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A new strategy for the stereoselective synthesis of 2,2′-bipyrrolidines

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Dedicated to Professor John B. Bremner on the occasion of his 66th birthday

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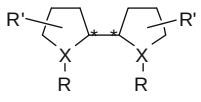
ABSTRACT

A new strategy for the stereoselective synthesis of the 2,2′-bipyrrolidine scaffold is presented using a metathesis reaction followed by asymmetric dihydroxylation for the introduction of the stereogenic elements. This straightforward high-yielding process is suitable for application to the synthesis of additional heterocycles.

Chiral bisamine compounds are commonly used as ligands in stereoselective metal-catalysed reactions, including allylic additions, reductions and asymmetric dihydroxylations.[1] Our interest in such compounds stems from the concept of invoking chiral discrimination in reactions based on helix sense as a design principle driven by the observation that all chiral molecules are also helical. Ligand types of interest to us include bisphosphines, bisarsines, bisamines and helical ligands that possess a mixture of heteroatoms with a view that a range of metal-ligand catalysed reactions could be investigated in the future. Our general target structures are encompassed by **1** where the helix is defined by the two stereogenic atoms which are flanked by the metal co-ordinating heteroatoms, thus forming the backbone 'arc' of helicity. The helical groove depth and degree of twist could be modulated by a range of substituents 'R'', including the presence of fused rings. Importantly, any single synthetic strategy towards these structures should not only be highly stereoselective, but also be flexible to allow the incorporation of a range of heteroatoms, for example, X = N or P or As atoms in a controlled fashion. Further, the same strategy should allow articulation to produce different ring sizes, fused-ring structures and a range of substituted ligands stereoselectively, and in an efficient manner.



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The starting point for our investigations was the stereoselective synthesis of the known 2,2′-bipyrrolidine and this is the subject of the work reported here. The most common syntheses of the 2,2′-bipyrrolidine parent structure involve dimerisation of monomers followed by resolution,[2,3] but given our requirement for a single stereoselective strategy to produce a range of derivatives, the lack of convergency of this approach was deemed impractical. Our attempts to reproduce the published 15-step chiral synthesis from tartaric acid[4] proved extremely unreliable and poor yielding rendering it of little use for our purposes. Therefore, we devised a new strategy for the stereoselective synthesis of the 2,2′-bipyrrolidine scaffold that utilises simple chemistry and starts from cheap and readily available materials. The key steps involved the formation of a symmetrical alkene using Grubbs' metathesis chemistry and Sharpless asymmetric dihydroxylation for the introduction of chirality—subsequent functional group manipulations use established, high yielding chemistry.[4] This Letter reports the synthesis of the protected 2,2′-bipyrrolidine **10** using this new strategy and is outlined in Scheme 1.

Pent-4-en-1-ol was protected and then subjected to metathesis using standard Grubbs' I reaction conditions[5] giving the dimer **2** in an optimised 75% yield with an *E*:*Z* ratio of 5:1 as determined by ^{1}H NMR analysis of the methylene peaks adjacent to the olefin (Scheme 1).[6] A small quantity (5%) of a by-product was also formed arising from reaction with the styrene generated from the catalyst. Asymmetric dihydroxylation utilised Sharpless conditions[7] with ADmix α and a mixture of the inseparable *E*:*Z* isomers of **2** yielding the diol **3** as a mixture of chiral and *meso* diastereomers in overall 86% yield and 86% ee as determined by chiral HPLC.[†] Similarly, the

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[†] ee values are determined based upon conversion of the *trans*-alkene.

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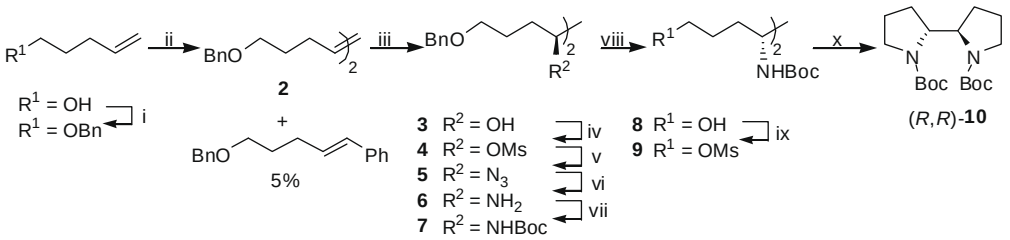
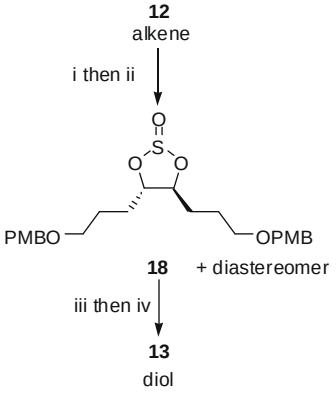


