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The development of a complementary pathway for the synthesis of aliskiren†

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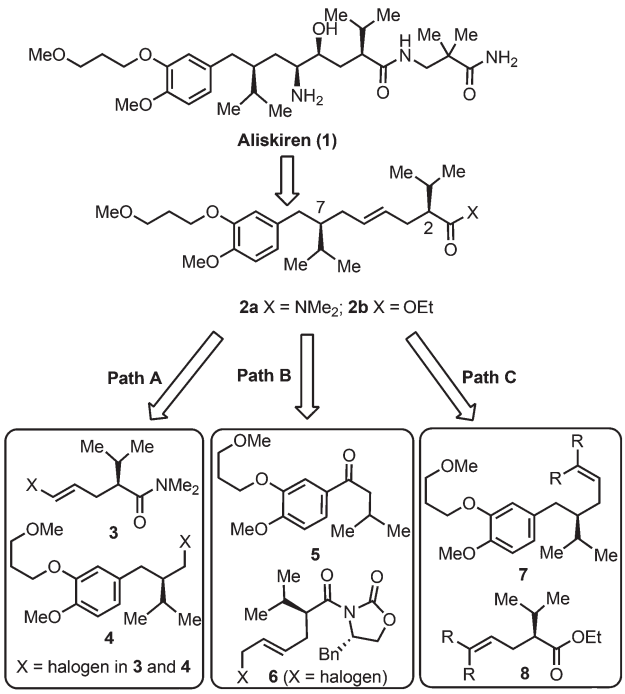
The synthesis of aliskiren (**1**), a recently marketed drug for the treatment of hypertension, is presented. The focus of our synthetic effort is to develop an efficient pathway for the synthesis of (2*S*,7*R*,*E*)-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy) benzyl)-*N*,*N*,8-trimethylnon-4-enamide (**2a**), which has been used as the advanced intermediate toward aliskiren. After an extensive investigation of three different strategies designed to construct the *E*-olefin functionality in **2a** by employing the olefin cross-metathesis, Horner–Wadsworth–Emmons (HWE), and Julia-type olefinations, we have established a new protocol for the synthesis of **2a** with a substantially improved overall efficiency in terms of the yield (*ca*. 33%), and diastereo- and *E*/*Z*-selectivity. The key transformations were the Evans chiral auxiliary-aided asymmetric allylation for the synthesis of the appropriate chiral intermediates in excellent enantiomeric purity of higher than 97% ee and a modified Julia–Kocienski olefination for the highly selective construction of *E*-**2a** with up to 13.6 : 1 *E*/*Z* ratio from the chiral intermediates. Consequently, the results provide an appealing option for the synthesis of aliskiren.

Introduction

Aliskiren **1** (Scheme 1) is a novel non-peptidic renin inhibitor[1] and has been marketed as an orally active drug for the treatment of hypertension.[2] This molecule features the presence of four chiral centers in an aliphatic carbon chain, which renders the synthesis of this molecule extremely challenging. Nevertheless, the structural complexity as well as the fascinating biological activity of aliskiren has stimulated tremendous interest of the community of synthetic and medicinal chemistry since its discovery.[3] Among a number of synthetic methods being reported,[3] the development of an effective approach for the construction of the advanced intermediate **2a** or **2b** (Scheme 1), whose structure contains two chiral centers and an *E*-olefin, has been the focus of many investigations because these intermediates can be flexibly converted into aliskiren with high regio- and stereoinduction.[3h]

So far, three typical strategies have been developed for accessing **2**. These include the coupling of vinyl halide **3** with a Grignard reagent generated from alkyl halide **4**[3r–t] (Path A), the base-promoted substitution reaction of aryl ketone **5** and allylic bromide **6**[3p,q] (Path B), or the cross-metathesis of olefins **7** and **8**[3d] (Path C). Notably, the third protocol (Path C)



Scheme 1 Structures of aliskiren **1**, the key intermediate **2** and the general synthetic strategies.

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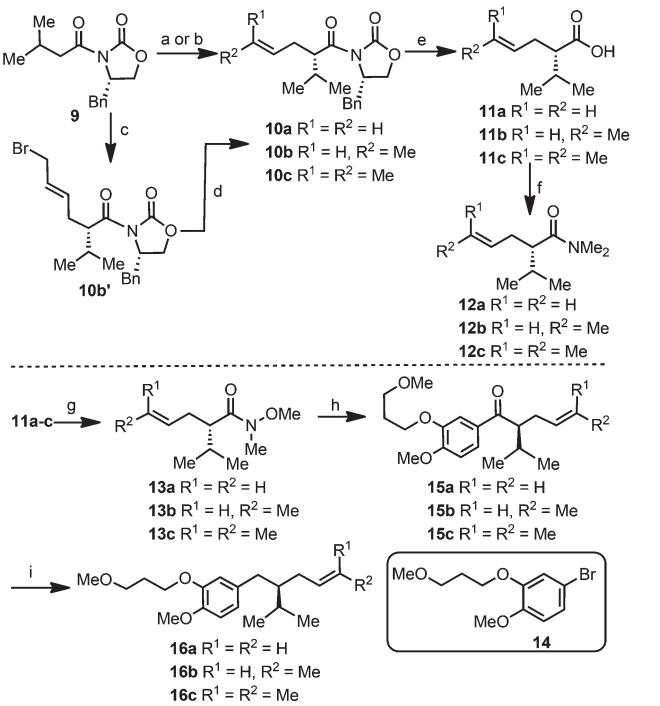
established by Hanessian[3d] could allow for a rapid synthesis of **2b** in five linear steps and in 38% overall yield from a known intermediate. Despite these important advances, the development of a more efficient synthesis remains highly desired resulting from at least one of the following concerns of the extant protocols such as the effective construction of C2 and C7 chiral centers, or the *E* olefin.

