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Total Synthesis

Formal Total Synthesis of Aliskiren

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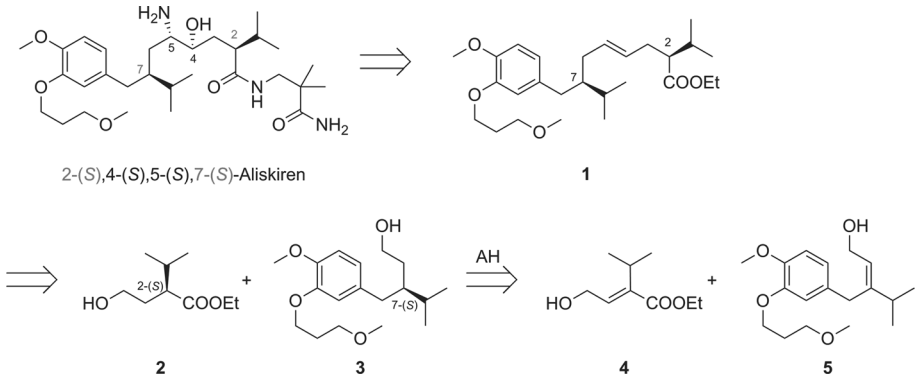
Abstract: The efficient and selective formal total synthesis of aliskiren is described. Aliskiren, a renin inhibitor drug, has received considerable attention, primarily because it is the first of the renin inhibitor drugs to be approved by the FDA. Herein, the formal synthesis of aliskiren by iridium-catalyzed asymmetric hydrogenation of two allylic alcohol fragments is reported. Screening a number of N,P-ligated iridium catalysts yielded two catalysts that gave the highest enantioselectivity in the hydrogenation, which gave the saturated alcohols in 97 and 93% *ee*. In only four steps after hydrogenation, the fragments were combined by using the Julia–Kocienski reaction to produce late-stage intermediate in an overall yield of 18%.

Introduction

Hypertension is the most modifiable risk factor in the treatment of heart disease. Therefore, inhibition of kidney-produced renin has become an emergent field of focus.[1] Aliskiren (Tekturna) is an efficient renin-inhibitor drug used to treat hypertension and renal failure (Scheme 1). It is also the first renin inhibitor to be administered orally. Hence, a simple and facile synthetic protocol for its preparation is widely sought after. Several synthetic methods for its preparation have been reported[2] and some patented.[3]



Scheme 1. Retrosynthetic approach to key intermediate **1**.

Aliskiren has four stereocenters: C-2, C-4, C-5, and C-7. Some emphasis has been directed to the enantioselective preparation of C-2 and C-7.[4] In these syntheses, the chirality induced at C-2 or C-7 or both has been utilized to direct stereoselectivity at C-4 and C-5. Thus, achieving high enantioselectivity at these points is crucial to the total synthesis of aliskiren. In a number of earlier reported syntheses, chiral auxiliaries (Evans' oxazolidinones) have been used to prepare both C-2 and C-7.[2a,c,d,4a] The two fragments are then joined by a Grignard reaction or an aldol condensation.

Organocatalysis has been employed by Hanessian and Chénard to prepare both C-2 and C-7 through an asymmetric allylation of isovaleraldehyde using MacMillan's catalyst.[2b,g] The two fragments were joined by Yamaguchi esterification followed by ring-closing metathesis to form a nine-membered unsaturated lactone. Hanessian and Chénard have also demonstrated a palladium-catalyzed asymmetric allylation protocol to prepare C-7. In this case, cross-metathesis was used to join the two fragments to produce late-stage intermediate **1** with an *E*:*Z* ratio of 86:14.[4b]

Attention has also been focused on the preparation of C-7 through asymmetric hydrogenation. Excellent results for the hydrogenation of the corresponding α,β-unsaturated esters and acid have been achieved by using iridium, ruthenium and rhodium, P,P-, and N,P-ligated catalysts.[5]

Asymmetric methods for the preparation of analogues of C-2 are scarce. Buchwald et al. have produced the corresponding aldehyde by an asymmetric hydroformylation reaction with 92% *ee* in 91% yield.[6] Peterson et al. have prepared the alcohol by enantioselective Brønsted acid catalyzed kinetic resolution with 52% *ee* and 56% conversion. However, long reaction times (72 h) were required.[7]

Iridium-catalyzed asymmetric hydrogenation is a valuable tool for the hydrogenation of unfunctionalized and functional-

