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Generation of All-Carbon Quaternary Stereocenters at the C-3 Carbon of Lactams via [3,3]-Sigmatropic Rearrangement and Revision of Absolute Configuration: Total Synthesis of (−)-Physostigmine

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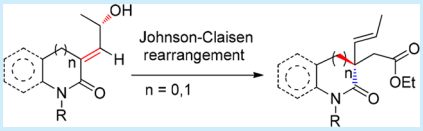
Supporting Information

ABSTRACT: A diastereoselective (up to >99%) route to all carbon quaternary stereocenters at the C-3 position of cyclic lactams has been developed via Johnson−Claisen rearrangement of γ-hydroxy-α,β-unsaturated lactams. It has been observed that olefin geometry plays an important role in the development of the absolute stereochemistry of the product. Dependence of product configuration on the olefin geometry is explained by postulating probable transition states. The success of this method has been shown for multigram-scale synthesis of these substituted lactams from commercially available cheap starting materials. The synthetic usefulness of this method is also demonstrated by carrying out the total synthesis of (−)-physostigmine.



3,3-Dialkyl-substituted cyclic lactams or their corresponding amines are privileged structural motifs constructing the core of many biologically active alkaloids (**1**−**2**)[1] and pharmaceuticals (**3**−**5**) (Figure 1).[2] Although few attractive chiral auxiliary based

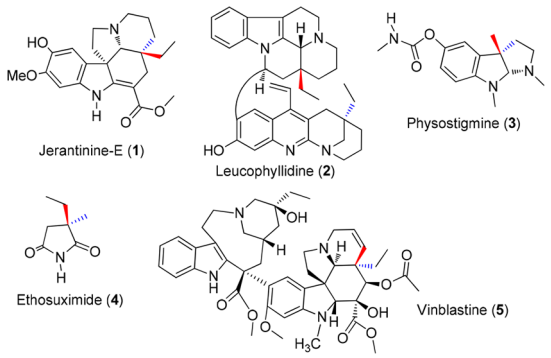


Figure 1. Representative examples containing all-carbon quaternary centers at the C-3 position of lactams/amines.

strategies for the construction of 3,3-dialkylated pyrrolidinone and piperidinone moieties are known, diastereoselectivities in most of these cases remains low to moderate.[3−5] Our own approach in this regard, using Birch reduction followed by alkylation of (*S*)-prolinol derived nicotinic acid derivative further functional group transformation, provides >99% ee of the 3,3-dialkylated piperidinone moiety. Moderate yield coupled with the limitation to only one enantiomer of the piperidinone moiety restricts its wide applicability.[6] Recently, palladium-catalyzed decarboxylative allylic alkylation of lactams to form 3,3-dialkyl-substituted lactams in good to excellent enantiomeric excess (88−99%) was reported.[7]

Because of our continuing interest in the synthesis of structurally complex biologically active alkaloids[6,8] and the challenge associated with the construction of 3,3-dialkyl cyclic lactams/amines, we evaluated using 3,3-sigmatropic shift (Johnson−Claisen rearrangement)[9,10] strategy from the substrate of type **6** for the construction of all carbon quaternary stereocenters at the C-3 position of cyclic lactams as shown in Scheme 1. We have reported this concept previously,[11] but during the synthesis of leucophyllidine (**2**)[12] we realized that the absolute configuration at C-3 position was incorrectly assigned.

Scheme 1. Proposed General Concept for the Construction of All-Carbon Quaternary Stereocenters of Lactams

Therefore, we disclose herein the correct assignment of absolute configuration at the C-3 position of lactams and the success of our concept as outlined above for preparing lactams of type **7** in high yield (88−97%) and excellent diastereoselectivity (up to >99%). It was also found that the stereochemistry of **7** is dependent both on the olefin geometry as well as on the configuration of the secondary alcohol **6** and the advantage of the same is exploited to produce both enantiomers of **7**. Application of this method is also demonstrated by developing a synthetic route to (−)-physostigmine.

