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Studies on the asymmetric Birch reductive alkylation to access spiroimines

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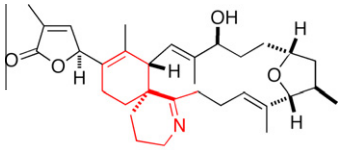
ABSTRACT

The asymmetric Birch reductive alkylation has been investigated to synthesize spiroimine analogs of the neurophycotoxin (−)-gymnodimine A **1**. Two types of chiral aromatic substrates, an acyclic benzamide **2** and a benzoxazepinone **3** were studied. We found that the chiral auxiliary of benzoxazepinone could be easily removed in a three step procedure to afford β-ketoester **14** that was converted into spiroimines **23**–**24** possessing antagonist effects on nicotinic acetylcholine receptors (nAChRs).

The asymmetric Birch reductive alkylation is a valuable method for the formation of chiral cyclohexa-1,4-dienes with a stereogenic quaternary carbon.[1] The availability of benzoic acid derivatives and the possibility to use a wide range of electrophiles bearing functional groups resulted in several applications of this reaction in the synthesis of natural products.[1b,2] During the course of our ongoing project on the synthesis of 6,6-spiroimine analogs of the neurophycotoxin (−)-gymnodimine A **1** (Fig. 1),[3] we therefore were interested in the asymmetric Birch reductive alkylation of chiral benzamides **2** and **3** to create the quaternary carbon of the spiroimine skeleton. This strategy complements the asymmetric allylic alkylation approach recently reported by our group.[3]

We began our investigations with (*S*)-2-methoxymethylpyrrolidine-derived benzamide **2** and benzoxazepinone **3** which were subjected to the Birch reduction under optimized conditions using potassium (3 equiv) in a 10/1 mixture of liquid ammonia and THF at −78 °C, in the presence of *t*-BuOH (1 equiv) (Table 1). The excess of potassium was then quenched with piperylene followed by addition of the electrophile bearing either an azido (entry 1) or a protected alkoxy group (entries 2–4). When the electrophile containing an acetate function was used, the crude mixture was directly treated with potassium carbonate in a mixture of THF/H_2O to afford the corresponding alcohols (entries 2 and 3). In these conditions, chiral cyclohexadienes **4a–b** and **5a–b** were obtained in excellent yields and diastereomeric ratios whatever the nature of the aromatic amides **2** or **3** and the electrophiles.

With compounds **4a–b** and **5a–b** in hand, we then turned our attention to the cleavage of the chiral auxiliary. A number of methods have been described to cleave the chiral amide of the Birch adduct.[1] The action of organometallic (MeLi)[4] or reducing agents ($LiAlH_4$)[5] were tested on substrate **4a**, but led to degradation or recovery of the starting material. Cleavage of the chiral auxiliary under acidic conditions was then examined on azido amide **4a** (Scheme 1).[6] Treatment of **4a** with 6 N HCl in refluxing methanol gave a 90/10 mixture of amide **6** and acid **7**, as determined by ^1H NMR. Other acidic conditions (12 N HCl, 2 N H_2SO_4) or prolonged reaction time did not improve the formation of acid **7** and led to complete degradation. We thus decided to obtain acid **7** from iodolactone **8** prepared in quantitative yield by treatment of **6** with iodine in aqueous THF.[7] Unfortunately, our attempts to fragment iodolactone **8** in the presence of metal (Li/NH_3 or Zn/EtOH) failed to give acid **7**.[8]



(–)-Gymnodimine A (**1**)

Figure 1. Structure of (−)-gymnodimine A (**1**).

We next investigated a second strategy based on the cleavage of the chiral auxiliary by lactonization (Scheme 2).[9] This would give spirolactone **9** that should be easily transformed into a spiroimine analog. However, treatment of alcohol **4b** with dry HCl (2 N in Et_2O) in toluene gave the enol ether **10**. The same reaction conducted with aqueous 2 N HCl in MeOH resulted in the degradation of the starting material.