After a careful analysis of the advantages and disadvantages of the reported approaches, we thought that the key for an efficient synthesis of **2** should rely on the establishment of such a pathway that is capable of not only installing the chiral centers with highly enantiomeric purity, but also constructing the olefin moiety in high *E*-selectivity. Thus, three possible routes were designed which we anticipated to construct the *E*-**2a** at the late stage through the olefin cross-metathesis, Horner–Wadsworth–Emmons (HWE), or Julia-type olefination by employing the appropriately synthesized chiral precursors. An extensive and detailed investigation into these synthetic routes led eventually to the discovery that a pathway involving the Evans asymmetric allylation and Julia–Kocienski olefination as the key transformations could be a highly appealing option for the efficient synthesis of **2a**. The notable advantages offered by this new approach are that **2a** could be furnished in excellent *E*/*Z* selectivity of up to 13.6 : 1 from the appropriately synthesized chiral precursors with excellent enantiomeric purity of higher than 97% ee. In addition, high overall yield of *ca.* 33% could be obtained for **2a** in ten linear steps from the commercially available materials. These advantages make the current approach one of the appealing options for the efficient synthesis of aliskiren. Finally, the synthesis of aliskiren from the advanced intermediate **2a** has also been successfully demonstrated according to the known methods.[3p,s] Herein, we present the detailed results of our investigation.



Scheme 2 Synthesis of olefins **12a–c** and **16a–c**. Reagents and conditions: (a) LiHMDS (1.2 equiv.), allyl bromide (1.5 equiv.), THF, −78 °C to rt, 96%; (b) LiHMDS (1.5 equiv.), 3,3-dimethylallyl bromide (1.5 equiv.), THF, −78 °C to rt, 96%; (c) LiHMDS (1.2 equiv.), *trans*-1,4-dibromo-2-butene (3.0 equiv.), THF, −78 °C to rt, 90%; (d) $NaBH_3CN$ (3.0 equiv.), THF, 60 °C, 94%; (e) LiOH (2.0 equiv.), H_2O_2 (4.0 equiv.), THF–H_2O, rt, 91% for **11a**; 88% for **11b**; 88% for **11c**; (f) $(COCl)_2$ (3.0 equiv.), DMF (cat.), CH_2Cl_2, then $Me_2NH{\cdot}HCl$ (2.0 equiv.), DMAP (5 mol%), Et_3N (4.0 equiv.), rt, 86% for **12a**; 69% for **12b**; 72% for **12c**; (g) $(COCl)_2$ (3.0 equiv.), DMF (cat.), CH_2Cl_2, then MeONH(Me)·HCl (2.0 equiv.), DMAP (2 mol%), Et_3N (4.0 equiv.), rt; (h) **14** (2.0 equiv.), *n*-BuLi (2.0 equiv.), THF, −78 °C; (i) $AlCl_3$ (2.0 equiv.), $LiAlH_4$ (1.0 equiv.), Et_2O, rt; three-step yield for **16a**: 70%; for **16b**: 38%; for **16c**: 26%.