Initially, we evaluated establishing the validity of the concept (Scheme 1) by constructing all-carbon quaternary stereocenters at the C-3 position of the piperidinone ring system. Toward this

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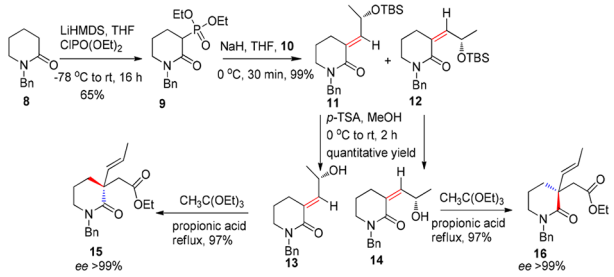
end, a multigram scale (25.0 g, 99% yield) preparative route for **11** and **12** (de = **11**:**12** = 1:1.5) was worked out using Wittig−Horner olefination[13] of **9** with −OTBS-protected L-lactaldehyde (**10**).[14] Precursor **9** was obtained in 65% yield by the reaction of the 1-benzylpiperidin-2-one (**8**) with LiHMDS followed by the addition of diethyl chlorophosphate (Scheme 2). Pure

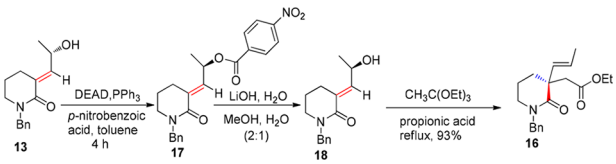
Scheme 2. [3,3]-Sigmatropic Rearrangement of 13 and 14



diastereomers were easily purified by column chromatography (230−400 mesh silica; EtOAc/*n*-hexane as an eluent). In order to proceed further with the 3,3-sigmatropic rearrangement, the silyl groups of **11** and **12** were deprotected separately using *p*-toluenesulfonic acid in methanol.

Compound **13** was subjected to standard Johnson−Claisen rearrangement (triethyl orthoacetate, propionic acid, reflux),[15,16] which gave **15** in 97% isolated yield and >99% enantiomeric purity (determined by chiral-phase HPLC analysis, Chiralcel OD-H, 2-propanol/*n*-hexane; 10:90).[17] Under the same reaction conditions, however, **14** produced the corresponding opposite isomer **16** in 97% yield and >99% enantiomeric excess. In order to confirm this observation, the configuration of secondary alcohol **13** was inverted by the Mitsunobu's reaction[18] followed by the ester hydrolysis using LiOH and H_2O. The resultant **18** on usual rearrangement produced **16** in 93% yield (ee = 97%) (Scheme 3).[19a]

Scheme 3. [3,3]-Sigmatropic Rearrangement of 18



This observation suggests that the stereochemistry of the Johnson−Claisen rearrangement does not depend only on the −C−OH stereochemistry but is also guided by the geometry of the olefin.[19b] These observations are tentatively explained with the help of the proposed transition states (TS, **13b**−**18b**) as shown in Figure 2. It appears that in **13b** suprafacial approach of the incoming $-CH_2CO_2Et$ group moves the **C3**−**C4** bond above the plane leading to the formation of **15**, whereas **16** is formed by involving **14b**, where owing to the *Z*-geometry of the olefinic bond the **C3**−**C2** bond is pushed above the plane by the $-CH_2CO_2Et$ group. Furthermore, through **18b** it may be clearly visualized that suprafacial attack of the incoming group forces **C3**−**C4** bond below the plane for the formation of **16**.

With this promising result in hand, we explored this strategy further with the pyrrolidinone derivatives **22** and **23** as well by following the identical experimental conditions as discussed above and obtained corresponding 3,3-dialkylated derivatives **24** and **25** as shown in Scheme 4.