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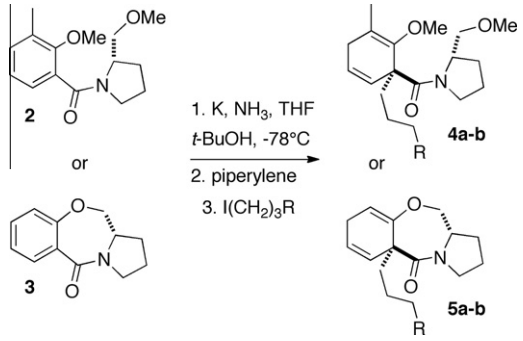
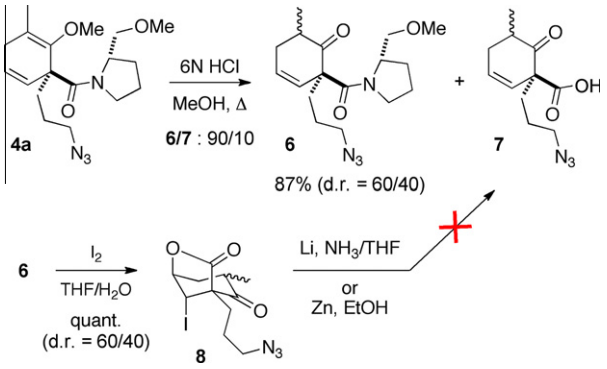
Table 1
Asymmetric Birch reductive alkylation of benzamides **2** and **3**



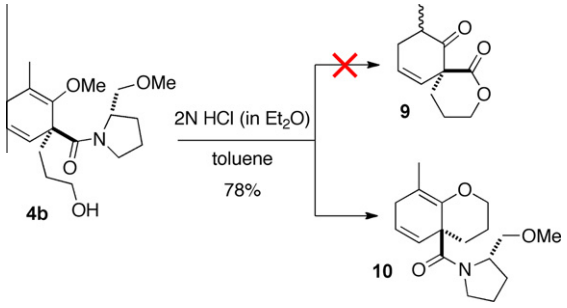
Entry	Substrate	Electrophile (R)	Product (R)	Yield[a] (%)	d.r.[b]
1	**2**	N_3	**4a** (N_3)	91	97/3
2	**2**	OAc	**4b** (OH)[c]	80[d]	97/3
3	**3**	OAc	**5a** (OH)[c]	91[d]	94/6
4	**3**	OBn	**5b** (OBn)	85	94/6

[a] Isolated yield.
[b] Determined by HPLC.
[c] The hydroxyl group was obtained after treatment with K_2CO_3 in THF/H_2O.
[d] Yield after deprotection.

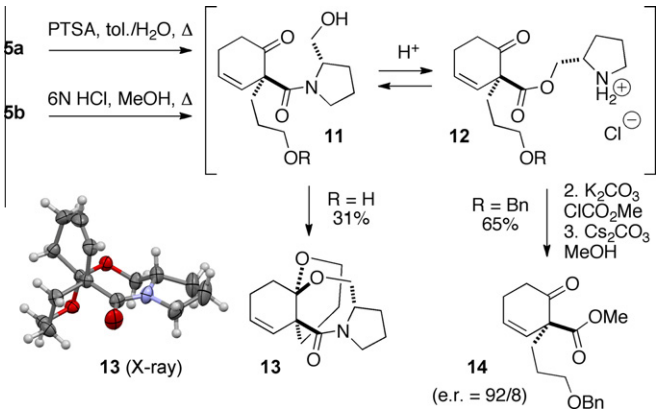


Scheme 1. Chiral auxiliary cleavage of benzamide **4a** by iodolactonization.