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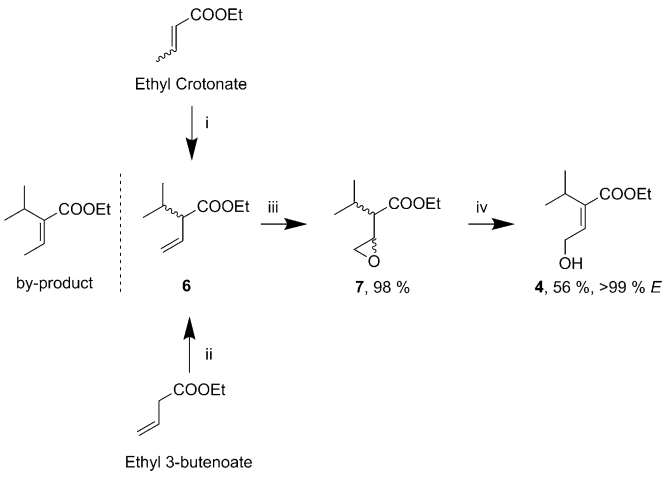
ized olefins.[8] Andersson et al. have studied this reaction and have not only expanded the substrate scope,[9] but also studied the mechanism and the origin of stereoselectivity.[10]

Here we report the formal synthesis of aliskiren through a convergent approach employing the asymmetric hydrogenation of two allylic alcohol fragments as key intermediates. These fragments were combined by using the Julia–Kocienski reaction to produce **1**, a late-stage precursor in the preparation of aliskiren.

Results and Discussion

The retrosynthetic analysis (Scheme 1) of aliskiren is shown in Scheme 1; precursor **1** resulted in synthons **2** and **3**. The fact that chirality in these fragments could easily be installed by using asymmetric hydrogenation made **4** and **5** synthetic targets.

We originally planned to prepare allylic alcohol **4** from ethyl crotonate by an alkylation, epoxidation, and rearrangement sequence (Scheme 2). The efficient and high-yielding preparation

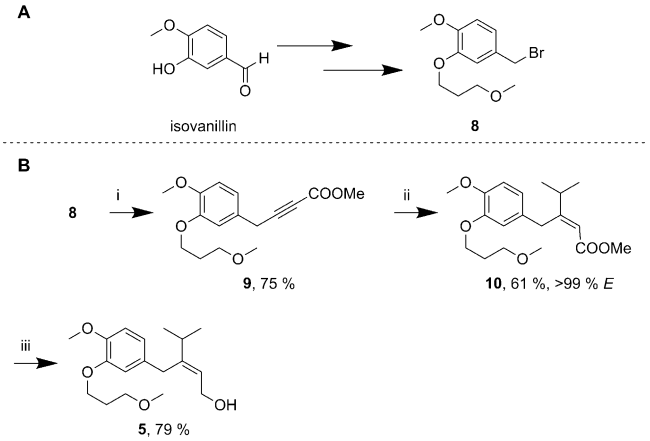


Scheme 2. Preparation of compound **4**. i) Literature: LDA, HMPA, *i*PrI, −78 °C, 4 h, 96%; this group: DMPU, DMSO, NMP, DMF, TMEDA, < 20%. ii) LDA, *i*PrI, −78 °C–RT, 4 h, 85%. iii) *m*CPBA, CH_2Cl_2, RT, 72 h. iv) K_2CO_3, EtOH, reflux, 4 h. DMPU: *N*,*N*′-dimethylpropylene urea, TMEDA: *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, HMPA: hexamethylphosphoramide, LDA: lithium diisopropylamide, *m*CPBA: *meta*-chloroperoxybenzoic acid, NMP: *N*-Methyl-2-pyrrolidone.

of **6** by deconjugative alkylation of commercial ethyl crotonate has earlier been reported by Herrmann et al. (Scheme 2 i).[11] They employed HMPA as an additive to form a strongly basic, non-nucleophillic complex with LDA. In an effort to avoid the use of significantly toxic or harmful substances such as HMPA, several other additives were screened as potential replacements. However, low conversions (determined by ^{1}H NMR spectroscopy) were obtained, and a significant amount of conjugated ester was formed as a byproduct. The best result was obtained with DMPU, albeit with a low yield of 20%. Instead, an alternative route (Scheme 2 ii), employing alkylation of ethyl 3-butenoate with LDA and *i*PrI was developed and enabled synthesis of **6** in high yield (85%), without the use of HMPA. This protocol allowed efficient preparation of **6** on a 23 g scale.