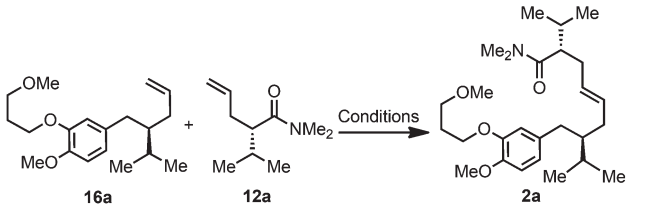
Results and discussion

Synthesis of 2a *via* the olefin cross-metathesis strategy

At the outset of our investigation, we planned to synthesize **2a** *via* the olefin cross-metathesis strategy. Although a general rule for accurately predicting the selectivity of olefin cross-metathesis such as homo- and heterogeneous selectivity, and *cis*/*trans* stereoselectivity remains unavailable,[4] intensive studies have demonstrated that the outcome of the cross-metathesis is markedly influenced by altering the steric and electronic properties of either reaction partners, or by choosing an appropriate catalyst.[5] Thus, a series of chiral olefin precursors with different steric bulkiness were synthesized by utilizing the Evans asymmetric allylation as the key transformation.[6] As outlined in Scheme 2, the reaction of commercially available **9** with allyl bromide (condition a) or 3,3-dimethylallyl bromide (condition b) proceeded smoothly to give **10a** and **10c**, respectively, in excellent yields. **10b** was readily prepared *via* a two-step procedure involving the allylation of **9** with *trans*-1,4-dibromo-2-butene, affording **10b′**, followed by reductive removal of the bromo group with $NaBH_3CN$.[7] Hydrolytic cleavage of Evans' chiral auxiliary in **10a–c** afforded the corresponding carboxylic acids **11a–c**, which could be synthesized on a scale of dozens of grams with constant efficiency and serve as the versatile intermediates for the preparation of various chiral precursors in our following studies. Accordingly, **11a–11c** were converted into the amides **12a–c** and Weinreb amides **13a–c**, respectively, through their acyl chlorides.[8] The Weinreb amides **13a–c** were further reacted with the aryl lithium, generated *in situ* from aryl bromide **14**[3d] and *n*-BuLi, to give the aryl ketones **15a–c**. The enantiomeric purity of compound **15a** was higher than 97% ee as determined by chiral HPLC analysis (see ESI†), reflecting that the Evans asymmetric allylation was a powerful option for the synthesis of chiral precursors. Finally, reduction of **15a–c** by a combined use of $LiAlH_4$ and $AlCl_3$ afforded the olefin **16a–c**.[3d,9]

With the two types of olefins **12** and **16** in hand, we investigated the cross-metathesis reaction. Screening of the catalysts and solvents were carried out using **12a** and **16a** as the model substrates. Some representative results are summarized in Table 1. The Grubbs 1st generation catalyst (1st G) was less effective with the best result obtained in 18% yield in CH_2Cl_2

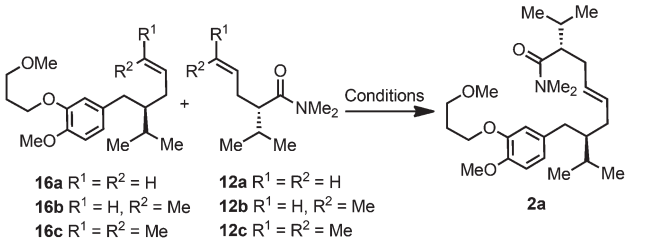
Table 1 Screening of catalysts and solvents[a]



Entry	Catalyst	Solvent	Yield[b] (%)	E/Z[c]
1	1st G	CH_2Cl_2	18	—[d]
2	2nd G	CH_2Cl_2	76	3.1
3	2nd G	*n*-Hexane	66	5.2
4	2nd H–G	CH_2Cl_2	65	3.3
5	2nd H–G	*n*-Hexane	56	3.3
6	2nd G	PE	66	5.5
7	2nd G	PhMe	53	4.2
8	2nd G	$(CH_2)_2Cl_2$	30	—[d]
9	2nd G	Cyclohexane	28	—[d]

[a] Reaction conditions: **16a** (0.5 mmol, 1.0 equiv.), **12a** (1.5 mmol, 3.0 equiv.) and the catalyst (5 mol %) under reflux. [b] Isolated yield. [c] E/Z ratio was determined by HPLC on a Hypersil ODS C18 column. [d] Not determined.

Table 2 Cross-metathesis of various combinations of **12** and **16** in the presence of a BQ additive[a]



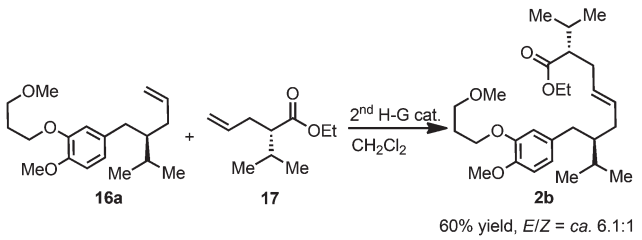
Entry	Substrate	Catalyst	Solvent	Yield[b] (%)	E/Z[c]
1	**12a**/**16a**	2nd H–G	PE	88	3.9
2	**12a**/**16a**	2nd G	PE	72	4.2
3	**12a**/**16b**	2nd H–G	PE	72	4.6
4	**12a**/**16b**	2nd G	PE	78	4.2
5	**12b**/**16a**	2nd H–G	PE	82	3.0
6	**12b**/**16a**	2nd G	PE	80	4.2
7	**12b**/**16b**	2nd H–G	PE	72	4.1
8	**12b**/**16b**	2nd G	PE	80	4.3
9	**12b**/**16b**	2nd H–G	CH_2Cl_2	68	5.7
10	**12b**/**16b**	2nd G	CH_2Cl_2	62	6.6
11	**12b**/**16b**	2nd G	CH_2Cl_2	62	7.0[d]
12	**12b**/**16b**	2nd G	CH_2Cl_2	67	6.8[e]
13	**12b**/**16b**	2nd G	CH_2Cl_2	66	6.7[f]

[a] Unless otherwise noted, the reaction conditions were: **16** (0.2 mmol, 1.0 equiv.), **12** (0.8 mmol, 4.0 equiv.), catalyst (5 mol%), BQ (50 mol%) in a solvent under reflux for 24 h. [b] Isolated yield. [c] The ratio of E/Z was determined by HPLC on a Hypersil ODS C18 column. [d] 60 mol% of BQ was used. [e] 70 mol% of BQ was used. [f] 80 mol% of BQ was used.

