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Synthesis of Enantiopure Bicyclic α,α-Disubstituted Spirolactams via Asymmetric Birch Reductive Alkylation

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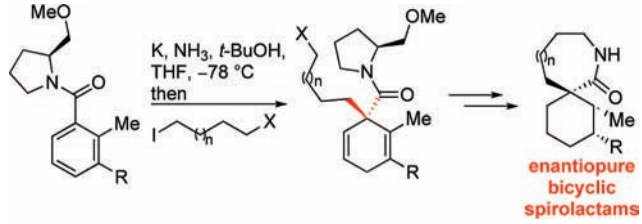
ABSTRACT



The synthesis of enantiopure bicyclic α,α-disubstituted spirolactams is described using a diastereoselective Birch reductive alkylation as the key step. Hydrogenation of the resultant alkylated cyclohexadienes followed by intramolecular cyclization provides access to enantiopure 8-azaspiro[5.6]dodecan-7-ones.

The stereoselective construction of quaternary spirocyclic carbon centers is a challenging problem in organic synthesis.[1] A limited number of methods for the stereoselective construction of bicyclic α,α-disubstituted spirolactams have been reported to date including use of a photochemical iron carbonyl [6 + 2] ene-type reaction,[2] reduction of a bridged bicyclic lactone,[3] and oxidative spirocyclization of a phenolic oxazoline.[4] In the case of spirolactams containing a 7-membered lactam ring, regioselective alkylation of an aminocaprolactam proceeding via a benzylidiene Schiff base intermediate has only furnished a racemic quaternary lactam.[5] The enantioselective synthesis of α,α-disubstituted 7,6-bicyclic spirolactams has only been reported by Murai et al.[6] and our research group[7] via asymmetric Diels−Alder addition of an α-methylene caprolactam to a diene using chiral copper (II) bisoxazoline catalysts. We herein report a new method for the stereocontrolled synthesis of α,α-disubstituted bicyclic spirolactams using a Birch reductive alkylation strategy to establish the key quaternary center.

The Birch reduction provides a valuable method for the formation of partially reduced 6-membered rings from aromatic compounds.[8] When combined with methods for the alkylation of the anions generated in situ, this provides a powerful method to access substituted carbocyclic rings. Schultz et al.[9] developed an asymmetric version of the Birch reductive alkylation using an (*S*)-2-methoxymethylpyrrolidine-derived benzamide. When using a 2-methyl-substituted chiral benzamide, the enolate generated undergoes alkylation *anti* to the side chain of the chiral auxiliary affording one diastereoisomer of the alkylated product. We therefore focused our attention on the synthesis of enantiopure methyl-substituted 6,6- and 7,6-spirolactams (Figure 1) that are valuable precursors to the spiroimine pharmacophore present in the shellfish toxins, the spirolides,

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(9) Schultz, A. G.; Macielag, M.; Padmanabhan, S.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828–7841.

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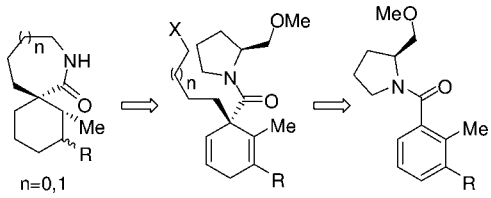


Figure 1. Retrosynthesis for α,α-disubstituted spirolactams.

and gymnodimine (Figure 2).[10] Additionally, spirolactams are an interesting pharmacophore to evaluate for their neuroprotective properties.[11]

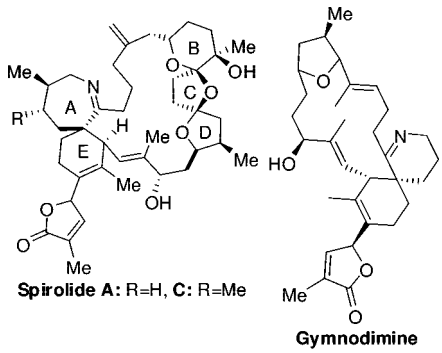
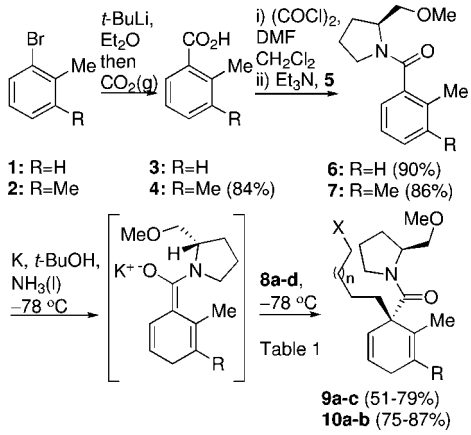


Figure 2. Structure of spirolides A and C and gymnodimine.

