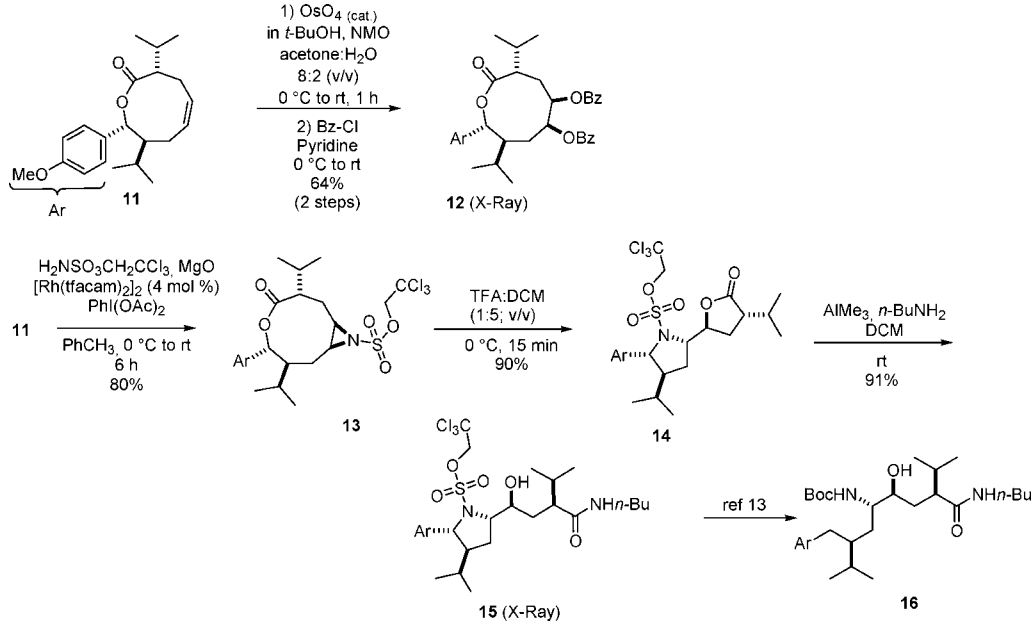
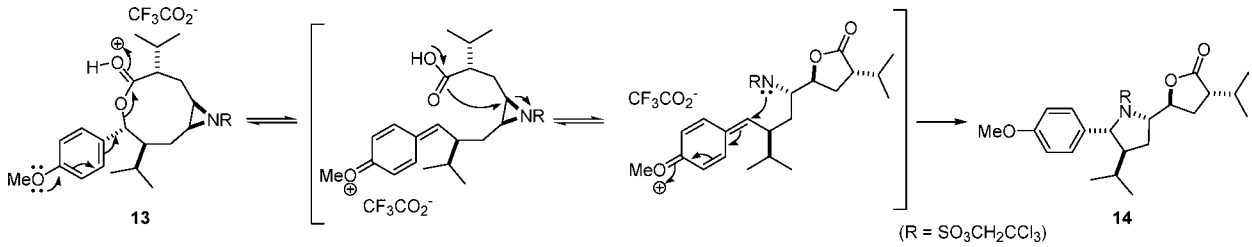
Scheme 1. Aliskiren Synthesis



Scheme 2. Model Synthesis



Scheme 3. Proposed Mechanism for Ring Contraction



was found that the most efficient method to cleave the benzylic bond in **9** was with Na/NH_3 in the presence of *t*-BuOH, which led to **10** in 70% yield. Finally, exposure of **10** to HCl in dioxane afforded aliskiren.[13]

An identical sequence with the *p*-methoxyphenyl lactone **11** allowed the establishment of absolute stereochemistry of earlier intermediates in the synthesis (Scheme 2). Remarkably, OsO_4-mediated dihydroxylation led to the (4*R*,5*S*)-diol as the only isolable diastereomer, as evidenced by an X-ray crystal structure of the corresponding dibenzoate ester **12** (Figure 2).[13] We had anticipated that the Du Bois[19] aziridination of **11** would also take place with the same facial selectivity, as was observed in the conversion of lactone **5** to the aziridine **6** (Scheme 1). Indeed, compound **13** was isolated in 80% yield as a single diastereomer. In the presence of TFA in dichloromethane, a double ring contraction took place to give pyrrolidine lactone **14** in near-quantitative yield (Scheme 3). Treatment with *n*-butylamine in the presence of $AlMe_3$ afforded the crystalline amide **15** whose structure and absolute stereochemistry were also ascertained from an X-ray analysis (Figure 2).[13] 8-Aryloctanoic acid *n*-butyl amides harboring various substituents in the aromatic moiety such as **16** are also potent low nanomolar inhibitors of renin.[5a]

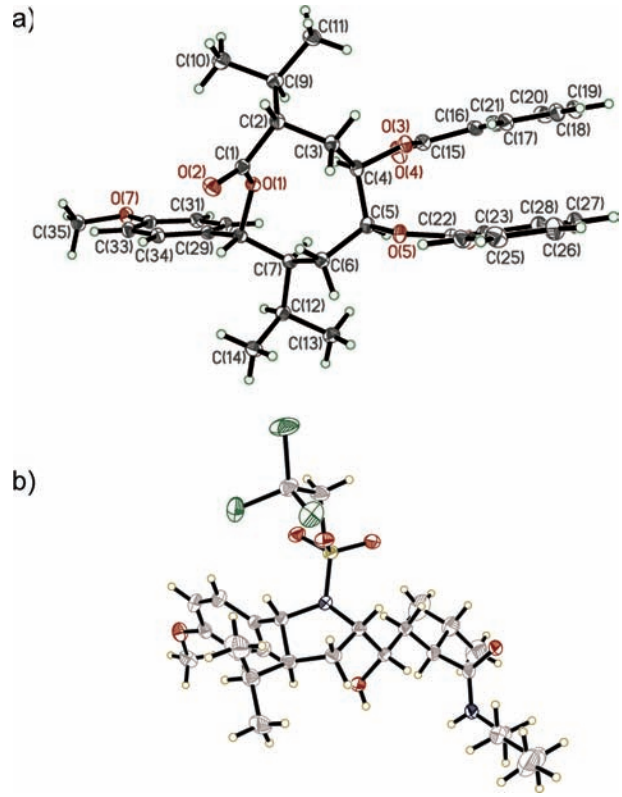


Figure 2. X-ray structures of (a) macrocycle **12** and (b) amide **15**.

In conclusion, we have described a concise and operationally simple original total synthesis of the antihypertensive drug aliskiren. The strategy relied on the facile and selective ring-closing metathesis reaction of the (*S*,*R*,*S*)-ester **4** to produce the nine-membered lactone **5** in excellent yield. A highly diastereoselective aziridination of the quasi C_2-symmetrical lactone **5** according to Du Bois[19] followed by a one-step formation of a pyrrolidine lactone generated the sulfamate **7**, which was converted to aliskiren in five steps. An identical sequence with the *p*-methoxyphenyl counterpart **11** led to **15**, which has been previously synthesized in a multistep process as the *N*-Boc analogue.[8a,21] Overall, our linear synthesis of aliskiren, comprising 11 steps, and achieved in an unoptimized overall yield of 7%, starting from a common precursor aldehyde **A**[12,14] is, to the best of our knowledge, the shortest to date. Improvements in the amide-forming step to **8** would further enhance the overall efficiency of the synthesis. Aspects pertaining to the selectivity of the RCM reaction with other catalysts and alternative synthetic strategies toward this unique class of synthetic protease inhibitors will be reported in due course.

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Supporting Information Available: Experimental details and analytical data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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