(entry 1). In contrast, the Grubbs 2nd generation catalyst (2nd G) exhibited a much higher activity, giving the cross-metathesis product **2a** in high yield and moderate to moderately high E/Z selectivity in CH_2Cl_2 and *n*-hexane solvents (entries 2 and 3). In addition, the Hoveyda–Grubbs 2nd generation catalyst (2nd H–G) could also affect the reaction although the overall efficiency was somewhat lower than the Grubbs 2nd generation catalyst (entries 4 and 5). Further examination of various solvents (entries 6–9) in the presence of the Grubbs 2nd generation catalyst revealed that petroleum ether (PE) was also a promising solvent (entry 6). Thus, through these preliminary studies, we found that CH_2Cl_2 or PE solvents coupled with the use of Grubbs 2nd or Hoveyda–Grubbs 2nd generation catalysts were a promising combination for the cross-metathesis reaction. Here, it should be mentioned that the structure of the major *E*-**2a** was determined by NMR and HRMS analyses using a sufficiently pure sample isolated carefully from the mixture of *E* and *Z*-**2a** by column chromatography on 200–300 mesh silica gel (E/Z >200 : 1 as determined by HPLC). The corresponding *Z*-**2a** was identified by the ^{1}H-NMR combined with HPLC-MS analyses of a mixture of *E*- and *Z*-**2a**. The data were identical to the reported literature.[3s]

Having discovered the suitable solvents and catalysts, we examined the effect of additives on the reaction since it has been observed that, in many cases, the efficiency of olefin cross-metathesis was dramatically influenced by varying the additives.[10] Accordingly, an array of Lewis and Brønsted acids, bases, and oxidants were extensively examined. Unfortunately, most of the acidic and basic additives exhibited a detrimental effect both to the yield and selectivity (data not shown). However, the addition of 1,4-benzoquinone (BQ) afforded an improved yield in PE although the E/Z selectivity was somewhat diminished (Table 2, entries 1 and 2). To improve the stereoselectivity, we inspected the cross-metathesis of the sterically more hindered olefins. However, the results showed that the reaction was less sensitive to the steric nature of the substrates in the PE solvent. Both the yield and E/Z selectivity under various combinations of olefins such as **12a** with 1-methyl olefin **16b** (entries 3 and 4), 1-methyl olefin **12b** with **16a** (entries 5 and 6), and 1-methyl olefin **12b** with 1-methyl olefin **16b** (entries 7 and 8) were almost identical to those afforded by the combination of 1-unsubstituted olefin **12a** and **16a**. Interestingly, an increased E/Z ratio was observed when the PE solvent was replaced by CH_2Cl_2 (entries 9 and 10), although the yield was somewhat diminished. At this conjuncture, the effect of the molar equivalents of BQ on the reaction was re-optimized in order to improve the overall efficiency (entries 10–13). We found that the use of 60 mol% of BQ could afford the best E/Z ratio of up to 7.0 : 1 without decrease in the yield (entry 11). Finally, it should be mentioned that ineffective cross-metathesis was observed when either of the 1,1-dimethyl olefins **12c** or **16c** was used as the cross-metathesis partner.

During the course of our investigation, we noted that Hanessian and co-workers employed a very similar cross-metathesis reaction as one of the key transformations in their synthesis of aliskiren.[3d] Namely, in the presence of 20 mol% of the Hoveyda–Grubbs 2nd generation catalyst, the cross-metathesis of **16a** and the olefin **17** bearing an ester functionality delivered the cross product **2b** in 60% yield and *ca.* 6.1 : 1 E/Z ratio under reflux for 3 days (Scheme 3). To compare with



Scheme 3 Cross-metathesis reaction reported by Hanessian *et al.*[3d]

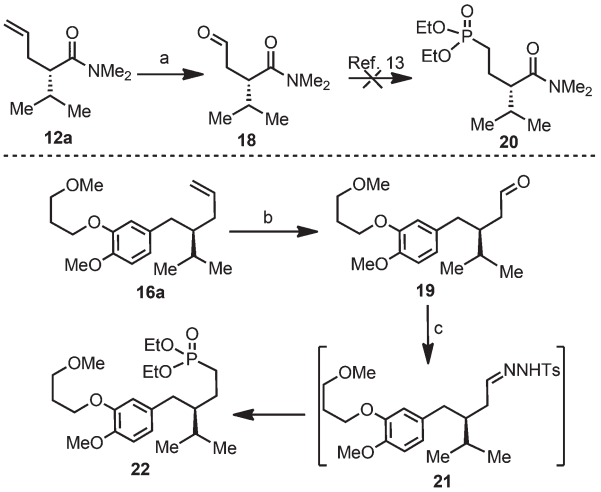
Hanessian's protocol, our cross-metathesis is somewhat more effective for the construction of analogue **2a** in terms of yield, *E*/*Z* selectivity, the catalyst loading (5 mol%) and the reaction time, presumably resulting from the different properties of amide olefin **12a** *vs.* the ester olefin **17** and the presence of a BQ additive in the reaction system. However, both the yield and *E*/*Z* selectivity of our procedure remained not sufficiently high. In addition, the need of 5 mol% of the Grubbs 2nd generation catalyst is still a high loading. These drawbacks are apparent obstacles when practical application for the synthesis of aliskiren is under consideration. As such, we decided to search an alternative pathway toward synthesizing **2a** more efficiently.