Starting from **6**, allylic alcohol **4** was prepared in two steps by a protocol developed by Valenta et al.[12] First, compound **6** was epoxidized with *m*CPBA to give **7** in a 1:5 *cis*:*trans* ratio (Scheme 2 iii). Next, base-catalyzed rearrangement with K_2CO_3 in refluxing ethanol afforded pure (*E*)-**4** after workup (56% yield).[13] A small amount of the corresponding unsaturated lactone, presumably formed by spontaneous cyclization of any (*Z*)-**4** formed in the reaction, was also observed in the crude reaction mixture. However, the volatile lactone was completely removed during workup, which involved evaporation of solvents.

Allylic alcohol **5** was prepared via bromide **8**, previously obtained by Maibaum et al. in four steps from isovanillin (Scheme 3 A).[14] Following a procedure established by Wulff

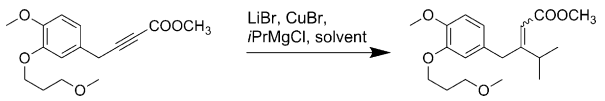


Scheme 3. Preparation of compound **5**. i) Methyl propiolate, CuI, K_2CO_3, CH_3CN, 40 °C, 24 h. ii) *i*PrMgCl, CuBr, LiBr, THF, −100 °C, 1 h. iii) DIBAL, THF, −78 °C–RT, overnight. DIBAL: diisobutylaluminium hydride.

et al., bromide **8** was treated with methyl propiolate, CuI, and K_2CO_3 to afford **9** (75% yield)[15] No allene byproducts could be observed in the crude reaction mixture. The *i*Pr group was installed by an organocuprate addition under optimized conditions (see below) yielding **10**, followed by reduction with DIBAL to give allylic alcohol **5**. The reduction proceeded smoothly, and only a quick purification by passage through a small plug of silica was required to afford pure (*E*)-**5** in 79% yield.

The stereoselectivity for introduction of the *i*Pr group by using an organocuprate was found to be very sensitive to the reaction conditions (Table 1). At temperatures above −50 °C, *E*:*Z* selectivity was poor (Table 1, entries 1 and 2). However, selectivity dramatically increased when the reaction was carried out below −50 °C (Table 1, entries 3 and 4). The use of THF as solvent is crucial; Et_2O had a negative effect on the selectivity, even at low temperature (−78 °C; Table 1, entry 5). When the reaction was carried out at −100 °C, essentially only the *E* product was produced (Table 1, entry 6). This protocol was also amenable to scale-up (Table 1, entry 7). In asymmetric catalytic hydrogenation it is often crucial that pure *E* or *Z* isomers be

Table 1. Optimization of the addition of the *i*Pr group to **9**.



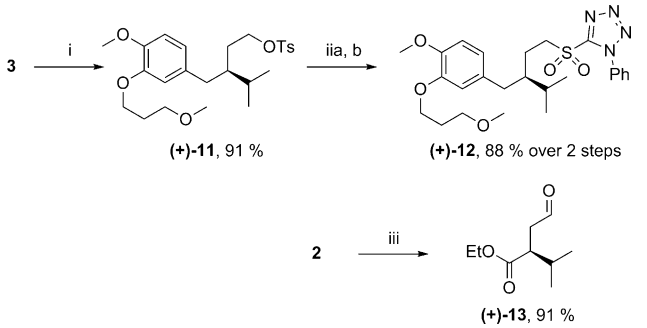
Entry	*T* [°C]	Solvent	Scale [mg]	*E*:*Z*
1	−78 to −30	THF	70	4:1
2	−40	THF	70	6:1
3	−50	THF	70	14:1
4	−78	THF	70	26:1
5	−78	Et_2O	70	4:1
6	−100	THF	70	99:1
7	−100	THF	3000	99:1

used. Thus, selective methods such as those developed herein for the synthesis of compounds **4** and **10** are necessary, as they avoid the tedious use of preparative chromatography or crystallization to separate such isomers.

Two catalysts **A** and **B** (Table 2) having an imidazole and a thiazole heterocyclic backbone, respectively, were evaluated in the hydrogenation of substrates **4** and **5**. Both of these substrates have purely aliphatic substituents and are typically challenging substrates for obtaining high enantiomeric excess in asymmetric catalytic hydrogenation. Screening was carried out with CH_2Cl_2 as solvent, and the results for the asymmetric hydrogenation of compounds **4** and **5** are presented in Table 2.

