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Synthesis of (−)-Lasubine(I) via a Planar Chiral [(η^6-arene)Cr(CO)$_3$] Complex

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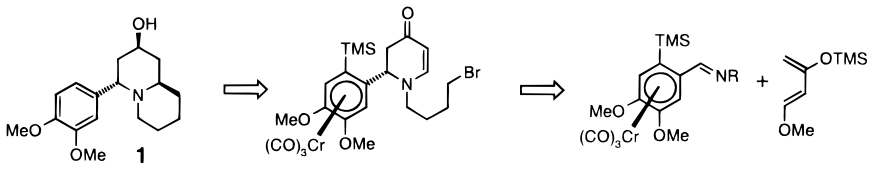
ABSTRACT



Key steps of the synthesis of the Lythraceae alkaloid (–)-lasubine(I) are the formation of an enantiopure planar chiral arylaldehyde tricarbonylchromium complex and highly diastereoselective aza-Diels–Alder cycloaddition and intramolecular radical cyclization reactions to afford a quinolizidinone intermediate. Ketone reduction, desilylation, and decomplexation yield the enantiomerically pure product.

Lasubine(I) (**1**), first isolated from the leaves of *Lagerstroemia subcostata* Koehne by Fuji et al. in 1978, is a phenylquinolizidine alkaloid from the Lythraceae family of alkaloids.[1] The literature contains a number of reports of racemic syntheses of **1**,[2] but to our knowledge there has been only a couple of reports on the synthesis of (−)-lasubine-(I).[3] The key step in Comins and LaMunyon's elegant approach is a highly diastereoselective nucleophilic addition to a chiral pyridinium salt.[3b] The new synthesis reported here entails diastereoselective sequential aza-Diels−Alder/intramolecular radical cyclization reactions[4] carried out with the enantiomerically pure planar chiral (arene)chromium complex (1*S*)-(+)-**3a**.

The requisite 4,5-dimethoxy-2-(trimethylsilyl)benzaldehyde (**2a**) was obtained in two steps in 66% yield by bromination of veratraldehyde followed by halogen/lithium exchange and silylation.[5,6] Complexation of the dimethyl acetal of **2a** followed by acetal hydrolysis afforded *rac*-**3a**, which was readily resolved via imine formation with L-valinol.[7] Alternatively, following a procedure described by Alexakis et al., we converted **2a** into the chiral aminal **4a**. Complexation of **4a** gave complex **5a** with a diastereomeric excess of 84%, and chromatography followed by hydrolysis afforded the enantiomerically pure (1*S*)-(+)-**3a** (Scheme 1).[8] The drawback of this more elegant synthesis is the modest yield (35%) obtained. The absolute configuration was assigned on the basis of comparison of the CD spectrum of (+)-**3a** with spectra of analogous planar chiral aryl aldehyde complexes of known configuration.[9]

Conversion of the aldehyde complex (+)-**3a** to the aldimine complex (+)-**6a** was quantitative.[4] Aza-Diels−Alder reaction with Danishefsky's diene mediated by $SnCl_4$ afforded the (+)-(2-aryl-2,3-dihydro-4-pyridinone)Cr(CO)$_3$ complex (+)-**7a**.[4] While a single diastereoisomer was formed in this reaction, the yield was a modest 48% (Table 1). In accord with literature precedent of addition reactions to *o*-silyl benzaldehyde complexes,[7] we attribute this to steric

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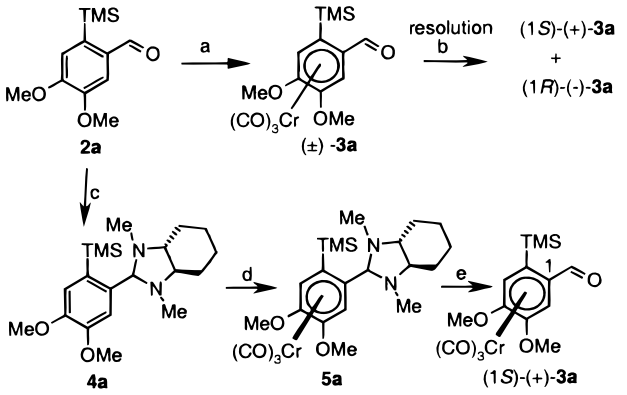
Scheme 1. Preparation of [(+)-(4,5-dimethoxy-2-(trimethylsilyl)benzaldehyde)$Cr(CO)_3$] (**3a**)[a]