Synthesis of 2a *via* the HWE olefination strategy

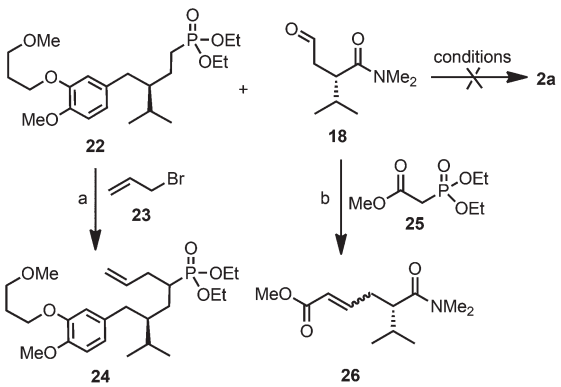
Considering that Horner–Wadsworth–Emmons (HWE) olefination has various advantages such as high *E*-selectivity and the ease of separation of the dialkyl phosphate by-product for the preparation of alkenes,[11] we investigated its application for the synthesis of **2a**. Accordingly, oxidation of the olefins **12a** and **16a** gave the aldehydes **18** (97% ee, see ESI†) and **19**, respectively, in high yield (Scheme 4). Here, it should be mentioned that for the oxidation of **16a**, the addition of an organic base such as 1,4-diazabicyclo[2,2,2]octane (DABCO) was crucial for improving the yield of **19** by suppressing the formation of various side products.[12]

For the transformation of **18** or **19** to the corresponding phosphonate esters **20** or **22**, we investigated the copper-catalyzed reductive coupling of dialkyl phosphite with *N*-tosylhydrazone generated *in situ* from aldehyde and *N*-tosylhydrazine as disclosed independently by Tang and Liang's groups.[13] This new protocol takes the advantage of furnishing the phosphonate esters directly from the aldehydes *via* a two-step one-pot operation without the isolation of *N*-tosylhydrazone intermediates. Therefore, if the protocol works well for our substrates, it would provide a straightforward option for the synthesis of the desired phosphonate esters **20** or **22** to compare with the conventional procedures, which, in principle, required a multi-step transformation involving the reduction of the aldehyde to alcohol, conversion of alcohol to halide followed by the Arbuzov reaction[14] or by the nucleophilic displacement of phosphinic halide with an organometallic reagent such as organolithium and Grignard reagent formed from the halide.[15] Initial trials showed that the copper-catalyzed coupling of dialkyl phosphite with the *N*-tosylhydrazone formed from the amide aldehyde **18** and *N*-tosylhydrazine for producing **20** was ineffective under the reported conditions presumably due to the influence of the amide functionality in **18**. However, **19** could be converted into the desired phosphonate ester **22** in moderate yield (40–55%) *via* a one-pot reaction through the intermediate **21**. After a further optimization of the reported reaction conditions, we could obtain **22** in 80% yield by replacing the K_2CO_3 or Cs_2CO_3 base with K_3PO_4 and the dioxane solvent with toluene, respectively.

Next, the HWE olefination of **22** and **18** was examined (Scheme 5). Disappointedly, extensive trials showed the reaction did not proceed under an array of conditions – by varying the bases, solvents, temperature and additives. **22** was recovered completely in many cases. In stark contrast, control experiments demonstrated that phosphonate **22** reacted uneventfully with allyl bromide **23** to give the allylated phosphonate **24** in



Scheme 4 Synthesis of **20** and **22**. Reagents and conditions: (a) OsO_4 (1 mol%), $NaIO_4$ (4 equiv.), THF–H_2O (2 : 1), 0 °C, 69%; (b) OsO_4 (1 mol%), $NaIO_4$ (4.0 equiv.), DABCO (4.0 equiv.), THF–H_2O (2 : 1), 0 °C, 89%; (c) $TsNHNH_2$ (1.0 equiv.), toluene, rt, 45 min; then $(EtO)_2P(O)H$ (5.0 equiv.), CuI (10 mol%), K_3PO_4 (6.0 equiv.), reflux, 80%.