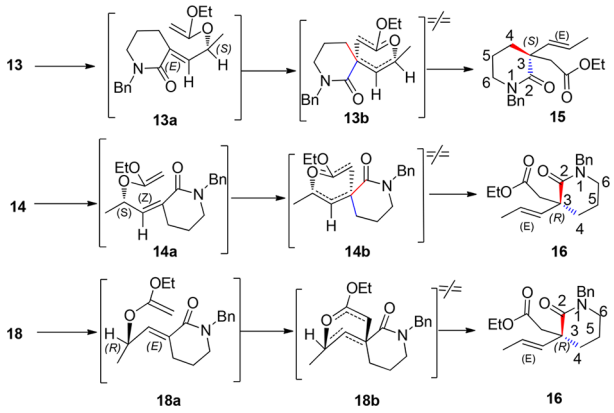
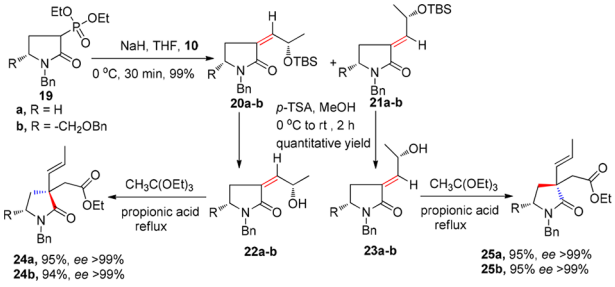


Figure 2. Transition state for [3,3]-sigmatropic rearrangement.

Scheme 4. [3,3]-Sigmatropic Shift of 22 and 23



Furthermore, we desired to extend this method to construct an oxindole framework containing all-carbon quaternary stetreocenters at the C-3 position. 3,3-Dialkyl-substituted oxindole derivatives serve as precursors for the synthesis of spirooxindoles, pyrroloindolines, and furanoindolines ring systems, which are privileged heterocyclic structural frameworks composed of a large number of biologically active natural products and pharmaceutically active agents.[20] Although there are several interesting approaches known for the construction of enantomerically pure 3,3-disubtituted oxindoles,[21−30] developing another conceptually new strategy, as shown in Scheme 6, would enhance the repertoire of synthetic methodologies in this field. Thus, in order to prepare oxindole rearrangement precursor **29** and **30**, Wittig−Horner olefination of **26a** produced **27a** and **28a** (1:4) in total 89% yield. Johnson−Claisen rearrangement of the corresponding −OTBS deprotected **29a** as well as **30a**, produced **31a** (ee = 77%) and **32a** (ee = 79%),[17] respectively, in excellent yield. It may be worth mentioning that, unlike in the case of **13**−**14** and **22**−**23**, here enantioselectivity was comparatively low. This result led us to speculate that isomerization of the olefin geometry during the reaction may possibly be responsible for this observation. Therefore, appropriate controlled experiments were carried out which ascertained that isomerization of the olefinic double bond does happen both in the presence of room light as well as with propionic acid.[31] The generality of this rearrangement was also established by studying various other substrates (**29b**−**d** and **30b**−**d**) as shown in Scheme 5.

Physostigmine (**3**), isolated from *Physostigma venenosum*,[32] is a clinically used molecule for the treatment of glaucoma and myasthenia gravis and also is a therapeutic agent for Alzheimer's disease.[33] Owing to interesting biological activities associated with this molecule, the attention of many synthetic chemists is drawn toward its asymmetric synthesis.[34] Because of our