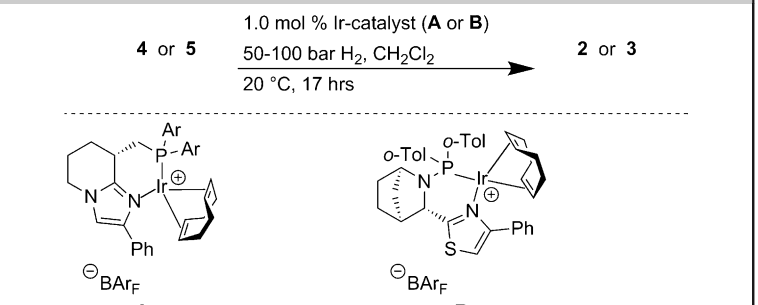
For both catalysts **A** and **B**, high conversions were obtained in the hydrogenations (Table 2, entries 1–4). Enantioselectivities were also good, whereby the best results for alcohol **4** were obtained with catalyst **A** (97% *ee*, 99% conversion), whereas for the hydrogenation of **5**, catalyst **B** gave the best results (93% *ee*, 99% conversion). Both results were reproducible on a 300 mg scale. In some reports, enantioselectivity can increase if hydrogenation is carried out in solvents such as $ClCH_2CH_2Cl$ and $CF_3C_6H_5$.[9i,16] A number of weakly coordinating solvents were tested but did not lead to any improvements of the enantioselectivities (for experimental details, see the Supporting Information).

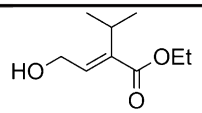
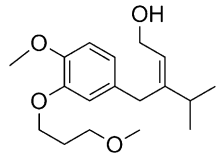
Our earlier work on the mechanism and origin of enantioselectivity in iridium-catalyzed hydrogenation have resulted in a selectivity model that rationalizes the observed enantioselectivities[10b,17] From the *S* configuration at C-2 and C-7 in aliskiren, it follows that both hydrogenated products **2** and **3** also should be *S*-configurated. In accordance with the model, catalyst **A** having 2-*S* configuration and catalyst **B** having 8-*S* configuration were needed to produce **2** and **3**, both of which are *S*-configurated. This assignment was indeed supported by experimental data (comparison of optical rotation data reported for **1**).[4b]



Scheme 4. Preparation of compounds **12** and **13**. i) TsCl, Et_3N, DMAP, CH_2Cl_2, RT, overnight. ii) a) 1-Phenyl-1*H*-tetrazole-5-thiol, K_2CO_3, CH_3CN, microwave, 90 °C, 20 min, filter; b) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (cat), H_2O_2, EtOH, reflux, overnight; iii) PCC, CH_2Cl_2, RT, overnight.

Table 2. Screening of asymmetric hydrogenation of compounds **4** and **5**.[a]

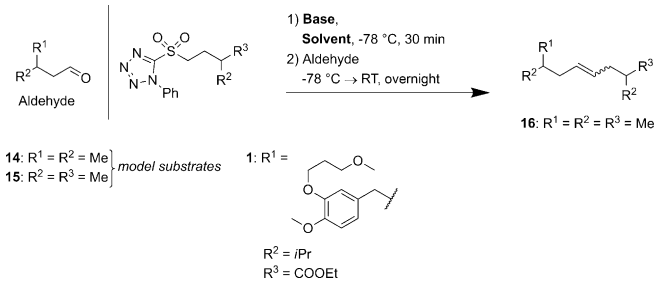


Entry	Catalyst	Substrate	Conversion[b] [%]	*ee*[c] [%]
1	**A**		99	97 −-*S*
2	**B**		77	72 −-*S*
3	**A**		99	83 +-*S*
4	**B**		99	93 +-*S*

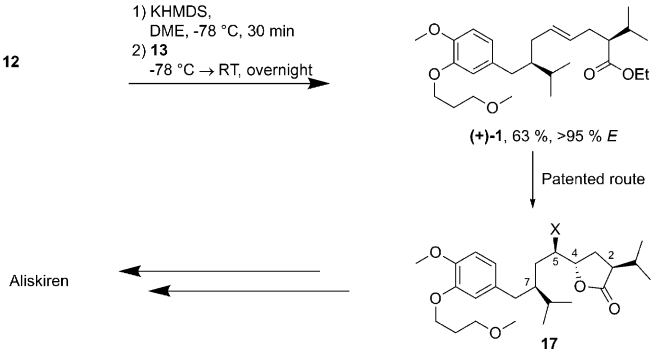
[a] Reaction conditions: 0.065 mmol substrate, 1.0 mol% catalyst, 0.5 mL CH_2Cl_2, 100 bar H_2 for **4**, 50 bar H_2 for **5**, 20 °C, 17 h. In the hydrogenation of **4**, 1.5 mg of polyvinylpyridine was added (see Supporting Information). [b] Determined by ^{1}H NMR spectroscopy. No side products were detected. [c] Determined by HPLC, SFC or GC on a chiral stationary phase.

