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Asymmetric Synthesis of 3-Substituted Isoindolinones: Application to the Total Synthesis of (+)-Lennoxamine

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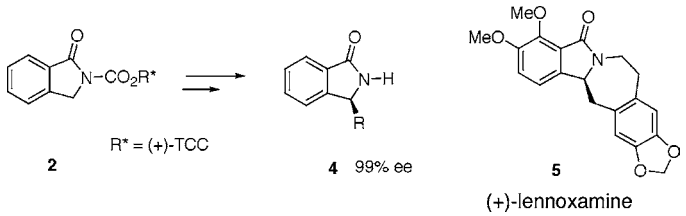
ABSTRACT



An anionic chiral auxiliary mediated asymmetric alkylation of carbamate 2 provides 3-substituted isoindolinones 4 in high ee. This methodology was used in the first asymmetric synthesis of (+)-lennoxamine.

Various heterocyclic compounds containing the isoindolinone skeleton (**1**) have important biological activities, and many of these have been prepared and examined as antihypertensive,[1] antipsychotic,[2] antiinflammatory,[3] anesthetic,[4] antiulcer,[5] and vasodilatory[6] agents. Antiviral,[7] antileukemic,[8a1,b] and platelet aggregation inhibitory[8c] properties have also been observed in this class of structures. Isoindolinones have been widely used as building blocks for the synthesis of various drugs[9] and natural products[10] and have recently found application as templates for combinatorial library preparation.[10c]

Although there are several methods available for making racemic 3-alkylisoindolinones, enantioselective syntheses are few. These involve a resolution of racemic material,[11] an intramolecular Heck reaction,[12] asymmetric Diels−Alder reactions,[13] a ring-closure procedure of chiral hydrazones,[14] chiral acyliminium ion reactions,[15] and a chiral appendage

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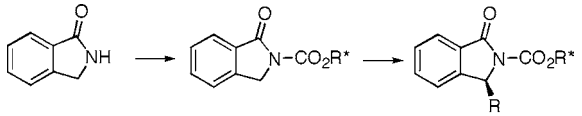
mediated carbanion method.[16] Both the carbocationic approach developed by Allin[15c] and the carbanion method reported by Royer[16] use an (*R*)-phenylglycinol unit as a chiral appendage to control diastereoselectivity. Modest to high stereoselectivity can be obtained using these two asymmetric methods. A disadvantage to using an incorporated phenylglycinol unit as the chiral appendage is that its cleavage is harsh (concentrated H_2SO_4)[15d] or tedious requiring three steps (mesylation, elimination, and acid hydrolysis).[15c] As a result of our interest in pursuing the synthesis of isoindoline-containing natural products, we decided to investigate an asymmetric synthesis of 3-substituted isoindolinones via a carbanion method using an easily cleaved and recoverable chiral auxiliary. Given our success at using (+)- and (−)-*trans*-2-(α-cumyl)cyclohexanol (TCC) as the chiral auxiliary for 1-acylpyridinium salt reactions,[17] we prepared *N*-acylisoindolinone **2** (R* = (+)-TCC) and studied its deprotonation and asymmetric alkylation (Scheme 1).

Scheme 1



Isoindolinone **1** was treated with *n*-butyllithium and (+)-TCC chloroformate to give the *N*-acyl derivative **2** in 90% yield. A deprotonation study indicated that NaHMDS was the base of choice. Anion formation at −78 °C in THF and addition of an electrophile provided the 3-substituted isoindolinones **3** in high yield and with excellent diastereoselectivity as shown in Table 1. The stereochemistry of **3d** was established by single-crystal X-ray analysis.

Table 1. Asymmetric Alkylation of **2**

entry	R-X	3	yield[a] (%)	$[\alpha]_D$[b]	de[c] (%)
1	CH_2=$CHCH_2Br$	**3a**	83	+35° (*c*, 1.35)	97
2	BnBr	**3b**	89	+91° (*c*, 0.70)	97
3	$(CH_3)_2CHI$	**3c**	76	+79° (*c*, 0.45)	97
4	MeI	**3d**	86	+38° (*c*, 0.86)	99
5	CH≡CCH_2Br	**3e**	84	+90° (*c*, 1.28)	98
6	$I(CH_2)_4Cl$	**3f**	74	+47° (*c*, 0.80)	97

[a] Yields are for the major diastereoisomer isolated. [b] The solvent was $CHCl_3$. [c] The de was determined by HPLC analysis of the crude product.