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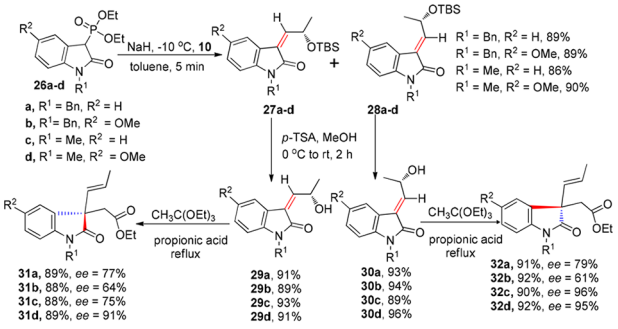
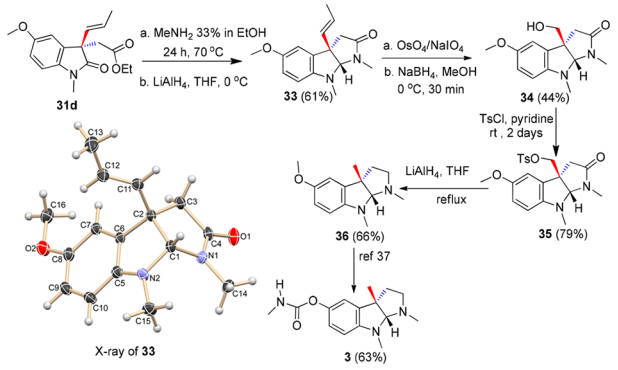
Scheme 5. [3,3]-Sigmatropic Rearrangements of Oxindole Derivatives 29 and 30



Scheme 6. Total Synthesis of (−)-Physostigmine

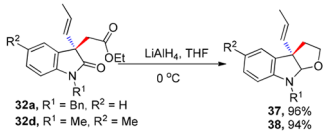


interesting strategy for easily constructing structural frameworks of type **31** and **32**, we were motivated to employ our strategy for the synthesis of **3**. In this context, **33** was prepared in 61% yield by the reaction of **31d**[35] with ethanolic methylamine followed by $LiAlH_4$ reduction. The absolute configuration of **33** was confirmed through X-ray crystal structure analysis (see the Supporting Information).

The oxidative cleavage of the olefinic double bond of **33** using $OsO_4/NaIO_4$ produced corresponding aldehyde, which upon reduction with $NaBH_4$ in methanol gave **34** in 44% yield. Tosylation (TsCl, pyridine) of **34** followed by reduction with LAH in refluxing THF produced (−)-esermethole[36] (**36**, 66%), which was transformed to **3** using previously reported protocols[37] (eight linear steps, 8.8% overall yield starting from **31d**). After **3** was synthesized successfully from **32d**, it was also visualized that the furanoindoline heterocyclic moiety could be constructed from **32** by simplifying its reduction. Furanoindoline structural motifs are recently being evaluated as drug candidates for the treatment of Alzheimer's disease.[38] Thus, reduction of **32a** as well as **32d** using LAH (THF, 0 °C) was carried out to obtain corresponding furanoindolines **37** and **38**, respectively, in excellent yield as shown in Scheme 7.

In conclusion, we have developed a conceptually new route for the construction of enantiomerically pure all carbon quaternary stereocenters at the C-3 position of cyclic lactams by Johnson−Claisen rearrangement of corresponding γ-hydroxy-α,β-unsaturated lactams. The success of this method has been demonstrated for the synthesis of both enantiomers on a multigram scale from a common precursor. The application of this method has been shown by the total synthesis of (−)-physostigmine. Further exploration of this method in the synthesis of other biologically active alkaloids is in progress.

Scheme 7. Synthesis of Furanoindolines



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03537.

Details of the experimental procedure and characterization data for all new compounds (PDF)

Accession Codes

CCDC 1585505 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(15) For details of the optimization study, see the Supporting Information.

(16) Compound **13** was successfully converted to **15** on a 10.5 g scale without affecting the yield and enantiomeric excess.

(17) See the Supporting Information for the preparation of the corresponding racemic compound.

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(31) (a) Controlled experiment by refluxing **29a** in toluene in the presence of propionic acid produced a mixture of **29a: 30a** (59:41) within 2 h which indicates that the enantioselectivity is not controllable and it could vary in case of oxindole ring system.. (b) DFT calculation study shows energy difference between **29d** and **30d** is only 3.31 kcal/mol (see Supporting Information)..

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