The final part of the synthesis consists of joining the two fragments into an *E* olefin by using the Julia–Kocienski reaction. Tosylation of **3** provided **11** in 91% yield (Scheme 4). The 1-phenyl-1*H*-tetrazole sulfone **12** was prepared by a two-step thiolation and molybdenum-catalyzed oxidation to produce **12** in 88% yield over two steps. Fragment **2**, on the other hand, was oxidized to the corresponding aldehyde **13** in good yield (91%).

For the Julia–Kocienski reaction, it is typically observed that the use of phenyl-1*H*-tetrazole as the heterocycle results in higher *E* selectivity compared to benzothiazole and pyridine derivatives. To test this hypothesis and to screen optimal conditions, two isoamyl units (Scheme 5: **14** and **15**) were chosen as model substrates. A variety of bases and solvents were screened, following a study by Morley



Scheme 5. Study of the Julia reaction using isoamyl units **14** and **15**.



Scheme 6. Preparation of **1** under optimized conditions and earlier reported synthesis of aliskiren (patented route, see ref. [3]). X = leaving group.

et al.,[18] and the results are presented in Table 3. Increasing the polarity of the solvent (toluene < Et_2O < THF < DME) had a positive influence on selectivity toward the *E* product (Table 3, entries 1–12). Potassium hexamethyldisilazide (KHMDS) was consistently better than its Li and Na analogues, regardless of solvent. With the exception of Et_2O as solvent (Table 3, entries 4 and 5), NaHMDS showed somewhat better *E* selectivity than LiHMDS (Table 3, entries 1 vs. 2, 7 vs. 8, and 10 vs. 11). The highest selectivity was obtained with a combination of DME and KHMDS (99% *E*). These conditions were selected to prepare **1** (Scheme 5). As anticipated, on combining fragments **12** and **13** under these conditions, only the *E* isomer was observed by NMR spectroscopy, and **1** was isolated in 63% yield.

Table 3. Screening results for isoamyl model substrates.

Entry	Solvent	M in MHMDS	*E*:*Z*	*E* [%]
1		Li	1.5:1	60
2	toluene	Na	1.7:1	63
3		K	7.0:1	88
4		Li	2.9:1	74
5	Et_2O	Na	2.1:1	68
6		K	6.3:1	86
7		Li	6.1:1	86
8	THF	Na	6.5:1	87
9		K	25.1:1	96
10		Li	8.1:1	90
11	DME	Na	14.8:1	94
12		K	88.2:1	99

From the late-stage intermediate **1**, aliskiren can be synthesized by the Novartis protocol (Scheme 6): hydrolysis of ester **1** to the acid followed by halolactonization to furnish **17**, which has the desired stereochemistry for the synthesis of aliskiren after inversion at C-5 by S_N2 substitution with azide.[3a–c] The stereospecific halolactonization starting from the corresponding dimethyl amide analogue of **1** has also been reported.[3g] Both protocols that enable the construction of the correct stereocenters at C-4 and C-5 rely on the use of pure *E* olefin and are readily amendable to the highly *E* selective Julia–Kocienski reaction used in this work.

Conclusion

Late-stage intermediate **1** in the synthesis of aliskiren was prepared in 11 steps with an overall yield of 18% starting from **6**. The chirality at C-2 and C-7 of aliskiren was set up by asymmetric hydrogenation of allylic alcohols **4** and **5**. High enantioselectivities (97 and 93% *ee*) were achieved by using chiral N,P ligated iridium catalysts. The product alcohols **2** and **3** were then modified and combined by Julia–Kocienski reaction to selectively produce the desired intermediate **1** in pure *E* configuration.

Experimental Section

All experimental details can be found in the Supporting Information, which contains compound characterization and copies of spectra of new compounds.

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Keywords: asymmetric synthesis · hydrogenation · iridium · olefination · total synthesis

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