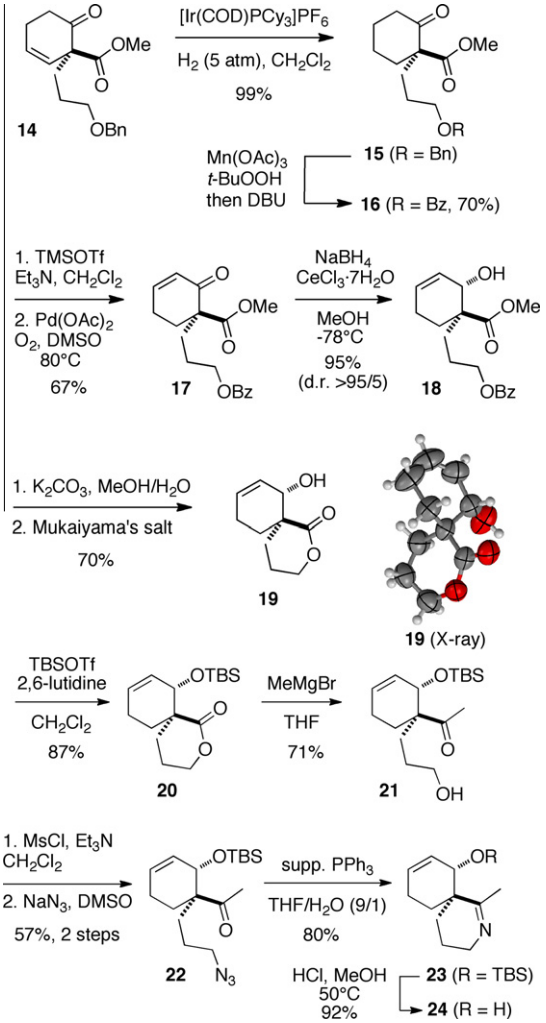
The observed difficulties to remove the prolinol derivative of benzamides **4a–b** led us to examine benzoxazepinones **5a–b** (Scheme 3). Hydrolysis of the enol ethers **5a** and **5b** under acidic conditions results in the formation of amide **11** which is in equilibrium with ester **12**. Treatment of **5a** by *para*-toluene sulfonic acid in a mixture of toluene/water gave ketal **13** in 31% yield,[10] which



Scheme 2. Attempt to cleave chiral auxiliary of **4b** with HCl.



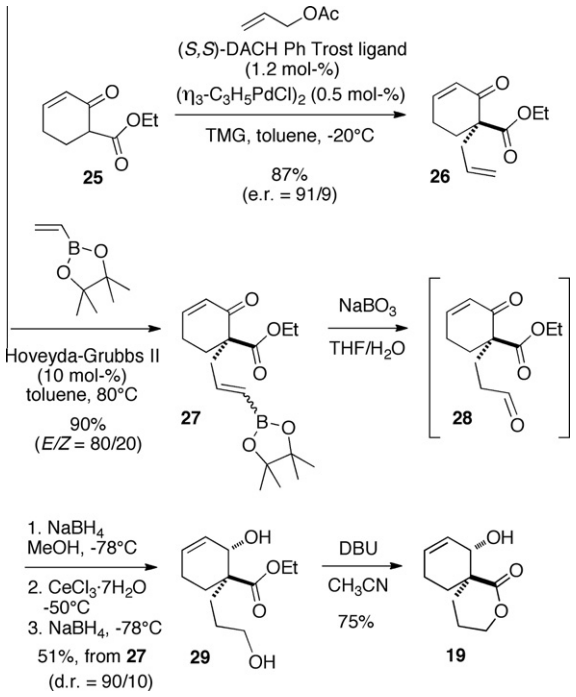
Scheme 3. Hydrolysis of benzoxazepinones **5a** and **5b**.



Scheme 4. Elaboration of β-ketoester **14** into spiroimines **23–24**.

structure and absolute configuration of **13** were confirmed by X-ray analysis.[11] Again, the formation of ketal **13** highlights the propensity of the alcohol to react onto the cyclic ketone to form a fused bicycle instead of a spirocycle, as already observed in the related cyclization of alcohol **4b** (Scheme 2).