Scheme 1. Reagents and conditions: (i) (a) NaH, THF, 0 °C, 30 min, (b) BnBr, 0 °C to rt, 23 h, 99%; (ii) 5 mol % Grubbs' 1, CH_2Cl_2, Δ, 5 h, 75% (*E*:*Z*, 5:1); (iii) ADmix α, methane sulfonamide, 1:1 $^tBuOH/H_2O$, 24 h, 86%; (iv) MsCl, Et_3N, CH_2Cl_2, 20 min, 76%; (v) NaN_3, DMF, 80 °C, 2 h, 71%; (vi) H_2(g), Pd/C, EtOH, 2 h, 100%; (vii) Boc_2O, Et_3N, Et_2O, 8 h, 59%; (viii) $H_{2(g)}$, Pd/C, EtOH, 1.5 h, 85%; (ix) MsCl, Et_3N, CH_2Cl_2, 20 min, 86%; (x) NaH, DMF, 2 h, 62%.

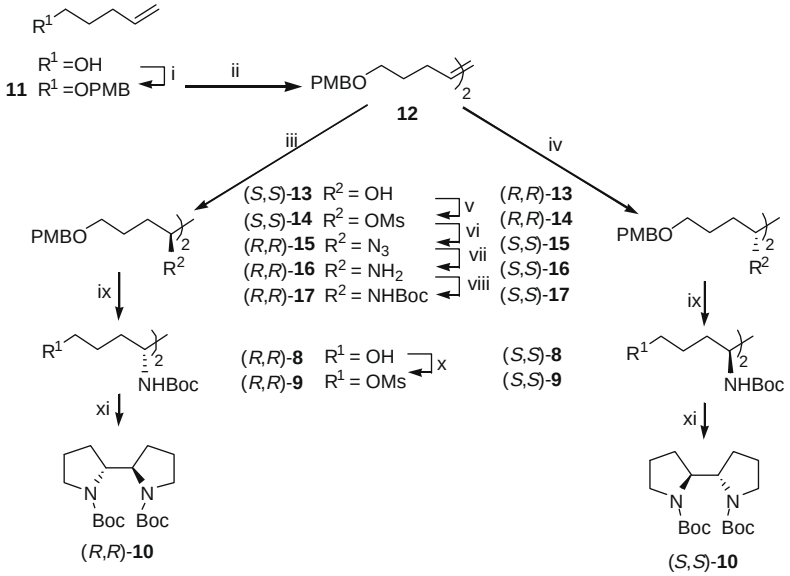
use of ADmix β resulted in an 80% yield of the alternative diol **3** with an ee of 81%. Attempts to separate the chiral and *meso* isomers using column chromatography were unsuccessful. The remainder of the synthesis to the bipyrrolidine utilised reported chemistry.[4] While these initial investigations established the viability of our strategy, the stereochemical outcome required improvement. The problem arose from the mixture of *meso* and chiral diols **3** being generated as a result of the inability to separate the *cis* and *trans* isomers of **1** from the metathesis reaction—this was largely due to the non-polar nature of the alkene making simple separation using silica gel problematic. Therefore, a more polar protecting group was chosen with the idea that silica gel separation might be feasible and the results of this sequence synthesising both the (*R*,*R*)- and (*S*,*S*)-bipyrrolidine **10** are summarised in Scheme 2.

Protection of pent-4-en-1-ol with PMBBr followed by metathesis gave the alkene **12** in an optimised 86% yield with an *E*:*Z* ratio of 3.5:1. Again, the isomers could not be separated using silica gel column chromatography. Attempts to optimise the formation of the *E*-isomer included the use of Grubbs' II catalyst which resulted in a mixture of products that were mostly non-symmetrical alkenes. The use of 10 mol % benzoquinone[8] in combination with Grubbs' II catalyst resulted in a poorer alkene yield (60%) with an *E*:*Z* ratio of 4:1, and additional impurities that could not be separated by column chromatography.

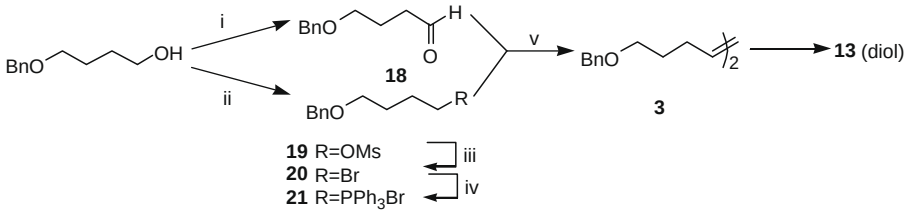
The asymmetric dihydroxylation of the alkene **12** was undertaken with ADmix α to give the (*S*,*S*)-diol **13** in a yield of 69% with an ee of 98%. The yield can be improved (90%) using longer reaction times but at the expense of stereochemical integrity (92%). In an



