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Asymmetric Intramolecular Aza-Michael Reaction in Desymmetrization Processes. Total Synthesis of Hippodamine and *epi*-Hippodamine

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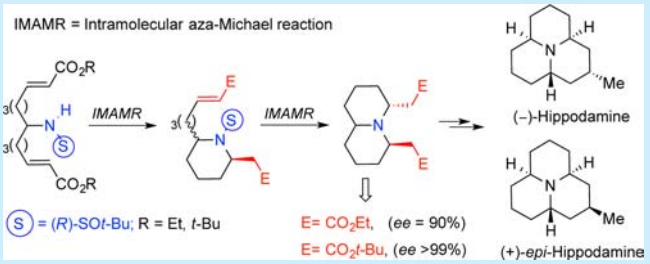
Supporting Information

ABSTRACT: The use of chiral sulfinyl amines both as nucleophilic nitrogen sources and chiral inducers has been described for the first time in a desymmetrization-type process involving an intramolecular aza-Michael reaction. The resulting product was employed as an advanced intermediate in the total synthesis of the natural product hippodamine and *epi*-hippodamine, taking advantage of the special symmetry of these molecules. In addition, this is the first asymmetric total synthesis of *epi*-hippodamine.



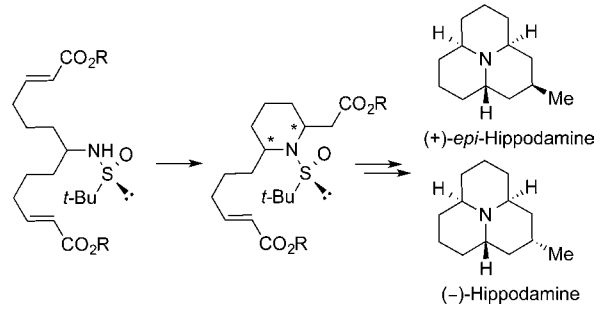
Chiral *N*-sulfinamides are among the most efficient and versatile auxiliaries developed to date.[1] Their success is due to several factors: (a) they can be prepared easily from aldehydes and ketones; (b) they are more electrophilic than the corresponding *N*-alkyl- or *N*-arylimines; (c) the sulfinyl auxiliary exerts powerful stereodirecting effects; and in addition, (d) this auxiliary is an excellent amine-protecting group easily removed under mild acidic conditions.

Since their introduction in organic synthesis, *N*-sulfinamides have played an important role in the asymmetric synthesis of a variety of structurally diverse nitrogen-containing molecules as they provide a general solution to the problem of the addition of organometallic reagents to chiral imines. Usually, after nucleophilic addition (A_N), once the sulfinyl group has exerted its directing effect, it is removed under acidic conditions and the free amino group is susceptible to further transformations. Despite the widespread use of these chiral auxiliaries, the behavior of *N*-sulfinylamines both as nitrogen-centered nucleophiles and chiral inducers has been explored to a much lesser extent. Most examples of this performance take advantage of the formation of a nitrogen amide after the addition of an organometallic reagent to the imine functionality that undergoes, in a tandem fashion, a subsequent nucleophilic nitrogen addition to an electrophile present in the substrate. In this context, several tandem A_N-intramolecular alkylations,[2] A_N-intramolecular aza-Michael reactions[3] (IMAMR), and Mannich-IMAMRs[4] have been reported in the literature. Furthermore, additional examples following a stepwise sequence have also been described. In these cases, after the isolation of the sulfinyl amine, treatment under basic conditions allowed further transformations in most cases involving intramolecular alkylations.[5]

Our research group directed previous efforts toward the evaluation of the sequence cross-metathesis/IMAMR of sulfinyl amines bearing a remote olefin either in a tandem or in a stepwise manner.[6] The overall process constitutes a useful route to access enantiomerically pure pyrrolidine and piperidine derivatives. In addition, this methodology has been successfully applied to the total synthesis of the natural product pinidinol. In the present paper, *N*-sulfinylamines acting both as nucleophilic nitrogen sources and chiral inducers were subjected, for the first time, to a desymmetrization process by means of an IMAMR.[7] The resulting disubstituted piperidines were used as intermediates in the total synthesis of the azaphenalene skeleton of the natural products hippodamine and *epi*-hippodamine (Scheme 1). It is worth mentioning that this is the first total synthesis of (+)-*epi*-hippodamine and the second of (−)-hippodamine.[8]