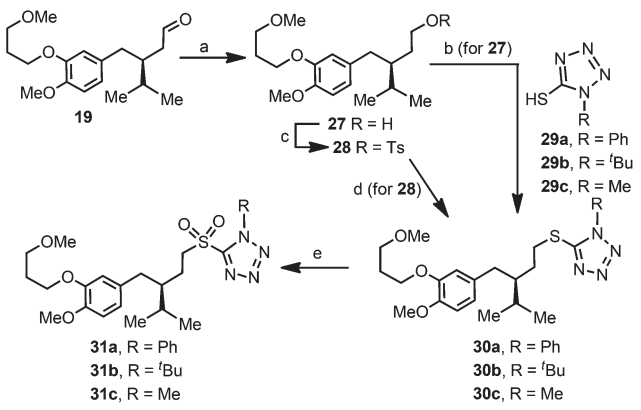
Scheme 5 HWE reaction of **18** and **22**, and control experiments. Reagents and conditions: (a) allyl bromide (5.4 equiv.), *n*-BuLi (1.5 equiv.), THF, –78 °C to rt, 69%; (b) **25** (1.5 equiv.), *n*-BuLi (1.5 equiv.), THF, –78 °C to rt, 74%.

69% yield. On the other hand, reaction of aldehyde **18** with methyl 2-(diethoxyphosphoryl)acetate **25** could also proceed efficiently to produce the α,β-unsaturated ester amide **26** in 74% yield. These results imply that the ineffective HWE reaction between **18** and **22** may be resulted from the increased steric bulkiness of both substrates. The detailed reasons deserve a further clarification in our laboratory. Thus, we had to give up this investigation and turn our attention to explore other possible approaches.

Synthesis of 2a *via* the Julia–Kocienski olefination

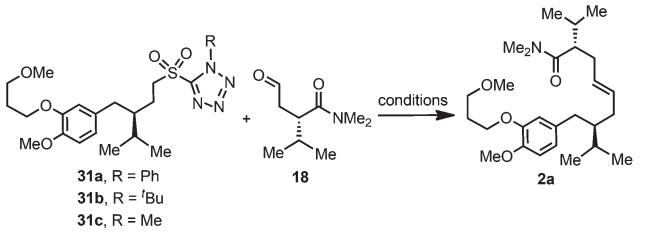
The Julia-type olefination is also one of the most popularly used protocols for accessing olefins.[16] Typically, the Julia–Kocienski olefination has been demonstrated to be a powerful tool for the synthesis of *E*-form of nonconjugated 1,2-disubstituted alkenes.[17] Owing to the exemplified advantages, we conceived to synthesize **2a** by employing the Julia–Kocienski reaction. Accordingly, the aldehyde **19** was reduced to alcohol **27** with $LiBH_4$ in quantitative yield (Scheme 6). Condensation of **27** with 1-phenyl-1*H*-tetrazole-5-thiol **29a** under Mitsunobu conditions[18] afforded the sulfide **30a** in high yield. Alternatively, the conversion of alcohol **27** into the corresponding tosylate **28** followed by the substitution reaction with **29a–c** was also an efficient option for the synthesis of various sulfides **30a–c**. Finally, oxidation of the sulfides[19] proceeded smoothly to give sulfones **31a–c**.

Next, we examined the Julia–Kocienski olefination of sulfones **31** with aldehyde **18**. The screening of the reaction conditions was carried out using **31a** and **18** as substrates. Some representative data are shown in Table 3. A brief screening of the solvents showed that THF was a better option in terms of yield and *E*/*Z* selectivity (entries 1–3). In addition, among the three bases being examined (entries 3–5), NaHMDS was the optimal one which could afford **2a** in high yield and moderate



Scheme 6 Synthesis of sulfones **31**. Reagents and conditions: (a) $LiBH_4$ (1.2 equiv.), THF, rt, quant.; (b) **29a** (2.0 equiv.), PPh_3 (1.5 equiv.), DEAD (2.0 equiv.), THF, −40 °C, 80%; (c) TsCl (1.1 equiv.), Et_3N (3 equiv.), DMAP (0.05 equiv.), rt, 96%; (d) K_2CO_3 (5 equiv.), **29** (2.0 equiv.), 50 °C, 95% for **30a**, 60% for **30b** and 85% for **30c**; (e) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (20 mol%), 30% H_2O_2 (20 equiv.), EtOH, rt, 94% for **31a**, for 90% **31b** and 98% for **31c**.

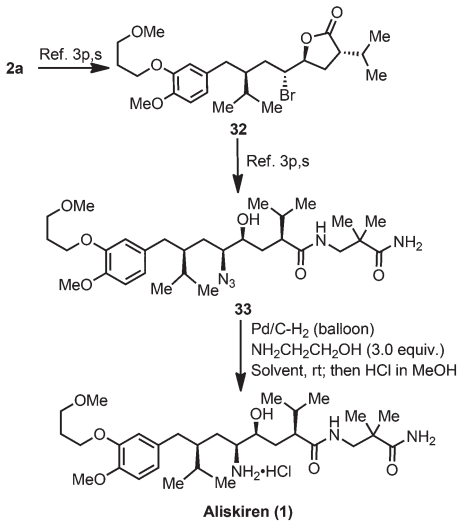
Table 3 Optimization of the Julia–Kocienski olefination of sulfone **31** and aldehyde **18**[a]