To avoid the formation of ketal **13**, we carried out the hydrolysis on benzoxazepinone **5b** (d.r. = 94/6) bearing the benzyloxy group (Scheme 3). The enol ether of **5b** was subjected to 6 N HCl in



Scheme 5. Enantioselective synthesis of lactone **19** by AAA.

refluxing methanol and the resulting ammonium **12** transformed into a methyl carbamate. Methanolysis in presence of cesium carbonate afforded the methyl ester **14**. Interestingly, this three step sequence gave β-ketoester **14** in a 65% yield (e.r. = 92/8),[12] without the need for temporary protection of the cyclic ketone.[13]

With a reliable synthesis of β-ketoester **14** in hand, we then turned to its transformation into the bioactive spiroimine analogs **23–24** possessing an antagonist effect on nAChRs (Scheme 4).[3]

Chemoselective hydrogenation of the double bond of **14** with Crabtree's catalyst gave the saturated ketone **15** in almost quantitave yield.[14] The benzyloxy ether of **15** was oxidized in the presence of a catalytic amount of $Mn(OAc)_3$ and *t*-BuOOH as cooxidant, then the crude mixture was treated with DBU to afford benzoate **16** in a 70% yield.[15] Dehydrogenation of **16** was achieved by the Saegusa reaction using Larock's conditions,[16] providing the cyclic enone **17** in a 67% yield. Diastereoselective reduction of **17** under Luche's conditions (d.r. >95/5) afforded allylic alcohol **18** in excellent yield (95%). Treatment of **18** with K_2CO_3 in aqueous methanol provided the corresponding seco-acid which was directly cyclized in the presence of Mukaiyama's salt[17] to give lactone **19** in a 70% yield. Gratifyingly, we obtained crystals of lactone **19** and X-ray analysis confirmed its relative configuration.[18] The allylic alcohol of lactone **19** was then protected with a silyl group before being subjected to ring opening with methyl magnesium bromide to produce the methyl ketone **21** in good yield. Transformation of the primary alcohol **21** into azide **22** and reduction with supported triphenylphosphine finished the synthesis of spiroimine **23**. The silyl group could also be removed under acidic conditions to afford the free alcohol **24** in a 92% yield.

In comparison to our strategy involving asymmetric allylic alkylation (AAA) of β-ketoester **25**,[3] a similar enantiomeric ratio (e.r. = 91/9) to the Birch alkylation (e.r. = 94/6) was obtained (Scheme 5). Cross-metathesis with vinyl pinacol boronate followed by oxidation with sodium perborate gave keto-aldehyde **28** which was reduced in diol **29** by a sequential one pot operation. The same key lactone intermediate **19** was finally obtained by treating **29** with DBU. Although the AAA is a shorter route to the common lactone **19**, it only allows the formation of 6,6-spiroimines. In contrast, the Birch reaction tolerates electrophiles with longer alkyl chain and could be used for the synthesis of the 6,7-spiroimines contained in spirolides and pinnatoxins.[19]

In conclusion, we have demonstrated that the asymmetric Birch reductive alkylation is a valuable strategy to create the quaternary carbon of spiroimine analogs of the neurotoxin gymnodimine A **1**. Although the acyclic amides **4a–b** could not be converted into an appropriate substrate for the synthesis of spiroimines, we have shown that the chiral auxiliary of cyclic amide **5b** bearing a protected alcohol could be easily removed in a three step sequence to afford the β-ketoester **14** in good enantiomeric ratio. β-Ketoester **14** was a suitable intermediate to access spiroimine analogs **23–24** possessing a biological activity.[3] In addition, our study highlights the difficulties to remove the chiral auxiliary after the asymmetric Birch reductive alkylation of benzamide derivatives. Thus, when planning this reaction, particularly with benzamides bearing an *ortho*-alkoxy group, the benzoxazepinones (i.e., **3**) or related acyclic 2-(methoxymethoxymethyl)pyrrolidine benzamides[2] should be considered as a starting material to easily remove the chiral auxiliary.

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