Chiral benzamides **6** and **7** were initially prepared via reaction of carboxylic acids **3** and **4** with oxalyl chloride and (*S*)-2-methoxymethylpyrrolidine **5**[12] to afford enantiopure monomethyl and dimethyl benzamides **6**[13] and **7** (Scheme 1). The

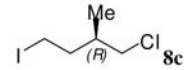
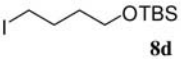
Scheme 1



selectivity of the Birch reductive alkylation of benzamides **6** and **7** was then studied using several electrophiles (Table 1).

Birch reduction of amide **6** was first performed using potassium (∼3 equiv) at −78 °C in liquid ammonia and THF

Table 1. Birch Reductive Alkylation of Chiral Benzamides **6** and **7**

entry	ST[a]	metal	electrophile[b]	product, yields (%)[c]	de (%)[d]
1	**6**	K	 **8a**	**9a**, 79	92
2	**6**	Na	 **8a**	**9a**, 19	61
3	**6**	K	 **8b**	**9b**, 74	92
4	**6**	K	 **8c**	**9c**, 51	94
5	**7**	K	 **8a**	**10a**, 75	92
6	**7**	K	 **8d**	**10b**, 87	100

[a] ST = starting material. [b] 1.5 equiv of electrophile used. [c] Isolated yield. [d] de of the (*S*,*S*)-diastereomer determined by ^{1}H NMR.

in the presence of *t*-BuOH (1 equiv). After 20 min, 4-chloro-1-iodobutane **8a**[14] (1.5 equiv) was added, affording alkylated product **9a** in 79% yield and 92% de (entry 1, Table 1).

The use of sodium under the same conditions resulted in a significant decrease in yield with moderate diastereoselectivity (61% de) (entry 2, Table 1). Using potassium as the reductant, only 1.5 equiv of the iodide was required to effect satisfactory alkylation.

Having established the optimum conditions, Birch reductive alkylation of benzamides **6** and **7** using several electrophiles was carried out to afford compounds **9b** and **10a**,**b** in good yield (74−87%) with high de (92−100%) in favor of the (*S*,*S*)-diastereoisomer (entries 3, 5, and 6, Table 1). Notably, cyclohexa-2,5-dienes **9a**−**c** and **10a**,**b** underwent oxidation at C4 to afford cyclohexadienones.[15] In order to apply this process to more complex substrates related to the spiroimine moiety of spirolide A, (*R*)-1-chloro-4-iodo-2-methylbutane **8c** was reacted with amide **6**, using the optimized conditions, to afford adduct **9c** in 51% yield in 94% de (entry 4, Table 1).

(*R*)-1-Chloro-4-iodo-2-methylbutane **8c** was obtained in 6 steps via diastereoselective alkylation[16] of amide **11** derived from (*S*,*S*)-pseudoephedrine (Scheme 2). Reduction of the pseudoephedrine amide **12** to alcohol **13** was effected using lithium amidotrihydroborate complex

(10) O'Connor, P. D.; Brimble, M. A. *Nat. Prod. Rep.* **2007**, *24*, 869–85.
(11) Jehle, T.; Lagrèze, W. A.; Blauth, E.; Knorle, R.; Schnierle, P.; Lücking, C. H.; Feuerstein, T. J. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2000**, *362*, 74–81.
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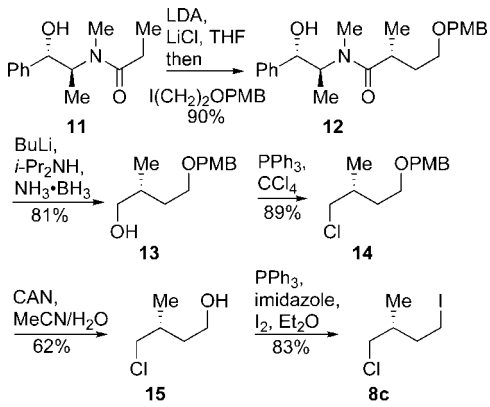
(LiH_2NBH_3) and the resultant alcohol **13** was converted in several steps to the unstable iodide **8c**.