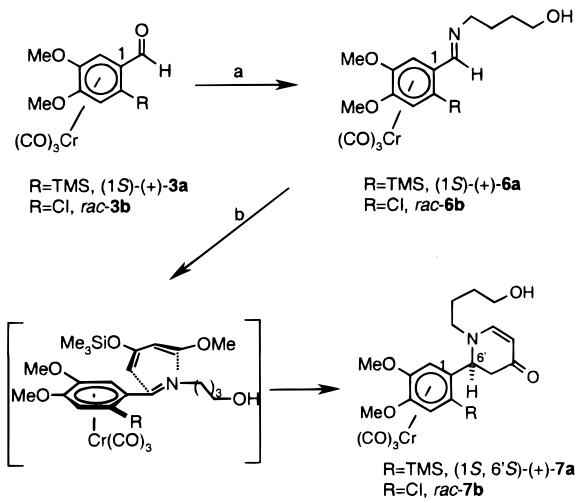
[a] Legend: (a) (i) $HC(COMe)_3$, MeOH, *p*TsOH, MS 4×81 Å, 98%, (ii) $Cr(CO)_6$, *n*Bu_2O, THF, 140 °C, 80%, (iii) HCl, THF, 98%; (b) (i) L-valinol, Et_2O, MS 4 Å (ii) column chromatography, then HCl, THF, ee >99%; (c) (*R*,*R*)-1,2-bis(methylamino)cyclohexane, MS 4 Å, Et_2O, 95%; (d) $Cr(CO)_6$, *n*Bu_2O, THF, 140 °C, 35%, de 84%; (e) column chromatography, then HCl, THF, 95%, ee >99%.

hindrance by the trimethylsilyl group in the diene approach to the imine *si*-face. Indeed, a smaller R group (e.g., R = Cl in *rac*-**3b**) resulted in a more efficient reaction (Table 1, entry 4).

Mesylate formation and substitution by bromide gave the complex (+)-**8a** (92% yield). The stage was now set for the intramolecular radical cyclization, which was carried out in refluxing benzene under nitrogen in the presence of tributylstannane and a catalytic amount of AIBN. In an earlier study, Beckwith et al. reported that radical cyclization in a phenyl-substituted dihydropyridinone lacking an amide oxygen atom proceeds with low diastereoselectivity (*trans*:*cis* = 3:1).[2b] With a $Cr(CO)_3$-complexed arene, diastereoselectivity is much higher for this transformation.[4] The complex *rac*-**8c** (R = H) afforded the quinolizidinone *rac*-**9c** with a 9:1 *trans*:*cis* selectivity, and the reaction with (+)-**8a** gave a single diastereoisomer ((−)-**9a**) in 90% yield.

Arguably, this high selectivity is the result of the preferred conformation at C(6′) (minimization of $A_{1,3}$ strain). Intramolecular radical addition to the C_β-*re* face of the enone is then much easier than to the C_β-*si* face, where the alkyl chain would bump into the $Cr(CO)_3$ group (Scheme 2).

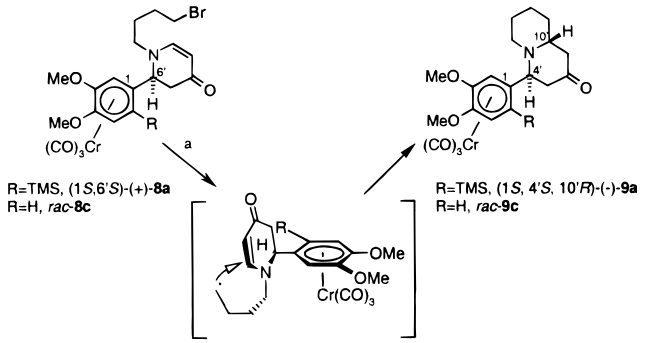
Table 1. Diastereoselective Aza-Diels−Alder Cycloaddition[a]



entry	R	amt of $SnCl_4$ (equiv)	yield (%)
1	TMS	1.0	15
2	TMS	1.6	48
3	TMS	2.0	35
4	Cl	1.2	70