Starting materials for the projected desymmetrization reaction were assembled from symmetric ketone **1**.[9] Its condensation with (*R*)-*N*-*tert*-butanesulfinamide in the presence of titanium(IV)

Scheme 1. Desymmetrization by Means of an Asymmetric IMAMR. Application to the Synthesis of the Azaphenalene Skeleton



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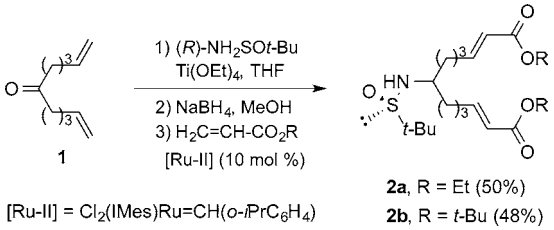
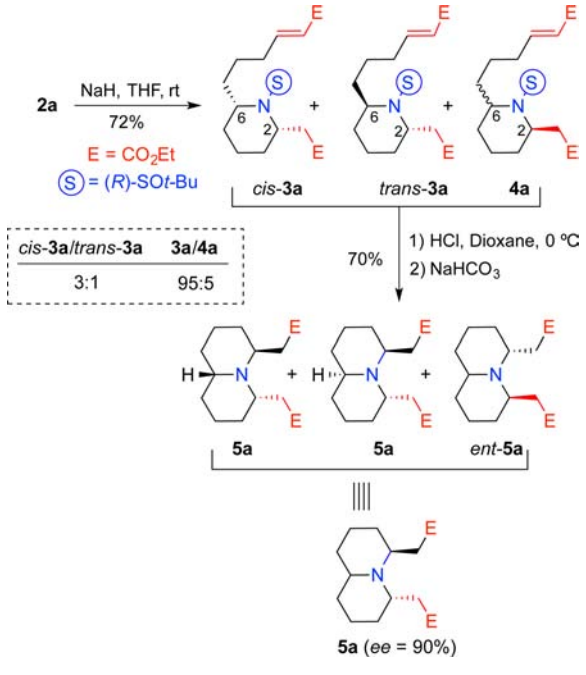
ethoxide followed by $NaBH_4$ reduction rendered the corresponding reductive amination product containing the chiral auxiliary. A double-direction cross-metathesis reaction with ethyl or *tert*-butyl acrylate afforded symmetric diesters **2** in acceptable overall yields (Scheme 2).[10] These substrates were subjected to the desymetrization process by means of an intramolecular aza-Michael reaction (IMAMR).

Scheme 2. Preparation of Desymmetrization Substrates 2



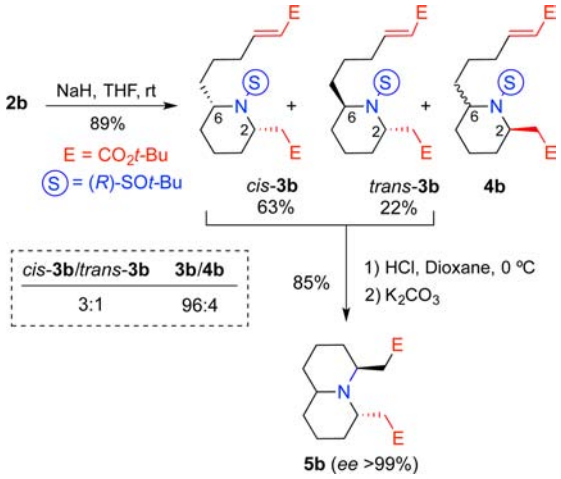
Several bases were tested in an initial attempt to cyclize **2a**, namely LDA, LiHMDS, NaHMDS, TBAF, KH, and NaH. Among them, the best results were obtained with NaH in THF at room temperature. Under these conditions, a nonseparable 3:1 mixture of diastereoisomers *cis*-**3a** and *trans*-**3a** was obtained as the major product. A small amount of the other two possible isomers **4a** was also detected in a 95:5 ratio (**3a**/**4a**).[11] This reaction mixture was treated with HCl in dioxane to remove the sulfoxide auxiliary, and upon basification with saturated aqueous $NaHCO_3$, a second intramolecular aza-Michael reaction took place spontaneously, rendering bicycles **5a** in 70% yield (Scheme 3). Interestingly, the symmetry of the final bicyclic structure plays an important role in this process.[12] Thus, compound **5a** is C_2-symmetric, and it means that the second cyclization of substrates *cis*-**3a** and *trans*-**3a** renders the same isomer **5a**. Likewise, **4a** would render the enantiomer of **5a**. Consequently, and considering the initial diasteroisomeric ratio, compound **5a** was obtained in 90% *ee*, as determined by chiral HPLC analysis (Scheme 3).