Scheme 3. Separation of stereoisomers via the corresponding sulfite. Reagents and conditions: (i) ADmix α or ADmix β, methane sulfonamide, $^tBuOH/H_2O$ (1:1), 17 h; (ii) $SOCl_2$, Et_3N, CH_2Cl_2, 72 h; (iii) chromatographic separation, (*R*,*R*)-**18** 58%, (*S*,*S*)-**18** 62% (yields are based on the two step conversion from the *trans* alkene **12**); (iv) NaOMe, MeOH, 116 h, (*R*,*R*)-**13** 77%, (*S*,*S*)-**13** 69%.



Scheme 2. Reagents and conditions: (i) (a) NaH, THF, 0 °C. (b) PMBBr, 0 °C to rt, 4 h, 73%; (ii) 2.5 mol % Grubbs' 1, CH_2Cl_2, Δ, 20 h, 86%, *E*:*Z*, 3.5:1; (iii) ADmix α, methane sulfonamide, ^tBuOH:H_2O (1:1), 24 h (69%, 98% ee) or 20 h (90%, 92% ee); (iv) ADmix β, methane sulfonamide, ^tBuOH:H_2O (1:1), 65 h (98%, 88% ee) or 24 h (93%, 70% ee); (v) MsCl, Et_3N, CH_2Cl_2; (*S*,*S*)-**14** 25 min, 99%; (*R*,*R*)-**14** 20 min, 95%; (vi) NaN_3, DMF, 80 °C, (*R*,*R*)-**15** 23 h, 73%; (*S*,*S*)-**15** 18 h, 76%; (vii) H_2(g), Pd/C, abs. EtOH, 2 h, (*R*,*R*)-**16** 6 h, 100%; (*S*,*S*)-**16** 3.5 h, 100%; (viii) Boc_2O, Et_3N, Et_2O, 35 °C, (*R*,*R*)-**17** 17 h, 40%; (*S*,*S*)-**17** 15 h, 75%; (ix) H_2(g), Pd/C, abs. EtOH, (*R*,*R*)-**8** 1.5 h, 85%; (*S*,*S*)-**8** 5 h, 95%; (x) MsCl, Et_3N, CH_2Cl_2, (*R*,*R*)-**9** 20 min, 86%; (*S*,*S*)-**9** 10 min, 76%; (xi) NaH, DMF, (*R*,*R*)-**10** 2 h, 62%; (*S*,*S*)-**10** 3 h, 76%.



Scheme 4. Synthesis of alkene **3** using the Wittig chemistry. Reagents and conditions: (i) DMP, CH_2Cl_2, 86%; (ii) MsCl, Et_3N, CH_2Cl_2, 30 min; (iii) LiBr, THF, 72 h, 82% over two steps; (iv) PPh_3, CH_3CN, Δ, 164 h then $KOH_{(aq)}$, THF, 3.5 h, 47% over two steps; (v) LiBr, PhLi, THF, −78 °C to rt, 30 min, then **18**, −78 °C to rt, 12 h, 30%, 97% *E*.

analogous fashion, the use of ADmix β yielded the (*R,R*) isomer in 98% yield with an ee of 88%. The chiral diols could not be separated from the *meso* diol at this stage. Subsequent mesylation of both the (*S,S*) and (*R,R*) isomers gave **14** (99% and 95% yields, respectively) and allowed for the incorporation of the heteroatom in an S_N2 reaction using sodium azide giving (*R,R*)-**15** (73%) and (*S,S*)-**15** (76%). Reduction of the azide derivatives using H_2 gas and palladium on carbon gave the amines (*R,R*)-**16** (100%) and (*S,S*)-**16** (100%) with no removal of the PMB protecting group evident. Boc protection of the amines proceeded under standard conditions giving (*R,R*)-**17** (40%) and (*S,S*)-**17** (75%). At this stage, separation of the *meso* from the chiral molecule was possible by recrystallisation from CH_2Cl_2/hexanes. Removal of the PMB protecting groups using H_2 gas and palladium on carbon proceeded smoothly [(*R,R*)-**8** (85%) and (*S,S*)-**8** (95%)] and subsequent mesylation gave the penultimate derivatives **9** in 86% (*R,R*) and 76% (*S,S*) yields. The ring-closing reaction proceeded by generation of the anion using NaH and produced the target *N*-Boc-protected bipyrrolidines (*R,R*)-**10** and (*S,S*)-**10** in 62% and 76% yields, respectively,[9] with excellent stereoselectivity [(*S,S*)-**10** $[\alpha]_D^{23}$ −43.7 (*c* 0.198, $CHCl_3$), cf. lit.[4] $[\alpha]_D^{23}$ −40.6 (*c* 0.36, $CHCl_3$)].