The high degree of asymmetric induction observed was anticipated on the basis of the molecular mechanics calculation depicted in Figure 1. The phenyl ring of the TCC auxiliary clearly blocks the bottom face of the stabilized anion.

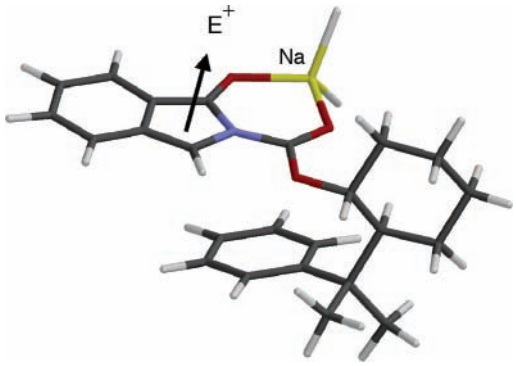
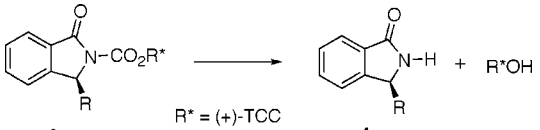


Figure 1. Low energy conformation of the sodium enolate of **2** (MMFF).

We next looked at the removal of the chiral auxiliary (Table 2). Initial attempts using lithium methoxide (entry 2) and K_2CO_3/MeOH (entry 5) resulted in efficient cleavage of the N-acyl group, but significant racemization at C-3 occurred. Fortunately, the racemization problem was circumvented by using magnesium methoxide in methanol at room temperature. In this manner, (*S*)-3-alkylisoindolinones **4** were isolated enantiopure in excellent yield. In addition, the TCC auxiliary can be readily recovered (90−95%). All of the products (entries 7−12) exhibited a minus specific rotation value which corresponds to the 3*S* configuration.[11,15e]

Table 2. Removal of the Chiral Auxiliary from **3**



entry	3	conditions	yield[a] (%)	$[\alpha]_D$[b]	ee[c] (%)
1	**3a**	LiOMe, MeOH, rt	0		sm
2	**3a**	LiOMe, MeOH, reflux	85		racemization
3	**3d**	10% HCl, MeOH, rt	0		sm
4	**3d**	K_2CO_3, MeOH, rt	0		sm
5	**3d**	K_2CO_3, MeOH, reflux	93		racemization
6	**3d**	LiOMe, 30% H_2O_2, rt	0		sm
7	**3a**	$Mg(OMe)_2$, MeOH, rt	92	−70° (*c* 0.63)	>99
8	**3b**	$Mg(OMe)_2$, MeOH, rt	99	−65° (*c* 0.53)	99
9	**3c**	$Mg(OMe)_2$, MeOH, rt	98	−40° (*c* 0.38)	>99
10	**3d**	$Mg(OMe)_2$, MeOH, rt	92	−34° (*c* 0.26)	>99
11	**3e**	$Mg(OMe)_2$, MeOH, rt	93	−57° (*c* 0.43)	99
12	**3f**	$Mg(OMe)_2$, MeOH, rt	90	−44° (*c* 0.40)	99

[a] Purified by radial PLC. [b] Solvent was CH_2Cl_2. [c] The ee was determined by chiral column HPLC analysis.

With the asymmetric synthesis worked out, we decided to test the methodology against the rigor of natural product

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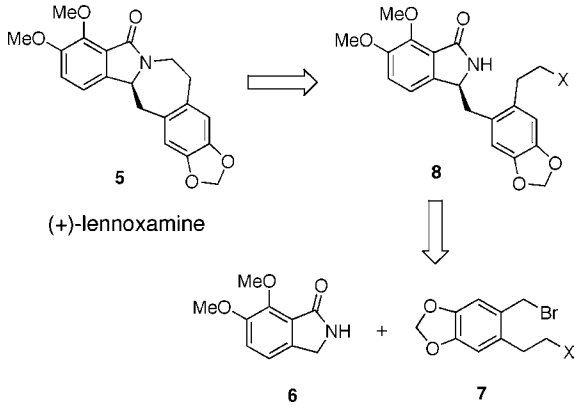
synthesis. We turned our attention to applying our method to the total synthesis of (+)-lennoxamine,[18] a naturally occurring isoindolobenzazepine alkaloid.