Entry	31	Base	Solvent	Add. (equiv.)	Yield (%)[b]	*E*/*Z*[c]
1	**31a**	LiHMDS	Toluene	—	86	2.1
2	**31a**	LiHMDS	DMF	—	57	2.4[d]
3	**31a**	LiHMDS	THF	—	86	3.3[e]
4	**31a**	NaHMDS	THF	—	82	5.1
5	**31a**	KHMDS	THF	—	73	3.4
6	**31a**	NaHMDS	DME	—	83	9.9[f]
7	**31b**	NaHMDS	DME	—	88	9.4
8	**31c**	NaHMDS	DME	—	92	7.4
9	**31a**	NaHMDS	THF	18-C-6 (2.0)	54	7.4
10	**31a**	NaHMDS	DME	18-C-6 (2.0)	58	14.5
11	**31a**	NaHMDS	DME	15-C-5 (2.0)	49	8.5
12	**31a**	NaHMDS	DME	18-C-6 (1.0)	70	13.9
13	**31a**	NaHMDS	DME	18-C-6 (0.5)	70	13.6
14	**31a**	**NaHMDS**	DME	**18-C-6 (0.25)**	**80**	**13.6**

[a] Unless otherwise noted, the reaction conditions: **31** (0.2 mmol, 1.0 equiv.), **18** (0.8 mmol, 4.0 equiv.), base (0.4 mmol, 2.0 equiv.), additive (*x* equiv.) in solvent from −78 °C (in THF) or −70 °C (in DME) to r.t. [b] Isolated yield. [c] The ratio of *E*/*Z* was determined by HPLC on a Hypersil ODS C18 column. [d] The reaction was performed from −40 °C to r.t. since the reaction mixture was slightly frozen under lower temperature. [e] Average value of two runs. [f] The reaction was performed from −55 °C to r.t. since the reaction mixture was slightly frozen under lower temperature. Abbr.: LiHMDS = lithium hexamethyldisilazide; NaHMDS = sodium hexamethyldisilazide; KHMDS = potassium hexamethyldisilazide; DMF = *N*,*N*-dimethylformamide; THF = tetrahydrofuran; DME = 1,2-dimethoxyethane; 18-C-6 = 18-crown-6; 15-C-5 = 15-crown-5.

E/*Z* selectivity (entry 4). On the basis of these preliminary results, the reaction parameters were re-examined using NaHMDS as the base. Delightedly, we found that the *E*/*Z* selectivity could be improved markedly from *ca.* 5.1 : 1 to 9.9 : 1 without affecting the yield when DME instead of THF was used as the solvent (entry 4 *vs.* 6). An investigation into the effect of different sulfones decorated by various R groups in the tetrazole moiety revealed that **31a** (R = Ph) and **31b** (R = ^{t}Bu) could afford the product in almost equally good efficiency as seen from the yield and *E*/*Z* selectivity (entries 6 and 7). However, **31c** (R = Me) gave a decreased *E*/*Z* ratio although the yield was slightly increased (entry 8). Considering that **31a** could be synthesized more efficiently than **31b** due to the higher yield for the preparation of its precursor **30a** (Scheme 6), sulfone **31a** was used as the substrate to screen the reaction conditions toward further improving the reaction efficiency. At this conjuncture, we inspected the effect of phase transfer catalysts such as crown ethers since a recent report[20] has exemplified that the presence of such additives could influence considerably the outcome of the Julia olefination. Indeed, we observed



Scheme 7 Synthesis of aliskiren (**1**).

that the addition of 2.0 equiv. of 18-crown-6 could lead to a substantial increase in *E*/*Z* selectivity either in THF or in DME (entries 4 *vs.* 9, and 6 *vs.* 10). Notably, the *E*/*Z* ratio was improved to 14.5 : 1 in DME, although the yield of **2a** significantly diminished in this solvent (entry 10). As a comparison, the addition of 15-crown-5 exhibited a detrimental effect both to the yield and stereoselectivity (entry 11). Finally, a brief optimization of the molar equivalents of 18-crown-6 (entries 12–14) revealed that the presence of 0.25 equiv. of 18-crown-6 could deliver **2a** not only in high yield (80%) but also in excellent *E*/*Z* selectivity (13.6 : 1) (entry 14).

Having established an efficient route for the synthesis of the advanced intermediate **2a**, we implemented the final synthesis of aliskiren (**1**) by referring to the reported procedures.[3p,s] Namely, bromolactonization of **2a** with NBS followed by a simple recrystallization of the crude product afforded pure lactone **32** (Scheme 7). The NMR spectroscopic and the specific rotation value of the intermediate **32** were consistent with the reported data {synth., $[\alpha]_D^{20}$ +39.2 (*c* 1.0, $CHCl_3$); Lit.,[3s] $[\alpha]_D^{25}$ +44.2 (*c* 1.0, $CHCl_3$)}. The data further confirmed that *E*-**2a** is obtained as the major product from the Julia–Kocienski olefination. Substitution of Br with NaN_3 and amidation of the lactone moiety in **32** proceeded uneventfully to give the azide **33**. Finally, hydrogenolysis of the N_3 group in **33** gave aliskiren **1**. Here, we should mention that, although not investigated carefully, it seems that the free aliskiren is not sufficiently stable during hydrogenolysis and the subsequent handling. A small amount of the less polar byproduct was often formed as indicated by the TLC monitoring. This may result from the partial oxidation of the product under ambient conditions. After some trials, it was found that the addition of ethanolamine in the reaction system and trapping the product with HCl solution in MeOH could afford pure aliskiren as its HCl salt. The NMR data of both the HCl and hemifumarate salt of aliskiren is identical to the reported data.[3j,u]