Scheme 3. Double Cyclization via IMAMR of Compound 2a (E= CO_2Et)



When substrate **2b**, bearing *tert*-butyl acrylate moieties, was subjected to cyclization under the optimized conditions, a 3:1 mixture of diastereoisomers*cis*-**3b** and *trans*-**3b** was obtained in 85% yield. In this case, these two diastereoisomers were easily separated by column chromatography, and they were independently cyclized. Selective removal of the *tert*-butyl sulfinyl group was achieved with HCl in dioxane at 0 °C without affecting the *tert*-butyl acrylate moieties present in the molecule. The second intramolecular aza-Michael addition took place upon basification with K_2CO_3 to give the *trans* isomer **5b** in 85% overall yield, either from *cis*-**3b** or *trans*-**3b**, in enantiomerically pure form (Scheme 4).

Scheme 4. Double Cyclization via IMAMR of Compound 2b (E = CO_2-*t*-Bu)



Piperidines *cis*-**3a,b** and *trans*-**3a,b** share the same configuration at C2, indicating that the selectivity of the first IMAMR, which involves the desymmetrization process, is very high. A possible explanation of this selectivity might be the participation of a rigid transition state. On the one hand, a chelate between the ester carbonyl, the sulfoxide, and the sodium amide would deliver the addition of the nitrogen nucleophile to the *si* face of the conjugated ester, opposite to the bulky *tert*-butyl group.[13] On the other hand, the substituent at C6 (R′) is too far away to affect the cyclization. Major products *cis*-**3a,b** are expected to arise from an equatorial disposition of this lateral chain, while the axial conformation would render isomers *trans*-**3a,b** (Scheme 5).

This relative stereochemical assignment was confirmed by means of a NOESY experiment on piperidine **6** obtained for derivatization of compound *cis*-**3b**. Hydrogenation of the double bond followed by removal of the sulfoxide auxiliary rendered 2,6-disubstituted piperidine **6**. The NOESY experiment showed a relative *cis* relationship for protons H_a and H_b at the 2 and 6 positions of the piperidine ring (Scheme 6).

The construction of the whole skeleton of the natural products started with enantiomerically pure quinolizidine derivative **5b**, which was subjected to a sequence Dieckmann condensation−decarboxylation rendering tricyclic ketone **7** in 60% yield (two steps). Subsequent Wittig reaction afforded olefin **8** in very good yield (87%) (Scheme 7).

Finally, hydrogenation of the double bond would give the desired products. Depending on the reaction conditions, it was possible to develop a diastereodivergent synthesis of hippod-

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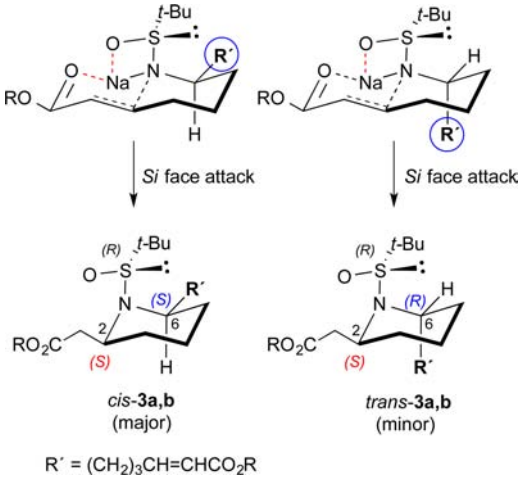
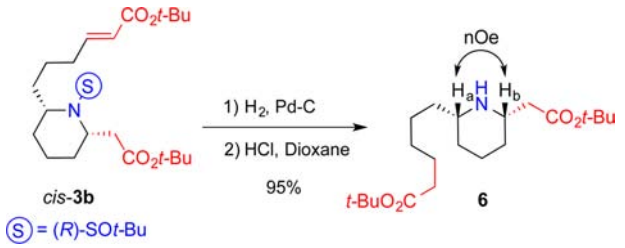
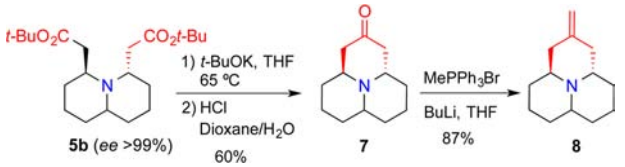
Scheme 5. Rationalization of the Stereochemical Outcome in the First IMAMR