[a] Legend for reaction: (a) 4-Aminobutan-1-ol, Et_2O, MS 4 Å, 98%; (b) Danishefsky's diene 2 equiv, $SnCl_4$, THF, −78 °C to room temperature, 16 h. The de value for all entries is >98%; it was determined by ^1H NMR for the crude product.

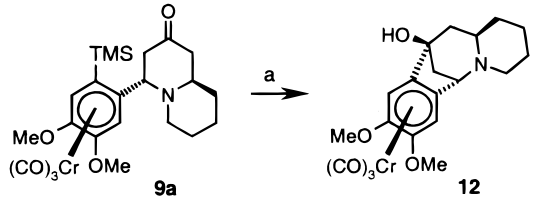
Scheme 2. Diastereoselective Radical Cyclization[a]



[a] Legend: (a) AIBN 5%, $HSnBu_3$ 1.5 equiv, benzene, reflux, 2 h, 90% yield, >98% de (−)-**9a**. dr = 90:10 for *rac*-**9c**.

The synthesis of (−)-lasubine(I) next requires desilylation of the arene in (−)-**9a**, diastereoselective ketone reduction, and decomplexation. However, attempted realization of this sequence resulted in an efficient but undesirable intramolecular cyclization to product **12** (Scheme 3).[10]

Scheme 3[a]

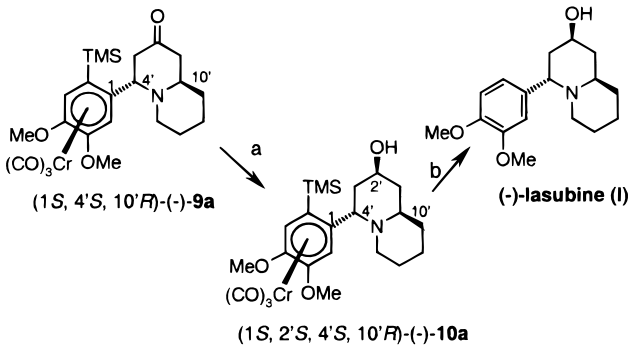


[a] Legend: (a) TBAF, THF, 85%.

Ketone reduction was therefore carried out first. As found in the reduction of the uncomplexed arene, the use of $NaBH_4$

(11) The intermolecular desilylation/carbonyl addition of $(CO)_3Cr-Ar-SiMe_3$ has precedent: (a) Effenberger, F.; Schoellkopf, K. *Chem. Ber.* **1985**, *118*, 4356. (b) Mandal, S. K.; Sarkar, A. *J. Org. Chem.* **1998**, *63*, 5672.

Scheme 4. Diastereoselective Ketone Reduction, Desilylation, and Decomplexation[a]



[a] Legend: (a) L-Selectride, THF, −78 °C, 94%, de >98%; (b) (i) TBAF, THF, 93%, (ii) light, air, CH_3CN, 0.5 h, 84%.

gave a 1:1 mixture of diastereomers but L-Selectride produced a single diastereoisomer.[2e] Desilylation of (−)-**10a** with TBAF in THF followed by an unusually rapid oxidative metal removal afforded enantiomerically pure (−)-lasubine-(I) in 84% yield (Scheme 4).[11]

In summary, an enantio- and diastereoselective synthesis of (−)-lasubine(I) has been achieved, providing a new and efficient route to quinolizidine alkaloids. The synthesis also shows how the stereodirecting and activating $Cr(CO)_3$ group is compatible with a variety of reaction conditions but is easily removed at the end of the sequence.

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Supporting Information Available: Experimental procedures and full characterization data for compounds **3a**−**10a** and (−)-lasubine(I). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Longer exposure to light/air led to rapid product degradation.