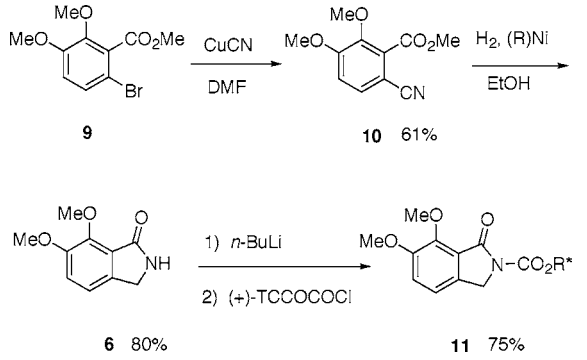
The synthesis plan followed the retrosynthetic analysis shown in Scheme 2. The known isoindolinone **6**[19] was

Scheme 2



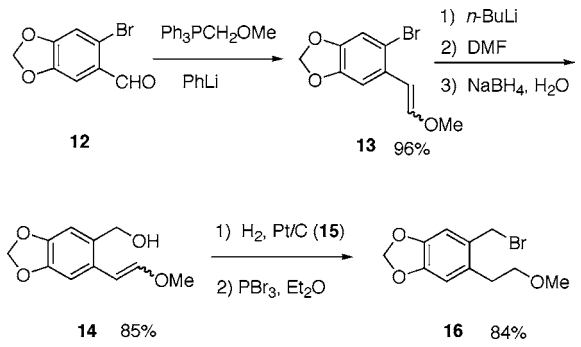
prepared in four steps from commercially available 2,3-dimethoxybenzoic acid by bromination using dibromodimethylhydantoin (DBDMH),[20] esterification, cyanation, and then hydrogenation as depicted in Scheme 3. *N*-Acylation as before provided the TCC-carbamate **11**. The required

Scheme 3



benzyl halide was synthesized from 6-bromopiperonal (**12**) in four steps (Scheme 4). Olefination using the Levine reagent[21] gave the vinyl ether **13** in high yield. One-pot

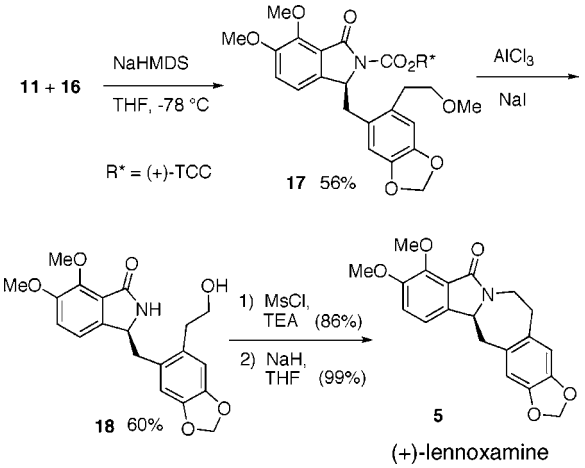
Scheme 4



lithium-bromide exchange, formylation, and reduction provided alcohol **14**. Hydrogenation of the vinyl ether and subsequent treatment of the resulting alcohol (**15**) with PBr_3 afforded the desired benzyl bromide **16**.

The joining of isoindolinone **11** and bromide **16** proved to be more problematic than anticipated. As a result of the presence of two methoxy groups in **11**, the anion formed on deprotonation was not very stable. The best conditions found for the alkylation step involved adding a mixture of **11** and **16** to 1.1 equiv of NaHMDS at −78 °C. In this manner, a 56% yield of **17** was isolated as a white solid (Scheme 5).

Scheme 5



Selective demethylation and chiral auxiliary cleavage was effected using $AlCl_3$/NaI[22] to give alcohol **18** in 60% yield. Finally, mesylation and cyclization using NaH provided (+)-lennoxamine (**5**) in high overall yield for the two steps. Our synthetic **5** (mp 232−234 °C, $[\alpha]^{23}_D$ +28 (*c* 1.0, $CHCl_3$)) was configurationally stable and shown to be enantiopure by chiral column HPLC analysis.

In summary, an efficient and practical asymmetric synthesis of 3-alkylisoindolinones has been developed. This

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method was used in the first enantioselective synthesis of the isoindolobenzazepine alkaloid, lennoxamine.

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Supporting Information Available: General experimental procedures for the preparation of **3** and spectral data for compounds **2**, **3**, **4e**−**f**, **5**, **11**, **13**−**18**. ORTEP plot and X-ray crystal data for **3d** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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