Scheme 2



Attention next turned to amide-directed hydrogenation of the cyclohexadiene using the protocol of Schultz et al.[17] Compounds **9a**, **10a**, and **10b** were subjected to hydrogenation over Crabtree's catalyst[18] ($[Ir(COD)PCy_3]PF_6$) (10 bar H_2) in CH_2Cl_2 for 10 h. Disappointingly, only starting material was recovered and hydrogenation over 10% Pd/C at (10 bar H_2) in $MeOH/CH_2Cl_2$ was also unsuccessful. Hydrogenation of compounds **9a** and **10a** was finally achieved using Adams' catalyst (PtO_2) (4−8 bar H_2) in acetic acid to effect reduction of either one or both of the double bonds. Alternatively, an azide group was introduced onto the alkyl substituent with the aim of effecting simultaneous reduction of the alkenes and the azide group to expedite the synthesis of the desired spirolactams (Scheme 3).

Scheme 3

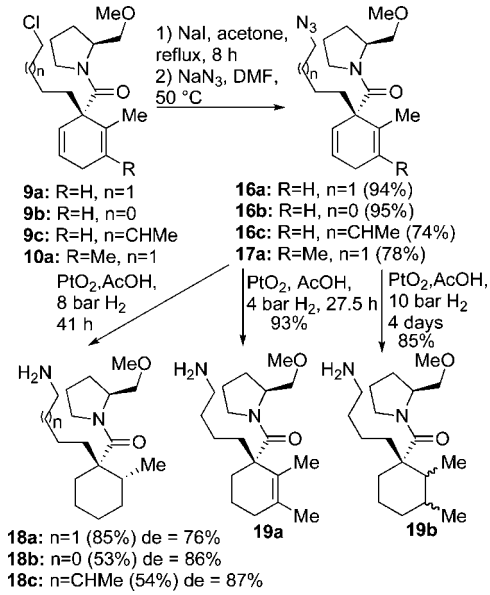
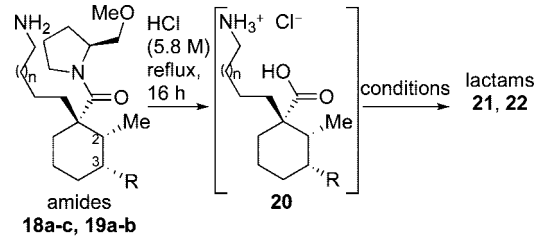
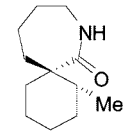
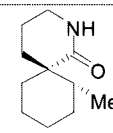
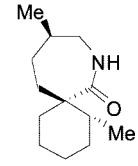
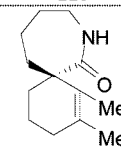
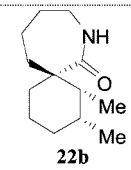


Table 2. Synthesis of Bicyclic Spirolactams



entry	amide	conditions[a]	yield (%) over 2 steps	lactam
1	**18a**	**A**	20[b]	
2	**18a**	**B**	26[b]	 **21a**
3	**18a**	**C**	14[b]	
4	**18a**	**D**	31[b]	
5	**18a**	**E**	23[b]	
6	**18b**	**B**	28[b]	 **21b**
7	**18b**	**D**	12[b]	
8	**18c**	**B**	33[b]	 **21c**
9	**19a**	**B**	<13[c]	 **22a**
10	**19b**	**B**	17[b]	 **22b**

[a] Conditions: (A) HATU (3 equiv), HOAt (3 equiv), DIPEA (10 equiv), CH_2Cl_2/DMF (2:1), rt, 41 h; (B) pyBOP (2 equiv), DMAP (2 equiv), *i*-Pr_2EtN (4 equiv), CH_2Cl_2/DMF (2:1), rt, 23 h; (C) pyBOP (2 equiv), DMAP (2 equiv), *i*-Pr_2EtN (6 equiv), CH_2Cl_2/DMF (2:1), rt, 72 h; (D) DPPA (6 equiv), Et_3N (6 equiv), THF, rt, 39 h;[25] (E) DPPA (8 equiv), Et_3N (6 equiv), THF, rt, 39 h. [b] Yield over two steps from amide **18a**−**c** and **19b** after chromatography. [c] Yield based on LC−MS analysis.