Conclusions

In conclusion, we have developed an alternative route for the synthesis of the advanced intermediate **2a** toward aliskiren. From the commercially readily available **9**, **2a** could be synthesized in 33% overall yield *via* a ten-step procedure. Although the steps of our synthesis are relatively longer and the overall yield is slightly lower than the protocol developed by Hanessian for the synthesis of analogue **2b** (5 linear steps from a known intermediate in 38% overall yield),[3d] the pathway developed herein could afford the product with a remarkably improved *E*/*Z* selectivity (*E*/*Z* = 13.6 : 1). Moreover, the enantiomeric purity of the key chiral precursors **16a** synthesized through the Evans chiral auxiliary-aided asymmetric allylation in this work is higher than that synthesized through the Stoltz Pd-catalyzed asymmetric protocol[3d,21] (97% *vs.* 90% ee). Owing to these advantages, we believe that the method presented in this work should be a complementary route for the synthesis of aliskiren. The synthesis of aliskiren from **2a** has also been demonstrated according to the known procedures.[3p,s] Further optimization of the process toward large scale synthesis is currently underway.

Experimental section

General methods

Unless otherwise noted, all solvents were purified according to the standard procedures. Allyl bromide, $(COCl)_2$, and $(EtO)_2POH$ were distilled prior to use. Other reagents were of reagent grade and used without purification. The ^{1}H-NMR spectra were recorded at 600, 400, or 300 MHz (Bruker AV) in $CDCl_3$ or DMSO-d_6. The ^{13}C-NMR spectra were recorded at 150 or 100 MHz in $CDCl_3$ or DMSO-d_6. The ^{31}P-NMR spectra were recorded at 162 MHz in $CDCl_3$. Chemical shifts are given in ppm relative to TMS or the appropriate solvent peak. Coupling constants (*J* values) are reported in hertz (Hz). High resolution mass spectra (HRMS) are measured using an IonSpec Ultima 7.0 TFT-ICR-MS instrument (IonSpec, USA) with a Waters Z-spray source. HPLC analysis was performed on Shimadzu (LC 20AD, UV detection monitored at 254 nm) or Shimadzu (LC 6AD, UV detection monitored at 254 nm). C18 column for *E*/*Z* selectivity measurements (Hypersil ODS 5 μm, 4.6 mm × 250 mm) was purchased from Dalian Elite Analytical Instruments Co., Ltd. A Chiralpak AD-H column for enantiomeric excess measurements was purchased from Daicel Chemical Industries, Ltd. The optical rotation value was measured by a Perkin Elmer 341LC polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell and are reported as: $[\alpha]_D^T$ (concentration in g per 100 mL, solvent). Column chromatography was performed on silica gel 100–200 mesh or 200–300 mesh.

General synthesis of 2a *via* the olefin cross-metathesis

A round-bottom flask equipped with a condenser and a magnetic stirrer bar was charged with **16** (1.0 equiv.), **12** (3.0 or 4.0 equiv.), additives (added or not) and 5 mol% of catalyst under

a nitrogen atmosphere. The reaction vessel was flushed with nitrogen. Then a solvent was added *via* a glass syringe. The resulting reaction mixture was refluxed for 24 h under a nitrogen atmosphere. The solvent was then removed under reduced pressure. The product was isolated by column chromatography on silica gel with ethyl acetate and hexane (v/v = 1 : 5) as an eluent to give **2a** as a slightly yellow oil.

General synthesis of 2a *via* the Julia–Kocienski olefination

A dried tube equipped with a magnetic stirrer was charged with **31** (0.2 mmol, 1.0 equiv.) and flushed with nitrogen. Then a dried solvent (2.5 mL) was added *via* a glass syringe. Unless otherwise noted, the solution was cooled to −70 °C and then a solution of the MHMDS base (0.4 mmol in solvent (1 mL), where M = Li, Na, or K) was added dropwise. After being stirred at −70 °C for 1 h, aldehyde **18** (0.8 mmol in solvent (1 mL)) was added dropwise. The resulting reaction mixture was stirred at −70 °C for 1 h and then allowed to warm gradually to room temperature and stirred for a few hours until **31** had disappeared, as monitored by TLC. The reaction mixture was quenched with brine and diluted with CH_2Cl_2. The organic layer was separated, dried over Na_2SO_4, filtered, concentrated and purified by flash column chromatography on silica gel with a mixed ethyl acetate and hexane (v/v = 1 : 2) as an eluent to give **2a** as a slightly yellow oil.

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