Scheme 6. Derivatization of *cis*-3b toward Piperidine 6



Scheme 7. Synthesis of Azaphenalene Scaffold 8

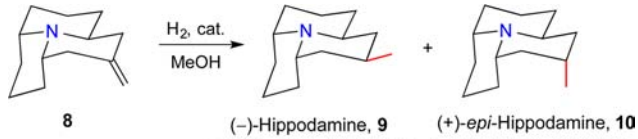


amine and *epi*-hippodamine. Hydrogenation with Raney Ni afforded a 2:1 mixture of hippodamine **9** and *epi*-hippodamine **10**, which were separated by column chromatography.[14] Comparison of the NMR data and optical rotation with those reported in the literature [found: $[\alpha]^{25}_{D}$ −1.5 (*c* 1.0 $CHCl_3$), lit.[8] $[\alpha]^{22}_{D}$ −1.2 (*c* 1.1 $CHCl_3$)] led us to conclude that the major product under these hydrogenation conditions was (−)-hippodamine **9** (Scheme 8). This finding, together with the previously mentioned NOESY experiment, prompted us to assign the absolute configurations for intermediate compounds **3**, **5**, **7**, and **8**.

On the other hand, the hydrogenation reaction in the presence of Pd/C yielded a 1:3 mixture of products **9**/**10**, while with Pearlman's catalyst, the selectivity toward *epi*-hippodamine **10** increased to a 1:10 ratio (Scheme 8).[15] After chromatographic separation, we found that NMR data of the major product **10** were in good agreement with those previously described.[16] Additionally, the optical rotation value for *epi*-hippodamine was found to be $[\alpha]^{25}_{D}$ +8.5 (*c* 1.0 $CHCl_3$).

In summary, by taking advantage of the unique symmetry of the alkaloid products hippodamine and *epi*-hippodamine, we were able to develop an efficient strategy for their asymmetric total synthesis. To this end, a desymmetrization process by means of an asymmetric intramolecular aza-Michael reaction was

Scheme 8. Final Hydrogenation Reaction for the Synthesis of Hippodamine 9 and *epi*-Hippodamine 10



cat.	9/10	yield (9+10)
Raney Ni	2:1	93%
Pd/C	1:3	92%
$Pd(OH)_2$	1:10	95%

used as the key step. The dual ability of *N*-sulfinyl amines to act as chiral auxiliaries and nucleophilic nitrogen sources was successfully exemplified with this interesting transformation. Moreover, it is important to point out that this is the second total synthesis of (−)-hippodamine **9** and the first of (+)-*epi*-hippodamine **10**, which led us to determine its optical rotation value.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data of all new compounds, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Prof. Iwao Ojima on the occasion of his 70th birthday.

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(11) A diastereoisomeric ratio of 70:26:4 (*cis*-**3a**/*trans*-**3a**/ *cis*+*trans*-**4a**) was determined by chiral HPLC (see HPLC traces in the Supporting Information)

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(13) When the reaction was performed in the presence of crown ether-15, a 3:1:2 mixture of *cis*-**3b**, *trans*-**3b**, and **4b** was obtained. This result indicates that the crown ether captures the sodium cation avoiding the formation of the chelate, which is reflected in a clear drop of the selectivity. This experiment supports the mechanistic proposal.

(14) Diasteroisomeric ratios of hippodamine/*epi*-hippodamine were determined by ^{1}H NMR.

(15) Hydrogenation with Pd−C or $Pd(OH)_2$ takes place through the less hindered face, while Raney Ni gives rise to the thermodynamic product with the methyl group in the equatorial position.

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