Chlorides **9a**−**c** and **10a** were thus converted to the corresponding iodides using sodium iodide in acetone and hence to the azides **16a**−**c** and **17a** using sodium azide in DMF in 74−95% yield over two steps. The monomethyl compounds **16a**−**c** were then reduced to amines **18a**−**c**

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in moderate yield (53−85%) with good selectivity (76−87% de) using 2.5 equiv of PtO_2 (8 bar H_2, AcOH, 26 °C, 41 h). In the case of dimethylsubstituted cyclohexa-2,5-diene **17a**, olefin **19a** was obtained in 93% yield using 1.2 equiv of PtO_2 (4 bar H_2, AcOH, 26 °C, 28 h). More forcing conditions (3.5 equiv PtO_2, 10 bar H_2, AcOH, 26 °C, 4 days) afforded dimethylcyclohexane **19b** as an inseparable mixture of diastereomers for which the de was determined upon subsequent cyclization to the spirolactam (60% de).

In comparison to amide-directed hydrogenations using homogeneous iridium catalysts, heterogeneous catalysts (PtO_2) deliver the opposite sense of facial selectivity with respect to the cyclohexa-1,4-diene ring system.[19] Hydrogenation of the cyclohexadienes took place *anti* to the amide functionality, and this was confirmed by X-ray analysis of 7,6-spirolactam **21a** obtained via hydrolysis and cyclization of amide **18a** (Figure 3).[20]

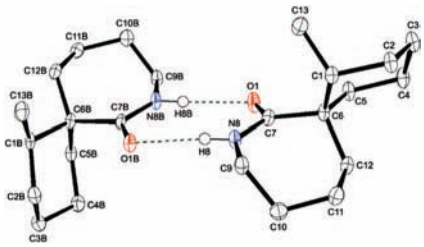

Figure 3. X-ray crystal structure of **21a**. Note the presence of two conformers differing in the conformation adopted by the six-membered ring. Ellipsoids are drawn at the 50% probability level.

Finally, removal of the sterically hindered chiral auxiliary needed to be addressed. Use of Schwartz reagent,[21] LiAlH$(OMe)_3$,[22] MeLi, or alkynyl boranes[23] all failed to affect conversion to an aldehyde or ketone. Only acidolysis under harsh conditions proved effective to convert the tertiary amide to a carboxylic acid in moderate yield (∼50%). Amides **18a**−**c**, **19a**,**b** were therefore hydrolyzed using 5.8 M HCl under reflux then dried on a freeze-drier to afford the corresponding crude amino acid hydrochloride salts **20**. The final intramolecular cyclization of the amino acids to form the bicyclic spirolactams was then attempted using several coupling reagents (Table 2). Use of PyBOP, DMAP, and *i*-Pr_2EtN in CH_2Cl_2/DMF[24] (conditions **B**) proved optimum to effect cyclization of the crude amino acids **18a**−**c** to spirolactam **21a**−**c** (entries 2, 6, and 8, Table 2). Spirolactam **22a**, however, was only obtained in poor yield (entry 9, Table 2) due to the sensitivity of the olefin to aqueous HCl.

In summary, a new method for construction of a range of enantiopure bicyclic α,α-disubstituted spirolactams has been developed using a diastereoselective Birch reductive alkylation to instal the quaternary center. Importantly, the synthesis of (1*R*,6*R*)-1-methyl-8-azaspiro[5.6]dodecan-7-one **21a** provides the core 7,6-ring system of the spiroimine unit of the spirolides and the introduction of an additional methyl group in (1*R*,6*R*,10*R*)-1,10-dimethyl-8-azaspiro[5.6]dodecan-7-one **21c** provides momentum for the synthesis of the challenging spiroimine unit of spirolide A.

Supporting Information Available: Experimental procedures, copies of NMR spectra for all compounds, and CIF file for the X-ray structure of compound **21a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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