In an attempt to improve the stereochemical efficiency of the sequence, we attempted to remove the *meso* isomer by converting the product from the dihydroxylation of the alkene **12** into the corresponding sulfite, followed by chromatographic separation[10] and hydrolysis back to the diol (Scheme 3). This three-step process provided the (*S,S*)-diol **13** in 43% overall yield with an ee of 96% and the (*R,R*)-diol **13** in 45% yield with an ee of 68%.

Although the diastereomeric separation of the chiral sulfites allows for the successful completion of the synthesis with good stereoselectivity, the sequence would clearly be more efficient if none of the *cis* alkene was produced in the first instance. Thus, we investigated the generation of alkene **12** using modified Wittig chemistry. Protected 4-benzyloxy-1-butanol was converted into the required aldehyde **18** using DMP in 86% yield (Scheme 4). The use of PCC for the oxidation gave lower yields and side products that were difficult to separate. The same alcohol was also converted into the bromide **20** in 82% yield via mesylation and bromination with LiBr. Synthesis of the phosphonium bromide salt **21** under the reported conditions[11] of xylenes at reflux (Table 1, entry 1) was sluggish and benzyltriphenylphosphonium bromide was formed unexpectedly as the major product. Decreasing the reaction time and temperature using toluene at reflux favoured the formation of the desired salt albeit in low yield (entry 2). The reaction was also slow in a polar solvent (entry 3), however, an extended reaction time afforded the phosphonium salt **21** in good yield with a small amount of the persistent by-product. In this case, the benzyl salt was removed by selective hydrolysis with $KOH_{(aq)}$ in THF, providing the pure phosphonium salt in an overall yield of 47% after hydrolysis.

Table 1
Optimisation of the generation of the the Wittig salt **21**; X = halogen

Entry	X	Solvent	Time (h)	Temperature	Yield[a] (%)	
					Butyl phos. halide	Benzyl phos. halide
1	Br	Xylenes	100	Reflux	36	46
2	Br	Toluene	6	Reflux	21	5
3	Br	Acetonitrile	164	Reflux	71	20
4	I	Benzene	21	Reflux	44	—
5	I	Toluene	158	80 °C	74	—

[a] Relative yields determined by ^1H NMR analysis of the salt mixture.

Due to the difficulties encountered with the benzyl salt by-product, we also investigated the reaction with iodine. Therefore, iodination of 4-benzyloxy-1-butanol was carried out under standard conditions with PPh_3, I_2 and imidazole in 94% yield. Although subsequent reaction with PPh_3 was still slow (entry 4), prolonged heating in toluene at 80 °C gave the phosphonium iodide salt in 74% yield with only a trace amount of the benzyl by-product detected by NMR (entry 5).

The *trans* selective modification of the Wittig reaction[12] using PhLi as the base and the bromide salt **21** furnished the alkene **3** in high stereoselectivity (97% *E*), albeit in a modest yield of 30% (Scheme 4). A secondary alcohol was also isolated as a by-product (25%) arising from attack of PhLi on the unreacted aldehyde. The same yield was also obtained with the iodide salt, although the stereoselectivity was slightly lower (94% *E*). The poor yields were a result of incomplete ylide generation presumably due to the competing acidity of the benzylic protons of the protecting group. The AD reaction was carried out using the *trans* alkene (97% *E*) to afford the (*S,S*)-diol in 77% yield (ee 87%) and the (*R,R*)-diol in 73% yield (ee 97%) using ADmix α and ADmix β, respectively.

Thus, we have demonstrated an efficient stereoselective synthesis of 2,2′-bipyrrolidine utilising cheap starting materials and straightforward chemistry. The key steps involved ensuring the integrity of the *trans* alkene to enable asymmetric dihydroxylation to produce chiral diols in good enantiomeric excess. Alternatively, any remaining *meso* isomers can be removed by recrystallisation partway through the sequence. Subsequent functional group manipulations have been shown by us, and others, to maintain the chirality through to the 2,2′-bipyrrolidines. The advantages of this new synthetic route are the extremely simple and highly reproducible reactions and the versatility of design which allows for the incorporation of different heteroatoms giving rise to a range of possible heterocycles using the identical strategy. Importantly, a range of substituted alkenes could be used in the initial stages and thus, this strategy could be used to give access to numerous different symmetrical systems, and by the early use of cross-metathesis reactions, it is possible to produce non-symmetrical heterocyclic systems. We are currently investigating the versatility of our stereoselective strategy through the synthesis of novel heterocycles.

Acknowledgements

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